Chrysin, an Important Active Ingredient of Honey: 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. Flavonoids are found primarily throughout the plant kingdom and are synthesized as secondary phenylalanine metabolites in plants. This chapter was mainly focused on the flavone chrysin (5,7-dihydroxyflavone), which occurs naturally in many plants, honey, and propolis. Chrysin has been known to have various pharmacological activities, including antioxidant, anti-inflammatory, anticancer, and antiviral activities through inhibiting multiple pathways.

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Keywords

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19.1 Introduction

Prehistoric evidence has demonstrated that humans use natural ingredients to cure different symptoms and even infectious and cancerous diseases (Dias et al. 2012). The use of natural products for medicinal purposes has a rich history. Such practices go back thousands of years from Sumerians, Akkadians, India, and China. Previously thought of as "traditional medicine" used by native or ancient cultures, herbal medicine has arisen as a common supplement or addition to conventional medicine (Rehman et al. 2018). Natural products historically used for treatment that include whole or portions of organisms such as plants (flowers, stems, or roots), animal products (glands or organs), microorganisms, or inorganic salts without thorough processing (Pan et al. 2013). The production and use of natural products for human well-being have developed and grown through the years by trial and error method (Cragg and Newman 2013). Based on the current statistics of the World Health Organization, approximately 70% of the global population are utilizing traditional medicine for certain type of primary health care (Ekor 2014). Botanical dietary supplements alone are projected to surpass $3 billion a year in the United States (Bailey 2020). The rich history of bioactive compounds used in medicine and the confirmation of their structural nature should be viewed as unsurprising because coevolution of flora and fauna has resulted in similarity with the building blocks inherent in both organisms (Hu et al. 2015). Natural products have structural diversity throughout many species in the world and therefore share comparable structural domains with biological targets. Phytochemicals can therefore fit in perfectly throughout the chemical area of target proteins, e.g., interaction with targets in human signal transduction pathways (Yi et al. 2018).

19.2 Chemistry and Occurrence

Flavonoids are secondary metabolites in plants. It has extensive class of polyphenolic compounds having a benzo–γ–pyrone complex with immense biological activities (Pietta 2000; Pasini et al. 2013). They are synthesized by phenylpropanoids pathway and are responsible for many pharmacological activities (Tian et al. 2014). Among the flavonoids, a hydroxylated flavone derivative is known as chrysin. Chrysin is mainly found in honey, propolis, and some plants (Hadjmohammadi et al. 2010; De Vries et al. 1997). Flavonoids are polyphenols with patterns of hydroxylation and when substituted it gives rise to various groups such as flavanones, anthocyanins, flavonols, flavones, isoflavonoids, and chalcones (Fig. 19.1).

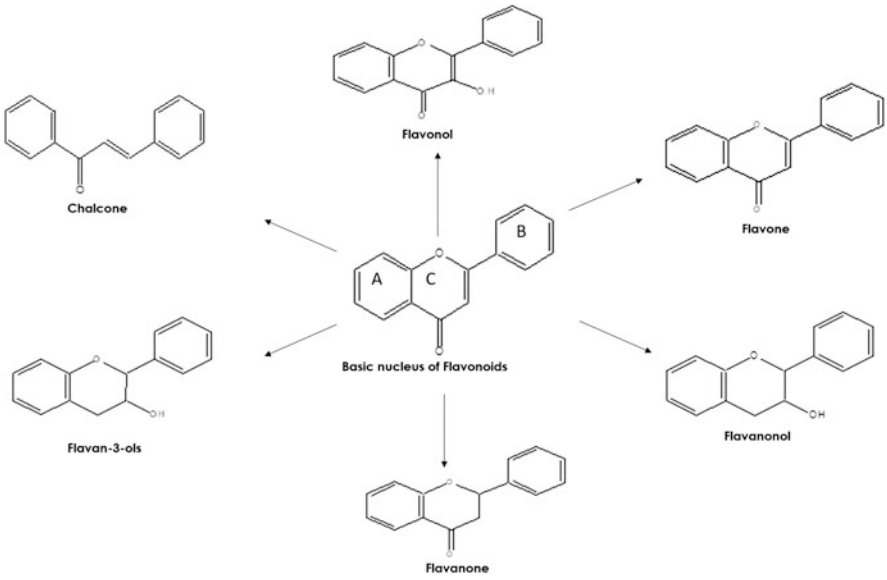

Fig. 19.1 Classification of flavonoids

Flavonoids have varied biological activities including but not limited to antiulcer, antioxidant, anti-atherosclerotic, antibacterial, anti-inflammatory, hepatoprotective, and anticancer, etc. (Beecher 2003; Mercan et al. 2006). They are also inhibitors for many enzymes, for example, cyclooxygenase, xanthine oxidase, phosphoinositide 3-kinase, and lipoxygenase (Walker et al. 2000; Panche et al. 2016). The functions of flavonoids in various bioactivities are shown in Fig. 19.2.

Chemically flavonoids were categorized on the basis of a 15-carbon structure composed of two benzene rings A and B as shown in Fig. 19.3a are attached by a heterocyclic pyrane ring (C) (Kumar and Pandey 2013). Chrysin (5,7-dihydroxyflavone or 5,7-dihydroxy-2-phenyl-4Hchromen-4-one) (Fig. 19.3b) is a naturally occurring flavone, found abundantly in plant extracts, honey, and bee propolis and many plant species. The IUPAC name used for chrysin is 5,7-dihydroxy-2-phenyl-4H-chromen-4-one (3) and with the chemical formula $C_{15}H_{10}O_4$ (Siddiqui et al. 2018). Chrysin has a characteristic feature which is the presence of double bond at C2–C3 in ring C and the lack of oxygenation at C-3. Chrysin, a dihydroxy flavone has a double bond between C-2 and C-3, and the ring B will be coplanar with the rings A and C due to conjugation. The exact mechanism for antioxidants always seemed to be correlated with the A-ring hydroxyl groups, although the influence of the A-ring on antioxidant activity is perhaps not clear. In addition, the C2–C3 double bond in carbonyl containing the C ring and the two hydroxyl groups in positions 3 and 4 in the B-ring are widely known as important structural patterns for the biological activities of flavonoids (Seetharaman et al. 2017; Naz et al. 2019).

