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A Review on Comprehensive Review of Rutin Derivatives and Their Biological Activities

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ABSTRACT:

Flavonoids are the largest group of naturally occurring plant polyphenols and are well known for exhibiting a broad spectrum of biological activities in both in vitro and in vivo experimental models. Among these compounds, rutin has attracted considerable attention because of its diverse pharmacological properties, including antioxidant, anti-inflammatory, antimicrobial, wound-healing, antimutagenic, and anti-HIV activities. To overcome the limitations associated with rutin and improve its therapeutic performance, researchers have developed various structural derivatives aimed at increasing its bioavailability, biological potency, and target selectivity. Studies on the structure–activity relationship (SAR) of rutin have provided valuable insights into how chemical modifications influence its biological functions, thereby supporting the rational design of more effective derivatives. Consequently, rutin and its derivatives have emerged as promising candidates for the development of novel therapeutic agents against a wide range of diseases. This review highlights the chemical characteristics, structure–activity relationships, and pharmacological potential of rutin and its potent derivatives, emphasizing their significance in modern drug discovery and development.

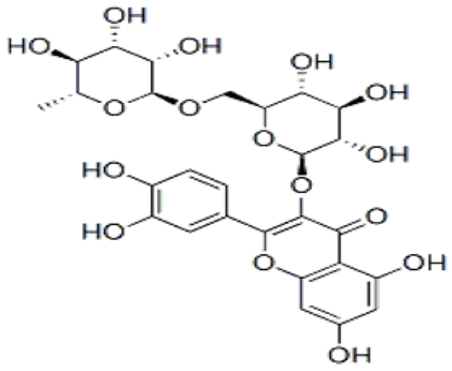
Keywords: Anti-inflammatory, Antimicrobial, Antioxidant, Chemical properties, Polyphenols, Rutin derivatives.

1. INTRODUCTION:

Rutin is a naturally occurring flavonoid that has gained significant attention because of its broad range of biological activities and promising therapeutic applications. It exhibits antimicrobial, anti-inflammatory, antioxidant, cytotoxic, and several other pharmacological properties, making it a valuable candidate for the prevention and treatment of various diseases. Due to its diverse biological effects, rutin has been widely investigated as a lead compound for the development of novel therapeutic agents. Computational approaches, particularly molecular docking studies, have further contributed to identifying structurally modified rutin derivatives with enhanced affinity toward specific molecular targets, provided that their mechanisms of action are clearly understood. Commonly known as vitamin P, rutin (3′,4′,5,7-tetrahydroxyflavone-3-O-rutinoside) is a naturally occurring flavonoid glycoside present in numerous plant species, especially buckwheat. Pharmacological investigations have demonstrated that rutin helps maintain capillary strength by reducing vascular permeability and fragility, thereby preventing haemorrhage and vascular damage. In addition, it possesses antibacterial, anti-inflammatory, analgesic, antioxidant, radioprotective, cardioprotective, diuretic, antispasmodic, cholesterol-lowering, and antiplatelet activities. Given its extensive therapeutic potential and increasing pharmaceutical importance, the development of simple, accurate, reliable, and sensitive analytical methods for rutin detection and quantification remains essential..[1] Several studies have demonstrated that rutin possesses potent antioxidant, anti-inflammatory,

anticarcinogenic, neuroprotective, antiproliferative, and antimetastatic activities, primarily through its ability to reduce oxidative stress and inhibit lipid peroxidation. Excessive production of reactive oxygen species (ROS) can damage cellular components, including DNA, proteins, and lipids, leading to chromosomal abnormalities, dysregulated gene expression, and abnormal cell growth and proliferation. ROS can also impair the function of endogenous antioxidant defences systems, thereby increasing cellular susceptibility to oxidative damage. Accumulating evidence has linked elevated ROS levels with the development and progression of several cancers, such as breast, lung, colorectal, liver, leukemia, and neuroblastoma. Lipid peroxidation is an oxidative process in which ROS attack membrane lipids, generating lipid peroxyl radicals and lipid hydroperoxides that compromise membrane integrity and cellular function. If left unchecked, this process can result in severe cellular injury and cell death. Rutin acts as an effective antioxidant by scavenging free radicals and suppressing lipid peroxidation, thereby protecting cells from oxidative damage. Furthermore, previous studies have indicated that rutin can modulate lipid metabolism, reduce tissue injury associated with ischemia–reperfusion, and alleviate edema and tissue sensitivity, highlighting its potential as a therapeutic agent against oxidative stress-related disorders. [2] To overcome the pharmacokinetic limitations of rutin, considerable research has focused on developing advanced drug delivery systems in recent years. These novel formulations have demonstrated improved pharmacokinetic behavior, leading to enhanced bioavailability and greater therapeutic effectiveness compared with conventional preparations. Despite these promising findings, further investigations are necessary to optimize strategies that increase the lipid solubility of rutin, thereby maximizing its absorption, therapeutic potential, and overall clinical efficacy.

