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Review article

Chrysin: Pharmacological and therapeutic properties

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ABSTRACT

Chrysin is a promising phytochemical that is categorized under the class of flavonoids based on its chemical structure. Naturally, it is widely present in propolis, honey, passion fruit, and even in mushrooms and other plant sources, whereas its synthetic counterparts are also being employed for pharmacological purposes. It has widely been employed in treatment of various degenerative disorders and provides cytotoxic and anti-inflammatory functions. Its antioxidant and disease preventing abilities are attributed to its structural diversity arising in ring-A and absence of oxygenation in B and C ring. In this review, the scientific studies are being reported emphasizing benefits and its allied health claims on chrysin in numerous metabolic malfunctions.

1. Introduction

The promising sources of dietary flavonoids are fruits and vegetables, due to which various health problems are removed. The flavonoids are vital components of various medicinal plants thereby exert different pharmacological benefits [1,2]. The flavonoid, chrysin (5,7-dihydroxy-2-phenyl-4H-chromen-4-one) belongs to a flavone class of polyphenolic compounds having 15-carbon skeleton, naturally. One of the major natural sources of chrysin includes passion fruit (*Passiflora*sp.), honey and propolis [3–5]. In honeydew honeys, the content of this flavonoid is around 0.10 mg/kg, while forest honeys may contain upto 5.3 mg/kg [6]. Chrysin and its derivatives are the principal components of Radix scutellariae, which is a highly known medicinal plan. However, nowadays chrysin obtained from propolis and honey makes great interest to researcher [7].

Alongside, passion flowers (*P. caerulea* L.), mushrooms such as *Pleurotusostreatus* and various other fruits are good sources of chrysin (Fig. 1). Although there is a wide use of medicinal plants containing chrysin for therapeutic purposes, the use of synthetic chrysin is also being practiced at larger scales. In this respect, various methods have been established to synthesize chrysin and, thus, the compound is commercially available at reasonable prices [8].

The IUPAC name of chrysin is 5,7-dihydroxy-2-phenyl-4H-chromen-4-one and 5,7-dihydroxyflavone (Fig. 2).

Structurally, chrysin holds two benzene rings (A & B) and one oxygen containing heterocyclic ring. It possesses 2–3 double bound carbon with a carbonyl group attached to the 4th carbon, while lacking a 3-carbon hydroxyl group. Based on this structural classification, chrysin falls under the class of flavones. It also contains –OH groups at 5th and 7th carbon atoms. Unlike various flavonoids, chrysin does not share any oxygenation in the Ring-B. Mainly, diversity in the ring-A oxygenation is responsible for various derivatives of chrysin like wogonin, baicalein, and oroxylin A [9].

Biological activities of chrysin are associated with absence of oxygenation in B and C-rings, that are accompanied by anti-inflammatory to antitoxic effects. It has also been anticipated that antioxidant activity

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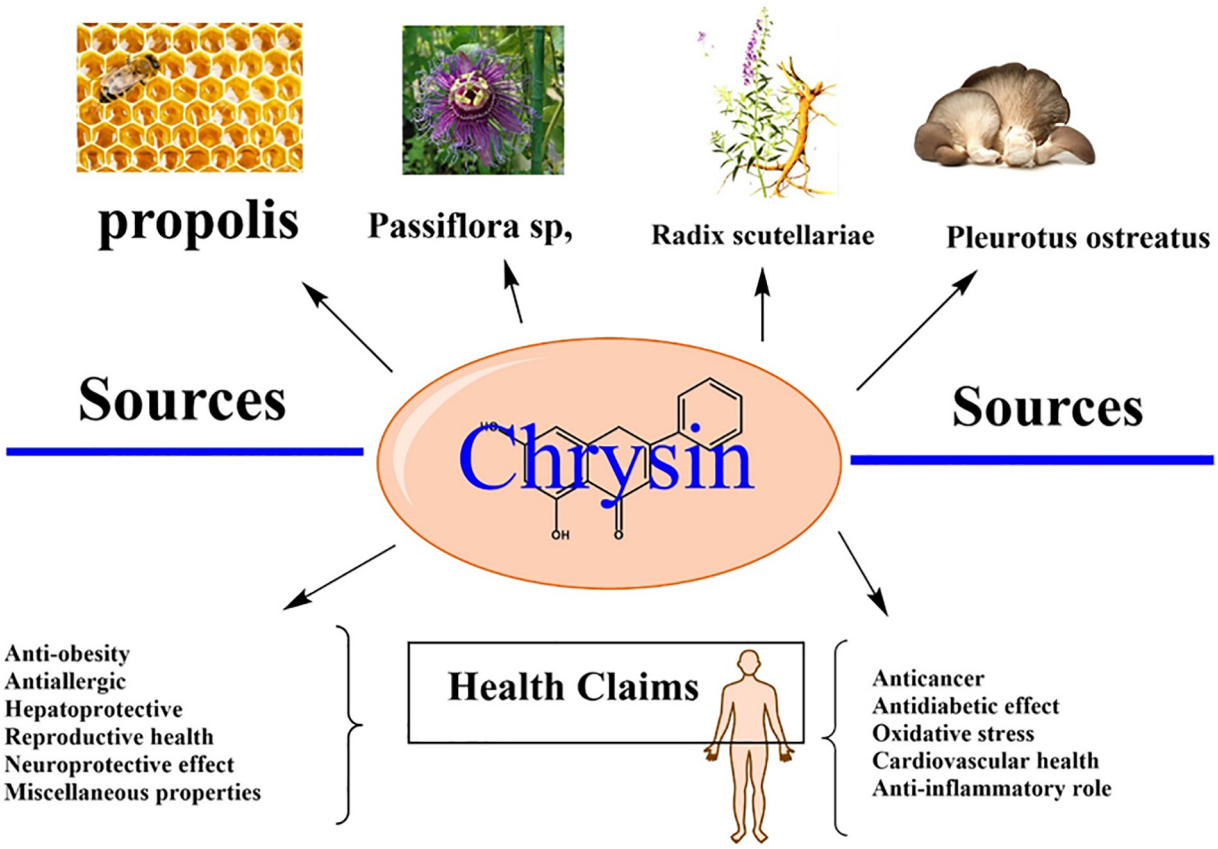

Fig. 1. Schematic of chrysin sources and its health claims.

