Nephrotoxicity and Neuropathy-Associated with Acyclovir Antiviral Remedy: Toxicological Mechanism and Ameliorative Role of Rutin and Quercetin

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Abstract

Background: Acyclovir is one of the most essential antiviral drugs in treating herpes virus infections like herpes simplex and herpes zoster. However, several clinical complications limit their uses, since after recovery these serious complications deteriorate patient quality of life. The most common and dangerous complications are nephrotoxicity and neuropathy. Acyclovir induced the abovementioned disorders by disrupting several physiological functions and molecular pathways such as promoting tissue oxidative burst, inflammation, apoptosis, endoplasmic reticulum stress, fibrosis, and blocking cellular autophagy in nephrons and neural cells. Nowadays, the protective usage of various bioactive compounds extracted from several medicinal plants is growing worldwide since they possess several beneficial pharmacological activities like anti-inflammatory, antioxidant, immunomodulatory, cytoprotective, and antiapoptotic properties. Thus, the current review summarizes the mechanism by which acyclovir induces renal impairment and neuropathy and the possible ameliorative effects of many bioactive compounds in mitigating these complications.

Keywords: acyclovir; apoptosis; nephrotoxicity; neuropathy; rutin; quercetin

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Introduction:

Acyclovir, an acyclic guanosine nucleoside analog is an antiviral agent that is active against herpes virus infections **(Rogers et al., 1983).**

The use of acyclovir (ACV) has become an established part of clinical practice, it is also being increasingly used in the treatment of herpes simplex and cytomegalovirus diseases in

immunocompromised hosts **(Dos Santos et al.,199).** Although herpes zoster is not a fatal disease, it can cause severe zoster-related pain including both acute zoster pain and chronic pain of post-herpetic neuralgia (PHN). Severe zoster-related pain can cause physical disability and emotional distress, impair quality of life, and create an economic burden on the individual and society. It is well-known that antiviral treatments are available to ameliorate acute zoster pain and prevent it **(Kim et al., 2012).**

Adverse effects of acyclovir include mild symptoms, such as nausea, vomiting, and diarrhea, to more severe symptoms, including neutropenia, hepatitis, and Stevens-Johnson syndrome, however drug- associated complications during pregnancy have not been documented **(Chang et al., 2002).** Acyclovir is a safe and efficacious drug for viruses such as herpes viruses, varicella zoster, and cytomegalovirus. The drug has little to no effect on healthy cells, targeting only those affected (**German, et al., 2023).** The main adverse reactions include nausea, vomiting, abdominal pain, diarrhea, dizziness, headache, urinary system damage, liver dysfunction, rashes, and allergic-like reactions. Therefore, the Chinese State Food and Drug Administration has issued a drug use warning for ACV **(Lu et al., 2014)**

The most common adverse effect of acyclovir a general malaise, while less commonly there can be abdominal pain, agitation, dizziness, anemia, or fatigue **(Taylor, 2019).** Many people worldwide use traditional medicine, which involves treating various illnesses with plants and herbs **(Emeka et al., 2018).** Furthermore, consuming plant-based diets is linked to a lower risk of several ailments, such as diabetes, cancer, cardiovascular disease, and hypertension **(Adams and Standridge, 2006 & Adelakun et al., 2018).** Sources of bioactive substances and secondary metabolites with proven medical advantages are plants. Alkaloids, phenolics, flavonoids, tannins, and steroids are among the several substances present in plants; these have been demonstrated to have certain medicinal effects against a variety of diseases **(Murevanhema et al., 2018).** Thus, the current review summarizes the mechanisms by which acyclovir induces nephropathy and neuropathy in patients and experimental animals and how the supplementation of several pants bioactive compounds mitigate these adverse effects.

Reno and neuro-toxicological mechanism of acyclovir.

Acyclovir is commonly used and has good general tolerance. However, despite its good safety profile, it can cause systemic adverse effects such as nephrotoxicity and neurotoxicity **(Nishii et al., 2021).** The adverse effects related to IV administration of acyclovir require caution when patients with renal impairment receive high drug doses. Neurological adverse events of the acyclovir are associated with the metabolite 9-carboxymethoxymethyl guanine (CMMG), mainly in older people and those ones with reduced renal function. Preexisting renal impairment and dehydration are associated with acyclovir crystalline nephropathy. The risk of nephropathy is usually reduced when acyclovir is slowed and infused over 1 h, combined with adequate hydration and dose adjustment based on renal function (**Assis et al., 2021).** Deposits and tubular obstruction crystal formation were more likely with rapid infusions, and high-dose therapy, and in the setting of volume depletion crystal formation often occurs early in the therapeutic course (first 1–2 days) **(Downes et al., 2020).**

Acyclovir-induced nephrotoxicity.

