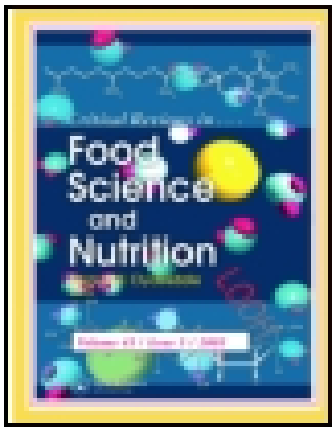


Critical Reviews in Food Science and Nutrition
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/bfsn20

Representative Literature on the Phytonutrients Category: Phenolic Acids

Andrea Roche[a], Erika Ross[a], Nicole Walsh[a], Kierin O'Donnell[a], Alyssa Williams[a], Marjorie Klapp[a], Nova Fullard[a] & Sari Edelstein PhD, RD[a]
[a] Simmons College, 300 The Fenway, Boston, Massachusetts, USA
Accepted author version posted online: 01 Apr 2015.

To cite this article: Andrea Roche, Erika Ross, Nicole Walsh, Kierin O'Donnell, Alyssa Williams, Marjorie Klapp, Nova Fullard & Sari Edelstein PhD, RD (2015): Representative Literature on the Phytonutrients Category: Phenolic Acids, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2013.865589

To link to this article: http://dx.doi.org/10.1080/10408398.2013.865589

Representative Literature on the Phytonutrients Category: Phenolic Acids

Andrea Roche, Erika Ross, Nicole Walsh, Kierin O'Donnell, Alyssa Williams, Marjorie Klapp, Nova Fullard, and Sari Edelstein

Simmons College, 300 The Fenway, Boston, Massachusetts, USA

Address correspondence to Sari Edelstein, PhD, RD, Simmons College, S-334, 300 The Fenway, Boston, MA 02115, USA. E-mail: dre@simmons.edu

T-617 521-2713

F-617 521-3002

Andrea Roche, MS

Simmons College, S-334

300 The Fenway

Boston, MA 02115

T-617 521-2713

F-617 521-3002

Andrea.roche@simmons.edu

Erika Ross, BS

Simmons College, S-334

300 The Fenway

Boston, MA 02115

521-2713

F-617 521-3002

Erika.ross@simmons.edu

Nicole Walsh, BS

Simmons College, S-334

300 The Fenway

Boston, MA 02115

T-617 521-2713

F-617 521-3002

Nicole.walsh@simmons.edu

Kierin O'Donnell, BS

Simmons College, S-334

300 The Fenway

Boston, MA 02115

T-617 521-2713

F-617 521-3002

Kierin O'Donnell@simmons.edu

Alyssa Williams, BS

Simmons College, S-334

300 The Fenway

Boston, MA 02115

T-617 521-2713

F-617 521-3002

Alyssa.williams@simmons.edu

Marjorie Clapp, BS

Simmons College, S-334

300 The Fenway

Boston, MA 02115

T-617 521-2713

F-617 521-3002

Marjorie.clapp@simmons.edu

Nova Fullard, BS

Simmons College, S-334

300 The Fenway

Boston, MA 02115

T-617 521-2713

F-617 521-3002

Nova.fullard@simmons.edu

Abstract:

Research concerning the benefits derived from dietary polyphenols, a significant class within the family of phytonutrients, has increased considerably in the last decade. Prior to the late 90ôs, the nutritional spotlight focused on the antioxidant capabilities of carotenoids, vitamins, and minerals. More recently, however, research has emerged in strong support of the antioxidant capacity of polyphenols and their role in the prevention and/or treatment of certain cancers, diabetes, cardiovascular diseases, and inflammation. Polyphenols are categorized according to the nature of their carbon skeleton, ranging from basic phenolic molecules to highly complex compounds, such as flavonoids, the most common and widely studied of all phenolic compounds. The most prevalent phenolic acids include ellagic acid, gallic acid, tannic acid, and capsaicin.

Key words: phytonutrients, phytochemicals, phenolic acids, ellagic acid, gallic acid, tannic acid, and capsaicin

Research concerning the benefits derived from dietary polyphenols, a significant class within the family of phytonutrients, has increased considerably in the last decade. Prior to the late 90ôs, the nutritional spotlight focused on the antioxidant capabilities of carotenoids, vitamins, and minerals. More recently, however, research has emerged in strong support of the antioxidant capacity of polyphenols and their role in the prevention and/or treatment of certain cancers, diabetes, cardiovascular diseases, and inflammation.[1]

Polyphenols are categorized according to the nature of their carbon skeleton, ranging from basic phenolic molecules to highly complex compounds, such as flavonoids, the most common and widely studied of all phenolic compounds. Phenolic acids are secondary metabolites that are commonly found in plant-derived foods. Of these, ellagic acid, gallic acid, tannic acid, and capsaicin are perhaps the most prevalent in the widest variety of foods from various teas and tropical fruits, to soy and wheat products.

