Toxic phytochemicals and their potential risks for human cancer

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Abstract

Consuming plants for their presumed health benefits has occurred since early civilizations. Phytochemicals are found in various plants that are frequently included in the human diet and are generally thought to be safe for consumption because they are produced naturally. However, this is not always the case and in fact many natural compounds found in several commonly consumed plants are potential carcinogens or tumor promoters and should be avoided.

Introduction

Consuming plants for medicinal purposes or to take advantage of their presumed health benefits, including cancer prevention or treatment, has been a common practice since early civilizations. Phytochemicals are present in fruits, vegetables and many other plants and are not essential nutrients, such as vitamins or minerals, but many are commonly consumed or used as herbal remedies or dietary supplements for perceived health benefits. Most phytochemicals in the United States are not subject to regulation by the Food and Drug Administration (FDA) and their potential toxicity is understudied. Over the past few decades, the use of phytochemical dietary supplements and herbal remedies has increased exponentially and this has been particularly apparent in Western countries where supplement use was reported by 49% of the U.S. population (44% of males, 53% of females) (1). In particular, many cancer patients use supplements in conjunction with traditional cancer treatment, but do not necessarily inform their physicians of their use (2–5). In spite of this popularity, only limited data are available regarding the safety and efficacy of most individual phytochemicals in preventing or treating chronic diseases such as cancer (6). Epidemiological studies indicate that many people who use dietary supplements assume that these compounds are safe and might be a more natural alternative to conventional medication (7). Indeed, some reports have suggested beneficial effects of phytochemicals, such as EGCG (epigallocatechin gallate) (8, 9) or resveratrol (10) in the prevention or treatment of cancer. Numerous dietary epidemiologic observations and animal studies for many dietary factors suggest possible protection against various cancers; but in general, these findings have not yet been validated in randomized human clinical trials. In fact, results of most dietary intervention clinical trials have been very disappointing. Dietary-based cancer prevention suffered a major setback in the mid 1990s in a cancer prevention trial in which βeta carotene actually was associated with an increased risk of lung cancer in smokers (11, 12). Results from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study) in Finland indicated that alpha-tocopherol had no effect on lung cancer incidence, but was associated with decreased prostate cancer risk (11). Unexpectedly, a higher incidence of lung cancer was also observed in men receiving βeta carotene compared to those who did not. Concurrently, in the U.S., the Beta Carotene and Retinol Efficacy Trial

(CARET) was initiated and involved smokers, former smokers, and workers exposed to asbestos and its purpose was to examine the effect of daily βeta carotene and retinol (vitamin A) supplementation on the incidence of lung cancer (13). Similar to the ATBC, the βeta carotene group had a higher risk of lung cancer compared with the placebo group. A later report indicated that plant foods have an important preventive influence in a population at high risk for lung cancer, but the effect is diminished with βeta carotene supplements (14).

In contrast with earlier research suggesting that dietary supplementation with selenium and vitamin E may lower the risk of prostate cancer (11, 15–18), initial results from the largest-ever prostate cancer prevention study, the Selenium and Vitamin E Cancer Prevention Trial (SELECT), showed that these substances did not help prevent prostate cancer (19). Clinical trials with St. John's Wort and garlic have generally shown no effect or an anti-cancer effect and these plants are not considered to be human carcinogens. Whether ginkgo is a carcinogen has been somewhat controversial. An NIH Toxicology report published in March of 2013 summarized the results of a 2-year rodent study on the toxicology of ginkgo, but the study was criticized because of the huge doses that were administered.

The Internet is full of 'pop science' touting the advantageous properties of many phytochemicals that have not been scientifically proven to be safe or effective. This review article highlights some of the phytochemicals that have been reported to act as carcinogens and appear to be most commonly consumed in food or used in herbal remedies. The review is divided into two parts: potential dietary carcinogens and carcinogens in herbal remedies. For example, capsaicin, phytoestrogens, bracken fern, and safrole are commonly consumed in many parts of the world and are linked to cancer development. Amygdalin, aristolochic acids, and some of the pyrrolizidine alkaloids are not regulated and are commonly used in herbal remedies. The emphasis of this review is to focus on food compounds or herbal remedies that have been shown or suspected to be human carcinogens.

