Neurochemistry International 143 (2021) 104939

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/neuint

Therapeutic potential of mangiferin in the treatment of various neuropsychiatric and neurodegenerative disorders

Vaibhav Walia, Sushil Kumar Chaudhary, Neeraj Kumar Sethiya *

Faculty of Pharmacy, DIT University, Dehradun, India

ARTICLE INFO

Keywords:
Alzheimer's
Anxiety
Biosynthesis
Depression
Mangiferin
Neuroaging
Neurodegenerative
Neuroinflammation
Neuropsychiatric
Parkinson's
Pharmacokinetics
Xanthone

ABSTRACT

Xanthones are important chemical class of bioactive products that confers therapeutic benefits. Of several xanthones, mangiferin is known to be distributed widely across several fruits, vegetables and medicinal plants. Mangiferin has been shown to exert neuroprotective effects in both in-vitro and in-vivo models. Mangiferin attenuates cerebral infarction, cerebral edema, lipid peroxidation (MDA), neuronal damage, etc. Mangiferin further potentiate levels of endogenous antioxidants to confer protection against the oxidative stress inside the neurons. Mangiferin is involved in the regulation of various signaling pathways that influences the production and levels of proinflammatory cytokines in brain. Mangiferin cosunteracted the neurotoxic effect of amyloid-beta, MPTP, rotenone, 6-OHDA etc and confer protection to neurons. These evidence suggested that the mangiferin may be a potential therapeutic strategy for the treatment of various neurological disorders. The present review demonstrated the pharmacodynamics-pharmacokinetics of mangiferin and neurotherapeutic potential in several neurological disorders with underlying mechanisms.

1. Introduction

Xanthones are the secondary metabolites having wide range of biological properties and diverse pharmacological potential in the treatment of various disorders. Structurally, xanthone are related to flavonoids. However, flavonoids exist frequently in nature, whereas xanthones have limited occurrence. Xanthone occur as mono- or polymethyl ethers or glycosides or polyhydroxylated compounds along with other functional groups in three ring systems (Negi et al., 2013; Shan et al., 2011). Among xanthones aryl C-glycosides present a unique class having C–C glycosidic bonds in their core skeleton, exhibit wide range of biological properties and possess remarkable stability toward both enzymatic and chemical hydrolysis and are the most suitable drug candidates (Levy and Tang, 1995; Wei et al., 2016). Dietary xanthone have been found active against various neurodegenerative disorders due to their anti-inflammatory, antioxidant and neuroprotective activities (Li et al., 2013b, 2014; Newman and Cragg, 2016).

Of several compounds belongs to this class, mangiferin (C-glucopyranoside of 1, 3, 6, 7-tetrahydroxyxanthone) is a yellow color polyphenolic natural xanthone and is the first xanthone which has been investigated widely for the pharmacotherapeutic effects (Sethiya et al., 2009a, b; Padmapriya et al., 2012; Jyotshna et al., 2016; Wu et al., 2010; Rashid and Sil, 2017). Chemically mangiferin is a stable C-glycoside, having highly condensed aromatic ring system with aglycone (1, 3, 6.7-tetrahydroxyxanthone) and glycone (pyranose) moiety (Bhatia et al., 1967). Mangiferin exhibit various properties including cytoprotection, scavenging action against reactive oxygen species (ROS), complexation with metal ions, etc. (Li et al., 2008). Further mangiferin exerts pharmacological activities including antioxidant, antiviral, immunomodulatory, antimicrobial, antiparasitic, anticancer, anti-diabetic, antiasthmatic, hepatoprotective, antiseptic, anti-inflammatory, etc. (Matkowski et al., 2013; Pal et al., 2014; Rashid and Sil, 2017). Particularly, mangiferin is known to interact with neural components, downregulate stress pathways, improve memory and counteract the neurodegeneration (Cao et al., 2017; Jung et al., 2009; Zajac et al., 2013; Bertolini et al., 2007) (*refer to* Fig. 1). It is also suggested that the mangiferin is a bioactive compound and could be a new drug or a leading compound for the treatment of wide range of diseases (Imran et al., 2017; Zhi-quan et al., 2011). However, despite of these evidence regarding the beneficial effect of mangiferin in pharmacotherapy, there is no detailed description of neurotherapeutic potential of mangiferin in literature. This narrative review describes the therapeutic

* Corresponding author.
E-mail addresses: vaibhav.walia00@gmail.com (V. Walia), sushil.chaudhary@dituniversity.edu.in (S.K. Chaudhary), neeraj.sethiya@dituniversity.edu.in, neeraj.sethiya@dituniversity.edu.in (N. Kumar Sethiya).

https://doi.org/10.1016/j.neuint.2020.104939
Received 29 June 2020; Received in revised form 2 November 2020; Accepted 12 December 2020
Available online 17 December 2020

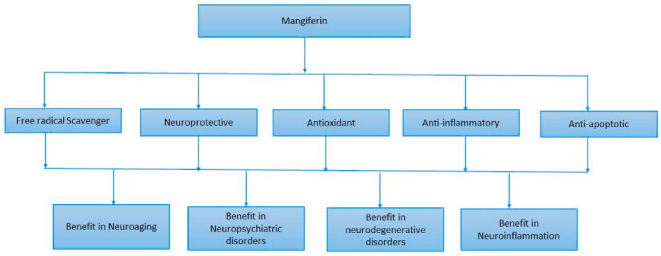

Fig. 1. Mangiferin and its role in therapeutics.

potential of mangiferin in the treatment of various neurological disorders with underlying mechanism of action.

2. Biological sources, distribution and biosynthesis of mangiferin

The presence of mangiferin has been confirmed in 96 species, 28 genera and 19 families of angiosperm (Sekar, 2015; Hostettmann and Hostettmann, 1989). Mangiferin is widely distributed in families including Anacardiacae, Aphloiaceae, Celastraceae, Bignoniaceae, Gentianaceae, Iridaceae, Malvaceae, Moraceae, Rubiaceae and Thymelaceae (Rashid and Sil, 2017). It is also reported in several monocots and ferns (Sekar, 2015). In ferns it is present in *Asplenium adiantum-nigrum*, *Davallia subsolida*, *Trichomanes reniforme*, Acystopteris sp., *Cystopteris* sp., Gymnocarpium sp. and *Woodsia* sp (Matkowski et al., 2013). However, mangiferin occurs in the forms of the isomangiferin in *Nanohammus rufescens*, *Nephrolepsis dryeri* and *Cardiomanes reniforrne* (Jyotshna et al., 2016). Mangiferin content varies from plant to plant such that *Anemarrhena asphodeloides* (0.41%), *Aphloia theiformis* (2.0–9.0%), *Aquilaria sinensis* (0.1%), *Arrabidaea patellifera* (0.1%), *Bombax malabaricum* (0.02%), *Cratoxylum cochinchinense* (0.23%), *Cratoxylum pruniflorum* (0.23%), *Cyclopia genistoides* (0.70%), *Hedysarum alpinum* (1.9%), *H. flavescens* (1.2%), *Hiptage madablota* (0.03%), *Hypericum aucheri* (0.21–0.31%), *Iris domestica* (0.31–3.60), *Mangifera pajang* (0.48%), *Phaleria cumingii* (0.46%), *Salacia reticulata* (1.4%), *Salacia chinensis* (1.6%) and *Swertia minor* (6.38%) (Nedialkov et al., 1998; Dimitrov et al., 2011; Matkowski et al., 2013; Jyotshna et al., 2016; Tangah et al., 2017). A very small amount of mangiferin has been reported in *Aquilaria sinensis*, *Arrabidaea patellifera*, *Arrabidaea samydoides*, *Belamcanda chinensis*, *Bersama Abyssinia*, *Bersama engleriana*, *Bombax ceiba*, *Canscora decussata*, *Cratoxylum cochinchinense*, *Curcuma amada*, *Cuscuta reflexa*, *Dendrophthoe falcate*, *Gnidia involucrate*, *Hibiscus liliastrum*, *Hypericum montbretii*, *Iris domestica*, *Mahkota dewa*, *Phaleria macrocarpa*, *Polygala hongkongensis*, *Polygala tenuifolia, Pueraria tuberosa*, *Rhynchosia suaveolens, Senecio mikanioides*, *Swertia ciliata* and *Zizyphus cambodiana* (Sethiya et al., 2012; Chauhan and Dutt, 2013; Demirkiran et al., 2013; Matkowski et al., 2013; Ou et al., 2013; Sekar, 2015; Bera et al., 2015; Rammohan et al., 2015; Bulugonda et al., 2017). Mangiferin content (more than 6%) has been found in young leaves of coffee plants (*Coffea pseudozanguebariae*) which is higher than that of *Cyclopia* genisloides and Mangifera *zeylanica* (Jyotshna et al., 2016). However, the main and the primary source of mangiferin is *Mangifera indica* and almost every part of it is used for the extraction and isolation of mangiferin. Further the content of the mangiferin is more in stem and bark as compared to other parts of this plants (Jyotshna et al., 2016).

The biosynthesis of mangiferin mainly occurs through shikimate and ketate pathways (Rashid and Sil, 2017). Mangiferin biosynthesis involves the synthesis of xanthone aglycone (1, 3, 6, 7-Tetrahydroxyxanthone) and glycosylation of aglycone with glucose unit. The ring A is formed by the acetate-malonate polyketide route whereas the ring B is come up with the shikimic acid pathway followed by the condensation of both to form benzophenone intermediate, maclurin, which reacts intramolecularly to form the tetraoxygenated xanthone. C-glycosylation takes place and direct phenolic oxidative coupling of corresponding 3-C-glucosylmaclurin provides mangiferin (Ehianeta et al., 2016; Fujita & Inoue, 1977, 1980, 1981) (refer to Figs. 2 and 3).

Mangiferin is sometime isolated as coloring matter known as isomangiferin (from bark) and homomangiferin (from leaves and twigs) (Wu et al., 2010). Isomangiferin is 4-C-glycoside regioisomer and homomangiferin is the 3-O-methyl derivative of mangiferin and mainly coexist with mangiferin (Aritomi and Kawasaki, 1970; Saleh and Ansari, 1975; Fujita and Inoue, 1982). However, the content of mangiferin is suggested to be high when both isomangiferin and homomangiferin are present together (Richardson, 1984).

3. Pharmacokinetics mangiferin

Mangiferin has poor solubility (0.111 mg/mL), low bioavailability, high hepatic first-pass metabolism and high P-$_{gp}$ efflux (Jain et al., 2013; Khurana et al., 2017) making its use in the therapeutics a challenging task. Mangiferin is poorly soluble in aqueous solutions but the solubility increases through its complexation with phospholipids (Ma et al., 2014). Further, complexation of with β-cyclodextrin improves thermal stability and water solubility of mangiferin (Yang et al., 2013). However, the administration of mangiferin in the form of the complexes improves the bioavailability and other of physical properties of mangiferin (Ma et al., 2014; Yang et al., 2013; Boonnattakorn et al., 2016). So, it is important to develop mangiferin derivatives with improved physicochemical properties and pharmacological activities (Ehianeta et al., 2016). In humans, the intestinal flora plays many important roles in the metabolism of mangiferin (Li et al., 2000). The metabolites form after the oral administration of mangiferin include glucuronide conjugate, methyl derivatives, dehydroxylated and sulphated compounds (Liu et al., 2011, 2012; Wang et al., 2007). Bock et al. (2008) demonstrated that the mangiferin concentrations in plasma and urine of the pigs administered with mangiferin (74 mg/kg daily for 11 days). The blood sample collected at day 9th and 11th of the study. The mean plasma mangiferin level was 7.8–11.8 μmol/L, in urine it was about 1.4% and 1.6% and in feces it was about 8.2% on days 9th and 11th day of study. The main metabolite was norathyriol. Subsequently, in another study mangiferin (10, 25 and 50 mg/kg, i.v.) was administered to rats followed by the blood collection at different time intervals for the estimation of mangiferin content using HPLC (methanol and glacial acetic acid in ratio 40:60). The results obtained demonstrated that mangiferin possess the dose dependency and fitted in two-compartment model. The concentration of mangiferin in retina was 5.69 ± 1.48 μg/ml and 0.30 ± 0.02 μg/ml after 30 min and 5.0 h of mangiferin (50 mg/kg, i.v.) administration (Hou et al., 2010; Zhang et al., 2010). In another study, pharmacokinetic profile of mangiferin in rats were determined by administering the rats with mangiferin (50–500 mg/kg, p.o.). The results showed undetectable levels of mangiferin in plasma suggesting poor bioavailability upon oral administration (Li et al., 2003). The pharmacokinetics was studied after single oral dose of mangiferin (0.9 g/kg) in 21 male Chinese volunteers. Plasma mangiferin concentration

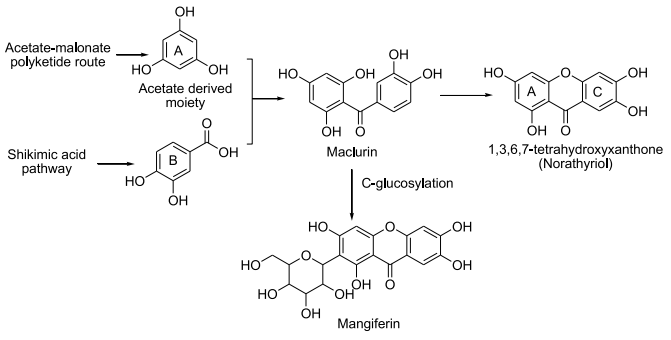

Fig. 2. Biological Synthetic pathway of mangiferin.

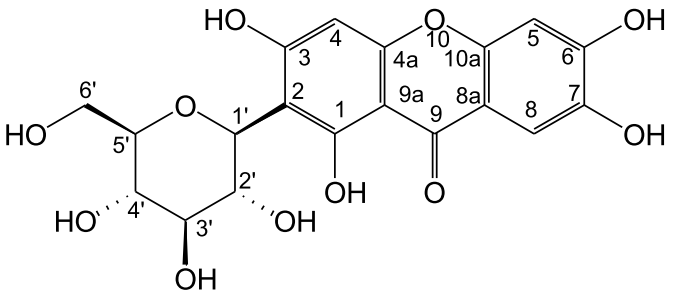

Fig. 3. Structure of mangiferin.

was 38.64 ± 6.75 ng/mL and elimination half-life was 7.85 ± 1.72 h after 1 h of mangiferin (0.9 g/p.o.) administration suggesting the absorption of mangiferin increases with dose and follows non-linearity (Hou et al., 2012). Another study reported that administration of mangiferin (17.5, 35 and 70 mg/kg) by intragastric administration resulted in the increase in C_{max} and AUC non-proportional to doses further suggested non-linearity in kinetics of mangiferin (Liu et al., 2010).

Various studies reported different perspectives regarding the entry of mangiferin in brain. The blood-brain barrier (BBB) consists of specialized tight junctions, specific transporters, a secretory body, and metabolic enzymes and acts as the interface for communication between CNS and peripheral circulation. BBB protect the brain and restricts the entry of various solutes and substance in brain (Abbott et al., 2006). Mangiferin, is a polar xanthones having mol. wt. 422 Da, and cannot traverse across BBB. But the exact mechanism why mangiferin cannot cross the BBB is not known (Zajac et al., 2013). However, some of the studies suggested that the mangiferin can cross the BBB. Interestingly, it was demonstrated that the oral administration of *Mangifera indica* L. extract daily for 7 days provides dose-dependently neuronal protection against the transient ischaemia and reperfusion injury in hippocampus of experimental animals. The study suggested that the *Mangifera indica* L. extract administered orally, absorbed through the BBB to confer neuronal protection (Martínez Sanchez et al., 2001). Li et al. (2008) determine mangiferin concentrations following single oral dose of Rhizoma Anemarrhenae (15 g/kg) extract. Mangiferin concentration was determined in different body tissues using RP-LC techniques. The result suggested traces of mangiferin in brain, indicating that mangiferin can pass through the BBB (Li et al., 2008). Thus, mixed results were reported in the literature regarding the ability of mangiferin to traverse across BBB. However, despite of these facts, mangiferin is known to possess the wide range of neurotherapeutic potential.

4. Toxicity studies

Mangiferin is non-toxic, non-mutagenic, non-genotoxic and non-embryotoxic but confers toxic effects on cancerous cells (Bulugonda et al., 2017; Matsushima et al., 1985; Gonzalez et al., 2007). The LD_{50} value for rats is 365 mg/kg and for mice is 400 mg/kg following i.p. administration (Bhattacharya et al., 1972; Jagetia and Baliga, 2005). Absorption index of mangiferin is about 0.1 (10%) (Dimitrov et al., 2011). Mangiferin (2000 mg/kg) administration resulted in transient dyspnoea, pain in flank position and pilo-erection. Further no abnormal clinical signs or haematological alterations were observed following oral administration of mangiferin (250–1000 mg/kg, p.o. for 28 days). However, mangiferin (1000 mg/kg, p.o. for 28 days) administration resulted in the vacuolar degeneration, necrosis and acinar cells apoptosis (Prado et al., 2015).

5. Mangiferin a promising antioxidant

Oxidative stress is the condition characterized by the increased production of ROS, the later confer damage to various cellular molecules and has been implicated in the pathogenesis of various pathologies (Gupta et al., 2014; Li et al., 2015). ROS are production occurs inside the mitochondria, produced under normal conditions and the production increases with the increase in age (Wei et al., 2001; Smith et al., 2007; Sohal et al., 1994; Sohal and Sohal, 1991) (refer to Fig. 4). The leakage of electron from electron transport chain (ETC) resulting in the release of free electron which is captured by molecular oxygen for the formation of superoxide radical (O^{2-}) which in the presence of enzyme in the presence enzyme superoxide dismutase (SOD) forms hydrogen peroxides (H_2O_2) which then decompose by the enzyme catalase to form hydroxyl radical (OH^-) (Finkel and Holbrook, 2000; Valko et al., 2007). Both O^{2-} and H_2O_2 are mainly responsible for oxidative damage to the cell (Balaban et al., 2005; Van Houten et al., 2006). ROS also inhibit the complex-I, II, and III of ETC and generally interferes with the mitochondrial energetics (Ghezzi and Zeviani, 2012). Aging is characterized by increased formation of ROS (Gerschaman et al., 1954; Harman, 1956). Age related increased production of ROS is responsible for increased damage to various proteins, lipids, DNA and mitochondrial dysfunction (Floyd and Hensley, 2002; Lin and Beal, 2006; Mattiazzi et al., 2002; Kirkinezos et al., 2005). Further most of neurodegenerative disorders develops in the aged individuals and are often associated with the mitochondrial dysfunctions (Hirai et al., 2001; Baloyannis, 2006; Harman, 1972). Aging associated mitochondrial dysfunctioning is associated with the neuronal cell loss and the development of forms of neurodegenerative diseases (Schon and Przedborski, 2011; Exner et al., 2012). Therefore, to counteract such events there is a need of developing the neuroprotective therapy (Guttmacher, 2003).

