Review Article

Emerging Utilization of Chrysin Using Nanoscale Modification

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Chrysin is a flavone found in several plants, mushroom, and honeycomb. This constituent is broadly used in herbal medicine in Asia. Since its biological activities were identified in various studies, the focus has shifted to the development of chrysin as a complementary medicine for health promotion. Chrysin is known to have chemopreventive and therapeutic effects in skin aging, atherosclerosis, inflammation, diabetes, AIDS, and cancer. However, its poor bioavailability is a bottleneck for pharmaceutical applications. To overcome the limitations and enhance the bioactive effects, methods like nanoencapsulation or conjugation have been attempted. In this review, current trends of chrysin use in the biomedical field are summarized.

1. Introduction

Flavonoids including flavones, flavanols, and flavans possess various biological activities. Their effects are utilized in herbal medicines. Chrysin (5, 7-dihydroxyflavone, Figure 1) is a flavone contained in several plants (*Passiflora caerulea* [1], *Passiflora incarnate* [2], *Oroxylum indicum* [3, 4], *Matricaria chamomilla* [5], etc.) and natural products (*Pleurotus ostreatus* [6], propolis [7, 8], honey [9], etc.).

Recently, chrysin was reported as a bioactive ingredient. In this review, the effects of chrysin are briefly summarized (Figure 2) and its complementary application is discussed. Finally, emerging nanoscale modification of chrysin is introduced.

2. Biological Activities of Chrysin

2.1. Effect on Inflammation. Inflammation is a protective reaction of the body to infection, physiological stress, drugs, and so on and activates the immune system. Acute inflammation is induced by mediators including arachidonic acid, platelet-activating factor, prostanoids, leukotrienes, lipoxins, interleukins, histamine, serotonin, and lysosomal hydrolases. Chrysin alleviates inflammation through inhibition of COX-2 [10], prostaglandin-E2 [11], histamine [12], NF- γ B

pathway [13–15], tumor necrosis factor- (TNF-) alpha [16, 17], iNOS [16], and cytokines (interleukin-1 β , interleukin-2, interleukin-6, and interleukin-12) [18] and activation of peroxisome proliferator-activated factor γ (PPAR γ) [19]. These reports suggest that chrysin could be a good agent in inflammatory diseases. When acute inflammation does not clear up, inflammatory cells persist and chronic inflammation promotes organ dysfunction [16, 20, 21]. Disabling inflammatory diseases include Parkinson disease [22], cancer [13], cerebral ischemia [23], allergy [12], and autoimmune neuritis [18]. The anti-inflammatory mechanism of chrysin could prevent inflammation-related diseases.

2.2. Effect on Atherosclerosis. Atherosclerosis and hypercholesterolemia are risk factors for coronary heart disease, which is a major cause of mortality. In atherosclerosis, a fibroinflammatory lipid plaque consisting of inflammatory cells, smooth muscle cells, lipid, and connective tissue accumulates in arteries. The major factor in atherosclerosis is oxidative metabolism of plasma lipoproteins. Oxidation of low-density lipoproteins by oxygen free radicals generates reactive oxygen species (ROS). Thus, ROS play a central role in the incidence of atherosclerosis. Overproduction of ROS also injures endothelial cells. Originally, ROS are intermediate products in oxidative phosphorylation and

FIGURE 1: Structure of chrysin.

FIGURE 2: Biological activities of chrysin as a complementary medicine.

are eliminated by sufficient levels of superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). However, oxidative stress-induced ROS accumulate and impair cells when these enzymes are depleted. Chrysin can scavenge ROS as chrysin increases SOD, GPx, and CAT [11, 24, 25]. Furthermore, chrysin controls cholesterol efflux [26] and suppresses TNF- α -induced adhesion molecule expression [27]. These activities of chrysin could prevent atherosclerosis.