Potential dietary carcinogens

A number of phytochemicals with potential carcinogenic effects are found naturally in many foods and seasonings that have been consumed for centuries by humans as food, supplements to maintain optimal health, or used as treatments for disease (Table 1).

Capsaicin

Perhaps one of the most controversial, in spite of being well-studied, phytochemicals is capsaicin. Capsaicin is the principal pungent component in the fruits of plants from the genus *Capsicum*, which are members of the nightshade family, *Solanaceae*. These plants are native to the Americas and have been cultivated as part of the diet since at least 7500 B.C. (20). Capsaicin gives chili peppers their intensity or 'hotness' when ingested or applied topically to the skin, and is the primary ingredient in pepper spray often used in law enforcement. Even though widely consumed, capsaicin has a long and checkered history as to whether its consumption or topical use is carcinogenic. Conflicting epidemiological and basic research studies suggest that capsaicin could have a role in either preventing cancer or causing cancer. Hundreds of basic research studies show that capsaicin suppresses growth of numerous types of cancer cell, suggesting that it has chemopreventive activities and these

studies have been well reviewed and will not be detailed herein (21–23). Animal studies have produced ambiguous results, with some studies showing a carcinogenic effect and some reporting a protective effect. In contrast, epidemiological studies seem to indicate that consumption of hot peppers, which contain variable levels of capsaicin, might be associated with an increased risk of cancer, especially of the gallbladder (24) or stomach (25). However, most of these studies have severe limitations and are descriptive, correlative studies with speculative conclusions. Thus a complete consensus as to whether the primary effect of capsaicin is cancer prevention or promotion has not yet been reached.

Capsaicin is unique among naturally occurring irritant compounds because the initial neuronal excitation it provokes is followed by a long-lasting refractory period during which time the previously excited neurons are no longer responsive to a broad range of apparently unrelated stimuli (26). This desensitization has been exploited for its therapeutic potential. Capsaicin-containing creams have been in clinical use for many years to relieve painful conditions such as rheumatoid arthritis, osteoarthritis and diabetic neuropathy (27). However, even in this area, evidence for the effectiveness or safety of capsaicin use in pain relief is controversial. We recently reported that capsaicin has a co-carcinogenic effect on 12-O-tetradecanoylphorbol-13-acetate (TPA)-promoted skin carcinogenesis *in vivo* and is mediated not only through the transient receptor potential vanilloid subfamily member 1 (TRPV1), but also through the tyrosine kinase epidermal growth factor receptor (EGFR) (28) and COX2 (29). These results suggest caution in the prolonged topical application of capsaicin, especially in the presence of a tumor promoter, which would include exposure to solar ultraviolet irradiation.

Cycasin

Cycasin and its metabolite, methylazoxymethanol (MAM), are typically extracted from the seeds and roots of cycad plants (30), which are cone-bearing plants common to the tropics and subtropics. The seeds and roots of cycads were used as food long before their toxicity was recognized and have also been a source of medicine for many people who live in proximity to these plants. However, the plants are highly poisonous and toxicity from seed ingestion is mainly caused by misuse as an edible food, as an agent to improve health, for cancer prevention, cosmetic use, and to treat gastrointestinal discomfort. MAM is a genotoxic metabolite that targets cellular processes involved in neurodegeneration and cancer development (31). This is based on the observation that a single systemic dose of MAM was shown to induce DNA damage in the brains of C57BL6 mice, which was linked with changes in gene expression associated with cancer (31). MAM was shown to induce a variety of tumors, primarily liver and renal cell carcinomas in nonhuman primates in a 32-year study conducted by the National Cancer Institute (NCI) in the U.S. (32) confirming the results of earlier studies (33). When given subcutaneously or intraperitoneally (IP) to newborn rats, tumors were detected in more than 80% of rats of both sexes and kidney tumors were the most common (34). However, whether cycasin acts directly as a carcinogen in humans is not yet clear and the seeds are still consumed in certain areas of the world.

