



Pharmacological Activity & Therapeutic Potential of Bioactive Flavonoid Rutin

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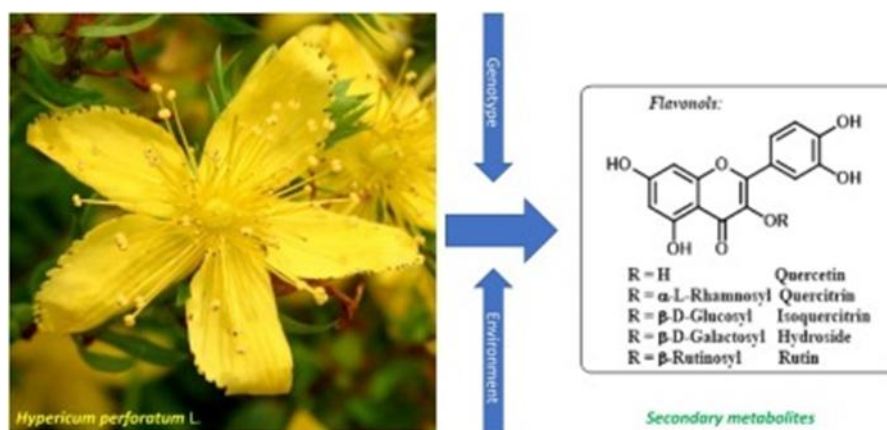
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ABSTRACT

Rutin is a naturally occurring flavonoid glycoside widely distributed in plants and plant-derived foods. It is recognized for its diverse pharmacological activities and considerable therapeutic potential. The present review summarizes the biological and pharmacological properties of rutin, with particular emphasis on its antioxidant, cytoprotective, anti-inflammatory, antimicrobial, cardiovascular, antiplatelet, antidepressant, and anti-ulcer activities. Rutin exhibits strong free-radical scavenging and antioxidant effects and has been reported to reduce reactive oxygen species and lipid peroxidation while enhancing endogenous antioxidant defenses. Its cytoprotective and anticancer potential has been associated with modulation of cell proliferation, apoptosis, oxidative stress, and cellular signaling pathways. Rutin also demonstrates anti-inflammatory effects through regulation of inflammatory mediators and pathways including NF- κ B and MAPK. Experimental studies further indicate cardioprotective, antithrombotic, neuroprotective, and gastroprotective effects. These diverse activities suggest that rutin may have potential in the prevention and management of oxidative stress-related and inflammatory disorders. However, further studies, particularly well-designed human investigations, are required to establish its therapeutic efficacy, mechanisms, safety, and clinical applicability.

INTRODUCTION

Flavonoids, polyphenolic compounds, are one of the important classes of plant derived chemicals that contain benzopyrone moiety. About 4000 types of flavonoids have been reported to be present in plants (Guardia et al., 2001). It is one of the flavonoids of a great importance in the pharmaceutical industry, and it is a component of many medicinal and therapeutic formulations patented in several countries (Gullon, Matkowski, Ghorbani, Sharma et al., 2008). Rutin is a kind of flavonoid glycoside, also known as vitamin P or purple quercitrin, present in more than 70 plants species and food products of plant origin especially buckwheat seeds, apricots, cherries, grapes, grapefruit, onion, plums, and oranges (Kreft S).



Rutin is a common dietary flavonoid and little or no dietary rutin is absorbed intact since gut microflora metabolizes it to a variety of compounds that may be absorbed (Yang et al., 2008). Microflora of the lower gut hydrolyzes rutin to its aglycone, quercetin, and the sugar residue, which are subsequently absorbed by the small intestine wall (Koval'skii et al., 2014).

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. Phytochemicals (plant-based products) have received wider significance in exploring potent therapeutic approaches against numerous carcinomas with enormous health benefits. (Ashrafizadeh, BSR et al., 2014).

