American Herbal Pharmacopoeia®
and Therapeutic Compendium

Cranberry Fruit

Vaccinium macrocarpon **Aiton**

Standards of Analysis, Quality Control, and Therapeutics

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To Dr Boxin Ou, whose many scientific accomplishments have enriched the world of medicinal plant research, this monograph is lovingly dedicated.

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NOMENCLATURE

Botanical Nomenclature

Vaccinium macrocarpon Aiton

Botanical Family

Ericaceae

Pharmacopoeial Nomenclature

Fructus macrocarponii

Pharmacopoeial Definition

Cranberry fruit consists of the fresh or dried whole, crushed, or powdered mature fruits of *Vaccinium macrocarpon Aiton* conforming to the methods of identification and standards provided.

Common Names

Wampanoag:	Ibimi; sasumuneash [sassamenesh] (Algonquin)
United States:	Cranberry (standardized common name); American cranberry, large cranberry (McGuffin et al. 2000)
Spain	Arandáno
France	Canneberge
Germany	Moosbeere (großfrüchtige), Kranbeere
Italy	Mirtillo rosso

HISTORY

The fruit of cranberry, or more specifically, the juice of cranberry, is by far the most popular and widely used botanical preparation for the prevention and treatment of urinary tract infections. Cranberry juice is popularly used among health practitioners, is given freely to residents of nursing care facilities, and is one of the most commonly used home remedies among consumers. Indigenous to North America, cranberry was consumed broadly by numerous Native Americans as a food and medicine, including by the Wampanoag, the first East Coast tribe encountered by the English (pilgrims) in Massachusetts. Cranberry's popular use as a food, especially as a sauce—considered integral to a uniquely North American holiday, Thanksgiving—is well known. In 1789, the fruit was so in demand that over-harvesting by early European immigrants forced the New Jersey legislature to restrict the harvesting of unripe berries (Eck 1931).

Nomenclatural History

The genus name of cranberry is believed to derive from the Latin *vaccinus*, meaning dun-colored, while the species name is from the Greek *makro*, or large, and karpós, meaning fruit. The common name cranberry is thought to be a derivation of the early name craneberry, which reportedly has two origins; the first a botanical reference regarding the stamens that resemble the beak of a crane; the second, due to the reported fondness of marsh cranes for the berry. Regardless of which is true, writings of the middle 1600s variably use the names cranberry, cramberry, and craneberry.

Native American Use

Native Americans living in northern regions commonly consumed various species of *Vaccinium*, including *Vaccinium macrocarpon*, *V. oxycoccos*, and *V. vitis-idaea* (also known as mountain cranberry or lingonberry) for their tart flavor and nutritive value. According to the oral history of the Wampanoag of Cape Cod, Massachusetts, the originating location of the first colonial Thanksgiving, cranberries (sasumuneash or ibimi) were cooked in stews. The name ibimi refers to the bitter or sour taste of the fruits (Whitman-Salkin 2013). The Ojibwa, Iroquois, Huron, Mi'kmaq (Micmac), Anticosti, Anishinaabe (Chippewa, Ojibwa), Algonquin (Moerman 2014), Cree, Malecite (Kuhnlein and Turner 1991), Potawatomi, Gitksan, Menomini (Smith et al. 1997), Coast Salish, Nlaka'pamux (Thompson) (Turner et al. 1990), Dena'ina, and Nuu-chah-nulth (Nootka, including Hesquiaht) (Turner and Efrat 1982), and Ditidaht (Nitinaht) (Turner et al. 1983) were all known to have eaten the *Vaccinium* fruits (Kuhnlein and Turner 1991).

Figure 1 Historical illustration of cranberry

Source: *Vaccinium macrocarpon.* Amanda Almira Newton 1913. US Department of Agriculture Pomological Watercolor Collection. Rare and Special Collections, National Agricultural Library, Beltsville, MD 20705.

The Anishinaabe (Ojibwa) of the Great Lakes region called the cranberry *a'ni-bimin*, which means "bitter berry." The Narragansett in the region of today's Rhode Island, called the berries *sasemineash*, and, according to Roger Williams in his 1643 Key *Into the Languages of America*, described cranberry as sharp and cooling and some fruits opening and others binding, being used for "feavors of diverse kinds." According to Le Sueur (1657–1704), the first European explorer through the Minnesota River Valley, recorded an Algonquin name of cranberry as *atoqua*, meaning "good fruit." (Le Sueur 1700).

Among the most common use of cranberries by Native Americans was as a fruit ingredient in pemmican, a mix of dried meat and berries, and as a supplemental winter fruit. Throughout their growing range, native peoples stored the berries under water or stored them fresh throughout the winter, often eating with oil or grease (Turner and Aderkas 2012). The Aquinnah Wampanoag, the tribe first encountered by the Pilgrims, have observed an annual harvest of cranberries in the dunes at least since 1931, a practice that continues today on the second Tuesday in October.

Unfortunately, there is no recorded medicinal use of cranberry among tribes of Massachusetts, one of the primary growing areas for native cranberry populations. The Montagnais of Nova Scotia steeped cranberry branches to make a tea for pleurisy (Moerman 2014). According to *Cranberries—The National Cranberry Magazine* (Tomlinson 1945) the fruits (sometimes unripe) were used medicinally as a poultice for wounds, and, mixed with cornmeal, as a drawing poultice for blood poisoning. First Nation peoples in Quebec crushed and applied cranberries to facilitate the healing of cancerous sores (decubitus ulcers) (Erichsen-Brown 1979). In the early 1800s, the Massachusetts Wampanoag petitioned the Massachusetts state legislature to guarantee access to the bogs that had been handed down to them by their ancestors for centuries. The fruits were a winter staple and, according to the petition, were used predominantly by the poorest women and children of the tribe (Eck 1931).

Early History of European Immigrants

In his detailed history of cranberry, *American Cranberry* (1931), Eck reports that Captain John Smith (1580–1631), the English explorer and seminal figure in the founding of America's first colony, Jamestown, Virginia, may have been the first European to write about the cranberry as he explored the New England coast in 1614. Eck wrote: "The Herbes and Fruits are of many sorts and kinds: as Alkermes, currants, mulberries… Of certain red berries, called Kermes…" According to Eck, early Colonists found cranberry growing profusely on peat bogs at Gay Head on the island of Martha's Vineyard (off Cape Cod, Massachusetts) and in marshes along the Sudbury, Concord, Charles, and Neponset rivers in Massachusetts, in the marshes of Barnegat Bay and the swamps of Great Pine Barrens (now known as the Pinelands) in New Jersey, northward into the Maritime provinces of Canada, as far south into the Carolinas, occurring sporadically in the Allegheny Mountains and from Southern Pennsylvania to peat swamps of Virginia. As Europeans migrated west, they found wild cranberries growing in the wetlands of Indiana, Michigan, Wisconsin, and Minnesota. Wild cranberries also grow into the boreal forests of Canada and west to the Haida Gwaii islands and Alaska.

In 1647, John Eliot (1604–1690), referenced as "the Apostle to the Indians," wrote of native First Nations people bringing the fruits to market and recorded the name as "craneberry (Eliot 1647)." John Josselyn in his *New-Englands Rarities Discovered* (1672) was the first to describe the botanical characteristics of the "cran berry" or "bear berry" (not *Arctostaphylos*, which is also known as "bearberry") as well as to present the earliest written record of the use of cranberry sauce, though according to Eck (1931), Native tribes prepared cranberry sauce with maple syrup. According to EH Durrell, president of the American Cranberry Association, a letter from a Mahlon Stacey living in Falls of the Delaware (present-day Trenton, New Jersey), provides an account of the earliest record of the pairing of cranberry sauce with turkey (1689), now a staple in Thanksgiving fare, and told of Native peoples gathering the fruits and giving them to the Europeans (Durrell 1902). Durrell himself writes: "The turkey dinner without cranberry sauce would not be a turkey dinner on the bill of fare of a first-class dinner other things and fruits might be stricken off, but not cranberry sauce; this is an indispensable, a desideratum."

For the European, the mix of cranberry with meat may have been a carryover of a common Elizabethan practice of pairing barberry fruits (*Berberis vulgaris*), fruits with a similar mix of tartness and sweetness (Sumner 2004). However, it is clear from many Native American traditions, including those of the Wampanoag, that cranberry was a favored pairing with meat. The importance of cranberry to early Europeans was highlighted when, in 1677, colonists sent 10 barrels of cranberries, along with American corn, and codfish to England as an appeasement to King Charles II for the illegal minting of the first Colonial coin, the pine tree shilling. Josselyn also provides one of the earliest records of the medicinal use of cranberry in *New-Englands Rarities Discovered* (1672). Describing the fruits as "of a sower and astringent taste," Josselyn writes: "They are excellent against the Scurvy… For the heat of fevers … and to allay the fervour of hot Diseases." Considering the Pilgrims landed in the East Coast winter in December 1620, it is almost certain that cranberry was seminal in attenuating the scurvy that undoubtedly afflicted the English immigrants in their long journey overseas.

Cranberry does not appear in many of the American materia medicas of the 1700s (e.g., *Pharmacopoeia Extemporaea* of Thomas Fuller 1730; *Physico-Medicum Lexicon* of John Quincy 1757). It does appear in the first herbal produced and printed in America, the *American Herbal* of Samuel Stearns (1801). Like Josselyn, Stearns credits this fruit as being anti-scorbutic, "good in the sarcy and similar complaints." He goes on to say; "they are much used at the table and when eaten freely prove laxative," and also records cranberry's use for fevers. John Monroe in his *The American Botanist and Family Physician* (1824) records

cranberry as "a very wholesome and agreeable tart, which is good in fevers, and helps the appetite." The renowned naturalist Constantine Rafinesque mentions cranberry, as *Oxycoca macrocarpa*, in his *Medical Flora* (1828), citing its use as a food in tarts and preserves, as well as medicinally as a mild laxative, refrigerant, diuretic, anti-pyretic, and anti-scorbutic, undoubtedly simply reflecting earlier records. Cranberry occasionally occupied a place in works on the domestic practice of medicine. For example, *Gunn's Family Physician* (1863) reported on the newly "discovered" use of a poultice of raw cranberry fruits as a treatment for cancerous tumors, recounting purported cures of one case each of breast and nasal carcinoma.

Use of Cranberry by Eclectic Physicians

Henry Hollembaek (1865) appears to be the first Eclectic practitioner to include cranberry, under the name of *Oxycoca macrocarpa*, in his writings. In his *American Eclectic Materia Medica* of 1865, Hollembaek lists its virtues as a "refrigerant, diuretic, antiseptic, laxative and mild astringent." Like Gunn, he also mentions a poultice of the berries for "mortification" and gangrene, as well as for local inflammation.

Foster (1899), in his *Practical Therapeutics* gleaned from domestic and Eclectic sources, reports that the berries are "astringent, detersive, antiscorbutic and refrigerant." Felter and Lloyd (1905), in their *King's American Dispensatory*, note the use of the fruit in domestic practice as a poultice for erysipelas, inflammatory swellings, swollen glands, indolent and malignant ulcers, tonsillitis, and for boils on the tip of the nose. Despite its medicinal use by Native Americans, European immigrants, and Eclectics, cranberry did not find its way into mainstream medical practice as it was not included in early editions of the *United States Pharmacopeia, National Formulary, or United States Dispensatory.*

Figure 1b Picking cranberries circa 1904, Harwich, Cape Cod, Massachusetts

Source: Courtesy of the Harwich Historical Society, Harwich, MA.

Medical and Popular Uses of Cranberry in the 19th and Early 20th Century

German physicians in the mid-1800s provided scientific evidence of the benefits of cranberries on the health of the urinary tract. It was observed that ingestion of cranberries increased urinary excretion of hippuric acid, which was believed to have strong antibacterial activity (Schneider 1974). Hippuric acid is a metabolite of benzoic acid, a compound in cranberry juice products. Benzoic acid has strong antibacterial activity and hippuric acid is bactericidal against *E. coli* and has a potential beneficial effect for reducing stone formation (Atanassova and Gutzow 2013). There are also data suggesting that increased hippuric acid excretion is correlated with decreased saturation and dissolution of oxalic acid in human urine (Atanassova and Gutzow 2013).

In a 1902 proceedings of the 32nd annual meeting of the American Cranberry Growers' Association, the taste, quality, and medical virtues of the cranberry were extolled by EH Durrell: "In taste it is incomparably and inexpressibly pleasant… The taste of the cranberry is so delicate, gratifying, charming, and exhilarating that among fruits it has no peers. It is a tonic. In some ways, it seems to regulate and tone up the system even in the absence of alcohol." Durrell reported on a minister friend of a "somewhat weak and frail constitution" who carried fresh fruits in his pocket, eating them frequently and "claimed he was much benefited." He further reported, perhaps with credulity, the use of the fruits for the prevention of typhoid, diphtheria, yellow fever, grip, and cholera, stating these diseases to be unknown among families who eat the fruit frequently and plentifully. Durrell also reported on a physician who considered cranberry to be a specific for erysipelas. Finally, in extolling its virtues, Durrell writes of cranberry; "No other fruit is so universally prized and appreciated by all classes of the American people as the cranberry. To the poor it is a joy; to the middle classes a delight; to the rich a necessity." Considering the conflicted reports of Durrell, whose job it was to promote use of the fruit, the veracity of such claims must be questioned but never the less is part of the colorful history of cranberry.

Early researchers (e.g., Blatherwick 1914; Blatherwick and Long 1923; Fellers et al. 1933) reported on the effect of cranberries on increasing urinary acidity. In 1931, researchers isolated an anthocyanin from cranberry, naming it "oxycoccicyanin," after the then Latin name *Oxycoccus macrocarpus*. This provided one of the earliest references postulating the presence of anthocyanins in cranberry (Grove and Robinson 1931).

The culinary attributes of cranberry have long been enjoyed in North America, and never more so than in World War II. In a 1945 edition of *Cranberries—The National Cranberry Magazine*, Lieutenant Colonel Cecil G Dunn of the Quarter Master Corps wrote a letter imploring cranberry growers that it was their duty to allocate a portion of their crops to the men and women serving overseas. Dunn wrote: "This office strongly feels that it is the privilege as well as the duty of each grower to voluntarily set aside a portion of his crop for use in serving the armed forces of this country… He must not fail them! Dehydration of cranberries has yielded

an excellent product, which is one of the most popular dehydrated items used by the armed forces (Dunn 1945)."

Recent History of Cranberry Use and Study

Numerous studies from 1959 to the 1980s continued to support the health benefits of cranberry juice, primarily for the urinary tract, as well as for other indications. One of the earliest formal investigations of the antibacterial activity of a dilute cranberry juice (1 part juice, 2 parts water) occurred in 1959 (Bodel et al. 1959). These researchers suggested that hippuric acid was the mechanism behind the ongoing folkloric use of cranberries in urinary tract infections and also reported on the successful prophylactic treatment of chronic pyelonephritis.

In subsequent studies, focus was placed on the antibacterial effects of cranberry in relationship to urinary tract health. A variety of mechanisms were reported, including the ability of cranberry to decrease urinary pH, which both increased the efficacy of other antibacterial agents (Brumfitt and Percival 1962) and was beneficial in preventing and treating some renal problems (Sternlieb 1963); inhibition of growth of E. coli (Kraemer 1964); antifungal activity (Swartz and Medrek 1968; Ujvary et al. 1961); reduction of urinary ionized calcium in patients with kidney stones (Light et al. 1973); and antiviral activity (Borukh et al. 1972; Konowalchuket and Speirs 1978; Ibragimov and Kazanskaia 1981). While many of these reports lacked the methodological strength of formal modern clinical studies, they clearly suggest a trend for benefit and clinical relevance.

A number of critical reviews of the cranberry literature, including meta-analyses, have been conducted (e.g., Jepson and Craig 2007, 2008). Cochrane Reviews of 2007 and 2008 (Jepson and Craig 2007, 2008) supported the efficacy of cranberry for the prevention of urinary tract infections, while later analyses by the same group (Jepson et al. 2012), that included the same studies as the earlier positive review, reported a lack of efficacy. Clearly, the overwhelming trend of the previous meta-analyses and individual studies supports efficacy. Numerous other health benefits and actions of cranberry have been investigated including for ulcer prevention, periodontal disease, cancer prevention, viruses, and cardiovascular disease risk factors, among others.

Cranberry ("juice preparation") was included in the 19th edition of the *United States Pharmacopeia-National Formulary* (1999). The American Herbal Pharmacopoeia developed a *Cranberry Fruit Monograph* and *Therapeutic Compendium* in 2002. Today, medical herbalists, a myriad of health care professionals, and consumers commonly use cranberry as a beverage, dietary supplement, and medicine.

IDENTIFICATION

Botanical Identification

Vaccinium macrocarpon Aiton. Trailing, often ascending, evergreen shrub to 5–20 cm tall; rhizomatous. **Stem:** Slender, glabrous to hairy, rooting at nodes. **Leaf:** Simple, alternate, subsessile; blade narrowly elliptic to elliptic, rarely oblong, (5-) 7–10 (-18) mm long, (2-) 3–4 (-5) mm wide; adaxially green, abaxially glaucous; margin entire, slightly revolute. **Inflorescence:** Flowers solitary in leaf axils of current year's shoots; bracteoles 2, greenish white, 1–2 mm wide; pedicels 2–3 cm, recurved, jointed to the flower. **Flower:** Bisexual, radially symmetric with a nectariferous disc surrounding the style; calyx 4-lobed, the lobes being relatively small; corolla white to pink, cup-shaped, 4-lobed with lobes much longer than cup, and strongly reflexed at anthesis; stamens 8, filaments with stiff hairs along margins, anthers dehiscent by apical pores; ovary inferior, style 1, stigma capitate. **Fruit:** Berry, 4-loculed, globose, 9–20 mm in diameter; glabrous; red to crimson, dark burgundy, or almost black; several- to many-seeded. Seed: Hard, reddish to yellow-orange 1–2.7 mm long x 0.5–1 mm in diameter; ovate to elliptic with an acute apex; beak laterally bent; surface finely striated or longitudinally wrinkled. **Chromosome number:** n = 12.

Distribution: Bogs, swamps, wet shores; restricted to acidic soils and peat. Flowers late spring–early summer. Native to eastern North America from Newfoundland south to North Carolina and west to central Minnesota. Cultivated and/or escaped in other parts of North America and in Britain and Europe, especially Germany, Switzerland, parts of Eastern Europe, and the Netherlands, Chile, China, and New Zealand (Aiton 1789 [original citation]; Vander Kloet 2009).

Macroscopic Identification

Fresh Fruit

Surface view: Berry globose to ellipsoidal; 9 to 20 mm in diameter; red, crimson, burgundy to almost black; glabrous, with a smooth lustrous surface.

Transverse section: Mesocarp and endocarp are off-white to dull-red. The mesocarp has large air pockets (up to 2 mm thick). The fruit is 4-locular, with each locule containing 1 to 5 seeds. Each seed is narrowly ovoid to elliptic with an acute apex, 1 to 2.7 mm long and approximately 1 mm wide, with a lustrous rose to red or orange-yellow testa that is longitudinally wrinkled. The endosperm is opaque white. Note: The fresh ripe berry of different cultivars will vary somewhat in shape, size, texture, and color.

Dried Fruit

Surface view: Globose to ellipsoidal; 7 to 11.5 mm wide and 10 to 15 mm long; dark red to almost black, with a smooth but deeply wrinkled, slightly lustrous surface. At the fruit apex is the dried, slightly raised nectariferous disc, 1.5 to 2 mm across, with a shallow depression in its center inside of which is a small protuberance from the remains of the style.

Table 1 Historical timeline of the use of cranberry *(Vaccinium macrocarpon)*

Native American Uses	Cranberries used by many tribes as food. First Nation peoples in Quebec applied crushed cranberries and juice to facilitate the healing of cancerous sores.
1620	Pilgrims learn to use cranberries from the Wampanoag of Massachusetts.
1647	John Eliot, "apostle to the Indians" reports on the trading of "craneberries" by Native Americans to English immigrants.
1677	Colonists send 10 barrels of cranberries, along with American corn, and codfish to England as an appeasement to King Charles II for illegally minting a Colonial coin, the pine tree shilling.
1789	To curb overharvesting, the New Jersey legislature imposes a fine for anyone picking unripe cranberries.
1800	The Massachusetts Wampanoag petition the Massachusetts state legislature to guarantee access to cranberry bogs for use by the tribe.
1810	Cultivation of cranberries begins.
1830	Rafinesque includes cranberry in his Medical Flora, attributing to it laxative, refrigerant, diuretic, antipyretic, and anti-scorbutic properties
1845	An Act for the Protection of Cranberries on Gay Head is put forth by Gay Head Indians on Martha's Vineyard.
1850	Seamen use cranberries to prevent scurvy.
1865	Henry Hollembaek is the first Eclectic physician to publish on the medicinal use of cranberry, describing its internal use as a "refrigerant, diuretic, antiseptic, laxative and mild astringent" and its topical use against gangrene and local inflammation.
1871	American Cranberry Growers Association formed in Massachusetts.
1905	In their King's *American Dispensatory*, Felter and Lloyd note the topical use of cranberry as a poultice for erysipelas, inflammation, swollen glands, indolent and malignant ulcers, tonsillitis, and boils on the tip of the nose.
1914–1933	Researchers report on the effects of cranberry on increasing urine acidity.
1945	Quarter Master Corps implores cranberry growers to allocate a portion of their crops for military rations.
1950s	Ocean Spray begins promoting the use of cranberry for the prevention of urinary tract infections and other health benefits and popularizes its use as a beverage and food.
1959–1980s	Series of investigations and case histories demonstrating and reporting health benefits of cranberry juice in the prevention of urinary tract infections, in renal health (pyelonephritis), inhibition of *Escherichia coli (E. coli)*, and in reducing kidney stones (calcium oxalate).
1984	Sobota reports that cranberry juice inhibits adherence of *E. coli* and certain other gram-negative bacteria to some types of epithelial cells, including uroepithelial cells.
1991	Ofek et al. report that cranberry contains two types of inhibitors to bacterial adherence: fructose and a large molecular weight inhibitor, which was not identified at the time.
1994	Avorn et al. conduct the first randomized, double-blind, placebo-controlled clinical trial of cranberry juice for the treatment and prevention of asymptomatic bacteriuria and pyuria (biomarkers for urinary tract infections). Consumption of 300 mL of a cranberry juice beverage daily for 6 months reduced bacteriuria and pyuria compared to placebo.
1998	Howell et al. utilized bioassay-directed fractionation of cranberry fruit to isolate PACs and determine that these compounds prevent P-fimbriated *E. coli* adhesion to bladder cells in vitro.
1999	Cranberry Liquid Preparation is entered into the *United States Pharmacopeia 24–National Formulary 19.*
2000	Foo et al. determine that cranberry PACs that prevent bacterial adhesion have the unusual double, A-type linkages.
2002	Monograph and therapeutic compendium developed by the American Herbal Pharmacopoeia. Continued research supports the use of cranberry juice products, as well as other preparations, for urinary tract health. Numerous other health benefits and actions are identified including periodontal disease, anti-cancer, antiviral, and cardiovascular, among others.
2005	Howell et al. determine that foods containing PACs with only B-type linkages do not elicit significant bacterial antiadhesion activity in urine, as the cranberry PACs with A-type linkages do.
2007–2012	Different meta-analyses of cranberry studies report both positive (Jepson and Craig 2007, 2008; Wang et al. 2012) and negative (Jepson et al. 2012) findings regarding the efficacy of cranberry for the prevention and treatment of urinary tract infections.
2013	Comprehensive summary report on the previous and ongoing research associated with the multiple health benefits of cranberries is published (Blumberg et al. 2013).
2015	First randomized placebo-controlled trial demonstrates clinical efficacy of whole cranberry powder for reducing recurrence of UTIs (Vostalova et al. 2015).

2a

2b

2c

2d

2e

Figures 2a-d Botanical characteristics of *Vaccinium macrocarpon*

Figure 2a Historical botanical illustration of cranberry
Figure 2b Cranberry flower
Figure 2c Native cranberry bog amidst sand dunes
Figure 2d Ripe cranberry fruits
Figure 2e Cranberry seeds.

Source: Courtesy of Figure 2a Kops J. 1800. Flora Batava. Figure 2b Erika Saalau-Rojas, University of Massachusetts-Amherst, Cranberry Station; 2c & d Wisconsin State Cranberry Growers Association, Wisconsin Rapids; 2e AHP.

The fruit base bears a small scar where the berry was attached to the pedicel.

Transverse section: Mesocarp and endocarp are dull red. The mesocarp has large air pockets, and is of varying thickness when dried, ranging 0.1 to 2 mm. In cross section, the

fruit is divided into 4 chambers (locules), each running the entire length of the fruit. The locules are separated by dull red, thin, translucent septa, and each locule contains 1 to 5 seeds.

Powder: Crimson.

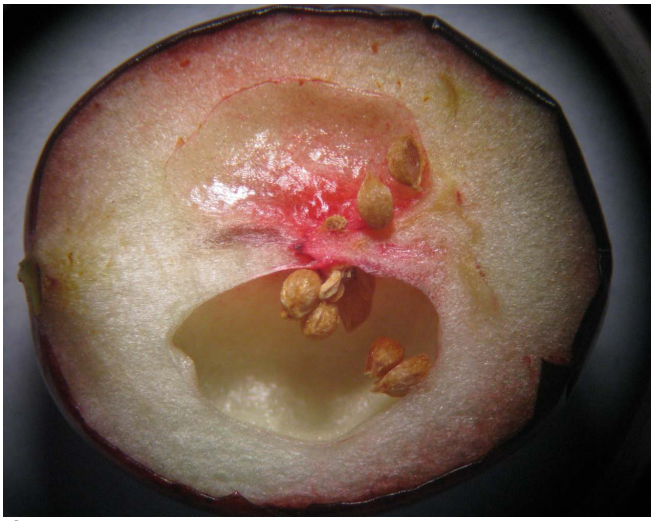
Organoleptic Characterization

Aroma: *Fresh:* Fruity; should have no smell of decay or fermentation.
Dried: Slightly fruity and sweet.

Texture: *Fresh:* Tender to firm.
Dried: Spongy, tough.

Taste: *Fresh and dried:* Very acidic, tart, with a mealy texture.

3a



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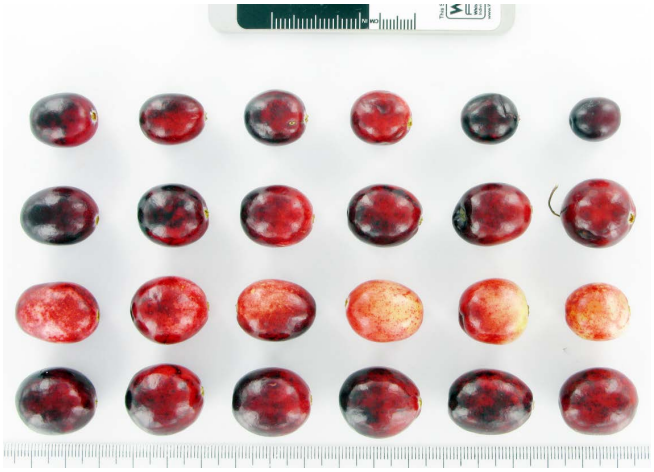

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3d

Figures 3a-d Macroscopic characters of fresh whole cranberry fruit, fresh fruit cross section, and seeds

Figure 3a Cranberry fruit close-up; note the cross where the flower was attached (left) and the point of attachment of the pedicel and berry (right).

Figure 3b Cranberry fruit cross section showing pericarp, white flesh, two seed chambers, and seeds (stereomagnification).

Figure 3c Fresh cranberry fruits.

Figure 3d Dried cranberry and cranberry powder.

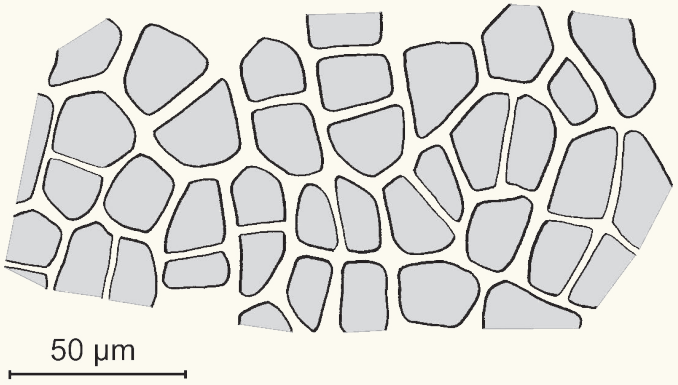
Microscopic Identification

Fruit: The exocarp consists of anthocyanin-colored polygonal cells covered by a thick cuticle. Groups of cells are separated by fairly thick, colorless walls, whereas the walls within the respective groups are very thin. The mesocarp consists of large, spherical, thin-walled cells in which small bundles of spirally thickened vessels are embedded.

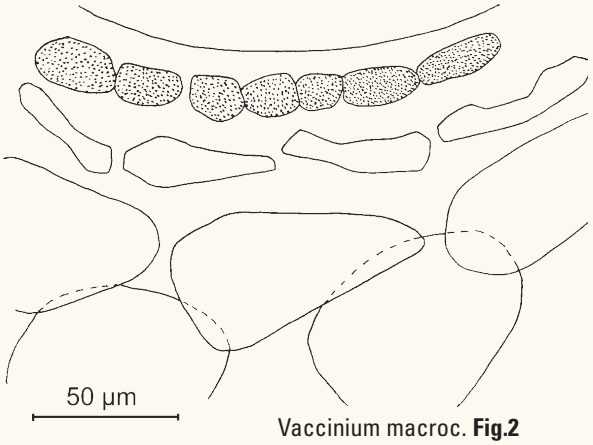
Seed (cross section): The epidermis of the testa is composed of radially elongated rectangular cells that are filled with mucilage. The walls are thickened in a U-shape, the thickest wall being the exterior one, the mucilage is radially striated, and in the center of the cell is a small lumen. Below the epidermis are several layers of polygonal cells with thick, brown, occasionally reticulately thickened walls.

These cells are from 250 to 350 μm long and approximately 80 μm broad. The innermost layer of the testa consists of compressed, rectangular cells with sinuous longitudinal walls. The voluminous endosperm is made up of small polygonal and oil-containing cells.

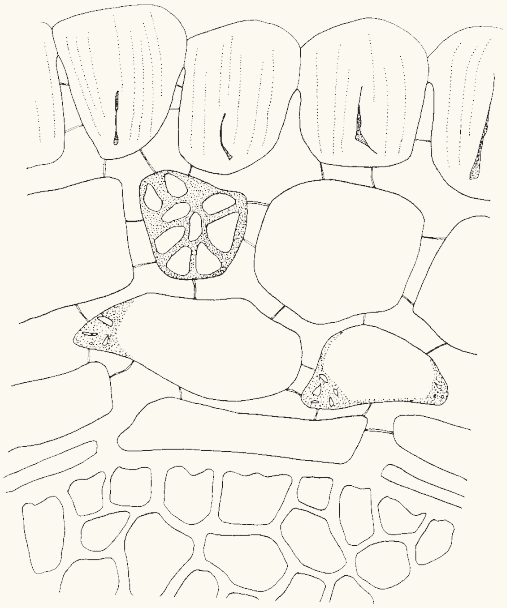
Powder: Numerous fragments of the exocarp with colorless cell walls and violet contents; thin-walled parenchyma of the mesocarp; thickened and pitted cells of the testa; oil droplets.



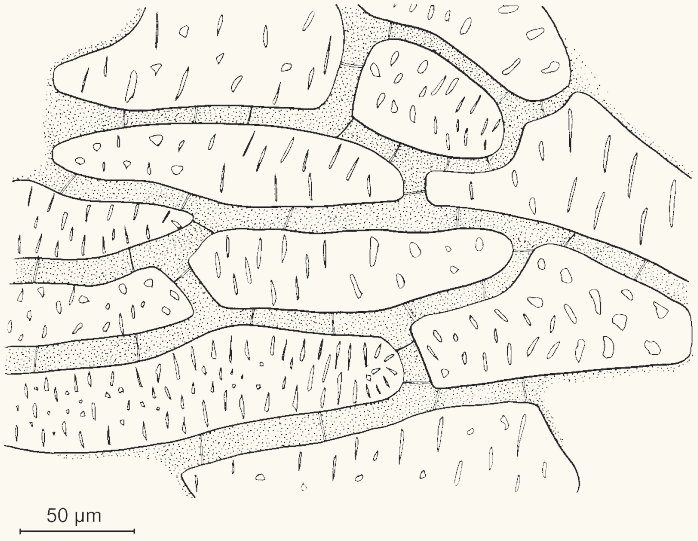
Vaccinium macroc. **Fig.1**



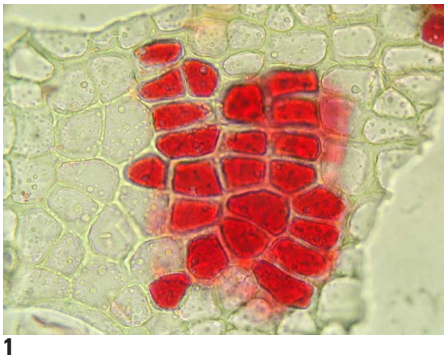
Vaccinium macroc. **Fig.2**



Vaccinium macroc. **Fig.3**



Vaccinium macroc. **Fig.4**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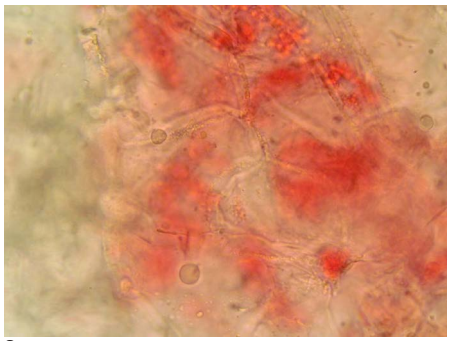
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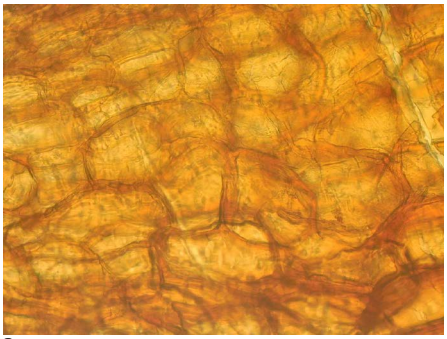
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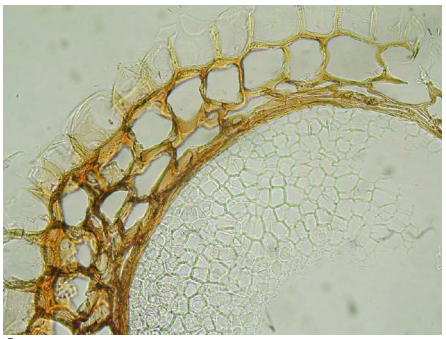
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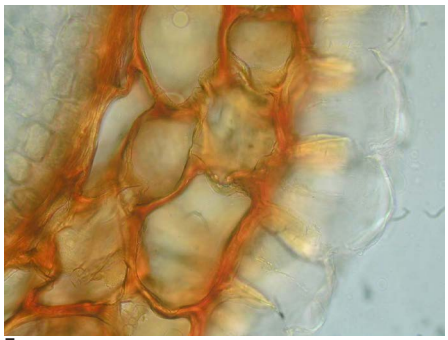
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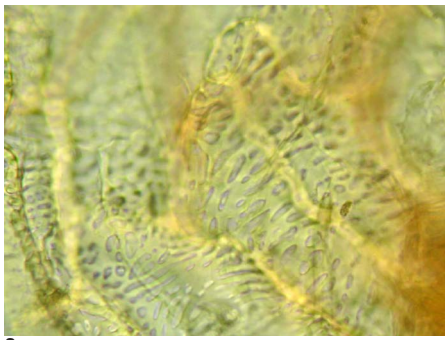
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Figure 4b Microscopic characters of cranberry fruit and seed (photographic images)

1. Powdered exocarp showing red pigment.
2. Powdered mesocarp.
3. Testa epidermis (surface view).
4. Testa (transverse view).
5. Detail of testa (transverse section).
6. Reticulately thickened cells of the testa (surface view).

COMMERCIAL SOURCES AND HANDLING

All commercial supplies of cranberry come from cultivated sources. Cranberry is grown almost entirely in northern North America, though it has been introduced to England, Europe, and parts of Asia and South America. The major producers are, in decreasing order of predominance: Wisconsin, Massachusetts, Canada (British Columbia and Quebec), New Jersey, Oregon, and Washington. Other growing regions include Delaware, Maine, Michigan, New York, Rhode Island, other Provinces of Canada (New Brunswick, Prince Edward Island, Newfoundland, Nova Scotia, Ontario) (Dorff 2014), and Chile. In 2013, the total US crop of cranberries was approximately 8.9 million barrels (one barrel holds 45 kg [100 lb] of fresh fruit) (USDA-NASS 2014) harvested from approximately 43,900 acres. There is a plethora of information regarding cranberry cultivation available online, predominantly from national authorities, state agricultural extension services, and cranberry associations, and includes best practices guidance for cultivation and integrated pest management practices (see Burgess 2007; McManus et al. 2011, among others).

Cultivation

In the wild, cranberries are adapted to the relative lack of available nutrients in their preferred sandy soils. Cranberry bogs initially developed from glacial deposits thousands of years ago, forming in *kettle holes*, which are basins lined with deposits of impermeable materials such as clay, which subsequently filled with organic matter and water. These unique biosystems gave rise to unique species, including the cranberry. Some bogs are thought to have formed more than 10,000 years ago.

Native soils in which cranberry vines grow are low in organic matter, with little clay. Since soils lose nutrients with every harvest, 3 organic fertilizers—nitrogen, phosphorus, and potassium—are often utilized. However, fertilization of cranberry plants is low in comparison with other crops (e.g., corn or soybeans). Cranberries are grown in beds that have been drained, cleared, and leveled, often with a layer of sand applied prior to planting selected vine cuttings. Cranberries require acidic soil with an optimal pH of 4 to 5.5 (Delahaut and Mahr 1998; Roper and Planer 1996; Salett 1998). The first commercial harvest may occur 3 years after planting, though it takes 5 to 7 years before full production potential is reached. A well-maintained bog can produce a viable crop annually for 60 to 100 years or more (Roper and Planer 1996; Salett 1998; WSCGA 2002). The average yield per acre nationwide 2014 was 211.6 barrels, with Wisconsin showing the highest yield per acre at 246.1 barrels (USDA-NASS 2015).

Inadequate fruit set is a major limiting factor on yields (Baumann and Eaton 1986; Birrenkott et al. 1991; Hagidimitriou and Roper 1994). Low pollination rates are one of the major reasons for inadequate fruit set (Samulis 1999). Cranberries are grown in a habitat where there are many different natural pollinators. However, growers have

found that to increase the rate of fruit set and ultimately yield, they must use commercial honeybees and bumble bees. Bees are introduced when approximately 10% of cranberries are blooming and growers typically employ between 1 to 5 hives per acre of producing bog.

Cranberry fruit anthocyanin content is affected by light, temperature, and pruning regime. Anthocyanin content is highest in plants that are grown in a sunny location (Sapers et al. 1986a) and increases with exposure to light during water immersion harvest. In one experiment, exposure to natural light increased the total anthocyanin level by 75.3% and 87.2%, respectively, after 24 and 48 hours, respectively, of water immersion as compared to controls in darkness and exposure to red light and far-red light (41.5% and 34.7%, respectively) (Zhou and Singh 2004). Under experimentally low diurnal light intensities, the highest anthocyanin content was found in berries grown at low temperatures (Hall and Stark 1972). In one study, unpruned vines produced fruit with a lower anthocyanin content than did pruned vines (Strik and Poole 1991). To achieve maximum color, growers will leave fruit on the vine as late into the growing season as possible. Growers must time harvest to achieve maximum color, while protecting the crop from potential damage due to onset of winter. Because of this, growers typically harvest berries before they have reached their maximum anthocyanin content (Farag et al. 1992). Pruning helps color development by allowing the berry to be more exposed to sunlight.

Many varieties of cranberry have been selected for juice yield and color, color being determined by anthocyanin content (Sapers et al. 1986b; Sapers and Hargrave 1987). Selection for color has been especially important commercially as high anthocyanin-yielding fruits often command a higher price (Farag et al. 1992).

Organic Cultivation: Cultivation of cranberry vines that meet organic certification criteria has been successful. As with many organic crops, production costs are higher and yields often lower than when chemical control methods are used. In consideration of best management practices, organic waste matter should be tested for heavy metal contamination before use (Colquhoun and Johnson 2010). Although comparable yields have been reported for organic and conventional cranberry cultivation, the organic yield in Wisconsin typically ranges from 60 to 120 barrels per acre, considerably less than the average (Zeldin 2008).

Irrigation

In addition to the plethora of irrigation information readily available from USDA, university extension services, and various associations, one study investigated the irrigation conditions for optimal cranberry yields based on soil water tension thresholds (SWT_1) that can inform timing for initiation of irrigation (Pelletier et al. 2015). According to this study, the four most important cranberry yield components in order of importance were; the number of marketable berries per quadrat (B_M/Q), the number of uprights per quadrat (U/Q); the number of marketable berries per upright (B_M/U); and the marketable fruit set (B_M/F). Significant reductions in B_M/Q, B_M/U and B_M/F were observed when SWT1 varied from 8.5 to 10.0 kPa, while a reduction in U/Q was associated with a SWT_1 of 5.5 kPa. According to this study, a SWT_1 ranging from 7.0 to 8.0 kPa significantly improved the principal yield components as defined.

Collection

Preharvest Considerations: The storage of fresh cranberries is affected by a number of environmental and cultural factors prior to harvest. Cultural practices include application of fungicides at time of bloom, which can reduce the chance of fruit decay. In commercial environments, fruit rot can reach as high as 50% at 3 years after discontinuation of fungicide use, compared with 2 to 10% in treated plots. As with many integrated pest-management techniques, appropriateness and effectiveness of such controls require precise timing (Forney 2003). In contrast, continued application of fungicides can potentially result in the development of resistance to the fungicide and lack of natural resistance through natural selection. Cultural practices that can help reduce fruit rot include the removal of plant debris from bog areas, water/flooding management, sanding, and avoiding over fertilization (since increased nitrogen can increase storage rot) (Forney 2003).

Harvest: Harvest occurs from September to November, approximately 11 to 13 weeks after full bloom or at desired stage of maturity. Harvest maturity is based on optimum color development, specifically the development of the red anthocyanin pigments characteristic of cranberry. Some classify maturity according to the following stages: stage I white berries, possessing appropriate size for the cultivar (beginning of ripening); II stage—50% reddish berries (light seeds); III stage—ripe berries (brown seeds); IV stage—soft overripe (Viskelis et al. 2009). Collection of immature fruits results in a reduction in physiological damage of fruits due to physical handling and decay; however, physiological breakdown due to other factors is less pronounced in mature fruits. Conversely, care must be taken not to harvest fruits that are over-mature (Eck 1931), as this can also result in physiological breakdown of the fruit.

Fruit destined for processing is generally 'water harvested'. During the 1960s, flooding was introduced as a harvest technique. Cranberries have natural air pockets that cause them to float. Bogs are flooded to a depth of 20 to 30 cm to lift the fruit, allowing the fruit to be knocked off with a harrow or water reel. The fruit then floats to the surface and is corralled by booms and removed by pumps or conveyor belts into bulk containers or directly into trucks (Delahaut and Mahr 1998; Roper and Planer 1996; Samulis 1999). In some growing areas where flooding is not possible, growers will harvest using a dry-rake method that mechanically rakes the fruit off the vine. More than 85% of cultivated cranberries are harvested for processing. Fifteen percent of the crop is sold as fresh fruit or fresh-frozen and this fruit must be harvested in a gentler fashion that maximizes keeping quality. There are two methods for harvesting fresh fruit: "dry" and

"wet". Dry harvesting can be done using a mechanical dry-picker that rakes the fruit off the vines with an action similar to a comb. After picking, the fruit is put into burlap sacks or wooden boxes for transport to packing facilities. Some growers utilize a 'wet' method where a shallow layer of water is used to flood the cranberry bed. As with processed fruit wet harvesting, the water lifts the fruit away from the vine surface, enabling a mechanical picker to more easily pull the fruit from the vine. The fruits are then dried, stored, and packaged immediately prior to shipping to market.

Harvest methods can affect the integrity of the fruits, which may in turn have a negative impact on long-term storage life of fruits. Water-reel harvested fruits typically are subject to greater levels of bruising than fruits harvested using water- or dry-rake methods. However, such fruits are acceptable for processing into juice and sauces. More than 85% of berries are harvested in this manner. Small volumes of fruit can be harvested with a hand scoop and have significantly longer keeping quality compared to mechanically harvested and water-picked fruits.

Dry-harvesting can be done by hand using a cranberry scoop, or mechanically. Mechanical dry-harvesters are used

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Figures 5a–q Cultivation, harvest, and processing of cranberry fruits

Figure 5a Cultivating cranberry starts.

Figure 5b Fruiting cranberry starts.

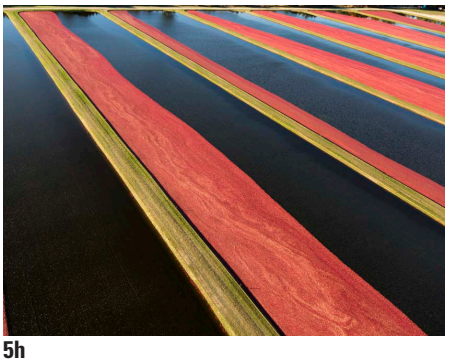
Figure 5c Cranberry fruiting in the bog after flooding and prior to detachment.

Figure 5d Mechanically detaching cranberry fruits from plants after flooding.

Figure 5e Cranberry fruits being mechanically harvested for use as fresh fruits, predominantly used for Thanksgiving and Christmas.

Figure 5f Worker uses a "cranboom" to corral fruit. The fruit is collected inside the boom and then removed from the bed.


5g


5h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5q

Sources: 5a–d Thomas Brendler, PlantaPhile, Collingswood, NJ; 5e-h, j, k Wisconsin State Cranberry Growers Association, Madison, WI; 5i, l–o Cranberry Marketing Association, Wareham, MA; 5p & q The Cranberry Network, Wisconsin Rapids, WI.

Figure 5g Boomed cranberries in preparation for removal from bog.
Figure 5h Aerial view of cranberries awaiting removal from bogs.
Figure 5i Worker rakes cranberries into berry pump for removal from bed and subsequent cleaning.
Figure 5j Berries removed from water by conveyor.
Figure 5k Washing fresh cranberries.
Figure 5l Receiving and processing station.
Figure 5m Filling cranberries into crates.
Figure 5n Crates of fresh dry-harvested cranberries in field.
Figure 5o Dry-harvested cranberries.
Figure 5p Cranberry bouncing apparatus (Baily Mills).
Figure 5q Cranberry fruit conveyor bouncer (Baily Mills).

to rake the fruit off the vines with an action similar to a comb, after which the fruit is put into burlap sacks or wooden boxes. Berries that are sold fresh, fresh-frozen, or dried are typically dry-harvested, though water-harvesting is increasing in use. Handpicked fruits are subject to significantly less decay and physiological breakdown compared to mechanically harvested and water-picked fruits.

