An Updated Review of Pharmacological, Standardization Methods and Formulation Development of Rutin

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Rutin is one of important bioflavonoids and biomarker that helps to increase the quality of the herbal product. It has a wide variety of pharmacological applications such as neuroinflammation, anti-hypercholesterolemic, neuroprotective, cardioprotective, wound healing, radioprotective, nephroprotective, hepatoprotective, antiplasmodial, antiarthritic, antiviral, antihypertensive, Antinociceptive, antimicrobial, gastroprotective, antiosteoporotic, anticancer, diuretic and anticonvulsant effect. The current review article helps to identify the current and future prospects of rutin. Most of the previous studies were more focus on their pharmacological activities and to understand their mechanism of action but less focus on its clinical trial, commercial potential and formulation development. This review article documents the pharmacological activities, standardization methods and formulation development over the last six years.

Keywords: Rutin, Standardization, Pharmacology, Formulation development.

The role of flavonoids can never be ignored in our daily life. They had a wide variety of application in our daily health care such as antioxidant,¹² anticancer,¹ neurodegeneration³ and cardiovascular disease⁵.⁶. They are commonly available in our food such as fruits, beverages, and vegetables. There is a different class of flavonoids such as flavones, flavonols, and flavanones. Quercetin, rutin, kaempferol belongs to most common available flavonoids in our diet. This review article is based on updated information about the pharmacological potential, standardization method and recent knowledge about formulation development of rutin. Google scholar is used as a search engine to find the information from 2012 till to date. The keywords used to find the information was rutin, standardization method of rutin, pharmacological activities of rutin and formulation development of rutin in recent years (2012-2017).

Pharmacological activities

Rutin possesses several pharmacological activities such as reducing oxidative stress, prevent neuroinflammation⁷, anti-diabetic⁸, aiding to reduce neurodegeneration⁹, cardioprotective activity¹⁰, wound healing activity¹¹, radioprotective activity¹², nephroprotective activity¹³, hepatoprotective activity¹⁴, antiplasmodial activity¹⁵, antiarthritic
activity\textsuperscript{17}, antiviral activity\textsuperscript{18}, improved endothelial functions\textsuperscript{19} and antinociceptive activities\textsuperscript{20}.

**Antioxidant**

The recent research on rutin was based on enhancing the activity and optimization of antioxidant potential. The formation of supramolecular inclusion complexes between rutin and four cyclodextrins, namely β-cyclodextrin (β-CD), (2-hydroxypropyl)-α-cyclodextrin (HP-α-CD), (2-hydroxypropyl)-β-cyclodextrin (HP-β-CD) and (2-hydroxypropyl)-γ-cyclodextrin (HP-γ-CD), and the effects of the complexation on the stability and antioxidant activity of rutin were investigated. Formation of such an inclusion complex conferred moderate degrees of protection to rutin from degradation by heat and UV radiation during storage, and significantly enhanced its antioxidant capacity\textsuperscript{21}. Enzymatic de-glycosylation enhance the antioxidant potential of rutin\textsuperscript{22}. Encapsulation of rutin with lipid-based onion-type multilamellar vesicles (MLVs) optimized the antioxidant activity\textsuperscript{23}. It considerably decreased lipid peroxidation in 6-hydroxydopamine (6-OHDA) toxicity induced in pheochromocytoma (PC-12) cells\textsuperscript{24}. Rutin has a protective effect against hydrogen peroxide-induced oxidative stress in human lens epithelial cells\textsuperscript{25}.

**Neurodegenerative effect**

Rutin can help to treat peripheral neuropathy in mice\textsuperscript{24}. Rutin showed neuroprotective effects in streptozotocin-induced diabetic rat’s retina\textsuperscript{26}. Rutin protects dopaminergic neurons from oxidative stress in an animal model of Parkinson’s disease\textsuperscript{27}. Rutin is an effective bioflavonoid against neurotoxicity in rats by activating the mitogen-activated protein kinase (MAPK) pathway and brain-derived neurotrophic factor (BDNF) gene expression\textsuperscript{28}. Rutin decreased the oxidative stress in seizure-induced mice by kainic acid\textsuperscript{29}. Rutin is an effective bioactive compound against neurotoxicity caused by acrylamide\textsuperscript{30}.

**Antidiabetic effect**

Rutin possesses the antidiabetic activity by stimulating β-cells to release more insulin\textsuperscript{31}. It showed anti-hyperglycemic activity in streptozotocin-induced diabetic rats\textsuperscript{32}.

**Cardioprotective effect**

Rutin possesses the cardioprotective effect but recent studies found that the effect was less effective than quercetin on isoproterenol-induced cardiac fibrosis in the rat\textsuperscript{10}. It was found to be an effective as protective agent in hypercholesterolemic male rat\textsuperscript{33}.

