Review
doi.org/10.1002/slct.202303306
Chemistry Europe
European Chemical Societies Publishing

www.chemistryselect.org

# Chrysin, The Flavonoid Molecule of Antioxidant Interest

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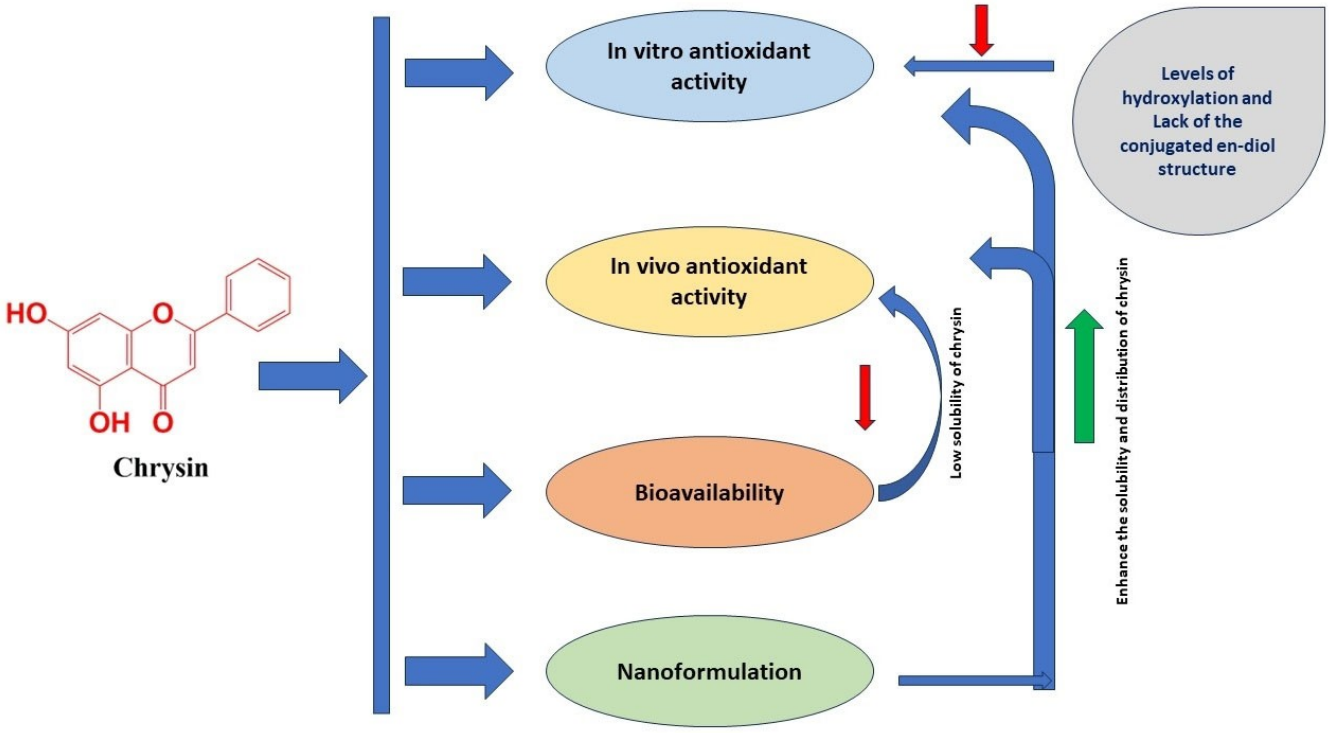

Chrysin, the natural bioactive flavone compound, has been identified in several edible materials such as honey, propolis, and passionflower with numerous biological potentials and pharmaceutical effects including antitumor, anti-inflammatory, antiviral and antioxidant. The compound has been reported to have lower *in vitro* antioxidant activity compared to other flavone-based structures such as quercetin, luteolin, and myricetin, which is mostly attributed to the higher hydroxylation and the presence of conjugated en-diol structures in these flavonoids and the lack of these structural features in chrysin. On the contrary to the *in vitro* antioxidant effect of chrysin, the compound has exerted remarkable *in vivo* antioxidant activities in several models related to the liver, brain, heart, kidneys, and other soft tissues. The current review includes a discussion of the *in vivo* and *in vitro* antioxidant activity of chrysin compared to other common flavonoids. The study also covers subjects linked to chrysin antioxidants, such as its metabolism, bioavailability, and current formulations that aim to increase chrysin antioxidant impact and overcome its low bioavailability.

## 1. Introduction

It is common knowledge that we require natural products in our lives, and that need is increasing daily as a result of how much food, medication, and industrial production are used globally.[1] Natural product elements, including those obtained from plant and animal sources, make significant contributions to the world's modern development, and returning to nature and protecting existing natural elements from extinction are global concerns.[2–4] Plants and their metabolites are the most commonly used natural components in the world, and research into improving plant production and protecting their diversity is critical to reducing monopolies and compensating for mankind's daily consumption. Through their use throughout history, people have observed and documented what is helpful and dangerous, and their conviction in the role that plants play in preventing and treating diseases has been established.[5–7] Because of their secondary metabolite content, medicinal plants have proven to play an important role in the global health system, according to research and applications.[8,9] Several classes of secondary metabolites of the alkaloids, volatile oils, flavonoids, saponins, bitter principles, and others have been identified, examined, and applied for the management of diseases, and examples of such secondary metabolites are too numerous to be discussed. One of the most widely distributed classes of natural products in plants is flavonoids. They are present in almost all greens and contribute to their known health benefits and disease-fighting activities.[10–13] Flavonoids have a defined role in plant physiological mechanisms, including protection against oxidative stress and microbial invasion.[14,15] On the other hand, greens, colored fruits, and medicinal plants rich in flavonoids are recommended for human protection against hazards or oxidative stress and to enhance overall human health.[7] These recommendations have been based on the high levels of usefulness and lower risk potential associated with these greens and fruits for human consumption. Flavonoid as pure entities have also been recommended for the same purposes. However, the level of toxicity of some pure flavonoids has been recorded.[16,17]

### 1.1. Chrysin Molecule

Chrysin is one of the flavonoids that have been chemically, physically, and biologically examined in several publications. As a pure flavonoid, chrysin has been isolated for the first time from the pine trees woods' at the concentration of 0.07% by Gösta Linstedt in 1949 at the KTH Royal Institute of Technology (Stockholm).[18] Afterword, chrysin has been isolated and identified from several plants and is considered one of the major products of honey, propolis, and passion flower species (*Passiflora caerulea* and *Passiflora incarnata*).[19–23] The chemical structure of chrysin, which has been characterized by NMR and mass spectrometry, indicates that chrysin is a simple compound with a di-hydroxy flavone structure, whereas two free hydroxy groups are attached to the carbons C-5 and C-7 in the A ring of the molecules (Figure 1). Based on the number and distribution of the hydroxyl groups in the chrysin structure, the compound is considered one of the lowest molecular weight and low hydroxylated flavonoids. These chemical features of chrysin gave the compound unique therapeutical, biological, and physical properties.

