

Rutin: Chemical properties, Pharmacokinetic properties and Biological activities

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ABSTRACT

INTRODUCTION

Herbal drugs are opening new visions and have been evolving as potential candidates for the treatment of various diseases (Abdo *et al.*, 2021; Elsayed *et al.*, 2022; Aboubakr *et al.*, 2023).

Currently, pharmaceutical industries have been concentrating on the phytomedicines because these are more affordable, closely match up with the patient's belief, concerns about adverse effects of synthetic medicines and lower phytochemical costs. Mainly, the plant secondary metabolites such as alkaloids, glycosides, flavonoids, terpenoids, are bioactive compounds with a variety of biological activities (Ravi *et al.*, 2018).

Recently, great interest in using herbal remedies as an antioxidant due to having fewer adverse effects compared to synthetic drugs in treating diseases (Erkan *et al.*, 2020), they are relatively low-cost, safe, nontoxic, and available in an ingestive form. So, they are mostly used for chronic diseases (Gaziano *et al.*, 2007). Flavonoids that have much attention for their potential pharmacological actions, in particular, rutin (3,3',4',5,7-pentahydroxy flavone-3-rutinoside), a non-toxic flavonoid glycoside which is present in orange, tomato, sweet, carrot, potato, apple peels and

Recently, due to their excellent safety history and potent therapeutic effects, medicinal plants have gained the interest of researchers. Herbal remedies have been utilized for centuries to both prevent and treat a variety of diseases. Flavonoids, among them, contain polyphenols, which are well known for having a wide range of beneficial medical effects. Rutin is Considered as one of the most important flavonoids and valuable phytochemicals in the pharmaceutical industry. The current study's objective was to evaluate rutin's advantages and disadvantages, utilizing the previously published researches. The pharmacokinetic properties and medical uses of this compound were investigated in details, with an emphasis on new findings, considering its potential relevance to numerous health benefits as antioxidant, hepatoprotective, nephroprotective, neuroprotective, anti-inflammatory, antimicrobial, antidiabetic, antitumor properties and testicular protective action. However, due to some drawbacks, like low absorption and poor solubility, its medicinal use is restricted. Furthermore, strategies to improve the pharmacokinetic profile of rutin are also suggested in light of its possible therapeutic use in the near future

Keywords: Rutin, Pharmacokinetic properties, Antioxidant, Hepatoprotective, Drug delivery.

black tea (Fabjan *et al.*, 2003). The present review highlights current information of rutin as anti-oxidative, hepatoprotective, neuroprotective, antidiabetic and anti-inflammatory, testicular protective action, antimicrobial, cardiovascular protection, and antitumor, moreover trials to enhance rutin absorption.

a. Chemical structure:

The *Ruta graveolens* plant is the source of the flavonoid derivative rutin (Enogieru *et al.*, 2018). It has been utilized for vascular conditions associated with capillary permeability since its discovery in 1842 (Frutos *et al.*, 2019).

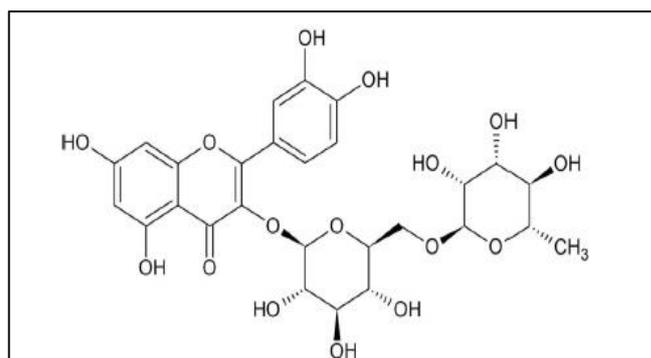


Fig. 1. Chemical structure of rutin (Semwal *et al.*, 2021).

b. Chemical properties of Rutin:

