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REVIEWS

Potential Therapeutic Applications of Some Antinutritional Plant Secondary Metabolites

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Plant-based formulations have been used since ancient times as remedial measures against various human and animal ailments. Over the past 20 years interest in traditional medicines has increased considerably in many parts of the world. Whereas modifications in lifestyles, including diet, have had a profound effect on the increased risks of various diseases, there is considerable scientific evidence, both epidemiological and experimental, regarding vegetables and fruits as key features of diets associated with reduced risks of diseases such as cancers and infections. This has led to the use of a number of phytometabolites as anticarcinogenic and cardioprotective agents, promoting a dramatic increase in their consumption as dietary supplements. There are changing perceptions regarding the therapeutic potential of various plant secondary metabolites (PSMs), some of which have also been known to possess certain antinutritional qualities. The knowledge gained at the cellular and molecular levels, and biological activities of PSMs including tannin−polyphenols, saponins, mimosine, flavonoids, terpenoids, and phytates, would be useful in planning for future epidemiological studies and human cancer prevention trials, especially when a large pure dosage is not the option to deliver the active compounds to many tissues. It is well observed that alteration of cell cycle regulatory gene expression is frequently found in tumor tissues or cancer cell lines, and studies have suggested that the herbal-based or plant-originated cell cycle regulators might represent a new set of potential targets for anticancer drugs. The recent upsurge of interest in this area of research and advances made therein indicate that the impact of a number of diseases affecting humans and animals may be lessened, if not prevented, by simple dietary intake of PSMs with putative therapeutic properties.

Keywords: Plant secondary metabolites; antinutritional factors; therapeutic applications

INTRODUCTION

Plants produce an amazing variety of metabolites that are gaining importance for their therapeutic and biotechnological applications (*1*). The evolution of new genes to synthesize novel secondary products in plants is an ongoing process that might account for most differences in gene function among the plant genomes. Among the thousands of metabolites, only a few are part of the "primary" metabolic pathways and the rest are termed as secondary as they have no specific function in the plants (*2*). Levels of secondary metabolites are both environmentally induced as well as genetically controlled.

The ability to synthesize toxic compounds has evolved to ward off pathogens (bacteria or fungi) or herbivores such as insects and animals or to suppress the growth of competitor neighboring plants (*3*−*5*). Bryant et al. (*6*) concluded that woody plants adapted to growing on low-resource sites (with low nutrient levels) are often more dependent on evolved chemical defenses to counteract their inability to grow rapidly beyond the reach of most browsing animals. The variety of herbivore-deterring phytometabolites is diverse and, depending on their structure, degree of polymerization, and concentration, may be genotoxic, hepatotoxic, pneumotoxic, neurotoxic, or cytotoxic to the susceptible host (*7*). Plant secondary metabolites (PSMs), such as polyphenols, have properties including antioxidant, antimutagenic, anticarcinogenic, antiinflammatory, and antimicrobial effects that might potentially be beneficial in preventing diseases and protecting the stability of the genome (*8*). Herbal medicines along with chemotherapy and radiotherapy have been recommended for patients who become resistant to radiotherapy and chemotherapy or who are not suited for conventional treatment due to old age and marked weakness. Traditional medicines all over the world are nowadays being reevaluated by extensive research on different plant species with reference to their therapeutic principles. The ability of certain PSMs such as polyphenolic compounds to act as scavengers of free radicals, besides their antioxidant and antimicrobial properties, is raising the possibility of their food and pharmaceutical applications.

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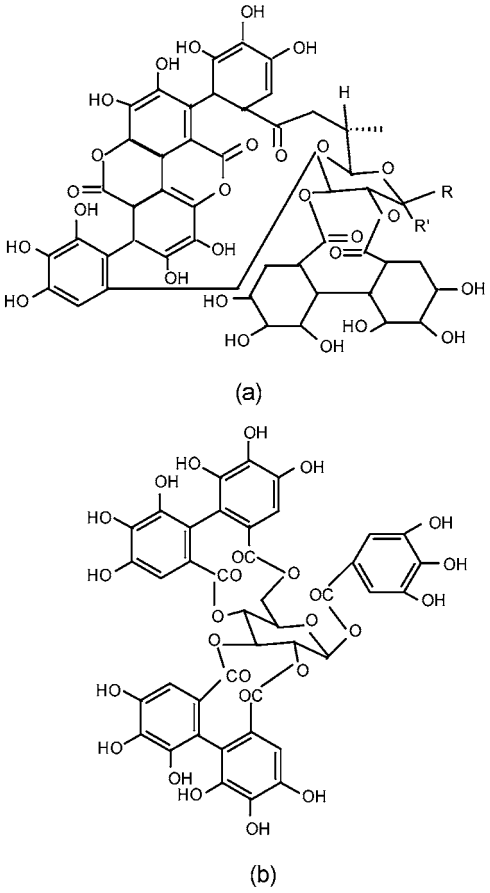

Figure 1. Hydrolyzable tannins: (a) punicalagin; (b) casuarictin, an ellagitannin.

Despite progress in conventional chemistry and pharmacology in producing effective drugs, the plant kingdom might provide a useful source of new medicines and pharmaceutical entities or, alternatively, may be used as simple dietary adjuncts to existing therapies (*9*). This paper reviews the chemistry, biochemistry, and potential therapeutic attributes revealed recently with scientific evidence of some of the most widely prevalent PSMs, already known for their antinutritional and toxic effects in vivo, which appear promising as prospective therapeutic agents. Wherever possible, relevant examples of their mode of action and applications to animal health have also been incorporated.

TANNIN−POLYPHENOLS

Tannins. Tannins are naturally occurring water soluble polyphenols of varying molecular weights and are the most abundant polyphenolic compounds with the ability to precipitate proteins from solutions (*10*). Chemically there are two main classes of tannins (**Figures 1** and **2**) widely distributed in vascular and woody plants including pteridophytes such as ferns (*11*). Hydrolyzable tannins (HTs) are esters of polyol (most often β-D-glucose) or hexahydroxydiphenic acid (ellagitannins). In plant cells, the tannins are located separately from the proteins and the enzymes of cytoplasm, but when tissue is damaged, for example, when animals feed, tannins may react with proteins, making them less accessible to the gastric juices of the animals. Tannins could intervene by binding to either digestive enzymes (e.g., trypsin) or the substrate (e.g., dietary proteins) or to both (*12*), thus rendering them unavailable to the host. Condensed tannins (CTs) or proanthocyanidins, the polymers of flavanol

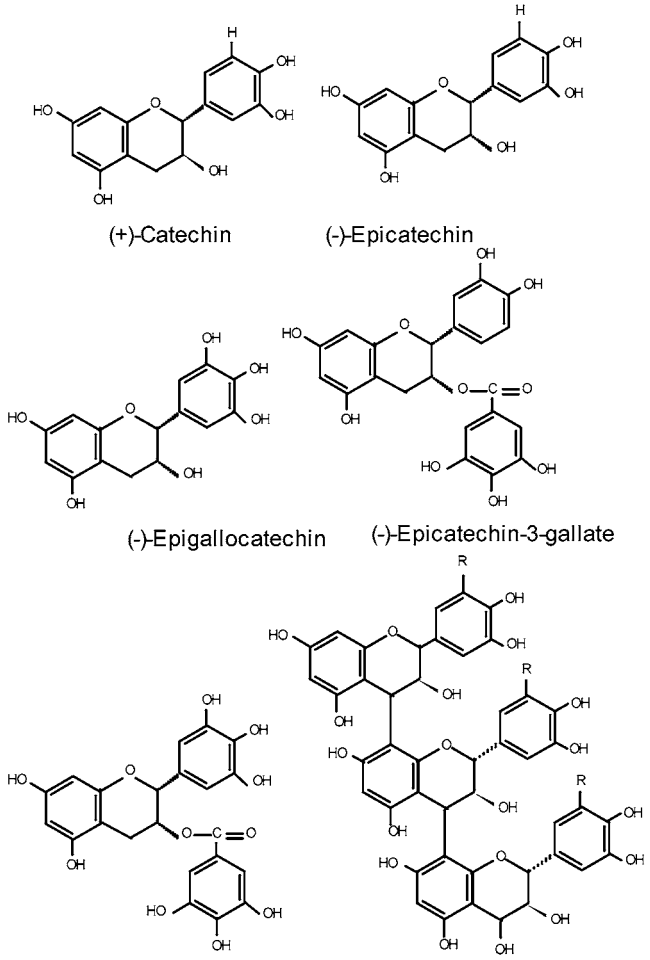

Figure 2. Catechins and proanthocyanidins (R = H, procyanidins; R = OH, prodelphinidins).

units, are probably the most extensively studied PSMs with reference to their physiological and nutritional consequences. Their adverse effects include inhibition of nutritionally and therapeutically relevant gastrointestinal (GI) microflora of the host through various mechanisms. CTs reduce the digestibility of proteins and carbohydrates in the rumen as the tannin−protein complex (T-PC) formed is stable over the pH range of 3.5−7.0 but dissociates at pH <3.0 and >8.0 (*13*). HTs and flavonols undergo extensive microbial metabolism in the GI ecosystem (**Figures 3** and **4**) (*14*, *15*). Recent findings provide evidence of GI degradation of dietary CTs into low molecular weight products (*16*) (**Figure 5**).

Tannin-containing plants have been put to use since ancient times. Oak (*Quercus robur*), rich in tannins (gallotannins, ellagitannins, monomeric and dimeric catechins, and leucocyanidins), has long been used for its medicinal properties. Tannins may be either procarcinogenic or anticarcinogenic and either mutagenic or antimutagenic. However, except for extreme cases such betel quid chewing, which enhances accumulation of mitochondrial DNA (mtDNA) deletions in oral cells (*17*), there appears to be no evidence that tannins are procarcinogenic in humans (*18*).