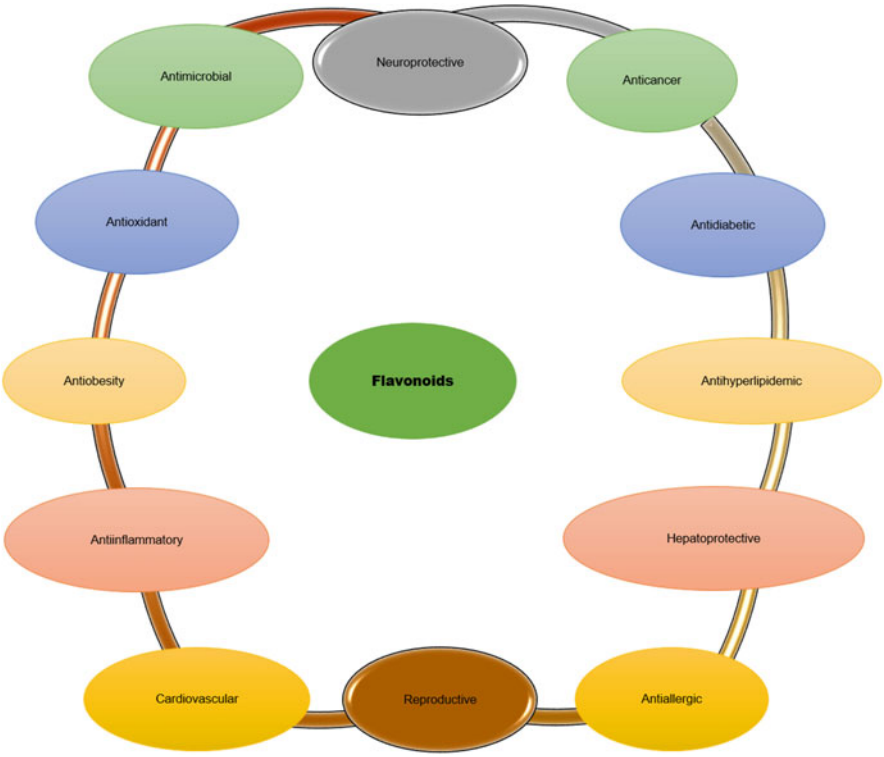

Fig. 19.2 Biological activities of flavonoids

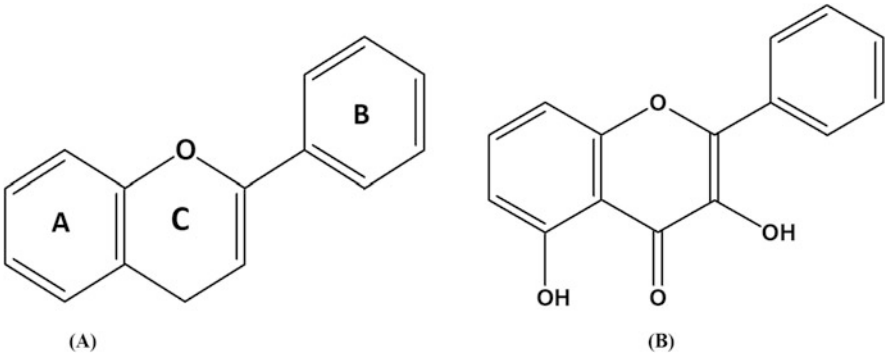

Fig. 19.3 (**a**) Chemical structure of flavonoids and (**b**) chrysin

Chrysin is a natural flavonoid with a wide spectrum of pharmacological behavior including anticancer neuroprotective, antidiabetic antihyperlipidemic anti-inflammatory, hepatoprotective, reproductive, cardiovascular, anti-allergic, anti-obesity, antioxidant as well as its antimicrobial action, they contain extensive

therapeutic activities that were found to be beneficial for the human well-being; therefore, the research conducted on flavonoids has grown immensely in the past few years as they have proven to function through physiological mechanisms as well as multiple significant signaling pathways that take part in numerous diseases implicating on human health (Pietta 2000).

19.3 Pharmacological Activities

19.3.1 Anticancer

Cancer is a real concern for public health around the world, it is a category of diseases identified by unmanageable proliferation as well as maturation of atypical cells that take over and metastasize to different areas of the human body (Salimi and Pourahmad 2018). Chrysin has proven to stimulate apoptosis and suppress proliferation in the majority of cancer cells and an efficient suppressor of tumor cell-induced angiogenesis (Jemal et al. 2011) and it is stronger and more efficacious than alternative flavonoids tested to treat leukemia cells, chrysin is to be expected to function inside the cell by triggering caspases and arresting AKT signaling. Furthermore, the relationships between structure and activity have shown that chrysin chemical structure contains the key structural components required by flavonoids to obtain efficacious cytotoxicity in leukemia cells (Fu et al. 2007).

In carcinoma cells and human tongue squamous cell chrysin causes amplified proline dehydrogenase/proline oxidase and the proline metabolism, therefore, a reduction in proline concentration, prolidase activity, and collagen biosynthesis (Celińska-Janowicz et al. 2018). Chrysin has a combined effect with metformin in which it suppresses the cyclin D1 gene and hTERT expression in breast cancer T47D cell lines (Campos et al. 2018). In addition to its combination effect with metformin, chrysin has a combined effect with cisplatin in where it considerably increases the HepG2 cancer cell apoptosis. The flavonoid has the ability to activate ERK1/2 which in turn steadies p53 gene expression, therefore, enhancing p53 phosphorylation in HepG2 cells (Li et al. 2015) Furthermore, alterations in b-arrestin-2 expression, an adaptable signaling molecule, second to chrysin addition affect multiple signaling pathways (Khan et al. 2011).

Treatment with chrysin decreases the action of NF-κB transcription factor, NF-κB is redox-active, and maintains the antioxidant armory. During renal carcinogenesis, chrysin suppresses biomarkers that encourage tumors and inflammation hence is a possible applicant for the hindrance of renal carcinogenesis (Rehman et al. 2013).

