

Onions – Phytochemical and Health Properties

Provided by the National Onion Association



Abstract

Onions have been valued for their medicinal qualities by many cultures around the globe. Numerous health benefits have been attributed to the vegetable, including prevention of cancer and cardiovascular disorders. Scientific studies have shown a positive relationship between vegetable intake and risk for these common diseases. This has led many researchers to test whether the proposed medicinal attributes of onions are valid. Some of these studies have shown that including onion in the diet:

- Was associated with a reduced risk of stomach cancer in humans.
- Was associated with a decreased risk for brain cancer in humans.
- Inhibited platelet-mediated thrombosis (a process leading to heart attacks and strokes).
- Reduced levels of cholesterol, triglycerides, and thromboxanes (substances involved in the development of cardiovascular disease) in the blood.
- Was associated with a reduction in symptoms associated with osteoporosis.

For a deeper understanding of these and other potentially beneficial qualities, scientists have studied specific compounds found in onion bulbs. Onions have a unique combination of three families of compounds that are believed to have salutary effects on human health — fructans, flavonoids and organosulfur compounds. Fructans are small carbohydrate molecules that help maintain gastrointestinal health by sustaining beneficial bacteria. A great deal of research has focused on one flavonoid, quercetin, which is found at particularly high levels in onions. It functions as an antioxidant, deactivating molecules that are injurious to cells in the body. Research studies have shown quercetin to:

- Decrease cancer tumor initiation.
- Promote healing of stomach ulcers.

- Inhibit the proliferation of cultured ovarian, breast, and colon cancer cells.

The organosulfur compounds are largely responsible for the taste and smell of onions. Research studies have shown organosulfur compounds to:

- Reduce symptoms associated with diabetes mellitus.
- Inhibit platelet aggregation (involved in thrombosis).
- Prevent inflammatory processes associated with asthma.

Many of these studies used non-human subjects. Others used experimental assays that mimic processes related to disease that occur in the body. More research is underway to assess the effects of dietary intake of onions on health in human subjects.

Introduction

For centuries consumption of fruits and vegetables has been attributed to beneficial health effects. Ames and Gold (1998) stated that approximately one-third of cancer risk in humans could be attributed to diet. Epidemiological studies have suggested that those persons in the lowest quartile of fruit and vegetable consumption have twice the risk of cancer as do those in the highest consumption quartile (Block et al., 1992). Free radical formation of reactive oxygen species (ROS) and subsequent oxidative stress have been correlated to many human disorders including those of the kidney, eye, lung, liver, nervous system, heart and cardiovascular system (Cutler et al., 1998). Therefore, foods in our diet that can aid in prevention of these diseases are of major interest to both the scientific community and the general public.

Biologically active plant chemicals other than traditional nutrients that have a beneficial effect on human health have been termed “phytochemicals”

(Hasler, 1998). Onions have received considerable attention for their healthful, functional benefits. Phytochemicals in onions include the organosulfur compounds such as cepaenes and thiosulfinates (Dorsch and Wagner, 1991; Goldman et al., 1996), the large class of flavonoids including quercetin and kaempferol (Dorant et al., 1994), and pigments such as anthocyanins found in red onions and red wine (Fitzpatrick et al., 1993). Much research has been conducted in recent years on the role of phytochemical compounds found in onions. Antioxidant activity (Gazzani et al., 1998a), vascular disease (Hertog et al., 1995; Da Silva 1998), and cancer prevention of the bladder (Malaveille et al., 1996), brain (Hu et al., 1999), breast (Challier et al., 1998), colon (Deschner et al., 1991), lungs (Khanduja et al., 1999), ovaries (Shen et al., 1999), and stomach (Dorant et al., 1996) are some of the focus areas receiving attention. Other potential benefits under current investigation include, but are not limited to, kidney function (Shoskes, 1998), anti-bacterial/fungal activity (Kim 1997; Fan and Chen, 1999), cataractogenesis (Sanderson et al., 1999), immune function (Chisty et al., 1996; Steerenberg et al., 1998), prebiotic effects (Gibson, 1998), diabetes (Sheela et al., 1995), and HIV suppression/AIDS blocking (Shimura et al., 1999).

Potential benefits of onion consumption to human health are still under investigation. Promising results have been obtained from epidemiological studies, *in vivo* research, and numerous *in vitro* investigations. Some *in vivo* research contradicts *in vitro* findings, while other researchers suggest a possible different mechanism of benefit. As with most unproven theories, there will be both supporting and dissenting evidence. Therefore, some findings are accepted while others need more research to support or refute the available evidence. The volume of scientific research concerning healthful benefits of onion phytochemicals continues to increase as more attention is focused on food in prevention and treatment of human diseases.

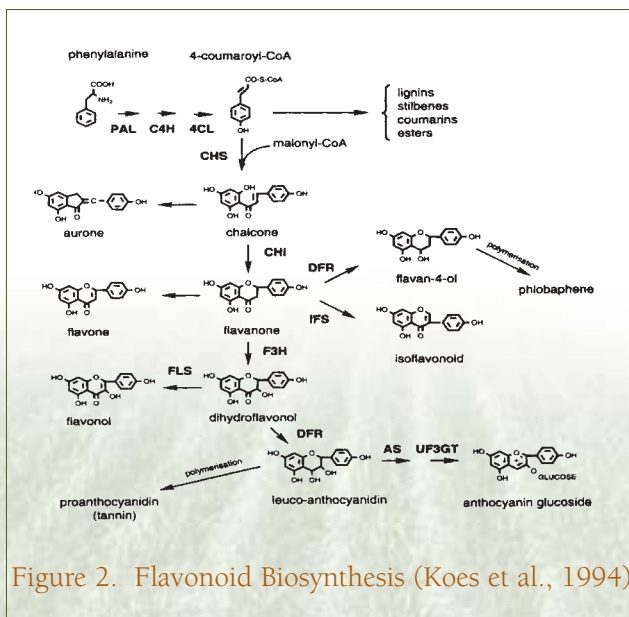
Phytochemical Synthesis

Flavonoids and organosulfur compounds are the two major classes of secondary metabolites found in onions believed to promote beneficial health effects. Their mode of action and biosynthetic pathways are quite different.