Tannins, primarily associated with plant defenses against insects and herbivores, may also exhibit a number of beneficial effects when they are part of the human and animal diet. Possibly, tannins may be beneficial to the host if they inhibit plant enzymes such as β-glucosidases and esterases that

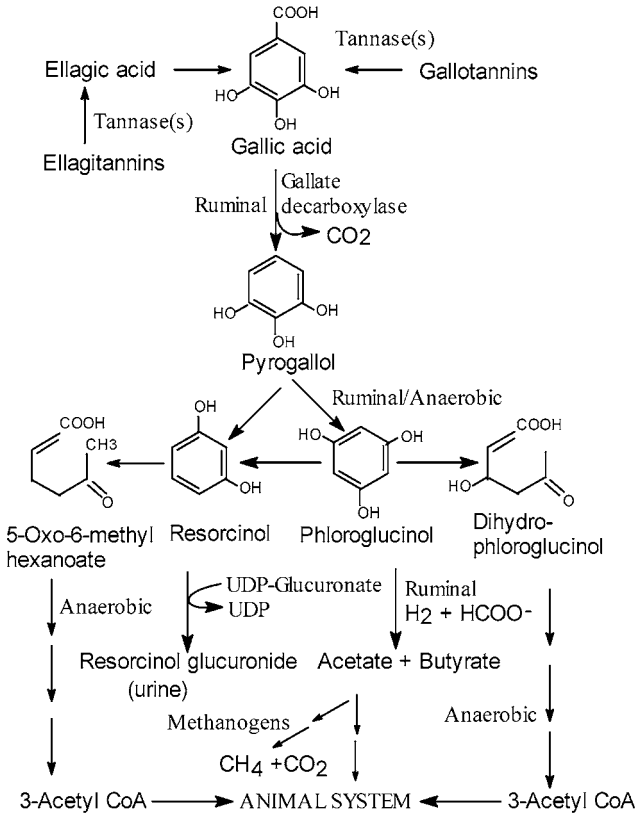

Figure 3. Pathways by which hydrolyzable tannins are degraded to simpler metabolites in an anaerobic or ruminal system

potentiate the toxic activity of plant phenolic compounds. Tannins from the bark of *Betula*, *Salix*, and *Pinus* species strongly precipitated β-glucosidases, although the magnitude of T-PC formation varied moderately between the species (*19*). CTs prevent bloat formation in ruminants (*20*) and protect dietary protein in the rumen, enhancing amino acid absorption and utilization by the ruminants (*21*). Forages containing moderate concentrations of CTs can have positive effects on sustainability and production in intensive grazing systems through increasing the efficiency of animal production by decreasing urinary nitrogen excretion and reducing chemical inputs such as detergents to control rumen bloat in cattle and anthelmintics (*22*).

Antiparasitic Attributes of Tannin−Polyphenols. Gastrointestinal (GI) parasites, especially the nematodes, pose a severe threat to animals, especially those having a poor nutritional status. Subclinical infections of GI nematodes such as *Trichostrongylus colubriformis*, *Ostertagia circumcincta*, and *Haemonchus contortus* depress live weight gain, feed intake, and wool and milk production and can impair soft tissue deposition and skeletal growth (*23*). Control of the GI nematodes for the past three decades has relied heavily on the use of anthelmintics. In tropical and subtropical regions of the world where marginal levels of nutrition lead to enhanced susceptibility to infections, mortality and morbidity due to nematode infections are still apparent (*24*, *25*). In the developed countries of the world anthelmintics are so intensively used that multiple drug resistance has made them ineffective, giving a clear indication that control programs based on their indiscriminate use are not sustainable. In view of the public concern over drug residues excreted in milk and meat products and their potential risk as environmental contaminants (*26*), there is an increasing demand for alternatives to chemoprophylaxis in order to reduce or even exclude the use of anthelmintic drugs to control parasites. In

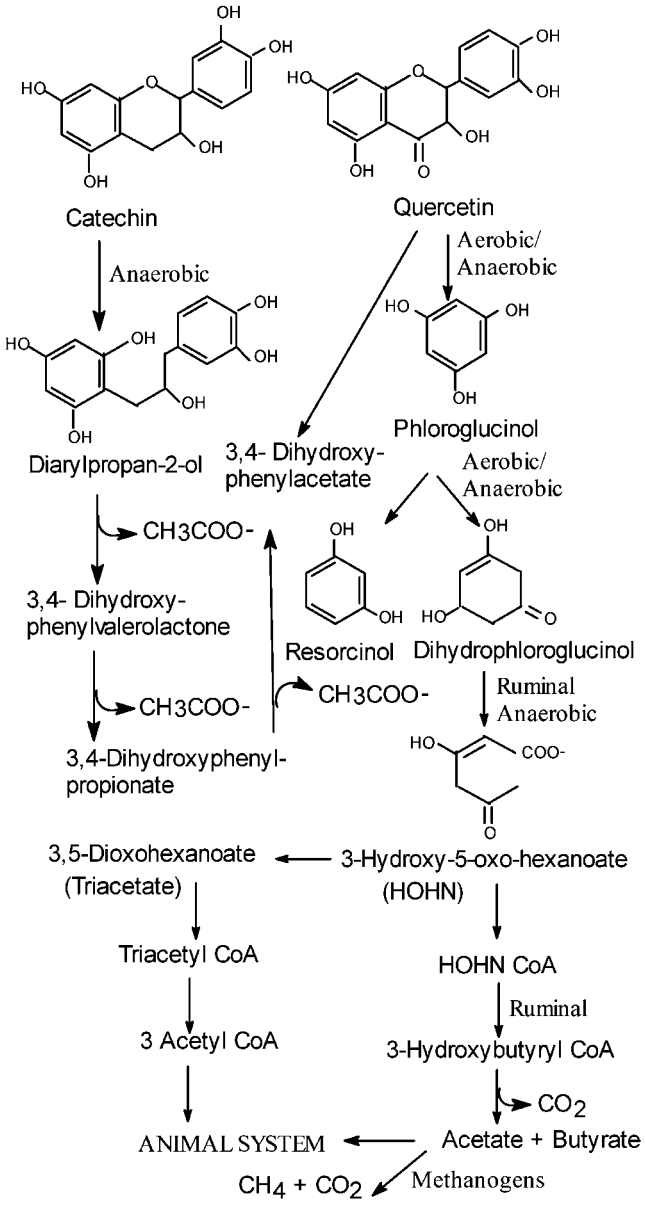

Figure 4. Pathways by which catechins (flavanol) and quercetin (flavonol) are degraded to simpler metabolites in an anaerobic or ruminal system.

the search for effective treatments, exploiting PSMs capable of reducing infection levels solely or in combination with limited drug use could be a novel practical approach.

It seems to be plausible that consumption of the dietary CTs may affect GI nematode number and animal production in a number of ways. Indirect effects could be mediated by a change in the supply of digestible proteins (DP), a change in the amino acid supply, particularly that of threonine and methionine/cystine, changes in mineral absorption, and interaction with intestinal mucosal epithelia. Direct effects would need to be mediated through tannin−nematode interactions to reduce nematode viability (*32*). There are reports suggesting that an increase in the supply of DP could improve the resistance and resilience of sheep to nematodes (*30*, *33*, *34*). Reduced nematode burden has been reported in sheep grazing on forages containing CTs (*35*, *36*). The effect was attributed to an improved protein supply in tannin-fed animals or the direct action of CTs against the nematodes. *Eucalyptus* species have proved to be effective against the abomasal nematode *H. contortus* (*37*), and inhibitory effects of several plant extracts against *T. colubriformis* larvae have been attributed to polyphenols present in these plants (*38*).

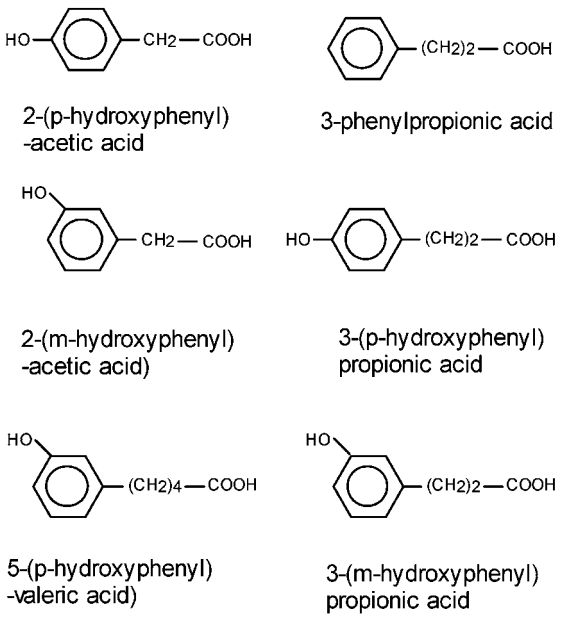

Figure 5. Proanthocyanidin metabolites formed by human colonic microorganisms.

A significant negative linear relationship has been observed between the concentrations of CTs in the diets of red deer and their burden of abomasal nematodes (*39*). A direct anthelmintic effect of quebracho extract has recently been reported toward *T. colubriformis* in infected sheep. Drenching young growing sheep previously infected with a single dose of *T. colubriformis* with quebracho extract at 8% of their food intake caused immediate reduction in total worm burden, fecal egg counts, and worm fecundity of female worms compared with the parasitic population in control sheep (*40*). The impact of CTs extracted from leguminous herbage on *T. colubriformis* larval migration suggests a possible role of forage CTs as a means to reduce dependence upon proprietary anthelmintics (*41*).

