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Review

Cranberry anti-cancer compounds and their uptake and metabolism: An updated review

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Abstract. Consumption of cranberry fruits or juice rich in polyphenols is associated with a wide range of potential health benefits. We and others have previously showed that cranberry juice concentrate and its phytochemicals, flavonols, anthocyanins and A-type proanthocyandins, may have potential to be chemopreventive agents. Although a number of cranberry constituents have been implicated in cancer prevention, our understanding about which metabolites are bio-available to reach target sites and thereby elicit cancer chemopreventive properties is still lacking. However, poor plasma bioavailability of cranberry constituents may be overcome by their potential interactions with gut microbiota by providing cancer prevention through induction of compositional and functional modifications of gut microbiota. Well-designed clinical trials evaluating metabolic and gut microbiome changes associated with cranberry consumption would provide useful information about the cancer patient's response to dietary intervention with cranberry constituents.

Keywords: Cranberry, polyphenols, chemoprevention, metabolism

1. Introduction

Cranberry (*Vaccinium macrocarpon* Ait. Ericaceae)- a fruit native to North America - offers a wide array of health benefits and has attracted much public interest as a functional food (whole, fortified or enriched food) with increasing scientific reports showing its potential health benefits [1]. It is widely believed that cranberry juice can help to treat and prevent urinary tract infections (UTIs) caused by *E. coli* [2]. Emerging evidence has also shown that cranberry juice and its phytochemicals have potential cancer chemopreventive effects both *in vitro* and *in vivo* [3–5].

Cranberry contains a diverse range of phytochemicals. Flavonols, proanthocyanidins (PACs), and anthocyanins are the major contributors to the observed anti-cancer properties of cranberry fruits or juice. Their underlying mechanisms of chemopreventive action may include induction of apoptosis in tumor cells [6], reduced ornithine decarboxylase activity [3], decreased expression of matrix metalloproteinase and anti-inflammatory activities [7]. In addition, other cancer preventive effects of cranberry have been attributed to modulating reactive oxygen

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species (ROS) [8]. Cranberry may also be cancer preventive through a combination of additive and/or synergistic effects [9]. While a multitude of mechanisms has been proposed, clinical use of cranberry polyphenols as anti-cancer agents has not been approved due to several unresolved challenges.

For a safe and effective use of cranberry products, understanding the pharmacokinetic properties (absorption, distribution, metabolism and elimination or excretion, ADME) of a heterogeneous mixture or a pure compound isolated from cranberry is essential. However, a lack of authentic proanthocyanidin standards and sufficient amounts of these compounds for *in vivo* studies continue to be important challenges. In addition, safety evaluation is essential for a dietary supplement to be tested in humans.

With regard to cancer chemopreventive effects of cranberry and its active phytochemicals, there have been a number of excellent reviews [10–12]. The beneficial effects of cranberry constituents could be due to their metabolites presented at the target sites. In doing so, they may bind to target proteins, or modulate the activity of genes. Considering the importance of metabolic transformation of dietary polyphenols, in this review we attempt to provide an updated insight into the current stage of knowledge on anti-cancer compounds of cranberry and their uptake and metabolism *in vitro* and *in vivo*.

2. Cranberry polyphenols with anti-cancer properties

We previously demonstrated that cranberry juice may be effective in preventing urinary bladder carcinogenesis [5]. Our work on toxicological assessment of cranberry juice concentrate in Fischer-344 rats also concluded that exposures to cranberry juice concentrates do not pose a significant toxicology risk in rodents [5]. Recent research reports have further demonstrated that cranberry fruit can be a potential natural source for cancer prevention. Daily consumption of cranberry fruit powder (1500 mg daily for 30 days) lowered prostate specific antigen (PSA) in patients with prostate cancer [13]. Another study showed that dietary feeding of frozen cranberry may have potential to inhibit development of intestinal tumor in $APC^{min/+}$ mice [14].

