BIOMEDICAL IMPORTANCE OF MORIN –A REVIEW

Abstract

Morin is a phytochemical compound, polyphenol in nature isolated from the members of Moraceae family and found to be in appreciable amounts in various parts of these plants. Morin exerts beneficial as pharmacological effects against various ailments in humans. It exhibits antidiabetic, antitumoral, antihypertensive, antioxidant, antibacterial and neuroprotective property. It is widely distributed in *Morus alba* (white mulberry) and fig (*Ficus carica*), in almond (*Prunus dulcis*) and other herbs and fruits. This study emphasizes on the importance of morin and its prospects in applications of medical field.

Keywords: Morin, antidiabetic, antihypertensive, antioxidant, antibacterial, neuroprotective

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I. INTRODUCTION

Bioactive compounds obtained from plants, yeast and microbes are either used naturally or as semi- synthetic derivatives are widely applied in medicine in pharmaceutical industry. Various drugs for modern lifestyle diseases are directly obtained from these. Morin (IUPAC Name- 3,5,7,2',4'-pentahydroxyflavone), is one of the phytochemicals obtained from nature. It belongs to flavanol category with hydroxyl group at 3,5,7,2',4' positions. It is an yellow pigment from the plants of family Moraceae. Morin is one of the important constituents of many plant preparations. It is recommended to treat various human pathologies by the traditional system of medicine.

II. ABSORRPTION AND METABOLISM OF MORIN

Morin is available as either free or glycosylated form in nature. The glycosylated, methylated or sulfated form of morin was hydrolyzed by the enzymes of the small intestine and get converted into aglycone for absorption. The absorption from intestinal lumen to enterocytes and from blood into cells is an energy- dependent process (**Calliet *et al.*, 2007)**. This occurs with the help of specific shuttle proteins. In a study on wistar rats it is found that the plasma concentration of morin does not exceed 1% even on high dosage application. This proves that morin has very low intestinal permeability due to its presence of Multidrug Resistance-Associated Protein-1, a carrier protein. Once absorbed they are again converted to their glycosylated, methylated or sulfated form **(Yu, Fong, & Cheng, 2006)**. Upon oral administration of high doses of morin, a significant increase in blood morin aglycone was detected, suggesting that the activity of glucuronyl transferase/ sulfotransferase enzymes in the gut is easily saturated. Other hepatic enzymes are also involved in morin metabolism in promyelocytic leukemia cells of human.

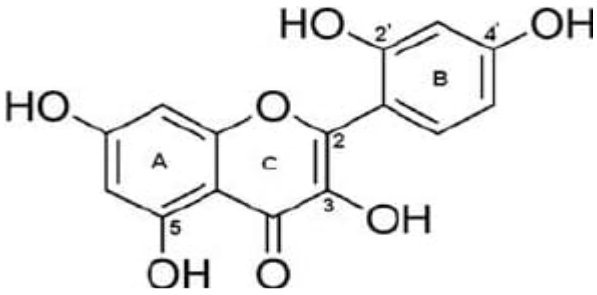

Figure 1: Structure of Morin

III. BIOMEDICAL PROPERTIES OF MORIN

1. **Anti-Hyperglycemic and Antidiabetic Activity:** Various in-vivo studies have shown that the Psidium guajava L. extracts are effective against diabetes as it contains high concentration of morin. It inhibits the activity of PTP1B which is involved in the regulation of the receptor signaling pathway. The extract shows a significant decrease in glycemia and lipid liver deposits in diabetic mice and in individuals with by maturity-onset diabetes and in healthy volunteers. Antihyperglycemic and antioxidant effects are seen in streptozotocin induced diabetic rats treated with the extract. Hence it suggests that these extracts containing morin can complement orthodox anti-diabetic therapies. In a study by **(Galvez *et al.*, 2001)**, it is found that morin increases glycogen synthesis and

decreases gluconeogenesis properties by acting as an insulin sensitizer. Morin-Zinc complexes have been found to strongly enhance the antidiabetic activity in diabetic rats. This acts by reducing the glycemic glucose, circulating lipids and lipoproteins fastly. It is also proved that there is no adverse effect in this complex **(Manna, Aggarwal, Sethi, Aggarwal, & Ramesh, 2007).** Morin activates insulin receptor signaling by directly inhibiting PTP1B enzyme or by increasing the transport of zinc ions into the cells. Morin also has the ability to inhibit the glycosylation process which results in protecting the organs from diabetic complications.