Gallic acid, a naturally abundant plant phenolic compound and a well-known component of HTs, along with some structurally related compounds is reported to be inhibitory against both the long slender bloodstream forms and the procyclic forms of *Trypanosoma brucei* brucei. The study on the comparison between the structure and trypanocidal activities of gallic acid and related compounds suggested that a pyrogallol moiety was responsible for the activity (*42*). Terpenoids and tannin-containing plant extracts have been reported to have antiplasmodial activities in vitro against some strains of *Plasmodium falciparum* (*43*).

Antimicrobial Properties of Tannin−Polyphenols. Tannins and related compounds are well-known to possess inhibitory activities against viruses, bacteria, fungi, and protozoa including GI microbes, which could be beneficial to human health. Tannic acid, methyl gallate, and propyl gallate, but not gallic acid, were found to inhibit the growth of a number of pathogenic intestinal bacteria in culture broth, namely, *Bacteroides fragilis*, *Clostridium clostridiiforme*, *C. perfringens*, *C. paraputrificum*, *Escherichia coli*, *Enterobactor cloacae*, and *Salmonella typhimurium* (*44*). Ellagitannin extracts have been reported to inhibit a range of pathogenic organisms including *Vibrio cholerae*, *Shigella dysenteriae*, and *Campylobacter* spp. (*45*, *46*). Tannins, methyl gallate, and gallic acid from *Galla rhois* were found to possess clear inhibitory effects against lactobacilli, bifidobacteria, and several pathogenic intestinal bacteria (*47*). Tannic acid enriched aqueous extract of certain medicinal plants such as bearberry and cowberry was found to be bacteriostatic against *Helicobactor pylori* (*48*). *Syzygium jambos* plant extracts having high tannin contents (77 and 83% for the aqueous and acetone extracts, respectively) showed antimicrobial activity against *Styaphylococcus aureus*, *Yersinia enterocolitica*, and a few other staphylococci (*49*). Phenols, tannins, and flavonoids present as major active constituents of some medicinal and edible plants have been reported to be antagonistic toward multidrug-resistant human pathogenic bacteria and yeasts of clinical origin (*50*−*52*). Isoterchebulin and 4,6-*O*-isoterchebuloyl-D-glucose, novel HTs isolated from the bark of *Terminalia macroptera*, were active against *Bacillus subtilis* and *Pseudomonas fluorescens* (*53*). Punicalagin, an ellagitannin from some Ethiopian medicinal plants has been reported to be inhibitory to pathogenic *Mycobacterium tuberculosis* strains (*55*). Ho et al. (*56*) have concluded that tannins from *Vaccinium vitis-idaea*, exhibiting antimicrobial activities against *Porphyromonas gingivalis* and *Prevotella intermedia*, could potentially be used for the treatment of periodontal diseases.

Anticarcinogenic Attributes of Tannin−Polyphenols. There has been a great interest in free radicals and oxygen species generated in vivo, which have been implicated in diseases such as cancer, atherosclerosis, and multiple sclerosis. Agents causing oxidative DNA damage usually increase the risk of cancer development (*57*). Most plant-derived polyphenols exhibit strong antioxidant properties (*58*) and inhibit lipid peroxidation and peroxygenases, thus scavenging free radicals such as hydroxyl, superoxide, and peroxyl, which are known to be important in cellular pro-oxidant states (*59*). *Terminalia catappa* is a popular folk medicine for preventing hepatoma and treating hepatitis in many parts of the world. Its major tannin component, punicalagin, has been seen to be active against bleomycin-induced genotoxicity in cultured ovary cells (*60*). HTs including ellagitannins have been found to exhibit higher cytotoxicity against human oral squamous cell carcinoma and salivary gland tumor cell lines than against normal gingival fibroblasts (*61*). Tannic acid, but not HT hydrolytic products (ellagic acid, gallic acid, and propyl gallate), affects the metabolic activation of a number of direct mutagens including 2-nitrofluorine (2NF), 4,4′-dinitro-2-biphenylamine, 1-nitropyrine, and 1,3-dinitropyrine (*62*). HTs (1-*O*-galloyl castalagin and casuarinin) from *Eugenia jambos*, an antipyretic and antiinflammatory herb of Asian folk medicine, could be the candidates for developing low-toxicity antitumor agents (*63*). Whereas the cytotoxicity of these compounds was substantially lower toward human lymphocytes and Chang liver cells, at least a 3-fold higher antiproliferative activity toward the cancer cells was observed. Apoptosis was induced in promyelocytic leukemia cell line HL-60 cells, treated with 6, 12, and 24 μM 1-*O*-galloyl castalagin and casuarinin for 48 h. Dietary polyphenols have been reported to be capable of modulating in vivo oxidative damage in the gastrointestinal tract of some rodents. These data support the hypothesis that dietary polyphenols might have both protective and therapeutic potential in oxidative damage related pathologies (*64*). The findings of Gronbaek et al. (*65*) on cancers of the upper digestive tract, showing protective effects of red wine that cannot be attributed to alcohol, are encouraging. They showed that phenolic polymers directly in contact with the digestive mucosa may well have anticarcinogenic action. Also, dietary antimutagens acting individually or in consortium may be useful in counteracting the effects of certain mutagens and carcinogens to which humans are commonly exposed. Pistafolia A, a novel gallotannin isolated from the leaves of *Pistacia weinmannifolia*, is capable of scavenging reactive oxygen species including hydroxyl radicals and superoxide anion and might be used as

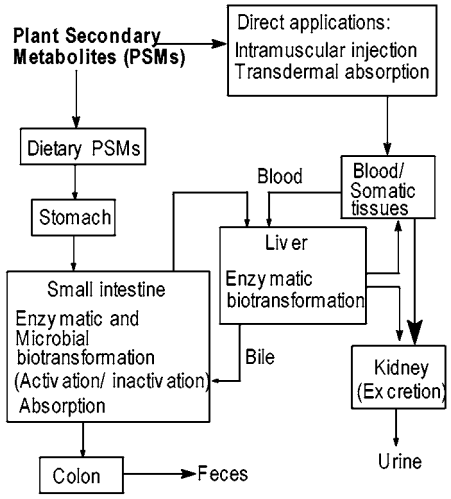

Figure 6. Possible routes of PSM intake, biotransformation, and absorption in the human body. The GI tract is the major site of microbial biotransformation, and enzymatic biotransformation occurs in the liver.

effective natural antioxidants for the prevention of neuronal diseases associated with the production of peroxynitrite and related reactive oxygen species (*66*). However, to define the protective and therapeutic potential of these compounds in oxidative damage related pathologies, further research will have to clarify whether these effects can be observed in other organs that are subjected to oxidative damage (such as the brain and heart), the role of the single components of the polyphenol crude extracts, and the related antioxidant potencies of each.

Catechins and Their Miscellaneous Therapeutic Uses. Catechins are a group of polyphenolic compounds, (−)-epigallocatechin-3-*O*-gallate (EGCG), (−)-epigallocatechin (EGC), (−)-epicatechin-3-*O*-gallate (ECG), and (−)-epicatechin (EC), which are abundantly present in vegetables and plant-derived beverages and foods (*67*). Chemically, catechins are polyhydroxylated flavonoids (**Figure 2**), which exhibit water soluble characteristics. Being important microconstituents of the human diet, for instance, with an average intake of 50 mg/ day in The Netherlands, catechins need to be taken into account when the relationship between diet and chronic diseases is investigated (*68*).

Dietary PSMs, including CTs and catechins, reaching the intestine undergo extensive microbial and enzymatic biotransformations (**Figure 6**). Catechins are conjugated to glucuronide, sulfate, and methyl groups in the gut mucosa, liver, and kidney, and their substantial levels are incorporated into the human body. As reported recently (*69*), substantial levels of catechins (EGCG) were found in human plasma 60 min after ingestion, although the basal levels after 12 h of fasting were below the detection limits (<2 pmol/mL). Glucuronides and sulfate conjugates of catechins, being highly polar, are rapidly removed from the bloodstream. Van Amelsvoort et al. (*70*) have reported that the catechin levels in plasma after ingestion were significantly different: EGC rose quickly with a short elimination half-time ($t_{1/2}$ elim = 1.7 h); ECG was intermediate in rise but slowest in decline ($t_{1/2}$ = 6.9 h); and EGCG was slowest in rise but intermediate in decline ($t_{1/2}$ = 3.9 h). At 24 h, EGC and EGCG had returned to base levels, but ECG was still elevated. This shows that catechins differ significantly in their pharmacological behaviors.

Because the antioxidant activity of catechins is dependent on the number of phenolic hydroxyl groups (*71*), nonconjugated forms of catechins appear to be more important with reference

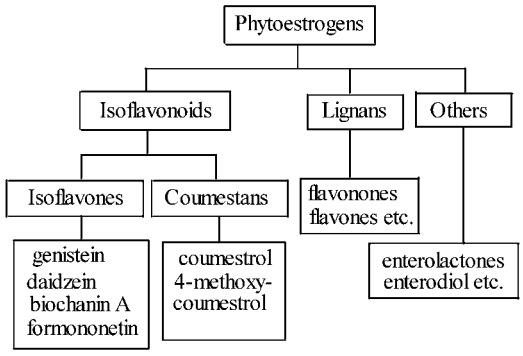

Figure 7. Classification of phytoestrogens.

to their antioxidant action. The antioxidant activity of catechins is thought to be due to their radical scavenging properties. It has been indicated that catechins are effective antioxidants in blood plasma, delaying the lipid oxidation and depletion of endogenous lipid soluble antioxidants, namely, α-tocopherol and β-carotene (*72*). The prevention of plasma lipid oxidation and lipid soluble antioxidant depletion by catechins could be a mechanism for the prevention or delay in the development of pathologies related to free radical damage (*72*). Studies have indicated that EGCG can preferentially induce apoptosis in T lymphocytes of leukemia patients (*73*) or cultured cancer cell lines (*74*, *75*). Investigating the specific anticancer activity of EGCG, Wang and Bechrach (*76*) concluded that, compared to normal controls, the transformed NIH-pATMras fibroblasts were sensitive to EGCG at a 5 μM concentration. Anticancer activity of the catechins tested was found to be selective and therefore might have a therapeutic value.

