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PHENYLPROPANOIDS AS NATURALLY OCCURRING ANTIOXIDANTS: FROM PLANT DEFENSE TO HUMAN HEALTH

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Abstract – Phenylpropanoids (PPs) belong to the largest group of secondary metabolites produced by plants, mainly, in response to biotic or abiotic stresses such as infections, wounding, UV irradiation, exposure to ozone, pollutants, and other hostile environmental conditions. It is thought that the molecular basis for the protective action of phenylpropanoids in plants is their antioxidant and free radical scavenging properties. These numerous phenolic compounds are major biologically active components of human diet, spices, aromas, wines, beer, essential oils, propolis, and traditional medicine. Last few years, much interest has been attracted to natural and synthetic phenylpropanoids for medicinal use as antioxidant, UV screens, anticancer, anti-virus, anti-inflammatory, wound healing, and antibacterial agents. They are of great interest for cosmetic and perfume industries as active natural ingredients. In the present review, the metabolic pathways of phenylpropanoid biosynthesis in plants and the mechanism of phenylpropanoid-mediated plant defense are described. Learning from plants, free radical-driven, molecular and cellular processes modulated by phenylpropanoids in human cell cultures in vitro and in the in vivo animal models of tumors, inflammation, and cellular damage are also reviewed.

Key words: Phenylpropanoids, metabolism, plant defense, UV-screen, antioxidants, phytoestrogens, anti-cancer, anti-inflammatory, and cytoprotective action

INTRODUCTION

Phenylpropanoids (PPs): metabolism and role in plant physiology

In the 19th century it was suggested that two major classes of metabolites exist in both plants and microorganisms: primary metabolites are essential for cell survival and propagation (carbohydrates, proteins, amino acids, lipids). Plants produce a great variety of other organic compounds that are not directly involved in primary metabolic processes of growth and development. The roles these secondary metabolites play in plants have only recently come to be appreciated. Secondary metabolites appear to function primarily in defense against predators and pathogens such as virus, mycoplasma, bacteria, and fungi. They also protect plants against herbivores both insects and mammals; against plant competitors, and abiotic stresses like UV light, ozone, and herbicides. They are of big importance for adaptation of plants to continuously changing environmental conditions, they provide reproductive advantages as attractants of pollinators and seed dispersers, they serve as signaling molecules and hormones, and they act to create competitive advantage by poisoning of rival species. Secondary metabolites provide two types of resistance: a passive one when the products present continuously regardless of the presence of stressors and an active resistance when the products produced in response to a damage cue from specific stressful agents. Among the cues can be cell wall fragments, insect saliva, and products of specific recognition genes, which initiate the biochemical signaling pathways for activation of defense genes. Secondary metabolites are derived from primary metabolites first of all amino acids and carbohydrates through methylation, hydroxylation, and glycosylation biochemical pathways. Up to date, a few thousands of different secondary metabolite structures have been identified in plants; the largest of them are the phenylpropanoids (PPs, synonym, phenylethanoids), isoprenoids and alkaloids. By chemical structure, secondary metabolites in plants are divided in several major classes such as:

- terpens (isoprenoids, terpenoids)
- PPs, phenylpropanoids and their derivatives (flavonoids, tannins, glycosides, and lignins)
- nitrogen-containing compounds (alkaloids and heterocyclic aromatics)

