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Review

Chrysin: Sources, beneficial pharmacological activities, and molecular mechanism of action

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ABSTRACT

In recent years, public and scientific interest in plant flavonoids has tremendously increased because of their postulated health benefits. This review was mainly focuses on the flavone chrysin (5,7-dihydroxyflavone), which occurs naturally in many plants, honey, and propolis. A number of in vitro and *in vivo* studies have revealed the therapeutic effects of chrysin against various diseases. In general, chrysin exhibits many biological activities and pharmacological effects, including antioxidant, anti-inflammatory, anticancer, and antiviral activities. Moreover, many studies have reported on the bioavailability of chrysin. Because of its compromised bioavailability and enhanced protein stability, chrysin solid lipid nanoparticle (SLN) synthesis avoids proteolytic degradation and sustained release of drug delivery. To clarify the mechanism of action of chrysin, researchers have investigated the structural binding relationship of chrysin through the docking computation method.

1. Introduction

Flavonoids are ubiquitous plant specialized metabolites that contain large groups of low-molecular-weight polyphenolic compounds, which present benefits to human health because of their biological properties. To date, approximately 5000 diverse flavonoids have been identified (Pietta, 2000). Nutritionists calculate the approximate average ingestion of flavonoids by humans on a normal diet to be 1–2 g/day (De Vries et al., 1997). Flavonoids are naturally occurring polyphenols with patterns of hydroxylation and substitutions that give rise to various subclasses including flavanones, anthocyanidins, flavonols, flavones, catechins (or flavanols), isoflavones, dihydroflavonols, and chalcones (Hodnick et al., 1988; Beecher, 2003) (Fig. 1). One such flavonoid that has received considerable attention is chrysin (5,7-di-OH-flavone). Chrysin, which has the ubiquitous 15-carbon flavone backbone, is one of the most important bioactive constituents of different fruits, vegetables, and even mushrooms. Chrysin has a common chemical structure, consisting of two fused rings, A and C, and a phenyl ring, B, attached to the second position of the C ring. It shares the

Abbreviations: AC, adenylyl cyclase; AGEs, advanced glycation end products; ACR, acrylamide; AHR, aryl hydrocarbon receptor; AMPK, AMP-activated protein kinase; AP-1, AR, aldose reductase activator protein 1; ATC, anaplastic thyroid cancer; ATP, adenosine triphosphate; B(a)P, benzo(a)pyrene; b-CD, b-cyclodextrin; BDE, bond dissociation energy; BDNF, brain-derived neurotrophic factor; BZD, benzodiazepine; CaM, calmodulin; CAPE, chrysin and caffeic acid phenethyl ester; CDDP, cisplatin; Ch-2, 5-hydroxy-7-methoxyflavone; Ch-4, 5,7-diacetylflavone; CHRY-DM, dimethoxylated chrysin; COX-2, cyclooxygenase-2; CPI, di-isopropyl chrysin-7-yl phosphate; CUMS, chronic unpredictable mild stress; CVDs, cardiovascular diseases; DEN, N-nitrosodiethylamine; DMBA, 7,12-dimethylbenza [a]anthracene; DMSO, dimethyl sulfoxide; DOX, doxorubicin; EAN, experimental autoimmune neuritis; EEP, ethanolic extract of propolis; EMT, epithelial–mesenchymal transition; EV71, enterovirus 71; Fe-NTA, ferric nitrilotriacetate; FSK, forskolin; GABA, gamma amino butyric acid; D-GalN, D-galactosamine; GSH, glutathione; PCA, protocatechuic acid; HIF-1A, hypoxia-inducible factor-1A; HOMO, highest occupied molecular orbital; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; LC-MS, liquid chromatography mass spectrometry; MD, molecular dynamics; MMP, human matrix metalloproteinase; MRP, multidrug resistance protein; NF-κB, nuclear factor κ-light-chain enhancer of activated B cells; NGF, nerve growth factor; Nrf-2, nuclear factor-erythroid 2-related factor 2; ODC, ornithine decarboxylase activity; PCNA, proliferating cell nuclear antigen; PDGF, platelet-derived growth factor; PGE2, prostaglandin E2; PPAR-γ, peroxisome proliferator-activated receptor-γ systolic arterial pressure; ROS, reactive oxygen species; SDE, *Scutellaria discolor* Colebr. extract; SRE, serum response element; STAT, signal transducer and activator transcription; SVGp12, human astroglia cells line; TNBC, triple-negative breast cancer; TNF, tumor necrosis factor; TNF-α, tumor necrosis factor-alpha; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; UPLC-MS, ultra-performance tandem mass spectrometry; VEGF, vascular endothelial growth factor; VSMC, vascular smooth muscle cell.