2. **Antioxidant Activity:** Reactive oxygen species (ROS) can damage the major biomolecules and regulates various cell signaling pathways when its production exceeds the activity of antioxidants. Morin, being a polyphenol and due to the presence of double bond between C2 - C3 atoms and the presence of hydroxy group at the C3 and 2' (of B ring) position makes it a strong antioxidant.it shows anti lipid peroxidation activity due to the presence of two hydroxy groups at 2'and 4' position of B ring. Morales *et al.*, have reported that the hydroxyl group in position 2' of B ring forms a hydrogen bond with the oxygen atom in position 1 of C ring, inducing rotation of the B ring, which acquires a planar configuration with respect to ring C. This in turn favors the transmission of electronic effects from the B ring to the double bond of C ring, thereby making morin as a free radical scavenger. Morin helps to prevent oxidized LDL uptake by macrophages, by inhibiting the oxidation of LDL. It thus suppresses the internalization process. It also contributes to atherosclerosis prevention. In a study demonstrated by Jonnalagadda *et al.*, 2013 It is shown that morin protects the rats from gentamicin induced nephrotoxicity which is caused by ROS that trigger and sustain chronic inflammatory response causing tubular necrosis. On pretreatment with morin strongly reduces the intestinal mucosal damage and inhibits inflammation and cells death by producing malodialdehyde and preventing the depletion of intra cellular reducing agents. It also prevents the cholesterol increase. The non- malignant cells are protected from cytotoxic activity of certain drugs (Kok L.D. *et al.,* 2003) and the cells are protected from the effects of chemotheraphy on administering morin. Morin has been observed to promote the expression of genes producing antioxidant response related proteins. Despite the absence of a structure that is a prerequisite in flavonoids for this property, morin was found to be a more potent anti-oxidant than any other in scavenging DPPH, ABTS and other free radicals (**Bors, Heller, Michel, & Saran, 1990**).

3. **Anti-Inflammatory And Antiallergic Activity:** Many invitro and in-vivo studies have shown that morin has anti-inflammatory properties, which acts by inhibiting the activated macrophages and the corresponding effectors that cause inflammation. The inhibition of Nf-kB, most significant effector was shown by Sunil K. *et al.,* 2007. Morin lowers the bowel deterioration and is also effective against liver inflammation in rats fed with high doses of fructose. It is also observed that the NO, TNF-α and IL-12 production are reduced in LPS activated macrophages by sulfate and glucuronide metabolites of morin, which shows the 1000 fold higher potency than morin.

Morin exhibits anti-allergic activity which was proven both in-vivo and invitro. The mechanism of reversible inhibition of Fyn kinase, one of the main effector of Syk kinase in mast cells is the function of morin. Through this process, the release of TNF-α, and IL- 6 & 8 and the degranulation of mast cells was inhibited.

4. **Anti-Tumour and Chemopreventive Activity:** Morin exerts anti-cancer activity by preventing the oncogene activation, reducing the damages in DNA molecules and by regulating the signalling pathways involved in proliferation and differentiation. It inhibits the activity of various carcinogenic chemicals. On treatment with morin, there is a significant decrease in tumour markers expression and oxidative stress in rats treated with anthracene. Similarly, morin blocks hepatocyte transformation caused by TPA.

5. **Inhibition of proliferation and apoptosis:** Morin inhibits cancer cell proliferation which is evident from the study performed by Brown J. *et al.*, 2003, in which morin arrests cell cycle at G2/M phase in human oral squamous carcinoma cells, without inducing the apoptosis process. But studies in human prostate cancer cells and in leukemia cells with morin have proved that morin induces caspase-3 and -9, Bax expression and suppresses the anti-apoptotic expression. It is also demonstrated that morin inactivates STAT3 signaling pathway. It thus promotes the apoptosis of cancer cells by 30% without affecting normal cells. Morin also prevents metal-catalyzed generation of free radicals by binding with the metal ions like iron, copper, cobalt, chromium and vanadium. This metal-morin complex also helps to remove free radicals effectively.

6. **Antihypertensive Activity of Morin:** Morin relaxes the vessels that are contracted by KCl, noradrenaline and phorbol ester derivatives and also improves the activity of classical anti-hypertensive drugs like isoprenaline and sodium nitroprusside **(Herrera M.D. *et al.*,)**. Hypertension induced by deoxycorticosterone acetate, causing renal and cardiac damages are reduced by morin pretreatment in rats. It acts by regulating the systolic and diastolic blood, decreasing serum insulin and triglyceride levels and by inhibiting endothelin-1 expression and thromboxane A2 (vasoconstrictor). It also aids in the production of nitric oxide, a vasorelaxant **(Taguchi *et al.*, 2014)**.

7. **Antibacterial Activity:** The antibacterial activity of morin-arabopyranoside present in the leaves extract of guava is found to act against Bacillus cereus and Salmonella enteritidis with a minimum inhibitory concentration of 300 and 150 micro g/ml **(Arima H. and Danno G.)**. **Kang S. S. *et al.*,** have reported that morin inhibits the two important enzymes that helps the adhesion of bacteria to the host cell which can establish an infection. The enzymes are sortase A and B, expressed in Staphylococcus aureus and other Gram-positive bacteria. *In vitro* studies showed that morin can inhibit the ATPase activity of the enzyme DNA helicase. This shows that the compound can act against both Gram-positive and Gram-negative bacteria **(Xu *et al.*, 2002)**.