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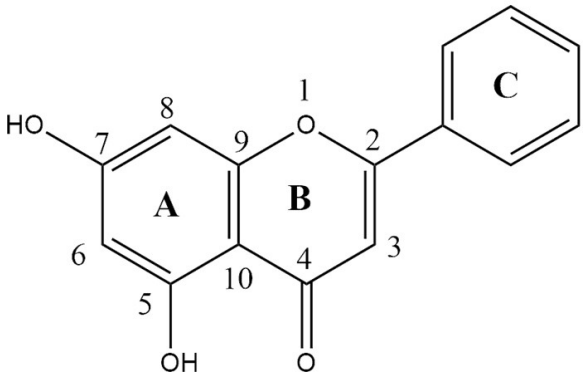


**Figure 1.** Structure of chrysin showing the number and positions of hydroxyls at the C-5 and C-7.

### 1.2. Biological Activities of Chrysin

Several biological activities have been reported for the chrysin, including antioxidant, anti-inflammatory, neuroprotection, anti-depressant, antiviral, antidiabetic, antiasthma, anticancer, anti-photoaging, and anti-melanogenesis activities.[20,24,25] Several studies have highlighted the beneficial pharmacological effects of chrysin, leading to recommendations for its consumption (Figure 2).

Chrysin has demonstrated its anticancer properties in various types of cancer, including colon cancer, gastro-intestinal cancer, breast carcinoma, esophageal carcinoma, tongue carcinoma, pancreatic exocrine cancer, liver cancer, urothelial carcinoma, prostate cancer, ovarian carcinosarcoma, cervical carcinoma, choriocarcinoma, bronchogenic carcinoma, pulmonary mucoepidermoid carcinoma, anaplastic thyroid cancer,

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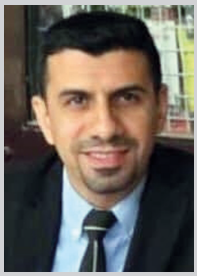

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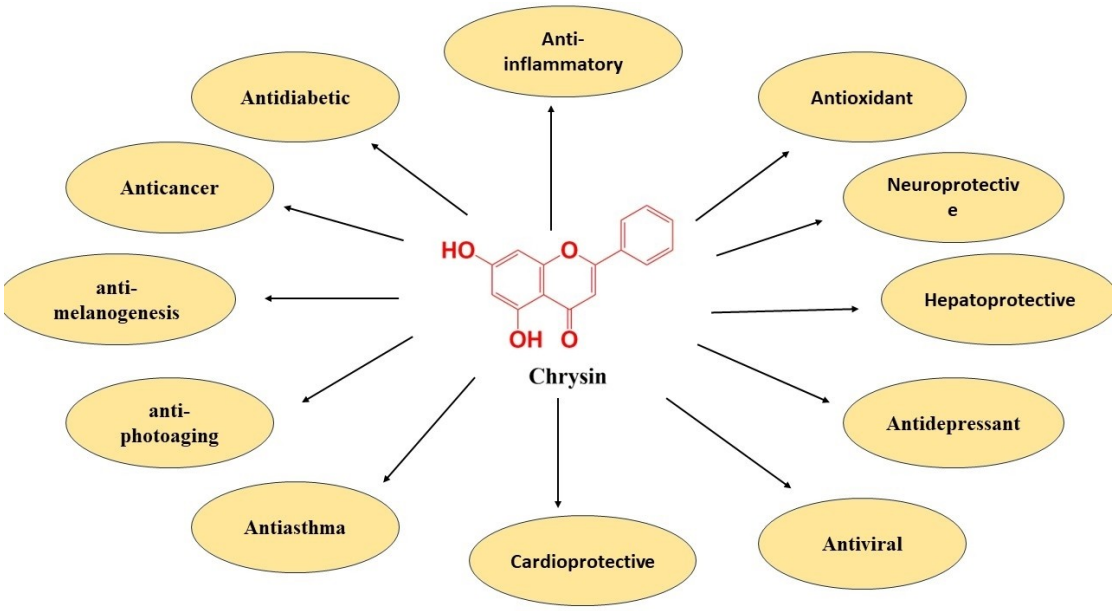


**Figure 2.** Pharmacological activities of chrysin in different organs of the body.

nasopharyngeal carcinoma, melanoma, uveal melanoma, glial tumor, carcinoids, blood-based cancers, osteoblast tumor, lymph angiogenesis, hematopoiesis, angiogenesis, and genotoxicity.[26–30] Chrysin's influence on a number of molecular pathways, including NF-κB, STAT3, Notch1, microRNA, and PI3K, has been linked to its anticancer potential. As a result, cancer growth and metastasis are inhibited.[30–33] Furthermore, chrysin has shown neuroprotective effects in a number of neurological conditions, including epilepsy, oxidative stress-induced apoptosis in neuronal cells, neuroinflammation, anxiety, depression, Guillain-Barre syndrome, multiple sclerosis, Huntington's disease, Parkinson's disease, Alzheimer's disease, aging-related cognitive deficits, memory impairment, hippocampal neurogenesis depletion, spinal cord injury, traumatic brain injury.[34,35] Chrysin has been investigated for its use in the treatment of cardiometabolic disorders like atherosclerosis, hypertension, hypercholesterolemia, cardiotoxicity, acute myocardial infarction, myocardial injury, vascular endothelial inflammation, arterial intima hyperplasia, platelet aggregation, and thrombosis because it has shown potential cardiovascular benefits. Moreover, several studies have revealed the benefit of using chrysin to treat type 2 diabetes, over-weight obesity, and metabolism associated syndromes.[36,37] Chrysin also confirmed hepatoprotective effects in numerous liver dysfunctions, including hepatotoxic activity, steatosis of the liver, non-alcoholic fatty liver disease, encephalopathy, fibrosis, and contraction of gallbladder smooth muscles.[38,39] A reno-protective properties of chrysin was demonstrated in a number of renal diseases, including nephrotoxicity, renal ischemia-reperfusion injury, diabetic nephropathy, sclerosis and fibrosis of renal glomeruli, chronic kidney disease, and hyperammonemia.[40] Additionally, chrysin has demonstrated gastrointestinal protective properties in cases of colitis, inflammatory bowel disease, diarrhea, and gastric ulcers.[41] In terms of the respiratory tract, chrysin has demonstrated protective effects for the respiratory tract against pneumonia, asthma, lung fibrosis, pulmonary edema, pulmonary arterial hypertension, and allergic inflammation as well as pulmonary hypertension, pleurisy, and lung injury[42,43] Additionally, endometriosis, early ovarian failure, ovarian torsion, reproductive toxicity, and benign prostate hyperplasia have all been linked to chrysin's protective effects on the reproductive system.[33] In diseases such diabetic retinopathy, cataracts, age-related macular degeneration, and uveitis, chysin has demonstrated ocular protective properties.[44] Chrysin has also shown skin-protective properties in cases of leishmaniasis, psoriasis, atopic dermatitis, photoaging, and melanogenesis.[45] Additionally, it has shown osteoprotective properties in the treatment of nociception, osteoporosis, and osteoarthritis. Furthermore, chrysin has exhibited antiviral effects against the influenza-A virus, enterovirus 71, chikungunya virus, and human immunodeficiency virus (HIV).[46–48] Given its diverse range of effects on multiple organs, chrysin can be recognized as a versatile flavonoid molecule with potential applications in the management of disorders affecting various organ systems (Figure 2). Its beneficial activities are largely attributed to its antioxidant and anti-inflammatory properties, which involve the regulation of *in vivo* antioxidant systems, oxidative stress factors, and pro-inflammatory mediators.