1.1 CHEMICAL STRUCTURE OF RUTIN:



1.2 CHEMICAL PROPERTIES OF RUTIN:

Property	Description
Chemical Name	Rutin (Quercetin-3-rutinoside)
Molecular Formula	$C_{27}H_{30}O_{16}$
Molecular Weight	610.52 g/mol
Chemical Class	Flavonoid glycoside

Property	Description
Appearance	Yellow to greenish-yellow crystalline powder
Solubility	It has low solubility in water but dissolves readily in ethanol, methanol, and alkaline media.
Melting Point	Approximately 190–200°C (with decomposition)
pH Stability	It remains stable under mildly acidic conditions but becomes unstable in strongly alkaline environments.
Hydrolysis	Under acidic conditions or in the presence of certain enzymes, rutin is hydrolyzed to yield quercetin and the disaccharide rutinose as its major degradation products.
Oxidation	It is prone to oxidation upon exposure to air and light.
UV Absorption	It exhibits distinct absorption peaks near 257 nm and 355 nm.
Reducing Property	Acts as an antioxidant by donating electrons and scavenging free radicals
Metal Chelation	Forms complexes with metal ions such as iron and copper
Chemical Reactivity	It possesses several phenolic hydroxyl groups that contribute to its antioxidant properties.
Storage Conditions	It should be kept in a well-sealed container and safeguarded from exposure to light, heat, and humidity.

Rutin is a naturally occurring flavonoid glycoside and one of the major secondary metabolites synthesized by plants. It is also commonly known by several other names, including rutoside, quercetin-3-*O*-rutinoside, sophorin, and vitamin P. Chemically, rutin is designated as 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[β-D-glucopyranosyloxy-(1→6)-α-L-rhamnopyranosyl]chromen-4-one and has the molecular formula $C_{27}H_{30}O_{16}$. It occurs as a yellow crystalline or yellow-colored powder with a molecular weight of 610.52 g/mol.[3] Flavonoids are a large class of plant-derived polyphenolic compounds characterized by a common 15-carbon (C6–C3–C6) structural framework. Their basic structure consists of two aromatic benzene rings, known as rings A and B, connected by a three-carbon bridge that forms a heterocyclic ring (ring C). The structural diversity of flavonoids arises from differences in the oxidation pattern of ring C, the presence or absence of double bonds, and the position of attachment between rings B and C. Based on these structural variations, flavonoids are classified into several subclasses, including flavonols, flavones, flavanones, flavanols, anthocyanidins, and isoflavones. Rutin is a flavonol glycoside that possesses this characteristic flavonoid backbone, with a rutinose sugar attached to the quercetin aglycone, contributing to its distinctive biological and pharmacological properties..[2]

2. STRUCTURAL ACTIVITY RELATIONSHIP:

Quercetin exhibits limited bioavailability due to its poor aqueous solubility and low solubility in several pharmaceutically acceptable solvents, which restrict its absorption and therapeutic effectiveness. [4] Quercetin, chemically known as 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one, is a prominent member of the flavonol subclass of flavonoids. Its molecular structure is characterized by five

hydroxyl groups positioned at the 3, 5, 7, 3′, and 4′ carbon atoms of the flavonol nucleus. These hydroxyl groups provide sites for the attachment of various sugar moieties through glycosylation, leading to the formation of numerous quercetin glycosides. Such structural modifications significantly influence the compound's physicochemical characteristics, stability, bioavailability, and pharmacological properties..[5] Antioxidants are compounds that protect biological systems and other chemical substances from oxidative damage caused by reactive oxygen species (ROS). These highly reactive molecules include singlet oxygen, hydroxyl radicals (•OH), superoxide anions ($O_2^{\bullet -}$), and lipid peroxyl radicals, all of which can damage cellular components and contribute to the development of various diseases. Rutin is a naturally occurring flavonoid glycoside that possesses significant antioxidant activity and is widely recognized for its ability to neutralize ROS and reduce oxidative stress..[6] The antioxidant and free radical scavenging properties of flavonoids are largely influenced by their chemical structure. Important structural features include the presence of multiple free hydroxyl groups, a double bond between C2 and C3 in the C ring, and hydroxyl groups located at the C-3, C-5, and C-7 positions. In addition, the existence of either a catechol-type dihydroxyl arrangement or a pyrogallol-type trihydroxyl arrangement on the B ring significantly enhances the antioxidant potential of flavonoid molecules. [7] Hyperglycaemia primarily results from the enzymatic action of α-glucosidase, which hydrolyzes terminal α-1,4-linked D-glucose residues to release free α-D-glucose during carbohydrate digestion. Therefore, inhibiting α-glucosidase has become an important therapeutic strategy for the management of diabetes mellitus, as it helps reduce postprandial blood glucose levels..[8] Experimental findings demonstrated that the compound exhibits stronger DPPH radical scavenging activity than quercetin. Computational analysis further indicated that this enhanced antioxidant performance is associated with its lower ionization potential (IP) and bond dissociation energy (BDE) compared with quercetin..[9]