Postharvest Pathology: Most postharvest diseases of cranberry are due to fungal infection, with the exception of ringspot, which is thought to be viral (Caruso and Ramsdell 1995; Prange and DeEll 1997). Some of these fungi are unique to cranberry. The most common of the storage rots include: end rot, black rot, viscid rot, yellow rot, and Botryosphaeria fruit rot (Eck 1931; Prange and DeEll 1997). According to one study (Stretch and Ceponis 1983), the longer that the detached fruit is left in bog water, the greater the incidence of black rot during storage.

Handling and Processing

Berries are cleaned and graded mechanically or with laser equipment, and then sold fresh or frozen for later processing into foods (jams, jellies, sauces, relishes, fillings), juices, or dietary supplements (Roper and Planer 1996). Approximately 93% of the annual domestic crop is processed prior to selling (Vandenberg and Parent 1999).

The primary causes of fruit loss during storage include decay, physiological breakdown, and physical damage. Decay can be caused by excessive handling (e.g. bouncing) or by a number of fungal organisms (e.g., *Allantophomopsis* spp.; black rot) (see *Physiological Breakdown* below).

In commercial juice production, cranberries are generally subjected to a freeze-thaw treatment before pressing. This disrupts the cellular structure of the berries, increasing juice yield up to 50% and anthocyanin extraction 15-fold. Thawing encourages the migration of anthocyanins from the exocarp into the mesocarp and endocarp, enhancing pigment extraction during pressing. Anthocyanin recovery (extraction efficiency) can be further increased by double pressing and tissue homogenization. Anthocyanin recovery is independent of cultivar, total anthocyanin content, juice yield (Sapers et al. 1983), berry size, and coloration (Sapers et al. 1986b).

Lastly, varying processing techniques can affect the constituent yield of various finished preparations and should be taken into consideration when choosing a preparation for therapeutic purposes (see Preparations).

Physiological Breakdown: Physiological breakdown is a result of excessive bruising due to handling, late harvest, prolonged immersion of free berries for 8 or more hours in flooded bogs, smothering of berries when held under conditions of poor ventilation, or excessive chilling (Ceponis and Stretch 1981; Forney 2003; Graham et al. 1967; Massey et al. 1981, among others). Such berries are soft and/or rubbery, the outer surface is dull, and there is a diffusion of the external skin pigments into the inner flesh (Ceponis and Stretch 1981).

Grading and Size: There are two US standards of grading for fresh cranberries. Fresh Cranberries US No. 1 (USDA 1997a) and Fresh Cranberries for Processing US No 1 (USDA 1997b): Fresh Cranberries US No. 1, which is based primarily on color, cleanliness and diameter: 75% or more of the fruit surface must be pink or red (must not be green, white, or speckled); size: the minimum diameter must be 10.3 mm (USDA 1997b) or no more than 115 berries in a cup (Cunningham et al. 2008); and the fruits must be free of defects, with no soft or decayed fruits (Prange 2014; USDA 1997a). Reddening of harvested berries can be increased by holding fruits, especially fruits harvested early at 7 to 10 °C for a few weeks rather than at lower temperatures (Wang and Wang 2009). There are also US standards for grades of frozen cranberries and for grades of canned cranberry sauce.

Cooling: Following harvest, for optimal storage time, fresh fruits should be cooled quickly and stored between 2 to 7 °C at a relative humidity of 90 to 95% (see Storage, below). Cranberry is sensitive to chilling. Storage near 0 °C for more than approximately 4 weeks can result in low-temperature breakdown. Symptoms of excessive chilling include: dull appearance to skin, rubbery texture, and increased decay (Mitcham et al. 1999). Decay due to excessive chilling can be minimized by intermittent warming to 21 °C for one day per month (Hruschka 1970).

Hot Water Treatments: Treatment with hot water can reduce the number of pathogens on fruits. Hot water treatments of 48.8 °C for 2.5 or 5 minutes and 51.7 °C for 2.5 or 5 minutes (stored at 21.1 °C) for cranberries resulted in a reduction of pathogens and fruit spoilage, especially in early harvested fruits (Forney 2003).

Drying

There are a number of drying techniques applied to cranberries, including: air-drying, oven-drying, dehydration, microwave-drying, vacuum-drying, and freeze-drying. The criteria used for optimal drying conditions are based on sensory characteristics (color, taste, texture, etc.), anthocyanin content, or both. In terms of preservation of anthocyanins, rehydration ratio, color, and taste, freeze-drying has been demonstrated to be best (Sunjka et al. 2008).

Pre-Drying Processing: When drying at home, only the freshest berries should be selected. The Washington State University Extension recommends choosing cranberries that are bright red or yellowish-red. Fresh cranberries are firm and not wrinkled. A wrinkled, soft cranberry indicates it is not fresh. Cranberries should be stored in the refrigerator until ready to dry.

Freeze-Drying: Frozen berries are placed in a vacuum chamber set to pull at about 120 m Torr and at 10 °C. Formal parameters of freeze-drying are provided by Rudy et al. (2015), who concluded that pulping the fruit prior to freeze-drying reduced the drying time by approximately 50% and resulted in greater preservation of redness of color, vita-

min C content, and greater antioxidant activity as compared to fruits dried whole. Similarly, Huemmer and Schreier (2008) reported freeze-drying to be optimal for preservation of PACs derived from *Pinus* species, though also noted that exposure to moisture must be avoided to prevent degradation reactions due to the fact that cell membranes are broken upon freezing.

Oven Drying: For home use, cranberries are typically parboiled or blanched prior to drying. This is done by boiling water, removing the water from the heat, and placing a quantity of berries in the water, leaving until the skin of all the berries cracks (pops). This allows for moisture to escape in the drying process and also denatures enzymes that can otherwise cause degradation when dried. After blanching, fruits should be rinsed with cool water in a colander and allowed to cool. The fruits should be laid out on an absorbent layer (paper towels or cotton towels) and carefully patted dry to remove excess moisture. Line a baking sheet with paper towels. Place the cranberries on the sheet in a single layer. Place another layer of paper towels over the berries, patting them dry as much as possible. Prepare another baking tray by laying some paper towels (absorbent layer) on the tray, covering this layer with a piece of parchment paper, and then over this, spread a layer of berries. Place in an oven preheated to 66 °C and dry for 6 to 10 hours or until desired dryness is reached. The tray should be rotated several times during the drying process. After drying, allow to cool to room temperature prior to packaging.

Dehydrator Drying: Freeze or parboil the berries as described above. If freezing, freeze for 2 hours. Place frozen berries in a dehydrator at 66 °C for the first hour then reduce to 57.2 °C for 10 to 16 hours or to desired dryness. Let the berries cool before storing. Dry cranberries should be of a similar chewy texture as raisins.

Storage

The use of refrigerators and proper temperature control is the primary post-harvest practice for extending shelf-life of fresh fruits. Optimum temperatures will vary according to cultivar, stage of harvest, and other cultivation practices. A variety of authors propose varying storage temperatures. The minimum and maximum storage temperatures are 2 °C and 5 °C, respectively (Hader et al. 1988; Hardenburg et al. 1986; Lidster et al. 1988; Spayd et al. 1990), with one study recommending 7 °C (Kasmire and Thompson 1992). Similar commercial sources provide guidance on storage humidity, but these values vary greatly from 70 to 75% to 80 to 90%, or 90 to 95%. High humidity can lessen the probability of undesirable weight loss, shriveling, and softening of the berries, but, with poor circulation, can result in increased decay. The most severe decay has been observed when cranberries were stored at 0 °C and 15 °C for 3 and 4 months (Wang and Wang 2009). Lower levels of humidity (75%) can lower the risk of decay. High humidity with good airflow may be optimal. Intermittent warming is also applied to reduce the chance of rot during chilled storage. For example, fruits stored at 0.6 °C or 3 °C and warmed to 21 °C for one day every 4 weeks, showed less physiological breakdown than those not warmed (Forney 2003).

Dried berries should be stored in airtight containers, protected from light, air, moisture, and insect infestation. Storage of cranberry products should minimize anthocyanin and vitamin C degradation. One study showed that in refrigerated fresh berries, 90% of the vitamin C remained after 2 to 3 months of storage, 73% after 4 months, 56% after 5 months, and 46% after 6 months (Murray 1997 and references therein). Shelf-life evaluation of pulsed electric field (PEF)-treated and aseptically packaged cranberry juice showed only minor loss of flavor, vitamin C, and pigment. The PEF technology is reported to inactivate microbial contamination with less impact on the visual quality and flavor of cranberry juice than heat-processing methods (Jin et al. 1998). In another study, the vitamin C content of cranberries decreased by an average of 90%, organic acids by 54%, and phenolic compounds by 60% over a 12-month period. The fresh cranberries were stored in glass jars in water. During six-month storage in closed PP (non-perforated polypropylene) boxes, vitamin C decreased by an average of 99%, organic acids by 30%, and phenolic compounds by 34%. Mold began to form after six months (Ruse et al. 2013).

There are some data to suggest that optimal atmospheric conditions for cranberry storage are approximately 21% O_2 and 30% CO_2 (Gunes et al. 2002). Cranberries can be stored under anaerobic conditions for up to 14 months at 3 °C at a low relative humidity (Stark et al. 1974). However, such fruits show a considerable amount of physiological breakdown and are only appropriate for use in processed cranberry products such as cranberry sauce. Another study reported that A and B-type PAC and flavonol concentrations in cranberry syrup stored at 25 ºC for 1 month were highly stable after application of gamma-irradiation at a dose of 5 kGy (Rodríguez-Pérez et al. 2015).

Generally speaking, cranberries are expected to remain stable under normal storage conditions for 2 to 4 months (Wang and Wang 2009). Following are food industry standards for shelf-life and storage conditions of fresh and various processed forms of cranberry:

Fresh Fruit: 60 to 120 days when stored at 2 to 4 °C and 90 to 95% relative humidity (Williams 1998). Treating with high-voltage electric fields (HVEF) (2, 5, or 8 kV/cm-[1]) for up to 90 minutes has been shown to increase the shelf-life of fresh berries (Palanimuthu et al. 2009).

Dried Sweetened Fruit: 24 months when stored in high-density 2-mL polybags inside a corrugated box in a cool, dry atmosphere at a temperature not exceeding 18 °C (65 °F) (DCP 2014).

Frozen Fruit: 24 months when shipped and stored in a high-density 2 mL polybag inside a corrugated box at 0 ºF ± 15 ºF (-18 ± -9 ºC) (OCS 2011).
Juice: 2 to 3 weeks once opened, if tightly capped and refrigerated.

Juice Concentrate (Brix [Bx] 50.0): Minimum 2 years if kept frozen at -18 + -9 °C (0 to +15 °F) in a 55-gallon open head metal drum with liners, filled to 50 gallons (DCP 2014).

Cranberry Puree (Bx 8.0): 24 months if kept frozen at -18 + -9 °C (0 to +15 °F) in 55 gallon drums (OCS 2013).

Spray-dried Juice Powder: 36 months when stored in a cool 10 to 21 °C (50–70 °F), dark, and dry area in a polybag sealed in a drum (Artemis 2015).

Spray-dried Juice Concentrate: 36 months when shipped and stored at 10 to 21 °C (50–70 °F), 50% relative humidity, packed in double poly-lined sealed drum with desiccant bags, protected from moisture and excessive heat (Artemis 2013).

Qualitative Differentiation

Fresh cranberry quality is based on intensity of color, glossiness, uniformity of size, texture, and freedom from defects (Forney 2003; Spayd et al. 1990). The anthocyanin content of cranberries is reflected in the intensity of color and is a major factor in determining crop value and optimal harvest times. Fruits should have an intense, red, shiny surface, be uniform in size, have good firmness and no wrinkles, and be free from noticeable defects. The inner flesh should be creamy white.

The United States Department of Agriculture (USDA 1997a) has standards for grades of fresh cranberries. Grade US No. 1 consists of cranberries that meet the following basic requirements: (1) One variety or similar varietal characteristics (color and shape); (2) Clean (e.g., free from dirt, dust, spray residue, or other foreign material); (3) Mature (e.g., should not show more than a slight amount of green); (4) Firm, not soft or decayed (no more than 3% soft or decayed fruits allowed); (5) Free from damage caused by moisture, bruises, freezing, smothering, scarring, sunscald, foreign material, disease, insects, or mechanical means; (6) Color: Fairly well colored and uniform in color (not more than 5% non-uniform colored fruits allowed for berries in transit or in containers) (Seelig 1974); and (7) Size: Berry diameter must not be less than 10.319 mm. No more than 3% of any lot may fail to meet the size requirements. In addition to these USDA standards, firm, ripe, undecayed berries have air pockets that allow them to bounce and float (Small and Catling 1999), allowing for qualitative differentiation using a bounce board or float test. A firm berry will bounce, whereas a soft berry will not. Soft berries are usually discarded.

Total anthocyanin content has been shown to vary by growing region with supplies grown in Oregon (70 mg/100 g), Washington (55 mg/100 g), and British Columbia (45 mg/100 g) yielding the highest concentrations, followed by Massachusetts (~42 mg/100 g), New Jersey (~37 mg/100 g), and Wisconsin (~35 mg/100 g).

Vitamin C and phenolic content also varies with varying cultivars and stage of ripeness. According to one study (Viskelis et al. 2009), phenolic content was highest in Black Veil cultivar (504 mg/100g) as the fruit matured; anthocyanin content increased with increased ripeness in Ben Lear and Black Veil cultivars; ascorbic acid content increased during ripening with increasing maturity, the highest concentration occurring in the Ben Lear cultivar (15.8 mg/100 g). In the same study, extracts of press cakes (a by-product of cranberry juice production; also known as pomace) were analyzed and the antioxidant and antimicrobial activity compared with the activity of extracts made from whole berries. All extracts from berries and their press cakes showed good radical scavenging activity and revealed antimicrobial properties against both gram-negative and gram-positive bacteria (e.g., *Bacillus cereus* [ATCC 10876] and *Micrococcus luteus* [ATCC 9341], among others).

Adulterants

Fruits: Due to widespread cultivation, adulteration of cranberry fruits with other species of *Vaccinium* is unlikely. However, blueberry (*V. corymbosum*) has occasionally been found as an adulterant in the United States, though this is a rare occurrence and is due to accidental mixup in contrast to an intentional adulteration.

Juice: There are older reports of adulteration of cranberry juice products with added colorants or acidulants (Hong and Wrolstad 1986b). Cranberry juice products have reportedly been adulterated with a 5% or less solution of enocyanin, an anthocyanin-containing pigment derived from grapes. In Europe, *V. uliginosum* has historically been reported as an adulterant of cranberry juice in, though not in recent years.Anthocyanin, anthocyanidin, and organic acid profiles can be used for authentication of cranberry preparations (Chandra et al. 2001; Coppola and Starr 1988; Coppola et al. 1995). Adulteration with enocyanin can be determined using HPLC to identify delphinidin-3-glucoside and petunidin-3-glucoside, 2 anthocyanins found in enocyanin but not in cranberry (Hale et al. 1986). Quinic acid, an uncommon fruit acid, has been extensively measured in cranberry juice, providing a useful marker for detecting juice adulteration and percentage of cranberry juice in products, because it is cost prohibitive to correct for quinic acid content (Coppola and Starr 1988; Coppola et al. 1995). The principal characteristics of an authentic single strength (7.5 °Bx) cranberry juice are reported to be as follows: Total organic acids, 2.2 to 3.3 g/100 g; relative percentages of organic acids: quinic 39%, citric 32%, and malic 27%; total anthocyanins by pH differential spectrophotometry, 19.0 to 53.3 mg/100 g; relative percentages of anthocyanidins: cyanidin 57%, peonidin 43%; total sugars, 3.6 to 5.0 g/100 g; relative percentages of sugars: glucose 79%, fructose 21% (Hong and Wrolstad 1986a).

Extract Powders: Adulteration is reported to occur in powder extracts and may be more prevalent than adulteration of juice products, due to the inability or misapplication of standard analytical methodologies to detect adulterants.

The most prevalent adulterant in cranberry extract products appears to be grape seed or grape skin extracts. Grape seed oligoprocyanidins (OPCs) are less expensive (currently by approximately 25 times) than PACs derived from cranberry juice. Several chemical methods can be used for detection of adulteration by comparing the chemical fingerprint of test samples with an authenticated reference material. These methods include: high performance thin-layer chromatography (HPTLC), high performance liquid chromatography (HPLC), and matrix-assisted laser desorption/ionization with time of flight mass spectrometry (MALDI-TOF-MS) (see Analytical). Other potential PAC-rich adulterants include peanut skins, black bean skins, plum, and mulberries and reportedly are mixed with authentic cranberry extracts in China (Kaufmann 2015; personal communication to AHP, unreferenced) and sold back to the American market. The most likely candidate ingredients for adulteration are those that are by-products of other industries, as is the case with the skins of peanuts and grape.

Sustainability

While there are about 48,000 acres of cranberries harvested each year in the US and Canada combined (CCCGA 2015.), there were only an estimated 283 acres of organic cranberries harvested in the United States in 2014 (USDA-NASS 2015). Organic cranberry production in Canada (mainly Quebec) has been estimated at about 400 acres (Zeldin 2008).

Surveys indicate that for every one acre of land under cranberry cultivation, the cranberry producer owns 6.3 acres that are not under cultivation. Because of this, cranberry agriculture plays a role in protecting land from overdevelopment and urban sprawl, provides habitat for wildlife, and preserves land for water collection and replenishment of aquifers. A small percentage of non-cultivated land is used as support land for cultivation, while the larger percentage of non-cultivated land preserves a relatively natural habitat for wildlife and intact ecosystems. Cranberry is also a water intensive crop that can affect ecosystems through water use and water diversion, natural habitat distortion and destruction, and use of pesticides, necessitating development of sustainable cultivation practices and water management practices (see Burgess 2007; Colquhoun and Johnson 2010; Harbut 2011; Pelletier et al. 2015, among others). Many such initiatives are underway by the cranberry industry at large and state agriculture departments. For example, according to a University of Wisconsin survey of 114 cranberry growers in Wisconsin, 77% hire integrated pest management consultants to minimize pesticide use; 88% use pest-control methods that are alternative to chemical pesticides; 88% test the soil to determine actual need for amendments rather than scheduled, but potentially unnecessary fertilization; 98% calibrate their fertilizer and pesticide application regularly; 36% test water content of the soil for optimizing flood conditions; 79% participate in recycling programs; and Wisconsin's cranberry crop travels an average of 35 miles to processing facilities, resulting in a relatively small carbon footprint associated with the crop (Colquhoun and Johnson 2010). In Massachusetts, distance from the cultivation site to the processing facility is less than 15 miles (Cape Cod Cranberry Grower's Association). According to the University of Wisconsin survey, many producers of fresh cranberries adhere to the Good Agricultural Practices (GAPs) of the European Union, which are generally more stringent than those in the US (Colquhoun and Johnson 2010). A similar survey in Massachusetts indicated 80% of producers have a USDA approved Conservation Farm Plan that assures farm improvements are done according to federal and state guidelines and 70% have received USDA funding to make improvements in how water is used on their farm.

Water Management: Cranberry cultivation is a water-dependent and water-intensive industry. Cranberries are included under a provision of US law that allows application of pesticides to waters of the US via a general permitting program authorized by the the National Pollutant Discharge Elimination System (NPDES) under the Clean Water Act. Cranberry growers are required to comply with the provisions of this permitting program, which greatly reduces the potential for contamination of waters of the US. Generally, vines require approximately one inch of water per week during the growing season. Additionally, cranberry cultivators can flood their bogs from late December to mid-March, depending on the weather, to protect the vines and buds from winter injury. The same bog may be flooded from April to mid-May for weed and pest control. Water usage for current cranberry cultivation, for example, in Massachusetts, is estimated at 41 to 45 billion gallons of water per year, most of which is recycled. Attempts are made to maximize use of water by channeling water from one growing area to another. Use of automated irrigation systems can save more than 9,000 gallons of water per acre on a frost night. Irrigation is conducted in the morning to minimize exposure to the plants and loss due to evaporation, drift, and run-off. Estimates show that only 40% of cranberry growing sites have adequate water supply throughout the season. Most cranberry acreage (84%) relies on ground water. Conservation plans to balance water use are in place and are constantly evolving (CCCGA 2001).

Loss and Preservation of Native Wetlands and Affects on Local Waterways: Surveys note that loss of wetlands due to cranberry farming is small compared to loss of wetland habitat due to other development including other agriculture. Similarly, as noted above, preservation of land for purposes of cranberry cultivation preserves wildlife habitats that may otherwise be subject to commercial development that has a greater negative environmental impact. In some states (e.g., Massachusetts) agricultural activities are governed under wetlands protection acts, which regulate activities that alter the function of wetlands.

Commercial cultivation of cranberries can result in changes in surrounding waters due to damming, which can change the temperature of stream water and negatively affect fish. Additionally, increased temperatures and pesticide and

fertilization runoff, most notably phosphorous, can increase algal growth, which can negatively affect native waterways. In native acidic soils, phosphorus is tightly bound to iron and aluminum and does not leach off into surrounding waters. When bogs are flooded, a chemical change occurs that releases the phosphorus, allowing it to be distributed, potentially to other waterways (CCCGA 2001). To minimize negative environmental impacts, formal programs regarding water quality and management are in place in most states that grow cranberries commercially. According to some surveys, 65% of Massachusetts cranberry growers have put in low phosphorous programs to prevent excessive phosphorous migration into surrounding lands and water.

Pesticides: There are a wide variety of pesticides used on cranberry crops including organophosphates, carbamates, pyrethroids, and biopesticides (EPA 2015). In addition to their affects on target pests, broad-spectrum pesticides may negatively affect beneficial insects that generally contribute to greater pest control through natural predation, often resulting in the need for less pesticide use. According to one report, organic farms averaged 27 to 45% more natural insect predators (beneficials) than conventional farms (Singleton and Mahr 2011). This does not necessarily correlate with better yield or quality of fruit, but represents an alternative agricultural practice.

Cranberries are susceptible to lepidopteran insect, fungal (especially fruit-rotting fungi), and weed pests (Salett 1998; Samulis 1999; Stanley 1992). In general, pesticides are used to control all 3 classes of pests (Cranberry Institute 2001). A variety of herbicides, insecticides, and fungicides may be applied to cranberry. Such pesticides are used within the context of integrated pest management programs that include introduction of natural predators and parasitoids, mating disruption, pruning, sanding (application of sand over vines), bog sanitation, improved water drainage, and increased scouting for potential pests, among other practices (Sandler 2008). While formal pesticide reduction programs are in place in all cranberry cultivation areas, studies show that, at least in one area (Washington state), pesticide levels from cranberry cultivation from 1996 to 2002 exceeded water quality standards despite implementation of IPM practices (Anderson and Davis 2000; Coots 2003; Davis et al. 1997). Aggressive efforts, most notably by the Cranberry Institute (Carver, MA), are in place to reduce pesticide use and develop alternative control methods for both weeds and insects. For guidance regarding appropriate pesticide controls see DeMoranville and Sandler 2000, among others.

Preparations

A variety of cranberry preparations are available, including fresh fruits, pure cranberry juice, cranberry juice beverages (e.g. diluted with water, sweetened, or mixed with other juices), dried cranberries, cranberry sauce, and cranberry dietary supplements (powders and tinctures) made from a variety of cranberry starting material including whole cranberries, cranberry juice, and cranberry pomace (micronized dried cranberry pulp and skins, seeds, stems; also known as press cake) (Roopchand et al. 2013). Generally speaking, the juice is rich in soluble PACs, which are rapidly bioavailable, while the press cake, which is a by-product of the juicing industry, is rich in larger, insoluble PACs that cannot be measured by DMAC (Roopchand et al. 2013) and may not be as bioavailable as PACs in juice products.

Commercial cranberry products that are used as therapeutic agents and/or as dietary supplements include liquid cranberry juice products of various dilutions, both sweetened and unsweetened, and cranberry juice concentrates in liquid and dry (powdered, flaked, or granulated) forms, the latter available in capsules, tablets, and teabag-infusion products, as well as products made from the pomace. The specific type of material a dietary supplement is made from (juice, seed, pomace, etc.) may not be disclosed on the packaging and varied greatly in price. Because of varying concentrations of compounds between the preparations, care must be taken when choosing a cranberry product specifically for therapeutic purposes.

Cranberry Juice Cocktail® (Ocean Spray) and cranberry dietary supplements are often used in studies regarding urinary tract health. A number of cranberry products, including fruits, juice, mash, depectinized mash, and pomace have been found to induce phase II xenobiotic detoxification processes (quinone reductase), suggesting a potential positive anticancer effect. The effect was found to be anthocyanin-concentration dependent, with fruits and depectinized mash exhibiting the greatest activity, and pomace and juice the least. The juice is lower in anthocyanins than whole fruit because the skins, which are rich in these pigments, are filtered out during the juicing procedure (Caillet et al. 2012). This suggests that whole fruits or whole fruit extracts are optimal for preserving the broad spectrum of cranberry constituents. Similarly, different processing techniques result in varying levels of degradation of the different constituents, with the greatest loss of phenolic compound observed with milling and depectinization. The amount of anthocyanins in juice is about 40% less than in whole fruits, and is further decreased (~20%) when the juice is concentrated, due to the sensitivity of anthocyanins to evaporation. Generally, cancer-protective effects diminish in the following order: fruit > mash = depectinized mash clarified juice > raw juice > pomace > juice concentrate (Caillet et al. 2011). This suggests that whole fruits or whole fruit extracts are optimal for preserving the broad spectrum of cranberry constituents.

Juice and Juice Concentrate Products

Cranberry juice is predominantly made from frozen fruits either by pressing or extracting in water. Each production batch is tested for brix, titratable acidity, haze, and color; Cranberry Juice Cocktail® (Ocean Spray) is typically used as the reference point. Cranberry juice concentrate is prepared by hot mash depectinization of fresh or frozen cranberries. The mash is then either filtered or pressed to recover the juice, which is then concentrated to 50 °Bx (Cunningham et al. 2008). The phenolic compounds in cranberry are easily oxidized and are affected by heat, light, and dissolved oxygen. Thus, care must be taken to protect these compounds

from degradation during the juicing process (Rein and Heinonen 2004; Wrolstad et al. 2005). On the other hand, commercially, pressed cranberry juice has a higher concentration of PAC monomers, dimers, and A-type trimers than fresh fruits (Prior et al. 2001), as PACs are extracted from all parts of the cranberry and are not subject to the same degradation issues as anthocyanins during the juicing process.

Some concentrates are spray dried onto carriers (e.g. magnesium oxide) and can be obtained from different starting materials, resulting in varied anthocyanin content.

Cranberry Juice Cocktail® and White Cranberry Juice Products

Cranberry Juice Cocktail® (Ocean Spray) is typically composed of 27% juice (7.5° Bx) with water and sweetener added. This beverage can be made either from juice, juice concentrate, or a blend of the two. The United States Department of Agriculture (USDA) mandates that such juice contain a minimum of 27% juice and 0.26% quinic acid (USDA 2001). Positive results regarding genitourinary health have been demonstrated for Cranberry Juice Cocktail® in a number of clinical investigations (see Therapeutics). Cranberry Juice Cocktail® typically has a shelf life of 6 to 12 months. White cranberry juice was introduced to the market in recent years. This is prepared from berries harvested several weeks early while in their white-color stage of development. White juice is less tart and less apt to stain clothing red. Some cranberry juice products are made from concentrate while others are not. Anthocyanin concentration of non-concentrate products can be twice as high as that of juice prepared from concentrate (8.3 and 4.2 mg/100 mL, respectively). The lower concentrations found in juice made from concentrate may be attributed to heating, pasteurization, bottling, distribution, and storage processes. Juice prepared from fresh fruits versus concentrate is similarly higher in total phenolic compounds, almost double, that of juice from concentrate, and higher than cranberry juice cocktail (27% juice) (50.2, 25.0, and 25.4 mg/100 mL, respectively) (Grace et al. 2012).

Cranberry Sauce

Cranberry sauce is produced by cooking whole cranberries in a kettle with cranberry pomace (by-product of juicing). The addition of pomace increases pectin, which is needed for gelling. Cranberry sauce can also be made at home by boiling whole cranberries (fresh or frozen) with water and sugar. One study found that cranberry sauce was able to prevent adhesion of certain pathogenic bacteria in vitro that are associated with causing urinary tract infections, but at 40 to 80% that of cranberry juice cocktail (based on PAC activity) (Howell 2000). One study analyzed the constituent profile of commercial versus homemade cranberry sauce. The homemade sauce was made by adding 340 g of fresh cranberries to a boiling mixture of sugar 200 g) and water (225 mL), boiled for 5 minutes, and then allowed to cool to room temperature. The homemade sauce was significantly higher in anthocyanins compared to canned whole berry sauce (15.9 and 9.6 mg/100 g, respectively), which had only traces of these compounds. These lower concentrations are likely due to the absence of skins in commercial products and may also be due to the higher concentration of berries used in home-made recipes compared to lower amounts used for commercial products. Other processing techniques may also affect constituent concentrations and compounds may degrade over time. Home-made cranberry sauce also contained significantly higher amounts of PACs compared to 2 commercial products (87.9 mg/g compared to 16 mg and 54.4 mg/100 g, respectively, as well as higher amounts of total phenolic compounds (150 mg/100 g versus 77.7 and 130.7 mg/100 g for the same two commercial products, respectively) (Grace et al. 2012).

Sweetened Dried Cranberries

Dried cranberries are produced from cranberries that are infused with sugar, and cranberry juice concentrate or another fruit juice, and then dried. Research suggests that consumption of sweetened dried cranberries, like other cranberry products, may play a role in maintaining urinary tract health (Burleigh et al. 2013; Greenberg et al. 2005). One analysis reported sweetened dried cranberries to contain relatively low amounts of anthocyanins (7.9 mg/100 g dry wt) and PACs (64.2 mg/100 g). According to one analysis, sweetened dried cranberries contained 219.6 mg/100 g total phenolics (Grace et al. 2012).

Cranberry Dietary Supplements

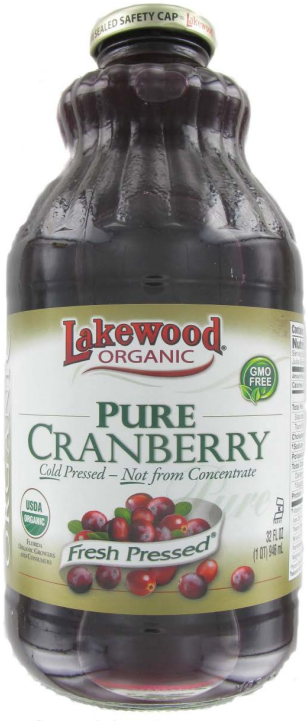
Cranberry supplements can be made in a variety of ways, including dry preparations made from whole cranberry fruit powder, juice, or pomace (typically frozen), or made from extracted material. The PAC and anthocyanin content of dietary supplement products will vary greatly depending on the starting material that was used to make the product. Select cranberry supplements have been shown to have therapeutic benefit in clinical trials (see Therapeutics). Some products blend various raw materials, predominantly to address price considerations, using 100% pomace (relatively low cost), 100% juice extract (relatively high cost), or a combination of both. Products often do not disclose the source of the material.

Cranberry Pomace (press cake)

Cranberry pomace, also known as press cake, is the pulpy residue that remains after juice has been extracted from fresh fruits, and consists of fruit pulp, seeds, and stems. This is a by-product of the juicing process and is also used in the manufacture of food and dietary supplement ingredients. Preservation of anthocyanin and flavonol content in pomace is dependent on temperatures used for processing. According to one study, pure pomace contains 6 anthocyanins (111.5 mg/100 g dw) including derivatives of cyanidin and peonidin. Thirteen flavonols were identified (358.4 mg/100 g dw), and the aglycones myricetin (55.6 mg/100 g dw) and quercetin (146.2 mg/100 g dw) were the most prominent. PACs with degrees of polymerization (DP) of 1 to 6 were identified (167.3 mg/100 g dw), the most abundant being an A-type of DP2 (82.6 mg/100 g dw)

6a

6b



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Figures 6a-j Common cranberry preparations

Figure 6a Fresh cranberries.
Figure 6b Dried cranberry fruits.
Figure 6c Cranberry juice (100%).
Figure 6d Cranberry juice cocktail (OceanSpray©).
Figure 6e Cooking cranberries.
Figure 6f Cranberry sauce (whole berry).
Figure 6g Cranberry sauce (jelly).
Figure 6h Cranberry tincture.
Figure 6i Cranberry pomace.
Figure 6j Cranberry fruit powder and extracts (1); fruit powder (2); (3); dry extract prepared from 70% ethanol native extract 20 to 35:1 herb to extract ratio (4) powdered extract, characterization undisclosed.

Source: Figures courtesy of: 6a Cranberry Marketing Committee, Wareham, MA; 6b–g AHP; 6h Herb Pharm, Williams, OR; 6i BNK Enterprises, LLC, Wisconsin Rapids, WI; 6j 1 & 2 Fruit d'Or, Villeroy, Quebec, Canada; 6j 3 Pharmatoka, Cedex, France; 6j 4 Naturex, South Hackensack, NJ.

(White et al. 2010a). However, the analytical methodology used in this study only distinguishes small oligomer A-type PACs and does not quantify larger PACs or PACs bound to cellulose, underestimating total PACs by approximately half (Feliciano et al. 2012). According to an analysis by the same group of researchers (White et al. 2011), the pomace contained approximately 15% of the total anthocyanins of the whole fruit. These larger PACs, which are difficult to isolate and quantify, are bound with cellulose within the press cake (Krueger et al. 2004; Krueger et al. 2013b; Reed et al. 2005), but may still be active in reducing E. coli in the gut (Feliciano et al. 2014). Conversely, due to the relative insolubility of the PACs in press cakes, they may not exhbit the same anti-adhesion activity in the urinary tract.

Pomace may be mixed with other materials, such as corn starch or soy protein isolate and mechanically extruded. Generally, flavonols increase with extrusion, while anthocyanin levels tend to decrease. Maximum preservation of anthocyanins was observed at 150 °C and 30% pomace. Antioxidant activity (based on ORAC) increased at temperatures of 170 °C and 190 °C. Increases in PACs and decreases in oligomers were also observed (White et al. 2010b). One study found optimal extraction conditions for preservation of PACs to be a 5:1 solvent:wet pomace ratio of cranberry pomace in 50% ethanol adjusted to pH2, incubated at 80 °C for 2 hours with agitation, and co-drying (37 °C) the pomace with a soy isolate, which increases the stability of cranberry's beneficial compounds (Roopchand et al. 2013).

Specific fractions of a pomace extract showed 3 to 4 times the phenolic acid, tartaric ester contents, and antioxidant activities, as well as 5 to 10 times the flavonols and anthocyanins of their respective juice powders (Harrison et al. 2013), and displayed similar ex vivo antimicrobial activity against *S. aureus* [ATCC 29213 and MRSA COL]. For an overview of the activity of cranberry press cakes see Viskelis et al. (2009).

CONSTITUENTS

The primary compounds of interest in cranberry are anthocyanins and PAC oligomers of both A-type (with at least one set of two bonds between monomer units) and B-type (with all single interflavan bonds). Bacterial antiadhesion activity has been demonstrated for A-type PACs (Howell et al. 2005), with an effect of clinical relevance regarding cranberry's putative beneficial affects on the genitourinary tract. PACs with only the B-type linkages have not demonstrated in vivo antiadhesion activity (Foo et al. 2000a, 2000b; Howell et al. 2005). Anthocyanins additionally elicit anticancer activity, possess cardioprotective effects, and are powerful antioxidants. Ursolic acid and polyphenols also contribute to the general health-promoting benefits of cranberry possessing anticancer, anti-inflammatory, and antioxidant activity (Blumberg et al. 2013). In addition to the bioactivity of these constituents, quantitation of specific compounds can also be used for quality assessment and the detection of adulterants of both crude fruits and finished preparations.

Macro Consituents

Cranberries contain a broad array of nutrients (see Table 2). Raw cranberries contain approximately 86.5% water and 13.5% solids (Kuzminski 1996). Among the organic constituents that make up the solids are carbohydrates, organic acids, terpenes, sterols and polyphenolic compounds (Howell 2007; Neto 2007a; Pappas and Schaich 2009). The pressed juice contains 5 to 7% solids, the majority of which is made up of sugars and organic acids (Cunningham et al. 2004; Kuzminski 1996; Leahy et al. 2001). The °Bx (sugar content) of the single strength juice can range from 6.5 to 8.7 °Bx, with the accepted industry standard being 7.5 °Bx (Cunningham et al. 2004; Hong and Wrolstad 1986a). Combined with a titratable acidity in the range of 1.9 to 2.9 g/100 mL, the resulting juice is a highly acidic, astringent, and generally unpalatable beverage (Hong and Wrolstad 1986a; Leahy et al. 2001). To make the beverage more palatable, due to the very low natural sugar in cranberries, juice manufacturers blend the single strength juice with water, sweeteners (sugar, other fruit juice concentrates, or non-nutritive sweeteners in low-sugar preparations), and ascorbic acid, to produce a cranberry juice cocktail drink (Cunningham et al. 2004; Hong and Wrolstad 1986a; Kuzminski 1996; Leahy et al. 2001). The percent concentrate used in the cocktails varies, although cocktail with around 27% pure juice is typical (Cunningham et al. 2004; Hong and Wrolstad 1986a; Leahy et al. 2001).

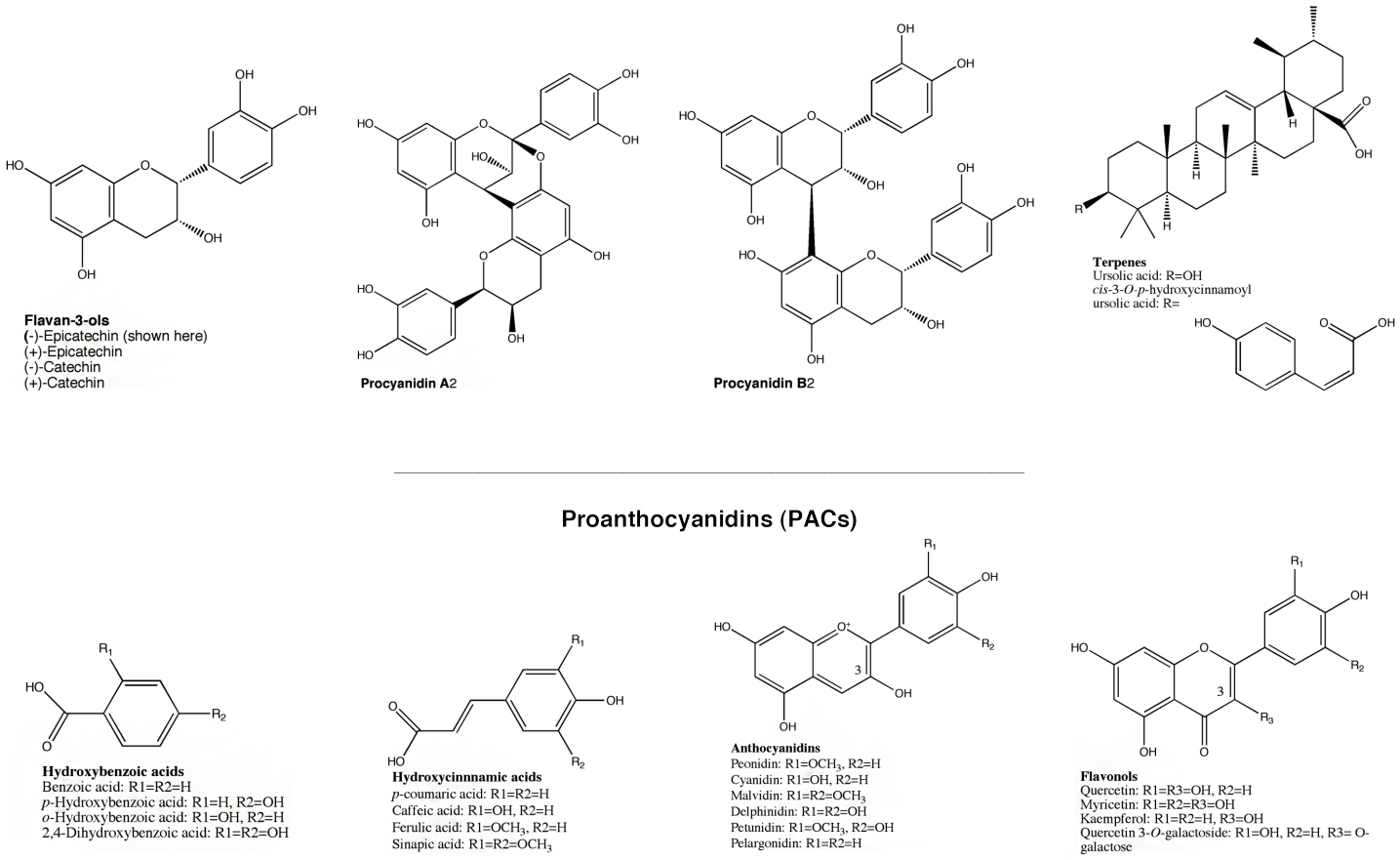

Figure 7 Primary cranberry constituents associated with bioactivity

Source: Blumberg et al. 2013, published in American Society for Nutrition. *Adv Nutr* 4: 618–632.

Anthocyanins

The red pigmentation of cranberry is primarily attributed to the presence of the following 6 anthocyanins, which mostly occur in the skin (1705.2 mg/100 g based on dry wt, while the peeled fruit [flesh] contained only 101.5 g/100 g) (Grace et al. 2012): cyanidin 3-*O*-galactoside, cyanidin 3-*O*-glucoside, cyanidin 3-*O*-arabinoside, peonidin 3-*O*-galactoside, peonidin 3-*O*-glucoside, and, peonidin 3-*O*-arabinoside (Figure 7) as originally described by Fuleki and Francis (1967, 1968a, 1968b) (see Table 3). Conversely, procyanidin A-2 dimer, quantified by LC-MS, was more concentrated in the flesh of the peeled fruit than in the skin (76.9 mg and 44.9 mg/100 g dry wt for flesh and skin, respectively). The anthocyanin galactosides are most predominant, followed by the anthocyanin arabinosides and very low levels of anthocyanin glucosides. Two anthocyanidins (cyanidin and peonidin), the aglycones of anthocyanins, may be generated by the loss of sugar moieties (galactose, glucose, and arabinose) as an effect of processing (White et al. 2011). The total anthocyanin content of fresh fruit is 25 to 100 mg/100 g (Vvedenskaya and Vorsa 2004; Wang and Stretch 2001), of canned juice is 8 to 24 mg/100 mL, and of Cranberry Juice Cocktail (Ocean Spray) is 6 to 10 mg/100 mL (Deubert 1978; Fuleki and Francis 1968a, 1968d; Sapers et al. 1986a; Schmid 1977). The total anthocyanin content in cranberry fruit and products are variable and depend upon variety, environment, growing practices, post-harvest storage conditions, and post-harvest processing. In edible fruits the reported anthocyanin values range between 13.6 to 140 mg/100 g (Cunningham et al. 2004; Pappas and Schaich 2009; Sapers and Hargrave 1987; Wu et al. 2006). Levels in juices are generally lower than in fruits with different ranges reported in the literature. Hong and Wrolstad (1986b) report levels in pressed juice ranging from 19 to 53 mg/100 mL for different cranberry varieties. In cranberry juice cocktails, Prior et al. (2001) report 1.3 mg/100 mL anthocyanins and Cunningham et al. (2004) report levels ranging from 8 to 25 mg/L. On average, the cyanidin:peonidin ratio is approximately 40:60 in fruits and 60:40 in juice (Lee 2013) and this value in addition to the detection of significant levels of the other anthocyanin types have been used as markers to detect cranberry product adulteration, although newer methods are more definitive (Feliciano et al. 2012a). Anthocyanin content is inversely correlated with berry size, can increase during storage, and

Table 2 **Nutrient content of cranberries and select cranberry products**

Nutrient	Whole raw (1 c or 95 g)	Dried sweetened (0.33 c or 40 g)	Juice, unsweetened (1 c or 253 g)	Juice (27%) cocktail (1 c or 253 g)
Energy (kcal)	44	123	116	137
Water (g)	83	6	220	218
Protein (g)	0.37	0.03	0.99	0.00
Carbohydrate (g)	11.59	32.94	30.87	34.21
Total lipid (g)	0.12	0.55	0.32	0.25
Fiber (g)	4.4	2.3	0.3	0
Potassium (mg)	81	16	194	35
Sodium (mg)	2	1	4	5
Selenium (µg)	0.1	0.2	0.4	0.5
Vitamin A (µg RAE)	3	0	6	0
Vitamin C (mg)	12.6	0.1	23.6	107.0
Vitamin E (mg α-tocopherol)	1.14	0.43	3.04	0.56
β-Carotene (µg)	34.2	0.0	68.3	13.0
Lutein + zeaxanthin (µg)	86.45	13.40	172.67	33.00

Source: McKay and Blumberg (2007).

Table 3 **Anthocyanins in Cranberry Juice Cocktail® (Ocean Spray)**

Anthocyanin	Amount mg/L	Relative ratio
Cyanidin-3-O-glucoside	2.0 ppm	1.0
Cyanidin-3-O-galactoside	0.1 ppm	0.05
Cyanidin-3-O-arabinoside	1.4 ppm	0.9
Peonidin-3-O-galactoside	2.8 ppm	1.4
Peonidin-3-O-glucoside	0.3 ppm	0.2
Peonidin-3-O- arabinoside	1.1 ppm	0.6

Source: Cunningham et al. 2008.

is positively correlated with antioxidant activity (Wang and Stretch 2001).

Proanthocyanidins (PACs)

Cranberry PAC oligomers, also referred to as condensed tannins or polyflavan-3-ols, are predominantly made up of epicatechin extender units. The stereochemistry of the flavonol monomers is predominantly of the 2,3-cis type with a small proportion of 2,3-trans units (Foo et al. 2000a, 2000b). Some studies also report the presence of epigallocatechin and catechin units in PAC oligomers (Foo et al. 2000a, 2000b; Howell et al. 2005; Neto et al. 2006; Porter et al. 2001; Reed et al. 2005). Total catechins in raw cranberry average 17 mg/100 g with epicatechin being the most abundant of these (Harnly et al. 2006). According to Gu et al. 2004, cranberry juice contains 6 mg/L of catechins. Oligomers and polymers with a degree of polymerization above 3 are more effective at preventing adherence of P-fimbriated *Escherichia coli (E. coli)* to uroepithelial cells in vitro than dimers (Howell et al. 2005). Cranberry PACs also increase extra-intestinal pathogenic *E. coli* (ExPEC) agglutination, reduce ExPEC gut epithelial cell invasion (Feliciano et al. 2013), and, in animals, improve the health of the gut mucosal layer by increasing oral mucin levels (Pierre et al. 2013) and intestinal secretory immunoglobulin A (Pierre et al. 2014).