Ellagic Acid

Ellagic acid is a phenolic acid that is naturally occurring in many foods that are derived from plants. The structure is made up of four aromatic rings. This acid can be found in various plant foods such as cranberries, strawberries, blueberries, blackberries, raspberries, pomegranates, walnuts, and pecans. Blackberries and raspberries hold the highest sources of ellagic acid at 1,500 ppm each and other berries like blueberries at less than 100 ppm per berry. The acid itself is not naturally occurring in plants, rather ellagitannins are present in plant foods. Ellagitannins form from polymers of Gallic Acid and hexahydroxydiphenoyl (HHDP) being linked to glucose centers. An HHDP molecule is formed when two Gallic acid groups are combined next to each other within a tannin molecule. Ellagic acid is the molecule formed from

HHDP groups cleaving from a tannin molecule and rearranging randomly. Essentially, ellagic acid is an ellagitannin attached to a sugar molecule. [2]

Ellagic acid has been shown to decrease blood pressure, have anticarcinogenic effects, decrease high blood cholesterol, has anti-inflammatory properties, and even reduce skin wrinkles from radiation. [3]

RESEARCH

The antiproliferative and antioxidant properties of ellagic acid have spurred preliminary research into the potential health benefits of its consumption**.** In the 1960s, Ellagic acid was studied for its effects on blood clotting. By the 1980s, it was being researched in laboratory studies for cancer prevention. Today, dietary supplements of ellagic acid are available but there is limited research as to its efficacy alone, or if benefits are derived from interactions of this acid with other compounds found in foods.[2]

Ellagic acid consumed from berries has been shown to reduce estrogen-mediated mammary tumorigenesis. In a recent study done, rats were placed on various diets, including blackberry powder, raspberry powder, and ellagic acid at 40 ppm. Two weeks later, the rats received 17ɒ-estradiol implants. Tumor volume and multiplicity were reduced significantly after 24 weeks. Ellagic acid at 40 ppm reduced tumor volumes by 75% and tumor multiplicity by 44% in ACI rats. Black raspberry induced diets reduced tumor growth by 69% and multiplicity by 37%. Rats consuming the blueberry powder diet only had a 40% reduction in tumor volume, demonstrating that blueberries only offer only a small amount of ellagic acid. Once the ellagitannin is consumed, the gut flora release the ellagic acid to be absorbed. Weight loss was also prevented with the use of ellagic acid supplementation. The study results revealed that there

is a significant prevention of estrogen-induced mammary tumors in females from ellagic acid use. There is a question as to whether ellagic acid has a higher bioavailability in black raspberries than in blueberries and if the anthocyanins in the blackberries work together to make a larger effect on tumors. Even though the blueberry serves as a poor source of ellagic acid, it has a high source of anthocyanins, a flavanoid, which may have had an effect on the tumor growth reduction. These dietary phenols have been shown to have a major affect on several types of cancer, whether acting solely or in unison.[4] However, it is questionable as to whether or not these results are able to be replicated or translated in humans.

Animal studies have demonstrated the use of ellagic acid in the prevention of colon cancer. A major effect has been seen on 1,2-dimethylhydrazine-induced colon cancer, which is induced to promote malignant neoplasms in the colon of rodents. Ellagic acid caused a decrease in protein expression and anti-inflammatory effect of several inflammatory mediators, such as COX-2 and TNF-Ű to inhibit transcription of these proteins. Ellagic acid blocks NF-kB activation in vitro to cause the decline in production of inflammatory mediators. NF-kB controls gene expression and is involved in several biological steps; inflammation, proliferation and apoptosis. This research is significant in light of the current increase in colorectal cancer in developing countries.[5]

Dietary ellagic acid has been tested to initiate decreased uptake of oxidized LDL, in the prevention of atherosclerosis. Foam cell formation of macrophages cause inflammation and initiate this process. A recent study involved incubated macrophages with ellagic acid. Western blot analysis and real time PCR were used for analysis. The result was the inhibition of lipid oxidation. In addition, ellagic acid promoted oxidized LDL-induced expression of ABCA1, a

membrane transporter found in high amounts in macrophages and responsible for cholesterol efflux. Oxidized lipid uptake was overall reduced. The use of ellagic acid may be useful in the treatment and prevention of atherosclerosis. [6]

Ellagic acid has been described as an inhibitor of tyrosinase or polyphenol oxidase (PPO) and, therefore, of melanogenesis. Ellagic acid demonstrates high antioxidant activity most likely due to its great number of hydroxyl groups. Ellagic acid can play a role in the pathway of melanin due to its inhibitory capabilities of tyrosine. PPO is actively involved in pigmentation. A study conducted in Spain revealed that ellagic acid is a substrate of polyphenol oxidase. This evidence coincides with another study done in Korea. The former study presents the use of ellagic acid for alleviating skin wrinkles and inflammation induced by UV-B radiation. While the latter study examined photoprotective effects of ellagic acid on collagen breakdown and inflammatory responses in UV-B irradiated human skin cells and hairless mice. UV skin damage causes DNA damage that further causes inflammation, photoageing, and photocarcinogenesis. Pomegranate extract, a high source of ellagic acid, recently showed that UV-A and UV-B skin induced damage was prevented in human skin fibroblast cells. In hairless mice, a topical application of ellagic acid was applied and resulted in the disappearance of pro-inflammatory cytokines and blocked infiltration of inflammatory macrophages after exposure to UV-B for 8 days. MMP (matrix metalloproteinases) were inhibited by ellagic acid; therefore, preventing collagen degradation in fibroblasts. Results from these studies show that ellagic acid efficiently enhanced the elastogenesis of aged skin. As a result, ellagic acid or dietary sources, such as berries, may provide ways to interrupt skin wrinkles and inflammation from chronic sun damage from UV-B rays.[7] [8]