With the exception of rutin, limited information is available regarding the ability of flavanol glycosides to inhibit lipid autoxidation, primarily because their poor solubility in lipid-based systems has restricted extensive investigation. [2,10,11] Previous studies have reported that rutin exhibits strong antioxidant activity, which has been attributed to the presence of its disaccharide glycosyl moiety. Similarly, a quercetin diglycoside was found to display antioxidant activity comparable to that of rutin, as illustrated in Figures 2a and 2b. These observations suggest that other quercetin glycoside derivatives may also contribute significantly to antioxidant activity..[12] The xanthine oxidase inhibition results indicate that the rutinoside moiety plays a vital role in enzyme inhibitory activity, as removal of this group markedly reduces potency. Among the synthesized compounds, RU3a3, which contains the rutinoside moiety, exhibited the strongest inhibitory effect with an IC_{50} value of 4.870 µM, whereas RU7c1 showed the weakest activity, displaying an approximately fivefold reduction in potency with an IC_{50} value of 19.377 µM. Hydrazine derivatives demonstrated greater inhibitory activity than the corresponding aniline derivatives, emphasizing the importance of the NH–NH_2 functional group. Nevertheless, replacing the sulfur-containing group with hydrazine, as observed in RU3a3 and RU3a2, resulted in reduced activity, while substitution of the phenyl group with sulfur, as in RU3a1, enhanced the inhibitory effect. In contrast, the introduction of an ester group led to a further decline in xanthine oxidase inhibitory activity..[13]

3. BIOLOGICAL ACTIVITY\SIGNIFICANCE:

3.1 Antioxidant:

Reactive oxygen species (ROS) are highly reactive molecules generated through normal metabolic processes within the body as well as through exposure to various external factors. These species include hydroxyl radicals (•OH), superoxide anions ($O_2^{\bullet -}$), and hydrogen peroxide (H_2O_2), all of which are capable of causing oxidative damage. When ROS production exceeds the body's antioxidant defense mechanisms, oxidative stress develops, leading to a wide range of pathophysiological conditions and contributing to the onset and progression of numerous diseases..[14] The antioxidant potential of the compounds was

determined using DPPH and ABTS radical scavenging assays. Both rutin and its glycoside derivative exhibited concentration-dependent antioxidant activity, with increasing concentrations resulting in enhanced free radical scavenging. Notably, the rutin glycoside demonstrated stronger antioxidant effects than rutin under the same experimental conditions..[15]

3.2 Anticancer:

Renal cell carcinoma (RCC) is the most common form of kidney cancer in adults and originates from the epithelial cells of the proximal convoluted tubules. It is characterized by a highly vascular nature and a strong tendency to metastasize to distant organs, including the lungs, liver, and bones. Histologically, RCC is classified into several subtypes, among which clear cell renal cell carcinoma (ccRCC) accounts for approximately 70–80% of all cases, making it the predominant subtype. The incidence of RCC varies across different populations and is influenced by factors such as age, sex, ethnicity, and geographic location. Although multiple treatment options—including chemotherapy, radiotherapy, targeted therapy, hormone therapy, and immunotherapy—are available, their clinical effectiveness is often limited by low response rates and the development of therapeutic resistance. Consequently, surgical resection remains the preferred treatment for patients with localized primary tumors. However, the success of surgery largely depends on tumor stage, histological grade, and the presence or absence of metastatic disease. Therefore, there is a pressing need to develop new therapeutic strategies that are safe, effective, and capable of improving outcomes in patients with RCC..[16]