Catechins and O-methylated derivatives of EGCG have been shown to exhibit various therapeutic effects such as antiinflammatory (*77*, *78*) and antigenotoxic activities against induced genotoxicity and scavenging activity against various free radical and reactive oxygen species that could lead to the development of atherosclerosis (*79*, *80*).

PHYTOESTROGENS

Phytoestrogens (PEs) are natural phytometabolites known to possess estrogenic activity (*81*) and comprise of a number of classes, including isoflavones, lignans, coumestans, and resocyclic acid lactones (**Figure 7**) (*82*, *83*). PEs are structurally or functionally similar to mammalian estradiol (**Figure 8**) (*84*). Various plants, specifically those belonging to the Leguminosae and Graminae families, which include important grain crops, vegetables, oilseeds, and livestock forage (*85*−*88*), are the major sources of various dietary PEs. Two of the major isoflavonoids in soybeans are daidzin and genistin, which are glycoside conjugates of daidzein (7,4′-dihydroxyisoflavone) and genistein (5,7,4′-trihydroxyisoflavone), respectively (*89*). Other isoflavonoids reported from the legumes are biochanin A, formononetin, and glycitein, which are methoxylated derivatives of genistein, daidzein, and 6,7,4′-trihydroxyisoflavone, respectively (*85*, *90*). Ginsenoside Rg1 derived from *Panax notoginseng*, found to exhibit estrogen-like activity, has been proposed to be classified as a novel class of PEs (*91*). Most of the isoflavones in plants conjugated almost exclusively to sugars are deglycosylated in the gut to their active forms (*88*, *92*, *93*). Gut flora may further metabolize daidzein into equol or *O*-desmethylangolensin and genistein into *p*-ethylphenol. Daidzein, genistein, equol, and *O*-desmethylangolensin are the major PEs detected in the urine and blood of humans and animals. As reported recently, isoflavone glycosides are not absorbed intact across

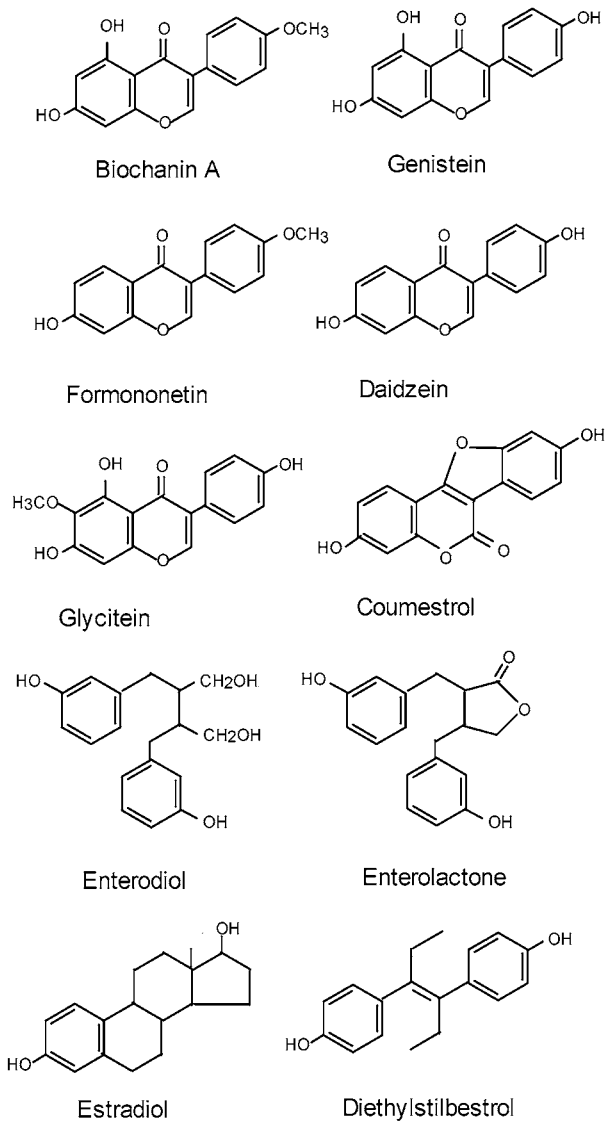

Figure 8. Phytoestrogens (isoflavones, coumestrol, and lignans) and their structural resemblance to estradiol and diethylstilbestrol (synthetic estrogens).

the enterocyte of healthy adults, and their bioavailability requires the initial hydrolysis of a sugar moiety by intestinal β-glucosidases for uptake to the peripheral circulation (*93*).

The dietary isoflavones exhibit a number of biological activities. Although little is known about the clastogenicity and mutagenicity of PEs in mammalian cells (*94*), prolonged ingestion of some varieties of clover enriched with estrogenic isoflavones can cause impaired fertility and related reproductive disorders in animals (*95*, *96*). Concern has been raised about coumestrol consumption in the human population because endocrine disorders have been observed in farm and laboratory animals exposed to coumestrol. Some studies suggest that neonatal exposure to coumestrol may affect sexual differentiation in rats (*97*). Whereas coumestans act as an estrogen mimic directly, formononetin is metabolized to estrogenically active compounds daidzein, equol, or *O*-desmethylanglolensein (**Figure 9**) (*98*). Kuiper et al. (*99*) measured the estrogenic potencies for both estrogen receptors ERα and ERβ and showed that the affinities were in the order of genistein > daidzein > biochanin A > formononetin. Although the estrogenic potency of industrially derived estrogenic chemicals is very limited, the estrogenic potency of phytoestrogens is significant, especially for ERβ, and they may trigger many of the biological responses that are evoked by the physiological estrogens (*99*).

Whereas a number of factors are responsible for the accumulation of PEs in plants (*100*, *101*), their biotransformation to the metabolites with altered chemical structures (**Figure 10**) (*102*−*104*) is critical for biological effects at the cellular levels. Hydroxylated hepatic metabolites of daidzien and genistein have been reported to possess biological properties other than those of their parent compounds (*105*). Earlier also, it was suggested that the isoflavone structure and 4′-hydroxyl groups were essential for differentiation−induction and growth inhibition effect, whereas trihydroxyl derivatives were good growth inhibitors (*106*).

Phytoestrogens as Anticarcinogens. Antioxidant species may act in vivo to prevent oxidative damage to DNA, proteins, and lipids, thus reducing the risk of coronary heart disease and cancers. Both scientific and lay publications on the proposed health-related and clinical benefits of PEs have attracted much attention from the medical scientific community. Consumption of soy products in some Japanese populations, with PE levels in the diet as much as 200 mg/day, has been related to a lower risk of hormone-dependent cancers and other chronic diseases (*107*). Many of the therapeutic effects of PEs have been related to the antioxidant action of these compounds (*108*, *109*). Genistein and daidzein are currently being extensively investigated through molecular, preclinical, and clinical studies to explore their potential health benefits. Considerable attention has been focused on PEs having a potential benefit in the prevention of atherosclerosis and arterial degeneration or as anticancer agents (*109*, *110*) or reduced risk of hormone-dependent cancers such as prostate and breast cancers (*111*).

Approximately 60% of breast cancer patients have hormone-dependent breast cancer containing estrogen receptors and therefore require estrogen for proliferation of these cancer cells. In tumors, the expression of aromatase, which converts androgen to estrogen, is up-regulated compared to surrounding noncancerous tissue (*112*, *113*). Aromatase suppression in postmenopausal women could be a potential chemopreventive modality against breast cancer. Almstrup et al. (*115*) have found that PEs, except genistein, were aromatase inhibitors at low concentrations (<1 μM) but estrogenic at higher concentrations (>1 μM).

