Drug Design, Development and Therapy Dovepress

Open Access Full Text Article REVIEW

Quercetin: A Flavonoid with Potential for Treating Acute Lung Injury

Ma Huang*, Xinxin Liu*, Yingcong Ren*, Qianxia Huang, Yuanzhi Shi, Ping Yuan, Miao Chen

Department of Critical Care Medicine, Affiliated Hospital of Zunyi Medical University, Zunyi City, Gui Zhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Miao Chen, Department of Critical Care Medicine, Affiliated Hospital of Zunyi Medical University, Zunyi City, Gui Zhou, People's Republic of China, Email chenmiao64@163.com

Abstract: In intensive care units, acute lung injury (ALI) is a syndrome that is frequently encountered. It is associated with a high rate of morbidity and mortality. Despite the extensive research conducted by the medical community on its treatment, no specific effective drugs have been identified. Quercetin is a natural flavonoid with many biological activities and pharmacological effects. Research indicates that Quercetin can modulate various targets and signaling pathways, inhibiting oxidative stress, inflammatory responses, ferroptosis, apoptosis, fibrosis, and bacterial and viral infections in ALI. This regulation suggests its potential therapeutic application for the condition. Currently, there is no comprehensive review addressing the application of Quercetin in the treatment of ALI. This paper begins with a classification of ALI, followed by a detailed summary of the mechanisms through which Quercetin may treat ALI to evaluate its potential as a novel therapeutic option.

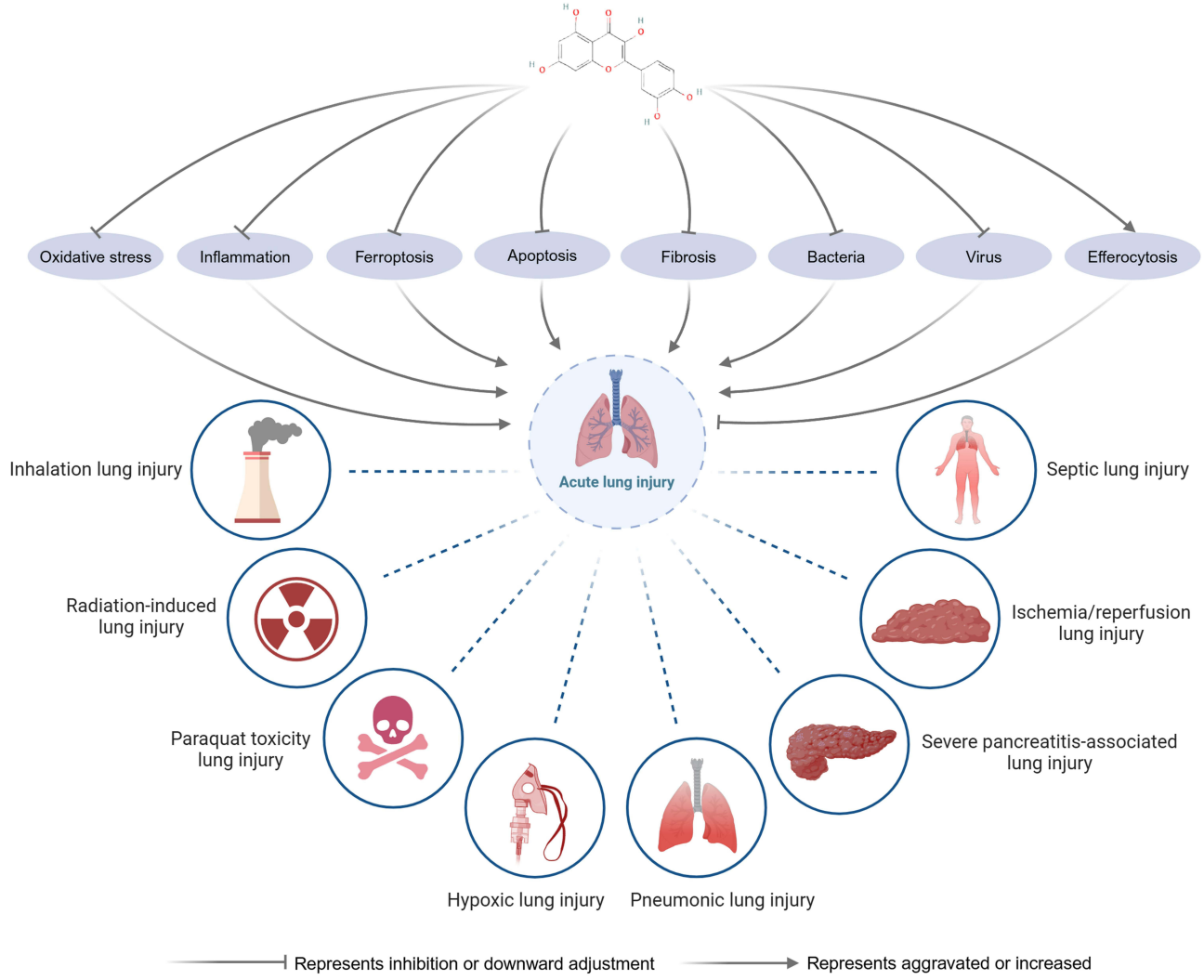
Keywords: quercetin, acute lung injury, treatment, oxidative stress, inflammation

