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Traditional uses and pharmacological properties of rutin

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ABSTRACT

Rutin, a bioactive flavonoid glycoside found in over seventy plant species, has attracted considerable interest because of its broad pharmacological profile. Traditionally derived from buckwheat seeds, citrus fruits and medicinal plants, rutin has been a keystone of therapeutic uses in Ayurveda, Traditional Chinese Medicine (TCM) and European herbal traditions. Modern studies validate its multifaceted bioactivities, such as strong antioxidant, anti-inflammatory, antimicrobial, neuroprotective, cardioprotective, and anticancer activities. Pharmacological studies demonstrate that rutin has broad-spectrum antimicrobial activity against bacterial and fungal pathogens such as *Staphylococcus aureus* (Rosenbach, 1884) and *Candida krusei* (Castellani, 1905) and synergistically improves standard antibiotic and antifungal treatments. Although having significant therapeutic promise, rutin's translation into the clinical setting is circumscribed by its limited aqueous solubility and bioavailability. Progress in recent nanoencapsulation and drug delivery techniques has endeavoured to obviate these barriers, optimizing their pharmacokinetics. By linking conventional medicinal heritage with contemporary pharmacological developments, rutin remains at the epicentre of scientific research, anticipating new therapeutic interventions in chronic disease treatment.

Key words: Antimicrobial, antioxidant, bioavailability, bioflavonoids, pharmacology, rutin, Structure- activity relationship, traditional medicine.

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1. INTRODUCTION

Nature provides a rich source of therapeutic agents, with plant-derived phytochemicals playing a crucial role in disease prevention and treatment. Over the past fifty years, plant-based drugs have transformed modern medicine. Herbal medicines and nutraceuticals are widely used globally, with up to eighty percent of people in developing countries relying on them for primary healthcare (34). Medicinal compounds fall into three major classes: alkaloids (vinblastine, pilocarpine), flavonoids (quercetin, rutin) and terpenoids (Taxol, digitoxin) (44). These compounds offer significant health benefits, particularly in managing cancer, cardiovascular diseases and diabetes.

Rutin, named after *Ruta graveolens* L. (Figure 1), is a flavonoid glycoside found in over seventy plant species, including buckwheat, citrus fruits, onions and grapes (41). Rutin is produced through the phenylpropanoid pathway and was initially found in buckwheat in the 19th century. Its numerous pharmacological characteristics include anti-inflammatory, neuroprotective, cardioprotective, antioxidant and anticancer activities. (14). Additionally, it offers protection against UV-induced skin damage and is used in cosmetics. Its weak solubility, however, limits its usage in pharmaceuticals. Because of its potent antioxidant and radical-scavenging properties, it is useful in a variety of therapeutic settings. (39).

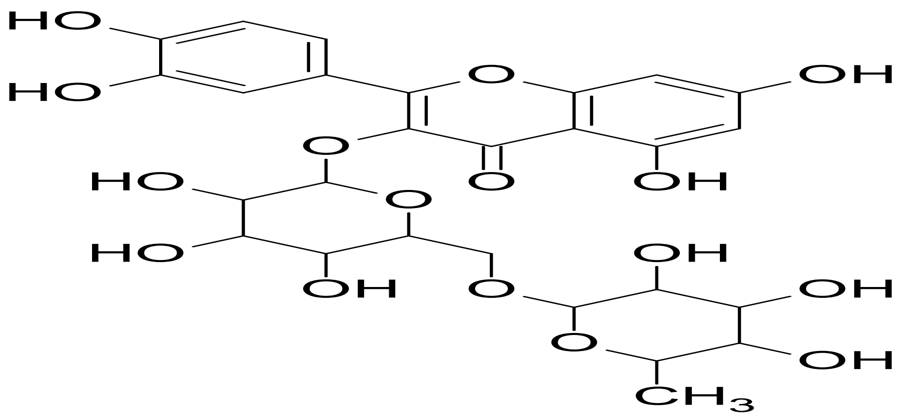

Figure 1. Structure of Rutin

Rutin, a key component of traditional medicine, offers numerous therapeutic benefits due to its anti-inflammatory, antioxidant and vasoprotective properties (34). It also boosts the bioavailability of co-administered medicines, hence increasing polyherbal efficacy. Rutin, as a bridge between traditional treatments and modern pharmacology, is still an important focus of scientific investigation (42). Rutin, which is commonly used in traditional medicine, strengthens blood vessels, preventing diseases such as varicose veins, hemorrhoids and hypertension (11). It has anti-inflammatory and pain-relieving effects that aid in the treatment of arthritis and rheumatism, as well as wound healing. Rutin promotes skin health by increasing collagen levels and minimizing bruising. It aids immunity, reduces allergies and asthma, preserves eye health and promotes blood sugar balance and liver detoxification, emphasizing its extensive therapeutic effects (29).