Rutin, a hydrophobic polyphenolic flavonoid phytochemical, has evinced various pharmacological properties (A. Ganeshpurkar). The secondary metabolite, rutin, is the principle active constituents in some of the medicinal plants of Sikkim. In this context, the new approach of rutin estimation could be able to establish the economic value of medicinal plants at cultivation or field area. (D.k.Pradhan et al.,2018). It is reportedly responsible for the bioactivity of many natural products which include anticancer, antigout, anti-inflammatory, antioxidant, anti-hypertensive, antidepressant, antidiabetic, antiaging, and antimicrobial properties (Arima, Dixit S., Gullon, Jarial R et al.,2020).

A high antioxidant capacity was attributed to rutin, in addition to presenting important biological activities (Abarikwu, Panchal).

PHARMACOLOGICAL ACTIVITIES

❖ Antioxidant Property

Rutin, known for its powerful antioxidant ability, is gaining attention as a molecule of interest because of its many pharmacological effects, which include regulating inflammation, managing diabetes, protecting blood vessels, exhibiting antimicrobial activity, and most importantly, possessing anticancer capabilities (Gosavi,H.D.).

Antioxidants are compounds that inhibit oxidation of other molecules and balance the oxidative state in the cells. They can prevent or slow damage to cells caused by free radicals, unstable molecules that the body produces as a reaction to environmental and other factors. They are sometimes also called as "free-radical scavengers." It is well-known that excessive free radical production and lipid peroxidation in vivo may cause many kinds of diseases. Due to antioxidative nature, rutin shows a wide range of pharmacological actions and has been used as protective agent in a number of diseases. Yang et al., (2008) using different assays analyzed the antioxidant activity of rutin and found that it has powerful antioxidant capacity against various antioxidant systems exhibiting strong radical scavenging activity as well as effective inhibition of lipid peroxidation. The study showed that rutin in vivo administration improved the antioxidant defense systems against iron overload-induced hepatic oxidative stress in rats. This protective effect in liver of iron-loaded rats may be due to both antioxidant and metal chelation activities.(Aziza et al., 2014).The finding suggested that the antioxidant capacity of rutin may be attributed to its electron or hydrogen donating power orhydroxyl scavenging ability (Kaur et al., 2015). Rutin's ability to reduce reactive oxygen species(ROS) generation and enhanced activity/levels of various antioxidants in the cells has also been reported (Gegotek et al., 2017).

Wang et al.(2012)demonstrated that rutin acted as a multifunctional agent by inhibiting α -amyloid aggregation and β cytotoxicity, preventing mitochondrial damage, reducing the production of malondialdehyde (MDA), ROS, nitric oxide (NO), glutathione disulfide(GSSG), inducible nitric oxidesynthase (iNOS), and pro-inflammatory cytokines, and increasing catalase, superoxide dismutase, reduced glutathione (GSH), and glutathione peroxidase levels. (Patil et al. 2017) reported the protective effect of rutin and quercetin against radiation-induced DNA damage in human lymphocytes, which may be attributed to antioxidant capacity of rutin involving scavenging of radiation-induced free radicals and also by the inhibition of radiation-induced oxidative stress.

The interaction between these internal and external factors is crucial, with oxidative stress—caused by an imbalance between the production of reactive oxygen species (ROS) and the body's ability to remove these reactive substances or repair the resulting harm—being a significant factor in the development of various diseases, particularly cancer6(Hwang,E.S.).

Rutin is known for its anti-inflammatory and vasoactive properties, as well as for its capability to diminish capillary permeability and to reduce the risk of arteriosclerosis, whereby reducing coronary heart disease, possibly through the diminishing of platelet aggregation [La Casa et al., 2000; Jiang et al., 2007]. There are also studies that show a doseresponse effect of rutin in inhibiting low-density lipoprotein (LDL) peroxidation [Jiang et al., 2007], and the antioxidant activity of rutin in Fenton reaction [Cailet et al., 2007]. These properties are potentially beneficial in preventing diseases and protecting the stability of the genome.