Melanoma tumors significantly showed a decrease in MMP-9, MMP-2, and TERT gene levels were markedly present in C57B16 mice with B16F10 melanoma tumors treated with nanoparticle-based chrysin; however, it exaggerated TIMP-2 and TIMP-1 genes expressions (Celińska-Janowicz et al. 2018; Choi and Yun 2011). Chrysin and curcumin nano-encapsulation enhanced the transmission of these compounds in colorectal cancer cells, Caco-2, and SW480 substantially inhibiting the maturation of cancer cells, as it reduces the expression of hTERT gene by

increasing the solubility as well as bioavailability of these therapeutic agents (Darwish et al. 2014). Among the different types of cancer chrysin has shown, therapeutic effects are against hepatocellular carcinoma (HCC) through multiple pathways. Cell apoptosis was encouraged; the combinations of VDAC-1 and HK-2 on mitochondria were substantially reduced moving Bax to the mitochondria from its original site the cytoplasm. Chrysin-mediated glycolysis suppression and cell apoptosis were severely damaged in exogenous overexpression cells HK-2. Further on it has been documented that tumor growth has been restrained in models of HCC xenograft as well as substantially decreased HK-2 expression with chrysin treatment (Davaran et al. 2018).

Ryu and their colleagues performed a study on PC-3 and DU145 cancer cell lines of the prostate, it was proven that chrysin induced fragmentation of the DNA as well as considerably induced apoptosis moreover inducing sub-G1 phase cell cycle cessation, and declining the extent of elevation of cell nuclear antigen proliferation. It accordingly caused the depletion of MMP conjointly with exaggerating lipid peroxidation and the yield of ROS as per the dose administered. Similarly, endoplasmic reticulum (ER) stress was aided by chrysin through inducing unfolded protein response (UPR) including translation eukaryotic initiation factor 2α (eIF2α), PRKR-like ER kinase (PERK), and 78 kDa glucose-regulated protein (GRP78). The intracellular signaling pathways mediated by chrysin-induced mitogen-activated protein kinases (MAPK), P38, and ERK1/2 proteins activated in association with inhibiting phosphoinositide 3-kinase (PI3K) and the majority of P70S6K, AKT, S6 proteins, and P90RSK (Durak et al. 2016). In conclusion, chrysin is an efficient inhibitor of tumor cell-induced angiogenesis; hence, it has the ability to postpone the formation of the tumor on the contrary to inhibiting the tumor formation (El-Bassossy et al. 2014).

Chrysin-loaded nanoparticles tumors were used in the treatment of breast tumors as it has been reported that the flavonoid enhances the pronouncement of TIMP-1 and 2 and decreases the pronouncement of MMP-2 and 9 therefore prevents the metastasis of the cancer (Eatemadi et al. 2016; Mohammadian et al. 2016). Chrysin provides optimum effects in breast cancer cell (BCC) lines when encapsulated as observed in the expression of the genes hTERT, BRCA1, and FTO. Likewise, in an alternative study, it had been determined that encapsulating chrysin in nanoparticles of PLGA-PEG amplified the expressions of three genes in the human gastric cell line, miR-34a, miR-22, and miR-126 (El-Sisi and Abdelsalam 2017). A concentration of chrysin (25 mg/kg and 50 mg/kg) was found to be very effective in opposition to MCF-7 breast cancer cells, it established extraordinary growth inhibition as well as induction of apoptotic (Mani and Natesan 2018).

Chrysin is a flavonoid with established anticancer activity and is effective on multiple different cell lines including prostate cancer, breast cancer, leukemia, melanoma, squamous cell, and finally colorectal cancer. Its anticancer activity makes it a flavonoid with momentous use therefore obtaining interest for its therapeutic use among scientists (Naz et al. 2019).

19.3.2 Neuroprotective

Chrysin has a wide variety of neuroprotective properties including neuroinflammatory where it showed substantial results in Parkinson's disease. Alzheimer also including antidepressant effects that were tested and proven on mice as well as its antiepileptic effects due to chrysin's containing a ligand for the benzodiazepine receptors (Nabavi et al. 2015). An increase in the production of oxidative stress may be the cause of the deleterious impact on signal transductions RhoA and ERK1/2 that aims for the modified cytoskeleton, most likely by acting on membranes, proteins, as well as DNA by stimulating lipid peroxidation.

Furthermore, astrocytes have shown effects on pro concentrations, they reorder their cytoskeleton, as well as make it across RhoA and ERK-mediated mechanisms. A type of polyvalent cells are astrocytes that are active in most of the processes that take place in the CNS, the effects of chrysin can be appreciated given how fragile the cytoskeleton astrocytes are (Loureiro et al. 2013). Oxidative stress was proven to reduce which therefore elevated the extent of brain damage. Furthermore, a decrease in cell death by the suppression of apoptosis was proven when exposed to chrysin, with lipid peroxidation induction that is associated with toxicity of acrylamide. The free radical scavenging effect of chrysin has been reported to be the most significant molecular mechanism in neuroprotection (Souza et al. 2015; Sathiavelu et al. 2009).

A report has shown oxidative stress and memory impairment is lowered effectively due to the administration of chrysin with reduced levels of brain-derived neurotrophic factor (BDNF) in matured mice's brain hence delegating as an antiaging agent (Zhang et al. 2015). In addition to chrysin acting as an antiaging agent, it contains antioxidant and antiapoptotic potential by inhibiting oxidative impairment, associating with tumor necrosis factor-alpha (TNF-α) and IL-β, and is in association with bcl-2 and caspases, hence elaborating motor as well as sensory functions (Kandhare et al. 2014).

Depression in experimental animals has been correlated with changes in brain neurotrophins in the brain and Na(þ), K(þ)-ATPase (Dubey et al. 2015). Mice that were put through chronic unpredictable mild stress for long periods of time which resulted in a substantial decrease in nerve growth factor (NGF) levels and BDNF, and Na(þ), K(þ)-ATPase activity in the forced swimming test the depressive statues were developed due to CUMS with considerable increase in corticosterone levels. Therapy with oral chrysin came to a decrease in the levels of BDNF and NGF levels, which is proportionate to fluoxetine. Furthermore, chrysin reduced the elevation in glutathione peroxidase (GPx), glutathione reductase (GR), and catalase (CAT) action in the experimental animals (Filho et al. 2015). In vivo, the primary mechanism that explains the antidepressant action of chrysin is the combination with the increase of BDNF and NGF, in addition to chrysin's potent antioxidant action.

Multiple members of flavonoid family contain neuroprotective effects as opposed to the oxidative attack on to the mesencephalic neuron dopamine (DA) after being exposed to *N*-methyl-4-phenyl-1,2,3,6- tetrahydropyridine hydrochloride (MPP). Chrysin can defend mesencephalic cultures from harm by MPP; this was demonstrated by DNA fragmentation studies as well as the use of DA neurons

tyrosine hydroxylase (TH) immunocytochemistry. To identify neuroprotective agents, MPP neurotoxicity is essential in vitro models. Due to the DA results, it has been concluded that chrysin is advantageous for the therapy of Parkinson's disease (Mercer et al. 2005).