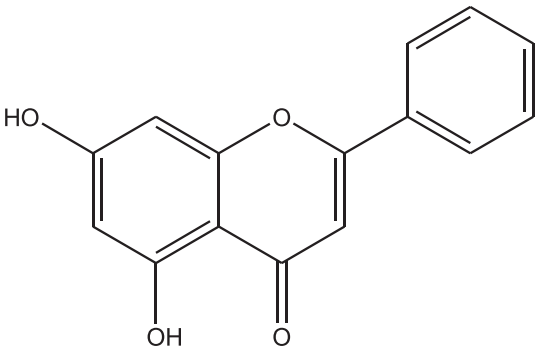

Fig. 2. Chemical structure of chrysin.

of different flavones is based on the structural diversity of these chemical entities. The presence of carbonyl group on C-4 and a double bond between C-2 and C3 (30, 40 hydroxylation) is essentially linked to antioxidant activity of chrysin. It has further been shown that flavonoids are quite effectual at low doses, whereas these may impose toxic effects on human body, if consumed in surplus or higher amounts. In this respect, each compound is accompanied by its effectual doses to be taken on daily basis to get beneficial effects and avoid toxic circumstances. The recommended daily amount of chrysin is considered to be 0.5–3 g. However, it can also induce toxicity in liver cell even in its daily concentrations as reported in literature [10]. The cytotoxic effects of chrysin administration are attributed to its peroxidase-like activity in hepatocytes causing the production of toxic by-products of chrysin. The chrysin affects *de novo* DNA synthesis ultimately decreasing the cellular numbers. In neutrophils, myeloperoxidase is believed to be responsible for chrysin-induced toxicity [11].

In the current review a comprehensive search was carried out with the keyword of "chrysin", in title, abstract and keywords of core electronic databases, including Medline, Scopus, Science direct, Embase, and Web of science. All English articles from the start date of inclusion of databases to 2018 were included.

2. Health claims

2.1. Anticancer

The suppression of hTERT and cyclin D1 gene expression in T47D breast cancer cell lines is due to the combined effect of metformin and chrysin [12], increased proline metabolism and proline dehydrogenase/proline oxidase, and decreased prolidase activity, collagen biosynthesis, and proline concentration in human tongue squamous cell and carcinoma cells (Table 1) [13].

The nanoparticle-based chrysin in C57B16 mice bearing B16F10 melanoma tumors was markedly presented reductions in the levels of MMP-9, MMP-2, and TERT genes, whereas it enhanced TIMP-2 andTIMP-1 genes expressions [13,30] (Table 2).

During an *in vivo* study, chrysin treatment (50 mg/kg b.w.) exhibited a dose-dependent inhibition of cancer cell growth in B16F10 melanoma cells of BALB/c mice by inducing cell cycle arrest at G2/M phase and apoptosis. Moreover, it inhibited 60% melanoma tumor growth after 14 days of treatment as compared to control which inhibited 71%. Moreover, the cytotoxic activity of macrophages, CTL, and NK were increased by administrating chrysin [31], in Caco-2 and SW480 colorectal cancer cells, nano-encapsulation of chrysin and curcumin improved the delivery of these phytochemicals that significantly inhibited the growth of cancer cells, while it decreased the hTERT gene expression *via* increased solubility and bioavailability of these therapeutic agents [32]. Hexokinase-2 (HK-2), which plays a vital role in glucose metabolism as well as in mediation of cell apoptosis, making it

Table 1
Health claims for chrysin.

Health claims	Mechanism	References
Anticancer	Suppresses hTERT and cyclin D1 gene expression	[14]
	Reduces the levels of MMP-2, MMP-9 and TERT genes whereas enhanced TIMP-1 and TIMP-2 genes expressions	[15]
	Prevents from lymphocytic leukemia (CLL) B-lymphocytes while showing significant increase in intracellular ROS, cytotoxicity, mitochondrial membrane potential (MMP) collapse, caspase 3 activation, ADP/ATP ratio.	[16]
	Inhibited complex II and ATPases	
	Prevents metastasis and cancer progression by enhancing the TIMP-1 & 2 expression and reducing MMP-2 & 9 expressions in breast tumor	[17]
	Activates MAPK and PI3K/AKT pathways in OV90 and ES2 cells	[18]
	Inhibits colon cancer cells lines *via* apoptosis, sufficiently reducing the volume of tumor	[8]
	Up-regulation of Bax and down regulation of the sall4	
	Increased ROS and cytoplasmic Ca^{2+} levels alongside induction of cell death and loss of MMP are involved in inhibition of ovarian cancer	
Antidiabetic	Protection of cognitive decline (DACD) *via* reduction of NF-κB p65 unit, TNF-α, IL-1β, IL-6 and caspase-3 in cerebral cortex and hippocampus	[19]
	Prevention of impaired insulin signaling molecules and glucose tolerance	[20]
	Restoration of increased Bax/Bcl-2 ratio and suppression of increased cytochrome *c* and Apaf-1 induction in renal podocytes exposed to high glucose concentrations	[21]
Antioxidant	Prevent lipid peroxidation, glutathione depletion and tumor necrosis factor-α level and reduced c-kit level.	[22]
	Increment in antioxidant enzymes, reduction of expression of p53, Bax, Puma, Noxa, cytochrome *c* and caspase-3, increment of expression of Bcl-2, inactivation of MAPK; p38 and JNK, reduction of NF-κB, expression of PTEN, and augmentation of VEGF/AKT pathway	[23]
	Control apoptotic damage to the cells by increasing caspase-3 activity and cytochrome *c* and Bax expressions while lowering the Bcl-2 expression	[1,24]
Anti-inflammatory	Reduced TNF-α, NF-κB p65 unit, interleukin-1β (IL-1β), IL-17A, interferon gamma (IFN-γ), IL-12 and IL-6	[25]
	Inhibitory agent against NF-Kb and peroxisome proliferator activated receptor gamma (PPAR-γ)	
	Down regulate the pro-inflammatory enzymes *i.e.* COX-2, myeloperoxidase (MPO), iNOS, prostanoids and phospholipase A2	
	Reduced IL-1β-induced production of NO, PGE2; expression of iNOS, MMP-3, COX-2, ADAMTS-4, ADAMTS-5 MMP-13, MMP-1 and degrade collagen-II, aggrecan.	[26]
	Blocked activation of NF-κB and degradation of IL-1β-stimulated IκB-α	
Antiallergic	Suppressed the eosinophil counts in BALF, total inflammatory cell and IgE levels in serum.	[7]
	Decreased airway mucus-producing goblet cells and eosinophilic inflammation induced by allergen.	
	Stimulate the immune system by triggering the immune response to allergens towards GATA-3, T-helper type 1 (Th1) profile by modifying the T-bet transcription factors	
Hepatoprotective	Reduced serum aspartate-amino-transferase and alanine-amino-transferase also give protection against extension of steatosis, centrilobular necrosis, and an alteration of hepatocyte ultrastructure	[27]
	Reduce hepatic α-SMA protein and TNF-α expression	
	Decreased hepatic fibrosis, down regulated the α-SMA, decreased number of TGF-β1 immunopositive cells and marked down regulated the TGF-β1	[9]
Neuroprotective	Prevention from oxidative stress, inhibition of the development of neurodegenerative histopathologies, reduction of TBARS levels and increment of GSH levels	[28]
Reproductive health	Effective to regulate normal testicular morphology and increased ovarian follicles in number	[12]
	Improved plasma membrane integrity, its functionality, increased sperm number, motility, semen concentration as well as fertility and hatchability	[5]
	Reduction in fatty acids ratio (n-6/n-3), MDA concentration and enhanced the blood testosterone level	
	Enhanced the sperm motility, decreased apoptosis, sperm abnormalities, dead sperm rate, and MDA levels in paracetamol testicular tissues	[2]
Cardiovascular health	Inhibit platelet accumulation and granule production which is induced by collagen, thrombin, ADP, and U46619	[29]
	Inhibited the collagen induced activation of PKC, Syk, PLCγ2, along with phosphorylation of ERK1/2 and Akt. Reduces the phosphorylation of FAK, Akt, FcγRIIa, and GSK3β in platelet spreading on immobilized fibrinogen	