There are 2 common series of PAC dimers. The B-type series are dimers linked either in the C4 to C6 or C4 to C8 position whereas the A-type series are dimers linked in the C4 to C8 position with an additional C2 to O to C7 ether linkage. Cranberry PAC oligomers with a degree of polymerization (DP) greater than 2 may incorporate both A-type and B-type interflavan linkages. By extension of this definition, and for purposes of discussing differences among oligomers, PAC that contain one or more A-type interflavan bonds in their structure are referred to as A-type PAC whereas PAC oligomers that contain only B-type interflavan bonds are referred to as B-type PAC (Krueger et al. 2013a). Feliciano et al. (2012a) applied a method to deconvolute matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) isotope patterns and determined that more than 91% of cranberry PAC molecules had at least one A-type linkage. The ratios of A-type to B-type linkages in PAC are product-specific and therefore constitute information that can be used to authenticate cranberry content. PACs are also soluble (extractable) and insoluble (non-extractable), depending on the history of the cranberry sample and the extraction solvent. Insoluble PACs are often bound to complex carbohydrate cell wall components or proteins. The average degree of polymerization of PACs differs and is variably reported as 4.7 (Foo et al. 2000a), 8.5 to 15.3 (Gu et al. 2003a), and up to 23 (Blumberg et al. 2013; Reed et al. 2005), in part due to variable findings using different analytical methods that employ thiolysis and phloroglucinolysis (Karonen et al. 2007; Zhou et al. 2011). Like anthocyanins, the amount of PACs found in cranberries can vary, partly due to variations in samples and due to differ-

ences in analytical methodologies. Based on HPLC-MS-MS analyses, Gu et al. (2004) reported PAC content of 418.8 ±75.3 mg/100 g of fresh fruit and 231 ± 2 mg/L in cranberry juice cocktail. Different values will be found using other analytical methods. In both matrices the majority of the PAC had a >10 degrees of polymerization.

The oligomeric pigments that are in cranberry are similar to structures found in wine (Krueger et al. 2004). Approximately 10% of the color in freshly prepared whole cranberry juice is due to polymeric material (Hong and Wrolstad 1986a) and this increases with age. MALDI-TOF MS was used to characterize the structural diversity of a series of anthocyanin-polyflavan-3-ol oligomers in cranberry fruit and spray dried juice powder. MALDI-TOF mass spectra provide evidence for a series of compounds corresponding to anthocyanins linked to PAC through a CH3-CH bridge (Krueger et al. 2004). Liquid chromatography electrospray ionization mass spectrometry (Tarascou et al. 2011) and MALDI Fourier transform ion cyclotron resonance MS have confirmed the presence of oligomeric anthocyanin-PACs in cranberry (Feliciano et al. 2012b). While mass spectrometry has the ability to detect these compounds, the absolute structure of the compounds cannot be elucidated by mass spectrometry alone.

Flavonols

The principal flavonols in cranberries are the galactosides, arabinosides, and rhamnosides of quercetin (177–250 mg/kg), myricetin (4–27 mg/kg), and kaempferol (1–3 mg/kg) (Bilyk and Sapers 1986; Cunningham et al. 2008; Puski and Francis 1967; Zheng and Wang 2003). More than 20 different flavonols occur in cranberries, with their relative proportions differing by cranberry variety (Pappas and Schaich 2009; Vvedenskaya and Vorsa 2004). Total flavonol content of cranberry fruit is in the range of 20 to 40 mg/100 g (Cunningham et al. 2003; Neto 2007b; Vvedenskaya et al. 2004; Zheng and Wang 2003). Both quercetin and myricetin occur mainly as monoglycosides in the fruit, with quercetin galactoside the most abundant form (Figure 7). Three flavonol aglycones may be generated by the loss of sugar moieties as an effect of processing (White et al. 2011). The flavonol profile of processed cranberry products such as juice and powder is similar to the fruit; however, these products also contain a significant amount of the flavonol aglycones (Vvedenskaya et al. 2004).

Organic Acids

Cranberries contain 3 primary organic acids (see Tables 5 and 6): quinic acid, citric acid, and malic acid (Coppola et al. 1978; Hong and Wrolstad 1986a). These acids account for a significant portion of the total solids in cranberry juice ranging from 2.2 to 3.57% (w/v) (Coppola et al. 1978; Jensen et al. 2002; Hong and Wrolstad 1986a). Cunningham et al. (2004) reported an average of 3.1% for single strength juice. Cranberries possess a relatively high level of quinic acid, with reported values ranging from 0.83 to 1.62% for fruit and a reported average of 1.05% in the single strength juice (Coppola et al. 1978; Hong and Wrolstad 1986a; Jensen et al. 2002; Kuzminzki 1996). The same acids are also present in cranberry juice in very consistent ratios. Hong and Wrolstad (1986b) reported that studies generally agree on mean percentages of individual acids that make up total acids: for quinic acid 40%; malic acid 28%; and citric acid 32%. The consistency of these ratios allows for their use for quality-control assessment of cranberry products (Hong and Wrolstad 1986a). Low concentrations of ascorbic acid (11–14 mg/100 g, in whole cranberries) (Kuzminski 1996; Licciardello et al. 1952), shikimic acid, and tartaric acid have been reported (Pappas and Schaich 2009). Processing of cranberries into juice can result in significant losses of ascorbic acid in unfortified cranberry juice and ascorbic acid concentrations have been reported to be much lower in these products (<2 mg/100 g) (Kuzminski 1996; Leahy et al. 2002; Licciardello et al. 1952; Pappas and Schaich 2009). To make up for these losses, cranberry products are typically fortified with ascorbic acid to levels equivalent to recom-

Table 4 Phytochemical content of cranberry foods

Cranberry Preparation	Flavan-3-olmonomers and dimers	Proanthocyanidins	Anthocyanins	Hydroxybenzoic Acids	Hydroxycinnamic Acids	Terpenes	Flavonols
Fruit mg/100 g mg/serving (80 g)	7–33 5.6–26.4	133–367 106–293	13–171 10.4–136.8	503–602 402–482	73–82 57.6–65.6	65–125 52–100	20–40 16–32
Juice mg/L mg/serving (200 mL)	6–35 7	89–230 17.8–46	27–132 5.4–26.4	64 12.8	12–19 2.4–3.8	Trace Trace	11–58 2.2–11.6
Canned sauce mg/100 g mg/serving (70 g)	112.8 78.9	16–54.4 11.2–38	0.6–11.8 0.4–8.3	476 333.2	47.5 33.2	1.1–22.8 0.8–16	– –
Sweetened dried fruit mg/100 g mg/serving (40 g)	– –	64.2 25.6	10.3 4.1	– –	– –	98.5–39.4	– –

Source: Modified from Blumberg et al. (2013).

mended daily intake (RDI) (Hong and Wrolstad 1986a; Licciardello et al. 1952; Pappas and Schaich 2009). Citric acid occurs at concentrations of 1.3% and 1.1% in the fruit and juice, respectively (Coppola et al. 1978; Jensen et al. 2002; Kuzminzki et al. 1996). Malic acid is present in lower concentrations with reported averages of 0.7% and 0.8% in the fruit and juice, respectively (Cunningham et al. 2004; Hong and Wrolstad 1986a). Shikimic acid is present in cranberry at low concentrations with reported averages of 0.03% in the fruit and 0.02% in the juice (Cunningham et al. 2004; Hong and Wrolstad 1986a). Cranberries are highly acidic, with a typical pH of ~2.5. Benzoic acid, a compound with antibacterial activity that is metabolized to hippuric acid, which is also bactericidal, occurs in cranberry fruits in trace amounts, may occur in larger amounts in cranberry preparations, and may be lacking in other preparations (see Table 5). More recent research in vitro suggests organic acids and their metabolites may play a role in the antiadhesion activity of cranberry (Gonzalez de Llano et al. 2015), though further confirmation of this is required.

Cranberries contain more than 20 simple phenolic acids, hydroxycinnamic acids, and triterpene organic acids (Pappas and Schaich 2009; Wang and Zuo 2011) and differ between preparations (see Table 5). More than 50% of these simple phenolics are esterified to sugars, cell wall polysaccharides, or other components (Zuo et al. 2002). Sinapic acid, *p*-courmaric acid, caffeic acid, and ferulic acid are the most prevalent hydroxycinnamic acids. Benzoic acid and salicylic acid are the most predominant phenolic acids; benzoic acid being the major aromatic compound in cranberry juice (Zuo et al. 2002), according to Turner (2006) occurring at 0.24%; according to Zuo et al. (2002) 4.7 g/kg fresh weight in fruits. However, because of the diversity of structures of cranberry phenolic acids, HPLC may result in an underestimation of total phenolics (Grace et al. 2012).

Oleanolic acid and ursolic acid (Markley and Sando 1934; Neto 2007b; Wu and Parks 1953) and 2 lipophilic triterpenes are present in the waxy coat of the fruit skin (Fellers and Esselen 1955). Whole cranberry fruit contains approximately 60 to 110 mg/100 g ursolic acid, but this compound is lacking in commercial juice (Neto 2007b). Ursolic acid has anti-inflammatory properties and several in vitro investigations reported ursolic acid and ursolic acid derivatives to have direct cytotoxic and antiproliferative activity against several cancer cell lines (He and Liu 2006; Huang et al. 2009; Murphy et al. 2003; Neto 2007b).

Table 5 Free and total phenolic compounds in fresh cranberry fruits, juice, and sauces samples

Phenolics	Concentration in fruits (µg/g)		Concentration in juice (µg/mL)		Concentration in fresh sauces (µg/g)	
	Free	Total	Free	Total	Free	Total
Benzoic acid	416.5 ± 32.4	5575.8 ± 363.4	234.6 ± 15.6	3256.7 ± 109.8	358.8 ± 44.9	4658.5 ± 478.4
o-Hydroxybenzoic acid	ND*	29.03 ± 2.32	14.12 ± 2.41	34.64 ± 3.43	2.33 ± 0.32	24.73 ± 3.53
trans-Cinnamic acid	1.08 ± 0.31	18.29 ± 1.33	0.78 ± 0.14	7.68 ± 1.23	0.87 ± 0.21	9.07 ± 2.21
m-Hydroxybenzoic acid	6.34 ± 0.34	14.82 ± 2.87	0.92 ± 0.21	3.72 ± 0.23	2.31 ± 0.12	6.35 ± 1.54
p-Hydroxybenzoic acid	5.77 ± 0.24	27.83 ± 3.89	0.37 ± 0.09	3.82 ± 0.43	1.09 ± 0.13	12.89 ± 3.76
p-Hydroxyphenylacetic acid	ND*	4.95 ± 0.43	ND*	2.69 ± 0.21	ND*	3.64 ± 0.98
o-Phthalic acid	6.34 ± 0.65	19.28 ± 2.43	ND*	23.96 ± 3.56	ND*	20.45 ± 4.74
2,3-Dihydroxybenzoic acid	1.63 ± 0.22	5.02 ± 0.89	7.99 ± 1.23	39.65 ± 4.63	0.93 ± 0.09	10.73 ± 1.89
Vanillic acid	8.98 ± 0.98	33.86 ± 3.11	0.95 ± 0.76	23.99 ± 2.45	3.32 ± 0.87	43.02 ± 6.43
o-Hydroxycinnamic acid	16.56 ± 1.21	92.43 ± 3.89	4.68 ± 1.01	140.68 ± 21.4	0.87 ± 0.23	90.93 ± 10.32
2,4-Dihydroxybenzoic acid	1.27 ± 0.11	24.32 ± 1.23	0.78 ± 0.11	7.83 ± 2.5	5.78 ± 1.09	15.68 ± 3.52
p-Coumaric acid	31.63 ± 2.43	329.6 ± 23.5	10.88 ± 2.32	210.88 ± 23.6	25.86 ± 4.87	289.76 ± 33.8
Ferulic acid	7.92 ± 1.08	94.23 ± 10.9	3.86 ± 0.87	13.78 ± 1.78	3.23 ± 0.77	32.43 ± 5.78
Caffeic acid	6.94 ± 1.11	202.5 ± 23.4	0.95 ± 0.21	40.75 ± 4.82	1.24 ± 0.13	31.64 ± 4.65
Sinapic acid	0.88 ± 0.13	28.34 ± 1.32	18.87 ± 3.56	218.87 ± 34.7	0.52 ± 0.12	20.72 ± 5.23
trans-Resveratrol	0.76 ± 0.11	47.03 ± 3.56	0.45 ± 0.23	40.43 ± 7.54	ND*	20.87 ± 4.34
(–)-Epicatechin	48.7 ± 3.98	122.79 ± 13.67	6.12 ± 1.21	36.92 ± 3.26	35.2 ± 3.7	72.77 ± 6.23
Catechin	3.62 ± 0.33	58.23 ± 7.55	2.86 ± 0.43	42.89 ± 6.87	3.66 ± 0.54	39.96 ± 4.53
Quercetin	1399.7 ± 34.7	3445.8 ± 108.6	193.8 ± 16.5	2983.5 ± 187.3	689.4 ± 78.4	3675.8 ± 387.9
Myricetin	789.6 ± 93.9	2108.4 ± 243.8	86.9 ± 3.4	1966.8 ± 194.3	426.8 ± 39.7	2026.3 ± 213.7

Volatile Oils

Fresh cranberries contain ~0.00011% volatile oils consisting of ≥68 compounds including monoterpenes (primarily α-terpineol at 24% of the total volatile oil, plus cineole 0.7%, carvacrol 0.5%, limonene 0.4%, linalool 0.3%, and others) and diterpenes (kaurene 1.1%, pimaradiene 1.0%, and manoyloxide 0.3%). Other terpenes reported in cranberries include α-pinene, β-pinene, myrcene, and nerol (Crouteau and Fagerson 1968; Hirvi et al. 1981). Terpenes contribute greatly to the flavor and aroma of the fruits. Isophorone, a compound found in very few plants to date, is present at 0.2% of the total volatile oil. Also present are aromatic compounds such as benzyl alcohol (9%), the above-mentioned carvacrol, various benzoic acid esters, 4-ethylguaiacol (0.7%), benzothiazole (0.6%), and eugenol (0.2%) (Anjou and Sydow 1967, 1968). Much of the data is outdated and would benefit from more modern analyses with current analytical technology.

Table 6 Vitamins found in cranberries

Vitamins	Concentration per 100 g fresh fruit
Ascorbic acid (vitamin C)	7.5–32 mg
Niacin	33–100 µg
Pantothenic acid	25 µg
Beta-carotene	40 IU
Thiamine (B-1)	13.5–30 µg
Pyridoxine (B-6)	10 µg
Riboflavin (B-2)	3-20 µg

Source: Fellers and Esselen 1955; Schmid 1977; Watt et al. 1975

Sugars and Complex Carbohydrates

Sugar in cranberry fruit are reported to occur at concentrations of 1.1% fructose and 4.3% glucose (Hong and Wrolstad 1986a). The cranberry cell wall consists of cellulose, pectin, and hemicellulose (Holmes and Rha 1978). Cranberry pomace (press cake) solids are 35% insoluble fiber (USDA-ARS 2004). The soluble fiber fraction of cranberries contains oligomeric saccharides with monomer units mostly of arabinose, glucose, galactose and rhamnose, with lesser amounts of xylose and mannose (Marlett and Vollendorf 1994). Interactions between carbohydrates and PACs, resultant of covalent bonding, give rise to insoluble PAC.

Cranberries have a high glucose:fructose ratio, which is unusual for fruit juices. This ratio has been used to detect adulteration of unsweetened single strength cranberry juice (Hong and Wrolstad 1988). Hong and Wrolstad (1986a) reported an average glucose:fructose ratio of 3.8, whereas Schmid (1977) reported glucose:fructose ratios ranging from 2.27 to 5.2. The detection of sorbitol in significant amounts can also be an indication of adulteration, as sorbitol is only found in cranberry in trace amounts (Hong and Wrolstad 1986a).

Vitamins

Cranberry contains a number of nutrients such as vitamin C and some B-vitamins (see Table 6). Vitamin C is easily degraded in processing, resulting in juice manufacturers fortifying their products with ascorbic acid. Cranberry seed also contains vitamin E (O'Brien 2004).

Seed Oil

Cranberry seeds contain fatty acids (~0.55%) (Rindt 2008), most notably linoleic, oleic, palmitic, and linolenic acids (Bhagdeo 2004). Fatty acid composition consists of saturated and unsaturated fats. Of the unsaturated fatty acids, from soxhlet and super critical CO_2 extracts, the seed oil contains methyl esters of omega-3 fatty acids such as α-linolenic acid, omega-6 fatty acids such as linoleic acid and eicosadienoic acid, and omega-9 fatty acids such as oleic acid, palmitoleic acid, and eicosenoic acid. In addition, several hydrocarbons were tentatively identified. An unknown alkyne, a hydrocarbon (possibly squalene), and possibly β-sitosterol were also found, along with tocopherols and amyrin. In vivo cholesterol lowering activity and improvements in high-density lipoprotein have been demonstrated for cranberry seed oil (Eno 2007).

ANALYTICAL

Because of the diversity of cranberry products in the market place and the fact that evidence suggests multiple compounds and their metabolites play a role in the overall activity of cranberry for its various effects, no single analytic technique is capable of addressing all of the authentication and quantification needs for each unique product. Some techniques are more suitable for identification (botanical, macroscopic, chemical, molecular), while others are more specific for quantification of specific compounds (spectrophotometric, chemical). Botanical and macroscopic identification are the most definitive assessment techniques for whole raw material. HPTLC, HPLC, and genetic assessment are most appropriate for identity of powdered material. HPTLC and HPLC are standard techniques that can be used for the identification of extracts, including the ability to detect some adulterations (e.g. grape skins or grape seeds to 15% adulteration) (AHP data, unreferenced; Brown and Chan 2015; Lee et al. 2013). MALDI-TOF-MS can differentiate cranberry PACs and grape OPCs by assessing the ratios of A-type to B-type linkages in PACs (Krueger et al. 2013b) with an A2 reference standard. In cranberry, these ratios are stable. Thus anomalies in these ratios can serve to detect some adulterations. Other mass spectrometry techniques, such as direct infusion electrospray ionization, have also been used to characterize PACs.

The most appropriate techniques for quantitation of specific compounds depend on the analytical endpoint. For quantitation of anthocyanins, HPLC is appropriate. For quantitation of PACs, spectrophotometric methods e.g., DMAC for soluble PACs, or a butanol-HCL for insoluble PACs (or other assays), are typically used.

Further complicating cranberry analysis is adulteration of cranberry extracts with a variety of adulterants that can include dyes, grape skin and seed extract, peanut skins, or

other substances that are naturally rich in PACs, such as mulberry, and plum. Care must be taken to ensure appropriate identification tests have been performed prior to quantification of specific compounds. Not all methods have been fully validated for their application. Therefore analysts must choose the most appropriate technique(s) and methodology for the desired analytical endpoint(s). Using varying techniques in tandem, such as HPTLC or HPLC for identification, HPLC for quantitation of anthocyanins or phenolics, DMAC for quantitation of soluble PACs, or butanol-HCL assays for quantitation of insoluble PACs, may be most appropriate for various aspects of cranberry quality control. The analytics of cranberry and its products will continue to develop with greater levels of validation and with greater clarity regarding activity of compounds.

High Performance Thin Layer Chromatography (HPTLC) for the Identification of Cranberry Fruit and Detection of the Anthocyanin Cyanidin-3-O-glucoside and the Flavonoid Hyperoside

This HPTLC method was developed by Camag (Muttenz, Switzerland) and detects the anthocyanidin cyanidin-3-O-glucoside chloride and the flavonoid hyperoside. The method can be used as an identifying fingerprint for freshly dried, liquid extract, and dry cranberry extract. The method may also be used to detect cranberry extract adulterated with grape skin (15%).

An HPTLC method for the detection and relative quantification of PAC is available but has not yet been validated (see Boudesocque et al. 2013).

Sample Preparation

Powder: 0.2 g of powdered material are mixed with 7 mL of water and sonicated for 10 minutes at room temperature. After centrifugation, 4 m of the supernatant are loaded onto a 6 mL SPE C18 cartridge that has been conditioned first with 3 mL of MeOH, dried, and then with 3 mL of water (not dried). The loaded and dried cartridge is washed with 1 mL of water-MeOH (80:20) and dried. The test solution is obtained by elution of the cartridge with 1 mL of methanol.

Liquid extract: 2 mL of the liquid extract are loaded onto a 6 mL SPE C18 cartridge that has been conditioned first with 3 mL of MeOH, dried, and then with 3 mL of water (not dried). The loaded and dried cartridge is washed with 1 mL of water - MeOH (80:20) and dried. The test solution is obtained by elution of the cartridge with 1 mL of methanol.

Notes: For sample preparations, during loading, cleanup, and elution, the flow rate of the solvent should not exceed 120 drops per minute (e.g. Finisterre C18). The wash volume can be collected into a vial for analysis of sugars if desired.

Standard Preparation

1 mg/mL in methanol of each standard.

Derivatization Reagent Preparation

Natural products (NP) reagent: 1 g of 2-aminoethyl diphenylborinate is dissolved in 200 mL ethyl acetate, prior to immersion into the reagent.

Anisaldehyde reagent: 10 mL of sulfuric acid are carefully added to an ice-cooled mixture of 170 mL of methanol and 20 mL of acetic acid. To this solution, 1 mL of anisaldehyde is added.

Reagent use: Preheat plate to 100 °C for 3 minutes before dipping into NP Reagent. Dip the warm plate in NP reagent (dipping speed: 5; time: 0). Document findings in white light and UV 366 nm. After documentation, dip the same plate in anisaldehyde (dipping speed: 5; time: 0) and heat at 100 °C for 3 minutes.

Chromatographic Conditions

Stationary Phase

HPTLC plates 10 x 10 cm or 20 x 10 cm silica gel 60 F254 (Merck or equivalent).

Relative Humidity

Condition the plate at a relative humidity of 33%.

Mobile Phase

Ethyl acetate, glacial acetic acid, formic acid, water (100:11:11:27).

Temperature

Ambient

Sample Application

Instrument: ATS4 (or equivalent).
Application: Apply 10 µL of the test solution, authenticated botanical reference material (e.g., AHP-Verified BRM), and/or 2 µL of each chemical standard as 8 mm bands, 2 mm apart from each other. Application position should be 8 mm from the lower edge of the plate and at least 15 mm from the left and right edges of the plate.

Note: The application volume of the liquid extracts, seeds, and fresh fruit was adjusted in order to have the same concentration (or same intensity of the zones) as the dry fruits.

Development

Instrument: Twin Trough Chamber (TTC or equivalent)
Open the chamber and place a correctly sized (10 x 10 cm; 20 x 10 cm) piece of filter paper in the rear trough. Pour an appropriate volume (10 mL for 10 x 10 cm, 20 mL for 20 x 10 cm TTC) of solvent into rear trough of the chamber so that the filter paper is thoroughly wetted and adheres to rear wall of the chamber. Pour an appropriate volume (5 mL for 10 x 10 cm, 10 mL for 20 x 10 cm TTC) of solvent into front trough of the chamber. Let saturate for 20 minutes. Measure and mark the developing distance 70 mm from the lower

edge of the plate. Introduce the plate into the chamber with the stationary phase towards the inside, close the chamber, and allow the solvent to reach the 70-mm mark. Remove the plate and dry for 5 minutes in a stream of cool air.

Application

Instrument: ATS4 (or equivalent)

Results

Compare to chromatograms provided.

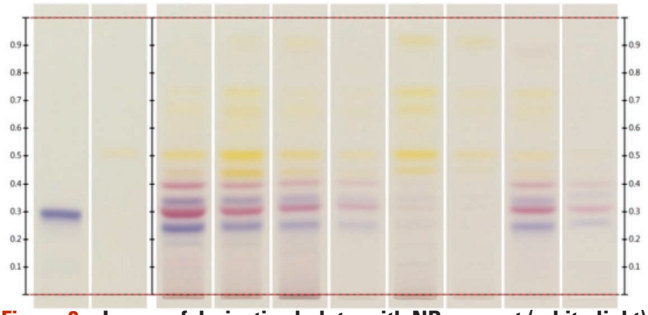

Figure 8a Image of derivatized plate with NP reagent (white light)

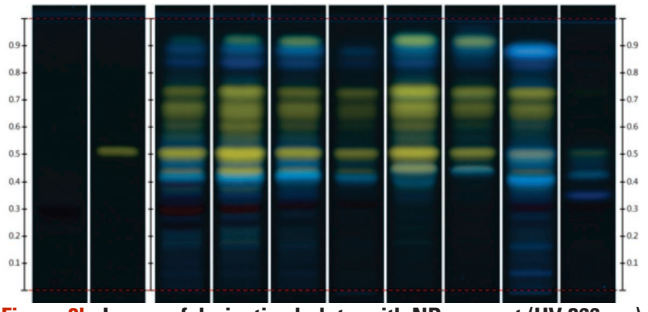

Figure 8b Image of derivatized plate with NP reagent (UV 366 nm)

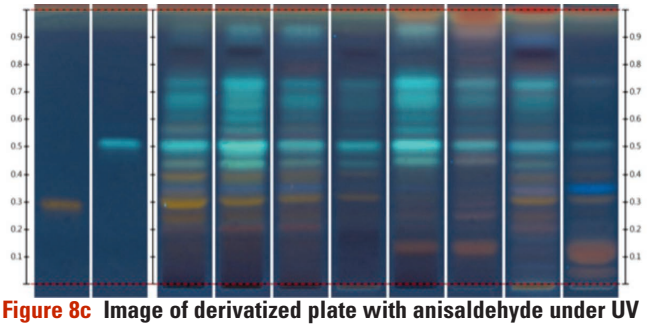

Figure 8c Image of derivatized plate with anisaldehyde under UV 366 nm

Lane Assignments

Lane 1 Cyanidin-3-O-glucoside chloride.
Lane 2 Hyperoside.
Lane 3 Dry fruit.
Lane 4 Dry fruit.
Lane 5 Fruit powder.
Lane 6 Fruit powder.
Lane 7 Liquid extract (tincture; 1:4; 52–62% ethanol).
Lane 8 Liquid extract (tincture; 1:4; 52–62% ethanol).
Lane 9 Cranberry seeds.
Lane 10 Fresh fruit.

Discussion of the Chromatograms

Figure 8a (derivatized, NP reagent, white light): The cyanidin-3-O-glucoside chloride standard (Lane 1) is observed as a blue zone at R_f 0.3. The hyperoside standard is observed as a very faint yellow zone at ~ R_f 0.52 (Lane 2). The profile of different dry fruits (Lanes 3–6) is relatively consistent showing the following banding pattern in ascending order: a violet zone at R_f 0.29, a magenta zone at R_f 0.3, a pale violet zone at R_f 0.33, a magenta zone at R_f 0.4, 2 orange-yellow zones at R_f 0.45 and 0.5, and 2 faint yellow zones in the upper R_f (0.68 and 0.73). The liquid extracts (tinctures; 52 to 62% ethanol; 1:4 herb to extract ratio; Lanes 7 & 8) show a profile that is similar to those of the dry fruits but show only very faint zone. The profile of the seed (Lane 9) looks similar to that of the dry fruits. The fingerprint of the fresh fruit (Lane 10) is almost identical to the lower part of the profile obtained from dry fruits, though the intensity of the zones is more faint.

Figure 8b (derivatized, NP reagent, UV 366 nm): The cyanidin-3-O-glucoside chloride standard (Lane 1) is not visualized at UV 366. The hyperoside standard is observed as a yellow zone at R_f 0.52 (Lane 2). There are zones corresponding to hyperoside in all samples. The profile of different dry fruits (Lanes 3–6) is relatively consistent showing the following fingerprint pattern in ascending order: in the lower R_f region faint yellowish and bluish zones between R_f 0.1 to 0.3 and a red zone at R_f 0.3 in some samples (Lanes 3–5,9); from the middle to upper R_f region, most samples are characterized by a bright blue zone at R_f 0.4, a yellow zone corresponding to position and color to hyperoside at R_f 0.52 in all samples, a cluster of 4 blue and yellow zones between R_f 0.55 to 0.72, and blue and yellow zones in the upper R_f at 0.85 to 0.9.

The liquid extracts (tinctures; 52 to 62% ethanol; 1:4 herb to extract ratio; Lanes 7 & 8) show a profile that is similar to those of the dry fruits in positioning and intensity with the exception of the absence of the deep red zone (R_f 0.3). The profile of the seed (Lane 9) looks identical to that of the dry fruits and shows a prominent blue zone at R_f 0.89 and the yellow zone at R_f 0.9 is lacking. The fresh fruit (Lane 10) shows an almost identical profile in the lower R_f region as dry fruits, though the intensity of the zones is more faint.

Figure 8c (derivatized, anisaldehyde reagent, UV 366 nm): After derivatization with anisaldehyde, both standards (Lanes 1 & 2) are visible. There are yellowish-orange zones at the position of cyanidin-3-O-glucoside chloride in all samples except for the liquid extracts (Lanes 7 & 8). The liquid extracts (tinctures; 52–62% ethanol; 1:4 herb to extract ratio; Lanes 7 & 8) and fresh fruit (Lane 10) show additional reddish-orange zones at ~R_f 0.1 and the fresh fruit shows no blue zones between R_f 0.6 and 0.7. Otherwise the patterns of zones are similar in position to those described above, with the zones in the middle to upper Rf region being more blue than yellow. The liquid extracts (Lanes 7 & 8) and the fresh fruit (Lane 10) show an additional orange zone at R_f 0.11 that is not observable in the other samples with this detection.

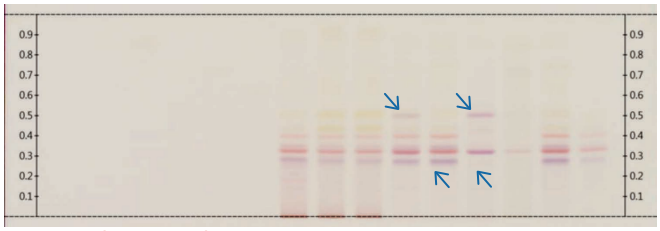

Figure 9a (WRT light):

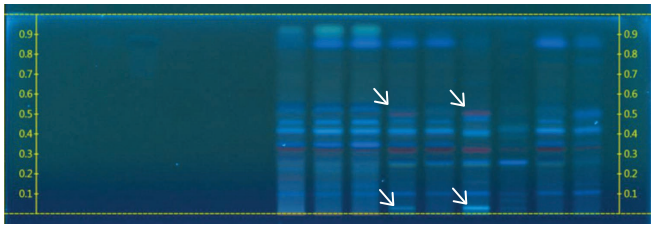

Figure 9c Image of the plate under UV 366 nm

Lane Assignments

Lane 1 (-) Epigallocatechin-3-O-gallate
Lane 2 Epicatechin
Lane 3 (+) Catechin
Lane 4 PAC A2
Lane 5 PAC B2
Lane 6 PAC C1
Lane 7 *V. macrocarpon* dried whole fruit
Lane 8 *V. macrocarpon* dried whole fruit
Lane 9 *V. macrocarpon* dried fruit
Lane 10 *V. macrocarpon* fruit powder w/ 15% grape skin
Lane 11 *V. macrocarpon* powder w/ 15% grape seed
Lane 12 Grape (*Vitis vinifera*) fruit skin powder
Lane 13 Grape seed skin powder
Lane 14 *V. macrocarpon* powder
Lane 15 *V. macrocarpon* seed (less seed oil) powder

Discussion of the Chromatograms

Figure 9a (WRT light): Prior to derivatization, the pink zone at R_f 0.5 (blue arrows) is due to adulteration of the cranberry fruit powder with 15% grape fruit skin powder (Lane 10). The fingerprint of grape skin alone (Lane 12) lacks a violet zone at 0.29 that is present in cranberry fruit. The fingerprint of grape seed (Lane 13) lacks most of the zones characteristic of cranberry fruit.

Figure 9b (derivatized, anisaldehyde reagent; WRT light): Zones due to catechin (Lane 3) and proanthocyanidins A2, B2, C1 (Lanes 4–6) are detected. The zone due to PAC-B2 (Lane 5, blue arrow; R_f 0.71) is seen in grape seed powder (Lane 13), grape skin powder (Lane 12), and the cranberry fruit sample adulterated with 15% grape seed (Lane 11). This zone is not observed in cranberry fruit adulterated with 15% of grape skin (Lane 10) and is absent in all other samples.

Figure 9c (UV 366 nm): The cranberry fruit sample adulterated with 15% of grape skin (Lane 10) shows a blue fluorescent zone just above the application position and a reddish zone at Rf 0.5 (blue arrows). Both zones are characteristic of grape skin powder (Lane 12).

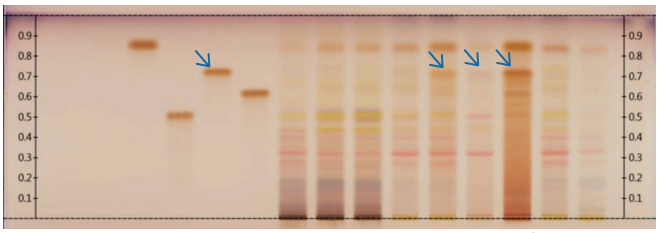

Figure 9b Image of derivatized plate under WRT light (anisaldehyde reagent)

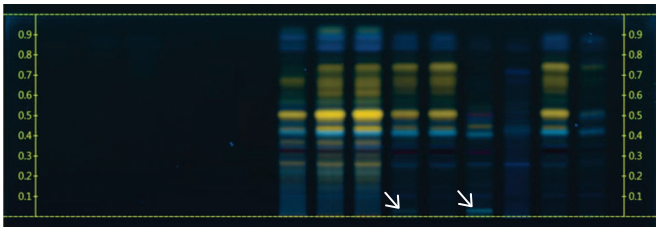

Figure 9d Image of derivatized plate under UV 366 nm (NP)

Figure 9d (derivatized, NP reagent; UV 366 nm): The blue fluorescent zone above the application position (blue arrows) is present in grape fruit skin powder (Lane 12) and is seen in the cranberry fruit sample adulterated with 15% of grape skin (Lane 10). The upper R_f region of the grape skin (Lane 12) and grape seed Lane 13) fingerprints alone do not show the same characteristic patterns as cranberry fruit and are easily distinguished.

High Performance Liquid Chromatography (HPLC) for the Quantitation of Anthocyanins in Freeze-Dried Cranberry Powder, Cranberry Juice, Cranberry Cocktail, and Cranberry Extract Powder

The following HPLC procedure can be used to quantify cranberry anthocyanins in selected raw materials and finished products. The method detects the following anthocyanins: cyanidin-3-*O*-galactoside (further C3Ga), cyanidin-3-*O*-arabinoside (C3Ar), cyanidin-3-*O*-glucoside (C3Gl), peonidin-3-*O*-galactoside (P3Ga), and peonidin-3-*O*-arabinoside (P3Ar). The method was subjected to a single-laboratory validation (SLV) according to AOAC International guidelines and has been shown to be appropriate for the analysis of the following preparations: freeze-dried cranberry powder, cranberry juices, cranberry juice cocktail, and cranberry extract powder (Brown and Shipley 2011). The limit of detection (LOD) and limit of quantitation (LOQ) were determined according to the guidelines of International Union of Pure and Applied Chemistry (IUPAC). Further work determined the method appropriate for identifying admixtures of cranberry fruit and grape fruit skins and seeds (potential adulterants). The occurrence of a prominent peak between C3Ga and C3G1 is anomalous and may be due to the presence of an adulterant (Lee et al. 2013).

Sample Preparation

Freeze Dried Raw Material and Powdered Extract: Grind freeze-dried cranberries and cranberry extract powder to <60 mesh (250 µm) powder. Weigh and place 0.250 g (+/-0.025 g) of the test article into a 50 mL conical tube, add 20 mL of extraction solvent, 2% (v/v) concentrated HCl in methanol solution, using a graduated cylinder, mix for 10 seconds with a vortex mixer, sonicate for 15 minutes, and shake at an angle at 180 rpm for 30 minutes. Mix the test solutions for 10 seconds with a vortex mixer and centrifuge at 5000 rpm for 5 minutes. Decant the supernatant to a 25 mL volumetric flask and bring to 25 mL volume with extraction solvent. Invert the flask 20 times to mix and filter approximately 1 mL of the solution through a 0.45 µm Teflon filter into an amber HPLC vial for analysis.

Juice (pure): Thoroughly mix the juice by inverting the container approximately 20 times or until no sediment is visible. Centrifuge 10 mL of juice at 5000 rpm for 10 minutes. Dilute 1000 µL of juice with 500 µL extraction solvent and filter approximately 1 mL of the solution through a 0.45 µm Teflon filter into an amber HPLC vial for analysis.

Juice Cocktail: Thoroughly mix the juice cocktail by inverting the container approximately 20 times or until no sediment is visible. Centrifuge 10 mL of cocktail at 5000 rpm for 10 minutes and filter approximately 1 mL of the solution through a 0.45-µm Teflon filter into an amber HPLC vial for analysis.

Standards Preparation

Reference standards for each of the 5 anthocyanins can be obtained from Cerilliant Corp. (Round Rock, Texas). Individual 1000 µg/mL stock solutions of each anthocyanin standard are prepared by weighing 10.0 ± 1.0 mg of each standard and placing the weighed amount into separate amber 10 mL volumetric flasks. Approximately 5 mL of a 2% (v/v) conc. HCl in methanol solution is added to each flask and sonicated until all solid material dissolves. The flasks are then brought to volume with the addition of 2% (v/v) concentrated HCl in methanol solution. A mixed anthocyanin reference standard solution can be prepared by transferring 400 µL of the C3Ga stock solution, 100 µL of the C3Gl stock solution, 400 µL of the C3Ar solution, 70 µL of the P3Ga solution, 30 µL of the P3Ar solution and 8100 µL of a 2% (v/v) HCl in methanol solution to a test tube. The tube is vortexed for 30 seconds to produce a mixed standard solution with the concentrations shown in Table 7 below.

Table 7 Anthocyanin concentrations in mixed standard solution

Anthocyanin	Theoretical concentration (µg/mL)	Purity (%)	Actual concentration (µg/mL)	Chemical formula
C3Ga	40	91.32	36.53	$C_{21}H_{21}ClO_{11}$
C3Gl	10	98.30	9.83	$C_{21}H_{21}ClO_{11}$
C3Ar	40	44.18	17.67	$C_{20}H_{19}ClO_{10}$
P3Ga	70	92.44	64.71	$C_{22}H_{23}ClO_{11}$
P3Ar	30	90.47	27.14	$C_{21}H_{21}ClO_{10}$

Preparation of Calibration Solutions

The mixed anthocyanin reference solution (as described above) is diluted with a solution of 2% (v/v) HCl in methanol, as per the dilution scheme presented below, mixed well, and stored at -20 °C when not in use.

Linearity 7—Pipette 500 µL of the mixed anthocyanin reference solution.

Linearity 6—Dilute 500 µL of linearity 7 solution with 500 µL of reference solution diluent.

Linearity 5—Dilute 500 µL of linearity 6 solution with 500 µL of reference solution diluent.

Linearity 4—Dilute 500 µL of linearity 5 solution with 500 µL of reference solution diluent.

Linearity 3—Dilute 500 µL of linearity 4 solution with 500 µL of reference solution diluent.

Linearity 2—Dilute 500 µL of linearity 3 solution with 500 µL of reference solution diluent.

Linearity 1—Dilute 500 µL of linearity 2 solution with 500 µL of reference solution diluent.

The final concentrations of the calibration standards produce standard curves that would capture the range of each of the primary anthocyanins typically found in cranberry fruit and their products. The approximate concentrations for each of the samples are presented in Table 8 below.

Table 8 Approximate concentrations (µg/mL) of individual anthocyanins at each linearity of the calibration curve

Linearity	[C3Ga]	[C3Gl]	[C3Ar]	[P3Ga]	[P3Ar]
7	36.53	9.83	17.67	64.71	27.14
6	18.27	4.91	8.84	32.35	13.57
5	9.13	2.46	4.42	16.18	6.78
4	4.57	1.23	2.21	8.09	3.39
3	2.28	0.61	1.10	4.04	1.70
2	1.14	0.31	0.55	2.02	0.85
1	0.57	0.15	0.28	1.01	0.42

Equipment and Instrumentation*

Analytical balance (range ± 0.1 mg).

Centrifuge: Eppendorf 5804 Table Top Centrifuge (VWR International, Edmonton, AB, Canada).

Wrist action shaker: Burrell Model BT Wrist Action Shaker (VWR International, Edmonton AB, CAN).

Syringes: 3 mL Luer-lok® fitted with PTFE filter, 0.45 µm and 0.2 µm pore size, 25 mm diameter (Fisher Scientific, Ottawa, ON, Canada) or equivalents.

Vortex mixer: Thermo Scientific Maxi Mix 1 (VWR International, Edmonton, AB, Canada).

Micropipettes: Eppendorf Reference Series, 100, 200, and 1000 µL (VWR International, Edmonton, AB, Canada).

HPLC system: Agilent 1100 Series liquid chromatograph equipped with quaternary pump and degasser (G1354A), temperature-controlled column compartment (G1316A), temperature controlled auto-sampler (G1327A), standard flow-cell 10 mm, 13 µl, 120 bar (G1315-60012), Diode-array detector (G1315B), HPLC 2D ChemStation Software (G2175AA), and online degasser (1322A) (Agilent

Technologies, Mississauga, ON, Canada).
Ultrasonic water bath: Bransonic 3510 (VWR International, Edmonton, AB, Canada).
Coffee grinder: Black and Decker smart grind.
* The specific equipment and instrumentation cited was used in the method validation. Equipment and instrumentation that provides the same performance can be used.

Reagents

HPLC grade methanol, acetonitrile, hydrochloric acid, phosphoric acid.
Ascorbic acid (purity ≥99.0%) (Sigma-Aldrich).
Phosphoric acid, 85% in H2O (purity ≥99%) (Sigma-Aldrich).
Reference standard diluent/Extraction solvent: 98:2 (v/v) methanol: concentrated HCl (HCl in H2O, 33 to 40%).
HPLC Mobile Phase A (MPA): 99.5:0.5 (v/v) water: concentrated phosphoric acid;
HPLC Mobile Phase B (MPB): 50.0:48.5:1.0:0.5 (v/v) water: acetonitrile: glacial acetic acid: concentrated phosphoric acid.
Extraction solvent: 2% (v/v) concentrated HCl in methanol solution.

Stability and Storage of Preparations

The anthocyanins are stable in solution when stored at 25 °C for at least 13 days.

Linearity and Analytical Range

The analytical range is approximately 0.57 to 36.53 µg/mL for C3Ga, 0.15 to 9.83 µg/mL for C3Gl, 0.28 to 17.67 µg/mL for C3Ar, 1.01 to 64.71 µg/mL for P3Ga, and 0.42 to 27.14 µg/mL for P3Ar. For solid materials, as prepared by the described method, this translates to 0.06 to 3.65 mg/g for C3Ga, 0.02 to 0.98 mg/g for C3Gl, 0.03 to 1.77 mg/g for C3Ar, 0.10 to 6.47 mg/g for P3Ga, and 0.04 to 2.71 mg/g for P3Ar.

Limits of Detection and Limits of Quantification

Variance checks showed that the method used was applicable for the analytes. The MDL and LOQ for each of the analytes are reported in Table 9 below.

Table 9 Method detection limit (MDL) and limit of quantification (LOQ) calculated for each of the analytes used in validation study

Analyte	MDL (µg/mL)	LOQ (µg/mL)
C3Ga	0.02	0.06
C3Gl	0.02	0.05
C3Ar	0.01	0.02
P3Ga	0.01	0.04
P3Ar	0.01	0.03

Chromatographic Conditions

Column:
Cosmosil 5C18-PAQ 4.6 mm x 150 mm, 5 µm (Nacalai USA Inc., San Diego, CA, US).

Column Temperature:
25 °C.

Mobile Phase:
Gradient:
HPLC Mobile Phase A (MPA): 99.5:0.5 (v/v) water: concentrated phosphoric acid;
HPLC Mobile Phase B (MPB): 50.0:48.5:1.0:0.5 (v/v) water: acetonitrile: glacial acetic acid: concentrated phosphoric acid.

Table 10 Mobile phase gradient

Time (min)	% Mobile phase A	% Mobile phase B
0	90	10
28	50	50
32	25	75
32.1	90	10
35	90	10

Flow Rate:
0.9 mL/min.

Injection Volume:
10 µL.

Detection:
520 nm (8 nm bandwidth), no reference.

Run Time:
35 minutes with 5 minutes-post time for column equilibration.

Table 11 Elution Order*

Compound	Time (min)
C3Ga	~15.8–15.9
C3Gl	~16.7–16.9
C3Ar	~17.7–17.9
P3Ga	~18.3–18.5
P3Ar	~20.2–20.4

* As determined in single lab validation (SLV). Elution values should be taken as relative as times will change with different columns and different plant and preparation matrices. Note shifting elution times between preparations (Figures 10a–c).

Calculations

Individual anthocyanins from solid samples are quantified in % w/w using the following equation:

$$\frac{P_0 - b_0}{m_0} \times \frac{V}{W} \times \frac{D}{10^4}$$

P0 = peak area of target analyte in sample chromatogram
b0 = y-intercept of calibration curve for the target analyte

m0 = slope of calibration curve for the target analyte
V = volume of test solution, in mL
W = dry weight of sample, in g
D = dilution factor

Individual anthocyanins from liquid samples are quantified in µg/mL using the following equation:

$$\frac{P_0 - b_0}{m_0} \text{ x}D$$

The calculations used to determine the Horwitz Ratio (HorRat), a normalized performance parameter used to evaluate overall method precision, are provided below.
RSDr (found, %):

$$RSDr = \frac{SD(r)}{mean} \text{ x}100$$

Where SD(r) = the population standard deviation.

PRSDr (RSDr calc, %):

$$PRSDr = 2C^{-0.5}$$

Where C = the concentration of the analyte expressed as a mass fraction.

4-(dimethylamino)cinnamaldehyde (DMAC) for Quantification of Soluble Proanthocyanidins (PACs) in Cranberry Juice, Concentrated Juice, and Juice Extract Powders

DMAC is one of a few methods used for the quantification of PACs and is only applicable when extracted material has been positively identified as being pure cranberry, because it gives one measure of PAC content (soluble PACs) and cannot differentiate between A and B-type PACs. DMAC is an aromatic aldehyde that reacts with flavan-3-ols and PACs to form a green chromophore with maximum absorbance at approximately 640 nm (Treutter 1989). This wavelength effectively excludes the spectra of anthocyanins, which are a source of interference in other quantifications for PACs. DMAC does not react with hydroxycinnamic acids, hydroxybenzoic acids, flavonones, and flavonols (McMurrough and McDowell 1978; Treutter 1989). DMAC is not an appropriate method for authentication of cranberry or cranberry extract as flavan-3-ols and PACs from any source (cranberry, grape, pine bark, apple, chocolate, peanut skins, etc.) will react with the DMAC reagent.

Some within the cranberry industry use DMAC with a procyanidin A2 dimer reference standard, to standardize the PAC content of extracts and finished products. While DMAC is useful for the quantification of cranberry PACs, there are several limitations to this methodology. DMAC is only capable of quantifying soluble PACs, or PACs that can be readily extracted from cranberry products. Insoluble PACs that remain bound to fruit cell wall constituents such as fiber, pomace, and protein are not quantified by DMAC (Roopchand et al. 2013). Therefore, DMAC quantitation of PACs is most appropriately applied to cranberry juice and cranberry juice powder extracts that contain water-soluble PACs and is not applicable for quantitation of PACs in products such as sweetened-dried cranberries, dried whole cranberry powder, and cranberry pomace (press cake). Because of this, DMAC quantitation results in an underestimation of total PACs (soluble plus insoluble) by approximately half. Additionally, the use of the procyanidin A2 dimer standard is biased toward quantification of PAC oligomers, because these products more closely reflect the structure and reaction kinetics of the A2 dimer (Krueger et al. 2013b). Such methods are designed primarily to ensure consistency of an extract and delivery of a consistent, though not absolute, dose of PACs. For accuracy, it is important to include the A2 reference standard when reporting DMAC results for quantification of PACs in cranberry juice products, as use of different standards will give different PAC levels on the same sample.