2.3. Effect on Diabetes. Diabetes, one of the lifestyle diseases, is described as a high glucose level in blood. Diabetes-induced complications depreciate the quality of the patient's life and often become the cause of death. The ethanolic extract of *Oroxylum indicum* Kurz, which includes chrysin, inhibits the activities of α -glucosidase, thus decreasing glucose absorption in blood. It also induces GLUT-4 translocation in 3T3-L1 adipocyte cells, suggesting an increase of glucose uptake into those cells [28]. Several studies showed that chrysin has hypoglycemic effects on diabetic mice [29, 30]. Pancreatic beta cells, the function of which is important to prevent diabetes mellitus, are protected by the antioxidant activity of chrysin [31]. The antioxidant effect of chrysin can assuage the complications of diabetes. Chrysin decreases malondialdehyde and increases CAT, SOD, and glutathione. Its effect ameliorates cognitive deficits [32] and renal dysfunction [33] in diabetic animal models. Chrysin decreases total cholesterol, triglyceride, and low-density lipoprotein in streptozotocin-nicotinamide induced diabetic rats [34]. Nitric oxide-releasing chrysin attenuates diabetes-induced

complications [35–38]. Because of these activities, chrysin derivatives have been synthesized for development as antidiabetes agents [38].

2.4. Effect on AIDS. Chrysin is known to inhibit casein kinase II involved HIV-1 transcription [39] and to suppress HIV replication in H9 cells [40]. Chrysin inhibits HIV expression in OM-10.1 cells or ACH-2 cells treated with TNF- α or phorbol myristate acetate (PMA) and 8E5 cultures [41]. Thus, chrysin has anti-HIV activity [41, 42].

2.5. Effect on Aging. Physiological functions degrade with advancing years. Among these functions, synthesis of sex hormones is important in the development of reproductive organs and maintenance of sexual function. With age, sex hormones decline and sexual function is enervated. Chrysin stimulates cyclic AMP-induced steroidogenesis in Leydig tumor cells and increases the expression of steroidogenic acute regulatory protein [43]. Moreover, chrysin ameliorates sexual functions in 2-year-old male rats, suggesting that chrysin can inhibit aromatase activities [44]. On the other hand, oral administration of chrysin to immature rats did not change sex hormone-induced uterine growth [45]. Urinary testosterone level was also measured in sportsmen drinking propolis including chrysin because aromatase inhibition can trigger the conversion of testosterone into estrogen. However, oral supplementation of propolis did not alter urinary testosterone levels [46]. These results may be due to poor absorption or bioavailability of chrysin *in vivo*. Nevertheless, chrysin was recently utilized as a testosterone booster supplement for bodybuilders and athletes [47].

Aged mouse brain shows memory declines, but chrysin prevents age-related cognitive decline by mitigating the decrease of brain-derived neurotrophic factor and ROS in the prefrontal cortex and hippocampus of aged mice [48].

Skin aging is also a matter of great interest. Ultraviolet (UV) exposure is a risk factor for skin aging. In particular, ROS promote photoaging by UV and induce cell damage. So ROS accumulation is observed in the aging process. Matrix metalloproteinase level is also increased by ROS. The antioxidant effect of chrysin inhibits the expression of matrix metalloproteinase and prevents UV-induced skin aging [49–51].

2.6. Effect on Cancer. Chrysin, a component of natural products, shows anticancer activities in various cancer cell lines [52, 53]. Several studies on chrysin have sought to explain the mechanisms of its anticancer effects, which include inhibition of the PI3K/Akt pathway, activation of caspase-3 and caspase-8 [54], and depletion of cellular glutathione [55]. Chrysin also increases mitochondrial membrane depolarization, Bax, and cleaved-PARP levels in cervical cancer cell lines [56]. Chrysin activates the transcription pathway mediated by TNF- α and TNF- β *via* aryl hydrocarbon receptor in colorectal cancer cells [57]. Chrysin, as an HDAC inhibitor, arrests the cell cycle through induction of p21 [58, 59] and then suppresses cellular proliferation. Also, chrysin as an aromatase inhibitor potentially reduces tumor growth in

estrogen receptor-positive breast cancer MCF-7 cells [60]. Chrysin derivatives have been synthesized and evaluated in the development of anticancer drugs [61].

