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ABSTRACT

Flavonoids are currently considered a special class of medicinal chemicals by the scientific community because of their wide range of therapeutic applications. Of them, rutin—also referred to as rutoside or vitamin P—has been studied for a variety of pharmacological effects. Rutin is an active component of numerous foods, including tea leaves, apples, and many others. These days, rutin's nutraceutical properties have been noted. The current review focusses on the most recent findings and the benefits of rutin for health. In addition, concerns related to safety pharmacology and SAR have also been addressed. Rutin's low bioavailability is a severe drawback that is mostly brought on by its low solubility in water, unstable nature, and restricted membrane permeability [table 1]. This is a significant component that prevents rutin from having any biological effects in vivo, even if it may exhibit bioactivity in several in vitro systems. Furthermore, rutin's low liposolubility makes it impractical for topical usage.

KEYWORDS: Rutin, organ protection, anticancer, antidiabetic, and antimicrobial.

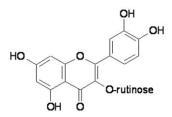
INTRODUCTION

Since ancient times, medicinal plants have played a crucial role in traditional medicine. Phytochemicals have been used in the drug discovery process to find novel leads.^[1,2]

Flavonol rutin (3,3',4',5,7-pentahydroxyflavone-3rhamnoglucoside) is widely distributed in plants, including buckwheat, apple, passion flower, and tea. It is an essential nutrient in food items.^[3]

Buckwheat contains rutin, a citrus flavonoid glycoside also known as rutoside, quercetin-3-rutinoside, and sophorin.^[4]

3,3',4',5,7-pentahydroxyflavone-3-rhamnoglucoside rutin According to Hosseinzadeh and Nassiri-Asl (2014), Figure 1 is a flavonoid of the flavonol-type, which is widely distributed throughout the kingdom of plants.^[5]



Chemical structure of rutin; Figure 1.

Pharmacology of action Central nervous system Prevention of neuroinflammation

Rutin has been shown to have a neuroprotective effect in cases of cerebral ischaemia. Rutin administration resulted in a reduction of "ischaemic neural apoptosis" because of the lipid and p53 expression embarrassment.^[6]

Increased levels of "endogenous antioxidant defence enzymes" in conjunction with peroxidation.^[7]

It has been discovered to be beneficial in oxidative, glutamate, and hypoxic stress.^[8]

Promotion of neural crest cell survival

Neural and mesenchymal potentials comprise the progenitor known as the neural crest. Rutin treatment of trunk neural crest cells improved their vitality without changing the differentiation and proliferation of the cells, which may have resulted from PI3K and ERK2 pathway modification.^[9]

Sedative activity

In tests of mice's locomotor activity, thiopental-induced sleep duration, and CNS activity, rutin was found to be involved. When rutin was administered intraperitoneally, the central nervous system was depressed. Studies found that the GABAA receptor's involvement made rutin's CNS depressive action improbable.^[10]

Anticonvulsant activity

Additionally having aniconvulsant properties, rutin does not appear to have any negative effects on the efficacy of antiepileptic medications that are administered, suggesting that it is safe for use in epileptic patients.^[11]

Anti-Alzheimer activity and treatment of hyperkinetic movement disorder

Rutin reduced TNF- α and IL-1 β production in microglia, which in turn inhibited the action of proinflammatory cytokines. The suppression of β -amyloid oligomeric cytotoxicity indicates that this action may be helpful in the treatment of Alzheimer's disease.^[12]

Antidepressant effects

Rutin extracted from Schinus molle was examined for "antidepressant-like effects" using the forced swimming and tail suspension tests in mice. In the tail suspension test, the immobility duration decreased. There was no alteration in locomotor activity. Research revealed that rutin's antidepressant-like effects are mediated by boosting serotonin and noradrenaline availability in the synaptic cleft.^[13]

Stroke

Stroke could be regarded as a crucial public health concern that looks to be an important cause of fatality and disability in adults globally.^[14]

Following "ischaemic injury" to the brain, two pathological phenomena that are seen include oxidative stress and inflammation.^[15]

Analgesic and antiarthritic activities

Analgesic and antinociceptive effects

Swiss albino mice were used in a hot plate test to investigate the analgesic properties of rutin, and this proved to be successful.^[16]

Additionally, it was verified that rutin has both central and peripheral antinociceptive properties.^[17]

Antiarthritic effects

By preventing "oxygen radical overproduction," rutin treatment was shown to significantly reduce rheumatoid arthritis and Fanconi anaemia in animals.^[18]

