Morin Hydrate: Botanical origin, pharmacological activity and its applications: A mini-review

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Abstract
Flavonoids are one of the secondary metabolites belongs to a polyphenolic group, and are commonly found from different parts of the plant sources like fruit, vegetables, nuts, stems, seeds, flowers, tea, wine, propolis and honey. Flavonoids have been used in different ailments like anti-inflammatory, antibacterial, and antiviral activity etc. In the past decade, Morin Hydrate (3,5,7,2',4'-pentahydroxyflavone) a polyphenol compound has been extensively studied for different pharmacological activities in various human disorders, with slight side effects. This mini-review summarises the origin, nomenclature and highlights of its pharmacological activities.

1. Introduction
Plants produce different types of low molecular weight products. Most of them are helpful in plant defence mechanisms. Among them, flavonoids are a group of secondary metabolites related to a polyphenolic group distributed widely in plant kingdom having 3000 types of flavonoids. Flavonoids are having the different pharmacological activities like antihepatotoxic, anti-inflammatory, anti-ulcer activity. In spite of the various bioflavonoids, Morin Hydrate was one of the bioflavonoid in nature has a marked attention in nature.

Morin Hydrate (3,5,7,2',4'-pentahydroxyflavone), was a yellow crystalline polyphenolic compound coming from branches of Morus alba L (white mulberry) and red Wine. It is ubiquitously distributed in the family of Moraceae [white mulberry (M. alba)] and in almond (Prunus dulcis, family Rosaceae), in sweet chestnut (Castanea sativa, family Fagaceae) and other fruits also. From long back onwards Morin Hydrate produces different types of pharmacological benefits such as free radical scavenging activity, xanthine–oxidase inhibitor property, anti-inflammatory activity, Protective effect of DNA from damage caused by free radical, prevention of low density lipoprotein oxidation, and anticancer activity. Morin Hydrate was used in food and traditional herbal medicines. Further studies indicate that its health benefits in vitro and in vivo.

In spite of the vast research progress made on Morin Hydrate pharmacological/biological activities, there is no such article which comprisesly explains its botanical origin, pharmacological activities. So, in this present Review paper we tried to compile the few pharmacological activities of Morin Hydrate.

2. Chemistry of Morin Hydrate
Synonym: 2', 3, 4', 5, 7-pentahydroxyflavone.
Linear formula: C15H10O7·XH2O

The Morin Hydrate structure [Fig. 1] represents an isomeric form of quercetin, both having OH in position 3, a resorcinol moiety, and a carbonyl group in position 4; the only difference between them is the hydroxylation pattern on B-ring, which is meta in Morin Hydrate but Ortho in quercetin. Even though quercetin is regarded as one of the flavonoid with the highest antioxidant potential because it has all those groups, as well as an ortho hydroxylation pattern on B-ring, it has been demonstrated a higher effectiveness of Morin Hydrate facing certain oxidative processes.

3. Pharmacological activities
An increasing number of studies showed that Morin Hydrate having the different pharmacological activities, including cardiovascular disease, diabetic mellitus, neurodegenerative disease, cancer and anti-inflammatory activities. As inflammation leads to the various oxidative stress related disorders, thus anti-oxidant and anti-inflammatory activities of Morin Hydrate play a critical role in
the therapeutic processing, even though the cellular mechanisms of action need to be processed.

3.1. Anti-oxidant and anti-inflammatory effects of Morin Hydrate in cardiovascular diseases

Cardiovascular Diseases (CVD) are the chief mortality causes worldwide. Myocardial infarction (MI) is one of the CVD disorder. MI is the condition in which there is imbalance between the coronary supply and its myocardial demand and causes necrosis of myocardial tissue. As Morin Hydrate is mostly ubiquitous in white mulberry and in almond shows cardiovascular benefit qualities in isoproterenol-induced myocardial infarction in rats due to its free-radical scavenging activity attributed by the polyphenolic group. Morin Hydrate showed the significant beneficial effect on lipid profiles, blood pressure, serum glucose levels from the high fat diet induced hypertensive rats. And also, Subhash and Subramanian showed that by the administration of Morin Hydrate (30 mg/kg) by oral administration offered the protection against hyperammonemia by acting through reducing of blood pressure, oxidative stress and by increasing the antioxidant system in ammonium-chloride induced hyperammonemic rats induced by at dose of 100 mg/kg/b.w i.p.

