MINIREVIEW

Bioavailability of chalcones

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Abstract

Epidemiological evidence suggests that diets rich in fruits and vegetables decrease the risk of premature mortality from major clinical conditions, including cancer and heart disease. However, it is not yet clear which components or combination of components in fruit and vegatables are protective and what is their mechanism of action is. Phenolic compounds are important compounds because of their contribution to human health and their multiple biological activities. Although these compounds are not a panacea for good health, some of their beneficialt activities presented in this short review showed their importance and their possible usage in the prevention of various diseases *(Tab. 1, Fig. 1, Ref. 42)*.
Key words: polyphenols, chalcones, cancer, heart disease, bioavailability.

In recent years, there has been is a growing interest in polyphenolic compounds and their presumed role in the prevention of various degenerative diseases, such as atherosclerosis, cancer and chronic inflammation.

The term polyphenolic compounds refers to the main classes of secondary metabolites in fruits, vegetables, and beverages (Tab. 1). Polyphenols are important compounds because of their contribution to human health and their multiple biological effects, such as antioxidant activity, antimutagenic and/or anticarcinogenic activities, and antiinflammatory actions. The importance of antioxidant activities of polyphenolic compounds and their possible usage in processed foods as a natural antioxidant have been appreciated more reached a new high in recent years.

Absorption, metabolism and bioavailability of food phenolics

Karakaya (2004) summarized the factors that effect the absorption, bioavailability and metabolism of food phenolic compounds. According to Karakaya, partition coefficients seem to play an effective role in the absorption of hydrophobic phenolics that have sugar or organic acid and ester linked substitutions in their structure, whereas hydrophilic phenolic having similar structure are degraded by the esterases produced by the colonic microflora in the colon and cannot be absorbed in the upper part of gastrointestinal tract (Scalbert and Williamson, 2000; Olthof et al, 2001; Rechner et al, 2001; Adam et al, 2002; Rondini et al, 2002). The number of sugar molecules seems to play an effective role in the absorption of phenolics. If the phenolics contain a sugar molecules, such as glucose, galactose, or xylose, they will be absorbed through the small intestine by the cytosolic ß-glucosidase/lactase phlorizin hydrolase. The absorption is also related to the specificity of the carriers (Hollman et al, 1997; Gee et al, 2000; Hollman and Arts, 2000; Hollman, 2001; Murota et al, 2002).

Phenolics, which have rhamnose in their molecule, cannot be absorbed through the small intestine. They are degraded by the action of rhamnosidases produced by the colonic microflore. Acylated flavonoids, such as (-)-epicatechin and (-)-epigallocatechin, are absorbed without deconjugation and hydrolysis (Manach et al, 1999; Hollman and Arts, 2000; Scalbert and Williamson, 2000). Isoflavone aglycones were absorbed from the stomach, while their glycosides were absorbed from the duodenum (Murota et al, 2002). Dihydrochalcones were absorbed in the small intestine of rats following the conjugation and, thus, could be recovered intact in plasma (Crespy et al, 2001 a, b; Glöck et al, 2001). Studies showed that phenolic compounds are metabolized by the deconjugation and reconjugation reactions. Phenolics are hydrolyzed to their free aglycones, then are conju-

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Tab. 1. Classification of polyphenolic compounds with characteristic samples.

Main structure	Class	Samples
C_6	Simple phenol	Catechol, hydroquinone, resorcinol
	Benzoquinones	
C_6-C_1	Phenolic acid	*p*-Hydroxybenzoic acid, salicylic acid
C_6-C_2	Phenylacetic acids	*p*-Hydroxyphenylacetic acid
C_6-C_3	Cinnamic acid	Caffeic acid, ferulic acid
	Phenylpropenes	Eugenol, myristicin
	Coumarins	Umbelliferone, aesculetin, scopolin
	Chromones	Eugenin
C_6-C_4	Naphthoquinones	Juglone
C_6-C_1-C_6	Xanthones	Mangostin, mangiferin
C_6-C_2-C_6	Stilbenes	Resveratrol
	Anthraquinones	Emodin
C_6-C_6-C_6	Flavonoids	
	Flavones	Sinensetin, nobiletin, tengeretin, isosinensitin, various polymethoxylated flavones
	Flavonols	Quercetin, kaempferol
	Flavonol glycosides	Rutin
	Flavanonols	Dihydroquercetin and dihydrokaempferol glycosides
	Flavanones	Hesperitin, naringenin
	Flavanone glycosides	Hesperitin, neohesperidin, narirutin, naringin, eriocitrin
	Anthocyanins	Cyanidin glycosides including acylated derivatives, glycosides of pelargonidin, peonidin, delphinidin, petunidin, malvidin including acylated forms, glycosides of cyanidin, cyanidin 3-glucoside and 3-rutinoside
	Flavanols(catechins)	(+)-Catechin, (-)-epicatechin, (+)-gallocatechin, (-)-epigallocatechin,
	Chalcones	Phloretin derivatives, phloridzin, arbutin, phloretin glucosides, chalconaringenin
	Isoflavones	Daidzein, genistein
$(C_6$-$C_3)_2$	Lignins	Pinoresinol
$(C_6$-C_3-$C_6)_2$	Biflavonoids	Agathisflavone