Introduction

In the ICU, acute lung injury (ALI) is a common syndrome that can lead to acute respiratory distress syndrome (ARDS).[1] According to recent statistics, the development of ALI/ARDS in the ICU is currently associated with mortality rates of 25–40%, and these rates are increasing. Both intrapulmonary and extrapulmonary factors can cause ALI/ARDS.[2,3] The pulmonary factors include the consequences of pneumonia, pulmonary contusion, hyperoxia, smoke inhalation, phosgene, inhalation of gastric contents, smoking, drowning, fat embolism, lung transplantation, radiation, chemical poisoning, and inappropriate mechanical ventilation. Extrapulmonary factors affecting ALI/ARDS encompass sepsis, severe shock, pharmacological agents, blood transfusions, burns, acute pancreatitis, race, hypoxia, alcoholism, advanced age (>65 years), acute exacerbations of chronic obstructive pulmonary disease (AECOPD), disseminated intravascular coagulation (DIC), and hyperthermia (Figure 1).[4–7] In particular, a classification mechanism for ALI is not present. This paper categorizes ALI into various types, including those caused by pneumonia, trauma, inhalation, mechanical ventilation, sepsis, pulmonary ischemia/reperfusion injury, hypoxia, pharmacological agents, blood transfusions, severe acute pancreatitis, toxins, radiological treatments, and fever (Figure 1). The pathogenesis of ALI/ARDS is complex, primarily encompassing inflammation,[7] oxidative stress,[8] apoptosis,[9] ferroptosis,[10] autophagy,[11] and fibrosis.[12] The development of ALI can be prevented by reducing or blocking these factors. The pathogenesis of ALI/ARDS is complex, primarily encompassing inflammation,[7] oxidative stress,[8] apoptosis,[9] ferroptosis,[10] autophagy,[11] and fibrosis.[12] The development of ALI can be prevented by reducing or blocking these factors (Figure 1). Treatment of ALI/ARDS is mainly symptomatic supportive therapy, including rehydration, anti-infection treatment, and iratory, nutritional, and organ function support.[5,13] However, the overall therapeutic effect is inadequate and fails to treat the underlying source of the disease. The discovery of specialized drugs for ALI/ARDS is thus critically needed. ALI therapy has been the subject of numerous studies during the last several decades. Quercetin has drawn interest because of its wide variety of bioactivities, pharmacological effects, and outstanding therapeutic effects on ALI.

Received: 3 October 2024
Accepted: 21 November 2024
Published: 6 December 2024

Graphical Abstract



Flavonoids are abundant in plants, where phytochromes mediate light radiation to stimulate their synthesis. They are low molecular weight metabolites of naturally occurring plant polyphenols, which are primarily found in vascular plants and have various pharmacological and biological effects.[14] Quercetin, one of the most powerful antioxidants among flavonoids, also known as oak extract and quercetin flavonoid, is one of the most powerful flavonoid antioxidants and is a secondary metabolite synthesized by most plants, including ancient plants such as ferns. Quercetin was initially identified in 1936 by Hungarian physiologist Albert Szent-György. Quercetin occurs in the stems, skins, flowers, leaves, buds, seeds, and fruits of plants, primarily as glycosides, and can be extracted through acid hydrolysis. Quercetin is present in various vegetables and fruits, including onions, cabbage, peppers, tomatoes, grapes, apples, mangoes, and plums. Furthermore, it is a primary component in over a hundred herbal medicines derived from medicinal plants, such as winterflower, mulberry parasol, prickly ginseng, astragalus, and ginkgo biloba.[15–17] Quercetin is a flavonoid present in dark-colored, nutrient-dense fruits and vegetables.