PPs belong to a large class of plant phenols produced through shikimic acid pathway. The synthesis of PPs has a common

initial step – deamination of phenylalanine to cinnamic acid catalyzed by phenylalanine ammonia lyase (PAL, EC 4-3.1-5), a family of enzymes with many isoforms responsive to different developmental and environmental stimuli. Several factors are known to affect the expression and activity of PAL. They are light, wounding (31), disease, gamma-ray irradiation, germination, development and differentiation, and the application of certain macromolecules (37). Many of plant-derived phenolic compounds (flavonoids, isoflavonoids, coumarines, and lignans) are secondary products of PPs metabolism (17, 18). For example, both resveratrol and flavonoids evolve from a common biosynthetic shikimic acid pathway. First, cinnamic and then, hydroxycinnamic acid are formed, both acids belonging to PPs. Then, chalcone synthase uses 3 cinnamoil radicals to produce flavonoids. Stilbene synthase uses 2 cinnamoil radicals to produce trans-3,4'-trihydroxystilbene, known as resveratrol. Resveratrol is a phytoalexin used by plants to protect themselves from fungi (19). Lignins are phenolic polymers playing an important role by reducing the permeability of the cell wall to water, by increasing the rigidity of cell wall, which is a part of the pathogen resistance mechanism. These plant polymers are products of the oxidative coupling of PPs monomers: peroxidase catalyses the oxidation of PPs to their phenoxyl radicals, and the subsequent non-enzymatic coupling controls the pattern and extent of polymerization that results in a vast structural diversity of natural lignins (88).

Plants normally increase several components of the antioxidant system in response to naturally occurring stresses such as stress at high altitude, chilling, draught, and nutrient deficiencies (46). More attention has been paid over the past five years to the effects of UV-B radiation on oxidative stress as well as to the role of PPs as antioxidants in plants. It has been shown that many plants respond to enhanced UV radiation by producing smaller and thicker leaves, by increasing the thickness of the cutin layer and the epidermal wall, and by increasing concentrations of UV absorbing compounds in the epidermal cells, waxes and leaf hairs, and activation of the antioxidant defense system (97). In higher plants, PPs, mainly, hydroxycinnamic acid, cinnamoyl esters, flavones, flavonols, and anthocyanins provide a UV-A and UV-B screen. Both soluble and insoluble PPs absorb efficiently in the range of 304-350 nm and 352-385nm, respectively. Although these compounds absorb UV light, they transmit visible and photosynthesis activating radiation into the mesophyl cells. Soluble flavonoids are actively and rapidly induced by UV-B exposure whereas cell wall bound PPs represent a more passive UV screening mechanism (58).

An almost ubiquitous feature of plant responses to incompatible pathogens or to elicitors is the activation of PPs metabolism in which PAL catalyses the first committed step of the core pathway of general PP metabolism. Branch pathways lead to the synthesis of compounds that have diverse defensive functions in plants such as cell wall strengthening and repair (lignin and suberin), antimicrobial activity (furanocoumarin, pterocarpan and isoflavonoid phytoalexins), and signaling (salycilic acid) (41). The resulting phenolics are often converted into more reactive species by phenol oxidases and peroxidases (30, 34). There are several PPs-based mechanisms of defense against pathogens, for example, construction of structural lignin-containing barriers preventing the pathogen penetration into the plant tissues. Another mechanism is the use of phytoalexin and scopoletin, which could act as broad-range antibiotics. Additionally, scopoletin being an efficient peroxidase substrate may act as scavenger of reactive oxygen species and thus prevent, or reduce, oxidative damage to infected plant cells (5). PPs exert direct antimicrobial activity and also serve in signaling and chemotaxis to both pathogenic and symbiotic microorganisms (16). Thus, fungal infection of cassava leaves and cultured cells led to a rapid oxygen radical overproduction (within 20 min), PAL mRNA accumulation (9 hours) and over-expression of peroxidase gene, after which an increase in the enzyme activities was observed (48 hours). As a result, the levels of PPs increased and fungitoxicity enhanced up to 20-fold (30). The endogenous signaling molecules for the induction of plant defense are several plant hormones, for example, analogues of jasmonic acid. These jasmonic acids are widely distributed in plants and affect a variety of processes, including fruit ripening, production of viable pollen, root growth, and plant response to wounding, abiotic stress, infections, and insects. Jasmonic acids are produced of linolenic acid from lipids of damaged plant membranes (63). The endogenously produced or exogenously applied jasmonic acid derivatives induce PAL

