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Efficacy of Morin as a Potential Therapeutic Phytocomponent: Insights into the Mechanism of Action

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ABSTRACT

Morin (3,5,7,29,49-pentahydroxyflavone) is a yellow colour natural bioflavonoid abundantly available in different species of Moraceae family. Besides this, Morin is also harvested from several other sources like tea, coffee, cereals, fruits and red wine. Anti-oxidant, anti-inflammatory, and antiproliferative potency of Morin is well established in both in vivo and in vitro experiments. Among all major sources of Morin, Almond (Prunus dulcis), Fig (Chlorophora tinctoria), and Indian guava (Psidium guajava) contains high quantity of it. Easy availability, less side effects and robust functional properties have encouraged the use of these plants in the traditional herbal medicine. In last few decades, the studies on Morin have opened up a whole new era in the therapeutic medicine. Besides anti-oxidant, anti-inflammatory, and antiproliferative activity, Morin has also been reported as a potential neuroprotective agent against many neurological diseases including Alzheimer's disease, Parkinson's disease, and cerebral ischemia. According to published reports, the underlying neuroprotective mechanism of Morin is focused mainly on its capacity to inhibit oxidative stress in brain. However, recent data also supports its efficacy in neuroprotection by effectively interacting in the β–amyloid pathways, inflammatory pathways, and apoptotic pathways. In the present review, we have accumulated all the protective contributions of Morin and intended to drag a mechanistic pathway containing the molecular events leading to the protection against various anomalies.

Keywords: Morin, Oxidative stress, Inflammation, Apoptosis, Neuroprotection

INTRODUCTION

Morin (3,5,7,2',4'-pentahydroxyflavone) is a plant derived flavonoid widely available from *Moraceae* family [1]. Use of Morin has been found to be effective in a wide range of disease pathologies, which includes Alzheimer's disease (AD) [2,3], Parkinson's disease (PD) [4,5], ischemia [6,7], diabetes [8-10], cancer [11-13], cardiovascular anomalies [14,15], and renal complications [16]. Morin is considered as a potent therapeutic drug suggested for all those diseases, which are mainly affected by free radical vandalism [17]. Progressive research has showed that, administration of Morin has not associated with any adverse side effects [18]. Moreover, it is comparatively cost-effective and easily available [19]. The protective efficacy of Morin is mainly attributed by its anti-oxidant properties and also the unique structural feature that assists Morin to interact with nucleic acids, enzymes and proteins [20]. Besides well-known anti-oxidant property of Morin, it has recently been highlighted for the therapeutic benefits in neurological anomalies [6]. Available reports are suggesting that, administration of Morin is effective against AD and PD pathology [2,5]. However, detail molecular mechanism of which is still equivocal. Morin is reported to confer

neuroprotection by influencing the pathways like inflammatory pathways [19,21,22], β-amyloid (Aβ) pathways [2], and apoptotic pathways [10]. Additionally, Morin also exhibits its efficacy in the recovery from psychomotor and cognitive abnormalities [23] as reported in various animal models. Along with neuroprotection, benefits of Morin administration in ischemia, diabetes, cancer, cardiovascular complications, are also have been discussed here in the present review to get a clear insight into the Morin mediated molecular mechanisms.

STRUCTURAL CHEMISTRY OF MORIN

Morin (2′,3,4′,5,7-pentahydroxyflavone) is a C15 flavonoid structure, containing three phenolic rings, which was first isolated in the year 1830 [24]. Traditionally flavonoids are conformationally flexible and the same is true for Morin (Figure 1). Such chemical nature is mainly due to the electronic and intermolecular environment. Additionally, Morin is having the competitive binding affinity to the serum thyroxin transport protein- transthyretin [25]. Reports have suggested that Morin could occupy the thyroxin-binding site in more than one orientation, which indicates the thyromimetic property of Morin. Furthermore, Morin is also known for insulin mimetic properties due to its unique structural configuration [9].

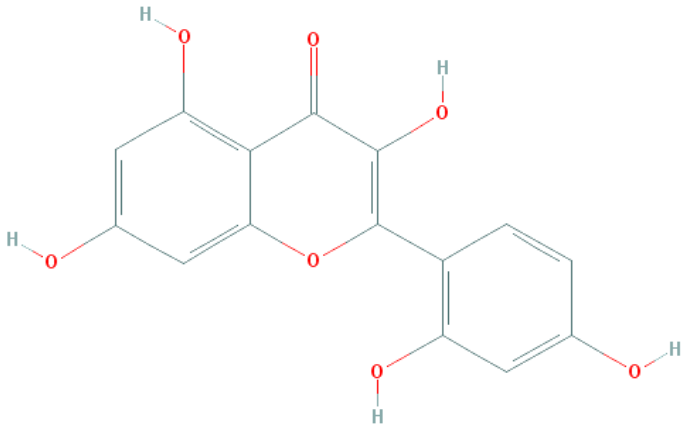

Figure 1 Structure of Morin (Source: Pubchem; https://tinyurl.com/y7j9l9rj)

AVAILABILITY AND NATURAL SOURCES OF MORIN

Available reports have listed several naturally occurring plants, which contain high quantity of Morin in different vegetative parts of the plant [26]. Brief descriptions of different natural sources of Morin have been discussed below.