The organosulfur compounds are believed to possess anti-inflammatory, anti-allergic, anti-microbial, and anti-thrombotic activity by inhibition of cyclooxygenase and lipoxygenase enzymes (Block et al., 1999). Most likely the compounds work through sulfur-sulfur or sulfur-oxygen linkages (Augusti, 1996). These compounds are formed when an onion is cut and the cell walls are disrupted (Figure 1). Allinase enzymes produce sulfenic acids via S-alk(en)yl cysteine sulphoxides (ACSOs) which rearrange to various compounds such as thiosulfinates, cepaenes, and onion lachrymatory factor (Block et al., 1996; Lancaster et al., 1998).



Flavonoids are phenolic compounds consisting of two aromatic rings held together by a C3 unit. The degree of oxidation of the C3 unit determines the subclass of flavonoid such as flavonols, flavanones, and anthocyanins. Flavonoid biosynthesis (Figure 2) begins with chalcone formation via chalcone synthase from malonyl CoA and coumaroyl CoA, a derivative of the amino acid phenylalanine. The chalcone is eventually isomerized to yield a flavanone. Specific enzymes then catalyze the formation of each flavonoid subclass (Koes et al., 1994; Formica and Regelson, 1995). Quercetin and kaempferol, the major flavonoids in onions, are found in the flavonol subclass. The degree of hydroxylation distinguishes them from one another. The beneficial health effects associated with these compounds such as reduced risk of coronary heart disease and different types of cancer are thought to be primarily from anti-oxidative activity including metal ion chelation and inhibition of lipid peroxidation (Formica and Regelson, 1995; Anonymous, 1998).



Cancer

The inhibitory effects of onion consumption on human carcinoma have been widely researched. Epidemiological data both support (Gao et al., 1999; Hu et al., 1999) and refute (Dorant et al., 1995) the concept that higher intake of onions is positively related to lower risk for carcinoma. In a review on the effects of quercetin, Hertog and Katan (1998) noted that persons in the highest consumption category versus the lowest had a 50% reduced risk of cancers of the stomach and alimentary and respiratory tracts. Organosulfur compounds such as diallyl disulfide (DDS), S-allylcysteine (SAC), and S-methylcysteine (SMC) have been shown to inhibit colon and renal carcinogenesis (Hatono et al., 1996; Fukushima et al., 1997). Mechanisms of protection ranged from induced cancer cell apoptosis (Richter et al., 1999) and gene transcription inhibition (Miodini et al., 1999) to protection against UV-induced immunosuppression (Steerenberg et al., 1998). Thus, closer examination of specific carcinomas and the potential effects of onion consumption is warranted.

Like onions, garlic is considered a dietary anticarcinogen. Song and Milner (2001) demonstrated that as little as 60 seconds of microwave heating or 45 minutes of oven heating could block the ability of garlic to inhibit *in vivo* binding of mammary carcinogen metabolites to rat mammary epithelial cell DNA. If garlic were allowed to sit at room temperature for 10 minutes prior to microwave heating, a total loss of anticarcinogenic activity was prevented. While this study was conducted with garlic and not onions, its implications for onions and health should not be ignored. The accumulation of health-promoting organosulfur compounds may be hastened by simply allowing chopped onions to rest at room temperature prior to cooking.

New evidence suggests that some of the most common organosulfur compounds in onions may

protect against cancer in rats. Fukushima et al. (2001) found that both cysteine and S-methylcysteine, two common organosulfur compounds found in onions, have chemopreventive activity for hepatocarcinogenesis and colon carcinogenesis in a rat model.

Stomach Cancer

Various researchers have suggested that allium vegetable consumption may have a strong impact on stomach cancer prevention. Based on epidemiological data, Dorant et al. (1996) published their findings of the Netherlands Cohort Study (NCS), research involving 3500 subjects over a 3.3 year period. This study analyzed onion, leek, and garlic supplement intake for 139 known stomach carcinoma cases and 3123 subcohort members. A high intake of onions (≥ 0.5 onion/day) was correlated with reduced risk of stomach cancer beyond the cardia. Neither leek consumption nor garlic supplement use was shown to have this reduced effect. Garcia-Closas et al. (1999) also found an inhibitory effect of flavonoid containing vegetables in gastric cancer in a hospital case control study in Spain. Their results showed that intake of kaempferol and quercetin were protective while that of carotenoids was not.

High intake (≥ 1 time/week) of allium vegetables such as onion, Welsh onion, and Chinese chives has been shown to decrease the risk of stomach cancer in China (Gao et al., 1999). The authors stated that high consumption of allium vegetables may decrease the risk of *Helicobacter pylori* infection, which has been linked to stomach cancer through ulcer formation. Quercetin has been shown to not only prevent the induction of gastric mucosal injury, but also to promote the healing of gastric ulcers through free radical scavenging (Suzuki et al., 1998). Thus, stomach cancer risk may be reduced by the antioxidative effects of quercetin and organosulfur compounds realized from high levels of onion consumption.