3.3 Xanthin Oxidase Inhibitors:

According to the work of Hui Xue, gout is a common inflammatory arthritis caused by the deposition of monosodium urate crystals within the joints, leading to severe pain, swelling, and inflammation. Xanthine oxidase (XO), a key enzyme in purine metabolism, plays a central role in the pathogenesis of gout by catalyzing the oxidation of hypoxanthine and xanthine to uric acid. Elevated uric acid levels promote hyperuricemia, which facilitates urate crystal formation and the subsequent development of gout. Beyond its involvement in gout, xanthine oxidase has also been associated with several metabolic disorders, including diabetes and cancer, through its contribution to oxidative stress and free radical generation. XO is a molybdenum-containing oxidoreductase enzyme with a molecular weight of approximately 300 kDa that catalyzes reactions producing both uric acid and reactive oxygen species. Because conventional purine-based xanthine oxidase inhibitors, such as allopurinol, are associated with various adverse effects, there is growing interest in identifying safer inhibitors from natural sources. Rutin, a naturally occurring plant flavonoid, possesses a broad range of pharmacological activities, including antioxidant, anti-inflammatory, and cytotoxic effects. Recent studies have demonstrated that rutin and several of its derivatives exhibit significant xanthine oxidase inhibitory activity, highlighting their potential as promising natural agents for the prevention and treatment of gout..[17]

3.4 Anticonvulsant Activity:

Epilepsy is one of the most common and serious neurological disorders, representing a significant public health concern worldwide. Epidemiological studies have highlighted its high prevalence and considerable impact on affected individuals and healthcare systems. Nearly 70% of patients with epilepsy achieve adequate seizure control through antiepileptic medications, which primarily act by regulating membrane ion channels or by modulating γ-aminobutyric acid (GABA)-mediated inhibitory neurotransmission and glutamatergic excitatory signaling..[18] Flavonoids are naturally occurring polyphenolic compounds characterized by a phenylbenzopyran backbone. They are classified into different subclasses based on the oxidation state of the heterocyclic ring and the number, type, and position of their substituent groups. In recent years, considerable attention has been directed toward the effects of flavonoids on the central nervous system (CNS). Among the various neurotransmitter systems, γ-aminobutyric acid type A

(GABA_A) receptors serve as the principal inhibitory receptors in the CNS and represent important pharmacological targets for the treatment of neurological disorders, including epilepsy, anxiety, insomnia, and alcohol dependence..[19]

3.5 Antimicrobial activity:

Several studies have identified quercetin and rutin as two of the most biologically active polyphenolic flavonoids found in nature. Investigations into the antimicrobial properties of quercetin have demonstrated its effectiveness against a variety of pathogenic bacteria. In vitro studies have shown that quercetin inhibits the growth of microorganisms associated with periodontal disease, including *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans*, as well as other clinically important pathogens such as *Clostridium botulinum* and *Staphylococcus aureus*. These findings suggest that quercetin possesses broad-spectrum antibacterial activity and may have potential applications in the prevention and treatment of bacterial infections.. [20] Species belonging to the *Ruta* genus represent a valuable natural source of biologically active compounds. Extracts, essential oils, and purified phytochemicals obtained from *Ruta* species have demonstrated diverse pharmacological and biological activities, showing potential for the treatment of various diseases as well as for pest control. These beneficial properties enhance the medicinal and economic importance of *Ruta* plants..[21 Antibacterial polyamide fibers can be produced using two principal approaches. The first involves incorporating inorganic antimicrobial agents, such as zinc oxide or silver nanoparticles, into the polyamide matrix during the fiber-spinning process, while the second method applies antibacterial agents to the fibers through wet finishing treatments. Among these techniques, the incorporation of inorganic antimicrobial additives during spinning is more widely adopted because of its simplicity and processing efficiency. Wet finishing methods employ a variety of antimicrobial substances, including cationic surfactants and non-surfactant compounds such as cetylpyridinium chloride and chlorhexidine, as well as chitosan, silver nanoparticles, and different metal salts to impart antibacterial properties to the fibers [22]

A study conducted by Sergio Dias da Costa Junior and colleagues investigated the antibacterial and antibiofilm effects of quercetin against drug-resistant *Staphylococcus aureus* and *Staphylococcus saprophyticus*. The minimum inhibitory concentration (MIC) was determined using the broth microdilution method. Quercetin demonstrated antibacterial activity against methicillin-susceptible *S. aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), vancomycin-intermediate *S. aureus* (VISA), oxacillin-resistant *S. saprophyticus*, vancomycin-resistant *S. aureus* (VRSA), and *S. saprophyticus* strains resistant to both oxacillin and vancomycin. The MIC values ranged from 125–150 µg/mL for MSSA, MRSA, and VISA, while higher concentrations of 500–1000 µg/mL were required for the more resistant *S. saprophyticus* and VRSA isolates. In addition to inhibiting bacterial growth, quercetin significantly reduced biofilm formation. Biofilms produced by *S. aureus* were suppressed at MIC/2 and MIC/4 concentrations, whereas *S. saprophyticus* biofilms were also notably reduced at MIC/2. These findings indicate that quercetin possesses considerable antibacterial and antibiofilm properties, highlighting its potential as a promising natural antimicrobial agent against resistant bacterial pathogens..[23]