followed by downstream enzymes such as caffeic acid *O*-methyltransferase. Among the PPs, chlorogenic acid (3-O-caffeoyl quinic acid) has been extensively investigated for its role in plant defense. It serves as a phytoanticipin in many plant species. Tobacco and cotton plants over-expressing PAL produce high levels of chlorogenic acid and exhibit markedly reduced susceptibility to fungal pathogens. For other PPs, malate esters such as 5-hydroxyferuloyl, caffeoyl, coumaroyl, feruloyl, and sinapoyl malates were induced by exogenous application of methyl jasmonate to *Brassica rapa* leaves (63). The host plant resistance to the stem borer that attacks maize strongly correlated with the cell wall PPs (p-coumaric, trans-ferulic, cis-ferulic, and diferulic acids) content (90).

Some plant derived PPs are of great importance also for physiology of herbivore insects. Thus, methyl eugenol, consumed by sexually mature male fruit fly and subsequently subjected to biotransformation into two other PPs (2-allyl-4,5-dimethoxyphenol and (E)-coniferyl alcohol), which are released as sex and aggregation pheromones during courtship and coupling (48).

Plant-derived PPs and their derivatives are among the most common biologically active components of food, spices, aromas, fragrances, propolis, wines, essential oils, beer, and traditional medicine. Taking into account numerous defensive roles of PPs and their derivatives in plants, these compounds are of great interest, especially for medicinal use as antioxidant, UV screens, anticancer, anti-virus (4), anti-inflammatory, wound healing, and antibacterial agents (See review 13). Much interest has been recently attracted to natural and synthetic PPs from cosmetic and perfume industries (95). PPs for biological experiments, medicinal and cosmetic use are mainly isolated and purified from plant extracts or from cultivated plant cells. Their chemical synthesis is complex and expensive. Although in order to increase specificity and activity, natural PPs sometimes are subjected to chemical modifications.

Molecular and cellular mechanisms underlying anti-inflammatory, chemopreventive, and cytoprotective activity of PPs and their derivatives

Numerous publications have been focusing on the molecular mechanisms of biological activity of natural and synthetic PPs. Several studies within the last few years have shown that resveratrol induces the accumulation of p53 and p21 (39), inhibits ribonucleotide reductase and DNA polymerase (24), induces nitric oxide production, and suppresses cell growth by arresting cells at the S and G_2 phases of the cell cycle in a number of animal cells (39, 45). It suppresses both the production of IL-1β and its effect on the activation of NF-κB, activates caspase 3, thus inducing apoptotic death in leukemia cells (19). The studies of immunomodulatory activity of resveratrol have shown that at the concentrations of 25-50 μM it suppressed significantly mitogen-, IL-2-, or alloantigen-induced proliferation of splenic lymphocytes and the development of antigen-specific cytotoxic T lymphocytes. It inhibited cytokine production by splenic lymphocytes and peritoneal macrophages. The PP inhibited proliferation of cultured keratinocytes and fibroblasts, presumably, by inactivation of arachidonic acid cascade (38, 76). These data could explain strong anti-inflammatory effect of resveratrol. Caffeic acid phenethyl ester (CAPE) is an active PP present in propolis, a resinous product derived from the bark of conifer trees and carried by honeybees to their hives. CAPE has anti-tumor and anti-inflammatory properties (23). CAPE inhibits the transcriptional activity of the COX-2 gene in epithelial cells (74), inducible nitric oxide synthase gene expression, and nitric oxide production in macrophage cell lines (93), suppresses the release of arachidonic acid and eicosanoid synthesis (74), and inhibits NF-kB activation (81). The PP-mediated inhibition of NF-kB transcriptional activity occurs without degradation of the cytoplasmic NF-kB inhibitory protein IkappaBalpha, suggesting that the molecular target for PPs is at a post-IkB degradation level (7, 81) Additionally, CAPE inhibited both the DNA-binding and transcriptional activity of nuclear factor of activated T-lymphocytes. Moreover, CAPE specifically inhibits both interleukin (IL)-2 gene transcription and IL-2 synthesis in stimulated T-cells (68). The PPs from Bupleurum fruticosum prevented cytokine IL-1, IL-6, TNFα, IL-8 release and prostaglandin E_2 synthesis (7). All these findings provide new insights into the molecular mechanisms involved in the immunomodulatory and anti-inflammatory activities of the PPs.