Phytoestrogens

The phytoestrogens are a group of phytochemicals purported to have both beneficial and, under certain conditions, less than desirable effects. Phytoestrogens gained their name because of their ability bind to estrogen receptors and stimulate receptor activity. Genistein is a polyphenol or isoflavone phytoestrogen that is found in soybeans and other plants, including red clover and fava beans. Lignans are another major class of phytoestrogens and matairesinol was one of the first plant lignan phytoestrogens identified in food and is found in numerous foods such as oil seeds, whole grains, vegetables, and fruits (35). Flax seed and sesame seed contain higher levels of lignans than most other foods. Demographic and anthropometric characteristics, a medical history, and 7-day records of diet were collected prospectively from participants (aged 40–79 years) in the European Prospective Investigation into Cancer and Nutrition-Norfolk (EPIC-Norfolk) and results indicated that dietary phytoestrogens might contribute to the risk of colorectal cancer among women and prostate cancer among men (36). On the other hand, both genistein and matairesinol have been shown to exert preventive effects against hormone-associated tumors, such as breast (37–39) and prostate (36) cancers in humans. However, many phytoestrogens seem to be able to negate the effectiveness of aromatase inhibitors, which are designed to reduce the levels of estrogens that can promote tumor growth in some types of breast cancer (40, 41). Local estrogen production is catalyzed by aromatase, which is regulated differentially in healthy and tumorigenic breast tissue. Soy supplements that have been used to alleviate menopausal symptoms can induce MCF-7 breast cancer cell growth by increasing breast cancer-associated aromatase expression and activity (40). Notably, genistein was reported to block the inhibitory activity of the aromatase inhibitors fadrozole (40) and letrozole (41) against MCF-7 breast cancer cell growth in culture and in a xenograft model, respectively. Thus, women who are taking an aromatase inhibitor might need to be cautioned against consuming soy products. Overall, the results supporting a cancer preventive role for phytoestrogens are not yet conclusive and whether lignans, such as matairesinol, can interfere with aromatase inhibitors in humans has not yet been established.

Ptaquiloside (Bracken fern)

A very commonly consumed but extremely toxic plant is the bracken fern. All parts of bracken fern, including rootstocks, fresh or dry leaves, fiddleheads and spores, contain toxic compounds that are poisonous to livestock and humans. Bracken contains a thiaminase, which splits the essential vitamin thiamine (B1) into its two inactive components, pyrimidine and thiazole, causing thiamine deficiency (42). Bracken fronds are still eaten as a vegetable in many parts of the world and particularly in Korea, Japan and parts of China. Evidence linking this plant to human health issues has been strengthened by epidemiological associations (43) and significant advances in understanding the chemical reactions between one of its most notorious components, ptaquiloside, and DNA (44).

Ptaquiloside is the primary carcinogenic component in bracken fern and when activated to a dienone (APT or activated ptaquiloside), forms DNA adducts and eventually leads to tumor development. It is the only known plant carcinogen that causes natural outbreaks of bladder and/or intestinal cancer in livestock (45). Rats given APT developed ischemic tubular necrosis in the kidney (46) and adenocarcinomas of the mammary glands (47). Squamous

cell carcinomas of the upper digestive tract of cattle have been associated with chronic bracken fern consumption (48) and milk from cows consuming bracken fern has been suggested as a vehicle for this carcinogen in humans (49). Others have shown that consumption of ptaquiloside-contaminated milk may contribute to human gastric cancer (43). However, the greatest risk to humans appears to be the direct consumption of the fern itself, a practice that continues in various countries throughout the world and is indeed promoted on the Internet with recipes for preparing bracken fiddleheads (http://honest-food.net/2011/06/24/bracken-fern-food-or-poison/). Bracken fern was shown to induce DNA damage and apoptotic death of normal human submandibular gland (HSG) cells and oral epithelium cells (OSCC-3) (50). Other studies reveal that the mere presence of bracken fern and its spores represents a greater risk of dying of gastric adenocarcinoma for people who live more than 20 years in such areas or are exposed in childhood (51).