In chemotherapy, metastasis is a problem that needs to be solved. Matrix metalloproteinase-9 (MMP-9) plays a key role in the metastatic cell invasion. Chrysin inhibits MMP-9 expression via suppression of ERK and JNK pathways in gastric cancer cells [62]. These activities of chrysin are of interest for its application in the pharmaceutical field. Furthermore, up to 3 g/day of chrysin showed no toxicity [47]. Although its advantages are attractive, chrysin has weaker therapeutic efficacy than commercial anticancer drugs. Generally, chrysin is ingested as a dietary food and utilized as a complementary medicine. Recently, the combination of chrysin and anticancer drug was shown to enhance cytotoxicity in various cancer cell lines and to be devoid of toxicity to normal cells. In human lung cancer H460 cell lines, chrysin improved the anticancer efficacy of doxorubicin and cisplatin by depletion of glutathione [63, 64]. In Hep G2 cells, the combination of chrysin and cisplatin enhanced p53 levels and induced apoptosis [65]. Also, chrysin increased the responsiveness in adriamycin-resistant cancer cells, indicating that chrysin could be developed as a chemosensitizer [66]. Moreover, the combination of chrysin and 1, 2, 3, 4, 6-penta-O-galloyl- β -D-glucose suppressed tumor growth through the reduction of S-phase kinase-associated protein 2 and low-density lipoprotein receptor-related protein 6 in triple-negative breast cancer [67].

3. Improvement Strategies for Chrysin

Although the bioactive effects of chrysin are diverse, its medicinal application is limited. One of the reasons is that chrysin has poor solubility as well as rapid metabolism and excretion [68]; the bioavailability of chrysin therefore needs to be enhanced. Nanoscale natural products are emerging as a good strategy. The nanoscale modification increases the ratio of surface area to volume and thus may improve solubility.

Bottom-up manufacturing method involves assembly of a nanoscale structure from small molecules (e.g., organic synthesis and self-assembly on protein) [69]. To improve the activities of chrysin, chemical conjugation with other chemicals was performed. Conjugation of chrysin with indole and barbituric acid increased the anti-inflammatory activity above that of chrysin itself [70]. Organogermanium had antioxidative activity like chrysin [71, 72]. And conjugation of chrysin-organogermanium had synergistic antioxidant effects and enhanced anticancer effects through apoptosis-associated mitochondrial function and antiangiogenesis [73]. Selenium containing chrysin showed significant cytotoxicity with 18-fold lower IC_{50} than that of chrysin. Moreover, the cytotoxic activity of selenium containing chrysin was superior to that of cisplatin, a commercial anticancer drug [74]. These results suggest that chrysin and other chemicals that have similar biological activity elicit increasing therapeutic efficacy with conjugation.

The other method for overcoming the disadvantages of chrysin is the utilization of a drug delivery system (DDS).

DDS have been used to solubilize a drug or modify the properties of a drug. Furthermore, DDS could be used to accumulate encapsulated drug at a target site (e.g., tumor). Nanoscale carriers include a drug reach and accumulate in tumor tissue much more than in normal tissues through the enhanced permeability and retention (EPR) effect [75]. Generally, this is called passive targeting. Recently, researchers have been concerned about manipulating nanoscale carriers in order to control drug release at the desired target site. Tumor specific antibodies or ligands are utilized in addition to the tumor microenvironment in order to achieve the active targeted delivery of drug. Eventually, DDS enhance the final concentration of drug at targeted site and improve the drug bioavailability. The technology of nanoscale modification as DDS is applied to infectious diseases as well as cancer therapy [76]. Use of natural products including chrysin as encapsulated materials has increased. Plant- or microorganism-derived materials are known to have biological activities and low toxicity compared to commercial drugs [77]. So natural products have been utilized as complementary medicine or preventive medicine. Recently, it was reported that nanoscale natural products are prospects for homeopathic medicine [69, 78–80]. Chrysin is also a good candidate for homeopathic medicine.

