

Therapeutic potential of Morin hydrate in Moraceae family to treat reproductive problems in domestic animals

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ABSTRACT

Reproductive disorders in domestic animals necessitate innovative therapeutic approaches. This review examines the therapeutic potential of morin hydrate (3,5,7,2',4'-pentahydroxyflavone), a flavonoid present in Moraceae family, to treat reproductive disorders in males and females. Morin hydrate is potent anti-inflammatory and antioxidant, mitigates oxidative stress and inflammation, which causes reproductive abnormalities. It has antimicrobial activity and inhibits pathogenic microorganisms. Morin also alleviates reproductive conditions (testicular abnormalities, ovarian cysts, ovulation failure and endometritis) enhance crucial enzyme activities and prevent lipid peroxidation, hence, beneficial to both male and female reproductive health.

Keywords: Animals, Antibacterial, antioxidant, Bioactive compound, Morin Hydrate, Reproductive disorders, Therapeutic intervention.

1. INTRODUCTION

Approximately 25% drugs are plant-derived compounds and 75% medicinal plants grow in India (29). Veterinary herbal medicines encompass plant-based therapeutic, prophylactic, or diagnostic applications in animal healthcare. The misuse of antibiotics not only leads to antibiotic resistance but also results in the persistence of toxic residues in meat. In contrast, herbal preparations have low toxicity, easy accessibility and fewer side effects than synthetic medicines (43,44). Many herbs, contain multiple ingredients with synergistic effects in a single medicinal preparation. Several plants and their extracts (rich in polyphenols, flavonoids, flavonols, carotenes and saponins) are used to treat various diseases. Flavonoids play significant role in influencing animal health (56).

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The Moraceae (mulberry or fig family), comprises about 50 genera and 1,400 species in tropical and subtropical regions (24). Morin (3,5,7,2',4'-pentahydroxyflavone) is natural polyphenolic flavonol found in fruits, stems and leaves (16,46) (Fig. 1,2). Morin exhibits higher biological activity in its hydrated form than non-hydrated form (34). Morin hydrate has pharmacological properties, [anti-inflammatory (60), antioxidant (32,60) and free radical scavenging activities (32)]. It has diverse biological activities, [anti-inflammatory, antioxidant and anticancer properties (27,49)].

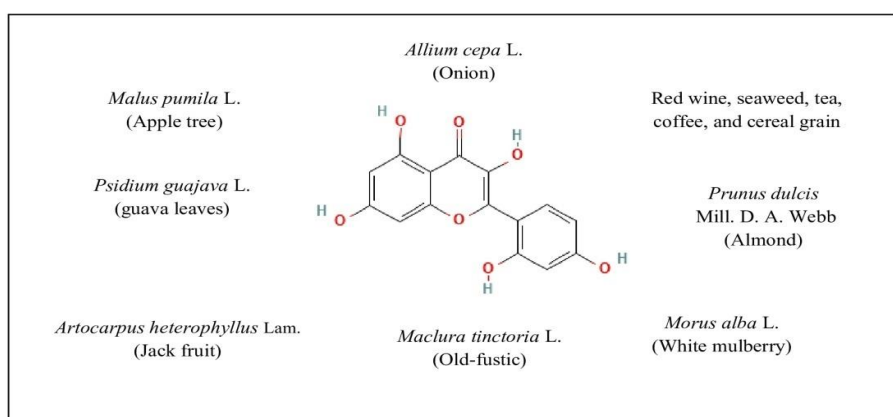


Figure 1. Schematic diagram illustrating various natural sources of morin hydrate and its chemical structure



Red mulberry (*Morus rubra* L.)



Fig (*Ficus carica* L.)



Jackfruit (*Artocarpus heterophyllus* Lam.)



Osage orange (*Maclura pomifera* (Raf.) Schneid.)

Figure 2. Representative plants from the family Moraceae.

Morin as a bioactive compound, exhibit a wide range of biological and pharmacological properties with low cytotoxicity (16). It has cytoprotective actions against peroxide-induced DNA and lipid damage, thus reducing intracellular reactive oxygen species (ROS) production (32).