The stages of inflammation. In the chronic stage of inflammation, rutin was the most active.^[19] Rutin has a therapeutic impact on Candida albicans-induced septic arthritis because of its antifungal and anti-arthritic properties.^[20]

Endocrine system

Antidiabetic effects A poisonous substance called streptozotocin is known to reduce insulin levels by killing pancreatic islets. Streptozotocin specifically targets pancreatic β -cells by lowering NAD and NADP levels and producing free radicals of nitrogen monoxide and oxygen. The main causes of hyperglycemia are

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increased glucose synthesis and reduced tissue uptake of glucose. $^{\left[21\right] }$

In one study, long-term rutin administration resulted in decreased plasma glucose, increased insulin levels, and restored glycogen content and glycolytic enzymes in streptozotocin-induced diabetic rats. When diabetic rats were given rutin, there was a notable regeneration of the pancreatic islets as well as a decrease in the amount of fat infiltrate.^[22,23]

Sources of Rutin Obtained in Familly Farming Products

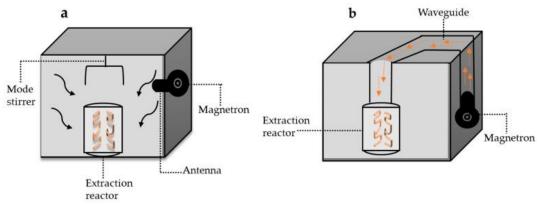
Fruits and vegetables are among the most widely consumed goods in the world and are an essential part of a healthy diet. In general, they are reasonably priced and serve as a symbol of customary farming methods for families and communities.^[24]

On the one hand, aromatic herbs are frequently employed as condiments and seasonings in the culinary arts to improve the mouthfeel of meals. These plants are also frequently employed in the agricultural and pharmaceutical industries as a source for treating a variety of illnesses because humans have been cultivating them since ancient times. Active ingredients found in aromatic plants have anti-inflammatory, antiinfectious, and calming effects, among many other qualities that make them beneficial for treating both physical and mental illnesses. They work as antiseptics, disinfectants, bactericides, and fungicides and are beneficial against influenza, gastrointestinal disorders, anxiety, seizures, rheumatic pain, muscle spasms, ulcerations, and haemorrhoids.^[25]

Thus, safe enzymes and solvents that enable selective extraction are used, along with modelling and optimisation of operational variables, to create effective rutin extraction processes. Rutin is frequently extracted using protic substances like ethanol, glycerol, or 1,3 butanediol because of the flavonoid's skeleton and many hydroxyl groups. According to reports, the extraction procedure is carried out at temperatures between 30 and 70 °C.^[26]

Microwave-Assisted Technologu in Rutin Extrction

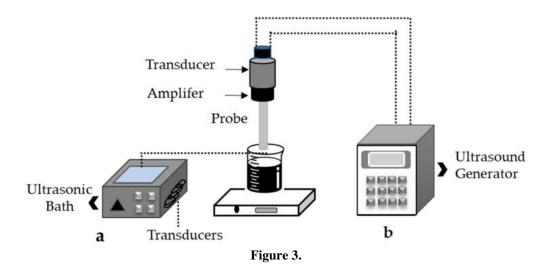
A viable substitute for traditional extraction techniques is the microwave-assisted extraction technique (MAE). Gedye and Giguere developed microwave energy as a revolutionary approach in organic synthesis in 1986. In order to extract biological matrices and prepare analytical samples, Ganzler applied (MAE).^[27] As seen in Figure 2, closed microwave equipment makes use of the parallel or perpendicular microwave radiation dispersion over the entire cavity; this closed system is employed to adapt the technology to high pressure. Conversely, as Figure 2b illustrates, the open system permits the occurrence of microwave radiation in a particular area of the cavity; hence, this system is typically utilised to operate at atmospheric pressure.^[28] Solvents including ethanol and water have been used to extract rutin utilising the microwave-assisted method. It was investigated how to extract bioactive chemicals from fig leaves. Since the solubility investigations showed that non-ionic solvents were more soluble than the metabolites to be extracted, the presence of several hydroxyl groups in the surfactant may cause the target compounds to form strong hydrogen bonds with one another, which would facilitate their capture.^[29]





Ultrasound- Assisted Technology in Rutin Extrection Utilised to aid in the extraction of biological substances, ultrasound technology is thought to be a productive and cost-effective substitute for conventional techniques.^[30]

