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MORIN HYDRATE: A PROMISING BIOFLAVONOID WITH DIFFERENT THERAPEUTIC EFFECTS

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Flavonoids are bioactive compounds derived from plants that significantly influence the health of individuals. Morin hydrate (MH) is a bioactive compound of botanical origin easily available in various plants' leaves, stems, fruits, and branches of the family Moraceae. MH can exert a beneficial impact on various disorders, owing to its antioxidative, anti-inflammatory, antidiabetic, cardioprotective, anti-arthritis, anti-tumor, nephroprotective, and protective effects in many neurodegenerative diseases. In many cases, MH exhibits systemic protective effects, mitigating the adverse effects of various medications without compromising their efficacy. It exhibits these potential pharmacological actions through different mechanisms such as influencing the activity of various enzymes, scavenging free radicals, enhancing or reducing the level of various inflammatory mediators, increasing or decreasing the expression of many proteins, and boosting or suppressing a variety of intracellular signaling cascades. Several findings indicate that MH can prevent a variety of human pathologies, either on its own or in conjunction with other medications. Moreover, many studies performed in vivo and in vitro showed that MH has very low toxicity levels and is well tolerated when taken over an extended period. This article presents recent studies on the biological and pharmacological properties, as well as the molecular mechanisms of MH to elucidate its many positive health impacts.

***Keywords**: Morin hydrate (MH), Flavonoids, Antioxidant, Anti-diabetic, Anti-inflammatory*

INTRODUCTION

Bioactive compounds derived from dietary plants and fruits have a growing attention recently owing to their potential to prevent numerous chronic diseases' complications with insignificant adverse effects[1]. MH (3,5,7,2′,4′-pentahydroxyflavone), is a member of the flavonoid family which has been separated as a yellow pigment[2, 3]. It is one of the essential components of many botanical preparations and has been suggested by traditional medicine to treat several human illnesses[4]. MH is considered a potentially effective therapeutic compound due to its antioxidant and anti-inflammatory properties[5-7]. MH is mainly found in plants of Moraceae, Rosaceae, and Fagaceae families. It mostly appears in Osage orange (*Maclura pomifera*), onion (*Allium cepa*), guava leaves (*Psidium guajava L.*), almond hulls, apple skin (*Malus pumila*), mill (*Prunus dulcis*), white mulberry (*Morus alba L.*), red wine, old fustic (*Maclura Tinctoria*), jackfruit (*Artocarpus heterophyllus*), seaweeds, coffee, tea, cereals and a variety of beverages[2, 3] **Fig. 1**.

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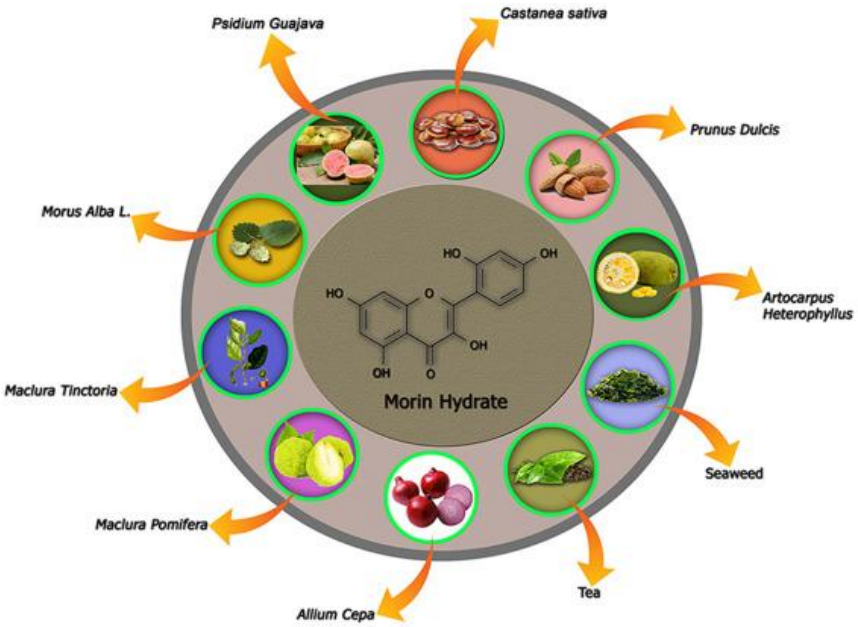

Fig. 1: Showing possible natural sources of MH[8].

Chemical structure

MH is a member of the flavonol class that has a 3-hydroxyflavon base and there are additionally three more hydroxy substituents at positions 2′, 4′, and 5 of this 7-hydroxy flavonol **Fig. 2**.

Physical properties

MH is a stable compound with a yellow color that has a bitter taste. It has a high solubility in alcohol, poor solubility in acetic acid and ether, good solubility in methanol and alkaline aqueous solutions, and moderate solubility in water emulsion[10]. In addition, the MH exact mass is 302.042653 g/mol, and its molecular weight is 302.2357 g/mol[9].

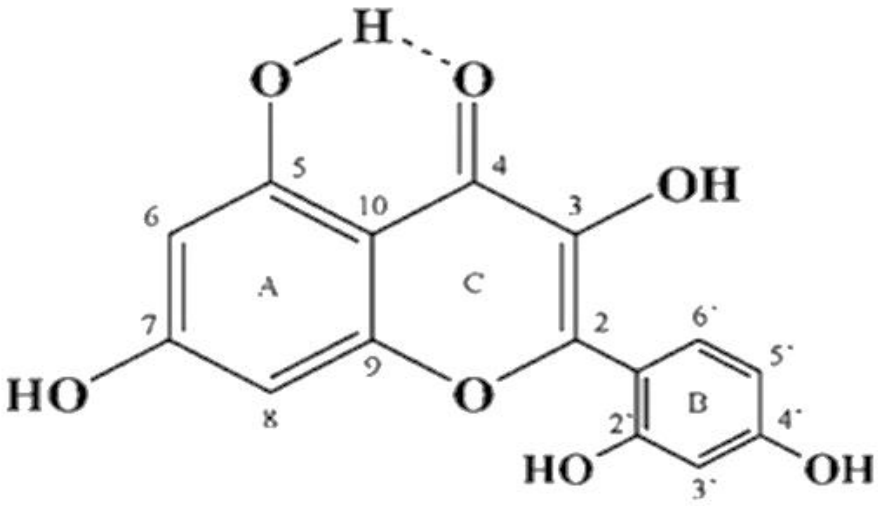

Fig. 2: Represents MH molecular structure [9].

Pharmacokinetics

Absorption

MH solubility and stability are two critical criteria for understanding the MH absorption profile. It has been shown that the solubility of MH is mainly dependent on the PH of the solvent used[11] so it is important to illustrate the effect of PH on MH solubility as the stomach and intestine are considered the main sites of its absorption. MH has low solubility in acidic to neutral medium due to the protonation or chelation with metal ions of the ring's B hydroxyl groups at positions 2' and 4' and the ring's C 3-OH group[12]. While, it is more readily soluble in basic medium which is mainly attributed to the deprotonation of ring's B hydroxyl groups at C7 of the benzoyl ring which generating MH molecules with more negatively charged species that responsible for its high solubility in basic PH[13]. Due to this low solubility of MH in aqueous solutions, a low oral bioavailability is observed and this sheds light on developing more formulation of MH to enhance its oral bioavailability[14]. The stability of MH is mainly affected by the PH and light more than temperature since MH has a low degradation rate in acidic and neutral mediums while rapid degradation was observed in basic medium[15]. Also, MH shows high stability in room temperature and dark conditions, while it is highly degraded in light condition[16, 17]. Another contributing factor to MH's low oral bioavailability is that it is subjected to intestinal and hepatic first-pass metabolism, leading to its rapid clearance *in vivo* with an insufficient plasma level for clinical efficacy[18]. Also, Multidrug Resistance-Associated Protein-1(MRAP-1), a transporter protein widely present on intestinal cell membranes which allows MH efflux, is primarily responsible for MH limited bioavailability[19].

Distribution

Once MH is orally ingested, it passes through the stomach unchanged and reaches the small intestine in the form of glycosylated, methylated, and sulfated derivatives. These derivatives of MH or free forms enter the gut, where they are transformed into their corresponding aglycone form by intestinal enzymes[20, 21], which allows the derivatives to be easily absorbed from the intestine. These absorbable aglycone derivatives bind with specific transport proteins, enabling them to pass from circulation through cell membranes more readily[22]. Based on several observations, regulation of MH intestinal absorption is accomplished by an energy-driven transport system that carries MH from the circulation into the interior of the cell, this energy-driven transport system is confirmed by a study on mammalian endothelial cells[23, 24]. The low intestinal permeability of MH is confirmed by various studies using human Caco-2 cells[19]. It was previously reported that MH, following IV injections, possesses a very short half-life (30 min) in the plasma[25].