1.1. Historical significance in various cultures

Rutin has a long history of use across Europe and Asia. In Eastern Europe, Russia and parts of Asia, buckwheat has been a staple crop and a traditional source of rutin, valued both nutritionally and medicinally. Southern Europe contributed rue (*Ruta graveolens* L.), revered in ancient Greek and Roman medicine for its symbolic and healing properties, with rutin as a key active component (41). In Asia, the Japanese pagoda tree (*Sophora japonica*) has been central to traditional Chinese and Japanese medicine, particularly for promoting vascular health and reducing bleeding. Tartary buckwheat (*Fagopyrum tataricum* L. Gaertn), notably rich in rutin, has been used in traditional Chinese medicine to support circulation and metabolic function. Modern scientific recognition of rutin emerged in the 20th century when Nobel laureate Albert Szent-Györgyi identified its synergistic role with vitamin C, coining the term "vitamin P" and cementing its place in supplements for capillary and vascular health (24).

2. PHARMACOLOGICAL PROPERTIES OF RUTIN

Rutin has large pharmacological effects (Figure 2) in the body.

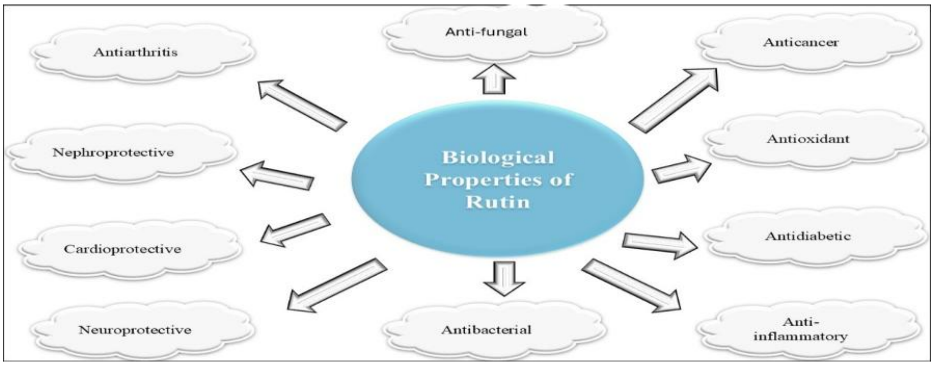

Figure 2. Summary of various biological processes of Rutin

2.1. Rutin as potential anticancer agent

Rutin exhibits potent anticancer properties through apoptosis induction, cell cycle arrest, oxidative stress modulation and immune enhancement (31). Rutin also enhances chemotherapy by acting as a chemosensitizer. Its bioavailability is increased by encapsulation techniques, which also increase its effectiveness against different cancer cells (19). Rutin exhibits anticancer effects by modulating oncogenic pathways like PI3K/Akt, MAPK and NF-κB, inhibiting tumor growth, inflammation and cell survival. It induces apoptosis via p53 activation, caspase-3 and ROS, and arrests the cell cycle at G1/G2-M phases. Its antioxidant and anti-inflammatory properties enhance chemotherapeutic efficacy, reducing resistance and side effects in cancer treatment (31). Rutin targets DNA damage response pathways (PARP-1, ATM, ATR), inducing genotoxic effects in cancer cells. Despite low bioavailability, nano-formulations are enhancing its clinical potential, showing promising preclinical results in glioblastoma, hepatocellular carcinoma and hormone-resistant cancers.

2.2. Anti-inflammatory potential

The anti-inflammatory and radical scavenging qualities of rutin promote the repair of ulcerative colitis and reduce severe vascular inflammation (43). Rutin acts as a multi-target anti-inflammatory agent by modulating several key pathways involved in chronic and oxidative stress-related inflammation. It inhibits the NF-κB signaling cascade, particularly NF-κB p65, thereby downregulating pro-inflammatory cytokines such as TNF-α, IL-1β, IL-8 and enzymes like COX-2 and iNOS (38). Rutin also mitigates oxidative stress by activating the Nrf2/HO-1 pathway, enhancing antioxidant defences through increased HO-1 expression (51). Additionally, it modulates the NLRP3 inflammasome via ASC protein regulation, reducing caspase-1-driven inflammation. In viral and immune responses, rutin influences Toll-like receptor (TLR) signalling, helping to balance antiviral immunity and cytokine storms, as seen in COVID-19 models (16). Compared to its aglycone quercetin, rutin offers better chronic anti-inflammatory effects due to its enhanced stability and bioavailability from the sugar moiety, making it particularly effective in sustained inflammatory conditions.