S. Al-Majmaie and co-workers investigated **rutin and its derivative, rutin 3′-methyl ether**, to evaluate their biological activities. [25] and 6-hydroxy-rutin 3',7-dimethyl ether[26] a novel flavonol glycoside, were identified from the methanol extract of Ruta chalepensis fruits that were harvested in Diyala, Iraq. They were able to clarify their structures by spectroscopic investigations, such as 1D, 2D, and HRESIMS NMR. Using a 96-well resazurin microtitre assay, the antimicrobial activity of compounds 1-3 was evaluated against four strains of both Gram +ve and Gram -ve bacteria as well as the single fungus strain, Candida albicans. [27]

In a study by Han Y and co-workers, rutin was isolated from *Artemisia princeps* Pamp. and used as the starting material for the synthesis of several novel derivatives containing a 1,4-pentadien-3-one structural unit. The synthesized compounds were structurally characterized using proton nuclear magnetic resonance (^1H NMR), carbon-13 nuclear magnetic resonance (^13C NMR), and electrospray ionization mass spectrometry (ESI-MS). Biological evaluation demonstrated that several of these derivatives exhibited good to excellent antiviral activity against *Tobacco mosaic virus* (TMV) and *Cucumber mosaic virus* (CMV) in vivo at a concentration of 500 μg/mL..[28]

O. Elansary H. and co-workers investigated the antibacterial potential of polyphenolic constituents isolated from *Ferocactus* species. Among the 21 compounds analyzed from the stem extracts, six were identified as polyphenols. These included four phenolic acids—protocatechuic acid, 3,4-dihydroxyphenylacetic acid, caffeic acid, and vanillic acid—and two flavonoids, rutoside and quercitrin. The identified polyphenolic compounds were associated with the antibacterial activity observed in the *Ferocactus* stem extracts..[29]

In a study conducted by O. Elansary H. and co-authors, the antibacterial properties of polyphenolic constituents isolated from *Ferocactus* species were investigated. Analysis of the stem extracts revealed 21 phytochemicals, of which six were identified as polyphenolic compounds. These consisted of four phenolic acids—protocatechuic acid, 3,4-dihydroxyphenylacetic acid, caffeic acid, and vanillic acid—and two flavonoids, rutoside and quercitrin. The presence of these polyphenols was considered to contribute to the antibacterial activity exhibited by the *Ferocactus* stem extracts..[29]

In a study by Ivanov M. and co-workers, the antifungal effects of several flavonoids against *Candida albicans* were investigated. The researchers evaluated the activities of luteolin, apigenin, and their glycosylated derivatives, including quercitrin, isoquercitrin, rutin, and apigetrin. In addition, the study assessed the influence of these compounds on the expression of the *CDR1* gene, which encodes an efflux pump, and the *ERG11* gene, involved in ergosterol biosynthesis. The cytotoxic effects of the flavonoids on primary liver cells were also examined. Among the tested compounds, luteolin, quercitrin, isoquercitrin, and rutin demonstrated the strongest inhibitory activity against *Candida albicans*, exhibiting the lowest minimum inhibitory concentrations (MICs). The minimum inhibitory concentration and minimum fungicidal concentration (MFC) were determined using a modified broth microdilution method..[31] In a study by Orhan D.D. and co-authors, the antimicrobial activities of isolated compounds were evaluated using the broth microdilution method against standard and drug-resistant strains of bacteria and fungi. The tested microorganisms included *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Bacillus subtilis*, and the fungal species *Candida albicans* and *Candida krusei*. The isolated compounds exhibited notable antibacterial and antifungal activities, particularly against drug-resistant isolates of *P. aeruginosa*, *A. baumannii*, *S. aureus*, and *C. krusei*. In addition, cinnamoyl-β-D-apiofuranosyl-5,7-dimethoxyflavanone-4′-O-β-D-glucopyranoside, 5,7,3′-trihydroxyflavanone-4′-O-β-D-glucopyranoside, and rutin demonstrated antiviral activity against HSV-1, with β-D-glucopyranoside derivatives showing particularly strong inhibitory effects..[32] Özçelik B. and co-workers investigated the antibacterial and antiviral potential of several flavonoid derivatives. Flavonoids are a large class of naturally occurring polyphenolic compounds biosynthesized from *p*-coumaroyl-CoA and malonyl-CoA, forming a characteristic chromane ring structure. More than 5,000 flavonoids have been identified from natural sources such as fruits, vegetables, beverages, and medicinal plants, with many occurring as water-soluble glycosides. These compounds are well known for their diverse biological activities, including antioxidant, anti-inflammatory, cardioprotective, antimicrobial, anticancer, hepatoprotective, and antiviral effects. In this study, four flavonoid derivatives—scandenone, tiliroside, quercetin-3,7-*O*-α-L-dirhamnoside, and kaempferol-3,7-*O*-α-L-dirhamnoside—were evaluated for their antibacterial, antifungal, and antiviral activities. Among the tested microorganisms, the compounds showed the strongest antibacterial effects against *Staphylococcus*