Metabolism and Elimination

After phase I metabolism, MH substrates undergo phase II metabolism, and the major metabolites of this phase are in the form of glucuronides and sulfate conjugates. This may be accomplished by the action of several enzymes including intestinal and hepatic enzymes (glucuronyl transferase and sulfotransferase) for phase II metabolism or hepatic cytochrome P450 enzymes (CYPs) that catalyze phase I metabolism[26]. The unabsorbed portions of MH are also converted to the absorbable aglycone form but through the action of the large intestine's bacteria[2]. MH also has a modulating effect on the transport proteins and may affect the kinetics of other drugs such as enhancement of the bioavailability of diltiazem, etoposide, nimodipine, and nicardipine which is mainly due to MH inhibitory effect of CYP isoenzymes (CYP3A4) and it can enhance the intestinal absorption of talinolol through the inhibition of P-gp[27]. The conjugates of MH are more soluble and readily detected in urine. This rapid excretion illustrates the reduced plasma half-life of MH[28, 29]. The overall kinetics of MH in human are showen in **Fig. 3**[30]**.**

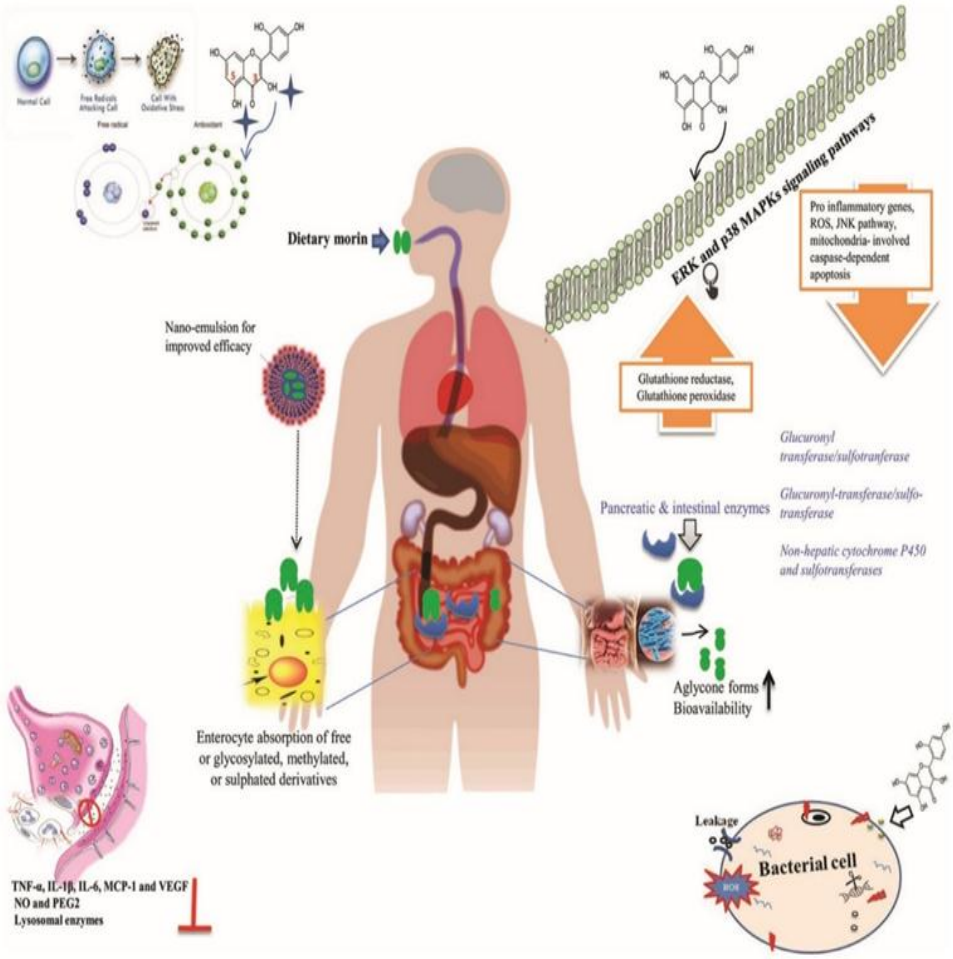

Fig. 3: Summarization of the kinetics of MH in human [30].

Mechanism of action

Antioxidant effects

Reactive oxygen species perform a crucial part in the signaling cascade that controls cellular homeostasis. There should be a balance between the cellular antioxidant enzyme activity and the formation of reactive oxygen species to maintain homeostasis within the cell. Damage of lipids, proteins, nucleic acids, and carbohydrates subsequently cell death occurs when the cellular antioxidant defense mechanism is disrupted by the overproduction of ROS[31, 32]. This oxidative damage of cells can be avoided through antioxidant enzymes that eliminate ROS and Nuclear factor-erythroid 2-related factor 2 (Nrf2)[33]. The antioxidant effect of MH owing to the existence of a double bond between the hydroxyl group and its C2-C3 atoms that act to activate the double bond of C-3. MH inhibition of lipid peroxidation is mainly due to ring's B two hydroxyl groups on the 2' and 4' positions. However, it appears that MH antiradical properties are due to the ring's B hydroxyl group at the 4' position[34-36]. The formation of a hydrogen bond between the ring's B hydroxyl group in position 2' and the oxygen atom in position 1 of the ring C causes a rotation of the ring B and takes a planar configuration regarding ring C[37, 38]. Concerning this arrangement, MH is an effective natural radical scavenger since it facilitates the transfer of electronic effects between the B ring and the C ring's double bond this was confirmed by Morales *et al* [39]. ROS is the major mechanism by which gentamicin causes cytotoxic effects. It triggers and maintains a persistent inflammatory response resulting in tubular necrosis[40]. In hepatic cells that received tert-butyl hydroperoxide, MH decreased ROS production and enhanced Nrf2 expression, along with its regulating genes HO-1 and NQO1this also been proved by Rizvi *et al.*[33]. *In vitro*, the investigation revealed that

through modulation of the Nrf2/ARE signaling cascade and enhancement of cellular antioxidants including superoxide dismutase (SOD) and catalase (CAT), MH protected pancreatic β-cells from DNA damage caused by oxidative stress[41]. According to these results, MH preserves Chinese hamster lung fibroblast V79-4 cells against DNA damage and death caused by mitochondrial dysfunction and overproduction of ROS. It also enhances heme oxygenase 1 (HO 1) gene expression that is linked to the overexpression and phosphorylation of Nrf2 and a suppression of Kelch-like ECH-associated protein 1 expression[42]. MH reduces intracellular overproduction of ROS, prevents DNA damage, reduces the production of pro-apoptotic proteins, and maintains mitochondrial function in rats' hepatic cells this has been indicated by Kapoor *et al.*[43]. Along with these findings, recent in vivo investigations show the use of 100 mg/kg b.w. of MH treatment preserves the rat liver against oxidative damage following cyclophosphamide[44]. Ray *et al.* had similar results with rabbits receiving cyclophosphamide/flutamide therapy. MH ceases the rise in cholesterol along with protecting against oxidative stress[45].

Anti-inflammatory effects

Chronic inflammation causes exacerbation of many pathologies like neurodegenerative disorders, diabetes, cancer, cardiovascular disease, and chronic bowel diseases[46]. Inflammation is modulated by a variety of pro-inflammatory agents, including transcription factors, chemokines, cytokines, and enzymes[47, 48]. Numerous studies show that MH serves as an efficient anti-inflammatory drug[49, 50]. According to prior *In vivo* study, MH can maintain intestinal cells from damage as it decreases the intestinal levels of IL-4 and MDA with less granulocyte infiltration in the mucosa of the intestine and alleviates colitis caused by trinitrobenzene sulfonic acid[51]. MH lowers proinflammatory mediators mRNA expression such as (TNF-α, IL-1β, COX-2, and IL-2) thus reducing the inflammation triggered by midbrain carotid artery occlusion (MCAO) in cerebral ischemic rats this has been proven by Chen *et al*[52]. In the LPS-mastitis model *in vivo* and peritoneal macrophages *in vitro* MH reduces mammary gland tissue damage through a dramatic reduction of levels of TNF-α, IL-1β, and IL-6 and MPO activity in mammary gland tissues and suppression of NF-κB and NLRP3 inflammasome signaling cascade[53]. In LPS-stimulated bovine mammary epithelial cells (bMEC), MH suppresses the activation of (NF-κB), p38, inhibitory kappa B (IκBα) protein, and extracellular signal-regulated kinase (ERK) and downregulates TNF-α, IL-6, and IL-1β expressions[54]. In chronic airway inflammation by ovalbumin, MH *in vivo* reduces the elevation of intracellular production of ROS, inflammatory mediators such as TNF-α, IL-4, MDA, IgE, and matrix metalloproteinase-9, and the percentage of inflammatory cells recruited into (BALF) preventing them from infiltrating the blood vessels and respiratory tracts and *in vitro*, it reduces the levels of proteins like IL-8, intercellular adhesion molecule-1, and phosphorylation of MAPK, suggesting that this cascade ROS/MAPK is the MH key mechanism in reducing inflammation of the airway as previously proved by Ma *et al.* [55]. *In vivo*, MH reduces inflammation and hepatic damage via suppression of NF-kB, iNOS, TNF-α, IL-1β, and IL-6 protein expression[56] **Fig. 4**.

Therapeutic potential

Anticancer effect

Evidence has shown that combining novel biologically active compounds with safe, natural therapeutic benefits is an effective strategy for treating different tumor types[57, 58]. Since oxidative stress can trigger cancer thus, the most recent research has proposed using novel antioxidants as a main natural cancer treatment strategy[59]. Flavonoids including MH are important naturally occurring antioxidants exhibiting significant anti-cancer effects[60, 61]. However, the use of MH in some cancers (*in vitro* and *in vivo* studies) is illustrated in **Table 1.**

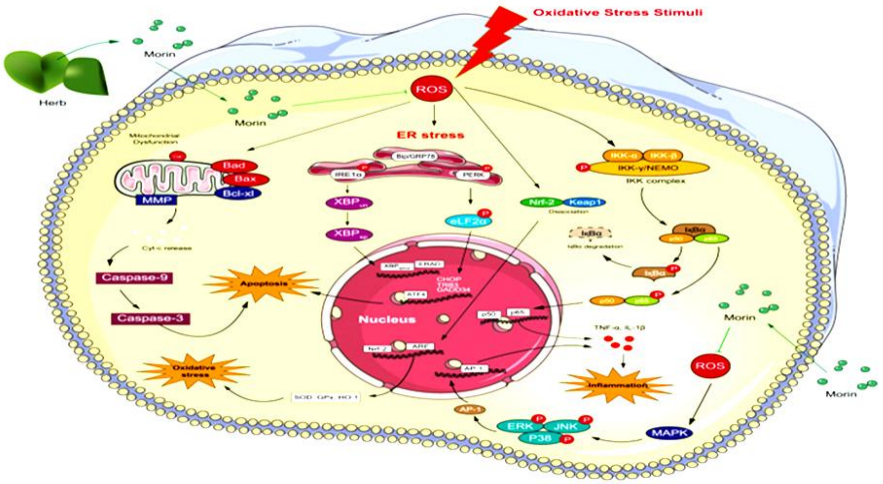

Fig. 4: Shows the MH impact on reducing oxidative stress, apoptosis, and inflammation on a molecular basis[8].