Rutin, also known as rutoside, quercetin-3-O-rutinoside, sophorin, or vitamin P, is a naturally occurring flavonoid glycoside that is one of the main secondary metabolites of plants. Chemically, it is referred to as 2-(3,4-dihydroxyphenyl)-5-[α -L-rhamnopyranosyl-(1-6)- β -D-glucopyranosyloxy]-5,7-dihydroxy-3-chromen-4H, chemical formula C₂₇H₃₀O₁₆. It is a yellowish powder. It has a 610.521 g/mol molar mass. It is not very soluble in water, but it dissolves readily in pyridine. Rutin has a pKa value of 6.17 and melts at 125 °C (Semwal et al., 2021).

c. Studies on metabolism and pharmacokinetic:

Previous studies have shown that rutin has a limited solubility and low bioavailability in biological systems. The report conducted by Carbonaro and Grant (2005), demonstrated that oral administration of rutin was used to assess its absorption in both isolated intestinal segments and blood in the small intestine. The analysis confirmed that it was poorly absorbed by the rat's small intestine, this could be to substance's degradation by the cecal bacteria (Manach et al., 1997). Following oral administration of 328 μ mol/kg to rats, the main metabolites seen were quercetin sulfates and glucuronides, while rutin was disappeared from the circulation (Yang et al., 2005). Other rutin metabolites such as homovanillic acid, 3,4-dihydroxyphenyl-acetic acid, 3,4-dihydroxytoluene, m-hydroxyphenyl-acetic acid, and quercetin were also reported (Pashikanti et al., 2010). About 10% of rutin is eliminated in urine, with the remainder going into feces (Choudhury et al., 1999).

d. Rutin biosynthesis and commercial manufacture

Rutin is a common flavonoid that is present in a wide range of plants and may be economically synthesized from a number of carefully selected plants. With a 3-5% rutin concentration, green buckwheat (*Fagopyrum esculentum*) was the first plant to be used commercially. Like other flavonoids, it is also produced by plants, starting with phenylalanine (Verhoeven et al., 2002). Its biosynthetic pathway yields naringenin via p-coumaric acid, and then dihydrokaempferol, dihydromyricetin, and dihydroquercetin. Finally, the method by which rutin and its aglycone, quercetin, are biosynthesised is known as the dihydroquercetin route (Fig. 2) (Yi et al., 2019).

e. Medical uses

Rutin provides a number of beneficial effects, including antibacterial, antiviral, antioxidant, vasoprotective, neuroprotective, anti-inflammatory, and anticancer properties (Li and Yang, 2020). Studies performed to determine rutin's potential as an analgesic have shown that the compound has a centrally calming and analgesic effect (Selvaraj et al., 2014). It affords defense against UV rays, which are known to induce skin cancer (Gegotek et al., 2017). Its antioxidant qualities make it very useful in the cosmetics sector (Kamel and Mostafa, 2015). However, its use in the pharmaceutical field is limited due to its low solubility both in water and oil (Park et al., 2013). Rutin also possess several other pharmacological activities

including anti-inflammatory, neuroprotective, cardioprotective, antiarthritis, antimicrobial, antiallergic, antiviral, hepatoprotective, anticancer, and gastroprotective effects. The most important properties of Rutin are antioxidative and radical-scavenging properties on oxidizing species such as hydroxyl radical, superoxide radical, and peroxy radical (Cui et al., 2014; Pan et al., 2014).

