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Pharmacological and bioanalytical aspects of galangin-a concise report

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ABSTRACT

Flavonoids are low molecular weight plant phytoconstituents, widely distributed in the leaves, seeds, bark and flowers of plants. It has various pharmacological activities and protects plants against ultraviolet radiation, pathogens, and herbivores. Most of the beneficial health effects of flavonoids are mainly due to its antioxidant properties. Galangin is a flavonol found in honey, *Alpinia officinarum*, *Helichrysum aureonitens* and in propolis. It showed anti-mutagenic, anti-clastogenic, anti-oxidative, radical scavenging, metabolic enzyme modulating activity and effective against certain types of cancers. The present review described the pharmacological activity and bioanalytical aspects of galangin, which may be benificial to the researchers who wants to explore the hidden potential of galangin.

1. Introduction

Flavonoids are polyphenolic compounds, mainly found in plants materials as well as in human diet. The bioavailability and biological properties of flavonoid have got great interest during the last two decades because of its unique properties. *In vitro* studies suggest it can protect body from reactive oxygen species (ROS) such as hydroxyl, alkoxyl, or peroxyl radicals. It can protect the body from aging, cancer, and cardiovascular diseases[1]. Flavonols are a major group of flavonoids, which is found mainly in the form of glycosides in plants. The most common aglycons are quercetin, myricetin, galangin and kaempferol attached with glucose, galactose and other sugar moieties. When flavonols are present in the diet as aglycons, they are partially absorbed in the stomach[2]. Galangin, a member of flavonol class of flavonoid, present in honey, *Alpinia officinarum*, *Helichrysum aureonitens* and in propolis (Natural composite balsam produced by honeybees from the gum of various plants) in the significant level (Figure 1). Galangin showed various pharmacological activity such as anti-mutagenic, anti-clastogenic, anti-oxidative, radical scavenging, metabolic enzyme modulating and anticancer activity[3-5]. Galangin has three hydroxyl groups on its carbon rings, has enzyme modulating activities and can suppress the genotoxicity of chemicals[6]. Previous studies demonstrated that, galangin is a potent inhibitor of the aryl hydrocarbon receptor. They have also been shown to possess a variety of biological activities at non-toxic concentrations in organisms[7].

2. Pharmacological activity of galangin

2.1. Antimicrobial activity

Antibacterial activity of galangin was investigated against 17 strains of 4-quinolone resistant *Staphylococcus aureus* using an agar dilution assay. The strain which possessed an amino acid alteration in the GrlB subunit of topoisomerase IV had increased susceptibility to galangin. The topoisomerase IV enzyme may therefore be implicated

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in the antibacterial mechanism of action of galangin[4]. Antimicrobial activity of galangin against 16 *Campylobacter jejuni* clinical isolates and several Gram-positive and Gram-negative human pathogens were investigated. Galangin showed highest percentage of sensitivity among *Campylobacter jejuni* strains[8]. Aggregatory effect of galangin on bacterial cell was investigated. In preparatory time-kill assays, galangin was found to reduce colony counts of *Staphylococcus aureus*. Light microscopy study showed significant increases in the number of large clusters of bacterial cells in populations treated with the flavonol[9]. The bioactivity of the flavonoids galangin 3-methyl ether was investigated *in vitro* against amastigote stages of *Leishmania amazonensis* and found to have significant activity[10]. A number of mechanisms are involved in the antimicrobial effects of herbs, including inhibition of beta -lactamase, which was found in the herbal phytoconstituents galangin[11].

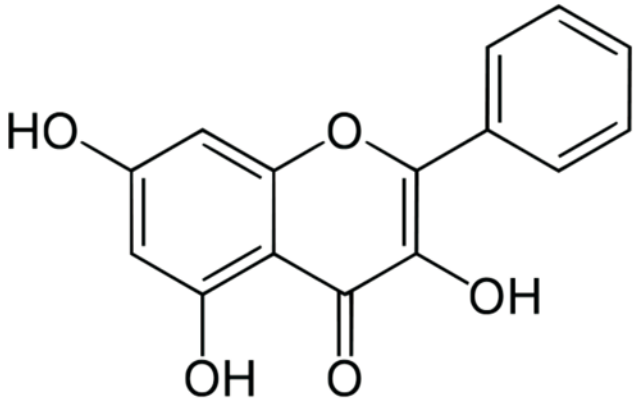

Figure 1. Chemical structure of galangin.