## 2. Antioxidant Activity of Chrysin

### 2.1. In vitro Antioxidant Activity of Chrysin

As mentioned before, chrysin belongs to the flavone class of flavonoids with a low number of hydroxylation, which are only represented by the presence of two hydroxy groups attached to the A-ring of the compound at the C-5 and C-7 positions

(Figure 1). Therefore, little scavenging activity of chrysin against 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radicals has been reported compared to the more hydroxylated flavones, e.g., luteolin, quercetin, and myricetin, which was explained by the lack of conjugated en-diol structure in the chrysin molecule[49] (Figure 3). Similar results for the radical scavenging of chrysin compared to quercetin and naringenin have been reported.[50] At the same time, chrysin has competitively inhibited the superoxide anion ($O_2^-$) generation, the effect of which is mostly attributed to the competitive inhibition of uric acid formation as a result of the xanthine oxidation with the free radicals, e.g., superoxide radicals and hydrogen peroxide, generated from xanthine oxidase oxidative conversions.[49,51–53] However, flavonoids having more than one conjugated en-diol group, like quercetin and myricetin, reduced $O_2^-$ generation by their ability to reduce the xanthine oxidase enzyme, leading to a decrease in free radicals generation.[49,54] Similar findings for the antioxidant activity of chrysin have been reported by Sim et al.,[55] as they reported the lower activity of chrysin, which lacks hydroxylation in the B-ring of the structure, towards scavenging stable free radicals, DPPH, and ordered the activity of tested flavones according to the presence and number of hydroxyl groups in the B-ring of the flavone structures. Accordingly, they have found that luteolin (ortho dihydroxy groups in the B-ring) was more active than apigenin (only one hydroxy group in the B-ring); however, the chrysin scavenging activity with no hydroxy groups in its B-ring structure was the least active molecule (DPPH scavenging activities of 96.2%, 10.2%, and 8.5%, respectively, at 1 mM concentrations of luteolin, apigenin, and chrysin).[55] In addition, different orders of activity have been reported by Sim et al.[55] in the superoxide anion ($O_2^-$) radical scavenging activity, which is generated in a hypoxanthine/xanthine oxidase system, as luteolin was the highest active scavenger for the superoxide radical (91.8% at 0.1 mM); however, chrysin has shown better activity (42.3% at 0.1 mM) compared to apigenin (15.7% at 0.1 mM),[55] which might support the competitive inhibition of xanthine oxidase as a mechanism for the chrysin antioxidant activity. The *in vitro* antioxidant activity of chrysin against the oxidative stress of tert-butyl hydroperoxide on the neuroblastoma cell line, SH-SY5Y, has been measured by Campos et al.[56] The results revealed that chrysin has the ability to antagonize the tert-butyl hydroperoxide in the SH-SY5Y cell line and induce potential *in vitro* and *in vivo* neuroprotection against $AlCl_3$-induced lipid peroxidation and Fenton reaction in the SH-SY5Y cells and impairment of the levels of antioxidant enzymes, SOD and CAT, in the *in vivo* mouse model.[56] This activity could be explained by the ability of chrysin to chelate the transition metal ions and

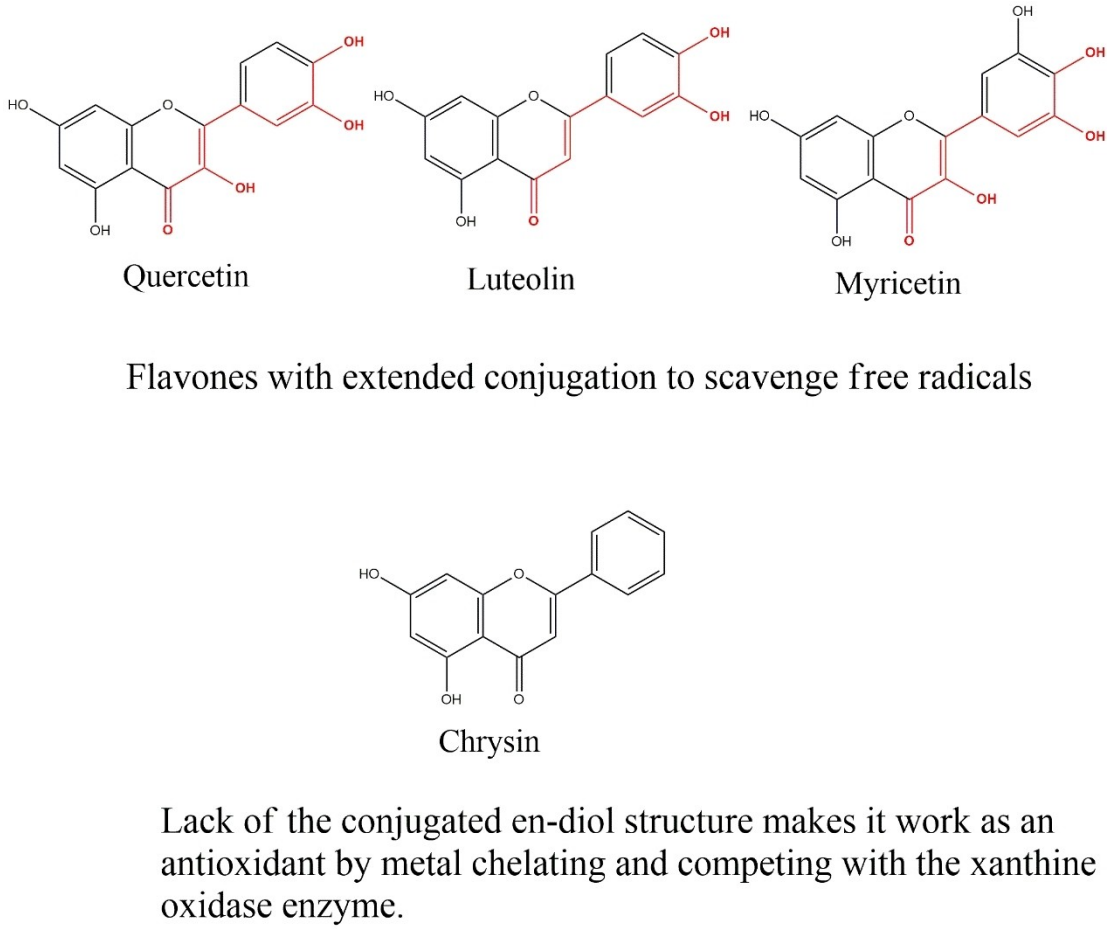


**Figure 3.** *In vitro* antioxidant activity of chrysin compared to other more hydroxylated flavones.

reduced the prooxidant enzymes,[37] as the chrysin also reported for its ability to regulated and restrained the transition metals levels, e.g., Fe, Cu, and Zn, in the rats brain leading to protection against cerebral ischemia reperfusion injury in the rats model.[57]

Therefore, the *in vitro* antioxidant activity of chrysin is mostly attributed to the metal chelating effect of the compound or the competition of the compound with the xanthine oxidase enzyme; however, the direct capturing activity of chrysin on the free radical is weak compared to the common antioxidant flavonoids (Figure 3).