Table 1: The use of MH in cancers (in vitro and in vivo studies)

Cancer type	Aim of the study	Outcomes
Breast cancer	MH role in 7, 12 dimethyl benz(a)anthracene (DMBA)-mammary carcinoma[62].	Inhibition upregulation of Bcl-2 and downregulation of Bax. Downregulation of NF-κB and pro-inflammatory markers including IL-1β, COX-2, TNF-α, and IL-2.
Ovarian cancer	Examine ovarian cancer growth and observe the tumor progression[63].	Mitigation of the growth of ovarian cancer through modulation of the NF-κB pathway, reduction in the tumor size, and inhibition of the inflammatory response.
Colorectal cancer	Explore MH chemo-preventive mechanism in dimethylhydrazine (DMH) colon cancer[64].	Suppression of the NF-κB pathway and its linked inflammatory mediators, including TNF-α, IL-6, COX-2, and PGE-2.
Liver cancer	Investigation of MH anti-cancer effect in rats received hepatocarcinogen diethyl nitrosamine (DEN) to induce liver cancer[65].	Decreased COX-2 and NF-κB-p65 protein expression, thus inhibiting inflammation and angiogenesis. Diminished matrix metalloproteins such as MMP-2 and MMP-9 levels.
Lung cancer	Investigating the impact of MH on A549 lung cancer cell line[66].	MH exhibits anti-tumor activity through suppression of MicroRNAs (miR-135b) expression, which specifically targets and inhibits the (cyclin G2) CCNG2 tumor suppressor gene.
Bladder cancer	Shin *et al*. investigated MH's impact on the EJ bladder cancer cell line and its underlying molecular mechanism[67].	G1-phase cell cycle arrest through downregulation of cyclin D1, cyclin E, CDK2, and CDK4 expression Inhibition of cell migration and invasion through AP-1, Sp-1, and NF-κB binding suppression. It decreases MMP-9 expression.
Prostate cancer	Investigate MH-enhancing effect on prostate cancer cells' chemo-sensitivity to paclitaxel and its molecular mechanism[68].	Suppression in cell viability in the cells treated with paclitaxel. Promoting prostate cancer cells' chemo-sensitivity to paclitaxel through downregulation of miR-155 expression a suppressor of GATA binding protein 3 (GATA3), thus restoring GATA3 expression.

Hepatoprotective effect

It has been found in CCl4-induced liver fibrosis that MH causes alleviation of liver fibrosis with less fiber tissue enlargement. Upregulation of Nrf2 and its related downstream antioxidant factors (HO-1 and NQO1) while downregulation of protein expression of α-SMA, collagen I, and collagen III[69]. MH has been found to suppress toll-like receptor 4 (TLR4) and the triggering receptor expressed on myeloid cells-1 (TREM-1) signaling cascades and enhance the expression of antioxidant proteins HO-1 and Nrf2[70]. Furthermore, MH reduces the inflammation in the damaged livers by (CCl4) through a reduction in levels of TNF-α, IL-1β, and IL-6 and the NF-κB) p65 and inhibitor of kappa B α (IκBα) expression this has also been proved by Li *et al.* [70]. MH in liver fibrosis triggered by (CCl4) causes a reduction in serum biomarkers of liver function and the liver index which was elevated by long-term CCl4 exposure. It also restored the hepatic GSH to normal and reduced hepatic levels of NO, MDA, and TNF-α. Furthermore, it downregulates NF-κB and iNOS protein expression[71].

Neuroprotective effect

A previous study indicates MH neuroprotective properties in Parkinson's disease and proposes that it can be beneficial in such neurodegenerative diseases this also has been confirmed by Zhang *et al.*[72]. MH decreased activation of astrocytes mediated by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), protected against dopaminergic neuronal losses in the substantia nigra and striatum, and improved motor dysfunction. Additionally, *in vitro*, MH protected primary cultured neurons against disruption of the mitochondrial membrane potential (MMP) and decreased ROS production and NF-κB activation mediated by 1-methyl-4-phenylpyridine (MPP+) as previously indicated by Lee *et al* [73]. In a different study, MH causes restoring the antioxidant defense balance through a decrease in MDA content, an increase in antioxidant levels (GSH, and Gpx), and SOD activity, improving neurological deficiencies, upregulating Bcl-2, downregulating proinflammatory cytokines, Bax, and caspase-3 mRNA expression, and alleviating focal cerebral ischemia induced by midbrain carotid artery occlusion (MCAO)[52]. Moreover, MH prevents oxidative stress, poly (ADP) ribose polymerase(PARP) over-activation, and neuroinflammation in peripheral neuropathy[74]. In addition, a previous study showed that micellar nanocarriers containing MH significantly improved the memory of Wister rats with Alzheimer's disease induced by aluminum[75].

Nephroprotective effects

The kidney is the body's most essential organ which eliminates medication residue, heavy metals, undigested food remains, and metabolic wastes take place so toxic metabolic product intoxication occasionally results in renal damage[76]. In a rat model, MH showed protective effects against nephrotoxicity induced by mercury chloride[77]. Also, MH protects rats from gentamicin-induced nephrotoxicity and oxidative stress. It causes a significant decrease in renal function markers such as blood urea nitrogen (BUN) and serum creatinine (Scr) and restoring in the antioxidant defense balance through the reduction of ROS production while the increase in the CAT and SOD enzyme activity and GSH levels this has been proved by Jonnalagadda *et al* [78]. As mentioned before by Apaydin *et al.* MH pretreatment prevented hepatotoxic and nephrotoxic changes in cisplatin-intoxicated rats[79]. Additionally, MH causes alleviation of ER stress, inflammation, and autophagy mediated by cisplatin through suppression of poly (ADP-ribose) polymerase 1(PARP-1) gene expression, attenuation of inflammatory responses, and reducing oxidative stress with subsequent decrease in cellular death in HEK-293 cells and mice kidneys[80]. MH causes a reduction in CYP2E1, phospho-NF-κB p65, Bax, phospho-p53, cleaved caspase3, and phospho-P38MAPK activation, improvement of histopathological alterations and lowering of TNF-α and IL-1β levels in kidney damage by cisplatin these results also have been proved by Wei *et al.*[81]. Nephroprotective impact of MH in kidney injury caused by gentamicin has been accomplished by ameliorating the histopathological changes and the increase in serum levels of albumin, urea, uric

acid, creatinine, and K^+ in young male rats[82]. In an earlier study, MH ameliorated the kidney histopathological changes and reduced the elevated levels of uric acid and serum creatinine levels, thiobarbituric acid reactive substances (TBARS), non-protein sulfhydryl, and CAT activity in the rats' diabetic nephropathy in STZ-induced diabetes[83].

Anti-diabetic effect

Several complications in body organs and systems are impacted by diabetes[84]. It has been found that MH can serve as a beneficial therapeutic remedy in diabetes and this was investigated using HepG2 cells in which we observed a significant enhancement in the synthesis of glycogen, phosphorylation of the insulin and Akt receptors, and inhibition of glucose production[85]. In streptozotocin (STZ) diabetic rats, MH has been found to cause hepatic hexokinase and glucose-6-phosphate dehydrogenase enzyme activation while a decrease in fructose-1,6-bisphosphatase and glucose-6-phosphatase levels, improvement in serum insulin level with a reduction in blood glucose level, and preservation of the normal histological appearance of pancreatic islets[86]. MH enhanced the SOD and CAT activity, reduced the levels of inflammatory markers TNFα, IL1β, and IL-6 and thiobarbituric acid reactive substances, and also reduced fasting glucose with a significant increase in levels of serum insulin. Furthermore, there has been a significant increase in the brain's GSH and neurotrophic factors (BDNF, NGF, and IGF-1) this has been indicated by a previous study on the brain of STZ diabetic rats[87].

Cardioprotective effect

Cardiovascular diseases (CVD) have great attention nowadays as they are the most common cause of mortality worldwide. In isoproterenol-induced myocardial infarction owing to MH free radical scavenging and antioxidant properties, it exhibits cardiovascular protective effects[88]. In fatty diet hypertensive rats, MH positively impacted lipid profile, blood pressure, and serum glucose levels[89]. Moreover, MH modulates alterations in lipid peroxidation and lipid metabolism and mitigates changes in electrocardiogram and myocardial injury induced by isoproterenol in rats[90]. MH supplementation decreased MDA level while increasing GPx level and SOD and CAT enzyme activities as previously proved in deoxycorticosterone acetate heart-damaged rats by Prahalathan *et al*.[91]. Improvement of heart function in mitochondrial ischemia-reperfusion injury (MIRI) through downregulation the protein expression of caspase-3, apoptotic protease activating factor-1, caspase-9, cytochrome c, reduction myocardial infarction's size along with lowering LDH activity, inhibition of mitochondrial permeability transition pore (MPTP) opening, increased cell viability and reduced cell apoptosis, and prevention the reduction of mitochondrial membrane potential[92]. Cardioprotective effects of MH have been accomplished by improvement in cardiac function through restoring myocardial architecture, enhancing SOD and CAT activity, and reducing MDA levels while increasing GSH levels, modulating the MAPK/NF-kB/TNF-a pathway, and improving hemodynamic parameters in isoproterenol-induced myocardial injury[93]. Another *in vivo* investigation established the anti-atherosclerotic activity of MH through a decrease in lipid accumulation and plaque formation within atherosclerotic mice without significantly affecting body weight and reduction in serum levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, and triglycerides. It has been indicated that neither dosage of MH exhibited notable toxicity in the mice[7].

Effect of MH in lung diseases

The lung is the human body's essential organ for exchanging gases. Any damage to lung tissue's ability to function properly could result in potentially fatal scenarios.