Lung Cancer

The same Netherlands Cohort Study used to evaluate stomach carcinoma risk (Dorant et al., 1996) was also used for analysis of risk of lung cancer. Although high onion intake was associated with lower lung cancer risk in stratified analysis, upon correction for dietary and non-dietary determinants of lung cancer, the correlation was not statistically significant (Dorant et al., 1994). It was postulated that dietary absorption of and/or quantity of flavonoids and organosulfur compounds in the onions consumed were inadequate to produce effective results. Khanduja et al. (1999) performed an *in vivo* study of quercetin effects on mice with N-nitrosodiethylamine-induced lung tumorigenesis. The flavonoid was found to decrease tumor incidence by 32% in the initiation phase, but had no effect on already present carcinomas. The mechanism of benefit was thought to be a consequence of antioxidant activity and suppression of lipid peroxidation. The researchers used a dosage of 9mg/mL H₂O but failed to quantify how much each mouse ingested daily per kg body weight. Therefore, it can be concluded that there is a possible inhibitory effect on lung carcinoma risk from ingestion of onions, but it is unknown if the levels needed are feasible to consume.

Bladder Cancer

Tobacco smoking has been cited as the major cause of urinary bladder cancer in humans (IARC, 1986 from Malaveille et al., 1996). Human urine was shown to contain dietary phenols that had an antimutagenic effect on a known tobacco-smoke related carcinogen (Malaveille et al., 1996; 1998). Extracts from onions and wine were shown to have corresponding effects as the phenols extracted from urine, suggesting both absorption of flavonoids after ingestion and a possible role in protection against tobacco carcinogens from dietary intake of vegetables.



Mechanisms of these effects were thought to alter absorption rates, modify enzymes that activate heterocyclic amines, and react with or tightly bind toxic substances or metabolites.

Colorectal Cancer

Both *in vitro* and *in vivo* studies were performed to study the effects of onion phytochemicals on colon cancer. The organosulfur compound S-allylcysteine (SAC) from garlic was shown to inhibit colon cancer precursors when administered orally to rats (Hatono et al., 1996). The mode of action was proposed to be activation of detoxification systems such as glutathione S-transferase (GST). Only the initiation phase of carcinogenesis was affected while promotion and differentiation were not affected. Quercetin, however, was shown to have a large inhibitory effect on colon tumor proliferation in mice suggesting protection at the promotion phase and not at initiation (Deschner et al., 1991).

Duthie and Dobson (1999) showed a protective effect of quercetin on oxidative attack of human colonocyte from peroxide attack. Antioxidant activity has been inversely associated with cancer formation (Newmark, 1996). Thus, colonocytes as well as all cells can benefit from quercetin's scavenging ability. Quercetin was also shown to be highly effective in inducing apoptotic cell death in colorectal tumor cells while sparing normal cells (Richter et al., 1999). Inhibition of epidermal growth factor (EGF) receptor kinase was thought to be the effective mechanism. Therefore, high dietary intake of onions may provide protection from colon cancer by inhibiting both initiation and proliferation through the effects of both organosulfur compounds and flavonoids.

Breast Cancer

In 1995 Dorant et al. published their results from the Netherlands Cohort Study which showed no relationship between high consumption of onions and risk of breast cancer in post-menopausal women. However, other researchers from Switzerland (Levi et al., 1993) and France (Challier et al., 1998) showed a significant decrease in risk of breast cancer with high intake (>16 times/week) of onions. It should be noted that these studies did not distinguish between pre- and post-menopausal women. Rodgers and Grant (1998) suggested that quercetin may have a significant anti-proliferative effect on breast cancer cells by increasing the activity of reductase enzymes known to inactivate cytotoxic carcinogenic compounds. They also stated that flavonoids may induce apoptosis in the cancer cell and synergistically increase the activation of quinoid anticancer drugs. This would increase the efficacy of the drugs and enable use of lower dosages so that negative side effects such as those seen with chemotherapy are diminished. Another investigation of the same type of breast cancer cell (MCF-7) suggested that the marked antiproliferation effect of quercetin was due to causation of conformational changes on the oestrogen receptor protein which inhibits gene transcription (Miodini et al., 1999).

Ovarian Cancer

An *in vitro* research study showed that quercetin had an antiproliferative effect on cells of ovarian carcinoma, one of the most common causes of death from cancer in women (Shen et al., 1999). Dose-dependent inhibition of kinase activity in the signal transduction pathway was noted as the mode of protective action. Of particular interest are the effects on ovarian carcinoma found with sequential administration of tiazofurin, an anticancer drug, and quercetin. Similar synergistic effects have been noted

for cancer cells of the colon (Rzymowska et al., 1999) and breast (Rodgers and Grant, 1998).

Brain Cancer

Guo et al. (1994) suggested that vegetable consumption may be inversely linked and salt preserved foods positively related to risk of brain cancer. A case control of 129 subjects in northeast China paralleled these findings (Hu et al., 1999). In particular, a strong inverse relationship to cancer risk was found with high consumption of onions. Both Guo et al., (1994) and Hu et al., (1999) postulated that N-nitroso compounds (NOCs) from salted foods may be the reason for increased risk of brain cancer. It has been shown that both organosulfur compounds (Shenoy and Choughley et al., 1992) and flavonoids (Law et al., 1999; Shutenko et al., 1999) found in onions have a protective effect against NOCs.

