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REVIEW ARTICLE

Morin combat against Oxidative stress induced different diseases in Experimental models: A Review

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ABSTRACT:
Phytochemicals including bioflavonoids are active metabolites extensively present in plants. It is potent antioxidants provide that beneficial effects against oxidative stress-related diseases. The present literature survey was carried out to explore the reported antioxidant activity of morin. Morin exerts different biological activities viz., antidiabetic, anti-inflammatory, antihypertensive, antitumoral, antibacterial, and neuroprotective effects by regulating the activity of different antioxidant enzymes. In addition, morin exerts various biological activities such as xanthine oxidase inhibition, protective effect of DNA from damage caused by free radical, free radical scavenging activity, cell proliferation inhibitor property, hepatoprotective, hypolipidemic, antidiabetic, and neuroprotective activity. From the literature review it was found that most of these activities of morin are due to increase in the endogenous antioxidant activities viz., superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Based on our findings, we enlighten the prospective role of morin hydrate as an antioxidant.

KEYWORDS: Morin, bioflavonoids, antioxidant, oxidative stress, free radical.

INTRODUCTION:
Reactive oxygen species (ROS) are chemically reactive molecules and free radicals containing oxygen[1]. Oxidative stress reflects a disturbance in the balance between the production of ROS and the biological system's potentiality to withdraw them[2]. ROS are adopted significantly in various cellular activities including signal transduction, immune response, and gene transcription[3]. Biomolecules like DNA, lipids, and proteins which have been intricate in the progress of aging over and above several ailments including respiratory, cardiovascular, cancer, digestive diseases, and neurodegeneration is due to an excess of ROS which causes oxidative damage[3,4]. Regulation of reducing and oxidizing (redox) state is unfavorable for cell activation, viability, proliferation, and organ functions[5].

Aerobic organisms have integrated antioxidant systems, which include certain enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx)[6], and nonenzymatic antioxidants such as flavones, anthocyanin, carotenoids and ascorbic acid[7] that are generally effective in blocking noxious effects of ROS[8]. However, in morbid conditions, the antioxidant systems can be overwhelmed. Oxidative stress can be extenuated by antioxidants, either extrinsically supplied or endogenously generated, that are efficient of scavenging ROS and alleviating the oxidation of cellular molecules[9].

It has been reported that the antioxidant activity of natural compounds isolated from plants, counterpoise free radicals[10,11]. Among them, flavonoids are a group of secondary metabolites with variable phenol groups. Moreover, they are the bioactive compounds present extensively in plants and have long received attentiveness in the progress of antioxidants[12-14]. Flavonoids are an essential component is related to a broad spectrum of health-promoting effects[15]. This is an account of their antioxidant, antimutagenic, anti-inflammatory, and anticarcinogenic properties combined

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with their capacity to modulate the functions of key cellular enzymes. They are also said to be effective inhibitors for some enzymes, such as cyclooxygenase (COX), xanthine oxidase (XO), phosphoinositide-3-kinase, and lipoxygenase[16-18]. Further, they exhibit the scavenging capability to oxygen radicals such as singlet oxygen, superoxide anion, and hydroxyl radicals[19]. The prime examples of potent antioxidant flavonoids are morin, rutin, and quercetin. Despite several bioflavonoids, morin hydrate was one of the bioflavonoid that has pronounced recognition in nature[20].

