From Soil to Snake Oil: Possibilities and Limitations in Food Functionality*

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Abstract

Plants are the foundation for a significant part of human medicine. Monomolecular drugs have been widely adopted, obscuring the collective wisdom of many traditional remedies. Plants contain secondary compounds that have the potential to influence human health. Functional foods deliver physiological benefits beyond nutrition. However, the functional constituents of many foods may be unknown. Uptake and assimilation of nutrients by plants may dictate the kinds and amounts of functional secondary compounds in crops. For example, sulfur (S) uptake may dictate the health functionality of *Brassicaceae* and *Alliaceae* crops. Competitive S and selenium (Se) uptake may further enhance or diminish the health functionality of these crops. Fertilization of *Brassica* crops with sodium selenate (Na_2SeO_4) can increase Se accumulation, but reduce glucosinolate concentration, thereby diminishing the benefits of these S-based compounds. Luxuriant fertility levels generally do not result in vitamin or secondary compound increases in crop plants, although mineral increases have been noted. The potential for improving and/or limiting food functionality through fertility practices will be considered from the perspective of nutrient uptake and assimilation.

Introduction

Food and health are inextricably connected, but their relationship is difficult to understand. If one judges a scientific field on the level of interest among the general public, nutrition and health come close to the top of the list. And in fact, many consumers are highly interested in matters of food and health. Some of this may stem from their desire to improve their health through dietary modification, and others may be interested in the potential healing benefits of foods. Unfortunately, there is so much conflicting information about diets and health that many readers find themselves overwhelmed by contradictory suggestions, unproven claims, and marketing efforts that seem to lack scientific foundations. It is not surprising that today's consumer faces a myriad of confusing recommendations and suggestions that do little to sort out fact from fiction. In fact, the modern field of food functionality has at times seemed to resemble the snake oil claims sales that characterized a number of natural product–health marketing efforts over the years. How much of this has a scientific foundation and the potential to positively impact human health?

Fortunately, the origin of many of our edible crop plants (and particularly horticultural crops such as vegetables) is connected to their use as both food and medicine. The medicinal or therapeutic value of a number of vegetable plants may have been an important factor in their domestication. For example, rice has been used by cultures throughout the world as a symbol of fertility. Throwing rice at weddings may have originated with the belief that rice protected the fertility of the newly married couple. Tomatoes were originally used to treat eye diseases and other ailments in addition to being a food crop. The vegetable alliums, including onion, garlic, and their relatives, have been used by cultures throughout the world to improve blood circulation, as well as additions to flavor food. This is also true of carrot and related members of the vegetable *Apiaceae*. Thus, plants and their use as both food and medicine are deeply woven into the fabric of many human cultures. Although we do not have information on the details of domestication history for these crops, it is possible that their potential value as foods enabled humans to make dual use of them, thereby improving their chances of becoming adopted by cultures.

Medicine, horticulture, and botany intersected in the recognition that plants can prevent, treat, and cure disease (Janick, 2002). The origins of all the healing arts begins with plant-based products, and thus horticulture and medicine have been linked since the beginning of these practices. The priest, physician, healer, shaman, botanist, and horticulturist were connected by their natural interest in plant materials. They also incorporated a magical or dimension of superstition to their healing practices. Janick (2002) has pointed out that the Egyptian word *pharagia*, which means making magic, is the origin of the Greek *pharmakon* and Egyptian *pharmaki,* serving as the origin of the word pharmacy.

However, the development of the scientific method transformed medicine into a scientific discipline by the 17th century. It was at this time that medicine and horticultural botany began to separate. Prior to

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their separation, documents known as herbals described the healing properties of many plants. Today, the herbal is a reminder of the primary linkage between horticulture, medicine, and human health, as it combines information about medical remedies, botanical features, and horticulture. As chemical methods of synthesis improved, highly purified monomolecular drugs became the norm (Lawson, 1998). Within the last 50 years, these pharmaceuticals have become standard in preventing, treating, and curing disease in the U.S. In my opinion, this has been a tremendous boon to public health and a fantastic success of modern medicine. However, it has also displaced some elements of our collective wisdom with regard to matters of food and health.