Ellagic acid has major benefits in the prevention of oxidative stress in the liver and heart tissue during chemotherapy treatment. A study performed in Turkey demonstrated the use of ellagic acid in this way on rats. The high use of cisplatin in chemotherapy can subside with very hypertoxic effects on patients. The suggestion of an antioxidant, such as ellagic acid, synergistically being used with this cytotoxin may reduce the harmful effects of this anticancer treatment. The study was performed on liver and cardiac tissue in rats. The first group received only cisplatin, the second group relieved only ellagic acid, and the third group received ellagic acid and cisplatin. There was also a control group that received only saline injections. Rats were euthanized at the end of the treatments and the liver and heart tissues were removed. Treatment with ellagic acid decreased the cisplatin-induced hepatocellular necrosis. Liver and heart tissue enzyme values were decreased when used with just cisplatin. These tissues include glutathione, glutathione-peroxidase, and catalase. With the use of ellagic acid, these tissue values rose. Malondialdehye, levels of lipid peroxidation, increased with just cisplatin but decreased in value with ellagic acid use in combination. Reduction in lipid peroxidation demonstrates the antioxidant effects of ellagic acid. Thus, ellagic acid can be used with cisplatin to improve stress parameters in liver and heart tissue. [9]

Ellagic acid has been studied in cardiac tissue of diabetic mice to test its anti-inflammatory and anti-coagulatory effects. Diabetes is an inflammation-prone condition due to the elaboration of inflammatory cytokines. Three groups of mice were sorted with different dietary intakes and supplemented for 12 weeks. The control group had a regular diet. A second group was supplemented with 2% caffeic acid, and the last group was supplemented with 2% ellagic acid. After 12 weeks, hypercoagulability, oxidative stress, and inflammation were

measured in the cardiac tissues of the mice. Mice supplemented with ellagic acid and caffeic acid experienced weight loss, elevated plasma insulin, and decreased plasma glucose levels in diabetic mice. AT-III inhibits the activity of a number of proteases in the coagulation cascade. AT-III and protein C are both anticoagulants. Ellagic acid elevated AT-III and protein c activities showing an anticoagulatory effect. In addition, ellagic acid suppressed cardiac mRNA expression of inflammatory cytokines such as IL-6. Triglyceride content was decreased in these cardiac tissues as well. These results show strategies for the prevention of diabetic cardiomyopathy.[10]

Ellagic acid has great health benefits and can be easily consumed on a daily basis in the American diet. This phytonutrient has preventative factors against some of the highest causes of death in the U.S.

Gallic Acid

The phytonutrient Gallic Acid is a polyphenol thought to have powerful health benefits. It is found in tea, mango, rhubarb and soy. This phenolic acid is synthesized as a byproduct in the pathway responsible for producing tannins in plants such as tea, cocoa and walnuts. This polyphenol is a byproduct of the Shikamate pathway responsible for producing tannins. This process in which tannins are produced contains the enzyme Shikamate Dehydrogenase (SDH) that is responsible for the step of the pathway that turns 3-dehydroshikamate (3DHS) into aromatic compounds such as L-tryptophan. 3DHS however, also has the ability to take a different route in the pathway and produce Gallic Acid via $NADP^+$, changing 3DHS from a ketone to an alcohol.[11]

RESEARCH

As most phytonutrients, gallic acid is known mainly for its antioxidant effect. It has long been in question, however, if phytonutrient properties are influenced by their combination with other nutrients in their native state or if they are as effective when isolated. Gallic acid has been tested in this respect, both independent of other compounds and as part of a plant based sugar solution. The scavenging properties have been tested on superoxide anion radical (O_2-) and on hydroxyl radical (OH). Many experiments have shown that although gallic acid alone had noticeable activity in the scavenging of the free radicals, this activity increased significantly when part of a sugar solution against hydroxyl radicals. This suggests that gallic acid in the presence of sugars, as it would be found in its natural state in fruit, may be beneficial when fighting off hydroxyl radicals. This data supports a popular supposition that obtaining nutrients from their source rather than a supplement would be more beneficial. In measuring gallic acid for its scavenging activity at high doses, it actually worked as a pro-oxidant, creating more free radicals. Valuable information from this research suggests that gallic acid is an effective antioxidant but as most antioxidants can have harmful effects in dangerously high doses. Consuming the nutrient through the consumption of plant products would be both a safe and effective way to obtain the benefits of Gallic Acid.[12]

This polyphenol is also widely known for its antioxidant activity as one of the polyphenols found in tea. Although found in a small amount, gallic acid can still be extracted from black tea such as Uva and C. Ptilophylla leaves. [13] Teaôs polyphenols including gallic acid have also been shown to have protective benefits for human liver cells. A study published in the *Journal of Medical Plants Research* tested its effects against liver cells exposed to hydrogen peroxide and carbon tetrachloride damage. Treatment of these exposed cells with antioxidants of

tea polyphenols, gallic acid or alpha tocopherol significantly decreased amounts of markers of apoptosis and lipid peroxidation such as levels of lactate dehydrogenase. Since hydrogen peroxide and carbon tetrachloride are compounds related to oxidative stress, the protective effect gallic acid and tea polyphenols have against their damage showcases the phytonutrientsô health benefits. [14]

Antioxidants can play an important role in the protection of many of our tissues, including brain tissue. Elements such as fluoride have been found to have especially high toxic effects on our brain tissue. Antioxidants such as gallic acid and vitamin C were both used in experiments to measure their protective effects against the damage done by fluoride. Both antioxidants proved worthy in the battle against lipid peroxidation in the brain, yet gallic acid displayed a stronger effect. [15] Neurological disorders such as Parkinsonôs disease also have shown beneficial effects of intake of antioxidants such as gallic acid since the death of neurons in the brain are related to oxidative stress. Gallic acid derivatives were tested in their ability to inhibit catalepsy in the same manner as drugs used to treat Parkinsonôs. The derivative Triacetoxy Butyl gallate displayed the most promising results. [16] The evidence of this study only adds to the neurological benefits of gallic acid as an antioxidant.