Morin hydrate or morin (3,5,7,2',4'-pentahydroxy flavone) is a flavonoid isolated as a yellow pigment from plants belonging to the Moraceae family[21]. It is one of the primary components of several preparations of botanical origin, and it is suggested by traditional medicine to treat various human diseases[22]. Morin has been shown to have effective antioxidant and metal ion-chelating capacities. Besides, it has various biological activities including antioxidant[23], anti-inflammatory[24], anti-mutagenesis[25], cardioprotective[26], antineoplastic[27], and anticancer[28] activities. Moreover, it is also an inhibitor of XO[29], cell proliferation[30] and, protein kinase C[31]. Further, morin has also been shown to act as a potent chemopreventive agent against oral carcinogenesis *in vitro* and *in vivo*[32]. Therapeutically, morin is considered a significant drug, which is recommended for all those diseases, which are mostly affected by the overproduction of ROS[33]. Ongoing research has demonstrated that the administration of morin has not associated with any adverse side effects. Moreover, it is comparatively cost-effective and easily available[34]. Therefore, this review enlightens the potential role of morin as an antioxidant in the pathogenesis of several redox imbalance-related diseases and the attenuation of oxidative stress-induced damages. Hence, the investigators explored that morin is taken into account as a potent drug due to its curative and preventive properties.

ANTIOXIDANT ACTIVITY OF MORIN:

Morin has demonstrated its protective potential against oxidative stress leading to attenuation of the disease condition. It has shown its antioxidant potential in the following models:

Morin as a hepatocellular protector:

It has been demonstrated that morin is an antioxidant-based cytoprotector both in cultured rat hepatocytes and in the rat liver during ischemia-reperfusion. Morin is in a very dose-dependent studythat prolongs hepatocyte survival without being affected by exposure. Also, the consequence of morin (2.5, 5.0 and 10μmol/kg;b.w.) excels given by Trolox, ascorbate, and mannitol. In a rat model of hepatic ischemia-reperfusion, the dose-dependent impact of morin on hepatic salvage has been noted. Mechanistically, morin is an unwonted antioxidant that seems to act both "preventively" (i.e. partially blocking radical formation from XO) and "curatively" (i.e. scavenging free radicals). It has been observed that morin being an efficacious curative radical scavenger, scavenges peroxyl radicals better than Trolox, ascorbate, and mannitol. Morin is a partial inhibitor of XO and may have certain relevance in the liver since the organ is fairly well endowed with XO. During hepatic ischemia-reperfusion, XO is a vital source of oxy-radicals[35].

Chronotherapeutic effects of morin on hyperammonemia:

Hyperammonemia is a metabolic condition characterized by elevated levels of ammonia concentration in blood, resulting from insufficient ammonia detoxification due to impairment in liver function. The study aimed to demonstrate the chronotherapeutic effect of morin on ammonium chloride (AC) (100mg/kg;i.p)-induced hyperammonemia in Wister rats.Morin (30mg/kg) was administered to rats at 6, 12, 18, and 24 hours in hyperammonemia. The impact of morin on AC-induced hyperammonemia was evaluated by studying the circulatory levels of enzymatic and nonenzymatic antioxidant such as GPx, reduced glutathione (GSH), SOD, CAT, and vitamins A, C, and E. Restoration in the levels of various component during morin treatment shows the potent antioxidant activity by offering possible role in reducing the oxidative stress by inducing cellular antioxidant enzymes[36].

Effects of morin on lipid peroxidation:

The protective effect of morin inthe progression and development of alcoholic liver disease (ALD) was studied in an experimental model. The recent analysis intended to inspect the effect of morin on oxidative stress and ethanol-induced dyslipidemia in plasma, erythrocytes and liver mitochondria of rats. Hepatotoxicity was induced in rats for 60 days by administering ethanol (6g/kg) daily. After 30 days of the experimental period, morin (15, 30, 60, and 120 mg/b.w.) was administered to the ethanol-fed rats and the treatment was continued up to the 60th day. An outstandingincrease in plasma alanine transaminases, γ-glutamyltransferase, aspartate aminotransferases, and alkaline phosphatase was observed in rats intoxicated with ethanol. Also, the administration of ethanol in rats showed significantly elevated levels of lipids and altered lipid profile levels in the plasma. As compared to control rats, the levels of thiobarbituric acid-reactive substances (TBARS) and lipid hydroperoxides were also significantly elevated in the plasma, erythrocyte, and

hepatic mitochondria of ethanol-fed rats. It has been noted that decreased levels of SOD, GPx, CAT, and GSH were observed in ethanol-administered rats. Oral supplementation of morin (60mg/kg) showed its high potentiality in reducing dyslipidemia and oxidative stress in plasma, erythrocytes, and liver mitochondrial in ALD by its potent hepatoprotective, hypolipidemic, and antioxidant effects[37].