Many of the compounds that have been identified as health-functional in vegetable crops have also been associated with defense against pathogens. Compounds such as flavonoids, carotenoids, terpenes, glucosinolates, isoflavones, and thiosulfinates may, through their inherent toxicity, confer significant opportunities for pest control. In addition, they may also deliver some of the bitterness and pungency to vegetables that we have come to associate with some crops, such as certain salad greens, peppers, vegetable brassicas, and vegetable alliums. It is possible that the astringency of these compounds, which protect the plants in their growing environment, may also protect humans from pathogens.

Onions and Cardiovascular Health

Onion was domesticated in the mountains of Asia from a wild progenitor that was likely perennial and formed many small bulbs. Selection pressure for a single, large, apically dominant bulb with a biennial life cycle enabled humans to develop a propagule that could serve as a storage vegetable (Goldman, 2001). The biennial life cycle requires storage of certain compounds during the over-wintering period, and the formation of the alk(en)yl-L-cysteine sulfoxides (ACSOs), also known as flavor precursors, may have been one of the ways in which onion bulbs stored S.

Tissue disruption initiates lysis of the ACSOs and causes formation of a variety of organosulfur compounds including the lachrymatory factor, which causes the familiar tearing in those chopping fresh onion, and thiosulfinates. Thiosulfinates are very unique molecules because they are responsible for a variety of activities, including both the flavor and medicinal properties that derive from alliaceous vegetables (Block, 1992). For example, the thiosulfinates have been shown to be important in onion-induced antiplatelet activity (Briggs et al., 2000). In addition, organosulfur compounds produced by alliums, particularly those that develop from disruption of the ACSOs, likely play a unique role in pest control and inhibit predation by would-be predators (Fenwick and Hanley, 1986).

Thus, the formation of thiosulfinates and other organosulfur compounds has a multiplicity of roles for onion: (i) they serve to deter pests, (ii) they confer desirable flavors to food and mask undesirable flavors; and (iii) they confer unique medicinal properties to onion consumers, many of which have yet to be fully understood.

At least 23% of the current U.S. population has some form of cardiovascular disease (AHA, 2000), and most of the U.S. public suffers from some narrowing of coronary arteries due to the presence of arterial plaque (discussed in Goldman, 2001). Cardiovascular disease, including heart attack and stroke, is the leading cause of death in the U.S. for men and women from all ethnic and racial groups studied. The primary forms of the disease include high blood pressure, coronary heart disease, and stroke. Persons with risk of heart disease are often prescribed antiplatelet agents such as aspirin to maintain blood flow and prevent thromboembolic events caused by aggregating platelets in the coronary arteries. Platelets play a key role in thrombosis and acute coronary syndromes because they facilitate blood coagulation. Platelets also play a major role in the development of atherosclerotic narrowing of coronary and cerebral arteries. The inhibition of platelet aggregation is directly associated with the maintenance of coronary arterial blood flow.

In 1998, we formed an interdisciplinary team to investigate cardiovascular health claims for onion. We have (i) determined allium-derived thiosulfinates differentially inhibit human platelet aggregation in vitro and are more potent than aspirin at similar doses (Briggs et al, 2001), (ii) developed a model reaction mixture for large-scale preparation of allium-derived organosulfur compounds such as thiosulfinates (Shen et al., 2000), which should facilitate clinical trials; (iii) determined that a chromosome region on linkage group E in onion accounted for a significant amount of the phenotypic variation for pungency, soluble solids, and in vitro antiplatelet activity (Galmarini et al., 2001), (iv) demonstrated that even minimal cooking times eliminate the in vitro antiplatelet potential of onion extracts, suggesting that fresh onion may be the only efficacious preparation for inhibition of platelet activity, (v) determined that S fertility at high levels (beyond 2 mM sulfate) in solution culture was not able to influence onion-induced antiplatelet activity (Orvis et al., 2001).