Safrole

Safrole (also known as shikimol) is found in a variety of spices, including cinnamon, nutmeg, black pepper and herbs such as basil. However, it is typically extracted from the root-bark or the fruit of sassafras plants as sassafras oil and has been widely used as a natural or synthetic flavoring agent. In the U.S, it was frequently used as a food additive in root beer and sassafras tea. Safrole was first shown to be a liver carcinogen in rats (52). In humans, epidemiological evidence indicates that individuals who chew betel nut or areca quid, which contains high levels of safrole, have an increased incidence of oral cancer (53), esophageal cancer (54) and hepatocellular carcinoma (55). This observation appears to be related to the formation of safrole-DNA adducts (53, 54), although some areca nut preparations include tobacco and caustic lime, which could also contribute to increased cancer risk.

Safrole is also associated with oral submucous fibrosis, a precancerous condition (56). However, the actual carcinogenicity of safrole in humans has been questioned because even though its tumorigenic metabolites, 1′-hydroxysafrole and 3′-hydroxyisosafrole, were observed in the urine of rats, they were not found in human urine (57). Notably, not all chemicals that act as carcinogens in rats or mice act as carcinogens in humans or vice versa. In addition, some work has shown that safrole causes marked changes in cellular calcium levels resulting in an inhibition of cancer cell growth. In particular, safrole induced death of human oral squamous cell carcinoma HSC-3 cells in culture and in mice by causing increases in cytosolic calcium levels (58). Similar effects on calcium levels and cell death were induced by safrole in MG63 human osteosarcoma cells (59) and PC3 prostate cancer cells (60). Safrole reportedly caused cell death by activating caspases in human tongue squamous carcinoma SCC-4 cells (61) and in A549 human lung cancer cells (62). Furthermore, safrole also induced apoptosis of human promyelocytic leukemia (HL-60) cells that was associated with increased production of reactive oxygen species (ROS) and Ca^{2+} levels and enhanced levels of the pro-apoptotic protein BAX and reduced levels of the anti-apoptotic protein BCL-2 (63). Safrole was also reported to alter immune modulation of T cells, B cells and macrophages in leukemic BALB/c mice and inhibited the growth of leukemia WEHI-3 cells *in vivo* (64). In contrast, increased calcium levels stimulated by

safrole appeared to enhance human oral cancer OC2 cell growth (65). Thus, whether safrole is a true carcinogen in humans is still debatable.

Nevertheless, safrole has been banned by the FDA in the U.S. and was also banned from use in soap and perfumes by the International Fragrance Association. In spite of these bans, safrole can still be purchased on the Internet as a primary ingredient in sassafras oil or brown camphor oil and instructions as to its synthesis from methylenedioxy compounds are also readily available. In addition, safrole is a precursor in the synthesis of the insecticide synergist piperonyl butoxide, which when added to insecticide mixtures, such as pyrethrin, pyrethroid, and carbamate insecticides, increases their potency (66–68). Many common insecticides and pesticides for home and garden use, mosquito and termite control, veterinary use, and human clothing and bedding use contain piperonyl butoxide, which is classified as a possible human carcinogen by the EPA (69). Safrole is also a primary ingredient in the illegal recreational drug MDMA or 'Ecstasy'. Thus, safrole still possesses a potential threat to human health.

Carcinogens in herbal remedies

Herbal medicines and remedies are widely available from a variety of sources and are virtually unregulated and many are contaminated with carcinogens (Table 2).

