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KRİSİN: POTANSİYEL FARMAKOLOJİK ve TOKSİKOLOJİK ETKİLERİ

ÖZET. Günümüzde sentetik kimyasal ilaçlara alternatif olarak bitki kökenli farmakoterapötik ajanların kullanımı artmaktadır. Oldukça fazla bitki bazlı biyoaktif bileşen bildirilmiş olsa da mavi çarkıfelek, bal ve propolis gibi bazı ürünlerde bulunan biyoaktif molekül krisin, son yıllarda dikkat çekici bir fitokimyasal haline gelmiştir. Krisin, birçok farklı farmakolojik etkiye sahip olmasının yanı sıra güçlü antioksidan, antikanserojenik ve anksiyolitik özellikleri ile öne çıkan önemli bir flavonoiddir. Bu derlemede krisinin fizikokimyasal, farmakokinetik, farmakodinamik özellikleri ve çeşitli hastalıklarda koruyucu ve faydalı özellikleri hakkında bilgi verilmesi amaçlanmıştır.

Anahtar Kelimeler: Krisin, Flavonoid, Bal, Propolis.

CHRYSIN: POTENTIAL PHARMACOLOGICAL and TOXICOLOGICAL EFFECTS

ABSTRACT. Recently, the use of pharmacotherapeutic agents of plant origin is increasing as an alternative to synthetic chemical drugs. Although quite a lot of plant-based bioactive ingredients have been reported, the bioactive molecule chyrisin, which is found in some products such as blue passionflower, honey and propolis, has become a remarkable phytochemical in recent years. Chrysin is an important flavonoid that stands out with its strong antioxidant, anticarcinogenic and anxiolytic properties as well as having many different pharmacological effects. In this review, it is aimed to give information about the physicochemical, pharmacokinetic, pharmacodynamic properties of chrysin and its protective and beneficial properties in various diseases.

Keywords: Chrysin, Flavonoid, Honey, Propolis.

Makale atıf

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INTRODUCTION

Dietary supplements from plant origin possess many pharmacological properties and are able to protect and cure diseases in humans and animals (Khan and Sultana, 2011).

Flavonoids constitute a group of important bioactive substances found in plants. Flavonoids are polyphenolic compounds, which are the most widespread chemical class of phytochemicals, especially those that have a multitude of health-beneficial effects. Flavonoids are widely found in plants (Samarghandian et al., 2017). Dietary sources of flavonoids include vegetables, spices, fruits and seeds. These substances appear to be credible to consume in the diet. A diet rich in flavonoids is thought to be beneficial (Kozlowska and Szostak, 2014). Flavonoids are recognized as important components used in different pharmaceutical, nutraceutical, medical and cosmetic applications. The effects of flavonoids are attributed to their anti-oxidant, anti-mutagenic, anti-inflammatory and anti-carcinogenic properties as well as their ability to modulate essential cellular enzyme functions (Metodiewa et al., 1997).

Chrysin is a phytochemical that has promising pharmacological and beneficial bioactivity, which is categorized under the flavonoids class. It is widely used in the treatment of different degenerative disorders (Naz et al., 2019).

Within the scope of this review, some current information about the structure, mechanism of action, important pharmacological properties of chrysin and its effects on human and animal health have been compiled.

Sources of Chrysin

Chrysin is a phytochemical found in mainly propolis, honey and some plant extracts, such as blue passionflower (*Passiflora caerulea*) (Mani and Natesan, 2018). High levels of chrysin have been described in honey and propolis (Siess et al., 1996). In addition, mushroom such as *Pleurotusostreatus* and *Radix scutellariae*, a medicinal plant, are important chrysin sources (Naz et al., 2019) (Figure 1).