Ultrasonic waves (>16 kHz) are transferred into a liquid medium during the sonication process, which causes cavitation phenomena. Because of the pressure variations and cycles of expansion and compression that take place during the process, this causes gas bubbles to form, grow, and burst. When high-power intensity (10–1000 W/cm2) and low frequencies (less than 100 kHz) are used during sonication, the collapse of bubbles results in high shear rates in solids and surfaces, which facilitates the extraction of chemicals. Localised high temperatures (<4727 °C) and pressures below 101 MPa are also produced. Figure 3 When high-power intensity (10–1000 W/cm2) and low frequencies (less than 100 kHz) are used for sonication, the collapse of bubbles results in high pressures (below 101 MPa) and localised high temperatures (less than 4727 °C).^[31]



Rutin, Industrial Application Rutin in the Food Industry

The study of phenolic compounds in relation to the food industry is concentrated on standardising transformation procedures that prevent the compound from degrading, substituting chemical additives, enhancing the nutritional value of food, and creating bioactive packaging. Despite the fact that rutin has many well-known health benefits, its use in the food industry is still limited because of its physicochemical properties in aqueous media and the bitter, astringent taste that phenolic compounds have. Moreover, rutin is prone to deterioration during processing, such as cooking, which explains this. Cooking is one of the common methods that has been observed to determine the amount of rutin. The amount of rutin in cooked asparagus.^[32]

Active Packaging

Packaging and container manufacturing have been researched with rutin compositions. Quercetin and rutin

were encapsulated in dipalmitoyl lecithin liposomes and subsequently integrated into edible carboxymethylcellulose films. Low polydispersity index (0.32 and 0.20), good encapsulation efficiency (88.9 and 74.1%), and a Z potential of 42.4 mV were all reported by the physicochemical characterisation. It was noticed that liposomes were appropriate for encapsulating rutin and regulating its release. In addition, the antioxidant efficacy of the flavonol rutin was proven.^[33]

Food Fortification

Enriching food matrices with bioactive chemicals is an important area of research, and although the number of studies on the subject is still low, the number of publications on the subject has increased. After adding rutin and quercetin to a spreadable cheese composition at a concentration of 0.5 g/100 g, researchers assessed the impact of temperature and melting duration (80 and 90 °C for 1.5 and 10 min) on the antioxidant capacity, total phenolic content, and rutin and quercetin retention. According to the study, the two flavonoids' content dramatically dropped, which had an impact on their antioxidant potential. Rutin was more affected by melting temperature than quercetin.^[34]

Cosmetic Applications

Recent years have seen a rise in interest in natural compounds with antioxidant activity and photoprotective potential because of their potential to enhance traditional sunscreen formulations. In sunscreen formulations containing 0.1% and 3% w/w rutin, the clinical safety, antioxidant potential, and sun protection factor (SPF) of rutin were assessed. Their research showed that the 3% rutin formulation could raise the SPF by up to 70%, proving that it was a safe and effective addition to sunscreen formulas. Additionally, compared to formulations lacking rutin, this formulation increased the removal of free radicals by 40%.^[35]

CONCLUSION

The information above makes it clear that rutin is a phytochemical with a variety of pharmacological effects. Given that rutin, one of the key ingredients in apples, exhibits a variety of biological functions, the proverb "an apple a day, keeps the doctor away" appears to be accurate. Therefore, rutin might be considered a "vital phytochemical" that requires further research in order to determine an effective safety profile in humans and get therapeutic advantages.

REFERENCES

- 1. Grdina D.J., Murley J.S., Kataoka Y. Radioprotectants: current status and new directions. *Oncology*, 2002; 63(Suppl 2): 2–10.
- Weiss J.F., Landauer M.R. Protection against ionizing radiation by antioxidant nutrients and phytochemicals. *Toxicology*, 2003; 189.
- Harborne J.B. Nature, distribution and function of plant flavonoids. *Prog. Clin. Biol. Res.*, 1986; 213: 15–24.