Quercetin can inhibit the polar transport of certain plant hormones, such as auxin. Its formula is $C_{15}H_{10}O_7$, with a molecular weight of 302.24 g/mol. Quercetin shows complete insolubility in cold and hot water while demonstrating high solubility in alcohol and lipids.[18–20] The compound features a benz(γ)-pyranone structure characterized by a C6-C3-

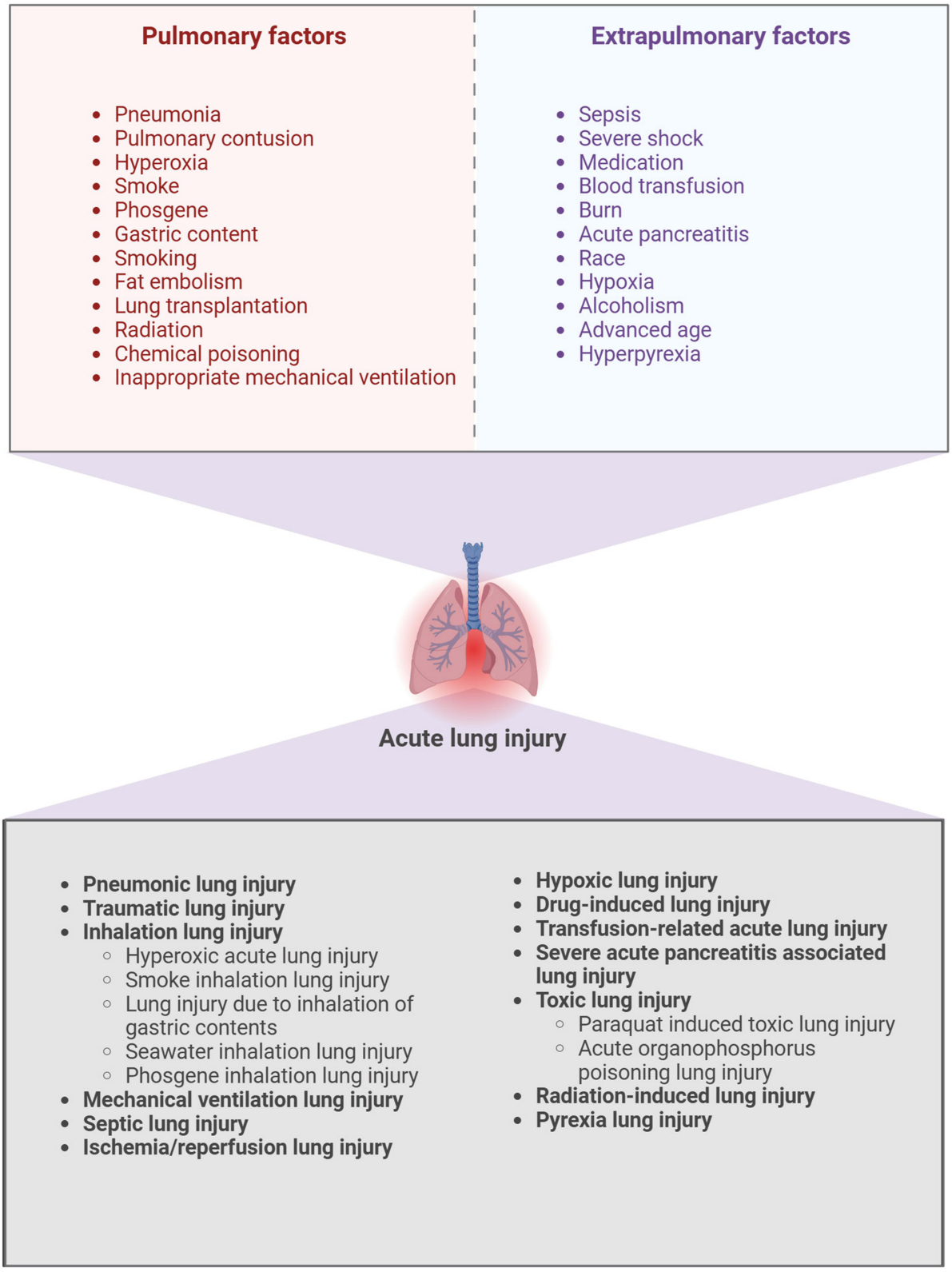


Figure 1 Causes and classification of acute lung injury.