8. **Anti-Uricemic Activity:** Morin has the ability to decrease the uric acid level in the serum of people with hyperuricemia, without impairing total serum antioxidant capacity. It acts by two different mechanisms. The conversion of xanthine into uric acid is reduced by inhibiting the enzyme xanthine oxidase. Or it may inhibit human urate anion transporter-1. In a study conducted by **Shi *et al.*, 2012**, it is found that the ethanolic extract of Ramulus Mori containing morin, mulberroside-A, oxyresveratol, etc., has the ability to regulate renal organic ion transporters and hence reduces the uric acid levels, protecting the kidney. Morin is also found to be less toxic and more potent, in comparison with other classical urate- lowering agents. Hence, it can be a good alternate source for the treatment of hyperuricemia.

9. **Neuroprotective and Anti- Amyloidogenic Activity:** Morin can act as a neuroprotective agent, protecting the neuronal cells from various damages. It exerts its action through various mechanisms. The nanomolar concentration of morin can protect the oligodendrocytes and cortical neurons from ROS accumulation. In mice treated with 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine, it is found that morin relives the symptoms of Parkinson's disease and prevents dopaminergic neuronal cell death **(Ibarretxe G. *et al.*, 2007)**. It also attenuates the ROS formation in PC12 cells, and also inhibits apoptosis. The action of enzyme glycogen synthase kinase 3 is inhibited by morin, which helps to treat the patients with Alzheimer's disease and tauopathies **(Gong *et al.*, 2011)**. Both in vivo and in vitro studies prove that inhibition of glycogen synthase kinase 3, will reduce the A β- induced tau hyperphosphorylation.

   Morin has the ability to disintegrate or inhibit assembly of amyloid and β-amyloid fibers. These are proteinaceous structures that appear in the late stages of various neurological diseases. The inhibition of β-amyloid peptide fibrillogenesis will protect the HT22 murine neuroblastoma cells from oxidative stress. The mechanism of this action was studied in *in-silico*, which showed that morin blocks the protein polymerization process by binding to the end of beta-amyloid growing fibrils. It also modifies tertiary and quaternary structures of newborn protofibrils, hence inhibiting their cytotoxicity and their conversion in mature amyloid fibrils **(Lemkul, Bevan, D.R. Morin 2014)**. Morin inhibits acetylcholinesterase activity thereby preventing the loss of Alzheimer's disease. In-silico studies revealed that morin targets the active site of β-secretase 1 and inhibits its activity **(Shimmyo *et al.*, 2008)**. Morin protects the membrane against perturbations induced by aggregates obtained from mutant and wild type of α-synuclein proteins.

10. **Inhibitory Activity of Morin on Enzyme Activity and Protein Function:** It is found that morin inhibits various key enzymes by competitively binding to the active site. It can inhibit cytochrome P450-2C9, monocarboxylate transporter-1, fatty acid synthase and some multidrug resistance proteins. Morin non-competitively inhibits RepA DNA helicase, PTP1B and urate anion transporter. According to **Iglesias *et al.*,** morin is able to inhibit phospholase A2 from *Crotalus durissus cascavella* venom by interacting with the hydrophobic catalytic site of the enzyme. But it does not alter its inflammatory and neurotoxic effects. Anyhow, morin can cause significant change in the secondary structure of protein albumin and effectively modulates its physiological functions **(Xie *et al.*, 2006)**.

11. **Toxicity of Morin:** Morin shows low cytotoxic effects in several studies demonstrated in animal models and cellular. However in in-vivo studies conducted in F344 rats, it shows no toxic effects and causes a mild increase in liver or kidney weight on supplying high doses. Hence, it was calculated that morin shows no adverse effects if the level does not exceed 300 mg/Kg of body weight/day **(Choi *et al.*, 2009)**.

IV. SUMMARY

The flavanoids are important compounds in drug development as they have various therapeutic and curative properties. Morin in such a case is an important compound in treating several diseases. Morin shows antioxidant property as it is a potent free radical scavenger. It also aids in prevention and treatment of neurodegenerative diseases through several mechanisms. It has anticholinesterase activity, anti-inflammatory activity. It inhibits

several regulatory enzymes that aids in releasing hypertension, controlling blood glucose levels in diabetes and in controlling the uric acid levels in serum. Apart from these, morin has anti-allergic and antibacterial properties. Morin acts as an anti-cancer agent by preventing the formation of ROS, induces the apoptosis of proliferating cells, and protects the cells from carcinogenic chemicals. Morin has the ability to reduce the side effects of chemotherapy. The cytotoxic effect of morin is negligible. All these properties make morin a powerful and less harmful compound and hence it can be used in drug preparation.

V. CONCLUSION

Though there are advancement in medical technologies, various diseases like cancer, neurodegenerative disease, diabetes are also prevailing. This emerges the production of new drugs from existing sources. Traditional medicine system has also contributed many drugs from natural sources to the society. In such a case morin is an interesting molecule with several healing properties. Antioxidant property of morin has influenced in many ways to treat cardiac diseases, cancer, neurodegenerative diseases. It is also found to interfere with various factors like proteins and helps to prevent and treat diabetes, hypertension, kidney failure, inflammation and bacterial diseases. Further research on the use of morin to develop natural drugs is warranted.

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