Amygdalin

Amygdalin is a glycoside initially isolated from the seeds of the tree *Prunus dulcis*, also known as bitter almonds. Several other related species in the genus of *Prunus* that contain amygdalin, include apricot and black cherry seeds (70). Amygdalin has been confused with laevomandelonitrile, also referred to as laetrile. Indeed, both amygdalin and laetrile have been promoted as vitamin B17, a cure for cancer, but are not actually a vitamin (71). Even though they are often referred to in the literature as the same chemical, amygdalin and laetrile are not the same chemical compound (72). Neither appear to be carcinogens but are widely touted as alternative cancer treatments that are claimed to be effective by many alternative therapists. However, both are totally ineffective and potentially toxic (73) as a possible cause of cyanide poisoning (74). Systematic reviews by the Cochrane Collaboration concluded that no sound data from any controlled clinical trial supports the claim that laetrile/amygdalin have beneficial effects for cancer patients (75, 76). The FDA prohibited the interstate shipment of amygdalin and laetrile in 1977. However, at least 27 U.S. states legalized the use of amygdalin within those states (77) and it is readily available for purchase on the Internet as an alternative cancer treatment.

Aristolochic acids

Aristolochic acids are a family of compounds that have been used since ancient times in traditional herbal medicines in many parts of the world (78). These compounds have been reported to have antibacterial, antiviral, antifungal and anticancer effects (79). Other traditional uses include treatment for snakebite, scorpion stings, fever, infection, diarrhea and inflammation (80). Several studies in animals and humans have confirmed that exposure to aristolochic acid is associated with a high incidence of cancers associated with the kidney

and urinary tract (81). Aristolochic acid has been used as an agent in weight loss plans, but was banned by the FDA in 2001 after a report that the use of the Chinese herb, *Aristolochia fangchi*, was associated with end-stage kidney failure and urinary system cancer in patients enrolled in a weight loss study in Belgian (82). However, aristolochic acids have been detected recently in some Chinese medicinal herbs and herbal products (83). It is found in wild ginger, which is distinct from the commercial species that is acquired from *Zingiber officinale* used in cooking today. Even though extensive warnings of the dangers of aristolochic acids have been published (84), this compound is still widely available for purchase on the Internet. In particular, consumption of aristolochic acid-containing Chinese herbal products, like Mu Tong, which is associated with an increased risk of cancer of the urinary tract in humans, can still be purchased on the Internet (85) as an antibiotic and to improve cardiac function.

Phorbol esters

Phorbol esters are the tetracyclic diterpenoids generally known for their potent tumour promoting activity. Phorbol 12-myristate 13-acetate (also known as 12-*O*-Tetradecanoylphorbol-13-acetate or TPA) is derived from the oil of the seeds of the Croton plant. This shrub, which is native to Southeast Asia, has been used by herbalists and homeopaths for years. The plant causes a skin rash similar to poison ivy, which led scientists to isolate the compounds that were biologically active. The phorbol esters mimic the action of diacylglycerol (DAG), an activator of protein kinase C, which regulates different signal transduction pathways and other cellular metabolic activities (86). The biological activities of the phorbol esters are highly structure specific, with the ester groups of these compounds recognized as being essential for their undesirable activities. Although TPA is used as a tumor promoter in many mouse cancer models, it has also been used to treat cancers. In particular, the oils from the seeds of the plant have been used as an effective cancer therapeutic agent in myelocytic leukemia patients, and have been indicated as a potential colorectal cancer therapeutic (87, 88). TPA has also been shown to increase white blood cell and neutrophil counts in patients with solid tumours (89). TPA also inhibits thyroid cancer cell proliferation and migration (90) and prostate cancer cell growth in combination with paclitaxel (91). However, it is also a potent tumour promoter in skin (92). Thus the evidence indicates that, if applied appropriately, TPA might be utilized effectively for treating leukemia and lymphomas even though it is a well-known tumour promoter in skin.