aureus and *Enterococcus faecalis*, while moderate activity was observed against *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Bacillus subtilis*. In contrast, *Proteus mirabilis* and *Pseudomonas aeruginosa* exhibited the greatest resistance to the tested flavonoid derivatives..[33]

Shu and co-workers investigated the antibacterial activity of quercetin against eleven major oral pathogenic microorganisms. Quercetin inhibited the growth of six of the tested species, including *Streptococcus mutans*, *Streptococcus sobrinus*, *Lactobacillus acidophilus*, *Streptococcus sanguinis*, *Aggregatibacter actinomycetemcomitans* (formerly *Actinobacillus actinomycetemcomitans*), and *Prevotella intermedia*, with activity determined by minimum inhibitory concentration (MIC) assays. Quercetin and its derivatives exhibited antibacterial effects against a broad range of bacterial species, although their potency varied depending on the microorganism tested. In addition, quercetin demonstrated significant activity against several Gram-positive bacteria, including *Enterococcus* species, methicillin-sensitive *Staphylococcus aureus* (MSSA), and methicillin-resistant *Staphylococcus aureus* (MRSA). The ability of quercetin to suppress the growth of multiple drug-resistant pathogens highlights its potential as a promising antimicrobial agent for combating antibiotic-resistant bacterial infections..[34]

Özçelik B. and co-workers evaluated the antibacterial activity of six flavonoids isolated from *Galium fissurense*, *Viscum album* ssp. *album*, and *Cirsium hypoleucum*. The tested compounds included 5,7-dimethoxyflavanone-4′-*O*-β-D-glucopyranoside, 5,7-dimethoxyflavanone-4′-*O*-(2″-*O*-(5‴-*O*-trans-cinnamoyl)-β-D-apiofuranosyl)-β-D-glucopyranoside, naringenin-7-*O*-β-D-glucopyranoside, 5,7,3′-trihydroxyflavanone-4′-*O*-β-D-glucopyranoside, rutin, and nicotiflorin. Their antimicrobial activity was assessed against extended-spectrum β-lactamase (ESBL)-producing multidrug-resistant *Klebsiella pneumoniae*. Although the flavonoids exhibited lower activity than the reference antibiotic ampicillin, all tested compounds demonstrated measurable in vitro antibacterial effects against the ESBL-producing *K. pneumoniae* isolates. Considering the intrinsic resistance of ESBL-producing bacteria to most β-lactam antibiotics, the observed antimicrobial activity suggests that these flavonoids may serve as promising lead compounds for the development of alternative therapies against multidrug-resistant bacterial infections..[35] Li B. and co-workers investigated the incorporation of rutin into cellulose acetate/poly(ethylene oxide) (CA/PEO) fiber membranes to overcome the compound's poor aqueous solubility and limited bioavailability. Rutin was encapsulated within the CA/PEO fiber matrix to produce a bioactive membrane, which was subsequently characterized for its surface morphology, encapsulation efficiency, antioxidant capacity, antibacterial activity, and drug-release behavior. In addition, the researchers evaluated the mechanical properties, thermal stability, and molecular interactions of the fabricated membranes. The findings indicated that rutin-loaded CA/PEO fiber membranes possess favorable physicochemical and biological properties, highlighting their potential as multifunctional bioactive materials for biomedical and pharmaceutical applications. [36]

In a study by Motallebi M. and co-workers, the influence of rutin on methylene blue (MB)-mediated photodynamic therapy (PDT) against *Pseudomonas aeruginosa* and *Staphylococcus aureus* was investigated. Rutin, a plant-derived flavonoid commonly found in tea, wheat, and apples, is recognized for its antimicrobial properties. The antibacterial effects of rutin, administered before or after MB-assisted PDT at 660 nm, were evaluated in both planktonic and biofilm bacterial cultures following minimum inhibitory concentration (MIC) and MTT assays. The results demonstrated that combining rutin with MB-mediated PDT significantly enhanced the reduction of bacterial biofilm formation and planktonic bacterial populations compared with treatment using methylene blue alone. Furthermore, the combined therapy showed no detectable cytotoxicity toward human dermal fibroblasts, suggesting that rutin-enhanced MB-mediated PDT may represent a safe and effective strategy for the treatment of bacterial wound infections..[37]