C6 carbon skeleton comprising two benzene rings linked by a three-carbon pyran ring. The quercetin molecule has a variety of biological activities and pharmacological effects due to its four phenolic hydroxyl groups, one enolic hydroxyl group, and one carbonyl structure.[21]

Table 1 Bioactivity and Pharmacological Effects of Quercetin

No.	Effects	No.	Effects	No.	Effects
1.	Anti-oxidative stress	11.	Anti-apoptosis	21.	Dilation of Coronary Arteries
2.	Anti-inflammatory response	12.	Inhibition of autophagy	22.	Lowering Blood Lipids
3.	Anti-tumor	13.	Anti-aging properties	23.	Anti-obesity
4.	Anti-allergic	14.	Lowering Blood Pressure	24.	Antiulcer activity
5.	Neuroprotection	15.	Lowering blood sugar	25.	Cardiotonic
6.	Anti-viral	16.	Immune Regulation	26.	Regulates intestinal flora
7.	Anti-bacterial	17.	Liver protection	27.	Antagonistic sedation
8.	Anti-fibrotic	18.	Kidney protection	28.	Heart protection
9.	Anti-scorch death	19.	Antidepressant	29.	Anti-Atherosclerosis
10.	Anti-ferroptosis	20.	Antiplatelet aggregation	30.	Suppress coughing

As a drug, Quercetin is safe and reliable with few side effects (Table 1).[22] For example, in an experimental study on quercetin toxicity, it was found that high doses of quercetin extract in rats (6 g/kg) did not induce organ damage or death. Subacute tests revealed no significant differences in histomorphology, blood biochemistry, or blood counts.[23] Further, after taking 5000 mg of quercetin orally every day for 28 days in succession,[24] individuals with chronic hepatitis C did not experience any negative side effects, according to clinical studies. In 2010, Quercetin received GRAS approval from the US The Food and Drug Administration (FDA) has approved certain substances in beverages, cereal products, pasta, processed fruits and juices, and gummies, permitting production from natural sources. Quercetin received approval for use in antioxidants, anti-allergy drugs, and as a supplement for COVID-19 DELTA variants.[25,26] Quercetin is used as a food additive in Japan and Korea. A review by Ding et al thoroughly summarized the safety and reliability of Quercetin based on results from Phase I and Phase II clinical trials. Individuals with conditions such as chronic obstructive pulmonary disease (COPD), tuberculosis, neo-coronary disease, cardiovascular disease, gastro-oesophageal reflux disease, hepatitis C, Alzheimer's disease, rheumatoid arthritis, age-related macular degeneration, nephropathy did not experience any adverse reactions following Quercetin application.[27]

The chemical structure of Quercetin confers various pharmacological effects.[23] The o-diphenol structure of the quercetin molecule and the hydroxyl group at C3 demonstrate significant reducing properties. This enables the scavenging of reactive oxygen species (ROS) radicals, chelation of metal ions, inhibition of oxidized low-density lipoprotein (Ox-LDL), modulation of signal transduction pathways, and regulation of glutathione (GSH) levels, enzyme activities, and antioxidant substances, thereby enhancing resistance to oxidative stress.[28–30] Quercetin can also inhibit the release of inflammatory factors and mediators, modulate inflammatory pathways, and thus play an anti-inflammatory role.[31] Quercetin influences the cell cycle in tumor cells, impacts tumor-related signal transduction pathways, and promotes tumor cell apoptosis, which inhibits cancer proliferation and metastasis.[32] It can inhibit histamine release and the formation of antigen-specific IgE antibodies, reduce leukotriene production, and improve Th1/Th2 balance, thereby exerting antiallergic effects.[33] Furthermore, it increases blood flow and energy metabolism in the brain, promotes neuronal regeneration, and inhibits neuroinflammation, resulting in cerebral neuroprotective effects.[34] In addition to the above pharmacological effects, Quercetin has antiviral, antibacterial, anti-fibrotic, anti-focal death, anti-obesity, antidepressant, and anti-aging properties, while inhibiting apoptosis, autophagy, and platelet aggregation, regulating the immune system, protecting against hyperlipidemia, hypertension, hyperglycemia, liver damage, and coronary artery disease.[35] Quercetin shows a wide array of pharmacological effects, and its lipophilicity facilitates the crossing of cell membranes, activating various intracellular signaling pathways.[36] This compound treats cardiovascular,[37] digestive,[38] renal,[39] endocrine,[40] nervous system,[41] and respiratory diseases.[42] Multiple studies demonstrate that Quercetin demonstrates significant therapeutic effects on various types of acute lung injury, including those caused by sepsis, radiological treatments, paraquat toxicity, inhalation, hypoxia, severe pancreatitis, pneumonia, and ischemia/reperfusion.