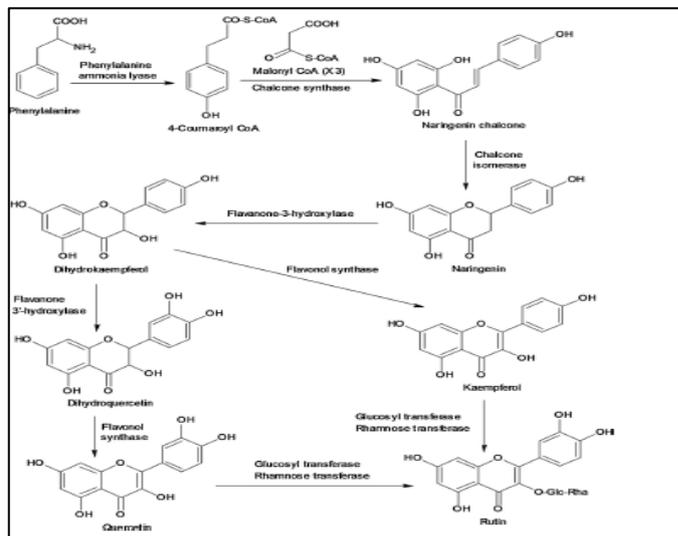


Fig.2. Biosynthesis of rutin from phenylalanine (Yi et al., 2019).

f. Toxicity investigations

In order to verify a sample's safety during the drug discovery process, its toxicity evaluation is a crucial prerequisite. Rutin can be regarded as safe for continued therapeutic usage based on previous investigations. Rutin's acute and long-term toxicity was evaluated in rats, guinea pigs, and rabbits; none of the test animals displayed any harmful symptoms (Wilson et al., 1947). Even 1% of rutin in the diet did not slow down the growth rate of albino rats, and after 400 days of this type of diet, histological analysis of the tissues revealed no signs of damage that could be directly linked to the rutin administration. The experimental animals' organ weights were within normal limits. Rats fed on a 1% percent rutin diet had the same length of estrous cycle as control animals, good reproduction, and healthy-looking offspring. According to the criteria used, rutin is neither hazardous in the short- or long-term (Wilson et al., 1947). Moreover, microbial metabolites found in the urine of human, accounted for as much as 50% of the 75 mg of rutin that had been ingested (Sawai et al., 1987).

g. Biological properties of rutin.

i. Antioxidant activity

antioxidants are compounds that prevent oxidation of other molecules and maintain the oxidative state in the cells. Wang et al. (2012) reported that rutin acted as a multifunctional agent by suppressing α -amyloid aggregation and β cytotoxicity, preventing mitochondrial damage, reducing the production of malondialdehyde (MDA), ROS, nitric oxide (NO), glutathione disulfide (GSSG), inducible nitric oxide synthase (iNOS), and pro-inflammatory cytokines, and increasing catalase, superoxide dismutase,

reduced glutathione (GSH), and glutathione peroxidase (GPx) levels.

The studies suggested that the antioxidant capacity of rutin may be attributed to its electron or hydrogen donating ability or hydroxyl scavenging power (**Kaur et al., 2015**).

Nowadays, there are a lot of antioxidant products available on the market; these products mostly contain flavonoids and polyphenols. These products are supposed to protect the body from oxidation by scavenging free radicals and other reactive oxygen species (ROS) (**Lobo et al., 2010**). Since rutin is one of the most potent antioxidants, it is frequently used as a benchmark for evaluating a sample's antioxidant impact. Numerous studies have confirmed its role in preserving erythrocytes and the liver by downregulating of iNOS expression. It's interesting to note that through preserving intracellular redox-homeostasis, it avoids oxidative stress and the issues that accompany it, such as GPx, glutathione reductase (GR), catalase (CAT), superoxide dismutase (SOD), and GST. It has also been shown to reduce ROS levels without being harmful, maintaining the erythrocyte's shape (**Singh et al., 2019**).

ii. Hepatoprotective activity

It has been demonstrated that rutin is a helpful flavonoid in reducing the hepatotoxicity caused by CCl₄ (**Khan et al., 2012**) and liver damaging resulted from biliary obstruction in rats (**Pan et al., 2014**). However, by lowering hepatic aminotransferase activity and inflammatory response, its protective efficacy against ethanol-induced hepatotoxicity was also demonstrated in human hepatoma (**Lee et al., 2019**). Rutin protected wistar rats against liver toxicity caused by doxorubicin by reducing liver lipid peroxide, increasing glutathione (GSH) content, and increasing GST, SOD, and GPx, activities (**Ahmed et al., 2022**).

iii. Nephroprotective activity

One of the most common pathologies seen is nephropathy. Rutin has a protective effect on hexachlorobutadiene-induced nephrotoxicity (**Sadeghnia et al., 2013**).