Lung inflammation may be induced by cigarette smoke. One hour before cigarette smoke exposure, MH administration can lessen lung inflammation this has been accomplished by a reduction in MPO activity, MDA levels, P13K/ATK/NF-κB singling pathway activation, the levels of inflammatory mediators in the BALF, and the number of neutrophils, macrophages, and total cells. It improved lung physiological alterations[94]. Through MH antioxidative and free radical

scavenging activity restoring miRNA expression alterations and reducing $PM_{2.5}$-induced toxicity can be achieved[95]. In chronic asthma *in vivo*, MH causes a reduction of intracellular overproduction of ROS, inflammatory mediators such as TNF-α, IL-4, MDA, IgE, and matrix metalloproteinase-9, and the percentage of inflammatory cells recruited into (BALF) preventing them from infiltrating the blood vessels and respiratory tracts. *In vitro*, MH shows a reduction in the levels of proteins like IL-8, intercellular adhesion molecule-1, and phosphorylation of MAPK. It has been suggested that ROS/MAPK cascade is the MH key mechanism in reducing inflammation of the airway[55]. MH significantly enhanced SOD activity, suppressed MPO activity, and reduced the inflammation through downregulating of lung NLRP3 inflammasome protein, lowering the levels of TNF-α, IL-1β, IL-18, and IL-6, and reducing the number of inflammatory cells in the BALF. indicating its beneficial impact on LPS-induced acute lung injury (ALI)[50].

Anti-arthritic effect

In vivo, in IL-1β-induced osteoarthritis, MH reduces inflammation through inhibition of gene expression of NF-κB, iNOS, and COX-2 and preventing NO and PGE2 production[96]. *In vivo*, MH suppressed cartilage degradation and hindered phosphorylation of p38 and extracellular signal-regulated kinase. Downregulation of matrix metalloproteinase (MMP-3 and MMP-13) while upregulation of tissue inhibitors of metalloproteinase -1, in rat chondrocytes induced with IL-1β[97]. According to a prior study, MH suppresses angiogenesis and hinders the PI3K/Akt pathway via binding to and stimulating the peroxisome proliferator-activated receptor-γ (PPARγ) and boosting the expression of PTEN, a PPARγ target gene. These results have proved that PPARγ is the MH key mechanism in synovial angiogenesis inhibition and subsequent protection against arthritis[98].

Anti-bacterial and antiviral effects

MH has been proven to be an effective inhibitor of various microorganisms. It has been established that MH may reduce the virulence of *Staphylococcus aureus*, which is frequently responsible for skin infections that can develop into lethal septicemia, necrotizing pneumonia, and endocarditis[99]. Moreover, infected mice treated with MH showed reduced inflammation and protected the new cells from influenza virus infection[100]. Using an A/PR/8 infection murine model, a combination of oseltamivir and MH causes hemagglutination by A/PR/8 was decreased with the use of MH. It also improved A/PR/8-infection symptoms, decreased lung levels of TNF-α, IL-1β, and CCL2, and inhibited virus replication[100].

Role of MH in other diseases

MH has been indicated to have a significant beneficial impact on different diseases. As shown by a previous study, MH has been proven to protect the gastric mucosa from indomethacin-induced inflammation by modulating the NF-κβ signaling pathway[101]. Moreover, Jiang *et al*. suggested that Morin could mitigate LPS-induced mastitis by preserving the integrity of the blood-milk barrier through the modulation of tight junction protein expression and blocking of intracellular signaling cascades of NF-κB, NLRP3, MAPK, and PI3K/AKT[102]. However, **Fig. 5**[8] and **Table 2** summarize the potential pharmacological action of MH.

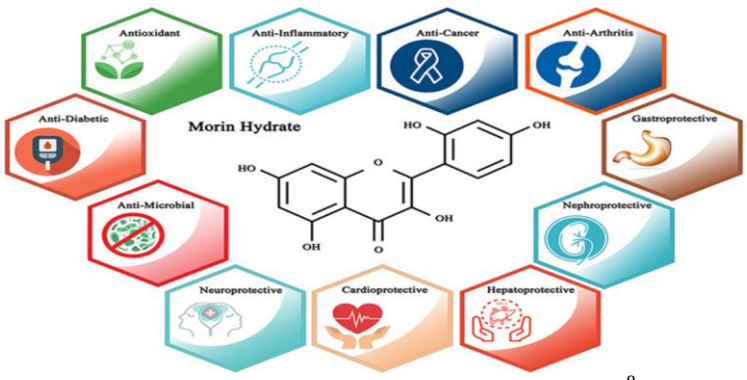

Fig. 5: Summary of MH pharmacological actions in preclinical studies[8].

Table 2: Summary of MH pharmacological actions in preclinical studies.

Pharmacological action of Morin hydrate	Aim of study	Outcomes
Hepatoprotective	1. The *in vivo* study aimed to assess MH effects on (DEN-induced) liver fibrosis rats, whereas the *in vitro* study investigated MH impacts on cultured LX-2 cells[103].	*In vivo*, downregulation of β-catenin, GSK-3β, and cyclin D1 protein expression.*in vitro*, inhibition of Wnt signaling and proliferation of cultured LX-2 cells along with induction of G1 cell cycle arrest.
	2. Explore MH impact on liver fibrosis in rats long-term exposed to CCL4[71].	Reduction in serum biomarkers of liver function and the liver index which was elevated by long-term CCl4 exposure. MH restored the hepatic GSH to normal and reduced hepatic levels of NO, MDA, and TNF-α. Furthermore, it downregulates NF-κB and iNOS protein expression.
	3. Investigate MH impact with its possible mechanism on hepatic fibrosis induced by CCL4[69].	Alleviation of liver fibrosis with less fiber tissue enlargement. Upregulation of Nrf2 and its related downstream antioxidant factors (HO-1 and NQO1) while downregulation of protein expression of α-SMA, collagen I, and collagen III.
	4. Investigate the underlying protective mechanism of MH against nonalcoholic fatty liver diseases[104].	Improvement in hepatic steatosis and other related metabolic disorders preventing them from progression through inhibition of LXR signaling as MH has been proven to be an antagonist of (LXRα and LXRβ).
Neuroprotective	Explore MH impact on focal cerebral ischemia induced by midbrain carotid artery occlusion (MCAO)[52].	Restoring the antioxidant defense balance through a decrease in MDA content, an increase in antioxidant levels (GSH, and Gpx), and SOD activity. Improvement in neurological deficiencies, Upregulation of Bcl-2, and downregulation of the proinflammatory cytokines, Bax, and caspase-3 mRNA expression.
Nephroprotective	1. Investigate MH protective impact on kidney damage caused by Cis[81].	Improvement of histopathological alterations, reduction of the kidney inflammatory mediators such as TNF-α and IL-1β levels, and downregulation of CYP2E1, NF-κB p65, P38, MAPK, Bax, caspase3, and p53 signaling cascades.
	2. *In vivo* and *in vitro* investigation of MH impact on Cis-induced nephrotoxicity[80].	Alleviation of Cis-induced ER stress, inflammation, and autophagy through suppression of PARP-1 gene expression, attenuation of inflammatory responses, and reducing oxidative stress with subsequent decrease in cellular death in HEK-293 cells and mice kidneys.
	3. Evaluate nephroprotective features of MH against nephrotoxicity by Gentamycin *in vivo*[78].	Significant decrease in the renal function markers such as (BUN) and (Scr). Restoring the antioxidant defense balance through the reduction of ROS production while the increase in the CAT and SOD enzyme activity and GSH levels.
	4. Determine MH impact on nephrotoxicity induced by Gentamycin[82].	Ameliorated the histopathological changes and increased the serum levels of albumin, urea, uric acid, creatinine, and K^+.

Table 2: Continued.

Anti-diabetic	1. Evaluation of MH regulatory effect on carbohydrate metabolic hepatic enzymes and its protective effect in STZ-diabetic rats[86].	Hepatic hexokinase and glucose-6-phosphate dehydrogenase enzyme activation while a decrease in fructose-1,6-bisphosphatase and glucose-6-phosphatase levels. Improvement in serum insulin level with a reduction in blood glucose level.
	2. Investigate the MH role in STZ diabetic rats and its impact on the brain[87].	Enhanced activity of SOD and CAT activity, it reduced the levels of inflammatory markers TNFα, IL1β, and IL-6 and thiobarbituric acid reactive substances, and also reduced fasting glucose with a significant increase in levels of serum insulin. Furthermore, there has been a significant increase in the brain's GSH and neurotrophic factors (BDNF, NGF, and IGF-1).
Cardioprotective	1. Explore the MH impacts on myocardial injury caused by ISO and the underlying mechanism[93].	Improvement in cardiac function through restoring myocardial architecture, enhancing SOD and CAT activity, and reducing MDA levels while increasing GSH levels, modulating the MAPK/NF-kB/TNF-a pathway, and improving hemodynamic parameters in isoproterenol-induced myocardial injury
	2. Prove MH benefits in ISO-stimulated myocardial infarction in rats[90].	MH lessened lipid peroxidation and modulated lipid metabolism while regulating the abnormalities in the ECG and biomarkers. A histopathological investigation showed that MH pretreatment prevented myocardial damage.
Anti-inflammatory in lung diseases	1. MH Attenuation of lung inflammation caused by CS and its underlying mechanism[94].	Reduced MPO activity, MDA, and P13K/ATK/NF-κB singling pathway activation It also reduced the levels of inflammatory mediators in the BALF, neutrophils, macrophages, and total cells. It improved lung physiological alterations.
	2. Investigate the MH role in chronic airway inflammation induced by OVA *in vivo* and in BECs *in vitro* [55].	*In vivo*, reduction of the elevation of intracellular production of ROS, inflammatory mediators such as TNF-α, IL-4, MDA, IgE, and matrix metalloproteinase-9, and the percentage of inflammatory cells recruited into (BALF) preventing them from infiltrating the blood vessels and respiratory tracts. *In vitro*, reduction in the levels of proteins like IL-8, intercellular adhesion molecule-1, and phosphorylation of MAPK.
	3. Explore the MH impact on LPS-induced ALI[50].	Enhancing SOD activity and suppressing MPO activity. Reduction in the inflammation through downregulating of lung NLRP3 inflammasome protein, lowering the levels of TNF-α, IL-1β, IL-18, and IL-6, reducing the number of inflammatory cells in the BALF.
Gastroprotective	Explore MH gastroprotection in Indomethacin(IND)-induced inflammation and apoptosis[101].	Restoring in the inflammatory damage, apoptosis, and neutrophil infiltration caused by IND in the gastric mucosa of rats. Reduction in ROS production, proinflammatory reactions, and NF-κB and (iNOS) activation. Enhancement of antioxidant enzymes.