gated by methylation, sulfation, glucuronidation, or a combination. Dietary phenolics are usually consumed in lower than hundreds of milligrams in a diluted dose and when food are administered at pharmacological dose they are found in the free form in the blood. The dose will also determine the primary site of metabolism. Large doses are metabolized primarily in the liver, however, small doses may be metabolized in the intestinal mucosa. The liver has a secondary role in the metabolism of small doses (Scalbert and Williamson, 2000). It was shown that phenol glycoside were first deglycosilated and then converted to glucuronides or sulfates, with or without methylation, in studies using rats or isolated rat intestine (Hollman et al, 1997; Manach et al, 1998; Shimoi et al, 1998; Gee et al, 2000; Sesink et al, 2001; Adam et al, 2002; Rondini et al, 2002; Murota et al, 2002). The existence of conjugation reactions in the metabolism of phenolics were also shown in human studies (Adlercreutz et al, 1995; Manach et al, 1998; Rechner et al, 2001; Felgines et al, 2002; Wu et al, 2002). However, the data available on phenolics bioavailability are still limited, Scalbert and Williamson (2000) proposed the possible pathway that allows the prediction of uptake of phenolics from the diet (Fig. 1).

Chalcones

Chalcones are flavonoids lacking a heterocyclic C ring. Among flavonoids this category of flavonoids have been identified as interesting compounds that is associated with several biological activities (Calliste et al, 2001). The most common chalcones found in foods are phloretin and its glucoside phloridzin (phloretin 2'-*0*-glucose), chalconaringenin, and arbutin. Phloretin and phloridzin are characteristic of apples. Chalconaringenin is characteristic of tomatoes, and arbutin is characteristic of pears. Arbutin is also found in strawberry and bearberry, in wheat, in wheat products, and in trace amounts in tea, coffee, red wine, and broccoli (Robards et al, 1999; Clifford, 2000). Studies on the bioavailability of chalcones from food sources are limited but tested synthetic chalcones have reported to have a wide ranges of biological properties. Chalcones are readily synthesized by the

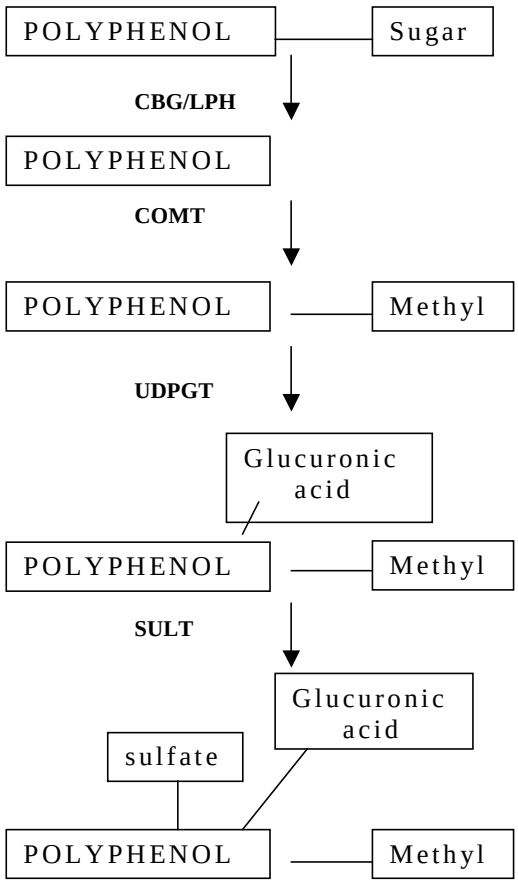

Fig. 1. Possible metabolic pathway of phenolics (Scalbert and Williamson, 2000). CBG – cytosolic ß-glucosidase, LPH – lactase phlorizin hydrolase, COMT – catechol-0-methyltransferase, UDPGT – glucuronosyltransferase, SULT – phenol sulfotransferases.

base-catalysed Claisen-Schmidt condensation of an aldehyde and an appropriate ketone in a polar solvent like methanol. The method is versatile and convenient, although yields may ve variable.