### 2.2. In vivo Antioxidant Activity of Chrysin

In contrast to the *in vitro* antioxidant activity of chrysin, several reports have confirmed the remarkable *in vivo* antioxidant potency of the compound, which participates in the chrysin protection effect against different organs toxicity (Table 1). In that context, chrysin has been reported to reduce oxidative stress and induce neuroprotection in the mouse model of middle cerebral artery occlusion by reducing the expression of NF-κB, cyclooxygenase-2 (COX-2), and nitric oxide synthase (iNOS).[35] In addition, chrysin has also enhanced the age-related memory decline in the aged mouse model, which was attributed to the antioxidant activity of the compound that proved its effect in increasing the levels of the protective antioxidant enzymes, CAT, SOD, and glutathione peroxidase (GPx), and reducing the free radical concentrations, which were assessed by the dichlorofluorescein assay in the prefrontal cortex and hippocampus of the aged mice.[58] Therefore, the protective effect of chrysin on the cognitive decline in aged mice has been attributed to the antioxidant activity of the compound and the compound's ability to increase the aged-related decline level of the brain-derived neurotrophic factor (BDNF).[58] The neuroprotective effect of chrysin is also attributed to the compound's ability to reduce the levels of transition metals, e.g., Fe, Cu, and Zn, associated with oxidative stress in the brain, an effect that is attributed to the protective effect of chrysin against the injury in cerebral ischemia reperfusion in the rat model.[57] Chrysin is also reported to protect against aluminum phosphide-induced cardiovascular complications by reducing oxidative stress and mitochondrial damage.[59] In that model, chrysin has induced potential changes in the antioxidant (e.g., GSH) and oxidizing (e.g., GSSG and MDA) biomarker contents.[59] In addition, chrysin has significantly reduced mitochondrial oxidative biomarkers such as lipid peroxidation, ROS formation, and MMP collapse (Collapse of mitochondrial membrane potential).[59] In another *in vivo* model, chrysin has enhanced the total antioxidant capacity of the rat's serum in a dose-dependent manner, which is similar to the effect of the hepatoprotective agent silymarin.[60] This effect of chrysin has been implicated in its activity to reduce the liver cell necrosis and hepatic injury of acute acetaminophen-induced hepatotoxicity in the rat model. It was reported that chrysin administrated in rats treated with 2,3,7,8- tetra-chlorodi-benzo-p-dioxin normalized the level of antioxidant enzymes (SOD, GPx and CAT) and enhanced the level of GSH in rats' kidneys and livers. Chrysin has also been shown to protect the liver, kidney, and brain tissues of rats from oxidative stress induced by D-galactose.[61] The treatment of rats with chrysin has induced higher levels of vitamin C and vitamin E in addition to the antioxidant enzymes SOD, CAT, GPx, glutathione-S-transferase (GSTs), and glutathione reductase in the rats homogenates compared to the D-galactose oxidatively stressed rats.[61] The administration of chrysin has restored all the antioxidant parameters to the normal levels which have been significantly affected by the administration of D-galactose. Also, administration of chrysin to the intact rats has not been affected any of the previous antioxidant biomarkers.[61] The *in vivo* reducing oxidative stress activity of chrysin has been also reported against several oxidative stress inducers, e.g., doxorubicin induced cardiotoxicity,[62] ferric nitrilotriacetate induced renal cancer,[63] methotrexate induced liver toxicity,[64] and cisplatin induced neurodegeneration.[64] Table 1 provides the mechanisms by which chrysin induces protection against several medicament-induced oxidative stresses. The information in Table 1 indicated the beneficial effect of chrysin on all types of oxidative stress that might be induced by several drugs like doxorubicin and cisplatin and indicated the possible role of chrysin and chrysin-rich foods as protectives against the possible toxicity of these drugs and improving their therapeutic index. According to the data in Table 1, chrysin induces *in vivo* antioxidant activity in different organs in a similar way to other flavones, like quercetin and luteolin.[65–69]

### 2.3. Comparing the in vitro and in vivo Antioxidant Activity of Chrysin

The last two sections involved with *in vitro* and *in vivo* antioxidant activity of chrysin, which indicated that chrysin induced remarkable *in vivo* antioxidant effect by different mechanisms in similar ways to other flavonoids like quercetin and luteolin, however, the *in vitro* free radical scavenging activity of the compound is comparatively lower than the more hydroxylated flavonoids and the flavones with the extended conjugated en-diol structure, like quercetin, myricetin, and luteolin. The literature contains very few studies comparing the *in vivo* antioxidant activity of chrysin with that of other flavonoids. Such an *in vivo* and *in vitro* antioxidant activity comparison of chrysin and quercetin has been investigated by Sirovina et al.[86] They have measured the chelating and scavenging abilities of both flavonoids *in vitro*, in addition to their ability to reduce lipid peroxidation *in vivo* in diabetic mice.[86] The results of Sirovina et al. have indicated the significantly higher iron chelating activity of chrysin compared to quercetin, with chelating $IC_{50}$ of 15.57 and 121.33, respectively. The DPPH free radical scavenging activity of chrysin has been very weak compared to the more hydroxylated flavonoid molecule, quercetin, with scavenging $IC_{50}$ of 41.0967 and 0.3288, respectively. On the other hand, both compounds, chrysin and quercetin, have reduced the levels of peroxidation in the mice's liver tissues, with no significant variations between

**Table 1.** *In vivo* antioxidant activity of chrysin, and its protection role against oxidative stress inducers.

| Oxidative Stress Inducers/Doses | Used Models | Route of chrysin administration | Duration of treatment and dose of chrysin | Role of Chrysin | Ref |
|---|---|---|---|---|---|
| Acetaminophen/single dose of 1500 mg/kg. | Rats model for induction the liver toxicity. | Oral gavage | Two weeks at the doses of 10, 20, and 40 mg/kg body weight. | Elevated the total antioxidant capacity of the rat's serum. Reduced the liver enzymes, i.e., ALT, AST, and ALP, levels after their elevation by the acetaminophen. Alleviates the liver cells necrosis and injury induced by acetaminophen. Decreasing the level of the inflammatory mediator, TNF-α. | [60] |
| Acetaminophen/single dose of 500 mg/kg. | Male rats' model for reproductive damage. | Oral gavage | One week at the doses of 25 and 50 mg/kg body weight. | Protected the testicular tissue, enhance the sperms motility, and reduced the MDA levels in the testicular tissue. | [70] |
| Doxorubicin/single intraperitoneal dose of 15–20 mg/kg. | Rats Model for cardiotoxicity and testicle damage. | Oral route | 25 and 50 mg/kg for 7–12 days. | Pretreatment by chrysin has attenuated the oxidative damage on the myocardial cells through reduction of the elevated levels of SOD, CAT, and GSH. Chrysin also reduced the lipid peroxidation, expression of inflammatory mediators, NF-κB, iNOS, COX-2, and TNF-α. | [62,71] |
| Cisplatin/single intraperitoneal dose of 7.5 mg/kg. | Rats model for nephrotoxicity. | Oral route | 25 and 50 mg/kg for 14 days. | Decreased the DNA damage, lipid peroxidation, and xanthine oxidase levels. | [72] |
| Cisplatin/single intraperitoneal dose of 7.5 mg/kg. | Rats model for colon toxicity. | Oral route | 25 and 50 mg/kg for 14 days. | Increased GSH accumulation, and levels of SOD, GPx, glucose-6 phosphate dehydrogenase (G6PD), glutathione reductase (GR), and CAT. Decreased lipid peroxidation and xanthine oxidase activity. | [73] |
| Ferric Nitrilotriacetate/ single intraperitoneal dose of 9 mg/kg. | Rats mode for cancer induction. | Oral gavage | 20 and 40 mg/kg for 20 days. | Decreased iNOS and COX-2, and lipid peroxidation, IL-6, TNF-α and prostaglandin E2. Increased GSH levels. | [63] |
| Methotrexate/single intraperitoneal dose of 20 mg/kg. | Rats model for liver toxicity. | Oral route | 40 and 80 mg/kg for 20 days. | Deceased lipid peroxidase, AST, ALT, lactate dehydrogenase, and MDA contents. Increased the levels of GSH, GR, SOD, CAT, and GPx. | [64] |
| Lead Acetate/ 7 days oral dose of 30 mg/kg. | Rats model for nephrotoxicity. | Oral route | 25 and 50 mg/kg for 7 days. | Chrysin has enhanced the CAT, SOD, GPx activities, and GSH accumulation. Chrysin has also protect the DNA from the toxic effects of lead acetate and reduces the levels of 8-hydroxy-2′-deoxyguanosine, NF-κB, IL-33, Prostaglandin E2, TNF-α, p53, and COX-2, and iNOS. | [74] |
| Isoproterenol/double subcutaneous doses of 85 mg/kg on 27th and 28th days of the treatment. | Diabetic rats (induced by streptozotocin) for inducing myocardial injury. | Oral route | 60 mg/kg for 28 days. | Chrysin has enhance the expression of peroxisome proliferator activated receptor-γ and reduced the expression of NF-κB, p65/IKK-β and TNF-α which reflect the reduction of myocardial inflammation. | [75] |