Isoproterenol [1-(3, 4-dihydroxyphenyl)-2-isopropylaminoethanol hydrochloride] was one of the synthetic catecholamine and β-adrenergic agonist, which has been documented to produce severe stress in the myocardium, resulting in MI, if administered in supramaximal doses. Isoproterenol (ISO)-induced cardiac necrosis include increased oxygen consumption, increased calcium overload and accumulation, increased myocardial CAMP levels, deranged electrolyte milieu, changes in the myo-cardial cell metabolism, alterations of membrane permeability, intracellular acidosis and increase in lipid peroxides. Al-Numair et al. showed that pre treatment of Morin Hydrate (20, 40 and 80 mg/kg, respectively) daily for a period of 30 days, decreases the activities of cardiac marker enzymes in serum and increased activities in the heart, and decreased activities of calcium-dependent adenosine triphosphatase and magnesium-dependent adenosine triphosphatase in the heart, and activity of the sodium potassium-dependent adenosine triphosphatase increased in the heart. And also, showed a significant decrease in glycoprotein levels in serum and heart. ISO produces the myocardial infarction via free radicals mediated β-adrenoceptor mechanism. In particular, Morin Hydrate (40 mg/kg) significantly (p < 0.05) decreases the isoproterenol induced myocardial infarction in rats. The observed effects may be due to its anti-oxidant, anti-inflammatory and free-radical scavenging activity of Morin Hydrate. Up to now, the molecular mechanism of actions are not elucidated, further studies are required to prove the molecular mechanisms of Morin Hydrate.

3.2. Xanthine oxidase and uricosuric activity

Gout is a general systemic joint disorder that affects the 1% of western population. Hyperuricemia was a hallmark of gout. A serum uric acid level of more than 9 mg/dl was considered as gouty arthritis and incidence was 4.9%. Pathologically production of gouty arthritis occurs due to over production or decreased excretion of purine metabolic end product i.e. uric acid. Recently, a urate-anion transporter (URAT1) was identified in the brush-border membrane of the proximal tubule in human kidney, mainly involved in the serum uric acid level through reabsorption of urate from the lumen to the cytosol in kidney tubules. Different mechanism of drugs are used in the treatment of gout. These include Xanthine oxidase inhibitors (e.g. allopurinol), inhibitors of urate reabsorption at proximal renal tubule like probenecid and benzbromarone are employed as hypouricemic agents. Moreover these agents along with hypouricemic activity posses some undesirable side effects like hepatotoxicity associated with the benzbromarone. Some natural herbs were exhibited the xanthine oxidase inhibitor activity, along with other types of mechanisms which were helpful in the treatment of gouty arthritis and hyperuricemia related disorders. Morin Hydrate, which is a natural Chinese herb having the xanthine oxidase inhibitor activity along with other type of mechanism involved to reduce the rheumatic disorders. Because, mainly it inhibits the urate reabsorption at the brush border of proximal renal tubule membrane vesicles, explains this effects on the kidney to inhibit the urate reabsorption. By Lineweaver–Burk plot mechanism Morin Hydrate explained the inhibition of the urate reabsorption through competition mechanism, with a Ki value of 17.4 μM. In addition, this Morin Hydrate also had the mixed type of xanthine oxidase inhibitor activity i.e. Ki and Kmax values were being 7.9 and 35.1 μM, respectively. By using oxonate-induced hyperuricemic rat model, Morin Hydrate showed the uricosuric activity. Based on this above information Morin Hydrate has been used in the treatment of rheumatic disorders, along with further investigation also.

3.3. Anti-inflammatory activity

Free radicals, nitric oxide, leukotrienes were the main inflammatory parameters in the intestinal inflammation. They are involved in the production of inflammatory mediators in the intestinal inflammatory conditions. Morin Hydrate shown to inhibit the leukotriene-β4 synthesis and inhibition of nitric oxide synthase activity. Moreover, it also inhibits the myeloperoxidase activity, which was evidently increased in the intestinal inflammation marker of neutrophil infiltration. Another anti-inflammatory activity attributed to the Morin Hydrate, due to its anti-inflammatory cytokine responsible for the induction of inducible nitric oxide Synthase (iNOS) activity in enterocytes.

In intestine, inflammatory bowel disease (IBD) is a chronic phase of inflammatory disorder associated with two closely related conditions, namely Crohn’s disease, and Ulcerative colitis. The main aetiological events occurred in the development of IBD was synthesis and up-regulation of pro-inflammatory mediators, such as reactive oxygen species, cytokines and platelet-activating factors. Now-a-days, the drugs used for the management of IBD are 5-amino salicylic acid and local or systemic glucocorticosteroids, to exert their benefit through various mechanisms. Rats were impart colitis by single injection of colonic instillation of 30 mg of the hapten trinitrobenzenesulphonic acid dissolved in 0.25 mL of 50% ethanol. And the colitic rats were treated with Morin Hydrate 25 mg/kg orally for 4 weeks. Morin Hydrate showed the beneficial effect on 4th week following colitis insult, both macroscopically and microscopically. The anti-inflammatory activity associated by it decreasing the colonic myeloperoxidase, which is previously attributed its action in experimental colitis. Different biochemical mediators are involved in the colonic inflammation are...
myeloperoxidase, leukotriene B4, interleukin-1β synthesis, glutathione and malondialdehyde levels and nitric oxide Synthase activity. The anti-inflammatory activity of Morin Hydrate was mainly due to its inhibition of synthesis of most important cytokine interleukine 1β and decreased in the nitric oxide Synthase, free radicals involved in the inflammatory cascade. The anti-inflammatory activity of Morin Hydrate against experimental colitis in rats, due to its ameliorative effect of such as free radicals, leukotriene B4, nitric oxide and interleukin-1. 34