- 4. Kreft S., Knapp M., Kreft I. Extraction of rutin from buckwheat (*Fagopyrum esculentum* Moench) seeds and determination by capillary electrophoresis. *J. Agric. Food Chem.*, 1997; 4.
- 5. Hosseinzadeh H, Nassiri-Asl M. Review of the protective effects of rutin on the metabolic function as an important dietary flavonoid. *J Endocrinol Invest.*, 2014; 37: 783–788.
- 6. Of flavonoids and polar metabolite profiling of Tanno-original and Tanno-high rutin buckwheat. *J Agric Food Chem.*, 2014; 62: 2701–2708.
- Khan M.M., Ahmad A., Ishrat T., Khuwaja G., Srivastawa P., Khan M.B., Raza S.S., Javed H., Vaibhav K., Khan A., Islam F. Rutin protects the neural damage induced by transient focal ischemia in rats. *Brain Res.*, 2009; 1292: 123–135.
- Pu F., Mishima K., Irie K., Motohashi K., Tanaka Y., Orito K., Egawa T., Kitamura Y., Egashira N., Iwasaki K., Fujiwara M. Neuroprotective effects of quercetin and rutin on spatial memory impairment in an 8-arm radial maze task and neuronal death induced by repeated cerebral ischemia in rats. *J. Pharmacol. Sci.*, 2007; 104: 329–334.
- 9. Nones J., Costa A.P., Leal R.B., Gomes F.C., Trentin A.G. The flavonoids hesperidin and rutin promote neural crest cell survival. *Cell Tissue Res.*, 2012; 350(2): 305–315.
- Fernández S.P., Wasowski C., Loscalzo L.M., Granger R.E., Johnston G.A., Paladini A.C., Marder M. Central nervous system depressant action of flavonoid glycosides. *Eur. J. Pharmacol.*, 2006; 539(3): 168–176.
- Nieoczym D., Socała K., Raszewski G., Wlaź P. Effect of quercetin and rutin in some acute seizure models in mice. *Prog. Neuropsychopharmacol. Biol. Psychiatry.*, 2014; 54: 50–58.
- 12. Nieoczym D., Socała K., Raszewski G., Wlaź P. Effect of quercetin and rutin in some acute seizure models in mice. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 2014.
- Machado D.G., Bettio L.E., Cunha M.P., Santos A.R., Pizzolatti M.G., Brighente I.M., Rodrigues A.L. Antidepressant-like effect of rutin isolated from the ethanolic extract from *Schinus molle* L. in mice: evidence for the involvement of the serotonergic and noradrenergic systems. *Eur. J. Pharmacol.*, 2008; 587(1–3): 163–168.
- Lloyd-Jones D., Adams H.P., Carnethon M., De Simone G., Ferguson T.B., Flegal K., Ford E., Furie K., Go A., Greenlund K., Haase N., Hailpern S., Ho M., Howard V., Kissela B., Kittner S., Lackland D., Lisabeth L., Marelli A., Mcdermott M., Meigs J., Mozaffarian D., Nichol G., O'donnell C., Roger V., Rosamond W., Sacco R., Sorlie P., Stafford R., Steinberger J., Thom T., Wasserthiel-Smoller S., Wong N., Wylie-Rosett J., Hong Y. Heart disease and stroke statistics 2009 update: a report from the American heart association statistics committee and stroke statistics subcommittee. *Circulation.*, 2009; 11: e71–e87.

- 15. Deb P., Sharma S., Hassan K.M. Pathophysiologic mechanisms of acute ischemic stroke: an overview with emphasis on therapeutic significance beyond thromlolysis. *Pathophysiology*, 2010; 17: 197–218.
- Rylski M., Duriasz-Rowińska H., Rewerski W. The analgesic action of some flavonoids in the hot plate test. *Acta Physiol. Pol.*, 1979; 30(3): 385–388.
- Selvaraj G., Kaliamurthi S., Thirungnasambandam R., Vivekanandan L., Balasubramanian T. Antinociceptive effect in mice of thillai flavonoid rutin. *Biomed. Environ. Sci.*, 2014; 27(4): 295–299.
- 18. Ostrakhovitch E.A., Afanas'ev I.B. Oxidative stress in rheumatoid arthritis leukocytes: suppression by rutin and other antioxidants and chelators. *Biochem. Pharmacol.*, 2001; 62(6): 743–746.
- Guardia T., Rotelli A.E., Juarez A.O., Pelzer L.E. Anti-inflammatory properties of plant flavonoids. Effects of rutin, quercetin and hesperidin on adjuvant arthritis in rat. *Farmaco.*, 2001; 56(9): 683–687.
- 20. Han Y. Rutin has therapeutic effect on septic arthritis caused by *Candida albicans*. Int. Immunopharmacol., 2009; 9(2): 207–211.
- 21. Chattopadhyay R. Hypoglycemic effect of *Ocimum* sanctum leaf in normal and streptozotocin diabetic rats. *Indian J. Exp. Biol.*, 1993; 31: 891–893
- 22. Stanley Mainzen Prince P., Kamalakkannan N. Rutin improves glucose homeostasis in streptozotocin diabetic tissues by altering glycolytic and gluconeogenic enzymes. J. Biochem. Mol. Toxicol., 2006; 20(2): 96–102.
- 23. Srinivasan K., Kaul C.L., Ramarao P. Partial protective effect of rutin on multiple low dose streptozotocin-induced diabetes in mice. *Indian J. Pharmacol.*, 2005; 37: 327–328.
- 24. Martin C. The interface between plant metabolic engineering and human health. *Curr. Opin. Biotechnol.*, 2013; 24: 344–353. doi: 10.1016/j.copbio.2012.11.005.
- 25. Tacherfiout M., Kherbachi S., Kheniche M., Mattonai M., Degano I., Ribechini E., Khettal B. HPLC-DAD and HPLC-ESI-MS-MS profiles of hydroalcoholic extracts of *Chamaemelum nobile* and *Mentha pulegium*, and study of their antihemolytic activity against AAPH-induced hemolysis. *S. Afr. J. Bot.*, 2022; 150: 678–690. doi: 10.1016/j.sajb.2022.08.001
- Lefebvre T., Destandau E., Lesellier E. Selective extraction of bioactive compounds from plants using recent extraction techniques: A review. J. Chromatogr. A., 2020; 1635: 461770. doi: 10.1016/j.chroma.2020.461770.
- 27. Smith L.A., Mills J. Concurrent and sequential networks—Implications for prwecrp management. *Eng. Manag. Int.*, 1986; 3: 279–282. doi: 10.1016/0167-5419(86)90024-4
- Chan C.-H., Yusoff R., Ngoh G.-C., Kung F.W.-L. Microwave-assisted extractions of active ingredients from plants. *J Chromatogr. A.*, 2011; 1218: 6213– 6225. doi: 10.1016/j.chroma.2011.07.040.