Quercetin exhibits potential therapeutic effects for ALI, attributable to its source, structural characteristics, safety profile, and pharmacological properties. However, a thorough investigation into its application for treating ALI has not

been conducted. This study systematically reviews research on Quercetin and ALI published over the last decade, evaluating advancements in the field and proposing novel treatment strategies for ALI.

Progress in Research on the Use of Quercetin in Various Types of Acute Lung Injuries

Use of Quercetin for Treating Septic Lung Injury

Sepsis can lead to significant lung injury. Oxidative stress, inflammatory cells, and mediators primarily contribute to this acute disorder. Controlling inflammation and oxidative stress is essential for preventing acute lung injury during septic lung injury.[43,44] Furthermore, ferroptosis and efferocytosis are involved.[45,46] Quercetin has been thoroughly investigated as a therapeutic agent for septic lung injury due to its ability to promote efferocytosis and mitigate inflammation, oxidative stress, and ferroptosis (Table 2).

Inhibition of the Inflammatory Response

Cyclic adenosine monophosphate (cAMP) is the most widely used second messenger. It is involved in regulating various physiological processes, including inflammation, calcium transport, cell growth, and apoptosis.[58] The cyclic adenosine monophosphate-activated exchange protein (Epac) operates downstream of cAMP and is involved in multiple effector and signal transduction mechanisms. cAMP can enhance the regulation of Epac. The cAMP/Epac signaling system modulates inflammation,[59] and its activation is essential for mitigating septic lung injury.[60] Wang et al conducted a study demonstrating that Quercetin activates the cAMP/Epac pathway, leading to the inhibition of inflammatory cytokine release in mouse lung tissue, the blockage of neutrophil recruitment, and a reduction in pathological changes linked to lung injury. In in vitro investigations using LPS-induced pulmonary epithelial cells (MLE-12), Quercetin was observed to modulate the cAMP/Epac pathway, inhibiting the production of chemokines from keratinocytes, therefore mitigating inflammation-induced cell damage and improving cell survival.[44]

Sirtuin 1 (SIRT1) is a deacetylase implicated in inflammation, oxidative stress, and apoptosis.[61] SIRT1 inhibits the activation of the NLRP3 inflammasome, which triggers the production of IL-1β, IL-18, and HMGB1, therefore initiating and amplifying the innate immune response.[62] Pyruvate kinase M2 (PKM2) is a crucial enzyme that regulates aerobic glycolysis, lactate synthesis, and metabolic transformation. The inflammatory response activates the PKM2 dimer, leading to its translocation to the nucleus, where it phosphorylates and activates transcription factors such as Nrf2, STAT3, and NF-κB, thereby regulating gene expression.[63] In a mouse model of septic lung injury, Quercetin increased SIRT1 expression in lung tissue, inhibited NLRP3 inflammasome activation, and reduced the release of pro-inflammatory factors (TNFα, IL-1β, and IL-6), preventing the up-regulation of nuclear PKM2 in the lung. Overexpression of SIRT1 inhibited the nuclear PKM2 accumulation and NLRP3 activation, resulting in improved anti-inflammatory effects of Quercetin. Inhibition of SIRT1 expression resulted in increased NLRP3 activation and nuclear accumulation of PKM2, therefore, preventing the anti-inflammatory effects of quercetin. These results suggest that Quercetin activates the SIRT1/PKM2/NLRP3 pathway, reducing the inflammatory response and alveolar wall damage, thus inhibiting septic lung injury.[47]

