Review Article

Enhancing health benefits of berries through phenolic antioxidant enrichment: focus on cranberry

Dhiraj A Vattem PhD[1,3], Reza Ghaedian PhD[2] and Kalidas Shetty PhD [1]

[1] Laboratory of Food Biotechnology, Department of Food Science, University of Massachusetts, Amherst,USA
[2] Decas Cranberry Products Inc.,Carver, MA 02330, USA
[3] Current Address: Molecular and Cellular Nutrition, Texas State University, San Marcos, TX 78666

Emerging epidemiological evidence is increasingly pointing to the beneficial effects of fruits and vegetables in managing chronic and infectious diseases. These beneficial effects are now suggested to be due to the constituent phenolic phytochemicals having antioxidant activity. Cranberry like other fruits is also rich in phenolic phytochemicals such as phenolic acids, flavonoids and ellagic acid. Consumption of cranberry has been historically been linked to lower incidences of urinary tract infections and has now been shown to have a capacity to inhibit peptic ulcer-associated bacterium, *Helicobacter pylori*. Isolated compounds from cranberry have also been shown to reduce the risk of cardiovascular diseases. Recent evidence suggests the ability of phytochemical components in whole foods in being more effective in protectively supporting human health than compared to isolated individual phenolic phytochemicals. This implies that the profile of phenolic phytochemicals determines the functionality of the whole food as a result of synergistic interaction of constituent phenolic phytochemicals. Solid state bioprocessing using food grade fungi common in Asian food cultures as well as cranberry phenolic synergies through the addition of functional biphenyls such as ellagic acid and rosmarinic acid along with processed fruit extracts have helped to advance these concepts. These strategies could be further explored to enrich cranberry and cranberry products with functional phytochemicals and further improve their functionality for enhancing health benefits.

Key Words: antioxidant activity, antimicrobial activity, free radical scavenging, cranberry, fruit phytochemicals, phenolic antioxidant, synergy, solid-state bioprocessing.

Introduction

Phenolic Phytochemicals

Phenolic phytochemicals are secondary metabolites of plant origin which constitute one of the most abundant groups of natural metabolites and form an important part of both human and animal diets.[1-3] These phenolic metabolites function to protect the plants against biological and environmental stresses and therefore are synthesized in response to pathogenic attack such as fungal or bacterial infection or high energy radiation exposure such as prolonged UV exposure.[4,5] Phenolic phytochemicals, because of their important protective biological functions, are ubiquitous in all plants and therefore find their place in almost all food groups. Common fruits such as apples, cranberries, grapes, raspberries, and strawberries and their beverages like red wine, apple and orange juices are rich sources of phenolic phytochemicals. In addition to fruits, vegetables such as cabbage and onion; food grains such as sorghum, millet, barley, peas, and other legumes[6] are also described as important sources of phenolic phytochemicals.

Phenolic phytochemicals from berries

There are numerous different types of phenolic phytochemicals which are classified according to their ring structure and the number of carbon atoms substituting the ring and linking them together (Table 1). Metabolic processing of phenolic phytochemicals in plants for their final biological function has led to chemical variations in basic phenolic structure. They vary structurally from being simple molecules (e.g phenolic acids with a single ring structure) (Fig. 1), biphenyls and flavanoids having 2-3 phenolic rings[7,8] (Fig. 1). Another abundant group of phenolic phytochemicals in fruits and vegetables often referred to as polyphenols contain 12-16 phenolic groups (Fig. 1). These polyphenols are classified as condensed proanthocyanidins, tannins which include galloyl and hexahydroxydiphenoyl (or ellagoyl) esters and their derivatives, or phlorotannins[7,8] (Fig. 1). Flavanoids and biphenyls are another important class of phenolic phytochemicals that are especially rich in fruits. Flavanoids like quercetin constitute the most abundant group of phenolic phytochemicals and are widespread in fruits. Structural variations within the rings resulting in an alteration in the extent of hydroxylation, methylation, isoprenylation, dimerization and glycosylation (producing O- or C-glycosides) subdivide the flavonoids into several families: flavonols, flavones, flavanols, isoflavones, anthocyanidins and others

Correspondence address:. K Shetty, Laboratory of Food Biotechnology, Department of Food Science, University of Massachusetts, Amherst, MA 01003, USA
Tel: +1-413-545 1022; Fax: +1-413-545-1262
Email: kalidas@foodsci.umass.edu
Accepted 13 December 2004

Table 1. The major classes of phenolic compounds in plants

Number of carbon atoms	Basic skeleton	Class
6	C_6	Simple phenols Benzoquinones
7	C_6-C_1	Phenolic acids
8	C_6-C_2	Acetophenones Tyrosine derivatives Phenylacetic acids
9	C_6-C_3	Hydroxycinnamic acids Phenylpropenes Coumarins Isocoumarins Chromones
10	C_6-C_4	Naphthoquinones
13	C_6-C_1-C_6	Xanthones
14	C_6-C_2-C_6	Stilbenes Anthraquinones
15	C_6-C_3-C_6	Flavonoids Isoflavonoids
18	$(C_6$-$C_3)_2$	Lignans
30	$(C_6$-C_3-$C_6)_2$	Biflavonoids
N	$(C_6$-$C_3)_n$ $(C_6)_n$ $(C_6$-C_3-$C_6)_n$	Lignins Catechol Flavolans (Condensed Tannins)