Bone Health

Bone fractures due to osteoporosis are a health care burden. Dairy and soy have both been proposed as dietary sources of compounds (calcium, phytoestrogens) with potential for improving bone health, but neither has been confirmed as helpful in clinical trials with humans. Muhlbauer and Li (1999) demonstrated that onion intake by rats was responsible for increasing bone mass, bone thickness, and bone mineral density. Onions inhibited bone resorption by 20% when consumed at a rate of 1g per day per kg of body weight. This was slightly higher than the rate of bone resorption obtained from the calcitonin that is typically used to treat postmenopausal osteoporosis. These findings suggest that onion intake may be a useful dietary approach to improving bone health.

Diabetes

Significant research has been done on the effect of onion consumption on diabetic conditions. The organosulfur compounds S-methylcysteine sulfoxide (SMCS) and S-allylcysteine sulfoxide (SACS) were linked to significant amelioration of weight loss, hyperglycemia, low liver protein and glycogen, and other characteristics of diabetes mellitus in rats (Sheela et al., 1995). They found that the use of SMCS and SACS (200mg/kg/day) gave results comparable to treatment with insulin or glibenclamide but without the negative side effect of cholesterol synthesis stimulation. Similarly, Baba Suresh and Srinivasan (1997) found that a 3% onion powder diet also reduced hyperglycemia, circulating lipid peroxides, and blood cholesterol (LDL-VLDL exclusively). *In vivo* analysis of the effects of quercetin on human diabetic lymphocytes showed a significant increase in the protection against DNA damage from hydrogen peroxide at the tissue level (Lean et al., 1999). Antioxidant activity was shown, but non-diabetic controls were not used and symptom relief was not mentioned. Further human studies should assess the ability of a high flavonoid diet to attenuate diabetic conditions.

Coronary Heart Disease

Reduction of heart disease via dietary intake of phytochemicals has been examined (Fitzpatrick et al., 1993; Hertog et al., 1995; Augusti, 1996). Researchers who studied 12,763 men from seven countries found an inverse relationship between flavonoid intake and coronary heart disease (Hertog et al., 1995). Inhibition of LDL oxidation and platelet aggregation were proposed as mechanisms of benefit against cardiovascular disease (Janssen et al., 1998). Quercetin exerts its beneficial effects on cardiovascular health by antioxidant and anti-inflammatory activities (Anonymous, 1998; Kuhlmann et al., 1998). Adenosine and paraffinic



polysulfides (PPS) are compounds isolated from onions with purported antiplatelet effects (Makheja and Bailey, 1990; Augusti, 1996; Yin and Cheng, 1998).

Lipid peroxidation is a self-propagating chain of highly reactive radicals that have drastic effects on membrane functions (Juurlink et al., 1998). Aldehydes derived from lipid peroxidation can diffuse within or escape the cell and attack targets far away from the site of origin (Uchida et al., 1999). LDL oxidation and endothelial cell damage is believed to be involved in the early development of atherosclerosis (da Silva et al., 1997; Kaneko and Baba, 1999). Researchers found that presence of quercetin significantly reduced LDL oxidation *in vitro* from various oxidases including 15-lipoxygenase, copper-ion, UV light, and linoleic acid hydroperoxide (Nègre-Salvayre and Salvayre, 1992; da Silva et al., 1998; Aviram et al., 1999; Kaneko and Baba, 1999). Besides the direct antioxidant effect, quercetin also inhibited consumption of *alpha*-tocopherol (Hertog and Katan, 1998; da Silva et al., 1998; Kaneko and Baba, 1999) and protected human serum paroxonase (PON 1) activities (Aviram et al., 1999). Thus, synergistic inhibition of oxidative stress was observed. McAnlis et al. (1999) found that despite the rise in plasma antioxidant capacity from ingestion of onions, LDL oxidation was not affected. This *in vivo* research suggested that quercetin, having a high affinity for protein, was bound to albumin and never incorporated into the LDL particle. The authors proposed that *in vitro* results are caused by flavonoids acting in an aqueous phase and do not give a true representation of *in vivo* effects. However, other research suggested that the protective effects of quercetin occur at the cellular level. Nègre-Salvayre and Salvayre (1992) found that the flavonoid protected cells from the cytotoxic effects of previously oxidized LDL. They suggested the mechanism of action was blocking of the intracellular transduction of the cytotoxic signal. Uchida et al. (1999) noted inhibition of transduction signals by quercetin on the lipid peroxidation-derived

oxidative stressor 4-hydroxy-2 nonenal (HNE).

Strokes and coronary heart disease can be caused by platelets in the blood adhering to the walls of blood vessels in the heart or brain and aggregating to the point of obstruction (Ali et al., 1999). Research on *in vivo* effects of onion consumption in rats showed significant inhibition of serum thromboxane, an inducer of platelet aggregation, levels with high doses (500mg/kg) (Bordia et al., 1996). Low doses (50mg/kg) showed little effect, but a benefit was proposed over long term consumption. Boiled onions, even at the high dosage level, showed no effect, suggesting degradation of effective compounds due to high temperatures. Similarly, raw Welsh onion extracts were shown to have vasorelaxing effects on precontracted aortic rings while boiled extracts caused vasoconstriction and were purported to induce thromboxane synthesis (Chen et al., 1999). In a subsequent study it was found that oral administration of raw Welsh onion juice in rats prolonged bleeding time, reduced platelet aggregation, and increased camp levels (Chen et al., 2000). However, boiled onion juice showed none of these effects. Again, change in thromboxane balance was thought to be the causative agent in the inhibition of platelet adhesion. Other researchers showed antiplatelet activity in rabbit plasma, but not in human plasma (Ali et al., 1999). The researchers suggested that varietal differences may play a role. Goldman et al. (1996) found that onions containing higher sulfur levels exhibited a greater antiplatelet effect than genotypes with low sulfur content. Janssen et al. (1998) performed both *in vitro* and *in vivo* studies. 2500 umol/L quercetin was shown to inhibit platelet aggregation by 95-97%, but 18 human subjects ingesting 114mg quercetin/day from onions showed no significant effects. Therefore, it was concluded that necessary concentration levels of quercetin for beneficial effects were too high to be obtained dietarily.