Almond (*Prunus dulcis*, syn. *Prunus amygdalus*)

The almond varieties are widely distributed in Middle East, Indian subcontinent and North Africa. Drup is the fruit type of this plant, hull of which contains high quantity of Morin [27].

Guava (*Psidium guajava* L.)

There are different varieties of guava plants available throughout the globe. *Psidium guajava* is the commonest form of similar kind. However, yellow guava or lemon guava is also found to be abundant in Caribbean, Central America and South America. In every variety of guavas, a high quantity of Morin is reported in their leaves. Along with Morin, several Morin like structural components such as Morin-3-O-lyxoside, Morin-3-O-arabinoside, quercetin, and quercetin-3-O-arabinoside, are also available from this plant [28].

Old fustic (*Chlorophora tinctoria* or *Maclura tinctoria*)

Old fustic or dyer's mulberry is a neotropical tree largely found in South America. The yellow pigment harvested from this plant is rich in flavonoid-Morin. Previously such product was used for the colouring purpose in American military apparel. However, leaf, bark, fruit, and other vegetative parts of the plant contain considerable quantities of Morin, which is now cultured and harvested for medicinal benefits [29].

Osage orange (*Maclura pomifera*)

Maclura pomifera is commonly called as the Osage orange, which is regarded as deciduous type of tree/shrub. Osage orange contains distinctive fruit, which turns into bright yellow-green when they are ripen. The fruits and other parts are known to contain Morin as the most abundant phytochemical compound [30].

Acridocarpus orientalis

This is a genus of plant belonging to the family *Malpighiaceae*. Leaf, fruit and bark of the plant contains yellow-pigmented flavonoid Morin. The said active phytochemical component is harvested from the plant throughout tropical and subtropical Africa [31].

Onion (*Allium cepa*)

Experimental evidences by Kim, et al. and some other recent reports [32,33] have shown the therapeutic potency of Morin extracted from onion peel. Morin from onion peel also reported to protect DNA from toxic exposure [34,35].

Apple (*Malus pumila*)

According to recent research, apple is the most flavonoid rich fruit in American daily diet. Apple contains high quantity of Morin in fruit skin [36].

Tea (*Camellia sinensis*)

Tea (green) is known to contain several flavonoids, which are potent oxidant killers and contain anti-inflammatory properties. Morin is one of the crucial phytochemicals in tea. Several reports on health benefits by tea are actually contributed by Morin with or without other associated phytochemicals [37].

Other beverages

Red wine: While compared with white wine, red wine contains significantly higher quantity of Morin and other flavonoids, which poses several health benefits, owing to its anti-oxidant, anti-inflammatory and anti-apoptotic properties. The abundance of Morin and other phytochemicals also enriches the taste and flavor of red wine, which provides a global acceptance for both recreational and health benefits [38].

Coffee: It is regarded as the most common source of Morin, which we take frequently in our daily diet. Morin from coffee has been reported to acts as a chemo-preventive agent against oral carcinogenesis *in vitro* and *in vivo* [39,40].

Cereal grains: Cereal grains are known to contain large amount of various flavonoid phytochemicals including Morin. Health benefits from cereals are appreciable [41].

MORIN METABOLISM AND BIOAVAILABILITY

Morin can be traced from the natural food as its glycosylated derivatives or as a free phytochemical [26,42,43]. During dietary intake it has been shown that, derivatives (glycosylated, methylated or sulphated forms) or free Morin flavonoid reach into gut. Where, upon hydrolyzation, it converts into its respective aglycone form [44], which assists the derivatives for easy uptake from gut. However, the unabsorbed portions are then reach into large intestine, where bacterial action forms the desired Morin aglycone, that after tagged with specific protein transported into cellular membrane [45]. Several experimental evidences have showed that, an energy-driven transport system is associated with the transport of Morin from circulation to the cell interior [45,46]. Many researchers have reported the very similar mechanism while enterocytic uptake of Morin occurs in gut. It is noteworthy that, Morin is having comparatively less permeability potency through intestinal membrane [47]. This is one of the reasons underlying the less bioavailability of Morin after administrating selective higher dose of Morin [48]. Moreover, Multidrug Resistance-Associated Protein-1(MRAP-1) activity in gut is another reason of Morin extrusion [49]. Experimentally, inhibition of MRAP-1 by selective chemical component has showed improved Morin uptake and the mechanisms of which provides the possibilities of regulation of biological action of Morin [47,49].