Acyclovir nephrotoxicity occurs in approximately 12-48% of cases and is associated with three patterns of kidney injury: tubular dysfunction, crystal-induced nephropathy, and acute tubulointerstitial nephritis **(Chávez-Iñiguez et al ., 2018).** In a study of adults, acute kidney (AKI) occurred in 13% of parenteral acyclovir treatment **(Ryan et al ., 2018).** Acyclovir-induced AKI has been reported to occur in 13–21% of patients and AKI occurred after a median of 2–9 days on acyclovir **(Barber et al., 2019).** When acyclovir is at supra-therapeutic levels, it can result in AKI due to the insoluble crystal of acyclovir in renal tubules **(Kim et al., 2012, Yildiz et al., 2013 and Kour et al., 2023).**

Preexisting kidney disease, older age, obesity, hypertension, longer duration of treatment, and concurrent use of nephrotoxic drugs are all associated with an increased risk of acyclovir-induced nephrotoxicity. The most characteristic symptoms of neurotoxicity are confusion, somnolence, and hallucination **(Kacirova et al., 2023).** Acute Kidney Injury is a significant adverse effect of intravenous acyclovir. Patients with pre-existing chronic renal disease or getting greater total dosages are more at risk, emphasizing the therapeutic significance of dosage modification based on optimum body weight and baseline renal function **(Ryan et al., 2018).**

Acyclovir causes multiple changes in the renal tubules and renal glomeruli including congestion, cellular infiltration, tubular degeneration, glomerular hypercellularity, and glomerular tuft shrinkage. **(Sodhi et al., 2003).** Studies have reported various forms of nephrotoxicity caused by ACV including crystal nephropathy, acute interstitial nephritis, acute tubular necrosis and obstructive nephropathy (**Lu et al., 2014 ; Vomiero et al., 2002;Yarlagadda and Perazella 2008 and Mulay and Anders 2017).** A well-known side effect of acyclovir is nephrotoxicity. The most common manifestation of acyclovir-induced kidney failure is obstructive nephropathy caused by the intratubular precipitation of crystals and characterized by hematuria, pyuria, and crystalluria **(Desrumaux et al., 2023).**

Acyclovir causes renal failure through a variety of mechanisms, including direct renal tubular toxicity with unique effects on epithelial cells of the kidney. crystal deposition in the kidney may promote the development of renal failure also induce crystal nephropathy so acyclovir renal injury associated with effects on the renal transporters, as well as on tubule cells **(Izzedine et al., 2005).** A direct toxic effect of acyclovir or an acyclovir metabolite on the podocytes: the aldehyde metabolite of acyclovir may be formed in glomerular cells, causing a similar toxic effect to that described in acute tubular necrosis Another possibility is that the 9-carboxy methoxymethyl guanine metabolite, known for its neurotoxicity, is formed in the glomerulus causing damage to the podocytes **(Kenzaka et al.,2021).**

It has been reported that urea crystallization is a secondary factor in ACV renal toxicity – the main agent being the aldehyde metabolite of ACV, which can damage renal tubules directly **(Gunness et al., 2011 and Yvin et al., 2020).** Because of its low solubility in urine, rapid or excessive intravenous infusion can cause crystal precipitation and blockage in the kidney tubules, leading to acute renal **(Delluc et al., 2004).** The most common manifestation of acyclovir-induced kidney failure is an obstructive nephropathy caused by the intratubular precipitation of crystals and characterized by hematuria, pyuria, and crystalluria, Other renal side effects of acyclovir are acute tubular toxicity and interstitial nephritis. Additionally, acyclovir can induce encephalopathy. The

neurotoxicity is caused by the accumulation of a toxic metabolite of acyclovir CMMG, which occurs mostly in patients with pre-existing renal dysfunction **(Desrumaux et al.,2023).**