a quite attractive target for cancer therapy. It has been reported that chrysin has antitumor activity against hepatocellular carcinoma (HCC) through multiple pathways. Upon treatment with chrysin, VDAC-1 combined HK-2 on mitochondria was significantly lowered transferring Bax to mitochondria from cytoplasm and encouraged cell apoptosis. In HK-2 exogenous overexpression cells, chrysin-mediated glycolysis suppression and cell apoptosis were intensely impaired. It has further been reported that chrysin treatment restrained tumor growth in HCC xenograft models and significantly reduced HK-2 expression in tumor tissues [33]. A peer of researchers, they investigated that chrysin prevented from the lymphocytic leukemia (CLL) B-lymphocytes *via* showing a significant increase in intracellular reactive oxygen species (ROS), cytotoxicity, mitochondrial membrane potential (MMP) collapse, caspase-3 activation, ADP/ATP ratio, and ultimately apoptosis. Additionally, in cancerous mitochondria, chrysin markedly inhibited complex II and ATPases [34]. In another study performed by Ryu and their colleagues on prostate cancer cells lines like PC-3 and DU145 cells, they evaluated that chrysin administration significantly induced apoptosis along with DNA fragmentation and causing sub-G1 phase cell cycle arrest, and decreased the levels of proliferating cell nuclear antigen. It also induced loss of MMP along with enhancing lipid peroxidation and production of ROS depending on dose. Likewise, chrysin encouraged endoplasmic reticulum (ER) stress *via* stimulation of unfolded protein response (UPR) involving eukaryotic translation initiation factor 2α (eIF2α), PRKR-like ER kinase (PERK) and 78 kDa glucose-regulated protein (GRP78). The chrysin-mediated intracellular signaling pathways stimulated mitogen-activated protein kinases (MAPK), activation of P38 and ERK1/2 proteins alongside suppressing phosphoinositide 3-kinase (PI3K) and the abundance of AKT, P70S6K, P90RSK and S6 proteins [28]. In a breast cancer study, chrysin-loaded nanoparticles (25 mg/kg) have been observed to prevent metastasis and cancer progression by enhancing the TIMP-1 & 2 expression and reducing MMP-2 & 9 expressions in breast tumor [35,36].

Antitumor effects of chrysin are improved when it is encapsulated as evident from the hTERT, BRCA1, and FTO gene expressions in breast cancer cell (BCC) lines. Similarly, in another study was explored that chrysin encapsulated in PLGA-PEG nanoparticles enhancing the expressions of miR-22, miR-34a, and miR-126 in human gastric cell line [37]. Chrysin (25 mg/kg and 50 mg/kg) is also effective against human breast cancer cells (MCF-7). These concentrations of chrysin showed a momentous growth inhibition and induction of apoptotic [22].

In another investigation, it has been established that combined treatment of silibinin and chrysin synergistically inhibited growth of T47D BCC and downregulated the hTERT and cyclin D1 levels [19]. Multiple studies regarding the anticancer role of chrysin reported that the compound (5.0, 10.0, and 20.0 μmol/L) possesses cytotoxic effects

Table 2
Dose-response relation and physiological effects of chrysin.

Form	Dose	Physiological effect	Reference
Chrysin	50 mg/Kg	Dose-dependent inhibition of cancer cells	[31]
Chrysin	10 mg/Kg	Restored the lowered VE-cadherin and ZO-1 junction proteins	[42]
Chrysin	20–80 mg/Kg	Ameliorated lipid malfunction	[43]
Chrysin	40 mg/Kg	Prophylaxis of testosterone-induced benign prostate hyperplasia	[48]
Chrysin	25–50 mg/Kg	Prevention from reduction of sperm count and sperm viability	[49]
Chrysin	50 mg/Kg	Protection against the elevation of serum CKMB and LDH	[24,50]
Chrysin loaded solid nanoparticles	5–10 mg/Kg	Improved antioxidant levels and non-antioxidant enzymes in hippocampus	[51]
Chrysin	1–10 mg/Kg	Protection of age-related memory decline	[52]
Chrysin	0.1–10 mg/Kg	Enhanced the concentrations of antioxidant enzymes	[53]
Chrysin	25–50 mg/Kg	Hepatoprotective	[54]
Chrysin	20–40 mg/Kg	Hepatoprotective and nephroprotective	[56]
Chrysin	10 mg/Kg	Reduced DNA fragmentation	[6]
Chrysin	10–20 mg/Kg	Inhibit inflammation induced by cigarette smoke and decrease phosphorylation of p38 and ERK	[62,63]
Chrysin	25–50 mg/Kg	Protected from myocardial damage	[24]
Chrysin	50 mg/Kg	Inhibited ovalbumin-induced AHR to acetylcholine chloride (ACh)	[54]
Chrysin	50–200 mg/Kg	Decrease hepatic fibrosis	[65]
Chrysin	25–100 mg/Kg	Reduce hepatic stress and lipid oxidation and improve antioxidant enzymes	[29,57]
Chrysin	25–50 mg/Kg	Hepatoprotective and improved antioxidant status	[1]
Chrysin	50 mg/Kg	Regulate normal testicular morphology and increased ovarian follicles	[25]
Chrysin	50 mg/Kg	Improved sperm motility and reduced abnormal sperms	[31]
Chrysin and celecoxib	25–50 mg/Kg + 5 mg/Kg	Decreased paw edema	[37]
Chrysin	30–100 mg/Kg	Protection against spinal cord injury	[49]
Chrysin	50 mg/Kg	Neuroprotection	[17]

in a concentration-dependent manner on human ovarian cancer SKOV3 cell line through multiple mechanisms including reduction the sphere forming rate of SKOV3-derived ovarian cancer stem-like cells, decreased the protein expressions of CK2α, CD133, and CD44 in SKOV3-derived ovarian cancer stem-like cell [38].

Chrysin has also been reported to exhibit anticancer role against different cancer cells lines. The treatment of 5-(2′-amino) phenyl-7-cyclohexanemethyl chrysin from 250 μM to 500 μM regulated the cell death, and upregulated the p53 apoptotic pathway regulator [39]. In are search study results showed that chrysin impart inhibitory effect on colon cancer cells lines *via* apoptosis, sufficiently reducing the volume of tumor, upregulation of the Bax and down regulation of the sall4 [8]. Primarily, increased ROS and cytoplasmic Ca^{2+} levels alongside induction of cell death and loss of MMP are involved in inhibition of ovarian cancer through chrysin. Moreover, chrysin activated MAPK and PI3K/AKT pathways in OV90 and ES2 cells [18,40]. So chrysin can suppress neoplastic pathways in different cancers including squamous cell, melanoma, colorectal, breast and prostate cancers.