THERAPEUTIC USE OF MORIN IN VARIOUS DISEASE PATHOLOGIES

Anti-oxidant activity of Morin has been reported to be effective against free radical scavengers in several disease profiles [8,17]. Anti-oxidant levels and activities have been reported to be enhanced in animal model of diabetes after

the treatment with Morin [7,17,34,42]. Administration of Morin has been reported to improve the pathological condition of hyperglycemia, glucose intolerance and insulin resistance [8,9]. Lipids and lipoproteins are the major causative entities for cardiovascular anomalies [50]. Morin is able to inhibit most of the effectors involved in inflammation, as a potent anti-inflammatory agent by inhibiting activated macrophage cells both *in-vitro* and *in-vivo* [4,21,22]. Morin administration has been found to be beneficial, as it has been reported to normalize abnormal bioprofiles immediately after dosing. Reduction in the levels of lipid peroxides is also evident after Morin administration [7,45]. It is well-known that, TNFα is an endogenous pyrogen, which is responsible for several pathogenic modulations like- fever, apoptotic cell death, cachexia, inflammation in host [51]. Levels of TNFα were found to be decreased after the administration of Morin [51,52]. Moreover, Morin administration was effective in reducing the elevated inflammatory cytokines IL-1β, and IL-6 [53]. Such contribution of Morin provides justifiable support for its anti-inflammatory properties. Morin also ameliorates high fructose-induced hepatic SphK1/S1P signaling pathway impairment and decrease NF-κβ activation in rodent and cellular models [54]. It is also reported to reduce hyperlipidemia and liver lipid accumulation in animal and cell line models [54,55]. Several other contributions of Morin have been documented in the last five decades. For the better understanding, here in this study we have segregated all those contributions under the disease head, which are briefly described in the following sections.

THERAPEUTIC EFFICACY OF MORIN IN ALZHEIMER'S DISEASE

The pathological hallmark of Alzheimer's disease (AD) is the toxic aggregation of amyloid beta (Aβ), which is the product of Amyloid precursor protein (APP) abnormally cleaved by β-secretase enzyme [56-58]. It has been observed that, neurons are extremely sensitive to the external and internal changes due to altered redox balance [59]. Such alteration for a longer time (chronic) influences inflammatory and further progress of similar pathology initiates apoptotic mechanisms [60]. Evidences have shown that, administration of Morin provides adequate neuroprotective effects in AD animal model as well as in AD patients [2,3,23,61]. One of the potential contributions of Morin is the inhibition of glycogen synthase kinase-3β (GSK 3β), which is regarded the determining enzyme in the occurrence of AD pathology [62]. It has been reported that inhibition of GSK 3β function can alter several crucial pathways in cellular environment [63,64]. Alteration in choline metabolism and microtubule dynamics are notable among them [62,65]. Further, such inhibition has been seen to trigger apoptotic mechanism and impairs the axonal transport, which in terms of neurological spectrum is having utmost importance [66,67]. In AD perspective, inhibition of GSK 3β has been reported to improve the cognitive condition among patients [68-70]. Morin at low concentration has showed (*in vitro*) remarkable inhibition of GSK 3β activity and thereby, reducing the pathogenic Aβ load in neuron, which further reduces the possibilities of Aβ-induced tau protein hyperphosphorylation [71]. However, another study has shown that, Morin with the similar dose spectrum significantly reduced phosphorylated tau content in rodent AD model [62]. The very same study also supports the earlier reports, which postulated the therapeutic concerns of Morin against tauopathies. Recent reports have documented the NF-kβ inhibitory properties of Morin [72]. By doing so, Morin also explores the possibilities to be an anti-inflammatory drug, as NF-kβ is one of the major target molecules for anti-inflammatory treatment [73,74]. Morin is known to disintegrate the aggregate prone Aβ fibers and such mechanism contributes to the anti-amyloidogenic action of Morin [2]. In another study, HT22 murine neuroblastoma cells with high ROS content (induced by Aβ fibrils) were treated with Morin and outcome of the study showed potential role of Morin in the inhibition of Aβ fibrilization [23]. However, all these results are at initial stage of investigation and underlying molecular mechanisms are yet to be established. There are some *in silico* studies, demonstrating the hypothetical molecular dynamics underlying the inhibition process of Aβ by Morin. Such approach has put forwarded a concept that, the binding of Morin to the Aβ fragments, blocks the site needed for polymerization and therefore exhibits anti-amyloidogenic activity at least in virtual platform [75]. Further work progress has highlighted that; Morin also alters the three-dimensional structure of protofibrils and Aβ fibers, which confers neuroprotection by inhibiting the cytotoxicity and Aβ aggregation [76]. AD patients are also reported with high acetylcholinesterase (AchE) activity and therapeutic approaches targeting AchE have been found to be beneficial against AD pathology [77]. Interestingly, Morin administration is also known for the very same outcome and therefore, a robust therapeutic intervention could be achieved with Morin administration. Experimental evidences have shown that, Morin is able to inhibit the putative enzyme β-Secretase 1, which is responsible for abnormal production of the amyloidogenic peptide [78]. Virtual studies have supported this notion and further showed that, there is high binding affinity of Morin on the active site of the enzyme β-Secretase 1. Such interaction is mainly targeted to the Asp228 residue (catalytic) of the enzyme [79]. Furthermore, Cadmium induced oxidative neuropathy has been reported to be ameliorated by the