Rutin was suggested as one of the most potent natural inhibitors of advanced glycation endproducts (AGEs) accumulation in human body, suggesting that its anti-glycation activity may mainly be due to its radical scavenging activity [Peng et al., 2008]. Up till now, only a few studies have been performed on humans in this respect. Probably, the first study was described by [Griffith et al.1944]. [He et al.1995] reported a hypocholesterolemic effect in humans after the intake of buckwheat products.

In this study, for the first time, the antioxidant activity of rutin was measured in parallel with buckwheat-originated material by means of spectrophotometric assays (2,2'-azinobis-(3-ethylbenzothiazoline-6-sulphonate) Radical Scavenging Activity, ABTS RSA; 2,2-diphenyl-1-picrylhydrazyl Radical Scavenging Activity, DPPH RSA, photochemiluminescence (PCL) and cyclic voltammetry (CV) methods. The contribution of rutin to the antioxidant capacity of buckwheat material might be a tool for a better selection of buckwheat-based material for different applications in functional food formulations and then for preventing many diseases resulting from the increased intake of buckwheat-based products [Danuta Zielińska].

❖ Cytoprotective Property

Cancer is caused by various factors including chemical carcinogenesis, viral infections, epigenetic changes, and somatic mutations [S.Sell,L.B.Alexandrov]. Two distinct models inform our current understanding of the transformation of normal cells into cancer cells.

Recently, a hybrid of these two models, the cellular plasticity model, was proposed. This model postulates that the “cell of origin” is not a CSC. Instead, this model contends that normal cells are inherently plastic and can undergo phenotypic changes when exposed to internal or external stimuli [P.B.Gupta 2020].

Assessing the antioxidant properties of Naringin and Rutin and investigating their oxidative DNA damage effects in breast cancer (Badhe Pravin).

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 antileukemic properties (Lin et al., 2012).

The antitumor activity of rutinsplatin combination against malignant murine ascites Dalton's lymphoma (DL) has been reported with increased cytotoxicity and apoptosis in DL cells resulting in increase in hosts, survivability. The treatment also caused a decrease in glutathione in tumor cells (Prasad and Prasad, 2018). (Calzada et al. 2018) have reported that rutin obtained from showed Schinus molle anticancer activity against human leukemic monocyte lymphoma U-937 cell line. Rutin isolated from the methanolic extract of straw has shown the anticancer and *Triticum aestivum* chemopreventive effect of rutin in dimethylbenz[a]anthracene (DMBA) and croton oil-induced skin carcinogenesis in Swiss albino mice (Dixit, 2014). In a different type of study, rutin encapsulated in low methoxyl pectin beads was found to exhibit anti-cancer activity higher than non-encapsulated rutin against three human cancer cell lines i.e. human colon adenocarcinoma (HT-29), human mouth epidermal carcinoma (KB) and hepatocellular carcinoma (HepG2) cells (Jantrawut et al., 2014). Rutin has also been used as a chemosensitizer for different cancer cell lines to increase the anticancer effect of different drugs on chemosensitized cells. Rutin was shown to sensitize human breast cancer cells to cyclophosphamide and successfully arrest cell cycle progression (Iriti et al., 2017).

Quercetin as one of the main components of rutin has also shown the anticancer and apoptosis-inducing effects in vitro in nine tumor cell lines and in mice bearing MCF-7 and CT-26 tumors (Hashemzaei et al., 2017). (Vadapalli et al. 2017) reported that rutin exhibited anti-proliferative activity on HeLa cell line by modulating haematological parameters, lipid peroxidation and augmenting antioxidant defense system in HeLa cell line-induced cervical cancer in rats. Recently, it was found that rutin and orlistat exert an in vivo anticancer activity against Ehrlich ascites carcinoma (EAC) and caused a decrease in carcinoembryonic antigen level, cholesterol content, fatty acid synthase expression and exerted antioxidant action with reduced malondialdehyde level and increased glutathione content. Further, both the drugs were cytotoxic to breast cancer cell lines MCF-7 and the pancreatic cancer cell line, Panc-1 in vitro by promoting apoptosis (Saleh et al., 2019).