The original DMAC method used for quantification of cranberry PACs was published by Prior et al. (2010b) as part of a multi-laboratory validation that included 5 laboratories. The SOPs of the Prior publication are available on the DMAC website www.dmac-asso.org. With the original method, intra-laboratory variation was a mean of 4.1 ± 1.7% RSD (range 2.3–6.1%) and inter-laboratory variability was 16.9 ± 8.5% RSD (range 8–32%). The inter-laboratory variation of almost 17% limited the viability of the original method. For purposes of this monograph, the method of Prior et al. (2010b) was modified by ICT Laboratories (Milford, MA; ICT study number ICT10002; Neotron SpA, Modena, Italy; report 14/10/LRA) for better performance in terms of linearity (R2 ≥ 0.995), repeatability (relative standard deviation [RSD] ≤ 3%), intermediate precision (RSD ≤ 5%), recovery within 90 to 100%, and robustness (≤3%) for dry cranberry extract. This modified method was validated according to International Conference on Harmonisation (ICH) Guideline Validation of Analytical Procedures: Text and Methodology Q2(R1). Furthermore, a multi-lab validation of this modified method showed an overall RSD of 2.03–3.37 %. Use of this validated method is recommended when DMAC results are desired. In addition to the limitations mentioned, this method requires specialized equipment that can take multiple readings rapidly. Accuracy of DMAC analysis requires strict controls of numerous parameters including development of color reaction.

Experimental Conditions for the Modified DMAC/A2 Method Apparatus: Perkin Elmer Lambda 40 double-beam UV-Visible spectrophotometer, or equivalent.

Reagents

4-dimethylaminocinnamaldehyde-DMAC (reagent grade; Sigma p/n 39421, or equivalent)

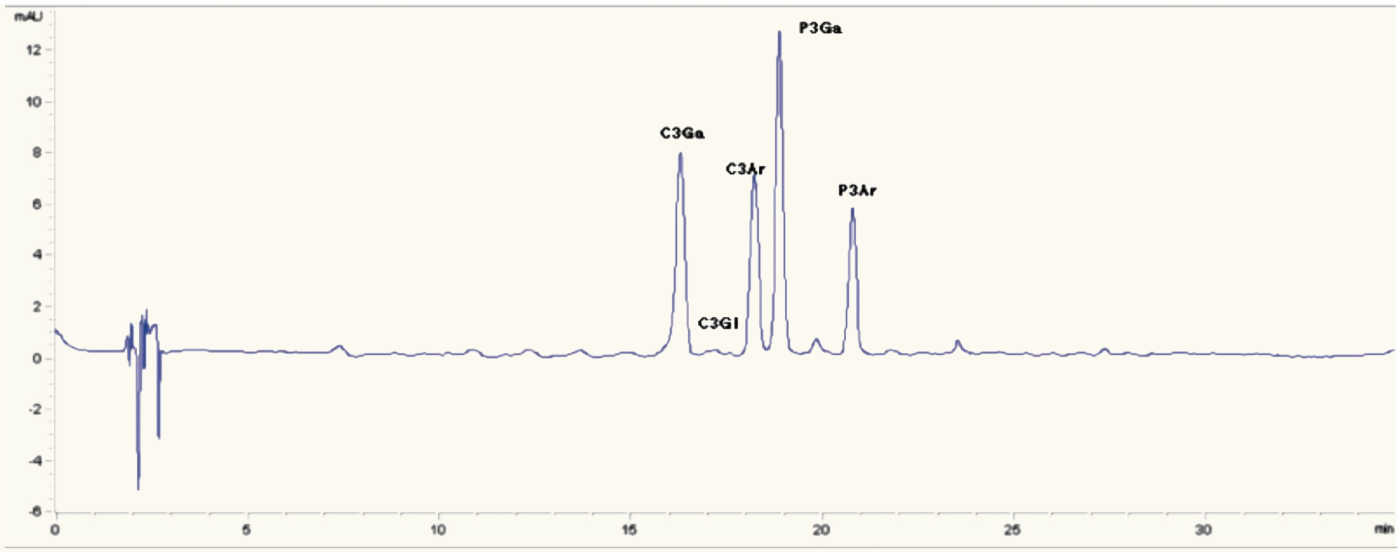

Figure 10a HPLC chromatogram of cranberry freeze-dried powder.

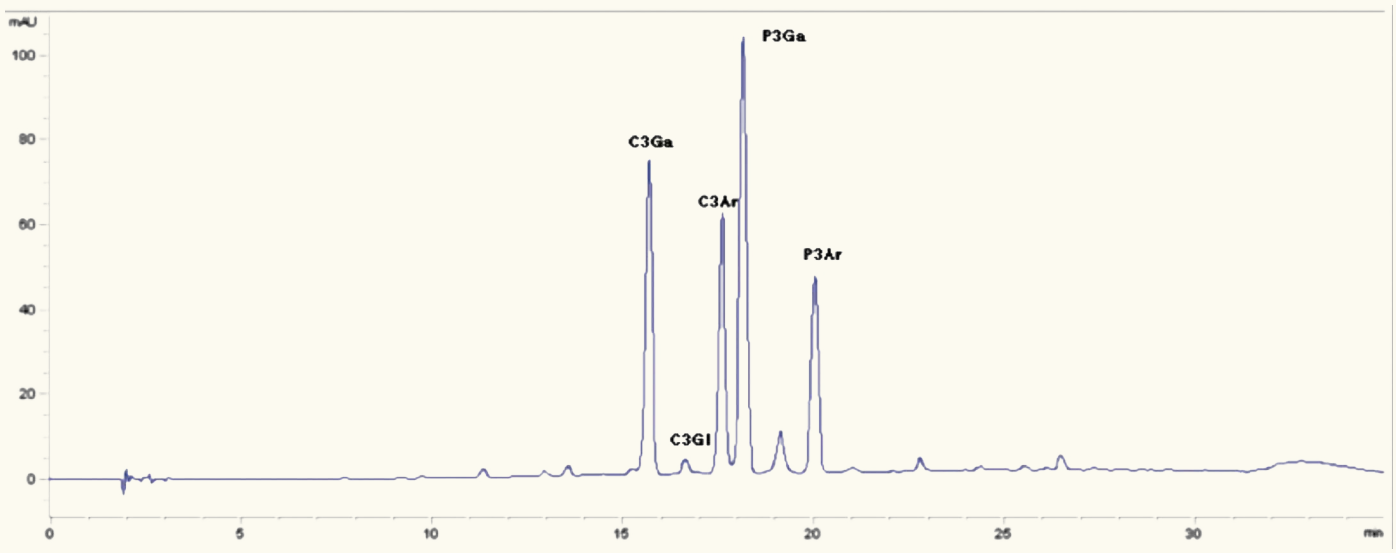

Figure 10b HPLC chromatogram of cranberry juice cocktail (27% cranberry juice; OceanSpray)

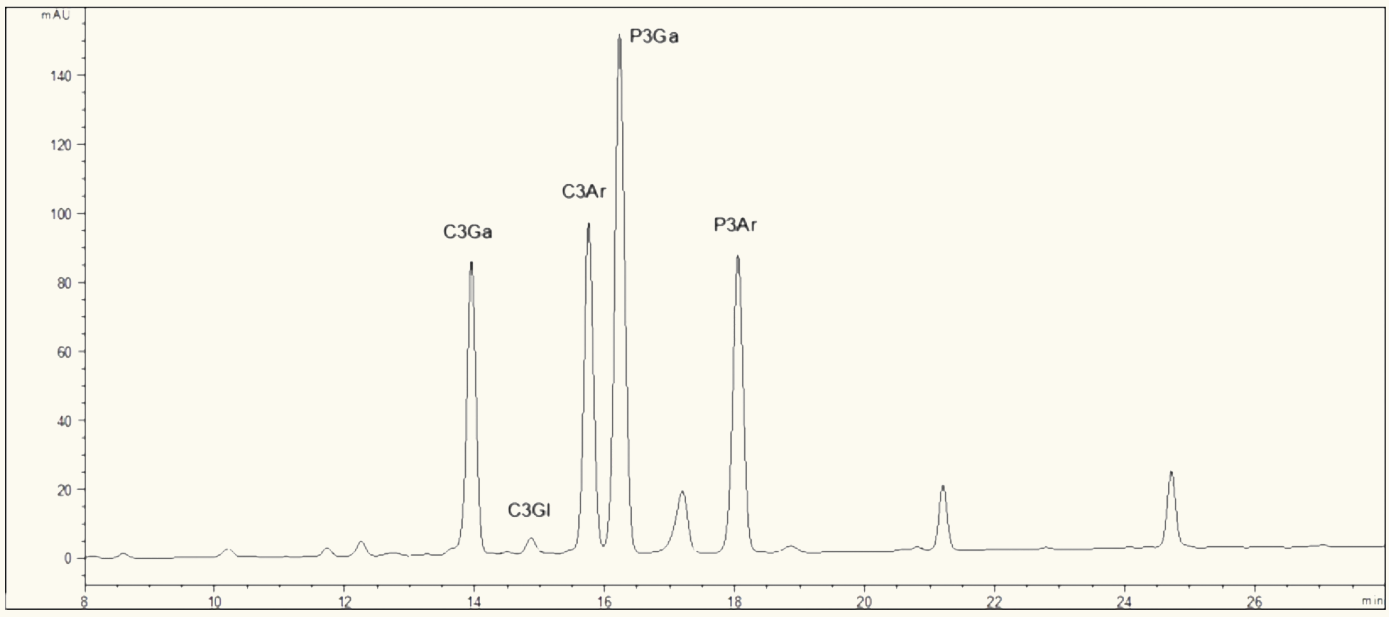

Figure 10c HPLC chromatogram of cranberry dry extract (70% ethanol; native extract 20–35:1 herb to extract ratio; Pharmatoka Labs, Rueil-Malmaison, France).

Methanol (HPLC grade).

Sulfuric acid (H2S04): reagent grade).

PACs extraction solvent: Methanol.
Reaction Solvent: Carefully measure 12.0 mL of H2S04 into a 50 mL flask. Slowly transfer H_2S0_4 by using a glass Pasteur pipette in a 1 L volumetric flask containing 500 mL of methanol. Add a stir bar and allow to stir at least 30 minutes until the heat generated by addition of H_2S0_4 is completely released. When the temperature of solution reaches room temperature, fill to the volume with methanol and allow stirring for a minimum 10 minutes. Transfer to a glass bottle labeled as 0.4N H_2S0_4 in methanol.

DMAC Solution: Accurately weigh 50 mg of 4-dimethylaminocinnamaldehyde (DMAC) into a 50 mL volumetric flask. Dissolve and dilute to volume with reaction solvent. Prepare fresh and use within 2 hours.

Reference Solutions
Standard stock solution: Prepare a Standard stock solution containing approximately 90 µg/mL of proanthocyanidin A2 (ChromaDex, Boulder, CO) in methanol (for example by weighing approximately 9 mg of proanthocyanidin A2 in 100 mL of methanol).

Prepare 5 reference solutions at different proanthocyanidin A2 concentrations by diluting Standard stock solution with methanol:
Standard 30 µg/mL: pipette 1.0 mL of Standard stock solution into a 15 mL tube and add 2.0 mL of methanol.
Standard 25 µg/mL: pipette 0.75 mL of Standard stock solution into a 15 mL tube and add 1.95 mL of methanol.
Standard 20 µg/mL: pipette 0.5 mL of Standard stock solution into a 15 mL tube and add 1.75 mL of methanol.
Standard 15 µg/mL: pipette 0.5 mL of Standard stock solution into a 15 mL tube and add 2.5 mL of methanol.
Standard 10 µg/mL: pipette 0.25 mL of Standard stock solution into a 15 mL tube and add 2.0 mL of methanol.

Test Solution
In duplicate, accurately weigh about 10 mg of cranberry extract into a 100 mL volumetric flask. Dissolve by sonication and dilute to volume with methanol. If necessary, place on a shaker for 30 minutes at 300 rpm to solubilize and/or extract and centrifuge to clarify the sample.

Procedures and Calculations
Turn on the spectrophotometer and select the reading absorbance at 640 nm.

Pipette 1.0 mL of DMAC solution in a cuvette and place it into the spectrophotometer (cover the top with parafilm). Use this solution as the compensation liquid (reference cuvette in double beam spectrophotometer);

Pipette 1.0 mL of DMAC solution into respective Eppendorf test tubes;

Pipette 0.2 mL of blank (Reaction Solvent), Reference solutions or Test solution(s) into respective Eppendorf test tubes, mix well by vortexing, transfer the solution into the sample cuvette.

Place the cuvette in the spectrophotometer and read the absorbance at 640 nm every 5 seconds for at least 300 seconds.

Record the highest absorbance value of each 300 seconds reading. Subtract the reference reading from the reference cuvette (double beam spectrophotometer should do it automatically). Take the readings within 5 minutes of the addition of the DMAC solution.

Determine regression line in the format y = bx between proanthocyanidin A2 concentration (y) and maximal absorbance at 640 run (x). The correlation factor r2 of the regression curve should be 0.99 (see 11).

From the regression line, calculate the proanthocyanidins % content (PAC%) expressed as proanthocyanidin A2 as follows:

$$PAC\% = \frac{C\ (\mu g/mL) \times V}{P\ (\mu g)} \times 100$$

where:
C (µg/mL) = Proanthocyanidins concentration in µg/mL obtained from the regression line;
V = dilution volume (mL) per l 00 mL.
P (µg) = Sample weight (in micrograms) of the test product.
Express the result as the average of the two determinations.

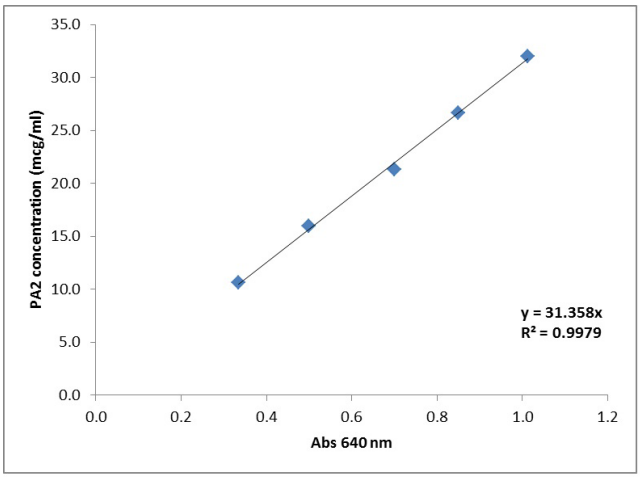

Figure 11 Typical proanthocyanidin A2 regression line for DMAC analysis

Limit Tests*

Foreign Organic Matter (fresh):	Free from insects and insect larvae (CFIA 2000). Not to exceed 0.1% infested with worms (USDA 1997).
Foreign Organic Matter (dry):	Not to exceed 3%.†

Fruit Deterioration (fresh at point of shipping):	Not to exceed 3% (USDA 1997).
Fruit Deterioration (fresh at destination):	Not to exceed 5% (USDA 1997).
Total Ash (dry):	8% (Khanega et al. 2015).
Acid-insoluble Ash (dry):	10% (Khanega et al. 2015).
Loss on Drying *(dry):	9% (Khanega et al. 2015).
Extractives (water; dry):	25% (Khanega et al. 2015).
Extractives (alcohol; dry):	77% (Khanega et al. 2015).

* Values given should be considered as approximate values that will change with harvest stage and different varieties.
† Estimate based on typical values of other fruits.

THERAPEUTICS

The primary health-promoting benefit for which cranberry consumption has been used is to maintain urinary tract health. Several clinical trials, including meta-analyses, support its use to prevent urinary tract infections (UTIs). Modern herbal practitioners and consumers similarly use cranberry, predominantly as juice products or dietary supplements, for UTI prevention and treatment, although data are lacking on its effectiveness for treatment. Additional work has investigated the use of cranberry as an antioxidant, antiviral, anticancer, anticariogenic, anti-ulcerogenic, cholesterol lowering, and vasorelaxant agent. To date, the majority of medical research on cranberry consists of observational clinical trials yielding mixed results or preclinical studies, the latter focusing on mechanisms of action, many of which are relevant to the putative benefits attributed to cranberry.

Pharmacokinetics

Cranberry fruit contains a wide array of compounds known for their potential therapeutic benefits (Iswaldi et al. 2012) (see Constituents) and includes flavonoids, phenolic compounds, anthocyanins, and PACs. Most notably, the A-type PACs (condensed tannins) are known for their antibacterial antiadhesion activities, anthocyanins and seed oils for their antioxidant activity, and organic acids for their antimicrobial activity. Large molecular weight polyphenols such as PACs are minimally absorbed due to nonhydrolyzable bonds between monomeric subunits and a propensity to bind proteins through hydrogen bonding (Hagerman and Butler 1981). Because of this poor absorption, more than 95% of PACs remain in the intestinal lumen during transit (Gonthier et al. 2003; Reed 1995; Scalbert et al. 2002). Research has shown that large molecular weight oligomers (trimer to hexamer) are hydrolyzed in gastric acid to mixtures of epicatechin, enhancing the potential for absorption (Baba et al. 2002; Spencer et al. 2000). More recently it was found that certain polyphenolic compounds in cranberry can be metabolized into simple phenolic acids by gut bacteria and that metabolization takes place in different parts of the gut (McKay et al. 2015). In the gut epithelium, liver, and other tissues, there are three types of polyphenolic/phenolic-derived metabolites which have been observed: (1) compounds found in their native form; (2) phase-1 metabolites formed by chemical modification, such as hydrogenation ($M+H_2$), dehydrogenation ($M-H_2$), hydroxylation (M+OH) and hydration ($M+H_2O$); and (3) phase-II metabolites formed by conjugation, such as methylation ($M+CH_3$), glucuronidation ($M+C_6H_8O_6$, and other conjugation reactions (Iswaldi et al. 2013).

Studies investigating the potential for interactions with conventional medications provide additional information regarding the pharmacokinetics of cranberry compounds. For example, in a study of Lilja et al. (2007) daily ingestion of cranberry juice did not inhibit the activities of CYP2C9, CYP1A2, or CYP3A4. Uesawa and Mohri (2006) reported that cranberry juice did inhibit the CYP3A-mediated metabolism of nifedipine in both rats and humans suggesting cranberry components are heavily metabolized in the liver and possibly in a dose-dependent fashion.

Proanthocyanidins

In one in vivo study cranberry PAC ingestion resulted in urine with bacterial antiadhesion activity (Howell et al. 2001). These researchers found that urine collected from mice that were fed purified cranberry PACs had bacterial antiadhesion activity against P-fimbriated *E. coli* (see Bacterial Antiadhesion Effects). In another study, rats fed 108 mg PACs/animal/day produced urine that prevented adhesion of *E. coli* by 83 and 52%, respectively (Risco et al. 2010). Very low levels of PAC A2 dimer (0.541 ± 0.10 ng/mL) have been found in rat plasma samples 1 h after cranberry administration Rajbhandari et al. (2011) and in low levels in human urine (McKay et al. 2015).

Other information on the pharmacokinetics of PACs can be gleaned from animal studies utilizing grape (*Vitis vinifera*) and other foods high in PACs. However, the applicability of data from grapes and other foods to cranberry pharmacokinetics is unclear due to structural differences between the PACs in different foods. PACs in cranberries have both A-type interflavan bonds with double linkages and B-type single linkages (Foo et al. 2000a; 2000b), whereas those in grapes have only the more common B-type single linkages. Though additional studies are needed, the A-type linkage may influence bioavailability, distribution, metabolism, and elimination of cranberry PACs. When 50 mg/kg of ^{14}C-labelled PACs from grapes were administered orally (po) to rats, 6% were excreted in expired air as $^{14}CO2$, 19% were eliminated in the urine, and 45% in the feces, suggesting that PACs or their metabolites may reach the human bladder and intestines (Harmand and Blanquet 1978). When

rats were administered intragastrically (ig) 250 mg/kg of a 25 mg/mL solution of grape PACs in drinking water by direct stomach intubation, PAC metabolites were detected in the plasma 15 minutes after administration (Koga et al. 1999). Laparra et al. (1977) analyzed mouse blood levels of ^{14}C-labelled grape PACs after a single oral dose and found that gastrointestinal absorption was rapid and peaked at 45 minutes. Evidence is emerging that certain PACs are broken down to smaller units that can be absorbed, but more research is needed to determine to what extent the complex A-type PACs from cranberry are metabolized. ^{14}C-labelled PAC polymers from goat willow leaf (*Salix caprea*) were almost totally metabolized after 48 hours of in vitro incubation in human fecal suspensions (Deprez 2000).

While it has generally been assumed that cranberry exerts its effect on UTIs directly through the urine, an alternative and untested hypothesis is that it also works preventatively through affecting adhesive properties of bacteria in the large intestine and colon (Kontiokari et al. 2001; Ofek et al. 1996; Sobota 1984; Zafriri et al. 1989). Very recent studies have suggested other possible mechanisms of action of cranberry components in the prevention of UTI (Krueger et al. 2013b; Shanmuganayugari et al. 2013) involving decreases of the relative levels of 8 proteins/peptides in the urine of human subjects post-supplementation with cranberry (Krueger et al. 2003). The functions of these proteins are not fully understood and the implications of these shifts in UTI are unclear. Recently, it has been shown that exposure of extraintestinal pathogenic *E. coli* to cranberry PACs inhibits their invasiveness into enterocytes, disrupts surface structures of the E. coli, and increases killing of *E. coli* by macrophages (Shanmuganayugari et al. 2013). The action of PACs (and their metabolites) on prevention of adhesion, invasion and immune function are pharmacologically more complex than previously thought, and require further study to determine more about the metabolism and precisely how these various biological activities exert effects in the urinary tract and gut to maintain urinary tract health.

Anthocyanins

Human Clinical Studies

In addition to PACs, cranberry fruit contains six known anthocyanin pigments (see Constituents). These compounds exhibit antioxidant activity (Wang et al. 1997). Limited data are available regarding the pharmacokinetics of cranberry anthocyanins. Milbury et al. (2010) studied the absorption and metabolism of anthocyanins from a cranberry juice drink (54% juice; 835 mg total polyphenols; 94.47 mg anthocyanins) in human subjects (n = 15) with coronary heart disease. All anthocyanins measured reached their highest concentration (0.56–4.64 nmol/L) in plasma within 1.5 hours after juice consumption. All individuals had increased concentrations of each anthocyanin in their 4-hour urine samples with the exception of cyanidin-3-glucoside. Total plasma concentrations and urinary anthocyanin recovery from cranberry juice was highly variable between individuals, ranging between 0.078 and 3.2% of the administered dose. The profile of anthocyanins detected in the plasma reflected the same relative concentrations present in the juice (cyanidin-3-galactoside, 18.7 mg; cyanidin-3-glucoside, 1.58 mg; cyanidin-3-arabinoside, 16.47 mg; peonidin-3-galactoside, 30.83 mg; peonidin-3-glucoside, 5.85 mg; and peonidin-3-arabinoside, 21.03 mg) and peonidin-3-galactoside predominated in urine.

In another human study (Ohnishi et al. 2006), 11 healthy volunteers consumed 200 mL of cranberry juice containing 650.8 µg total anthocyanins (Cranberry UR-100, Kikkoman Corporation, Chiba, Japan). Urine samples were collected within 24 h before and after consumption. Six of the 12 anthocyanins identified in the juice were quantified in urine. Peonidin 3-O-galactoside, the second most plentiful anthocyanin in the juice, was found at the greatest concentration at 41.5 ± 6.2 nmol/ 24 h (56.1% of total anthocyanins) and total urinary anthocyanin levels reached a maximum between 3 and 6 h after ingestion and were almost completely exhausted within 12 h. Recovery of total anthocyanins in the urine over 24 h was approximately 5.0% of the amount consumed. In contrast to the aforementioned findings, Duthie et al. (2006) did not observe any change in plasma phenols, anthocyanins, or catechin levels of healthy individuals who consumed 750 mL/day of cranberry juice for 2 weeks. Bioavailability of anthocyanins may be inferred from clinical feeding studies conducted on other anthocyanin-rich fruits such as elderberry (*Sambucus spp.*) (mainly cyanidin 3-glucoside and cyanidin 3-sambubioside), grape, and bilberry (*Vaccinium myrtillus*). It has been reported that elderberry anthocyanins can be absorbed in their unchanged glycosylated form. Intact anthocyanins were detected in the plasma and urine of an elderly man who consumed 25 g of elderberry extract containing 1.5 g total anthocyanins after fasting overnight (Cao and Prior 1999). While anthocyanins were not found in samples taken prior to consumption, detection levels of at least 100 µg/L were reported in plasma samples taken 30 minutes following consumption. In a follow-up investigation, these same researchers studied 4 elderly females who consumed 12 grams of elderberry extract containing 720 mg of anthocyanins (Cao et al. 2001). Ten blood samples and 6 urine samples were obtained over 24 hours following consumption. Diet was controlled to provide no additional anthocyanins and to be low in other flavonoids throughout the study period. Using HPLC, 5 compounds were detected in the plasma samples and 6 in the urine. These included cyanidin 3-sambubioside and cyanidin 3-glucoside, which accounted for 92.5% of the total anthocyanins. Others included cyanidin aglycone and malvidin hexoside. Maximum plasma anthocyanin concentration varied from 55.3 to 168.3 nmol/L. The mean maximum plasma concentration (C_{max}) of total anthocyanins was 97.4 nmol/L and was reached within 71.3 minutes (T_{max}), which is similar to that observed in subjects consuming cranberry juice (Milbury et al. 2010). The elimination of plasma anthocyanins appeared to follow first-order kinetics. The elimination half-life ($t_{1/2}$) of plasma total anthocyanins was 133 minutes. The anthocyanins were excreted into the urine at a rate of 77 µg/hour during the first 4 hours and 13 µg/hour during the second 4 hours. The total amount of

anthocyanins excreted in the urine over a 24-hour period was 397.0 ± 45.1 µg. Peonidin and cyanidin galactosides and arabinosides were the most abundant observed (McKay et al. 2015; Milbury et al. 2010; Ohnishi et al. 2006).

Anthocyanins seem to be unique compared to other flavonoids, in that they are absorbed intact, but they can be methylated and conjugated as seen with other flavonoids (Wu et al. 2005; 2006). Anthocyanins from black raspberry were excreted as intact and methylated derivatives in human urine and reached a maximum concentration during the 4 to 8 hour period after black raspberry ingestion (Tian et al. 2006). Sulfate conjugates, another common form of metabolites found with other flavonoids, have been reported as metabolites of anthocyanins in 2 human studies following either strawberry or blackberry consumption, but the concentrations of the sulfated forms were present at extremely low concentrations (Felgines et al. 2003; 2005).

Animal Study

Intact peonidin 3-*O*-galactoside and cyanidin 3-*O*-galactoside were identified in rat urine within 1 hour after oral gavage of a cranberry concentrate (1 g/bw). This demonstrated rapid metabolism and elimination into the urine. Because of the low plasma concentrations of intact anthocyanins, they may not be acting directly through an antioxidant mechanism in blood but rather through local action on bladder tissue (Rajbhandari et al. 2011).

Flavonols

Human Clinical Studies

In addition to anthocyanins and PACs, cranberry fruit has a diverse phytochemical profile of phenolic acids and flavonols. Cranberries are one of the leading fruit sources of quercetin on a weight basis. In human subjects (n = 4), a total of 32 metabolites of polyphenols from cranberry were tentatively identified in human urine following consumption of a cranberry syrup (0.6 mL/kg) (Iswaldi et al. 2013), including phase I and phase II metabolites, such as methylated and glucuronide forms. Of the flavonols, methoxyquercetin 3-*O*-galactoside, myricetin, and quercetin were identified in human urine. The compounds reached a peak in the urine by 4 hours and then began declining by 6 hours following the consumption of cranberry syrup (Iswaldi et al. 2013).

Animal Studies

Quercetin, 3'-O-methylquercetin (isorhamnetin), myricetin, kaempferol, together with 13 conjugated metabolites of quercetin and methylquercetin were identified in rat urine after cranberry treatment (Rajbhandari et al. 2011). Very low levels of isorhamnetin (0.48 ± 0.09 ng/mL) and no quercetin were found in plasma samples after 1 hour of cranberry administration. However, using liquid chromatography-tandem mass spectrometry (LC-MS/MS) and MRM analysis of the methanolic extract of urinary bladder, it was shown that chronic administration of cranberry concentrate to rats resulted in accumulation of quercetin and isorhamnetin in cells of the bladder (Rajbhandari et al. 2011).

Phenolic Acids

Many dietary flavonoids are poorly absorbed from the gastrointestinal tract. However, colonic bacteria can convert flavonoids into simple phenolic acids, which can be absorbed into the circulation and may contribute to health-promoting effects (Gao et al. 2006). However, the extent and importance of absorption of many of these phenolic acids is not known, not only because the colon lies at the distal end of the gastrointestinal tract, but also because of the difficulty in assessing all the breakdown products of the parent polyphenols. Phenolic acids, which are much smaller and simpler in structure than flavonoids, are probably among the major end products of the metabolism of flavonoids or other polyphenol metabolism by the intestinal microbes. Presence of large amounts of monophenolic acids have been demonstrated previously in the colon of healthy humans (Jenner et al. 2005).

Various phenolic acids have been shown to have positive health effects. For instance, ferulic acid (4-hydroxy-3-methoxycinnamic acid) has been shown to reduce hypertension (Suzuki et al. 2002), lipid peroxidation (Balasubashini et al. 2004), oxidative impairments (Thyagaraju and Muralidhara 2008), and enhance insulin secretion (Adisakwattana et al. 2008) in rats, while *p*-methoxycinnamic acid has been found to stimulate insulin secretion from the pancreatic β-cells in rats (Adisakwattana et al. 2008). Caffeic acid has been shown to improve glucose utilization and reduce plasma glucose in diabetic rats (Hsu et al. 2000), while chlorogenic acid attenuates hypertension and endothelial cell function in spontaneously hypertensive rats (Suzuki et al. 2006). O-Coumaric acid was found to be effective in improving the symptoms of metabolic syndrome and obesity (Hsu et al. 2009; Hsu and Yen 2007). 3,4-Dihydroxybenzoic acid (protocatechuic acid; 3,4-DHBA) is another phenolic acid found in many edible and medicinal plants. It is a major metabolite of cyanidin-3-glucoside metabolism and has been shown to have many health effects, including chemoprevention (Krajka-Kuźniak et al. 2008; Lin et al. 2007; Liu et al. 2009) and improvement of antioxidant status (Vitaglione et al. 2007), a major factor involved in many chronic diseases.

Parent flavonoids in the diet are often deglycosylated before absorption and are often conjugated by methylation, glucuronidation, sulfation, etc. during the absorption process (Fardet et al. 2008; Fleschhut et al. 2006; Gu et al. 2007; Jaganath et al. 2006; Mullen et al. 2008; Ward et al. 2004). Phenolic acids can also be conjugated in a similar manner during the absorption process. While several studies have reported free (Jaganath et al. 2006) or total phenolic acids (Gu et al. 2007; Ward et al. 2004; Wu et al. 2009), little is known about their conjugated counterparts. Since phenolic acids and other metabolites formed by the intestinal microflora and/or those produced in host tissues are excreted in the urine (Gonthier et al. 2003; Scalbert et al. 2002), the identification and quantification of the amount and form of phenolic acids excreted in urine after ingestion of plant polyphenols is important.

Human Clinical Studies

There is relatively little information available from cranberries or other berries as to whether specific phenolic acids are formed in the metabolic process. A recent study investigated the pharmacokinetics of phenolic compounds in humans (n = 11) given cranberry juice (240 mL of 100% juice; Knudsen. Oroville, CA), sauce (55 g; Wegman's, Rochester, NY), and fruits (dried Cranberry Crasins, Ocean Spray, Middleboro, MA) (Wang et al. 2012a). Total phenolic consumption was 2.184, 0.496, and 0.611 g for the juice, sauce, and fruits, respectively. Only 4 phenolic acids including benzoic, 4-hydroxybenzoic, 3-methoxy-4-hydroxybenzoic, and 4-hydroxycinamic acids were identified in plasma samples without hydrolysis. Six other compounds including 2-hydroxybenzoic, 3-hydroxybenzoic, and 4-hydroxyphenylacetic acids and catechin were identified in the same plasma samples after hydrolysis. Significant increases in the sum of plasma phenolics were observed with different concentration peaks (between 0.5 and 2 hours) for individual subjects. Some of the phenolics, such as cinnamic, 3-methoxy-4-hydroxybenzoic, 4-hydroxycinamic acids, and catechin, showed second plasma concentration peaks. All cranberry-derived phenolics increased significantly in urine samples after the intake of each cranberry product (juice, sauce, or fruit). Quercetin and myricetin, which were abundant in cranberry foodstuffs, were not found in either plasma or urine samples (Wang et al. 2012a).

McKay et al. (2010) conducted a single-dose, pharmacokinetic study to characterize the bioavailability of cranberry flavonoids and phenolics acids from cranberry juice cocktail (CJC) (Ocean Spray, Inc) in 10 healthy adults. The subjects had a body mass index (BMI) of 18.5 to 29.9, and were 50 to 70 years of age. Subjects were put on a low polyphenol diet and after a 2-day run-in period consumed 237 mL of low-calorie, sugar-free cranberry juice cocktail (54% juice). Blood samples were collected at specified time points before and up to 24 h after juice consumption. Marked variation maximal plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) of cranberry bioactives was reported as follows: sinapic acid at 18.6 ng/mL at 30 min; homovanillic acid at 54.1 ng/mL at 6 h; protocatechuic acid at 1.3 µg/mL at 10 h; myricetin at 18.3 ng/mL at 2 h; quercetin at 0.4 µg/mL at 8 h; and kaempferol at 18.4 ng/mL at 2 h. These data suggest that different phenolic constituents in CJC are absorbed and metabolized at different locations in the gastrointestinal tract. Further analyses of the same data (McKay et al. 2015), reported peak plasma concentrations of phenolics of 34.2 µg/mL between 8 and 10 h; peak concentration in urine was 269.8 µg/mg creatinine, and appeared 2 to 4 h earlier. These metabolites were correlated with plasma antioxidant activity (assessed with ORAC and TAP assays) showing cranberry phenolic compounds to be bioavailable and active as antioxidants in healthy adults. Additionally, the presence of PAC A2 dimers was observed for the first time and occurred after the flavonoids and phenolics to similarly varied degrees (T_{max} in four subjects at 10 h; 2 subjects between 10–24 hours; and one subject at 2 h).

In a study of Valentova et al. (2007), dried cranberry juice (1200 mg/d) was given in capsules (200 mg/per capsule) to volunteers for 8 weeks. An increase in urine levels of total phenols, hippuric, salicyluric, and dihydroxybenzoic acids and quercetin glucuronide was observed. Liu et al. (2015) reported an increased excretion of hippuric acid and plasma citric acid levels after consumption of a cranberry juice concentrate (57% juice) by 18 healthy female subjects. The authors suggest these metabolomic changes may contribute to the putative health benefits attributed to cranberry.

Pedersen et al. (2000) reported a small but significant ($P < 0.05$) increase in total phenols in plasma within 1 hour of consumption of 500 mL of cranberry juice cocktail (Ocean Spray®) compared to either blueberry juice or a control (sugar water) in human subjects (n = 9). Interestingly, even though blueberry juice had a higher amount of total phenols (2589 µg gallic acid equivalent [GAE]/mL) compared to those in cranberry juice (893 µg GAE/mL), only the cranberry juice showed a significant increase in plasma phenol levels and a significant increase ($P < 0.001$) in antioxidant capacity of plasma as determined by both ESR spectroscopy and change in FRAP value. No change in urine levels of total phenols up to 4 hours after drinking was observed.

Other human investigations with single subjects offer additional pharmacokinetic information. In an assessment by Zhang and Zuo (2004), a single subject consumed 1.8 L of cranberry juice cocktail (Ocean Spray; 27% juice). Benzoic acid, *o*-hydroxybenzoic acid, 2,3-dihydroxybenzoic acid, ferulic acid, and sinapic acid were detected in plasma 45 minutes after drinking, with benzoic acid predominating at 4.40 and 3.11 µg/mL at 45 and 270 min, respectively. Interestingly, two phenolic acids, *p*-hydroxyphenylacetic and 2,4-dihydroxybenzoic acid, have been identified in plasma after cranberry juice consumption, but not in the juice itself. These researchers did not analyze metabolites in urine.

Animal Studies

In rats fed 3 different levels of a cranberry concentrate powder (Prior et al. 2010a), urinary excretion of 3-hydroxycinnamic, 4-hydroxycinnamic, 3,4-dihydroxybenzoic, and 3-hydroxybenzoic acids increased in a linear manner with increased dietary intake of the cranberry powder. For most phenolic acids, the percentage of phenolic acids excreted in the conjugated form was approximately constant across levels of cranberry in the diet and ranged from 65 to 100% for the individual phenolic acids. However, a few phenolic acids were excreted only in the free form while others were nearly completely conjugated. Thus, measurement of just the free form may not accurately reflect the amount excreted. Future studies investigating the health effects, bioactivity, or bioavailability of parent polyphenols should also consider the contribution of their metabolites, not just the parent compound(s). Relative to feeding blueberry, black raspberry, or cranberry, the greatest increase in the excretion of phenolic acids with cranberry feeding was observed in hippuric acid (HA), 4-hydroxycinnamic acid (4HCA), and 3-methoxy, 4-hydroxybenzoic acid (VA) (Khanal et al. 2013).

Older literature indicates that cranberry consumption resulted in the formation and excretion of hippuric acid (Bodel et al. 1959). The authors suggested that hippuric acid is formed by the transformation of quinic acid, possibly carried out by intestinal bacteria. In one of the early cranberry pharmacokinetic studies, Blatherwick and Long (1923) found that the consumption of 305 g of cranberry sauce by a single subject increased hippuric acid in the urine from a basal value of 0.78 to 4.74 g. Later, however, Kubota and Ishizaki (1991) demonstrated that benzoic acid is excreted in the urine as hippuric acid. Benzoic acid is present in whole cranberry juice products but may not be present in other preparations. Benzoic acid has strong antibacterial activity. Hippuric acid has been shown to reduce the saturation of urinary calcium oxalate with a potential beneficial effect on reducing stone formation (Atanassova and Gutzow 2013).

Seed Oils

Cranberry seeds contain a number of oils with potential health benefits (e.g., antioxidant effects), including high levels of (-)-linolenic acid (30.9 g/100 g fat), tocopherols, and tocotrienols (Parry et al. 2006; Yu et al. 2005). No data exist on the pharmacokinetics of cranberry seed oils. However, Burton et al. (1988) reported that the mid-gut is the site of greatest tocopherol absorption in rats. Hayes et al. (1993) found that tocotrienols were deposited along with triglycerides in the adipose tissues of hamsters. Tocopherols were the only tocol readily detected in all tissues except adipose during tocotrienol supplementation in hamsters. Thus, it is possible that the oils found in cranberry seeds are absorbed and could deliver medicinal benefits. However, in this regard, more work specifically on cranberry is needed.

Effects of Cranberry on Urinary Tract Infections and Urinary Tract Health

Consumption of cranberries and cranberry products has been widely recommended for the maintenance of urinary tract health in general (Bone and Morgan 1999; Henig and Leahy 2000; Kerr 1999; Patel and Daniels 2000; Reid, 1999; Wang et al. 2012b), as well as for the prevention and prophylactic treatment of urinary tract infections (UTIs) (Bonetta and Di Pierro 2012; Haverkorn and Mandigers 1994; Hess et al. 2008; Rogers 1991; Stothers 2002; Walker et al. 1997, among others). There are an almost equal number of studies with comparable numbers of subjects that report positive and negative outcomes. A variety of preparations have been used in the various studies including cranberry juice, cranberry juice cocktail (~27% juice), and varying cranberry extracts (see review of select studies below and Table 12). Some studies do not fully characterize the preparations used, while other studies report low compliance and high dropout rates (see Jepson et al. 2012). Patients with recurrent UTIs appear to prefer "natural" therapies such as cranberry in order to avoid prophylactic antibiotic use (Mazokopakis et al. 2009; Nowack and Schmitt 2008) underscoring the importance for health care providers to understand the benefits, limitations, dosage, and product characterizations to maximize the efficacy of cranberry preparations. The most common dose used in early studies was approximately 300 mL of cranberry juice cocktail that, when calculated, delivers approximately 36 mg of soluble PACs (analyzed according to DMAC with an A2 standard). A variety of mechanisms for cranberry's putative effects have been articulated. For many years, it was assumed that hippuric acid excreted in the urine following cranberry consumption was responsible for the effect on prevention of UTIs as hippuric acid can be bacteriostatic against *E. coli* (at concentrations of 1–2 mg/L; Bodel et al. 1959; Hamilton-Miller 1976). In human trials, urinary pH levels were somewhat reduced following consumption of cranberry juice, but to achieve a bacteriostatic effect, urinary pH must be reduced to at least 5.0 with a minimum hippuric acid concentration of 0.02 M (Bodel et al. 1959; Blatherwick 1914; Blatherwick and Long 1923; Jackson and Hicks 1997; Kinney and Blount 1979; Nickey 1975; Papas et al. 1966; Schultz 1984a; Schultz 1984b). To attain these levels, humans would need to consume at least 1500 mL of cranberry juice per day (Kahn et al. 1967). To date, researchers have not yet elucidated an exact in vivo mechanism of action, although there is substantial in vitro and ex vivo evidence indicating that cranberry and cranberry A-type PACs stimulate an activity that results in inhibiting bacteria, particularly *E. coli*, from adhering to uroepithelial cells (Gupta et al. 2007; Howell et al. 1998; Sobota 1984; Zafriri et al. 1989), prevent formation of bacterial biofilms (LaPlante et al. 2012), hinder motility, and downregulate the enzyme urease and the transcription of flagellin, which are important virulence factors (McCall et al. 2013). In addition to other potentially bioactive compounds, cranberries contain a rich and diverse mixture of polyphenolic compounds. More research is needed to determine if and how these compounds contribute to the antiadhesion effect and modulate other systems to help prevent UTIs, such as through the immune system or by reducing uropathogenic bacteria invasion in the GI tract (Feliciano et al. 2014). It is likely that a suite of compounds contributes to cranberry's biological activity. More recently, focus has been given to PACs as the primary compounds with clinically relevant antiadherence activity. Preliminary in vitro data suggest phenolics may have a role to play (Gonzalez de Llano et al. 2015) but requires confirmation.

Live bacteria must attach and gain entry to uroepithelial cells in the urinary tract to grow and cause infection, and they do so by binding to certain cell receptors with filamentous appendages called pili or fimbriae. The antiadhesion activity of cranberry was first recognized by Sobota (1984). A series of experiments using cranberry juice and uropathogenic strains of *E. coli* demonstrated that cranberry juice contains one or more compounds that inhibit in vitro bacterial adherence to uroepithelial cells (Howell et al. 1998; Zafriri et al. 1989). It appears that by preventing the *E. coli* from adhering to uroepithelial cells, the bacteria will not grow and cause infection, but be flushed out in the urine stream. Since this mechanism is not killing the bacteria, it is unlikely to result in bacterial resistance to cranberry. Antiadhesion activity of cranberry has been demonstrated in humans (Di Martino et al. 2006; Howell et al. 2005;

Howell et al. 2010; Lavigne et al. 2008; Tempera et al. 2010; Valentova et al. 2007).

Human Intervention Trials

UTIs are the most common bacterial infection in the ambulatory setting in the United States (Schappert and Rechtsteiner 2011). Although both males and females can develop a UTI, infections occur more frequently in women (Foxman and Brown 2003). It is estimated that more than 50% of women will experience at least one UTI in their lifetime (Griebling 2005), and 20 to 30% of women who experience a UTI will have 2 or more recurrent episodes (Foxman 1990). Other populations at higher risk for developing UTIs include children, pregnant women, the elderly, patients with spinal cord injuries, catheterized patients and those with chronic and/or immune-compromising diseases such as diabetes and HIV/AIDS (Foxman 2002). Foxman et al. (2015), found that administration of the equivalent of two 8-oz servings of cranberry daily in solid dosage form (capsule; TheraCran, Theralogix, LLC, Rockville, MD) for 6 weeks significantly (P =0.008) reduced the incidence of UTIs in post-surgical catheterized subjects (n = 160) by approximately 50% as compared to placebo controls. Subjects in this study were instructed to take the capsules morning and evening with an 8-oz glass of water beginning at time of discharge, and were specifically asked to avoid any other cranberry product or vitamin C supplementation for the duration of 4 to 6 weeks, or until their post-operative visit. There were no differences in adverse effects, including GI upset in this study.

A recent review of clinical studies (Micali et al. 2014) and evaluation of the cranberry efficacy/safety ratio in the prevention of UTIs supports the use of cranberry in the prevention of recurrent UTIs in young and middle-aged women (see Afshar et al. 2012; Ferrara et al. 2009; Kontiokari et al. 2001; Salo et al. 2012; Stothers 2002; Uberos et al. 2012; Walker et al. 1997; Table 12). However, evidence of its clinical efficacy among other groups remains controversial (Micali et al. 2014). Past clinical reviews have been mixed with several suggesting that cranberry may help prevent infections, particularly in women with recurrent UTIs (Jepson and Craig 2008; Wang et al. 2012b), with one review finding no benefit for cranberry (Jepson et al. 2012). Risk ratios of <1.0 (calculated relative risk of developing UTIs in the treated vs control groups) were interpreted as positive outcomes by Wang et al. (2012b) but not by Jepson et al. (2012) with different confidence intervals reported in each study. Compliance in some studies included in the Cochrane Review (Jepson et al. 2012) was low, but may have been confounded by the use of poor compliance measures. Most of the studies used cranberry products that were not standardized to A-type PACs and may not have had sufficient amounts of bioactive PAC to achieve clinical efficacy. It is important to note that cranberry is a food that comes in different product forms (juice, powder, dried, etc.) making it difficult to use a meta-analysis to compare results from multiple trials that each used different product forms (Howell 2013). Additionally, the choice of study subjects is particularly important, as the pathogenesis of UTI is specific to different patient groups. Several studies completed since the Cochrane Review (Jepson et al. 2012) had positive outcomes for cranberry in preventing UTI recurrence and are included in the most recent review of Micali et al. (2014). However, more work is needed to determine the optimal dose, frequency of administration, length of consumption, subject characteristics, and product form.

Importantly, the Cochrane Review (Jepson et al. 2012) concluded that in studies comparing low-dose antibiotics to cranberry for UTI prevention, there was little difference between cranberry and antibiotic prophylaxes, with both being similarly effective. In fact, in a study conducted by Beerepoot et al. (2011), antibiotic prophylaxis resulted in trimethoprim-sulfamethoxazole (TMP-SMX) resistance in 86.3% of fecal and 90.5% of asymptomatic bacteriuria *E. coli* isolates after one month on low-dose TMP-SMX, while in the cranberry group (1000 mg CranMax®; Pharmachem Labs; Kearny, NJ, 23.7% of fecal and 28.1% of asymptomatic bacteriuria *E. coli* isolates were TMP-SMX resistant. These same researchers also found increased resistance rates for trimethoprim, amoxicillin, and ciprofloxacin in these *E. coli* isolates after one month in the TMP-SMX group (see Interactions). Due to the very low risk of resistant bacterial strain development, cranberry was recommended by these study authors as a viable alternative to low-dose antibiotics to prevent UTI. Since the increasing prevalence of *E. coli* resistance to first-line antimicrobials in the treatment of acute UTI in women is also a serious problem (Stapleton 2013), use of cranberry to prevent initial infections may help reduce the need for subsequent antibiotic treatments and slow the pace of resistance development. According to the World Health Organization (WHO 2014) Antimicrobial Resistance Global Report on Surveillance, resistance to fluoroquinolones for controlling UTIs is very widespread, and compared with the 1980's, resistance rates have gone from 0 to 100% in many parts of the world. Cranberry products, therefore, may be a prudent nutritional therapy that can help maintain urinary tract health (Blumberg et al. 2013).