administration of Morin [80], which also have shown the additional benefit in the use of Morin as a therapeutic drug. The above discussion directs to the obvious conclusion that, Morin is having potential therapeutic benefits for AD and further research could consider Morin as a therapeutic drug alone or with suitable combination of other effective drugs.

Protective role of Morin in Parkinsonian pathology

Parkinson's disease (PD) is a progressive neurodegeneration characterized by redox imbalance and nigrostriatal neurodegeneration [80-82]. Morin has been reported to inhibit ROS formation, caspase-3 activation and apoptosis in PC12 cell-line intoxicated with MPP+ (1-methyl-4-phenylpyridinium ion) [83]. The study also has documented the efficacy of Morin as an effective drug for the symptomatic rectification of PD [83]. In summary, the outcome of that study highlighted that, Morin is having the ability to rescue dopaminergic neurons from the neurotoxic insult of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). Several other studies have demonstrated that, Morin and other bioflavonoids are potent to normalize the dopamine level, which is an additional benefit in the PD therapeutics [84,85]. ROS mediated over activation of AMPA receptor is responsible for several detrimental changes in neuron [86,87]. Studies have shown that, Morin is capable of normalizing the said anomaly with minimal dose administration spectrum [88,89]. Another study also reported the possible role of Morin in normalization of membrane integrity in α-synuclein mutants [90]. Reports also indicating the potential contribution of morin along with some other phenolic compounds in the maintenance of membrane integrity after being insulted with α-synuclein aggregates [5,90]. Morin attenuates the toxic insult of endogenous neurotoxin 6-OHDA (6-hydroxydopamine) and thereby rescues the dopaminergic neurons of substantia nigra pars compacta [83,91]. Studies have shown that, through this mechanism, Morin also ameliorates the behavioral deficits in 6-OHDA intoxicated rodents [84,92]. Similar activity of Morin is also evident in other neurotoxins and snake venom-induced toxicity [18,93,94]. It has been reported that, not only dopamine, Morin also normalizes the serotonin and other neurotransmitter levels in various regions of PD-toxin induced rodent animals [18,95]. Besides detoxification, Morin also have shown its efficacy to inhibit the activity of MAO-B (monoamine oxidase-B), which has added the additional benefit in the neuroprotective mechanism by Morin [96]. However, the mechanism by which Morin interact with α-synuclein and Lewy body are equivocally reported. More studies are the urgent need of time to explore the interaction, which could add more information for the future therapeutics.

Efficacy of Morin in the therapeutics of cerebral ischemia

Cerebral ischemia (CI) is another disease profile, where redox imbalance, neurochemical anomalies and inflammatory responses have been frequently reported [97,98]. Several therapeutic paradigms have been described previously to cope up with the severity of seizure [99], ischemia and ischemic stroke [100,101]. Administration of Morin has shown remarkable outcome in CI by reducing the cerebral infract volume and redox imbalance in neuron [6,7,102]. In a comparative analysis, Morin has shown greater efficacy than traditionally prescribed drugs like paracetam or protocatechuic acid, which has been experimentally evident from the improvement in histochemical as well as psychomotor anomalies in rodent models of CI [103-105]. Additionally, apoptotic genes were found to be down-regulated after Morin administration in CI animals [95,106-108], which adds additional support to the neuroprotection in CI pathology. It is presumable that, Morin mediated anti-oxidant defense is one of the crucial mechanism which also reduces the inflammatory responses of inducible nitric oxide synthase, myeloperoxidase, cyclooxygenases, NF-κβ and tumor necrosis factor-β (TNF-β) [21,44,54,109,110]. Together, Morin induced neuroprotection in CI accounts a large spectrum of protective mechanisms like restoration of anti-oxidants, inhibition of lipid peroxidation, inflammation, and apoptosis. Therefore, future therapeutics could consider Morin as a 'wonder drug' and could formulate novel therapeutic approaches by adding additional bioactive components or synthetic approaches documented earlier [111-117], specifically for the amelioration of ischemic conditions.