Mangiferin is a well-known antioxidant and exhibit tremendous free radical scavenging action on ROS (Joubert et al., 2008; Rodriguez et al., 2006; Wu et al., 2008; Martin et al., 2008; Bera et al., 2015). Further therapeutic potential of mangiferin is mainly explained in context of its free radicals scavenging activity and its antioxidant potential (Narkhede et al., 2016; Yang et al., 2016). Mangiferin possess free radical-scavenging activity and antioxidant potential due to the presence of C-glycosyl linkage and polyhydroxy components (Asensio et al., 2000; Telang et al., 2013; Bors et al., 1990). It has been reported that the presence of catechol moiety containing four hydroxyl groups makes mangiferin an efficient antioxidant and anti-free radical molecule (Matkowski et al., 2013). Mangiferin due to the presence of two hydroxyl groups at ortho position in catechol moiety forms complex with iron (Dar et al., 2005; Pardo-Andreu et al., 2005, 2006, 2006a, 2007). Mangiferin confers protection against oxidative stress and enhances the levels of endogenous antioxidants such as glutathione (GSH) (Li et al., 2013a; Muruganandan et al., 2002; Ling et al., 2009; Joubert et al., 2008; Bertolini et al., 2007; Sato et al., 1992; Salvi et al., 2002).

Li et al. (2018) evaluated the antioxidant potential of mangiferin and its derivatives using ferric reducing antioxidant power (FRAP) assay and reported IC_{50} values for mangiferin, iso-mangiferin, neo-mangiferin, 7-O-methylmangiferin (45.8 ± 0.9 μM, 50.5 ± 1.9 μM, 5432.6 ± 345.4 μM, 5881.7 ± 315.3) respectively (Li et al., 2018). Mangiferin exerts

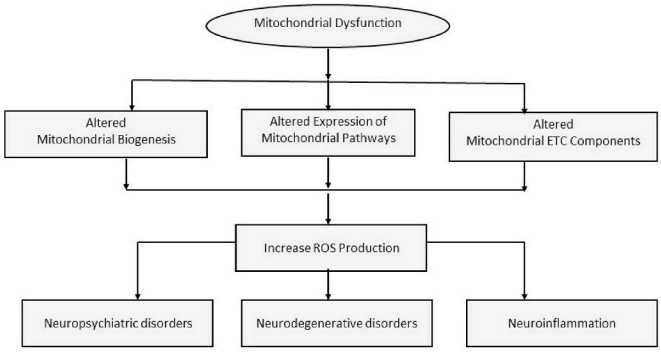

Fig. 4. Mitochondrial dysfunctioning & production of ROS

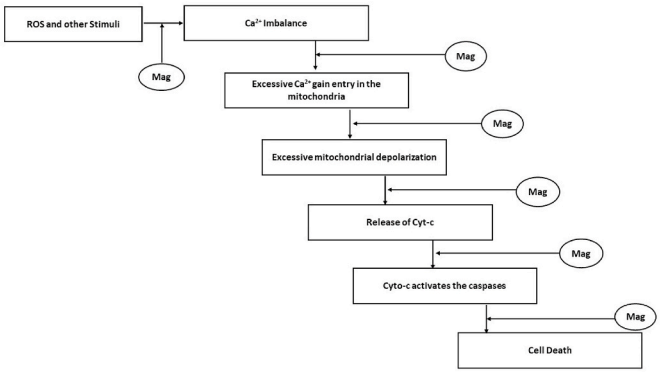

Fig. 5. Cytoprotective action of mangiferin.

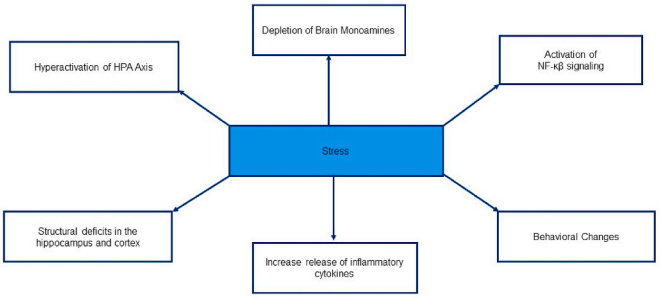

Fig. 6. Stress mediated pathological alterations.

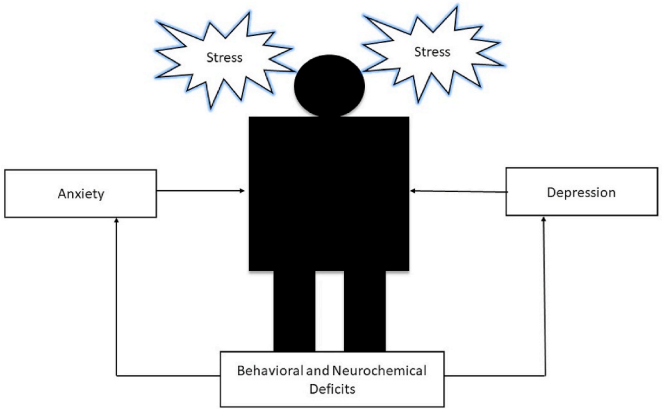

Fig. 7. Stress evoke anxiety and depression: Two pathologies link together.

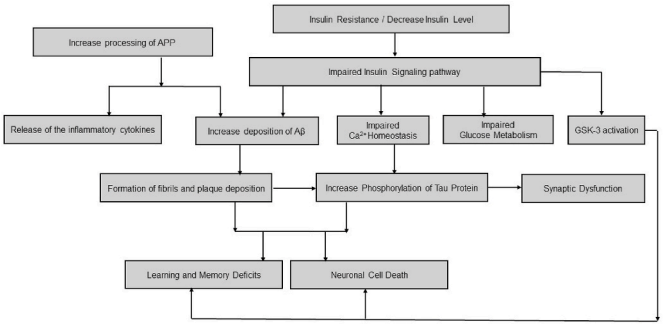

Fig. 8. Behavioral deterioration & neuronal degeneration in Alzheimer's disease.

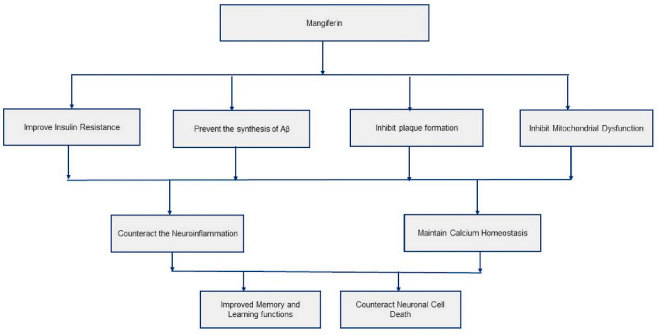

Fig. 9. Mangiferin as a promising therapy for Alzheimer's disease.

strong DPPH scavenging activity ($EC_{50} = 5.8 \pm 0.96$ μg/ml or 13.74 μM) and suggested that the presence of free hydroxyl groups and catechol moiety are essential for antioxidant activity (Dar et al., 2005). In another study also the mangiferin exerted potent DPPH radical scavenging activity (IC_{50} value = 2.45 ± 0.08 mM) (Pardo Andreu et al., 2006). Further mangiferin is suggested to be a better antioxidant than the flavonoids or phenylpropanoic acids in DPPH scavenging activity (Matkowski, 2009; Ling et al., 2009; Dar et al., 2005; Joubert et al., 2008; Pauletti et al., 2003).

Mangiferin forms complexes with iron and inhibit formation of Fe^{2+} ion (Kostyuk et al., 2007). Fe^{2+} is known to participate in Fenton-Haber-Weiss reactions responsible for the formation of OH^- radical. In deoxyribose assay, OH^- are generated in a reaction mixture (ascorbate, H_2O_2 and Fe^{3+}-EDTA) responsible for the degradation of mangiferin. Fe^{3+} ions form complex with deoxyribose, subsequently reduced to Fe^{2+} by the ascorbate. Fe^{2+} so formed favors the formation of OH^- ions by the degradation of H_2O_2. Mangiferin because of its iron chelating activity, forms chelate with Fe^{3+} and inhibit its binding with deoxyribose and subsequent formation of OH^- ions (Martinez et al., 2000). Mangiferin not only stimulates Fe^{2+} autoxidation, but also form a stable complex with Fe^{3+}, inhibiting its reduction and redox cycling to Fe^{2+} (Pardo Andreu et al., 2005). Mangiferin shows inhibiting capacity against OH^- radicals through its chelating capacity (Stoilova et al., 2008). Beside this mangiferin also acts as a scavenger for OH^- radicals (Martinez et al., 2000). In contrast to typical OH^- scavengers, mangiferin does not interfere with reaction between 2-deoxyribose and OH^- radicals suggesting that mangiferin acts by preventing OH^- formation from Fe^{3+}-EDTA plus ascorbate rather than by trapping OH^- radicals (Pardo Andreu et al., 2006).

Mangiferin (30 mg/kg, p.o.) treatment counteracted doxorubicin induced oxidative stress, lipid peroxidation and suppression of SOD activity (Zelko et al., 2002; Mohamed et al., 2011; Siswanto et al., 2016). Mangiferin (50 μM) reversed the cytotoxic effects of magnesium chloride by increasing the levels of endogenous antioxidants (Agarwala et al., 2012). Administration of mangiferin (100 mg/kg, p.o. for 6 days) decreased the ROS formation and inhibit the Pb(II)-induced NF-kβ pathway, mitogen-activated protein kinases (MPAKs) and apoptotic cell death (Pal et al., 2014). Mangiferin possess ROS scavenging capacity and ferric reducing ability of plasma (FRAP) comparable with vitamin C and E (Luo et al., 2012). Mangiferin prevented ROS and ROS mediated oxidative tissue damage more as compared to vitamin C, E, quercetin, curcumin and β-carotene (Sanchez et al., 2000; Martinez et al., 2000; Ghosh et al., 2012). Mangiferin enhances cellular antioxidant defense (Das et al., 2012) and increases the levels of SOD, CAT, and glutathione peroxidase (Sellamuthu et al., 2013). Mangiferin is also devoid of prooxidant activity and is thus superior to the conventional antioxidants (Martinez et al., 2000).

Mangiferin inhibit the phospholipid peroxidation in spontaneous autoxidation system greater than other plant extracts in TBARS assay (Martı'nez et al., 2000). Mangiferin inhibits lipid peroxidation induced by Fe^{2+}-citrate (50 mM) in rat liver mitochondria (IC_{50} value = 7.89 ±

1.19 mM and complete protection against peroxidation at 50 mM) (Pardo Andreu et al., 2005). Fe^{2+}-citrate induces mitochondrial dysfunctions due to lipid peroxidation. Mangiferin inhibit the mitochondrial swelling and prevent the dissipation of mitochondrial membrane potential induced by Fe^{2+}-citrate (50 mM) in dose-dependent manner and shows full protection at 10 mM concentration (Pardo Andreu et al., 2005). Mangiferin reduced formation of OH^- ions (through Haber-Weiss-type reaction) responsible for mitochondrial membrane peroxidation (Pardo Andreu et al., 2005) and also confers protection against H_2O_2 induced lipid peroxidation in erythrocytes (Jagetia and Venkatesha, 2005; Pardo-Andreu et al., 2006; Rodriguez et al., 2006).

Therefore, mangiferin confer protection against oxidative stress, and free from prooxidant effects and thus a superior antioxidant than the conventional antioxidants.

6. Mangiferin in neuroaging

Neuroaging is often understudied, under-expressed and underdefined in literature and thus the exact mechanism is still not known. Neuroaging is the condition characterized by decrease neuronal volumes, neuronal loss in specific areas, alterations in cortical thickness, impaired glial activity and control, etc. (Morrison and Hof, 1997; Pakkenberg and Gundersen, 1997; Resnick et al., 2003; Erraji-Benchekroun et al., 2005). It has been reported that the oxidative stress mainly contributes to neuronal aging or brain aging (Gerschman et al., 1954; Harman, 1956; Cadet, 1988). Aging is the main cause of neuronal degeneration and characterized by the presence of protein misfolding, aggregation of misfolded protein, oxidative stress, metal dyshomeostasis, mitochondrial dysfunction, impaired phosphorylation etc. (Zhang, 2005). However, the neuronal aging or brain aging is not always associated with the loss of neurons in brain areas, but in normal conditions it involves cognitive decline (Gallagher et al., 1996). Neuroaging also involve increase threshold for long term potentiation (LTP) induction and the lowering of threshold for long term depression (LTD) induction suggesting that a shift in LTP/LTD balance results in the declination of synaptic transmission and excessive synaptic depression (Barnes, 1994; Foster et al., 2001). Further this shifts in synaptic plasticity during aging is due to the reduced influx of Ca^{2+} through NMDARs and increased influx Ca^{2+} through voltage operated calcium channels (Barnes, 1994; Bodhinathan et al., 2010; Lehohla et al., 2008; Norris et al., 1996; Potier et al., 2000; Shankar et al., 1998; Thibault and Landfield, 1996) resulting in the disruption of neuronal Ca^{2+} homeostasis and cell death (Toescu and Verkhratsky, 2004; Toescu and Vreugdenhil, 2010). Excessive Ca^{2+} levels is also responsible for overloading of Ca^{2+} into mitochondria responsible for mitochondrial dysfunction (Petrosillo et al., 2004), and the release of cytochrome *c* (Vercesi et al., 1997; Iverson and Orrenius, 2004) further responsible for the initiation of apoptotic signaling pathway (Boehning et al., 2003) suggesting severe mitochondrial dysfunction an underlying event responsible for the neuronal degeneration (Gerlach et al., 1991; Kong and Xu, 1998; Panov et al., 2005). Further increase Ca^{2+} levels and substantial loss of Ca^{2+} buffering protein (i.e. calretinin and parvalbumin) has been observed during normal aging and in AD and PD patients (Iacopino and Christakos, 1990; Riascos et al., 2011; Iacopino and Christakos, 1990; Yamada et al., 1990; Tsuboi et al., 2000).

Mangiferin possess anti-ROS properties (Duang et al., 2011) and is a promising antioxidant agent (Stoilova et al., 2005). Mangiferin also abolished the oxidative damage mediated by the glutamate in the cortical neurons and the treatment with the mangiferin (100 nM) inhibit the glutamate induced ROS productions in the cortical neurons (Campos-Esparza et al., 2009). Mangiferin also attenuates the activation of NMDA receptor activation and inhibit the cytosolic Ca^{2+} overloading. Mangiferin (100 nM) treatment inhibit the glutamate induced calpain activity [In glutamate plus glycine group calpain activity was 139.6 ± 0.8% whereas mangiferin (100 nM) + glutamate plus glycine group calpain activity was 86.6 ± 4.0%]. Mangiferin (1–104 nM) attenuates neuronal cell death in primary neuronal cell culture caused by the activation of NMDA receptors (glutamate 50 μM + glycine 10 μM for 10 min). Mangiferin (100 nM) decreases mitochondrial membrane depolarization induced by the activation of glutamate receptors by glutamate (50 μM) in the presence of glycine (10 μM) for 10 min in cortical neurons (Campos-Esparza et al., 2009). It has also been reported that the mangiferin (10 mM) pretreatment for 2 h inhibit the MeHg induced increase in Ca^{2+} concentrations in IMR-32 cells. Mangiferin (10 mM) pretreatment significantly delayed the MeHg (10 mM) induced mitochondrial membrane potential collapse but did not inhibit the disruption of same as compared to control. Mangiferin (10 mM) also counteracted the release of cytochrome *c* release and caspase-3 expression in MeHg (10 mM) treated IMR-3 cells (Das et al., 2011). Mangiferin counteracts the deleterious effects of oxidative stress (Li et al., 2016) and prevents age specific changes in various enzymes (Ochocka et al., 2017), alleviates cognitive impairment (Liu et al., 2013), ameliorates morphological damages in hippocampus (Li et al., 2013), reduces the intracellular Ca^{2+} concentration and may contribute neuroprotective effects (Martinez et al., 2001) (refer to Fig. 5).

7. Mangiferin in the treatment of neuropsychiatric disorders

Anxiety is a coping strategy often characterized by the specific neuronal and behavioral changes in response to a potential or actual stressor (Steimer, 2002). Anxiety develops when an individual fail to cope up with the stressor. Depression is a psychiatric disorder characterized by depressed mood, anhedonia, loss of energy and low self-esteem (Wong and Licinio, 2004). Anxiety is considered as a part of depression, mainly coexist with depression making depression with anxiety in rare cases (Brown et al., 1996; Morilak and Frazer, 2004). In laboratory animals' anxiety related behavioral alteration can be determine using behavioral paradigms such as elevated plus maze (EPM) and light and dark box (LDB) (Pellow et al., 1985; Crawley and Goodwin, 1980; Walia et al., 2019b). In animals, the depression related behavior can be determined using tail suspension test (TST) and forced swim test (FST) (Steru et al., 1985; Porsolt et al., 1977a, b). It has been reported that the chronic anxiety makes the patients susceptible for depression and increase the chance of relapse also (Schapira et al., 1972; Flint and Rifat, 1997; Regier et al., 1998).

Stress induces a behavioral state similar to anxiety and depression (Bohus et al., 1993; Caspi et al., 2003; Vollmayr and Henn, 2003; Joo et al., 2009; Qin et al., 2011; Kumar and Goyal, 2008) (refer to Figs. 6 and 7). Stress causes reversible atrophy of hippocampus (McEwen and Sapolsky, 1995) and cortical areas (Lucassen et al., 2001). Stress causes permanent loss of neurons in rodents (McEwen and Sapolsky, 1995) and potentiated the lipopolysaccharide (LPS)-induced nuclear factor kappa beta (NF-kb) activation in frontal cortex and hippocampus of brain (Munhoz et al., 2006). Stress is known to activate hypothalamus-pituitary-adrenal (HPA) axis responsible for the release of corticotrophin-releasing hormone (CRF) which then stimulate the release of adrenocorticotrophin hormone (ACTH), further responsible for the release of glucocorticoids and catecholamines. Stress is thus characterized by the elevated plasma glucocorticoids which are responsible for hippocampal atrophy, inhibition of glucose transport in neurons, decreases ATP levels of neuronal cells, increase calcium mobilization and reduced reuptake of glutamate further responsible for glutamate excitotoxicity and neuronal cell death (Munhoz et al., 2008). Further both anxiety and depression are characterized by the elevated levels of glucocorticoid (Airan et al., 2007; Grippo et al., 2005; Popa et al., 2008). Also, the administration of glucocorticoid induces a state analogous to anxiety and depression in terms of structural, functional, behavioral and neurochemical alterations (Murray et al., 2008; Zhao et al., 2008; Gourley et al., 2008). Stress is also characterized by the increased release of inflammatory cytokines (such as TNF-α and IL-1) (Dunn et al., 1999) and exposures to only 30 min of restraint stress increase the expression of TNF-α convertase enzyme (TACE) in the brain

cortex (Madrigal et al., 2002) responsible for the cleavage of pro-TNF-α into TNF-α (Black and White, 1998). TNF-α so released is responsible for the activation of NF-kb pathway resulting in the inducible degradation of Iκbα and the release of free nuclear factor of kappa beta (NF-kb) followed by its translocation inside the nucleus (Hayden and Ghosh, 2014). Exposure to restraint stress of 4 h is responsible for the activation of NF-kb pathway in brain (Madrigal et al., 2009). NF-kb is an inducible transcription factors, present in association with Ikb proteins. NF-kb when activated translocate inside the nucleus and is responsible for the transcription of iNOS gene (Madrigal et al., 2009). Thus the activation of NF-kb pathway is responsible for the increased expression of inducible nitric oxide synthase (iNOS) (Madrigal et al., 2001) and thus considered as a key regulator of iNOS (Xie et al., 1994). iNOS is a high-output isoform of NOS (Nathan and Xie, 1994) induced by the exposure to the restraint stress of 6 h, responsible for the increased production of NO for longer period of time (Madrigaal et al., 2009). Beside iNOS, COX-2 expression is also dependent upon NF-kb pathway (Appleby et al., 1994). COX-2 is constitutively expressed in brain but is induced by cytokines, lipopolysaccharides, etc. (Yamagata et al., 1993; Nogawa et al., 1998). It was observed that the COX-2 activation precedes NOS-2 (Yamagata et al., 1993). The specific blockade of NMDA receptors during 6 h stress procedure inhibits the expression of COX-2 (Madrigal et al., 2003). COX-2 is associated with the production of ROS and could act as a source of O^{2-} for the formation of $ONOO^{-}$ formation (Vane et al., 1998).