In a study, rutin demonstrated ameliorative activity against oxonate-induced hyperuricemia and renal dysfunction in mice. Administration of rutin resulted in a decrement in levels of serum urate, creatinine and blood urea nitrogen, serum and kidney uromodulin levels, and increased urine uromodulin, urate and creatinine excretion in hyperuricemic mice.

In the kidney of hyperuricemic mice, there was a considerable elevation of the mRNA and protein levels of the organic anion transporter 1 and the organic cation/carnitine transporters, and a significant downregulation of the mRNA and protein levels of mouse glucose transporter 9 and urate transporter 1 (**Chen et al., 2013**).

In a fructose-fed rat model for hyperuricemia, rutin blocked the Nucleotide-binding oligomerization domain

(NOD)-like receptor and aided in the improvement in the signaling and reduced lipid accumulation in the kidney of rats (**Hu et al., 2009**).

Cisplatin caused oxidative stress and elevated ROS generation are the fundamental causes of cisplatin-induced nephrotoxicity, when rutin administered simultaneously to cisplatin intoxicated rats, it showed nephro-protective properties (**Alhoshani et al., 2017**).

iv. Testicular protective action.

Flavonoids possess an amphipathic quality that allows them to pierce lipid bilayer membranes and prevent oxidative damage. This property may shield spermatozoa and the acrosome membrane altogether, ensuring the sperm acrosome response necessary for fertilization (**Moretti et al., 2012**). Testicular lactate dehydrogenase (LDH), acid phosphatase (ACP), and alkaline phosphatase (ALP), which were found to be highly related to spermatogenesis, were significantly increased after administration of rutin to cadmium-intoxicated rats. This showed that rutin had a beneficial effect on testicular and spermatogenesis maturation defects (**Abarikwu et al., 2013**). The increased number of comets, tail lengths, tail moment, and tail percentage in rats exposed to cisplatin were all reversed by rutin administration (**Jahan et al., 2018**).

According to **Moretti et al. (2012)**, rutin provided a protective effect against lipid peroxidation-induced damage to human sperm. Rutin also demonstrated potential in reducing cyclophosphamide-induced reproductive toxicity (**Abarikwu et al., 2012**) and protecting testicular tissue and fertility from oxidative stresses associated with type 1 diabetes (**Akondi et al., 2011**). Rutin and kolaviron alone or in combination reversed busulfan-induced increase in oxidative stress along with sperm quality of treated rats (**Abarikwu et al., 2022**).

v. Neuroprotective action

Peripheral neuropathy in mice is ameliorated by rutin (**Magalingam et al., 2013**). Rutin showed neuroprotective effects in the retina of rats with streptozotocin-induced diabetes. (**Ola et al., 2015**). Rutin is an efficient bioflavonoid against neurotoxicity in rats because it stimulates the production of the brain-derived neurotrophic factor (BDNF) gene and the mitogen-activated protein kinase (MAPK) pathway as discussed by **Khan et al. (2012)**.

vi. Activity against microbes

Many bacterial strains have been studied in relation to rutin's antibacterial activity. It has demonstrated a strong inhibitory effect on the development of bacteria, such as *Escherichia coli* (**Araruna et al., 2012**). When measured in honey, rutin has been demonstrated to have suppressive properties against *Klebsiella* sp., *Shigella sonnei*, and *Proteus vulgaris* (**Pimentel et al., 2013**). Research on rutin's and other polyphenols' antibacterial qualities across the food chain suggests that flavonoids may be beneficial for food

preservation. (Stojković & colleagues, 2013). Additionally, rutin showed antifungal efficacy against the *Candida gattii* strain at a minimum inhibitory dose of 60 µg/ml (Johann et al., 2011).