Another extensively studied PP is chlorogenic acid, the ester of caffeic and quinic acids. It is one of the most abundant PPs in

human diet and has been reported to decrease the incidence of chemical carcinogenesis in several animal models of cancer. Using the model of TPA- and UVB-induced neoplastic transformation of JB6P+ cells, Feng and co-authors (22) have shown that chlorogenic acid strongly inhibited NF-kB and AP-1, decreased the phosphorylation of p38 kinase as well as MAPK kinase 4, and activated Nrf2. The transcription factor Nrf2 plays an essential role in the antioxidant response element (ARE)-mediated expression of phase 2 detoxifying enzymes and stress-inducible genes (47, 79). Normally, Nrf2 is located in cytoplasm bound to the Keap1 protein. Many natural molecules, such as PPs, isothiocyanites, and bioflavonoids induce the dissociation of Nfr2 from Keap 1, then, Nfr2 is translocated into nucleus favoring the expression of ARE-regulated cytoprotective genes encoding the phase 2 enzymes (heme oxygenase-1, glutathione-S-transferase A1, and NAD(P)H:quinone oxidoreductase 1). The induction of phase 2 and antioxidant enzymes by chemicals or dietary factors, first of all, PPs, to prevent carcinogenesis has been often linked to cancer chemoprevention (See review 15).

Anti-inflammatory and potential anti-allergic properties of 1'S-1'-acetoxychavicol acetate and 1'S-1'-acetoxyeugenol acetate, PPs isolated from the rhizomes of *Alpinia galanga*, were studied in RBL-2H3 cell cultures. Both PPs were extremely effective (IC_{50} = 15 and 19 µM, respectively) in the inhibition of antigen-IgE-mediated cell degranulation and pro-inflammatory cytokine (TNF-α and IL-4) release. Both the 1'- and 4-acetoxy groups were essential for this kind of biological action (72).