Antibacterial activity of Morin

Morin is a potential bioflavonoid against bacterial diseases [18,118-120]. Such antibacterial efficacy of Morin is chiefly attributed by the putative enzymatic inhibition in bacteria [121]. It has been reported that, Sortase A- the crucial enzyme secreted by bacteria, is responsible for the host surface adhesion process, which secures the pathogen on host surface and assists in the invasion process [122-124]. Morin inhibits that particular enzyme activity and thereby hindering in the establishment process of the bacteria. Further, Morin also inhibits the ATPase activity of DNA

helicase RepA, which reduces the growth of the bacteria [125]. Morin derivatives and analogous structures also have showed better anti-bacterial activity in both cellular and rodent model system. Morin-3-O-arabinoside and Morin-3-O-lyxoside extracted from *P. guajava* have shown effective antibacterial effect in securing stored food quality by inhibiting the growth of *B. stearothermophilus, B. ther-mosphacta, E. coli, L. monocytogenes, P. fluorescens, enterica, S. aureus, and V. cholera* [126,127]. Depending upon available information it is presumable that, Morin is an effective antibacterial phytocomponent, which is having potential industrial efficacy to improve the shelf-life and the safety of foods, thereby preventing from food-borne diseases.

Protective effect of Morin in diabetic pathology

Several reports have documented antidiabetic activity of natural products earlier [128-130]. However, in quantitative approach, methanolic extract of *P. guajava* L. has showed high concentration of Morin [131,132]. From the very same species, PTP1B inhibiting activity and related improvement in insulin receptor signalling has been reported, which directly supports the notion of antidiabetic activity of Morin [131,133]. Studies in animal model have shown that, *P. guajava* extracts reduces hyperglycaemia and lipid deposits in liver [133]. Apart from this finding, *P. guajava* L. extracts showed antidiabetic and anti-oxidant effects in streptozotocin-induced rat model of diabetic complications [134-136]. In another study, Morin administration has showed increased insulin receptor activation with decreased gluconeogenesis potency [137]. Several reports have documented the insulin mimetic effect of Morin, which also promotes the crucial influence in the normalization of blood glucose level [9,138]. The effect of Morin has been found to be similar with the conventionally used antidiabetic drug- Glibenclamide [139], which shares common functional attributes in terms of rescuing pancreatic insulin-producing cells from cell death, sustaining insulin release, and by increasing the glycogen synthesis in liver [140]. Studies have shown that, Morin with zinc provides better functional attributes [141,142]. In chronic spectrum, administration of Morin-Zinc complex showed decreased glucose level, improvement in insulin production, reduction in glycosylated hemoglobin content, and lipid profile [143-145]. Depending upon the administration type (with or without Zinc), Morin enhances the insulin receptor mediated signaling and efficiently reduces the blood glucose levels [146-149]. Furthermore, Morin has been reported to inhibit the protein glycosylation, which in turn reduces various inflammatory markers in the central nervous system and circulation as well [150,151]. Inhibition of protein glycosylation also responsible for the increased level of circulatory neurotrophic factors [146], which adds beneficial contribution to maintain healthy neuronal environment. Together, all these contributions establish the efficacy of Morin as an adequate substitute for traditional synthetic antidiabetic drugs.

Anti-gout activity of Morin

Uric acid (UA) is regarded as the primary anti-oxidant of blood, excess of which has been reported to remove through excretion [152,153]. However, in diseased condition, UA synthesis increases exponentially, as a result, elimination of excess UA from circulation becomes difficult. The excess UA accumulated in different joints, which lead to chronic inflammation and pain. This pathological scenario is clinically diagnosed as Gout or hyperuricemia [154]. In such situation, UA becomes the prime causative factor for intolerable pain, systemic inflammation, and damages in kidney. Studies have shown that, Morin is effective against such increased UA mediated complications [155]. Morin efficiently reduces the serum level of UA either by inhibiting xanthine oxidase or by inhibiting urate anion transporter-1 [153,156]. These pathways reduce the synthesis of UA and reabsorption of UA respectively. Further studies have showed that, Morin administration reduces plasma UA, without hampering the anti-oxidant balance in the cell [157,158]. Moreover, Morin administration showed no side effects and restores adequate UA level in circulation. In case of inhibition of urate anion transporter-1, Morin showed profound efficacy, which is even better than the prescribed drug of similar attribute like Probenecid and Sulfinpyrazone [159,160]. Hence, further studies could establish Morin as the most suitable alternative medicine for anti-Gout therapy.