2.2. Antidiabetic effect

Diabetes mellitus (DM) is a metabolic disorder that disturbs the overall physiology of the body alongside glucose metabolism. It also affects other organs' functions and physiological process that worsen the overall health of an individual. The normality of glomerular filtration barrier is maintained by highly specialized cells known as glomerular epithelial podocytes. It has been noticed that elevated glucose exposure causes apoptosis in glomerular podocytes which can be attenuated by treating with chrysin. The primary mechanism involved in such effect has been identified to be reduction of DNA fragmentation. Further, restoration of increased Bax/Bcl-2 ratio and suppression of increased cytochrome *c* and Apaf-1 induction in renal podocytes exposed to high glucose concentrations (Fig. 3).

The oral administration of chrysin (10 mg/kg) continued for 10 weeks resulted in significant control of proteinuria and abnormal alteration in glomerular ultrastructure in diabetic mice. It also improved the slit diaphragm protein (podocin/nephrin) induction in diabetes affected glomeruli. It was also noticed that the rate of unfolded protein response was elevated to ER stress as depicted by PERK-eIF2α-ATF4-CHOP upregulation. Moreover, blocking of ER stress responses related with apoptotic events in podocytes was sufficiently associated with chrysin treatment. Besides, *in vitro* and *in vivo* treatment with chrysin caused a significant reduction in synthesis of slit diaphragm proteins [21].

In another investigation, streptozotocin-induced diabetic rats showed significant improvement in cardiac functionality upon treatment with chrysin. The ameliorative effect was delivered by chrysin through lowered inflammatory markers *via* inhibited expression of nuclear factor kappa B (NF-κB)p65/IKK-β and TNF-α levels. Besides, chrysin reduced apoptotic events characterized by Bcl-2 expression augmentation and lowered expressions of Bax and caspase-3. Similarly, it normalized alterations in expression of numerous enzyme systems and reduce peroxidation, thus inhibiting nitro-oxidative stress. The cardioprotective effects of chrysin were also found, when administered with GW9662 that raised the oxidative stress and inflammatory biomarkers, while the chrysin treatment (60 mg/kg) significantly attenuated the myocardial injuries in diabetic rats induced by isoproterenol *via* inhibition of AGE-RAGE mediated inflammation and oxidative stress and PPAR-γ activation [41]. Diabetic retinopathy (DR) is a chronic diabetes, which is due to abnormal retinal function. The study conducted by Kang and allies showed the positive effects of chrysin when administered to human retinal endothelial cells in glucose exposed eyes of diabetic mice. They deduced that chrysin suppresses apoptotic events in retinal endothelial and increased inhibition of VEGF and its receptor-2 and HIF-1α. Oral dose of chrysin accounting for 10 mg/kg resulted in restoration of decreased VE-cadherin and ZO-1 junction proteins possibly maintaining pericytes and endothelial cells interaction. The treatment also controlled the apoptosis by upregulation of Ang-1 & 2 and Tie-2 in diabetic mouse's eye [42].

For streptozotocin (STZ)- induced diabetic rats, the results of a research study exhibited that different doses of chrysin (20, 40, and 80 mg/kg/day) amended the raised levels of low density lipoprotein, malondialdehyde (MDA), triglycerides, cholesterol, and enhanced the concentrations of high density lipoproteins, total protein, GST, SOD and catalase [43]. In another study, it was observed that negative impacts on blood glucose, insulin, and lipid profile were significantly controlled by chrysin treatment in high fat and sucrose diet induced diabetic rats. Chrysin treatment was also related to prevention of impaired insulin signaling molecules and glucose tolerance [20]. Chrysin has also been shown to ameliorate negative impacts of diabetes on renal health indicators. Kang found that chrysin inhibited glucose induced renal EMT *via* blockage of expressions of mesenchymal markers. The treatment

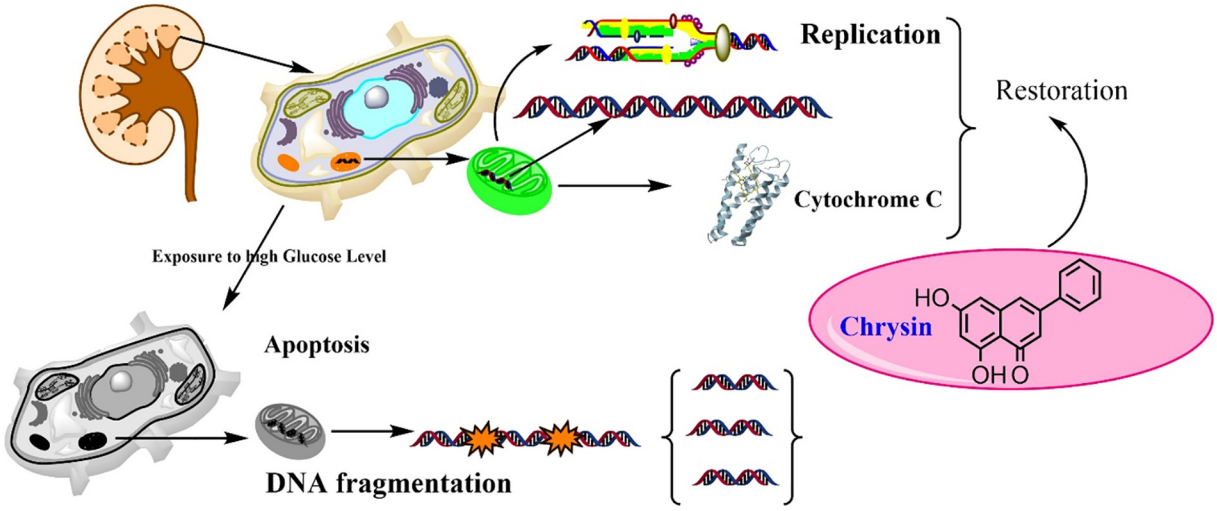

Fig. 3. Schematic of high Blood Sugar affection on kidney cells and protecting activity of Chrysin *versus*.

also reversed the downregulation of E-cadherin and N-cadherin induction in RPTEC. Additionally, the production of collagen IV and deposition of collagen fiber in kidneys of mouse were also inhibited through chrysin administration. It blocked the tubular cell migration, while decreasing the matrix metalloproteinase-2 activity. Furthermore, it restored the ZO-1 proteins and downregulation occluding in diabetic mice [44]. Besides, multiple other studies have also confirmed the antidiabetic role of chrysin like protection of cognitive decline (DACD) *via* reduction of NF-κB p65 unit, TNF-α, IL-1β, IL-6, and caspase-3 in cerebral cortex and hippocampus [45]. In another study, the alloxan-induced diabetic Swiss albino mice were treated with chrysin and quercetin by intraperitoneal administration. The study showed that 7-day treatment of these flavonoids significantly reduced the lipid peroxidation status in liver tissues of the rats and decreased the degree of vacuolization in liver tissue and number of vacuolated hepatic cells [46]. To sum up chrysin showed to be able to suppress the metabolic pathways involved in diabetic nephropathy, retinopathy, cardiac myopathy and dyslipidemia.