3.6 Antioxidant Property:

Rutin has attracted considerable attention for its potential therapeutic role in the management of neurodegenerative disorders. Many neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and prion diseases, share common pathological features such as neuronal degeneration, apoptosis, mitochondrial dysfunction, oxidative stress, and chronic inflammation. Among these mechanisms, oxidative stress is considered a major contributor to the initiation and progression of these disorders. Owing to its potent antioxidant and neuroprotective properties, rutin has been extensively investigated for its ability to reduce oxidative damage and mitigate the pathological processes associated with neurodegenerative diseases..[38] Alexander Victor and co-workers reviewed the biological significance of quercetin, emphasizing its broad therapeutic potential as a natural antioxidant. Antioxidants protect cells from oxidative damage caused by reactive free radicals, and quercetin, a flavonoid abundantly present in fruits and vegetables such as onions, grapes, berries, cherries, broccoli, and citrus fruits, is recognized for its potent free radical-scavenging activity. In addition to its antioxidant properties, quercetin has demonstrated protective effects against tissue injury induced by various toxic agents and pharmaceuticals.

In another study, Sung Sook Choi and colleagues compared the biological activities of rutin and rutin glycoside, focusing on their in vitro antioxidant capacity, anti-inflammatory effects, platelet aggregation, and blood coagulation. Rutin glycoside, consisting of mono- and diglucosyl derivatives of rutin, was synthesized through enzymatic transglycosylation. The results showed that rutin glycoside exhibited stronger free radical-scavenging activity than rutin in antioxidant assays. Moreover, rutin glycoside displayed lower cytotoxicity toward murine RAW264.7 macrophage cells, whereas rutin showed comparatively greater toxicity, indicating that glycosylation improved both the antioxidant performance and safety profile of rutin..[15]

Tanja Pivec and co-workers investigated the relationship between the antioxidant properties of water-soluble rutin derivatives and their potential application in wound healing. Although rutin is a well-established plant-derived flavonoid with strong antioxidant activity, its limited water solubility restricts its use in pharmaceutical and cosmetic formulations. To overcome this limitation, the researchers enzymatically polymerized rutin in an aqueous medium without using organic solvents, producing a water-soluble polymer known as polyrutin (PR). The chemical structure of PR was characterized using ^1H NMR and Fourier-transform infrared (FTIR) spectroscopy, while its molecular weight was determined by size-exclusion chromatography (SEC). Potentiometric charge titration was employed to evaluate its acid–base properties. Furthermore, the antioxidant capacity of PR was comprehensively assessed by measuring its ability to scavenge the stable free radical ABTS, neutralize biologically relevant reactive species including superoxide ($O_2^{\bullet -}$), nitric oxide (NO•), and hydroxyl radicals (OH•), as well as its iron (Fe^{2+})-chelating activity. The findings demonstrated that enzymatic polymerization enhanced the water solubility of rutin while preserving its strong antioxidant and free radical-scavenging properties, highlighting the potential of polyrutin for wound-healing and other biomedical applications..[39] Jingqiu Wang and co-workers investigated the antioxidant, anti-inflammatory, and anticancer activities of kaempferol and its glycosylated derivatives. Although both kaempferol and its glycosides are widely found in nature and are known to possess diverse biological activities, comparative studies evaluating their pharmacological properties remain limited. In this study, the researchers compared the biological effects of kaempferol (Kae), kaempferol-3-*O*-rhamnoside (Kae-3-*O*-Rha), kaempferol-7-*O*-glucoside (Kae-7-*O*-Glu), and kaempferol-3-*O*-rutinoside (Kae-3-*O*-Rut). Their findings highlighted differences in the antioxidant, anti-inflammatory, and anticancer activities among these compounds, demonstrating that glycosylation significantly influences the biological efficacy of kaempferol derivatives..[40]