A ligand allocated for the benzodiazepine receptors is chrysin, both central (Ki ¼ 3 microM, competitive mechanism) and peripheral (Ki ¼ 13 microM, mixed-type mechanism). The flavonoid has been proven to enhance tonic–clonic seizures expression caused by pentylenetertrazol when administrated intracerebroventricularly with the righting reflex restored to normal in all the mice treated therefore confirming a myorelaxant effect in chrysin (Medina et al. 1990). Another study conducted proved that treatment with extracts of natural sources containing chrysin as the primary component maintained the brain levels of serotonin and noradrenaline (Singh et al. 2012). Therefore, this indicates that chrysin may be used as a substitute of the standard diazepam treatment, which aggravates postictal depression (Sampath et al. 2011).

19.3.3 Antidiabetic

A metabolic disorder known as diabetes mellitus (DM) disrupts the glucose metabolism as well as the general physiology of the body, it results from the action of insulin and defects of its secretion, and diabetes mellitus is characterized by hyperglycemia. Diabetes mellitus decreases the general health of the patient by impacting other organs' functions and physiological process. Glomerular epithelial podocytes are a highly specialized cell that maintains the normality of glomerular filtration barrier although high glucose levels cause apoptosis in those specialized cells, which can be decreased by subjecting them to chrysin mainly by DNA fragmentation. Additionally, by increasing the Bax/Bcl-2 ratio back to its normal state and decreasing the rate of induction of cytochrome c and Apaf-1 in renal podocytes that are under the influence of exceeding glucose concentrations.

Oral administration of chrysin in diabetic mice resulted in substantial management of proteinuria as well as atypical transformation in glomerular ultrastructure. Furthermore, the flavonoid increased the extent of unfolded protein feedback to ER stress as shown by PERK-eIF2α-ATF4-CHOP increase. Inhibition of ER stress feedback by apoptotic episodes in podocytes as well as a major decrease in the synthesis of slit diaphragm is associated with chrysin treatment (Kang et al. 2017). Chrysin was tested on rats and found significant results by reestablishing normal renal function and pathology. TNF-α expression is inhibited due to chrysin which correlates to its nephroprotective action (Ahad et al. 2014).

Diabetes causes vascular problems due to hyperglycemia. HepG2 cells medicated with, positive reference, rosiglitazone, and chrysin, chrysin derivatives were used and monitored to obtain their hypoglycemic effects. An O7-nitrooxyalkyl nitric oxide (NO) donor moiety is connected to the parent moiety chrysin, and its O7-[(nitrooxyl) alkyloxycarbonyl] methyl derivatives were produced. Moreover, a new class of hybrid ester prodrugs was produced. The methyl analog of (nitrooxyl)

ethoxycarbonyl is the prevalent suppressers of AR and AGE, and chrysin is a strong suppresser of AGE. In the presence of L-cysteine, all the hybrid ester prodrugs moderately release NO. The O7-nitrooxyethyl chrysin derivatives O7-[(nitrooxyl) butoxy carbonyl] methyl analog and O7 [(nitrooxyl)hexoxycarbonyl] methyl analog (5c) significantly stimulate the glucose uptake of HepG2 cells. These prodrugs which are a hybrid ester NO donor provide an upcoming drug design idea for the advancement of prophylactic or pharmacological agents for diabetes implicated vascular complications (Zou et al. 2010).

Abnormal retinal function is caused by chronic diabetes known as diabetic retinopathy (DR). Positive effects were obtained when chrysin was administered to human retinal endothelial cells inserted in glucose-bared eyes of diabetic mice, it was reported that the flavonoid stimulated the suppression of VEGF and its receptor-2 and HIF-1α as well as inhibited apoptotic events in retinal endothelial, chrysin also managed apoptosis by increasing Tie-2 and Ang-1 and 2 in the eyes of diabetic mice. An oral administration of chrysin of 10 mg/kg restored the drop of the junction proteins, VE-cadherin, and ZO-1 likely upholding endothelial cells and pericytes interaction (Goes et al. 2018).

Another antidiabetic roles of chrysin inlist the preservation of cognitive descend (DACD) by the decrease of NF-κB p65 unit, TNF-α, IL-1β, IL-6, and caspase-3 in hippocampus and cerebral cortex as proven by multiple studies (He et al. 2012). Liver tissues lipid peroxidation status were substantially decreased as well as the extent of vacuolization in liver tissue and a decline in the number of vacuolated hepatic cells after 7 days of administration of the flavonoid through the intraperitoneal of the diabetic Swiss albino mice that were induced with alloxan (Sirovina et al. 2013).

Varied doses of chrysin produced attenuated the elevated levels of deficient density lipoprotein, triglycerides, malondialdehyde (MDA), cholesterol, and elevated the high-density lipoproteins concentrations, GST, total protein, SOD, and catalase on streptozotocin (STZ)-induced diabetic rats (Samarghandian et al. 2017). Treatment with chrysin was also associated with the hindrance of defective insulin-stimulating molecules as well as the tolerance to glucose. Furthermore, it has been reported that undesirable effects on blood glucose, insulin, and lipid profile were substantially regulated by chrysin treatment diabetic rats subjected to high fat and sucrose diet (Satyanarayana et al. 2015).

19.3.4 Antihyperlipidemic

In women, dyslipidemia upholds a high-risk factor for coronary heart disease. It has been observed that chrysin is commensurate to the standard drug simvastatin. The amplification of triglyceride, non-HDL cholesterol levels, and plasma total cholesterol, can be restricted by chrysin as it contains antihyperlipidemic action. A likely cause of chrysin hypolipidemic effect is its possession of antioxidant action (Zarzecki et al. 2014).

It has been proven that chrysin contains antiatherogenic action in addition to its antioxidant effects. It has been reported that the administration of chrysin resulted in a substantial decrease of lipid profile mean serum levels parameter albeit HDL–cholesterol were found to be elevated. Furthermore, decrease in hepatic marker enzymes was observed in alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and lactate dehydrogenase, in correlation with a contrary substantial increase in mean hepatic levels of lipoprotein lipase (LPL), 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA reductase), enzymatic (catalase, superoxide dismutase, and glutathione peroxidase), as well as nonenzymatic antioxidants (reduced glutathione and vitamins C and E) (Anandhi et al. 2014).