Propolis shows many biological activities such as anti-inflammatory, antitumor, antioxidant, antibacterial, antifungal and antiviral activities (Drago et al., 2007). Some of these effects have been reported to be due to chrysin found in propolis. Studies have also shown that amount of chrysin in propolis is up to 28 g / L (Mani and Natesan, 2018). It was accounted for that chrysin content could be found as 5.3 mg / kg in forest honey and 0.10 mg / kg in honey (Hadjmohammadi et al., 2010). It has also been stated that various mushrooms from Lesvos island in Greece contain chrysin and the level

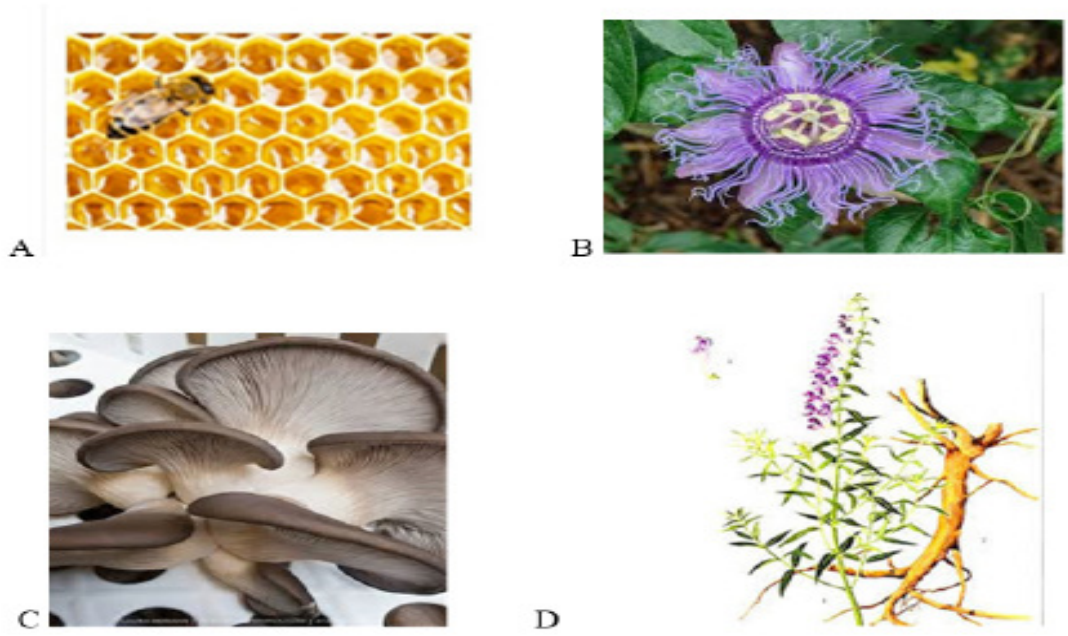

Figure 1. Chrysin sources: A. Propolis, B. Passiflora Sp., C. Pleurotus ostreatus, D. Radix scutellariae (Naz et al., 2019).

of chrysin individually varies between 0.17 mg / kg in Lactarius deliciosus and 0.34 mg / kg in Suillus bellinii (Kalogeropoulos et al., 2013).

Another important source of chrysin is Passiflora plant which belongs to Passifloraceae family (Passion flower family), that contains about 500 species (Hickey and King, 1988). Chrysin extract obtained from the genus Passiflora was shown to have anti-depressive, anxiolytic (Missassi et al., 2007), sedative, (Guerrero and Medina, 2017), anti-spasmolytic, anti-asthmatic effects and shows protective effects on sleep and respiratory disorders (Miroddi et al., 2013). Chrysin, a naturally occurring monovalent in Passiflora caerulea, is a ligand for central and peripheral benzodiazepine receptors (Medina et al., 1990).