2. MITIGATE INDUCED INFERTILITY

Male infertility often results from testicular abnormalities (testicular degeneration) and defective sperm, which is associated with inflammation and oxidative stress. Oxidative stress (imbalance between pro-oxidants such as reactive oxygen species (ROS) and antioxidants) can lead to testicular abnormalities and defects in sperm. Reactive oxygen species (ROS) are correlated with male infertility, affecting sperm cells with high levels of unsaturated fatty acids in their cytoplasmic membranes, making them susceptible to lipid peroxidation, when exposed to ROS (3). Uncontrolled oxidative stress can lead to membrane lipid peroxidation, resulting in testicular damage and loss of function (40). Such injuries can result in decreased rates of fertilization and implantation, disrupted fetal development, and increased chances of abortion. In females, oxidative stress causes ovarian cysts, ovulation failure and endometritis (1,10).

Maintaining redox homeostasis, is crucial for reproductive health, relies on a balance between antioxidants and ROS. The use of antioxidant-containing herbal remedies, such as morin, has been suggested to treat infertility (4). Plant-derived pure molecules and herbal extracts are protective against various illnesses, including reproductive system (48). Phenolic compounds and flavonoids found in these medicinal plants are believed to exhibit potent antioxidant activity and play a role in anti-mutagenic or protective actions by stabilizing reactive molecules and reducing DNA damage (5).

Morin administration serves as a protective measure against oxidative stress in the testes, enhancing the activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH) (39). Morin has been shown to positively influences the glutathione (GSH) levels, a key antioxidant that plays a crucial role in maintaining cellular redox balance (26). Morin co-treatment reduces lipid peroxidation and limits the formation of free radical derivatives (39). It mitigate heat-induced testicular damage by enhancing testosterone levels and alleviating oxidative stress. Morin hydrate promotes germ cell proliferation, upregulates the anti-apoptotic marker Bcl-2, and decreases caspase-3 expression, a critical enzyme in apoptosis (30). Several studies have confirmed its *in-vivo* anti-lipoperoxidation effects, demonstrating morin's protective role in maintaining testicular health (6,25).

3. ROLE IN COMBATING INFLAMMATION

Inflammation plays a significant role in reproductive health, influencing critical processes [(ovulation, implantation and pregnancy, as well as sperm production, function and ejaculation (57)]. Inflammatory effects on the reproductive tracts, tissues, platelets, leukocytes, blood plasma and endothelial cells can be induced by infectious agents like bacteria, leading to the release of inflammatory mediators (42). Ovulatory abnormalities such as premature ovarian failure and anovulation, linked to female infertility, are associated with inflammation. Cytokines, leukotrienes, histamines and prostaglandins are responsible for ovarian inflammation, impacting ovarian function and quality (57).

Endometritis, a leading cause of infertility in cows, mares, sows and bitches (21,23,36,41), is linked to inflammation. Bacterial infections of the endometrium in dairy cattle commonly cause metritis and endometritis, releasing intracellular cytokines TNF- α , IL-1, IL-6 and IL-8 (11,15,17,57). In case of cystic ovary and ovarian inactivity, higher levels of pro-inflammatory markers such as IL-6 and TNF- α have been observed (10,50,13). The concentration of inflammatory cytokines, particularly TNF- α , may impair ovarian function, inhibiting follicular development and affecting sperm quality. Chronic inflammation driven by higher TNF- α levels can lead to endometritis, ovarian dysfunction and impaired embryo implantation, ultimately contributing to infertility or reproductive failure (51).

Morin is potent anti-inflammatory and antibacterial phyto-component. It suppresses the production of inflammatory mediators like interleukins (IL-6, IL-8), TNF- α and nitric oxide (NO) by inhibiting NF- κ B activation and lipopolysaccharide (LPS)-induced inflammation (18,20). It also reduces the production of prostaglandin E2 (PGE2), thus mitigating inflammatory responses (45). Its inhibitory effect on various microorganisms, including *Staphylococcus aureus*, promotes bacterial aggregation, inducing cell membrane leakage, intervening in biofilm growth and down-regulating resistant mechanisms (61). Morin's inhibits bacterial enzymes involved in host surface adhesion and invasion processes, and also influences the ATPase activity of DNA helicase RepA, reducing bacterial growth (14,59).

Morin's is a promising therapeutic agent in combating bacterial infections associated with reproductive health issues, such as mastitis or metritis (49). Further research and exploration of morin's potential in addressing inflammatory reproductive disorders are warranted.