Cranberry's efficacy against tumor development *in vivo* will depend largely on the bioavailability of its phytochemicals to the various tissues, but some of the cranberry components undergo rapid metabolism and elimination, indicating that they have poor bioavailability [15].

2.1. Flavonols

Flavonols are a class of flavonoids that have a 3-hydroxyflavone backbone. Quercetin, and myricetin (Fig. 1) are the main flavonols in cranberry and their levels vary among cultivars. They are mostly present in glycosylated forms. Less ripe fruits contain smaller amounts of flavonols in cranberry, compared to ripe ones [16]. Sugars often associated with these compounds are glucose, galactose, rhamnose, arabinose and glucuronic acid. The specificity of the sugar moiety and its attachment position to flavonol may play a role in the bioavailability *in vivo* [17].

3. Quercetin

Cranberry fruit contains glycosides (galactose, glucose, rhamnose and rutinose) of quercetin, with quercetin 3-galactoside being the predominant form. Quercetin has been shown to be a growth inhibitor against various cancers *in vitro* and *in vivo* [18–26]. Such inhibitory effects have been shown to depend on the form of quercetin. For example, compared to its rutinoside and rhamnoside, the aglycone quercetin has higher cytotoxic effects against human leukemia HL-60 cells [19]. Recent studies demonstrated quercetin's synergistic anti-cancer effects with 10-hydroxy camptothecin in MCF-7 cells, indicating its potential application of drug combination in cancer therapy [21]. While a number of reports demonstrate anti-cancer effects of quercetin, the underlying mechanism(s)