2.3. Antihypertensive and vasorelaxant effects

Significant hypotensive and vasorelaxant effects are shown by rutin (7). It exerts antihypertensive effects through multiple complementary mechanisms. It inhibits key regulators of blood pressure, including angiotensin-converting enzyme (ACE), angiotensin II type 1 receptor (ATR1) and the mineralocorticoid receptor (MCR), reducing vasoconstriction and sodium retention mechanisms comparable to conventional ACE inhibitors like lisinopril (8). Rutin also combats oxidative stress in vascular endothelial cells by decreasing reactive oxygen species (ROS) and nitrotyrosine levels, thereby improving vascular reactivity and baroreflex sensitivity. It enhances nitric oxide (NO) production, promoting endothelium-dependent vasodilation and maintaining vascular tone. Additionally, its antioxidant activity preserves NO bioavailability, sustaining its vasorelaxant effects. By inhibiting vasoconstrictor pathways and supporting vascular health, rutin demonstrates significant potential as a natural antihypertensive agent (50).

2.4. Antibacterial properties

Rutin exhibits potent antibacterial activity against a wide range of Gram-positive and Gram-negative bacteria. It has been identified in plant extracts such as *Pteris vittata* L. and *Castanea sativa* (26). Rutin's antibacterial efficacy is further enhanced when combined with other flavonoids, including quercetin and morin, especially against pathogens such as *Salmonella enteritidis* (Danysz, 1894), *Bacillus cereus* (Frankland and Frankland 1887) and methicillin-resistant *Staphylococcus aureus* (MRSA). Rutin exerts its broad-spectrum antibacterial effects through multiple pathways. It disrupts bacterial cell membranes and walls, compromising structural integrity and increasing bacterial vulnerability to environmental stressors (48). Rutin interferes with bacterial metabolism by binding to essential enzymes and inhibiting efflux pumps, boosting antibiotic efficacy (28). Its antioxidant properties stabilize bacterial membranes and prevent oxidative damage. Rutin shows synergistic effects with antibiotics like amikacin, especially against Gram-negative bacteria (26).

2.5. Antifungal properties

Rutin possesses significant antifungal properties and enhances the effectiveness of conventional antifungal agents. When co-administered with amphotericin B, rutin improves therapeutic efficacy against *Cryptococcus neoformans* (Sanfelice Vuillemin) while reducing associated toxicity (15). Rutin isolated from *Polygala paniculata* L. has demonstrated activity against *Cryptococcus gattii* (Vanbreuseghem, Kwon-Chung and Bennett) and its anti-arthritic and antifungal effects have also been observed in models of *Candida albicans*-induced septic arthritis (18). Furthermore, rutin extracted from tobacco leaves has shown inhibitory effects on *C. albicans* and antibacterial activity against *Staphylococcus aureus* (Rosenbach, 1884), *Bacillus subtilis* (Ehrenberg, 1835), *Escherichia coli* (Theodor Escherich, 1885) and *Klebsiella oxytoca* (Flügge 1886) (1). Rutin inhibits fungal growth by suppressing cell replication, with an IC_{50} of about 110 μM against Candida species. Its antifungal potency is enhanced by structural modifications like imidazole or benzimidazole, improving solubility and bioactivity. Rutin disrupts fungal cell membranes and metabolic functions, causing cell dysfunction and apoptosis (48).

2.6. Neuroprotective properties

Rutin's antioxidant, anti-inflammatory and antiapoptotic properties confer significant neuroprotective benefits (4). Rutin alleviates the progression of various neurological disorders, including Parkinson’s disease, Alzheimer’s disease and prion-related conditions. It also improves cognitive function and protects hippocampal neurons from dexamethasone-induced neurotoxicity. Rutin exerts several neuroprotective molecular pathways (40), it mitigates oxidative stress by scavenging free radicals, increasing the levels of antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GSH-Px) and decreasing lipid peroxidation markers like malondialdehyde (MDA) (7). Rutin suppresses neuroinflammation by inhibiting the NF-κB pathway and pro-inflammatory cytokines (30). It promotes neuronal survival by upregulating Bcl-2 and downregulating Bax and caspases. Rutin enhances synaptic plasticity, learning and memory by activating the BDNF/TrkB/ERK/CREB pathway and inhibiting p38 MAPK, supporting its potential in treating neurodegenerative diseases (46).