A successful strategy includes the selection of suitable carriers that could encapsulate the respective drugs. Based on the literature analysis, DDS for chrysin have utilized liposome [13], micelles [81], and nanoparticles [82–84] as carriers. Until now, chrysin-incorporated polymer as a nanoscale medicine was made from poly(ϵ -caprolactone) (PCL), polylactide-glycolic acid (PLGA), and polyethylene glycol (PEG). By improving the drug-loading contents, chrysin modified polymer increased chemotherapeutic efficacy. Chrysin interacted with PEG-PCL and formed polymer micelles composed of a single layer. With solubilization of chrysin, the micelle enhanced doxorubicin-induced cytotoxicity [81]. Moreover, chrysin was bound to the terminal group of methoxy PEG (mPEG) and doxorubicin was incorporated into mPEG-chrysin conjugate [82]. In micelles modified with chrysin, the chain lengths of their components were important. So mPEG (2 k)-PCL (5 k)-chrysin micelles were optimized to maximize the anticancer effect *in vitro* [85]. Chrysin has been used in attempts to enhance chemotherapeutic efficacy in various cancer cell lines.

To reduce the toxicity, carriers should be degradable in the body. One such carrier is PLGA-PEG, an FDA-approved polymer. Chrysin encapsulated into PLGA-PEG exhibited increased solubility and cytotoxicity in breast cancer T47D cells [83, 84]. The IC_{50} s of PLGA-PEG with chrysin and pure chrysin were 44.8 and 46.7 μ M, respectively, in T47D cells [66]. Moreover, PLGA-PEG with chrysin decreased cyclin D1, a protooncogene, more than pure chrysin [66]. In Zarghami et al.'s study [83, 86], chrysin-curcumin in PLGA-PEG also inhibited the proliferation of breast cancer cells by decreasing cyclin D1 expression. This result with this technology suggests that bioavailability of chrysin is improved by PLGA-PEG [86].

Until now, chrysin has been modified for anticancer therapy in most studies, but various nanoparticles including

TABLE 1: Summary of modified chrysin for improvement strategies.

Methods	Structure	Pharmaceutical application	Ref. number
Conjugation	Chrysin-indole-barbituric acid	Anti-inflammatory activity	[70]
	Chrysin-organogermanium	Antioxidant activity Anticancer effect	[71–73]
	Chrysin-selenium	Anticancer effect	[74]
Encapsulation	Liposome	Anticancer effect	[22]
	Micelle (PEG-PCL)	Enhancement of chemotherapeutic efficacy	[81]
	Nanoparticles (PLGA-PEG)	Anticancer effect	[82–84]
	Nanoparticles (PLGA)	Prevention of <i>S. Typhimurium</i> infection	[87]

chrysin, have the potential to be used for other applications. For example, PLGA-honeybee, a complex of chrysin and other components, was utilized for prevention of *S. Typhimurium* infection [87].

4. Conclusions

The technology of nanoscale modification could overcome obstacles in the development of functional dietary supplements and medicines. Nanoscale material changes the original material's physicochemical properties, (especially, solubility). In this review, chrysin is described as a good example of nanoscale modification. Chrysin, a natural flavonoid, possesses various biological activities and shows promise as a complementary medicine. However, the limitations of chrysin (poor solubility in water and low stability in the body) are a hurdle in terms of application. To enhance the bioavailability, chemical conjugation using bottom-up manufacturing and encapsulation using nanoparticles were designed and applied (Table 1). These trials could be developed for the commercial exploitation of chrysin. Hereafter nanoscale modification could be increased in the pharmaceutical field, although scale-up processing and quality control remain to be solved.

Abbreviations

TNF:	Tumor necrosis factor
ROS:	Reactive oxygen species
SOD:	Superoxide dismutase
GPx:	Glutathione peroxidase
CAT:	Catalase
PPAR:	Peroxisome proliferator-activated receptor
PMA:	Phorbol myristate acetate
UV:	Ultraviolet
HIV:	Human immunodeficiency virus
HDAC:	Histone deacetylase
MMP-9:	Matrix metalloproteinase-9
PEG:	Polyethylene glycol
PLGA:	Poly(lactic-glycolic acid)
PCL:	Poly- ϵ -caprolactone
DDS:	Drug delivery system.

Competing Interests

The author declares that there are no competing interests.

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