2.2. Anticancer activity

Galangin suppresses beta-catenin response transcription, which is aberrantly up-regulated in colorectal and liver cancers, by promoting the degradation of intracellular beta-catenin. Galangin down-regulated the intracellular beta-catenin levels in cancer cells with inactivating mutations of adenomatous polyposis coli or Axin[5]. Galangin was found to be effective as anti-proliferative, and apoptotic agent in Bcr-Abl expressing K562 and KCL22 cells and in imatinib mesylate resistant K562-R and KCL22-R cells. Galangin arrests the cells in G_0-G_1 phase of cell cycle and a decrease in pRb, cdk4, cdk1, cycline B levels. It also caused a decrease in Bcl-2 levels and markedly increased the apoptotic activity of imatinib both in sensitive or imatinib-resistant Bcr-Abl$^+$ cell lines[12]. The effects of galangin on the proliferation of an ER-, AhRhigh line and Hs578T were studied. Galangin inhibited transition of cells from the G_0/G_1 to the S phases of cell growth. Galangin is a strong inhibitor of Hs578T cell proliferation that likely mediates this effect through a relatively unique mechanism[7]. The influences of galangin on induction of differentiation in a human esophageal adenocarcinoma (OE33) cell line were studied. Galangin inhibits proliferation of OE33 cells in a dose-and time-dependent manner. The results showed that up-regulation of 14-3-3 sigma and down-regulation of cyclin B1 and cyclin D1 at the mRNA and protein levels were observed in OE33 cells treated with galangin[13]. The *in vitro* preferential cytotoxicity of galangin was evaluated against a PANC-1 human pancreatic cell line. Galangin displayed the most potent preferential cytotoxicity in the nutrient-deprived medium and triggered apoptosis-like morphological changes in PANC-1 cells[14]. Galangin was found to be inhibitory effect against cancer cells[15]. Effect of galangin on the viability of A549 cells and on TNF- alpha inhibitory activity was investigated. Based on MTT assay, it was found that galangin can inhibit growth of human lung cancer cells. It also significantly inhibited TNF- alpha gene expression in A549 cells[16].

2.3. Antioxidant activity

In vitro and *in vivo* antioxidant activity indicate that galangin has anti-oxidative and free radical scavenging activity and is capable of modulating enzyme activity and suppressing the genotoxicity of chemicals[3]. Liposomes containing flavonols (galangenin) was evaluated for their antioxidant activity and found to have significant antioxidant activity and is dependent on concentration and chemical structure of active compound[17]. Honey is rich in phenolic compounds (galangin), which act as natural antioxidants and are becoming increasingly popular because of their potential role in contributing to human health[18]. Antioxidant activity of galangin was measured and found to showed significant DPPH radical scavenging activity[19]. A comparison of alizarin red and fluorescein as target molecules in oxygen radical absorbance capacity-like methods is reported and showed that galangin decreased alizarin red initial consumption rate[20]. Galangin was found to have significant antioxidant potential[21]. Honey has been used since long time both in medical and domestic needs. Antioxidant property of honey was investigated and found to have significant antioxidant activity[22]. Antioxidant activity of various components of propolis was investigated and found that galangin possessed significant antioxidant activity[23]. Mitochondria are important intracellular sources and targets of ROS. Antioxidant activity of galangin on Fe^{2+}/citrate-mediated membrane lipid peroxidation in isolated rat liver mitochondria was investigated. Results suggest that 2,3-double bond in conjugation with the 4-oxo function in the flavonoid structure are major determinants of the antioxidant activity of flavonoids in mitochondria[24]. The modulatory effect of galangin on rabbit PMN oxidative metabolism, specifically stimulated via Fc gamma R, CR or both classes of receptors, was evaluated by luminol- and lucigenin-dependent chemiluminescence assays[25].