Prostate cancer is another leading cause of malignancy in men, with >180400 newly diagnosed cases annually, resulting in ~31000 deaths each year (*116*). A high consumption of PEs is inversely correlated with the incidence and mortality rate of prostate cancer. Studies have shown that genistein inhibits prostate cancer cell growth in vitro and in vivo and decreases secreted and intracellular levels of the androgen-related protein prostate-specific antigen (PSA). Elucidating the mechanism by which genistein modulates PSA protein expression in prostate cancer cells, Davis et al. (*117*) have reported that expression of PSA is transcriptionally regulated by genistein in prostate cancer cells. Low-dose genistein induces cyclin-dependent kinase inhibitors and cell cycle arrest in human prostate cancer cells. Physiologic concentrations of genistein (<20 μM) decreased LNCaP viable cell number in a dose-dependent manner, induced a G1 cell-cycle block, decreased prostate-specific antigen mRNA expression, and increased p^{27KIP1} and p^{21WAF1} (mRNA and protein synthesis). No effect on apoptosis or mRNA expression of the apoptosis- and cell-cycle-related markers, *bcl-2*, *bax*, *Rb*, and proliferating cell nuclear antigens was observed (*118*). Combined with radiation, genistein was found to inhibit prostate carcinoma calls. Genistein at 15 μM caused a significant

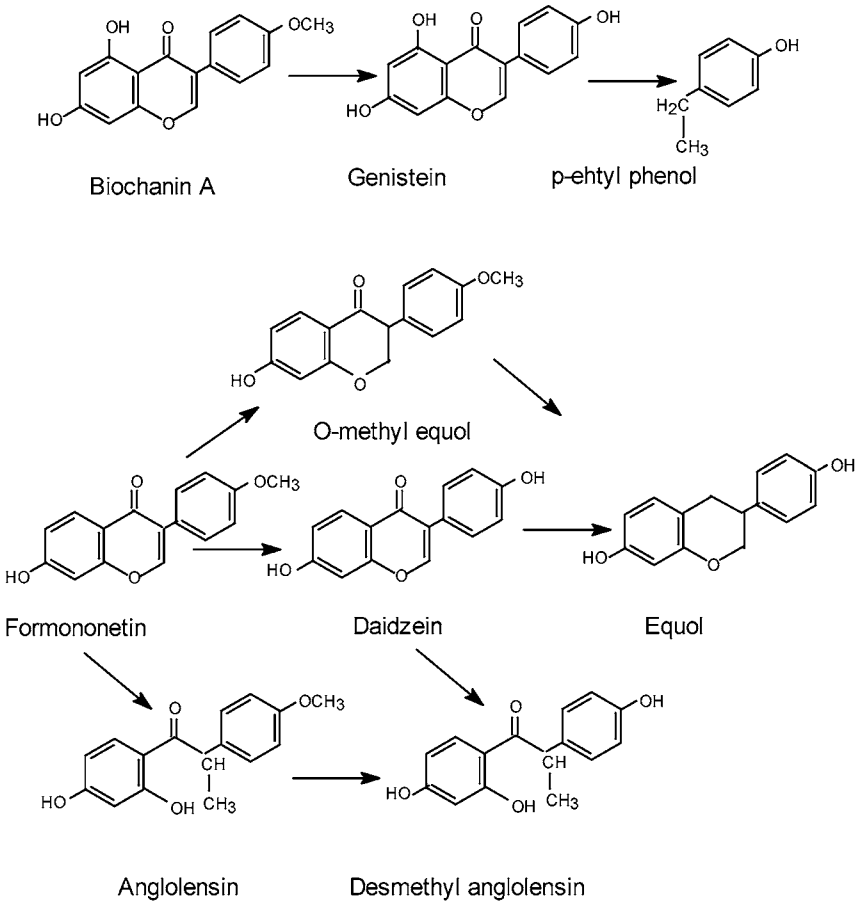

Figure 9. Ruminal metabolism of phytoestrogens. The major metabolic pathway of formononetin is via daidzein to equol rather than via *O*-methylequol to desmethylanglolensin.

inhibition in DNA synthesis, cell growth, and colony formation in the range of 40−60% and potentiated the effect of low doses of 200−300 cGy photon or 100−150 cGy neutron radiation (*119*). The effect of combined treatments was more pronounced than with genistein or radiation alone. Genistein-induced glutathione peroxidase activation might be another important anticarcinogenic activity of PEs against prostate cancer cells (*120*). The relationship between thyroid cancer risk and dietary PEs has not been thoroughly investigated. Findings from a multiethnic population-based case-control study of thyroid cancer suggest that thyroid cancer prevention via dietary modification of soy and/or PEs intake may be possible but warrants further studies at this time (*121*).

Biochanin A, equol, myricetin, and quercetin have been identified as potent topoisomerase II inhibitors, similar in activity to the epidophylotoxins widely used in cancer therapy (*122*−*124*). Coumestrol has been reported as an effective inducer of DNA strand breaks, micronuclei, and mutations in the HGPRT gene of Chinese hamster ovary cells (*125*), suggesting that it may have both mutagenic and clastogenic effects in cultured human lymphoblastoid cells. Other prohealth and clinical attributes of these phytometabolites, namely, estrogen receptor binding, natural killer cells activation, and a beneficial role in chronic renal diseases, have been the objectives of various recent investigations (*126*−*128*). Some of the potential therapeutic applications of phytoestrogens and other PSMs along with possible modes of action are presented in Table 1.

Phytoestrogens and Postmenopausal Health. As aging progresses, the level of sex hormones declines in the human body. Both natural and artificial menopause can cause estrogen deficiency. The lack of estrogen can directly worsen the quality of life, and epidemiological evidence suggests its association with the development of certain diseases (*129*). Over the past 20 years there has been increasing interest in menopause and hormone replacement therapy (HRT) regarded as the preferable choice for pharmacological prevention of osteoporosis in women (*130*) and the risk of coronary heart disease (CHD) (*131*). Hormone replacement with natural estrogens has been proven to be successful for various indications: it reduces menopausal vasomotor and psychological symptoms, thus improving the quality of life (*129*). A recent study (*132*) on the effectiveness and safety of the isoflavone dietary supplement Promensil from red clover on menopausal hot flush symptoms has revealed that treatment with 80 mg of isoflavones per day had resulted in reduction in hot flushes. A significant decrease in hot flushes of 44% between the active and placebo group demonstarates the effectiveness of PEs in the management of hot flushes (*132*). Although doses have not been established, menopausal symptoms, CHD risk, and osteoporosis risk appear to be reduced with PEs (*132*). Phytoestrogen supplementation offers a potential alternative or complementary treatment/or therapy to conventional HRT for osteoporosis prevention. Also, the rates of breast, endometrial, and ovarian cancers are low in Asian cultures, where the diet is rich in soy isoflavones (*133*). Isoflavones with estrogen-like properties, and because of favorable side-effect profiles, could be an ideal alternative to HRT with respect to cardiovascular benefits. Research has been concentrated on phytoestrogens in the belief that delivery of these phytometabolites via the diet would be more acceptable than pharmaceutical regimens (*134*).

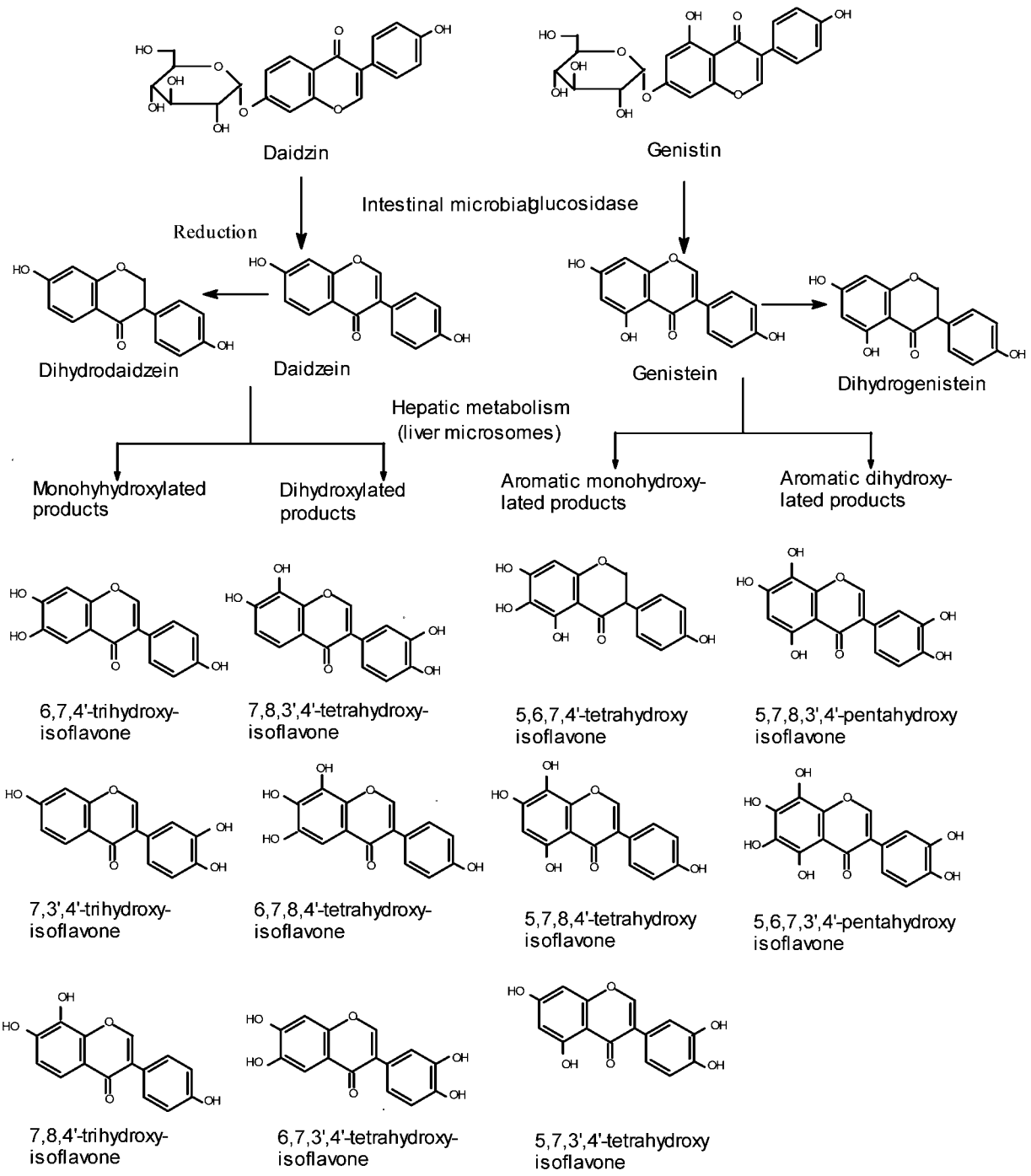

Figure 10. Proposed intestinal microbial and hepatic metabolic pathways of daidzein and genistein to products with altered structures and functions [Hur et al. (*104*) and Kulling et al. (*105*)].