An essential enzyme in heme catabolism, HO-1 is associated with several in vivo anti-inflammatory molecular mediators. HO-1 has anti-inflammatory and anti-oxidative stress actions by activating inflammatory and oxidative stress signaling pathways in cells and tissues under stress and protecting cells from oxidative damage.[64] Research has indicated that inflammatory pathways mediated by HO-1 play a crucial role in septic lung injury. Quercetin increased HO-1 expression in the lungs of a septic lung injury mouse model, reducing the release of inflammatory factors and the lung wet-to-dry ratio in BALF. It increased the HO-1 expression in lung AMJ2-C11 cells stimulated by LPS in an in vitro experiment. It decreased the cells' inflammatory response and improved their survival rate by preventing the release of pro-inflammatory molecules (TNF-α, IL-1β, and IL-6). When applied in reverse, the HO-1 inhibitor's protective impact on cells was diminished.[48]

In addition to regulating the above pathways to inhibit the inflammatory response, Quercetin can also regulate the Notch1,[54] SCAP/SREBP2/NLRP3,[55] PTEN/β-catenin, AKT/GSK-3β,[53] TLR4/Myd88,[56] and Nrf-2/ARE pathways[57] to

Table 2 Results of in vitro and in vivo Studies on the Treatment of Septic Lung Injury with Quercetin

No.	Model(in vivo/in vitro)	Signal Pathway	Mechanism	Findings (in vivo/in vitro)	Reference
1.	C57BL/6 male mice/lung epithelial cells	cAMP/Epac	Inflammatory response	In vivo experiments, quercetin inhibited the release of inflammatory cytokines, blocked neutrophil recruitment, and attenuated pathological changes in lung injury in mouse lung tissues. In vitro experiments, quercetin reduced cellular damage and increased cell viability.	[44]
2.	C57BL/6 male mice/J774A.1 cells	SIRT1/PKM2/NLRP3	Inflammatory response	In vivo experiments, quercetin reduced alveolar wall destruction and attenuated inflammatory damage in lung tissue in mice. In vitro experiments, quercetin decreased the release of inflammatory factors in cells and enhanced cell viability.	[47]
3.	C57BL/6 male mice/Lung AMJ2-C11 cells	HO-1	Inflammatory response	In vivo experiments, quercetin reduced the release of inflammatory factors in mouse BALF, decreased the wet and dry specific gravity of the lungs, and mitigated pulmonary edema. In vitro experiments, quercetin suppressed the release of pro-inflammatory factors (TNF-α, IL-1β, IL-6) from cells, alleviated the inflammatory response of cells, and enhanced cell survival.	[48]
4.	C57BL/6 male mice/alveolar epithelial cells	Sirt1/Nrf2/Gpx4	Ferroptosis	In vivo experiments, quercetin decreased the levels of TNF-α, IL-6, IL-1β, and mitigated the pathological changes associated with lung injury in BALF. In vitro experiments demonstrated that quercetin enhanced the proliferative capacity of alveolar epithelial cells and strengthened the alveolar epithelial barrier	[49]
5.	SD male rat	Nfr2/HO-1	Ferroptosis	Quercetin decreased the levels of pro-inflammatory factors (TNF-α, IL-6, IL-1β) in BALF, suppressed the expression of ROS and MDA, and elevated the levels of SOD and GSH in lung tissue.	[50]
6.	C57BL/6 male mice/MLE-12cells	SIRT1/AMPK	Endoplasmic reticulum stress, Oxidative stress	In vivo experiments, quercetin alleviated oxidative stress and mitigated inflammatory damage in mouse lungs. In in vitro experiments, quercetin downregulated the expression of PDI, CHOP, GPC78, ATF6, PERK, and IRE1A, while upregulating the levels of MMP and superoxide dismutase. Additionally, quercetin reduced the production of ROS and MDA, as well as the release of inflammatory factors within cells.	[51]
7.	C57BL/6 male mice	NF-κB	Oxidative stress	Quercetin decreased the expression of COX-2, HMGB1, and iNOS, as well as NF-κB p65 phosphorylation in mouse lungs. It also reduced the release of inflammatory factors (TNF-α, IL-6, NO), enhanced lung permeability, and decreased the recruitment of neutrophils and macrophages in BALF.	[52]
8.	SD male rat	PTEN/β-catenin AKT/GSK-3β	Oxidative stress, Inflammation, Apoptosis	Quercetin reduced inflammatory cell infiltration in lung tissue, lowered lung injury score, decreased lung dry and wet specific gravity, reduced apoptosis rate, downregulated apoptosis-related protein expression, and decreased levels of inflammatory factors in lung tissue. Additionally, it enhanced antioxidant capacity and improved the survival rate of rats.	[53]
9.	Alveolar macrophages	PPARγ/LXR-α	Efferocytosis	Quercetin decreases serum levels of inflammatory factors, inhibits inflammatory cytokine storms, and mitigates pathological damage resulting from inflammation in lung tissue.	[46]