Mangiferin is known to have a good impact on the mood and behavior. Mangiferin (50 and 100 mg/kg, i.p.) treatment induced tremors, piloerection, compulsive gnawing, and increased motor activity in rats. Mangiferin (50 mg./kg, i.p.) significantly increased the effect of pentobarbital (30 mg/kg, i.p.) on sleeping time and potentiated the effect of ethanol (20%, 4 g/kg, i.p.) on the righting reflex of rats. Mangiferin (50 and 10 mg/kg, i.p.) exhibited a dose-related inhibition of reserpine (5 mg/kg i.p.) induced ptosis, sedation, and depression of locomotor activity in the rats. Mangiferin (25–100 mg/kg, i.p.) potentiated the amphetamine (40 mg/kg, i.p.) induced toxicity in rats (Bhattacharya et al., 1972).

Mangiferin has been shown to confer the beneficial effect in the stress and the stress evoked pathologies. It is reported that the oral administration of mangiferin (15, 30 and 60 mg/kg, daily for 7 days) in the stressed rats (acute stress of 6 h) inhibit the stress induced increase in plasma corticosterone (Plasma corticosterone levels: control = 265.0 ± 62.2 ng/mL; acute stress = 509.2 ± 32.7 ng/mL; mangiferin 15 mg/kg = 199.7 ± 32.4 ng/mL, mangiferin 30 mg/kg = 201.3 ± 81.3 ng/mL, mangiferin 60 mg/kg = 177.6 ± 66.1 ng/mL) (Marquez et al., 2012). Beside this mangiferin (60 mg/kg, po) administration prior to acute stress inhibit the expression of TNF-α, activation of NF-kb pathway, iNOS and COX-2 in the brain of stressed rats (Marquez et al., 2012). Mangiferin (1–50 μM) decreases the expression of COX-2 and COX-2 mediated production of PGE_2 production in rat microglial cells induced by LPS (10 ng/ml) in microglia cells (Bhatia et al., 2008). Garrido et al. (2004) suggested that *M. indica* extract pre-treatment inhibit the production of TNF-α (IC_{50} value = 76.0 ± 0.5 mg/ml) and total NO^{2-} levels (IC_{50} value = 84.0 ± 0.1 mg/ml) respectively. Mangiferin attenuates the corticosterone induced anxiety and depression related behavioral and biochemical alterations. Administration of mangiferin (40 mg/kg, p.o. daily for 21 days) prior to the corticosterone (40 mg/kg, s.c. for 21 days) reverses the corticosterone induced anxiety like behavior in LDB and EPM and corticosterone induced depression like behavior in TST and FST in treated mice (Luo et al., 2017). Mangiferin administration also counteracts the corticosterone induced increased levels of IL-1β and TNF-α in the hippocampus of brain (Luo et al., 2017). Mangiferin (40 mg/kg, p.o.) pretreatment daily prior to the corticosterone administration counteracted the corticosterone induced increase in hippocampal nitrite levels (Luo et al., 2017). Mangiferin also attenuate the LPS induced behavioral and biochemical alterations in experimental animals. It has been suggested that the administration of LPS (0.83 mg/kg, i.p.) to the is responsible for the anxiogenic behavior in mice in EPM and LDB. Administration of mangiferin (40 mg/kg, p.o. daily for 14 days) prior to the LPS treatment reversed LPS induced anxiety in mice in EPM and LDB tests. Administration of mangiferin (40 mg/kg, p.o. daily for 14 days) prior to the LPS treatment reversed LPS induced depression like behavior in TST and FST. Daily administration of mangiferin (40 mg/kg, po) for 14 days to the LPS treated mice increased the consumption of sucrose solution and thus counteracted LPS induced anhedonic behavior in mice (Jangra et al., 2014). Sethiya et al., suggested that the mangiferin is a constituent of *Canscora decussata* and *canscora decussata* and reverses the anxiety related behavior in behavioral paradigms of anxiety (Sethiya et al., 2010). Administration of hydroethanol stem bark extract of *M. indica* (HeMI) (3.125, 6.25, 12.5 and 25 mg/kg, p.o.) reverses the anxiety related behavior in EPM test. HeMI (12.5 and 25 mg/kg, p.o.) significantly reduced the immobility period of mice in FST as compared to control group whereas in TST only HeMI (25 mg/kg, p.o.) decreased the immobility period of mice significantly as compared to control. Pretreatment of flumazenil (3 mg/kg, i.p.) counteracted the effect of HeMI (3.125 mg/kg, po) in EPM test (Ishola et al., 2016) suggesting the involvement of GABA-BZ-Cl^{-} pathway. The antidepressant like effect of the HeMI (25 mg/kg, po) was abolished by the pretreatment of pCPA (100 mg/kg, i.p daily for 4 days) suggesting the involvement of serotonergic in the antidepressant like effect. (Ishola et al., 2016). Also, the administration of mangiferin (62.5, 125, 250, and 500 mg/kg, p.o.) decreases the immobility period of mice in dose dependent manner in Porsolt's test (FST) significantly as compared to control mice. Further the repeated administration of the mangiferin (250 mg/kg, p.o. for 7 and 14 days) reduced the immobility period of the mice in Porsolt's test compared to control. The antidepressant like effect was more as compared to the imipramine (50 mg/kg, i.p.). Mangiferin at these doses did not influence the locomotor activity of mice in actophotometer test. Mangiferin treatment shows the MAO-A and B inhibitory action (IC_{50} value = $4.1 \pm 0.3 \times 10^{-4}$ M and 1×10^{-3} M) (Dimitrov et al., 2014). These lines of evidence suggested that the mangiferin might be a potential therapy for the treatment of neuropsychiatric disorders in near future.

8. Mangiferin in the treatment of neurodegenerative disorders

Neurons are vulnerable to oxidative stress and oxidative stress contributes to the age specific to neuronal cell death in many neurodegenerative disorders (Coyle and Puttfarcken, 1993; Andersen, 2004; Nabavi et al., 2015). Mangiferin has been reported to possess antiapoptotic actions (Campos-Esparza et al., 2009) and confer neuroprotective action (Gottlieb et al., 2006) suggesting the therapeutic potential for the treatment of neurodegenerative disorders like Alzheimer's disease (AD) and Parkinson's disease (PD) (Lemus-Molina et al., 2009).

8.1. Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by memory and learning impairment (Waldemar et al., 2007). AD generally affect the people in late stage of life and is the main cause of dementia in approx. 60–80% individuals of age above 65 years (Plassman et al., 2007). Approx.1–6% of AD cases has younger onset [known as early onset AD (EOAD)] while nearly 60% cases has late-onset AD (LOAD) (Campion et al., 1999; Brickell et al., 2006). EOAD is accompanied by lesser memory deficits, more hippocampal atrophy, language problems and altered visuospatial presentations as compared to LOAD patients (Gerritsen et al., 2016; Caso et al., 2015; Cerami et al., 2013). Pathological hallmark of AD is the deposition of amyloid beta (Aβ) plaques, synthesized by the action of enzyme β-secretase and γ-secretase upon amyloid precursor protein (APP) (Kamal et al., 2001; Cole and Vassar, 2007; Gustaw et al., 2008). Aβ in its monomeric form is not toxic however when aggregates it exerts toxicity (Wegiel et al., 2007; Hartley et al., 1999) particularly to the cholinergic neurons responsible

for cholinergic dysfunction, cognitive impairment and memory loss in AD patients (Boncristiano et al., 2002; Bronfman et al., 2000; Francis et al., 1999; Blusztajn and Berse, 2000; Wong et al., 1999; Bell et al., 2006; Terry et al., 1991; Selkoe, 2002) (refer to Fig. 8). Aβ accelerate the production of ROS, resulting in the impaired mitochondrial dynamics, synaptic dysfunction, lipid peroxidation and neurotoxicity in AD (Christen, 2000; Beal, 2005; Baloyannis et al., 2004; Garcia-Matas et al., 2010). Aβ further phosphorylates tau proteins responsible for disruption of cytoskeletal network and neuronal cell death (Iqbal et al., 1998; Brion et al., 2001; Tamagno et al., 2003).

Mangiferin is known to exert the beneficial effects in the AD and related pathologies (refer to Fig. 9). It has been reported that the administration of mangiferin (40 mg/kg, p.o.) ameliorates $AlCl_3$-induced neurotoxicity in the. Administration of mangiferin (40 mg/kg, p.o. for 21 days) to $AlCl_3$ (100 mg/kg, p.o. for 42 days) treated mice resulted in the significant reduction in the retention latency, decreases the number of crossings over a platform position, and thus improved the memory outcomes in MWM test (Kasbe et al., 2015). Further the administration of mangiferin (40 mg/kg, p.o.) to $AlCl_3$ treated mice counteracted the $AlCl_3$ induced decrease preference for novel objects (Kasbe et al., 2015). Administration of mangiferin (20 and 40 mg/kg, p.o.) to $AlCl_3$ treated mice significantly decreased the brain nitrite levels (Kasbe et al., 2015) suggesting the beneficial effect of mangiferin against the $AlCl_3$ induced neurotoxicity, nitrostative stress and memory impairment. Kumar et al. demonstrated that the administration of alcoholic extract of mango fruit (MI extract) (250 and 500 mg/kg, p.o. daily for 7 days) to the scopolamine (1 mg/kg, i.p.) treated mice significantly decreased the transfer latency (TL) in EPM test and increased the step down latency in passive avoidance test scopolamine treated young mice compared with respective controls suggesting that the MI extract promotes the retention of memory (Kumar et al., 2009).

The anti-dementic effect of mangiferin was also studied in the senescence-accelerated mouse prone 8 (SAMP8) mouse (lifespan of 12 months, accelerated aging within 4–6 months, activity loss, hair loss, higher level of soluble Aβ and Aβ deposition, increased phosphorylated τ and CDK-5 expression, progressive dementia, learning and memory impairment) which is considered as an ideal model for senile dementia (Takeda et al., 1997; Morley et al., 2000; Pallas et al., 2008). Du et al. demonstrated that the administration of mangiferin (200 mg/kg, p.o. for 60 days) to SMAP-8 mice resulted in the restoration of the ability to navigate the platform in MWM test as compared to the respective control. Mangiferin treatment to the SMAP-8 mice decreased the level of Aβ1-40 and Aβ1-42, promote the recovery of cerebral cortex and hippocampus and restored the structure of mitochondrial crista nearly normal with only mild swelling. These findings suggests the beneficial effects of the mangiferin in senile dementia and aging also (Du et al., 2019). Mangiferin treatment ameliorate the neuronal structural alterations, dystrophies in APP/PS1 and improve episodic and spatial memory in APP/PS1 treated mice (Infante-Garcia et al., 2017). Mangiferin significantly reduced cell damage in rat cortical slices mediated by Aβ oligomers exposure. Aβ (5 μM) increases the neuronal $[Ca^{2+}]_{mit}$ by 2.35-fold and the preincubation with mangiferin did not affect the $[Ca^{2+}]_{mit}$ overload but decreased the $[Ca^{2+}]_{cyt}$ overload from 2 to 2.3-fold suggesting that the mangiferin prevent the Aβ oligomers induce mitochondrial dysfunction and neuronal cell death (Alberdi et al., 2018).

In context of cholinergic dysfunction, mangiferin (20 mg/kg, p.o.) counteracted the scopolamine-induced cholinergic dysfunctions, inhibit the enzyme AChE and stimulate cholinergic receptor to promote the improvement of long-term memory and the counteraction of cholinergic and memory deficits induced by the scopolamine treatment (Jung et al., 2009). Also, the chronic administration of mangiferin (40 mg/kg, p.o.) to AlCl3 treated mice inhibit the activity of AChE (Kasbe et al., 2015) suggesting that the mangiferin inhibit the $AlCl_3$ induced AChE expression.

Insulin signaling in the brain is known to regulate glucose uptake, glucose level, behavior, memory, and cognitive functions (Derakhshan and Toth, 2013; Benedict et al., 2004; Kern et al., 1999; Park et al., 2000). Binding of insulin to its receptors resulting in the activation of PI3K/AKT pathway (Lemmon and Schlessinger, 2010) responsible for the inhibition of Bax, Bad, caspase-9, and glycogen synthase kinase-3 (GSK-3) to halt the cellular apoptosis and to promote the cellular survival (Boucher et al., 2014; De Meyts 2016; Kim and Feldman, 2012; Levenga et al., 2017; Manna and Jain, 2013; Noguchi and Suizu, 2012). Insulin prevents the formation of Aβ fibril, clears Aβ across the BBB and thus prevents Aβ neuronal damage (Rensink et al., 2004; Ribe and Lovestone, 2016; Barroso et al., 2013). Thus impaired insulin signaling and the emergence of insulin resistance results in the sustained activation of enzyme GSK-3β and increased release of TNFα and IL-6 responsible for oxidative stress, metabolic disturbance, neuroinflammation, and subsequent neuronal damage (Lyman et al., 2013; Beurel and Jope 2009; Wang et al., 2010; Duarte et al., 2012; de la Monte and Wands 2005; Correia et al., 2012; Gasper et al., 2016). It has been reported that the administration of mangiferin (10 and 20 mg/kg, i.p. daily for 21 days) to the STZ treated rats resulted in the lowering of glucose level and lipid level in STZ treated rats (Muruganandan et al., 2005). Oral administration of mangiferin (20 mg/kg, i.p. for 4 weeks) to STZ treated rats improves the insulin sensitivity, lipid profile, and adipokine levels (Saleh et al., 2014). Mangiferin thus ameliorate the insulin resistance by reducing the FFA levels and by inhibiting the accumulations of TG (Zhang et al., 2019). Administration of mangiferin (15 mg/kg, p.o. daily for 7 weeks) mitigates insulin resistance (in rat model of fructose-induced metabolic syndrome) by increasing the clearance of plasma NEFA, improve OGTT and decreases TG accumulation (Zhou et al., 2016). Mangiferin improves the glucose utilization and insulin sensitivity by up-regulation of AMPK phosphorylation (Wang et al., 2014). Administration of mangiferin (40 mg/kg, p.o.) also reduced the $AlCl_3$ induced increased release of IL-1β and TNF-α (Kasbe et al., 2015).

These lines of evidence suggested the beneficial effects of the mangiferin in the treatment of AD and AD related dementia (*refer to* Fig. 6).

8.2. Parkinson's disease (PD)

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive degeneration of dopaminergic neurons in substantia nigra (SN) region of midbrain (Dauer and Przedborski, 2003) resulting in the development of motor dysfunctions in PD patients (Walia et al., 2019a). PD generally affect the individuals in later stages of life (Olanow and Tatton, 1999; Tanner, 2003). The prevalence rate of familial PD is approx. 5% whereas that of sporadic PD is 95% (Farrer, 2006; Tanner, 2003). PD related motor dysfunctions include bradykinesia, postural imbalance, resting tremor, rigidity, etc. (Clarke, 2002). In PD, neuronal damage is prominent mainly in striatum, basal ganglia (BG) and subthalamic nucleus (STN) (Forno, 1996; Hornykiewicz and Kish, 1987). The exact mechanism of neuronal degeneration in PD is not known completely, but the mutation and impaired expression of various genes might be the possible cause of PD (Mizuno et al., 2001; Van Den Eeden et al., 2003). α-synuclein is a synaptic protein and the aggregation of misfolded α-synuclein has been implicated in the pathogenesis of PD (Campelo et al., 2017). Further the aggregation of α-synuclein contributes to mitochondrial dysfunction (Ved et al., 2005), membrane disruption (Conway et al., 2001) and lysosomes dysfunction (Martinez-Vicente et al., 2008) all of which contributes to the neuronal degeneration in PD. Also, the α-synuclein protofibrils themselves are responsible for the modulation of vesicular membranes and transport of dopamine (Lotharius and Brundin, 2002). Dopamine also interact with α-synuclein to confer neurotoxicity (Caudle et al., 2008; Chen et al., 2008; Edwards, 1993; Pardo et al., 1995).

Mangiferin might be the future therapeutic option for the treatment of PD and has shown beneficial effects in various models of PD. Mangiferin shows the neuroprotective effect against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced PD in mice. MPTP is a

lipid-soluble compound, readily crosses BBB, captured into lysosomes and astrocytes, oxidized by MAO-B resulting in the formation of 1-methyl-4-phenylpyridinium (MPP^+) that inhibit the complex-I of mitochondrial ETC, inhibit the ATP production in neuronal cells responsible for neuronal damage. MPP^+ also increases the oxidative stress and disrupt the neuronal calcium homeostasis resulting in the neuronal cell damage. (Sian et al., 1999; Matsui et al., 2009; Walia et al., 2019a). Mangiferin inhibit the conversion of MPTP into MPP^+ by inhibiting the enzyme MAO-B (Dimitrov et al., 2014). Kavitha et al. demonstrated that the administration of mangiferin (40 mg/kg, po, daily for 14 days) to the MPTP (30 mg/kg, i.p. for 5 days daily) treated mice inhibit the expression of MAO-B as compared to control mice respectively (Control: 3.19 ± 0.24 mU/mg protein; MPTP: 5.34 ± 0.41 mU/mg protein; mangiferin (40 mg/kg, p.o. for 14 days) alone: 3.02 ± 0.23 mU/mg protein and mangiferin (40 mg/kg, p.o. for 14 days) + MPTP was 4.25 ± 0.30 mU/mg protein). Mangiferin (40 mg/kg, p.o.) treatment to the MPTP treated mice restore the expressions of Bax and Bcl-2 and attenuate the MPTP-induced GSH depletion, lipid peroxidation, oxidative damage and depletion of striatal DA (Kavitha et al., 2013). Mangiferin treatment to MPTP treated mice resulted in the increased performance in swim test, increased swim score, increased hanging time and decreased cataleptic time significantly as compared to MPTP alone treated mice (Kavitha et al., 2013). Mangiferin also counteracted the MPP^+-induced cell death and oxidative stress in murine neuroblastoma cell line N2A cells (Amazzal et al., 2007).