A pilot study by Greenberg et al. (2005) (n = 5) suggested that consumption of a single serving of sweetened dried cranberries (Craisins® Ocean Spray) may elicit bacterial antiadhesion activity in human urine and may be a healthy snack with specific genitourinary benefits.

Cranberry and Urinary Tract Health in the Elderly

One of the earliest large, double-blind, placebo-controlled randomized clinical trials evaluated a low calorie 27% cranberry juice cocktail for its effect on bacteriuria (defined as $>10^5$ cfu/mL of urine) and pyuria (white blood cells in urine) in 153 elderly women over a 6-month period (Avorn et al. 1994). Participants consumed either 300 mL/day of cranberry juice cocktail or 300 mL/day of a placebo drink. After 48 weeks of treatment, bacteriuria and pyuria were reduced by nearly 50% in the group that consumed cranberry juice cocktail with their odds of remaining bacteriuric-pyuric at only 27% of the odds of the control group (P =0.006). In another study (randomized, controlled,

crossover), Haverkorn and Mandigers (1994) administered 30 mL/day of cranberry juice diluted in water to 17 elderly men and women for 4 weeks. Participants consuming the cranberry treatment had fewer occurrences of bacteriuria compared to those who drank water (P =0.004), confirming Avorn's findings that cranberry juice consumption reduces frequency of bacteriuria in the elderly. An uncontrolled study of 28 elderly patients in a long-term care facility found that cranberry juice was effective in preventing UTIs (Gibson et al. 1991). Participants drank 120 to 180 mL of cranberry juice cocktail almost daily for 7 weeks. UTIs were prevented in 19 of the 28 participants. A retrospective cross-sectional study and a longitudinal cohort study (Dignam et al. 1998) were carried out in a long-term care facility in which there was a 20-month pre-intervention period when UTI rates were recorded, and an 8-month intervention period when cranberry juice or cranberry capsules were given to participants (only 4% received the capsules instead of the juice). The cross-sectional study involved 538 elderly people (77% women and 23% men). During the 20-month pre-intervention period, UTIs were reduced significantly between these 2 periods (P =0.008), with 545 UTIs compared with 164 UTIs during the 8-month intervention period when cranberry juice was consumed. In the longitudinal cohort study, 113 residents participated. There were 103 UTIs during the pre-intervention period and 84 UTIs during the intervention period, which represented a trend toward reduction in UTIs.

A double-blind, randomized, placebo-controlled pilot study aimed at identifying the optimal dose of cranberry capsules needed to reduce the incidence of bacteriuria plus pyuria was conducted over a 1-month period in elderly nursing home patients (Bianco et al. 2012). Subjects (n = 80) were given either 3 cranberry capsules (108 mg PAC determined by DMAC assay); 2 cranberry capsules (72 mg PAC) plus one placebo; or one cranberry capsule (36 mg PAC) plus 2 placebos; or 3 placebo capsules for 30 days, measuring episodes of bacteriuria and pyuria at days 7, 14, 21, and 28. In those consuming cranberry, a dose-dependent trend towards a reduction in bacteriuria and pyuria (particularly with *E. coli*) was observed, most notably in women. Cranberry did not affect bacteriuria with pathogens other than *E. coli*. The effects of the 2-capsule dose were comparable to those of the 3 capsule dose. Neither the long-term sustainability of the reduction in bacteriuria and pyuria, nor effects on clinical outcomes related to UTI (e.g., hospitalization, antibiotic therapy) was determined.

A double-blind, randomized placebo-controlled multicenter trial (n = 928) was conducted to determine the efficacy of cranberry (undisclosed characterization and dose taken twice daily for 12 months) in reducing the incidence of UTIs in residents of long-term care facilities (703 women, median age 84 years) in the Netherlands (Caljouw et al. 2014). Subjects were stratified by low or high UTI-risk (including long-term catheterization, diabetes mellitus, and ≥1 UTI in the preceding year). Of the total subjects, 516 were stratified as having a high risk for UTI; 412 were considered low risk. Compared to placebo, a 26% reduction in UTI was observed in the high-risk group, while no difference was observed in the low-risk group. One limitation of this study is that the actual incidence of UTIs was lower in the cranberry compared to placebo group.

In a recent study by Barnoi et al. (2015), prophylactic administration of 120 mg cranberry (preparation not characterized) daily significantly reduced the incidence of UTI as compared to a control group of patients with in-dwelling catheters (12.9% versus 38.75%, respectively; n = 31 in treatment and control groups; P =0.04).

Cranberry in Women with Recurrent UTIs

Cranberry products have been evaluated in 5 clinical trials to determine their efficacy in preventing recurrent UTIs in women. Three of the trials had a successful primary outcome regarding cranberry consumption and the prevention of recurrent UTIs (Kontiokari et al. 2001; Stothers 2002; Walker et al. 1997), while the other studies did not demonstrate a significant effect (Barbosa-Cesnik et al. 2011; Stapleton et al. 2012). Only 3 trials were randomized, double-blind, placebo-controlled (Barbosa-Cesnik et al. 2011; Stapleton et al. 2012; Walker et al. 1997), but none was adequately powered statistically. All trials recruited healthy women, ages 18 to 72 years, with a history of at least one UTI within the previous year. Cranberry regimens and dosing varied greatly among these studies. Walker et al. (1997) provided participants with 400 mg of encapsulated cranberry solids taken once per day for 3 months. Kontiokari et al. (2001) used cranberry-lingonberry juice made from concentrates, primarily containing cranberry: 7.5 g cranberry concentrate and 1.7 g lingonberry concentrate diluted in 50 mL water once daily for 6 months. Kontiokari et al. (2001) also compared 100 mL of a probiotic milk drink containing *Lactobacillus* for 5 days/wk for one year to 150 women who were recruited with UTIs; an open group served as open controls. After 6 months, the women on the cranberry treatment experienced 56% fewer UTIs (defined as $>10^5$ cfu/mL) than the control group (P =0.02). After 12 months, the cumulative occurrence of the first episode of UTI was still significantly different between the groups (P =0.048), suggesting that cranberry juice drink was effective in preventing UTI, while the probiotic drink was not. The Stothers (2002) study had 2 cranberry treatment arms, administered as a juice or tablet. Participants in the juice arm consumed 250 mL of "pure, unsweetened" cranberry juice 3 times/day, and the tablet arm received a 1:30 parts concentrated cranberry juice tablet twice per day for 12 months. A double-blind, placebo-controlled, crossover study by Walker et al. (1997) found that dried cranberry powder was effective in reducing UTI occurrence. Women between the ages of 28 and 44 with a history of recurrent UTIs were recruited to take two 400-mg cranberry extract pills per day for 3 months (and 3 months of placebo). While taking cranberry pills, 7 out of the 10 women experienced fewer UTIs. Only 6 UTIs occurred among the 10 subjects on cranberry supplementation, while 15 UTIs occurred among the 10 subjects on the placebo. The authors concluded that cranberry extract pills were more effective than placebo in reducing UTI occur-

rences (P <0.005). Participants in the Barbosa-Cesnik et al. (2011) study consumed two 240 mL cranberry beverage per day for 6 months; these subjects entered the trial with acute UTIs. Participants in the study of Stapleton et al. (2012) consumed the same juice beverage, assigned to one 120 mL/day or 240 mL/day for 6 months. Papas et al. (1966) conducted an uncontrolled study in which 480 mL/day of cranberry juice cocktail was administered for 21 days to 60 patients (44 women and 16 men) diagnosed with acute UTI. After 3 weeks, 53% of the participants experienced fewer UTIs following cranberry juice consumption. Six weeks after discontinuation of cranberry treatment, bacteriuria returned in most subjects. Each study reported total PAC concentration but used different methods to quantify PACs, thus giving inaccurate and varied results that are inconsistent with current quantification methods.

A recent study in which women with recurrent UTI were given 42 g dried cranberries/day for 2 weeks followed by observations for 6 months showed that women taking dried cranberries had significantly lower incidence of UTI, with a mean UTI rate at 6 months decreasing from 2.4 to 1.1 compared to a historical control group enrolled in a previous vaccine control study (Burleigh et al. 2013). Those women in the dried cranberry group also had a significant reduction in *E. coli* in a rectal swab taken post-consumption. Recently, Takahashi et al. (2013), provided 125 mL/day of cranberry juice (Group A) compared with placebo (Group P) for 24 weeks to women between 20 to 79 years with recurrent UTI. In the subgroup of females aged 50 years or more, there was a significant difference in the rate of relapse of UTI between groups A and P (log-rank test; P =0.0425). A study by Sengupta et al. (2011) found symptomatic relief and significant reduction (P <0.05) in the subjects positive for *E. coli* in both the high dose (1000 mg) and low dose (500 mg) treatment groups given a standardized cranberry powder for 90 days, compared to baseline evaluation in a randomized clinical trial of 60 female subjects between 18 to 40 years of age.

In a recent randomized placebo-controlled trial, 164 women with a history of at least 2 symptomatic UTIs in the previous 12 months, were given 500 mg of "whole cranberry fruit powder" consisting of the "peel, seeds, and pulp" (Naturex-DBS, Sagamore, MA) delivering 2.8 mg PACs daily (determined by DMAC using the A2 standard) for 6 months. There were 78 women in the treatment group and 86 in the placebo group. Consistent with numerous other individual trials, there were significantly fewer recurrent UTIs in the treatment versus placebo groups (10.8% vs. 25.8%, respectively, P =0.04). The authors reported there were no anthocyanins or PACs detected in plasma or urine, no significant differences in urinary phenolics between the groups, and speculated that PACs were not correlated with the effects, rather suggesting that other compounds, such as ursolic acid, may play a role (Vostalova et al. 2015). This is the first such trial demonstrating the efficacy of a whole cranberry powder.

Cranberry and Recurrent UTIs in Pregnancy

Asymptomatic bacteriuria, defined as $>10^5$ CFUs/mL of uropathogenic bacteria in the urine, without the traditional symptoms associated with UTIs, is of particular concern in pregnant women due to their association with pre-term delivery and low birth weight (Romero et al. 1989; Sheiner et al. 2009). Untreated, asymptomatic bacteriuria in pregnancy may progress to a UTI, particularly pyelonephritis (Kass 1960), which is associated with increased risk to both the neonate and the pregnant woman (Farkash et al. 2012).

The first study published to investigate the effect of cranberry on ASB/UTI in pregnant women did not find a statistical difference in asymptomatic bacteriuria, UTI, or neonatal outcomes among participants who were compliant with zero, one, or two 8 oz. servings of a cranberry beverage per day. The beverage treatments were reduced to 2 servings per day (Wing et al. 2008), and although this study was underpowered, women compliant with two 8 oz servings of cranberry per day experienced a 57% reduction in asymptomatic bacteriuria and 41% reduction in UTIs, indicating that cranberry may be efficacious in preventing asymptomatic bacteriuria and UTIs in pregnant women. Further studies would help solidify this area of importance for pregnant women and UTI prevention. A recent literature review of pregnant women taking cranberry supplement compared with antibiotics showed no adverse effects on the mother or infants including no increased risk of malformations nor any of the following pregnancy outcomes: stillbirth/neonatal death, preterm delivery, low birth weight, small for gestational age, low Apgar score, and neonatal infections, suggesting that cranberry consumption during pregnancy has no safety concern (Heitmann et al. 2013). Although an association was found between use of cranberry in late pregnancy and vaginal bleeding after pregnancy week 17, further sub-analyses of more severe bleeding outcomes did not support a significant risk (see Precautions and Safety). This review provided no characterization of the products or doses utilized and are juxtaposed against one formal study (Wing et al. 2008) and other reviews (Nordeng et al. 2011) showing no such effect.

Recurrent UTIs in Children

Recent trials in the pediatric population have demonstrated a benefit from cranberry consumption. The 5 available trials used a variety of cranberry products: 7.5 g cranberry concentrate plus 1.7 g of lingonberry concentrate diluted in 50 mL of water per day for 6 months (Ferrara et al. 2009); commercially available cranberry juice containing 8.2 g of cranberry concentrate per 200 mL water administered at 5 mL/kg body weight per day for 6 months (Salo et al. 2012)

a cranberry syrup containing 36 mg PAC (Ellura®/Urell®; Pharmatoka Labs, Rueil-Malmaison, France) measured by DMAC with A2 reference standard) administered at 5 mL per day depending on body weight (Uberos et al. 2012); and cranberry juice containing 37% PACs (PAC quantitation not specified) administered at 2 mL/kg body weight for one year (Afshar et al. 2012). The primary outcomes analyzed

demonstrated that cranberry treatment was efficacious in reducing UTI risk by 65% (Afshar et al. 2012) and preventing UTI recurrences (Ferrara et al. 2009). The primary outcome of reducing the number of children who experienced a recurrent UTI was not statistically significant in the Salo et al. (2012) trial. Cranberry treatment did, however, significantly reduce the number of recurrent UTIs and the number of days on antibiotics. In the trial of Uberos et al. (2012), cranberry prophylaxis was safe and effective having non-inferiority with respect to trimethoprim in recurrent UTI in relation to vesico-urethral reflux in 192 children ages 1 month to 13 years. In a follow-up analysis of their work (Uberos et al. 2015), the authors reported cranberry intake was correlated with high levels of hydroxycinnamic and hydroxybenzoic acids in urine and suggested these metabolites may play a therapeutic role in the UTI preventive effects of cranberry in vivo. One group of subjects was given a 3% glucose solution of cranberry extract (Urell®, Pharmatoka Labs, Rueil-Malmaison, France) yielding 4732 µg/mL of PACs at a dose equivalence of 5.6 mg/kg of extract; the other group was given trimethoprim in a similar syrup base at a concentration of 8 mg/mL and 0.1% CC-1000-WS (E-120) at a dose of 1.6 mg/kg. Subjects included 85 children less than 1 year of age, 53 of whom were treated with trimethoprim and 32 with cranberry syrup and 107 children over 1 year of age, 64 of whom were treated with trimethoprim and 43 with cranberry syrup. There were marked differences in efficacy in children under one year of age and those over, as well as between treatment groups. In the trimethoprim group, rates of UTI in males and females under one year of age were 19% and 43%, respectively. Interestingly, gender associated efficacy was reversed in the cranberry group, the UTI rates in male and female children under one year of age being 46% and 17%, respectively. When adjusting for gender differences, in those under one year of age, the overall rates of UTI recurrence in the trimethoprim group was 28% and in the cranberry group 35%. Similarly, a reversal of the rate of efficacy was observed in children over one year of age, the UTI rate being 35% in the trimethoprim group and 26% in the cranberry group. These researchers concluded that overall, cranberry syrup was similar in efficacy and safety to trimethoprim, but that in children under one year of age trimethoprim was more effective than cranberry syrup. Conversely, cranberry was slightly more effective than trimethoprim in reducing the incidence of multi-resistant bacteria in urine culture, with 22.9% of the cranberry group displaying positive cultures compared to 33.3% in the trimethoprim group.

A recent meta-analysis of the use of cranberry in the prevention of UTIs in children concluded that cranberry products are effective in otherwise healthy children and at least as effective as antibiotics in children with urogenital abnormalities. A dosage and frequency recommendation is confounded by the variability of products and dosages used in the trials included in this analysis (Durham et al. 2015).

Cranberry and Urinary Tract Health in Neurogenic Bladder and Spinal Cord Injury

Neurogenic bladder is the result of problems with nerves in the body that control how the bladder stores and empties urine. Results of intervention trials using cranberry juice for UTI prevention in patients with neurogenic bladders are not clear. One double-blind, placebo-controlled, crossover study did not find a significant reduction in bacteriuria in children ages 2 to 18 years with neurogenic bladders after 60 mL/day cranberry juice concentrate consumption (Schlager et al. 1999) (equal to 300 mL/day of cranberry juice cocktail) or a placebo for 3 months with another 3-month crossover. The authors suggest that the voiding dysfunction associated with neurogenic bladder may have overshadowed the effect of cranberry in this population. In a crossover study by Foda et al. (1995), cranberry juice consumption did not significantly reduce UTIs in a pediatric population with neurogenic bladders. Participants (n =21) consumed either 15 mL/kg/day of body weight/day of cranberry juice cocktail or 15 mL/kg of body weight/day of water for 6 months, with a 6-month crossover. There was no significant difference in UTI reduction between cranberry juice consumption and water consumption in this group of participants. However, in an uncontrolled study, Rogers (1991) administered 360 to 480 mL/day of cranberry juice to 17 children with neuropathic bladders for one week and 540 to 660 mL/day during the second week. All urine samples had reduced red and white cell counts, suggesting reductions in UTIs following cranberry consumption.

The evidence for effectiveness of cranberry supplementation on UTI prevention and bacteriuria in spinal cord-injured individuals is inconclusive. Two studies found no reduction in bacteriuria or pyuria with cranberry supplementation (Linsenmeyer et al. 2004; Waites et al. 2004), and one study did not result in a longer UTI-free period on cranberry compared to placebo (Lee et al. 2007). However, a crossover, double blind, randomized, placebo-controlled trial of 47 subjects with spinal cord injury and neurogenic bladder did find a reduction in symptoms and a 60% reduction both in the number of UTI and of subjects who experienced any UTI over a 6-month trial in those subjects receiving a daily 500-mg cranberry tablet taken twice per day compared to placebo. Subjects taking cranberry did not experience a reduction in urinary pH. UTI was nearly eliminated among subjects in the cranberry group with a glomerular filtration rate (GFR) above 75 mL/min−1. The authors hypothesized that the combination of bacterial adhesion inhibition and a high urinary filtration rate worked together to prevent bacterial biofilm formation and eliminate the bacterial pathogens (Hess et al. 2008). Bacterial biofilm load was significantly reduced in a study of 15 spinal cord-injured participants who consumed 3 glasses of cranberry juice on days 7 and 15 compared to those that consumed 3 glasses of water on those days. The results in the cranberry group were due to a reduction of both gram-negative and gram-positive bacterial adhesion to cells (Reid et al. 2001). These findings suggest that different risk factors or populations studied may contribute to some of the inconsistent results found with cranberry prophylaxis. However, a nutritional approach utilizing cranberry to reduce the incidence of UTIs has signifi-

cance due to the potential for reducing antibiotic treatment and the consequent development of resistance to these drugs (Blumberg et al. 2013).

Other Urinary Tract Effects

Administration of a daily cranberry encapsulated powder containing 36 mg PAC, as measured by DMAC with the A2 standard significantly decreased asymptomatic bacteriuria in patients with an ileal enterocystoplasty (bladder replacement) (Botto and Neuzillet 2010). There have been several clinical reports of cranberry juice having a beneficial effect on reducing catheter-obstructed mucus production in enterourocytoplasties (Rosenbaum et al. 1989) and in catheterized children (Rogers 1991), as well as reducing urine odor (DuGan and Cardaciotto 1966; Kraemer 1964). *E. coli* alkalinizes and ferments the urine with a subsequent release of ammonia. Cranberry juice lowered urinary pH sufficiently (from 6.6 to 5.8) to retard this bacterial action and reduce the ammonia smell (Kraemer 1964). DuGan and Cardaciotto (1966) found that ammonia odor and burning sensation while urinating were reduced following administration of 90 mL/day for one week, with a weekly increase of 30 mL/day until a maximum dosage of 180 mL/day was reached after 3 weeks. Ammonia odor was actually measured in the air and was reduced, especially in the female group, after the intervention period. Conversely, no beneficial effect was observed in in-home subjects (n = 11) with in-dwelling catheters (Lin et al. 2014). In this study, no significant differences were observed on urinalysis, urine culture, and biochemical blood tests compared to controls. Subjects consumed 300 mL cranberry juice cocktail and 2200 mL of water.

There is mixed evidence on the effects of cranberry juice consumption and kidney stone formation stones with some reporting a risk a potential but slight increased risk of stone formation (e.g. Gettman et al. 2005) and others reporting decreased risk (Light et al. 1973; Zinsser et al. 1968). Most of these opinions are based on biomarkers of stone formation rather than clinical outcomes showing an increase or decrease in stones. Findings on all biomarkers used have been mixed with reports of urinary calcium excretion increasing, decreasing, or remaining unchanged; urinary oxalate excretion to decrease or increase; and urinary citrate to increase or remain unchanged with consumption of cranberry juice (see Gettman et al. 2005). These variations are likely due to differences in the preparations consumed.

Regarding calcium oxalate stones, concerns have been raised about high intakes (1 L or more/day) of cranberry juice due to the potential of oxalate and uric acid stones forming in acidic urine (Rogers 1991). In one early investigation, cranberry juice consumption of up to 2.4 L/day significantly reduced urinary ionized calcium associated with calcium-containing renal stones by 50% (P =0.001) (Light et al. 1973). Further more, Brinkley et al. (1981) reported that cranberry juice contained low or negligible amounts of oxalate and was safe for patients with calcium kidney stones. In contrast, Gettman et al. (2005; see *Association between cranberry consumption and increased kidney stone formation* below) reported that cranberry juice consumption increases the risk of calcium oxalate and uric acid stone formation but decreases the risk of brushite stones. These authors also concluded that cranberry juice CBJ "probably does not substantially affect the risk of stone formation. Similarly, Terris et al. (2001) reported a potential increase in oxalate stone formation based on increases in urinary excretion of calcium, sodium, and phosphate, lithogenic ions, in normal volunteers, though increases in magnesium and potassium, antilithogenic ions, was also observed.

Regarding struvite stones, bacteria in the urine can alkalinize and facilitate the formation of struvite calculi (Zinsser et al. 1968). In another early study, patients (53) who consumed 946 mL/day of cranberry juice over 9 years reportedly had a 60% improvement with no stone formation, 32% had no increase in stone size, and 8% had new stones form or an increase in stone size (Zinsser et al. 1968). This effect was assumed to be due to urinary acidification by cranberry juice but could have been associated with decreases in stone formation due to urinary tract infection (Light et al. 1973).

In a recent investigation, Rafsanjany et al. (2015) investigated the in vitro, in vivo, and ex vivo antiadhesin activity of cranberry extracts, one enriched and the other devoid of PACs. Four males were given 600 mg of a cranberry extract containing 1.24% PACs (as determined by LC-MS and calculated as cyanidin), and another devoid of PACs (as determined by TLC), for seven days. Urine samples were taken at days 0, 3, and 7 and antiadhesin assays were conducted. Significant (P <0.01) reductions in bacterial adhesion were reported at days 3 (-39%) and 5 (-48%) compared to the control (day 0) for both cranberry preparations. This investigation confirms earlier in vitro findings (e.g., see Feliciano et al. 2013) that high PAC extracts can result in a clumping (agglutination) of bacteria on the surface of bladder cells and that non-PAC preparations also selectively inhibit bacterial adhesion (e.g., Type 1 *E. coli*; Hotchkiss et al. 2015; Zafriri et al. 1989). These researchers cautiously interpret that part of the in vitro bacterial antiadhesion activity of cranberry is due to tannin-induced agglomeration, a novel theory. These investigators further confirm that PACs inhibit bacterial adhesion to urinary bladder cells but emphasize that PAC metabolites (e.g., catechol, myricetin, phenylacetic acid, 3,4-dihydroxyphenylacetic acid,) may have a greater role in bacterial antiadhesion activity than previously reported (Kimble et al. 2014; de Llano et al. 2015). Other research similarly confirms that compounds in addition to PACs exhibit antiadhesin activity (see Hotchkiss et al. 2015; Zafriri et al. 1989). In the study of Rafsanjany et al. (2015), neither the PAC extract nor the PAC-depleted extract influenced biofilm or curli development. In contrast to the findings of other studies, these investigators also reported that P-fimbriae-mediated adhesion was not influenced by these cranberry preparations.

In Vitro, Ex Vivo, and Animal Studies

Bacterial Antiadhesion and Other Potential Mechanisms

The results of in vitro studies on cranberry indicate there may be multiple mechanisms contributing to the fruit's

beneficial effects, with a significant number of investigations focusing on bacterial antiadhesion. There are many in vitro and ex vivo studies on cranberry, cranberry products, and isolated cranberry A-type PACs demonstrating significant antiadhesion effects on mainly *E. coli* bacteria. There are 2 major uropathogenic *E. coli* fimbrial types, P-type (or pyelonephritis-associated pili [PAP]), which are mannose-resistant, and Type 1, which are mannose-sensitive. The bacterial antiadhesion effect of cranberry targets P-fimbriated *E. coli* (Sobota 1984), which are associated with both cystitis and pyelonephritis (Dowling et al. 1987).

There are different types of cranberry compounds that have been implicated in the antiadhesion effect: fructose and high molecular weight compounds identified as A-type PACs (Howell et al. 1998; Zafriri et al. 1989) and phenolic compounds. Binding studies demonstrate that fructose has a high affinity to the Type 1 FimH adhesin, although 15-fold less than its natural mannose ligand (Bouckaert et al. 2005). Incomplete metabolism of fructose in the liver can lead to its urinary excretion, but is normally only clinically significant at very high sugar doses (Tasevska et al. 2005) or in diabetics (Kawasaki et al. 2002). Thus it is unlikely that the fructose in cranberry elicits a significant in vivo antiadhesion effect in most people. The majority of research has focused on the A-type PACs as the key compounds responsible for preventing adhesion of P-type *E. coli* (Ermel et al. 2012; Foo et al. 2000a, 2000b; Howell et al. 2005; Howell 2007). Recently, Gupta et al. (2012) showed cranberry PAC extracted from dried juice prevented the in vitro binding of both sensitive and multi-drug resistant P-fimbriated *E. coli* at concentrations of 10 to 50 µg/mL/day. Purified cranberry PACs fed to mice for 20 days at 0.122 or 0.522 mg/day in water elicited significant bacterial antiadhesion activity in urine when compared to the urine collected from control mice that were consuming plain water ($P < 0.01$) (Howell et al. 2001).

In another animal study, urine from rats fed 118 mg PACs/animal/day in oral suspension form or tablets prevented adhesion of *E. coli* by 83% and 52%, respectively (Risco et al. 2010). PACs appear to prevent bacterial adhesion in multiple ways, including causing morphological changes in the bacteria such as elongation or fimbrial compression, preventing binding to uroepithelial cells (Ahuja et al. 1998; Liu et al. 2006). In another animal study, rats were administered 1 mL of either diluted (25%) or pure cranberry juice three times daily. Significant decreases in *E. coli* hemagglutination, urothelium adhesion, and biofilm formation along with significant increases in nematode killing were observed with both cranberry preparations. There was greater activity of the pure juice over the diluted cranberry juice preparation (Chen et al. 2013).

In a study of Gonzalez de Llano et al. (2015), a variety of phenolic compounds and their metabolites (catechol, benzoic acid, vanillic acid, phenylacetic acid, and 3,4-dihydroxyphenylacetic acid; 100 to 500 µM) showed in vitro antiadhesion activity against *E. coli* in uroepithelial cells. According to the authors this is the first time antiadhesion activity was demonstrated for these compounds. However, these phenolics are also metabolites of A-type PACs so such an activity is not surprising. Additionally, the authors acknowledge that in vivo relevance has not been established. The study also confirmed the antiadherence activity of PACs (500 µM).

A group of researchers used atomic force microscopy to elucidate the effects of cranberry products on the ability of bacteria to attach to uroepithelial cells (Liu et al. 2006; 2010). In initial studies, the researchers found that the cranberry products decreased the attachment of *E. coli* HB101pDC1, a fimbriated strain, but not *E. coli* HB101, a non-fimbriated strain (Liu et al. 2006). Later they found that bacterial exposure to increasing concentrations of cranberry juice cocktail (27% cranberry by weight) or incubation in isolated cranberry PAC (345.8 µg/mL/day) resulted in a decrease of bacterial attachment to uroepithelial cells for the P-fimbriated strain (Pinzon-Arango et al. 2011).

Results of in vitro studies are helpful in determining mechanisms and potency of products prior to ingestion; but, to more accurately determine efficacious dosages and persistence of cranberry, studies using hemagglutination or bladder cell adhesion assays that measure the ex vivo urinary antiadhesion activity following consumption are important. Sobota (1984) found that urine collected from mice that ingested cranberry juice cocktail in place of water for 14 days significantly inhibited adherence of P-fimbriated *E. coli* to uroepithelial cells ($P < 0.01$). This antiadhesion effect was also detected in human urine in 15 of the 22 subjects, 1 to 3 hours following ingestion of 450 mL of cranberry juice cocktail (Sobota 1984). Since then, other studies have also found ex vivo bacterial antiadhesion activity in human urine following cranberry consumption (Di Martino et al. 2006; Howell et al. 2010; Tempera et al. 2010; Valentova et al. 2007). Lavigne et al. (2008) found that urine from subjects consuming 3 capsules of cranberry preparation caused a highly significant reduction in bacterial adherence to T24 cells as compared with placebo ($P < 0.001$) with a dose-dependent decrease in bacterial adherence. The ex vivo antiadhesion activity in urine was also demonstrated following ingestion of different dosages of cranberry juice powder standardized for PAC content (Howell et al. 2010). Dosages of cranberry powder containing 36 or 72 mg PAC levels/day as measured by DMAC method with a procyanidin A2 reference standard (Prior et al. 2010a) elicited significantly higher antiadhesion activity in urine using both the hemagglutination and human T24 epithelial cell line bioassays at 6 hours than powder dosages containing 18 mg of PAC ($P = 0.002$) (Howell et al. 2010).

Biofilms are typically associated with catheter-associated UTIs, but have recently been implicated in the etiology of recurrent UTI (Anderson et al. 2004). Biofilms, sessile communities of bacteria, form an extracellular matrix for functional and structural integrity and have altered phenotypes associated with long-term persistence (Dolan et al. 2010). Ex vivo biofilm studies have demonstrated that urine from cranberry juice consumers can prevent biofilm formation in uropathogenic *E. coli* (Camesano et al. 2011; Di Martino et al. 2005), implying that active compounds are present in the

urine following cranberry consumption.

Flagellum-mediated motility has been suggested to enable uropathogenic *E. coli* to reach the upper urinary tract. It was proposed that inhibition of flagellum-mediated motility might be a key mechanism by which cranberry PACs prevent UTIs. The authors of a study using *E. coli* strain CFT073 grown in the presence of dehydrated crushed cranberries or purified cranberry PACs results in a reduction of fliC (flagellin gene) expression by almost 2.4-fold (Hidalgo et al. 2011). Additionally, the study showed that 0.1 to 10 mg/mL/day of cranberry PACs can slow or completely prevent swimming or swarming motility of the bacteria. Chan et al. (2013) reported a similar action of cranberry powder and cranberry PACs to downregulate the expression of the flagellin gene of *E. coli* CFT073 and Proteus mirabilis HI4320 in vitro in a silicone gel model. Interestingly, these researchers suggest the application of cranberry compounds into medical devices (e.g., catheters) as a way to reduce the migration of bacterial pathogens.

Additional research is needed to determine more specifics on cranberry and bacterial adhesion and other potential mechanisms of action in support of urinary tract health. Questions remain regarding the specific in vivo antiadhesion mechanism due to lack of both bioavailability of larger polymeric A-type PACs (which are prevalent in cranberry skins, thus limiting their solubility) and published ex vivo antiadhesion data from clinical trials.

Recently, A-type PAC dimers have been shown to be bioavailable in small concentrations (Zampariello et al. 2012) with maximal urinary concentrations of A2 PACs averaging 24.4 ng/mg creatinine at 11 hours post-cranberry consumption. There are very few studies that have focused on metabolism of A-type PACs (e.g., Iswaldi et al. 2013; Rajbhandari et al. 2011). This area needs further study to more clearly determine the quantity and size of A-type PAC molecules that enter the urine following metabolism (see Pharmacokinetics). It is clear that the antiadhesion effects are complex and multi-faceted. It is also possible that an antiadhesion response may be induced indirectly in the urine following gut binding of larger PACs, or that these larger PACs bind directly to uropathogenic rectal *E. coli*, preventing fimbrial adherence to uroepithelial receptors following introduction of these bacteria into the urinary tract. Gut colonization by extra-intestinal pathogenic *E. coli* serves as a source of bacteria for subsequent UTIs, thereby increasing recurrence risk. Cranberry A-type PACs have also been shown to inhibit invasion of these *E. coli* into gut cells, potentially reducing the reservoir of bacteria for future infections (Feliciano et al. 2014).

Summary

The accumulative in vivo data, including numerous positive clinical studies with almost 3,000 thousand subjects, along with strong mechanistic rationale, suggest efficacy of cranberry and its preparations for maintaining urinary tract health and the potential to reduce UTIs. Conversely, an almost equal number of studies with more than 1600 subjects failed to show efficacy in UTI prophylaxis or treatment, perhaps partially due to the use of ineffective products or insufficient doses.

Efficacy of cranberry for urinary tract health is likely due to multiple effects that include antiadhesion activity, modulation of bacterial motility, bactericidal activity, immune modulation, and urine acidification. A-type PACs are predominantly associated with the antiadhesion activity, with suggestions that 36 mg of PACs daily (as determined by DMAC with the A2 reference standard) is the target dose. This 36-mg dose is the amount of PACs in a typical 300 mL serving of cranberry juice cocktail (27% juice) as determined by the DMAC method (A2 reference standard), which showed efficacy in prevention of bacteriuria in elderly women (Avorn et al. 1996). Another well-designed clinical trial established the efficacy of whole cranberry fruit (delivering 2.8 mg PACs daily) in reducing recurrent UTIs (Vostalova et al. 2015). Other mechanistic data suggest that phenolics, metabolites of A-type PACs, may play a greater role than previously believed (Gonzalez de Llano et al. 2015; Rafsanjany et al. 2015). Still additional data report on antiadhesin activity of xyloglucan oligosaccharides (Hotchkiss et al. 2015), further establishing that a suite of compounds contributes to the overall activity of cranberry. Efficacy has been demonstrated for a variety of preparations including dried fruit, cranberry juice, cranberry juice cocktail, cranberry juice extracts, solid extracts, and a syrup. An important aspect of cranberry as a nutritional approach in potential prevention of UTIs is in lessening the need for conventional antibiotic therapy that leads to resistant bacterial strains. With very rare exceptions, cranberry has been demonstrated to be safe in adults, children, the elderly, and in pregnancy.

As reflected in the findings of the latest Cochrane review (Jepson et al. 2012), more rigorous randomized controlled clinical trials are needed as all studies to date can be criticized for having some methodological flaws.

Table 12 **Clinical trials of cranberry preparations in the prevention of urinary tract infections (UTIs)**

Reference	Study design	Patient population	Product and daily dosage	Treatment duration	Outcome
Rogers 1991	OBS	Children with neuropathic bladders; *n* = 17	CJ, 360–480 mL for 1 week and 540–660 mL for the 2nd week	2 weeks	Observed reduction in red and white cell counts; *E. coli* still present in samples at end of study
Avorn et al. 1994	DBRPCT	Elderly women; *n* =153	CJC (27%, saccharin-sweetened), 300 mL	6 months	Lower odds ratio for bacteriuria with pyuria in treatment group (P =0.004)
Haverkorn and Mandigers 1994	RX, control water	Elderly men and women; *n* = 17	CJ, 30 mL	1 month	Fewer incidences of bacteriuria (P =0.004)
Foda et al. 1995	PCTX	Children with neuropathic bladders; *n* = 21	CJC, 15 mL/kg	6 months	No reduction in incidence of UTIs
Walker et al. 1997	DBRPCTX	Women (28–44 years) with history of recurrent UTI; *n* = 10	CE (Cranactin®), 1 capsule equivalent to 400 mg cranberry solids daily	3 months	Significantly fewer UTIs in treatment group (P =0.005)
Dignam et al. 1998	OBS, cross-sectional	Elderly men / women; *n* = 538	CJ, 120 mL or 6 Azo-cranberry capsules	8 months	Fewer UTIs during the treatment period (*P* =0.008)
Dignam et al. 1998	OBS, longitudinal	Elderly men / women; *n* = 113	CJ, 120 mL or 6 Azo-cranberry capsules	16 months	No reduction in incidence of UTIs
Schlager et al. 1999	DBPCTX	Children with neurogenic bladders; *n* = 15	CC; 60 mL (= 300 mL CJC)	3 months	No reduction in bacteriuria
Kontiokari et al. 2001	PRCT, 3 arm, Control Lactobacillus rhamnosus drink	Young women suffering from UTI at recruitment; *n* = 150	Cranberry-lingonberry concentrate, 50 mL in 200 mL water	6 months	56% fewer UTIs in cranberry group after 6 months (*P* =0.02)
McGuinness 2002	PRCT, control beetroot powder	Multiple sclerosis patients; *n* = 126	Cranberry containing tablet product (NOW Natural Foods): 8000 mg tablet, one tablet/daily	6 months	No significant advantage of cranberry over control
Stothers 2002	DBRPCT	Women (21–57 years) with history of UTIs; *n* = 150	CJ or CE, brands and dosage unspecified	1 year	Mean number of symptomatic UTIs reduced in both cranberry groups (*P* ≤0.05)
Linsenmeyer et al. 2004	PRCTX	Patients with neurogenic bladders secondary to spinal cord injury; *n* = 21	Cranberry tablets: 400 mg standardized tablets	9 weeks	No statistically significant treatment (favorable) effect for cranberry supplement beyond placebo
Waites et al. 2004	PRCT	Men and women at least one year post spinal cord injury; *n* = 48	Concentrated cranberry extract: 2 g in capsule form	6 months	No reduction in bacteriuria and pyuria
McMurdo et al. 2005	PRCT	Elderly men and women; *n* = 376	Cranberry juice: 300 mL	35 days	Between-group differences not significant

Table 12 Continued

Reference	Study design	Patient population	Product and daily dosage	Treatment duration	Outcome
Lee et al. 2007	PRCT, control methenamine hippurate	Men and women with spinal cord injury; n = 305	Treatment group 1 Methenamine hippurate: 2 g; cranberry: 1600 mg Treatment group 2 Methenamine hippurate: 2 g; cranberry placebo Treatment group 3 Cranberry: 1600 mg; Methenamine hippurate placebo	6 months	No difference in UTI-free period with either treatment
Bailey et al. 2007	OBS	Women with a history of recurrent infections of a minimum of 6 UTIs in the preceding year; *n* = 12	One capsule twice daily containing 200 mg of a concentrated cranberry extract standardized to 30% phenolics	3 months	No UTIs during study period
Hess et al. 2008	RCTX, control rice flour	Men and women with spinal cord injury; *n* = 47	Cranberry tablet: 500 mg twice daily	6 months	Reduction in the likelihood of UTI and symptoms for any month while receiving the cranberry tablet (P <0.05 for all)
Wing et al. 2008	PRCT, 3 arm	Women < 16 weeks gestation; n = 115	Treatment group 1 Cranberry juice: 240 mL at breakfast, placebo juice at other meals Treatment group 2 Cranberry drink: 240 mL, 3 times/daily, reducing to twice daily after 52 enrollments because not well tolerated Control group Placebo: 3 daily doses of matched juice product	~5 months	Non-significant trend for reduction in asymptomatic bacteriuria and symptomatic urinary tract infections in pregnancy
Ferrara et al. 2009	PRCT, 3 arm	Girls 3–14 years; *n* = 80	Cranberry-lingonberry concentrate (97.5 g and 1.7 g respectively); Lactobacillus GC drink	6 months	Significant reduction in the risk of repeated UTIs in the cranberry group (P <0.05) compared with the Lactobacillus group and the control group

Table 12 Continued

Mazokopakis et al. 2009	OT	Post-menopausal women with recurring UTI; *n* = 10	Four cranberry capsules per day (Natural Cranberry Extract, 400 mg with vitamin C vegetable, capsules, Solgar, Inc, Leonia, NJ)	6 months	No symptomatic UTI during trial, almost all urine cultures were sterile
McMurdo et al. 2009	PRCT	Women >45 years with at least 2 antibiotic treated UTIs in previous 12 months; **n** = 120	Cranberry tablet: 500 mg, 100 mg of trimethoprim	6 months	Study underpowered; trimethoprim had a limited advantage over cranberry, but more adverse effects; cranberry group experienced fewer infections with *E. coli*
Cadkova et al. 2009	PT	Women during perioperative period leading to gynecological surgery; **n** = 286	Cranberry extract capsules (equivalent to 17,000 mg of fresh fruit) twice daily, 4 days before and 5 days after the surgery	6 days	No effect on the number of post-surgical UTIs
Vidlar et al. 2009	RCT	Men, aged 45–70 years; *n* = 42	1500 mg of the dried powdered cranberries or no treatment	6 months	Significant improvement in International Prostate Symptom Score, QOL, urination parameters including voiding parameters, and lower total PSA level for cranberry group
Botto and Neuzillet 2010	OT	Asymptomatic bacteriuria in patients with an ileal enterocystoplasty; *n* = 15	36 mg/daily PAC (Urell, Pharmatoka)	32.8 months (median)	Significant decrease in the number of positive urine cultures during cranberry compound treatment
Juthani-Mehta et al. 2010	PRCT, 3 arm	Elderly men and women >60 years of age with dementia; *n* = 56	Cranberry capsule: 1 x 650 mg once or twice daily	6 months	No difference between the 3 groups
Essadi and Elmehashi 2010	PCT, control water: 250 mL 4 times/ daily	Pregnant women; *n* = 544	Cranberry juice: 250 mL 4 times/ daily	12 months	To little information to assess
Uberos et al. 2012, 2015	PRCT, control trimethoprim 8 mg/kg	Children aged from 1 month to 13 years, with recurrent UTI; **n** = 192	Cranberry syrup: 0.2 mL/kg yielding 36 mg PACs (Urell, Pharmatoka) Trimethoprim	12 months	Similar efficacy between trimethoprim and cranberry
Barbosa-Cesnik et al. 2011	PRCT, control matched for flavor and color	Women 18–40 years, with UTI symptoms; *n* = 319	Low calorie cranberry cocktail: 240 mL twice daily	6 months	Among otherwise healthy college women with an acute UTI, drinking cranberry juice did not result in a decrease in the 6-month incidence of a second UTI
Sengupta et al. 2011	PRCT, 3 arm	Females with a history of recurrent UTIs; *n* = 60	Cranberry: 500 and 1000 mg/daily, 1.5% PAC	3 months	Significant reduction (P <0.05) in the subjects positive for E. coli in both the high-dose and low-dose treatment groups

Table 12 Continued

Beerepoot et al. 2011	PRCT, control trimethoprim-sulfamethoxazole 480 mg	Premenopausal women >18 years with at least 3 symptomatic UTIs in the year prior to enrollment; *n* = 221	Cranberry extract: 500 mg twice daily (9.1 mg/g type A PAC)	12 months	Trimethoprim-sulfamethoxazole is more effective than cranberry capsules to prevent recurrent UTIs; authors suggest that non-antibiotic therapies additionally beneficial to prevent antibiotic resistance
Bonetta and Di Pierro 2012	PCT	Patients with external beam radiotherapy; *n* = 370	200 mg of a highly standardized enteric-coated cranberry extract titered as 30% proanthocyanidins	~7 weeks	Significantly fewer lower urinary tract infections in the cranberry group
Salo et al. 2012	PRCT	Children; *n* = 255	Cranberry juice 5 mL/kg up to 300 mL 1–2 doses daily	6 months	No significant reduction in the number of children who experienced a recurrence of UTI; reduction in actual number of recurrences
Afshar et al. 2012	RCT	Children; *n* = 40	2 cc/kg cranberry juice containing 37% PAC (method not given) Placebo: same volume of juice with no PAC or other cranberry products	12 months	65% reduction in risk of urinary tract infection (P =0.045)
Stapleton et al. 2012	RCT	Premenopausal women with a history of recent UTI; *n* = 176	4 oz of cranberry juice, 8 oz of cranberry juice, or placebo	5.6 months (median)	Strong (though not significant) reduction in P-fimbriated E. coli; no significant reduction in UTI risk
Bianco et al. 2012	DBRPCT, 4 arm	Elderly; *n* = 80	108, 72, and 36 mg PAC, placebo	1 month	Dose-dependent trend toward decrease in bacteriuria and pyuria
Cowan et al. 2012	PRCT, control placebo juice	Adults >18 years with cervical or bladder cancer requiring radiation therapy; *n* =113	Cranberry juice twice daily (volume and concentration not stated)	6 weeks	Significant decrease of UTI and urinary symptoms (*P* =0.240)
Mutlu and Ekinci 2012	RCTX	Children with neurogenic bladder; *n* =20	One cranberry capsule (no further information given), placebo	12 months	Significant reduction in UTIs (P =0.012); significant decrease in pyuria (*P* =0.000)

Table 12 Continued

Takahashi et al. 2013	PRCT	Outpatients aged 20–79 years with acute exacerbation of acute uncomplicated cystitis or chronic complicated cystitis (including self-catheterization) who had a past history of multiple relapses of UTI; *n* = 213	125 mL cranberry juice or placebo	24 weeks	Significant reduction (P =0.0425) in rate of relapse of UTIs in females 50 years or more
Gallien et al. 2014	DBRCT	Multiple sclerosis patients; *n* = 171	Cranberry powder 18 mg proanthocyanidins sachets twice daily	12 months	No reduction in incidence of UTIs
Caljouw et al. 2014	DBPCT	Elderly long-term care facility patients stratified to high- or low risk for UTIs; *n* = 928	Undisclosed cranberry preparation and dose given twice daily	12 months	26% reduction in incidence of UTIs in high risk subjects (n = 516); no difference in low-risk subjects
Lin et al. 2014	OBS; control (catherized patients)	Elderly long-term care facility; patients with long-term in dwelling catheter; *n* = 11	Cranberry juice (300 mL daily; characterization not disclosed) along with 2200 mL water	6 months	No reduction in asymptomatic bacteriuria or incidence of UTIs
Mathison et al. 2014	DBRCTX	Healthy adults; *n* = 12	Cranberry leaf extract beverage, low-calorie cranberry juice cocktail, or placebo	Single dose	Cranberry showed significant (*P* <0.05) ex vivo antiadhesion activity against P-fimbriated E. coli in urine compared with placebo.
Vostalova et al. 2015	Single center; DBRPCT	Women, 18–75 yr; cranberry n = 78; placebo n = 86; history of at least 2 symptomatic UTIs treated with antibiotics in previous 12 months	Cranberry powder; 500 mg daily yielding 2.8 mg PACs daily.	6 months	Significant reduction in UTI recurrence in cranberry (10.8%) over placebo (25.8%) (*P* = 0.04)

DB = double blind; R = randomized; CT = controlled trial; PCT = placebo-controlled; PT = prospective trial; X = crossover; OBS = observational; PG parallel group; CJC = Cranberry Juice Cocktail® (Ocean Spray®, CJC ~27% cranberry juice); CJ = cranberry juice of unknown concentration from unknown manufacturer; CE = cranberry extract; CC = cranberry juice concentrate; OT = open trial *no results published.