Free radical scavenging, antioxidant, and metal chelating properties of PPs

There is a large amount of evidence that PPs and their glycosidated forms (PPG), like other plant polyphenols, are powerful antioxidants either by direct scavenging of reactive oxygen and nitrogen species, or by acting as chain-breaking peroxyl radical scavengers (See as reviews 14, 52). Polyphenols such as PPs, PPG and bioflavonoids with two adjacent –OH groups, or other chelating structures, can also bind transition metals, first of all iron and copper, in forms poorly active in promoting free radical chain reactions (27). Recently, PPs and their derivatives have been reported to possess multiple beneficial effects for human health. Indeed, they have been found to be effective in the chemoprevention of tumors (57); some have anti-inflammatory activity (61), while others have anti-thrombotic (96), wound healing (40), and cardio-protective actions (53). The majority of these health effects have been attributed to free radical scavenging, antioxidant and chelating properties of PPs (14, 52). Resveratrol is a potent inhibitor of copper initiated LDL oxidation (25) even more effective than flavonoids (26). Brito and co-authors (8) have shown that resveratrol inhibits peroxynitrite- and ferrylmyoglobin-stimulated LDL oxidation. PP glycosides from Orobanche caerulescens were five times more effective than resveratrol in the inhibition of human LDL oxidation (64). As a consequence, PPs suppressed endothelin-1 secretion by endothelial cells treated with Cu-oxidized LDL (70). Since ET-1 plays an important role in atherosclerosis, the PPs tested were proposed for the prevention of atherosclerosis (33). A comparison of different derivatives showed that 4'-OH is a sole reactive phenolic group responsible for the antioxidant activity of resveratrol. Cos et al. (11) measured the antioxidant activities of numerous PPs such as caffeic and chlorogenic acids and found them excellent inhibitors of microsomal lipid peroxidation with IC_{50} values ranged from 1.5 to 11.5 µM. Corresponding IC_{50} value for rutin was 26.5 µM. PPG extracted from the leaves of *Ligustrum purpuracens* used in China for the preparation of kundigcha (bitter tea) were identified as acteoside, isomers of ligupurpuroside, and osmanthuside B. The inhibitory effect of these substances on oxidation of human LDL (Cu-induced) and alpha-tocopherol (peroxyl radical-induced) was dose-dependent at micromolar concentrations and comparable with that of (-)-epicatechin gallate, a green tea antioxidant (99). Seven PPs from fresh rhizome of smaller galanga were extremely effective as inhibitors of autoxidation of methyl linoleate (65). *Ballota nigra* is a European medicinal plant with neurosedative properties. Its active substances are verbascoside, forsythoside, arenareoside, ballotetraside, and caffeoyl malic acid possessing scavenging properties against superoxide, hydrogen peroxide, hypochlorite, and hydroxyl radicals generated in cell-free systems and released from stimulated neutrophils. Their inhibitory concentrations were comparable to those of known antioxidant drugs, such as mesna and N-acetyl cysteine (12). In addition, the *Ballota nigra* PPs effectively

protected human LDL from Cu-induced oxidation without chelating copper ions (91).

Effects to Enzymes

PPs may act as nonsteroidal anti-inflammatory drug (NSAID)-like compounds as was revealed by the analysis of LPS-induce gene expression of cyclooxygenase-2 in cultivated macrophage line RAW 264. The COX-2 gene expression was dramatically inhibited by the synthesized dimer of ferulic acid (36). Plant-derived PPGs (derivatives of methoxyphenol and methoxycinnamic acid) were found as effective as arbutin in the selective inhibition of both tyrosinase activity and melanin synthesis in cultivated melanocytes without cytotoxic effects (95). PPGs from the roots of *Harpagophytum procumbens* inhibited human neutrophil elastase with IC_{50} 70 – 400 μM (6). Acteoside and its isomer showed potent inhibition of HIV-1 integrase with IC_{50} values 8-14 μM (49). PPs isolated from the rhizomes of *Alpinia galanga* inhibited NO production by LPS-stimulated mouse peritoneal macrophages with IC_{50} equal to 2.3 μM for 1'S-1'-acetoxychavicol acetate; 11,0 μM for 1'S-1'-acetoxyeugenol acetate; and 20 μM for both trans-*p*-hydroxycinnamaldehyde and trans-*p*-coumaryl diacetate (77). The structure-activity studies of the most potent inhibitor 1'S-1'-acetoxychavicol acetate showed that the *para* or *ortho* substitution of the acetoxyl and 1-acetoxypropenyl groups at the benzene ring was essential (71). Similarly, sesquiterpene PP derivatives isolated from the water/methanol extracts of the roots of *Ferula fucanensis* inhibited NO production and inducible NO synthase gene expression by a murine macrophage-like cell line (RAW 264.7), activated by a mixture of LPS + INF-gamma (78). In contrast, Xiong et al. (102) failed to find any effect of PPs such as acteoside, echinacoside, tubuloside, and cistanoside on the expression of iNOS mRNA, the iNOS protein level, or the iNOS activity in LPS-stimulated J774.1 macrophages. However, these PPs were effective NO scavengers, which may contribute to their anti-inflammatory action. The enhanced vasoconstriction induced by acteoside was attributed to inhibition of endothelial NO-synthase through activation of K^+ channels (94,100). In the early work, Farah and Samuelsson (21) found that coniferaldehyde, scopoletin, sinapaldehyde, and syringaldehyde inhibited prostanglandin synthase in a dose-dependent manner. Compared to aspirin, the inhibitory action of coniferaldehyde and scopoletin was about five times higher. In an attempt to find tumor inhibitors of plant origin, several PPs including verbascoside, calceolariosides A and B, forsythiaside, and acteoside have been found inhibitors of protein kinase C within the micromolar range of concentrations (0.6 – 9.3 μM) interacting directly with an active center of the enzyme and competing with ATP (35,105).