Rotenone has been reported to induce various degrees of Parkinsonism in rats (Phinney et al., 2006). Mangiferin (2.5, 5, 10, 20 and 40 mg/ml) treatment for 4 h to SK-N-SH cells followed by the incubation with rotenone (100 nM) for 24 h showed the dose-dependent protection against rotenone induced neuronal cell death (Kavitha et al., 2014). mangiferin (20 mg) treatment prior to rotenone counteracted the deleterious effect of the rotenone (Kavitha et al., 2014). Rats injected with rotenone in the SN region and ventral tegmental area (VTA) produces behavioral and neuronal deficits (Erbas et al., 2012) and oxidative damage in the dopaminergic neurons of midbrain region (Testa et al., 2005). Rotenone resulted in the inhibition of complex-1 of mitochondrial ETC resulted in the ATP depletion and damage to the dopaminergic neurons in the SN region of midbrain (Sherer et al., 2003; Testa et al., 2005). Rotenone treatment is also responsible for the increase mitochondrial membrane permeability, mitochondrial swelling, and opening of mitochondrial permeability transition pores (Kurosaki et al., 2004), release of mitochondrial cytochrome *c* and the latter binds to apoptotic protease-activating factor-1 (Apaf-1) leading to the caspase-3 activation (Tatton et al., 1999) resulting in the neuronal death in PD (Hartley et al., 1994). Mangiferin treatment counteracted the rotenone induced inhibition of oxidative phosphorylation, neuronal ATP depletion, prevent the release of cytosol cytochrome *c* and subsequent activation of caspase 3 to prevent the neuronal cell death in PD (Kavitha et al., 2014).

Beside MPTP and rotenone, mangiferin has also been reported to counteract the neurotoxicity induced by 6-hydroxydopamine (6-OHDA). 6-OHDA is used frequently for the induction of PD in rodents and confer neurotoxicity by ROS formation and inhibition of complex I and IV of mitochondrial ETC (Glink et al., 1997). It has been observed that the administration of 6-OHDA (40 μmol/L) results in dopaminergic neuronal cell loss and motor dysfunctions as seen in PD patients (Rodriguez-Pallares et al., 2007; Simola et al., 2007). Rao et al. demonstrated the neuroprotective effect of mangiferin against 6-OHDA neurotoxicity in rats mesencephalic cell culture (containing neuronal and non-neuronal cells). It was observed that mangiferin (10, 30, and 100 μM) alone treatment did not affect the cell viability of mesencephalic cells. However, mangiferin (10, 30, and 100 μM) treatment prior to 6-OHDA (40 μM) exposure resulted in the gradual and significant increase in cell survival particularly at concentration 30 and 100 μM. Mangiferin (30 μM) treatment prior to 6-OHDA (40 μM) treatment decreased the cellular apoptosis and decreased the nitrite level significantly as compared to 6-OHDA treated cells (Rao et al., 2012). Beside this mangiferin inhibit the production of O^{2-} radical and alleviate the neuronal cell loss in response to disruption of intracellular calcium signaling in cell cultures (Campos-Esparza et al., 2009). Mangiferin maintain Ca^{2+} homeostasis, intracellular antioxidant activities, and improve the mitochondrial function to confer neuroprotection in PD (Das et al., 2017).

9. Mangiferin counteracts neuroinflammation in several neurological disorders

Neuroinflammation is a condition characterized by the increased production of inflammatory cytokines and emergence of neuropsychiatric and neurodegenerative disorders (Rhie et al., 2020). In CNS, these cytokines are produced by group of specialized microglial cells (Graeber, 2010; Wake et al., 2009). The increased activation of microglia cells has been observed in the neurodegenerative disorders like AD and PD (Amor and Woodroofe, 2014). The activated microglia cells resulted in the recruitment and infiltration of monocytes into the brain resulting in the enhanced production of pro-inflammatory cytokines (Peraçoli et al., 2003). Increased activation of microglia cells and levels of pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) has been reported in brain of aged individuals (Niraula et al., 2016; Bruunsgaard et al., 2001; Ward et al., 2015) further responsible for the emergence of several neurological disorders (Miller and Raison, 2016). Earlier it was thought that the peripherally produced pro-inflammatory cytokines cannot gain access to brain, however it has been reported that these cytokines can enter into brain due to the altered permeability of BBB (Lacroix and Rivest, 1998; Wong et al., 1996; Quan and Banks, 2007). Thus, increased activation of microglia cells, cytokine levels and corresponding neuroinflammation is responsible for the age associated neuronal damage (von Bernhardi et al., 2015; Zilka et al., 2012). Altered function of microglia cells has been implicated in the pathogenesis of AD. Microglia cells play an important role in the phagocytosis and clearance of Aβ (Mandrekar et al., 2009; Koenigsknecht and Landreth, 2004). The special types of receptors present on the surface of microglia cells, recognize Aβ fibrils, engulf and transport it to the endolysosomal system (Bamberger et al., 2003; Paresce et al., 1997). However, it has been reported that Ab fibrils so internalized, can remain intact without getting metabolized for 72 h or may be resecreted also (Paresce et al., 1997; Chung et al., 1999). Thus, microglia cells protect the neurons against the Ab toxicity. However, in the presence of inflammatory cytokines, microglial cells loss their activity resulting in the retention and deposition of Aβ and corresponding progression of AD (Koenigsknecht-Talboo et al., 2005; Zelcer et al., 2007; Yamamoto et al., 2008). Beside this, microglia cell has been implicated in the pathogenesis of PD characterized by the damage of the dopaminergic neurons in the SN region of midbrain (Rocha et al., 2015), increased expression of misfolded α-synuclein (Ward et al., 2015; Grimmig et al., 2016; Yamada, 1992) and increased production of inflammatory cytokines (Zhang et al., 2005; Beraud et al., 2012). Further the over-activation of microglia cells, proinflammatory cytokines and neuroinflammation has been observed in PD brain (Ferrari et al., 2006; McCoy et al., 2006; McGeer et al., 1988; Hirsch and Hunot, 2009). Neuroinflammation is also involved in the pain and related response (Sawynok, 2003). Inflammatory cytokines (such as TNF-α, IL-1, IL-6 and IFN-γ) contributes to the activation of HPA axis, impairment of 5-HT signaling pathway and the behavioral alterations analogous to anxiety and depression (Dantzer, 2001; Salim et al., 2012; Dorr, 1993; Guo et al., 2014; Nunes et al., 2002; Kim et al., 2002; Maes et al., 1993, 1995, 1997, 1999).

Mangiferin inhibit the activation of microglia cells and confer protection against glial cell induced neuroinflammation (Bhatia et al., 2008; Prabhu et al., 2006). It has been reported that the stem extract of *M. indica* (4 μg/ml) reduces the expression of NF-kb, mRNA, NOS-2, COX-2, IL-β, TNF-α but did not affect the expression of IL-6 mRNA and TGF-b (Leiro et al., 2004). Mangiferin (10 μM) inhibits LPS induced activation of NF-κβ pathway and production of cytokines production

(Jeong et al., 2014; Telang et al., 2013; Das et al., 2012). Administration of doxorubicin (DOX) (15 mg/kg, i.p.) increases the expression of TNF-α level in brain. Administration of mangiferin (60 mg/kg, p.o.) prior to DOX decreased the levels and expression of TNF-α level (Siswanto et al., 2016). TNF-a promotes the activation and translocation of NF-kb inside the nucleus responsible for the increase expression of enzyme iNOS further responsible for the increase production of NO for longer time period (Alderton et al., 2001; Bogdan, 2001). Mangiferin treatment reduces the levels and expression of TNF-α, inhibit the activation and translocation of NF-kβ, inhibit the iNOS expression and subsequently reduced the NO production (Garrido et al., 2004; Martin et al., 2008a). It has been reported that the daily immobilization of 6 h for 7 days increases the levels of glucocorticoids and pro-inflammatory cytokines (IL-1β, TNF-α NF-kb, iNOS and COX-2) in brain. Administration of mangiferin prior to the stress exposure ameliorate the stress induced increase in the levels of pro-inflammatory cytokines (Marquez et al., 2012). Mangiferin also inhibit NF-kb dependent COX-2 and iNOS expression and their downstream signaling molecules (Garcia et al., 2002, 2003; Bhatia et al., 2008). Mangiferin further inhibits COX-2 mediated production of PGE_2 and LTB_4 (Garcia et al., 2002, 2003; Bhatia et al., 2008). Mangiferin thus inhibit the synthesis of inflammatory mediators and suppress the pain (Garrido-Suarez et al., 2010). Mangiferin attenuates neurogenic and inflammatory pain induced by capsaicin, acetic acid and formalin treatment. Mangiferin (30 and 100 mg/kg, p.o.) exerted antinociceptive effects without the activation of opioid receptors and thus free from the central side effects (Lopes et al., 2013). However, mangiferin fails to demonstrate the antinociceptive effects in the tail flick test and Eddy's hot-plate test which are known to involve the spinal and supraspinal mechanisms of nociception (Yaksh and Rudy, 1976). Mangiferin activate peripheral opioid receptors, decreases the excitability of sensory nerves, inhibits the release of pro-inflammatory cytokine and exerts anti-inflammatory and antinociceptive effects without any central action (Lopes et al., 2013). It has also been reported that the mangiferin treatment ameliorate the neurological dysfunction and neurological pain in contusive SCI rats (Luo et al., 2015). Mangiferin also exerted neuroprotective effect by preventing Wallerian degeneration in mononeuropathic rats (Garrido--Suarez et al., 2014). These lines of evidence suggested that the mangiferin counteract the neuroinflammation (He et al., 2014; Li et al., 2017) and subsequently inhibit the neuroinflammation induced neuropathologies.

10. Conclusion

Mangiferin belongs to the class of the xanthone and exhibit wide range of the pharmacological properties. Previous studies has suggested that the mangiferin can pass through the BBB and this fact made it a compound of interest for the treatment of neurological disorders. Mangiferin counteracts the deleterious effects of oxidative stress and is thus considered as a promising antioxidant. Mangiferin has been reported to be a better antioxidant than the flavonoids or phenylpropanoic acids in DPPH scavenging activity. Mangiferin possess ROS scavenging capacity and ferric reducing ability of plasma (FRAP) comparable with vitamin C and E and prevented ROS production and ROS mediated oxidative tissue damage more as compared to vitamin C, E, quercetin, curcumin and β-carotene. Mangiferin enhances cellular antioxidant defense (i.e. increases the levels of SOD, CAT, and glutathione peroxidase). Further mangiferin is devoid of prooxidant activity and is thus superior to the conventional antioxidants. Mangiferin also prevents the age specific changes in various enzymes, alleviates cognitive impairment, ameliorates morphological damages in hippocampus and reduces the neuronal intracellular Ca^{2+} concentration to confer neuroprotective effects. Mangiferin attenuate the corticosterone and LPS induced anxiety and depression related behavioral and biochemical alterations in various studies. Mangiferin mediated antinociceptive effects is devoid of the opioid receptor activation and thus free from the central side effects. Mangiferin counteracts the effect of MPTP, rotenone and 6-OHDA on dopaminergic neurons. Mangiferin treatment also counteracted neuronal ATP depletion, prevent the release of cytosol cytochrome *c* and subsequent activation of caspase 3 to prevent neuronal cell death in PD. Mangiferin significantly reduced cell damage in rat cortical slices mediated by Aβ oligomers exposure and prevent Aβ induce mitochondrial dysfunction and neuronal cell death in AD models. Mangiferin mitigates insulin resistance and improves insulin sensitivity by up-regulation of AMPK phosphorylation. Mangiferin inhibit the activation of microglia cells and confer protection against glial cell induced neuroinflammation. Thus, mangiferin could be new drug for the treatment of neurological disorders in near future.

Funding support

No funding was received for this work.

Research ethics

The present work do not involve the human volunteer and any animal experimentation.

Declaration of competing interest

None.

References

Abbott, N.J., Rönnbäck, L., Hansson, E., 2006. Astrocyte–endothelial interactions at the blood–brain barrier. Nat. Rev. Neurosci. 7 (1), 41.

Agarwala, S., Mudholkar, K., Bhuwania, R., Satish Rao, B.S, 2012. Mangiferin, a dietary xanthone protects against mercury-induced toxicity in HepG2 cells. Environ. Toxicol. 27 (2), 117–127.

Airan, R.D., Meltzer, L.A., Roy, M., Gong, Y., Chen, H., Deisseroth, K., 2007. High-speed imaging reveals neurophysiological links to behavior in an animal model of depression. Science 317 (5839), 819–823.

Alberdi, E., Sánchez-Gómez, M.V., Ruiz, A., Cavaliere, F., Ortiz-Sanz, C., Quintela-López, T., Capetillo-Zarate, E., Solé-Domènech, S., Matute, C., 2018. Mangiferin and morin attenuate oxidative stress, mitochondrial dysfunction, and neurocytotoxicity, induced by amyloid beta oligomers. Oxidative Med. Cell. Longev. 2018, 2856063.

Alderton, W.K., Cooper, C.E., Knowles, R.G., 2001. Nitric oxide synthases: structure, function and inhibition. Biochem. J. 357 (3), 593–615.

Amazzal, L., Lapôtre, A., Quignon, F., Bagrel, D., 2007. Mangiferin protects against 1-methyl-4-phenylpyridinium toxicity mediated by oxidative stress in N2A cells. Neurosci. Lett. 418 (2), 159–164.

Amor, S., Woodroofe, M.N., 2014. Innate and adaptive immune responses in neurodegeneration and repair. Immunology 141 (3), 287–291.

Andersen, J.K., 2004. Oxidative stress in neurodegeneration: cause or consequence? Nat. Med. 10 (7), S18–S25.

Appleby, S.B., Ristimäki, A., Neilson, K., Narko, K., Hla, T., 1994. Structure of the human cyclo-oxygenase-2 gene. Biochem. J. 302 (3), 723–727.

Aritomi, M., Kawasaki, T., 1970. A mangiferin monomethyl ether from Mangifera indica L. Chem. Pharmaceut. Bull. 18 (11), 2224–2234.

Asensio, J.L., Cañada, F.J., Cheng, X., Khan, N., Mootoo, D.R., Jiménez-Barbero, J., 2000. Conformational differences between O-and C-glycosides: the α-O-Man-(1→ 1)-β-Gal/α-C-Man-(1→ 1)-β-Gal case-A decisive demonstration of the importance of the exo-anomeric effect on the conformation of glycosides. Chem. Eur. J. 6 (6), 1035–1041.

Balaban, R.S., Nemoto, S., Finkel, T., 2005. Mitochondria, oxidants, and aging. Cell 120 (4), 483–495.

Baloyannis, S.J., 2006. Mitochondrial alterations in Alzheimer's disease. J. Alzheim. Dis. 9 (2), 119–126.

Baloyannis, S.J., Costa, V., Michmizos, D., 2004. Mitochondrial alterations Alzheimer's disease. Am. J. Alzheimer's Dis. Other Dementias 19 (2), 89–93.

Bamberger, M.E., Harris, M.E., McDonald, D.R., Husemann, J., Landreth, G.E., 2003. A cell surface receptor complex for fibrillar β-amyloid mediates microglial activation. J. Neurosci. 23 (7), 2665–2674.

Barnes, C.A., 1994. Normal aging: regionally specific changes in hippocampal synaptic transmission. Trends Neurosci. 17, 13–18.

Barroso, E., del Valle, J., Porquet, D., Santos, A.M.V., Salvadó, L., Rodríguez-Rodríguez, R., Palomer, X., 2013. Tau hyperphosphorylation and increased BACE1 and RAGE levels in the cortex of PPARβ/δ-null mice. Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. 1832 (8), 1241–1248.

Beal, M.F., 2005. Mitochondria take center stage in aging and neurodegeneration. Ann. Neurol.: Official Journal of the American Neurological Association & the Child Neurology Society 58 (4), 495–505.