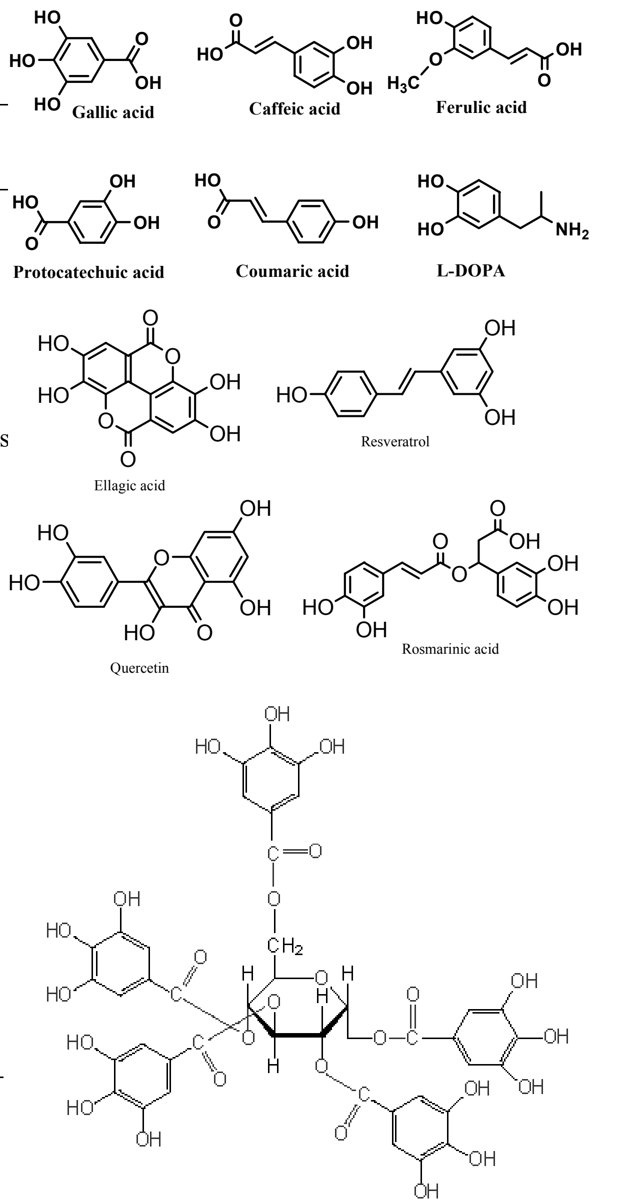


Figure 1. Common simple phenol, biphenyls, flavavoids and tannins in plants

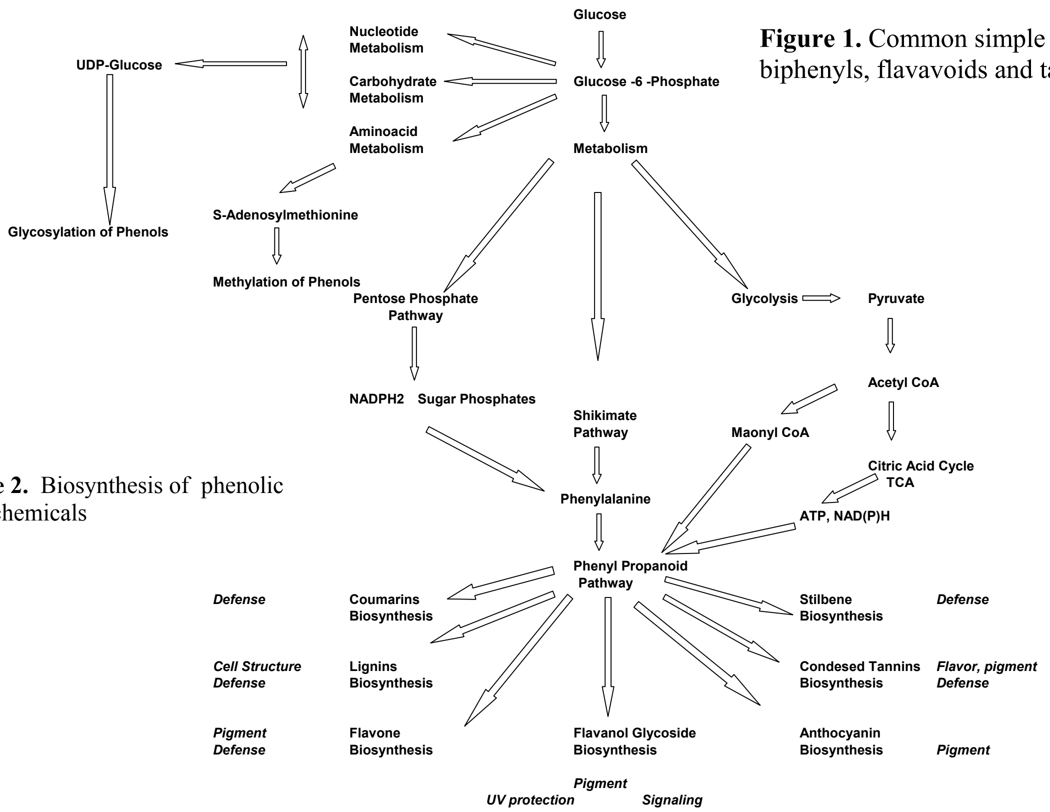


Figure 2. Biosynthesis of phenolic phytochemicals

(Fig. 2).[2,9] All the phenolic phytochemicals are derived from a common biosynthetic pathway, incorporating precursors from both the shikimate and/or the acetate-malonate pathways[1,9] (Fig. 2). To increase the solubility and target the phenolics to specific parts of the plant and prevent its enzymatic and chemical degradation, phenolic phytochemicals are often esterified with sugars and other chemical components such as quinic acid through the hydroxyl groups of the phenolic ring.

Berries like many other fruits are rich in phenolic compounds and these include biphenyls, flavonoids and phenolic acids. They are typically rich in flavonoids and biphenyls such as ellagic acid (Fig. 1) and represent a large group of secondary plant metabolites.[10] The diversity and complexity of the flavonoids found in berries depends on at least two factors: (i) different variety of aglycones and the high number of glycosides, sometimes in acylated form, and (ii) condensation into complex molecules. Recent research has determined the antioxidant activity of different phenolic compounds[11-13] and attempt has been made to define the structural characteristics which contribute to their activity.[12,14]

Phenolic acids present in berries are hydroxylated derivatives of benzoic acid and cinnamic acid.[15] The other simple phenolics in berries include caffeic, chlorogenic, ferulic, sinapic, and *p*-coumaric acids.[16] Berries have been described to exhibit a wide range of biological effects, including antioxidant[17-19] and anticarcinogenic properties.[22] A high free radical scavenging activity of berry extracts toward chemically generated active oxygen species has been described in several studies.[17-19] In terms of health benefits, increased fruit consumption in daily diets has shown to significantly reduce the incidence and mortality rates of cancer, cardiovascular disorders, and other degenerative diseases caused by oxidative stress.[20-23] Further, epidemiological evidence suggests that high consumption of flavonoids which are an important component of berries may provide protection against coronary heart disease, cardiac stroke,[24-26] lung cancer,[22,26,27] and stomach cancer.[28]

Cranberry

Cranberry *(Vaccinium macrocarpon)* which is also known as American cranberry belongs to the family Ericaceae, which also includes blueberry (*V. angustifolium*) and bilberry (*V.myrtillus*). The American cranberry is a prominent agricultural food crop produced in Massachusetts, Wisconsin, Michigan, Canada, New Jersey, Oregon, and Washington. The crop size is approximately 500 million pounds annually and is processed into three basic categories: fresh (5%); sauce products, concentrate, and various value-added applications (35%); and juice drinks (60%).[29] Even though cranberry has been historically associated with positive health benefits, scientific investigation into positive health benefits of cranberry (*Vaccinium macrocarpon*) has recently received more attention.[30,31] Extensive processing of cranberry for different products such as juice yields cranberry pomace as a byproduct with limited applications. Pomace is mainly composed of the skin, flesh and seed of the fruit. It is rich in fiber and has relatively small amounts of protein and carbohydrates.[32] Traditionally it has been used as an ingredient in animal feed, however due to its low protein and carbohydrate content it has little nutritive value. Its disposal into the soil or in a landfill poses considerable economic loss and potential environmental problems due to its low pH.[32] However such fruit processing residues are attractive and potentially cheap sources of natural antioxidants with potential health benefits as food and feed ingredients.[33-37] Evidence indicates increased antioxidant activity in rat plasma after oral administration of grape seed extracts.[38] Identification of polyphenolic compounds from apple pomace[39] has also been reported. Phenolics are ubiquitous in plants, but seeds and skins are especially rich sources of phenolics[33,38,40-42] probably because of the role in protecting the fruit and the seed to ensure healthy propagation of the species. However, several phenolics that are found in pomace and other plant products exist in conjugated forms either with sugars (primarily glucose) as glycosides or other moieties. This conjugation occurs via the hydroxyl groups of the phenolics, which reduces their ability to function as good antioxidants since availability of free hydroxyl groups on the phenolic rings is important for resonance stabilization of free radicals. Lowered antioxidant capacity has direct implications on decreasing functionalities for health benefit when these phenolics are ingested via food. Therefore, if free phenolics are released from their glycosides or other conjugates then the antioxidant and thus their function for health benefit could be enhanced. Enzymatic hydrolysis of these phenolic glycosides appears to be an attractive means of increasing the concentration of free phenolic acids in fruit juice and wines to enrich taste, flavor, and aroma, also potentially increasing functional value for health and wellness.[43-45]

Biological functionality of phenolic phytochemicals in nutritional management of oxidative and infectious diseases

Reactive oxygen species have been implicated in the development of several oxidation- linked diseases such as cancer, cardiovascular diseases (CVD) and diabetes. Recent epidemiological studies have indicated that diets rich in fruits and vegetables are associated with lower incidences of oxidation-linked diseases such as cancer, CVD and diabetes. These protective effects of fruits and vegetables are now linked to the presence of antioxidant vitamins and phenolic phytochemicals having antioxidant activity, which support the body's antioxidant defense system.[46-48]

Phenolic phytochemicals exhibit a wide range of biological effects and can broadly be divided into two categories. The first and the well described mode of action of these phenolic phytochemicals in managing oxidation stress-related diseases are due to the direct involvement of the phenolic phytochemicals in quenching the free radicals from biological systems. It is well-known that free radicals cause oxidative damage to nucleic acids, proteins, and lipids. Oxidation of biological macromolecules as a result of free radical damage has now been strongly associated with development of many physiological conditions which can manifest into disease.[46,47,49,50-52] Phenolic phytochemicals, due to their phenolic ring and hydroxyl substituents, can function as effective antioxidants due to their ability to quench free electrons. Phenolic antioxidants can therefore scavenge the harmful free radicals and thus inhibit their oxidative reactions with vital biological molecules.[17]