Chemical Structure and Physical Properties

Chrysin is a natural polyphenolic compound consisting of 15 carbon skeletons. Structurally, chrysin consists of 2 benzene rings (A, B) and 1 oxygen-containing heterocyclic ring (C). While the 3rd carbon lacks the hydroxyl group, it has 2-3 double-bonded carbons with one carbonyl group connected to the 4th carbon. Chrysin contains 2 fused rings A and C and a phenyl ring B. A ring posseses the flavone structure (Figure 2) having an extra hydroxyl group. Chrysin is classified within the flavones. It has also –OH groups on the 5th and 7th carbon atoms. Different from other flavonoids, chrysin does not have any oxygen containing groups in ring-B. Primarily, the diference in A ring oxygenation give rise to chyrsin derivatives (wogonin, oroxylin A and baicalein) (Figure 3) (Pusz et al., 2000; Muñoz et al., 2016).

Chrysin ($C_{15}H_{10}O_4$) is derived from phenylalanine. Phenylalanine is initially converted into cinnamic acid by the action of phenylalanine ammonia-lyase enzyme. A series of enzymatic reactions then produce chrysin (Pusz et al., 2000).

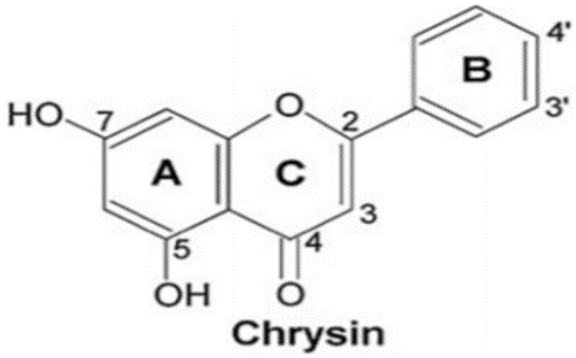

Figure 2. Chysin (5,7-Dihydroxyflavone) (Pusz et al., 2000; Muñoz et al., 2016).

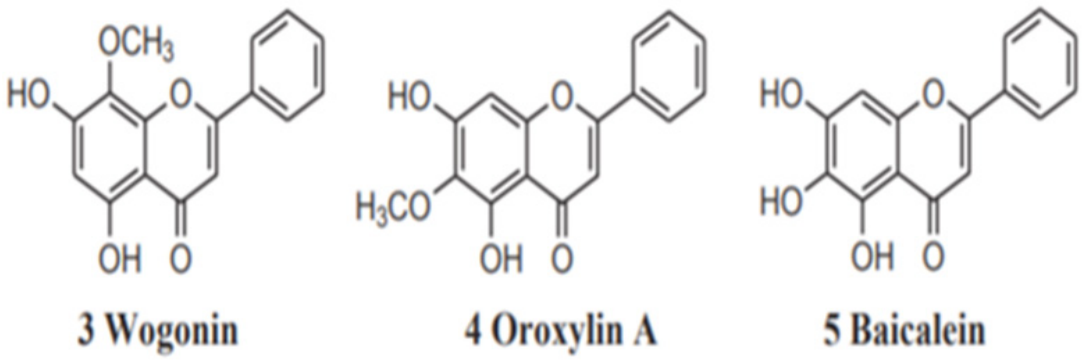

Figure 3. Chrysin derivatives (Nabavi et al., 2015).

Pharmacokinetics

Flavonoids are metabolized in the gastrointestinal lumen, intestinal wall cells and liver. A common feature of flavonoids is that they are found in the bloodstream as glucuronide and sulphate conjugates (Erlund, 2004). Conjugation process of flavonoids takes place in the small intestine and liver. The process involves sulfation, glucuronidation and methylation. This detoxification process limits their potential toxic effects and facilitates the elimination of chyrisin via bile and urine by increasing their hydrophilicity (Crespy et al., 2003). Flavonoids are secreted via bile into the duodenum. It undergoes enzymatic degradation by glucoronidase in the distal parts of intestines, which can then be reabsorbed. The enterohepatic recycling may give rise to the presence of flavonoids in the body for a longer period of time (Manach et al., 2004).