Bell, K.F., Ducatenzeiler, A., Ribeiro-da-Silva, A., Duff, K., Bennett, D.A., Cuello, A.C., 2006. The amyloid pathology progresses in a neurotransmitter-specific manner. Neurobiol. Aging 27 (11), 1644–1657.
Benedict, C., Hallschmid, M., Hatke, A., Schultes, B., Fehm, H.L., Born, J., Kern, W., 2004. Intranasal insulin improves memory in humans. Psychoneuroendocrinology 29 (10), 1326–1334.
Bera, S., Chaudhuri, S., Dutta, D., 2015. Assessment of free-radical scavenging activities of mangiferin from Curcuma amada obtained by non-conventional extraction methods: a comparative study. Indian J. Biotechnol. 14, 179–185.
Béraud, D., Maguire-Zeiss, K.A., 2012. Misfolded α-synuclein and toll-like receptors: therapeutic targets for Parkinson's disease. Park. Relat. Disord. 18, S17–S20.
Bertolini, F., Novaroli, L., Carrupt, P.A., Reist, M., 2007. Novel screening assay for antioxidant protection against peroxyl radical-induced loss of protein function. J. Pharmaceut. Sci. 96 (11), 2931–2944.
Beurel, E., Jope, R.S., 2009. Lipopolysaccharide-induced interleukin-6 production is controlled by glycogen synthase kinase-3 and STAT3 in the brain. J. Neuroinflammation 6 (1), 1–11.
Bhatia, H.S., Candelario-Jalil, E., de Oliveira, A.C.P., Olajide, O.A., Martínez-Sánchez, G., Fiebich, B.L., 2008. Mangiferin inhibits cyclooxygenase-2 expression and prostaglandin E2 production in activated rat microglial cells. Arch. Biochem. Biophys. 477 (2), 253–258.
Bhatia, V.K., Ramanathan, J.D., Seshadri, T.R., 1967. Constitution of mangiferin. Tetrahedron 23 (3), 1363–1368.
Bhattacharya, S.K., Ghosal, S., Chaudhuri, R.K., Sanyal, A.K., 1972. Canscora decussata (Gentianaceae) xanthones III: pharmacological studies. J. Pharmaceut. Sci. 61 (11), 1838–1840.
Black, R.A., White, J.M., 1998. ADAMs: focus on the protease domain. Curr. Opin. Cell Biol. 10 (5), 654–659.
Blusztajn, J.K., Berse, B., 2000. The cholinergic neuronal phenotype in alzheimer' s disease. Metab. Brain Dis. 15 (1), 45–64.
Bock, C., Waldmann, K.H., Ternes, W., 2008. Mangiferin and hesperidin metabolites are absorbed from the gastrointestinal tract of pigs after oral ingestion of a Cyclopia genistoides (honeybush tea) extract. Nutr. Res. 28 (12), 879–891.
Bodhinathan, K., Kumar, A., Foster, T.C., 2010. Redox sensitive calcium stores underlie enhanced after hyperpolarization of aged neurons: role for ryanodine receptor mediated calcium signaling. J. Neurophysiol. 104 (5), 2586–2593.
Boehning, D., Patterson, R.L., Sedaghat, L., Glebova, N.O., Kurosaki, T., Snyder, S.H., 2003. Cytochrome c binds to inositol (1, 4, 5) trisphosphate receptors, amplifying calcium-dependent apoptosis. Nat. Cell Biol. 5 (12), 1051–1061.
Bogdan, C., 2001. Nitric oxide and the regulation of gene expression. Trends Cell Biol. 11 (2), 66–75.
Bohus, B., Koolhaas, J.M., Heijneri, C.J., de Boer, O., 1993. Immunological responses to social stress: dependence on social environment and coping abilities. Neuropsychobiology 28 (1–2), 95–99.
Boncristiano, S., Calhoun, M.E., Kelly, P.H., Pfeifer, M., Bondolfi, L., Stalder, M., Sommer, B., 2002. Cholinergic changes in the APP23 transgenic mouse model of cerebral amyloidosis. J. Neurosci. 22 (8), 3234–3243.
Boonnattakorn, R., Sane, A., Chonhenchob, V., 2016. Antioxidant microemulsion-based ethylene vinyl acetate film containing mangiferin and surfactants. In: MATEC Web of Conferences, vol. 67. EDP Sciences, p. 6101.
Bors, W., Heller, W., Michel, C., Saran, M., 1989. Oxygen radicals in biological systems. Methods Enzymol. 186, 343–355.
Boucher, J., Kleinridders, A., Kahn, C.R., 2014. Insulin receptor signaling in normal and insulin-resistant states. Cold Spring Harbor Perspectives in Biology 6 (1) a009191.
Brickell, K.L., Steinbart, E.J., Rumbaugh, M., Payami, H., Schellenberg, G.D., Van Deerlin, V., Bird, T.D., 2006. Early-onset Alzheimer disease in families with late-onset Alzheimer disease: a potential important subtype of familial Alzheimer disease. Arch. Neurol. 63 (9), 1307–1311.
Brion, J. P., Anderton, B. H., Authelet, M., Dayanandan, R., Leroy, K., Lovestone, S.,... & Tremp, G. (2001, February). Neurofibrillary tangles and tau phosphorylation. In Biochemical Society Symposia (vol. 67, pp. 81–88).
Bronfman, F.C., Moechars, D., Van Leuven, F., 2000. Acetylcholinesterase-positive fiber deafferentation and cell shrinkage in the septohippocampal pathway of aged amyloid precursor protein london mutant transgenic mice. Neurobiol. Dis. 7 (3), 152–168.
Brown, C., Schulberg, H.C., Madonia, M.J., Shear, M.K., Houck, P.R., 1996. Treatment outcomes for primary care patients with major depression and lifetime anxiety disorders. Am. J. Psychiatr. 153 (10), 1293–1300.
Bruunsgaard, H., 2001. Pedersen M, pedersen BK. Aging and proinflammatory cytokines. Current Opinion in Hematology 8, 131–136.
Bulugonda, R.K., Gangappa, D., Beeda, H., Philip, G.H., Rao, D.M., Faisal, S.M., 2017. Mangiferin from Pueraria tuberosa reduces inflammation via inactivation of NLRP3 inflammasome. Sci. Rep. 7, 42683.
Cadet, J.L., 1988. Free radical mechanisms in the central nervous system: an overview. Int. J. Neurosci. 40 (1–2), 13–18.
Campêlo, C.L., Cagni, F.C., de Siqueira Figueredo, D., Oliveira Jr., L.G., Silva-Neto, A.B., Macêdo, P.T., de Oliveira Godeiro Jr., C., 2017. Variants in SNCA gene are associated with Parkinson's disease risk and cognitive symptoms in a Brazilian sample. Front. Aging Neurosci. 9.
Campion, D., Dumanchin, C., Hannequin, D., Dubois, B., Belliard, S., Puel, M., Raux, G., 1999. Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum. Am. J. Hum. Genet. 65 (3), 664–670.
Campos-Esparza, M.R., Sánchez-Gómez, M.V., Matute, C., 2009. Molecular mechanisms of neuroprotection by two natural antioxidant polyphenols. Cell Calcium 45 (4), 358–368.
Cao, C., Su, M., Zhou, F., 2017. Mangiferin inhibits hippocampal NLRP3 inflammasome and exerts antidepressant effects in a chronic mild stress mice model. Behav. Pharmacol. 28 (5), 356–364.
Caso, F., Agosta, F., Mattavelli, D., Migliaccio, R., Canu, E., Magnani, G., Falini, A., 2015. White matter degeneration in atypical Alzheimer disease. Radiology 277 (1), 162–172.
Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., Poulton, R., 2003. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301 (5631), 386–389.
Caudle, W.M., Colebrooke, R.E., Emson, P.C., Miller, G.W., 2008. Altered vesicular dopamine storage in Parkinson's disease: a premature demise. Trends Neurosci. 31 (6), 303–308.
Cerami, C., Crespi, C., Della Rosa, P.A., Dodich, A., Marcone, A., Magnani, G., Perani, D., 2015. Brain changes within the visuo-spatial attentional network in posterior cortical atrophy. J. Alzheim. Dis. 43 (2), 385–395.
Chauhan, R.S., Dutt, P., 2013. Swertia ciliata-A new source of mangiferin, amaroswerin and amarogentin. Journal of Biologically Active Products from Nature 3 (2), 161–165.
Chen, L., Ding, Y., Cagniard, B., Van Laar, A.D., Mortimer, A., Chi, W., Zhuang, X., 2008. Unregulated cytosolic dopamine causes neurodegeneration associated with oxidative stress in mice. J. Neurosci. 28 (2), 425–433.
Christen, Y., 2000. Oxidative stress and Alzheimer disease. Am. J. Clin. Nutr. 71 (2), 621S–629S.
Chung, H., Brazil, M.I., Soe, T.T., Maxfield, F.R., 1999. Uptake, degradation, and release of fibrillar and soluble forms of Alzheimer's amyloid β-peptide by microglial cells. J. Biol. Chem. 274 (45), 32301–32308.
Clarke, C.E., 2002. Medical management of Parkinson's disease. J. Neurol. Neurosurg. Psychiatr. 72 (Suppl. 1), i22–i27.
Cole, S.L., Vassar, R., 2007. The Alzheimer's disease β-secretase enzyme, BACE1. Mol. Neurodegener. 2 (1), 22.
Conway, K.A., Rochet, J.C., Bieganski, R.M., Lansbury, P.T., 2001. Kinetic stabilization of the α-synuclein protofibril by a dopamine-α-synuclein adduct. Science 294 (5545), 1346–1349.
Correia, S.C., Santos, R.X., Carvalho, C., Cardoso, S., Candeias, E., Santos, M.S., Moreira, P.I., 2012. Insulin signaling, glucose metabolism and mitochondria: major players in Alzheimer's disease and diabetes interrelation. Brain Res. 1441, 64–78.
Coyle, J.T., Puttfarcken, P., 1993. Oxidative stress, glutamate, and neurodegenerative disorders. Science 262 (5134), 689–695.
Crawley, J., Goodwin, F.K., 1980. Preliminary report of a simple animal behavior model for the anxiolytic effects of benzodiazepines. Pharmacol. Biochem. Behav. 13 (2), 167–170.
Dantzer, R., 2001. Cytokine-induced sickness behavior: mechanisms and implications. Ann. N. Y. Acad. Sci. 933 (1), 222–234.
Dar, A., Faizi, S., Naqvi, S., Roome, T., Zikr-ur-Rehman, S., Ali, M., Moin, S.T., 2005. Analgesic and antioxidant activity of mangiferin and its derivatives: the structure activity relationship. Biol. Pharm. Bull. 28 (4), 596–600.
Das, J., Ghosh, J., Roy, A., Sil, P.C., 2012. Mangiferin exerts hepatoprotective activity against D-galactosamine induced acute toxicity and oxidative/nitrosative stress via Nrf2–NFκB pathways. Toxicol. Appl. Pharmacol. 260 (1), 35–47.
Das, S., Paul, A., Mumbrekar, K.D., Rao, S.B., 2017. Harmonization of Mangiferin on methylmercury engendered mitochondrial dysfunction. Environ. Toxicol. 32 (2), 630–644.
Das, S., Rao, B.N., Rao, B.S., 2011. Mangiferin attenuates methylmercury induced cytotoxicity against IMR-32, human neuroblastoma cells by the inhibition of oxidative stress and free radical scavenging potential. Chem. Biol. Interact. 193 (2), 129–140.
Dauer, W., Przedborski, S., 2003. Parkinson's disease, mechanisms and models. Neuron 39 (6), 889–909.
de la Monte, S.M., Wands, J.R., 2006. Molecular indices of oxidative stress and mitochondrial dysfunction occur early and often progress with severity of Alzheimer's disease. J. Alzheim. Dis. 9 (2), 167–181.
De Meyts, P., 2016. The insulin receptor and its signal transduction network. In Endotext [Internet]. (MDText. com, Inc).
Demirkiran, O., Mesaik, M.A., Beynek, H., Abbaskhan, A., Choudhary, M.I., 2013. Immunosupressive phenolic constituents from Hypericum montbretii spach. Record Nat. Prod. 7 (3), 210.
Dimitrov, M., Nikolova, I., Benbasat, N., Kitanov, G., Danchev, N., 2014. Acute toxicity, antidepressive and MAO inhibitory activity of mangiferin isolated from Hypericum aucheri. Biotechnol. Biotechnol. Equip. 25 (4), 2668–2671.
Dorr, R.T., 1993. Interferon-α in malignant and viral diseases. Drugs 45 (2), 177–211.
Du, Z., Fanshi, F., Lai, Y.H., Chen, J.R., Hao, E., Deng, J., Hsiao, C.D., 2019. Mechanism of anti-dementia effects of mangiferin in a senescence accelerated mouse (SAMP8) model. Biosci. Rep. 39 (9).
Duang, X.Y., Wang, Q., Zhou, X.D., Huang, D.M., 2011. Mangiferin: a possible strategy for periodontal disease to therapy. Med. Hypotheses 76 (4), 486–488.
Duarte, A.I., Moreira, P.I., Oliveira, C.R., 2012. Insulin in central nervous system: more than just a peripheral hormone. Journal of aging research 2012, 384017.
Dunn, A.J., Wang, J., Ando, T., 1999. Effects of cytokines on cerebral neurotransmission. In: Cytokines, Stress, and Depression. Springer, Boston, MA, pp. 117–127.
Edwards, R.H., 1993. Neural degeneration and the transport of neurotransmitters. Ann. Neurol. 34 (5), 638–645.
Ehianeta, T.S., Laval, S., Yu, B., 2016. Bio- and chemical syntheses of mangiferin and congeners. Biofactors 42 (5), 445–458.
Erbas, O., Oltulu, F., Taşkiran, D., 2012. Amelioration of rotenone-induced dopaminergic cell death in the striatum by oxytocin treatment. Peptides 38 (2), 312–317.

Erraji-Benchekroun, L., Underwood, M.D., Arango, V., Galfalvy, H., Pavlidis, P., Smyrniotopoulos, P., Sibille, E., 2005. Molecular aging in human prefrontal cortex is selective and continuous throughout adult life. Biol. Psychiatr. 57 (5), 549–558.
Exner, N., Lutz, A.K., Haass, C., Winklhofer, K.F., 2012. Mitochondrial dysfunction in Parkinson's disease: molecular mechanisms and pathophysiological consequences. EMBO J. 31 (14), 3038–3062.
Farrer, M.J., 2006. Genetics of Parkinson disease: paradigm shifts and future prospects. Nat. Rev. Genet. 7 (4), 306–318.
Ferrari, C.C., Pott Godoy, M.C., Tarelli, R., Chertoff, M., Depino, A.M., Pitossi, F.J., 2006. Progressive neurodegeneration and motor disabilities induced by chronic expression of IL-1 beta in the substantia nigra. Neurobiol. Dis. 24 (1), 183–193.
Finkel, T., Holbrook, N.J., 2000. Oxidants, oxidative stress and the biology of ageing. Nature 408 (6809), 239–247.
Flint, A.J., Rifat, S.L., 1997. Two-year outcome of elderly patients with anxious depression. Psychiatr. Res. 66 (1), 23–31.
Floyd, R.A., Hensley, K., 2002. Oxidative stress in brain aging: implications for therapeutics of neurodegenerative diseases. Neurobiol. Aging 23 (5), 795–807.
Forno, L.S., 1996. Neuropathology of Parkinson's disease. JNEN (J. Neuropathol. Exp. Neurol.) 55 (3), 259–272.
Foster, T.C., Sharrow, K.M., Masse, J.R., Norris, C.M., Kumar, A., 2001. Calcineurin links Ca2+ dysregulation with brain aging. J. Neurosci. 21 (11), 4066–4073.
Francis, P.T., Palmer, A.M., Snape, M., Wilcock, G.K., 1999. The cholinergic hypothesis of Alzheimer's disease: a review of progress. J. Neurol. Neurosurg. Psychiatr. 66 (2), 137–147.
Fujita, M., Inoue, T., 1980. Biosynthesis of mangiferin in Anemarrhena asphodeloides Bunge. I. The origin of the xanthone nucleus. Chem. Pharm. Bull. 28 (8), 2476–2481.
Fujita, M., Inoue, T., 1977. Biosynthesis of mangiferin in Anemarrhena asphodeloides: intact incorporation of C6-C3 precursor into xanthone. Tetrahedron Lett. 18 (51), 4503–4506.
Fujita, M., Inoue, T., 1981. Further studies on the biosynthesis of mangiferin in Anemarrhena asphodeloides: hydroxylation of the shikimate-derived ring. Phytochemistry 20 (9), 2183–2185.
Fujita, M., Inoue, T., 1982. Studies on the constituents of Iris florentina L. II. C-glucosides of xanthones and flavones from the leaves. Chem. Pharmaceut. Bull. 30 (7), 2342–2348.
Gallagher, M., Landfield, P.W., McEwen, B., Meaney, M.J., Rapp, P.R., Sapolsky, R., West, M.J., 1996. Hippocampal neurodegeneration in aging. Science 274 (5287), 481–485.
Garcıa, D., Delgado, R., Ubeira, F.M., Leiro, J., 2002. Modulation of rat macrophage function by the Mangifera indica L. extracts Vimang and mangiferin. Int. Immunopharm. 2 (6), 797–806.
Garcia, D., Leiro, J., Delgado, R., Sanmartin, M.L., Ubeira, F.M., 2003. Mangifera indica L. extract (Vimang) and mangiferin modulate mouse humoral immune responses. Phytother Res.: An International Journal Devoted to Pharmacological & Toxicological Evaluation of Natural Product Derivatives 17 (10), 1182–1187.
García-Matas, S., de Vera, N., Aznar, A.O., Marimon, J.M., Adell, A., Planas, A.M., Sanfeliu, C., 2010. In vitro and in vivo activation of astrocytes by amyloid-β is potentiated by pro-oxidant agents. J. Alzheim. Dis. 20 (1), 229–245.
Garrido, G., Delgado, R., Lemus, Y., Rodrıguez, J., Garcıa, D., Núñez-Selles, A.J., 2004. Protection against septic shock and suppression of tumor necrosis factor alpha and nitric oxide production on macrophages and microglia by a standard aqueous extract of Mangifera indica L. (Vimang®): role of mangiferin isolated from the extract. Pharmacol. Res. 50 (2), 165–172.
Garrido-Suarez, B.B., Garrido, G., Castro-Labrada, M., Merino, N., Valdés, O., Rodeiro, I., Hernández, I., Godoy-Figueiredo, J., Ferreira, S.H., Delgado-Hernández, R., 2014. Anti-hypernociceptive effect of mangiferin in persistent and neuropathic pain models in rats. Pharmacol. Biochem. Behav. 124, 311–319.
Garrido-Suarez, B.B., Garrido, G., Delgado, R., Bosch, F., Rabí, M.D.C., 2010. A Mangifera indica L. extract could be used to treat neuropathic pain and implication of mangiferin. Molecules 15 (12), 9035–9045.
Gaspar, J.M., Baptista, F.I., Macedo, M.P., Ambrósio, A.F., 2016. Inside the diabetic brain: role of different players involved in cognitive decline. ACS Chem. Neurosci. 7 (2), 131–142.
Gerlach, M., Riederer, P., Przuntek, H., Youdim, M.B., 1991. MPTP mechanisms of neurotoxicity and their implications for Parkinson's disease. Eur. J. Pharmacol. Mol. Pharmacol. 208 (4), 273–286.
Gerritsen, A.A., Bakker, C., Verhey, F.R., de Vugt, M.E., Melis, R.J., Koopmans, R.T., Ramakers, I.H., 2016. Prevalence of comorbidity in patients with young-onset Alzheimer disease compared with late-onset: a comparative cohort study. J. Am. Med. Dir. Assoc. 17 (4), 318–323.
Gerschman, R., Gilbert, D.L., Nye, S.W., Dwyer, P., Fenn, W.O., 1954. Oxygen poisoning and x-irradiation: a mechanism in common. Science 119 (3097), 623–626.
Graeber, M.B., 2010. Changing face of microglia. Science 330 (6005), 783–788.
Grimmig, B., Morganti, J., Nash, K., Bickford, P.C., 2016. Immunomodulators as therapeutic agents in mitigating the progression of Parkinson's disease. Brain Sci. 6 (4), 41.
Grippo, A.J., Sullivan, N.R., Damjanoska, K.J., Crane, J.W., Carrasco, G.A., Shi, J., Van de Kar, L.D., 2005. Chronic mild stress induces behavioral and physiological changes, and may alter serotonin 1A receptor function, in male and cycling female rats. Psychopharmacology 179 (4), 769–780.
Guo, J., Lin, P., Zhao, X., Zhang, J., Wei, X., Wang, Q., Wang, C., 2014. Etazolate abrogates the lipopolysaccharide (LPS)-induced downregulation of the cAMP/pCREB/BDNF signaling, neuroinflammatory response and depressive-like behavior in mice. Neuroscience 263, 1–14.
Gupta, D., Radhakrishnan, M., Kurhe, Y., Thangaraj, D., Prabhakar, V., Kanade, P., 2014. Antidepressant-like effects of a novel 5-HT3 receptor antagonist 6z in acute and chronic murine models of depression. Acta Pharmacol. Sin. 35 (12), 1493–1503.
Gustaw, K.A., Garrett, M.R., Lee, H.G., Castellani, R.J., Zagorski, M.G., Prakasam, A., Friedland, R.P., 2008. Antigen–antibody dissociation in Alzheimer disease: a novel approach to diagnosis. J. Neurochem. 106 (3), 1350–1356.
Guttmacher, A.E., Collins, F.S., Nussbaum, R.L., Ellis, C.E., 2003. Alzheimer's disease and Parkinson's disease. N. Engl. J. Med. 348, 1356–1364.
Harman, D., 1972. The biologic clock: the mitochondria? J. Am. Geriatr. Soc. 20 (4), 145–147.
Harman, E., 1956. Protein oxidation in aging and age-related diseases. Gerontology 11, 298–300.
Hartley, A., Stone, J.M., Heron, C., Cooper, J.M., Schapira, A.H.V., 1994. Complex I inhibitors induce dose-dependent apoptosis in PC12 cells: relevance to Parkinson's disease. J. Neurochem. 63 (5), 1987–1990.
Hartley, D.M., Walsh, D.M., Chianping, P.Y., Diehl, T., Vasquez, S., Vassilev, P.M., Selkoe, D.J., 1999. Protofibrillar intermediates of amyloid β-protein induce acute electrophysiological changes and progressive neurotoxicity in cortical neurons. J. Neurosci. 19 (20), 8876–8884.
Hayden, M.S., Ghosh, S., 2014. Regulation of NF-κB by TNF family cytokines. Semin. Immunol. 26 (3), 253–266.
He, L., Peng, X., Zhu, J., Chen, X., Liu, H., Tang, C., Peng, Y., 2014. Mangiferin attenuate sepsis-induced acute kidney injury via antioxidant and anti-inflammatory effects. Am. J. Nephrol. 40 (5), 441–450.
Hirai, K., Aliev, G., Nunomura, A., Fujioka, H., Russell, R.L., Atwood, C.S., Shimohama, S., 2001. Mitochondrial abnormalities in Alzheimer's disease. J. Neurosci. 21 (9), 3017–3023.
Hirsch, E.C., Hunot, S., 2009. Neuroinflammation in Parkinson's disease: a target for neuroprotection? Lancet Neurol. 8 (4), 382–397.
Hornykiewicz, O., Kish, S.J., 1987. Biochemical pathophysiology of Parkinson's disease. Adv. Neurol. 45, 19–34.
Hostettmann, K., Hostettmann, M., 1989. Xanthones. In: Plant Phenolics, Harbone, J.B. (Eds.), Methods in Plant Biochemistry, vol. 1. Academic Press, London, pp. 493–508.
Hou, S., Wang, F., Li, Y., Li, Y., Wang, M., Sun, D., Sun, C., 2012. Pharmacokinetic study of mangiferin in human plasma after oral administration. Food Chem. 132 (1), 289–294.
Hou, Y., Fan, S., Zhang, H., Gu, Y., Yu, X., Li, B., 2010. Pharmacokinetic study of mangiferin in rat plasma and retina using high-performance liquid chromatography. Mol. Vis. 16, 1659.
Iacopino, A.M., Christakos, S., 1990. Specific reduction of calcium-binding protein (28-kilodalton calbindin-D) gene expression in aging and neurodegenerative diseases. Proc. Natl. Acad. Sci. Unit. States Am. 87 (11), 4078–4082.
Imran, M., Arshad, M.S., Butt, M.S., Kwon, J.H., Arshad, M.U., Sultan, M.T., 2017. Mangiferin: a natural miracle bioactive compound against lifestyle related disorders. Lipids Health Dis. 16 (1), 84.
Infante-Garcia, C., Ramos-Rodriguez, J.J., Delgado-Olmos, I., Gamero-Carrasco, C., Fernandez-Ponce, M.T., Casas, L., Garcia-Alloza, M., 2017. long-term Mangiferin extract treatment improves central pathology and cognitive deficits in APP/PS1 mice. Mol. Neurobiol. 54 (6), 4696–4704.
Iqbal, K., Alonso, A.D.C., Gong, C.X., Khatoon, S., Pei, J.J., Wang, J.Z., Grundke-Iqbal, I., 1998. Mechanisms of neurofibrillary degeneration and the formation of neurofibrillary tangles. Ageing & Dementia. Springer, Vienna, pp. 169–180.
Ishola, I.O., Awodele, O., Eluogu, C.O., 2016. Potentials of Mangifera indica in the treatment of depressive-anxiety disorders: possible mechanisms of action. J. Compl. Integr. Med. 13 (3), 275–287.
Iverson, S.L., Orrenius, S., 2004. The cardiolipin–cytochrome c interaction and the mitochondrial regulation of apoptosis. Arch. Biochem. Biophys. 423 (1), 37–46.
Jagetia, G.C., Baliga, M.S., 2005. Radioprotection by mangiferin in DBAxC57BL mice: a preliminary study. Phytomedicine 12 (3), 209–215.
Jagetia, G.C., Venkatesha, V.A., 2005. Effect of mangiferin on radiation-induced micronucleus formation in cultured human peripheral blood lymphocytes. Environ. Mol. Mutagen. 46 (1), 12–21.
Jain, P.K., Kharya, M., Gajbhiye, A., 2013. Pharmacological evaluation of mangiferin herbosomes for antioxidant and hepatoprotection potential against ethanol induced hepatic damage. Drug Dev. Ind. Pharm. 39 (11), 1840–1850.
Jangra, A., Lukhi, M.M., Sulakhiya, K., Baruah, C.C., Lahkar, M., 2014. Protective effect of mangiferin against lipopolysaccharide-induced depressive and anxiety-like behaviour in mice. Eur. J. Pharmacol. 740, 337–345.
Jeong, J.J., Jang, S.E., Hyam, S.R., Han, M.J., Kim, D.H., 2014. Mangiferin ameliorates colitis by inhibiting IRAK1 phosphorylation in NF-κB and MAPK pathways. Eur. J. Pharmacol. 740, 652–661.
Joo, Y., Choi, K.M., Lee, Y.H., Kim, G., Lee, D.H., Roh, G.S., Kang, S.S., Cho, G.J., Choi, W.S., Kim, H.J., 2009. Chronic immobilization stress induces anxiety- and depression-like behaviors and decreases transthyretin in the mouse cortex. Neurosci. Lett. 461 (2), 121–125.
Joubert, E., Richards, E.S., Merwe, J.D.V.D., De Beer, D., Manley, M., Gelderblom, W.C., 2008. Effect of species variation and processing on phenolic composition and in vitro antioxidant activity of aqueous extracts of Cyclopia spp. (honeybush tea). J. Agric. Food Chem. 56 (3), 954–963.
Jung, K., Lee, B., Han, S.J., Ryu, J.H., Kim, D.H., 2009. Mangiferin ameliorates scopolamine-induced learning deficits in mice. Biol. Pharm. Bull. 32 (2), 242–246.
Kamal, A., Almenar-Queralt, A., LeBlanc, J.F., Roberts, E.A., Goldstein, L.S., 2001. Kinesin-mediated axonal transport of a membrane compartment containing β-secretase and presenilin-1 requires APP. Nature 414 (6864), 643–648.
Kasbe, P., Jangra, A., Lahkar, M., 2015. Mangiferin ameliorates aluminium chloride-induced cognitive dysfunction via alleviation of hippocampal oxido-nitrosative