The literature data have demonstrated that cinnamic acid and its esters possessed remarkable anti-fungal properties against dermatophyte *Malassezia furfur* (32). This effect depended on the inhibition of 17-beta hydroxysterol dehydrogenase (17betaHSD), which is involved in the biosynthesis of steroids from the cell wall of fungi. The 17betaHSD inhibition occurs when PPs bind to the active center of the enzyme between nicotinamide moiety and tyrosine 212 thus, blocking the enzyme activity (29). The 17betaHSD is involved in the biosynthesis of steroid hormones in humans as well. Namely, 17betaHSD converts androstenedion into testosterone. The structural features of phytoestrogens, inhibitors of both oxidation and reduction catalyzed by the fungal 17beta HSD, are similar to the reported structural features of phytoestrogen inhibitors of human 17betaHSD types 1 and 2 as well (54). An attempt to discover new more potent topical antifungal drugs for the treatment of dermatomycoses (103) resulted in an array of slightly chemically modified PPs, which were highly effective against a broad spectrum of dermatophytes with MIC values between 0.5 and 50 microg/mL.

Estrogenic/Antiestrogenic Action of Phenylpropanoids

It is thought that some beneficial health effects of PPs such as reducing the risk of cancer, osteoporosis and cardiovascular diseases may depend on their action as estrogen agonists/antagonists via estrogen receptors (53). Estrogen receptor, a nuclear steroid receptor, binds estrogens and regulates the transcription of estrogen-responsive genes by interacting directly with DNA at estrogen response elements (ERE) of their promoters. Another pathway is to interact with transcription factors, such as AP-1 or NFκB bound to their cognate DNA sequences (83). There are two subtypes of estrogen receptor (ERα and ERβ) (55). ERα is mainly involved in promoting cell proliferation, whereas ERβ has a

counterproliferative, cytoprotective effect (59, 66, 67). ERα and ERβ differ in their biochemical action and tissue distribution. Ligands that bind ERα and ERβ may exhibit both agonism and antagonism depending on the type of estrogen responsive tissue, the ligand structure and concentration. The chemical structure of a ligand is an important determinant of its estrogen receptor affinity. Thus, the possession of two phenolic rings as well as a hydroxyl group at position 3 are necessary to recognize estrogen receptors and favor ER-ligand activities (20). There are numerous naturally occurring plant derived estrogens so called phytoestrogens, ligands for ER (9). Practically all of them belong to PPs group. The most known phytoestrogens are isoflavonoids (genistein, daizein, equol), lignans (enterolactone, enterodiol), coumestans (coumestrol), flavonoids (kaempherol, quercetin), stilbenes (resveratrol) (28), and PP glycosides (acteoside and martynoside). Majority of phytoestrogens compete better with estradiol for binding to the estrogen receptor beta than to ER alpha demonstrating estrogenic action at low concentrations (< 10^{-6}M) and antiestrogenic-cytotoxic action at high concentrations (>10^{-6}M) (55, 66). Two PP glycosides, acteoside and martynoside, isolated from the fresh aerial parts of *Verbascum macrurum* have been thoroughly investigated for their selective estrogen receptor modulating action (85). Both substances at concentration 10^{-9} – 10^{-7}M showed remarkable modulation of ERα and ERβ receptors transfected in Hela cells. Martynoside at low concentrations exhibited strong estrogenic effect on osteoblasts, antiestrogenic effect in MCF-7 breast cancer cells, and antiproliferative effect in endometrial cancer cells. Naturally occurring PPs, hinokiresinol and nyasol were found to possess appreciable estrogen receptor binding activity. The isomer cis-hinokiresinol displayed the highest activity, one order of magnitude greater than that of genistein. Binding to estrogen receptor, the PPs stimulated the proliferation of estrogen-dependent T47D breast cancer cells, and the stimulation was blocked by estrogen antagonist. So the PPs were the agonists of estrogen receptor (75).