Table 2: Continued.

Anti-arthritis	1. Explore the MH effect in synovial angiogenesis and subsequent arthritis and its underlying mechanism[98].	Suppression of angiogenesis and hindering the PI3K/Akt pathway through binding to and stimulating the PPARγ, boosting the expression of PTEN, a PPARγ target gene.
	2. Investigation of MH antiarthritic effect in different models[97].	*In vivo*, MH suppressed cartilage degradation. MH hindered p38 and extracellular signal-regulated kinase from being phosphorylated when exposed to IL-1β. It also increases the expression of (TIMP-1) and inhibits the expression of (MMP-3 and MMP-13).
Antimicrobial	Investigate MH impact on *S. aureus* pneumonia and haemolytic activity of α-hemolysin[99].	MH mitigates Hla's cytolytic activity, lessens lung cell damage in humans, and prevents *S. aureus* pneumonia-related mortality in a mouse infection model. The catalytic inhibition's molecular mechanism presents Morin's direct binding to Hla's "Stem" domain, specifically residues I107 and T109. This conformational change prevented the heptameric transmembrane pore's ability to self-assemble, thereby reducing Hla's biological activity associated with cell lysis.

Abbreviations

GSK-3β, glycogen synthase kinase-3β; **CCl4**, carbon tetrachloride; **NF-κB p65**, nuclear factor kappa B; **MAPK**,P38 mitogen-activated protein kinase; **Cis,** cisplatin; **ROS**, reactive oxygen species; **OVA**, ovalbumin; **MDA**, malondialdehyde ;**Bax**, Bcl-2-associated X protein; **TNF-α**, tumor necrosis factor-α; **NQO1**,quinone oxidoreductase 1; **HEK**, human embryonic kidney epithelial cells ;**HO-1,**heme oxygenase ;**BECs**, human bronchial epithelial cells; **ISO,** isoproterenol; **LPO**, lipid peroxidation; **Scr** , serum creatinine; **CS**, Cigarette smoke; **BALF**, bronchial alveolar lavage fluid ; **MPO**, myeloperoxidase; **Keap1**, Kelch-like ECH-associated protein1; **BUN**, blood urea nitrogen **i.p**, intraperitoneal; **LXR**, liver x receptor; **SOD**, superoxide dismutase; **CAT**, catalase ; **GSH**, reduced glutathione; **Nrf2**, nuclear erythroid-related factor 2; **ECG**, electrocardiogram ;**LPS**, lipopolysaccharides; **PPARγ** , peroxisome proliferator-activated receptor-γ; **OA**, osteoarthritis ;**MMP**, matrix metalloproteinase ; **TIMP-1,** tissue inhibitors of metalloproteinase ; **iNOS** ,inducible nitric oxide synthase ; **TBARS**, thiobarbituric acid reactive substances **STZ**, streptozotocin; **PPAR-γ**, peroxisome proliferator-activated receptor gamma.

MH safety and toxicity

A previous study had shown that plasma levels of MH remain below 1% after oral intake of high doses (200 mg/kg), this is due to its poor bioavailability and low membrane permeability[2]. Although parenteral administration of MH exhibits enhanced absorption and achievable therapeutical plasma level of MH, marked limitations are observed in these formulations such as low patient compliance, high cost, and safety considerations[18]. Therefore, MH, in modifying nano-emulsifying formulations for clinical application, was observed to demonstrate enhanced oral bioavailability, increased therapeutic efficacy, and low toxicity, even at elevated doses of 200 mg/kg[105]. This low toxicity of MH has been documented in several studies on animal models and also in human clinical trials, and oral administration of MH at long-term doses did not result in mortality or abnormal clinical signs[106].

Through investigation in clinical trials, more studies are needed to detect the accurate dose of MH to be safely used in various conditions since MH can interact with other

polyphenols, food products, and responsible genes, it also may affect the kinetic profile of concomitant drugs that depend on CYP isoenzymes in their metabolism or drugs substrate to P-glycoprotein (P-gp) due to its inhibitory effect on both (CYP isoenzymes, CYP3A4) and (P-gp). So, the kinetics of these concomitant drugs with MH should be adjusted carefully to obtain sufficient therapeutic clinical application in various acute and chronic diseases [27]. Previous *in vivo* and *in vitro* studies on MH prevention and treatment of calcium oxalate urolithiasis revealed that MH exhibits a good safety profile and beneficial therapeutic efficacy[107].

Conclusion

MH has been proven to have significant beneficial impacts on the health of both human and animal models. Owing to MH's numerous pharmacological actions it can be considered a potential therapy in a variety of chronic and lifestyle-associated degenerative diseases and different tumor types. These actions of MH have been reported to be attributed to several mechanisms such as enhancing or reducing the level of various inflammatory mediators, increasing or decreasing the gene expression of many intracellular regulatory proteins, influencing the activity of many enzymes, scavenging free radicals, and boosting or suppressing a variety of intracellular signaling cascades. Additionally, as stated by the results of the studies mentioned above MH is considered a therapeutically potent compound that may prove beneficial in the future for the development of novel herbal drugs and dietary supplements to improve human health with fewer side effects and minimal toxicities.

REFERENCES

1. X.Yan, M. Qi, P. Li, Y. Zhan and H. Shao, "Apigenin in cancer therapy: anti-cancer effects and mechanisms of action", ***Cell & Biosci,*** 7(1), 50 (2017).
2. A. Caselli, P. Cirri, A. Santi and P. Paoli, "Morin: a promising natural drug", ***Curr Med Chem,*** 23(8), 774-791 (2016).
3. J. Venu Gopal, "Morin Hydrate: Botanical origin, pharmacological activity and its applications: A mini-review", ***J Pharmacogn***, 5(3), 123-126 (2013).
4. R.M.P. Gutiérrez, S. Mitchell and R.V. Solis, "Psidium guajava: A review of its traditional uses, phytochemistry and pharmacology", ***J Ethnopharmacol***, 117(1), 1-27 (2008).
5. M.-A.M. Hassan, A.M. Gad, E.T. Menze, O.A. Badary and R.N. El-Naga, "Protective effects of morin against depressive-like behavior prompted by chronic unpredictable mild stress in rats: Possible role of inflammasome-related pathways", ***Biochem Pharmacol***, 180, 114140 (2020).
6. Q. Meng, L. Pu, Q. Lu, B. Wang, S. Li, B. Liu and F. Li, "Morin hydrate inhibits atherosclerosis and LPS-induced endothelial cells inflammatory responses by modulating the NFκB signaling-mediated autophagy", ***Int Immunopharmacol***, 100, 108096 (2021).
7. Y. Zhou, Z.-Q. Cao, H.-Y. Wang, Y.-N. Cheng, L.-G. Yu, X.-K. Zhang, Y. Sun and X.-L. Guo, "The anti-inflammatory effects of Morin hydrate in atherosclerosis is associated with autophagy induction through cAMP signaling", ***Mol Nutr Food Res,*** 61(9), 1600966 (2017).
8. S.A. Rajput, X.-q. Wang and H.-C. Yan, "Morin hydrate: A comprehensive review on novel natural dietary bioactive compound with versatile biological and pharmacological potential", ***Biomed Pharmacother***, 138, 111511 (2021).
9. K. Sinha, J. Ghosh and P.C. Sil, "Morin and Its Role in Chronic Diseases", in: S.C. Gupta, S. Prasad, B.B. Aggarwal (Eds.), Anti-inflammatory Nutraceuticals and Chronic Diseases, ***Springer International Publishing, Cham***, (2016), pp. 453-471.
10. A. Bhattarai and H. Wilczura-Wachnik, "Size and diffusion phenomena of AOT/alcohol/water system in the presence of morin by dynamic light scattering", ***Int J Pharm,*** 478(2), 610-616 (2015).
11. H.-R. Park, S.-E. Im, J.-J. Seo, B.-G. Kim, J.A. Yoon and K.-M. Bark, "Spectroscopic Properties of Morin in Various CH3OH–H2O and CH3CN–H2O Mixed Solvents",