2.3. Oxidative stress

Chrysin administration significantly ameliorated sperm parameters, protecting the reproductive system against varicocele damages. For that reason, chrysin might be an alternative adjuvant therapy to improve sperm quality in men presenting this condition [47]. Chrysin at dose (50 mg/kg) significantly protected from the testosterone-induced benign prostate hyperplasia (BPH) in rats through various mechanisms such as prevention from (i) elevation of lipid peroxidation, (ii) depletion of glutathione, (iii) inhibition of superoxide dismutase and catalase activities, (iv) restoration of cleaved caspase-3 level, and (v) restoration of reduced Bax/Bcl-2 ratio and mRNA expression of p53 and p21. Moreover, prevention from the enhancement of binding activity of mRNA expression of insulin-like growth factor 1 (IGF-1), NF-κB p65 subunit, and insulin-like growth factor 1 receptor (IGF-1R) were reported after chrysin treatment [48]. The orally administrated of nitrofurazone (50 mg/kg/day) to rats significantly induced testicular damage whereas on other side, the combining effects of chrysin (25 and 50 mg/kg/day, *p.o.*) and mirtazapine (15 and 30 mg/kg/day, *p.o.*) have been found to attenuate the elevation of serum acid phosphatase enzyme activity and markedly prevented from the reduction of sperm count and sperm viability. Chrysin and mirtazapine also work efficiently to prevent from the lipid peroxidation, glutathione depletion, and elevated TNF-α level and reduced c-kit level in rat testes. Moreover, this combining effect considerably decreased the levels of caspase-3 in testicular tissue [49].

In a study reported by the Mantawy and colleagues, they investigated the preventive role of chrysin against doxorubicin-induced chronic cardiotoxicity in male Sprague-Dawley rats. Administration of chrysin (50 mg/kg) provided protection against the elevation of serum CKMB and LDH as well as histopathological changes. Reduction in lipid peroxidation, enhancement of antioxidant enzymes, reduction of expression of p53, Bax, Puma, Noxa, cytochrome *c* and caspase-3, increment of expression of Bcl-2, inactivation of MAPK; p38 and JNK, reduction of NF-κB, expression of PTEN, and augmentation of VEGF/AKT pathway were prime functions of chrysin in rats [24,50].

Chrysin-loaded solid lipid nanoparticles (SLNs) (5 mg/kg and 10 mg/kg) expressively improved the antioxidant levels and non-antioxidant enzymes in hippocampus caused by amyloid-β25–35 (Aβ25–35). Chrysin decreased the lipid peroxidation, acetylcholinesterase and neuronal damage as well as vetoed from the memory loss [51]. Another study also indicated that orally administrated chrysin to rats provided protection of age-related memory decline, enhancement in levels of superoxide dismutase, catalase, glutathione peroxidase, attenuation of elevated level of reactive oxygen species, and inhibition of Na(+), K(+)-ATPase activity as well as mitigation of reduction of levels of brain-derived neurotrophic factor (BDNF) in aged mice [52]. In this regard, chrysin has also been found to protect from the oxidative damage induced by methylmercury in Wistar rats. The treatment of chrysin at different doses (0.10, 1.0, and 10 mg/kg/b.w.) significantly enhanced the concentrations of antioxidant enzymes studied the effects of orally administrated chrysin (25 and 50 mg/kgb.w.) against the hepatotoxicity induced by intraperitoneal administration of cisplatin (7.5 mg/kgb.w.). Amelioration of cisplatin-induced lipid peroxidation, xanthine oxidase activity, reduction of glucose-6 phosphate dehydrogenase, and quinone reductase was reported after chrysin treatment. In addition, chrysin also attenuated expression of iNOS, COX-2, and levels of NFκB and TNF-α along with hepatic tissue damage [53,54]. Oral administration of chrysin to rats against cisplatin [cis-diamminedichloroplatinum (II) (CDDP)] induced oxidative stress in the jejunum significantly attenuated CDDP-induced goblet cell disintegration, enhanced expression of phospho-p38MAPK & p53, and apoptotic tissue damage [55]. The administration of different doses of chrysin (20 and 40 mg/kg b.w.) prevented the liver and kidney of Wistar rats against oxidative stress by inhibiting cytochrome P450 2E1, alcohol dehydrogenase, and xanthine oxidase. It also lowered the levels of serum aspartate aminotransferase, alanine aminotransferase, blood creatinine, urea nitrogen, and lactate dehydrogenase [56]. To summarize chrysin showed to be able to inhibit the oxidative stress pathways in different animal models of oxidative injury in heart, prostate, reproductive system and hippocampus.

2.4. Cardiovascular health

Chrysin effectively inhibit platelet accumulation and granule production which is induced by collagen, thrombin, ADP and U46619. Additionally, chrysin limit the adherent platelets and also reduces the spread of single platelet on immobilized fibrinogen. It is revealed from biochemical tests that chrysin inhibited the collagen-induced activation of PKC, Syk, PLCγ2, along with phosphorylation of ERK1/2 and Akt. Moreover, chrysin also reduced the phosphorylation of FAK, Akt, FcγRIIa, and GSK3β in platelet spreading on immobilized fibrinogen [29]. In another trail (*in vitro*) data reported that chrysin also inhibited the thrombus formation and platelet functionality [57]. Lo and colleagues showed that chrysin concentration dependently has been found to inhibit the chemotaxis and PDGF proliferation and also decreased PDGF signaling in vascular smooth muscle cell (VSMC). Chrysin is also effectively decreaseH_2O_2 signaling, NADPH oxidase activation, and PDGF-induced reactive oxygen species production, but, on the other side, it did not interfere with the binding of PDGF with VSMCs. Chrysin inhibit PDGF-induced oxidation of protein tyrosine phosphatase (PTP) active site and relief PDGF-induced inhibition of PTP. It also inhibits PDGF receptor auto-phosphorylation which is induced by vanadate (PTP inhibitor) [58]. Effect of chrysin rather than antioxidant *N*-acetylcysteine and flavonoid (−)-epigallocatechin-3-gallate on the activity of PTP and PDGF signaling was inhibited due to intracellular glutathione (GSH) depletion which is due to the effectiveness of chrysin on glutaredoxin/GSH system for reactivation of PTP [58]. The study revealed that chrysin inhibited lipopolysaccharide (LPS)-induced angiogenesis in chorioallantoic membrane (CAM) of chicken as well as human umbilical endothelial cells (HUVEC). Chrysin also reduced LPS-induced neovascular density of CAM, making down regulation of VEGFR-2 (KDR), VEGF gene expression, but not VEGFR-1 (Flt-1). Furthermore, chrysin concentration independently reduced auto-regulation loop of IL-6/IL-6R in LPS-treated HUVEC in humans [26]. A group of scientists reported that chrysin concentration (10 □M) increased L-NAME-sensitive endothelial NO release which lead to cGMP accumulation in aortic rings with endothelium. It also induced aortic and endothelium dependent relaxation. Additionally, it stimulated the release of NO and effectively mediate through phosphatidylinositol (PI) 3 kinase [59]. A group of researchers reported that chrysin enhances relaxation of acetylcholine under control conditions or after a specified period of incubation with anion superoxide producing xanthine oxidase/hypoxanthine. It also increased relaxation which is induced by sodium nitroprusside, 3 morpholinosydnonimine, and 8-bromoguanosine-3′: 5′-cyclic monophosphates [34]. On the other hand, chrysin is effective in prevention from damage through tissue due to bioactivation by S-adenosyl methionine (SAM), which is methyltransferase dependent. It has been investigated that administration of chrysin (10 mg/kg) significantly reduced DNA fragmentation in liver, brain tissue, blood, lipid peroxidation, and protein carbonyls. It considerably reduced micronuclei generated in bone marrow cells of humans [6]. So chrysin suppress the pathways involved in thrombosis and platelet aggregation aortic endothelia injury and cardiac oxidative stress.