Cytoprotective action of PPs connected to their antioxidative and chelating capacity

Three PPs, namely, 4-O-E-p-methoxycinnamoyl-alpha-L-rhamnopyranoside ester, *p*-methoxycinnamic acid and isoferulic acid have been found equally protective against CCl_4-induced hepatototoxicity (60). This model system is widely used for the study of in vitro and in vivo iron-independent lipid peroxidation and the effects of antioxidants. The alpha, beta-unsaturated ester moiety seemed to be essential for exerting hepatoprotection. Along with cytoprotection, all three PPs studied preserved normal levels of GSH and MDA and normal activities of glutathione disulfide reductase and glutathione-S-transferase in hepatocytes. The inhibition of hepatic apoptosis and the subsequent liver failure induced by D-galactosamine and LPS in mice has been shown for acteoside pre-administered subcutaneously (101). E-p-methoxycinnamic acid isolated from the roots of Scrophularia buergeriana protected cultural cortical neurons against free radical-mediated glutamate-induced cytotoxicity. The same compound was effective *in vivo* in the mouse model of amnesia induced by scopolamine (50, 51). The cognition-enhancing efficacy of the PP was superior to velnacrine, a conventional drug to treat Alzheimer disease. That allowed to suggesting its therapeutic value in alleviating certain memory impairments in dementia. Verbascoside and acteoside were found protective against 1-methyl-4-phenylpyridin ion-induced neurotoxicity in cultured neurons (87, 92). They attenuated neuronal apoptosis, caspase-3 activation, and the collapse of mitochondrial membrane potential. The data strongly indicated that both PPs may be feasible for the treatment of oxidative stress-related neurodegenerative diseases. 1'S-1'-acetoxychavicol acetate and 1'S-1'-acetoxyeugenol acetate markedly inhibited the ethanol-, aspirin-, and HCl-induced gastric mucosal lesions increasing the glutathione levels and endogenous prostaglandin production. The acetoxy group was of great importance for the gastroprotective action of the compounds (73). There is mountain of evidence that oxidized low-density lipoproteins (Ox-LDL) might be involved in the pathogenesis of atherosclerosis. In the model systems, Ox-LDL induce cytotoxicity in cultured endothelial cells. PP glycosides and caffeoyl-1-malic acid inhibited both the LDL oxidation by Cu^{2+} and 2,2'-azobis(2-amidinopropane) dihydrochloride and preserved cultural bovine aortic endotheliocytes against structural and functional damage triggered by Ox-LDL (69).

The photoprotective properties of PPs are commonly recognized. Verbascoside and linarin acetate protected against UV-B induced cellular

death, and verbascoside showed the largest sun protection factor (SPF) (3). Another PP, caffeic acid ester was found more effective than alpha-tocopherol in the protection of human diploid fibroblasts against UV-C- induced cytotoxicity, presumably due to its free radical scavenging and antioxidant activity (82).