19.3.5 Anti-Inflammatory

Chrysin exhibits impressive anti-inflammatory properties that are well documented, investigated, and characterized. This is backed by deducting studies proposing that chrysin's identified association with the COX-2 binding site which is enough to prove the anti-inflammatory action of this flavonoid. An escalation in levels of proinflammatory cytokines and reduced amount of anti-inflammatory cytokines was observed which majorly mediate neuroinflammatory responses (Xiao et al. 2014). An alternative study proved that the flavonoid suppressed the discharge of proinflammatory cytokines inclusive of tumor necrosis factor-alpha (TNF-α) and interleukin-1beta (IL-1β) as well as and nitric oxide (NO) in lipopolysaccharide (LPS)-stimulated microglia. In addition to nitric oxide (NO) and proinflammatory cytokines, chrysin demonstrated an ability to inhibit the expressions of inductive NO synthase (iNOS) and cyclooxygenase-2 (COX-2). c-Jun N-terminal kinase (JNK) and nuclear factor-kB (NFkB) are enzymes with a significant impact on neuroinflammation and considered key mediators, both with the potential of being suppressed by chrysin (Ha et al. 2010). Nevertheless, another studied had resulted in alternative results that showed that the treatment with chrysin on mice was not able to regulate constitutively or TNF-α induced NF-κB action in main cultures of mouse cortical astrocytes, hence it has been concluded that chrysin is not as likely that it targets NF-κB signaling in astrocytes (Spilsbury et al. 2012).

Chrysin anti-inflammatory activity is associated with inflammatory cytokine management. The flavonoid activates macrophages through the NF-κB pathway which inhibits the yield of inflammatory cytokine IFN-c and TNF-α (Xiao et al. 2014; Galijatovic et al. 1999). Prostaglandin-E2, COX-2, and NF-κB are three other factors inhibited by chrysin, hence owing this action to its notorious anti-inflammatory action (O'Leary et al. 2004). The pharmacological action of chrysin substantially reduces inflammation and modulates macrophage standards by the inhibition of inflammation. Furthermore, chrysin takes part in the stimulation of PPAR-g functions as well as advancing the PPAR-g effects; it additionally encourages specific gene expressions. When taking all results into consideration, the conclusion this study has reached supports the newly found function of chrysin

as an effective regulator of PPAR-g transcriptional activity and in inflammatory diseases it is used as a therapeutic molecule (Feng et al. 2014).

Chrysin was also found effective in the treatment of osteoarthritis (OA) chondrocytes by stimulating IL-1β. In an alternative report, it was proved that chrysin could decrease IL-1β-induced yield of PGE2, NO; decreases the expression and effect of MMP-3, iNOS, MMP-1, COX-2, ADAMTS-5, ADAMTS-4, MMP-13, as well as diminish collagen-II, aggrecan. With an additional effect on NF-κB and IL-1β-stimulated IκB-α, chrysin blocks the activation of NF-κB as well as causes the deterioration of IL-1β-induced IκB-α (Zheng et al. 2017).

In addition, the flavonoid decreased iNOS-stimulated expression by LPS, the therapy suppressed LPS—caused phosphorylation of JAK-STATs, nuclear translocation of STAT1 and STAT3, suppresses the discharge of TNF-α, IL-6, MCP-1 as well as the yield of ROS in RAW264.7 cells. This is significant as ROS is enforced as an upstream signal to moderate the initiation of JAKSTATs signaling pathway. Hence chrysin acts by inhibiting the action of JAK-STATs moderated by ROS to decrease LPS-stimulated inflammatory feedback in cells of RAW264.7 (Qi et al. 2018).

Inflammatory cytokines are substantially released in human volunteers exposed to cigarette smoke, the inflammatory cytokines include IL-1β, TNF-α, and IL-8 in bronchoalveolar lavage fluid and in the lung tissue MPO expression was observed, when chrysin was administrated in varied doses through the intraperitoneal, the inflammation resulting from cigarette smoke was inhibited as an outcome of inhibiting the inflammatory cytokines TNF-α, IL-8, and IL-1β including the MPO release; in addition, chrysin caused the reduction in the extent of phosphorylation p38 and ERK (Shen et al. 2015; Rauf et al. 2015).

Doxorubicin (DOX) is known to be a chemotherapeutic drug with one of the most efficient and effective however its efficiency relays on the occurrence of cardiotoxicity. As mentioned earlier, chrysin contains many biological activities in the exception of anti-inflammatory including its anticancer as well as its antioxidant effect. The natural flavone has the ability to significantly protect the heart from damages caused by doxorubicin and the induced elevation of the enzymes serum creatine kinase isoenzyme-MB (CK-MB), lactate dehydrogenase (LDH) in addition to, myofibrillar disarray. The risk of oxidative stress was reduced by chrysin treatment. Furthermore, chrysin counteracts doxorubicin's inflammatory response by inhibiting the increase caused by the drug, the inflammatory response is caused by the following components; nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), expression of nuclear factor kappa-B (NF-κB), nitric oxide as well as tumor necrosis factor-alpha (TNF-α) (Shen et al. 2015). Another negative effect caused by doxorubicin is apoptosis induced by DOX it acts by augmenting cytochrome c and caspase-3 activity, Bax expression while reducing Bcl-2 expression therefore damaging the tissues. It has been noted that chrysin substantially reduced such apoptotic actions caused by doxorubicin. Therefore, it has been deducted from the above mentioned that chrysin contains protective action in the defense of doxorubicin-induced acute cardiotoxicity by decreasing apoptotic tissue damage as

well as reducing inflammation, oxidative injury (Rauf et al. 2015; Mantawy et al. 2014).

In conclusion, chrysin contains potent anti-inflammatory effects; it suppresses the releases of inflammatory cytokines in addition to cyclooxygenase action. The flavonoid has the potential to provide a novel pharmacological approach for autoimmune neuropathies as well as documented neuroprotective effects especially when it comes to its neuroinflammatory action.