Onions have long been known as a blood thinner, and part of the reason for this is their ability to inhibit platelet aggregation. Briggs et al. (2001) found that raw onion administered to canines inhibited platelet-mediated thrombosis, even at very low doses. They used an *in vitro* coronary thrombosis model developed by Dr. John Folts at the University of Wisconsin to collect these data. Their findings suggested that raw onion may be useful in preventing *in vivo* thrombosis, but they also reported that the platelet inhibitory properties of this extract were far greater in dog blood than in human blood, suggesting canines have high levels of sensitivity to onion compounds.

Rats fed 2g/kg dry onion for six days while feeding on an atherogenic diet showed significant reductions in both serum cholesterol and triglyceride levels as compared to those only eating the atherogenic diet (Lata et al., 1991). Likewise, students fed a high fat diet one day, and the same diet plus 100g onions another showed a significant decrease in serum triglycerides, but not cholesterol, from the onion supplemented diet (Sainani et al., 1978). Investigators from both studies showed a possible inhibitory benefit of onion consumption on atherosclerosis formation.

It is evident that there are several different mechanisms by which consumption of onions may exhibit protective effects against coronary heart disease. More research must be done to elucidate the realized benefits from dietary onion intake on coronary heart disease.

Immunosuppression

Quercetin's anti-inflammatory effect on prostaglandins, leukotrienes, histamine release and subsequent antiasthmatic activity has been investigated (Wagner et al., 1990; Anonymous, 1998). Inflammation is part of the body's natural

immune response to trauma (Marieb, 1995). Thiosulfinates and capsaenins responsible for the anti-inflammatory activities also cause inhibition of the immune response (Dorsch et al., 1990; Chisty et al., 1996). Quercetin also affects immunosuppression (Shoskes, 1998; Steerenberg et al., 1998). The flavonoid has been shown to create a beneficial effect in aiding renal transplantation (Shoskes, 1998). Quercetin was shown to suppress both immune and non-immune injury responses, the key risk factors in chronic graft loss. This showed promising application as it was noted that current drugs and treatments may worsen harmful, non-immunological reactions (ischemia, hypertension, hyperlipidemia) to the transplant.

Alternately, quercetin has been shown to prevent immunosuppression induced by UV exposure to mice (Steerenberg et al., 1998). The researchers noted the conflict in findings with other studies and offered an explanation that the immune response was reduced by anti-inflammatory activity via the arachidonic acid pathway.

Morphine Withdrawal

The *in vitro* effect of quercetin on morphine withdrawal has been examined. Capasso et al. (1998) found that withdrawal symptoms, measured by naloxone contraction, were reduced on a dose-dependent manner (2.7×10^{-6} M for IC 50). Previously, Capasso and Sorrentino (1997) showed that arachidonic acid and its metabolites (prostaglandins and leukotrienes) are involved in the development of morphine withdrawal. Onion capsaenins and thiosulfinates have been shown to inhibit cyclooxygenase and 5-lipoxygenase activity (Wagner et al., 1990) suggesting one mechanism for benefit. The anticholinergic effects of quercetin also were hypothesized to attenuate morphine withdrawal, normally thought to be exacerbated by acetylcholine stimulation (Capasso et al., 1998).



HIV

Suppression of human immunodeficiency virus type 1 (HIV-1) replication is a target for anti-AIDS drugs (Shimura et al., 1999). Viral protein R (*vpr*) has been shown to control the rate of replication of HIV-1 (Cohen et al., 1990). Therefore, suppression of this gene is a probable target for inhibition of the development of AIDS. Westervelt et al. (1992) showed that disruption of the functionality of the *vpr* gene attenuated HIV-1 replication. It was also shown that quercetin may diminish virus replication by inhibiting *vpr* function (Shimura et al., 1999). At 10 μ M dosage, quercetin provided 92% inhibition of *vpr*-induced cell cycle abnormality.

Cataracts

Cataracts, characterized by lens opacification, have been shown to be instigated by oxidative stress, primarily from hydrogen peroxide (H₂O₂) (Spector, 1995). Quercetin is known to scavenge the free radical superoxide anion, a major *in vivo* source of H₂O₂ (Juurlink et al., 1998). Opacity induced in rat lenses by exposure to H₂O₂ was almost entirely reversed after incubation with 30 μ M quercetin for 4 hours (Sanderson et al., 1999). Pretreatment of lenses with quercetin before oxidation was shown to provide 46% protection as compared to control. Further tests showed that the mode of action was not inactivation or removal of H₂O₂ by free radical scavenging, but that quercetin inhibited opacification by protecting modification of lens membrane channel proteins by an influx of Ca²⁺ and Na⁺ ions. Daily consumption of more than 500mL of tea, a large source of quercetin, was associated with decreased risk of cataracts (Robertson et al., 1991). It has been reported that the percentage of quercetin absorbed from onions is approximately twice that of tea (de Vries et al., 1998). Therefore, high daily intake of onions may provide a nutritional benefit against the risk of cataract formation.