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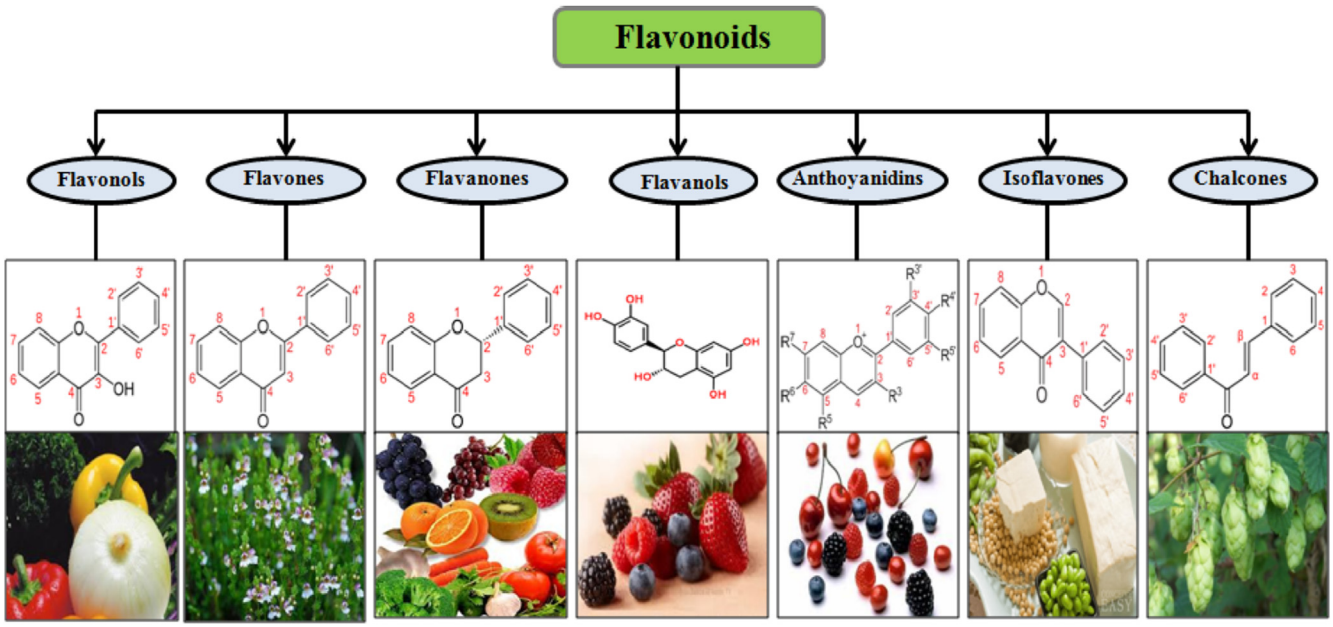

Fig. 1. Classification of flavonoids.

common flavone structure, with an additional hydroxyl group at the 5th and 7th positions of the A ring (Fig. 2). Chrysin is converted from the amino acid phenylalanine. The phenylpropanoids are a diverse family of organic compounds that are synthesized by plants from the amino acids phenylalanine and tyrosine. Their name is derived from the six-carbon aromatic phenyl group and the three-carbon propene tail of cinnamic acid, which is synthesized from phenylalanine in the first step of phenylpropanoid biosynthesis. Phenylalanine is first converted to cinnamic acid by the action of the enzyme phenylalanine ammonia-lyase. A series of enzymatic reactions lead to chrysin synthesis. Compared to the other flavonoids, chrysin is the least studied flavonoid by spectroscopic techniques (Pusz et al., 2000; Muñoz et al., 2016). The presence of hydroxyl and keto functional groups may result in the formation of strong supramolecular synthons, with coformers having complementary functional groups, thus offering a great opportunity to design nutraceutical cocrystals of chrysin.

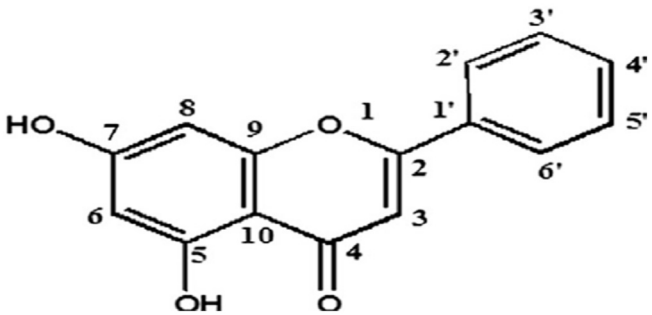

Fig. 2. Structure of chrysin.

2. Chrysin

2.1. Source of chrysin

Chrysin is a dietary phytochemical that is abundantly present in many plant extracts, including propolis, blue passion flower (*Passiflora caerulea*), and honey, which have great economic value and medicinal impact.

2.2. Propolis

Propolis (also known as “bee glue”) is the general name for the resinous substance collected by honeybees (*Apis mellifera* L.) from various plants. The word propolis is derived from the Greek words *pro* (defense) and *polis* (the city), i.e., defense of the city (or the hive). Propolis may vary in color from light yellow to dark brown depending on its source and age. It is hard and brittle when cold but becomes soft and very sticky when warm (Koltay, 1981). Some remarkable points emerge from the work that has been conducted for the propolis constituents. So far, flavonoid pigments are the