3.4. Anti-cancer activity

For decades, increasing studies focussed the potential anti-cancer activity of Morin Hydrate, in various kinds of cancers. For example, Morin hydrate, showed the anti-inflammatory activity in the acute phase of trinitrobenzoic acid induced colitis in rats, 31 exhibited the chemoprotective effect of chemically produced rat tongue carcinogenesis, 32 and inhibit the phorbol-ester induced transformation of rat hepatocytes. 33 Moreover, Morin Hydrate inhibits the peroxisome-proliferated activator receptor induced peroxisome proliferator-activated receptor alpha activation by inhibiting the lipoygenase pathway. 34 It also showed the inhibitory activity in release of inflammatory cytokines such as IL-8, interleukin (IL)-6, and tumour necrosis factor (TNF) from mast cells. 35

Morin Hydrate has shown its anticancer activity in cancer models like inhibit the growth of C6 rat glioma cells and murine melanoma cells. 30 The role of transcription factor nuclear transcription-KB (NF-KB) is involved in various kinds of cell proliferation, cell survival, tumor-igensis, and inflammation. By using the DNA binding assay study that induction of NF-KB activation pathway induced by tumour necrosis factor (TNF), phorbol 12-myristate 13-acetate, ceramide, lipopolysaccharide, interleukin-1, and H2O2 was suppressed by Morin Hydrate, through inhibition of IkB (inhibitory subunit of NF-KB) kinase, leads to suppression of phosphorylation and degradation of IkBα and consequent p65 nuclear translocation. Morin Hydrate also inhibited the NF-KB dependent reporter gene expression activated by TNF receptor, TNF, TNFR-associated factor 2, TNFR1-associated death domain, NFkB inducing kinase, IkB kinase, and the p65 subunit of NF-KB. Morin Hydrate also inhibits the NF-KB related products that are involved in the cell survival i.e. inhibitor of apoptosis protein 1 & 2, survivin, X-chromosome linked IAP, and Bcl-xl, invasion (matrixmetalloproteinase-9) and proliferation (cyclin D1and cycloxygenase-2) were down-regulated by Morin Hydrate. 36

3.5. In nephotoxicity

During the metabolic process we require the various metals for the enzymatic and non-enzymatic process in organic and inorganic form. But, the requirement of metals is in a limited range. However, various heavy metals are available in earth, mercury is a one among them. Mercury is a wide-spread environmental pollutant causes severe alterations in humans and animals. 37 Human beings are mostly exposed to heavy metals through the diet and inhalation. 38 Morin Hydrate at 200 mg/kg, i.p. for 10days simultaneously, showed the protection from mercuric chloride induced nephrotoxicity at dose of 5 mg/kg, i.p. for 5 days. Morin Hydrate significantly (p < 0.01). 39 Moreover, it showed the protection from serum markers like LDH, AST, ACP levels in significantly (p < 0.05), which are increased in renal nephritis and renal infarction. 39

4. Further studies

From the different studies reviewed in this article, Morin Hydrate has been useful in the management of different human disorders. Despite the in vivo and in vitro studies trying to elucidate the mechanisms of Morin Hydrate, and more studies are required to elucidate molecular mechanism of it. Moreover, clinical experiments are required urgently to provide a basis for prospective usefulness of Morin Hydrate in the treatment and mitigation of human diseases.

Conflicts of interest

The author has none to declare.

References

28. Salzman AL, Denenberg AG, Ueta I, O’Connor M, Linn SC, Szabo Á. Induction
and activity of nitric oxide synthase in cultured human intestinal epithelial
29. Stenson WF. Inflammatory mediators in inflammatory bowel disease. Curr Opin
30. Travis SP, Jewell DP. Salicylates for ulcerative colitis and their mode of action.
flavonoid morin on chemically induced rat tongue carcinogenesis. Int J Cancer.
1999;83:381–386.
33. Hsiang CY, Wu SL, Ho TY. Morin inhibits 12-O-tetradecanoylphorbol-13-
acetate-induced hepatocellular transformation via activator protein 1
signaling pathway and cell cycle progression. Biochem Pharmacol. 2005;69:
1603–1611.
34. Thuillier P, Brash AR, Kehrer JP, et al. Inhibition of peroxisome proliferator-
activated receptor (PPAR)-mediated keratinocyte differentiation by lip-
35. Kempuraj D, Madhappan B, Christodoulou S, et al. Flavonols inhibit proin-
flammatory mediator release, intracellular calcium ion levels, and protein kinase
36. Chen YC, Shen SC, Chow JM, Ko CH, Tseng SW. Flavone inhibition of tumor
37. Sembulingam K, Sembulingam P. In: Essential of Medical Physiology. 4th ed. J. P.
38. Goldstein RS, Schnellmann RG. Toxic responses of the kidney. In: Klaffen CD,
Amdur MS, Doull, eds. Casarett and Doull’s Toxicology. 5th ed. NY: Mc Growhill,
Effect of MORIN on mercury chloride induced nephrotoxicity. Theecoscan.