J Photochem Photobiol B, 91(2) 280-290 (2015).
12. Q.K. Panhwar, S. Memon and M.I. Bhanger, "Synthesis, characterization, spectroscopic and antioxidation studies of Cu(II)–morin complex", ***J. Mol. Struct,*** 967(1) 47-53 (2010).
13. M. Tungjai, W. Poompimon, C. Loetchutinat, S. Kothan, N. Dechsupa and S. Mankhetkorn, "Spectrophotometric characterization of behavior and the predominant species of flavonoids in physiological buffer: determination of solubility, lipophilicity and anticancer efficacy", ***Drug Deliv J,*** 2(1),10-19 (2008).
14. A.Y. Waddad, S. Abbad, F. Yu, W.L.L. Munyendo, J. Wang, H. Lv and J. Zhou, "Formulation, characterization and pharmacokinetics of Morin hydrate niosomes prepared from various non-ionic surfactants", ***Int J Pharm,*** 456(2), 446-458 (2013).
15. A. Jangid, D. Kulhari and H. Kulhari, "Determination of solubility, stability and degradation kinetics of morin hydrate in physiological solutions", ***RSC Adv,*** 8(50), 28836-28842 (2018).
16. S. Ramešová, R. Sokolová, I. Degano, J. Bulíčková, J. Zabka and M. Gál, "On the stability of the bioactive flavonoids quercetin and luteolin under oxygen-free conditions", ***Anal Bioanal Chem,*** 402(2), 975-82 (2012).
17. X. Liang, Z. Liu, H. Shi, Y. Zhang, S. Wang, K. Bi, X. Chen, "Degradation kinetics of larotaxel and identification of its degradation products in alkaline condition", ***J Pharm Anal***, 7(2), 118-122 (2017).
18. J. Li, Y. Yang, E. Ning, Y. Peng, J. Zhang, "Mechanisms of poor oral bioavailability of flavonoid Morin in rats: From physicochemical to biopharmaceutical evaluations", ***Eur J Pharm Sci***, 128, 290-298 (2019).
19. X.-J. Tian, X.-W. Yang, X. Yang and K. Wang, "Studies of intestinal permeability of 36 flavonoids using Caco-2 cell monolayer model", ***Int J Pharm***, 367(1), 58-64 (2009).
20. A. Choudhury, I. Chakraborty, T. Banerjee, D. Vana, D. Adapa, "Efficacy of Morin as a Potential Therapeutic Phytocomponent: Insights into the Mechanism of Action", ***IJCMR,*** 6, 175-194 (2017).
21. C. Manach and J.L. Donovan, "Pharmacokinetics and metabolism of dietary flavonoids in humans", ***Free Radic Res,*** 38(8) 771-786 (2004).
22. A.K. Ratty and N.P. Das, "Effects of flavonoids on nonenzymatic lipid peroxidation: Structure-activity relationship", ***Biochem Med Metab Biol,*** 39(1) 69-79 (1988).
23. C. Manach, A. Scalbert, C. Morand, C. Rémésy and L. Jiménez, "Polyphenols: food sources and bioavailability", ***Am J Clin Nutr,*** 79(5) 727-747 (2004).
24. T. Walle, "Absorption and metabolism of flavonoids", ***Free Radical Biol Med,*** 36(7), 829-837 (2004).
25. J. Zhang, X. Shuai, J. Li, N. Xiang, T. Gong and Z. Zhang, "Biodistribution, hypouricemic efficacy and therapeutic mechanism of morin phospholipid complex loaded self-nanoemulsifying drug delivery systems in an experimental hyperuricemic model in rats", ***J Pharm Pharmacol,*** 68(1), 14-25 (2016).
26. S. Barnes, J. Prasain, T. D'Alessandro, A. Arabshahi, N. Botting, M.A. Lila, G. Jackson, E.M. Janle and C.M. Weaver, "The metabolism and analysis of isoflavones and other dietary polyphenols in foods and biological systems", ***Food Funct,*** 2(5), 235-44 (2011).
27. S.M. Pathak and N. Udupa, "Pre-clinical evidence of enhanced oral bioavailability of the P-glycoprotein substrate talinolol in combination with morin", ***BDDCS,*** 31(2-3), 202-214 (2010).
28. A. Goyal, N. Dubey, A. Agrawal, A. Verma and R. Sharma, "Therapeutic potential of morin: Special focus on cognitive dysfunction, diabetes mellitus and cancer", ***Pharmacol Res - Mod Chin Med,*** 9, 100318 (2023).
29. B.G.-V. Meerveld, K. Venkova and K. Connolly, "Efficacy of repifermin (keratinocyte growth factor-2) against abnormalities in gastrointestinal mucosal

transport in a murine model of colitis", ***J Pharm Pharmacol***, 55(1), 67-75 (2003).
30. K. Thakur, Y.-Y. Zhu, J.-Y. Feng, J.-G. Zhang, F. Hu, C. Prasad and Z.-J. Wei, "Morin as an imminent functional food ingredient: an update on its enhanced efficacy in the treatment and prevention of metabolic syndromes", ***Food Funct***, 11(10), 8424-8443 (2020).
31. M. Valko, D. Leibfritz, J. Moncol, M.T.D. Cronin, M. Mazur and J. Telser, "Free radicals and antioxidants in normal physiological functions and human disease", ***Int J Biochem Cell Biol,*** 39(1), 44-84 (2007).
32. A.M. Radi, E.T. Mohammed, A.I. Abushouk, L. Aleya and M.M. Abdel-Daim, "The effects of abamectin on oxidative stress and gene expression in rat liver and brain tissues: Modulation by sesame oil and ascorbic acid", ***Sci Total Environ***,701, 134882 (2020).
33. F. Rizvi, A. Mathur, S. Krishna, Mohammad I. Siddiqi and P. Kakkar, "Suppression in PHLPP2 induction by morin promotes Nrf2-regulated cellular defenses against oxidative injury to primary rat hepatocytes", ***Redox Biol***, 6, 587-598 (2015).
34. O. Farkas, J. Jakus and K. Héberger, "Quantitative Structure – Antioxidant Activity Relationships of Flavonoid Compounds", ***Mol,*** 9(12), 1079-1088 (2004).
35. A.M. Mendoza-Wilson, H. Santacruz-Ortega and R.R. Balandrán-Quintana, "Spectroscopic and computational study of the major oxidation products formed during the reaction of two quercetin conformers with a free radical", ***Spectrochim Acta A Mol Biomol Spectrosc***, 81(1), 481-488 (2011).
36. K.L. Wolfe and R.H. Liu, "Structure−Activity Relationships of Flavonoids in the Cellular Antioxidant Activity Assay", ***JAFC,*** 56(18), 8404-8411 (2008).
37. J. Morales, G. Günther, A.L. Zanocco and E. Lemp, "Singlet oxygen reactions with flavonoids. A theoretical–experimental study", ***PloS One,*** 7(7), e40548 (2012).
38. S. Burda and W. Oleszek, "Antioxidant and Antiradical Activities of Flavonoids", ***J Agric Food Chem***, 49(6), 2774-2779 (2001).
39. C.A. Rice-Evans, N.J. Miller and G. Paganga, "Structure-antioxidant activity relationships of flavonoids and phenolic acids", ***Free Radic Biol Med***, 20(7), 933-956 (1996).
40. A.A. Banday, N. Farooq, S. Priyamvada, A.N.K. Yusufi and F. Khan, "Time dependent effects of gentamicin on the enzymes of carbohydrate metabolism, brush border membrane and oxidative stress in rat kidney tissues", ***Life Sci,*** 82(9), 450-459 (2008).
41. P. Vanitha, S. Senthilkumar, S. Dornadula, S. Anandhakumar, P. Rajaguru and K.M. Ramkumar, "Morin activates the Nrf2-ARE pathway and reduces oxidative stress-induced DNA damage in pancreatic beta cells", ***Eur J Pharmacol,*** 801, 9-18 (2017).
42. M.H. Lee, H.J. Cha, E.O. Choi, M.H. Han, S.O. Kim, G.Y. Kim, S.H. Hong, C. Park, S.K. Moon, S.J. Jeong, M.J. Jeong, W.J. Kim andY.H. Choi, "Antioxidant and cytoprotective effects of morin against hydrogen peroxide-induced oxidative stress are associated with the induction of Nrf-2‑mediated HO-1 expression in V79-4 Chinese hamster lung fibroblasts", ***Int J Mol Med,*** 39(3), 672-680 (2017).
43. R. Kapoor and P. Kakkar, "Protective role of morin, a flavonoid, against high glucose induced oxidative stress mediated apoptosis in primary rat hepatocytes", ***PLoS One,*** 7(8), e41663 (2012).
44. A. Merwid-Ląd, M. Trocha, E. Chlebda-Sieragowska, T. Sozański, M. Szandruk, J. Magdalan, D. Ksiądzyna, M. Pieśniewska, L. Fereniec-Gołębiewska, J. Kwiatkowska and A. Szeląg, "The impact of morin, a natural flavonoid, on cyclophosphamide-induced changes in the oxidative stress parameters in rat livers", ***Adv Clin Exp Med,*** 23(4), 505-509 (2014).
45. S. Ray, P. Chowdhury, B. Pandit, S.D. Ray and S. Das, "Exploring the antiperoxidative potential of morin on cyclophosphamide and flutamide-induced lipid peroxidation and changes in