It is also known that consumption of natural dietary antioxidants from fruits and vegetables has been shown to enhance the function of the antioxidant enzyme-linked defense response mediated by glutathione, ascorbate, superoxide dismutase, catalase and glutathione-s-transferase interface.[53-56] Therefore, the second and more significant mode of action of phenolic phytochemicals is the ability to modulate cellular physiology both at the biochemical/physiological and at molecular level linked to the above antioxidant enzyme response pathway. This mode of action is a result of the structure-function activity that modulate antioxidant response-linked metabolic pathways. These phenolic phytochemicals, because of their structural similarities with several key biological effectors and signal molecules, are able to participate in induction-repression of gene expression or activation-deactivation of proteins, enzymes and transcription factors of key metabolic pathways.[49,57-59] They can critically modulate cellular homeostasis as a result of their physiochemical properties such as size, molecular weight, partial hydrophobicity and ability to modulate acidity at biological pH through enzyme coupled reactions. As a consequence of many modes of action of phenolic phytochemicals they have been shown to have several different functions. Several studies have demonstrated anticarcinogenic properties of phenolic phytochemicals such as gallic acid, caffeic acid, ferulic acid, catechin, quercetin and resveratrol.[60-62] It is believed that phenolic phytochemicals might interfere in several of the steps that lead to the development of malignant tumors, including, inactivating carcinogens, inhibiting the expression of mutant genes.[63] Potential anti-carcinogenic functions of phenolic phytochemicals have also been shown due to their ability to act as antimutagens in the Ames test.[60-62] Many studies have also shown that these phenolic phytochemicals can repress the activation of pro-carcinogens[2,64] and can activate enzymatic systems (Phase II) as well as prevent oxidative damage to the DNA which has been shown to be important in the in the age-related development of some cancers.[65] Other phenolics, such as caffeic and ferulic acids, and important biphenyls such as resveratrol (Fig. 1) found in fruits, have been shown to inhibit the development of cancer in tissue cultures in the presence of carcinogens.[66,67] Resveratrol and other phenolic antioxidants have also been shown to prevent development of CVD by inhibiting LDL oxidation *in vitro*[68] and preventing platelet aggregation. Phenolic phytochemicals have also been able to reduce blood pressure and have anti-thrombotic and anti-inflammatory effects[69,70]. They can also inhibit the activity of α-amylase and α-glucosidase, which are resposible for postprandial increase in blood glucose level, which has been implicated in the manifestation of type-II diabetes and cardiovascular diseases.[71,72] The ability of phenolic phytochemicals in managing infectious diseases has also been well described. Antibacterial, antiulcer activity antiviral and antifungal properties[73-76] of the phenolic extracts have been suggested. Immune modulatory activities such as anti-allergic[77] properties by suppressing the hypersensitive immune response and the TNF-α mediated proinflammatory pathways have also been shown to be mediated by phenolic phytochemicals.[78]

Cranberry and health benefits

Cranberry and their products have been associated historically with many positive benefits on human health. For many decades, cranberry juice has been widely used, particularly in North America, as a folk remedy to treat urinary tract infections (UTIs) in women and other

Table 2. Important phenolic phytochemicals in cranberry with their structures:

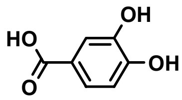
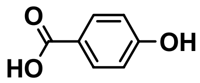
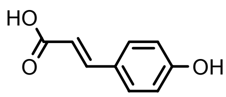
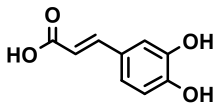
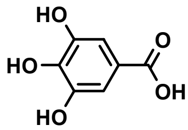
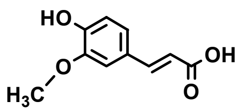
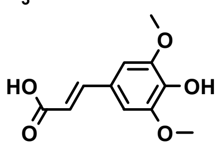
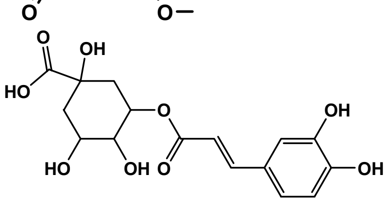
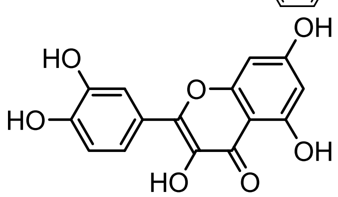
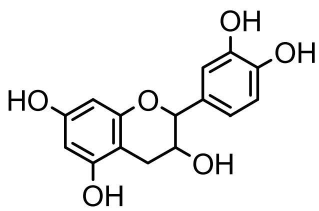
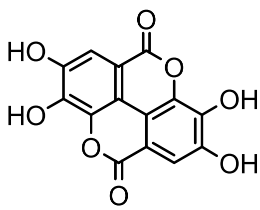
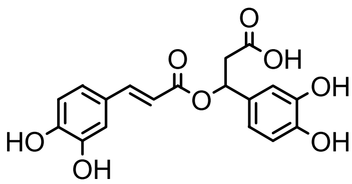
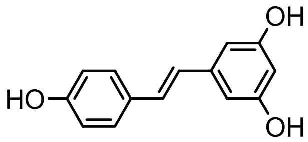
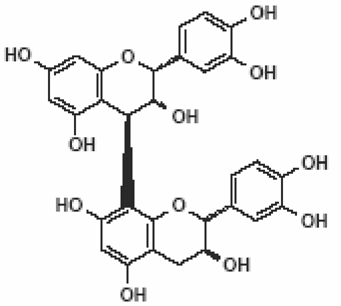
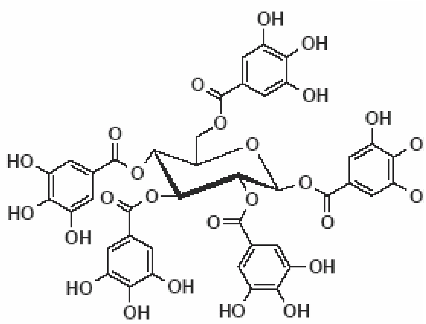
Protocatechuic acid	
Para-hydroxybenzoic acid	
Coumaric acid	
Caffeic acid	
Gallic acid	
Ferulic acid	
Sinapic acid	
Chlorogenic acid	
Quercetin	
Catechin	
Ellagic acid	

Table 2. continued

Rosmarinic acid	
Resveratrol	
Condensed tannins	
Hydrolyzabl e Tannins-	

gastrointestinal (GI) disorders.[79,80] These infections have now been shown to be caused by the infections of the GI tract by *Escherichia coli* and other pathogens. Recent clinical studies have established a positive link between cranberry consumption and prevention of urinary tract infection with the consumption of cranberry juice.[81] Cranberry, like other fruits and berries is rich source of many bioactive components including phenolic phytochemicals such as phenolic acids, flavanoids, anthocyanins and their derivatives.[82] p-Hydroxybenzoic acid , a phenolic acid present at high concentrations in cranberry (Table 2) was previously believed to be the primary bioactive component in preventing urinary tract infections.[30] This was believed to be due to the bacteriostatic effect of hippuric acid which is formed from metabolic conversion of p-hydroxybenzoic acid in liver. Hippuric acid when excreted into the renal system causes acidification of urine and thus prevents the growth of *Escherichia coli* on the urinary tract.[30]

Anti-adhesive properties of cranberry phenolics: implications on urinary and gastrointestinal tract infections

Recent research has now suggested that adherence of the pathogen to the host tissue is also one of the most important step required for the colonization of bacteria and their subsequent infection. A majority of infectious diseases including UTI that are caused by microorganisms have now been shown to involve the adherence of the pathogen to the host tissue.[83,84] Investigations into the mechanism of adherence to host tissue has led to an understanding that these are mediated by specific glycoprotein receptors called "fimbriae" or "lectins" on the bacterial cell surface which can specifically bind to sugars present on the mucosal or intestinal cell surfaces of the host tissue.[83,84] Many soluble and non-digestible sugars and oligosaccharides fructose and manno-oligosaccharides can act as decoy sugars and forcing the bacteria to bind to them instead of the host cell. Inability of the pathogen to bind to the cell surface causes the microorganism to be washed away by the constant peristaltic motion in the intestine. This type of binding however, occurs only via a specific type of fimbriae called type 1 (mannose sensitive) fimbriae.[83,84] Recent investigations have shown that type P fimbriae [α-Gal(1→4) β-Gal] mediated adhesion which is mannose resistant is also involved in the adherence of bacterial adhesion. Components of fruit juices including cranberry juice have been proposed to inhibit bacterial adherence to the epithelial cells by competing to bind with both these fimbriae.[83,84] In addition to the extensive studies done on the inhibition of the adherence of components of *Escherichia coli* to host mucus cells, recent *in-vitro* studies indicate a high molecular weight component in cranberry to inhibit the siallylactose specific (S-fimbriae) adhesion of *Helicobacter pylori* strains to immobilized human mucus, erythrocytes and cultured gastric epithelial cells. It is suspected that these high molecular weight components from cranberry can inhibit the adhesion of *Helicobacter pylori* to the stomach *in vivo* and therefore may have a potential inhibitory effect on the development of stomach ulcer.[85,86] Certain high as well as low molecular weight preparations of cranberry juice were also effective in decreasing the congregation and salivary concetration of *Streptococcus mutans* which causes tooth decay.[87,88] The formation of catheter blocking *Proteus mirabilis* biofilms in recovering surgical patients was also significantly decreased by the consumption of cranberry juice.[89] Adherence of *Fusobacterium nucleatum* to Buccal cells was also reduced by the high molecular weight extract from cranberry juice.[87,88] Low and high molecular weight components (condensed and hydrolysable tannins) from cranberry (Table 2) are also suspected to have anti-viral properties because of the ability of tannins and other polyphenols to form non-infectious complexes with viruses. Cranberry and its products are also known to inhibit many fungi belonging to *Candida sp.* and *Microsporum sp.* and *Trycophyton sp.*[90,91]