In an effort to develop potent anti-inflammatory and cancer chemopreventive agents were synthesized a series of chalcones (Won et al, 2005). These products were tested for their inhibitory effects on the activation of mast cells, neutrophils, macrophages, and microglial cells. It is conceivable that mast cells, neutrophiles, and macrophages are important players in inflammatory disorders. Activation of microglial cell also play a crucial role in inflammatory diseases of the CNS. Thus, inhibition of the activation of these inflammatory cells appears to be an important therapeutic target for small molecule drug design for the treatment of inflammatory diseases. Nitric oxide (NO) plays a central role in macrophage-induced cytotoxicity and expressed NO may contribute to the pathophysiology of septic shock. The excessive production of NO also can destroy functional normal tissues during acute and chronic inflammation, stimulates the production of a wide variety of inflammatory mediators such as tumor necrosis factor (TNF-α) and interleukin 1ß (IL-1ß) (Laskin and Pendino, 1995). This phenomenon is also closely related mechanistically to carcinogenesis. Thus, inhibitors of NO production in macrophages are potential anti-inflammatory and cancer chemopreventive drugs. Won et al (2005) suggests that 2',4-dihydroxychalcone, 2'-hydroxy-2-thienylchalcone, 2'-hydroxy-3-tienylchalcone, and 2',5'-dihydroxy-indol-3-yl-chalcone have anti-inflammatory effects and 2'-hydroxy-3,4-dichlorochalcone and 3,5-di-tert-butyl-2',4,5'-trihydroxychalcone are potential anti-inflammatory and cancer chemopreventive agents.

Some chalcones have been observed to inhibit NO production in lipopolysaccharide (LPS) and interferon-activated microglial cells (Rojas et al, 2002). These chalcones with methoxy substituents on ring B and fluorinated substitutionsents on ring A did not scavenge NO radicals but inhibited the expression of inducible nitric oxide synthase (iNOS), the enzyme responsible for NO production when cells were confronted by inflammatory stimuli. The potent inhibitory effect of 2',5'-dihydroxychalcones on NO production in LPS-activated macrophage, probably through the suppression of iNOS protein expression reported Ko et al (2003). In this study demonstrated that most of the 2',5'-dihydroxychalcones have also anti-inflammatory effects.

Some interesting finding were reported for a series of 2',5'-dihydroxychalcones. Most of the chalcones exhibited cytotoxic activity against a variety of tumour cell lines (B16 murine melanoma, HCT 116 human colon cancer, A31 human epidermoid carcinoma), as well as a non-tumour endothelial cell line (HUVEC human umbilical venous endothelial cells) in the low micromolar range (Nam et al, 2003). The formation of new blood vessels from endothelial cells (angiogenesis) is a prerequisite for solid tumour growth and inhibition of angiogenesis would limit the growth and proliferation of cancer tumours. Thus, this report suggests that chalcones may be angiogenesis inhibitors (Nam et al, 2003).

Recent reports documenting the potential of chalcones interfering at the transcription level by inhibiting the p53-MDM2 interaction (Stoll et al, 2001; Kumar et al, 2003). Chalcones were shown to bind to the tryptophan pocket of p53 binding site of MDM2 (mouse double minute 2) oncogene and to promote dissociation of the p53/MDM2 complex. The MDM2 oncogene is over-expressed in human breast cancer. It inhibits the tumor suppressor protein p53 by binding to the p53 transactivation site, leading to disregulation of the cell cycle. Thus, disruption of the p53/MDM2 complex is considered an attractive target in cancer therapy.

Particularly interesting properties of chalcones are induction of apoptosis (De Vincenzo et al, 2002; Saydam et al, 2003) and their ability to uncouple mitochondrial respiration thus causing a collapse in mitochondrial membrane potential (Sabzevari et al, 2004). The authors noted that chalcones with fewer hydroxyl groups on rings A and B were more effective in this regards, as compared to chalcones with more hydroxyl groups. This difference was attributed to the acidity of the phenolic hydroxyl groups. One of the most widely cited mechanisms by which chalcones exert their cytotoxic activity is that of interference with the mitotic phase of the cell cycle. Edwards et al (1990) proposed a hypothetical basis for the anti-mitotic activity of chalcones. Indeed, they found a large number of methoxylated chalcones with antimitotic activity against HeLa cells.