2.4. Antiinflamatory activity

Topical anti-inflammatory activity of selected flavonoids commonly found in propolis was investigated. The reduction in croton oil-induced oedema in a mouse model, after topical application of galangin for 3 h, was more than 50%, while after 6 h of treatment the reduction was less than 50%[26]. Various fractions obtained from *Parthenium hysterophorus* showed antiinflammatory activity and contain gangline as active constituent[27]. Inhibition of human neutrophil degranulation by galangin was evaluated using released elastase as a biomarker. Inhibitory potency of galangin was found to be significant[28].

2.5. Enzyme modulating activity

Galangin, a dietary flavonoid, inhibited cytochrome P450 1A1 (CYP1A1) expression induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). This inhibitory activity remained after permeating human intestinal epithelial Caco-2 cell monolayers, but was reduced when galangin permeated TCDD-pretreated Caco-2 cells[29]. Flavonoids were tested for their potential function in inhibiting acetylcholinesterase (AChE) activity from the brain *in vitro*. Among all the tested flavonoids, galangin showed an inhibitory effect on AChE activity with the highest inhibition[30]. Structure-function relationships for the inhibition of human cytochrome P450s 1A1, 1A2, 1B1, 2C9, and 3A4 by 33 flavonoid derivatives were studied, galangin was found to be the most potent in the tested compounds[31]. Modifications of beta-naphthoflavone (beta-NF)-induced CYP1A1 expression by flavonoids in mouse hepatocytes in primary culture were investigated. Galangin enhanced beta -NF-induced CYP1A1 expression at 24 h, but considerably suppressed it at 9 h[32]. The effect of flavonoids on coumarin 7-hydroxylation, an activity marker of an important human liver cytochrome P450 isoform, cytochrome P450 2A6 (CYP2A6), was investigated. Galangin was found to have significant activity[33]. Effect of a group of 20 structurally related flavonoids on the production of vascular endothelial growth factor (VEGF) induced by hypoxia in NCI-H157 cells were investigated. Structure-activity relationships demonstrated that galangin induced HIF-1 alpha expression while reducing those of VEGF[34]. Dietary benefits of bioflavonoids to the inhibition of ATP synthase were investigated and found that galangin has significant inhibitiory potential[35]. Galangin reversibly inhibited human butyrylcholinesterase (BChE, EC 3.1.1.8) and found to be the most potent BChE inhibitor among the tested flavonoids, which showed 12 times higher preference for binding to BChE than to the related enzyme human acetylcholinesterase (AChE, EC 3.1.1.7)[36].

2.6. Effect on metabolic process

Effects of galangin on oxidative stress, inflammatory cytokine levels and NF-kappa B activation in fructose-fed rat liver were investigated. Galangin prevented the rise in plasma glucose, insulin and triglycerides and improved insulin sensitivity, however, treatment with galangin downregulated the expression of these cytokines. Translocation of NF-kappa B into the nucleus was also increased in fructose diet-fed animals, which was prevented by galangin[37]. Fluorescence quenching was used to show that the flavonols galangin, bearing different numbers of hydroxyl substituent on the aromatic rings, may inhibit dNTP binding of the primary replicative DnaB helicase of *Klebsiella pneumoniae* (KpDnaB). Galangin significantly decreased the binding ability of KpDnaB to dATP, whereas the binding affinity of KpDnaB to dGTP that was almost unaffected[38]. A series of fluorescence polarisation measurements showed that flavonoids structure-dependently acted on the deeper regions of lipid bilayers to decrease membrane fluidity. Galangin meeting such a structural requirement inhibited the proliferation of tumour cells together with rigidifying cell membranes[39]. The bioavailability of flavonoids in biological samples has conventionally been quantified by high-performance liquid chromatography and mass spectrometry. The autofluorescence of galangin appeared stronger in the nucleus than cytoplasm, suggesting that they are incorporated into the cells and accumulated in the nucleus[40]. The effects of Chinese propolis and its constituents galangin against tunicamycin-induced neuronal cell death in SH-SY5Y cells was invetigated[41]. Hypoxia-inducible factor-1 alpha (HIF-1 alpha) is the regulatory subunit of the heterodimeric transcription factor HIF-1 that is the key regulator of cellular response to low oxygen tension. Galangin induces HIF-1/2 alpha accumulation and this effect is completely reversed by additional iron ions[42]. The interactions of some natural flavonols (galangin, kaempferol and quercetin) with alpha, beta- and gamma-Cds have been investigated[43]. Effect of the flavonoid galangin in isolated rat thoracic aortic rings was investigated. Galangin relaxed aortic rings with or without endothelium. Galangin inhibited the contractile response to PE, either in presence or in absence of external calcium, and to KCl. Galangin caused nitric oxide release from aortic rings[44]. The impacts of Zn^{2+} ion on interactions of flavonols galangin with bovine serum albumin in aqueous solution were studied by fluorescence quenching technique. The results exhibited that Zn^{2+} ion affected significantly the interactions and the effect was distinct for the flavonol bearing different number of B-ring hydroxyl[45]. Propolis, the material used by bees to protect their hives, is a glue-like substance composed of plant resins, bee waxes and pollens. The propolis from Amaicha del Valle and galangin were found to be stable from room temperature to 120℃[46].