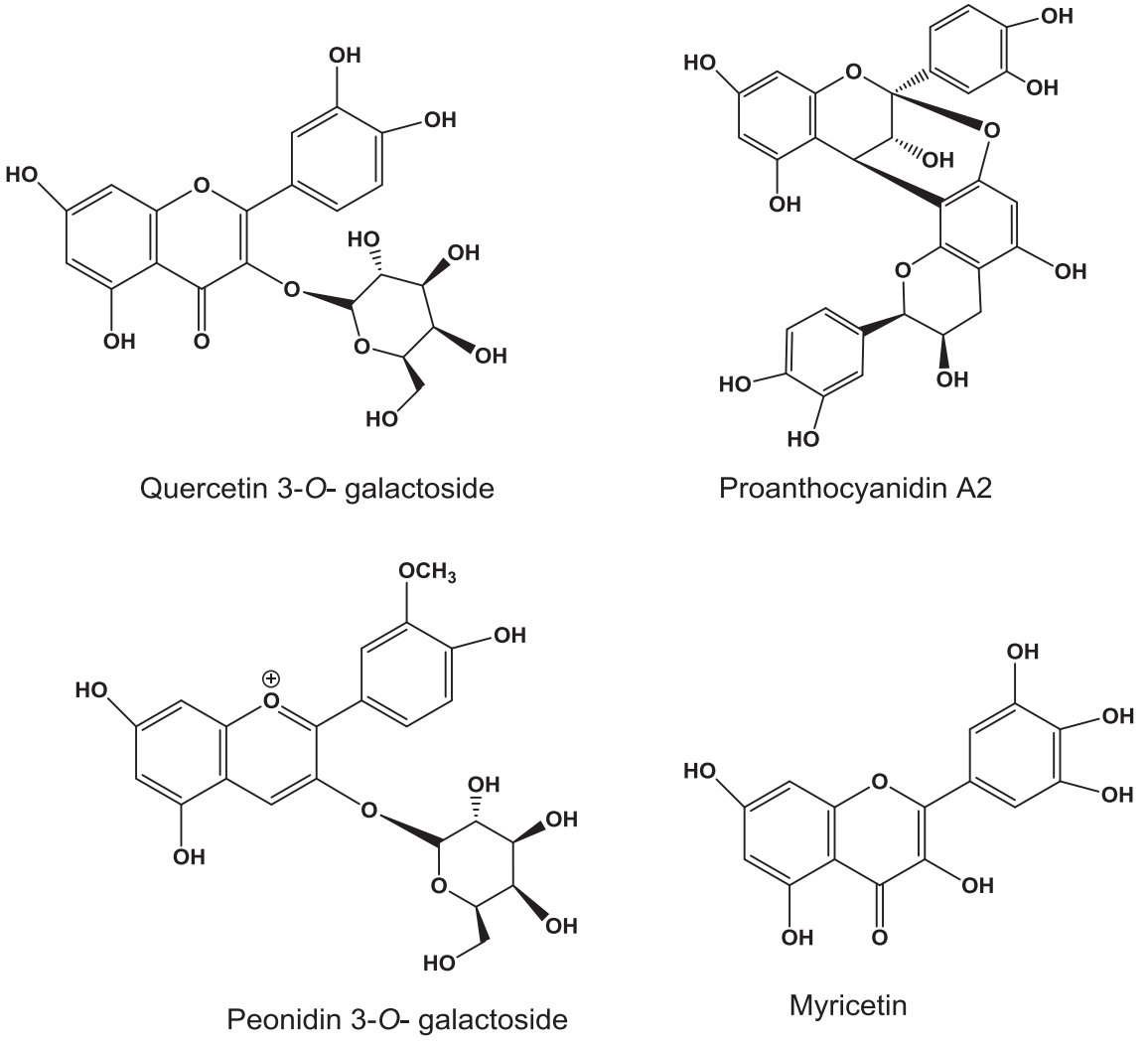

Fig. 1. Structures of major cranberry polyphenols.

by which it exerts cancer chemoprevention are not yet understood [22]. Nonetheless, it interacts with multiple cellular targets influencing the activity of diverse signaling pathways [23].

Regarding the potential toxicity of quercetin *in vivo*, previous studies have shown that quercetin is not carcinogenic when rats were fed with 5.0% (w/w) quercetin in diet [18, 24].

While quercetin intake is negatively correlated with the incidence of a number of cancers, its low bioavailability is a problem and combination therapy may provide solutions [25]. Uptake, metabolism, pharmacokinetics and biological effects of quercetins depend on their chemical structures and the biological systems being tested. Like other flavonoids, quercetin undergoes phase II metabolism, glucuronidation, methylation and sulfation. Quercetin-3-O-β-glucuronide (Fig. 2), the major metabolite of quercetin in circulation, may be hydrolyzed to the aglycone quercetin at target sites [27]. Phase II metabolites of quercetin and methylquercetin (quercetin sulfates, methylquercetin sulfate, quercetin diglucuronide, methylquercetin diglucuronide, methylquercetin glucuronide sulfate) were detected in the urine sample collected over 14 h after cranberry powder treatment in rats [15].