2.5. Anti-inflammatory role

Pro-inflammation and inflammation of cytokines are linked with different chronic diseases. Chrysin plays significant role to reduce inflammation of immune system to reduce damage produce through macrophages, neutrophils and other immune-inflammatory responses. Additionally, there is a number of positive effects of chrysin is reported *i.e.* reduction of tumor necrosis, alpha (TNF-α), NF-κBp65 unit, interleukin-1β (IL-1β), IL-17A, interferon gamma (IFN-γ), IL-12, and IL-6. Furthermore, chrysin is one of the effective inhibitory agents against NF-KB and peroxisome proliferator activated receptor gamma (PPAR-γ), which plays significant role in down regulation of pro inflammatory enzymes *i.e.* cyclooxygenase-2 (COX-2), myeloperoxidase (MPO), inducible nitric oxide synthase (iNOS), prostanoids, and phospholipase A2 [25]. Chrysin dose such as 1, 5, and 10 μM was used to treat human osteoarthritis (OA) chondrocytes for 120 min which stimulate IL-1β for 24 h. In another study, chrysin was reported to reduce IL-1β-induced production of NO, PGE_2; expression of iNOS, MMP-3, COX-2, ADAMTS-4, ADAMTS-5, MMP-13, MMP-1, and degrade collagen-II, aggrecan. Additionally, it also blocked activation of NF-κB and degradation of IL-1β-stimulated IκB-α [60]. Qi and coworkers expounded that chrysin dose, such as10, 30, and 60 μg/mL, reduced iNOS-induced expression by LPS. Besides, chrysin treatment inhibited LPS-induced phosphorylation of JAK-STATs, nuclear translocation of STAT1 and STAT3, release of TNF-α, MCP-1, IL-6 and ROS production in RAW264.7 cells; ROS acted as an upstream signal to mediate the activation of JAK-STATs signaling pathway. Chrysin blocked the activity of JAK-STATs mediated by ROS to reduced LPS-induced inflammatory response in cells of RAW264.7 [61].

The exposure of cigarette smoke to experimental subjects (volunteers) caused a significant enhancement in the release of inflammatory cytokines such as TNF-α, IL-1β, and IL-8 in bronchoalveolar lavage fluid and MPO expression in lung tissue, whereas intraperitoneal administration of different doses of chrysin (10, 20 mg/kg·d) inhibit inflammation induced due to cigarette smoke, MPO expression, and inflammatory cytokines release. It also decreased the levels of phosphorylation p38 and ERK respectively [62,63].

One of the most effective chemotherapeutic drugs is doxorubicin (DOX), although its therapeutic effectiveness depends on occurrence of cardiotoxicity. As discussed earlier, chrysin is natural flavones which possess several biological activates and act as anti-inflammatory, anticancer, and antioxidant. Chrysin (25–50 mg/kg on daily basis) for 12 days considerably protect myocardial damage induced by DOX (15 mg) which is due to increase level of lactate dehydrogenase (LDH), serum creatine kinase isoenzyme-MB (CK-MB), and myofibrillar disarrangement. In this way chrysin treatment reduces the risk of oxidative stress. Moreover, DOX also triggered inflammatory responses by increasing cyclooxygenase-2 (COX-2), nitric oxide synthase (iNOS), expression of nuclear factor kappa-B (NF-κB), tumor necrosis factor-alpha (TNF-α) and nitric oxide, chrysin also inhibit all the above mentioned inflammatory responses. Likewise, DOX-induced apoptosis damage tissues by increasing cytochrome *c* and Bax expression, caspase-3 activity and decreasing Bcl-2 expression. It is worth mentioning that the treatment with chrysin significantly reduced these DOX apoptotic actions. The entire abovementioned finding shows that chrysin have protective effect against DOX-induced acute cardiotoxicity *via* reducing inflammation, oxidative injury and apoptotic tissue damage [24]. To conclude chrysin suppress inflammatory cytokines release and cyclooxygenase activity that cause its anti-inflammatory effect.

2.6. Anti-obesity

In 3T3-L1 adipocytes, chrysin is effective to improve brown fat specific markers expression, while it improves protein levels of proliferator peroxisome activated receptor (PPAR)α, PPARδ, PPARγ, phosphorylated acetyl-CoA carboxylase, phosphorylated AMP-activated protein kinase (p-AMPK), lipase (hormone sensitive), carnitinepalmitoyltransferase 1, perilipin, acyl-coenzyme A oxidase 1, uncoupling protein 1 (UCP-1), proliferator peroxisome activated receptor-1 α (PGC-1α), fat oxidation, thermogenesis, lipolysis as well as decrease lipogenesis. Improved expression of brown fat-specific markers and UCP-1 was due to the AMPK activation induced by chrysin based on the information that suppression of AMPK by dorsomorphin eliminated expression of UCP-1, PR domain-containing 16 and PGC-1α, while the 5-aminoimidazole-4-carboxamide ribonucleotide activator improved expression of brown marker proteins [51]. In another study done by Feng and their coworkers, they addressed that chrysin improved high fat diet induced muscular steatosis, hepatic in obese rats without affecting their body weight. Chrysin reduced macrophages permeation into adipose

tissue in obese rat. Additionally, chrysin was able to induce anti-inflammatory M1, M2 phenotype in peritoneal macrophages of obese rat and cultured macrophages (*in vitro*) as a result chrysin changed M1/M2 status. Moreover, result revealed that chrysin regulated phenotypes of macrophages by improving transcription of (PPARγ) activity and its target genes expression [52].