Effects of morin in cardiovascular diseases:

Myocardial infarction occurs when there is a deprived of oxygen supply to heart which leads to irreversible death (necrosis) of the heart muscle. As morin hydrate is chiefly ever-present in almondand white mulberry exhibits cardiovascular protective effect in isoproterenol-induced MI in rats because of its free radical scavenging activity ascribed by the polyphenolic group of morin. Morin hydrate showed the distinguished advantageous effect on blood pressure, lipids, andserum glucose levels in high-fat diet-induced hypertensive rats[38].

Antioxidant and cytoprotective effects of morin:

The robust antioxidant ability of morin was determined by SOD-like activity and 2,2'-azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid) ($ABTS^{\bullet+}$) radical scavenging activity. Also, it has been investigated that in Chinese hamster, morin protects lung fibroblast V79-4 cellsfrom death and oxidative stress-induced DNA damage by the repression of ROS generation and mitochondrial dysfunction. However, the treatment of V79-4 cells with morin remarkably enhanced the expression of heme oxygenase-1 (HO-1) which was associated with the upregulation and phosphorylation of nuclear factor-erythroid 2-related factor 2 (Nrf2) and the downregulation of Kelch-like ECH-associated protein 1 expression. Moreover, the efficiency of morin ameliorated oxidative stress-induced DNA damage through activation of the Nrf2/HO-1 pathway and intrinsic free radical scavenging activity[39].

Morin attenuates doxorubicin-induced heart and brain damage:

Doxorubicin (DOX) is an anthracycline, one amongst the most potent antineoplastic agent and hence causes some toxicant effects including cognitive impairment and mainly cardiotoxicity. The protecting effects of morin against DOX-induced neurotoxicity and cardiotoxicity were evaluated in experimental rats. Morin was orally administered to rats at a dose of 50 and 100mg/kg for 10 days and DOX was administered 40 mg/kg single intraperitoneal dose on the 8^{th} day of the trial.According to the obtained data, a single dose of DOX (40mg/kg) significantly enhanced the malondialdehyde (MDA) levels and decreased SOD, CAT and GPx enzyme activities. The results recommend that morin may protect against DOX-induced oxidative stress by elevating GSH levels, decreasing MDA levels, and enhancing antioxidant enzyme activities compared to DOX-administrated groups[40].

Anti- atherosclerotic effect of morin:

In an *in vivo* study, anti-atherosclerotic activity of morin was demonstrated in two completely different doses (30 mg/kg, 100mg/kg) to observe the toxicity and effectiveness in mice. Results indicated that either low and high doses of morin reduced the lipid accumulation and plaque formation in atherosclerosis mice without a significant decrease of body weight and demonstrated that the two doses of morin had no remarkable toxicity on mice. Moreover, administration of morin consequently decreases serum levels of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglycerides (TG) are the four main independent factors in cardiovascular disease. Also, the decrease of the respective lesion area of the aortas was shown in the morin treated group, with the decrease of serum lipid levels consistently. Oxidation of LDL initiates inflammatory responses. Oxidized LDL is taken up by macrophages kick off the development of atherosclerotic lesions. There is strong evidence reveals that lipid molecules influence the regulatory mechanisms of inflammatory reaction that would possibly be mediatedby peroxisome proliferator-activated receptors (PPARs). In the present study, morin significantly suppressed the expression of TNF-α and intercellular cell adhesion molecule-1 (ICAM-1) in the serum of treated mice[41].

There are myriad of evidence suggests that morin is a potential antioxidant. Thus, the anti-atherosclerotic activity of morin probably due to its antioxidant effect which may further attenuated the inflammatory process.