The beneficial effects of chrysin depend on its bioavailability, their *in vivo* achievable concentrations and the solubility of these compounds. Walle et al., (1999) reported that chrysin has poor intestinal absorption. In a study, it was reported that plasma concentrations of unchanged chrysin were very low after administration of a single oral dose (Walle et al., 2001). Chrysin's maximum concentration in serum ranges from 12 to 64 nM due to its poor intestinal absorption (Kao et al., 1998). It was reported that plasma protein binding of chrysin is more than 99% (Boulton et al., 1998). Using these values, Walle et al. (2001) indicated that the oral bioavailability of chrysin was 0.003-0.02%. In general, chrysin treatment can be employed by micromolar range.

PHARMACOLOGICAL EFFECTS

Due to the lack of oxygenation in the B and C rings in the chemical structure of chrysin, it has been associated with various pharmacological activities ranging from antioxidant effects to anticancer effects with protective effects against some diseases (Habtemariam, 1997).

Anticarcinogenic Effect

Chrysin has become an important flavonoid studied for its anti-carcinogenic effects. In many cancer cell types tested, chrysin was reported to inhibit cell proliferation. It also induces apoptosis in these cancer cell lines. Chrysin has been shown to be more effective than other flavonoids tested on leukemia cells, where chrysin was reported to act through caspase activation and inactivation of Akt (activation via phosphorylation prevents apoptosis) signal in cells (Khoo et al., 2010).

Zhang et al. (2004) showed that chrysin exhibit potential anti-cancer effects in human cervical carcinoma. Chrysin and phosphorylated chrysin were shown to inhibit the growth of cervical cancer cells through induction of apoptosis and downregulation of proliferating cell nuclear antigen in the cells. Chrysin derivatives are more effective and may be a new potential anticancer drug.

Li et al. (2010) found that chrysin significantly sensitized cancer cells in the human liver cancer cell line (HepG2), human nasopharyngeal carcinoma cell line (CNE-1) and the human colorectal cancer cell line (HCT-116) to Tumor necrosis factor- α (TNF-α)-induced apoptosis.

In a study investigating the effect of 22 flavonoids on human leukemia cells (U937), galangin, apigenin, fisetin, alpha-naphtho-flavone, quercetin, chrysin, luteolin, genistein and 3,7-dihydroxyflavone reduced cellular viability of U937 cells. Nevertheless, only fisetin, luteolin, quercetin, apigenin, galangin and chrysin induced oligonucleosomal DNA fragmentation. Viability of U937 cells was shown to be effectively reduced by chyrsin. Chrysin increased the effects of TNF-α in inducing apoptosis in cells (Monasterio et al., 2004).

Woo et al. (2004) reported that chrysin induces apoptosis via activation of caspase-3, leading to signaling and downregulation of apoptosis protein inhibitor (XIAP) in U937 cells. All these studies show that chrysin exhibits a potential anti-leukemic activity and can be used as a potential agent in leukemia. The inhibitory effects of chrysin, on proliferation of leukemia cells appear to be dose-dependent (Chang et al., 2007).

Although many studies indicated that chrysin results in apoptosis in different tumor cell lines, the mechanism of apoptosis is unknown. Previous studies are contradictory in this respect. Therefore, it has been reported that more studies are needed to determine the potential molecular target of chrysin, which plays a role in modulating apoptosis in human cancer (Khoo et al., 2010).

Anxiolytic Effect

Chrysin has a sedative and its anxiolytic effect which are associated with gamma aminobutyric acid (GABA)

-benzodiazepine (BZD) receptors. Chrysin's anxiolytic effect is reported to be due to BZD receptor activation (Zanoli et al., 2000).

Zanoli et al. (2000) investigated the behavioral impacts of acute administration of chrysin and apigenin found in Passiflora incarnata and Matricaria chamomilla in rats. The findings show that chrysin and apigenin can similarly reduce locomotor activity at 25 mg / kg. Nevertheless, chrysin has been reported to exhibit an anxiolytic effect at a dose of 1 mg / kg, while apigenin is unable to show the same effect.