Antioxidant Activity

Antioxidant activity from a high intake of fruits and vegetables has been reported to prevent alteration of DNA by reactive oxygen species (ROS) and subsequent cancer development (Wardlaw, 1999). Flavonoids, ubiquitous in the plant kingdom, have been widely studied for their antioxidative effects (Rice-Evans et al., 1995; Hertog and Katan, 1998).

Onions are known to contain anthocyanins and the flavonoids quercetin and kaempferol (Bilyk et al., 1984; Rhodes and Price, 1996). However, anthocyanin pigments, concentrated in the outer shell of red onions, are only minor constituents of the edible portion (Rhodes and Price, 1996). Kaempferol, while detectable in certain onion varieties, is present in much smaller quantities than quercetin (Bilyk et al., 1984; Rice-Evans et al., 1995). Therefore, quercetin is the major flavonoid of interest in onions. Mechanisms of action include free radical scavenging, chelation of transition metal ions, and inhibition of oxidases such as lipoxygenase (de Groot and Rauen, 1998; Suzuki et al., 1998; Lean et al., 1999). The effects of organosulfur compounds on reactive nitrogen species (RNS) will be discussed in a separate section.

The antioxidative effects of consumption of onions have been associated with a reduced risk of neurodegenerative disorders (Shutenko et al., 1999), many forms of cancer (Hertog and Katan, 1998; Kawaii et al., 1999), cataract formation (Sanderson et al., 1999), ulcer development (Suzuki et al., 1998), and prevention of vascular and heart disease by inhibition of lipid peroxidation and lowering of low density lipoprotein (LDL) cholesterol levels (Frèmont et al., 1998; Aviram et al., 1999; Kaneko and Baba, 1999). Another antioxidant effect of onions and their extracts includes the reduction of rancidity in cooked meats (Jurdi-Haldeman et al., 1987). The authors found that addition of onion juice to cooked ground lamb reduced the 'warmed

over' flavor due to oxidative rancidity and resulted in a more preferable product as evaluated by a sensory panel.

Inhibition of oxidases, enzymes that liberate free radicals, can be direct or indirect (de Groot and Rauen, 1998). Protection from arachidonic acid metabolites and lipoxygenase activity is important in prevention of vascular disease (Juurlink et al., 1998). Quercetin has been shown to not only directly inhibit the lipoxygenase enzyme, but to also suppress consumption of *alpha*-tocopherol and to preserve human serum paraoxonase (PON 1), both potent antioxidants against lipid peroxidation (da Silva et al., 1997; Aviram et al., 1999). Metal chelation involves formation of a complex with the flavonoid and prevention of catalytic radical production, whereas free radical scavenging activities relate to the flavonoid donating a hydrogen atom and creating a more stable radical (de Groot and Rauen, 1998). Structural qualities of quercetin and other flavonoids that provide for effective free radical scavenging are:

- Presence of *ortho*-dihydroxyl (catechol) structure in B ring
- 2,3-double bond in conjunction with 4-oxo function in C ring and
- Additional presence of 3- and 5-hydroxyl groups (Yokozawa et al., 1999; Kaneko and Baba, 1999).

Rice-Evans et al. (1995) found that removal of the 2,3-double bond in the C ring, as in catechin and epicatechin, resulted in a 50% decrease in antioxidant activity. There is some debate about the exact mechanism of flavonoids. Direct scavenging of superoxide and hydroxyl anions has been reported (Yuting et al., 1990; Suzuki et al., 1998; Shutenko et al., 1999). However, Sestili et al. (1998), in an experiment designed to distinguish the mechanism of action, found that quercetin effectively protected DNA strand scission from *tert*-butylhydroperoxide, which can only be explained by iron chelation. Copper chelation has also been exhibited to have

anti-peroxidative effects (Frèmont et al., 1998). Nègre-Salvayre and Salvayre (1992) and McAnlis et al. (1999) reported that although direct protection of quercetin against oxidative LDL modification had been found *in vitro*, the flavonoid exerted its protective effect *in vivo* at the cellular level by preventing cell damage from already oxidized LDL. Therefore, depending on the location of protective action (cellular, nuclear, or plasma) a different antioxidative mechanism may take place.

Comparison studies of the antioxidative activities of different vegetables have been examined (Gazzani et al., 1998a; Gazzani et al., 1998b; Yin and Cheng, 1998). It has been found that most vegetables contain antioxidant activity, which is associated with epidemiological hypotheses relating high vegetable intake with lower risk of disease (Block et al., 1992; Cao et al., 1996; Gazzani et al., 1998a). Green and black tea have been shown to have high antioxidant activities, probably due to their high content of quercetin (Hertog et al., 1993; Cao et al., 1996). Polyphenolic compounds of red wine have been linked to vasorelaxation and decreased risk of coronary heart disease (Fitzpatrick et al., 1993). Researchers comparing antioxidant activity measured in Trolox equivalents equates 1 glass (150mL) red wine with 2 cups tea, 5 portions onion (~100g/portion), 7 glasses orange juice, and 20 glasses apple juice (Paganga et al., 1999). Absorption and bioavailability of flavonoids in onions have been shown to be more effective than from other sources (i.e. tea and apples) (de Vries et al., 1998). This is discussed in more detail in another section of this review.