Other health benefits of cranberries

Recent studies have reported on the radical-scavenging activities of the various flavonol glycosides and anthocyanins in whole cranberry fruit and their considerable ability to protect against lipoprotein oxidation *in vitro*. The flavanoid and hydrocinnamic acid derivatives in cranberry juice reduced the oxidation of LDL and LDL mobility.[92] In an *in vitro* study cranberry extracts significantly inhibited both H_2O_2 as well as TNFα induced vascular endothelial growth factor (VEGF) expression by the human keratinocytes.[93] Matrigel assay using human dermal microvascular endothelial cells showed that edible cranberries impair angiogenesis.[93] It is therefore believed that cranberry juice may also have beneficial effect on cardiovascular health.[94,95] Cranberry and cranberry extracts have been shown to have anticancer activity. Phenolic extracts from berries of *Vaccinium* species were able to modulate the induction and repression of ornithine decarboxylase (ODC) and quinone reductase that critically regulate tumor cell proliferation.[96] Cranberry extracts showed antitumor activity by inhibiting the proliferation of MCF-7 and MDA-MB-435 breast cancer cells in *in vitro* assays. Cranberry extracts also exhibited a selective tumor cell growth inhibition in prostate, lung, cervical, and leukemia cell lines.[96,97]

Innovative strategies to enrich cranberry with phenolic antioxidants to enhance functionality

A large variety of phenolic phytochemicals are present in plants and especially in fruits, such as cranberry which have several health benefits. The phenolic phytochemicals are generally present in their glycosidic and non-glycosidic forms. The glycosides are mainly confined to hydrophilic regions in the cells such as in vacuoles and apoplasts probably because of their higher water solubility.[98,99] Glycosylation of the hydroxyl groups on the phenolic ring of a phenolic phytochemical renders the molecule more water-soluble and less reactive toward free radicals.[6] Glucose is the most commonly involved sugar in glycoside formation, although phenolic glycosides of galactose, rhamnose, xylose and arabinose and disaccharides such as rutinose have also been reported to be present in plants.[6] Polymeric phenolics such as tannins exist primarily as condensed tannins (Table 2) or proanthocyanidins and are formed biosynthetically by the condensation of single catechins and flavanols. They are present either as soluble tannins or bound to the cell wall. Hydrolysable tannins (Table 2) are esters of a sugar with either gallic acid (gallotannins) or ellagic acid (ellagitannins). Tannins though have higher antioxidant properties than individual simple phenolics, are usually not bioavailable and are to some extent anti-nutritive in their function because of their ability to bind and precipitate biological macromolecules such as proteins and carbohydrates.[73] The total phenolic phytochemical content in plant foods also varies greatly. Their presence in plant foods is largely influenced by genetic factors and environmental conditions. Other factors, such as cultivar, variety, maturity, processing, and storage, also influence the content of plant phenolics.[100-102] The effects of processing and storage on the changes and content of polyphenols in cranberry,[103] plum,[104] and grape juice[105] have been evaluated.

As a consequence of evidence that consumption of fruits and vegetables has been linked to decreased incidences of chronic diseases, there has been a constant increase in the demand for diets rich in phenolic phytochemicals. Vast variation in the amounts of phenolic antioxidants available via diet[106] coupled with reduced bioavailability and functionality has led to an urgent need to develop innovative strategies to enrich the diets with phenolics and specifically phenolic antioxidants with consistent phytochemical profile for enhanced health benefits.

Strategies for enrichment

Among many strategies two important strategies to enrich phenolic antioxidants are: (i) Genetic improvement of fruits and vegetables to produce plants that will yield fruits and vegetables with higher phenolic concentration and (ii) Bioprocessing of botanicals using solid-state systems and synergies to generate phytochemical profiles with improved health benefits. Currently in terms of genetic improvement breeding strategy coupled with micropropagation using tissue culture is being developed.[107-109] These strategies along with genetic modification using recombinant DNA could be directed towards phytochemical enrichment and quality improvement. However, such methods present important issues such as regulation of key metabolites by multiple genes and biochemical pathways, acceptance of genetically modified foods and relative time and economic considerations that are involved.[110] A second exciting strategy that can be used is the bioprocessing of botanicals using solid-state systems using food grade microorganisms common in Asian food systems and synergies to generate phytochemical profiles with enhanced functionality and health benefits. This strategy can be for juice and pulp as well as pomace that remains after juice is extracted from the fruits. Fermentation of fruit juice such as grape juice to wine has already been shown to improve it nutritive and health promoting activity.[111-113] Solid-state bioprocessing done on the pulps using food grade fungi typical of Asian tempeh and soy products can result in enrichment of the pulps with phenolic antioxidants and functionally important phenolic phytochemicals and also improve phytochemical profile consistency.

Solid-state bioprocessing

Fermented foods have been consumed by humans all over the world for centuries. Most fermentation processes are conducted with liquid nutrient broths. Well-known examples in the food industry are the production of yoghurt, beer, wine, lactic acid, and many food flavors.[114] However, partial fermentation and aerobic microbial growth-based bioprocessing has also been used for processing food and food wastes in Asia for 2000 years. Here, instead of a nutrient broth, moist solid nutrients with minimal water are used as a substrate for microbial growth and this process is referred to as solid-state bioprocessing. Microbial fermentation and aerobic microbial growth on foods in solid-state for preservation of food and flavor enhancement has been done for centuries and some of the common examples for these processes include manufacture of cheese and bread.[115] Other well-known examples are the production of French cheeses such as Roquefort and the production of fermented sausages. In Asia, solid-state bioprocessing has been used for food processing for over 2000 years for the production of fermented foods such as Tempeh, *natto*, and soy sauce.[116] The preservation of fish and meat by solid-state bioprocessing has also reported to be carried by early human civilizations.[116,117] Fruit wastes have been extensively used as substrates for solid-state bioprocessing. These wastes have mostly been used for the production of fertilizers, animal feed, as a growth substrate for mushrooms, ethanol production, production of organic acids such as citric acid, tartaric acid and lactic acid and for the production of various kinds enzymes such as pectinases.[32,114] Solid-state bioprocessing of fruit substrates has also been carried out for several decades to produce compounds like gallic acid and vinegar.[115,114] Recent research has also shown that consumption of microbial bioprocessed foods, especially solid-state bioprocessed, has health benefits.[118,119] Solid-state bioprocessing of fruit wastes such as cranberry pomace using food grade fungi *Rhizopus oligosporus* and *Lentinus edodes* has shown to enrich phenolic antioxidants and improve phytochemical consistency. These studies have shown that during the course of solid-state growth the antioxidant activity and phenolic content of the pomace extracts increase several fold.[43,44] The process resulted in enrichment of functional phenolics to a level found usually in fresh fruits and their juice products. It is suspected that the increase in phenolic and antioxidant activity could have been due to the production of various hydrolyzing enzymes by the fungi during the course of solid-state growth. These fungal hydrolases such as glucosidase and fructo-furanosidases could possibly be hydrolyzing the glycosidic linkages between the phenolic moieties and sugars. A similar observation in the increase in phenolic aglycones was observed during the fermentation of soy milk for the production of tofu.[120] Also it is suggested that the fungus in adapting itself to utilize the fruit substrates may produce various other types of hydrolases such as laccases and lignocellulases. The activity of these enzymes is suspected to be responsible for the increase in the polymeric phenolics and potentially contribute to enhanced functional activity of such phenolic antioxidants. Enrichment of the solid-state bioprocessed fruit wastes such as cranberry pomace with ellagic acid after bioprocessing has been reported.[43,44] This may have resulted due to the hydrolysis of ellagotannins by tannin hydrolyzing enzymes produced by the fungus (Table 2). Further, it is suspected that phenolic enrichment could also occur through the contribution from the growing fungal species. The endogenous phenolics present in the fruit wastes could be toxic to the growing fungus. In an attempt to adapt and utilize the substrate for growth, the fungus could be detoxifying the phenolics biochemically using a variety of enzymatic systems present in the fungus. The fungal detoxification can occur by a variety of mechanisms including methylating or demethylating the phenolic ring and/or by hydroxylation.[121,122] Recent studies have shown methylated phenolic phytochemicals have excellent antibacterial properties against gram positive bacteria.[122] Hydroxylation of the phenolic ring by the fungal system during its growth increases their antioxidant properties[17] and therefore, phenolics resulting from biotransformation occurring during the solid-state bioprocessing may improve their functionality and be beneficial for human health.