Rutin has also been demonstrated for chemopreventive activity in many animal models such as azoxymethane-induced colonic tumorigenesis in mice and rats (Mahmoud et al., 2000), dimethylbenz[a]anthracene (DMBA) and N-nitrosomethylurea treated mammary glands of rats and DMBA-treated skin of cancer (Verma et al., 1988).

Apoptosis is a process of eliminating damaged cells and is executed by a family of caspases. It is regulated by apoptotic gene expression such as p53 and Bax [N. Kim-Campbell]. p53 gene mutation is the most common genetic irregularities related to apoptosis in human tumors. Rutin (900 µm) was found to downregulate the expression of mutant p53 protein in human prostate cancer cell lines (DU-145, PC-3, and LNCaP) [A. Satari, K. Yamada & K. Yoshida]. G1 and G2 phases of the cell cycle controlled by the p53 gene are a main regulatory mechanism in cellular proliferation [S. S. Baghel].

❖ Anti-Inflammatory Properties

In recent years, increasingly numbers of studies addressing the anti-inflammatory effects and mechanism of rutin have been published. Rutin can suppress the production of TNF- α and activation of nuclear factor kappa B (NF- κ B) by LPS and play an important role in the therapy for vascular inflammatory diseases. [Lee W et al. 2012]. In order to contribute to the anti-inflammatory mechanism revelation for the better evaluation of the use of rutin in clinic, this study aimed to a) to evaluate the anti-inflammatory activity of rutin in LPS-induced RAW 264.7 cells and b) to explore the regulatory effect on TLR4-MyD88-TRAF6-NF- κ B signalling pathway by analysis of the expression of related genes and proteins. In recent years, increasingly numbers of studies addressing the anti-inflammatory effects and mechanism of rutin have been published. Rutin can suppress the production of TNF- α and activation of nuclear factor kappa B (NF- κ B) by LPS and play an important role in the therapy for vascular inflammatory diseases [Lee W et al., 2012]. In addition, rutin may be a promising modulator in attenuating cyclophosphamide induced inflammation by downregulating the levels of inflammatory markers, such as TNF- α and IL-6, and expression levels of p38-mitogen-activated protein kinase (MAPK), NF- κ B, iNOS and COX-2 [Tian CL et al., 2012]. Rutin ameliorates CCl4-induced inflammation by significantly decreasing the p53, TNF- α and IL-1 β activities and MAPK phosphorylation in mouse kidneys [Ma JQ et al.]. However, there is no evidence that rutin can exhibit the anti-inflammatory activity through the tolllike receptor 4 (TLR4) myeloid differentiation factor 88 (MyD88)-TNF receptor, associated factor 6 (TRAF6)-NF- κ B signalling pathway. The present study provides an important evidence that rutin could display a better anti-inflammation effect, and the major mechanisms were also revealed, including diminution of the expression levels of iNOS gene and protein; and regulation of TLR4-MyD88-TRAF6-NF- κ B signalling pathway by increasing I κ B gene expression and reducing the expression levels of TLR4, MyD88, TRAF6 and p65 gene expression, and the phosphorylation levels of I κ B and p65 and the expression levels of TLR4, MyD88 and TRAF6 proteins (Chunlian Tian et al., 2012).

The production levels of NO, PGE2 and cytokines are closely related to signalling pathways. Therefore, the anti-inflammation mechanisms of rutin were further demonstrated based on the TLR4-MyD88-TRAF6-NF- κ B signalling pathway in this study. The expression levels of TLR4, MyD88 and TRAF6 genes were reduced ($P < 0.01$) by 20, 50 and 100 µm of rutin with a dose dependence. In addition, the regulation effects of rutin on the expression levels of TLR4, MyD88 and TRAF6 proteins were same with the tendency of gene expression levels. These results indicated that rutin could

exhibit the anti-inflammatory action by inhibiting the expression levels of TLR4, MyD88 and TRAF6 genes and proteins in LPS-induced RAW 264.7 cells. There were many reports on the regulation of flavonoids on TLR4-MyD88-TRAF6 signalling pathway.[**Chunlian Tian et al.,2012**]