Postmenopausal HRT has been seen as a specific treatment for symptoms in the short term and preventive therapy in the long term. In an investigation on experimental evidence concerning whether soy phytoestrogens (SPE) inhibit postmenopausal atherosclerosis progression/extent and their effectiveness relative to traditional estrogen replacement therapy, Clarkson et al. (*134*) have reported that conjugated equine estrogens (CEE; Premarin) and SPE significantly reduced the extent of common carotid and internal artery atherosclerosis. The isoflavones with their inhibitory effects on natural and platelet-derived growth factor (PDGF)-BB-induced smooth muscle cells (SMC) proliferation may be useful in attenuating such proliferation, a basic mechanism involved in atherosclerotic vascular change, thereby preventing atherosclerotic cardiovascular diseases (*135*). Standardized soy extract (Soyselect) may be a safe and efficacious therapy for the relief of hot flushes in women who refuse or have contraindications for HRT (*136*). Research into alternatives to estrogen for menopausal women is of clinical, scientific, and health policy importance (*137*). Hence, these therapies have additional benefits of being acceptable to women of various ethnicities and cultures.

SAPONINS

Saponins are glycosidic compounds of steroid (C_{27}) (*138*) or triterpenoid (C_{30}) (*139*) sapogenin nucleus with one or more side chains of carbohydrates (**Figure 11**). Many forage legumes grown in temperate areas contain various saponins and have

Table 1. Occurrence, Therapeutic Applications, and Possible Modes of Action of Some Antinutritional PSMs

PSM	major sources	therapeutic applications	modes of action	references
tannin–polyphenols	vascular woody plants and ferns, etc.	anticancer applications	antioxidant effects: delayed lipid peroxidation, depletion of endogenous lipid-soluble antioxidants, free radical scavenging properties	*27*, *57*, *58*, *66*, *72*
			angiogenesis inhibition and anti-inflammatory effects	*8*, *28*, *29*
			interaction with ultimate carcinogens, prevention of genotoxicty through inhibition of clastogenicity, gene mutations. and DNA breaks	*30*, *60*
			lowered metabolic activation of mutagens and down-regulation of CJIC during cancer promotion phases	*31*, *62*
			induction of apoptosis in cancer and leukaemia cells	*63*, *73*, *74*
		cardioprotective effects	prevention of lipoprotein oxidation	*214*
		antiparasitic action	direct tannin toxicity against gastrointestinal nematodes	*35*, *215*
			inhibition of nematode larval motility and helminth larval migration	*38*, *41*
			disruption of mechanical integrity of parasite cuticle	*216*
			enhanced host immunity against parasites	*217*
			inhibition of intracellular survival of pathogens (*Leismania donovani* amastigotes)	*218*
		antimicrobial effects	antimicrobial effects through depletion of iron and other metal ions vital for microbial growth	*54*
			bacterial DNA gyrase supercoiling inhibition	*219*
			inhibition of virus adsorption to the target cells	*220*
			inhibition of HIV-reverse transcriptase and HIV replication in lymphocytes	*221–223*
			inhibited expression of HIV antigen in lymphotropic virus type-I (HTLV-I) positive MT-4 cells	*224*
			inhibition of Epstein–Barr virus (EBV) DNA polymerase	*225*
			inhibition of HIV-1 protease (HIV-1 PR)	*226*
saponins	higher plants and some marine animals	anticancer uses	antioxidant actions	*167*
			growth inhibition and reverse transformation of melanoma (B16) cells	*156*
			depressed tumor cell proliferation, induction of cell differentiation and apoptosis in cancer cells	*169*, *226*
			intranucleosomal DNA fragmentation in cancer cells	*160*
			down-regulation of cyclin/cdk complex kinase activity, decreased phosphorylation of pRb and inhibition of E2F release	*158*
			cytotoxocity against cancer cells	*161*, *168*
			prevents down-regulation of gap junctional intercellular communication during the cancer promotion phase	*31*
		immunomodulatory uses	*iscom* induced high titers of serum antibodies and high numbers of IgG-Sc in the spleen; modulation of Ig G2a subclass augmented cellular and humoral responses	*277–229*
			viral capsid protein synthesis inhibition and some antiviral activities against HIV	*230*, *231*
		cardioprotective effects	hypocholesterolemic effects on plasma total and LDL cholesterol concentrations	*232*, *233*
		antidiabetic effects	enhanced insulin secretion and sensitivity	*234*
			reduced glucose absorption	*235*
			improved glucose tolerance	*236*
		analgesic and anti-inflammatory effects	action on leukotrienes in the metabolic pathway of arachidonic acid	*237*
mimosine	*Leucaena leucocephala*, *Mimosa pudica*	anticancer applications	targeting of serine hydroxymethyltransferase activity	*181*
			inhibition of initiation and elongation steps of DNA synthesis and induction of DNA breaks in cancer cells	*178*, *186*
			suppression of the expression of cyclin D1 and up-regulated expression of CDKI p21WAF1 in lung cancer cells, blocked cell proliferation by multiple mechanisms	*182*, *183*
			up-regulation of p27 protein levels through transcriptional and post-transcriptional regulatory mechanisms	*185*
			enhancement of radiation sensitization of cancer cells	*187*
		anti-inflammatory effects	inhibition of monocyte chemotactic proteins-1 (MCP-1) and MIP-2, chemokine transcription, and translation in the infected host	*238*

Table 1 (Continued)

PSM	major sources	therapeutic applications	modes of action	references
phytoestrogens	leguminous forage seeds, foods	anticancer effects	inhibition of aromatase, protein tyrosine kinase and S6 activities	*114*, *241*
			inhibitory effects on angiogenesis	*242*
			inhibition of DNA topoisomerase II	*121*, *243*
			induction of apoptosis in cancer cells	*244*
		prevention of prostate cancer cells	stimulation of adherence of prostate cancer	*245*
			suppression of cyclin-B expression, induction of cyclin-dependent kinase inhibitor p21	*246*
			genistein and radiation combined inhibition of DNA synthesis, cell division, and growth of cancer cells	*118*
			cellular growth inhibition through inhibited mitogenic signaling pathway(s) and altered cell cycle regulators	*247*
		prevention of gastro-intestinal cancer	inhibition of cell proliferation, induction of apoptosis and altered expression of C-*myc* oncogene in the colon and large bowel cancer cells	*248*, *249*
			inhibition of nonoxidative ribose synthesis in MIA pancreatic adenocarcinoma cells	*250*
		cardioprotective effects	improvment of cardiovascular risk factors, lowering plasma cholesterol levels and atherosclerosis, platelet aggregation inhibition	*251*, *252*
			prevention of glucose mediated LDL oxidation and atherogenic LDL formation	*239*, *240*
phytic acid	cereals, nuts, oilseeds, and pollen spores	anticancer applications	impairment of epidermal growth factor receptor (EGFR or erB1) and associated mitogenic signaling in prostate carcinoma cells	*253*
			inhibition of the AP-1 and NF-κ B transcription activities and radiation-induced signal transduction	*254*
			prevention of lipid peroxidation and suppressing the generation of highly reactive oxygen species	*196*, *255*

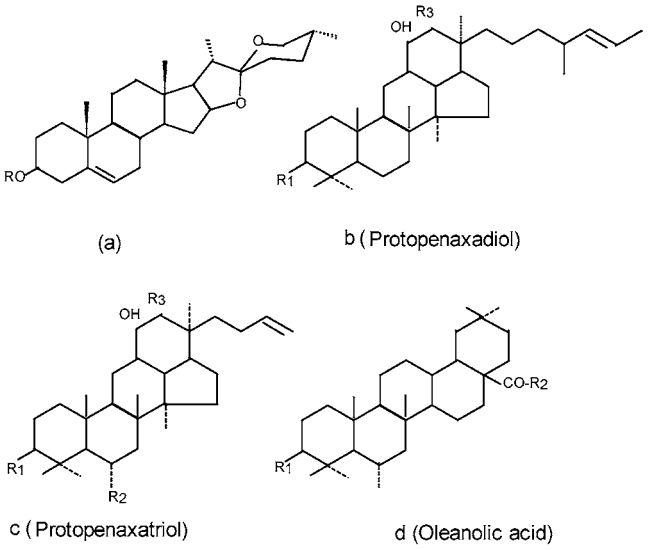

Figure 11. (a) Typical structure of a steroidal saponin (R = sugars), sapogenin (R = H), and ginseng saponins (b–d).

varieties of biological effects with both positive and negative implications. As a consequence of their amphiphilic nature and surface active properties, saponins are excellent foaming agents, forming very stable foam. Their biological value is closely related to chemical structure, which determines the polarity, hydrophobicity, and acidity of the compounds.

Yucca and quillaja saponins have both current and potential importance in animal and human nutrition. On the negative side, saponins inhibit the productive performance of nonruminant animals (*140*). Prolonged intake of saponin-enriched forage by animals has been found to reduce the ruminal protozoal number, reduce degradation of feed protein, decrease amounts of the microbial proteins flowing to the intestine and, hence, reduced apparent digestibility (*141*, *142*). Steroidal saponins of *Yucca schidigera* had adverse effects on ruminal bacteria, namely, *Streptococcus bovis*, *Prevotella bryanti*, and *Ruminobacter amylophilus* (*143*). Saponins present in various pastures and range weeds have been implicated in various toxicological problems. At high concentration, saponins can cause cell damage by disrupting cell membranes or inducing apoptosis (*144*). Saponins are also known to react with membrane sterols, disrupt membrane function, and, consequently, arrest cell growth (*145*).