Effects on Cardiovascular Health Cranberry Polyphenols: Effects on Cardiovascular Risk Factors

A continually increasing body of scientific evidence supports a positive relationship between the dietary consumption of foods that are high in polyphenolic compounds (e.g., flavonoids, phenolics, anthocyanidins), compounds found in cranberry, and reduced risk factors for cardiovascular disease (see Blumberg et al. 2013; Cassidy et al. 2011; 2013; Jennings et al. 2012; Hooper et al. 2008; Khoo and Falk 2014; Krueger et al. 2014; McCullough et al. 2012; Mink et al. 2007; Wallace 2014). Health effects associated with cranberry compounds include the inhibition of low-density lipoprotein oxidation (oxLDL), platelet aggregation and adhesion (Basu et al. 2010; Basu and Lyons 2012), and inflammatory response of vascular tissues and increases in endothelium-dependent vasodilation, as well as reductions in arterial stiffness (Dohadwala et al. 2011; Jennings et al. 2012) and blood pressure (Cassidy et al. 2011; Jennings et al. 2012). Current research specifically supports the function of polyphenols in modulating signal transduction through direct action on receptors and enzymes, which in turn influence redox reactions in the body (Scalbert et al. 2005; Stevenson and Hurst 2007).

Most findings correlating polyphenol consumption with cardiovascular protective effects are drawn from epidemiological data and dietary surveys, as well as systematic reviews, most of which do not specifically include cranberry. Thus a direct extrapolation of such findings to cranberry cannot be made. However, specifically regarding cranberry, well-controlled clinical trials have emerged supporting the effects of cranberry polyphenols in modulating cardiovascular risk factors such as hypertension, dyslipidemia, C-reactive protein, and oxidative stress markers such as LDL oxidation. Specific cardio-related risk factors that have been favorably influenced by cranberry or its constituents include arterial stiffness, diabetes, dyslipidemia, endothelial dysfunction, hypertension, inflammation, oxidative stress, and platelet function, suggesting potential benefit in atherogenesis, lesion progression, myocardial infarction, arterial plaque rupture and thrombosis (Blumberg et al. 2013). Additional in vitro, ex vivo, and cell culture investigations provide mechanistic support for a number of cardio-protective actions specifically for cranberry and its constituents, including anti-inflammatory and antioxidant activity of polyphenols (see Antioxidants Effects of Cranberry) and suggest the potential for high in vivo bioactivity.

Care is warranted in the interpretation of a number of polyphenol study findings as many of these employed a variety of products analyzed by a variety of non-homogenous methodologies and assessed by non-validated assays. Additionally, bioactivity of phenolic compounds is dependent on a number of factors including but not limited to the amount consumed, the molecular structure of compounds, constituent co-factors, absorption, and individual metabolism. While the parent structures of polyphenols are only minimally absorbed, absorption of metabolites formed in gut flora is enhanced. What has not yet been determined is the level and type of the most protective polyphenols in the diet, though a number of studies compare the flavonoids, phenolic, and PAC composition of cranberry to other flavonoid-rich foods (see Phenolic Composition of Cranberry and Del Rio et al. 2013; Khoo and Falk 2014; Wallace 2014, among others). Additionally, a number of studies utilize products that have been fortified with vitamin C or other antioxidants and so require specific consideration when interpreting results.

Flavonoid Consumption Patterns

The total daily intake of flavonoids in the American diet is estimated to be between 189.7 to 209 mg/day (Chun et al. 2007; 2010). The total daily intake of PACs in the American diet is variably estimated at a low mean of 57 mg/d (Gu et al. 2004) to a mean of 95 mg/d (Wang et al. 2011). Relative to dietary surveys of other nations, these values are considered low; for example, the estimated dietary flavonoid intake in Spain, with a primarily Mediterranean diet pattern and its associated health benefits, was 313.26 mg/day (Zamora-Ros et al. 2010), whereas PAC consumption was 189 mg/d (Santos-Buelga and Scalbert 2000). The primary dietary sources of PACs reported in the US are from apples, wine, and fruit (unspecified), all of which yield similar concentrations of flavonoids per 100 g as cranberry (Khoo and Falk 2014). Additionally, cranberry is one of only a few fruits that contain a large portion of free versus bound phenolics and a broad array of flavonols, procyanidins, and anthocyanins (Sanchez-Patan et al. 2012), as well as high concentrations of A-type PAC (Gu et al. 2004).

Phenolic Composition of Cranberry

The composition of cranberries and some cranberry preparations is very well characterized (see Constituents). Whole cranberries contain a higher amount of total phenolic compounds per serving (507–709 mg gallic acid equivalents/100 g) than other common fruits including blueberries (258–531 mg/100 g), apples (185–347 mg/100 g), red grapes (175–370 mg/100 g), and strawberries (132–368 g/100 g) (Sun et al. 2002; Vinson et al. 2001; Wu et al. 2004). Chen et al. (2001) reported a total phenolic concentration of 413 mg/L in freshly squeezed cranberry juice (100%) and 51 mg/L in a 27% cranberry juice cocktail (Ocean Spray®). According to Vinson et al. (2005), dry cranberries contain 870 mg catechin equivalents/100 g total phenols. Most of the phenolics (91.3–96.2%) in cranberries are present in a soluble free form (Sun et al. 2002; Vinson et al. 2005) and are among few fruits containing a large proportion of free phenolics versus phenolics bound to carbohydrates and proteins. The two major classes of phenolics identified in cranberries are phenolic acids (44%) and flavonoids (56%) in freshly squeezed juice (Chen et al. 2001). The most abundant phenolic acid identified by Zuo et al. (2002) was benzoic acid (4.7 g/kg fresh weight) followed by the hydroxycinnamic acids *p*-coumaric (0.25 g/kg fresh wt), sinapic (0.21 g/kg), caffeic (0.16 g/kg), and ferulic acids (0.088 g/kg). Some assays report cranberries as yielding among the highest concentration of

phenolic compounds of common fruits including apple, red grape, strawberry, pineapple, banana, peach, lemon, orange, pear, and grapefruit, which similarly correlated with the highest antioxidant activity (TOSC assay 177.9+/- 4.3 µmol vitamin C equivalent of fruit) and antiproliferative effects (against human liver cells; EC50 of 14.5 +/- 0.5 mg/mL) of the same fruits (Sun et al. 2002).

Antioxidants Effects of Cranberry

A number of human intervention studies investigated the antioxidant activity of either cranberry juice, capsules of dried cranberry juice, or dried cranberry extract. The length of the intervention period was relatively short, including acute (4–7 h) and sub-chronic (2–12 wk) studies. The antioxidant capacity was assessed by measuring plasma oxidized LDL or by using a variety of in vitro assays (FRAP, metmyoglobin, AOPP, and Fremy's salt). Two acute studies showed a beneficial effect for drinking cranberry juice (240–500 mL, single dose) on plasma antioxidant capacity, by reducing Fe^{+3} (FRAP assay) (Pedersen et al. 2000; Vinson et al. 2008) and Fremy's salt (Pedersen et al. 2000). However, the results across the literature are inconsistent. Subjects consuming greater amounts of cranberry juice (750 mL/d) for a longer period of time (two weeks) did not show an increase in plasma antioxidant capacity as measured by FRAP assay, the same assay used in the acute study (Duthie et al. 2006). Blood taken after an overnight fast showed no significant differences in the levels of total phenolic or total anthocyanin content (Duthie et al. 2006). The main difference among the acute and longer-term studies was the timing of blood draws from the subjects. In the acute studies, blood was drawn a few hours after the cranberry juice was consumed, while in the two-week study, blood was drawn after an overnight fast, suggesting immediate but not long-term antioxidant effects.

The antioxidant capacity of cranberry has been strongly correlated with its phenolic content in in vitro assays. All three of the aforementioned studies used cranberry juice fortified with vitamin C, which may contribute to some antioxidant activity, though a different study by Vinson et al. (2008) showed that the antioxidant capacity of cranberry juice is not based solely on its vitamin C content. Subjects who consumed 240 mL of cranberry juice containing vitamin C (80 mg) and high fructose corn syrup had an increase in their plasma antioxidant capacity up to 6 hours after intake, while subjects drinking the control juice, which contained high fructose syrup with the same amount of vitamin C, was pro-oxidant. Unfortunately, plasma levels of vitamin C were not assessed in this study.

In a long-term placebo controlled study, Basu et al. (2011) studied 36 women with metabolic syndrome for 12 weeks and found that the subjects consuming 240 mL of low calorie cranberry juice had significantly higher plasma antioxidant capacity and lower plasma malondialdehyde (MDA), a marker for oxidative stress. A cranberry leaf extract beverage was administered to 12 healthy humans (6 males/6 females). Participants consumed a low-polyphenol diet 2 days before each sampling and there was a 1-week washout period between beverages. Plasma glutathione peroxidase activity was significantly elevated ($P < 0.05$) and low calorie cranberry juice cocktail consumption (Ocean Spray; yielding 229 mg total phenolics, 119 mg proanthocyanidins, and 17.4 mg total anthocyanins based on 240 mL of juice product) significantly increased ($P < 0.05$) glutathione concentrations and superoxide dismutase activity compared with placebo. Cranberry leaf extract beverage and low calorie Cranberry Juice Cocktail consumption had no effect on the inflammatory biomarkers measured as compared with placebo. Neither the low calorie cranberry juice nor the leaf extract (with anthocyanins) had a significant effect on plasma 8-OHdG concentrations (Mathison et al. 2014). Similar findings were reported by Duthie et al. (2006).

In the study by Pedersen et al. (2000), nine female subjects consumed 500 mL of Cranberry Juice Cocktail® (Ocean Spray®). Increased plasma antioxidant capacity and a corresponding increase in plasma phenolic concentrations was observed, but the authors attributed the higher antioxidant capacity to be primarily due to the juice being fortified with vitamin C.

In a study of Valentova et al. (2007), 65 healthy women were given either 400 or 1200 mg of a dried cranberry juice containing 3% total phenolics daily for 8 weeks and were assessed for protein oxidation. No significant antioxidant effect was observed at the 400 mg dose, whereas the 1200 mg dose did result in a significant ($P < 0.05$) drop in protein oxidation leading the authors to suggest an antiatherogenic effect. The 1200 mg dose was estimated to yield a daily intake of 35 mg total phenols, 7.8 mg of anthocyanins, and 14.4 mg of PACs. In this particular study, vitamin C was ruled out as contributing significantly to the observed antioxidant effect.

In the randomized, double-blind, placebo-controlled trial of Basu et al. (2011), subjects ($n = 15$) with metabolic syndrome were given either low calorie Cranberry Juice Cocktail® (480 mL/day; Ocean Spray® yielding 229 mg total phenolics and 12.4 mg total anthocyanins) or placebo (480 mL/day) for 8 weeks. Compared to placebo, which showed no effect, cranberry juice significantly ($P < 0.05$) increased plasma antioxidant capacity (1.5 ± 0.6 to 2.2 ± 0.4 µmol/L [means ± SD]) and decreased oxidized low-density lipoprotein and malondialdehyde (120.4 ± 31.0 to 80.4 ± 34.6 U/L and 3.4 ± 1.1 to 1.7 ± 0.7 µmol/L, respectively [means ± SD].

Oxidized LDL-C

Oxidation of LDL particles in the arterial wall is considered a key event in the development of atherosclerosis and polyphenolic compounds (e.g., flavonoids) commonly found in fruits and vegetables possess strong antioxidant activity. As noted above, part of the effects associated with decreased risk of cardiovasculature morbidity and mortality are due to the antioxidant activity of polyphenols. Mechanisms to prevent oxLDL are diverse and include anti-oxidative mechanisms such as scavenging of free radicals, chelation of metals, sparing of vitamin E and carotenoids in the LDL particle, increase in redox state, down-regulation of oxidation path-

ways in macrophage, endothelial cells, and smooth muscle cells; inhibition of oxidative enzymes; changes in LDL levels; and changes in oxLDL scavenging and elimination (Aviram and Fuhrman 1998; McKay and Blumberg 2007; Reed 2002). Although binding of antioxidants to the LDL particle may be more effective, general increases in plasma antioxidant levels may be relevant to anti-oxidative effects as some increase may occur within the atherosclerotic plaque (Reed 2002; Steinberg 2009). While there is a strong correlation between circulating oxLDL levels and cardiovascular disease such that it has been proposed as a risk factor to predict disease, there is little evidence that lowering oxLDL levels prevent disease (Holvoet 2008).

Human Clinical Studies

The ability of cranberry products to reduce oxLDL was investigated in 6 clinical trials. Four of the 6 trials reported decreased oxLDL levels. In an intervention study, Ruel et al. (2005) reported a reduction in plasma oxLDL levels (-9.9% ± 17.8%, P =0.0131) and an increase in antioxidant capacity (+6.5% ± 10.3%, P =0.0140) from baseline after consumption of low-calorie cranberry juice (7 mL/kg body weight per day) for 14 days in 21 male subjects. The study did not include a placebo control. No improvement of plasma lipoprotein-lipid or inflammatory marker concentrations was observed and so the physiological relevance of this finding requires further investigation, though the effect is suggestive of being cardio protective.

In a later study, Ruel et al. (2008) reported significant dose-response decreases in oxLDL from baseline after challenge with light cranberry juice for 12 weeks in 30 subjects. Subjects were asked to consume increasing daily doses of cranberry juice cocktail (125, 250, and 500 mL/d) over 3 successive periods of 4 weeks; significance was reached at 250 mL/d (P <0.05) and 500 mL/d (P <0.001). The study also found significant decreases in intercellular adhesion molecule-1 (ICAM-1) (P <0.0001) and vascular cell adhesion molecule-1 (VCAM-1) (P <0.05), two other markers of inflammation.

Lee et al. (2008) investigated a number of markers associated with cardiovascular disease risk including total cholesterol, LDL/HDL levels, and oxLDL in type-2 diabetics in 30 subjects. Cranberry extract powder was administered at doses of three 500 mg capsules per day. After 12 weeks, LDL was significantly decreased from (-0.4 ± 0.1 vs 0.2 ± 0.1 mmol/L, P <0.001) and total cholesterol and total HDL cholesterol ratio also decreased significantly (P <0.001 and P =0.032, respectively) over placebo. While there was a trend towards a reduction in oxLDL, it was not significant.

Basu et al. (2011) investigated the effects of low calorie cranberry juice (480 mL/day) or placebo (480 mL/day) for 8 weeks on a number of cardiovascular risk factors including oxLDL in women (n = 36) with metabolic syndrome. Compared to placebo, cranberry juice significantly increased plasma antioxidant capacity (1.5 ± 0.6 to 2.2 ± 0.4 µmol/L [means ± SD], P <0.05) and decreased oxLDL and malondialdehyde (120.4 ± 31.0 to 80.4 ± 34.6 U/L and 3.4 ± 1.1 to 1.7 ± 0.7 µmol/L, respectively [means ± SD], P <0.05) at 8 weeks. In a placebo-controlled study by Juturu et al. (2011a), the effects of a low-calorie cranberry beverage on oxLDL were investigated on 140 subjects. While there was no effect of oxLDL, when the cranberry group was compared to placebo, within-group comparison of week 12 to week zero showed that oxLDL was decreased in the cranberry group and the decrease was 5-fold greater than that in the placebo group. In another study by Flammer et al. (2013), no change in oxLDL was reported in 32 subjects given low-calorie cranberry juice cocktail (230 mL twice daily). As this was a secondary endpoint, this and other similarly designed studies may have been underpowered to detect changes in oxLDL levels, though a trending is evident for a cardioprotective effect.

Another double-blind, placebo-controlled study similarly showed that consumption of low-calorie cranberry juice cocktail (240 mL daily for 8 weeks) improved several risk factors of cardiovascular disease in adults (n = 29 in treatment group; n = 27 in placebo group), including in triglycerides, C-reactive protein, glucose, insulin resistance, and diastolic blood pressure. In subjects consuming the cranberry juice, median CRP concentrations were 44% lower and had significantly lower fasting plasma glucose concentrations than the placebo group. Fasting serum insulin and other markers of inflammation (IL-6, IL-10, IL-1β, and TNF-α) were not significantly different between groups. The authors suggested that the magnitude of the change in blood pressure observed is consistent with that obtained with a low sodium diet and other dietary interventions (e.g., Dietary Approaches to Stop Hypertension Trial diet) and resulted in an estimated 15% decrease in risk of stroke and a 10% decrease in risk of coronary heart disease (Novotny et al. 2015).

Animal Studies, In Vitro, and Ex Vivo Assays

The antioxidant potency of cranberry juice was investigated in 2 animal studies (Deyhim et al. 2007; Villareal 2007) using orchidectomized (ORX) rats. Orchidectomized (ORX) rats are good models for addressing issues in cardiovascular disease in general because they have high cholesterol and triglyceride levels and a suppressed antioxidant capacity. Both studies used the same design: cranberry juice at concentrations of 27% and 45% administered for 4 months. At the end of the treatment period, cranberry juice reversed the orchidectomy-induced antioxidant suppression as evidenced by reduced plasma nitrite plus nitrate and decreased MDA in a dose-dependent manner (Deyhim et al. 2007). However, cranberry juice had no impact on liver and plasma cholesterol levels of ORX rats, only reducing triglycerides in liver but not in plasma. The authors concluded that drinking cranberry juice increased antioxidant status while decreasing peroxidation without affecting cholesterol homeostasis, despite a significant decrease in triglyceride concentration in the liver. In another publication of the same design, the authors reported that cranberry juice (27%) increased plasma antioxidant capacity (P <0.05) and improved red blood cell (RBC) resistance slightly, and cranberry juice (45%) protected RBC against pro-oxidant-

induced hemolysis compared to control ($P < 0.05$) (Villareal 2007).

The in vitro antioxidant activity of cranberry has shown some correlation with compounds found in cranberry. For example, total phenolic content has shown good correlation with the DPPH ($R^2 = 0.72$) (Amakura et al. 2000) and the ORAC ($R^2 = 0.76$) assays (Kalt et al. 2007). Anthocyanin content was weakly correlated ($R^2 = 0.43$) and PACs had no correlation ($R^2 = 0.12$) with the ORAC assay (Kalt et al. 2007). Although the results on PACs are inconsistent; another study reported a proanthocyanidin fraction of cranberries accounting for up to 54% of the total antioxidant activity measured by the ORAC assay (Prior et al. 2001).

A variety of studies have compared the in vitro antioxidant activity of cranberry and other fruits (see Khoo and Falk 2014). In different studies, cranberry showed the highest antioxidant activity among 13 berries and 24 different fruits when measured by ORAC (Boivin et al. 2007; Wu et al. 2004) and TOSC assays (Sun et al. 2002). Sun et al. (2002) reported that cranberry had the highest antioxidant activity, total phenolic content (527.2 ± 21.5 mg/100 g), and free phenolic (507.0 ± 21.1 mg/100 g) content compared to ten other fruits. The extraction method across the studies differed and may have contributed to the findings and one study reported that cranberry elicits the highest in vitro antioxidant capacity during the green stage (Celik et al. 2008).

Sun et al. (2014) demonstrated that a proanthocyanidin-enriched cranberry extract (Decas Botanical Synergies; Carver, MA), increased the lifespan of worms and flies when added as 2% of the diet by weight/volume. The extract included ≥4.0% proanthocyanidin. The mechanism underlying the prolongevity effects of cranberry was associated with reductions in a number of markers of oxidative stress and insulin signaling including reductions in phosphorylation of extra-cellular signal-regulated kinases (ERK), lipid peroxidation, and mitogen-activated protein kinase (MAPK) signaling, and slight increases in phosphorylation of protein kinase B, a kinase involved with cellular survival by decreasing apoptosis. In this study, cranberry supplementation extended the lifespan of test models in all life stages and was interpreted by the investigators as supporting a longevity promoting effect of cranberry. Zhu et al. (2011), using the same preparation and testing model, found cranberry to delay age related functional decline of pancreatic cells in rats.

Of three studies using cell culture, two reported positive effects for cranberry components. Youdim et al. (2002) investigated the protective effects of anthocyanin and hydroxycinnamic acids (HCA) from cranberry against a H_2O_2-challenge to human microvascular endothelial cells (HMVEC). The results showed a significant dose response in the reduction of dichlorofluorescein susceptibility to H_2O_2 in cells following supplementation with HCA ($P < 0.05$) but not with anthocyanins. On the other hand, anthocyanins were more protective than HCA against inflammatory insults. Joseph et al. (2004) measured calcium flux and cell viability in cos-7 cells. Cranberry did not protect cell viability after exposure to dopamine (1 mM, 4h) or Aβ 25–35 (100 µM, 24h), but did protect against calcium flux. Wolfe and Liu (2007) developed a new assay called the cellular antioxidant activity assay (CAA), which they report as a more biologically relevant method than in vitro assays because it accounts for some aspects of uptake, metabolism, and location of antioxidant compounds within cells. Extracts of several berries were analyzed by this method and cranberry had the second highest antioxidant activity with $EC_{50} = 11.31 \pm 0.29$ mg/mL (CV = 2.59%), being lower than blueberry, but higher than apple and red and green grapes.

Although the bioavailability of flavonoids is low (see Pharmacokinetics), a review by Stevenson and Hurst (2007) showed that the signal transduction mechanisms leading to anti-inflammatory actions are more relevant to the bioactivity of these compounds. Research over the past decade has delineated the role of flavonoids in modulating major signaling pathways, such as inhibiting NF-kB activation, which attenuates the inflammatory response induced through NF-kB pathways and for activation of MAP Kinase (mitogen activator kinase), which is involved in vascular gene regulation (Dezeil et al. 2010). Modulation of these two pathways are the proposed mechanisms by which flavonoids such as quercetin and catechin can alter expression of important markers of cardiovascular health, including iNOS, COX-2, advanced glycation end products, and the adhesion molecules VCAM-1 and ICAM-1. Guha et al. (2013) showed that cranberry extracts influence oxidative stress through modulation of daf-16 and osr-1 in a *C. elegans* model.

Cranberry action against human LDL oxidation was first demonstrated by Wilson et al. (1998) using a preparation yielding 1548 mg gallic acid equivalent/liter (Northland Cranberries Inc, Wisconsin Rapids, WI). Because oxLDL changes its electrical charge and the migration of the particle in an electric current, the investigators measured the relative electrophoretic mobility (REM) of LDL treated with cranberry relative to the LDL oxidized by cupric ions in the absence of an antioxidant. LDL from 5 male volunteers was incubated with cranberry homogenate diluted at 0%, 0.100%, 0.050%, 0.010%, or 0.005% and further oxidized by cupric sulfate. Compared to the REM for the oxidized LDL without cranberry 100%, the REM for cranberry homogenate at 0.050% and 0.100% dilutions were significantly lower ($P < 0.001$) at 82.2 ± 2.9% and 72.4 ± 3.5%, respectively. Cranberry at 0.100% dilution inhibited thiobarbituric acid reactive substances (TBARS) formation significantly ($P < 0.001$) from 69.0 ± 7.5 to 13.1 ± 7.2 MDA/100 µL solution.

Vinson et al. (2001) evaluated the ex vivo antioxidant activity of cranberry and apple homogenates. The concentration of 102 µM for cranberry and 114 µM for apple was required to increase the lag time of oxidation by 50% (CLT_{50}) of LDL plus very low-density lipoprotein (VLDL). Cranberry had a higher antioxidant capacity than apple at a lower concentration (50 µM) while similar results were obtained for cranberry and apple at a higher concentration (100 µM). In another study, the same research group reported the concentration to inhibit LDL and VLDL oxidation by 50% (IC_{50}) to be 0.75 and 0.44 µM for dried and frozen cranberry, which were much lower than those values for ascorbic acid (1.47 µM) and tocopherol (2.38 µM)

(Vinson et al. 2008). Cranberry, cranberry juice (100%), and cranberry juice cocktail (27%) had IC_{50} values of 1.54 µM, 2.16 µM, and 3.77 µM, respectively. In this study, dried and frozen cranberry showed higher antioxidant activity compared to vitamin C and vitamin E. The lag time of LDL oxidation increased in a dose-dependent manner: at 100 µM of cranberry extract there was a 2-fold increase in the time required for LDL to be oxidized, while at 200 µM the time increased by 3-fold. Cranberry extract of Early Black variety inhibited and prolonged the lag time of LDL oxidation in a dose-dependent manner (Chu and Liu 2005). Doses of 1, 2.5, and 5 mg/mL inhibited LDL oxidation by 50.7%, 71.4%, and 94.7%, respectively, and delayed oxidation by 2, 4, and 6 hours, respectively. Cranberry extract (10 mg/mL) completely inhibited LDL oxidation. The EC50 value as measured by the LDL Oxidation Model for Antioxidant Capacity (LOMAC) was 1.46 mg/mL. The EC50 of LDL oxidation for vitamin C was 84.1 µM and for vitamin E was 125.7 µM, meaning that the antioxidant activity of 100 g cranberries (~ 1 serving, 95 g) against LDL oxidation was equivalent to 1000 mg vitamin C or 3700 mg vitamin E. Cranberry also induced LDL receptors and increased cholesterol uptake by hepatocytes.

Comparing the effect of various cranberry fractions, Porter et al. (2001) reported that fractions containing PACs were the most effective in increasing the lag time of LDL oxidation. The degree of polymerization and the nature of the interflavan bond influenced antioxidant properties; pentamer through nonamer PACs with more double linked A-type interflavan bonds had higher antioxidant potency. There was a significant ($P < 0.05$) increase in the lag time of LDL oxidation of flavonol fraction of cranberry compared to the control, but no improvement was observed with hydroxycinnamic acid fraction.

Isolated compounds from cranberry of 'Stevens' variety were evaluated for their LDL oxidation inhibition potency by using the VLDL + LDL assay (Yan et al. 2002). The following EC_{50} values were reported for cyanidin 3-galactoside (1.45 µM) > quercetin dihydrate (2.33 µM) > myricetin (3.35 µM) > myricetin 3-arabinoside (3.54 µM) > quercetin 3-galactoside (4.32 µM) > myricetin 3-galactoside (5.53 µM) > quercetin 3-arabinoside (6.13 µM) > quercetin 3-rhamnoside (9.2 µM). The results show that the compounds cyanidin 3-galactoside and quercetin dihydrate isolated from cranberry were more effective in scavenging radicals and preventing LDL oxidation than vitamin E (EC_{50} = 2.92 µM).

Seeram et al. (2008) evaluated the ability of cranberry juice to inhibit LDL oxidation by the peroxides and MDA methods. Three brands of cranberry juices were tested (Northland 100% Cranberry Juice, RW Knudsen Just Cranberry, and Ocean Spray Pure Cranberry). On average, cranberry juices inhibited LDL oxidation by 39%. Both methods had similar results, but results from different juice brands had a large variation in inhibition of LDL oxidation (peroxides) ranging from 18 to 58% and 21 to 50% inhibition of LDL oxidation (malondialdehydes). In this study, cranberry was in the median range of antioxidant effects relative to other fruit juices. In a study of Chu and Liu (2005), cranberry extract was shown to increase the surface expression of LDL receptors and uptake of LDL-C in cultured hepatocytes, which would be expected to lower plasma LDL-C concentrations. In addition to the antioxidant activity demonstrated for cranberry juice, cold-pressed cranberry seed oil significantly ($P < 0.05$) protected human LDL from Cu^{2+}-induced oxidation, with reductions in TBARS of 2.84 mg/g oil (Yu et al. 2005).

Dyslipidemia

Decreases in total cholesterol (Total-C), LDL-C, Total-C:HDL-C ratio, and triglycerides, as well as increases in HDL-C, are considered salutary. Clinical trials with cranberry showed that LDL-C was decreased in 2 studies of weak to moderate power and short duration (Caron et al. 2005; Vinson et al. 2003) in diabetic subjects (Lee et al. 2008), and in a within-group analysis of the Juturu et al. (2011a) trial (trend only). In the remaining 9 studies, LDL was either unchanged or not measured (Basu et al. 2011; Chambers and Camire 2003; Dohadwala 2011; Juturu et al. 2011a, 2011b; Novotny et al. 2012a; Ruel et al. 2005, 2006; Ruel and Couillard 2007).

HDL-C was increased in 5 studies (Dohadwala 2011; Juturu et al. 2011a; Ruel et al. 2005, 2006; Vinson et al. 2003), in a within-group analysis (Novotny et al. 2012a) (trend only), and unchanged or not measured in 8 studies (Basu et al. 2011; Caron et al. 2005; Chambers and Camire 2003; Duthie et al. 2006; Flammer et al. 2013; Juturu et al. 2011a; Lee et al. 2008; Ruel et al. 2005). There may have been a correlation between duration of study and positive effect, as well as the health status of subjects. The positive studies were generally conducted for 12 weeks or longer and the unchanged studies were generally of shorter duration or utilized diabetic subjects or subjects with metabolic syndrome. Only 3 studies measured apolipoprotein (apoA-1), the HDL-C carrier protein, and 2 of the 3 reported increased levels supporting the effect seen in the increased HDL-C levels (Juturu et al. 2011a; Ruel et al. 2006).

All but one study measuring triglycerides reported that triglycerides was unchanged or increased (if the cranberry juice contained high fructose corn syrup). Novotny et al. (2012a) observed a decrease in triglycerides after 8 weeks of treatment with low-calorie cranberry juice. In ovariectomized rats treated with cranberry juice at 7 mg/kg for 8 weeks, Yung et al. (2012) observed decreased Total-C, LDL-C, LDL-C/HDL-C ratio, and triglycerides levels.

Vascular Health/Hypertension

Human Clinical Studies

Vasodilation is critical to reducing blood pressure and increasing blood flow. Impairment of vasodilation is a hallmark of cardiovascular disease. Vasodilation can be mediated by nitric oxide (NO) produced from the activity of NO synthase. Inhibition of angiotensin converting enzyme (ACE-1) reduces formation of the vasoconstrictor, angiotensin II; therefore, high ACE-1 inhibitory activity demon-

Table 13 Comparison of in vitro antioxidant activities of cranberry and other fruits

Rank	ORAC (μmol TE/mL)	ORAC (μmol TE/mL)	ORAC (μmol TE/mL)	ORAC (μmol TE/mL)	TOSC (μmol vit C/mL)	Radicals O2 and H2O2 (% inhibition)	TBARS PAOXI x 10-3 (IC50 μM)	DPPH assay (EC50 mg/mL)
	Boivin et al. 2007	Wu et al. 2004	Prior et al. 2001	Kalt et al. 2007	Sun et al. 2002	Wang and Jiao 2000	Vinson 2001	Amakura et al. 2000
1	Cranberry (26.9)	Cranberry (94.56)	Blueberry (44.5)	Partridgeberry (116)	Cranberry (177)	Blackberry (64–66)	Cherry (0.10)	Blackberry (2.06)
2	Strawberry (22.6)	Blueberry (92.60)	Cranberry (37.4)	Bilberry (95.4)	Apple (97.6)	Strawberry (64–65)	Red grape (0.27)	Black currant (2.45)
3	Raspberry (≈22.5)	Black Plums (73.39)	Blueberry (35.8)	Blueberry (75.6)	Red grape (64.7)	Blueberry (60–61)	Blueberry (0.22)	Lingonberry (2.64)
4	Black currant (≈18.7)	Plums (62.39)		Lingonberry (73.4)	Strawberry (64.4)	Cranberry (59–60)	Strawberry (0.12)	Strawberry (4.52)
5	Blackberry (≈18.5)	Blueberry (62.20)		Blueberry (68.4)	Peach (49.5)	Raspberry (57–61)	White grape (0.20)	Raspberry (4.63)
6	Serviceberry (14.6)	Blackberry (53.48)		Blueberry (50.5)	Lemon (42.8)		Cranberry (0.75)	Bayberry (4.86)
7	Blueberry (≈10.3)	Raspberry (49.25)		Cranberry (45.1)	Pear (34.2)		Banana (0.39)	Cranberry (6.11)

Antioxidant activities are ranked from highest to lowest, with number 1 being the highest.

The IC_{50} represents the concentration of a compound that is required for 50% inhibition. The EC_{50} represents the plasma concentration/AUC required for obtaining 50% of the maximum effect in vivo.

Source: Modified from Khoo and Falk 2014.

strates a potential role in management of hypertension.

Novotny et al. (2012b) observed a decrease in diastolic blood pressure in an 8-week, randomized, double-blind, placebo-controlled study on 56 subjects consuming low-calorie cranberry juice (unknown dose), but no change in systolic blood pressure. Diastolic blood pressure was decreased by 3 mm Hg over the 8-week period (within group analysis) and by 4 mm Hg at 8 weeks (compared to placebo). Dohadwala et al. (2011) reported on an acute treatment study using 15 subjects with proven coronary heart disease (CHD) without placebo control, and a chronic treatment study on 44 subjects with proven CHD in a randomized, double-blind, placebo-controlled crossover trial, both using a double-strength cranberry juice (54% juice yielding 835 mg polyphenols and 94 mg anthocyanins; 480 mL/d) for 4 weeks (2-week clearance before crossover). Vascular function was measured in both parts of the study. In the acute treatment study, brachial artery flow-mediated dilation was significantly (P =0.01) improved 4 hours after the initial cranberry dose, and pulse amplitude tonometry (lnPAT ratio) was significantly (P =0.001) improved both 2 hours and 4 hours after cranberry consumption. A modest decrease in resting brachial artery blood flow was also reported. In the chronic treatment study, only carotid-radial pulse wave velocity, a measure of arterial stiffness, an increasingly important risk factor, was significantly (P =0.003) improved 12 hours after cranberry consumption. No effects were found in brachial diameter, flow-mediated dilation, or hyperemic flow. The discrepancies between the acute and chronic studies may indicate that the effects do not persist for 12 hours or more after the challenge.

Flammer et al. (2013) observed no change in reactive hyperemia-peripheral arterial tonometry (RH-PAT) index in patients with peripheral arterial dysfunction and cardiovascular risk factors after 4 months of consuming a double-strength (54%), low-calorie cranberry juice (230 mL twice daily). RH-PAT mainly assesses the microcirculation as distinguished from brachial artery measures. There was no change in blood pressure. Although no effects were observed in the numbers of circulating endothelial progenitor cells (EPC), the researchers observed a decrease in endothelial progenitor cells expressing osteocalcin markers. Elevated EPC osteocalcin may be associated with abnormal repair and vascular calcification in atherosclerotic plaque formation.

Cassidy et al. (2011) studied participants from the Nurses' Health and Health Professionals Follow-up studies and found that participants in the highest quintile of anthocyanin intake (predominantly from blueberries and strawberries) had an 8% reduction in risk of hypertension (relative risk [RR]: 0.92; 95% CI: 0.86, 0.98; P =0.03) compared with that for participants in the lowest quintile of anthocyanin intake; in participants <60 y of age; and 0.96 (0.91, 1.02) in participants >60 y of age (for age interaction P =0.02).

Seven studies reported no effects on either systolic blood pressure (SBP) or diastolic blood pressure (DBP) after challenge with cranberry products, potentially due to lack of pharmacological relevance, the administration of ineffective products, inadequate study design, methodology, or lack of statistical power (Basu et al. 2011; Dohadwala et al. 2011; Flammer et al. 2013; Hakkinen and Auriola 1998; Juturu et al. 2011a; Ruel and Couillard 2005; Ruel et al. 2005, 2007).

Animal and Ex Vivo Studies

In one animal study, cranberry juice infusion at 1:100 dilution of estimated blood volume reduced mean arterial blood pressure in anaesthetized rats by 16% compared to baseline (Maher et al. 2000). However, heart rate increased during the study to a greater extent for rats infused with cranberry juice than rats infused with saline. In the same study, intact rat aortic rings that had been exposed to phenylephrine underwent a 56.7 ± 0.26% relaxation after exposure to cranberry juice; denuded rat aortic rings showed an 8.9 ± 0.06% relaxation. This vasodilatory effect was mediated by NO, as treatment with the competitive inhibitor of NO synthase, N^{ω}-nitro-L-arginine methyl ester (L-NAME), reversed cranberry-induced vasodilation of intact rings (0.54 g) and increased tension in denuded rings (0.04 g). L-arginine reversed the effects of N^{ω}-nitro-L-arginine methyl ester (L-NAME).

In ovariectomized rats treated with cranberry juice at 7 mg/kg for 8 weeks, Yung et al. (2012) observed improved endothelium-dependent relaxation in aortic rings and restored serum levels of eNOS, renin-angiotensin system markers, and markers of NADPH oxidase-mediated oxidative stress. A water extract of 100% cranberry was the strongest inhibitor of ACE-1 when compared with extracts containing cranberry with oregano (*Origanum vulgare*), rosemary (*Rosmarinus officinalis*), and rhodiola (*Rhodiola rosea*). Of the combined extracts, the extract containing 75% cranberry and 25% rosemary had the highest ACE-1 inhibitory activity. The data suggest that cranberry juice reduced blood pressure in rats, relaxed rat aortic rings in a NO-mediated mechanism, and inhibited production of the vasoconstrictor angiotensin II.

Caton et al. (2010) compared the effects of different cranberry juice preparations to other fruit extracts on the production of endothelin-1 (ET-1) in cultured bovine aortic endothelial cells. The decrease in ET-1 synthesis and ET-1 mRNA were correlated with oligomeric procyanidin content; monomer, dimer, and trimer had little effect, while tetramer, pentamer, hexamer, and heptamer produced concentration-dependent decreases with decreasing IC_{50} levels, respectively (e.g., IC_{50} value equivalent to ≈ 2 µL/mL). The effect was not as great as that observed for red wine, but was 10-fold greater than that observed for green tea (*Camellia sinensis)*. In the same study, Kruppel-like factor 2 (KLF2) production, a key endothelial transcription factor with anti-atherosclerotic activity, was inversely correlated with the ET-1 changes. The procyanidin-rich cranberry extracts induced concomitant morphological changes with reorganization of the actin cytoskeleton. The changes were independent of antioxidant activity.

The data on effects of cranberry and cranberry foods on vascular/endothelial health are somewhat limited, but studies with other flavonol-rich foods support the potential for cranberry flavonols to enhance vascular/endothelial function. Such data have to be interpreted with caution because the bioavailability and bioactivity of flavonols and their oligomers (procyanidins) are influenced by their chemical composition, isomeric form, and chain length, as well as interactions with other food constituents and metabolites (Wallace et al. 2009). Flavonols from other food sources have been shown to regulate blood levels of NO, which plays a role in increasing vasodilation. Human and animal studies have shown that consumption of a flavonol-rich diet improves vascular health and blood flow for 1 to 30 days (Balzer et al. 2008; Fisher and Hollenberg 2005; Schroeter et al. 2006; Sorond et al. 2008). Flavonol-rich diets are also associated with reduced risk of hypertension (Buijsse et al. 2006; Hertog 1995).

Anti-platelet Aggregation

Flavonoids have anti-platelet activation and anti-platelet aggregation abilities (Cos et al. 2004) that may occur through mechanisms such as increasing prostacyclin (Facino et al. 1999), inhibiting phosphodiesterases that degrade cAMP, and up-regulating nitric oxide (Freedman et al. 2001).

One human interventional study examined the ability of cranberry juice to decrease platelet-rich plasma aggregation responses. The study showed that cranberry juice consumption reversed platelet-rich aggregation responses to adenosine diphosphate. The lack of detail in the study made it difficult to evaluate the results (Wilson and Marley 2001). Although there are few studies examining cranberries or cranberry products on platelet aggregation, there is considerable supportive evidence related to inhibition of platelet aggregation and anti-thrombotic activity using other flavonoid-rich foods (Akhlaghi and Bandy 2009; Nardini et al. 2007; Natella et al. 2006; Reed 2002) but, as previously stated, such evidence should be interpreted with caution due to the variability in flavonoid content, bioavailability, and interactions with other food components.

Anti-inflammatory Effects

The inflammatory response comprises a complex signaling array that includes inflammatory signaling molecules known as cytokines and chemokines, immune cells, such as neutrophils and macrophages, cellular adhesion molecules, matrix metalloproteinases, and various complex intracellular regulatory pathways (Packard et al. 2009; Reed et al. 2002). Inflammation is a primary mechanism underlying the pathophysiology of cardiovascular disease (Pearson et al. 2003).

Compounds in cranberry may inhibit atherosclerosis through inhibiting inflammation in the vascular system (Neto 2007a). Anti-inflammatory actions can reduce vascular permeability and reduce adherence to the endothelium. The in vitro data show a consistent inhibition of cytokines, chemokines, and cellular adhesion molecules by cranberry compounds. The majority of studies examined the effects of periodontal pathogens and human gingival fibroblasts or macrophages, which showed a beneficial activity for cranberry (PACs) (Faghali et al. 2012). Possible mechanisms of action of cranberry PACs include the inhibition of bacterial and host-derived proteolytic enzymes, host inflammatory response, and osteoclast differentiation and activity. However, only 2 of these studies examined endothelial cells or aortic cells.

The evidence for a connection between cranberry compounds and the inflammatory response and atherosclerosis in clinical trials is still lacking. There is one weak study reporting a reduction in ICAM-1 (Ruel et al. 2008), one well-designed study reporting an increase in ICAM-1 (Juturu et al. 2011a) and 2 well-designed studies reporting no effect after 12 weeks of exposure to cranberry products (Dohadwala et al. 2011). One well-designed study observed an increase in sICAM-1 compared to baseline and a decrease in C-reactive protein (CRP) compared to placebo (Novotny et al. 2012a). No effects were reported for VCAM-1, or E-selectin. Similar reductions in CRP were noted by Duffey and Sutherland (2015) from data drawn from the National Health and Nutrition Examination Survey (2005–2008). Adults (n = 330 of a total of 10,334) who consumed approximately 14 ounces of cranberry juice cocktail daily had significantly lower CRP levels than non-consumers (P =0.015). Flammer et al. (2013) found that, although the endothelial function was not affected by cranberry juice consumption, the fraction of osteocalcin-expressing endothelial progenitor cells was decreased, which is a potential beneficial effect.

Summary

There is growing evidence from in vitro, ex vivo, animal, and human studies that foods and beverages rich in polyphenols, including cranberry and cranberry products, can support a healthy cardiovascular system. Well-controlled human studies specifically with cranberry or cranberry constituents support an effect of modulating cardiovascular risk factors that include hypertension, dyslipidemia, C-reactive protein, and oxidative stress markers such as oxidation of LDL cholesterol.

Numerous studies specifically demonstrate the in vitro and in vivo antioxidant potential of cranberry and elucidate the pharmacokinetics of cranberry antioxidants and some studies show modulation of endogenous antioxidant systems (e.g., glutathione) in vivo. Most antioxidant assays of cranberry and its compounds were conducted with in vitro assays, which may not be predictive of in vivo antioxidant activity or changes in health status. Never the less, there is ample evidence for general and specific cardiovascular health benefits of cranberry and its compounds, most notably cranberry phenolics.

More research is needed to better define the amount and types of polyphenols involved in cardiovascular preventive mechanisms and the bioavailability of the specific flavonoids, including well-designed clinical trials containing larger numbers of subjects and longer exposure periods. Current research firmly establishes that polyphenols, such as those found in cranberry, contribute to the known benefits of consuming a diet rich in fruits and vegetables, and should be part of a healthy balanced lifestyle to maintain a healthy cardiovascular system.

Anticancer Properties of Cranberry

A number of compounds contained within cranberry have been studied and shown to have in vivo and in vitro anticancer activity. There are no clinical studies that investigated the use of cranberry for the prevention or treatment of cancer.

The only clinical work relevant to cancer involves studies demonstrating a potential for antioxidant activity (e.g., Duthie et al. 2006; Pedersen et al. 2000, among others). Preclinical research suggests potential anticancer activity associated with a variety of effects including antioxidant, antiangiogenic, cytotoxic, immune modulating, and phase II detoxification (see Neto 2007b; Neto et al. 2008). Limited animal data suggest a potential benefit of cranberry in tumor prevention and regression, most notably in bladder cancer, and a plethora of in vitro data suggest potential benefit in cancer prevention (see Neto et al. 2007b; Neto et al. 2008 for a review). While degradation of compounds during processing predictably can reduce efficacy in general, evaporation to obtain a cranberry juice concentrate has been specifically shown to result in a diminishment of anticancer activity (see Caillet et al. 2011; Cote et al. 2010).

Additionally, cranberry has been shown to inhibit *Helicobacter pylori*, which is a risk factor for gastric cancer (see Effects of Cranberry on *Helicobacter pylori*).

Human Studies

Although no clinical studies evaluating the effect of cranberry on development of specific cancers have been reported to date, a 2006 study of cranberry juice supplementation on antioxidant biomarkers measured endogenous and induced oxidative DNA damage in lymphocytes, a biomarker for carcinogenesis (Duthie et al. 2006). Twenty healthy female volunteers (age 18–40) consumed 750 mL cranberry juice/day or a placebo for 2 weeks. Fasted blood was collected 1 week prior to the study and at 0, 7, and 14 days. DNA strand breakage was assessed in isolated lymphocytes using alkaline single-cell gel electrophoresis, both in the presence and absence of 200 uM H_2O_2. No significant differences in endogenous or induced DNA strand breakage or levels of oxidized pyrimidines between treatment and control groups were found over the study period, suggesting that short-term supplementation with cranberry juice in young, healthy volunteers had no cytoprotective effect.

Animal Studies

Animal model studies suggest that cranberry treatment may be effective in reducing tumor incidence and severity of some cancers. A 2006 study reported that administration of a PACs-rich fraction (100 mg/kg body weight) from whole cranberries by intraperitoneal injection (10x over 24 d) decreased the rate of growth and size of DU145 prostate, HT-29 colon, and U87 glioblastoma explants in female Balb/c mice over a period of several months (Ferguson et al. 2006). A flavonoid-rich aqueous extract of cranberry press cake extract also inhibited growth of the glioblastoma, with a 40% reduction in the time required for tumors to reach milestone sizes observed for both treatments vs control. In a 2009 study, Balb/c nu/nu mice were injected with SGC-7901 human gastric cancer cells that had been pretreated for 48 hours with an 80% acetone extract of whole cranberries at doses of 5 to 40 mg/mL, which are concentrations sufficient

to cause significant cell death. Tumor xenograft development was delayed and tumor size and volume reduced by nearly 50% relative to control in the 20 mg/mL treatment group. No tumors developed in the 40 mg/mL treatment group (Liu et al. 2009). These doses substantially reduced proliferation and increased apoptosis in SGC-7901 cells after 48 h in vitro. The chemical composition of the extract was not reported.

The effect of non-dialyzable material (NDM) obtained by dialysis of cranberry juice on lymphoma development was investigated in immune competent, syngeneic mice (Hochman et al. 2008). Balb/c female mice inoculated with Rev-2-T-6 lymphoma cells received intraperitoneal injections at a nontoxic dose (7x for 2 weeks) and were monitored for up to 100 days after treatment. No tumors were detected in the cranberry-treated group throughout the study, whereas 80% of control mice developed palpable tumors. The NDM-treated mice generated antibodies against Rev-2-T-6 cells, suggesting an increase in immune response to the lymphoma. While cranberry NDM has not been fully characterized, its mass range is reported as >12 K and it is thought to be at least partly composed of PAC oligomers; the identities of its metabolites were not reported.

The effect of cranberry juice concentrate taken orally on bladder cancer was studied in female Fischer 344 rats. Tumors were induced with nitrosamine over 8 weeks, then doses of either 1.0 mL or 0.5 mL undiluted juice concentrate were administered daily via gavage for 6 months. At the end of the study, a 31% reduction in bladder tumor weight, and a 38% reduction in number of cancerous lesions occurred in the higher dosage group, compared to control (Prasain et al. 2008). The authors did not identify the active constituent, but were able to detect quercetin and methylquercetin in the bladder 12 hours after gavage. The findings suggest that metabolites of cranberry given orally are bioavailable to the bladder in sufficient quantity to inhibit tumorigenesis.