Essential oils extracted from more than 25 different medicinal plants have been screened for their inhibition of platelet degranulation and damage in guinea pig and rat plasma (96). Since a significant correlation (54-86%) between antiplatelet potency and PPs content in the oils was found, the key role for this moiety in the control of hemostasis was suggested. As a confirmation of the importance of PP moieties in defining this kind of biological activity, traditional Chinese medicine preparations (Dang Gui, Duh eng, and Da hua hong jing) identified as remedies to prevent blood stasis and thrombus formation were analyzed for their structure/effect relationships. The PPs isoeugenol, ferulic acid, elemicin, myristicin, ethyl gallate, and dihydroxyacetophenon were recognized as essential platelet protecting compounds. Many of these substances share both the shikimic acid biosynthetic pathway and a common PP backbone (106).

Anti-tumor activity of PPs in cultured cancer cells

Six new PPs have been recently isolated from the ethanol extract of *Smilax china* stems, widely used in traditional Chinese medicine (56). They were highly cytotoxic to several human tumor cell lines. Moreover, they significantly inhibited angiogenesis in confrontation cultures consisting of stem cell-derived embryoid bodies and prostate tumor spheroids by decreasing expression of matrix metalloproteinase–2 and 9 and reducing intracellular ROS levels (98). Induction of apoptosis in promyelocytic leukemia HL-60 cells by micromolar concentrations of acteoside has been reported (42). Antiproliferative effect against cultured murine melanoma, human adenocarcinoma, and uterine carcinoma cells has been shown for PP glycosides such as acteoside, isoacteoside, martynoside, diacetylmartinoside, and chlorogenic acid (1,80). Resveratrol, a chemopreventive molecule, inhibited the proliferation of tumor cells of different etiologies. It blocked the cell cycle and induced apoptosis in MCF-7 breast tumor cells interacting with the estrogen receptor ERα-dependent phosphoinositide 3-kinase pathway (86). Interesting that resveratrol induced apoptotic death in MCF-7, which was mediated by Bcl-2 downregulation. Therefore, Bcl-2 and NF-kB have been considered as potential targets for the chemopreventive activity of resveratrol in estrogen-responsive tumor cells. Resveratrol was found to inhibit growth and induce apoptosis in human cancer cells through both CD95-dependent and –independent mechanisms (19, 45). Exposure of human gastric adenocarcinoma cells to verbascoside resulted in the tumor cell re-differentiation, the lack of their malignant phenotype, and the reduction of their tumorigenicity (62). Recent results suggested that verbascoside-mediated cell differentiation and apoptosis may be affected by telomere-telomerase-cell cycle dependent mechanism (104). The authors have shown that verbascoside inhibited telomerase activity, reduced telomere length, and arrested tumor cell cycle in G2/M phase. Ito and co-authors (43) have shown some years ago that several PPs isolated from plants of Rutaceae possessed remarkable inhibitory properties on Epstein-Barr virus early antigen activation induced by TPA. Later on, six PPs from Illicium tashiroi plants showed similar effect in the culture of Raji cells (44), two of them, having prenyl group, were two-fold more active anti-tumor promoting inhibitors than β-carotene, a commonly used standard reference in cancer prevention studies.

In vivo anti-tumor action of PPs

The PPGs with antioxidant activities, such as acteoside and martynoside, exhibited antiproliferative, cytotoxic, antimetastatic and immunomodulatory properties (2, 62, 84). Caffeic acid and its phenethyl ester, being administered subcutaneously or orally, suppressed the growth and metastasis of HepG2 tumor xenografts in nude mice *in vivo* (10). The anti-tumor effects were explained by selective suppression of the angiogenic enzyme matrix metalloproteinase-9 activity and its transcriptional down-regulation via NFκB pathway. Acteoside exhibited antimetastatic effect in a mouse model of lung metastasis of injected intravenously B16 melanoma cells (84). There is a growing interest in lignans and their synthetic derivatives in cancer chemotherapy. Although their molecular backbone consists only of two phenylpropane units (C6-C3), lignans show enormous structural and biological diversity. According to mountain of publications,

lignans possess remarkable anticancer, antioxidant, antimicrobial, anti-inflammatory, and immunosuppressive properties (For review see 89).

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