Gallic acid has been known as a phytonutrient displaying antioxidant properties but a study published in the *British Journal of Nutrition* experimented with the theory that it also has anti-obesity properties. Past experiments have demonstrated that gallic acid has the ability to prevent adipogenesis in human cell lines. In this study rats that were fed high fat diets were broken up into three categories in which one received no gallic acid supplementation and the other two groups received either high or low dose supplements. The results of the study showed promising

evidence for gallic acid as a supplement to improve the health condition of those consuming a high fat diet. The rats that were fed a high fat diet with supplemented gallic acid had lower overall body weight, hepatic weight, adipose tissue weight, serum triacylglyceride levels, serum phospholipid levels and serum cholesterol levels than those who received the high fat diet not supplemented with gallic acid. These discoveries could open doors for more research into gallic acid as beneficial in terms of lipid related disease such as fatty liver disease. [17]

Many other disease states have also been correlated with health benefits from gallic acid, especially those undergoing chemotherapy. Gallic acid as a treatment has even been tested as one alternative. Four groups of cancerous human cells (known as A549 cells) were tested amongst three different concentrations of gallic acid with one group being a control. After 24 hours, the four groups of cells were tested for various levels of apoptosis by measuring lactate dehydrogenase, DNA fragmentation and caspase enzyme. All of these are markers of cell death. The results of the study showed that the two higher doses of gallic acid at 10 and 20 ug/mL were effectively displaying anticarcinogenic properties by inducing apoptosis as evidenced by increased lactate dehydrogenase and increased DNA fragmentation. [18]

Aside from being found as an effective treatment for cancer cells and decreased absorption of fat, gallic acid is also been widely studied for its cardiovascular benefits. Gallic acid was tested against the effects of isoproterenol (ISO), a catecholamine known for its relation to myocardial infarction (MI), in rats. Four groups of rats were observed with a control group; one receiving gallic acid supplementation, another receiving ISO via saline, and a group receiving both Gallic Acid supplementation and ISO via saline. Two doses of ISO were administered to the appropriate groups and after 12 hours the data was collected. Classic serum

markers for MI such as CK-MB and Lactate Dehydrogenase were measured in all groups. The administration of isoproterenol significantly increased the serum markers of MI in the rats receiving only ISO in comparison to groups that did not receive ISO. In the group receiving both ISO and Gallic Acid the serum markers were significantly decreased, suggesting that these rats' risk of MI was decreased. With the only difference in the groups being supplementation of gallic acid, it can be concluded that the polyphenol has cardiovascular benefits in protection against MI. [19]

Ellagic acid is a component of some nuts, especially walnuts, and has been thought to exert anti-atherogenic, anti-carcinogenic and antioxidative properties. [20, 21] Specifically, researchers examined the role of walnuts in endothelial and bone cell function, the former of which has been recognized as an early step in inþammation and atherogenesis. They examined the effect of walnut methanolic extract and ellagic acid on the expression of vascular cell adhesion molecule (VCAM)-1 and intracellular adhesion molecule (ICAM)-1 in human aortic endothelial and skeletal cells. Their results confirmed that methanolic extract from such nuts has a high anti-inþammatory potential as well as osteoblastic activity that can be attributed partly to ellagic acid. [22] This suggests that a walnut-enriched diet may have a remarkable effect on cardio-protection and bone loss, an effect perhaps mediated by its major component ellagic acid.

Regarding anti-carinogenic effects, ellagic acid has been shown to act as a scavenger to "bind" cancer-causing chemicals, making them inactive. It is a well-known antioxidant, known as a potent anti-carcinogenic, anti-mutagenic compound. [23] Research shows that ellagic acid inhibits the growth of cancer cells. It also causes apoptosis, or normal cell death in those cancer cells. [24]

Unfortunately, studies have shown that ellagic acid has poor absorption and rapid elimination after consumption. [25] It is absorbed rapidly from the gastrointestinal tract. One study revealed that only 15 minutes following oral administration, ellagic acid from pomegranate juice was absorbed and available in the blood serum with about 50% bound to plasma protein and a half-life of 8.4 hours.[26]

Therefore, various studies have shown that consumption of foods rich in gallic acid may have great health benefits. The phytonutrient shows great promise in the prevention of obesity, as a powerful antioxidant and in the treatment of cancer and CVD.

Tannic Acid

An important, but often misunderstood group of phenolic acids is that of tannins, which can be further classified into two subgroups: hydrolyzable tannins and proanthocyanidins, or condensed tannins. While hydrolyzable tannins are of limited distribution in nature, proanthocyanidins are plentiful. Found in tea, chocolate, wine, vegetable extracts, and fruit, they have been touted as having antimicrobial compounds, antioxidant capabilities, anti-inflammatory, and anti-cancer fighting agents. [27]

However, conflicting studies pertaining to the benefits of tannins do exist in the scientific community. Traditionally, their astringent qualities and protein complexing abilities have led some to classify tannins as anti-nutritional [28]. It is only in recent years that new extraction techniques and advancements in the classification of tannin structure have enabled researchers to better understand the complexities and benefits of tannins.

Tannins are astringent, bitter-tasting plant polyphenols that bind and precipitate proteins. The term tannin was introduced by M. Seguin in 1796 to denote the substances present in plant

extracts, which have the ability to convert animal hides into leather by preventing the putrefaction of proteins present in the skin. Tannins show very high variability in their structures, with several hundred unique molecules detected in plants, and possess molecular weights ranging from 500 to 3000. [29]

Tannins are widely dispersed in the animal kingdom, with high concentrations in fruits and berries (persimmons, cranberries, and apples); nuts and seeds (grape seeds, almonds, cocoa beans); trees and leafs (Maritime pine, cinnamon bark, and parsley); and legumes (peas, Jamapa beans). The major contributors of tannin in the US market are grapes, apples, and chocolate [27]. Once ingested, tannins have a unique binding effect on saliva proteins, which results in the dry, bitter taste in the mouth. In plants, tannins act as defense compounds that counteract the bacteria and fungi by interfering with their surface proteins [29].