❖ Anti-Fungal & Anti-Microbial Property

Secondary metabolites are small molecules responsible for various biological activities, acting as antibiotic, antifungal and antiviral agents to protect plants from pathogens. There are large groups of secondary metabolites, which include alkaloids and flavonoids (Simões CMO), described mainly by their antimicrobial (Djipa CD, Esquenazi D) and antioxidant potential (Barreiros ALBS). The antibacterial properties of rutin have also been proven, which may find practical applications in the era of antibiotic resistance. Previous scientific research has demonstrated the antimicrobial activity of rutin against both Gram-positive and Gram-negative bacterial strains. [**Rodríguez-Valdovinos, L.F.; Medina-Medrano, Jhanji, R.; Singh,A, Jhanji, R.; Bhati.V, Wang.Z et al.,2002**]

Rutin was observed to be inactive against HSV, S. aureus 6583, E. coli 95, and C. albicans as speculated by **Ilic et al.,2004**. According to the other reports, the same compound tested by the plaque reduction method showed no activity against HSV-1 (Selway, 1986; Lyu et al.,2005). These inconsistencies may be due to variations within each assay.

Our results suggest that quercetin and rutin enhance the antifungal activity of amB. Additional in vivo tests are required to perform synergy tests and to evaluate the antimicrobial potential of these compounds for optimize the therapeutic conduct and reduce the toxic effects of the drug quercetin and rutin are potential therapeutic agents for use in combination with amd since it has the advantage of reducing the toxicity of the drug and also improves their antifungal activity.[V. M. Oliveiraa].

❖ Cardiovascular Property

Ischemic heart disease is one of the primary reasons for 'morbidity and mortality' all along the globe. The pathophysiology underlying damage at a cellular level raised due to ischemia is multifaceted. Reactive oxygen species are identified to participate and play a key task in the pathogenesis of several diseases (**Li and Jackson, 2002**). It is well known that ischemic tissues produce 'oxygen-derived free radicals' that are known to cause oxidative damage to membrane lipids, proteins, and carbohydrates that predispose to 'qualitative and quantitative alterations' of the myocardium (Burton et al., 1984). Rutin was studied for cardioprotective effect by ischemia-reperfusion-induced myocardial infarction in normal and streptozotocin diabetic rats. Rutin administration significantly offered cardioprotection and restricted infarcts size in normal and diabetic rats (**Annapurna et al., 2009; Krishna et al., 2005**). The mechanism lying behind this protection could be attenuation of lipid peroxidation in myocardial tissues (**Ali et al., 2009**). Isoproterenol is β -adrenergic agonist used to treat bradycardia and heart block (**Shen, 2008**). However, frequent administration of it may lead to cardiac toxicity observed by an increase in the activity of serum cardiac marker enzymes viz lactate dehydrogenase, aspartate transaminase, creatine kinase, and alanine transaminase along with significant decrease in the activity of these enzymes in the heart. Rutin restored the levels of cardiac marker enzymes along with a reduction in lipid peroxidation. The study suggests the cardioprotective effect is due to the virtue of the antioxidant effect of rutin (**Chan et al., 2009**). Repression of isoproterenol-induced increase in angiotensin II and aldosterone in plasma was observed after administered by rutin. Along with this, overexpression of transforming growth factor β 1, connective tissue growth factor, and excessive deposition of extracellular matrix in isoproterenol-treated myocardial tissues was observed in the group of animals treated with rutin (**Li et al., 2013**).