In a recent investigation effect of solid-state bioprocessing of cranberry pomace using food grade fungi *R. oligosporus* and *L. edodes* on anti-microbial activity against *L. monocytogenes* and *Vibrio parahaemolyticus, Escherichia coli O157*: H7 and *Helicobater pylori* was investigated.[124-126] Increase in total phenolics, antioxidant activity and enrichment of ellagic acid in the extracts due to fungal bioprocessing increased the antimicrobial activity against *L. monocytogenes.* The gram negative bacteria *V. parahaemolyticus, E. coli O157: H7* and *H. pylori* were more sensitive to the presence of ellagic acid content and antioxidant activity in a partially hydrophobic environment. The differential sensitivities of the tested microorganisms to various functional phenolic attributes of the extracts may indicate different mechanisms by which these extracts mediate their antimicrobial activity. Antimicrobial sensitivity of all the microorganisms to the presence of ellagic acid could be due to disruption of membrane integrity, blocking ion channels in the membrane or by inhibiting ATP synthesis by quenching the flow of electrons through the electron transport chain in the bacterial membrane.[127,128] The antimicrobial activity in some extracts was also observed after a sharp decrease in total phenolics and ellagic acid content. This could be due to mobilization of simpler phenolics such as protocatechuic acid, chlorgenic acid and further modification and polymerization of simpler phenolics into polyphenols by the fungal systems. The advantages of the solid-state bioprocessing strategy to improve biological functionality is that the fungi such as *R.. oligosporus* and *L. edodes* and other fungi used in this solid-state growth process have long history of use in food cultures in Asia and are generally recognized as safe (GRAS). This approach can easily be adapted to different substrates as well as be extended to liquid fermentation of juices to develop food and ingredients with enhanced functionality.

Cranberry synergies with functional phytochemicals and other fruit extracts

Recent research has documented the evidence that whole foods and not single compounds have a better functionality in maintaining our health against many of the oxidation-linked diseases. Studies on the effect of wine has shown that resveratrol is responsible for the decrease in atherogenesis in rats.[66,67] However, when resveratrol was used as a supplement in diet such an effect was not seen. Other researchers have shown that the combination of resveratrol and quercetin exerts a synergic effect in the inhibition of growth and proliferation of human oral squamous carcinoma cells.[129] When investigating the *in vivo* antioxidant assays with red wine it was observed that different phenolics in wine could play a co-antioxidant role.[130] Synergistic interactions between wine polyphenols, quercetin and resveratrol were found to decrease the inducible nitric oxide synthase (iNOS) activity in cell culture systems.[131] This suggests that the phytochemical profile in which the specific functional phenolic is present plays an important role in determining its functionality. Synergy can be defined as the ability of two or more functional components such as antioxidants in a phytochemical background to mutually enhance their functionalities. Typically, in a whole food background such as red wine, resveratrol is present in a background containing several simple as well as polyphenolics such as gallic acid, protocatchuic acid and hydrolyzed tannins. Each phenolic phytochemical has its own mode of action against a particular target. These modes of actions could be due to their ability to function as classical antioxidants or because of their ability to modulate cellular physiology by disrupting membrane functions or by altering the redox balance and energy metabolism of the cell.[128] However when they are present together their ability to function together rapidly improves the overall result of maintaining the cellular homeostasis especially in eukaryotes or killing the pathogenic prokaryotic bacteria. Also, it was observed that co-administration of coffee with ellagic acid enhanced the anti-genotoxic effect compared with that of either coffee or the ellagic acid alone suggesting that there is a significant synergistic interaction between coffee and the dietary constituents for antigenotoxic effects against different mutagens.[132] The conditions created due to the mode of action of one phenolic significantly improves the chances of the other phenolics to function effectively, thereby reducing the overall dosage required to observe the desired positive effect. This may be one of the reasons why whole foods have a better functionality in maintaining human health compared to the consumption of supplements. This synergy concept can also be artificially duplicated and this provides another way to significantly enhance the functionality of foods. Synergistic supplementation of foods such as fruit beverages with flavanoids and other functional phenolic phytochemical can be used to significantly improve their specific functionality.

In a recent study the potential antimutagenic properties of cranberry phenolics, ellagic acid, rosmarinic acid and their synergistic interactions on enhancing antimutagenic properties in *S. typhimurium* tester system against mutagens sodium azide and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) was investigated.[133] Ability of these phytochemical treatments to protect oxidative damage to DNA was also investigated using the super-coiled DNA strand scission assay. Results showed that ellagic acid was most effective in inhibiting the mutations in *S. typhimurium* system, whereas rosmarinic acid and ellagic acid were equally effective in protecting the DNA from oxidative damage. The antimutagenic functionality of cranberry powder made from juice extracts was significantly enhanced when 30 % (w/w) of phenolics in cranberry powder (Table 2) were substituted with rosmarinic acid and ellagic acid possibly due to synergistic redox modulation which could have influenced mutagen function. It was suggested that the synergistic mixture of cranberry phenolics with rosmarinic acid could also be protecting the cell from mutations by modulating DNA repair systems.[133] A recent study investigated the synergistic interaction of cranberry, blueberry, grape seed extract and oregano extracts on inhibiting *H. pylori.*[134] The results showed that the anti-*H. pylori* activity of cranberry juice extract was significantly improved by its synergistic blending with blueberry, grape seed extract and oregano extract. Lower efficacy of purified phenolics in inhibiting *H. pylori* compared with fruit powder at similar dosage levels suggests a synergistic mode of functionality of these individual phenolics in whole food background was supe-rior. Consumption of blends of fruit juices with biologically active biphenyls or other fruit as well as herb extracts can impart unique functional attributes and could be a more effective strategy in developing diet-based management of *H. pylori* infections as well as other oxidation linked diseases including mutagen and DNA damage induced carcinogenesis.