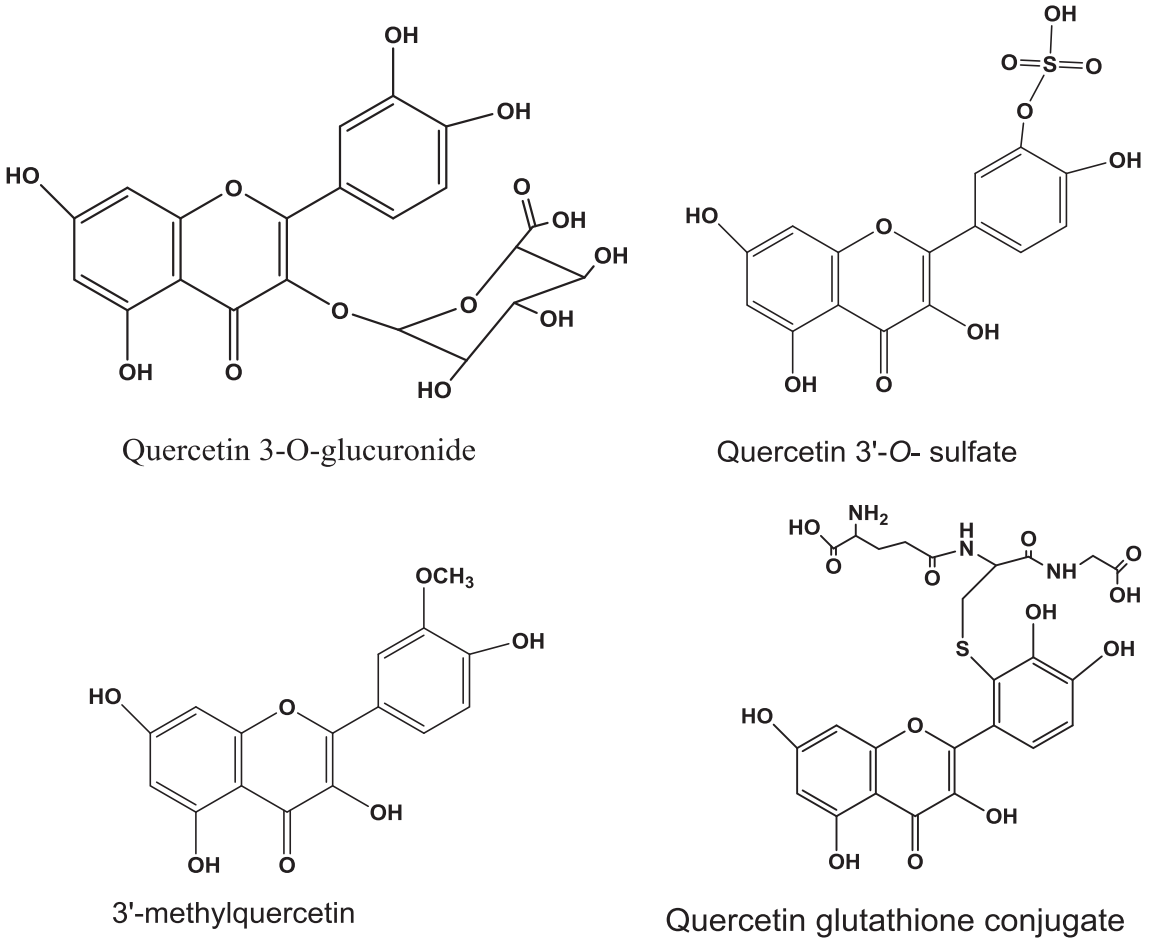

Fig. 2. Representative structures of quercetin phase II metabolites.

Interestingly, in our studies, no free quercetin in plasma and urine was found: only low levels of methylated quercetin [15]. Intact quercetin 3-rhamnoside and quercetin-3-galactoside were detected in the urine treated with cranberry juice [15]. These results suggest that the glycosidic moiety plays a role in the absorption.

Although quercetin-3-O-glucoside is a minor flavonoid in cranberry, it is more bioavailable than its aglycone quercetin. The higher absorption of quercetin glucoside compared to aglycone is partly due to its absorption in the small intestine via the sodium-dependent glucose transporter (SGLT1) [28, 29]. Another possible mechanism is the hydrolysis of quercetin-3-glucoside by lactose phloridzin hydrolase present in the brush border membrane of the small intestine releasing the aglycone and sugar [30].

Cranberry constituents that are not absorbed in the small intestine may undergo metabolism by gut microbiota; however, the absorption ability of the colon is less efficient than that of the small intestine, albeit that transit time through the colon is much longer than through the small intestine. Inter-individual variability in gut microbiota and their interaction with host is another important issue related to polyphenol bioavailability and their potential health beneficial effects. An acute double-blind randomized control trial with cranberry juice showed that due to variations in the gut microbiome, inter-individual variation of plasma metabolites was broad and metabolite

dependent [31]. Recent investigation on the relationship between quercetin metabolism, gut microbiota composition and dietary intake in elderly population indicate that specific fecal microbiota composition is correlated positively or negatively with quercetin concentration. It means metabolic fate of quercetin on the lower gut depends on the composition of microbiota [32]. Differences in phase II-enzyme polymorphism, in addition to the microbial composition of the gut microbiota, may be responsible for the inter-individual variation in the bioavailability of cranberry polyphenols [33].