John Folts, one of our team members, has developed a well-accepted and widely used canine model for investigation of in vivo platelet activity and platelet-vessel wall interactions. Through this model, our team has been able to begin realistically testing whole foods for their suspected health functional characteristics. Our work shows that surprisingly low doses of fresh onion administered both intravenously and intragastrically abolish platelet-mediated thrombosis in stenosed canine coronary arteries (Briggs et al., 2001). This finding suggests the potential for significant cardiovascular health benefit. However the magnitude, duration, and bioactive principles remain unclear. Furthermore, preliminary tests with cooked onion revealed no abolishment of platelet-mediated thrombosis, suggesting fresh onion may be the only dietary strategy for platelet inhibition from onion.

Cultivar differences for antiplatelet activity have been well documented (Goldman et al., 1995, 1996). One possible explanation for this finding is variation among candidate genes in the S biosynthetic pathway. Orvis (2000) used more than 25 cloned genes from this pathway from a variety of organisms including *Arabidopsis*, barley, maize, and onion as restriction fragment length polymorphism (RFLP) probes in an onion population segregating for antiplatelet activity, pungency, and soluble solids. Very few polymorphisms were detected among segregating progeny, indicating widespread conservation of the S biosynthetic pathway genes across disparate species. This finding suggests differences among cultivars may be due to factors other than differences in S biosynthetic genes.

Galmarini et al. (2001) identified a quantitative trait locus (QTL) that explained phenotypic variation for antiplatelet activity in a segregating onion population. The probe that revealed this QTL showed high homology to an invertase. Invertases are responsible for hydrolyzing fructans, which are primary storage carbohydrates in onion. Fructan polymerization and hydrolysis affect the osmotic potential of onion bulb cells and, as such, are associated with the bulbing process. Thus, one possible explanation for genetic variation in onion for antiplatelet activity may be variation in carbohydrate genes, which can influence water uptake, bulb size, and the concentration of organosulfur compounds in the bulb. More research must be conducted to determine if carbohydrate genes are indeed candidate genes for medicinal traits such as antiplatelet activity.

Selenium and Chemoprevention

Carcinogenesis involves prolonged and cumulative cell injury resulting in the development of a malignant cell or cells. Chemoprevention is the attempt to intervene in the precancerous stages of carcinogenesis by introducing natural or synthetic compounds (Greenwald, 1996). In chemoprevention, emphasis is placed on the beginnings rather than the endings of human disease. Many standard chemotherapeutic agents are toxic to both cancerous and healthy cells, but chemopreventative compounds must be nontoxic and free of side effects since they are intended to be administered to healthy individuals over long periods of time (Greenwald, 1996). Vegetables and fruits, already an integral part of the human diet, have offered a wealth of phytochemicals with potential in chemoprevention. The vegetable *Brassicas*, for example, contain dithiolthiones which in synthetic form inhibit lung, colon, mammary gland, and bladder tumors in laboratory animals. Like other natural chemopreventatives, this synthetic compound activates enzymes found in the liver, which detoxify carcinogens. The isothiocyanate sulforophane, recently isolated from broccoli, is thought to function in a similar manner.

Organosulfur compounds from allium species have been shown to inhibit carcinogenesis by acting as blocking agents and effectively preventing carcinogen activation (Wattenberg, 1992; Fenwick and Hanley, 1985a,b,c). The similarity in biochemical activity between S and Se led to manipulation of nutrient uptake to produce seleniferous Alliaceous plants, which in turn may be useful in supplementing Se in humans and animal diets. Selenium may be more active than S analogues in chemoprevention in studies using Se-enriched garlic. Further investigation revealed Se-enriched garlic was superior to unenriched garlic in suppression of mammary tumors in cancer-treated mice (Ip et al., 1992). Selenoamino acids have been identified in Se-enriched and unenriched garlic, and in Se-enriched onion (Cai et al. 1995a,b). Cai et al. (1995b) proposed enhanced levels of selenocysteine were responsible for a reduction in mammary tumor growth in carcinogen-treated mice fed a Se-enriched garlic diet, although clinical evidence has yet to be produced.