Various challenges are presented in the study of tannins, as their molecules are unevenly distributed in the plant species they inhabit, making it virtually impossible to find any two plant species with the identical tannin pool. However, the two main categories that influence nutrition are hydrolyzable tannins and proanthocyanidins, also called condensed tannins. [30]

Hydrolyzable tannins are compounds containing a central core of glucose or another polyol esterified with gallotannins, or with ellagitannins [27]. The most famous source of gallotannins is tannic acid, which is obtained from the twig galls of *Rhus semialata*. They are hydrolyzed by mild acids or mild bases to yield carbohydrate and phenolic acids, and do not regularly occur in nature [28].

Proanthocyanidins exist in abundance in nature. Proanthocyanidins are oligomeric and polymeric end products of the flavonoid biosynthetic pathways. They are present in the fruits,

bark, leaves and seeds of many plants, where they provide protection against predation due to their astringent nature. At the same time, they give flavor and bitterness to beverages such as wine, fruit juices and teas, and are increasingly recognized as having beneficial effects on human health. In fact, some researchers have deemed proanthocyanidins as the ñnew frontier in flavonoid research.ò [31].

RESEARCH

The past few years have seen important developments in the understanding of the biosynthesis of proanthocyanidins and the health benefits derived from purified fractions of fruits, leaves and bark. Initially, the research was focused on validating the potential benefits of grapes, wine, and juices, but more recently, as the mechanisms behind the metabolism of proanthocyanidins is uncovered, these potent polyphenols are believed to benefit various aspects of human health. [27]. For example, one study found that feeding rats proanthocyanidins in grape seed flour for three weeks resulted in improved cardiac recovery during reperfusion after ischemia [31]. Additionally, it has been purported that proanthocyanidins may have greater antioxidant potential than that of Vitamins C, E and B-carotene [31]. They also affect the inflammatory process via calcium-dependent release of nitric oxide and protect against H2O2-induced lipid peroxidation [29]. And, with regard to anti-cancer protection and their role in cardiovascular disease, proanthocyanidins have evidenced anticancer properties by mitigating tumor development through induction of apoptosis or inhibition of cell proliferation [27].

It is thought that proanthocyanidins exhibit cardioprotective properties through different mechanisms of action, including inhibition of LDL oxidation and endothelium-dependent relaxation of blood vessels [32].

Tannins found in wine affect the color, aging ability and texture. Tannic acid is most notable during wine tasting by the tactile drying sensation, astringency and sense of bitterness that leaves the mouth quite dry. This is due to the tendency of tannins to react with proteins such as those found in saliva.[33] Tannins are found in the skin, stems, and seeds of wine grapes but may also be introduced to the wine through the use of oak barrels and chips. The natural tannins found in grapes are known as proanthocyanidins, and also provide the notable red anthocyanin pigment of many wines. The amount of tannins found in grapes varies depending on the variety. Muscadine, Cabernet Sauvignon, Nebbiolo, Tannat and Syrah tend to be the most tannic grape varieties. The tannins derived from oak influence are known as "hydrolysable tannins" being created from the ellagic and gallic acid found in the wood.[34]

Research has shown that consumption of tannins in the form of proanthocyanidins, have a beneficial effect on vascular health. The mechanism involves the action of tannins in suppressing the production of the peptide responsible for hardening arteries. Additionally, wines from the regions of southwest France and Sardinia are particularly rich in proanthocyanidins, reflective of regions with low risk of heart disease and long life spans.[35]

The current data supporting the protective effects of tannins against diseases has produced new expectations for advancements in health. This has, of course, generated great interest from the food and nutritional supplement industry regarding the utilization and development of tannin-rich products, medications, or supplements. While substantial research has illustrated the health benefits of proanthocyanidins, several important questions still remain about the biosynthesis of these molecules and how they affect various genes, and whether or not they are safe for human consumption in large doses. In addition to the questions that remain,

conflicting research pertaining to tannins also exists and must be reconciled before moving forward in a wholehearted approach. Future research should be aimed at gaining a greater understanding for the metabolism of tannins so that additional evaluations may be performed in the general population to test for specific disease risks. Additionally, the astringency, taste, and color of tannins must also be considered as food must not only be good for oneôs health, but must be palatable and aesthetically pleasing to consumers.

Capsaicin

Among various spices, the fruit of Capsaicin is the mostly widely used spice. [36] It is a major capsaicinoid derived from the dried fruit of chili pepper and is synthesized in the interlocular septum of chili peppers by addition of branched-chain fatty acid to vanillylamine. Capsaicin belongs to the genus Capsicum. The potential benefits of capsaicin are widespread. In particular its medicinal uses include topical application involving neurological treatment, as well as treatment of arthritis have been reported. Furthermore, benefits relating to cardiovascular health, promotion of apoptosis and respiratory and gastrointestinal health have also been reported. The mechanism of action in capsaicin is experienced with a burning and painful sensation from the compounds interaction with sensory neurons. Its tangible properties are a direct result of the compoundsô selective binding to a vanilloid receptor subtype 1 (VR1). It is at this point of contact where pain and heat arise from. By binding to VR1 receptor, the capsaicin molecule produces the same sensation that is produced by excessive heat or abrasive damage; thus the burning sensation caused by capsaicin.[37]