Anticarcinogenic Attributes of Saponins. Despite the known antinutritional attributes of saponins, the beneficial effects, for instance, hypocholesterolemic (*146*), anticarcinogenic (*147*), and immunostimulatory properties (*148*), are being currently investigated. Experimental and epidemiologic carcinogenesis studies showing that >90% of cancer incidents are associated with mutagens and mitogens (*149*) suggest a search for agents that inhibit or reverse cellular processes derived from mutagenesis and mitogenesis. Absorbed sapogenins undergo metabolism in the liver and are excreted into the bile as episarcosapogenin or epismilagenin conjugates. The binding of bile acids by saponins has other important clinical implications. There is a strong association between the colon cancer incidence, secondary bile acids, and high cholesterol metabolites (*150*, *151*). It has been found that saponins from different dietary sources decrease intestinal absorption of cholesterol and reduce the availability of the endogenous and exogenous neutral steroids, primary bile acids to form secondary bile acids through the action of intestinal microflora, thus preventing the development of colorectal cancer (*152*, *153*). At concentrations of 150−600 ppm, soybean saponins have been shown to exhibit a

dose-dependent growth inhibiting effect on human carcinoma (HCT-15) cells, with significant reduction in their viability (*154*).

The active component in several herbal medicines that have been used as chemotherapeutic agents in Eastern countries was shown to be saponins. Ginseng species (e.g., *Panax ginseng*, *P. quiquefolius*, *P. japonocus*, *P. pseudoginseng*, *Eleutheroccus senticosus*, etc.) are widely employed in Chinese medicine, Eastern Asia regions, and Oriental medicine as tonic or adaptogenic and as treatment of cancer, diabetes, and hepatic and cardiovascular diseases (*155*, *156*). These species share many common phytometabolites incuding alkaloids, phytosterols, amino acids, and 0.5−3% of saponins (*157*). Ginsenosides, the ginseng saponins (**Figure 11**) constituting 2−4% of its dry weight, are claimed to be responsible for most, if not all, of the pharmacological activities of ginseng. Ginsenoside Rh2 (G-Rh2) isolated from the root of *P. ginseng* inhibited the growth of MCF-7 human breast carcinoma cells through induction of protein expression of p21 and reducing the protein levels of cyclin Cdk, resulting in the down-regulation of cyclin/Cdk complex kinase activity, decreased phosphorylation of pRb, and inhibition of E2F release (*158*). Apart from triterpenoid saponins in ginseng, acetylenic alcohols obtained from ginseng, especially panaxytriol, showed anticancer activity against melanoma B16 when intramuscularly administered (*159*). 20-*O*-(*β*-D-Glucopyranosyl)-20(*S*)-protopanaxadiol (IH-901), a novel intestinal metabolite of ginsenosides Rb1, Rb2, and Rc, is of particular interest in cancer chemoprevention and treatment. IH-901 has been reported to exert significant cytotoxic activity against cancer cell lines (HL-60 cells) by inducing internucleosomal DNA fragments. The treatment of HL-60 cells with IH-901 led to activation of caspase-3-protease and subsequent proteolytic cleavage of poly(ADP-ribose) polymerase. These results may provide a pivotal mechanism for the use of IH-901 in the prevention and treatment of leukemia (*160*). Some steroidal saponins showed higher cytotoxic activity against human oral squamous cell carcinoma cell lines (HSC-2) compared to normal human gingival fibroblasts HGF (*161*). The tumor specificity of saponins has been reported to exceed that of tannins and flavonoids, suggesting that an oxidation-mediated mechanism was not involved in the cytotoxicity induced by the steroidal saponins (*161*).

Yunnan Bai Yao, a Chinese herbal drug, used as a hemostatic agent and to promote wound healing (*162*), contains the saponin formosanin-C (*163*). Saponins extracted from *Agave centala* and *Asparagus curillus* also significantly inhibited the growth of human cervical carcinoma (JCT-26) and p-388 leukemia cells (*164*). A fraction of phytochemical concentrate (PCC) of soybean molasses repressed experimentally induced genomic DNA damage, clastogenic damage, and point mutation in mammalian cells (*165*). PCC-100, a chemically defined fraction of PCC, was found to exhibit the greatest levels of antimutagenic activity against 2-acetoxyacetylaminofluorene (2AAAF) in Chinese hamster ovary cells and to repress the genotoxic capacity of dietary carcinogen 2-amino-3-methylimidazo-(4,5-*f*)quinoline (IQ) in human lymphocytes (*166*). PCC-100 was shown to consist of a group B soyasaponin and 2,3-dihydro-2,5-dihydroxy-6-methyl-4*H*-pyran-4-one (DDMP) soy saponins. Purified soyasapogenol B aglycon prepared from fraction PCC-100 demonstrated significant antigenotoxic activity against 2AAAF (*167*). A steroidal cytotoxic glycoside, neohecogenin (chloromaloside A), isolated from *Chlorophytum malayense* was found to exhibit in vitro cytotoxicity against several human cancer cell lines (*168*). Dioscin, a saponin extracted from the root of *Polygonatum zanlanscianense* exerted significant inhibitory effects on the growth of the human leukaemia cell HL-60, inducing differentiation and apoptosis and thus revealing the importance of saponins in related cancer treatment (*169*). A new paradigm is emerging whereby the pharmacological effects of traditional herbs such as ginseng can be understood in the light of their polyvalent action as demonstrated by ginseng saponins, with their positive antimutagenic, anticancer, antiinflammatory, antidiabetic, and neurovascular effects (*170*).

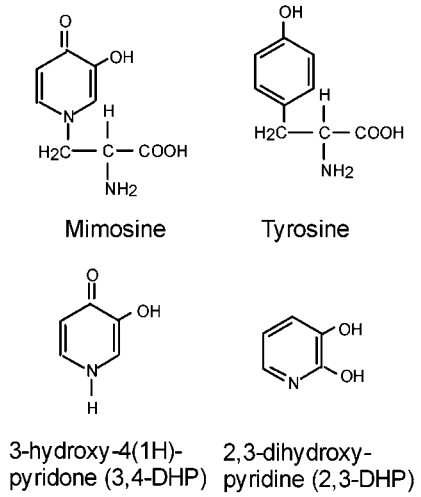

Figure 12. Mimosine and its metabolites produced by intestinal bacteria or autolysis. Mimosine is a structural analogue of tyrosine.

MIMOSINE

Mimosine [*β*-[*N*-(3-hydroxy-4-oxypyridyl)]-α-aminopropionic acid] is found in the plants of Mimosaceae, which include *Leucaena leucocephala*, *L. glauca*, and other legumes including *Mimosa* spp. The presence of mimosine and its intermediate metabolite, 3-hydroxy-4-(1*H*)-pyridone (3,4-DHP) (**Figure 12**), generated either by the action of GI bacteria or by autolysis, severely limits the potential attributes of *L. leucocephala* as a supplement in human (*171*) and animal diets (*172*). Mimosine and 3,4-DHP have been shown to reduce feed intake and to cause alopecia, renal and liver dysfunction, general inefficiency in various domestic species, and, in extreme cases, death (*173*). In addition, mimosine has been reported to influence various serum enzyme activities and to possibly interfere with the metabolism of some amino acids, notably glycine (*174*). Furthermore, 3,4-DHP has been classified as a thiouracil-type goitrogen with a general peroxidase inhibiting action (*175*).

Mimosine and Cancer Therapy. Cell growth and differentiation are the processes intimately associated with carcinogenesis and regulated by tyrosine kinases and other signaling proteins (*176*). Natural or synthesized agents that can inhibit cell cycle progression at specific points or the chemicals that affect DNA synthesis are potentially useful for the development of anticancer drugs and effective tools for the investigation of DNA metabolism.

Despite the mechanism of mimosine not being very clear, interest in mimosine, reported to be an effective mammalian cell synchronization agent and inhibitor of DNA synthesis in cells, is steadily growing. During the past few years a number of papers have appeared on mimosine being used for synchronization of mammalian cells at the G1/S phase of the cell cycle. In addition to its effect on DNA replication, mimosine has also been shown to inhibit deoxyhypusyl hydroxylase and thus prevent the formation of hypusine (*177*), a rare amino acid found only in the eukaryotic initiation factor eIF-5a (*178*). Mimosine

is a folate antagonist, with its effect being cell specific. The effect on folate metabolism is associated with the decreased cytoplasmic serine hydroxymethyl transferase (cSHMT) transcription by chelating iron (*179*). Alteration in the folate levels is of significant concern with reference to carcinogenesis. Leleu et al. (*180*) have reported that diminished folate status was associated with a decrease in the development of azoxymethane (AOM)-induced colorectal cancer. Mimosine inhibits cell cycle progression by depleting purine deoxyribonucleotide pools through inhibition of the folate-dependent enzyme cSHMT (*181*) or may arrest the growth by activating the expression of p^{21CIP1}, a cyclin-dependent kinase inhibitor (CDK I), and by inhibiting the activity of cyclin E-associated kinases in human breast cancer cells. Mimosine was found to decrease cyclin D1 protein levels and inhibit cyclin D1-associated kinase activity in H226 human lung cancer cells (*182*). Furthermore, anticancer effects of this compound on H226 cancer cells have demonstrated that mimosine inhibits cyclin D1 and induces p^{21WAF1} expression in vivo. Moreover, in addition to lung cancer, as mimosine also inhibits the proliferation of a number of cancer cell types in vitro, it is possible that mimosine may be useful for the therapies of these cancers (*183*). Collectively these results show that mimosine exerts anticancer effects in vivo and might be useful in the therapy for lung cancer, the leading cause of cancer-related deaths in many developed countries (*183*). The cyclin-dependent kinase inhibitor p^{27Kip1} observed throughout the G1 and early S phases plays an important role in cell cycle progression by negatively regulating the activity of cyclin−cdk complexes (*184*). Wang et al. (*185*) have proposed that mimosine blocks the cell cycle in the late G1 phase by up-regulation of p^{27Kip1} protein levels through transcriptional and posttranscriptional regulatory mechanisms. Treatment of mammalian cells with mimosine generates DNA breaks, and it has been indicated that inhibitory effects of mimosine on DNA synthesis and cell cycle may be as a result of the introduction of breaks into DNA (*186*). Molecular mechanisms that induce DNA breakage are not fully understood. One possible mechanism postulated was that, being a strong chelating agent, mimosine could bind iron and copper ions and thus facilitate the oxidative generation of free radicals (*186*).