In addition, rutin has been reported to exert its antiapoptotic effects by inhibiting apoptotic molecules such as caspase-3/-7/-9, and the elevation of antiapoptotic proteins including HMGB1 and Bcl-2. The beneficial effects of rutin on the heart, liver, and kidneys have been confirmed by histopathological examinations in a variety of studies. Rutin elicited significant cardioprotective, nephroprotective, and hepatoprotective effects that were mainly mediated by its antioxidant and anti-inflammatory properties. Considering these findings, further evaluation of this natural compound's ability to overcome the toxic effects of various toxicants is recommended. Studies focusing on the protective effects of rutin against chemical and natural toxins. Based on the results, rutin could be a promising component in the prevention and treatment of several toxicities, including hepatotoxicity, nephrotoxicity, and cardiotoxicity, and protect organs against many agents that produce free radicals. Although the biological effects of rutin on ROS-induced skin aging have been reported in a human study, further research on the protective effects of rutin and its mechanisms in human are needed to confirm animal studies. [Sohrab Rahmani]

In a diabetic cardiomyopathy-induced cardiac dysfunction model, the administration of rutin at 60 mg/kg for 6 weeks had significantly increased the phosphorylation of Akt in diabetic ApoE knockout mice, as opposed to the untreated diabetic group (**Huang et al., 2017**). In another study, rutin isolated from *Lonicera japonica* increased Akt phosphorylation in H₂O₂-mediated injury in H9c2 cells. The Akt activation by rutin was associated with a reduction in microtubule-associated protein light chain 3 (LC3), Atg5 and p62 protein expressions, the pattern of expressions of which was similar both in-vivo and in-vitro (**Ma et al., 2017**). This finding further suggests that rutin may act either directly as a parent compound on cells or after undergoing metabolism in vivo. This is suggestive that rutin itself is protective. The conversion of auto phagosomal attached protein, LC3 and turnover of LC3-II is suggestive of increased formation of autophagosome (**Li et al., 2016**), while p62 may act in a feed-forward loop to regulate autophagy (**Mans et al., 2017**). Therefore, rutin may be able to balance autophagic response to enhance cardiac cell survival which plays an essential role in cardiac remodeling process.

❖ Anti-platelets & Anti-thrombosis

Platelets are one of the principal blood cells which adhere to the damaged vessel wall at the site of injury in primary hemostasis [K. Ghoshal]. Following a vascular lesion, platelets become activated resulting in adhesion to the exposed extracellular matrix underlying the endothelium, formation

of a platelet plug. During this process, platelet surface-expressed glycoproteins (GP) [C.N. Morrell]. Activated platelets express these receptors and secrete granular contents such as von Willebrand factor (vWF), P-selectin, and ADP facilitating aggregates [Ed Nignpense].

In this study, rutin glycoside showed antioxidant and anti-inflammatory effects similar to or slightly different from rutin, indicating its potential for antithrombotic effects. Subsequently, platelet aggregation and blood coagulation were investigated in vitro and in vivo to compare and estimate the antithrombotic effects of rutin and rutin glycoside. Treatment of rutin and rutin glycoside similarly reduced platelet aggregation rate and delayed PT and APTT in blood coagulation in vitro. The repeated administration of rutin and rutin glycoside for 21 days was also effective on platelet aggregation rate in vivo. However, unlike in vitro, the PT and APTT of both the rutin and rutin glycoside group was not significantly delayed in an in vivo blood coagulation test (Choi, S.-S.).

Rutin inhibits platelet aggregation, as well as decreasing capillary permeability, making the blood thinner and improving circulation. There is also some evidence that rutin can be used to treat hemorrhoids, varicosis, and microangiopathy (Heather et al., 1995).