Higher serum concentrations of acyclovir are associated with the development of crystalluria and can result in a greater risk of acute kidney injury **(Zelnicek,2023 and Rao et al.,2015).** The use of intravenous acyclovir can be particularly complicated in pediatric patients with evolving renal impairment **(Steinberg et al., 2015).** Acute kidney injury secondary to the precipitation of acyclovir crystals in the kidneys is well-known and mainly observed in the setting of dehydration or pre-existing renal impairment. A case of acute kidney injury secondary to intravenous administration of acyclovir was described in a 64-year-old female with transversal myelitis and no prior medical history. She developed a rapid rise in the plasma creatinine level only seven hours after the primary drug administration **(Rantanen et al., 2014).** One pediatric cohort study described an AKI incidence in 35%in children treated with intravenous Acyclovir, **(Rao et al., 2015)**

In fact, the presumed mechanism of ACV-induced renal damage was first demonstrated by animal studies. Rats that received intravenous ACV (20 mg/kg /day) developed an obstructive nephropathy secondary to drug crystal formation in collecting ducts **(Dos Santos et al., 1997).** Cytotoxicity studies showed that acyclovir induced human renal proximal tubular cell death, *in vitro* The results suggest that acyclovir induces direct insult to human renal proximal tubular cells and the toxicity may be caused by the parent drug's acyclovir aldehyde metabolite **(Gunness**, 2011).

Acyclovir precipitate as crystals in the urinary system, causing damage to the tubular epithelium and obstruction of renal tubules This most often manifests as AKI, but chronic kidney disease can develop, depending on the rapidity and extent of crystal formation. Volume depletion is the major risk factor for crystal nephropathy, resulting in supersaturation of the urine and crystal formation in renal tubules; metabolic derangements and urinary pH may also predispose patients to crystal formation. Crystal-induced tubule cell damage stimulates inflammation and necrosis, while obstruction of the tubular lumen, if significant, can affect the hydrostatic pressure within the kidney and promote the release of signals that decrease GFR(**Downes et al., 2020).**

Renal damage from ACV has been a major factor limiting its clinical application. nephrotoxicity of ACV may be associated with oxidative stress high-dose ACV is associated with renal toxicity after a single intravenous injection or successive administration **(Shen et al., 2020).**

Nephrotoxic mechanisms of acyclovir.

A study reported a 6-year-old boy with leukemia with non oliguric acute renal failure in normal hydration status after using acyclovir treatment. He had no preexisting renal impairment, and there were no additional symptoms. laboratory findings revealed impairment of proximal tubule function, in addition to distal tubule. So, renal functions should be monitored carefully during treatment with acyclovir, and asymptomatic nephrotoxicity must be kept in mind. **(Genc et al., 2010**). Direct tubular toxicity is another important mechanism for Acyclovir-induced nephrotoxicity. Preclinical models in rats have shown a dose-dependent elevation in urinary N-acetyl-b-D-glycosaminidase activity, which is a marker of renal tubular damage **(Xing et al., 2016)**. Cytotoxicity studies showed that acyclovir induced human renal proximal tubular (HK-2)

cell death, 'in vitro', and that the degree of this toxicity was significantly reduced by co-exposure to 4-methyl pyrazole. The results suggest that acyclovir induces direct insult to human renal proximal tubular cells and the toxicity may be caused by the parent drug's noxious acyclovir aldehyde metabolite. Transepithelial transport studies illustrated that acyclovir does not inhibit the transport of creatinine **(Gunness et al., 2011).**

Nephrotoxicity is a well-known side effect of intravenous acyclovir treatment but occurs rarely by oral treatment. A 76-y-old healthy male, with normal baseline renal functions (blood creatinine 0.6 mg%), received oral acyclovir at a dose of 800 mg five times daily for 10 days for treatment of herpes zoster ophthalmicus. He developed renal failure with blood creatinine levels of 3 mg% and his renal function failed to improve within eight months of the end of treatment (**Sodhi et al.,2003)**. Crystalluria has long been thought to be the aetiology of acyclovir-induced nephrotoxicity. Clinical evidence of nephrotoxicity in the absence of crystal formation, on the other hand, suggested that acyclovir could elicit direct injury to renal tubular cells (**Gunness et al.,2011).**