PHYTIC ACID

Phytic acid (PA), *myo*-inosito l,2,3,4,5,6-hexakisdihydrogen phosphate (IP6), is an essential microconstituent of plant cells (*188*, *189*). IP6 is localized in cotyledons of legumes and oilseeds, where it is found as crystalline globoids immersed in protein bodies (*190*). It has been regarded as ANF due to its ability to complex with pectin and divalent cations such as Ca^{2+}, Fe^{2+}, Zn^{2+}, and Mg^{2+} (**Figure 13**) to generate insoluble complexes in the digestive tract and hinder mineral metabolism in man and other monogastric animals. Its interaction with proteins categorizes phytate as an enzyme inhibitor, especially an α-amylase inhibitor, which limits starch digestion and lowers blood glucose (*191*). Nevertheless, IP6 is receiving attention owing to its role in cancer prevention and/or therapy and its hypocholesterolemic effects (*192*, *194*). In addition to its anticancer properties, extracellular functions have been observed for IP6, including enhancing superoxide production and phagocytosis by neutrophils in the presence of microbial stimuli. Exposure of neutrophils to low levels of IP6 appears to modulate selective neutrophil functions (*193*). High levels of endogenous sodium phytate reduce iron-induced oxidative injury and reverse iron-dependent augmentation of colorectal tumorigenesis in rats (*195*). Intrinsic phytate from a corn−soy diet was reported to

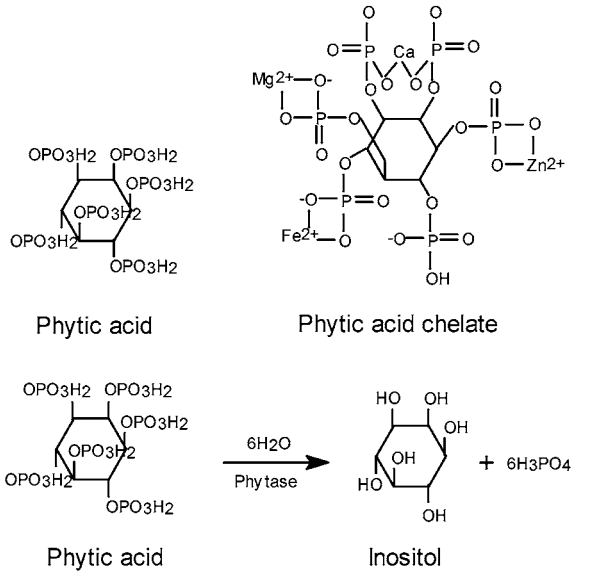

Figure 13. Phytic acid, phytic acid chelate, and enzymatic hydrolysis of phytic acid.

exert beneficial effects in the prevention of lipid peroxidation in the colon associated with a moderately high level of dietary iron (*196*). Wheat bran (WB) and its component phytic acid have been shown to decrease early biomarkers of colon carcinogenesis. Jenab and Thompson (*197*) have concluded that WB, partly due to its dietary fiber and endogenous and exogenous IP6, when added to a low fiber diet can increase cell apoptosis and differentiation and favorably affect colon morphology, such as reducing crypt cell height and crypt density.

Miscellaneous PSMs and Their Therapeutic Relevance. Alternative medicines such as herbal products are increasingly being explored for preventive and therapeutic applications in humans and animals, but several weeds and problem plants also could be rich and viable sources of novel therapeutic products. It is likely that new important drugs remain hidden in plants in primary tropical rainforests, several weeds, and noxious plants infesting degraded areas, and traditional medicinal plants could be fountain sources of novel therapeutic compounds. Apart from Poaceae, which is ranked as the number one family for the world's worst weeds, other major weed families are Asteraceae, Fabaceae, Convolvulaceae, Euphorbiaceae, Chenopodiaceae, Malvaceae, and Solanaceae (*198*). Stepp and Moerman (*199*) have presented data showing the significant representation of weeds in the medicinal flora, and the frequency with which weeds appear in pharmacopoeias along with explanations based on human and biochemical ecology.

Lantana camara, for example, is a noxious bush that originated in tropical America and spread to many subtropical areas of the world such as India, Southeast Asia, Polynesia, and Australia (*200*). It is a rich source of a number of biologically active triterpenoid compounds with the major toxic ones being lantadene A (angelate) and lantadene B (dimethylacrylate) (**Figure 14**), the concentrations of which vary with the cultivar (*201*). Different parts of lantana are used in folklore and traditional systems of medicine for the treatment of various problems such as itches, cuts, ulcers, swellings, eczema, malaria, tetanus, and rheumatism (*202*). The lantadenes, pentacyclic triterpenes from lantana, have a number of biological activities. Lantadenes have been shown to inhibit the activity of EBV, with lantadene B being most active (*203*). Lantadenes have been found to inhibit carcinogenesis of experimentally induced mouse skin papilloma (*204*). A number of pharmacological properties,

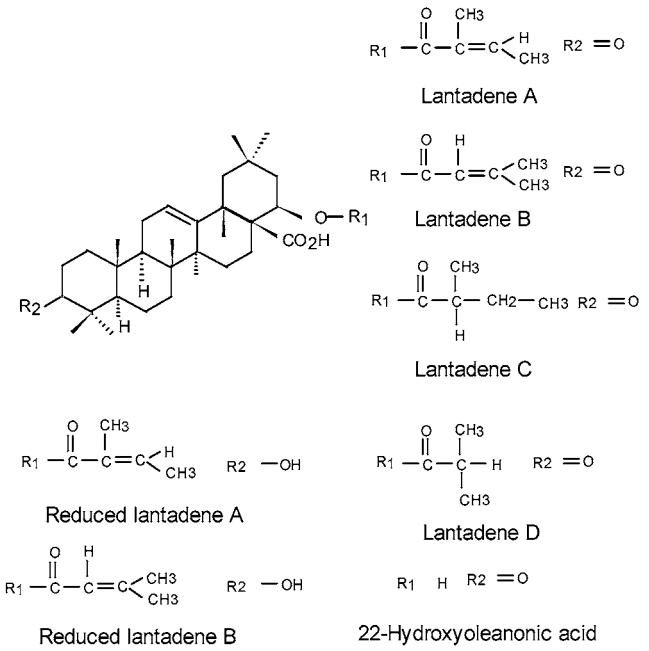

Figure 14. Chemical structures of lantadenes.

such as antitumor, anti-AIDS, antiinflammatory, and antibacterial, have been attributed to the pentacyclic triterpenoids (*205*−*207*). Methanolic extracts of *L. camara* leaves inhibited human thrombin, and the activity was associated with a series of 5,5-*trans*-fused cyclic lactones containing euphane triterpenes (*208*, *209*). Pentacyclic triterpenes are attracting increasing attention in the development of novel antiinflammatory drugs (*210*).

A number of alkaloids prevalent in *Senecio* and *Eupatorium* spp. have been reported to show anticancer activities. Several species of Asteraceae are effective against blood parasites. Neurolenin B and derivatives of *Eupatorium inulaefolium* at concentrations lower (0.057 ppm) than chloroquine (0.156 ppm) exhibited significant parasiticidal action against *Plasmodium falciparum* (*211*). Goitrogenic PSMs, the glucosinolates (thioglycosides, glucobrassicans), present in several cruciferous plants are implicated in anticancer activity. Glucosinolates and their highly reactive metabolites, such as isothiocyanates, can protect against cancer by modulating carcinogen metabolism (*212*). Isothiocyanates also inhibit mitosis and stimulate apoptosis in human tumor cells in vitro and in vivo (*213*).

On the basis of the antioxidative and other biological activities in animal studies, and some clinical and epidemiological studies, a number of plant metabolites have been proposed to be beneficial to human health. These views are further strengthened by the identification of possible mechanisms of action and target sites in the body. However, inadequate knowledge regarding the bioavailabilty and biotransformation of various dietary PSMs in humans has limited our understanding of their possible beneficial health effects. There is a need to carry out more clinical trials with proper selection of biomarkers for determining the bioefficacy of various PSMs. Hence, with increasing understanding, evidence-based incorporation of traditional herbs as complementary medicine into the mainstream medical science has tremendous potential for exploitation soon. Also, antioxidant PSMs could be new and potent therapeutic agents if their pharmacological properties including oral absorbance and plasma stability are improved through chemical modification. It is now essential that biologists and medical scientists integrate this knowledge in the conception of their experiments and in the interpretation of the results.

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