Antidepressant Effect

Chrysin's therapeutic role as an antidepressant has been evaluated using animals previously exposed to chronic unpredictable mild stress (CUMS). It has been shown that CUMS applied to female mice for 28 days caused a significant decrease in nerve growth factor (NGF) levels and brain-derived neurotrophic factor (BDNF) and Na, K-ATPase activity (Filho et al., 2015). CUMS additionaly increased the development of depressive states with significant increases in corticosterone levels in the forced swimming test and sucrose preference test, while oral chrysin administration (20mg / kg) mitigated the reduced NGF and BDNF levels in CUMS treated mice compared to fluoxetine. Chrysin also decreased the increased catalase, glutathione peroxidase, glutathione reductase and activities in mice exposed to CUMS. Chrysin showed an antidepressant effect equivalent to fluoxetine in mice by affecting behavioral, neurotrophic and biochemical parameters. It has also been noted that up-regulation of NGF and BDNF levels confers the antidepressant impacts of chrysin in mice (Jesse et al., 2015).

Antioxidant Effect

Oxidative stress indicates the imbalance between reactive oxygen species (ROS) and antioxidant defense within the cell which could harm membrane lipids and causes oxidative damage in DNA and proteins (Karrari et al., 2013). Chrysin has been shown to scavenge ROS, reduce lipid peroxidation, stimulate antioxidant enzymes such as glutathione peroxidase, catalase and superoxide dismutase and protect cell components from oxidative damage (Farkhondeh et al., 2019).

Khan et al. (2012) studied the effect of chrysin against oxidative stress, apoptotic response and colon damage caused by cisplatin (CDDP) in Wistar rats. Chrysin administration prevented oxidative stress in the liver and kidneys of Wistar rats by inhibiting xanthine oxidase, cytochrome P450 2E1 and alcohol dehydrogenase. Xanthine oxidase is an enzyme that contributes to the formation of reactive oxygen species (Koca and Karadeniz, 2003). Flavonoids have been reported to inhibit xanthine oxidase and scavenge the superoxide radical. The mechanism of action as antioxidants appears to be related to hydroxyl groups on the A-ring, but the effect of A-ring arrangement on antioxidant activity is not clear (Cos et al., 1998).

Oxidative damage is the primary machanism of methylmercury (MeHg). It has been reported that MeHg causes a significant increase in DNA damage associated with oxidative stress. It has been reported that when animals are exposed to metal in the presence of chrysin, chrysin has a protective effect against DNA damage (Manzolli et al., 2015).

Oxidative stress is an important factor in varicocele-related infertility and therefore antioxidant therapy is recommended. Chrysin application significantly improved sperm parameters by protecting the reproductive system against varicocele damage. Therefore, it has been reported that chrysin may be an alternative treatment to enhance sperm quality in varicocele (Missassi et al., 2017).

Neuroprotective Effect

Microglia activation is an significant factor in neuroinflammation and all neurodegenerative diseases and especially in Parkinson and Alzheimer's disease. Therefore, suppression of microglial activation is important for the healthy neuronal cells. One study reported that chrysin treatment significantly prevented the release of pro-inflammatory cytokines inluding nitric oxide, TNF-α and interleukin-1 in lipopolysaccharide stimulated microglia. It has also been reported that inducible Nitric Oxide Synthase (iNOS) and Cyclooxygenase-2 (COX-2) expressions are significantly inhibited by chrysin. In addition, chrysin inhibit c-Jun N-terminal kinase and Nuclear Factor kappa B (NFκB) activations, which are the main mediators of neuroinflammation (Elmore et al., 2015).

Ha et al. (2010) reported that chrysin exerted neuroprotective effect by blocking LPS-induced inflammatory response, NF-κB and c-Jun N-terminal

kinase (JNK) activation in BV2 microglia cells. Therefore, the authors reported that chrysin may have anti-inflammatory properties in the brain microglia.