RESEARCH

Many studies have been conducted on the medical uses of capsaicin. In particular, the uses of the compound as an anticancer agent has been explored extensively. Research on the anticancer effects include human breast cells, prostate cells, colon cells, as well as gastric cells. Recent research demonstrated that inhibition of human non-small lung cancer (H460) cells correlated with levels of capsaicin content in hot peppers. The research conducted found that capsaicin triggered cancer cell death by attacking the mitochondria of the cancer cells. These findings encouraged further research into other cancer drugs to be developed that target the mitochondria. [38]

Similarly, two researchers on separate occasions both showed that 50 μM of capsaicin inhibited human breast cancer (MCF-7) cells, as well as induced apoptosis. In a more recent study, it was demonstrated that inhibition of tumor growth in human breast cells (MDA-MB-231 MCF-7) correlated with levels of capsaicin content present in hot peppers. Results showed that extracts from 10 pepper varieties induced growth arrest and apoptosis in cancer cells with no significant effect on normal breast epithelial cells. [39] [40] [41] Results showed capsaicin induced apoptotic cell death. These findings are significant in the fight against cancer and further emphasizes the consumption of vegetables and fruits which are known to possess phytochemicals.

Topical creams containing capsaicin are used to treat general pain management including peripheral neuropathic pain and arthritis. In a randomized double-blind study, 281 patients suffering from chronic soft tissue pain were treated either with a cream containing capsaicin 0.05% or placebo. All outcome measures had significantly more improvement in the capsaicin-treated group compared with the placebo-treated group. In general, capsaicin cream is generally

well tolerated and may be effective for people suffering from arthritis and neuropathic disorders.[42]

In spite of the numerous reported benefits associated with capsaicin, it also contains a moderate amount of risks. Capsaicin is a highly irritant compound and requires safe handling procedures. It causes a burning or stinging pain to the skin, and if ingested in large amounts can produce nausea, vomiting, abdominal pain and burning diarrhea. Eye exposure produces intense tearing, pain, conjunctivitis and blepharospasm. [43]

Capsaicin Capsaicin has anti-inflammatory, antioxidant, anti-proliferative and anticancer potentials. Other potential benefits of capsaicin should be explored with the aim of broadening our understanding of the molecular mechanism associated with its anticancer properties. At this time, the only data-driven recommendation is that a diet rich in vegetables, fruits, seeds, and spices, that contain capsaicin and a variety of similar phenolic compounds, may be effective for the prevention of some types of cancer.

CONCLUSION

A growing reverberation pertaining to the benefits of polyphenols can be heard not only around the scientific community, but also that of the culinary and general public. Vitamin and mineral supplementation is already quite commonplace, while new evidence is being pursued on the protective effects of polyphenols and the promises they hold for disease prevention. Therefore, it may not be too far off that phenolic acids are in fact classified as nutrients. The research behind phenolic acids has just begun to take shape as scientists are starting to understand the gene regulation and metabolic pathways involved in the digestion of these

polyphenols. Numerous studies have found that they exhibit biological and pharmacological activities especially as anti-inflammatory, antioxidant and cancer prevention capabilities. A true nutritional role for phytochemicals is becoming more probable every day as research uncovers more of their remarkable benefits. In fact, phytochemicals may indeed be classified as essential nutrients. As new research illuminates the potential benefits of phenolic acids, it is important to continue experiments seeking methods that utilize these valuable food sources.

REFERENCES

[1] Scalbert, Augustin. "Polyphenols: Antioxidants and beyond." The American Journal of Clinical Nutrition 81.1 (2005).

[2] D. A. Vattem and K. Shetty (2005). "Biological Function of Ellagic Acid: A Review". Journal of Food Biochemistry 29 (3): 234ï 266.

[3] Ascacio-Valdés JA et al. (2011) Review: Ellagitannins: Biosynthesis, biodegradation and biological properties Journal of Medicinal Plants Research Vol. 5(19):4696-4703

[4] Aiyer HS ; Srinivasan C ; Gupta RC. Dietary berries and ellagic acid diminish estrogen-mediated mammary tumorigenesis in ACI rats. Nutrition And Cancer 2008; Vol. 60 (2), pp. 227-34.

[5] Umesalma S ; Sudhandiran G. Differential inhibitory effects of the polyphenol ellagic acid on inflammatory mediators NF-kappaB, iNOS, COX-2, TNF-alpha, and IL-6 in 1,2-dimethylhydrazine-induced rat colon carcinogenesis. Basic & Clinical Pharmacology & Toxicology 2010 Aug; Vol. 107 (2), pp. 650-5.

[6] Aviram M, Rosenblat M, Gaitini D et al. (June 2004). "Pomegranate juice consumption for 3 years by patients with carotid artery stenosis reduces common carotid intima-media thickness, blood pressure and LDL oxidation". Clin Nutr 23 (3): 423ï 33.

[7] Muñoz-Muñoz JL ; Garcia-Molina F ; Garcia-Molina M ; Tudela J ; García-Cánovas F ; Rodriguez-Lopez JN. Ellagic acid: characterization as substrate of polyphenol oxidase.IUBMB Life (2009) Feb; Vol. 61 (2), pp. 171-7.

[8] Bae JY ; Choi JS ; Kang SW ; Lee YJ ; Park J ; Kang YH. Dietary compound ellagic acid alleviates skin wrinkle and inflammation induced by UV-B irradiation. Experimental Dermatology (2010) Aug; Vol. 19 (8), pp. e182-90.