In vivo beneficial effects of cranberry constituents depend on how they interact with target cells [34]. Understanding the intracellular metabolism of target compounds helps determine the underlying biological mechanism associated with cancer chemoprevention. In our lab we previously performed uptake and metabolism studies of quercetin and its metabolites in bladder cancer cells [35]. These studies showed that quercetin 3-O-glucuronide enters and remains intact but inactive in SW-780 cells. In contrast, quercetin 3-O-glucoside, quercetin, methylquercetin and myricetin exert cell growth inhibition [35].

Biological activities of polyphenols may be mediated by intracellular metabolites (including quinone/quinone methide species). In our studies, quercetin 3-O-galactoside and 3-O-glucoside differ from each other in terms of bladder cancer cell growth inhibition and cellular metabolism [35]. Compared to quercetin 3-O-glucoside, quercetin 3-O-galactoside (Fig. 2) undergoes less metabolic biotransformation (methylation, glucuronidation and quinone formation) and shows a weak cell growth inhibitory effect in SW-780 cells [35].

Glutathione is an abundant intracellular antioxidant and plays important roles in detoxifying of xenobiotics, including polyphenols. We and others have detected glutathionylated products of quercetin (Fig. 2) [34–36]. Quinone-like metabolites can be produced which may have role(s) in cell growth inhibition in the quercetin-treated cells. We detected two peaks of quercetin glucuronides (*m/z* 498) and one less mass unit (*m/z* 478) in the lysate of SW-780 bladder cancer cells treated with quercetin [35]. MS/MS of the precursor ions *m/z* 479 and 478 produced intense fragment ions *m/z* 303 and 302, respectively corresponding to aglycone quercetin (*m/z* 303) and the proton stabilized quinone species (*m/z* 302) [34, 35].

4. Myricetin

Myricetin (Fig. 1) is considered as a multi-targeted natural product with potential anti-migratory and anti-invasive effects based on *in vitro* cellular assays [37]. Recent preclinical studies showed that myricetin represses the malignant progression of prostate cancer [38]. It induces apoptosis in colon cancer cells by increasing the expression of nucleoside diphosphate kinase and other caspase-regulated apoptotic proteins [39]. Myricetin's potential anti-metastatic effects have been studied in a mouse model [40]. In this study, myricetin suppressed breast cancer metastasis to the lung, indicating its potential to be developed as a therapeutic agent for breast cancer. In our studies, myricetin showed potent cell growth inhibitory effects in bladder cancer cells, but low inhibitory activity in normal cells, indicating its selective cytotoxicity for cancer cells but not normal cells [35].

Not much is known about the uptake and metabolism of myricetin. Human urine contains myricetin-3-galactoside and myricetin-arabinoside after ingestion of cranberry juice [41]. 3,5-Dihydroxyphenylacetic acid has been identified as its microbial metabolite in rats [42].

5. Cranberry proanthocyanidins

Cranberry fruits are a rich source of A-type proanthocyanidins and they may play a role in resistance to fruit rot [43]. Structurally, A-type PACs contain a double inter-flavanyl linkage compared to B-type PACs that have a single interflavanyl bond. Cranberry oligomers contain at least one A-type ether linkage (C_2-O-C_7) along with B-type linkages (Fig. 1). Their contents vary among cultivars growing in different regions. For example, Howes

had the highest total proanthocyanidins (76–92 g kg–1) and Ben Lear had lower PAC content than others when eight cultivars were analyzed for PACs [43]. Processing cranberries also affects proanthocyanidin content [44].