**Table 1.** continued

| Oxidative Stress Inducers/Doses | Used Models | Route of chrysin administration | Duration of treatment and dose of chrysin | Role of Chrysin | Ref |
|---|---|---|---|---|---|
| | | | | Chrysin enhanced the expression of Bcl-2 expression and decreased Bax and caspase-3 expressions, which indicated that chrysin ameliorates the myocardial apoptosis. Chrysin was also reduced the levels of 8-Oxo-2′-deoxyguanosine, nitrotyrosine, thiobarbituric acid reactive substances, and eNOS; and increase the levels of GSH and manganese superoxide dismutase (MnSOD). | |
| Cyclophosphamide/ single intraperitoneal dose of 200 mg/kg 7th day of experiment. | Rats model for hepatotoxicity and nephrotoxicity. | Oral route | 25 and 50 mg/kg for 7 days. | Chrysin reduced the elevated levels of NF-κB, TNF-α, IL-1β, IL-6, iNOS, COX-2, ALT, ALP, AST, urea, creatinine, MDA, and hepatorenal deterioration. Also increased the levels of SOD, CAT, and GPx, and GSH. | [76] |
| Indomethacin/ single oral dose of 48 mg/kg. | Rats model for gastric ulcer induction. | Oral route | Single dose of 25, 50 and 100 mg/kg. | Over expression of PPAR-ɣ associated with enhancing the mRNA expression of M2 macrophages marker genes (Arg-1 and CD206) and downregulation of M1 macrophages marker genes (IL-6 and CCL3). Chrysin also induced angiogenesis by upregulation of vascular endothelial growth factor, (bFGF) and cluster of differentiation-31. Chrysin has also reduced the levels of TNF-α and IL-1β, and NF-κB; Enhance the GSH and reduced the MDA levels. | [77] |
| Acrylamide/ 50 μM. | Human lymphocytes model for oxidative damage and genotoxicity. | Direct treatment of cells | 10, 25, and 50 μM. | Chrysin increased the GSH and reduced the GSSG levels. Reduced ROS, LPO, and MMP collapse. | [78] |
| Streptozotocin/ single intraperitoneal dose of 60 mg/kg. | Rats lenses of streptozotocin-induced type 1 diabetic. | Oral route | 50 and 100 mg/kg for 28 days. | Chrysin increased the reduced glutathione level in the rat's lenses and did not affect the polyol pathway in the diabetic rats. | [79] |
| MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)/ two intraperitoneal doses of 40 mg/kg at 16 h interval on day 3 and 4 of the treatment | Mouse model for Parkinson's induction. | Oral route | 50, 100, and 200 mg/kg for 5 days. | Increased the concentration of GSH, SOD and reduced the expression of LPO levels. | [80] |
| Bleomycin/ single intratracheal instillation at 5 mg/kg. | Rats model for pulmonary fibrosis induction. | Oral route | 50 mg/kg for 6 weeks. | Reduced the lipid peroxidation, iNOS, NO, and thioredoxin-interacting protein (TXNIP). Increasing SOD and GSH levels. | [81] |
| Aggregated Amyloid-β25–35/ | Rats model for neurotoxication | Oral route | 50 and 100 mg/kg for 21 days. | Reduced lipid peroxidation and acetylcholine esterase. Increased CAT, SOD, GSH. | [82] |

**Table 1.** continued

| Oxidative Stress Inducers/Doses | Used Models | Route of chrysin administration | Duration of treatment and dose of chrysin | Role of Chrysin | Ref |
|---|---|---|---|---|---|
| Intracerebroventricular injection of 10 μg/rat. | and Alzheimer's induction. | | | | |
| Atherogenic Diet for 15 days. | Rats model for induction of atherosclerosis. | Oral route | 200 mg/kg for 15 days. | Induced significant reduction in the lipid profile and hepatic biomarkers (ALT, AST, and ALP) and induced hepatic levels of lipoprotein lipase, 3-hydroxy3-methylglutaryl-coenzyme A reductase, CAT, SOD, GPx and increased the levels of GSH, vitamin C and vitamin E. | [83] |
| Carbon Tetrachloride/ 2 mL/kg prepared as 50% CCl4 in olive oil. | Rats model for soft tissues toxicity. | Intraperitoneal | Two doses of 200 mg/kg. | Reduced the liver enzymes ALT, AST, ALP, and LDH to the normal levels and increased the concentration of GSH, vitamin C, and vitamin E non-enzymatic antioxidant compounds. Chrysin also increased the levels of CAT, SOD and Gpx and return the iNOS expression to the normal levels. | [84] |
| AlCl3/daily doses of 100 mg/kg for 90 days. | Mouse model of neurotoxicity | Oral route | 10, 30 and 100 mg/kg for 90 days. | Chrysin elevated the CAT and SOD levels and reduced the lipid peroxidation, protein carbonylation. | [56] |
| Methylmercury/ 30 μg/kg. | Rats model for Genotoxicity | Oral gavage | 0.1, 1 and 10 mg/kg for 45 days. | Chrysin restored the GSH levels after depletion with methylmercury. | [85] |

them.[86] These results explained the *in vivo* antioxidant activity of chrysin, which might be attributed to the chelating activity of the compound, leading to the reduction of metal ions involved in the Fenton reaction and oxidative stress induction.[87] It also seems that chrysin has the *in vivo* ability to reduce the synthesis of free radicals; however, its ability to neutralize the developed reactive oxygen species is low compared to the flavonoids with hydroxyl groups in the B-ring.