[9] Yüce A ; Ateкkahin A ; Ceribaкi AO. Amelioration of cyclosporine A-induced renal, hepatic and cardiac damages by ellagic acid in rats. Basic & Clinical Pharmacology & Toxicology (2008) Aug; Vol. 103 (2), pp. 186-91.

[10] Chao PC ; Hsu CC ; Yin MC. Anti-inflammatory and anti-coagulatory activities of caffeic acid and ellagic acid in cardiac tissue of diabetic mice. Nutrition & Metabolism 2009 Aug 14; Vol. 6, pp. 33.

[11] Muir, R., Ibanez, A., Uratsu, S., Ingham, E., Leslie, C., McGranahan, G., Neelu, B., Goyal, S., Joseph, J.,Jemmis, E., Dandekar, A. (2011) Mechanism of Gallic Acid Biosynthesis in Bacteria (*Escherichia coli*) and Walnut (*Juglans Regia*) *Plant Molecular Biology* 75:555-565

[12] Lo Scalzo, R. (2010) Measurement of free radical scavenging activity of gallic acid and unusual antioxidants as sugars and hydroxyacids *Electronic Journal of Environmental, Agricultural and Food Chemistry* ISSN 1579-4377

[13] Wang, Y., Yang, X., Li, K., Li, C., Li, L., Li, J., Huang, H., He, Y., Ye, C., Song, X. (2010) Simultaneous determination of theanine, gallic acid, purine alkaloids, catechins, and theoflavins in black tea using HPLC *International Journal of Food Science & Technology* 45 1263-1269

[14] Li, T., Zhang, X., Zhao, X., (2010) Powerful protective effects of gallic acid and tea polyphenols on human hepatocytes injury induced by hydrogen peroxide or carbon tetrachloride in vitro *Journal of Medicinal Plants Research* 4(3) 247-254

[15] Nabavi, S.F., Habtemariam, S., Jafari, M., Sureda, A., Nabavi, S.M. (2012) Protective role of gallic acid on sodium fluoride induced oxidative stress in rat brain *Bulletin of Environmental Contamination and Toxicology* 89; 73-77

[16] Kasture, V.S., Kasture, S.B., Sahu, R.K., Kumar, A., Musmade, D.S. (2012) Synthesis and antioarpkinson activity of gallic acid derivatives *Medicinal Chemistry & Drug Discovery* 3(2) 134-139

[17] Chin-Lin Hsu, Gow-Chin Yen. Effect of gallic acid on high fat diet-induced dyslipidaemia, hepatosteatosis and oxidative stress in rats. British Journal Of Nutrition (impact factor: 3.01). 11/2007; 98(4):727-35.

[18] Elango, S., Balwas, R., Padma, V.V., (2011) Gallic acid isolated from pomegranate peel extract induces reactive oxygen species mediated apoptosis in a549 cell line *Journal of Cancer Therapy* 2, 638-645

[19] Priscilla, D.H., Prince, P.S.M., (2010) Gallic acid pretreatment ameliorates lipids, lipoproteins and HMG-CoA reductase in normal and isoproterenol induced myocardial infarction in male Wistar rats *Journal of Pharmacy Research* 3(5) 960-964

[20] Anderson KJ, Teuber SS, Gobeille A, Cremin P, Waterhouse AL & Steinberg FM (2001). Walnut polyphenolics inhibit in vitro human plasma and LDL oxidation. J Nutr 131, 2837 ï 2842.

[21] Mertens-Talcott SU, Talcott ST & Percival SS (2003) Low concentrations of quercetin and ellagic acid synergistically inþuence proliferation, cytotoxicity and apoptosis in MOLT-4 human leukemia cells. J Nutr 133, 2669 ï 2674.

[22] Papoutsi Z ; Kassi E ; Chinou I ; Halabalaki M ; Skaltsounis LA ; Moutsatsou P. Walnut extract (Juglans regia L.) and its component ellagic acid exhibit anti-inflammatory activity in human aorta endothelial cells and osteoblastic activity in the cell line KS483. The British Journal Of Nutrition [Br J Nutr] 2008 Apr; Vol. 99 (4), pp. 715-22.

[23] Suzuki, M., N. Kumazawa, S. Ohta, A. Kamogawa and M. Shinoda, 1990. Protective effects of antioxidants on experimental liver injuries. Yakugaku Zasshi, 110: 697-701.

[24] Loarca, P.G., P.A. Kuzmicky, E.G. de Mejia and N.Y. Kado, 1998. Mutat Inhibitory effects of ellagic acid on the direct-acting mutagenicity of aflatoxin B1 in the Salmonella microsuspension assay. Mutat. Res. Fundam. Mol. Mech. Mutag., 398: 183-187.

[25] Lei F, Xing DM, Xiang L, Zhao YN, Wang W, Zhang LJ, Du LJ. Pharmacokinetic study of ellagic acid in rat after oral administration of pomegranate leaf extract. J Chromatogr B Analyt Technol Biomed Life Sci. 2003 Oct 25;796(1):189-94.

[26] Abdul-Wahab R. Hamad, Waleed M. Al-Momani, Sana Janakat and Sawsan A. Oran, 2009. Bioavailability of Ellagic Acid After Single Dose Administration Using HPLC. Pakistan Journal of Nutrition, 8: 1661-1664.

[27] Cos, P., and T. De Bruyne,. "Proanthocyanidins in Health Care: Current and New Trends." *Current Medicinal Chemistry* 10 (2003): 1345-359.

[28] Cannas, Antonello. " Tannins: fascinating but sometimes dangerous molecules.ò

Department of Animal Science - Cornell University. Cornell University, 26 Mar. 2009. Web. 29 Nov. 2011. <http://www.ansci.cornell.edu/plants/toxicagents/tannin.html>.