In Vitro Anticancer Studies

The first report of in vitro anticancer effects for *Vaccinium* species fruits appeared in 1996, showing that extracts of cranberry and other species of *Vaccinium* inhibited ornithine decarboxylase (ODC) expression and induced the xenobiotic Phase II detoxification enzyme quinone reductase (QR) (Bomser et al. 1996). Inhibition of MDA-MB-435 estrogen-receptor negative and MCF-7 estrogen receptor positive breast tumor cell growth was reported for cranberry juice (Guthrie 2000) and cranberry press cake extracts (Ferguson et al. 2004). In a comparison study of the soluble phenolic extracts of several common fruits, cranberry showed the strongest inhibition of HepG2 human liver cancer cell growth (Sun et al. 2002). A study of Martin et al. (2015) suggests that hepatoprotective activity may be due to the ability of cranberry polyphenols to modulate endogenous antioxidant defenses (e.g. modulation of glutathione, ROS, and MDA).

Apoptosis, cell cycle arrest, reduced migration and invasion of specific tumor cells

Investigation of whole cranberry and various constituents in a variety of tumor cell lines has shed some light on specificity and possible cellular mechanisms of action. Studies in prostate, esophageal, colon, ovarian, and other cell lines point to induction of apoptosis, cell cycle arrest, and modulation of signaling pathways linked to proliferation and migration of tumor cells.

Prostate: Inhibition of prostate tumor cell growth has been observed for whole cranberry extract, cranberry powder, polyphenolic extracts, PAC fractions, and ursolic acid derivatives isolated from the fruit. Several studies by Neto et al. (2006) employed extracts and PAC fractions from whole cranberry fruit, characterized by MALDI-TOF MS analysis to contain dimers through octamers of epicatechin, with one A-type linkage (Neto et al. 2006). Whole-cranberry fruit extract, a flavonol fraction containing primarily quercetin glycosides, and the PAC fraction reduced viability of androgen-independent DU145 prostate carcinoma cells by 50% over 24 h at concentrations between 10 to 50 mg/mL (MacLean et al. 2011). A possible mechanism of action is induction of apoptosis, which can occur by multiple pathways. A 24-hour treatment of DU145 cells (derived from brain metastasis and used in models of prostate cancer) with whole cranberry extract, flavonol, or PAC fractions for 24 hours at 10 to 50 µg/mL induced significant increases in apoptosis based on DNA fragmentation (MacLean et al. 2011). Protein expression measurements showed that whole-cranberry treatment increased release of cytochrome-C, required for apoptosome assembly, with associated upregulation of Par-4 and Bax, and proteolytic cleavage of Bid to tBid, from the mitochondria into the cytosol as early as 6 h after treatment, activating caspase-9. PAC and flavonol-enriched fractions also activated caspase-8 and caspase-9 six to twelve hours after treatment, contributing to increased apoptogenic activity (MacLean et al. 2011). Effects of whole-cranberry extract on the DU145 cell cycle include decreased cells in the G2-M phase, and increased cells in the G1 phase following 6 h treatment. These alterations in cell cycle were coupled with cell cycle associated proteins including CDK4 and cyclins A, B1, D1, and E and increased p27 expression (Deziel et al. 2012). In separate studies, treatment with an acidic methanol extract of whole cranberry also inhibited the growth of androgen-dependent LNCaP prostate cells, as well as several other cell lines; IC50 = 100 µg/mL for a 48-hour treatment of LNCaP (Seeram et al. 2006).

Cranberry was found to inhibit expression of matrix metalloproteinases (MMPs), gelatinases that degrade the extracellular matrix, promoting invasion, migration, and metastasis, a common occurrence in androgen-independent prostate cancers (Yousif et al. 2002). Whole- cranberry fruit extract was observed to inhibit MMP-2 and MMP-9 expression in DU145 cells at 100 to 500 µg/mL (Neto et al. 2006). Treatment of DU145 cells with PACs isolated from whole-cranberry fruit at 25 mg/mL rapidly and significantly reduced the activity of MMP-2 and -9 (Deziel et al. 2010), accompanied by increased expression of TIMP-2 (tissue inhibitor of MMP) and decreased expression of EMMPRIN

(extracellular MMP inducer). PAC treatment increased phosphorylation of p38, ERK1 and ERK2, signaling proteins associated with the mitogen-activated protein kinase (MAPK) pathway, and expression of signaling proteins in the phosphatidylinositol-3-kinase (PI-3) pathway (Deziel et al. 2010). Another cranberry constituent that strongly inhibited MMP-2 and MMP-9 expression in DU145 cells was ursolic acid, which was inhibitory at 10 µg/mL; its hydroxycinnamate esters inhibited MMP-2 by 50% at 1 µg/mL (Kondo et al. 2011).

Colon: Studies show that cranberry constituents, including ursolic acid and its esters (Kondo et al. 2011; Murphy et al. 2003), water-soluble polyphenolic extracts (Seeram et al. 2004), and oligomeric PACs (Liberty et al. 2009; Neto et al. 2006) inhibit the growth and proliferation of human colon cancer cell lines. As was observed with prostate tumor cells, the antiproliferative effects may be due in part to induction of apoptosis. Both ursolic acid and PACs induced a dose-dependent increase in apoptosis in HCT-116 and HT-29, both colon adenocarcinoma cells, based on DNA fragmentation (Liberty et al. 2009). A study by Parry et al. (2006) evaluated the antiproliferative activity of several berry seed flours on HT-29 cells. Seed flours are a by-product of cold-pressing the seeds to make seed oils and may be a good source of omega-3 fatty acids. The cranberry seed flour tested contained 6.8% oil by weight, and the oil was relatively high in polyunsaturated fatty acids including α-linolenic acid [18:3(n-3)] with over 30 g/100 g of oil. Treatment with an acetone extract of cranberry seed flour at doses of 3 mg/mL or 6 mg/mL seed flour equivalents reduced HT-29 cell proliferation by 75% and 39% respectively vs control after 24 hours (Parry et al. 2006). A variety of cranberry preparations (puree, depectinized puree, pomace, raw or filtered juice, and juice concentrate) were extracted with various solvent mixtures to yield water-soluble, apolar, and anthocyanin-rich fractions. The compositions of the extracts were not reported. Antiproliferative activity was evaluated against 2 colon cancer cell lines (HT-29 and LS-513). While several extracts inhibited cell proliferation over 48 hours, no correlation with total phenolics content was found (Vu et al. 2012).

Esophageal: Kresty et al. (2008) investigated the effects of a cranberry PAC-rich extract (PAC) on proliferation of SEG-1 human esophageal cells, a Barrett's-associated adenocarcinoma of the distal esophagus, and associated mechanisms. Pretreatment with PACs at 50 µg/mL inhibited acid-induced proliferation within 3 to 6 hours in an in vitro model designed to simulate acid reflux, a risk factor for esophageal cancer. A significant increase in apoptosis (>50%) was detected within 24 hours, along with increased cell cycle arrest in G1 phase. A subsequent study by these investigators found that expression of a number of previously identified dysregulated miRNAs in Barrett's esophagus and esophageal adenocarcinoma tissues was altered by treatment with 70% aqueous acetone extract of whole cranberry containing PACs (Kresty et al. 2011a). Computational analysis of gene expression in three cell lines identified multiple signaling pathways altered by cranberry treatment. Several of the miRNAs modulated by cranberry in esophageal adenocarcinoma cell lines are known to also be inversely dysregulated in premalignant esophageal pathologies, suggesting chemopreventive potential at both early stages during the development of esophageal premalignancy and later stages characterized by neoplastic transformation and progression to adenocarcinoma.

According to Caillet et al. (2011), the cancer chemopreventive effects of cranberry decrease with processing. A number of cranberry preparations were screened for their ability to induce the phase II xenobiotic detoxification enzyme quinone reductase (QR) (Caillet et al. 2011), which can deactivate cancer causing free radicals (Cuendet et al. 2006). The results showed that the anthocyanin-rich extract (E3) at 25 mg/mL was the most effective among the three fruit extracts with a maximum QR induction of 19.04 II(QR)/mg of dry matter. Among all extracts, the extract rich in apolar phenolic compounds (E2) of depectinized mash presented between 3.12 and 25 mg/mL the highest QR induction with values ranging from 20.34 to 24.45 II(QR)/mg of dry matter. In contrast, extracts of pomace have shown a weak QR induction and the highest concentrations (between 6.25 and 200 mg/mL) of anthocyanin-rich extract (E3) of pomace inhibited the QR activity. Evaporation into a juice extract, which is often done for the manufacture of powders for use in food supplements, had an especially detrimental effect on cranberry's ability to induce QR detoxification systems (Caillet et al. 2011).

Additional evidence for anti-proliferative and pro-apoptotic properties of cranberry extracts in vitro was reported using breast, oral, and lung cancer cell lines. An 80% aqueous acetone extract of whole cranberry fruit at doses of 10 to 50 mg/mL reduced proliferation and increased apoptosis levels in MCF-7 breast cancer cells by 25%, with arrest of the cell cycle in G1 phase and downregulation of cyclin D1 and CdK4 proteins (Sun and Liu 2006). A study in oral squamous cell carcinoma cell lines by Chatelain et al. (2011) found that a commercial cranberry extract induced visible phenotypic changes to cell morphology including increased cell clustering and cell–cell adhesion; inhibiting proliferation of SCC25 tongue cancer cells in doses >50 µg/mL, and CAL27 tongue cancer cells in doses of >10 µg/mL; RT-PCR analysis confirmed an upregulation of apoptosis initiator caspase-2 and apoptosis effector caspase 8 within 24 hours of treatment. Further evidence was provided by Kresty et al. (2011b), who demonstrated similar actions in H460 lung cancer cells. Cranberry PACs induced apoptosis 6 to 24 hours after treatment, down-regulated expression of several IAPs (inhibitor of apoptosis proteins) and other anti-apoptotic molecules, and increased expression of P21, which has been linked to apoptosis resistance.

Further in vitro mechanisms of actions

Early studies by Bomser et al. (1996) identified cranberry as a potential inducer of quinone reductase (QR). A variety of cranberry preparations (puree, depectinized puree, pomace,

raw or filtered juice, and juice concentrate) were extracted with various solvent mixtures to yield water-soluble, apolar, and anthocyanin-rich fractions (as above, colon cancer section). The compositions of the extracts were not reported. Extracts were evaluated for their ability to induce QR in Hepa1c1c7 murine hepatoma cells. Water-soluble extracts were superior to apolar extracts, and as the level of processing increased, particularly in the preparation of juice concentrate, QR-inducing efficacy was observed to decrease (Caillet et al. 2011). A follow-up study evaluated multiple fractions from each preparation and found a wide range of QR induction; however, the constituents were not characterized (Caillet et al. 2012). Cranberry may act alone and in combination with platinum drugs or cyclophosphamide to limit proliferation of cancer cells. Treatment of platinum-resistant SKOV-3 human ovarian adenocarcinoma cells with a sublethal concentration of paraplatin together with a cranberry PAC fraction improved its ability to inhibit cell proliferation (Singh et al. 2009). Cranberry PAC treatment alone induced apoptosis and blocked cell cycle progression and AKT pathway activation in SKOV-3 cells, and blocked vascular endothelial growth factor (VEGF)-stimulated receptor phosphorylation in endothelial cells, suggesting antiangiogenic potential (Kim et al. 2011). In neuroblastoma cell lines (SH-SY5Y, SMS KCNR, IMR-32), an isolated PAC fraction containing a range of oligomer sizes exhibited dose-dependent inhibition of cell viability (Singh et al. 2012) with cell cycle arrest, upregulation of cyclin-D1 within 18 hours and CDK-4 within 6 h, and downregulation of CDK-6 and p27 expression. Activation of pro-apoptotic and deactivation of various pro-survival factors was found. An interesting finding was that a cranberry PAC extract in combination with cyclophosphamide decreased glutathione-S-transferase levels associated with many drug-resistant cancers, and increased uptake of cyclophosphamide occurred in cranberry PAC-treated SMS-KCNR cells.

A comparison study of juices freshly prepared from edible berries (Boivin et al. 2007) suggests that NFκB inhibition may play a role in cranberry's anticancer activity in vitro. A 50-µL/mL dose of juice inhibited proliferation of MCF-7 and MDA-MB-231 breast, PC-3 prostate, Caco-2 colon, and AGS stomach adenocarcinomas by over 50%. This was accompanied by reduced expression of several cell-cycle regulators. Moreover, in PC-3 cells, cranberry juice was among the most effective inhibitors of TNF-induced expression of both COX-2 and an NFκB-dependent reporter gene. This finding suggests that anti-inflammatory properties of cranberry juice may play a role in reduced tumor cell proliferation in vitro. The role of pro-oxidant ROS generation by polyphenols in cytotoxicity was evaluated in HSC-2 human oral carcinoma cells. Cranberry juice extract was characterized as a mild pro-oxidant, and treatment with doses of 100 µg/mL or more reduced cell proliferation, with observed morphological changes consistent with apoptosis, but no correlation with ROS generation was observed (Babich et al. 2012). However, Singh and others observed a loss of the mitochondrial transmembrane depolarization potential and excess generation of ROS in the treatment of neuroblastoma cells with isolated cranberry PACs (Singh et al. 2012).

In vitro antiangiogenic activity due to inhibition of vascular endothelial growth factor (VEGF) has also been observed with a mixture of berries (Roy et al. 2002). While cranberry was not studied alone, flavonoids and antioxidant activity similar to those in cranberry were considered to be at least partially responsible for this effect.

Characterization of anti-proliferative constituents

A bioassay-guided fractionation approach was used to investigate in vitro anti-tumor activities of whole-cranberry fruit isolates. An ethyl-acetate extract of whole-cranberry fruit inhibited growth of human tumor cell lines in vitro (Yan et al. 2002). Murphy et al. (2003) identified 2 hydroxycinnamate esters of ursolic acid which inhibited the growth of several human tumor cell lines, including MCF-7 breast, HT-29 colon, DU145 prostate, H460 lung, ME180 cervical epidermoid and K562 leukemia. Screening by the NCI Developmental Therapeutics Program found the esters, particularly the cis isomer inhibited growth of a broad range of tumor cell lines at doses <5 µM (Kondo et al. 2011). Polyphenolic-rich extracts with anti-proliferative properties have also been reported. A cranberry-fruit fraction containing catechin dimers and oligomers and quercetin glycosides inhibited ODC activity in murine epidermal cell line ME-308 (Kandil et al. 2002). A water-soluble polyphenolic extract from commercial cranberry powder containing a variety of organic acids, anthocyanins and other polyphenols inhibited proliferation of several human tumor cell lines including CAL27 and KB oral, HT-29, HCT-116, SW480 and SW620 colon, and RWPE-1, RWPE-2 and 22Rv1 prostate lines (Seeram et al. 2004). Inhibition by the combined extract was greater than that of individual subfractions, suggesting possible synergistic effects of the polyphenols. Neto et al. (2006) isolated and characterized a whole-cranberry fruit PAC subfraction which selectively inhibited the proliferation of H460 human large-cell lung carcinoma, HT-29 colon adenocarcinoma and K562 chronic myelogenous leukemia cells in vitro; MALDI-TOF-MS found the fraction contained PAC oligomers composed primarily of four to seven epicatechin units with one or more A-type linkages. A fraction with similar composition showed a variety of anti-proliferative effects in neuroblastoma cell lines in a study by Singh et al. (Singh et al. 2012).

Summary

Clinical data regarding potential anticancer activity of cranberry are lacking. However, the limited animal data and plethora of in vitro anticancer data of cranberry and its constituents suggest multiple possible mechanisms of action, including antioxidant, anti-angiogenic, and free-radical squelching activity and reduction of potentially carcinogenic metabolites from the intestines underscoring a potential role in both cancer prevention and treatment. To date, however, there is no evidence to suggest that oligomeric compounds reach tissues such as the brain, breast, lungs, and prostate. Thus, cranberry, and its many prepara-

tions, should be considered as a general healthy part of a diet rather than as a functional intervention for the prevention or treatment of cancer. While the in vitro work is promising, any vivo relevance remains in question. Further in vivo study using well-characterized cranberry preparations is warranted.

Affects of Cranberry on Helicobacter pylori

Adhesion of *Helicobacter pylori (H. pylori)*, a gram-negative bacterium, to stomach epithelial cells is associated with gastrointestinal diseases including gastric, duodenal and peptic ulcers, gastric cancer, and gastric lymphoma (Evans and Evans 2000; Walsh and Peterson 1995). Eradication of *H. pylori* from the gastric mucosa may be an effective way of preventing infection. Cranberry extract containing PACs prevents H. pylori from attaching to isolated stomach cells (Burger et al. 2000). A few clinical trials have demonstrated anti-bacterial effects of cranberry against *H. pylori*, both with and without concomitant antibiotic therapy, with positive results suggesting its potential application in supporting a healthy gastrointestinal system. Other data show that cranberry extract can inhibit the secretion of interleukin-8 from stomach cells, an inflammatory mediator associated with *H. pylori* infection.

Human Clinical Trials

One randomized controlled trial (RCT) investigated the potential additive effects of cranberry and antibiotic therapy against *H. pylori* (Shmuely et al. 2007). In this study, 889 patients were treated for *H. pylori* infection with a triple antibiotics therapy for one week. Of these subjects, 177 additionally received 250 mL cranberry juice or placebo twice daily, then only cranberry juice or placebo for another 2 weeks. Overall, there was no statistically significant difference in *H. pylori* eradication between all 3 arms. A gender-specific analysis revealed a significantly higher eradication rate for the cranberry arm in female subjects (non-significant in males), compared to placebo and antibiotics treatment only, suggesting an additive effect.

A double-blind placebo-controlled clinical trial was conducted on patients infected with *H. pylori*. Those in the cranberry group consumed two 250 mL servings of cranberry juice cocktail (27% cranberry) per day for 90 days, and those in the placebo group drank the same amount of a placebo beverage (Zhang et al. 2005). The overall rate of *H. pylori* eradication was significantly higher in the cranberry group (14.3%) compared to placebo (5.2%).

Gotteland et al. (2008) investigated modulation of *H. pylori* colonization with cranberry juice and the probiotic *Lactobacillus johnsonii* La1 in a RCT with 295 asymptomatic Chilean children infected with *H. pylori*. The study included 4 arms: Cranberry juice (CB; 200 mL) with La1 (La1; 80 mL); placebo juice with La1; cranberry juice with heat-killed lactobacillus; and placebo juice with heat-killed La1 for 3 weeks with a follow-up test to detect presence of *H. pylori* after a one-month washout. Eradication rates were significantly higher for all treatment groups compared to controls ($P < 0.01$) as follows: Lactobacillus 14.9%; cranberry juice 16.9%; cranberry juice/lactobacillus 22.9%; control 1.5%. No significant synergistic inhibitory effect on *H. pylori* colonization, however, was observed for the combination of cranberry juice and lactobacillus.

Animal and In Vitro Studies

Chatterjee et al. (2004) tested the in vitro bactericidal effects of cranberry extract alone or in combination with the antibiotic clarithromycin (PBS cell suspensions in Lennox broth). A dose-dependent inhibition of *H. pylori* was observed, which was further enhanced by the addition of clarithromycin. Other studies have focused on the inhibitory effect of cranberry juice on adhesion of *H. pylori* strains to immobilized human mucus, erythrocytes, and cultured gastric epithelial cells (Burger et al. 2000; Burger et al. 2002; Shmuely et al. 2004; Vattem et al. 2005). These data were confirmed in similar investigations of antibacterial, bacterial antiadhesion and growth-inhibiting effects of various berry phenolics, including cranberry (Matsushima et al. 2008, 2013; Nohynek et al. 2006; Puupponen-Pimia et al. 2005; 2005b). Matsushima et al. (2013), reported that a cranberry powdered extract (Kikkoman Corporation, Tokyo) containing 5.4% total polyphenols and 11.2% total organic acids and a cranberry juice concentrate (Nippon Del Monte Corporation, Tokyo) (both at 1 mg/mL) inhibited interleukin-8 secretion from stomach cells in mice. Lin et al. (2005) observed inhibition of *H. pylori* from a mixture of cranberry and oregano extracts and hypothesized that the activity was likely due to inhibition of urease and proline dehydrogenase at the plasma membrane. *H. pylori*-infected mice that consumed cranberry juice (0.5 mL/mouse daily for 30 days); showed a marked 80% clearance of H. pylori 24 hours after treatment, and eradication of 20%, 4 weeks after treatment ceased (Xiao and Shi 2003). No relationship between the antiadhesion effect of the cranberry and bacterial resistance to antibiotics was observed, which suggests a synergistic effect from the combination of antibiotics and cranberry preparations on eradication of *H. pylori*.

Summary

These data demonstrated that cranberry consumption alone can reduce *H. pylori* colonization but may not fully eradicate it. Special populations in which antibiotic treatment is not indicated, such as pregnant women or the elderly, may particularly benefit from cranberry therapy. Additional clinical trials are needed to determine specific dosage effects and persistence of cranberry products either alone or in combination with antibiotics on *H. pylori* colonization and eradication. However, given that the standard therapy for treatment of ulcers is extensive, often requiring multiple courses of antibiotics and proton pump inhibitors over several months, the use of cranberry may be warranted.

Affects of Cranberry on Gut Health

Besides its beneficial affects on *H. pylori*, cranberry exerts protective effects on the gut when given in conjunction with elemental enteral nutrition (EEN; liquid diet), which has a propensity to adversely affect mucus production and secre-

tion, which in turn has the potential to impair gut immunity. In two animal studies (Pierre et al. 2013, 2014) animals given a liquid diet displayed adverse changes in intestinal mucosal immunity (decreased tissue interleukin-4 and 13, phosphorylated signal transducer and activator of transcription, and polymeric immunoglobulin receptors). When EEN was given in conjunction with presscake-derived PACs (50 and 100 mg/kg/bw for 5 days), the observed alterations in gut integrity due to EEN were reversed, specifically, increases in oral mucin (Pierre et al. 2013) and intestinal secretory immunoglobulin (Pierre et al 2014) levels.

Affects of Cranberry on Oral Health

Many studies have reported on the potential of cranberry polyphenols (e.g., PACs) for preventing or treating oral diseases, including dental caries, periodontal diseases, and candidiasis. However, controlled clinical studies to support such beneficial effects are lacking. Cranberry polyphenols are well known to possess in vitro inhibitory effects on microbial biofilm (dental plaque) formation (Bodet et al. 2008; Bonifait and Grenier 2010), which is an important etiological factor in the development of dental caries. In regard to periodontal diseases, polyphenols from cranberry inhibit adherence, biofilm formation, and proteolytic activities of periodontopathogens, in addition to reduce the host inflammatory response, as well as the production and activity of host-derived proteolytic enzymes that mediate the destruction of periodontal tissue components (Feghali et al. 2012). Table 14 and 15 summarize the beneficial properties of cranberry polyphenols that may contribute to reduce the incidence/severity of dental caries and periodontal diseases. An additional rationale for the use of cranberry polyphenols in dentistry is their potential for reducing the need for antibiotics, thus helping to prevent the development of bacterial resistance associated with conventional antibiotic use in periodontics.

Conversely, it is questionable whether consumption of cranberry juice on its own can benefit oral health given the short contact time between the oral surfaces (teeth and gingiva), the pathogenic microorganisms, and the bioactive cranberry constituents. In addition, the sugar added to cranberry drinks and the acidity of these beverages may have an adverse effect by contributing to the demineralization of tooth enamel. Given that, purified compounds from cranberry (e.g., PACs) may be used to supplement oral hygiene products, which, if effective, could also be applied locally to diseased sites.

Etiology of Dental Caries, Periodontal Diseases, and Candidiasis

The human oral cavity is a complex microbial ecosystem colonized by more than 700 microbial species. The dental biofilm that develops on the hard and soft tissues of the oral cavity is composed of bacteria, epithelial cells, proteins, enzymes, and food debris, all of which are embedded into an extracellular polysaccharide matrix (Marsh 2005). The dental biofilm is responsible for the two major bacterial infections of the oral cavity: dental caries and periodontal diseases.

Dental caries is one of the most common diseases among humans. It is a multifactorial disease characterized by acid demineralization of the tooth enamel. The organic acids produced by cariogenic bacteria, including *Streptococcus mutans* and *Streptococcus sobrinus*, following fermentation of food carbohydrates (principally sucrose), reduce the pH of the biofilm below 5.5 (Marsh 2004). Such acidic conditions cause the dissolution of tooth enamel.

Periodontal diseases affect the tissues that surround and support the teeth. These conditions evolve episodically, with phases of active destruction, latency, and healing. In gingivitis, the inflammatory process is limited to the free gingiva, whereas periodontitis is a progressive disease that affects all of the tooth-supporting tissues, including the periodontal ligament and the alveolar bone. Two principal factors are involved in the pathogenesis of periodontal diseases: the microbial factor and the host factor. Bacterial species most commonly associated with periodontal diseases include *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola* for the chronic form of periodontitis, and *Aggregatibacter actinomycetemcomitans* for the aggressive form of the disease (Feng and Weinberg 2006). The second factor involves the host immune response to the above periodontopathogens resulting in the over-production of pro-inflammatory cytokines, prostanoids, and MMPs, which can modulate the progression and severity of periodontitis (Paquette and Williams 2000).

Oral candidiasis is an opportunistic fungal infection of the oral cavity caused by an overgrowth of *Candida* species, the most common being *Candida albicans* (Samaranayake et al. 2009). Several factors that induce changes in the oral environment can predispose to oral candidiasis and include: antibiotics, corticosteroids, xerostomia, diabetes mellitus, nutritional deficiencies, and immunosuppressive diseases and therapy (Zunt 2000).

Effects of Cranberry on Dental Caries

The two major biofilm-producing species associated with dental caries are *S. mutans* and *S. sobrinus*. Cranberry polyphenols may limit dental caries by inhibiting several mechanisms contributing to the cariogenic potential of these bacterial species: production of organic acids, formation of biofilms, and bacterial coaggregation.

Human Studies

In the single placebo-controlled trial available, Weiss et al. (2004) investigated in a population of 59 patients over a six-week period, the effect of using a mouthwash supplemented with non-dialysable material (NDM) prepared from cranberry juice concentrate. Total bacteria and *mutans* streptococci counts were significantly reduced in the experimental group compared to control. However, no clinical changes in the plaque and gingival indices were observed. In support of these in vivo results, in vitro experiments (reported in the same study) showed that the cranberry NDM fraction inhibits the adhesion of *S. sobrinus* to a saliva-treated hydroxylapatite surface.

In Vitro and Animal Studies

The polysaccharides glucan and fructan play a primary role in the adhesion of bacteria to dental surfaces and in the maturation of the biofilm. Various researchers have proposed that the ability of cranberry polyphenols to inhibit the adhesion of S. mutans to dental biofilm depends on inactivation of glucosyltransferase and fructosyltransferase, two extracellular enzymes produced by *S. mutans* that catalyze the formation of glucan and fructan, respectively (Duarte et al. 2006; Feldman et al. 2009; Gregoire et al. 2007; Steinberg et al. 2004).

The glucan-binding proteins found on the surface of *S. mutans* also contribute to the formation of the dental biofilm (Banas and Vickerman 2003). Koo et al. (2006), using hydroxylapatite surfaces pretreated with glucan, found that cranberry juice (25% cranberry) significantly inhibited the adhesion of S. mutans to glucan. The same juice also significantly reduced the activities of surface-adsorbed glucosyltransferases B and C. Yamanaka et al. (2004) similarly assessed the effect of cranberry juice on the ability of several oral species of *Streptococcus* to adhere to hydroxylapatite beads that had been pretreated with saliva. When the bacteria were exposed to cranberry juice, their adhesion to the beads decreased significantly. Furthermore, the cell surface hydrophobicity of bacteria declined in the presence of increasing concentrations of cranberry juice. In the same study, the authors found that cranberry NDM prevented biofilm formation by all oral streptococci tested (*S. sobrinus*, *S. mutans*, *Streptococcus criceti*, *Streptococcus sanguinis*, *Streptococcus oralis*, and *Streptococcus mitis*). Additional studies subsequently confirmed the ability of cranberry extracts to prevent the formation of biofilm by cariogenic streptococci (Duarte et al. 2006; Yamanaka-Okada et al. 2008). Interestingly, it has also been reported that the cranberry polyphenols induce desorption of *S. sobrinus* from an artificial dental biofilm (Steinberg et al. 2005) and inhibit the metabolic activity of a *S. gordonii* biofilm, thus reducing acid production (Babu et al. 2012). Lastly, cranberry NDM has been shown to prevent coaggregation of different oral streptococci species (Sethi and Govila 2011; Steinberg et al. 2004). All the above observations suggest that cranberry polyphenols can inhibit the colonization of dental surfaces by cariogenic streptococci and thereby slow down the development of cariogenic dental plaque. Koo et al. (2010) showed in an animal model with Sprague-Dawley rats that topical application of a purified cranberry PAC fraction onto teeth surfaces significantly reduced biofilm formation as well as severity of smooth- and sulcal-surface caries induced by *S. mutans*.

Periodontal Diseases

Cranberry polyphenols have been shown to exert effects on the two primary etiological factors involved in the pathogenesis of periodontitis. On the one hand, they can negatively affect some important biological properties of periodontopathogens involved in host colonization and tissue destruction. On the other hand, cranberry polyphenols may also target the host immune response thus reducing inflammation-related periodontal tissue damages. This dual effect associated with cranberry polyphenols makes these components of high interest.

Affects on Periodontopathogens

Labrecque et al. (2006) first showed that cranberry NDM is a potent inhibitor of biofilm formation by *P. gingivalis*, while it has no effect on growth and viability of the bacterium. Cranberry NDM also prevented significantly the attachment of *P. gingivalis* to surfaces coated with type I collagen (Labrecque et al. 2006). Moreover, cranberry NDM dose-dependently inhibits proteolytic enzymes of *P. gingivalis*, *T. forsythia* and *T. denticola* thus reducing the proteinase-mediated destructive process occurring in periodontitis (Bodet et al. 2006a). Inhibition of proteolytic and adherence activities of periodontopathogens by cranberry polyphenols have been subsequently confirmed by La et al. (2010) and Polak et al. (2013).

Affects on the Inflammatory Response to eriodontopathogens

Macrophages and monocytes, which are found in higher numbers in active periodontal sites than in inactive sites (Zappa et al. 1991), play a crucial role in the host inflammatory response to periodontal pathogens (Cekici et al. 2014). The continuous high secretion of cytokines and chemokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-α (TNF-α by host cells under inflammatory conditions modulates periodontal tissue destruction (Cekici et al. 2014). Bodet et al. (2006b) found that cranberry NDM inhibits the production of these pro-inflammatory cytokines by macrophages following their stimulation with lipopolysaccharides of various periodontopathogens, including *A. actinomycetemcomitans*, *F. nucleatum*, *P. gingivalis*, *T. denticola*, and *T. forsythia*. In gingival fibroblasts, cyclooxygenase-2 expression and the secretion of IL-6, IL-8, and prostaglandin E_2 (PGE_2) in response to *A. actinomycetemcomitans* LPS were also significantly reduced by this fraction (Bodet et al. 2007a). Cranberry polyphenols appear to act by inhibiting cellular signalling proteins, leading to a reduction in the regulation of the activating protein-1 (AP-1), an important transcription factor for the genes coding for pro-inflammatory mediators (Bodet et al. 2007a).

More recently, Lombardo et al. (2015), showed that cranberry PACs (25 and 50 mg/mL), and epigallocatechin-3-gallate (EGCG) (1 and 5 mg/mL) derived from green tea (*Camellia sinensis*), showed a synergistic effect in reducing inflammatory cytokines in oral mucosal cells in vitro.

Affects on Matrix Metalloproteinases (MMPs) Release and Activity

MMPs released by host mucosal and immune cells have been associated with tissue destruction in periodontal disease (Sorsa et al. 2006). Cranberry PACs were reported to inhibit MMP-1, -3, -7, -8, -9, and -13 secretions by macrophages and gingival fibroblasts stimulated with LPS from periodontopathogens (Bodet et al. 2007b; La et al. 2009). The inhibition of MMP secretion was associated

with reduced phosphorylation of key intracellular kinases and the inhibition of NF-κB p65 activity (La et al. 2009). Cranberry polyphenols also inhibited the activity of recombinant MMP-1 and MMP-9 (La et al. 2009). Taken together, these data support the potential of cranberry PACs for the development of novel host-modulating strategies to inhibit MMP-mediated tissue destruction during periodontitis.

Affects on Bone Resorption

Receptor activator of nuclear factor κB ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) stimulate the production of pre-osteoclasts from hematopoietic monocyte/macrophage precursors (Teitelbaum 2000). Once activated, resorptive osteoclasts promote the dissolution of the inorganic phase of bone, exposing the organic matrix. Demineralization occurs by the acidification of the osteoclast extracellular microenvironment, which mobilizes bone minerals. The exposed organic component is then degraded by proteases such as cathepsin K and MMPs (Teitelbaum 2000). Cranberry PACs are not cytotoxic to osteoclast cells, but they can inhibit their differentiation into bone resorbing cells, even in the presence of osteoclastogenesis mediators, and reducing MMP secretion, chemokine production, and bone resorption (Tanabe et al. 2011). The impact of cranberry PACs on MMP production/activity in osteoclasts is vital for preventing the resorption of the collagen-rich bone organic matrix.

Candidiasis

Feldmann et al. (2012) showed that cranberry PACs, while not affecting growth of *Candida albicans*, prevented biofilm formation and adherence to oral epithelial cells. An anti-inflammatory effect was also observed in an oral epithelial cell model stimulated with *C. albicans* (Feldmann et al. 2012).

Summary

Based on the numerous in vitro studies available, cranberry polyphenols, specifically the PACs, appear to have a strong potential for preventing and/or treating oral infections, including dental caries and periodontal disease. However, results obtained from these studies are difficult to extrapolate to in vivo use, since the oral environment could interfere with the biological properties of these molecules. Clinical studies in this area are therefore warranted.

Potential Antiviral Effects of Cranberry

Human enteric viruses are increasingly recognized as significant causes of non-bacterial gastroenteritis worldwide. Outbreaks are associated with human noroviruses, hepatitis A virus, Aichi virus, rotavirus, astrovirus, sapovirus, adenovirus, hepatitis E virus, parvoviruses, and other small round structured viruses (D'Souza et al. 2007). Cranberry juice, cranberry extract, and some cranberry constituents exhibit in vitro antiviral effects.

Table 14 Summary of beneficial effects of cranberry polyphenols for dental caries and periodontal diseases

Dental caries	Periodontal diseases
Reduction in production of extracellular polysaccharides	Inhibition of formation of biofilm and adhesion by periodontopathogenic bacteria
Inhibition of acid production by cariogenic bacteria	Inhibition of proteolytic activities of bacterial and tissue origin
Inhibition of function of proteins that bind to glucans	Inhibition of cytokine production by immune and mucosal cells
Reduction in formation of dental biofilm	Inhibition of production of matrix metalloproteinases by immune and mucosal cells

Source: Bonifait and Grenier (2010).

Table 15 Properties of cranberry NDM and PAC on periodontal health

Cranberry Fraction		
Property	**NDM[a]**	**PAC[b]**
Concentration in cranberry juice cocktail	1.5 mg/mL	2.9 mg/mL
Concentration required to inhibit adhesion of P-fimbriated *E. coli*	23.5 µg/mL	60 µg/mL
S. mutans	130 µg/mL	500 µg/mL
***P. gingivalis* biofilm**	62.5 µg/mL	NT
Oral bacteria coaggregation	200–500 µg/mL	NT
Concentration required to inhibit the enzymatic activity of *S. mutans* GTF or FTF	1000 µg/mL	500 µg/mL
Periodontopathogen proteases	10–100 µg/mL	NT
Concentration required to inhibit acid production by *S. mutans*	NT	500 µg/mL

Source: [a] Data from Bodet et al. (2006a); Labrecque et al. (2006); Ofek et al. (1991; 1996); Weiss et al. (1998); Zafriri et al. (1989); [b] Data from Dixon et al. (2005); Duarte et al. (2006); Foo et al. (2000a); Howell et al. (2005).
NT: not tested, GTF and FTF: Glucosyltransferase and fructosyltransferase.

Human noroviruses cannot yet be cultivated in the laboratory. Therefore, inactivation effects are determined by cultivable surrogates such as feline calicivirus (FCV-F9), murine norovirus (MNV-1), and bacteriophage MS2 at high (~7 $\log_{10}$ plaque forming units (PFU)/mL) or low (~5 $\log_{10}$ PFU/mL) titers. When these surrogates were treated in vitro with commercial cranberry juice at 0.15, 0.30, or 0.60 mg/mL cranberry PAC for 1 h at room temperature, low titer FCV-F9 was reported to be reduced to undetectable levels (Su et al. 2010a). MNV-1 titers were also reported to be reduced by 2.06 log10 PFU/mL by cranberry juice, and by 2.63, 2.75, and 2.95 $\log_{10}$ PFU/mL with 0.15, 0.30, and 0.60 mg/mL cranberry PAC, respectively. Bacteriophage MS2 titers were also reported to be reduced by 1.14, 0.55, 0.80,

and 0.96 $\log_{10}$ PFU/mL with cranberry juice, 0.15, 0.30, and 0.60 mg/mL cranberry PAC, respectively. Treatments of high titer viruses showed decreased effects, although similar reduction trends were observed for each of the three viruses compared to their low titers. Furthermore, in a time-dependence study, treatment of ~5 $\log_{10}$ PFU/mL viral titers in vitro with cranberry juice at pH 2.6, cranberry juice at pH 7.0, 0.30 mg/mL cranberry PAC, or 0.60 mg/mL cranberry PAC over 1 h at room temperature, showed maximal reduction effects for FCV-F9 titers causing ~5 $\log_{10}$ PFU/mL reduction within 30 min. MS2 titers were found to decrease the least among the three tested viruses. In general, viral reduction was found to occur within the first 10 min of treatment resulting in ≥50% of the total reduction (Su et al. 2010a; 2010b).

In order to understand the mechanism of action of cranberry PAC, transmission electron microscopy studies carried out by these researchers showed slight structural changes for FCV-F9 treated with cranberry juice and cranberry PAC. These findings showed that cranberry juice and cranberry PACs had antiviral effects against the tested human enteric virus surrogates over 1 h.

In addition, Lipson et al. (2007a) showed that cranberry juice at 20% concentration and cranberry PAC (0.2%) had antiviral activity against waterborne rotavirus SA-11, bacteriophages T2 and T4, and bovine reovirus. These researchers demonstrated that rotavirus SA-11 treated with cranberry extract had single-shelled or anomalous virus-like particles, while the control samples contained the typical double-shelled, icosahedral "wheel-like" particles. They also showed that bacteriophage T4 treated with cranberry juice was incapable of attaching to its bacterial host (Lipson et al. 2007b).

Some research has also been done with cranberries and viruses other than enteric viruses. Weiss et al. (2005) showed that high molecular weight constituents from cranberry (at 250 µm/mL) inhibited influenza virus adhesion and reduced viral infections. In vitro studies of polio virus type 1 with cranberry drink at natural pH 2.6 and adjusted pH of 7.0 (undiluted and 1:4 dilution) resulted in survival of 21% and less than 1%, respectively (Konowalchuck and Speirs 1978). Other researchers showed that cranberry extracts prepared using 95% ethanol (concentration undisclosed) exhibited in vitro inhibitory activity against Epstein-Barr virus early antigen induction using Raji cells, although to a lesser extent than beetroot extract (Kapadia et al. 1996).

Other Effects

A number of other beneficial effects are associated with cranberry consumption (see Table 16). Xiao et al. (2015) investigated the effects of dried cranberries (0.011% phenolics and 0.7% cranberry fiber) and a cranberry extract (0.011% phenolics and 0.04% cranberry fiber) in reducing inflammation in an animal model of colitis. Compared to controls, both preparations attenuated many of the metrics associated with the disease. Cranberry extract (not dry cranberries) reduced measures of inflammatory response. Both cranberry extract and dried cranberries significantly reduced serum levels of TNF-α and IL-1β. Both preparations protected against the shortening of the colon (a maker of inflammation in colitis) induced by dextran sulphate. Dry cranberries (not extract) showed significant reductions in myeloperoxidase (MPO) activity (a marker of inflammation) and reduced structural damage to intestinal tissue. Using various concentrations of these cranberry preparations, the authors concluded that both fiber and polyphenolic compounds contributed to the positive effects observed.

Cranberry juice consumption increased the absorption of vitamin B-12 in hypochlorhydric elderly patients, likely due to the acidity of the juice (Saltzman et al. 1994).

Conclusion

The benefits of cranberry on urinary tract health has been supported in formal human clinical research for almost 25 years and many decades of empirical use prior to that. It is clear from the totality of data that multiple compounds contribute to the overall health benefits of cranberry including PACs, PAC metabolites, organic acids, and sugars. In addition to the beneficial effects of cranberry on the health of the urinary tract, a number of other health benefits are supported by either clinical or pre-clinical data, including clinical data demonstrating a reduction in risk factors for cardiovascular disease (e.g., improved cholesterol profiles, antioxidant activity, decreased blood pressure and platelet aggregation), reduction in *H. pylori*, and a reduction in cariogenic biomarkers. Pre-clinical research suggests benefit in reducing cancer risk (colon, esophageal, prostate) and anti-inflammatory activity with potential benefits in reducing atherosclerosis and colitis. As with all medicinal products, appropriate characterization of preparations is needed to ensure benefit.

In conclusion, the health benefits of cranberry consumption are very broad, while risk of adverse effects and toxicity is very low (see Safety).

Indications Supported by Clinical Trials

Beneficial for the prevention of recurrent urinary tract infections (UTIs); helps reduce the adhesion of certain *E. coli* bacteria to urinary tract walls.

Actions

Prevents P-fimbriated and type 1-fimbriated uropathogenic strains of *E. coli* from adhering to mucosal cells in the urinary tract; reduces bacterial biofilm formation in the urinary tract, anti-inflammatory, antioxidant.

Indications Supported by Modern Research

Prophylactic against recurrent urinary tract infections; prevents P-fimbriated and type 1-fimbriated uropathogenic strains of *E. coli* from adhering to mucosal cells in the urinary tract; reduces bacterial biofilm formation in the urinary tract, anti-inflammatory, antioxidant.

Dosages

The recommended daily intake of cranberry for maintenance of urinary tract health is based on clinical and ex vivo

Table 16 **Studies on other health effects of cranberry preparations**

Effect investigated	Study type	Sample size	Product and dosage	Outcome	Reference
Antioxidant	Clinical, U	9	CJ; 500 mL in 1 dose	Increased plasma antioxidant capacity	Pedersen et al. 2000
Urine odor reduction	Clinical, U	220	CJ; 90 mL daily for 1 week; increased weekly by 30 mL up to 180 mL	Reduction of urine odor	DuGan and Cardaciotto 1966
Treatment of skin afflictions in urostomy patients	Clinical, U	13	CJ; 160-320 mL daily for an average of 6 months	Improvement in peristomal skin condition	Tsukada et al. 1994
Reduction of catheter complications	Clinical, U	5; 20	CJ, 2 glasses or 500 mL daily for 2 weeks	Reduction of catheter-induced mucus formation	Rogers 1991; Rosenbaum et al. 1989
Effect on struvite kidney stones	Clinical, U	53	CJ; 946 mL daily for 9 years	60% with no stone recurrence; 32% with no increase in stone size; 8% with new stones or an increase in stone size	Zinsser et al. 1968
Effect on calcium oxalate kidney stones	Clinical, U	4	CJC; 1.5–4 L over one day	Increase in urinary calcium excretion in 2 of 4 subjects at the 2 L dose (P =0.01)	Kahn et al. 1967
Effect on calcium oxalate kidney stones	Clinical, U	15	CJ; 2–5 pt daily duration variable	50% reduction in urinary ionized calcium (P =0.001) in patients with calcium oxalate stones (n = 10) and no change in normal patients (n = 5)	Light et al. 1973
Effect on calcium oxalate kidney stones	Clinical, U	8	CJ; 500 mL single dose	No change in urinary oxalate; increase in urinary calcium excretion (P <0.05)	Brinkley et al. 1981
Effect on calcium oxalate kidney stones	Clinical, U	5	CE; 900 mg daily for 7 days	Increase in urinary oxalate (P =0.01), Na (P =0.03), Mg (P =0.02), and K (P =0.006)	Terris et al. 2001

Key: U = uncontrolled; CJ = cranberry juice of unknown concentration from unknown manufacturer; CJC = Cranberry Juice Cocktail® (manufactured by Ocean Spray®, CJC contains approximately 27% cranberry juice); CE = cranberry extract

data from trials conducted with different cranberry product forms. Dosages will vary by product and brand. The preparations used in most positive studies yielded a minimum dose of 36 mg PAC per serving (measured by DMAC method using A2 reference standard) suggesting this is a target dose to achieve*

Commercial juice drink (27% cranberry):	300–500 mL/ day
Dried cranberries:	30–40 g/day
Cranberry sauce (whole or jellied):	45 g/day
Encapsulated powder:	
Juice-based	200–3500 mg/day
Whole berry or skin-based press cake:	500–1000 mg/day

Substantiation for Structure and Function Statements

Supports healthy urinary tract. Provides antioxidants for the maintenance of cardiovascular health.

SAFETY PROFILE

Cranberry is a very safe herb to consume both as a food and in therapeutic preparations. Its safety is well established in cultural use throughout the world and is formally generally recognized as safe (GRAS). When consumed both as a food and in therapeutic preparations it generally lacks any adverse effects. Long-term human studies indicate a high level of safety for cranberry and its preparations whether

used as foods or dietary supplements. In clinical trials, most adverse effects have been related to the gastrointestinal tract (e.g., nausea, diarrhea) and are transient. Occasional anomalous adverse events have been reported (see Adverse Effects). All of these side effects resolve with discontinuation of cranberry consumption. Some authors caution about a potential correlation between cranberry consumption and increased risk of the development of kidney stones. Research findings regarding this are mixed (see discussion below). Concern was also raised that cranberry consumption can increase the effects of the blood thinner warfarin. Though there are a number of case histories suggesting a caution is warranted, formal investigations have found this caution to be unfounded. Cranberry is safe in pregnancy and lactation and is widely used in the elderly population.

Adverse Effects

Adverse Events Observed in Clinical Trials

The following adverse effects were reported in clinical studies:

Nausea (Basu et al. 2011); nausea, vomiting, and/or diarrhea (Juthani-Mehta et al. 2010); nausea, diarrhea, constipation, and rash (Lee et al. 2007); nausea, diarrhea, constipation, rash or urticaria, vomiting, and vaginal complaints (Beerepoot et al. 2011); mild nausea, and increased frequency of bowel movements (Stothers and Stothers 2001); gastrointestinal upset including nausea, vomiting, and diarrhea (Wing et al. 2008); constipation, heartburn, loose stool, vaginal itching and dryness, migraine (Stapleton et al. 2012); gastrointestinal upset, increased nocturia, sensitive and swollen nipples (McMurdo et al. 2009); gastrointestinal upset (Takahashi et al. 2013); gastrointestinal upset, skin redness and itching (McMurdo et al. 2005); mild gastrointestinal problems (Mazokopakis et al. 2009); abdominal discomfort (Linsenmeyer et al. 2004); diarrhea, headache, and heartburn (Efros et al. 2010); abdominal bloating (Campbell et al. 2003); dyspepsia (Dohadwala et al. 2011); gastric pain (Bonetta and Di Pierro 2012); general weakness and lower abdominal pain (Sengupta et al. 2011). No adverse effects were reported in approximately 60 other studies.