Chemoprotection is an approach that seeks to arrest or reverse the process of carcinogenesis through the use of pharmacological agents. Chemoprotection may occur by various mechanisms and chemoprotective by chalcones may be a consequence of their antioxidant properties, mediated via inhibition or induction of metabolic enzymes, by exert an anti-invasive effect or a reduction in nitric oxide production. One report noted that chalcones with good antioxidant activities were cytotoxic against tumour cell lines and reduced ascites tumours development in mice (Anto et al, 1995). 2'-Hydroxychalcone was identified as a superior antioxidant compared to the unsubstituted chalcone and 2',2-dihydroxychalcone in another investigation (Dinkova-Kostova et al, 2001).

Phloretin [(ß-4-hydroxyphenyl)-1-(2,4,6-trihydroxypropiophenone)] and its glucoside, phloridzin (phloretin-2-ß-D-glucose) are dihydrochalcones which do not have α-ß double bound. Phloretin is a potent antioxidant in peroxynitrite scavenging and the inhibition of lipid peroxidation (Rezk et al, 2002). The concentration of phloretin needed to scavenge of the peroxynitrite (IC_{50}) is 3.1 μM and the concentration of phloretin needed to inhibit 50 % of the lipid peroxidation is 24 μM. Occupation of 2-OH by glucose decreased the antioxidant activities of phloridzin 18 times in comparison to phloretin. The hydroxyl groups of the sugar moiety have no role in the antioxidant activity of phloridzin, since the IC_{50} of glucose is more then 1000 μM for either peroxynitrite scavenging or inhibition of lipid peroxidation. Phenol is a very poor antioxidant. Introducing more OH groups in *meta* position, similar to the A-ring of phloretin, gives resorcinol or phloroglucinol that have a substantial higher antioxidant activity compared to phenol, however, it is still far less then that of phloretin. In comparison with structurally related compounds it was found that the activity of phloretin does not reside only in the three hydroxyl groups of ring A. Their activity is enhanced by the carbonyl group in phenol (giving 2-hydroxyacetophenone) reduces the antioxidant activity, whereas introduction of the same group in phloroglucinol (giving 2,4,6-trihydroxyacetophenone) increases the antioxidant activity. The activity of 2,4,6-trihydroxycetophenone is comparable of that of phloretin. Surprisingly, the antioxidant activity of 2,6-dihydroxyacetophenone is comparable to the of 2,4,6-trihydroxyacetophenone, whereas 2,4-dihydroxyacetophenone is a very poor antioxidant. The potent activity of 2,6-dihydroxyacetophenone is due to stabilisation of its radical via tautomerisation. The antioxidant pharmacophore in the dihydrochalcone phloretin, i.e., the 2,6-dihydroxyacetophenone group, is different from the antioxidant pharmacophores previously reported in flavonoids.

The potent antioxidant activity of several hydroxychalcones were evaluated for their ability to scavenge DPPH (1,1-diphenyl-2-picrylhydrazyl radical) and hydroxyl free radicals (Calliste et al, 2001). However, when were tested for antiproliferative activity against a human breast cancer cell line (MCF-7), no activity was observed for naringenin chalcone and phloretin. The other chalcones (including 2'hydroxychalcone) showed a biphasic response-antiproliferative activity at high concentrations (10.50 μM) and promoting cell growth at lower concentrations (0.01–1 μM).

Cytochrome P450 enzymes activate a large number of procarcinogens to reactive intermediates that subsequently interact with cellular nucleophiles to trigger carcinogenesis. Thus, compounds that inhibit these enzymes are potentially useful chemoprotective agents. Chalcones were found to be good inhibitors of CYP 1A activities in hepatic microsomes isolated from mice (Machala et al, 2001). Prenylated chalcones were found to have anti-invasive properties (Mukherjee et al, 2001). Anti-invasive properties may involve interference with the formation of cellular protein complexes that are involves in invasion. The exact nature of these complexes was not known but the authors proposed that activation of E-cadherin/catenin, which is known to have invasion suppressor properties, was not involved (Parmar et al, 2003).

Chalcones inhibiting TNF-α induced VCAM-1 (vascular cell adhesion molecule-1 expression at IC_{50} values in the micromolar range have also been reported (Meng et al, 2004). The authors noted a "methoxy effect" in their structure-activity analysis, namely that the presence of at least two methoxy groups on ring A led to compounds with good inhibitory potency.

Chalcones continue to attract considerable scientific attention because of their association with a variety of biological activities. In this article have been reviewed only some of them. Chalcones normally exert their activities in the middle to low micromolar range, with fewer examples of activity in the nanomolar range. Skilful structural manipulation of the chalcone framework may yet narrow its range of biological activity and enhance its potency for a targeted pharmacological profile.

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