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- Yu L., Meng Y., Wang Z.L., Cao L., Liu C., Gao M.Z. Sustainable and efficient surfactant-based microwave-assisted extraction of target polyphenols and furanocoumarins from fig (*Ficus carica* L.) *J. Mol. Liq.*, 2020; 318: 114196. doi: 10.1016/j.molliq.2020.114196.
- Chemat F., Rombaut N., Sicaire A.-G., Meullemiestre A., Fabiano-Tixier A.-S., Abert-Vian M. Ultrasound assisted extraction of food and natural products. Mechanisms, techniques, combinations, protocols and applications. A review. *Ultrason. Sonochem.*, 2017; 34: 540–560. doi: 10.1016/j.ultsonch.2016.06.035.
- Gallo M., Ferrara L., Naviglio D. Application of Ultrasound in Food Science and Technology: A Perspective. *Foods.*, 2018; 7: 164. doi: 10.3390/foods7100164.
- Drinkwater J.M., Tsao R., Liu R., Defelice C., Wolyn D.J. Effects of cooking on rutin and glutathione concentrations and antioxidant activity of green asparagus (*Asparagus officinalis*) spears. J. *Funct. Foods.*, 2015; 12: 342–353. doi: 10.1016/j.jff.2014.11.013.
- 33. Silva-Weiss A., Quilaqueo M., Venegas O., Ahumada M., Silva W., Osorio F., Giménez B. Design of dipalmitoyl lecithin liposomes loaded with quercetin and rutin and their release kinetics from carboxymethyl cellulose edible films. *J. Food Eng.*, 2018; 224: 165–173. doi: 10.1016/j.jfoodeng.2018.01.001.
- Přikryl J., Hájek T., Švecová B., Salek R.N., Černíková M., Červenka L., Buňka F. Antioxidant properties and textural characteristics of processed cheese spreads enriched with rutin or quercetin: The effect of processing conditions. *LWT—Food Sci. Technol.*, 2018; 87: 266–271. doi: 10.1016/j.lwt.2017.08.093
- Tomazelli L.C., de Assis Ramos M.M., Sauce R., Cândido T.M., Sarruf F.D., de Oliveira Pintoa C.A.S., de Oliveira C.A., Rosado C., Velasco M.V.R., Baby A.R. SPF enhancement provided by rutin in a multifunctional sunscreen. *Int. J. Pharm.*, 2018; 552: 401–406. doi: 10.1016/j.ijpharm.2018.10.015. [
- 36. Weiss J.F., Landauer M.R. Protection against ionizing radiation by antioxidant nutrients and phytochemicals. *Toxicology.*, 2003; 189: 1–20.
- 37. Arora R., Gupta D., Chawla R., Sagar R., Sharma A., Kumar R. Radioprotection by plant products: present status and future prospects. *Phytother. Res.*, 2005; 19: 1–22.