A number of previous studies have shown that cranberry proanthocyanidins are potential chemopreventive or cytotoxic against cancer cells [12, 45–47]. Wang et al. demonstrated that quercetin aglycone and PAC DP-9 induce cytotoxicity and cell cycle arrest and increase cisplatin sensitivity in ovarian cancer cells [48]. Similarly, a cranberry proanthocyanidin (PAC-1A) has been shown to have chemotherapeutic potential to treat a broad spectrum of neuroblastomas, including highly malignant tumors that show resistance to cyclophosphamide by increasing its cellular uptake and retention [49]. Cranberry proanthocyanidins have been found to be among the most active constituents [12]. Kresty et al. showed potential preventive or therapeutic effects in human esophageal adenocarcinoma cell lines and esophageal tumor xenografts in athymic NU/NU mice [46]. Although PACs inhibit the growth of a number of cancer cells lines, proanthocyanidin A2 showed no potent growth inhibitory activities in bladder cancer cells [35].

Cranberry constituents including PAs may provide benefits on gastrointestinal cancer and UTIs, as well as systemic inflammatory activities mediated via the gut microbiome [50].

The low bioavailability of cranberry PAs in circulating plasma indicates that the major part of their uptake and metabolism takes place in the colon where the specific resident microbiota produce metabolites that can undergo further metabolism upon entering the systemic circulation.

6. Anthocyanins

Anthocyanins (the glycosides of anthocyanidins) are water-soluble flavonoids which impart visible pigmentation (absorb light at around 500 nm) in fruits and vegetables. Daily intake of anthocyanins in the United States is in the range of 200 mg which is about 9-fold higher than other flavonoids [51]. Cranberry contains glycosides of six aglycones - cyanidin, peonidin, malvidin, pelargonidin, delphinidin and petunidin - and the 3-O-galactoside of peonidin (Fig. 1). Cyanidins are the major anthocyanins (about 55%) in cranberry [52]. Anthocyanins are potential cancer chemopreventive agents due to a broad range of activities, including anti-oxidant, anti-inflammatory and anti-mutagenic properties [53]. However, compared to anthocyanins, anthocyanidin aglycones show more potent cancer cell growth inhibitory activities *in vitro* [54]. Our lab previously examined growth inhibitory effects of the anthocyanins, cyanidin 3-O-glucoside, cyanidin 3-O-galactoside, and peonidin 3-glucoside, in bladder cancer cells. They all had weak activities, however [35].

Difference in the anti-cancer effects of anthocyanins is due to the different substituents on their B-ring; B-ring anthocyanins with ortho-dihydroxyphenyl substituents show the most potent activity [55]. There is an excellent updated review on effects of anthocyanins on the prevention and treatment of cancer by Lin et al., (2017) [53]. There has been considerable interest in cancer chemopreventive effects of anthocyanins because of their easily accessible source, low toxicity and large consumption via the diet [56].

Although anthocyanins are absorbed rapidly, overall, plasma bioavailability of anthocyanins is generally <1% of the consumed amounts [57]. The food matrix also plays a role in determining their bioavailability [56]. We detected peonidin 3-O-galactoside and cyanidin-3-O-galactoside in rat urine after cranberry treatment [15]. Peonidin 3-O-galactoside was detected in urine within 24 h as the most abundant anthocyanin in healthy volunteers consuming 200 mL of cranberry juice; urinary output of anthocyanins reached a maximum between 3–6 h after ingestion [58]. In another pharmacokinetic study of cranberry anthocyanins in humans, galactosides, glucosides and arabinosides of cyanidin, peonidin and malvidin were detected in urine after consumption of cranberry juice [59]. Contrary to others' work, Kalt et al. (2014) detected a large number of anthocyanin phase II metabolites, especially aglycone glucuronides, following ingestion of blueberry juice in humans, indicating that anthocyanins are more bioavailable than previously suggested [60]. Another clinical study on metabolism of cyanidin-3-glucoside indicated that anthocyanins are metabolized to a structurally diverse range of metabolites (phase I, phase 2, degradants and bacterial metabolites) with dynamic kinetic profiles [61].