### 2.4. Mechanisms of Chrysin Antioxidant Activity Compared to Other Flavones

There are two primary processes that have been documented for the antioxidant activity of flavonoids: the transition-metal chelating mechanism, which suppresses the generation of free radicals, and the direct free radical scavenging mechanism, which involves hydrogen-atom transfer (electron transfer).[88] The position and number of hydroxyls in the flavonoid structure have a great influence on the antioxidant activity. The presence of a 4-keto group, a 2,3-double bond, hydroxyl groups at the C-5 and C3, and ortho-dihydroxy catechol in ring B have been reported as characteristic antioxidant features of the flavonoids.[89] Due to its lack of the 3-OH and catechol ring, chrysin only has a little effect of radical scavenging action, returning only to the presence of the 4-keto and 2,3 double bond system.[88] The 7-OH hydroxyl group of chrysin likely has a role in the scavenging activity of the compound through its involvement in the formation of the intermediate chrysin-radical.[90] The reason behind the lower free radical scavenging effect of chrysin might also be that its 5-OH group is regularly involved in hydrogen bonding with the neighboring carbonyl group at position C-4 and has not participated in the radical scavenging effect of the compound.[91] However, the hydroxyls on the B- and/or C-rings in other flavones like quercetin, luteolin, and apigenin are mostly involved in the oxidation and stabilization processes of these flavonoids by the free radicals, enhancing their free radical scavenging effect compared to chrysin.[92] On the other hand, Selvaraj et al. have suggested that the 5-OH of chrysin could have a potential role in the free radical scavenging effect of the compound, the effect of which is mostly attributed to the electron transfer following the formation of chrysin-phenolate in an alkaline medium[88] (Figure 4). Even so, chrysin with a lack of hydroxylation on the B- and C-rings of the structure is a weak free radical scavenger compared to the flavones containing these hydroxyls in their structures, e.g., luteolin, myricetin, quercetin, and apigenin.

Several antioxidant assays have indicated the ability of chrysin to inhibit the generation of superoxide anion ($O_2^-$) through competitive binding of chrysin with the xanthine substrate to the active side (cavity) of the xanthine oxidase enzyme, the effect which inhibits the enzyme and involved in the reduction or inhibition of $O_2^-$ generation.[49,51–53,93] The mechanisms by which chrysin inhibits xanthine oxidase involve

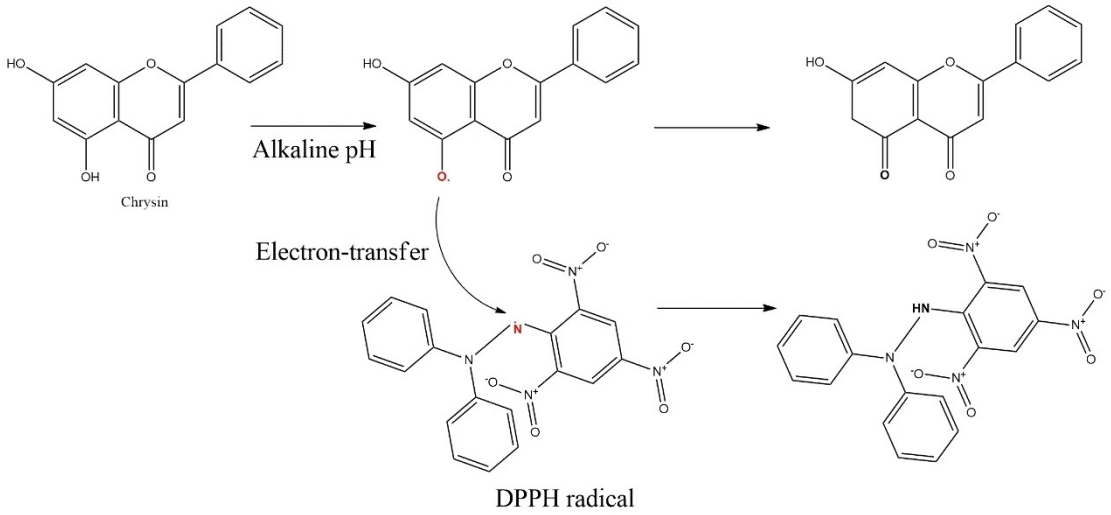


**Figure 4.** Proposed free radical scavenging mechanism of chrysin involving the 5-OH group in the alkaline medium.

enzyme conformation alterations, with α-helix and β-sheet expansions and β-turn and random coil structures decreasing, as indicated by the circular dichroism analysis.[94] In addition, van der Waals forces and hydrogen bonding between chrysin hydroxyls and several xanthine oxidase amino acid residues, e.g., valine, phenylalanine, glutamic acid, leucine, serine, arginine, and threonine, have been reported by chemical modeling simulation studies as possible interactions between chrysin and xanthine oxidase.[93,94] By this mechanism, chrysin exhibited a much better reduction effect on the generation of superoxide anion ($O_2^-$) compared to apigenin.[55] However, compared to quercetin, chrysin has been reported to have a lesser anti-$O_2^-$ generation effect.[95] Contrarily, chrysin had less free radical scavenging action in comparison to flavones that had a higher hydroxyl content, particularly those flavones that had a conjugated en-diol structure within the molecule.[49]

Part of the chrysin antioxidant effect could also be returned to the compound activation of the antioxidant enzymes, including SOD, CAT, GPx, G6P, MnSOD, and GR. Chrysin has also been reported to increase the levels of blood antioxidant components such as GSH, vitamin C, and vitamin E. In addition, chrysin has been induced reduction in the expression of inflammatory mediators, like NF-κB, iNOS, COX-2, and TNF-α, the effect which also related to the *in vivo* antioxidant activity of chrysin.[60,62,64,70–72,74] Furthermore, chrysin have been also decreased the elevated levels of xanthine oxidase, DNA damage, and lipid peroxidation in several stressed animal models[72] (Table 1). Through such effects, chrysin has the potential to elevate the overall antioxidant capacity of the body, protect soft tissues like the brain, heart, kidneys, and liver, prevent DNA damage, and prevent protein modification.

## 3. Metabolism and Bioavailability of Chrysin

Flavonoids are a large group of natural polyphenols present in most plants, including medicinal and edible plants. The literature evidenced the presence of more than seven thousand different structures of flavonoids, including aglycones and glycosylated molecules with different levels of polarity and solubility. This large variation in flavonoids as a class of natural products primarily influenced the bioavailability of these compounds and their availability in biological systems.[6,96,97] Thereby, the bioavailability of flavonoids is an important factor affecting the efficacy and biological activities of each individual flavonoid compound.[98] Compared to other flavonoids like quercetin, myricetin, luteolin, and kaempferol, chrysin has low hydroxylation levels in its three rings, A, B, and C (Figure 1). In addition, chrysin is an aglycone compound that lacks any connections to sugar molecules. These two structural features of chrysin affect the compound's solubility in aqueous media and subsequently affect its bioavailability and efficacy.[99,100] In the study by Walle et al., 400 mg of chrysin was given to a group of healthy individuals to determine its distribution and metabolites. The majority of the chrysin has been passed in the feces without modifications, according to the HPLC examination of the volunteer's plasma, urine, and feces sample. Chrysin and its glucuronide have also been discovered in urine samples, with concentrations ranging from 0.2 to 3.1 mg and 2 to 26 mg, respectively. A nanogram concentration of chrysin as a sulfated metabolite has also been found in the plasma of chrysin-administered individuals.[101] Furthermore, the experiment of Labib et al., indicated that chrysin has not been changed to any metabolites by the pig intestinal flora under anaerobic experimental conditions; however, more hydroxylated flavonoids like quercetin, hesperetin, and naringenin have been converted to several metabolites, e.g., phloroglucinol, 3-(3-hydroxyphenyl)-propionic, and 3-phenylpropionic acid, by the microflora under the same experimental conditions.[102] Similar findings have also been reported by Griffiths et al., who report that neither an increase in the size or intensity of hippuric acid spots in the test urine samples, nor any phenolic acid metabolites of chrysin, were observed in the urinary excretion of rats administered chrysin (200 mg) by stomach tube. Furthermore, Griffiths et al.

reported that incubation of chrysin with the microflora at the recommended conditions did not result in the development of any metabolites.[103] These results might indicate that chrysin, unlike other flavonoids, induces *in vivo* antioxidant activity through its intact structure and not through its metabolites. The promising activity and poor bioavailability of chrysin have encouraged researchers to try to enhance the compound's availability in the biological system through the incorporation of chrysin in different nanoforms.