[29] Bele, Archana. "The Potential of Tannins: A Review." *Asian Journal of Plant Sciences* 9.4 (2010): 209-14.

[30] Salminen, Juha-Pekka. "Chemical Ecology of Tannins and Other Phenolics: We Need a Change in Approach." *Functional Ecology* 25.2 (2011): 325-38.

[31] Reed, Jess. "Cranberry Flavonoids, Atherosclerosis and Cardiovascular Health." *Critical Reviews in Food Science and Nutrition* 42.Sup3 (2002): 301-16.

[32] Kumar et al. (2011). A review on molecular characterization of pepper for capsaicin and oleoresin. Int. J. Plant Breed. Genet. 5, 99-110.

[33] Sarni-Manchado, Pascale; Cheynier, Véronique; Moutounet, Michel (1999). "Interactions of Grape Seed Tannins with Salivary Proteins". Journal of Agricultural and Food Chemistry 47 (1): 42ï 7. doi:10.1021/jf9805146. PMID 10563846

[34] J. Robinson (ed) "The Oxford Companion to Wine" Third Edition pg 680 Oxford University Press 2006 ISBN 0-19-860990-6

[35] Corder R, Mullen W, Khan NQ et al. (November 2006). "Oenology: red wine procyanidins and vascular health". Nature 444 (7119): 566. doi:10.1038/444566a. PMID 17136085.

[36] Chhabra et al. (2012). Capsaicin: A promising therapy - A critical reappraisal. Int. J. Nutr. Pharm. Neur. Dis. 2(1), 8-15.

[37] Athanasiou, et al. (2007). Vanilloid receptor agonists and antagonists are mitochondrial inhibitors: How vanilloids cause non-vanilloid receptor mediated cell death. Biochemical and biophysical research communications 354(1), 50.

[38] Chou et al. (2009). Capsaicin-induced apoptosis in human breast cancer MCF-7 cells through caspase-independent pathway. Oncol. Rep. 21, 665ï 71.

[39] Hwang et al. (2009). Anti-inflammatory and anticarcinogenic effect of genistein alone or in combination with capsaicin in TPA-treated rat mammary glands or mammary cancer cell line. Ann. N.Y. Acad. Sci. 1171, 415ï 20.

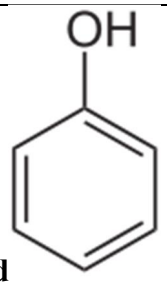
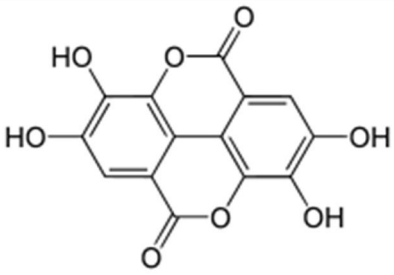
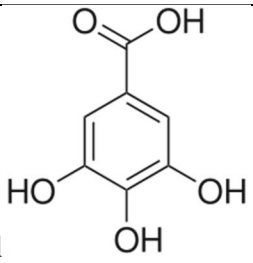
[40] Dou et al. (2011). Tumor cell growth inhibition is correlated with levels of capsaicin present in hot peppers. Nutrition and Cancer, 63(2), 272-281.

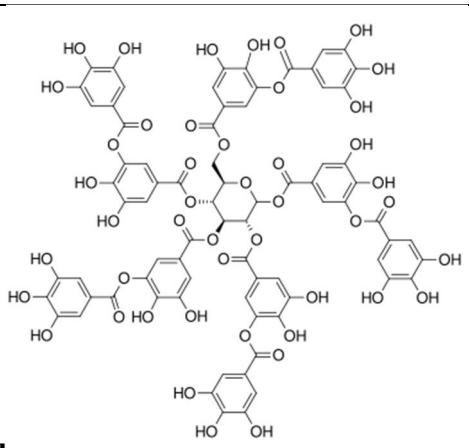
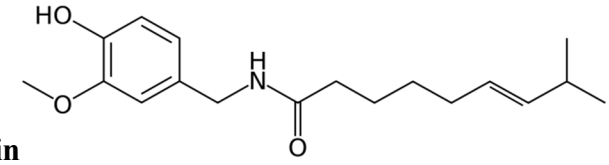
[41] [Chrubasik S ; Weiser T ; Beime B. Effectiveness and safety of topical capsaicin cream in the treatment of chronic soft tissue pain. Phytotherapy Research: PTR, 2010 Dec; Vol. 24 (12), pp. 1877-85.

[42] Altman RD ; Barthel HR. Topical therapies for osteoarthritis. Drugs [Drugs] 2011 Jul 9; Vol. 71 (10), pp. 1259-79.

[43] Goldfrank, L. R., & Flomenbaum, N. (2006). Goldfrank's toxicologic emergencies. (6 ed., p. 1167). New York: McGraw-Hill.

Table 1: The most prevalent phenolic acids include ellagic acid, gallic acid, tannic acid, and capsaicin. Created by the author.

Molecular Structure	**Found in Common Foods**
 **Phenol acid**	mostly fruit and vegetables in various forms
 **Ellagic acid**	cranberries, strawberries, blueberries, blackberries, raspberries, pomegranates, walnuts, and pecans
 **Gallic acid**	white tea, blackberries, raspberries and some wine

 **Tannic Acid**	high concentrations in fruits and berries (persimmons, cranberries, and apples); nuts and seeds (grape seeds, almonds, cocoa beans); trees and leafs (Maritime pine, cinnamon bark, and parsley); legumes (peas, Jamapa beans); grapes, apples, and chocolate
 **Capsaicin**	Chili peppers