4. TREAT HEAVY METAL-INDUCED REPRODUCTIVE DISORDERS

Heavy metals, [lead (Pb), cadmium (Cd), mercury (Hg), and inorganic arsenic (As)], are highly toxic. These metals accumulates in soft tissues like the testes, liver and kidneys and also in hard tissues such as bones. Their sources are coal mines, smelters, refineries, pesticides and volcanic eruptions. Heavy metals contaminate soils and plants, entering into the animal body via grazing or through cutaneous route (58). Chronic exposure to these metals cause reproductive abnormalities (cryptorchidism and hypospadias), along with structural damage to the seminiferous tubules and the hemato-testicular barrier in male (38). Additionally, heavy metals interfere with steroidogenesis and can cross the placenta, causing fetal abnormalities and embryotoxicity (35).

4.1. Cadmium

It is most toxic, induces testicular disorganization, reduces circulating testosterone and increases oxidative stress within 24-48 h of exposure. It also leads to the downregulation of germ cell proliferation markers, impairing normal sperm production and contributing to infertility (33).

4.2. Lead (Pb)

It accumulates in the epididymis and accessory glands, suppressing testosterone synthesis, with Leydig cells being particularly affected. Lead toxicity results in a higher percentage of abnormal sperm (54,55). Both Cd and Pb contribute to oxidative stress in ruminant semen, with cadmium being more detrimental to gonadal structures

by damaging vascular endothelium and blood-testis barrier (BTB) integrity causing germ cell loss and reduced sperm count (22,52). *In-vitro* studies on Cd and Pb exposure show adverse effects on oocyte maturation, fertilization and embryonic development across animal species (7,31,37). Lead poisoning in cattle disrupts prostatic function, leads to prostate hyperplasia, and reduces sperm motility, and in cows, it can cause infertility, premature calving or abortion (2).

4.3. Arsenic (As) and Mercury (Hg)

These pass through the placenta, posing high risk of stillbirth, fetal deformity and multiorgan damage in developing fetuses and miscarriages (19,58).

Morin hydrate upregulates testicular vis fatin expression, crucial for steroidogenesis, proliferation and apoptosis regulation in the testes and ovaries. It improves circulating testosterone, testicular histology and sperm parameters, offering a protective effect against heavy metal-induced toxicity (8). Morin also helps preserve testicular structure and mitigates oxidative damage (25). Specifically, it antagonizes Bax upregulation and Bcl-2 downregulation, protecting against lead-induced oxidative stress and reduces cytochrome c release from mitochondria (53). The Morin hydrate mitigates heat-induced testicular impairment, influences essential processes such as testosterone synthesis, germ cell proliferation and the reduction of oxidative stress (28). Its antioxidant properties further enhance its protective role, offering a therapeutic strategy to treat reproductive damage caused by stressors, including heavy metal toxicity and heat exposure. Morin's hydroxyl groups form complexes with metals, limiting gastrointestinal absorption and accelerating their elimination via urine (12). Thus Morin hydrate is a promising therapeutic approach to mitigate reproductive damage caused by heavy metals and other xenobiotics, including stressors like heat-induced testicular impairment.

CONCLUSIONS

The therapeutic potential of morin (3,5,7,2',4'-pentahydroxyflavone) as an antioxidant and anti-inflammatory agent is described, yet its precise molecular mechanisms remain underexplored. Its ability to counteract oxidative stress, mitigate inflammation, and neutralize xenobiotics and heavy metals underlines its versatility in addressing a range of pathophysiological conditions. Morin protects reproductive organs from heavy metal-induced toxicity, preserve testicular structure and improve steroidogenesis. Morin regulate oxidative stress, suppress apoptosis and improve sperm parameters by modulating key molecular pathways involved in apoptosis and inflammation, such as Bcl-2 and Bax. Further research is essential to elucidate its full spectrum of therapeutic benefits, particularly in reproductive health, where its antioxidant properties can mitigate heat stress and heavy metal-induced damage. Expanding the understanding of morin's mechanisms will pave the way to treat variety of disorders, including those related to reproductive toxicity.

DECLARATION

We declare that all authors of this Ms. have made substantial contributions. We did not exclude any author who substantially contributed to this Ms. We have followed our ethical norms established by our respective institutions.

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AUTHOR'S CONTRIBUTION

In the present review, Akhter Rasool and Sarath Thulsiraman analysed the herbs, phytochemicals, and nanoparticles used for the treatment of obesity and was the primary contributor in making the manuscript. The systematic evaluation was carried out by Porteen kannan, Puli Vishnuvardhan Reddy, Akshata Patil and Jan Mohd Muneeb. The final manuscript was read and approved by all authors.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

ETHICAL STATEMENT

This is to inform you that in this study, we have not been involved in any animal and human studies.

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