## 4. Chrysin Metal Complexes for Enhancing the Antioxidant Activity

Several complexes of chrysin have been synthesized to improve the antioxidant activity of the compound. For example, the chrysin-Cu (II) complex has been synthesized by Lin et al. to improve the xanthine oxidase inhibition of the chrysin.[93] They have found that the synthesized complex (chrysin-Cu (II)) exhibited xanthene oxidase inhibition much higher than the free flavone, chrysin. According to the chemical modeling, it has also been found that the complex is introduced into the xanthene oxidase active cavity, while Cu (II) serves as a bridge.[93] Computational analysis has indicated that replacing the ketonic oxygen group of chrysin with selenium or sulfur analogues results in enhancing the scavenging activity of chrysin.[104] Experimentally, the chalcogenation of chrysin with selenium or sulfur has been reported to enhance the DPPH-free radical scavenging activity and antioxidant activity of chrysin compared to the oxo-analogue of the compound.[91] The synthesized vanadyl (IV) complex of chrysin has been prepared for antioxidant comparison with pure chrysin by Naso et al.[105] The complex has exerted better $ABTS^{+}$ (diammonium-2,2′ Azino-bis(3-ethylbenzothiazoline-6-sulfonate) and hydroxy radical ($OH^{\bullet}$) scavenging activity compared to the plain chrysin.[105] Halevas et al. have synthesized chrysin and quercetin Zn(II) complexes with the ancillary aromatic chelator 2,2′-bipyridine for biological evaluations. The chrysin complex has free radical scavenging activity comparable to vitamin C and significantly inhibits the DPPH free radical compared to the plain chrysin at all the tested concentrations (0–200 μg/mL).[106] However, complexation of quercetin with Zn(II) and 2,2′-bipyridine has resulted in reducing the free radical scavenging of the compound.[106] Jiang et. al., have synthesized chrysin Organogermanium, Ge (IV) complex and tested its antioxidant activity compared to chrysin. The results again supported the higher antioxidant activity of the chrysin metallic complex, which was evaluated against DPPH free radical and by using normal breast epithelial cells oxidative stress model.[107] When compared to free chrysin, chrysin metal complexes are mostly found to be more antioxidant activity. The enhanced antioxidant activity of the chrysin complexes could be attributed to the metal ions' electron-withdrawing effect, which makes it easier for the hydrogen of the 7-OH of chrysin to be released and scavenge the free radicals.[106]

## 5. Chrysin Nano-formulation for Enhancing its Bioavailability and Antioxidant Activity

The antioxidant properties of chrysin, along with its anti-inflammatory effect, make it a superior therapeutic candidate in different kinds of diseases such as oxidative stress and apoptosis in neuronal cells, epilepsy, various neurological diseases, skin protective effects, multiple sclerosis, Alzheimer's disease, aging, cognitive deficits, Parkinson's disease, anxiety, depression, hepatotoxicity, nephrotoxicity, gastrointestinal protective effects, Guillain-Barre syndrome, and multiple types of cancer cell lines due to its activity to inhibit cell proliferation and induction of cell death via the apoptosis pathway (Figure 2).[34,36,38–41,43,45,56,108,109] However, the poor water solubility of chrysin limits its bioavailability, biocompatibility, and biomedical applications, emphasizing a large problem in its therapeutic applications.[110]

Chrysin nanoparticles compared to bulk chrysin have bee, and TNF-α, in the popolysaccharide induced elevation of cytokines in the J774A1 cell line model.[111] The chrysin conjugated gold nanoparticles has been prepared as evaluated for the potential antimicrobial, cytotoxic, and *in vitro* antioxidant activities.[112] The results of antioxidant activity have demonstrated significantly higher capture of free radicals by the chrysin-conjugated gold nanoparticles compared to pure chrysin, with DPPH scavenging effects of 91.3 and 52.1%, respectively. The increased antioxidant activity could be attributed to the synergistic effect of gold nanoparticles, which have shown a scavenging effect of 74.9% against DPPH radical molecules.[112] The study has also shown superior antimicrobial and cytotoxic effects of the chrysin-gold nanoparticles compared to pure chrysin.[112]

Recently, the biological activity of bioactive molecules and numerous medications has been enhanced and sustained in potency using biodegradable polymeric nanocapsules,[98,113] which have unique adjustable electrical conductivity and biodegradability features, making them attractive in many applications (Figure 5).

Two of the most widely utilized polymers in recent years are polyvinyl alcohol (PVA) and poly (D,L-lactic-co-glycolic acid) (PLGA).[114] Synthetic polymers such as poly (D,L-lactide), poly (D,L-glycolide), co-polymer poly (lactide-co-glycolide), poly (alkyl cyanoacrylates), and polycaprolactone are also examples of biodegradable polymers. They are regarded as safe, and a few biodegradable polymer products have received approval for pharmaceutical use from both the European Medicines Agency and the United States Food and Drug Administration.[115–117] The chrysin-conjugated poly (D,L-lactic-co-glycolic acid) and polyvinyl alcohol have been prepared by Sulaiman et al. and evaluated for their antioxidant and cytotoxic effects, which revealed the enhanced bioavailability of the prepared nano-chrysin and its DPPH-free radical scavenging and cytotoxic effects compared to the raw chrysin materials.[118] The nano-chrysin has been synthesized and evaluated for its *in vitro* antidiabetic and antioxidant activities by Khalid and Naseem.[119] The results have proven that the reduced nano-