Acyclovir has been associated with a multitude of nephrotoxicity symptoms, including crystal nephropathy, acute interstitial nephritis, acute tubular necrosis, and obstructive nephropathy, according to studies. Direct assault on renal tubular cells and oxidative stress have been proposed as methods by which ACV induces nephrotoxicity. ACV also had a deleterious effect on kidney redox state, reducing antioxidants (SOD) Superoxide dismutase, (CAT) Catalase activity, GSH Glutathione, and GPx (Glutathione peroxidase) and elevating (MDA) Malondialdehyde levels. The activation of oxidative stress as a result of ROS reactive oxygen species production by ACV may have impaired kidney antioxidant concentrations. The released ROS may have depleted kidney antioxidants and promoted the oxidation of renal lipids (polyunsaturated fatty acids), increasing MDA levels. It's possible that oxidative damage is a key indicator of ACV-induced renal impairment **(Adikwu et al., 2021).**

Although the rapid onset of AKI when using acyclovir the mechanism. have concluded that crystalluria and tubular obstruction of this relatively less soluble parenteral drug causes rapid renal impairment Other potential mechanisms of acyclovir-induced AKI expand on these observations. The lack of crystalluria in numerous case reports and histology reflective of tubulopathy in the face of non-oliguric renal impairment **(Steinberg et al., 2015).**

The precursor acyclovir aldehyde metabolite that is produced by alcohol dehydrogenase in a stoichiometric manner can be toxic to renal tubule cells and may explain dose-dependent nephrotoxicity **(Gunness et al., 2011).** Proteomics experiments of acyclovir-induced AKI in mice demonstrated the increased kidney production of peroxiredoxins and several other antioxidant and anti-inflammatory proteins in a dose-dependent fashion, whereas decreased expression of vascular endothelial growth factor and its receptor potentially may relate to reduced tissue repair capability **(Lu et al., 2014).** Kidney failure secondary to acute tubular necrosis is the main presentation of acyclovir nephrotoxicity also reported a severe and uncommon presentation of acyclovir nephrotoxicity Its classical presentation is acute kidney injury secondary to acute tubular necrosis (ATN), which has been related to its concentration within tubular cells **(Yvin et al., 2020).**

The use of slow infusions and optimization of hydration status and urine output before administration decreases the formation of crystals and reduces toxicity with intravenous acyclovir

(Downes et al., 2020). Aggressive hydration with intravenous fluids throughout the treatment course appears to mitigate a significant portion of nephrotoxicity from foscarnet **(Cheung et al., 2000)**.

All patients had a positive response with return to a normal renal function after hydration, lengthening of drug infusion time, and adjustment of the drug dosage **(Sandery et al., 2020)**. Renal damage indexes and urinary metabolic profiles in rats induced by ACV administration (in different concentrations and for different durations) used metabolomics technology to elucidate the time-effect relationship and dose-effect relationship of biomarkers to ACV-induced nephrotoxicity **(Xing et al., 2016)**. The treatment of acyclovir-induced nephrotoxicity is mainly supportive, and the drug should be discontinued or reduced (**Yildiz et al., 2013).**

How to reduce acyclovir-induced nephropathy.

It is recommended to administer Acyclovir as a slower infusion rather than a rapid bolus and to avoid excessively high dosages when possible. It is also paramount to achieve and maintain adequate hydration throughout the course of treatment, including at initiation, to limit the potential for crystal nephropathy. **(Izzedine et al., 2005).** Dose reduction or slowing the rate of infusion, along with administration of intravenous fluids, may decrease the risk of crystal formation by promoting urine flow (**Downes et al., 2020).** Maintaining a high urinary flow is important to prevent the formation of acyclovir crystals in the kidneys **(Fleischer et al., 2010).** In cases of acyclovir-induced renal failure, volume repletion with intravenous fluid therapy and loop diuretics may be used to flush out the medication **(Smith et al ., 2010).**

Acyclovir-induced neurotoxicity.

Neurotoxicity of acyclovir results from an accumulation of the antiviral and its metabolites in the bloodstream. This can be observed in the elderly or patients with chronic renal failure, generally in dialysis patients. Acute renal failure results from intratubular crystallization of acyclovir **(Delluc et al., 2004). Desrumaux et al., (2023)** presented a 49-year-old woman without preexisting renal failure, with an acute kidney injury and encephalopathy after acyclovir treatment.

Use of acyclovir and its congeners, like, valacyclovir and ganciclovir, especially in patients with end-stage renal disease can be problematic due to their reduced ability to excrete the drug. These patients are prone to drug toxicity that can cause alteration of mental status and encephalopathy. This can happen in patients with acute or chronic kidney disease **(Sadjadi et al., 2018).** Although recommendations exist about dose modification with kidney failure, neurotoxicity still happens, when the acyclovir dose is not modified for kidney function **(Onuigbo et al., 2009)**.