Protective effect of Morin against cardiovascular anomalies

Hypertension, Obesity, increased lipid profile, and diabetes are the most common lifestyle disorders, which imply the possible risk for critical cardiovascular diseases (CVD) [161-163]. CVD is reported to be influenced by several exogenous and endogenous factors, which include genetic malfunction, endothelial dysfunction, inflammation, and ROS production [152]. Conventionally, anti-oxidant therapy is the most common form of therapeutic approach prescribed throughout the world [129,164,165]. Concerning hypertension, Morin administration has been found to be

effective as it expands the diameter of the blood vessel and effectively recapitulates the function of traditional drugs like Isoprenaline and Sodium nitroprusside [166]. In animal model of hypertension (induced by deoxycorticosterone acetate-salt), Morin treatment showed positive result and restored the psychomotor behaviors [16,167]. Similar studies also have established that, Morin significantly decreases the systolic and diastolic blood pressure in rodent model of hypertension [167]. In fructose diet induced hypertensive model, Morin treatment showed reduction of blood pressure, normalization of lipid profile and decreased endothelin-1 expression [168]. Increased production of vasorelaxant (nitric oxide) and decreased production of vasoconstrictor (thromboxane A2) are also evident from Morin administration [169]. All these contributions depict that, Morin administration could effectively reduce the risks of CVD pathologies and further studies could postulate Morin as a potential drug for anti-CVD therapy.

Anti-cancer activity of Morin

Cancer is one of the leading causes of global mortality, which appears when oncogenes gets activated or massive DNA damage occurs [170-173]. Such anomalies trigger the fate of the cell towards uncontrolled proliferation and invasion [162]. Among numerous suggested natural compounds, Morin is found to be most promising, which showed profound anticancer activity by reducing DNA damage and modulating signalling pathways responsible for proliferation and differentiation [95,174,175]. Morin is having the potency to inhibit carcinogenic activity of malformed cells and also has been reported to stop the tumor formation induced by carcinogenic chemical compounds [165]. In rat model of carcinogenesis (induced by 7,12-dimethylbenz(a)-anthracene), Morin administration have showed reduced oxidative stress, decreased expression of tumor markers and inhibition of tumor growth [176]. Similar result has been found in another study, where carcinogenesis was induced by 12-O-tetradecanoyl-phorbol-13-acetate and after Morin treatment, restriction in carcinogenic transformation in liver cells was reported [177,178]. Morin also exerts notable effect by regulating the signalling pathways and changes the cellular fate against carcinogenesis. Morin is capable of arresting the affected cells in G2/M phase for long time. Such activity generally stops the carcinogenic progress of cell but do not cause the cell death by apoptosis [179]. Furthermore, Morin has been reported to induce apoptosis in prostate cancer (LNCaP) and leukemia (HL-60) by activating caspase-3 and Bax, which in turn increases the expression of caspase-9. Effective involvement of caspase-3 and caspase-9 stimulates cytochrome c to be released from mitochondria. However, gross outcome after Morin involvement is the decreased expression of anti-apoptotic Bcl-2, which triggers the fate of the cell towards death by apoptosis [180,181]. Even in myeloma cells, administration of Morin has found to be effective as it triggers the affected cell towards apoptosis via inhibition of STAT3-mediated pathway by SHP-1 [182]. Morin is having affinity for naturally occurring metal ions and it has been reported that, the activity of Morin increases once it forms a complex with available metal ions namely, zinc, copper, iron, vanadium, cobalt, and chromium. Haber-Weiss reaction is the crucial step, which needs Morin-metal ion complex to scavenge the ROS content in cytosol. Morin plays another critical role by regulating the expression of cytochrome P450-2C9 and cytochrome P450-3A4 enzymes, which are crucial in toxic metabolites generation from xenobiotic metabolism [24,183,184]. Most of such xenobiotic metabolites are carcinogenic by nature and their related conversion warrants the effective involvement of cytochrome P450 family enzymes. Morin has been reported to inhibit such enzymatic action and thereby, promoting the anticancer effects [185,186]. P-glycoprotein plays essential role to keep aside the target organ from the chemotherapeutic drug, which results into the failure of cancer chemotherapy [187]. Morin administration has been reported to improve the bioavailability of chemotherapeutic drugs by inhibiting P-glycoproteins [188-190]. Taken together, Morin plays a robust protective role in reducing carcinogenic progress. Hence, future therapeutics could consider Morin (with or without metal ions) as a novel drug for anticancer therapy.