3. Analytical techniques

High-performance liquid chromatography (HPLC) method was developed and used for the determination of galangin of Rhizoma *Alpiniae Officinarum* using phenomenex Gemini

C18 column and methanol-0.4% phosphoric acid (60:40) as a mobile phase whereas detection wavelength was 360 nm[47]. The analysis of flavonoids (galangin) in unifloral honeys by HPLC coupled with coulometric electrode array detection was developed[48]. Flavonoids (galangin) from 20 propolis extracts have been determined using HPLC analysis[49]. Ultra performance liquid chromatography coupled with photodiode array detector was used to identify and quantify the phenolic compounds in the spice extracts in China. Galangin was identified as the principal phenolic component and the main contributor to the antioxidant capacity[50]. The chromatographic analysis showed the presence of galangin of propolis on *Lactobacillus fermentum*[51]. The flavonoid profiles of seven types of Slovenian honey were analysed and was found to contain significant amount of galangin[52]. Propolis ethanolic extract was separated and purified by liquid-liquid extraction and thin layer chromatography and the most active band was subjected to HPLC-MS/MS to identify the antifungal compounds. Galangin was found to be the most bioactive components found in the extract[53]. Thin layer chrommatography, ultra violet-high phase liquid chromatography and gas chromatography-mass spectrometry of propolis extract was carried out and found to contain galangin as main active constituents[54]. Analysis of polyphenol content of fruit and leaves of *Ficus carica* L revealed the presence of galangin as a main phytoconstituents[55]. Total phenolic content was measured by the Folin-Ciocalteu methods using a mixture of pinocembrin and galangin as internal standards[56]. Phenolic compounds present in *Lolium multiflorum* Lam. were isolated and characterized as galangin[57]. A simple, sensitive and specific high-performance liquid chromatography-UV method has been developed for the quantification of the bioactive phenolic compounds in Chinese propolis, galangin was found to be as one of the main active phytoconstituents[58]. The chemical characterization as well as the assessment of geographical origin of propolis from several areas of the Provincia de San Juan (Argentina) is reported. Six main flavonoids were isolated and identified from the propolis samples and galangin was found to be one of the active constituents[59]. Seven phenolic compounds in bee pollen sample were detected by HPLC analysis and found to present galangin as active constituents[60]. Aqueous acetone extracts prepared from five *Indigofera* species of Burkina Faso, namely *Indigofera colutea* (Burm.) Murril., *Indigofera macrocalyx* Guilld et Perr., *Indigofera nigritana* Hook f., *Indigofera pulchra* willd. and *Indigofera tinctoria* L., were investigated for their phytochemical composition and found to contain galangin as one of the active constituents[61]. Determination of the flavonoids in monofloral sage (*Salvia officinalis* L.) honey which is characteristic and specific for the area of Croatian coast and islands. HPLC analysis showed that all examined sage honey samples contain galangin as active component[62]. The chemical profile of propolis samples from the same colonies of *Apis mellifera* in San Juan, Cuyo Region, Western Argentina, was compared every month during one year using 2 collection methods. All samples showed a similar profile and galangin were identified as the bioactive flavonoid in all samples[63]. Propolis is a sticky and resinous substance that honey bees collect from different plant sources. After extraction and separation of waxes and lipids, the samples were analysed by gas chromatograph mass spectrometer (GC-MS) and obtained mass spectra were compared with standards. The results showed the presence of galangin-3-methyl ether as one of the constituents[64]. Flavonoids galangin were analysed in grape, pistacio and propolis samples from Sicily, Italy, by HPLC[65]. A rapid fingerprint method was developed for investigating and inferring geographical origin of Chinese propolis by using HPLC-ultraviolet detection (HPLC-UV). 120 samples were analyzed, galangin was found to be present in the sample[66]. Chemical composition of propolis from three different arid and semiarid regions of Sonora, Mexico were investigated and found to contain galangin as active constituents[67]. A reverse phase LC-DAD-MS method for quantification of phenolic acids and flavonoids in propolis raw materials was developed. European, Chinese and Argentinean propolis contain significant amount of galangin[68]. The application of mixed micellar electrokinetic chromatography for the seperation of galangin was developed and used[69]. Three spectrophotometric methods for the quantitative determination of different flavonoid groups and total phenolics in *Croatian propolis* samples were optimised and validated using galangin as a standard[70]. LC-DAD-ESI/MS was used to identify 23 flavonoids in the extract of Mexican oregano (*Lippia graveolens* H.B.K.), a spice and herb, used in the USA and Mexico. The identification of galangin was confirmed by direct comparison with standards[71]. A new method for simultaneous determination of flavonols (Galangin) by HPLC was developed and validated[72]. Effects of grape varieties (Cabernet Sauvignon and Merlot), harvest dates, fermentation conditions and types of oak barrels on the concentrations of flavonols and flavones composition were investigated and found to contain galangin in the significant amount[73]. Galangin were detected in the apple and parsley extracts[74]. Chromatographic analysis of commercial propolis extracts was able to detect 35 compounds, among which galangin was found to be present in significant level[75]. Galangin was isolated from propolis extracts from the province of Tucumn (Argentina) samples and *Zuccagnia punctata* exudates[76]. The chemical composition of the Iranian propolis was investigated using thin layer chromatography and spectrophotometric methods and found to contain galangin in Iranian propolis[77]. Chemical analysis showed the presennce of the galangin as a active constituents in propolis extract[78].