vii. Cardiovascular activity

Cardiovascular issues are associated with poor heart function and are primarily caused by coronary artery disorders (Mendis et al., 2011). Numerous recent studies have shown that rutin can offer protection against a range of heart diseases through a number of different mechanisms (Siti et al., 2020). After oral administration of 50 mg/kg of rutin, rats with hemolytic and circulatory disorders demonstrated improved Cd/Pb-induced cardiovascular and erythrocyte membrane-bound ATPase activity. It recovered the Ca²⁺ and Na⁺/K⁺-ATPase activities that had been weakened by Pb and Cd exposure (Oluranti et al., 2022). Furthermore, the defense toward 5-fluoro uracil (5-FU) mediated cardiotoxicity was also demonstrated in rats at dosing of 50 and 100 mg/kg (Sengul et al., 2021).

viii. Antidiabetic actions

Over the past ten years, a substantial number of natural compounds that were first screened for antidiabetic effect have been studied therapeutically and then manufactured as medications to treat type 2 diabetes. Rutin exhibits several antidiabetic effects, including as reducing the absorption of carbohydrates in the small intestine, inhibiting tissue gluconeogenesis, boosting tissue glucose uptake, protecting pancreatic beta cells, and elevating insulin secretion (Al-Ishaq et al., 2019). Additionally, the antidiabetic potential of rutin was studied using a number of experimental models. Oral rutin therapy reduced postprandial blood sugar levels in diabetic rats produced by alloxan compared with acarbose (Calzada et al., 2017). This substance might have regulated the enzymatic mechanisms connected to the immune-mediated, hyperglycemic, and inflammatory reactions associated with diabetes mellitus (DM). Streptozotocin (STZ)-induced diabetic rats showed significant reductions in glucose, low-density lipoprotein (LDL) levels, and liver enzymes with rutin treatment (Chielle et al., 2016).

ix. Anti-hypercholesterolemic properties.

Rutin is a "specific and non-toxic modulator" of hypercholesterolemia. Rutin significantly reduced animals' plasma triglyceride levels in a study that used a Golden Syrian hamster model that provoked hypercholesterolemia (Kanashiro et al., 2009). Furthermore, rutin reduced total cholesterol and high-density lipoprotein (HDL) levels (Da Silva et al., 2001). A reduction in the bloodstream concentrations of triglyceride (TG), total blood cholesterol (TC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and LDL was observed in male wistar rats co-treated with a high-cholesterol diet along rutin supplementation (Al-Rejaie et al., 2013). Long-term flavonoid intake, such as that of rutin, may improve cardiovascular health, according to Kalgaonkar et al. (2010).

x. Anti-inflammatory properties

Pretreatment with rutin inhibited the bisphenol A-glycidyl methacrylate--induced generation of proinflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 in macrophages. Rutin also suppressed the bisphenol A-glycidyl methacrylate-induced secretion of NO and expression of (iNOS) in a concentration-dependent manner (Huang et al., 2023).

Due to its ability to reduce NF-κB activation and TNF-α generation, rutin may be used to treat vascular inflammatory conditions. Human synovial fluid phospholipase A2 (PLA2) activity is a key inflammatory enzyme that contributes to the synthesis of arachidonic acid (AA), rutin has been shown to effectively decrease its activity (Lindahl, and Tagesson, 1997).

According to research findings, rutin shields rats from nephrotoxicity, which results in inflammation, histopathological changes, and tubular cell death by lowering oxidative stress and the expression of markers linked to inflammation and death, such as TNF-α, NF-κB, and caspase-3 proteins (Arjumand et al., 2011).

xi. Gastrointestinal defense

hemorrhagic lesions were significantly lessened when rutin was administered prior to therapy. Histologically, the glandular portion's natural histological structure was preserved by pre-treating it with rutin before indomethacin. This resulted in less leucocyte cell infiltration at the junction of the glandular and non-glandular regions. Due to its antioxidant properties, rutin considerably improved the oxidative stress indicators that were negatively impacted by indomethacin therapy (Abdel-Raheem, 2010).

xii. Anti-tumor action

Many recent researches have demonstrated the efficacious chemopreventive qualities of rutin (Gong et al., 2010). Additionally, rutin has been shown to inhibit the expansion of cancer cells by halting their cell cycle and/or causing them to die, as well as the growth, blood vessel development, as well as dissemination of colorectal cell lines (Araújo et al., 2011). In a study on human leukemia HL-60 cells in a mouse, rutin suppressed the growth of the tumors, indicating that it has anti-leukemic properties (Lin et al., 2012).

xiii. Immune system activation.