References

1. Mann J. *Secondary Metabolism*. Oxford Chemistry Series, Clarendon Press: Oxford, 1978.
2. Bravo L. Phenolic phytochemicals: chemistry, dietary sources, metabolism, and nutritional significance. Nutr Rev 1998. 56: 317-333.
3. Crozier A, Burns J, Aziz AA, Stewart AJ, Rabiasz HS, Jenkins GI, Edwards CA, Lean MEJ. Antioxidant flavonols from fruits, vegetables and beverages: measurements and bioavailability. Biol Res 2000; 33: 79-88
4. Shetty K. Biotechnology to harness the benefits of dietary phenolics; Focus on Lamiaceae. Asia Pac J Clin Nutr l997; 6: 162-171
5. Briskin DP. Medicinal plans and phytomedicines. Linking plant biochemistry and physiology to human health. Plant Physiol 2000; 124: 507-14
6. Urquiaga I, Leighton F. Plant Polyphenol Antioxidants and Oxidative Stress. Biol Res 2000; 33: 55-64.
7. Harborne JB. Plant phenolics. In: Bella EA, Charlwood BV, eds. Encyclopedia of Plant Physiology, Springer-Verlag 1980; 8: 329-395.
8. Haslam E. Practical polyphenolics: from structure to molecular recognition and physiological action. Cambridge University Press: Cambridge UK, 1998.
9. Strack D. Phenolic metabolism. In: Dey PM, Harborne JB, eds. Plant Biochemistry. San Diego, California, USA: Academic Press, 1997; 387-416.
10. Zuo Y, Wang C, Zhan J. Separation, characterization, and quantitation of benzoic and phenolic antioxidants in American cranberry fruit by GC-MS. J Agric Food Chem 2002; 50 (13): 3789-94.
11. Guo C, Cao G, Sofic E, Prior RL. High-performance liquid chromatography coupled with coulometric array detection of electroactive components in fruits and vegetables: relationship to oxygen radical absorbance capacity. J Agric Food Chem 1997; 45: 1787-1796.
12. Cao G, Sofic E, Prior R. L. Antioxidant and prooxidant behavior of flavonoids: Structure-activity relationships. Free Radical Biol Med 1997; 22: 749-760.
13. Foti M, Piattelli M, Baratta MT, Ruberto G. Flavonoids, coumarins, and cinnamic acids as antioxidants in a micellar system structure-activity relationship. J Agri and Food Chem 1996; 44: 497–501.
14. ‚Velioglu YS, Mazza G, Gao L, Oomah BD. Antioxidant activity and total phenolics in selected fruits, vegetables, and grain products.J Agric Food Chem 1998;46:4113-4117.
15. Macheix JJ, Fleuriet A, Billot J. Fruit Phenolics. CRC Press: Boca Raton, FL, 1990.
16. Larson RA. The antioxidants of higher plants. Phytochemistry 1988; 27: 969-978.
17. Rice-Evans CA, Miller NJ, Paganga G. Antioxidant Properties of Phenolic Compounds. Trends In Plant Science 1997; 2: 152-159
18. Wang SY, Lin H. Antioxidant activity in fruits and leaves of blackberry, raspberry, and strawberry varies with cultivar and developmental stage. J Agric Food Chem 2000; 48: 140-146.
19. Kähkönen MP, Hopia AI, Vuorela HJ, Rauha J-P, Pihlaja K, Kujala TS, Heinonen M. Antioxidant activity of plant extracts containing phenolic compounds. J Agri Food Chem 1999; 47: 3954–3962.
20. Knekt P, Ja¨rvinen R, Reppa¨nen R, Helio¨vaara M, Teppo L, Pukkala E, Aroma A. Dietary flavonoids and the risk of lung cancer and other malignant neoplasms. Am J Epidemiol 1997; 146: 223-230.

21. Gillman MW, Cupples LA, Gagnon D, Posner BM, Ellison RC, Castelli, WP, Wolf PA. Protective Effect of fruits and vegetables on development of stroke in Men. J Am Med Assoc 1995; 273: 1113-1117.
22. Joshipura KJ, Ascherio A, Manson JE, Stampfer MJ, Rimm EB, Speizer FE, Hennekens CH, Spiegelman D, Willett WC. Fruit and vegetable intake in relation to risk of ischemic stroke. J Am Med Assoc 1999; 282:1233-1239.
23. Cox BD, Whichelow MJ, Prevost AT. Seasonal consumption of salad vegetables and fresh fruit in relation to the development of cardiovascular disease and cancer. Pub Health Nutr 2000; 3:19-29.
24. Strandhagen E, Hansson PO, Bosaeus I, Isaksson B, Eriksson H. High fruit intake may reduce mortality among middle-aged and elderly men. The study of men born in 1913. Eur J Clin Nutr 2000; 54: 337-341.
25. Hertog MG, Feskens EJ, Hollman PC, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. Lancet 1993; 342 (8878): 1007-11.
26. Keli SO, Hertog MGL, Feskens EJM, Kromhout D. Dietary flavonoides, antioxidant vitamins, and incidence of stroke: the Zetphen study. Arch Intern Med 1996; 156: 637-642.
27. Le Marchand L, Murphy SP, Hankin JH, Wilkens LR, Kolonel LN. Intake of flavonoids and lung cancer. J Natl Cancer Inst 2000; 92 (2): 154-60.
28. Garcia-Closas R, Gonzalez CA, Agudo A, Riboli E. Intake of specific carotenoids and flavonoids and the risk of gastric cancer in Spain. Cancer Causes Control 1999; 10 (1): 71-75.
29. National Agricultural Statistics Service (NASS). Agricultural Statistics board. Cranberries. Annual Reports, Fr Nt 4, Washington D.C: USDA, 2001.
30. Marwan AG, Nagel CW. Characterization of cranberry benzoates and their antimicrobial properties. J Food Sci 1986; 51: 1069-1070.
31. Chen H, Zuo Y, Deng Y. Separation and determination of flavonoids and other phenolic compounds in cranberry juice by high-performance liquid chromatography. J Chromatogr A 2001; 13; 913 (1-2): 387-95.
32. Zheng Z, Shetty K. Cranberry processing waste for solid-state fungal inoculant production. Proc Biochem 1998; 33: 323-329.
33. Rodríguez de Sotillo D, Hadley M, Holm ET. Potato peel waste, stability and antioxidant activity of a freeze-dried extract. J Food Sci 1994; 59: 1031–1033.
34. Rodríguez de Sotillo D, Hadley M, Holm ET. Phenolics in aqueous potato peel extract, extraction, identification and degradation. J Food Sci 1994; 59: 649–651.
35. Sheabar FZ, Neeman I. Separation and concentration of natural antioxidants from the rape of olives. J Am Oil Chemists' Society 1988; 65: 990–993.
36. Yamaguchi F, Yoshimura Y, Nakazawa H, Ariga T. Free radical scavenging activity of grape seed extract and antioxidants by electron spin resonance spectrometry in an H_2O_2/NaOH/DMSO system. J Agric Food Chem 1999; 47: 2544–2548.
37. Koga T, Moro K, Nakamori K, Yamakoshi, J, Hosoyama H, Kataoka S, Ariga T. Increase of antioxidative potential of rat plasma by oral administration of proanthocyanidin-rich extract from grape seeds. J Agric Food Chem 1999; 47: 1892–1897.
38. Lu Y, Foo LY. The polyphenol constituents of grape pomace. Food Chem 1999; 65: 1–8.
39. Lu Y, Foo LY. Antioxidant and radical scavenging activities of polyphenols from apple pomace. Food Chem 2000; 68: 81–85.
40. Peleg H, Naim M, Rouseff RL, Zehavi U. Distribution of bound and free phenolic acids in oranges (*Citrus sinensis*) and grapefruits (*Citrus paradisi*). J Sci Food Agric 1991; 57: 417-26.
41. Meyer AS, Jepsen SM, Sørensen NS. Enzymatic release of antioxidants for human low-density lipoprotein from grape pomace. J Agric Food Chem 1998; 46: 2439–2446.
42. Bocco A, Cuvelier ME, Richard H, Berset C. Antioxidant activity and phenolic composition of citrus peel and seed extracts. J Agric Food Chem 1998; 46: 2123–2129.
43. Zheng Z, Shetty K. Solid-state bioconversion of phenolics from cranberry pomace and role of *Lentinus edodes* beta-glucosidase. J Agric Food Chem 2000; 48: 895-900.
44. Vattem DA, Shetty K. Solid-state production of phenolic antioxidants from cranberry pomace by *Rhizopus oligosporus*. Food Biotech 2002; 16 (3): 189-210.
45. Vattem DA, Shetty K. Ellagic acid production and phenolic antioxidant activity in cranberry pomace (*Vaccinium macrocarpon*) mediated by *Lentinus edodes* using solid-state system. Proc Biochem 2003; 39 (3): 367-379.
46. Jakus V. The role of free radicals, oxidative stress and antioxidant systems in diabetic vascular disease. Bratisl Lek Listy 2000; 101 (10): 541-551.
47. Offen D, PM Beart, NS Cheung, CJ Pascoe, A Hochman, S Gorodin, E Melamed, R Bernard, O Bernard. Transgenic mice expressing human Bcl-2 in their neurons are resistant to 6-hydroxydopamine and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine neurotoxicity. Proc Natl Acad Sci 1998; 95: 5789-5794.
48. Barbaste M, Berke B, Dumas M, Soulet S, Delaunay JC, Castagnino C, Arnaudinaud V, Cheze C, Vercauteren J. Dietary antioxidants, peroxidation and cardiovascular risks. J Nutr Health Aging 2002; 6(3):209-23.
49. Droge W. Free radicals in the physiological control of cell function. Physiol Rev 2002; 82 (1): 47-95.
50. Morel Y, Barouki R. Repression of gene expression by oxidative stress. Biochem J 1999; Sep 15; 342 Pt 3:481-96.
51. Schwarz KB. Oxidative stress during viral infection: a review. Free Radic Biol Med 1996; 21 (5): 641-9.
52. Götz J, CI va Kan, HW Verspaget, I Biemond, C B Lamers, RA Veenendaal. Gastric mucosal superoxide dismutases in *Helicobacter pylori* infection. Gut 1996; 38: 502-506
53. Block G, Patterson B., Subar A. Fruit, vegetables, and cancer prevention: a review of the epidemiological evidence. Nutr Cancer 1992; 18: 1-29.
54. Serdula M K, Byers MAH, Simoes E, Mendlein JM, Coates R J. The association between fruit and vegetable intake and chronic disease risk factors. Epidemiology 1996; 7:161-165
55. Tapiero H, Tew KD, Ba GN, Mathe G. Polyphenols: do they play a role in the prevention of human pathologies? Biomed Pharmacother 2002; 56 (4):200-7.
56. Duthie GG, Gardner PT, Kyle JA. Plant polyphenols: are they the new magic bullet? Proc Nutr Soc 2003; 62 (3): 599-603.
57. Lusini L, Tripodi SA, Rossi R, Giannerini F, Giustarini D, del Vecchio MT, Barbanti G, Cintorino M, Tosi P, Di Simplicio P. Altered glutathione anti-oxidant metabolism during tumor progression in human renal-cell carcinoma. Int J Cancer 2001; 91 (1): 55-9.
58. Mates JM, Sanchez-Jimenez F. Antioxidant enzymes and their implications in pathophysiologic processes. Front Biosci 1999; 4: D339-45.
59. Mates JM, Perez-Gomez C, Nunez de Castro I. Antioxidant enzymes and human diseases. Clin Biochem. 1999; 32 (8): 595-603.