stress, proinflammatory cytokines and acetylcholinesterase level. J. Trace Elem. Med. Biol. 31, 107–112.
Kavitha, M., Manivasagam, T., Essa, M.M., Tamilselvam, K., Selvakumar, G.P., Karthikeyan, S., Thenmozhi, J.A., Subash, S., 2014. Mangiferin antagonizes rotenone: induced apoptosis through attenuating mitochondrial dysfunction and oxidative stress in SK-N-SH neuroblastoma cells. Neurochem. Res. 39 (4), 668–676.
Kavitha, M., Nataraj, J., Essa, M.M., Memon, M.A., Manivasagam, T., 2013. Mangiferin attenuates MPTP induced dopaminergic neurodegeneration and improves motor impairment, redox balance and Bcl-2/Bax expression in experimental Parkinson's disease mice. Chem. Biol. Interact. 206 (2), 239–247.
Kern, W., Born, J., Schreiber, H., Fehm, H.L., 1999. Central nervous system effects of intranasally administered insulin during euglycemia in men. Diabetes 48 (3), 557–563.
Khurana, R.K., Kaur, R., Kaur, M., Kaur, R., Kaur, J., Kaur, H., Singh, B., 2017. Exploring and validating physicochemical properties of mangiferin through GastroPlus® software. Future Ccience OA 3 (1). FSO167.
Kim, B., Feldman, E.L., 2012. Insulin resistance in the nervous system. Trends Endocrinol. Metabol. 23 (3), 133–141.
Kim, Y.K., Suh, I.B., Kim, H., Han, C.S., Lim, C.S., Choi, S.H., Licinio, J., 2002. The plasma levels of interleukin-12 in schizophrenia, major depression, and bipolar mania: effects of psychotropic drugs. Mol. Psychiatr. 7 (10), 1107–1114.
Kirkinezos, I.G., Bacman, S.R., Hernandez, D., Oca-Cossio, J., Arias, L.J., Perez-Pinzon, M.A., Moraes, C.T., 2005. Cytochrome c association with the inner mitochondrial membrane is impaired in the CNS of G93A-SOD1 mice. J. Neurosci. 25 (1), 164–172.
Koenigsknecht, J., Landreth, G., 2004. Microglial phagocytosis of fibrillar β-amyloid through a β1 integrin-dependent mechanism. J. Neurosci. 24 (44), 9838–9846.
Koenigsknecht-Talboo, J., Landreth, G.E., 2005. Microglial phagocytosis induced by fibrillar β-amyloid and IgGs are differentially regulated by proinflammatory cytokines. J. Neurosci. 25 (36), 8240–8249.
Kong, J., Xu, Z., 1998. Massive mitochondrial degeneration in motor neurons triggers the onset of amyotrophic lateral sclerosis in mice expressing a mutant SOD1. J. Neurosci. 18 (9), 3241–3250.
Kostyuk, V., Potapovich, A., Korkina, L., 2007. Plant polyphenol-metal complexes: effects on reactive oxygen species and cytoprotection against oxidative damage. In: Proc. European Meeting of the Society for Free Radical Research. Vilamoura, Algarve, Portugal, pp. 131–135.
Kumar, A., Goyal, R., 2008. Quercetin protects against acute immobilization stress-induced behaviors and biochemical alterations in mice. J. Med. Food 11 (3), 469–473.
Kumar, S., Maheshwari, K.K., Singh, V., 2009. Effects of Mangifera indica fruit extract on cognitive deficits in mice. J. Environ. Biol. 30 (4).
Kurosaki, R., Muramatsu, Y., Kato, H., Araki, T., 2004. Biochemical, behavioral and immunohistochemical alterations in MPTP-treated mouse model of Parkinson's disease. Pharmacol. Biochem. Behav. 78 (1), 143–153.
Lacroix, S., Rivest, S., 1998. Effect of acute systemic inflammatory response and cytokines on the transcription of the genes encoding cyclooxygenase enzymes (COX-1 and COX-2) in the rat brain. J. Neurochem. 70 (2), 452–466.
Lehohla, M., Kellaway, L., Russell, V.A., 2008. Effect of ageing on Ca 2+ uptake *via* NMDA receptors into barrel cortex slices of spontaneously hypertensive rats. Metab. Brain Dis. 23 (1), 1–8.
Leiro, J., Arranz, J.A., Yáñez, M., Ubeira, F.M., Sanmartin, M.L., Orallo, F., 2004. Expression profiles of genes involved in the mouse nuclear factor-kappa B signal transduction pathway are modulated by mangiferin. Int. Immunopharm. 4 (6), 763–778.
Lemmon, M.A., Schlessinger, J., 2010. Cell signaling by receptor tyrosine kinases. Cell 141 (7), 1117–1134.
Lemus-Molina, Y., Sanchez-Gomez, M.V., Delgado-Hernandez, R., Matute, C., 2009. Mangifera indica L. extract attenuates glutamate-induced neurotoxicity on rat cortical neurons. Neurotoxicology 30 (6), 1053–1058.
Levenga, J., Wong, H., Milstead, R.A., Keller, B.N., LaPlante, L.E., Hoeffer, C.A., 2017. AKT isoforms have distinct hippocampal expression and roles in synaptic plasticity. Elife 6, e30640.
Levy, D.E., Tang, C., 1995. The chemistry of C-glycosides. Pergamon Press, Oxford 13, 1–290.
Li, G., Thomas, S.P., Johnson, J., 2013a. Polyphenols from the mangosteen (Garcinia mangostana) fruit for breast and prostate cancer. Front. Pharmacol. 4, 80.
Li, H., Wang, Q., Ding, Y., Bao, C., Li, W., 2017. Mangiferin ameliorates Porphyromonas gingivalis-induced experimental periodontitis by inhibiting phosphorylation of nuclear factor-κB and Janus kinase 1–signal transducer and activator of transcription signaling pathways. J. Periodontal. Res. 52 (1), 1–7.
Li, J., Li, W., Jiang, Z.G., Ghanbari, H.A., 2013b. Oxidative stress and neurodegenerative disorders. Int. J. Mol. Sci. 14 (12), 24438–24475.
Li, S., Chen, G., Zhang, C., Wu, M., Wu, S., Liu, Q., 2014. Research progress of natural antioxidants in foods for the treatment of diseases. Food Science & Human Wellness 3 (3–4), 110–116.
Li, X., Jiang, Q., Chen, B., Luo, X., Chen, D., 2018. Structure–activity relationship and prediction of the electron-transfer potential of the xanthones series. Chemistry Open 7 (9), 730–736.
Li, Y.J., Sui, Y.J., Dai, Y.H., Deng, Y.L., 2008. LC determination and pharmacokinetics study of mangiferin in rat plasma and tissues. Chromatographia 67 (11–12), 957–960.
Li, Y., Meselhy, M.R., Wang, L.Q., Nakamura, N., Hattori, M., 2000. Biotransformation of a C-glycosylflavone, abrusin 2"-O-β-D-Apioside, by human intestinal bacteria. Chem. Pharmaceut. Bull. 48 (8), 1239–1241.
Li, Y.J., Bi, K.S., 2003. RP-HPLC determination and pharmacokinetic study of mangiferin in rat plasma after taking traditional Chinese medicinal preparation: zhimu decoction. Chromatographia 57, 767–770.
Lin, M.T., Beal, M.F., 2006. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature 443, 787–795.
Ling, L.T., Yap, S.A., Radhakrishnan, A.K., Subramaniam, T., Cheng, H.M., Palanisamy, U.D., 2009. Standardised Mangifera indica extract is an ideal antioxidant. Food Chem. 113 (4), 1154–1159.
Liu, H., Wang, K., Tang, Y., Sun, Z., Jian, L., Li, Z., Huang, C., 2011. Structure elucidation of in vivo and in vitro metabolites of mangiferin. J. Pharmaceut. Biomed. Anal. 55 (5), 1075–1082.
Liu, H., Wu, B., Pan, G., He, L., Li, Z., Fan, M., Huang, C., 2012. Metabolism and pharmacokinetics of mangiferin in conventional rats, pseudo-germ-free rats, and streptozotocin-induced diabetic rats. Drug Metab. Dispos. 40 (11), 2109–2118.
Liu, Y., Xu, F., Zeng, X., Yang, L., Deng, Y., Wu, Z., Li, X., 2010. Application of a liquid chromatography/tandem mass spectrometry method to pharmacokinetic study of mangiferin in rats. J. Chromatogr. B 878 (32), 3345–3350.
Liu, Y.W., Zhu, X., Yang, Q.Q., Lu, Q., Wang, J.Y., Li, H.P., Wei, Y.Q., Yin, J.L., Yin, X.X., 2013. Suppression of methylglyoxal hyperactivity by mangiferin can prevent diabetes-associated cognitive decline in rats. Psychopharmacology (Berlin) 228, 585–594.
Lopes, S.C., da Silva, A.V.L., Arruda, B.R., Morais, T.C., Rios, J.B., Trevisan, M.T.S., Santos, F.A., 2013. Peripheral antinociceptive action of mangiferin in mouse models of experimental pain: role of endogenous opioids, KATP-channels and adenosine. Pharmacol. Biochem. Behav. 110, 19–26.
Lotharius, J., Brundin, P., 2002. Pathogenesis of Parkinson's disease: dopamine, vesicles and [alpha]-synuclein. Nat. Rev. Neurosci. 3 (12), 932.
Lucassen, P.J., Vollmann-Honsdorf, G.K., Gleisberg, M., Czéh, B., De Kloet, E.R., Fuchs, E., 2001. Chronic psychosocial stress differentially affects apoptosis in hippocampal subregions and cortex of the adult tree shrew. Eur. J. Neurosci. 14 (1), 161–166.
Luo, F., Lv, Q., Zhao, Y., Hu, G., Huang, G., Zhang, J., Sun, C., Li, X., Chen, K., 2012. Quantification and purification of mangiferin from Chinese Mango (Mangifera indica L.) cultivars and its protective effect on human umbilical vein endothelial cells under H(2)O(2)-induced stress. Int. J. Mol. Sci. 13 (9), 11260–11274.
Luo, G.Q., Liu, L., Gao, Q.W., Wu, X.N., Xiang, W., Deng, W.T., 2017. Mangiferin prevents corticosterone-induced behavioural deficits via alleviation of oxido-nitrosative stress and down-regulation of indoleamine 2, 3-dioxygenase (Ido) activity. Neurol. Res. 39 (8), 709–718.
Luo, Y., Fu, C., Wang, Z., Zhang, Z., Wang, H., Liu, Y., 2015. Mangiferin attenuates contusive spinal cord injury in rats through the regulation of oxidative stress, inflammation and the Bcl-2 and Bax pathway. Mol. Med. Rep. 12 (5), 7132–7138.
Lyman, M., Lloyd, D.G., Ji, X., Vizcaychipi, M.P., Ma, D., 2014. Neuroinflammation: the role and consequences. Neurosci. Res. 79, 1–12.
Ma, H., Chen, H., Sun, L., Tong, L., Zhang, T., 2014. Improving permeability and oral absorption of mangiferin by phospholipid complexation. Fitoterapia 93, 54–61.
Márquez, L., García-Bueno, B., Madrigal, J.L., Leza, J.C., 2012. Mangiferin decreases inflammation and oxidative damage in rat brain after stress. Eur. J. Nutr. 51 (6), 729–739.
Madrigal, J.L., Hurtado, O., Moro, M.A., Lizasoain, I., Lorenzo, P., Castrillo, A., Leza, J. C., 2002. The increase in TNF-α levels is implicated in NF-κB activation and inducible nitric oxide synthase expression in brain cortex after immobilization stress. Neuropsychopharmacology 26 (2), 155–163.
Madrigal, J.L., Moro, M.A., Lizasoain, I., Lorenzo, P., Castrillo, A., Boscá, L., Leza, J.C., 2001. Inducible nitric oxide synthase expression in brain cortex after acute restraint stress is regulated by nuclear factor κB-mediated mechanisms. J. Neurochem. 76 (2), 532–538.
Madrigal, J.L., Moro, M.A., Lizasoain, I., Lorenzo, P., Fernández, A.P., Rodrigo, J., Leza, J.C., 2003. Induction of cyclooxygenase-2 accounts for restraint stress-induced oxidative status in rat brain. Neuropsychopharmacology 28 (9), 1579–1588.
Maes, M., Bosmans, E., De Jongh, R., Kenis, G., Vandoolaeghe, E., Neels, H., 1997. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. Cytokine 9 (11), 853–858.
Maes, M., Bosmans, E., Meltzer, H.Y., Scharpé, S., Suy, E., 1993. Interleukin-1 beta: a putative mediator of HPA axis hyperactivity in major depression? Am. J. Psychiatr. 150 (8), 1189–1193.
Maes, M., Meltzer, H.Y., Bosmans, E., Bergmans, R., Vandoolaeghe, E., Ranjan, R., Desnyder, R., 1995. Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. J. Affect. Disord. 34 (4), 301–309.
Maes, M., Song, C., Lin, A.H., Bonaccorso, S., Kenis, G., De Jongh, R., Scharpé, S., 1999. Negative immunoregulatory effects of antidepressants: inhibition of interferon-γ and stimulation of interleukin-10 secretion. Neuropsychopharmacology 20 (4), 370–379.
Mandrekar, S., Jiang, Q., Lee, C.D., Koenigsknecht-Talboo, J., Holtzman, D.M., Landreth, G.E., 2009. Microglia mediate the clearance of soluble Aβ through fluid phase macropinocytosis. J. Neurosci. 29 (13), 4252–4262.
Manna, P., Jain, S.K., 2013. PIP3 but not PIP2 increases GLUT4 surface expression and glucose metabolism mediated by AKT/PKCζ/λ phosphorylation in 3T3L1 adipocytes. Mol. Cell. Biochem. 381 (1–2), 291–299.
Martin, F., Hay, A.E., Cressend, D., Reist, M., Vivas, L., Gupta, M.P., Hostettmann, K., 2008. Antioxidant C-glucosylxanthones from the leaves of Arrabidaea patellifera. J. Nat. Prod. 71 (11), 1887–1890.
Martínez Sanchez, G., Candelario-Jalil, E., Giuliani, A., León, O.S., Sam, S., Delgado, R., Núñez Sellés, A.J., 2001. Mangifera indica L. extract (QF808) reduces ischaemia-induced neuronal loss and oxidative damage in the gerbil brain. Free Radic. Res. 35 (5), 465–473.