**Wound healing activity**

Rutin containing hydrogel was found to be an effective bio compound in healing the wound\textsuperscript{11}. The roots and leaves of *Tephrosia purpurea* possess 2.5% of rutin and was found as an effective wound healing agent in streptozotocin-induced diabetic rats\textsuperscript{34}. Rutin was also identified as bioactive compounds in the polyherbal formulation of *Clinacanthus nutans* and *Elephantopus scaber* in healing the wound using high-performance liquid chromatography\textsuperscript{35}.

**Nephroprotective activity**

Rutin has a protective effect on hexachlorobutadiene-induced nephrotoxicity\textsuperscript{36}.

**Hepatoprotective effect**

Rutin was found to be an effective flavonoid in reducing hepatotoxicity caused by CCl\textsubscript{4}\textsuperscript{15} and liver injury induced by biliary obstruction in rats\textsuperscript{37}. A Recent study reveals that it alters the expression of genes in the IL-6/STAT3 pathway in reducing hepatotoxicity caused by CCl\textsubscript{4}\textsuperscript{38}.

**Radioprotective effect**

Rutin plays an important role as a radio modulator effect in Swiss albino mice when exposed to gamma radiations\textsuperscript{13}. Monoglucosyl rutin is an enzymatically modified form of rutin that is found be an effect radioprotector in mammalian cells\textsuperscript{19}.

**Miscellaneous activities**

The antiproliferation of rutin in human neuroblastoma cells LAN-5 were detected by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay through inducing G2/M cell cycle arrest and promoting percentage of cell death in LAN-5 cells. Rutin also possesses antitumor activity and can be used as a potential chemotherapeutic agent.

![Structure of Rutin](image-url)
The quercetin analog rutin was the most active flavonoid against Plasmodium falciparum parasites\(^\text{16}\). Standardization of Rutin

Rutin in the polyherbal formulation of Azadirachta indica and Gynura procumbens ethanolic extracts was standardized by TLC-densitometry\(^\text{41}\). High-performance liquid chromatography was found to be the most used method of standardization using C18 column. It was identified and quantified in the polyherbal formulation of Clinacanthus nutans and Elephanopus scaber using high-performance liquid chromatography. The mobile phase was a binary mixture of methanol-water, 1:1 (v/v), adjusted to pH 3.0 with glacial acetic acid was used\(^\text{42}\). Erythroxylum suberosum extract possesses rutin. Aqueous phosphoric acid (1%) (solvent A) and acetonitrile (solvent B) was used as a solvent system in HPLC\(^\text{43}\). Rutin was identified from Strychnos nux-vomica extract using High-performance thin layer chromatography (HPTLC)\(^\text{44}\). It was quantified from Lepidagathis prostrata using silica gel plate as a stationary phase and ethyl acetate, n-butanol, formic acid, water in the ratio (5:3:1:1) as mobile phase in HPTLC\(^\text{45}\).

Formulation Development of Rutin

Rutin has been used in different formulation nowadays. Rutin hydrogel was effective in healing the wound\(^\text{11}\). Rutin is poorly soluble in water. Liposome hydrogel can function as potential drug delivery systems to enhance transdermal permeation of the water-insoluble antioxidants such as quercetin and rutin\(^\text{46}\). Rutin loaded nanoemulsions were prepared by spontaneous emulsification method and high-pressure homogenization (HPH) technique using selsol 218 and tocopheryl polyethylene glycol 1000 succinate (TPGS) (1:1), solutol HS15 and transcutol P as oil phase, surfactant and co-surfactant will increase the solubility and permeability of rutin\(^\text{47}\). Rutin loaded nanophytosomal formulation was found to be the useful carrier to improve the bioavailability and antioxidant properties\(^\text{48}\). Elastic liposome containing rutin helps to improve the skin permeation effect\(^\text{49}\). Self-emulsifying drug delivery systems of rutin were prepared by polyethylene glycol (PEG 6000), polyvinylpyrrolidone (PVP K30 and PVP K17) or sodium deoxycholate by co-precipitation method to improve the bioavailability of bioactive compound\(^\text{50}\). Rutin-encapsulated chitosan nanoparticles can be helpful...
as neuroprotective and readily available to the brain in the treatment of Cerebral Ischemia\textsuperscript{81}. Rutin nanocrystals produced by the smart crystal help in enhancing skin penetration\textsuperscript{2}. Nanostructured lipid carriers (NLCs) contains rutin can be useful as photoprotective cream. Apifil/TiO\textsubscript{2} rutin NLC is found be effective as sun protective cream\textsuperscript{83}.

**CONCLUSION**

Rutin is found to be one of a member of an essential flavonoid used in our daily routine. The current research is more focus on optimization of its pharmacological activities and formulation development. There is a lot of effort going on to enhance its pharmacokinetic profile. The commercial potential of rutin is still yet to be explored. There are limited studies on a clinical trial. Most of the preclinical studies are limited on animal models. It is need of time to make use of its pharmacological activity by developing different pharmaceutical dosage form and standardization of new rutin based formulation.

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