Neurotoxic mechanism of acyclovir.

Acyclovir can induce encephalopathy. The neurotoxicity is caused by the accumulation of a toxic metabolite of acyclovir (CMMG) **(De Deyne et al.,2006 and Kenzaka et al., 2021**). A case of acyclovir-induced nephrotoxicity and neurotoxicity that were reversible with cessation of treatment and hemodialysis so monitoring of renal function is essential for an early diagnosis of acyclovir-induced nephrotoxicity **(Nazliel et al., 2013)**. Severe toxicity, involving predominantly the central nervous system, can occur in patients with preexisting renal impairment receiving acyclovir, A case of severe acyclovir-induced neurotoxicity in a young patient without a history of renal impairment

was reported **(Delerme et al., 2002)**. A case of acyclovir-induced acute kidney failure and mild encephalopathy in a young and healthy woman without pre-existing renal failure was reported by **(Desrumaux et al.,2023)**.

Renal failure also causes multiple physiological changes involving CNS dysfunction, such as uremic encephalopathy, which is associated with problems of cognition and memory, with progression to delirium, convulsions, and coma **(Ohtsuki et al., 2002)**. **Onuigbo et al., (2009)** reported two patients on dialysis who exhibited significant neurotoxicity with encephalopathy after acyclovir was given at the usual adult dose.

Well-known side effects of acyclovir are nephrotoxicity and neurotoxicity present a case of acyclovir-induced acute kidney failure and mild encephalopathy in a young and healthy woman without pre-existing renal failure **(Desrumaux et al., 2023)**. **Habib and Saad (2023)** demonstrated that nephrotoxicity and neurotoxicity in obese patients .Incidence of neurotoxicity (confusion, lethargy, seizures, etc.) at any time starting after 24h of acyclovir initiation and up to 5 days or until the end of therapy.

Pharmacological properties of medicinal plants in modulating nephrotoxicity and neuropathy.

Plants' Nutritional and Therapeutic Qualities Food comes from two main sources: plants and animals, with plants providing the majority of the food. Plant-based foods include fruits, leaves, and other vegetables in our daily diet **(Tshiyoyo et al., 2022).** Plants are important for many reasons than just nutrition; they are frequently beneficial for health. Humans look to nature for potential remedies when seeking pharmaceuticals to heal illnesses **(Petrovska, 2012).** A flavonoid called quercetin is widely found in practically all fruits, vegetables, herbs, spices, dietary items, and cosmetics (Lesjak et al., 2018; Andres **et al., 2018).** It may change into a variety of compounds that include antibacterial, antioxidant, anti-inflammatory, and anti-carcinogenic qualities **(Lee et al., 2019).**

One of the most abundant naturally occurring polyphenols in our foods. Its occurrence as a secondary plant metabolite is widespread in the plant kingdom, where it is mostly present in the form of quercetin glycosides (quercetin molecule conjugated with sugar residues). In this form, quercetin is a common constituent of the human diet via vegetables and fruits (e.g., onions and apples **(Andres et al., 2018)**.

The impacts of quercetin have been documented in a large body of research that includes both human and animal studies as well as in vitro investigations. The chemical is thought to provide several benefits, including immunoprotected, anti-inflammatory, antioxidant, and even anticarcinogenic properties. As a result, the advantages of using quercetin have been explored, for example, cancer prevention or with inflammation, viral infections, asthma, diabetes, and cardiovascular illnesses **(Sharma et al.,2018).** Because of its supposed potential as an ergogenic drug, quercetin has also attracted research. Research on athletes' post-exercise inflammation, oxidative stress, immune system, endurance, and decreased rates of disease have all been studied **(Nieman and David, 2010).**

Quercetin, a potential poly-phenolic flavonol, found in onions, apples and berries, has been implicated against cancer proliferation, chronic inflammation and various other oxidative manifestations **(Sharma et al.,2018).** Some of quercetin's earliest viral studies show quercetin has antiviral activity against enveloped viruses including herpes virus simplex 1, parainfluenza type 3, pseudorabies, and Sindbis. The mechanism of action may involve interference with viral nucleic acid synthesis **(Heijnen et al.,2018).** Naturally occurring quercetin is present (primarily as glycosides) in many fruits (e.g., apples, cranberries, cherries, grapes) and vegetables (e.g., onion, peppers, asparagus), and other food items such as wine and black or green tea. **(D'Andrea and Gabriele. 2015).**