19.3.6 Hepatoprotective

Chrysin is used in liver as hepatoprotective and antihyperlipidemic effects. Evidences shown in hepatotoxicity of rats that chrysin decreases degrees of triglycerides, cholesterol, free fatty acids, phospholipids, very low and low-density lipoprotein-C, and the degree of high-density lipoprotein-C is increased in the tissues and plasma (Pushpavalli et al. 2010). TNF-α mediates the hepatoprotective activity of chrysin as it lessens soluble TNF-α formation by preventing the activity of TNF-α converting enzyme (Hermenean et al. 2017). In liver damage, Chrysin is additionally seen as viable which is initiated via carbon tetrachloride. The increment degree of centrilobular necrosis, steatosis, serum aspartate–aminotransferase, alanine–aminotransferase, change in hepatocyte ultrastructure, growth of hepatic α-smooth muscle actin protein, tumor necrosis factor-α through intraperitoneal CCl_4 infusion causes liver damage. The outcomes indicate that it diminished serum aspartate–aminotransferase, alanine–aminotransferase and convey assurance against enhancement of steatosis, centrilobular necrosis, and a change of hepatocyte ultrastructure which caused a decrease in hepatic TNF-α interpretation and α-SMA protein. In an investigation, chrysin shielded from the TGF-β1 interfered hepatic stellate cells incitement on fibrogenesis on rats. Chrysin diminished α-SMA, hepatic fibrosis, TGF-β1 immunopositive cells, and TGF-β1 when contrasted with different flavonoids. In addition, these portions significantly diminished mRNA of Smad 2 liver ((Khan et al. 2011; Anandhi et al. 2013). Nephron and hepatotoxicity marker activity degrees were seen in D-GaIN. Albumin serum total protein and A/G proportion are likewise influenced (Tahir and Sultana 2011). In different examination, chrysin diminished hepatic marker enzymatic activities and by-products of lipid peroxidation (Ravishankar et al. 2017; Liu et al. 2016). In addition, chrysin was exposed to albino rats in contrast to the hepatotoxicity lured through dispensation of cisplatin (Lo et al. 2012). The impact of chrysin on methotrexate lured hepatic oxidative stress was watched in other investigation. In rats, cell death is essentially caused by diminish in alanine transaminase, activity of lactate dehydrogenase, aspartate aminotransferase, and malondialdehyde content just as enhanced glutathione reductase, superoxide dismutase, activity of catalase, glutathione peroxidase, and diminished content of glutathione (Ali et al. 2014). Similarly, chrysin in contrast to CCl4 incited toxicity in Wistar male rat's downregulated the mRNA interpretation of the iNOS gene (Lotfi-Attari et al. 2017). To condense chrysin prevents damage in liver in various design of cisplatin, hepatotoxicity, and methotrexate related to

damage in the liver. As a result, it shows that chrysin associated with hepatoprotective, it lessens serum alanine aminotransferase and aspartate aminotransferase, which gives assurance in contrast to expansion of centrilobular necrosis, steatosis, and a change of ultrastructure of hepatocyte. Diminish hepatic α-SMA protein and TNF-α articulation (Hermenean et al. 2013). Diminished hepatic fibrosis, down directed the α-SMA, diminished number of TGF-β1 immunopositive cells, and set apart down controlled the TGF-β1 (Balta et al. 2015).

19.3.7 Reproductive

Campos and collaborators talked in an investigation, they assessed that chrysin has a defensive job against the reproductive abnormities (Campos et al. 2018). Chrysin is supplemented in a male and female gerbils which are 90-day-old displayed prostate gland stromal remodeling and epithelial hyperplasia. It is really the advancement of the organelles, which are engaged with the secretory biosynthetic pathway in epithelial cells. The increase in ovarian follicles and normal testicular morphology is managed by chrysin (Zeinali et al. 2017). It improved the sperm abnormalities, motility, dead rate, diminished cell death, and MDA degrees in paracetamol testicular tissues harm rats (Shen et al. 2001). Ciftci and colleagues made an investigation, they elucidated that chrysin usage indicated a decrease in TBARS, enriched glutathione degree, sperm motility, concentration, and decrease in abnormal sperm rate (Ciftci et al. 2018) in Wistar rats, chrysin and celecoxib separately were administered orally and information discovered that diminished paw edema was practically identical to celecoxib. In addition, through backing down histopathologic and gonadosomatic index by spermatogenesis protection, they also diminished testicular damage. The serum testosterone, interpretation of steroidogenic acute regulation mRNA and FSH is upregulated by the two agents. Through inversion of TNF-α, myeloperoxidase, COX-2 protein interpretation, and enhancing of iNOS and IL-10 chrysin inhibited inflammation. It was accompanied that the mitigation of the testicular damage with restraint of oxidative stress by means of diminishing testicular nitric oxide and lipid peroxides. Caspase-3 and FasL mRNA interpretation was effectively downregulated by the two agents to increase cell survival if there should be an occurrence of apoptosis (Mohammadian et al. 2016). As a result, normal testicular formation and enhanced ovarian follicles are controlled (Campos et al. 2018), additionally, fatty acids proportion (n-6/n-3) and MDA accumulation are reduced and the blood testosterone degree is intensified. Enhanced the sperm abnormalities, motility, dead rate, lowered cell death, and degrees of MDA in paracetamol testicular tissues as well as increases fertility and hatchability (Altawash et al. 2017; Aksu et al. 2016; Testai et al. 2013). Chrysin administration essentially enhances parameters of sperm and securing the reproductive system. Because of that reason, chrysin can be a different remedy for men to enhance the quality of sperm (Missassi et al. 2017). In rats, the induced testosterone benign prostate hyperplasia is essentially protected by chrysin through many processes, for example, prevention from enhancing of lipid peroxidation, glutathione deficiency, prevention of catalase

activities and superoxide dismutase, regaining of separated caspase-3 degree, and regaining of decreased Bax/Bcl-2 proportion and mRNA interpretation of p53 and p21. In addition, it was reported that after chrysin treatment, inhibition from the improvement of attaching of mRNA activity interpretation of like insulin growth factor 1, like insulin growth factor 1 receptor and NF-κB p65 subunit (Shoieb et al. 2018; Russo et al. 2012). In rats, the administration of nitrofurazone induced testicular damage, whereas it has been found out that the combining results of chrysin and mirtazapine lessen the rise of serum acid phosphatase enzyme action and especially inhibited from the decrease of the viability and count of sperm. They also work proficiently to inhibit from the lipid peroxidation, deficiency of glutathione, and in rat testes, raised TNF-α degree and diminished c-kit degree. This connecting reaction impressively diminished the caspase-3 degrees in tissue testicular (Jiang et al. 2014; Tian et al. 2014).