cholesterol profile in rabbit model", ***Acta Pol Pharm***, 67(1), 35-44 (2010).
46. D.B. Lowe and W.J. Storkus, "Chronic Inflammation and Immunologic-Based Constraints in Malignant Disease", ***Immunotherapy***, 3(10), 1265-1274 (2011).
47. S.M. Abou-Zeid, A.I. Ahmed, A. Awad, W.A. Mohammed, M.M.M. Metwally, R. Almeer, M.M. Abdel-Daim and S.R. Khalil, "Moringa oleifera ethanolic extract attenuates tilmicosin-induced renal damage in male rats via suppression of oxidative stress, inflammatory injury, and intermediate filament proteins mRNA expression", ***Biomed Pharmacother***, 133, 110997 (2021).
48. J. Bai, Y. Zhang, C. Tang, Y. Hou, X. Ai, X. Chen, Y. Zhang, X. Wang and X. Meng, "Gallic acid: Pharmacological activities and molecular mechanisms involved in inflammation-related diseases", ***Biomed Pharmacother,*** 133, 110985 (2021).
49. G.M. Raso, R. Meli, G. Di Carlo, M. Pacilio and R. Di Carlo, "Inhibition of inducible nitric oxide synthase and cyclooxygenase-2 expression by flavonoids in macrophage J774A.1", ***Life Sci,*** 68(8), 921-931 (2001).
50. Z. Tianzhu, Y. Shihai and D. Juan, "The Effects of Morin on Lipopolysaccharide-Induced Acute Lung Injury by Suppressing the Lung NLRP3 Inflammasome", ***Mediators Inflamm***, 37(6), 1976-1983 (2014).
51. M.A. Ocete, J. Gálvez, M.E. Crespo, T. Cruz, M. González, M.I. Torres and A. Zarzuelo, "Effects of morin on an experimental model of acute colitis in rats", Pharmacology 57(5) 261-70 (1998).
52. Y. Chen, Y. Li, H. Xu, G. Li, Y. Ma, Y.J. Pang, "Morin Mitigates Oxidative Stress, Apoptosis and Inflammation in Cerebral Ischemic Rats", ***Afr J Tradit Complement Altern Med***, 14(2), 348-355 (2017).
53. S. Yu, X. Liu, D. Yu, E. Changyong and J. Yang, "Morin Protects LPS-Induced Mastitis via Inhibiting NLRP3 Inflammasome and NF-κB Signaling Pathways", ***Mediators Inflamm***, 43(4), 1293-1303 (2020).
54. J. Wang, C. Guo, Z. Wei, X. He, J. Kou, E. Zhou, Z. Yang and Y. Fu, "Morin suppresses inflammatory cytokine expression by downregulation of nuclear factor-κB and mitogen-activated protein kinase (MAPK) signaling pathways in lipopolysaccharide-stimulated primary bovine mammary epithelial cells", ***J Dairy Sci Biotechnol***, 99(4), 3016-3022 (2016).
55. Y. Ma, A. Ge, W. Zhu, Y.-N. Liu, N.-F. Ji, W.-J. Zha, J.-X. Zhang, X.-N. Zeng and M. Huang, "Morin Attenuates Ovalbumin-Induced Airway Inflammation by Modulating Oxidative Stress-Responsive MAPK Signaling", ***Oxid Med Cell Longev***, 2016(1), 5843672 (2016).
56. M. Rudrapal, G. Rakshit, R.P. Singh, S. Garse, J. Khan and S. Chakraborty, "Dietary Polyphenols: Review on Chemistry/Sources, Bioavailability/Metabolism, Antioxidant Effects, and Their Role in Disease Management", ***Antioxidants,*** 13(4), 429 (2024).
57. R. Montaser and H. Luesch, "Marine Natural Products: A New Wave of Drugs?", ***Future Med Chem,*** 3(12), 1475-1489 (2011).
58. T. Rengarajan, N. Nandakumar, P. Rajendran, L. Haribabu, I. Nishigaki and M.P. Balasubramanian, "D-pinitol promotes apoptosis in MCF-7 cells via induction of p53 and Bax and inhibition of Bcl-2 and NF-κB", ***Asian Pac J Cancer Prev***, 15(4), 1757-1762 (2014).
59. A. Ahmadi and A. Shadboorestan, "Oxidative stress and cancer; the role of hesperidin, a citrus natural bioflavonoid, as a cancer chemoprotective agent", ***Nutr Cancer,*** 68(1), 29-39 (2016).
60. V. Sivaramakrishnan, P.N.M. Shilpa, V.R. Praveen Kumar and S. Niranjali Devaraj, "Attenuation of N-nitrosodiethylamine-induced hepatocellular carcinogenesis by a novel flavonol—Morin", ***Chem Biol Interact***, 171(1), 79-88 (2008).
61. Q. Zhang, F. Zhang, K. Thakur, J. Wang, H. Wang, F. Hu, J.-G. Zhang and Z.-J. Wei, "Molecular mechanism of anti-cancerous potential of Morin extracted from mulberry in Hela cells", ***Food Chem Toxicol***, 112, 466-475 (2018).

62. R.N. Kumar, K.N. Kumar, K. Salini and S.N. Devaraj, "Morin accelerates proliferative inhibition via NF-κB mediated transcriptional regulation of apoptotic events during chemical carcinogen induced mammary cancer in rats", ***Biomed & Prev Nutr,*** 4(2), 277-290 (2014).
63. M. Xu and Y. Zhang, "Morin Inhibits Ovarian Cancer Growth through the Inhibition of NF-κB Signaling Pathway", ***Curr Med Chem Anticancer Agents,*** 19(18), 2243-2250 (2019).
64. S.H. Sharma, J.S. Kumar, D.R. Chellappan and S. Nagarajan, "Molecular chemoprevention by morin – A plant flavonoid that targets nuclear factor kappa B in experimental colon cancer", ***Biomed Pharmacother***, 100, 367-373 (2018).
65. V. Sivaramakrishnan and S. Niranjali Devaraj, "Morin regulates the expression of NF-κB-p65, COX-2 and matrix metalloproteinases in diethylnitrosamine induced rat hepatocellular carcinoma***", Chem Biol Interact,*** 180(3), 353-359 (2009).
66. D. Yao, H. Cui, S. Zhou and L. Guo, "Morin inhibited lung cancer cells viability, growth, and migration by suppressing miR-135b and inducing its target CCNG2", ***Tumor Biology,*** 39(10) 1010428317712443 (2017).
67. S.-S. Shin, S.Y. Won, D.-H. Noh, B. Hwang, W.-J. Kim and S.-K. Moon, "Morin Inhibits Proliferation, Migration, and Invasion of Bladder Cancer EJ Cells via Modulation of Signaling Pathways, Cell Cycle Regulators, and Transcription Factor-Mediated MMP-9 Expression", ***Drug Dev Res,*** 78(2), 81-90 (2017).
68. B. Li, X. Jin, H. Meng, B. Hu, T. Zhang, J. Yu, S. Chen, X. Guo, W. Wang, W. Jiang and J. Wang, "Morin promotes prostate cancer cells chemosensitivity to paclitaxel through miR-155/GATA3 axis", ***Oncotarget***, 8(29), 47849-47860 (2017).
69. L. Sang, X.M. Wang, D.Y. Xu, L.X. Sang, Y. Han and L.Y. Jiang, "Morin enhances hepatic Nrf2 expression in a liver fibrosis rat model", ***World J Gastroenterol,*** 23(47), 8334-8344 (2017).
70. X. Li, Q. Yao, J. Huang, Q. Jin, B. Xu, F. Chen and C. Tu, "Morin Hydrate Inhibits TREM-1/TLR4-Mediated Inflammatory Response in Macrophages and Protects Against Carbon Tetrachloride-Induced Acute Liver Injury in Mice", ***Front Pharmacol***, 10, 1089 (2019).
71. G.H. Heeba and M.E. Mahmoud, "Therapeutic potential of morin against liver fibrosis in rats: Modulation of oxidative stress, cytokine production and nuclear factor kappa B", ***Environ Toxicol Pharmacol,*** 37(2), 662-671 (2014).
72. Z.-t. Zhang, X.-b. Cao, N. Xiong, H.-c. Wang, J.-s. Huang, S.-g. Sun and T. Wang, "Morin exerts neuroprotective actions in Parkinson disease models in vitro and in vivo", ***Acta Pharmacol Sin***, 31(8), 900-906 (2010).
73. K.M. Lee, Y. Lee, H.J. Chun, A.H. Kim, J.Y. Kim, J.Y. Lee, A. Ishigami and J. Lee, "Neuroprotective and anti-inflammatory effects of morin in a murine model of Parkinson's disease", ***J Neurosci Res***, 94(10), 865-878 (2016).
74. P. Komirishetty, A. Areti, R. Sistla and A. Kumar, "Morin Mitigates Chronic Constriction Injury (CCI)-Induced Peripheral Neuropathy by Inhibiting Oxidative Stress Induced PARP Over-Activation and Neuroinflammation", ***Neurochem Res***, 41(8), 2029-2042 (2016).
75. M. Singh, V. Thakur, R. Deshmukh, A. Sharma, M.S. Rathore, A. Kumar and N. Mishra, "Development and characterization of morin hydrate-loaded micellar nanocarriers for the effective management of Alzheimer's disease", ***J Microencapsul,*** 35(2), 137-148 (2018).
76. L.R. Johnson, "Essential medical physiology", ***Elsevier*** (2003).
77. R. Venkatesan, A.M. Sadiq, J.S. Kumar, G.R. Lakshmi and R. Vidhya, "Effect of Morin on mercury chloride induced nephrotoxicity", ***Ecoscan,*** 4, 193-196 (2010).
78. V.G. Jonnalagadda, S. Pittala, M. Lahkar and V. Pradeep, "Ameliorative effect of morin hydrate, a flavonoid against gentamicin induced oxidative stress and nephrotoxicity in sprague-dawley rats",