Quercetin, a flavonoid compound, has demonstrated nephroprotective effects against various drugs and chemicals that can cause kidney injury. Several studies have shown that quercetin can protect the kidneys from damage induced by compounds **(Alasmari,2021).** The flavonoid quercetin is frequently found in low amounts as a secondary plant metabolite in fruits and vegetables. Isolated quercetin is also marketed as a dietary supplement, mostly as the free quercetin aglycone, and frequently in daily doses of up to 1000 mg d–1 exceeding usual dietary intake levels **(Andres et al., 2018). Chaudhary et al., (2015).**

Renal and neural protective mechanism of quercetin.

The proposed mechanisms for quercetin's nephroprotective effects include its potent antioxidant properties, ability to reduce oxidative stress, and modulation of glutathione metabolism and antioxidant enzyme activities in the kidney. Quercetin has been shown to effectively protect against cell death and damage induced by these nephrotoxic agents **(Sujana et al., 2021).** Quercetin inhibits beta-secretase-1 (BACE-1) enzyme activity, which plays a key role in the production of amyloid-beta (Aβ) peptides that accumulate in the brains of Alzheimer's patients **(Khan et al., 2019).**

Neuroprotection by quercetin has been reported in several in vitro studies. It has been shown to protect neurons from oxidative damage while reducing lipid peroxidation. In addition to its antioxidant properties, it inhibits the fibril formation of amyloid-β proteins **(Khan et al., 2019).** Learning, memory, and cognitive functioning in AD have all improved when quercetin has been used therapeutically By inhibiting AChE and secretase enzymes in vitro models, quercetin treatment prevented acetylcholine breakdown and reduced Aβ formation, according to research by **(Khan et al., 2009) and Shimmyo et al., 2008).**

Quercetin inhibits AChE secondary to hydrophobic interactions and strong hydrogen bonding with the enzyme, reducing the hydrolysis of ACh, thus increasing ACh levels in the synaptic cleft, as reported by **(Abdalla et al., 2013).** One of the most powerful antioxidants derived from plants, quercetin is a major flavonoid that is more frequently present in edible plants **(Brüll et al., 2015).**

Quercetin functions as an anti-infective, anti-inflammatory, anti-carcinogenic, and psychostimulant agent, among other positive impacts on human health. Additionally, it promotes mitochondrial biogenesis and suppresses platelet aggregation and lipid peroxidation **(Li et al., 2016).**

Quercetin's neuroprotective properties have been documented in several studies using both in vitro and in vivo models of neurodegenerative illnesses, including ischemia, Parkinson's disease, traumatic damage, and cognitive decline (**Rishitha et al., 2018).** Among the phytochemicals, quercetin is a potent antioxidant. It has been shown to effectively reduce the concentrations of superoxide anion free radicals, and its antioxidant potential makes it a versatile choice in the management of various disorders, including AD (**Alok et al., 2014).** Studies have shown that quercetin has direct radical scavenging action. The presence of two pharmacophores in its structure is responsible for its antioxidant activities: one is a catechol group in the B ring, and the other is the OH group at position C-3. Quercetin also modulates the cell's antioxidant pathways, by inducing Nrf-2-ARE and paraoxonase 2 (PON2), which is an antioxidant enzyme **(Costa et al., 2016).**

Quercetin has been reported to have anti-inflammatory actions and is a suitable candidate among phytochemicals for future studies on its efficacy to reverse neuroinflammation **(Testa et al., 2014).** Quercetin can also protect against neuronal damage and death by modulating various signaling pathways involved in inflammation, oxidative stress, and apoptosis **(Chiang et al., 2023).**

Renal and neural protective effect of rutin

Rutin is a flavonoid glycoside found in a variety of plants, including citrus fruits, buckwheat, and the leaves and petioles of certain plants. Here are the key points about rutin **National Center for Biotechnology Information (2024).** Rutin is a plant pigment, or bioflavonoid, that is also found naturally in common foods like apple peels, black tea, asparagus, buckwheat, onions, green tea, figs, and most citrus fruit. Rutin has potent antioxidant activity through its ability to scavenge free radicals like hydroxyl, peroxynitrite, superoxide, and nitric oxide radicals **(Choi et al., 2021).**