Martínez, G., Delgado, R., Pérez, G., Garrido, G., Núñez Sellés, A.J., León, O.S., 2000. Evaluation of the in vitro antioxidant activity of Mangifera indica L. extract (Vimang). Phytother Res.: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives 14 (6), 424–427.
Martinez-Vicente, M., Talloczy, Z., Kaushik, S., Massey, A.C., Mazzulli, J., Mosharov, E. V., Dauer, W., 2008. Dopamine-modified α-synuclein blocks chaperone-mediated autophagy. J. Clin. Invest. 118 (2), 777.
Matkowski, A., Kus, P., Goralska, E., Wozniak, D., 2013. Mangiferin–a bioactive xanthonoid, not only from mango and not just antioxidant. Mini Rev. Med. Chem. 13 (3), 439–455.
Matkowski, A., Kuś, P., Janda, B., Oleszek, W., Woźniak, D., 2009. Isolation and antioxidant activity evaluation of mangiferin from Belamcandae rhizoma. Acta Biochim. Pol. 56, S3.
Matsui, H., Taniguchi, Y., Inoue, H., Uemura, K., Takeda, S., Takahashi, R., 2009. A chemical neurotoxin, MPTP induces Parkinson's disease like phenotype, movement disorders and persistent loss of dopamine neurons in medaka fish. Neurosci. Res. 65 (3), 263–271.
Matsushima, T., Araki, A., Yagame, O., Muramatsu, M., Koyama, K., Ohsawa, K., Tomimori, H., 1985. Mutagenicities of xanthone derivatives in Salmonella typhimurium TA100, TA98, TA97, and TA2637. Mutat. Res. Fund Mol. Mech. Mutagen 150 (1–2), 141–146.
Mattiazzi, M., D'Aurelio, M., Gajewski, C.D., Martushova, K., Kiaei, M., Beal, M.F., Manfredi, G., 2002. Mutated human SOD1 causes dysfunction of oxidative phosphorylation in mitochondria of transgenic mice. J. Biol. Chem. 277 (33), 29626–29633.
McCoy, M.K., Martinez, T.N., Ruhn, K.A., Szymkowski, D.E., Smith, C.G., Botterman, B. R., Tansey, K.E., Tansey, M.G., 2006. Blocking soluble tumor necrosis factor signaling with dominant-negative tumor necrosis factor inhibitor attenuates loss of dopaminergic neurons in models of Parkinson's disease. J. Neurosci.: The Official Journal of the Society for Neuroscience 26 (37), 9365–9375.
McEwen, B.S., Sapolsky, R.M., 1995. Stress and cognitive function. Curr. Opin. Neurobiol. 5 (2), 205–216.
McGeer, P.L., Itagaki, S., Boyes, B.E., McGeer, E.G., 1988. Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. Neurology 38 (8), 1285–1291.
Miller, A.H., Raison, C.L., 2016. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat. Rev. Immunol. 16 (1), 22.
Mizuno, Y., Hattori, N., Kitada, T., Matsumine, H., Mori, H., Shimura, H., Shimizu, N., 2000. Familial Parkinson's disease. Alpha-synuclein and parkin. Adv. Neurol. 86, 13–21.
Mohamed, R.H., Karam, R.A., Amer, M.G., 2011. Epicatechin attenuates doxorubicin-induced brain toxicity: critical role of TNF-α, iNOS and NF-κB. Brain Res. Bull. 86 (1–2), 22–28.
Morilak, D.A., Frazer, A., 2004. Antidepressants and brain monoaminergic systems: a dimensional approach to understanding their behavioural effects in depression and anxiety disorders. Int. J. Neuropsychopharmacol. 7 (2), 193–218.
Morley, J.E., Kumar, V.B., Bernardo, A.E., Farr, S.A., Uezu, K., Tumosa, N., Flood, J.F., 2000. β-Amyloid precursor polypeptide in SAMP8 mice affects learning and memory. Peptides 21 (12), 1761–1767.
Morrison, J.H., Hof, P.R., 1997. Life and death of neurons in the aging brain. Science 278, 412–419.
Munhoz, C.D., Lepsch, L.B., Kawamoto, E.M., Malta, M.B., de Sá Lima, L., Avellar, M.C. W., Scavone, C., 2006. Chronic unpredictable stress exacerbates lipopolysaccharide-induced activation of nuclear factor-κB in the frontal cortex and hippocampus via glucocorticoid secretion. J. Neurosci. 26 (14), 3813–3820.
Murray, F., Smith, D.W., Hutson, P.H., 2008. Chronic low dose corticosterone exposure decreased hippocampal cell proliferation, volume and induced anxiety and depression like behaviours in mice. Eur. J. Pharmacol. 583 (1), 115–127.
Muruganandan, S., Srinivasan, K., Gupta, S., Gupta, P.K., Lal, J., 2005. Effect of mangiferin on hyperglycemia and atherogenicity in streptozotocin diabetic rats. J. Ethnopharmacol. 97 (3), 497–501.
Muruganandan, S., Gupta, S., Kataria, M., Lal, J., Gupta, P.K., 2002. Mangiferin protects the streptozotocin-induced oxidative damage to cardiac and renal tissues in rats. Toxicology 176 (3), 165–173.
Nabavi, S.F., Braidy, N., Gortzi, O., Sobarzo-Sanchez, E., Daglia, M., Skalicka-Woźniak, K., Nabavi, S.M., 2015. Luteolin as an anti-inflammatory and neuroprotective agent: a brief review. Brain Res. Bull. 119, 1–11.
Narkhede, K.P., Kulkarni, A.R., 2016. Attenuation of neuronal damage by mangiferin in experimentally induced cerebral ischemia in rats. Int. J. Res. Pharm. Sci. 7 (4), 1–7.
Nathan, C., Xie, Q.W., 1994. Nitric oxide synthases: roles, tolls, and controls. Cell 78 (6), 915–918.
Nedialkov, P., Kitanov, G., Tencheva, J., 1998. HPTLC densitomeric determination of justicidin B in Linum in vitro cultures. Acta Pharm. 48, 211–214.
Negi, J.S., Bisht, V.K., Singh, P., Rawat, M.S.M., Joshi, G.P., 2013. Naturally occurring xanthones: chemistry and biology. J. Appl. Chem. 2013.
Newman, D.J., Cragg, G.M., 2016. Natural products as sources of new drugs from 1981 to 2014. J. Nat. Prod. 79 (3), 629–661.
Niraula, A., Sheridan, J.F., Godbout, J.P., 2017. Microglia priming with aging and stress. Neuropsychopharmacology 42 (1), 318–333.
Nogawa, S., Forster, C., Zhang, F., Nagayama, M., Ross, M.E., Iadecola, C., 1998. Interaction between inducible nitric oxide synthase and cyclooxygenase-2 after cerebral ischemia. Proc. Natl. Acad. Sci. Unit. States Am. 95 (18), 10966–10971.
Noguchi, M., Suizu, F., 2012. Regulation of AKT by phosphorylation of distinct threonine and serine residues. Adv. Med. Biol. 139–162.
Norris, C.M., Korol, D.L., Foster, T.C., 1996. Increased susceptibility to induction of long-term depression and long-term potentiation reversal during aging. J. Neurosci. 16 (17), 5382–5392.
Nunes, S.O.V., Reiche, E.M.V., Morimoto, H.K., Matsuo, T., Itano, E.N., Xavier, E.C.D., Costa, F.B., 2002. Immune and hormonal activity in adults suffering from depression. Braz. J. Med. Biol. Res. 35 (5), 581–587.
Ochocka, R., Hering, A., Stefanowicz–Hajduk, J., Cal, K., Barańska, H., 2017. The effect of mangiferin on skin: penetration, permeation and inhibition of ECM enzymes. PloS One 12 (7).
Olanow, C.W., Tatton, W.G., 1999. Etiology and pathogenesis of Parkinson's disease. Annu. Rev. Neurosci. 22 (1), 123–144.
Ou, S., Li, L., Ke-yuan, W., Fang-hua, L., 2013. Extraction of mangiferin from the leaves of *Aquilaria sinensis* (Lour.) gilg. China Forestry Science & Technology 5, 101–104.
Padmapriya, K., Dutta, A., Chaudhuri, S., Dutta, D., 2012. Microwave assisted extraction of mangiferin from. Curcuma Amada 2, 27–30.
Pakkenberg, B., Gundersen, H.J.G., 1997. Neocortical neuron number in humans: effect of sex and age. J. Comp. Neurol. 384 (2), 312–320.
Pal, P.B., Sinha, K., Sil, P.C., 2014. Mangiferin attenuates diabetic nephropathy by inhibiting oxidative stress mediated signalling cascade, TNFα related and mitochondrial dependent apoptotic pathways in streptozotocin-induced diabetic rats. PloS One 9 (9), e107220.
Pallas, M., Camins, A., Smith, M.A., Perry, G., Lee, H.G., Casadesus, G., 2008. From aging to Alzheimer's disease: unveiling "the switch" with the senescence-accelerated mouse model (SAMP8). J. Alzheim. Dis. 15 (4), 615–624.
Panov, A., Dikalov, S., Shalbuyeva, N., Taylor, G., Sherer, T., Greenamyre, J.T., 2005. Rotenone model of Parkinson disease multiple brain mitochondria dysfunctions after short term systemic rotenone intoxication. J. Biol. Chem. 280 (51), 42026–42035.
Pardo Andreu, G., Delgado, R., Velho, J., Inada, N.M., Curti, C., Vercesi, A.E., 2005. Mangifera indica L. extract (Vimang) inhibits Fe2+-citrate-induced lipoperoxidation in isolated rat liver mitochondria. Pharmacol. Res. 51 (5), 427–435.
Pardo-Andreu, G.L., Cavalheiro, R.A., Dorta, D.J., Naal, Z., Delgado, R., Vercesi, A.E., Curti, C., 2007. Fe (III) shifts the mitochondria permeability transition-eliciting capacity of mangiferin to protection of organelle. J. Pharmacol. Exp. Therapeut. 320 (2), 646–653.
Pardo-Andreu, G.L., Delgado, R., Núñez-Sellés, A.J., Vercesi, A.E., 2006a. Dual mechanism of mangiferin protection against iron-induced damage to 2-deoxyribose and ascorbate oxidation. Pharmacol. Res. 53 (3), 253–260.
Pardo-Andreu, G.L., Sánchez-Baldoquín, C., Ávila-González, R., Delgado, R., Naal, Z., Curti, C., 2006. Fe (III) improves antioxidant and cytoprotecting activities of mangiferin. Eur. J. Pharmacol. 547 (1–3), 31–36.
Paresce, D.M., Chung, H., Maxfield, F.R., 1997. Slow degradation of aggregates of the Alzheimer's disease amyloid β-protein by microglial cells. J. Biol. Chem. 272 (46), 29390–29397.
Park, C.R., Seeley, R.J., Craft, S., Woods, S.C., 2000. Intracerebroventricular insulin enhances memory in a passive-avoidance task. Physiol. Behav. 68 (4), 509–514.
Pauletti, P.M., Castro-Gamboa, I., Siqueira Silva, D.H., Young, M.C.M., Tomazela, D.M., Eberlin, M.N., da Silva Bolzani, V., 2003. New antioxidant C-glucosylxanthones from the stems of Arrabidaea samydoides. J. Nat. Prod. 66 (10), 1384–1387.
Peraçoli, M.T., Kurokawa, C.S., Calvi, S.A., Mendes, R.P., Pereira, P.C., Marques, S.A., Soares, Á.M., 2003. Production of pro-and anti-inflammatory cytokines by monocytes from patients with paracoccidioidomycosis. Microb. Infect. 5 (5), 413–418.
Petrosillo, G., Ruggiero, F.M., Pistolese, M., Paradies, G., 2004. Ca2+-induced reactive oxygen species production promotes cytochrome c release from rat liver mitochondria via mitochondrial permeability transition (MPT)-dependent and MPT-independent mechanisms ROLE OF CARDIOLIPIN. J. Biol. Chem. 279 (51), 53103–53108.
Phinney, A.L., Andringa, G., Bol, J.G., Wolters, E.C., van Muiswinkel, F.L., van Dam, A.M. W., Drukarch, B., 2006. Enhanced sensitivity of dopaminergic neurons to rotenone-induced toxicity with aging. Park. Relat. Disord. 12 (4), 228–238.
Plassman, B.L., Langa, K.M., Fisher, G.G., Heeringa, S.G., Weir, D.R., Ofstedal, M.B., Steffens, D.C., 2007. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology 29 (1–2), 125–132.
Popa, D., Léna, C., Alexandre, C., Adrien, J., 2008. Lasting syndrome of depression produced by reduction in serotonin uptake during postnatal development: evidence from sleep, stress, and behavior. J. Neurosci. 28 (14), 3546–3554.
Potier, B., Poindessous-Jazat, F., Dutar, P., Billard, J.M., 2000. NMDA receptor activation in the aged rat hippocampus. Exp. Gerontol. 35 (9–10), 1185–1199.
Prabhu, S., Jainu, M., Sabitha, K.E., Devi, C.S., 2006. Cardioprotective effect of mangiferin on isoproterenol induced myocardial infarction in rats. Indian J. Exp. Biol. 44 (3), 209–215.
Prado, Y., Merino, N., Acosta, J., Herrera, J.A., Luque, Y., Hernández, I., Rodeiro, I., 2015. Acute and 28-day subchronic toxicity studies of mangiferin, a glucosyl xanthone isolated from Mangifera indica L. stem bark. J. Pharmacy Pharmac. Res. 3 (1), 13–23.
Qin, M., Xia, Z., Huang, T., Smith, C.B., 2011. Effects of chronic immobilization stress on anxiety-like behavior and basolateral amygdala morphology in Fmr1 knockout mice. Neuroscience 194, 282–290.
Quan, N., Banks, W.A., 2007. Brain-immune communication pathways. Brain Behav. Immun. 21 (6), 727–735.
Rammohan, A., Gunasekar, D., Reddy, N.V., Vijaya, T., Deville, A., Bodo, B., 2015. Structure elucidation and antioxidant activity of the phenolic compounds from Rhynchosia suaveolens. Natural Product Communications 10 (4), 1934578X1501000418.
Rao, V.S., Carvalho, A.C., Trevisan, M.T.S., Andrade, G.M., Júnior, H.V.N., Moraes, M.O., Santos, F.A., 2012. Mangiferin ameliorates 6-hydroxydopamineinduced cytotoxicity