Modulatory effects of morin on hyperglycemia:

Protective role of Morin against Hydrogen peroxide (H_2O_2), Streptozotocin (STZ), and Methyl methanesulfonate (MMS) induced genotoxicity in pancreatic β-cells (INS-1E cells) were demonstrated using COMET assay. Morin protects the pancreatic β-cells against oxidative stress stress-induced DNA damage by activating the Nrf2 signaling pathway. In addition, it also increased the intracellular SOD and CAT and attenuated glucose-stimulated insulin secretion following exposure to STZ[42].

Besides, morin (15 and 30mg/kg) played a protective role against STZ-induced diabetic nephropathy in rats. Morin significantly attenuated the elevated serum creatinine and uric acid levels. In renal tissue, morin

reduced the levels and activities of elevated TBARS, nucleic acids, total glutathione, non-protein sulfhydryl, and CAT in diabetic rats. Also, it prevents the histopathological alterations in the kidney of diabetic rats[43].

Ameliorative effect of morin neuropathy:

Further, protective effect of morin was investigated in experimentally-induced diabetic neuropathy in rats. In this study, STZ was administered single 65mg/kg b.w. injection intraperitoneally to induce diabetes. After 3 weeks of administration of STZ injection, diabetic rats were given morin (15 and 30mg/kg/day) orally for 5 successive weeks. At the end of the treatment, pain threshold behaviour tests were performed. In sciatic nerve, nerve growth factor (NGF), insulin growth factor (IGF-1), and inflammatory cytokines (TNF-α, IL-1β, IL-6), GSH, SOD, CAT levels, and TBARS were evaluated. I was found that morin significantly reduced the levels of inflammatory cytokines and TBARS and enhanced NGF and IGF-1 levels in sciatic nerves diabetic animals. Treatment with morin also improved the levels of GSH, CAT, and SOD in the sciatic nerve of diabetic rats. Hence these assessments exhibit the protective effect of morin through reduction of oxidative stress and inflammatory process and recommend the curative potentiality of morin in the reduction of diabetic neuropathy[44].

The antioxidant activities of morin hydrate in various diseases are recapitulated in Table 1.

Table 1: Effect of morin on endogenous antioxidants in different key models

Key Models	Activity	References
Hepatic ischemia reperfusion	Inhibition of xanthine oxidase and free radical scavenging activity	35
Hyperammonemia	Increased GSH levels and SOD, CAT, GPx activities	36
Alcoholic liver disease	Enhanced SOD, GPx activities and GSH levels	37
Myocardial infarction	Free radical scavenging activity, Enhanced the SOD and CAT activity and antioxidant enzymes and the level of GSH	38
Cancer	Enhanced SOD activity, expression of heme oxygenase‑1, and free radical scavenging activity	39
Cardiotoxicity and Neurotoxicity	Increasing GSH levels, decreasing MDA levels and enhancing antioxidant enzyme activities	40
Atherosclerosis	Decreases serum levels of LDL-C,HDL-C, TC, and TG Suppressed the expression of TNF-α, ICAM-1,and inflammatory cytokines	41
Hyperglycemia	Protect β-cells against oxidative stress stress-induced DNA damage Reduced kidney TBARS in diabetes rats	42, 43
Diabetic neuropathy	Decreases glucose, cytokines and TBARS Increases GSH, NGF and IGF-1	44

CONCLUSION:

In conclusion, studies assessing the antioxidant properties induced by morin have presently expanded to a wider range of therapeutic applications.Several studies on experimental animals have been reported but so far but no reports of morin on human patient are published. Few tests performed on human patients confirm the data obtained with animal models and, despite they are still insufficient to select morin as a true natural drug, but they are an excellent starting point for further investigations. Therefore, morin could be used in combination with other drugs to prevent several human diseases.

CONFLICTS OF INTEREST:

The authors declare that they have no conflicts of interest.

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