19.3.8 Cardiovascular

In myocardial damage, chrysin is used to improve it and the mechanism of activity is by peroxisome proliferator-initiated receptor-g activation, which thus constricted propelled end product of glycation (AGE)/RAGE-intervened oxidative stress, inflammatory, and cell death reaction. Besides, past examinations gave the essential proof that chrysin considerably alleviates platelet-derived growth factor and H_2O_2 lured prevention of PTP action. It influences glutathione in the reactivation system for PTP reactivation, initiating to dephosphorylation of activated PDGFR and its downstream protein enzymes (Rani et al. 2016). Practically, PDGF lured proliferation and movement in vascular smooth muscle cells is suppressed by chrysin. The prohibition impact of chrysin is definite even when chrysin is included after PDGF induction (Lo et al. 2012; Testai et al. 2013). By restraining p53-dependent apoptotic pathway, oxidative stress, and MAPK and NF-κB pathways, chrysin defend in contrast to doxorubicin lured cardiomyopathy while increasing the vascular endothelial growth factor pathway (Mantawy et al. 2017; De Vries et al. 1997). Chrysin successfully restrains platelet aggregation and granule creation which is actuated by thrombin, collagen, U46619, and ADP. Moreover, it restricts the adhesive platelets and decreases the spread of single platelet on immobilized fibrinogen. In biochemical tests, it showed that the collagen lured activation of PLCγ2, PKC, Syk, along with Akt, and phosphorylation of ERK1/2 is inhibited by chrysin. The phosphorylation of GSK3β, FAK, FcγRIIa, and Akt in platelet permeating on immobilized fibrinogen is also decreased by chrysin (Liu et al. 2016). In an investigation conducted in vitro, the data collected showed that chrysin prevented the development of thrombus and platelet functionality (Ravishankar et al. 2017). In another investigation done by Lo and colleagues, they revealed that chrysin concentration dependently has been formed to prevent the PDGF proliferation and chemotaxis and also reduced PDGF signaling in vascular smooth muscle cell. It effectively reduces NADPH oxidase activation, H_2O_2 signaling, and PDGF lured reactive oxygen species formation, whereas it did not interact with the bounding of PDGF with

VSMCs. The PDGF lured oxidation of protein tyrosine phosphatase active site and support PDGF lured prevention of PTP is prevented by chrysin. The PDGF receptor autophosphorylation that is influenced by vanadate and is also prevented by chrysin (Lo et al. 2012). Action of chrysin rather than antioxidant *N*-acetylcysteine and flavonoid (−)-epigallocatechin-3-gallate on the action of PTP and PDGF signaling was prevented because of intracellular glutathione deficiency which is because of the efficiency of chrysin on glutaredoxin system for reactivation of PTP (Ali et al. 2014). The research showed that in chorioallantoic branch of chicken and human umbilical endothelial cells chrysin prevented lipopolysaccharide lured angiogenesis. Chrysin also decreased LPS lured neovascular density of 58CAM, making downregulation of VEGFR-2, VEGF gene interpretation, but not VEGFR-1. Moreover, the concentration of chrysin independently diminished autoregulation loop of IL-6/IL-6R in LPS conducted HUVEC in humans (Lotfi-Attari et al. 2017). A report made by members of scientists that LNAME-sensitive endothelial NO relief that introduces to cGMP aggregation in aortic rings with endothelium increased by chrysin. It also influenced aortic and endothelium-dependent relaxation. Furthermore, it activated the relief of NO and mediates efficaciously through phosphatidylinositol 3 kinase (Villar et al. 2004). A report made that chrysin improves relaxation of acetylcholine under situations which are under control or incubation with anion superoxide after a specific period generating xanthine oxidase. It also enhanced relaxation, which is influenced by 3 morpholinosydnonimine, 8-bromoguanosine- 3′: 5′-cyclic monophosphates, and sodium nitroprusside (Duarte et al. 2001). Chrysin is beneficial in the prevention from tissue damage because of bioactivation by *S*-adenosyl methionine. An examination has been made that administration of chrysin decreased DNA fragmentation in brain, liver, lipid peroxidation, blood, and protein carbonyls. The micronuclei achieved in bone marrow cells of humans is significantly decreased (Babangida et al. 2018). So the thrombosis and platelet accumulation aortic endothelial damage and cardiac oxidative stress pathways are restrained by chrysin. As a result, chrysin prevents platelet aggregation and granule formation which is influenced by thrombin, collagen, U46619, and ADP prevented the collagen lured activation of Syk, PKC, along with phosphorylation of ERK1/2, PLCγ2, and Akt. The phosphorylation of Akt, FAK, GSK3β, and FcγRIIa in platelet permeating on immobilized fibrinogen is decreased (Liu et al. 2016; Kandemir et al. 2017).

19.3.9 Antiallergic

On BALB/c female mice chrysin was conducted, ovalbumin lured airway hyperresponsiveness shows that it decreased OVA and reduced eosinophils, interleukin-4, IL-13 in bronchoalveolar lavage fluid, and total serum immunoglobulin IgE. Additionally manages the degree of BALF interferon-γ, reduced infiltration of inflammatory cell, goblet cell hyperplasia, and indication of α-SMA over bronchioles. Furthermore, chrysin reduces the extracellular signal monitored kinase and phosphorylation of Akt degree that is correlated to proliferation of ASMC (Yao et al. 2016). In BALB/c mice, it also inhibits ovalbumin lured AHR to acetylcholine

chloride. It merits referencing that chrysin in BALF extensively suppresses the eosinophil counts, IgE degrees in serum, and total inflammatory cell. An investigation of tissue of the lungs reported that chrysin generously reduced eosinophilic inflammation induced by allergen and airway mucus-producing goblet cells. Moreover, by causing the immune response to allergens against GATA-3, T-helper type 1 profile by adjusting the T-bet transcription factors in allergic mice, it activates the immune system (Manzolli et al. 2015; Bae et al. 2011). They also suppress the discharge of systemic hypersensitivity serum histamine and immunoglobulin E-mediated anaphylaxis and decreases discharge of histamine from mast cells. These results are intensive when compared with the known anti-allergic drugs such as cromolyn. Furthermore, pro-inflammatory cytokines gene expression in mast cells and the inhibited reaction was caspase-1 relative and NF-κB is inhibited by chrysin (Khan et al. 2012). Chrysin also caused lessening in infiltration of status of perivascular lung blood vessels, bronchi status, leucocytes, alveolar macrophages activation, inflammation, alveoli stability, and also reduces cellular injury factors in bronchoalveolar hyperresponsiveness rats. Furthermore, it was reported that treatment with chrysin has its anti-asthmatic capacity. It can be because of adjustment of Th1/Th2 polarization by means of prevention of NF-κB, activated protein, and nitric oxide synthase (Mantawy et al. 2014; Wadibhasme et al. 2011).