60. Yamada J, Tomita Y. Antimutagenic activity of caffeic acid and related compounds. Biosci Biotechnol Biochem 1996; 60 (2): 328-9.
61. Mitscher LA, Telikepalli H, McGhee E, Shankel DM. Natural antimutagenic agents. Mutat Res 1996; 350: 143-152.
62. Uenobe F, Nakamura S, Miyazawa M. Antimutagenic effect of resveratrol against Trp-P-1. Mutat Res 1997; 373: 197-200.
63. Kuroda Y, Inoue T. Antimutagenesis by factors affecting DNA repair in bacteria. Mutat Res 1988; 202 (2): 387-91.
64. Kanai S, Okano H. Mechanism of protective effects of sumac gall extract and gallic acid on progression of CC14-induced acute liver injury in rats. Am J Chin Med. 1998; 26: 333-341.
65. Halliwell B. Establishing the significance and optimal intake of dietary antioxidants: The biomarker concept. Nutr Rev 1999; 57: 104-113.
66. Clifford A.J, Ebeler SE, Ebeler JD, Bills ND, Hinrichs S.H, Teissedre P-L, Waterhouse AL. Delayed tumor onset in transgenic mice fed an amino acid-based diet supplemented with red wine solids. Am J Clin Nutr 1996; 64: 748-756.
67. Jang M, Cai L, Udeani GO, Slowing KV, Thomas C, Beecher CWW, Fong HHS, Farnsworth NR, Kinghorn AD, Mehta RG, Moon RC, Pezzuto J.M. Cancer chemo-preventive activity of resveratrol, a natural product derived from grapes. Science 1997; 275: 218-220.
68. Frankel EN, Kanner J, German JB, Parks E, Kinsella JE. Inhibition of oxidation of human low-density lipoprotein by phenolic substances in red wine. Lancet 1993; 341: 454-457.
69. Gerritsen ME, Carley WW, Ranges GE, Shen C-P, Phan SA, Ligon GF, Perry C.A. Flavonoids inhibit cytokine-induced endothelial cell adhesion protein gene expression. Am J Pathol 1995; 147: 278-292.
70. Muldoon MF, Kritchevsky SB. Flavonoids and heart disease. BMJ 1996;. 312 (7029): 458-9.
71. McCue PP, Shetty K. Inhibitory effects of rosmarinic acid extracts on porcine pancreatic amylase in vitro. Asia Pac J Clin Nutr 2004; 13 (1): 101-106.
72. Andlauer W, Furst P. Special characteristics of non-nutrient food constituents of plants--phytochemicals. Introductory Lecture. Int J Vitam Nutr Res 2003; 73 (2): 55-62.
73. Chung KT, Wong TY, CI Wei, YW Huang, Lin Y. Tannins and human health: a review. Crit Rev Food Sci Nutr 1998; 8: 21-464
74. Ikken Y, Morales P, Martínez A, Marín ML, Haza AI, Cambero MI. Antimutagenic effect of fruit and vegetable ethanolic extracts against N-nitrosamines evaluated by the Ames test. J Agric Food Chem 1999; 47: 3257-3264.
75. Vilegas W, Sanomimiya M, Rastrelli L, Pizza C. Isolation and structure elucidation of two new flavonoid glycosides from the infusion of *Maytenus aquifolium* leaves. Evaluation of the antiulcer activity of the infusion. J Agric Food Chem 1999; 47: 403-406.
76. Abram V, Donko M. Tentative identification of polyphenols in *Sempervivum tectorum* and assessment of the antimicrobial activity of *Sempervivum* L. J Agric Food Chem 1999; 47: 485-489.
77. Noguchi Y, Fukuda K, Matsushima A, Haishi D, Hiroto M, Kodera Y, Nishimura H, Inada Y. Inhibition of Df-protease associated with allergic diseases by polyphenol. J Agric Food Chem 1999; 47: 2969-2972.
78. Ma Q, Kinneer K. Chemoprotection by phenolic anti-oxidants. Inhibition of tumor necrosis factor alpha induction in macrophages. J Biol Chem 2002; 277 (4): 2477-84.
79. Mowrey DB. The scientific validation of herbal medicine. NewYork: McGraw-Hill, 1990; 255-264.
80. Yan X, Murphy BT, Hammond GB, Vinson JA, Neto C. Antioxidant activities and antitumor screening of extracts from cranberry fruit (*Vaccinium macrocarpon*) J Agric Food Chem 2002; 50: 5844 -5849.
81. Griffiths P. The role of cranberry juice in the treatment of urinary tract infections. Br J Community Nurs 2003; 8 (12): 557-61.
82. Vvedenskaya IO, Rosen RT, Guido JE, Russell DJ, Mills KA, Vorsa N. Characterization of flavonols in cranberry (Vaccinium macrocarpon) powder. J Agric Food Chem 2004; 52 (2):188-95.
83. Zafriri D, Ofek I, Adar R, Pocino M, Sharon N. Inhibitory activity of cranberry juice on adherence of type 1 and type P fimbriated *Escherichia coli* to eukaryotic cells. Antimicrobial agents and chemotherapy 1989; 33 (1): 92-98.
84. Sharon N, Ofek I. Fighting infectious diseases with inhibitors of microbial adhesion to host tissues. Crit Rev Food Sci Nutr 2002; 42 (3 Suppl): 267-72.
85. Burger O, Ofek I, Tabak M, Weiss EI, Sharon N, Neeman I. A high molecular constituent of cranberry juice inhibits *Helicobactor pylori* adhesion to human gastric mucus. FEMS Immunology and Medical Microbiology 2000; 29; 295-301.
86. Burger O, Weiss E, Sharon N, Tabak M, Neeman I, Ofek I. Inhibition of Helicobacter pylori adhesion to human gastric mucus by a high-molecular-weight constituent of cranberry juice. Crit Rev Food Sci Nutr 2002; 42 (3 Suppl): 279-84.
87. Weiss EI, Lev-Dor R, Kashamn Y, Goldhar J, Sharon N, Ofek I. Inhibiting interspecies coaggregation of plaque bacteria with a cranberry juice constituent. J Am Dent Assoc 1998; 129 (12): 1719-23.
88. Weiss EL, Lev-Dor R, Sharon N, Ofek I. Inhibitory effect of a high-molecular-weight constituent of cranberry on adhesion of oral bacteria. Crit Rev Food Sci Nutr 2002; 42 (3 Suppl): 285-92.
89. Morris NS, Stickler DJ. Does drinking cranberry juice produce urine inhibitory to the development of crystalline, cather-blocking *Proteus mirabilis* biofilms? BJU International 2001; 88: 192-197.
90. Swartz JH, Medrek TF. Antifungal properties of cranberry juice. Appl Microbiol 1968; 16 (10): 1524-7.
91. Cavanagh HM, Hipwell M, Wilkinson JM. Antibacterial activity of berry fruits used for culinary purposes. Med Food 2003; 6 (1): 57-61.
92. Wilson T, Porcari JP, Harbin, D. Cranberry extract inhibits low-density lipoprotein oxidation. Life Sci 1998; 62: 381-6.
93. Bagchi D, Sen CK, Bagchi M, Atalay M. Anti-angiogenic, antioxidant, and anti-carcinogenic properties of a novel anthocyanin-rich berry extract formula. Biochemistry (Mosc) 2004; 69 (1):75-80.
94. Reed JD, Krueger CG, Porter ML. Cranberry juice powder decreases low density lipoprotein cholesterol in hyper-cholesterolemic swine. FASEB J 2001; 15 (4,5): 54.
95. Reed J. Cranberry flavonoids, atherosclerosis and cardio-vascular health. Critical Rev Food Sci Nutr 2002; 42 (Suppl.): 301-316.
96. Bomser J, Madhavi DL, Singletary K, Smith MA. In vitro anticancer activity of fruit extracts from *Vaccinium* species. Planta Med 1996; 62 (3): 212-6.
97. Krueger CG, Porter ML, Weibe DA, Cunningham DG, Reed JD. Potential of cranberry flavonoids in the prevention of copper-induced LDL oxidation. Polyphenols Communications 2000; 2: 447-448.