2.7. Cardioprotective effects

Rutin offers strong cardioprotection through antioxidant, anti-inflammatory and antiapoptotic effects (38). It reduces oxidative stress, inflammation and fibrosis in sepsis-induced cardiac injury and improves heart function in drug-induced cardiotoxicity. Along with quercetin, it alleviates myocardial stress and suppresses fibrosis, highlighting its therapeutic potential in cardiac disorders (2). Rutin provides cardioprotection by enhancing antioxidant defenses through upregulation of enzymes like SOD, CAT, GPx and GST. It also activates Nrf2/HO-1 and SIRT1/Nrf2 pathways, reducing oxidative stress, lipid peroxidation and myocardial cell injury (38). Rutin reduces inflammation by suppressing cytokines like TNF-α, IL-6, IL-1β and TGF-β1 and inhibiting mediators such as COX-2, iNOS and TLR4, protecting against myocardial damage. It also prevents cardiac fibrosis by downregulating MMP-2, MMP-9, CTGF and TGF-β1, helping to inhibit pathological heart remodelling (45).

2.8. Antidiabetic effects

Rutin exhibits potent antidiabetic effects through multiple interconnected mechanisms that target glucose metabolism, insulin function and the prevention of diabetic complications (13). Rutin improves glycemic control by enhancing glucose uptake, reducing carbohydrate absorption and stimulating insulin secretion. It protects pancreatic β-cells, prevents liver hypertrophy and inhibits pro-inflammatory cytokines. As a key compound in *Morus alba* L., rutin contributes to its antidiabetic effects by inhibiting α-glucosidase and α-amylase, reducing postprandial hyperglycemia and supporting sustained insulin production (25). Rutin enhances glucose uptake by promoting GLUT-4 translocation through PI3K, PKC and MAPK pathways. It suppresses hepatic gluconeogenesis by downregulating enzymes like G6Pase (glucose-6-phosphatase) and PEPCK (phosphoenolpyruvate carboxykinase) (27). Rutin reduces oxidative stress, sorbitol and AGE formation and inflammatory cytokines, improving glycemic control, insulin sensitivity and organ protection (33).

3. TOXICITY AND POTENTIAL SIDE EFFECTS

Rutin is generally well-tolerated, with a favourable safety profile at typical dietary doses. However, high-dose supplementation may lead to mild, transient side effects, including gastrointestinal issues (nausea, bloating, diarrhea), neurological symptoms (headache, dizziness, fatigue) and, rarely, hypersensitivity reactions (rash, itching, or angioedema) (5). Musculoskeletal complaints like muscle stiffness have been reported anecdotally. Caution is advised when rutin is used alongside antithrombotic medications (e.g., warfarin, aspirin, clopidogrel), as it may increase bleeding risk. Due to limited data, its use during pregnancy and lactation is not recommended without medical supervision (41). Further research is needed to fully understand its drug interactions and long-term safety.

4. MECHANISM OF ACTION OF RUTIN

4.1. Molecular targets

Rutin exerts broad therapeutic effects by targeting various enzymes, receptors and signalling pathways. It reduces inflammation by inhibiting COX-1, COX-2, LOX, xanthine oxidase and aldose reductase (49). It interacts with adenosine, estrogen, and GABA/NMDA receptors for neuroprotection and hormone-related cancer treatment. Rutin also modulates MMPs, suggesting anticancer potential (14). It regulates key pathways-suppressing NF-κB, MAPK/ERK and PI3K/Akt, while activating Nrf2/ARE and modulating JAK/STAT-supporting its antioxidant, anti-inflammatory and immune-regulating properties (32).

4.2. Pharmacokinetics

Rutin has low oral bioavailability due to poor solubility, low lipophilicity and extensive metabolism (3). It is partially absorbed and hydrolyzed by gut microbiota into quercetin, which is more bioavailable. Only about 17% reaches systemic circulation, with absorption affected by diet and microbiome. In the liver, it's metabolized into derivatives distributed to the brain, liver and kidneys. Strategies like liposomes, nanoparticles and phospholipid complexes enhance uptake (47). Rutin and its metabolites have a half-life of twenty-six- thirty-two h and are excreted via urine and feces.

4.3. Structure-activity relationship (SAR) of rutin

Rutin's pharmacological activity is closely linked to its chemical structure, particularly its hydroxyl groups, glycosylation and conjugation (22). The rutinose moiety at C3 enhances stability and water solubility but limits lipophilicity and absorption. Its catechol structure enables metal chelation and ROS stabilization, contributing to antioxidant effects.