Pyrrolizidine Alkaloids

Pyrrolizidine alkaloids (PAs), named for the inclusion of a pyrrolizidine nucleus–a pair of linked pyrrole rings, are present in teas and are probably the most commonly used herbs today. PA-containing plants are widespread in the world and are likely the most common poisonous plants affecting livestock, wildlife and humans. PAs are produced by plants as a defense mechanism against insect herbivores and more than 660 PAs have been identified in over 6,000 plants, including 3% of the world's flowering plants (93), and most of them are toxic (94). As a result, honey (95, 96), milk (97, 98), grains and eggs (99, 100) have been found to contain PAs. However, in contrast to the regulations that exist for herbs and medicines, no international regulation of PAs in food currently exist (101).

PAs reportedly cause liver cancer (102) in rodent and primate animal models. These compounds require metabolic activation to generate pyrrolic metabolites (dehydro-PAs) that bind cellular protein and DNA, leading to genotoxicity and cancer. In particular, dehyro-PAs are the active metabolites responsible for skin cancer formation mediated through the generation of reactive oxygen species to initiate lipid peroxidation (103).

One of the most popular PAs is comfrey (*Symphytum officinale*), a well-known medicinal perennial herb, which is characterized as having been "one of the most popular herbal teas in the world (104)." Comfrey has been consumed for over 2000 years and contains PAs that are capable of inducing tumour development (105). Notably, the differentially expressed genes in livers from rats that have been fed comfrey compared to control livers are involved in metabolism, injury of endothelial cells, and liver abnormalities, including liver fibrosis and cancer development (106). Comfrey is readily available for purchase on the Internet and is sold as a topical application that can heal wounds and abraded skin, and for the treatment of broken bones, torn cartilage, tendon damage, lung congestion and ulceration of the gastrointestinal tract (www.takeherb.com/search/search.php?keywords=comfrey). In 2001, the FDA issued a warning against the consumption of herbal products containing comfrey.

Riddelliine is isolated from plants grown in the western United States and is a prototype of genotoxic PAs. Riddelliine can alter the expression of genes involved in cancer, cell death, tissue development, cellular movement, tissue morphology, cell-to-cell signaling and interaction, and cellular growth and proliferation (107). Riddelliine was found to be highly mutagenic in rat liver endothelial cells, which might be partially responsible for the tumourigenic specificity of this agent (108). Notably, the carcinogenesis-related gene expression patterns resulting from treatments with comfrey or riddelliine are very similar (109). However, most reports agree that riddelliine is toxic, but the safety and use of comfrey is still controversial.

Tussilago farfara, commonly known as coltsfoot, is a perennial, herbaceous plant that invades areas throughout much of the eastern United States. It has been used medicinally as a cough suppressant, but also contains tumourigenic PAs (110). Senecionine and senkirkine, present in coltsfoot, have the highest mutagenetic activity of any known PA (111). In spite of the dangers and warning, coltsfoot is also available for purchase on the Internet as a dietary supplement and as an herbal remedy for respiratory ailments (www.takeherb.com/search/search.php?keywords=coltsfoot).

Conclusion

Phytochemicals are found naturally in many plants and their consumption in fruits and vegetables is generally believed to provide beneficial health effects. Evidence from laboratory and epidemiology studies suggest that phytochemicals may reduce the risk of cancer, possibly due to antioxidant and anti-inflammatory effects. On the other hand, consumption of certain phytochemicals may act as carcinogens or tumor promoters. The Internet offers an enormous marketplace for such products. Clinically relevant adverse reactions to unconventional remedies purchased through the Internet have been reported (112, 113). Importantly, even herbal products that pose unacceptable health risks to

consumers, including remedies containing the carcinogenic aristolochic acids (82) can be readily found on the Internet. A U.S. study identified 19 products containing aristolochic acids and 95 products suspected to contain these acids for sale on the Internet, 2 years after the FDA had issued warnings and an import alert regarding the dangers of such products (114). Furthermore, the quality and accurateness of herbal information on the Internet is variable and poor (115–117). Consumers need to be aware that dietary supplements containing phytochemicals or other compounds are virtually unregulated and manufacturers do not have to show evidence of safety or health benefits before the product is marketed.