Reactive Nitrogen Species

Reactive nitrogen species (RNS) give rise to, and act much like reactive oxygen species in causing oxidative damage to cellular proteins, tissues, and DNA (Juurlink et al., 1998). Guo et al. (1994)



and Hu et al. (1999) described N-nitroso compounds (NOCs) as having an association with increased risk of brain cancer. Quercetin has been shown to reduce the level of peroxynitrate, an extremely powerful oxidant in the brain, by scavenging superoxide anion (Shutenko et al., 1999). Thus, cellular modification, lipid peroxidation, and risk of neurodegenerative disease in the central nervous system may be diminished (Juurlink et al., 1998). Law et al. (1999) also noted lower incidence of cell necrosis and lipid peroxidation levels due to the action of quercetin in scavenging non-enzymatically nitrogen derived radicals. Researchers on NOC formation proposed that sulphur containing compounds in onion juice were the causative agents in the observed inhibition of nitrosation reactions (Shenoy and Choughuley, 1992). The inhibitory effects of specific sulphhydryl compounds also were shown. Therefore, both flavonoids and sulphur containing compounds found in dietary onions may decrease the risk of nitrosamine formation and possible cellular damage and cancer development.

Absorption/Bioavailability

In order to validate epidemiological findings that consumption of vegetables, including onions, lowers the risk for human disease, absorption of the functional flavonoids in adequate amounts must be shown. Daily flavonoid intake from the human diet has been estimated to be between 25mg and 1g with quercetin constituting the majority of that intake, estimates ranging between 16 and 500mg per day (Deschner et al., 1991; Hertog et al., 1993; Rodgers and Grant, 1998; Richter et al., 1999). Tea, onions, and apples are believed to be the largest sources of dietary flavonoids contributing 48, 29, and 7 percent, respectively (Hertog et al., 1993). Total quercetin content in the edible portion of onions varies, but has been noted as high as 345mg/kg (Bilyk et al., 1984; Patil et al., 1995a; Patil and Pike, 1995). Kaempferol is found in much

smaller amounts (~1-7mg/kg) and, therefore, onions may not constitute a significant source (Bilyk et al., 1984).

Absorption into the body and type of isoform present are major concerns involving the affectivity of quercetin. Quercetin exists in the free aglycone form (no sugar attached) and in glycosilated forms (sugar attached) (de Groot and Rauen, 1998). Eighty percent of the quercetin in onions exists as mono- and di-glucosides that undergo autolysis upon processing (i.e. chopping) and accumulate after 24 hours as mainly mono-glucosides and the aglycone (Rhodes and Price, 1996). da Silva et al. (1998) found these two forms of quercetin to be more efficient in inhibiting lipoxygenase induced LDL oxidation than ascorbic acid and *alpha*-tocopherol. Hollman et al. (1997) reported that the absorption of quercetin from onions was faster and more complete than from apples or tea. Another study mirrored these results, where it was shown that absorption of quercetin from onions was two and three times more absolute than from tea and apples, respectively (de Vries et al., 1998). Thus, although tea may provide a larger source of quercetin, onions may be a better mode for dietary absorption and subsequent nutritional benefit.

Peak quercetin plasma concentrations occur within two hours after ingestion. This suggests that absorption takes place primarily in the stomach and/or small intestine (Aziz et al., 1998; McAnlis et al., 1999). Quercetin is liberated from its glycosilated form by glycosidases of colonic microflora (Deschner et al., 1991). These findings give credibility to researchers who have shown reduced risk of stomach (Garcia-Closas et al., 1999) and colon (Duthie and Dobson, 1999) cancers with increased dietary intake of onions. The exact amount necessary to be eaten has not been determined, but researchers have suggested that consumption of more than one-half onion per day has an inhibitory effect against some

cancers (Dorant et al., 1994). This finding was based on epidemiological data.

Quercetin is one of the most well-studied flavonoids and is particularly high in onions. Quercetin is thought to be protective against coronary heart disease, stroke, and certain cancers. But most flavonoids, including quercetin, have very low oral bioavailability. Thus their absorption from food may be limited. Walle et al. (2001) examined radio-labeled quercetin that had been administered orally and intravenously (IV) to normal, healthy volunteers. Total recovery of the labeled carbon in the quercetin was very low. These workers found that a large fraction of the quercetin dose was recovered as carbon dioxide in the expired air from volunteers after both oral and IV doses. Thus, much more work must be done to determine the metabolism of quercetin *in vivo* in order to estimate its potential for human health.

Fortunately for home cooks, Markis et al. (2001) discovered that quercetin in onions was completely unaffected by chopping; however, boiling for 60 minutes reduced the overall flavonol content of onions by 20.6%. Thus, chopped fresh onions retain much of their antioxidant capacity in *in vitro* assays, while boiled onions do not.

Red and yellow onions contain anthocyanins in their skins, which have been shown to be very useful antioxidants in the human diet. Anthocyanin content decreased in red onions when bulbs were stored for six weeks under various conditions mimicking home storage. Gennaro et al. (2002) discovered decreases in anthocyanins were from 64-73%. Antioxidant activity similarly declined from 29-36%. These workers found that low temperature storage, such as that obtained by a root cellar, was beneficial for preserving anthocyanins.

The composition of flavonoids in onions has been studied to some extent, but the types of

flavonoids in particular onions has not been well documented. Sellappan and Akoh (2002) showed that *Vidalia* onions contain quercetin as well as the flavonoids myricetin and kaempferol. Each of these flavonoids has been suggested to possess useful antioxidant properties in animal and human systems.

O'relly et al. (2001) studied the effects of a high flavonoid diet enriched with onions and black tea on indices of oxidative damage *in vivo* compared with a low-flavonoid diet. Plasma concentrations of quercetin were higher in the high flavonoid treatment in all 32 subjects, but there was no effect on lipid peroxidation. While such effects had been demonstrated *in vitro*, the biomarkers used in this study did not reveal an effect of the onion flavonoids consumed *in vivo*.