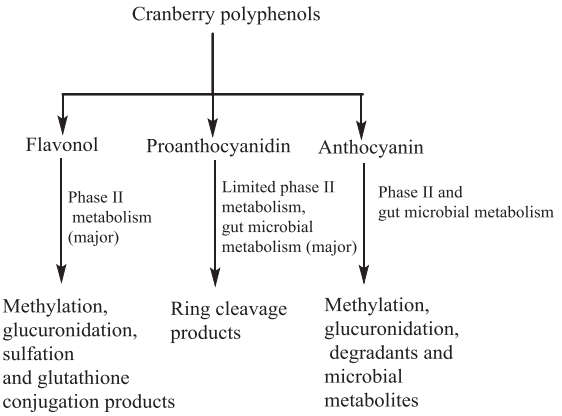

Fig. 3. Biotransformation of cranberry polyphenols *in vitro* and *in vivo*.

Because absorption of anthocyanins is an important issue if they are to be used as chemo-preventive agents, future studies focusing on enhancing their absorption is needed [62].

7. Conclusions and future prospectus

Although many preclinical studies have supported the cancer inhibitory potential of cranberries and their products, it is less clear whether the cancer chemo-preventive effects of cranberry are due to unmetabolized cranberry flavonoids or their upper intestinal and hepatic phase I and phase II metabolites. In addition, the role of specific gut bacteria in metabolism of cranberry polyphenols and the gut microbial metabolites that are absorbed into systemic circulation in exerting cancer chemoprevention remain to be elucidated, which are important issues in understanding the underlying mechanisms of action of cranberry. A summary of biotransformation of cranberry polyphenols is given in Fig. 3.

The bioavailability and activity of polyphenols found in fruits such as cranberry generally depend on not only in their content, but also on the extent to which they are metabolized by the gut microbiota, taken up into the blood and their hepatobiliary transport and metabolism by the liver. Although the gut microbial metabolism of dietary polyphenols is considered as an essential part of personalized nutrition approaches, whether gut microbiota regulate cranberry's chemo-preventive effects is largely unknown, partly because of the complex gut microbiota composition, which is further confounded by their interactions with the host. In addition, cranberry constituents may alter activities of fecal and host colonic mucosal enzymes, thereby altering cranberry and non-cranberry metabolites. Specific bacterial enzymatic activities such as glucosidases, esterases, demethylation, etc., may play important role in bio-activation or deactivation of cranberry metabolites. Therefore, future studies on effects of cranberry metabolites on the specific gut bacterial enzymatic activities are needed. Encouragingly, a recent randomized, double blind, cross-over feeding trial to evaluate cranberries' impact on gut microbiota has been reported [63]. These studies show that animal-based diets containing meat, dairy products and simple sugars altered gut microbiota composition to a less favorable profile and cranberries attenuate the impacts of animal diet.

Our current knowledge of gut microbial polyphenols metabolism generally is mainly based on interactions between single compounds and selected bacterial populations. To gain a comprehensive knowledge on interactions between cranberry constituents and the gut microbiome, metabolomics may provide functional endpoints associated with cancer chemo-prevention by cranberries. With regard to comprehensive analysis, recent high

resolution mass spectrometry-based metabolomics studies show that cranberry juice consumption alters plasma levels of endogenous and hepatic or bacterial metabolites of cranberry in young women [64]. Such studies would help capture molecular signature that could lead to potential biomarker identification for cranberry chemoprevention. More specifically, by comparing metabolic profiles between cranberry-treated and untreated animals in specific animal models of cancers, we would know to what extent cranberry and non-cranberry metabolites are generated by colonic microbiota and their potential chemopreventive roles.

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Conflict of Interest

The authors have no conflict of interest to report.

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