MOLECULAR MECHANISMS OF MORIN MEDIATED PROTECTION

Present study draws a mechanistic hypothetical pathway, which relates all the protective contribution by Morin, depending upon available research and studies. As majority of the pathological progress warrants the effective involvement of ROS and inflammation [191-196], the very same has been reported to be reduced after Morin administration. The molecular mechanisms of such anti-oxidant and anti-inflammatory properties are the regulated actions of Morin, which acts through controlling various cell-signaling pathways [180,197,198]. It has been reported that, excess ROS formation provokes the up-regulation of anti-oxidant enzyme synthesis to rescue the cellular ambient environment from free radical activity. Morin has been reported to stimulate the expression of anti-oxidant proteins like Superoxide dismutase, Catalase, Heme oxygenase-1, Glutathione peroxidase and Glutathione reductase [199]. Plenty of evidences have shown that, phytochemical compounds can reduce the ROS load in cell and can secure

the cell viability [200]. Chemical structure of Morin is the answer for its robust functional contributions. Presence of double bond at C2-C3 position and a hydroxyl group at C3 position plays a crucial role in this regard. However, hydroxyl groups at 2′ and 4′ positions (ring B) also play notable role in the reduction of lipid peroxidation. The same 4′ hydroxyl group is also reported for its contribution in radical scavenging activity of Morin. It is notable that, 2′ hydroxyl group structurally separates Morin from other similar phytocomponents like Myricetin, Quercetin etc., which are also responsible for the effective and conclusive free radical scavenging activity of Morin [201,202]. Even in some *in silico* studies, it has been shown that rotation of B ring owing to the presence of hydrogen bond formation (2′ hydroxyl group with position 1 of the C ring) favours the transmission of electrons from B to C ring (forms double bond) and such mechanism provides Morin an effective scavenging ability [203,204]. In doing so, Morin attenuates the risks of lipid peroxidation and related atherosclerosis. Similar mechanism also assists to normalize the lipid profile in body. While other studies have experimentally proved that, Morin reduces the lipid peroxidation by 2,2'-azo-bis-(2-amidinopropane) dihydrochloride and prevents the cellular accumulation of oxidized LDL by reducing CD36 expression on membrane. Morin also prevents the damage caused by oxidative action of peroxyl radicals generated by 2,2'-azo-bis (2-amidinopropane) dihydrochloride, xanthine oxidase plus hypoxanthine system, menadione, 3-morpholinosydnonimine-N-ethylcarbamide (SIN-1), and N-nitrosodiethylamine [205,206]. Morin has been reported to have profound nephroprotective activity, which is accompanied by the anti-oxidant and anti-inflammatory properties [207]. The study was conducted with Gentamicin and it caused severe ROS generation and inflammatory responses, which dragged the cellular fate towards tubular necrosis. After Morin administration, all the anomalies were ameliorated, and normal kidney function was evident [198]. Morin also protects the lung cells from H_2O_2 or γ-irradiation mediated DNA damage and related pathological implications [106,208,209]. Besides these, Morin also maintains mitochondrial dynamics, inhibits the release of pro-apoptotic proteins [10], and prevents DNA damages [141], all of which have been evident in toxin-induced diabetic rodent model [9,132]. Moreover, Morin scavenges ROS and reduces inflammatory entities in cyclophosphamide-induced liver toxicity [210,211]. Similar reduction in xanthine oxidase level by Morin helps to reduce the risk of ischemic-reperfusion [15,153,155,157]. Excess metal ions in body provoke ROS level through Fenton reaction [212]. Studies have shown that, herbal polyphenols are potent in reducing the ROS by chelation. Especially, Morin forms stable complex with such metal ions and thereby reducing the load of free metals from cytosol and extracellular spaces [213,214]. Further, the complex of Morin and metal ions has been reported to be more active than free Morin, which adds additional benefits in Morin mediated protection. Intriguingly, Morin has been found to be more efficacious than traditionally prescribed drugs like Trolox, mannitol, and ascorbate [15,215,216].

Development of many diseases such as diabetes, cancer, chronic bowel disease, cardiovascular, and neurodegenerative disorders [217,218] are induced due to chronic inflammation [219]. Inflammation is regulated at a molecular level through molecules and factors namely pro-inflammatory transcription factors, cytokines, chemokines, enzymes, matrix metalloproteinases, etc. [220,221]. Morin, through inhibition of activated macrophages, inhibit anti-inflammatory agents both *in vitro* and *in-vivo* [8,222,223]. Upon *in vivo* administration, Morin reduced colitis triggered by treatment with trinitrobenzene sulfonic acid thereby protecting intestinal cells from damage [224]. Rats when administered with Morin showed positive response while compared with control. The ameliorative responses were recorded in reducing bowel pressure, granulocyte infiltration in intestinal mucosa, and reduction in levels of leukotriene B4 and malondialdehyde levels [208]. Inflammatory response of essential transcription factors like NF-kB is also found to be reduced upon treatment with Morin [73,109], which confirms that Morin not only inhibits IkBα kinase pathway favoring the stabilization of IkBα but also down-regulates the expression of nitric oxide synthase, COX-2, IL-6, IL-8, and TNF genes [44,54,139,174]. Outcomes remain unaffected when same experiment is repeated using LPS-stimulated RAW 264.7 cells and macrophages in mice models [209,225]. In case of rats fed with high fructose diet, SphK1/S1P-NF-kβ signaling pathway is activated triggering liver inflammation, insulin resistance, and increased fat deposits [226,227]. Morin was found effective in such a case causing down-regulation of SphK1 besides blocking NF-kB nuclear translocation, inhibiting secretion of IL-1β, IL-6 and TNF-α by hepatocytes. NF-kβ activation along with decreased levels of TNF-α, IL-1β, IL-6, and iNOS is observed upon pre-treatment with Morin, which protects mice from hepatic damage [228]. Possible mechanism of protection by Morin has been presented in the Figure 2.