Gresa-Arribas et al. (2010) examined the neuroprotective effect of chrysinin on the experimental neuroinflammation model in their study. Chrysin administration has been found to inhibit TNF-α and nitric oxide production, as well as iNOS expression in microglial cells stimulated by both LPS and interferon. Proinflammatory enzyme cyclooxygenase-2 was not changed. Chrysin pretreatment has also been reported to reduce neurotoxicity because of microglial activation in primary murine neurons.

Rashno et al. (2019) investigated the motor and cognitive dysfunctions induced by traumatic brain injury (TBI) and the possible mechanisms of chrysin. Findings have shown that treatment with chrysin improves memory and learning impairments and improves motor coordination impairment in rotarod testing after TBI. Both anti-oxidative and anti-apoptotic properties of chrysin could be a possible factors improving cognitive / motor deficits and preventing the neuronal cell death after TBI.

Jiang et al. (2014) investigated the effectiveness of chrysin in Wistar rats with spinal cord injury (SCI). In rats with SCI, an increase in NF-κB p65 units, TNF-α, IL-1β, IL-6, production and caspase-3, NO, iNOS was reported in the spinal fluid. However, chrysin administration has been found to significantly enhance healing of neuronal function and suppress the iNOS pathway along with inflammatory factors in rats with SCI. The results indicated that chrysin improves neural function and this may be associated with inhibition of inflammation and the iNOS pathway.

Vedagiri and Thangarajan (2016) investigated the therapeutic role of Chrysin-loaded solid lipid nanoparticles (SLNs) in alleviating neuron damage on Alzheimer's disease (AD) induced by amyloid-25-35 '(Aβ25-35), a neurotoxic agent, in rats. It has been stated that after 21 days of application of chrysin loaded solid lipid nanoparticles, antioxidant levels in the hippocampus significantly increased. Chrysin has been reported to reduce neuronal damage, acetylcholinesterase and lipid peroxidation as well as decreased memory loss.

Anti-inflammatory Effect

Chrysin's anti-inflammatory mechanism are based on its agonistic activity on peroxisome proliferator-activated receptors gamma (PPARc) and ultimately downregulating iNOS and COX-2 production (Bae et al., 2011). The anti-inflammatory effect of chrysin may be linked to the selective elimination of macrophages (Hougee et al., 2005).

Rauf et al. (2015) investigated the effects of chrysin on classical inflammation models in male mice. It has been stated that in the pain induction caused by the release of cyclooxygenase products, chrysin acts by inhibiting the enzymes involved in the formation of these products. In addition, in the analysis of the receptor ligand complex, it was reported that chrysin interacted weakly with the COX-1 binding site, while exhibiting a notable interaction with COX-2. The results obtained indicate that *in vivo* chrysin exhibits anti-inflammatory activity, by interacting with the COX-2 binding site.

Yao et al. (2016) investigated the effects of chrysin on chronic asthma model and allergic airway inflammation. Chrysin reduces the increase in the number of inflammatory cells in bronchioalveolar lavage fluid. Histological studies have shown that chrysin can reduce the infiltration of inflammatory cells in the airway. Chrysin administration significantly reduced both respiratory tract inflammation and histopathological alterations in the lung tissue, demonstrating that chrysin could be a promising agent for the treatment of chronic asthma.

Yao et al. (2014) studied the neuroprotective effect of chrysin in the mouse with middle cerebral artery occlusion (MCAO). The results indicated that chrysin significantly reduced neurological disorder scores and volume of infarct compared to the control group. It has been noted that increases in glial cell count and proinflammatory cytokine secretion due to ischemia / reperfusion, are improved by chrysin treatment. Inhibition of IL-1A, IL-1-, IL-6, IL-12, IL-17A, TNF-α and IFN was observed after chrysin administration. In addition, chrysin was shown to inhibit the upregulation of MCAO-induced NF-κB, COX-2, and iNOS. Due to the anti-oxidative and anti-inflammatory effects, chrysin is an good candidate for cerebral ischemia / reperfusion injury.