Int J Pharm Pharm Sci, 6(1), 851-856 (2013).
79. F.G. Apaydın, K. Kaltalıoğlu, B. Balabanlı and Ş. Coskun Cevher, "Morin and Hesperidin Ameliorate Cisplatin-Induced Hepatotoxicity and Nephrotoxicity in Rats: A Histopathological Study", ***GUJS,*** 31(2), 399-406 (2018).
80. M.P. Singh, A.K. Chauhan and S.C. Kang, "Morin hydrate ameliorates cisplatin-induced ER stress, inflammation and autophagy in HEK-293 cells and mice kidney via PARP-1 regulation", ***Int Immunopharmacol***, 56, 156-167 (2018).
81. Z. Wei, X. He, J. Kou, J. Wang, L. Chen, M. Yao, E. Zhou, Y. Fu, C. Guo and Z. Yang, "Renoprotective mechanisms of morin in cisplatin-induced kidney injury", ***Int Immunopharmacol***, 28(1) 500-506 (2015).
82. H.A. Khattab, "Effect of Morin against gentamicin-induced nephrotoxicity in young male rats", ***EJHM,*** 49(1), 705-717 (2012).
83. A.M. Aleisa, S.S. Al-Rejaie, H.M. Abuohashish, M.M. Ahmed and M.Y. Parmar, "Nephro-protective role of morin against experimentally induced diabetic nephropathy", ***Dig J Nanomater Biostruct***, 8(1), 395-401 (2013).
84. M. Ghasemi-Dehnoo, H. Amini-Khoei, Z. Lorigooini and M. Rafieian-Kopaei, "Oxidative stress and antioxidants in diabetes mellitus", ***Asian Pac J Trop Med,*** 13(10), 431-438 (2020).
85. P. Paoli, P. Cirri, A. Caselli, F. Ranaldi, G. Bruschi, A. Santi and G. Camici, "The insulin-mimetic effect of Morin: A promising molecule in diabetes treatment", ***Biochim Biophys Acta,*** 1830(4), 3102-3111 (2013).
86. P. Vanitha, C. Uma, N. Suganya, E. Bhakkiyalakshmi, S. Suriyanarayanan, P. Gunasekaran, S. Sivasubramanian and K.M. Ramkumar, "Modulatory effects of morin on hyperglycemia by attenuating the hepatic key enzymes of carbohydrate metabolism and β-cell function in streptozotocin-induced diabetic rats", ***Environ Toxicol Pharmacol,*** 37(1), 326-335 (2014).
87. M.S. Ola, A.M. Aleisa, S.S. Al-Rejaie, H.M. Abuohashish, M.Y. Parmar, A.S. Alhomida and M.M. Ahmed, "Flavonoid, morin inhibits oxidative stress, inflammation and enhances neurotrophic support in the brain of streptozotocin-induced diabetic rats", ***Neurol Sci,*** 35(7), 1003-1008 (2014).
88. K.S. Al-Numair, G. Chandramohan, M.A. Alsaif, C. Veeramani and A. Newehy, "Morin, a flavonoid, on lipid peroxidation and antioxidant status in experimental myocardial ischemic rats", ***Afr J Tradit Complement Altern Med,*** 11(3), 14-20 (2014).
89. D.G. Kang, M.K. Moon, E.J. Sohn, D.H. Lee and H.S. Lee, "Effects of Morin on Blood Pressure and Metabolic Changes in Fructose-Induced Hypertensive Rats", ***Biol Pharm Bull,*** 27(11), 1779-1783 (2004).
90. B.K. Pogula, M.K. Maharajan, D.R. Oddepalli, L. Boini, M. Arella and D.Q. Sabarimuthu, "Morin protects heart from beta-adrenergic-stimulated myocardial infarction: an electrocardiographic, biochemical, and histological study in rats", ***Plant Physiol Biochem***, 68(3), 433-446 (2012).
91. P. Prahalathan, S. Kumar and B. Raja, "Morin attenuates blood pressure and oxidative stress in deoxycorticosterone acetate-salt hypertensive rats: A biochemical and histopathological evaluation", ***Metab***, 61(8), 1087-1099 (2012).
92. S. Liu, N. Wu, J. Miao, Z. Huang, X. Li, P. Jia, Y. Guo and D. Jia, "Protective effect of morin on myocardial ischemia‐reperfusion injury in rats", ***Int J Mol Med,*** 42(3), 1379-1390 (2018).
93. V.K. Verma, S. Malik, S.P. Narayanan, E. Mutneja, A.K. Sahu, J. Bhatia and D.S. Arya, "Role of MAPK/NF-κB pathway in cardioprotective effect of Morin in isoproterenol induced myocardial injury in rats", ***Mol Biol Rep***, 46(1), 1139-1148 (2019).
94. B. Cai, X. Gan, J. He, W. He, Z. Qiao, B. Ma and Y. Han, "Morin attenuates cigarette smoke-induced lung inflammation through inhibition of

PI3K/AKT/NF-κB signaling pathway", ***Int Immunopharmacol,*** 63, 198-203 (2018).
95. I. Veerappan, S.K. Sankareswaran, R. Palanisamy, "Morin Protects Human Respiratory Cells from PM2.5 Induced Genotoxicity by Mitigating ROS and Reverting Altered miRNA Expression", ***Int J Environ Res Public Health***, 16(13), 2389 (2019).
96. W.-P. Chen, Y.-L. Wang, J.-L. Tang, P.-F. Hu, J.-P. Bao and L.-D. Wu, "Morin inhibits interleukin-1β-induced nitric oxide and prostaglandin E2 production in human chondrocytes", ***Int Immunopharmacol,*** 12(2), 447-452 (2012).
97. W.-P. Chen, P.-F. Hu, J.-P. Bao and L.-D. Wu, "Morin exerts antiosteoarthritic properties: an in vitro and in vivo study", ***Exp Biol Med (Maywood)*** ,237(4), 380-386 (2012).
98. M. Yue, N. Zeng, Y. Xia, Z. Wei and Y. Dai, "Morin Exerts Anti-Arthritic Effects by Attenuating Synovial Angiogenesis via Activation of Peroxisome Proliferator Activated Receptor-γ", ***Mol Nutr Food Res***, 62(21), 1800202 (2018).
99. J. Wang, X. Zhou, S. Liu, G. Li, L. Shi, J. Dong, W. Li, X. Deng and X. Niu, "Morin hydrate attenuates Staphylococcus aureus virulence by inhibiting the self-assembly of α-hemolysin", ***J Appl Microbiol,*** 118(3), 753-763 (2015).
100. E.H. Hong, J.H. Song, S.R. Kim, J. Cho, B. Jeong, H. Yang, J.H. Jeong, J.H. Ahn, H. Jeong, S.E. Kim, S.Y. Chang, H.J. Ko, "Morin Hydrate Inhibits Influenza Virus entry into Host Cells and Has Anti-inflammatory Effect in Influenza-infected Mice", ***Immune Netw,*** 20(4), e32 (2020).
101. K. Sinha, P. Sadhukhan, S. Saha, P.B. Pal and P.C. Sil, "Morin protects gastric mucosa from nonsteroidal anti-inflammatory drug, indomethacin induced inflammatory damage and apoptosis by modulating NF-κB pathway", ***Biochim Biophys Acta,*** 1850(4), 769-783 (2015).
102. A. Jiang, Y. Zhang, X. Zhang, D. Wu, Z. Liu, S. Li, X. Liu, Z. Han, C. Wang, J. Wang, Z. Wei, C. Guo and Z. Yang, "Morin alleviates LPS-induced mastitis by inhibiting the PI3K/AKT, MAPK, NF-κB and NLRP3 signaling pathway and protecting the integrity of blood-milk barrier", ***Int Immunopharmacol,*** 78, 105972 (2020).
103. P. MadanKumar, P. NaveenKumar, S. Manikandan, H. Devaraj and S. NiranjaliDevaraj, "Morin ameliorates chemically induced liver fibrosis in vivo and inhibits stellate cell proliferation in vitro by suppressing Wnt/β-catenin signaling", ***Toxicol Appl Pharmacol,*** 277(2), 210-220 (2014).
104. M. Gu, Y. Zhang, C. Liu, D. Wang, L. Feng, S. Fan, B. Yang, Q. Tong, G. Ji and C. Huang, "Morin, a novel liver X receptor α/β dual antagonist, has potent therapeutic efficacy for nonalcoholic fatty liver diseases", ***Br J Pharmacol,*** 174(18), 3032-3044 (2017).
105. J. Zhang, Q. Peng, S. Shi, Q. Zhang, X. Sun, T. Gong and Z. Zhang, "Preparation, characterization, and in vivo evaluation of a self-nanoemulsifying drug delivery system (SNEDDS) loaded with morin-phospholipid complex", ***Int J Nanomedicine,*** 6(null), 3405-3414 (2011).
106. Y.M. Cho, H. Onodera, M. Ueda, T. Imai and M. Hirose, "A 13-week subchronic toxicity study of dietary administered morin in F344 rats", ***FCT,*** 44(6), 891-897 (2006).
107. M. Ponugoti, C. Guntupalli and N. Malothu, "Morin hydrate mitigates calcium oxalate urolithiasis by inhibiting oxalate synthesis and modulating crystal formation", ***Urolithiasis***, 52(1) 127 (2024).
108. S. Ali, A. Rahman, R. Shahbakht, R. Akhtar and R. Ma, "Impact of Plant-Originated Morin Hydrate on Human and Animal Health", ***IJAB,*** 1(1), 1-9 (2023).

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نشرة العلوم الصيدلية
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مورين هيدرات: بيوفلافونويد واعد ذو تأثيرات علاجية مختلفة

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الفلافونويدات هي مركبات نشطة بيولوجيا مشتقة من النباتات التي تؤثر بشكل كبير على صحة الإنسان. مورين هيدرات هو فلافونويد حيوي طبيعي، مستخرج بشكل رئيسي من عائلة موراسيا، ومتوفر بسهولة في الأوراق والفواكه والسيقان وأغصان النباتات المختلفة.

تشير مجموعة متنوعة من الأدلة إلى أن مورين هيدرات قد يكون له تأثير مفيد على الأمراض المختلفة التي تصيب الإنسان. يُظهر مورين تأثيرات مضادة للأكسدة، ومضادة للالتهابات، ومضادة لمرض السكرى، وواقية للقلب، ومضادة لالتهاب المفاصل، ومضادة للورم، ومضادة لامراض الكلي، ومضادة للبكتيريا من خلال التأثير على نشاط الإنزيمات المختلفة. علاوة على ذلك، يُظهر مورين هيدرات أيضًا آثاره الدوائية من خلال التأثير على مجموعة متنوعة من مسارات الإشارات الخلوية، بما في ذلك العامل النووي NF-ˊkappa-B، والبروتين المرتبط بـ ECH الشبيه بـ Kelch 1 / العامل المرتبط بالكريات الحمراء النووية ٢ (Keap1 / Nrf2). ، كيناز يانوس / محول الإشارة، بروتين كيناز المنشط بالميتوجين (MAPK)، ومنشط بروتينات النسخ (JAKs / STATs). في كثير من الحالات، يُظهر مورين هيدرات تأثيرات وقائية جهازية، مما يخفف من الآثار الضارة لمختلف الأدوية دون المساس بفعاليتها. علاوة على ذلك، أظهرت العديد من الدراسات التي أجريت في الجسم الحي وفي المختبر أن مورين هيدرات لديه مستويات سمية منخفضة ويمكن تحمله جيدًا عند تناوله على مدى فترة طويلة. تشير العديد من النتائج إلى أنه يمكن استخدام مورين هيدرات لمنع مجموعة متنوعة من الأمراض البشرية، إما بمفرده أو بالاشتراك مع أدوية أخرى. يعرض هذا المقال دراسات حديثة حول الخصائص البيولوجية والدوائية، بالإضافة إلى الآليات الجزيئية للمورين هيدرات لتوضيح آثاره الصحية الإيجابية العديدة.