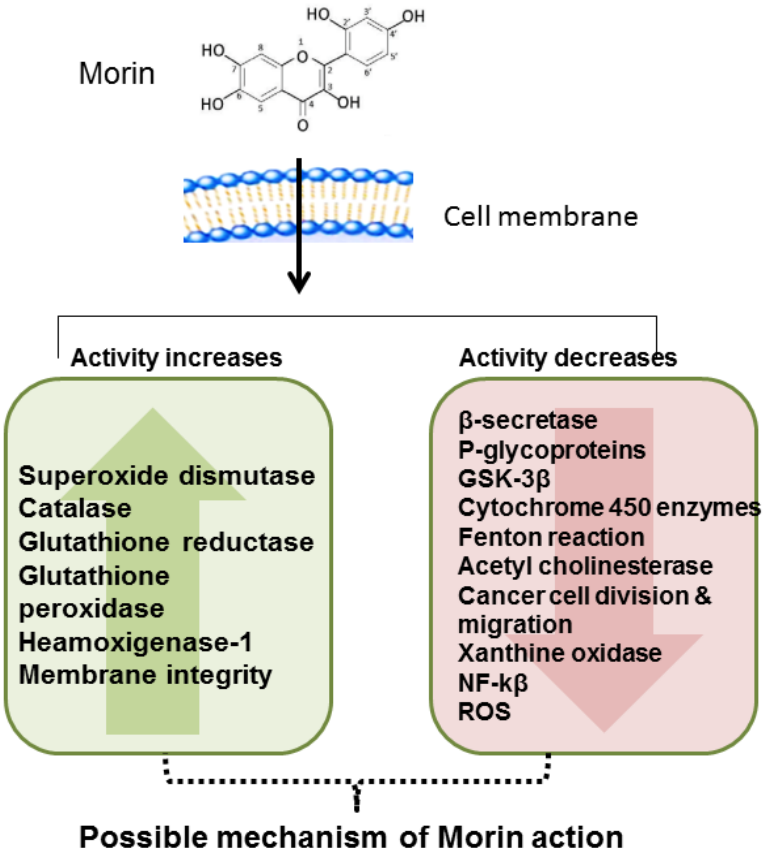

Figure 2 Possible molecular mechanism of Morin action

CONCLUSION AND FUTURE PROSPECTIVES

Lack of adequate knowledge about actual molecular mechanisms, hinders the application of Morin as a therapeutic drug for many lifestyle disorders. Since the ancient time of human history, nature has provided the sufficient remedies in the form of herbal products. Even now-a-days, initial clue for remedies and drug development largely depends on the ancient herbal knowledge [89]. In this regard, Morin serves as a 'Wonder Drug', with robust protective efficacy in several lifestyle disorders. Majority of such attributes are due to its anti-oxidant and anti-inflammatory activities. There are several other bioactive components which are also serving the similar purpose; however, Morin is different from them in several aspects. Firstly, the chemical structure with effective radical scavenging properties and secondly, Morin do not undergo auto-oxidation like other phytochemical compounds. Moreover, there is no higher dose dependent toxicity reported during or after Morin administration. Morin covers a large number of targets, which include oxidants, xenobiotics, excess of metals, radiations, pro-inflammatory factors. Furthermore, Morin can interact directly with proteins and enzymes, which results into modulation in signalling pathways and related changes in cellular metabolism.

Overall, *in vitro, in vivo* results, molecular docking studies, and clinical evidences suggest that Morin could be a promising therapeutic agent against extended range of diseases and disorders, which includes cancer, cardiovascular diseases, neurological impairments, diabetes, toxin-induced liver and kidney damage, inflammation and oxidative radical-induced pathology. Available reports on cellular and animal models have provided sufficient clinical outcomes, which could influence researchers to study further and establish the druggability of Morin for the benefits of mankind. The present study could assist in the very same process by providing a gross notion on the molecular mechanisms of Morin action. Further studies on translational and computational methodologies to uncover the therapeutic effects of Morin should be investigated.

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