98. McClure JW. Physiology and functions of flavonoids. In: JB Harborne, ed.. The Flavonoids. Academic Press: New York, USA , 1975; 45–77.
99. Wollenweber E, Dietz VH. Occurrence and distribution of free flavonoid aglycones in plants. Phytochemistry 1981; 20: 869–932.
100. Kähkönen MP, Hopia AI, Heinonen M. Berry phenolics and their antioxidant activity. J Agric Food Chem 2001; 49: 4076-4082.
101. Onyeneho SN, Hettiarachchy NS. Antioxidant activity, fatty acids and phenolic acids compositions of potato peels. J Sci Food Agric 1993; 62: 345-50.
102. Torres AM, Mau-Lastovicka T, Rezaaiyan R. Total phenolics and high-performance liquid chromatography of phenolic acids of avocado. J Agric Food Chem 1987; 35: 921–925.
103. Gil MI, Holcroft DM, Kader AA. Changes in strawberry anthocyanins and other polyphenols in response to carbon dioxide treatment. J Agric Food Chem 1997; 45:1662-7.
104. Raynal J, Moutounet M, Souquet JM. Intervention of phenolic compounds in plum technology. 1. Changes during drying. J Agric Food Chem 1989; 37: 1046–1050.
105. Spanos GA, Wrolstad RE. Phenolics of ale, pear, and white grape juices and their changes with processing and storage, a review. J Agric Food Chem 1992; 40: 1478–1487.
106. Kris-Etherton PM, Hecker KD, Bonanome A, Coval SM, Binkoski AE, Hilpert K.F, Griel AE, Etherton TD. Bioactive compounds in foods: their role in the prevention of cardiovascular disease and cancer. Am J Med 2002; 30: 113 Suppl 9B: 71S-88S.
107. De Lumen BO, Galvez AF, Revilleza MJ, Krenz DC. Molecular strategies to improve the nutritional quality of legume proteins. Adv Exp Med Biol 1999; 464: 117-26.
108. Tabe LM, Wardley-Richardson T, Ceriotti A, Aryan A, McNabb W, Moore A. Exceptional activity of ellagic acid. Proc Natl Acad Sci 1982; 79: 5513-5517.
109. Viera Diaz J. Genetic improvement of legumes Arch Latinoam Nutr 1996; 44 (4 Suppl 1): 41S-43S.
110. Brar DS, Ohtani T, Uchimiya H. Genetically engineered plants for quality improvement. Biotechnol Genet Eng Rev 1996; 13: 167-79.
111. Auger C, Caporiccio B, Landrault N, Teissedre PL, Laurent C, Cros G, Besancon P, Rouanet J.M. Red wine phenolic compounds reduce plasma lipids and apolipoprotein B and prevent early aortic atherosclerosis in hypercholesterolemic golden Syrian hamsters (Mesocricetus auratus). J Nutr. 2002; 132 (6):1207-1213.
112. Mattivi F, Zulian C, Nicolini G, Valenti L. Wine, biodiversity, technology, and antioxidants. Ann N Y Acad Sci 2002; 957: 37-56.
113. Waterhouse AL. Wine phenolics. Ann N Y Acad Sci. 2002; 957: 21-36.
114. Raimbault M. General and microbiological aspects of solid substrate fermentation. Electronic J Biotech 1998; 1 (3): 1-15.
115. Aidoo KE, Hendry R, Wood BJ. Solid state fermentation. Ad Appl Microbiol 1982; 28: 201-237.
116. Pandey R. Recent progress developments in solid-state fermentation. Process Biochem 1992; 27:109-117.
117. Wang SY, Stretch A. W. Antioxidant capacity in cranberry is influenced by cultivar and storage temperature. J Agric Food Chem 2001; 40: 969-974.
118. Shekib LA. Nutritional improvement of lentils, chick pea, rice and wheat by natural fermentation. Plant Foods Hum Nutr 1994; 46 (3): 201-5.
119. Hadajini S. Indegenous mucana tempe as functional food. Asia Pac J Clin Nutr 2001; 10 (3): 222-225.
120. Zheng GL, Zhou YG, Gong WG. Isolation of soybean isoflavones from Tofu wastewater. ACTA Academiae Medicinae Zhejang 1997; 8:23–25.
121. Morrissey P, Osbourn AE. Fungal resistance to plant antibiotics as a mechanism of pathogenesis. Microbiol Mol Biol Rev 1999; 62 (3):708–724.
122. Osbourn AE. Antimicrobial Phytoprotectants and Fungal Pathogens: A Commentary. Fungal Genetics Biol 1999; 26: 163-168.
123. Vattem DA, Lin Y-T, Labbe RG, Shetty K. Antimicrobial activity against select food-borne pathogens by phenolic antioxidants enriched in cranberry pomace by solid-state bioprocessing using food grade fungus *Rhizopus oligosporus*. Process Biochem 2004; 39: 1939-1946.
124. Vattem DA, Lin Y-T, Labbe RG, Shetty K. Phenolic antioxidant mobilization in cranberry pomace by solid-state bioprocessing using food grade fungus *Lentinus edodes* and effect on antimicrobial activity against select food borne pathogens. Innovative Food Sci Emerging Tech 2004; 5: 81-91.
125. Shetty K, Wahlqvist ML. A model for the role of proline-linked pentose phosphate pathway in phenolic phyto-chemical biosynthesis and mechanism of action for human health and environmental applications. Asia Pac J Clin Nutr 2004; 13:1-24.
126. Vattem DA, Lin Y-T, Labbe RG, Shetty K. Enrichment of phenolic antioxidants and anti-*Helicobacter pylori* properties of cranberry pomace by solid-state bio-processing. Food Biotech 2005 (In press).
127. Shetty K, Labbe RL. Food-borne pathogens, health and role dietary phytochemicals. Asia Pac J Clin Nutr 1998; 7: 270-276.
128. Shetty K, Wahlqvist ML. A model for the role of the proline-linked pentose-phosphate pathway in phenolic phytochemical bio-synthesis and mechanism of action for human health and environmental applications. Asia Pac J Clin Nutr 2004; 13: 1-24.
129. Elattar TMA., Virji AA. The effect of red wine and its components on growth and proliferation of human oral squamous carcinoma cells. Anticancer Res 1999; 19: 5407-5414.
130. Carbonneau MA, Léger CI, Descomps B, Michel F, Monnier L. Improvement in the antioxidant status of plasma and low-density lipoprotein in subjects receiving a red wine phenolics mixture. J Am Oil Chemists' Soc 1998; 75: 235–240.
131. Chan MM, Mattiacci JA, Hwang HS, Shah A, Fong D Synergy between ethanol and grape polyphenols, quercetin, and resveratrol, in the inhibition of the inducible nitric oxide synthase pathway. Biochem Pharmacol 2000; 60 (10): 1539-48.
132. Abraham SK. Anti-genotoxic effects in mice after the interaction between coffee and dietary constituents. Food Chem Toxicol 1996; 34 (1):15-20.
133. Vattem DA, Jang H-D, Levin R, Shetty K .Synergism of cranberry phenolics with ellagic acid and rosmarinic acid for antimutagenic and DNA-protection functions. J Food Biochem 2004. Submitted
134. Vattem DA, Lin Y-T, Ghaedian R, Shetty K. Cranberry synergies for dietary management of *Helicobacter pylori* infections. Process Biochem 2004;40(6): 2059-2065