Sulfur and Selenium Relationships

Sulfur, an important constituent of the glucosinolates that form in *Brassica* species, may have an inverse relationship with Se uptake. For example, Charron et al. (2001) found that Na_2SeO_4 fertilization increased Se accumulation and decreased glucosinolate concentration in rapid-cycling *Brassica oleracea*. For hydroponically cultivated onion, Barak and Goldman (1997) found that increasing levels of sulfate (SO_4)-S decreased selente (SeO_4)-Se. When the antagonistic relationship between these two elements was expressed as a molar ratio, S/Se in plant dry matter was nearly identical to S/Se in solution culture with a slight preference for S when S/Se in solution culture is low. Thus, SO_4 and SeO_4 uptake must be considered jointly when attempting to produce a reliable source of organoselenium compounds in plants. Such SO_4/SeO_4 antagonistic uptake interactions have been noted in single cells (Smith, 1976), excised roots (Legett and Epstein, 1956), and whole plants (Bell et al., 1992), even at the field level (Severson and Gough, 1992).

Kopsell and Randle (2001) selected for high and low Se accumulation in a rapid-cycling *Brassica oleracea* population. They conducted two cycles of selection and found gains of 4.8% and 4% per cycle for high and low Se accumulation, respectively. These findings demonstrate the potential for manipulating Se uptake in rapid-cycling plants through breeding. Kopsell et al. (2000) found that increasing selenium in solution culture was associated with increases in leaf Se, potassium, and S, while leaf boron, iron, and phosphorus decreased. This indicates that plant mineral composition may be affected by Se in solution culture.

It is interesting to speculate how Se might influence onion flavor, since it will substitute for S in the ACSO's or flavor precursors. Kopsell and Randle

(1999a,b) found that Se did not affect the content of total ACSO in several onion cultivars grown in nutrient solutions. However, it did affect the levels of several individual ACSOs. They found that Se decreased gamma-L-glutamyl-S-(1-propenyl)-L-cysteine sulfoxide and trans(+)-S-(1-propenyl)-L-cysteine sulfoxide content in all four cultivars tested. They also reported that (+)-S-Methyl-L-cysteine sulfoxide content was higher, while (+)-S-propyl-L-cysteine sulfoxide content was lower with the added Se for two cultivars. Barak and Goldman (1997) found that Se lowered total bulb S content in all onion cultivars, and increased the percentage of total S accumulated as SO_4^{2-} in three cultivars. The effect of Se on the flavor pathway was similar to that found when onions were grown under low S-concentrations. Kopsell and Randle (1999a,b) showed that root, stem, and leaf tissues of rapid-cycling *Brassica oleracea* responded in positive, linear fashion to increasing Se.

Conclusions

Fertilization of crops for improved health functionality may be possible. However, certain challenges have already been identified. For example, competitive S and Se uptake has the potential to either enhance or diminish the health functionality of vegetable alliums and *brassicas*. Fertilization of *Brassica* crops with Na_2SeO_4 can increase Se accumulation, but reduce glucosinolate concentration, thereby potentially diminishing the benefits of these S-based compounds. Luxuriant fertility levels generally do not result in vitamin or secondary compound increases in crop plants, although mineral increases have been measured and may be worth pursuing. In general, it would appear that strategies designed to improve the health functionality of crops must take into account the entire balance of nutrient uptake in the plant. Focusing on a single nutrient or a single pathway in order to enhance secondary compounds may have significant tradeoffs for other biosynthetic pathways. Functionality must be examined in an interdisciplinary context in order for significant progress to be made in improving human health.

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