3.7 Anticancer activity:

Shirin Asgharian and co-workers reported that several flavonoids are capable of modulating key signaling pathways associated with proto-oncogenes. Proto-oncogenes encode proteins such as growth factors, protein kinases, membrane proteins, cell surface receptors, and nuclear transcription factors that regulate cell proliferation and survival. Among these, the proto-oncogenes *c-Fos*, *c-Jun*, and *c-Myc* play pivotal roles in inflammation, tumor initiation, and cancer progression. The study also demonstrated that rutin exerts anticancer effects by inducing cytotoxicity through multiple mechanisms, including DNA damage, activation of the mitochondrial apoptotic pathway, and modulation of upstream apoptotic signaling. Furthermore, rutin enhanced the activity of antioxidant enzymes while reducing intracellular reactive oxygen species (ROS) levels, thereby contributing to its therapeutic potential against cancer..[41] Ayan Mukherjee and co-workers reported a synthetic strategy for the selective modification of quercetin at the C-3′ position to improve its solubility and lipophilicity. The regioselective substitution at the C-3′ position, in preference to the C-5 position, was confirmed by X-ray crystallographic analysis. The anticancer potential and underlying mechanism of the synthesized derivatives were evaluated using both in vitro and in vivo models of colon cancer. Human HCT-116 colon cancer cells were employed for the in vitro studies, while mice bearing CT-26 tumors served as the in vivo experimental model. The introduction of weakly basic and ester-containing alkyl side chains significantly enhanced the solubility, lipophilicity, and cellular uptake of quercetin. As a result, these semi-synthetic derivatives exhibited improved physicochemical properties and demonstrated greater anticancer efficacy against colon cancer compared with the parent compound..[42]

Amir Imani and co-workers reviewed the anticancer potential of rutin, emphasizing its well-recognized antioxidant properties and broad pharmacological applications in cancer research. Unlike many conventional chemotherapeutic agents that are associated with significant adverse effects, rutin has emerged as a relatively safe natural compound with promising anticancer activity. Numerous in vitro and in vivo studies have demonstrated that rutin suppresses tumor development by regulating multiple cellular signaling pathways, including NF-κB, Wnt/β-catenin, PI3K/Akt, JAK/STAT, MAPK, p53-dependent and p53-independent pathways, as well as apoptosis-related mechanisms. These findings highlight the multifaceted molecular actions of rutin in cancer prevention and therapy.

In another study, M.M.S. Kinthada Prakash and colleagues investigated quercetin-derived thiosemicarbazone compounds because of their potential chemotherapeutic applications. Thiosemicarbazones have attracted considerable interest owing to their broad spectrum of biological activities, including antiprotozoal, antiviral, antimalarial, and antitumor effects. Derivatives of quercetin containing thiosemicarbazone moieties have been explored for their potential use in the treatment of cancers such as advanced testicular cancer, advanced breast cancer, Hodgkin's lymphoma, and lymphocytic lymphoma. To evaluate their DNA-cleavage properties, the nuclease activity of the synthesized ligands and their metal complexes was examined against pBR322 plasmid DNA using agarose gel electrophoresis in both the presence and absence of hydrogen peroxide (H_2O_2). The results indicated that the ligands exhibited no significant nuclease activity at micromolar concentrations under either experimental condition.

.[43] Udaya Rajesh R. and co-workers reported that quercetin exhibits inhibitory effects on pancreatic cancer cell proliferation in both in vitro and in vivo experimental models using the MIA PaCa-2 cell line. Pancreatic ductal adenocarcinoma is recognized as one of the most aggressive malignancies and often develops resistance to conventional chemotherapeutic agents such as gemcitabine and other cytotoxic drugs. Due to these limitations, there is a strong interest in identifying new therapeutic strategies for its treatment. In this context, quercetin has demonstrated promising anticancer potential, suggesting its usefulness as a candidate compound for pancreatic cancer therapy..[44] Rajesh Prasad and co-workers reported that rutin exhibits notable anticancer, chemopreventive, and chemosensitizing activities across

multiple cancer types. In their study, rutin administered intraperitoneally at a dose of 120 mg/kg every four days significantly suppressed the growth of human leukemia HL-60 xenograft tumors in mouse models and also demonstrated anticancer effects against human neuroblastoma LAN-5 cells. The underlying mechanism was associated with rutin-induced cell cycle arrest at the G2/M phase and the activation of apoptotic pathways in LAN-5 cells. Additionally, rutin showed strong cytotoxic activity against human colon adenocarcinoma SW480 cells in vitro, while exhibiting anticancer and anti-angiogenic effects in vivo without causing noticeable toxicity in tumor-bearing nude mice. [45]

4.CONCLUSION:

To address pharmacokinetic limitations, phytochemicals play a crucial role in drug development, as they can be chemically modified to generate derivatives with improved structural and functional properties. Rutin and its derivatives, in particular, have shown considerable therapeutic potential, with enhanced analogues demonstrating promising activity in the treatment and prevention of microbial infections, inflammatory conditions, and carcinogenesis. Further research is needed to improve the safety profiles, bioavailability, and overall efficacy of these compounds to support their development as effective therapeutic agents.

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