Protective Effect in Cardiovascular Diseases

In humans and animals, many flavonoids and other polyphenols have been shown to have beneficial effects on cardiovascular disease as well as cancer chemopreventive

properties (Middleton et al., 2000).

Chrysinin has been reported to have antiplatelet activity. Nevertheless, the mechanism resulting in the inhibition of platelet function is unknown. In a study conducted on 16 healthy volunteers, chrysin was reported to inhibit platelet aggregation and granule production induced by ADP and U46619. From biochemical tests, chrysin has been shown to inhibit collagen-induced activation of PLCγ2, Akt, Syk, phosphorylation of ERK1 / 2 and PKK. Chrysin has been reported to reduce platelet adhesion and spreading of platelets to the fibrinogen-coated surface and also strongly suppresses platelet aggregation and secretion in vitro (Liu et al., 2016).

Mantawy et al. (2014) investigated the effect of chrysin against doxorubicin (DOX)-induced cardiotoxicity. Chrysin significantly ameliorated myocardial damage such as conduction abnormalities, increased lactate dehydrogenase and serum creatine kinase-MB isoenzyme. In addition, while DOX decreased Bcl-2 expression, it caused apoptotic tissue damage by increasing Bax and cytochrome c expressions and caspase-3 activity. Chrysin pretreatment significantly improved these apoptotic effects of DOX. Overall, the results show that chrysin has a strong protective effect on cardiotoxicity induced by doxorubicin via decreasing oxidative stress, inflammation and apoptotic tissue damage.

Anti-osteoporotic effect

In a recent study, chrysin at doses of 50 and 100 mg/kg has been shown to have a potential anti-osteoporotic effect by improving bone mineral content and reducing excessive changes in bone-remodeling markers in ovariectomized rats. Chrysin also improved sensitivity and function of estrogen receptors showin estrogen-like effect. In addition, chrysin at these doses prevented body weight gain, uterine weight loss, and it increased femur dry weight, femur ash weight, bone ash calcium, and phosphorous levels in a dose-dependent manner (İbrahim et al., 2021).

TOXICOLOGICAL EFFECTS

It was reported that flavonoids are highly effective at low doses, but when consumed in excess or in higher amounts, they can have toxic effects on the human body. In this context, effective doses to be taken daily are important in order to obtain useful effects and to prevent toxic situations. 0.5 to 3 g chrysin is recommended for daily intake. On the other hand, as reported in the literature, it can induce liver cell toxicity even at daily concentrations (Tsuji and Walle, 2008).

The cytotoxicity caused by chrysin is related to its peroxidase-like activity in hepatocytes, resulting in the production of toxic byproducts of chrysin. Chrysin *de novo* affects DNA synthesis and reduces cell numbers. In neutrophils, myeloperoxidase is considered to be the main factor for chrysin toxicity (Brown et al., 2007).

CONCLUSION

Chrysin is an important phytochemical whose pharmacotherapeutic effects have been studied extensively in recent years. Chrysin is an abundant flavonoid found in honey, propolis, radix scutellariae, passiflora plant. Chrysin has favorable membrane transport features, yet intestinal absorption and bioavailability is low because of the effective glucuronidation and sulfation in these cells. Chrysin stands out with its anticarcinogenic, anxiolytic and antioxidant properties. It has a powerful antioxidant and radical scavenging effect with the OH group in the Chrysin A ring. The above-mentioned positive effects are due to this high antioxidant property as well as the fact that it affects many molecular and biological reactions in the cell. Chrysin has been shown to have no significant toxicity in toxicity studies. Due to the important pharmacological effects of chrysin and its beneficial effects against various diseases, it is considered that the studies on chrysin will continue to attract attention in the future.

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