4. Discussion

Fruit and vegetable intake is associated with a reduced

risk of cancer and cardiovascular disease and these protective effects are mainly because of its beta-carotene and phenolic constituents. Flavonoids are a broad class of low molecular weight, secondary plant phenolics having flavan nucleus. It is widely distributed in the leaves, seeds, bark and flowers of plants. More then 4 000 flavonoids have been identified till date. In plants, flavonoid affords protection against ultraviolet radiation, pathogens, and herbivores. Most of the beneficial health effects of flavonoids are mainly due to its antioxidant and chelating abilities[79]. The intake of flavonoids is mainly depending on the consumption of vegetables and fruits. The health benefits of flavonoids are well known, they are used in food, cosmetics, and various other preparations. Flavonoid have various pharmacological activity such as free radical scavenging, antioxidant power, vasodilatory, anticarcinogenic, antiinflammatory, antibacterial, immune-stimulating, antiallergenic, antiviral, and estrogenic effects, as well as being inhibitors of several enzymes such as phospholipase A2, cyclooxygenase, lipoxygenase, glutathione reductase, and xanthine oxidase[80-82]. Galangin is a flavonol class of flavonoid phytoconstituents and found to be present in the significant amount in honey, *Alpinia officinarum*, *Helichrysum aureonitens* and in propolis. It have various pharmacological activity such as anti-mutagenic, anti-clastogenic, anti-oxidative, radical scavenging, metabolic enzyme modulating activities and anticancer activity against certain human cancers[3-5]. The present review gives an idea about its pharmacological activity and bioanalytical aspects, which can be helpful to the researchers for the development of molecule to combat different type of diseases.

Conflict of interest statement

We declare that we have no conflict of interest.

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