Acknowledgments

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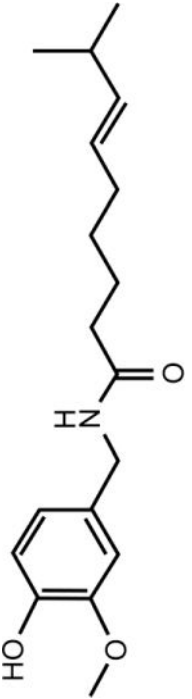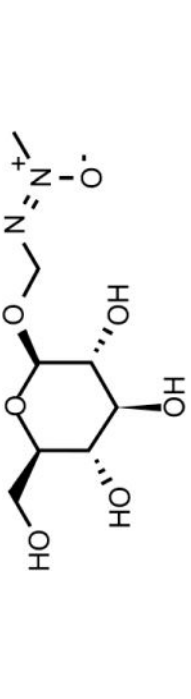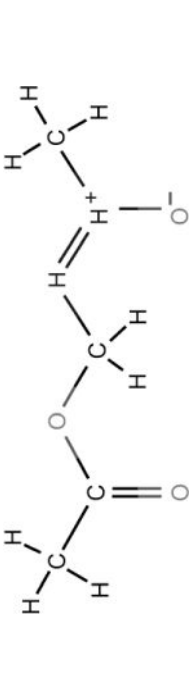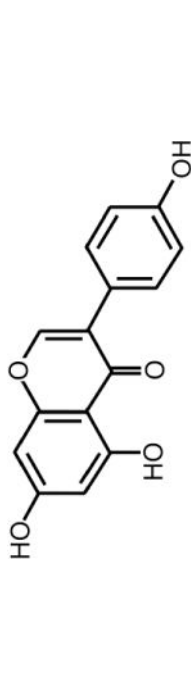
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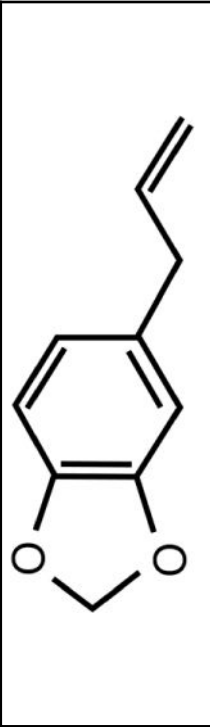
Table 1