and oxidative stress in ketamine model of schizophrenia. Pharmacol. Rep. 64 (4), 848–856.
Rashid, K., Sil, P.C., 2016. Identification and extraction of antidiabetic antioxidants from natural sources. Discovery & Development of Antidiabetic Agents from Natural Products: Natural Product Drug Discovery 63.
Regier, D.A., Rae, D.S., Narrow, W.E., Kaelber, C.T., Schatzberg, A.F., 1998. Prevalence of anxiety disorders and their comorbidity with mood and addictive disorders. Br. J. Psychiatr. 173 (S34), 24–28.
Rensink, A.A., Otte-Höller, I., de Boer, R., Bosch, R.R., Hans, J., de Waal, R.M., Kremer, B., 2004. Insulin inhibits amyloid β-induced cell death in cultured human brain pericytes. Neurobiol. Aging 25 (1), 93–103.
Resnick, S.M., Pham, D.L., Kraut, M.A., Zonderman, A.B., Davatzikos, C., 2003. Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. J. Neurosci. 23 (8), 3295–3301.
Rhie, S.J., Jung, E.Y., Shim, I., 2020. The role of neuroinflammation on pathogenesis of affective disorders. J. Exercise Rehabilitation 16 (1), 2–9.
Riascos, D., De Leon, D., Baker-Nigh, A., Nicholas, A., Yukhananov, R., Bu, J., Geula, C., 2011. Age-related loss of calcium buffering and selective neuronal vulnerability in Alzheimer's disease. Acta Neuropathol. 122 (5), 565.
Ribe, E.M., Lovestone, S., 2016. Insulin signalling in Alzheimer' s disease and diabetes: from epidemiology to molecular links. J. Intern. Med. 280 (5), 430–442.
Richardson, P.M., 1984. The taxonomic significance of xanthones in ferns. Biochem. Systemat. Ecol. 12 (1), 1–6.
Rocha, N.P., de Miranda, A.S., Teixeira, A.L., 2015. Insights into neuroinflammation in Parkinson's disease: from biomarkers to anti-inflammatory based therapies. BioMed Res. Int. 2015.
Rodríguez, J., Di Pierro, D., Gioia, M., Monaco, S., Delgado, R., Coletta, M., Marini, S., 2006. Effects of a natural extract from Mangifera indica L, and its active compound, mangiferin, on energy state and lipid peroxidation of red blood cells. Biochim. Biophys. Acta Gen. Subj. 1760 (9), 1333–1342.
Rodriguez-Pallares, J., Parga, J.A., Muñoz, A., Rey, P., Guerra, M.J., Labandeira-Garcia, J.L., 2007. Mechanism of 6-hydroxydopamine neurotoxicity: the role of NADPH oxidase and microglial activation in 6-hydroxydopamine-induced degeneration of dopaminergic neurons. J. Neurochem. 103 (1), 145–156.
Saleh, N.A.M., El–Ansari, M.A.I., 1975. Polyphenolics of twenty local varieties of Mangifera indica. Planta Med. 28 (6), 124–130.
Salim, S., Chugh, G., Asghar, M., 2012. Inflammation in anxiety. Advances in Protein Chemistry & Structural Biology 88, 1–25.
Salvi, A., Brühlmann, C., Migliavacca, E., Carrupt, P.A., Hostettmann, K., Testa, B., 2002. Protein protection by antioxidants: development of a convenient assay and structure-activity relationships of natural polyphenols. Helv. Chim. Acta 85 (3), 867–881.
Sánchez, G.M., Candelario-Jalil, E., Giuliani, A., León, O.S., Sam, S., Delgado, R., Núñez Sellés, A.J., 2001. Mangifera indica L. extract (QF808) reduces ischaemia-induced neuronal loss and oxidative damage in the gerbil brain. Free Radic. Res. 35 (5), 465–473.
Sato, T., Kawamoto, A., Tamura, A., Tatsumi, Y., Fujii, T., 1992. Mechanism of antioxidant action of pueraria glycoside (PG)-1 (an isoflavonoid) and mangiferin (a xanthonoid). Chem. Pharmaceut. Bull. 40 (3), 721–724.
Sawynok, J., 2003. Topical and peripherally acting analgesics. Pharmacol. Rev. 55 (1), 1–20.
Schapira, K., Roth, M., Kerr, T.A., Gurney, C., 1972. The prognosis of affective disorders: the differentiation of anxiety states from depressive illnesses. Br. J. Psychiatr. 121 (561), 175–181.
Schon, E.A., Przedborski, S., 2011. Mitochondria: the next (neurode) generation. Neuron 70 (6), 1033–1053.
Sekar, M., 2015. Molecules of interest–mangiferin–A review. Annual Research & Review in Biology 307–320.
Selkoe, D.J., 2002. Alzheimer's disease is a synaptic failure. Science 298 (5594), 789–791.
Sellamuthu, P.S., Arulselvan, P., Kamalraj, S., Fakurazi, S., Kandasamy, M., 2013. Protective nature of mangiferin on oxidative stress and antioxidant status in tissues of streptozotocin-induced diabetic rats. ISRN Pharmacology 2013.
Sethiya, N.K., Nahata, A., Dixit, V.K., 2010. Anxiolytic activity of Canscora decussata in albino rats. J. Compl. Integr. Med. 7 (1), 19.
Sethiya, N.K., Nahata, A., Dixit, V.K., Mishra, S.H., 2012. Cognition boosting effect of canscora decussata (a South Indian Shankhpushpi). Eur. J. Integrative Med. 4 (1), e113–e121.
Sethiya, N.K., Nahata, A., Mishra, S.H., Dixit, V.K., 2009. An update on Shankhpushpi, a cognition-boosting Ayurvedic medicine. Zhong Xi Yi Jie He Xue Bao 7 (11), 1001–1022.
Shan, T., Ma, Q., Guo, K., Liu, J., Li, W., Wang, F., Wu, E., 2011. Xanthones from mangosteen extracts as natural chemopreventive agents: potential anticancer drugs. Curr. Mol. Med. 11 (8), 666–677.
Shankar, S., Teyler, T.J., Robbins, N., 1998. Aging differentially alters forms of long-term potentiation in rat hippocampal area CA1. J. Neurophysiol. 79 (1), 334–341.
Sherer, T.B., Betarbet, R., Testa, C.M., Seo, B.B., Richardson, J.R., Kim, J.H., Miller, G.W., Yagi, T., Matsuno-Yagi, A., Greenamyre, J.T., 2003. Mechanism of toxicity in rotenone models of Parkinson's disease. J. Neurosci.: The Official Journal of the Society for Neuroscience 23 (34), 10756–10764.
Sian, J., Youdim, M.B.H., Riederer, P., et al., 1999. MPTP-induced parkinsonian syndrome. In: Siegel, G.J., Agranoff, B.W., Albers, R.W., et al. (Eds.), Basic Neurochemistry: Molecular, Cellular and Medical Aspects, sixth ed. *Lippincott-Raven, Philadelphia*.
Simola, N., Morelli, M., Carta, A.R., 2007. The 6-hydroxydopamine model of Parkinson's disease. Neurotox. Res. 11 (3–4), 151–167.
Siswanto, S., Arozal, W., Juniantito, V., Grace, A., Agustini, F.D., 2016. The effect of mangiferin against brain damage caused by oxidative stress and inflammation induced by doxorubicin. HAYATI J. Biosci. 23 (2), 51–55.
Smith, D.G., Cappai, R., Barnham, K.J., 2007. The redox chemistry of the Alzheimer's disease amyloid β peptide. Biochim. Biophys. Acta Biomembr. 1768 (8), 1976–1990.
Sohal, R.S., Sohal, B.H., 1991. Hydrogen peroxide release by mitochondria increases during aging. Mech. Ageing Dev. 57 (2), 187–202.
Sohal, R.S., Ku, H.H., Agarwal, S., Forster, M.J., Lal, H., 1994. Oxidative damage, mitochondrial oxidant generation and antioxidant defenses during aging and in response to food restriction in the mouse. Mech. Ageing Dev. 74 (1), 121–133.
Stoilova, I., Gargova, S., Stoyanova, A., Ho, I., 2005. Antimicrobial and antioxidant activity of the polyphenol mangiferin. Herba Pol. 1 (51).
Stoilova, I., Jirovetz, L., Stoyanova, A., Krastanov, A., Gargova, S., Ho, L., 2008. Antioxidant activity of the polyphenol mangiferin. EJEAFChe 7 (13), 2706–2716.
Takeda, T., Hosokawa, M., Higuchi, K., 1997. Senescence-accelerated mouse (SAM): a novel murine model of senescence. Exp. Gerontol. 32 (1–2), 105–109.
Tamagno, E., Parola, M., Guglielmotto, M., Santoro, G., Bardini, P., Marra, L., Danni, O., 2003. Multiple signaling events in amyloid β-induced, oxidative stress-dependent neuronal apoptosis. Free Radical Biol. Med. 35 (1), 45–58.
Tangah, J., Bajau, F.E., Jilimin, W., Chan, H.T., Wong, S.K., Chan, E.W.C., 2017. Phytochemistry and pharmacology of Mangifera pajang: an iconic fruit of Sabah, Malaysia. Sys. Rev. Pharm. 8 (1), 86.
Tanner, C.M., 2003. Is the cause of Parkinson's disease environmental or hereditary? Evidence from twin studies. Adv. Neurol. 91, 133.
Tatton, W.G., Olanow, C.W., 1999. Apoptosis in neurodegenerative diseases: the role of mitochondria. Biochim. Biophys. Acta Bioenerg. 1410 (2), 195–213.
Telang, M., Dhulap, S., Mandhare, A., Hirwani, R., 2013. Therapeutic and cosmetic applications of mangiferin: a patent review. Expert Opin. Ther. Pat. 23 (12), 1561–1580.
Terry, R.D., Masliah, E., Salmon, D.P., Butters, N., DeTeresa, R., Hill, R., Katzman, R., 1991. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann. Neurol.: Offi. J. Am. Neurol. Assoc. the Child Neurol. Soc. 30 (4), 572–580.
Testa, C.M., Sherer, T.B., Greenamyre, J.T., 2005. Rotenone induces oxidative stress and dopaminergic neuron damage in organotypic substantia nigra cultures. Brain Res. 134 (1), 109–118.
Thibault, O., Landfield, P.W., 1996. Increase in single L-type calcium channels in hippocampal neurons during aging. Science 272 (5264), 1017–1020.
Toescu, E.C., Vreugdenhil, M., 2010. Calcium and normal brain ageing. Cell Calcium 47, 158–164.
Toescu, E.C., Verkhratsky, A., 2004. Ca2+ and mitochondria as substrates for deficits in synaptic plasticity in normal brain ageing. J. Cell Mol. Med. 8 (2), 181–190.
Tsuboi, K., Kimber, T.A., Shults, C.W., 2000. Calretinin-containing axons and neurons are resistant to an intrastriatal 6-hydroxydopamine lesion. Brain Res. 866 (1–2), 55–64.
Valko, M., Leibfritz, D., Moncol, J., Cronin, M.T., Mazur, M., Telser, J., 2007. Free radicals and antioxidants in normal physiological functions and human disease. Int. J. Biochem. Cell Biol. 39 (1), 44–84.
Van Den Eeden, S.K., Tanner, C.M., Bernstein, A.L., Fross, R.D., Leimpeter, A., Bloch, D. A., Nelson, L.M., 2003. Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. Am. J. Epidemiol. 157 (11), 1015–1022.
Van Houten, B., Woshner, V., Santos, J.H., 2006. Role of mitochondrial DNA in toxic responses to oxidative stress. DNA Repair 5 (2), 145–152.
Vane, J.R., Bakhle, Y.S., Botting, R.M., 1998. Cyclooxygenases 1 and 2. Annu. Rev. Pharmacol. Toxicol. 38 (1), 97–120.
Ved, R., Saha, S., Westlund, B., Perier, C., Burnam, L., Sluder, A., Liu, L., 2005. Similar patterns of mitochondrial vulnerability and rescue induced by genetic modification of α-synuclein, parkin, and DJ-1 in Caenorhabditis elegans. J. Biol. Chem. 280 (52), 42655–42668.
Vercesi, A.E., Kowaltowski, A.J., Grijalba, M.T., Meinicke, A.R., Castilho, R.F., 1997. The role of reactive oxygen species in mitochondrial permeability transition. Biosci. Rep. 17 (1), 43–52.
Vollmayr, B., Henn, F.A., 2003. Stress models of depression. Clin. Neurosci. Res. 3 (4–5), 245–251.
Von Bernhardi, R., Eugenín-von Bernhardi, L., Eugenín, J., 2015. Microglial cell dysregulation in brain aging and neurodegeneration. Front. Aging Neurosci. 7, 124.
Wake, H., Moorhouse, A.J., Jinno, S., Kohsaka, S., Nabekura, J., 2009. Resting microglia directly monitor the functional state of synapses in vivo and determine the fate of ischemic terminals. J. Neurosci. 29 (13), 3974–3980.
Waldemar, G., Dubois, B., Emre, M., Georges, J., McKeith, I.G., Rossor, M., Winblad, B., 2007. Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. Eur. J. Neurol. 14 (1), e1–e26.
Walia, V., Gakkhar, A., Garg, M., 2019a. Parkinson's disease: a progressive disorder of the nervous system that affects movement. In: Handbook of Research on Critical Examinations of Neurodegenerative Disorders. IGI Global, pp. 252–273.
Walia, V., Garg, C., Garg, M., 2019b. NO-sGC-cGMP signaling influence the anxiolytic like effect of lithium in mice in light and dark box and elevated plus maze. Brain Res. 1704, 114–126.
Wang, H., Ye, G., Ma, C.H., Tang, Y.H., Fan, M.S., Li, Z.X., Huang, C.G., 2007. Identification and determination of four metabolites of mangiferin in rat urine. J. Pharmaceut. Biomed. Anal. 45 (5), 793–798.
Wang, M.J., Huang, H.Y., Chen, W.F., Chang, H.F., Kuo, J.S., 2010. Glycogen synthase kinase-3β inactivation inhibits tumor necrosis factor-α production in microglia by modulating nuclear factor κB and MLK3/JNK signaling cascades. J. Neuroinflammation 7 (1), 99.

Ward, R.J., Dexter, D.T., Crichton, R.R., 2015. Ageing, neuroinflammation and neurodegeneration. Front. Biosci. 7, 189–204.
Wegiel, J., Kuchna, I., Nowicki, K., Frackowiak, J., Mazur-Kolecka, B., Imaki, H., deleon, M., 2007. Intraneuronal Aβ immunoreactivity is not a predictor of brain amyloidosis-β or neurofibrillary degeneration. Acta Neuropathol. 113 (4), 389–402.
Wei, M.C., Zong, W.X., Cheng, E.H.Y., Lindsten, T., Panoutsakopoulou, V., Ross, A.J., Korsmeyer, S.J., 2001. Proapoptotic BAX and BAK: a requisite gateway to mitochondrial dysfunction and death. Science 292 (5517), 727–730.
Wei, X., Liang, D., Wang, Q., Meng, X., Li, Z., 2016. Total synthesis of mangiferin, homomangiferin, and neomangiferin. Org. Biomol. Chem. 14 (37), 8821–8831.
Wong, M.L., Licinio, J., 2004. From monoamines to genomic targets: a paradigm shift for drug discovery in depression. Nat. Rev. Drug Discov. 3 (2), 136–151.
Wong, M.L., Rettori, V., Amer, A.S., Bongiorno, P.B., Canteros, G., McCann, S.M., Licinio, J., 1996. Inducible nitric oxide synthase gene expression in the brain during systemic inflammation. Nat. Med. 2 (5), 581–584.
Wong, T.P., Debeir, T., Duff, K., Cuello, A.C., 1999. Reorganization of cholinergic terminals in the cerebral cortex and hippocampus in transgenic mice carrying mutated presenilin-1 and amyloid precursor protein transgenes. J. Neurosci. 19 (7), 2706–2716.
Wu, J.F., Chen, S.B., Gao, J.C., Song, H.L., Wu, L.J., Chen, S.L., Tu, P.F., 2008. Xanthone glycosides from herbs of Polygala hongkongensis Hemsl and their antioxidant activities. J. Asian Nat. Prod. Res. 10 (7), 665–670.
Xie, Q.W., Kashiwabara, Y., Nathan, C., 1994. Role of transcription factor NF-kappa B/Rel in induction of nitric oxide synthase. J. Biol. Chem. 269 (7), 4705–4708.
Yaksh, T.L., Rudy, T.A., 1976. Analgesia mediated by a direct spinal action of narcotics. Science 192 (4246), 1357–1358.
Yamada, T., McGeer, P.L., Baimbridge, K.G., McGeer, E.G., 1990. Relative sparing in Parkinson's disease of substantia nigra dopamine neurons containing calbindin-D28K. Brain Res. 526, 303–307.
Yamada, T., McGeer, P.L., McGeer, E.G., 1992. Lewy bodies in Parkinson's disease are recognized by antibodies to complement proteins. Acta Neuropathol. 84 (1), 100–104.
Yamagata, K., Andreasson, K.I., Kaufmann, W.E., Barnes, C.A., Worley, P.F., 1993. Expression of a mitogen-inducible cyclooxygenase in brain neurons: regulation by synaptic activity and glucocorticoids. Neuron 11 (2), 371–386.
Yamamoto, M., Kiyota, T., Walsh, S.M., Liu, J., Kipnis, J., Ikezu, T., 2008. Cytokine-mediated inhibition of fibrillar amyloid-β peptide degradation by human mononuclear phagocytes. J. Immunol. 181 (6), 3877–3886.
Yang, X., Zhao, Y., Chen, Y., Liao, X., Gao, C., Xiao, D., Yang, B., 2013. Host–guest inclusion system of mangiferin with β-cyclodextrin and its derivatives. Mater. Sci. Eng. C 33 (4), 2386–2391.
Yang, Z., Weian, C., Susu, H., Hanmin, W., 2016. Protective effects of mangiferin on cerebral ischemia–reperfusion injury and its mechanisms. Eur. J. Pharmacol. 771, 145–151.
Zajac, D., Stasinska, A., Delgado, R., Pokorski, M., 2013. Mangiferin and its traversal into the brain. In Respiratory Regulation-The Molecular Approach 105–111.
Zelcer, N., Khanlou, N., Clare, R., Jiang, Q., Reed-Geaghan, E.G., Landreth, G.E., Tontonoz, P., 2007. Attenuation of neuroinflammation and Alzheimer's disease pathology by liver x receptors. Proc. Natl. Acad. Sci. Unit. States Am. 104 (25), 10601–10606.
Zelko, I.N., Mariani, T.J., Folz, R.J., 2002. Superoxide dismutase multigene family: a comparison of the CuZn-SOD (SOD1), Mn-SOD (SOD2), and EC-SOD (SOD3) gene structures, evolution, and expression. Free Radical Biol. Med. 33 (3), 337–349.
Zhang, H., Hou, Y., Liu, Y., Yu, X., Li, B., Cui, H., 2010. Determination of mangiferin in rat eyes and pharmacokinetic study in plasma after oral administration of mangiferin-hydroxypropyl-beta-cyclodextrin inclusion. J. Ocul. Pharmacol. Therapeut. 26 (4), 319–324.
Zhang, H.Y., 2005. One compound multiple targets strategy to combat Alzheimers disease. FEBS (Fed. Eur. Biochem. Soc.) Lett. 579, 5260–5264.
Zhang, Q., Kong, X., Yuan, H., Guan, H., Li, Y., Niu, Y., 2019. Mangiferin improved palmitate-induced-insulin resistance by promoting free fatty acid metabolism in HepG2 and C2C12 cells via PPARα: mangiferin improved insulin resistance. J. Diabetes Res. 2019, 2052675.
Zhang, W., Wang, T., Pei, Z., Miller, D.S., Wu, X., Block, M.L., Zhang, J., 2005. Aggregated α-synuclein activates microglia: a process leading to disease progression in Parkinson's disease. Faseb. J. 19 (6), 533–542.
Zhao, Y., Ma, R., Shen, J., Su, H., Xing, D., Du, L., 2008. A mouse model of depression induced by repeated corticosterone injections. Eur. J. Pharmacol. 581 (1–2), 113–120.
Zhi-quan, W., Jia-gang, D., Li, Y., 2011. Pharmacological effects of mangiferin. Chinese Herbal Med. 3 (4), 266–271.
Zhou, L., Pan, Y., Chonan, R., Batey, R., Rong, X., Yamahara, J., Wang, J., Li, Y., 2016. Mitigation of insulin resistance by mangiferin in a rat model of fructose-induced metabolic syndrome is associated with modulation of CD36 redistribution in the skeletal muscle. J. Pharmacol. Exp. Therapeut. 356 (1), 74–84.
Zilka, N., Kazmerova, Z., Jadhav, S., Neradil, P., Madari, A., Obetkova, D., Novak, M., 2012. Who fans the flames of Alzheimer's disease brains? Misfolded tau on the crossroad of neurodegenerative and inflammatory pathways. J. Neuroinflammation 9 (1), 47.