Rutin is an important bioflavonoid that has demonstrated several pharmacological benefits including antioxidants, anti-inflammatory, cardio protecting and exerts renal protective effects on the ischemia/ reperfusion-induced renal injury rutin has also exhibited protective effect against brain damage in rats with chronic cerebral hypoperfusion **(Radwan & Fattah, 2017).** The hepatoprotective, Renoprotective, and cardioprotective effects of rutin are reviewed **by (Rahmani et al., 2022).**

Vancomycin-induced nephrotoxicity: Co-administration of rutin and vancomycin in rats significantly suppressed the vancomycin-induced increases in blood urea nitrogen, creatinine, and N-acetyl-beta-d-glucosaminidase. Rutin also reduced vancomycin-induced oxidative stress, inflammation, and apoptosis in the kidneys **(Rahmani et al., 2022).** Rutin has been shown to ameliorate cisplatin-induced elevation in serum creatinine and urea, disturbances in blood count, and increases in inflammatory and apoptotic markers in the kidneys of rats **(Radwan and Fattah,,2017).**

Compared to the well-known antioxidant quercetin, rutin showed more variable antioxidant effects depending on the concentration. At lower concentrations (10 μM), rutin exhibited strong free radical scavenging **(Pravin et al., 2024).**

for its neuroprotective effects against various neurodegenerative disorders. Several studies have demonstrated that rutin exerts its neuroprotective properties through its potent antioxidant, anti-

inflammatory, and anti-apoptotic activities **(Budzynska et al., 2019)** examine the neuroprotective effects of rutin against colistin-induced neurotoxicity in rats **(Çelik et al., 2020).** Rutin has been reported to exert diverse biological effects such as antitumor and antimicrobial mainly associated to its antioxidant and anti-inflammatory activities. Mental, neurological, and behavioral disorders are an important and growing cause of morbidity. Most of these disorders combine a high prevalence, early onset, progressive clinical course, and impairment of critical brain functions making them a major contributor to the global disease burden **(Budzynska et al., 2019).**

Pharmacological studies have reported the beneficial effects of rutin in many disease conditions, and its therapeutic potential in several models of neurodegenerative diseases (NDs), including Alzheimer's disease, Parkinson's disease, Huntington's disease, and prion diseases **(Enogieru et al., 2018).**

Pharmacological uses of rutin

Rutin, a bioflavonoid found in various plants, has several uses and potential health benefits. Here are some of the key uses and applications of rutin:

A- Cardiovascular Health **(Gotter, 2017)**

1. **Blood Vessel Strength and Flexibility**: Rutin is believed to strengthen and increase the flexibility of blood vessels, which can help ease conditions such as bruises, spider veins, varicose veins, and hemorrhoids.

2. **Blood Clot Prevention**: There is evidence that rutin can prevent the formation of blood clots in certain animals, suggesting it may reduce the risk of blood clots and related conditions.

3. **LDL Cholesterol Reduction**: Rutin has been shown to lower LDL cholesterol levels, which can be beneficial for individuals with diabetes and hypertension.

B- Anti-Inflammatory and Antioxidant Properties

1. **Anti-Inflammatory Effects**: Rutin has anti-inflammatory properties, which can help alleviate symptoms of conditions like ulcerative colitis by inhibiting the NF-κB pathway and regulating intestinal microbial levels.

2. **Antioxidant Properties**: Rutin acts as a powerful antioxidant, protecting against oxidative stress and improving overall health.

C- Other Uses

1. **Osteoarthritis**: Rutin, when taken in combination with trypsin and bromelain, has been found to be effective in relieving pain and improving knee function in people with osteoarthritis.

2. **Post-Surgical Lymphedema**: Rutin has been used to reduce swelling in the arm after breast surgery.

3. **Mucositis Prevention**: Rutin is used to prevent a side effect of cancer treatment called mucositis, which involves swelling and ulcer formation in the mouth or digestive tract

Conclusion.

Acyclovir is a vital antiviral remedy against herpes virus infection, but it induces several detrimental side effects among them are nephrotoxicity and neuropathy which can potentially mitigated by the coadministration of this remedy with various plats bioactive compounds like rutin and quercetin. These bioactive compounds also, improve the sensitivity of the acyclovir resulting in better recovery with minimal side effects.

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