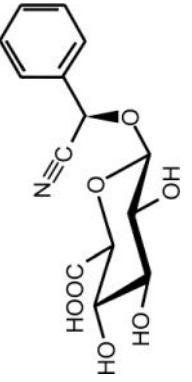| Dietary Phytochemical/source	Chemical Name	CAS Number	Chemical Formula	Chemical Structure
Capsaisin (Chili Pepper)	8-methyl-N-vanillyl-trans-6-nonenamide	404-86-4	$C_{18}H_{27}NO_3$	
Cycasin	(methyl-ONN-azoxy)methyl b-D-glucopyranoside	14901-08-7	$C_8H_{16}N_2O_7$	
Methylazoxymethanol –MAM (Cycas Seed)	Methyl-ONN-azoxymethanol	590-96-5	$C_2H_6N_2O_2$	
Phytoestrogens Genistein (soybeans, fava beans, red clover)	4',5,7- trihydroxyisoflavone	446-72-0	$C_{15}H_{10}O_5$	
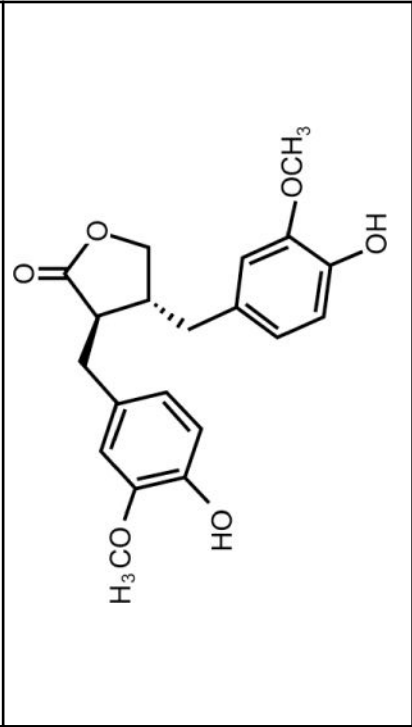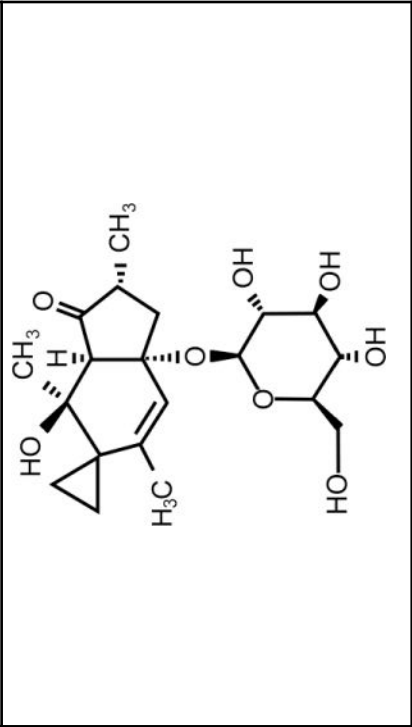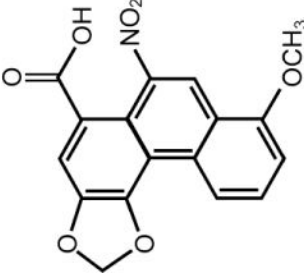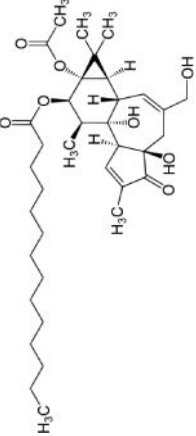
Dietary Phytochemical/source	Chemical Name	CAS Number	Chemical Formula	Chemical Structure
Phytoestrogens (Lignans matairesinol) (Sesame, flax seed)	(3R,4R)-3,4-bis[(4-hydroxy-3-methoxyphenyl)methyl] oxolan-2-one	580-72-3	$C_{20}H_{22}O_6$	
Ptaquiloside (Bracken Fern)	(2'R)-7'aβ-(β-D-glucopyranosyloxy)-1',3'aβ,4',7'a-tetrahydro-4'α-hydroxy-2'β,4',6'-trimethylspiro[cyclopropane-1,5'[5H]inden]-3'(2'H)-one	87625-62-5	$C_{20}H_{30}O_8$	
Safrole (Sassafrass Plant)	5-(2-propenyl)-1,3-benzodioxole	94-59-7	$C_{10}H_{10}O_2$	

Table 2

Herbal Phytochemical/source	Chemical Name	CAS Number	Chemical Formula	Chemical Structure
Amygdalin Seed (Cherry seed)	[(6-O-b-d-glucopyranosyl-b-D-glucopyranosyl) oxy] (phenyl) acetonitrile	29883-15-6	$C_{20}H_{27}NO_{11}$	
Aristolochic Acids (Wild ginger Mu Tong)	8-methoxy-3,4-methylenedioxy-10-nitrophenanthrene-1-carboxylicacid	313-67-7	$C_{17}H_{11}NO_7$	
Phorbol ester (Croton Plant)	Phorbol-12-myristate-13-acetate (12-O-tetradecanoylphorbol-13-acetate)	16561-29-8	$C_{36}H_{56}O_8$	
Pyrrolizidine alkaloids (Coltsfoot Flower Comfrey Leaf Ragwort Riddell)	2,3,5,6,7,8-Hexahydro-1H-pyrrolizine	643-20-9	C_7H_{13}	