The flavonoid backbone aids enzyme binding, supporting anti-inflammatory action. Structure-activity relationship (SAR) studies show that methylation or acylation of hydroxyl groups can improve metabolic stability but reduce antioxidant activity (23).

5. CLINICAL APPLICATION AND CURRENT RESEARCH

Rutin has gained significant attention in both clinical and research settings due to its diverse pharmacological properties. A list of its clinical applications and current research has been presented in Tables 1 and 2.

Table 1. List of clinical trials and research conducted using rutin

Activity Studied	**Human Volunteers**	**Dose**	**Study Period**	**Parameters Evaluated**	**Study Outcome**	**Ref**
Antioxidant and Cardioprotective	30 healthy volunteers	500 mg/day	5 weeks	lipid profile, oxidative stress markers (MDA, SOD, GPx)	A notable decrease in oxidative stress and an enhanced lipid profile	20
Anti-Inflammatory in Osteoarthritis	120 patients with knee osteoarthritis	250 mg/day	8 weeks	Pain score (WOMAC), inflammatory markers (CRP, IL-6)	Reduced pain and inflammation	17
Neuroprotective in Alzheimer's Disease	50 patients with mild cognitive impairment	500 mg/day	12 weeks	Cognitive function, oxidative stress markers	Decreased oxidative damage and enhanced cognitive performance	33
Anti-diabetic (Glycemic Control)	75 type 2 diabetes patients	500 mg twice daily	10 weeks	Fasting blood glucose, HbA1c, insulin resistance	Improved glycemic control, reduced insulin resistance	37
Antihypertensive (Blood Pressure Control)	90 hypertensive patients	500 mg/day	12 weeks	Blood pressure, endothelial function (NO levels)	Reduced systolic and diastolic blood pressure	21
Anti-cancer (Breast Cancer Adjuvant Therapy)	50 breast cancer patients	1 g/day	16 weeks	Tumor markers, apoptosis markers	Increased apoptosis, reduced tumor progression	10

Table 2. Clinical Application of Rutin

Application	Details	Evidence Level	Ref
Neurodegenerative Disorders	Alzheimer's disease (reduces β-amyloid toxicity) and tardive dyskinesia	Preclinical models show improved cognition and motor function	12
Epilepsy	Adjunct therapy without drug interactions	Demonstrated safety in animal models	35
Arthritis	Reduces inflammation and cartilage degradation in rheumatoid/septic arthritis	Effective in adjuvant-induced arthritis models	7
Cancer	Adjuvant in chemotherapy (e.g., colorectal, leukemia) and radioiodine therapy	Enhances survival and reduces tumor growth in murine models	23
Ocular Disorders	Improves retinal blood flow and function recovery	Validated in electroretino-graphy studies	6
Pulmonary Protection	Prevents acute lung injury by suppressing neutrophil infiltration and cytokine release	LPS-induced lung injury models show reduced oxidative damage	12
Varicosities/Hemorrhoids	Improves vascular integrity and reduces inflammation	Included in over-the-counter supplements	9

6. CONCLUSIONS

This study focuses on rutin as a potential, non-toxic nutraceutical with a diverse pharmacological profile that includes antioxidant, anti-inflammatory and protective effects. Regular eating of rutin-rich foods may help with disease prevention and management. Rutin has sparked growing scientific interest due to its diverse biological activities. Future research is likely to focus on identifying its underlying molecular mechanisms, enhancing bioavailability and understanding its metabolism, particularly the function of gut bacteria. Another interesting option is the development of improved drug delivery technologies, such as nanoparticles and liposomes, to improve rutin solubility, stability and targeted efficacy. Rutin has a lot of potential as an adjuvant in pharmaceuticals, and researchers are investigating its epigenetic effects and ability to modulate gene expression. Co-delivery strategies with other drugs may also result in synergistic therapeutic benefits. Advances in synthetic biology may allow for the scalable production of rutin through microbial engineering or plant-based systems and structural modifications could lead to more potent derivatives. Rutin may also play a role in veterinary medicine, particularly in reducing oxidative stress in animals. Altogether, rutin represents a multifaceted compound with significant therapeutic and commercial potential, warranting deeper investigation across multiple scientific disciplines.

AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration with all authors. All authors finally approved and drafted the manuscript.

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DECLARATION

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

ETHICAL STATEMENT

In this study, we did not involve any animal and human studies.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

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