❖ Anti-depressants

A widely approved mechanism of depression is depletion of monoamines levels including serotonin. In diabetes, changes in serotonin receptor modulation and serotonin depletion were detected [Prabhakar V, Gupta D]. Another suggested mechanism for serotonin depletion is inhibition of enzymes responsible for serotonin synthesis [Elesawy BH]. In agreement, hippocampal serotonin level in the diabetic group was reduced. However, rutin treatment in diabetic rats was found to increase hippocampal serotonin levels in comparison with the diabetic group. Rutin's antidepressant effect is attributed to restoration of serotonin level at the synapse via exerting antioxidant and anti-inflammatory effects [Ismail Abo El-Fadl HM]. Moreover, as our study reported, the improvement in FST results in the diabetic β rutin group confirms the antidepressant effect of rutin. Another suggested mechanism of depression in diabetes is depletion of BDNF. This factor is an essential neurotrophic factor that affects synaptic plasticity, dendritic and axonal morphology, and a number of intracellular signaling events [Moghbelinejad S]. It was found that depression associated with diabetes has been accompanied with reduction of BDNF in the hippocampus [Ge H]. Our study agreed with this finding, where the diabetic group showed significant decrease in hippocampal BDNF. However, rutin treatment alleviated BDNF. Rutin's ability to restore BDNF hippocampal level could be due to activated BDNF gene expression in the hippocampus of rodents and attenuation of oxidative stress as previously showed [Moghbelinejad S, Ola MS].

❖ Anti-ulcer Activity

In recent years several investigations conducted and explored the varied biological impacts of rutin, including but not limited to anti-carcinogenic, anti-thrombotic, cardio-protective, and neuroprotective activities, as well as enhancements to liver health and integrity [A. Ganeshpurkar, O.M. Ahmed] where rutin has the potential to offer various health benefits to humans and is found abundantly in the plant kingdom. In addition to their gastro-protective properties, it has been found to facilitate the healing of gastric ulcers. Moreover, a study showed that rutin has a protective effect against indomethacin-induced gastropathy, probably through inhibiting neutrophil infiltration, suppression of oxidative stress generation, and replenishing nitrite/nitrate levels regardless of gastric acidity [M. Raish]. The authors suggest that this may be due to the ability of rutin to inhibit the production of free radicals and to increase the production of prostaglandins. Another study found that rutin might shield against gastric ulcers induced by the medication indomethacin in rats. This effect could be linked to rutin's ability to boost mucus production while inhibiting pepsin, a digestive enzyme that can contribute to ulcers [J.S. Shah]. Further research found that rutin can attenuate the development of gastric ulcers in rats induced by immobilization stress. They suggest that this may be due to the ability of rutin to activate the Nrf2/HO-1 signaling pathway, which is involved in the protection against oxidative stress [M. Raish]. However, in this study, we reviewed the data on the gastro-protective effect of rutin against the pathophysiology of PUD. We assume these polyphenolic compounds may serve as promising alternatives for suppressing or modulating peptic ulcers and could potentially revolutionize the treatment of peptic ulcers, particularly in the context of commonly used antibiotics.

In addition, the involvement of oxygen derived free radicals are well established in the pathogenesis of ischemic injury of gastrointestinal mucosa and in other models of mucosal damage induced by non-steroidal anti-inflammatory drugs, ethanol, and H.pylori (Drake et al., 1998). Also, the gastric cancer risk is reduced by ascorbic acid (AA) intake in a dose-dependent way, and in H. pylori-infected patients, the ascorbic acid levels are lower than in the normal population. Decreases of AA and the increases of the oxidized form of AA, dehydroascorbic acid (DHAA), were detected in the acute and chronic inflammation, peptic ulcer, gastritis, and H. pylori infection in stomach. Low reducing capacity of rutin implies the rescue of AA from DHAA at low level in vivo. In addition, the cellular tissue damage by free radicals involves lipid peroxidation, which destroys cell membranes with the release of intracellular components, such as lysosomal enzymes, leading to further tissue damage. The radicals also promote mucosal damage caused by degradation of the epithelial basement membrane components, complete alteration of the cell metabolism and DNA damage. The levels of malondialdehyde (MDA), a final product of lipid peroxidation by oxidants, are thought to reflect free radical mediated cell membrane damage in patients with peptic ulcer and gastritis. Rutin completely inhibited the colonization of H. pylori at the dose of 50 μ M, and this effect was equivalent in that of ampicillin (10 μ g/ml). H. pylori is believed to be a major cause of peptic ulcer and gastric cancer as well as bacterial gastrointestinal infections.

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