19.3.10 Anti-obesity

Chrysin is effective in 3T3-L1 adipocytes, it improves interpretation of specific markers of brown fat, protein degrees of proliferator peroxisome stimulated receptor α and receptor 1 *α*, phosphorylated acetyl-CoA carboxylase, PPARδ, phosphorylated AMP-stimulated protein kinase, PPARγ, lipase, perilipin, acyl-coenzyme A oxidase 1, carnitine palmitoyltransferase 1, uncoupling protein 1, fat oxidation, thermogenesis, lipolysis, and also reduces lipogenesis. Improvement of specific markers of brown fat and UCP-1 was because of the chrysin, which activates AMPK based on that inhibition of AMPK by dorsomorphin eliminate interpretation of PR domain-containing 16, UCP-1, and PGC-1α, although 5-aminoimidazole-4-carboxamide ribonucleotide activator enhanced interpretation of brown marker proteins (Vedagiri and Thangarajan 2016; Kang et al. 2015). Chrysin also increased large fat diet lured muscular steatosis, without affecting the weight of hepatic in obese rats. It reduces macrophages permeation into adipose tissue and induces anti-inflammatory M1, M2 phenotype in the obese rat-cultured macrophages, and peritoneal macrophages and as an outcome it changes M1/M2 status. Moreover, chrysin improves transcription of PPARγ activity and its target genes expression as a result it regulates phenotypes of macrophages (Souza et al. 2015).

19.3.11 Antioxidant

Chrysin has likewise been appeared to defend toward hydrogen peroxide lured cell death and constrict neuronal death in many tests conducted in vitro (Souza et al. 2015; Pichichero et al. 2010). An investigation made in mice in vivo, it was shown that chrysin decline age linked improved in oxidative stress and increased cognitive declaring and lessening in derived neurotrophic factor of brain (Souza et al. 2015). Oral administration of chrysin effectively constricted the enhancement in the formation of free radical and prevented the catalase, superoxide dismutase activities, and glutathione peroxidase, and K(þ), Na(þ) ATPase degrees and in the aged mice prevents the activities of GPx, SOD, and CAT. In mice, Chrysin alters the action of K (þ), Na (þ) ATPase, and reduced degrees of BDNF in the hippocampus and prefrontal cortex. Chrysin can also inhibit age-linked declaring in memory because of its strong antioxidant actions and transition production of BDNF (Lirdprapamongkol et al. 2013; Souza et al. 2015). The homeostasis of antioxidant and oxidant status, which is regulated by lipid peroxidation and antioxidants during carcinogenesis, is improved when chrysin is administrated (Li et al. 2011; Karthikeyan et al. 2013). Both in vitro and in vivo, tumor production by the means of apoptosis associated with the activation of Notch1 signaling pathway is inhibited (Yu et al. 2013). Chrysins, primary mechanism of action contains a reduction in proliferation of cell, induction of cell death by apoptosis, and inflammation lessening (Xue et al. 2016; Khan et al. 2012; Kalogeropoulos et al. 2013). The transformers in a versatile signaling molecule, b-arrestin-2 interpretation, subsequent to chrysin supplementation regulate many signaling pathways (Khan et al. 2011). Chrysin and cisplatin on combination are considerably enhancing the death cells of HepG2 cancer cells. The p53 gene interpretation by stimulating ERK1/2 is stabilizing by both of them, which then stimulates p53 phosphorylation in HepG2 cells (Rehman et al. 2013). Treatment with chrysin conserves the armory antioxidant and restrains the redox-active transcription factor NF-κB activation. Chrysin is a prospective for the inhibition of renal carcinogenesis during renal carcinogenesis, it suppresses many biomarkers of tumor promotion and inflammation (Fu et al. 2013). Chrysin can be an efficacious preventor of tumor cell lured angiogenesis (El-Sisi et al. 2017). It is confirmed that chrysin has the prospective to detain tumor development rather than prevent tumor production. As a result, chrysin inhibits lipid peroxidation, deficiency of glutathione, and degrees of tumor necrosis factor-α and decrease c-kit degree (Mantawy et al. 2017). Antioxidant enzymes are increased, interpretation of p53, Bax, Puma, Noxa, caspase-3, and cytochrome c is decreased, interpretation of Bcl-2 is increased, inactivation of JNK, MAPK, and p38 decreases NF-κB, interpretation of PTEN, and enhancement of VEGF/AKT pathway (Izuta et al. 2008). Restraint apoptotic damage to the cells by enhancing the action of cytochrome c and caspase-3 and Bax interpretation at the same time lessening the Bcl-2 interpretation.

19.3.12 Antimicrobial

It is reported that chrysin acquires both antifungal and antibacterial activities. Nevertheless, higher concentration of chrysin is needed to produce the inhibitory action (Mercan et al. 2006). A report made by Chabot et al. that in the fungus *Gigaspora margarita* Becker and Hall, chrysin decreases the spore germination (Chabot et al. 1999).

19.4 Conclusion

The prevention and cure of diseases that use phytochemicals, especially flavonoids, are well known. Fruits and vegetables are really a common source of flavonoids. Wide range of flavonoids present in nature has its own physical, chemical, and physiological properties. Chrysin, a naturally occurring polyphenol, tends to have multiple pharmacological effects, such as anticancer, antidiabetic, neuroprotective, antiallergic, antihyperlipidemic, antimicrobial, anti-obesity, anti-inflammatory, hepatoprotective, cardiovascular, reproductive, and antioxidant activities. The molecular mechanisms influencing the pleiotropic actions of chrysin are complex, including configurations of cell signaling pathways at different stages of numerous diseases. Though, chrysin is plagued by bioavailability issues, close to other polyphenols, which should be resolved prior to clinical trials. The bioavailability of chrysin has to be optimized in order to increase the effectiveness of chrysin as a pharmaceutical molecule.

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