One case of hyperkalemia was reported in a man who consumed approximately 2 L of cranberry juice daily for several days. Causality could not be determined due to concomitant medications (Thomson and Perry 2001). In another report that was likely causal, diarrhea, hyperglycemia, and metabolic acidosis was reported in an infant given 150 mL of cranberry juice (Garcia-Calatayud et al. 2002).

Cranberry Consumption and Kidney Stone Formation

Long-term studies provide conflicting data regarding an association between cranberry juice or extract consumption and calcium oxalate kidney stone formation (Brinkley et al. 1981; Gettman et al. 2005; Kahn et al. 1967; Leahy et al. 2001; Light et al. 1973; Massey et al. 1993; Terris et al. 2001; Zinnsser et al. 1968). This is partially fueled by the fact that fresh cranberries, 100% cranberry juice, and cranberry juice cocktail contain oxalic acid (1.72 mg/100 g; 0.52 mg/100 g; 0.79 mg/8 oz, respectively) (Leahy et al. 2001). There is some evidence for increased oxalate risk for stone formation with cranberry consumption, e.g., increased urinary oxalate levels along with excretion of calcium, phosphate, and sodium ions (Gettman et al. 2005; Terris et al. 2001). However, there is no clinical evidence of increased kidney stone formation associated with cranberry consumption. Conversely, there is also evidence correlating cranberry consumption with a decrease in the development of oxalate, brushite, and struvite stones.

In 5 healthy volunteers who were administered cranberry concentrate tablets (type and dose not listed) daily for 7 days, urinary oxalate levels increased significantly ($P = 0.01$) by an average of 43.4% as compared to baseline values. The excretion of calcium, phosphate, and sodium ions, all of which may contribute to kidney stone formation, also increased. Levels of magnesium and potassium, both of which may inhibit stone formation, also increased (Terris et al. 2001). This study has been criticized for failing to measure oxalate content of the study material and failure to assess dietary intake of calcium and vitamin C, contributors to urinary oxalates (Leahy et al. 2001). Moreover, dietary oxalate ingestion is reported to have a negligible impact on stone formation (Taylor and Curhan 2007). Other sources suggest that dietary oxalate appears to contribute only about 10% of the urinary oxalate in healthy non-stone-forming individuals who eat Western-type diets (Williams and Wandzilak 1989). In 12 healthy male volunteers eating a standardized diet, administration of 330 mL of cranberry juice daily decreased urinary pH from 6.35 to 6.18, increased excretion of oxalic acid from 0.344 mmol/day to 0.392 mmol/day, and increased the relative supersaturation of uric acid from 0.67 to 0.99. The researchers concluded that since cranberry juice acidifies urine, the juice could be useful in the treatment of brushite and struvite kidney stones (Kessler et al. 2002).

In a study examining the ability of 7 "oxalate-rich" foods to enhance urinary oxalate excretion, cranberry juice was categorized as a low oxalate food (2–26 mg oxalate) as compared with other foods—for example, spinach (1236 mg oxalates). Urinary oxalate increased by 29.3 mg over 8 h after the ingestion of spinach, and increased by less than 4.2 mg from consumption of other food items, including cranberry juice. Among all the items tested, only spinach was deemed capable of causing hyperoxaluria in normal subjects (Brinkley et al. 1981). In a crossover study, healthy volunteers with no history of kidney stones were administered 500 mL of cranberry juice diluted with 1500 mL of tap water, or 2000 mL of tap water, daily for 2 weeks, with a 2-week wash-out period before crossing to the opposite treatment group. The ingestion of cranberry juice decreased oxalate and phosphate excretion while increasing citrate excretion. There was a decrease in the relative supersaturation of calcium oxalate, which tended to be significantly lower than that induced by water alone. The researchers concluded that cranberry juice has antilithogenic properties and deserves consideration as a conservative therapeutic protocol in managing calcium oxalate urolithiasis (McHarg et al. 2003).

Another study of 24 people was conducted to determine the biological markers for a potential increased risk of oxalate stone development with high cranberry juice consumption. Half of the subjects had calcium oxalate stone formation and half were normal. The two groups underwent two 7-day phases of study in random order while on a controlled diet. Study subjects ingested 1 L of cranberry juice or 1 L of deionized water daily for 7 days. Cranberry juice was found to significantly increase urinary calcium (from 154 to 177 mg/day) and urinary oxalate (from 26.4 to 29.2 mg/day), thereby increasing urinary saturation of calcium oxalate by 18%. Urinary citrate was unchanged and urinary magnesium increased slightly. Urinary pH decreased (from 5.97 to 5.67), and urinary ammonium, titratable acidity and net acid excretion increased during cranberry juice ingestion. Urinary uric acid decreased (from 544 to 442 mg per day), as did serum levels of uric acid. Thus, the urinary saturation of brushite and monosodium urate was reduced by cranberry juice, but the amount of undissociated uric acid increased. The researchers concluded that cranberry juice increases the risk of calcium oxalate and uric acid kidney stone formation but decreases the risk of brushite stones (Gettman et al. 2005).

In one placebo-controlled study of children (n = 171), cranberry juice (5 mL/kg po for 3 months) was well tolerated and compliance with the cranberry regimen over the 3-month treatment period exceeded that recorded for long-term antimicrobial prophylaxis (Kontiokari et al. 2005). In another study of children (n = 295), no adverse effects were reported in subjects consuming 200 mL of cranberry juice daily for 3 weeks (Gotteland et al. 2008).

Contraindications

None noted in the literature.

Precautions

There are no formal data supporting the efficacy of cranberry for the treatment of urinary tract infections. Despite this, practitioners use cranberry juice and other cranberry products for this purpose. If used, cranberry should only be attempted for the treatment of simple cystitis. Serious conditions such as pyelonephritis must be ruled out and monitored for. A physician should be consulted if UTI symptoms persist for 24 to 48 hours despite treatment with cranberry. If fever, chills, malaise, or aching arise, a physician should be consulted immediately. UTI, even when asymptomatic, is an indication for treatment with standard antibiotic therapy and is considered to increase the risk of preterm birth. Women experiencing or suspecting a UTI in pregnancy should consult with a qualified health care provider. Individuals on blood-thinning medications should have international normalized ratio (INR) values checked before, after, and throughout a period that involves consumption of cranberry preparations that is greater than what is typically consumed when INRs are stabilized.

Due to a single report of cranberry increasing the risk of bleeding in pregnant women, cranberry juice or other cranberry preparations should not be used for self-medication of urinary tract infections or suspected UTIs in pregnant women. In a single survey, spontaneous vaginal bleeding was reported in pregnant women self-medicating with cranberry, though no clinically significant risk was observed (Heitmann et al. 2013). A systematic review by Duguoa et al. (2008), reported there is no direct evidence of safety or harm to the mother or fetus as a result of consuming cranberry during pregnancy. Despite the lack of clinically significant adverse outcomes, increased bleeding in pregnancy is a serious event and should be referred to a qualified health care professional.

Case histories suggest a rare, potentially idiosyncratic, but potentially serious interaction between cranberry and warfarin (see Interactions below). Patients consuming warfarin should be aware that consumption of abnormally large quantities of cranberry could result in a bleeding event (see Interactions below). No concern has been noted with consumption of up to 480 mL daily and, as reviewed in Therapeutics, cranberry has a myriad of cardiovascular and antioxidant health benefits and should not be limited due to this concern.

Interactions

Positive Interactions

Both positive and negative cranberry-drug interactions have been reported. On the positive side, cranberry can counter the negative GI effects of elemental enteral nutrition (EEN) in animals (Pierre et al. 2013, 2014; see Effects of Cranberry on Gut Health above). In another pre-clinical study, a cranberry proanthocyanidin fraction (corresponding to catechin derived from cranberry juice (50 mg mL-*1*) significantly ($P < 0.05$) enhanced the antivirulence activity of the fluoroquinolone antibiotic ciprofloxacin (cipro; 1.5 mg mL-1) and the macrolide antibiotic azithromycin against *P. aeruginosa* (Vadekeetil et al. in press). In a clinical study of Beerepoot et al. (2011), a lower incidence of antibiotic resistance was evident when cranberry (500 mg twice daily; CranMax; pomace and juice product) was given in conjunction with trimethoprim-sulfamethoxazole (TMP-SMX; 480 mg once daily). After 1 month, of administration, TMP-SMX resistance to fecal and *E. coli* isolates was evident in 86.3% and 90.5% of subjects given TMP-SMX alone, respectively, compared to 23.7% and 28.1%, respectively, when cranberry was given in conjunction with TMP-SMX. The authors concluded that antibiotic resistance did not increase in the cranberry group.

In another study, specific fractions of a pomace extract displayed ex vivo antimicrobial activity against *S. aureus* [ATCC 29213 and MRSA COL] and further showed an additive antibiotic effect when the specific fractions were combined with β-lactam (i.e., amoxicillin and cefaclor). The authors suggest that cranberry pomace may be applied to reduce the development of antibiotic resistant *Staphylococcus* in animal food production (Harrison et al. 2013).

Negative Interactions

There have been several case histories suggesting potentially dangerous interactions between cranberry and the blood-thinning agent warfarin. This concern led to an FDA-imposed warning that accompanied Bristol-Meyers Squibb Medication Guide for warfarin (Coumadin®) cautioning health professionals and patients about this potential. Subsequently, FDA authorized the removal of this warning due to a lack of clinically relevant interactions based on formal pharmacodynamics investigations (Ansell 2009; Mellen 2010).

To date, 6 cases of possible potentiation of warfarin effects with cranberry product use have been reported in the literature, including a fatality from bleeding in an elderly man taking warfarin, phenytoin, and digoxin since suffering an embolic intracerebral stroke 4 years previously (Griffiths et al. 2008) (see Table 17). These events most often occurred in the elderly and are relatively rare considering the widespread consumption of cranberry juice in the elderly population. In each of the cases reported, patients had elevated INR levels associated with consumption of cranberry. Significant bleeding events occurred approximately 2 weeks after increased cranberry consumption began. In patients taking warfarin, a patient's coagulation rates are regularly checked by the INR. The target INR range for most patients on warfarin is 2.0 to 3.0 (Cushman et al. 2011), with values over 3.0 indicating a prolonged coagulation time and increased risk of bleeding events. The reported cases had confounding factors, such as changes in diet or a history of recent infection, which may also affect the INR level. In 3 reported cases, INR levels returned to within the therapeutic target range after discontinuation of cranberry consumption (relatively large amounts of juice or sauce) (e.g., Grant 2004; Mergenhagen and Sherman 2008; Welch and Forster 2007), providing perhaps the strongest evidence supporting that a clinically significant interaction can occur in some patients.

Following the case reports of cranberry and warfarin interactions, several human studies were completed (see Table 18). One of the studies shows a lack of interaction between cranberry and warfarin in 10 healthy volunteers (Lilja et al. 2007) and others in patients stable on warfarin doses (Ansell et al. 2009; Ansell 2011; Li et al. 2006; Mellen et al. 2010). However, the methodological quality of some of these studies has been criticized, citing too short of a study duration (usually 1 to 2 weeks) to detect a consistent clinically relevant interaction, a low patient population, or too low of a dose of warfarin to be clinically relevant (see Abdul et al. 2008). One study showed a significant ($P < 0.05$) 30% increase in the area under the INR–time curve when cranberry juice concentrate (equivalent to 57 g of cranberry fruit) was administered along with a high single dose of warfarin (25 mg). None of the subjects experienced major bleeding events or INR readings above 4. Two subjects developed rashes and 1 subject experienced nasal bleeding (presence of dried blood) at approximately 72 h after warfarin treatment. No significant changes in the maximum INR were observed. Cranberry did not alter S- or R-warfarin pharmacokinetics or plasma protein binding. Cranberry showed some evidence of VKORC1 (not CYP2C9) genotype-dependent interactions with warfarin. Subjects who carry the VKORC1 variant type (CT and TT alleles) were more prone to interactions with warfarin and cranberry in that cranberry significantly increased the effects of warfarin, suggesting that lower doses of warfarin are needed if taken concomitantly with a consistently characterized cranberry preparation. There was also an insignificant decrease in the activity of clotting Factor II, Factor VII, and Factor X when warfarin was co-administered with cranberry (Abdul et al. 2008).

In addition to the published case reports and clinical data, the Committee on Safety of Medicines (UK) as of 2003 received 7 other reports of possible warfarin-cranberry juice interactions through the formal Yellow Card reporting system of herbal practitioners. The reports suggested changes in INR or bleeding (Suvarna et al. 2003).

In a prospective open-label study of 10 male patients stable on warfarin, no statistical difference in prothrombin time was observed after consumption of 240 mL of pure cranberry juice twice daily for 7 days (Mellen et al. 2010). In another study of patients with a stable INR on warfarin, ingestion of 240 mL cranberry juice daily for 2 weeks resulted in a mild increase in INR in 8 of 30 patients. The mean INR level was increased only on the 12th day of treatment. Cranberry juice had no effect on plasma levels of warfarin. These researchers concluded that the transient change on one study day likely would not represent a clinically relevant event and suggested that contrasting case reports may reflect chance temporal changes in INR (Ansell et al. 2009; Ansell 2011).

In a randomized, double-blind, placebo-controlled, cross-over study, patients with atrial fibrillation on stable doses of warfarin for at least 3 months were randomized to receive either 250 mL of cranberry juice daily or placebo for 7 days, then placebo for 7 days, or vice-versa, with a washout period of 7 days. The baseline INR was 2.28 ± 0.54 for the cranberry group and 2.13 ± 0.50 for the placebo group. For all test points, the INR did not change significantly from baseline. At day 7 on cranberry juice, the INR was 2.23 ± 0.53 for the cranberry-first group and 2.16 ± 0.40 for placebo-first group. The mean differences between the cranberry and placebo groups were not statistically significant (Li et al. 2006).

In a study of healthy volunteers ($n = 10$) taking 600 mL cranberry juice and 10 mg racemic R-S-warfarin daily for 10 days, a slight decrease (7%, $P = 0.051$) in the area under the time-concentration curve of S-warfarin was observed. There were no clinically significant effects of cranberry juice on the anticoagulant effect of warfarin after 10 days of treatment, as measured by thromboplastin time (Lilja et al. 2007).

In an open-label, 3-treatment, randomized crossover clinical trial with 12 healthy male subjects, a single dose of 25 mg warfarin was administered alone or after 2 weeks of treatment with 1000 mg cranberry juice concentrate (equivalent to 57 g of cranberries) daily. Warfarin enantiomer concentrations, INR, platelet aggregation, and clotting

factor activity were measured to assess pharmacokinetic and pharmacodynamic interactions. Cranberry extract significantly increased the area under the INR–time curve by 30% when administered with warfarin compared to warfarin alone. Maximum average INR levels were 2.6 (range 2.3–3.0) for warfarin alone and 2.8 (range 2.5–3.1) for warfarin and cranberry. Cranberry did not alter S- or R-warfarin pharmacokinetics or plasma protein binding (Abdul et al. 2008).

An in vitro and in vivo evaluation of 5 different commercial preparations of cranberry juice, including pure cranberry juice, pure cranberry juice concentrate, cranberry juice cocktail, and cranberry-apple juice blends, investigated the potential effects of the cranberry preparations on S-warfarin 7-hydroxylation via CYP2C9 activity. The juices were tested at different dilutions in vitro in human liver microsomes. One of the 5 juices significantly inhibited S-warfarin 7-hydroxylation in vitro in a concentration-dependent manner, indicating a potential for an in vivo interaction. This juice was then administered double-strength to 16 healthy volunteers before and after administration of single doses of 10 mg of S/R-warfarin. Relative to water, consumption of multiple glasses of double-strength juice had no significant impact on the total exposure of S-warfarin. However, the absorption of S-warfarin with the selected juice was slower as compared to water. The median time to the maximum plasma concentration (t_{max}) increased by 2 hours, and geometric mean S-warfarin maximum plasma concentration (C_{max}) decreased by about 30%. Similar changes occurred with R-warfarin. No elevation in INR was reported in any of the study subjects (Ngo et al. 2010).

In a pharmacological study of healthy volunteers, no effects of cranberry juice (200 mL daily for 10 days or 2 doses of 240 mL) were observed on the drug-metabolizing isoenzymes CYP3A4, CYP2C9, or CYP1A2 (Greenblatt et al. 2006; Lilja et al. 2007).

In an open-label, randomized, three-way crossover study, 12 healthy male volunteers received a single dose of 200 mg of the immune-suppressant cyclosporine with 240 mL of pomelo juice, cranberry juice, or water under fasting conditions. While pomelo juice significantly increased blood levels of cyclosporine, cranberry juice had no clinically significant effects on cyclosporine (Grenier et al. 2006).

The β-lactam antibiotics amoxicillin and cefaclor are commonly used at low doses to prevent recurrent urinary tract infections. In a crossover study, 18 healthy female volunteers received, on 4 separate occasions, a single oral test dose of amoxicillin at 500 mg and 2 g with or without 8 oz cranberry juice cocktail. In a parallel study, 500 mg of cefaclor was administered with or without 12 oz cranberry juice cocktail. Cranberry juice cocktail delayed the absorption of both antibiotics but had no effect on the total absorption or renal clearance (Li et al. 2009).

Ansell (2011), in summarizing the cranberry-warfarin case histories and formal data, noted there was "no creditable scientific evidence to link an interaction between the moderate consumption of cranberry juice and warfarin." Ansell further reports that six of the seven interaction studies that assessed those studies in which valid and accepted pharmacodynamic and/or pharmacokinetic endpoints were used concluded that a cranberry juice-warfarin interaction is unlikely. In the seventh study, Ansell criticizes the finding based on the use of an abnormally single high dose of warfarin (25 mg) and the use of inappropriate and an unconventional area under the curve (AUC)-based pharmacodynamics parameter. Ansell does, however, note that interactions associated with large doses of cranberry cannot be ruled out and states that there are concerns with doses of up to two 8-oz glasses of juice daily. These studies examined 75 patients and healthy volunteers. A separate review of all 16 suspected reports from the UK reported to the Medicines and Healthcare products Regulatory Agency (MHRA 2003) through the Yellow Card program found that the cases were poorly documented.

Pregnancy, Mutagenicity, and Reproductive Toxicity

Several reviews report that cranberry is among the most commonly used herbs in pregnancy. In pregnancy, cranberry is primarily used to prevent or treat urinary tract infection and vaginal thrush (Broussard et al. 2010; Forster et al. 2006; Holst et al. 2009; Kennedy et al. 2013; Louik et al. 2010; Nordeng et al. 2011). When consumed according to typical consumption patterns as a beverage or in therapeutic doses, cranberry and its preparations are generally safe for consumption in pregnancy, though in a single survey, spontaneous vaginal bleeding has been reported (see discussion below).

In formal studies and reviews, no differences in obstetric or neonatal outcomes were observed in pregnant women taking 240 mL cranberry juice cocktail, placebo, or a combination of both. In one study, pregnant women were randomized to receive research-grade cranberry juice cocktail (27% cranberry juice, 80 mg of PACs) 3 times daily (n = 58), cranberry juice cocktail once daily and placebo twice daily (n = 57), or placebo 3 times daily (n = 63) beginning around week 16 of pregnancy and continuing until delivery. Parameters included pre-term delivery, route of delivery (spontaneous vaginal, instrumented vaginal, or Cesarean), birth weight, 1- and 5-minute Apgar scores, and neonatal ICU admissions. Of the women enrolled, 53% of the cranberry group, 61% of the cranberry-plus-placebo group, and 68% of the placebo group completed the study. Gastrointestinal upset (nausea, vomiting, and diarrhea) was reported as a significant reason for withdrawal from the study, although information on the rate of GI upset in each of the treatment groups was not listed (Wing et al. 2008).

In a related pilot study on the same preparation and population, no adverse effects were reported. Pregnant women (late first trimester to early second trimester) were randomized into 3 treatment arms, each taking investigational material twice daily (morning and evening): Cranberry twice daily (n = 10); cranberry in the morning, placebo in the evening (n = 9); and placebo twice daily (n = 8) (Wing et al. 2010).

In a study on the use of herbal products during pregnancy in Norway, 600 women were interviewed within 5

Table 17 **Case reports of interactions of cranberry products and warfarin**

Case	Previously stable INR	Cranberry form/ dose	INR	Complication	Report limitations	Reference
70 yo man with a history of atrial fibrillation, taking digoxin, phenytoin, and warfarin as a primary therapy and cephalexin for a chest infection. Had a poor appetite after a chest infection and ate "next to nothing" for 2 weeks.	Previously stable	470 mL of cranberry juice daily for 2 weeks prior to admission	>50	Died from a gastrointestinal and pericardial hemorrhage.	Poor appetite with minimal food intake would lead to vitamin K deficiency. Recent antibiotics could disrupt gastrointestinal Vitamin K biosynthesis. Infection would create a hypermetabolic state with increased clotting factor degradation. Patient was taking digoxin and phenytoin, which are also known to inhibit warfarin and prolong INR.	(Griffiths et al. 2008; Suvarna et al. 2003)
69 yo man with atrial fibrillation, a prosthetic heart valve, and recurrent urinary tract infections.	N/A	2 L (8.5 c) daily	On admission, INR was 12 and normalized to 2.0 after administration of vitamin K. When warfarin restarted, INR was 8 to 11 and only corrected to INR 3 after cessation of cranberry juice.	Blood in the urine and postrectal bleeding from a colovesical fistula (abnormal connection of the bladder and intestines).	High cranberry juice consumption. Recent antibiotics could disrupt gastrointestinal Vitamin K biosynthesis. UTI would create a hypermetabolic state with increased clotting factor degradation. Incomplete medication list and baseline INR not noted. Warfarin doses before, during, or after CJ discontinued not provided.	(Grant 2004)
71 yo man with a history of arteriovenous malformation (abnormal connection between arteries and veins) admitted for hemoptysis, hematochezia, and shortness of breath, who on admission received gatifloxacin for presumed exacerbation of chronic bronchitis.	N/A	700 mL (3 c) daily for 2 weeks before admission	>18	Hemoglobin 8.8 g/dL (baseline 15.3 g/dL) and an INR >18.	Patient was treated for bronchitis on admission, suggesting an infection that could create a hypermetabolic state with increased clotting factor degradation. Medical history and medication list not included.	(Rindone and Murphy 2006)
75 yo man with atrial fibrillation, taking digoxin, was found to have elevated INR on routine blood work one week after Thanksgiving.	10 mo	Cranberry sauce 113 g (0.5 c) daily for 7 consecutive days	Increased from baseline 2 to 3 to INR 4.8	No bleeding or bruising events. One week after discontinuing cranberry sauce INR returned to baseline and remained stable over the next month.	The many dietary changes that come from eating a Thanksgiving meal can affect INR. Cranberry sauce and not cranberry juice was consumed.	(Mergenhagen and Sherman 2008)

Table 17 Continued

77 yo man with a history of a mechanical aortic valve, heart failure (taking digoxin) was found on routine blood work to have elevated INR. His only reported change was addition of cranberry juice to diet.	6 mo	0.5 L (2 c) daily for 4 weeks (stopped 2 days before blood work)	Increased INR 5.9	Nosebleeds, "red mark in eye." With discontinuing CJ, INR returned to baseline.	Cranberry juice was discontinued prior to elevated INR.	(Welch and Forster 2007)
78 yo man with a history of atrial fibrillation (taking digoxin) with a recent cold was found on routine blood work to have an elevated INR. He reported taking an extra dose of coumadin, self-medicating his cough, and drinking large amounts of cranberry and apple juice	3 mo	0.5 gallons (8 c) daily for 1 week	INR 6.45	None	Illness and extra coumadin dose may be responsible for elevated INR. The patient had been taking large amounts of cranberry juice and may have had dietary changes during his illness.	(Paeng et al. 2007)

Adapted from: Zikria et al. (2010).

days after giving birth. Of the 600, 39.7% had used at least one herbal product during pregnancy. Ginger, iron-rich herbs, echinacea, and cranberry were the most commonly used herbal products, with 6.2% of women (n = 37) having taken cranberry. A review of the birth records of women who had taken herbal products, including cranberry, indicated no adverse effects on pregnancy outcome, including birth weight, gestational length, neonatal complications, or on delivery characteristics including analgesic use during delivery, and rates of Cesarean section (Nordeng et al. 2011). This same research group published a follow-up of women (n = 919 of 68,522 women surveyed) who had used cranberry while pregnant. No increased risk of adverse effect was observed regarding congenital malformations, stillbirth, neonatal death, low birth or gestational weight, preterm birth, low Apgar scores, neonatal infections, or maternal vaginal bleeding in early pregnancy. Increased vaginal bleeding in women who used cranberry to treat a UTI was observed after 17 weeks (roughly mid-pregnancy) but this did not require hospitalization and was not accompanied by any significant risk in terms of outcomes (Heitmann et al. 2013). Despite the lack of clinically significant adverse outcomes, increased bleeding in pregnancy is a serious event and should be referred to a qualified health care professional.

In a survey of 392 Italian women interviewed within 3 days after childbirth, 27.8% were found to have used at least one herbal product during pregnancy. The most commonly used products were chamomile (n = 48), licorice (n = 15), fennel (n = 13), aloe (n = 11), valerian (n = 11), echinacea (n = 10), almond oil (n = 10), propolis (n = 7), and cranberry (n = 5). Birth outcomes of those who used herbs were compared with those who did not use herbs. Use of these herbs was correlated with a higher rate of infants who were small for gestational age (11.9% as compared to 5.3%), while significant differences were not observed in other outcome measures such as gestational age, birth weight, Apgar score, malformations, problems at birth, and drugs at birth (Cuzzolin et al. 2010). No additional analysis of the cranberry-consuming individuals was provided.

Lactation

No data available. Based on its widespread consumption as a food, no negative effects with normal to therapeutic doses are to be expected.

Carcinogenicity

In a study with male Wistar rats, 3 commercial extracts of cranberry (NutriCran90S, HI-PAC 4.0, and PACRAN) were incorporated into the diet for 14 weeks by mixing 1500 mg cranberry extract per kg of feed. The animals were sacrificed

Table 18 **Summary of studies examining a potential cranberry juice-warfarin interaction from the literature**

Reference	Study design	Subjects	Intervention	Duration	PK Result	PD Result
Li et al. 2006	X	7 (warfarin for AF)	Warfarin + cranberry juice/placebo add doses given	Extended	Not determined	No effect (INR)
Greenblatt et al. 2006	X	14 healthy volunteers	Flurbiprofen (single dose) (preceded by cranberry juice, placebo, grape juice, tea or fluconazole)	Short-term include actual duration	No effect	N/A
Lilja et al. 2007	P	10 healthy volunteers	R-S warfarin, tizanidine, midazolam (5 days) + cranberry	Extended	No effect	No effect (thromboplastin time)
Abdul et al. 2008	ORX	12 healthy male volunteers	Single dose 25 mg warfarin, alone or after 2 weeks of cranberry juice concentrate capsules or garlic tablets	Extended	No effect	INR AUC increased by 28% (max 8% difference at any individual time point) in warfarin/cranberry juice group
Ansell et al. 2009	P	30 patients (16 placebo; 14 cranberry juice) AF (9), DVT (9), PE (4), VHD (3), CVD (4), CHF (1)	Cranberry juice vs placebo	Extended	No effect	No significant effect on INR
Ushijima et al. 2009	O; 2 –period; X >2 weeks wash-out period	6 male, 2 female healthy volunteers, mean age 30.5 (range 23–44 years)	Cranberry juice vs water with or without diclofenac (a medication metabolized by CYP2C9)	Medium duration (5 days), dosing of cranberry juice 180 mL, twice a day	No effect in healthy volunteers	No interaction with diclofenac in vivo, although inhibition of CYP2C9 in microsomal preparation in vitro
Mellen, et al. 2010	O prospective	10 patients, (62–86 years), on warfarin for AF (3), PE (5), DVT-stroke or DVT and AF (1 each)	On stable warfarin dose, INR 2 to 3.	Cranberry juice (100%), 240 mL, twice/ day x 7 days	N/A	No significant difference found in the mean PT at baseline vs anytime during the study

PK = pharmacokinetic; PD = pharmacodynamic; AF = atrial fibrillation; DVT = deep vein thrombosis; PE = pulmonary embolism; VHD = valvular heart disease; CVD = cerebrovascular disease; CHF = congestive heart failure; AUC = area under the curve; PT = prothrombin time. O = open; P; = parallel; R =randomized; X = crossover.

at the end of the study and no evidence of genotoxicity was found in the alkaline version of the Comet assay (Palikova et al. 2010).

Influence on Driving

Based on its widespread consumption as a food, no negative effects are to be expected at either food or therapeutic doses.

Overdose

No data available.

Treatment of Overdose

No data available.

Toxicology

In an 8-week study, 65 healthy female volunteers were randomized into 3 groups to receive placebo, 400 mg, or 1200 mg of dried cranberry juice daily. No significant changes in basic biochemical and hematological parameters were observed, including cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triacylglycerols, alanine aminotransferase, aspartate aminotransferase, D-glutamyl transferase, urea, creatinine, uric acid, and advanced oxidation protein products levels (Valentova et al. 2007).

In a study with male Wistar rats, 3 commercial extracts of cranberry (NutriCran90S, HI-PAC 4.0, and PACRAN) were incorporated into the diet for 14 weeks by mixing 1500 mg cranberry extract per kg of feed. A control group received standard feed. Average daily doses of anthocyanins were 0.57 (NutriCran90S group), 0.81 (HI-PAC 4.0 group), and 0.09 mg/kg/day (PACRAN group). Average daily doses of phenolics were 0.03 (control group), 0.47 (NutriCran90S group), 0.72 (HI-PAC 4.0 group), and 0.60 mg/kg/day (PACRAN group). The animals were sacrificed at the end of the study and clinical chemistry (including liver enzymes), hematology, histopathology, and cytochrome P450, were evaluated. Hematological parameters, body weight, and food consumption were unaffected by intake of cranberries. Plasma alkaline phosphatase was significantly decreased in the NUTRICRAN90S group. No changes in gross pathology, organ weights, or histopathology were observed in any of the groups. No changes were observed in total cytochrome P450 levels in the liver (Palikova et al. 2010).

Classification of the American Herbal Products Association (AHPA)

Safety class 1: Herbs that can be safely consumed when used appropriately. Interaction class A: Herbs for which no clinically relevant interactions are expected (Gardner et al. 2013).

TRADITIONAL WESTERN HERBAL MEDICINE SUPPLEMENT

Unlike many herbs that are used for a broad variety of clinical conditions, cranberry is primarily used for the prevention and treatment of UTIs and the deodorization of urine in those who are incontinent or in long-term care facilities (Der Marderosian 1977; Muller and Clauson 1997). While it does have other potential therapeutic benefits, these are far overshadowed by its use for its beneficial effects on the genito-urinary system, both among practitioners and those self-treating.

Figure 12 Historical illustration of cranberry.

Source: Bartons Flora of North America (1817).

Traditional Use of Cranberry for Urinary Tract Health

The clinical use of cranberries to treat UTIs is prevalent among contemporary herbalists, naturopathic physicians, midwives, and other allied natural health care practitioners. Many practitioners prefer to recommend the use of cranberry prophylactically in women with recurrent bladder infections in order to avoid the overuse of antibiotics and the resultant development of antibiotic-resistant bacteria. This has become common practice in many long-term elder care facilities. Naturopathic physician Bill Mitchell (2003) reported 500 mg 3 times daily of encapsulated powder with

"plenty of water" to be effective for bladder infections. Additionally, or alternatively, Mitchell recommended 30 drops of goldenseal (*Hydrastis canadensis*) and 60 drops of pipsissewa (*Chimaphila umbellata*) be added to 1 cup of cranberry juice 3 times daily. Because of the potential negative consequences of sugar, many natural health practitioners recommend use of unsweetened cranberry juice, encapsulated or tableted cranberry juice concentrates, or extracts for urinary tract health. Mitchell further records that noted naturopathic physician John Bastyr recommended a dose of 4 cups of cranberry juice daily for bladder infections. Aviva Romm, in her *The Natural Pregnancy Book* (1997), recommends that a dose of 8 oz of unsweetened cranberry juice every 4 hours be taken with an additional 8 oz of water four times daily for a total of 64 oz of fluid. This can dilute the urine and reduce the burning sensation associated with UTIs. Herbal practitioners also frequently prescribe cranberry after a course of antibiotics to prevent UTI recurrence.

Natural health care practitioners frequently recommend a prophylactic dose of cranberry juice in the range of 90 to 250 mL unsweetened juice daily (Muller and Clauson 1997), whereas the treatment range for cystitis or urethritis is from 360 to 1500 mL daily, prescribed as one 8 oz glass of juice every 2 or 4 hours, sometimes alternating with 8 oz of water (Muller and Clauson 1997; Romm 1997). This is continued for 3 to 5 days beyond the duration of symptoms. Bone and Morgan (1999) give the dosage in clinical trials as 75 mL daily of pure cranberry juice (approximately equivalent to 300 mL daily of CJC). In recent years, concentrated preparations have become available in tablets and capsules. Although the prescribed dosage may vary among practitioners, approximately 400 mg of cranberry dry extract are given 2 (Bone and Morgan 1999) or up to 3 (Yarnell 1997) times daily for those unable to consume the recommended quantities of juice. For a 25:1 dry extract preparation (fresh weight), dosages of 400, 800, and 1200 mg are equivalent to 10, 20, and 30 g of fresh berries daily (Bone and Morgan 1999). The typical dose of cranberry juice cocktail in early studies was 300 mL (27% juice), which yielded approximately 36 mg of PACs. This dose and characterization is used as a benchmark by some making cranberry products (e.g. Salo et al. 2012; Uberos et al. 2012).

Among modern herbal practitioners, cranberry is often combined with other botanicals to prevent and treat UTIs. These include uva ursi (*Arctostaphylos uva-ursi*), pipsissewa (*Chimaphila umbellata*), marshmallow root (*Althaea officinalis*), buchu (*Barosma betulina*), *Echinacea* spp., quaking aspen (*Populus tremuloides*), horsetail (*Equisetum arvense*), kava (*Piper methysticum*), and licorice (*Glycyrrhiza glabra*) (Mills and Bone 2000; Weiss 1988; Yarnell 1997). These botanicals offer therapeutic actions beyond the bacterial anti-adherence activity of cranberry alone, including demulcent, anti-microbial, diuretic, and immune stimulating effects. Some herbalists have reported concerns that cranberry might diminish the effectiveness of uva ursi (Mills and Bone 2000; Weiss 1988); since there is evidence that the antimicrobial effectiveness of uva ursi requires an alkaline urinary environment (Blumenthal et al. 1998; ESCOP 2003; Frohne 1970; Kedzia et al. 1975). Currently, a conclusion concerning such an antagonistic effect cannot be made.

In addition to the standard use of cranberry for urinary tract health based on the traditional western and modern understanding of cranberry's actions (astringent tonic, antiseptic, etc.), Western herbalists have also begun characterizing the fruit according to traditional Chinese principles, though a consensus of this has not yet been reached. Margi Flint, in her *The Practicing Herbalist* (2010), specifically provides a principle of differentiation in recommending cranberry in those with bladder infections manifesting as a cold (yin-type) where urinary excretion is characterized by a clear, in contrast to, a deep yellow urinary stream. Other herbalists classify cranberry as "cold" and therefore specific for inflammatory (excess heat) bladder conditions, as well as for bladder infections arising form internal deficiencies, cautioning against the use of cranberry if coldness predominates (Brien 2015, personal; communication to AHP, unreferenced). Garran (2008) in his *Western Herbs According to Traditional Chinese Medicine: A Practitioner's Guide*, records the use of cranberry for incontinence and excessive urination, both of which can be associated with bladder infections.

Other Uses of Cranberry by Traditional Practitioners

Eclectic physicians considered cranberry fruit to be an anti-inflammatory, using it both as a drink and a poultice for a variety of conditions including tonsillitis, sore throat due to scarlet fever, swollen cervical glands, and indolent and malignant ulcers (Felter and Lloyd 1905; Hollembaek 1865). Hollembaek (1865) recommended the bruised berries as a poultice for local inflammation as well as the prevention of gangrene. The drink was considered to be an anti-scorbutic, antiseptic, diuretic, laxative, refrigerant, and mild astringent, the latter property accounting for its use as an anti-diarrheal agent (Foster 1899; Hollembaek 1865; Rafinesque 1830). In King's *American Dispensatory* (1866), King instructed for ripe cranberries to be bruised to form a cataplasma [poultice] (cataplasma oxycocci). This was to be applied around the throat in quinsy (swollen or abscessed tonsils), in scarlatina (scarlet fever), and other diseases. In this regard, King noted that he knew of "no more useful agent" and that "its action is very prompt, relieving in a few hours." King described other reputed uses of the cataplasm in "cancerous ulcers, erysipelatous inflammation, and gouty rheumatisms." The later edition of King's *American Dispensatory* by Felter and Lloyd (1905) instructs for half of a fresh cranberry be mixed with flour and applied "to the tip of the nose for treating the pain and redness of boils on the tip of the nose." This topical use of cranberry may correlate partly with evidence of the antiadhesion activity associated with cranberry in UTIs, *H. pylori*, and dental caries. "Herbal Ed Smith" recommends the use of cranberry as a mouthwash in conjunction with spilanthes (*Spilanthes acmella*), myrrh (*Commiphora habessinica*), thyme (*Thymus vulgaris*), cinnamon (*Cinnamomum aromaticum*), clove (*Syzygium aromaticum*), and peppermint (*Mentha piperita*)

(extract of alcohol [50–60%], water, glycerine) mixing 1 mL of the extract in 2 ounces of water and swishing thoroughly after brushing and flossing.

Perhaps the earliest "health food preparation" of cranberry was recorded by Dr O Phelps Brown in *The Complete Herbalist* (1867) as *cranberry water*. Brown instructs to put a teaspoon of cranberries into a cup of water and mash them. In another pan, 2 quarts of water are boiled with one large spoonful of corn or oatmeal and a bit of lemon peel. To this, the cranberries were to be added with enough sugar to maintain the tart flavor and a wine-glassful of sherry. This mixture was then boiled gently for 15 minutes and strained. Brown provides no specific indications for this particular recipe and only records it in his section *Things for the Sick-Room*.

In addition to its prominent use for urinary tract health, Bastyr instructed for fresh cranberries to be applied directly to severe dermatitis of the scalp (Mitchell 2003), this obviously being a recommendation based on early use by eclectic physicians noted above.

While not traditionally used, a recent study reported that cranberry leaves yielded the highest concentration of polyphenols (predominantly PACs) among several fruits tested (mean value 11,095.46 mg/100 dm) suggesting a possible use in a manner similar to uva ursi (*Arctostaphylos uva-ursi*) (Teleszko and Wojdylo 2015). There is also data showing that home made berry products (sauces specifically) can yield higher concentrations of anthocyanins and proanthocyanins than typically yielded in commercial products, which due to processing and long-term storage, can result in a loss of these important compounds (Grace et al. 2012).

When characterizing cranberry according to traditional Chinese principles, other potential uses emerge based predominantly on the cooling, astringing nature of the fresh fruits. Garran's review (2008) reports that cranberry; "Supplements the kidneys and restrains essence" for "incontinence, excessive urination, and excessive sweating", and "strengthens the kidney and liver" for "yin vacuity for the kidneys and liver...impotence, lower back pain, dizziness, and night sweats.", correlating it closely with the traditional use of the Chinese herb shan zhu yu (*Cornus officinalis*). Others (e.g., Brien 2015, personal; communication to AHP, unreferenced) support this characterization further describing that it drains heat through diuresis and is also appropriate for restraining other leakages such as seminal emissions, leucorrhea, drooling, and excess mucus in the GI tract.

Actions

Anti-inflammatory (internally and topically), anti-scorbutic, antiseptic, astringent (mild), diuretic, febrifuge, laxative, nutritive, refrigerant, urinary tract antiseptic.

Indications Supported by Traditional or Modern Experience

Primarily used for simple cystitis, as a urinary tract astringent and antiseptic, and for general urinary tract health.

INTERNATIONAL STATUS

United States

Dietary Supplement: Cranberry preparations can be labeled and marketed as dietary supplement products (USC 1994), requiring FDA notification and substantiation to support permissible nutrient content and/or structure/function claim statements (FDA 2000). Quality: A quality standards monographs for Cranberry Liquid Preparation is provided in the Dietary Supplements section of the *United States Pharmacopeia-National Formulary* (USP-NF) (USP-NF 2012).

Food: Cranberries and cranberry products labeled and marketed without health claims or structure/function claim statements are conventional food products. Quality: For use as a conventional food, the "United States Standards for Grades of Fresh Cranberries" (USDA 1997a), the "United States Standards for Grades of Fresh Cranberries for Processing" (USDA 1997b), and the "United States Standards for Grades of Frozen Cranberries" (USDA 1997b) are available from the United States Department of Agriculture.

Australia

Cranberry is a substance that may be used as an active ingredient in "Listed" medicines in the Australian Register of Therapeutic Goods (ARTG) for supply in Australia (TGA 2007). Quality: Where an active ingredient is covered by a monograph in the BP, PhEur or USP, then this is the minimum standard that must be applied in its entirety, otherwise a justification is required (ARGCM 2015). Indications: No standard indications. Product-specific depending on the evidence submitted with a listed medicine application. For example, one listed medicine contains 500 mg per capsule of the branded ingredient CranMax®(Pharmachem Labs; Kearny, NJ), a press cake-juice powder product, and was authorized with the indications: "Reduce the incidence of the symptoms of cystitis. Cranberry has traditionally been used for the maintenance of urinary tract health. Research has shown its ability to discourage the adherence of harmful bacteria to the urinary tract wall and thus promote urinary health. A clinical trial conducted on the extract used [in this product] has shown benefits in management of cystitis. The deodorising properties of cranberry also make it useful in masking urinary odour in incontinence". Similar indications are allowed on another cranberry extract standardized to deliver 36 mg PACs (Ellura®; Pharmatoka, Rueil-Malmaison, France) (TGA 2012).

Canada

Natural Health Product (medicinal ingredient): Cranberry (fresh or dried fruit, fruit juice, juice cocktail, dried fruit juice or extract) is regulated as a medicinal ingredient of Natural Health Products (NHPs) requiring pre-marketing authorization and issuance of product license for over-the-counter (OTC) human use. The Natural Health Products Directorate (NHPD) published separate labeling standards

monographs for cranberry fruit (NHPD 2011a) and dried cranberry juice (NHPD 2011b). Quality: The finished product must comply with the minimum specifications outlined in the current NHPD Compendium of Monographs (NHPD 2007a). The medicinal ingredient may comply with the specifications outlined in the Cranberry Liquid Preparation monograph published in the USP (NHPD 2007b; NHPD 2011a; NHPD 2011b). Indications: (1) Traditionally used in herbal medicine to help prevent (recurrent) urinary tract infections (UTIs); (2) Used in herbal medicine to help prevent recurrent urinary tract infections (UTIs) in women; (3) Provides antioxidants for the maintenance of good health (NHPD 2011a; NHPD 2011b). "Helps reduce the adhesion of certain *E. coli* bacteria to the urinary tract walls".

Natural Health Product (non-medicinal ingredient): Certain forms of cranberry are permitted for specified uses as non-medicinal components of NHPs as long as they occur at sub-therapeutic levels. The defined substances "Vaccinium Oxycoccos (Cranberry) Fruit Extract" and "Vaccinium Macrocarpon (Cranberry) Fruit Juice" are permitted for use as flavor-enhancing components of oral-ingestion NHPs, while the substance "Vaccinium Macrocarpon (Cranberry) Fruit Extract" is permitted for use as a skin-conditioning agent of topical-application NHPs (NHPD 2012).

Food: Cranberries and cranberry products labeled and marketed without NHP claim statements are conventional food products. Quality: For the use of cranberry fruit as an ingredient of conventional food products, Canada's "Grades and Standards for Cranberries" is available in the "Fresh Fruit and Vegetable Regulations" published by the Minister of Justice.

European Union

Herbal Medicinal Product: Depending on the dosage strength and indications for use, cranberry preparations may be regulated as foodstuff, botanical food supplements, or as Herbal Medicinal Products (HMPs), the latter requiring pre-marketing authorization and product licensing or registration (EPCEU 2004). Quality: For cranberry to be used as an active ingredient of a licensed or registered HMP, compliance with pharmacopoeial-quality standards would be required and manufactured under pharmaceutical GMPs. Presently there are no European pharmacopoeial standards for cranberry. Indications: Presently, the European Medicines Agency (EMA) has initiated the development of a Community Herbal Monograph for cranberry.

Food with Nutrition or Health Claims: Although the European Food Safety Agency (EFSA) has, as of 2012, rejected various proposed health claims related to PACs from cranberry-fruit food supplements such as "defense against bacterial pathogens in the lower urinary tract," "gum protection," and "heart health," (EFSA 2011) national authorities have authorized a health claim for at least one specific strength of cranberry products. The French regulatory authority authorized the following health claim for cranberry products that provide at least 36 mg of North American cranberry PACs per day; "Helps reduce the adhesion of certain *E. coli* bacteria to the urinary tract walls". AFSSA provides examples that fulfill the requirement, such as 29 g of fresh or frozen cranberries provide 36 mg of PAC, 39 g cranberry puree provides 36 mg of PAC, and 27 g of dried sweetened cranberries provide 36 mg of PAC (AFSSA 2007). Subsequently, the French Directorate General of Competition, Consumption and Fraud Repression (DGCCRF) provided new requirements for determining PAC content. Following the publication by USDA-ARS of a new analytical method called BL-DMAC, the DGCCRF issued a statement that PAC values are to be quantified according to the BL-DMAC method. If reference to analyses based on other protocols is made, the marketer "will have to be able to justify the pertinence of his choice regarding the nutritional labeling and the proposed claim" (DGCCRF 2010).

Cosmetic: The defined ingredient "Vaccinium Macrocarpon Fruit Extract" is permitted for astringent function, "Vaccinium Macrocarpon Fruit Juice" (expressed from the fruit) for skin-conditioning function, "Vaccinium Macrocarpon Fruit Powder" (obtained from the dried, ground fruit) for antioxidant function, and "Vaccinium Macrocarpon Fruit Water" (aqueous solution of the steam distillate obtained from the fruit) for masking and perfuming functions in cosmetic products (ECHCD 2012).

World Health Organization

A monograph for *Fructus Macrocarponii*, the fresh or dried ripe fruit of *Vaccinium macrocarpon*, is published in the *WHO Monographs on Selected Medicinal Plants* Volume 4. Medicinal uses supported by clinical data: Orally as adjunct therapy for the prevention and symptomatic treatment of urinary tract infections in adults. Two clinical trials have assessed the effect of the fruit juice in pediatric populations, but the results were negative. Results from clinical trials involving the use of cranberry for the treatment of children with neurogenic bladder were also negative and do not support the use of cranberry products in pediatric populations for this indication. Uses described in traditional medicine: Treatment of asthma, fever, loss of appetite, scurvy and stomach ailments, as well as gallbladder and liver disease, and for treatment of wounds (WHO 2009).

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