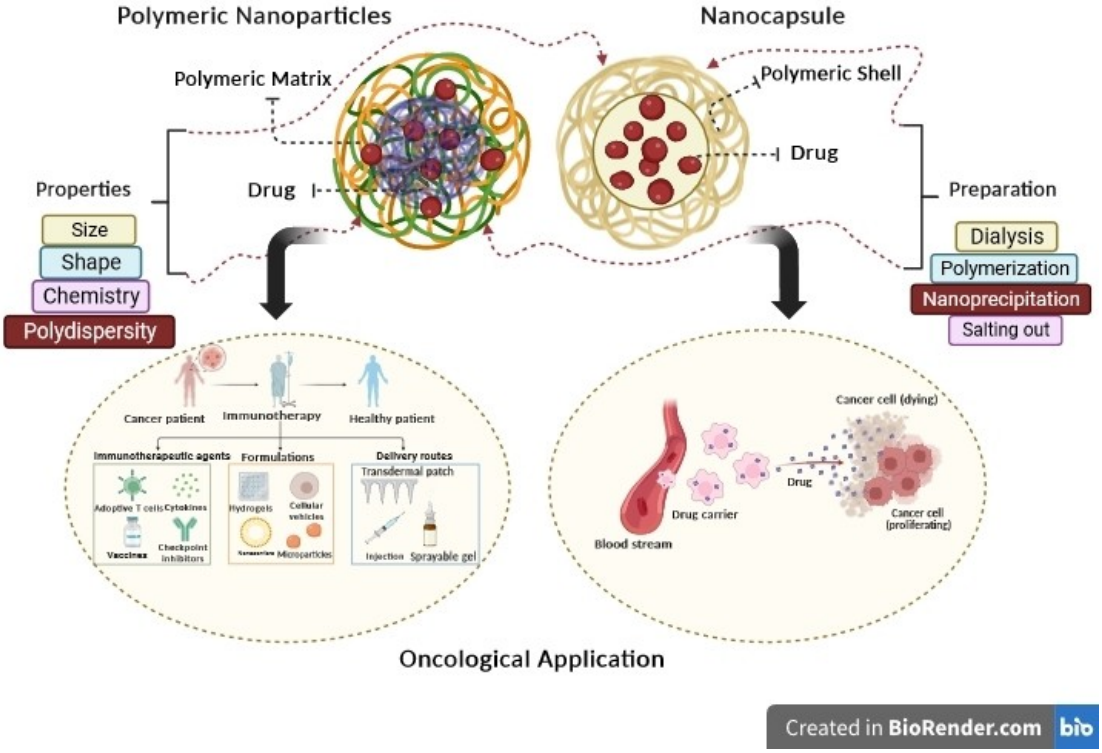


**Figure 5.** Summary of the key characteristics of nanoscale polymers.

form of chrysin has better activities compared to the bulk form of the compound, which might be attributed to the improvement in the compound's solubility.[119]

Chrysin nanoparticles have also been evaluated for their antioxidant activity *in vivo* in several animal models. For example, an efficient solid lipid nanoparticles (SLN) of chrysin has been formulated to enhance the bioavilability of the compound and for the treatment of Alzheimer diseases.[82] The formulation (chrysin-SLN), compared to the pure chrysin, has restored the deteriorated levels of the antioxidant enzymes, i.e., SOD and CAT, antioxidant compounds, such as GSH, and the elevated levels of lipid peroxidation and acetylcholine esterase, which have been induced by the Amyloid-β25–35 and resulted in the reduction of memory retention in rats.[82,120] Chrysin-loaded chitosan NPs were evaluated in zebrafish as neuroprotective agents against amyloid-β-induced toxicity. The nanocomposite aids in maintaining synaptic connections, memory, and cognition, all of which are otherwise hampered by amyloid-β toxicity. Moreover, lowering amyloid-aggregates was associated with a reduction in neuronal death and the production of ROS. Additionally, chrysin-loaded nanoliposomes were reported to reduce the signs of cadmium-induced toxicity when given to mice at levels of 2.5 and 5 mg/kg. Chrysin-loaded nanoliposomes altered liver enzymes, reduced hepatic oxidative stress, and enhanced the morpho-histological structure of the jejunum (the height and width of the intestinal villi), as well as promoted the deposition of antioxidant minerals.[121] The protective effect of nano-chrysin conjugated poly (lactic-co-glycolic acid) against neuronal damage induced by pentylenetetrazole in rats as a kindling model for epilepsy has been studied by Zhang et al.[122] Compared to the pure chrysin, the formulation has reduced the oxidative stress in the rats by elevating the SOD and GSHPx levels, reduced MDA, and induced Nrf2, heme oxygenase1 (HO-1), and NAD(P)H quinone oxidoreductase 1 as protective factors against epilepsy.[122]

## 6. Conclusions

One of the significant bioflavonoids with distinct biological and therapeutic activities is chrysin. The compound, which is extensively present in medicinal plants, is the main flavonoid in honey, propolis, and passionflower. When compared to other flavones like quercetin and luteolin, the chemistry of chrysin molecules indicated a lack of conjugated en-diol structures and low levels of hydroxylation. The compound has only two hydroxyls attached to the C-5 and C-7 to the ring A. The *in vitro* antioxidant activity of chrysin is related to the metal chelating effect of the compound or the competition of the compound with the xanthine oxidase enzyme; however, the direct capturing activity of chrysin on the free radical is weak compared to the common antioxidant flavonoids. However, chrysin induces *in vivo* antioxidant activity in a similar way to other flavones, like quercetin and luteolin, and has a beneficial effect against oxidative stress inducers such as doxorubicin and cisplatin. The study of chrysin metabolism indicated that unlike other flavonoids, chrysin has not been changed to any metabolites, e.g., phloroglucinol, 3-(3-hydroxyphenyl)-pro-

pionic, and 3-phenylpropionic acid, by the animal intestinal flora, which might indicate that chrysin induces *in vivo* antioxidant activity through its intact structure and not through its metabolites. The poor bioavailability of chrysin has been improved by incorporating the compounds through several research trials into many types of nanoparticles, which have enhanced the solubility, bio-accessibility, and bioavailability of the compound compared to bulk chrysin materials.

## 7. Abbreviations

| | |
|---|---|
| NMR | Nuclear Magnetic Resonance |
| NF-kB | Nuclear factor kappa B cell |
| STAT3 | Signal transducer and activator of transcription 3 |
| Notch 1 | Neurogenic locus notch homolog protein 1 |
| PI3K | Phosphoinositide 3-kinase |
| HIV | Human immunodeficiency virus |
| DPPH | 1,1-diphenyl-2-picrylhydrazyl |
| SOD | Superoxide dismutase |
| CAT | Catalase |
| COX-2 | Cyclooxygenase-2 |
| iNOS | Nitric oxide synthase |
| GPx | glutathione peroxidase |
| BDNF | Brain-derived neurotrophic factor |
| GSH | Glutathione |
| GSSG | Glutathione disulfide |
| MDA | Malondialdehyde |
| ROS | Reactive oxygen species |
| MMP | Mitochondrial membrane potential |
| GSTs | Glutathione-S-transferase |
| AST | Aspartate aminotransferase |
| ALP | Alkaline phosphatase |
| TNF-α | Tumor necrosis factor alpha |
| G6PD | Glucose-6 phosphate dehydrogenase |
| GR | Glutathione reductase |
| LPO | Lipid peroxidation |
| HPLC | High-performance liquid chromatography |
| PVA | Polyvinyl alcohol |
| PLGA | poly (D,L-lactic-co-glycolic acid) |
| SLN | Solid lipid nanoparticles. |

## Funding

This research received no fund.

## Declarations

**Ethics Approval**

Not applicable.

## Consent to Participate

Not applicable.

## Consent for Publication

Not applicable.

### *Author Contributions*

H.A.M, conceptualization; H.A.M, G.M.S., S.A., A.Z.Al-S., F.A.E., and E.A.R, wrote the main manuscript text; H.A.M, G.M.S., S.A., A.Z.Al-S., prepared figures, H.A.M, and E.A.R, reviewed the manuscript.

### *Acknowledgements*

The authors extend their appreciation to the institutes and organizations that they were belonging to. The authors also thank Prof. Dr. Riaz Khan for revising the English language of the manuscript.

### *Conflict of Interests*

The authors declare no conflict of interest.

### *Data Availability Statement*

All the data are available in the manuscript.

**Keywords:** Anticancer · Cytotoxicity · Chrysin, 5,7-dihydroxyflavone, antioxidant · *in vitro* antioxidant · Nanotechnology

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Manuscript received: August 20, 2023