2.7. Antiallergic

A study conducted on female BALB/c mice, ovalbumin (OVA)-induced airway hyperresponsiveness (AHR)result revealed that chrysin effectively reduced OVA and decreased eosinophils (inflammatory cells), IL-13 in bronchoalveolar lavage fluid (BALF), interleukin (IL) -4, and total serum immunoglobulinIg E (IgE). Chrysin also regulated the level of interferon-γ (IFN-γ) in BALF, decreased infiltration of inflammatory cell, goblet cell hyperplasia, and expression of α-SMA around bronchioles. Likewise, extracellular signal-regulated kinase (ERK) and phosphorylation levels of Akt decreased by chrysin, which is related to ASMC proliferation [64]. A group of researchers found chrysin (50 mg/kg) to significantly inhibit ovalbumin-induced AHR to acetylcholine chloride (ACh) in BALB/c mice (OVA). It is worth mentioning that chrysin considerably suppressed the eosinophil counts in BALF, total inflammatory cell, and IgE levels in serum. Histological studies of lung tissue disclosed that chrysin substantially decreased airway mucus-producing goblet cells and eosinophilic inflammation induced by allergen. Additionally, chrysin also stimulate the immune system by triggering the immune response to allergens towards GATA-3, T-helper type 1 (Th1) profile by modifying the T-bet transcription factors in allergic mice [54]. A number of studies indicated that chrysin suppressed the release of serum histamine, systemic hypersensitivity and immunoglobulin E-mediated anaphylaxis. These effects are stronger as compared to one of the well-known anti-allergic drugs *i.e.* cromolyn. Chrysin also decreased release of histamine from mast cells. Intracellular calcium modulation mediated the inhibitory effect of chrysin on histamine release. Moreover, chrysin suppressed pro-inflammatory cytokines gene expression in mast cells such as IL-1β, TNF-α, IL-6, and IL-4. Likewise, the inhibitory effect of chrysin on the pro-inflammatory cytokine was caspase-1 dependent and NF-κB [53]. Chrysin (3, 10, and 30 mg/kg, *p.o.*) caused a marked reduction in infiltration of leucocytes, inflammation, status of perivascular lung blood vessels, bronchi status, alveolar macrophages activation, alveoli integrity as well as reduced cellular injury factors; *i.e.* alkaline phosphatase, lactate dehydrogenase, and total protein in bronchoalveolar hyper-responsiveness rats. Moreover, treatment with chrysin pointed out to its anti-asthmatic potential. It may be due to alteration of Th1/Th2 polarization through inhibition of nitric oxide synthase, NF-κB and activated protein [24].

2.8. Hepatoprotective

Chrysin is found effective against liver damage induced by carbon tetrachloride (CCl_4). Liver damage is actually due to increase level of serum aspartate-amino-transferase, alanine-amino-transferase, steatosis, centrilobular necrosis, alteration in hepatocyte ultrastructure, augmentation of hepatic α-smooth muscle actin (α-SMA) protein, tumor necrosis factor-α (TNF-α) through intraperitoneal CCl_4 injections (dose: 1 ml/kg). The results showed that chrysin reduced serum aspartate-amino-transferase and alanine-amino-transferase also give protection against extension of steatosis, centrilobular necrosis, and an alteration of hepatocyte ultrastructure as well as also caused reduction in hepatic α-SMA protein, and TNF-α expression [65]. Being a hepatoprotective agent, in a study on rats, chrysin protected from the TGF-β1-mediated hepatic stellate cells (HSCs) stimulation on fibrogenesis. Chrysin (50–200 mg/kg) expressively decreased hepatic fibrosis, α-SMA, TGF-β1 immunopositive cells, and TGF-β1 as compared to other flavonoids. In addition, these doses considerably decreased mRNA in liver of Smad 2 [65]. D-GalN rats were observed to exhibit high level of nephron and hepatotoxicity marker activities alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transpeptidase, alkaline phosphatase, total bilirubin level, uric acid, urea, creatinine, and lipid profile. It also affected albumin serum total protein and A/G ratio [56]. In another study, chrysin (25, 50, and 100 mg/kg) reduced hepatic marker enzymatic activities and lipid peroxidation by products *i.e.* conjugated dienes, lipid hydroperoxides, thiobarbituric acid reactive substances (TBARS), increased free radical scavenging enzymatic activates such as superoxide dismutase, glutathione peroxidase, catalase, while non-enzymatic antioxidants reduced vitamin C, glutathione, and vitamin E [29,57]. Similarly, albino rats were subjected to oral administration of chrysin (25 and 50 mg/kg by b.w.) against the hepatotoxicity induced through administration of cisplatin (7.5 mg/kgb.w.) [58]. In another study, effect of chrysin on methotrexate-induced hepatic oxidative stress was observed. Apoptosis in rats significantly caused decreased in lactate dehydrogenase activity, aspartate aminotransferase, alanine transaminase, and malondialdehyde content as well as increased glutathione reductase, superoxide dismutase, catalase activities, glutathione peroxidase, and reduced glutathione content [1]. Likewise, chrysin against CCl_4 induced toxicity in male Wistar rats downregulated the mRNA expression of the iNOS gene [26]. To summarize chrysin inhibit liver injury in different model of hepatotoxicity including cisplatin and methotrexate associated liver injury.

2.9. Reproductive health

A study discussed by Campos and coworkers, they evaluated the protective role of chrysin against the reproductive abnormalities [12]. The supplementation of chrysin (50 mg/kg/day) in ninety-day-old male and female gerbils exhibited stromal remodeling and epithelial hyperplasia in male and female prostate gland. It is actually the development of the organelles which are involved in the secretory bio-synthetic pathway in female and male epithelial cells. Chrysin is effective to regulate normal testicular morphology and increased ovarian follicles in number [25]. It enhanced the sperm motility, decreased apoptosis, sperm abnormalities, dead sperm rate, and MDA levels in paracetamol testicular tissues damage rats [62]. In a study done by Ciftci and coworkers, they explicated that chrysin utilization (50 mg/kg) showed a marked decline in TBARS, improved glutathione levels, sperm motility, concentration and reduction in abnormal sperm rate [31]. Chrysin and celecoxib at the dose 25 and 50 mg/kg and 5 mg/kg respectively, were administered orally to Wistar rats and data revealed that decreased paw edema in Wistar rats which was comparable to celecoxib. Moreover, chrysin and celecoxib reduced testicular injury through retreating histopathologic and gonadosomatic index by spermatogenesis protection. Both agents upregulated serum testosterone, expression of steroidogenic acute regulatory (StAR) mRNA and FSH. Chrysin inhibited inflammation through reversal of TNF-α, myeloperoxidase, COX-2 protein expression, and elevation of iNOS and IL-10. Mitigation of the testicular damage was accompanied with inhibition of oxidative stress *via* decreasing testicular nitric oxide and lipid peroxides. Both agents effectively downregulated caspase-3 and FasL mRNA expression in order to increase cell survival in case of apoptosis [37].