Rats fed a normal diet with rutin supplementation experienced an immunomodulatory effect that raised the proportion of natural killer (NK)-cells and neutrophil leukocytes while lowering the relative lymphocyte amount (Thushina et al., 2015). Rutin elevates immunoglobulin levels, improves delayed type hypersensitivity reaction triggered by sheep red blood cells, and increase in the titer of antibodies in the hemagglutination test (Ganeshpurkar and Saluja, 2017).

3. Enhancements to the pharmacokinetic properties of rutin.

It is evident that rutin's low solubility and bioavailability and limited membrane permeability impede its therapeutic usage (Gullon et al., 2017; Yang et al., 2005).

Efforts are being made to overcome these drawbacks to improve rutin's pharmacokinetic qualities, several novel drug delivery strategies have been created recently. Different carriers, including liposomes, polymeric micelles, and nanoparticles for rutin, have been used to generate these systems. Furthermore, it was demonstrated that the curative efficacy of rutin was effectively boosted by these particular carriers (Semwal et al., 2021). Nanocarriers overcome permeability barriers to improve the uptake and accessibility of loaded active compounds because of their high level of solubility and nanosize (Chivte et al., 2017). Moreover, nanoparticles (NPs) decrease first-pass metabolism and raise oral bioavailability, which improves the oral absorption of loaded substances during small intestine transit because they circumvent the liver through lymphatic transport (Amjadi et al., 2019). The rutin-loaded nanoparticles were more advantageous than pure rutin because they lessened the harm that diabetes caused to the pancreas, kidney, and liver. The results confirmed the biochemical findings that phytosomes loaded with rutin were superior to rutin alone in treating patients (Amjadi et al., 2021). Furthermore, on a study of protection of pure rutin and rutin nano-complex against CCL4 induced hepatotoxicity, groups treated with rutin nano-complex (equivalent to 100 and 200 mg/kg of rutin) had a hepato-protective effect and improved GSH, GPx, GST, GRD, SOD, and CAT levels more effectively than groups treated with pure rutin at the same dose levels (Ravi et al., 2018). Furthermore, ethylene glycol dimers loaded with rutin have been shown to enhance cardiac histology in diabetic rats more efficiently than rutin alone (Bhattacharjee and Chakraborti, 2017).

CONCLUSION

As evident from aforementioned data, rutin is a phytochemical with several pharmacological activities. Hence, rutin can be considered as a 'vital phytochemical' which is needed to be studied comprehensively to establish effective safety profile in human to get therapeutic benefits, help in prevention and treating a variety of illnesses and toxicities.

List of abbreviations

AA	Arachidonic acid
ACP	Acid phosphatase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATPase	Adenosine triphosphatase
BDNF	Brain-derived neurotrophic factor
CAT	Catalase
DM	
FU	Diabetes Mellitus
Fluorouracil	

GPx	Glutathione peroxidase
GR	glutathione reductase
GSH	Glutathione
GST	Glutathione s-transferase
HDL	high density lipoprotein
HL-60	Human leukemia-60
IL	Interleukin
iNOS	Inducible nitric oxide synthase
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
MAPK	Mitogen-activated protein kinase
mRNA	Messenger ribonucleic acid
NK	Natural killer
NOD	Nucleotide-binding oligomerization domain
NPs	Nanoparticles
PLA2	Phospholipase A2
ROS	Reactive oxygen species
SOD	Superoxide dismutase
STZ	Streptozotocin
TC	Total cholesterol
TG	Triglyceride
TNF- α	Tumor necrosis factor-alpha
UV	Ultraviolet.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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