Food Safety

Onions, along with garlic, leeks, and chives, may be an important part of our cuisine because of their positive effects on food safety. Billing and Sherman (1998) suggested that there is a strong relationship between climate and spiciness of cuisine. They further suggested that this relationship may be due to the adaptive value of seasoning and that antimicrobial compounds in these spices, such as the organosulfur compounds in onions, may reduce the rate of food-borne illness. Even though some authors have taken issue with their findings (McGee, 1998), it is possible that consumers of onion-containing foods may benefit from the unique antimicrobial properties conveyed by this vegetable.

Probiotic Effects

Onions store their carbohydrates as fructans, which are fructose polymers held together by beta linkages. They may offer useful probiotic effects in



the human gut, including the improvement of intestinal flora, improved absorption of calcium and magnesium, and other health benefits. This area of research is just beginning for onions, and it is likely to offer many new promising health functionalities for onion consumers. Jaime et al. (2001) found large variability among onion cultivars for their composition of fructans, dry matter, and soluble solids. This variability will affect not only the length of time these onions can be stored, but their ability to deliver the useful benefits of the fructans. Although these data are promising, much more work must be done to evaluate onions for their potential as a probiotic.

Varietal Differences

Quantities of phytochemicals in onions can vary greatly due to varietal differences (Bilyk et al., 1984). Geographical location, storage, and genetic factors have all been determined to affect the levels of quercetin found in onions (Patil et al., 1995a; Patil et al., 1995b). Quercetin content is highest in the dry skin and decreases from the outer to inner rings (Patil and Pike, 1995). Yellow, red, and pink onions have been shown to contain higher amounts of quercetin than white varieties, but it was determined that color is not the limiting factor (Patil et al., 1995a). However, accessibility to light (i.e. skin color) has been associated with flavonoid development (Patil and Pike, 1995). Storage temperature and duration have been shown to have significant effects on quercetin content, but a relative pattern was not elucidated (Patil et al., 1995b). Differences in concentration due to growing location were also found, but identification of exact environmental factors was not determined (Patil et al., 1995b). High bulb sulfur content and percent solids were associated with increased antiplatelet activity (Goldman et al., 1996). Therefore, highly pungent genotypes may confer more health benefits than mild varieties. Tannins and anthocyanins from

the skin of red onion have been reported to have antioxidant activity (Augusti, 1996), but no appreciable amounts remain in the edible portion once the outer skin has been removed (Rhodes and Price, 1996). In view of these findings, conditions may be manipulated and certain strains chosen to produce onions with superior phytochemical properties.

Antibacterial/Antifungal

Although thought to be less active than garlic, onions have been shown to possess antibacterial and antifungal properties (Hughes and Lawson, 1991; Augusti, 1996). Onion oil has been shown to be highly effective against gram positive bacteria, dermatophytic fungi, and growth and aflatoxin production of *Aspergillus* fungi genera (Zohri et al., 1995). In fact, Welsh onion extracts have been proven to be more inhibitory toward aflatoxin production than the preservatives sorbate and propionate at pH values near 6.5, even at concentrations 3-10 fold higher than maximum levels used in foods (Fan and Chen, 1999). Organosulfur compounds were cited as protective agents by researchers finding antibacterial effects of onion extract against oral pathogenic bacteria (Kim, 1997). The possibility arises for protection against dental caries. It should be noted that no protection was found in extracts obtained from grated onion kept at 37°C for over two days. Enzymatic destabilization of thiosulfates was proposed for the change in effectiveness.

The organosulfur compounds of onions also have been credited with antiasthmatic effects (Dorsch and Wagner, 1991; Augusti, 1996). Thiosulfates formed from onion tissue degradation (i.e. chopping) have been credited in inhibition of arachidonic acid metabolic pathways and subsequent anti-inflammatory and antiasthmatic effects (Wagner et al., 1990). In addition to inhibitory effects

against pathogenic bacteria, onions have been found to promote beneficial microorganisms. Onions contain fructooligosaccharides (FOS), prebiotics which are non-digestible ingredients fermented by *bifidobacteria* in the body that help maintain the health of the gut and colon (Gibson, 1998). Onions are composed of 2.8% FOS (wet wt.) when compared to 1.0% FOS in garlic, 0.7% in rye, and 0.3% in bananas. Oligosaccharides have been proposed as a key food ingredient for the future.

Onion Future Directions

Imai et al.(2002) found that the lachrymatory factor produced by onions and known as the compound that makes one's eyes water when onions are chopped was produced by a specific enzyme, lachrymatory factor synthase, rather than as just a byproduct of other reactions. The identification of this enzyme raises questions about the possibility of modifying onions to produce no-tear onions, although it is quite likely that flavor would also be affected. Nevertheless, many consumers were intrigued when this discovery was announced, as it suggested the possibility of very mild no-tear onions in the marketplace.

Conclusion

In summary, the health benefits of dietary consumption of onions have been reviewed. Organosulfur compounds such as diallyl sulfide and thiosulfates, as well as flavonoids such as quercetin, have been the focus of much research pertaining to antioxidant activity, cancer prevention, coronary heart disease, and many other factors relating to human disease. Researchers using epidemiological data have shown a relationship between increased onion consumption and lower risk of certain cancers, especially in areas of the body involved in the digestive system. Other

research focused on lipid and cellular oxidation and subsequent damage to cellular function and overall health. *In vitro* and *in vivo* results both support and refute claims regarding the potential benefits from phytochemicals found in onions. Many promising aspects concerning high daily intake of onions have been elucidated. However, it is apparent that more research is still needed in order to clearly identify *in vivo* health benefits from increased onion consumption in the human diet.

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