2.10. Neuroprotective effect

6-Hydroxidopamine (6-OHDA) in Parkinson's disease induced behavioral alterations and apomorphine induced behavior in mice. 6-OHDA oral administration increased the levels of interferon-□, TNF-α, IL-2, IL-6, IL-1β, NF-□B, while decreased antioxidant potential, IL-10 levels, antioxidant reactivity in striatum along with modification in calcium-binding protein B (S100B), nerve growth factor, brain-derived neurotrophic factor and cell line-derived glial neurotrophic factor levels [66]. The result pointed out to fact that ammonium chloride (NH_4Cl) mediated the neuroinflammation in hyperammonemic rats. In this

experiment, NH_4Cl was injected *i.p.* to male albino (Wistar rats) can able to down regulate the glutamine synthetase (GS) expression and glial fibrillar acidic protein (GFAP), while upregulated IL-1β, TNF-α, p65 NF-κB, IL-6, iNOS, and COX-2 expression. Oral treatment of chrysin to hyperammonemic rats significantly restored brain ammonia level, water content and GFAP, GS, IL-1β, IL-6, p65 NF-κB, TNF-α, COX-2 as well asiNOS expression [66]. Chrysin using 30 and 100 mg/kg markedly protected against spinal cord injury (SCI) in Wistar rats through various mechanisms such as (i)reduction of water content of spinal cord, TNF-α, IL-6, NF-κB p65 unit, iNOS, IL-1β, NO production, and caspase-3, (ii) recovery of neural functions, (iii) suppression of iNOS pathway [49]. Similarly, the neuroprotective role of chrysin (50 mg/kg) against global cerebral ischemia and reperfusion (I/R) in a C57BL/J6 mouse model was accompanied with prevention of oxidative effects, inhibition of the development of neurodegenerative histopathologies, reduction of TBARS levels and increment of GSH levels [17].3-Nitropropionic acid (3-NP) is an irreversible mitochondrial complex-II inhibitor that has been able to produce transcriptional dysregulation, oxidative damage, bioenergetics failure in the same manner of Huntington's disease (HD) pathogenesis and protein aggregation. 3-NP at a dose 10 mg/kg (b.w.i.p.) administration showed significant alterations including oxidative damages to biomolecules, mitochondrial dysfunction as a result of this modification cell death occur. Oral administration of chrysin at the dose of 50 mg/kg b.w. orally for 14 days improved and regulated mitochondrial activities. Moreover, chrysin also abolished oxidative stress markers, such as nitrite, protein carbonyls, lipid peroxidation by remarkably improving the antioxidant status of catalase, superoxide dismutase, and reduced glutathione in striatal mitochondria. No doubt, chrysin prevents from apoptosis by upregulating the expression of Bcl-2 mRNA and downregulating the mRNAs pro-apoptotic (Bax, Bad) in 3-NP-induced condition. Furthermore, the results addressed that chrysin-based solid lipid nanoparticles (SLNs) (50 and 100 mg/kg) enhanced the decreased levels of antioxidant enzymes and non-antioxidant enzymes in hippocampus [51], while it decreased the lipid peroxidation and acetylcholinesterase in the Aβ25–35-injected volunteers [67]. Chrysin in combination with protocatechuic acid (PCA) result in greater cell viability and decrease the release of lactate dehydrogenase from 6-hydroxydopamine-treated PC12 cells. The combination of two compounds considerably reduced chemically induced dopaminergic both in mice and zebrafish. The combining effect of these compounds result in (a) increased transcriptional activity along with improve expression of nuclear factor-erythroid 2-related factor 2 protein (b) variation of cellular redox status with improve hallmark antioxidant enzymes; *i.e.* superoxide dismutase, heme oxygenase-1, and catalase (c) reduced the levels of MDA (a lipid peroxidation product). This combination of compounds also inhibited NF-κB activation and iNOS expression [67].

In male C57/BL6 mice of middle cerebral artery occlusion (MCAO), chrysin considerably reduced neurological deficit and infarct volumes. It also significantly improved the number of glial cells and secretion of pro-inflammatory cytokines. Additionally, chrysin decreased MCAO-induced upregulation of COX-2, NF-κB, and iNOS [64]. Acrylamide (ACR) produces neurotoxicity, which is associated with severe peripheral and central neuronal degeneration. Result revealed that administration of chrysin (0.5–5 μM) remarkably decreased ACR-induced neurotoxicity with the passage of time in dose-dependent manner in experimental Wistar rats [68]. Guillain-Barré syndrome (GBS) is a post-infectious, immune-mediated, acute, demyelinating disease of nerve and peripheral roots. In case of prevention, chrysin was orally administered (50 mg/kg on daily basis) at once which reduced inflammatory cell permeation and sciatic nerves demyelination in experimental autoimmune neuritis (EAN). In the sciatic nerves, chrysin decreased the expression of iNOS, COX-2 and NF-κB. Furthermore, chrysin inhibited the splenic mononuclear cell secretion of IL-1β, IL-6, IL-2, interferon γ, TNF-α, IL-12 and increased the level of IL-4 [69].

2.11. Miscellaneous properties

In a study conducted on male Sprague Dawley rats, oral administration of chrysin protect from renal toxicity induced due to frequent administration of paracetamol through various physiological mechanisms such as reduction of creatinine, serum urea, and also downregulate the increase level of inflammatory markers, *i.e.* TNF-α, IL-1β and IL-33. Additionally, it decreased the elevated autophagic tissue damage through increase light chain 3B (LC3B) expression and cysteine aspartate-specific protease-3 (caspase-3) activity [70].

The anti-inflammatory effect of chrysin on osteogenesis was analyzed in preosteoblast MC3T3-E1 cells. The findings disclosed that chrysin is also able to induce osteogenic differentiation even when osteogenic agents are not present. Chrysin administration improved transcription factors expression (Osx and Runx2) and bone formation genes marker (OCN, Col1A1, OPN) along with enhancement in the formation of mineralized nodes. In the process of osteogenic differentiation, the chrysin specially activate ERK1/2, while p38 MAPKs and JNK are not activated. Further researches enlighten that co-treatment of inhibitors *i.e.* PD98059, U0126 or ICI182780 (ER antagonist) with chrysin significantly abolished the ERK1/2 activation and chrysin-induced osteogenesis. So, it was concluded that the effect of chrysin on osteogenesis is ER and ERK1/2-dependent. Thus, chrysin has a significant role to improve osteogenesis for the prevention of osteoporosis as well as its treatment [14].

3. Conclusion

Chrysin is a promising bioactive flavonoid with aforementioned significant health effects and its synthetic counterparts are being utilized as a pharmaceutical drug for the treatment of various illnesses. Being vital in its pharmaceutic applications, chrysin plays an important role in prevention from cancer, oxidative stress, inflammatory disorders, diabetes mellitus, cardiovascular diseases, obesity, and allergic events. Scientific studies have also proved its neuroprotective and hepatoprotective functions along with boosting reproductive health as evident from numerous animal models. Nonetheless, this compound could be of paramount importance and its dietary inclusion may avoid various degenerative disorders making people less likely to develop life threatening diseases. In dietary modules of humans, chrysin-containing foods may be devised as a prophylactic strategy among the masses to avoid diseases, but it needs certain controlled experimental trials and safety studies. The scientific studies summarized in this article will assist in designing targeted clinical settings for dietary implementation of designer products containing chrysin as a remedial measure. Such clinical settings will further open new horizons for application of nutraceuticals in routine meals to aid in maintaining, improving, and protecting health of individuals.

Declaration of competing interest

We declare no conflict of interest in submission of this review manuscript.

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