10.	SD male rat	Notch1	Inflammatory response	Quercetin suppresses macrophage infiltration, inhibits the pro-inflammatory phenotype, and reduces inflammatory injury in lung tissue.	[54]
11.	C57BL/6 male mice	SCAP/SREBP2/NLRP3	Inflammatory response	Quercetin decreases the release of inflammatory factors (IL-1β, IL-6, TNF-α) in the lungs, mitigates damage to lung tissue structure, reduces intra-alveolar hemorrhage and inflammatory cell infiltration, alleviates alveolar interstitial edema, and lowers the total cell count and total protein concentration in BALF.	[55]
12.	SD male rat	TLR4/Myd88	Inflammatory response	Quercetin can enhance arterial blood gases, decrease alveolar damage, and reduce the serum release of inflammatory factors (TNF-α, IL-6, IL-1β).	[56]
13.	SD male rat	Nrf-2/ARE	Oxidative stress	Quercetin decreases the wet/dry ratio of the lungs, enhances arterial blood gases, suppresses the expression of NF-κB/p65 and ICAM-1, and reduces the release of pro-inflammatory factors (IL-1β, TNF-α).	[57]

https://doi.org/10.2147/DDDT.S499037

reduce the release of inflammatory factors and mediators, thereby exerting anti-inflammatory effects and thus attenuating septic lung injury.

Inhibition of Ferroptosis

Ferroptosis is a form of cell death characterized by iron accumulation and lipid peroxidation.[65] Disruption of intracellular iron homeostasis can trigger the Fenton reaction, leading to lipid peroxidation and inducing cell death. In septic lung injury, disrupted iron metabolism, lipid peroxide accumulation, and reduced lung antioxidant capacity contribute to endothelial damage in lung capillaries, increased vascular permeability, and reduced effective ventilation, ultimately resulting in intractable hypoxemia.[66] Therefore, inhibiting ferroptosis is another way to treat septic lung injury. SIRT1 is a deacetylase that regulates various transcription factors to exert anti-oxidative stress, anti-inflammatory, anti-apoptotic, and anti-aging effects. It depends on Nrf2 activation, which induces its translocation from the cytoplasm to the nucleus, resulting in the related protein expression. Activation of the SIRT1/Nrf2 signaling pathway reduces ROS production and activates antioxidant production, thus attenuating iron death.[67] Gpx4, a downstream target of Nrf2, is a mammalian membrane peroxidase critical for ferroptosis. In in vivo experiments in mice, Quercetin up-regulated SIRT1 activation of the Nrf2/Gpx4 pathway to inhibit ferroptosis, reducing the TNF-α, IL-6, and IL-1β levels in the BALF and consequently attenuating the inflammatory response of the lungs.[50] In in vitro experiments, Quercetin modulated the Sirt1/Nrf2/Gpx4 pathway to inhibit ferroptosis, thus improving the proliferative capacity of alveolar epithelial cells and the alveolar epithelial barrier. However, when a SIRT1 inhibitor was added to both in vitro and in vivo experiments, the protective effect of Quercetin on the lung was reversed. The Nfr2/HO-1 pathway plays an essential role in oxidative stress, with Nrf2 participating in the antioxidant response and HO-1 contributing to cellular protection from oxidative damage.[49] In a study by Li et al. Quercetin was also found to activate the Nfr2/HO-1 pathway to inhibit ferroptosis in rat lungs, thereby attenuating oxidative stress and the inflammatory response and consequently reducing septic lung injury.[68]

Inhibition of Oxidative Stress

Oxidative stress is caused by the imbalance between the reactive oxygen/nitrogen species and the antioxidant defence mechanism, resulting in excessive ROS production and an over-oxidized state. This in turn damages biomolecules, such as nucleic acids, lipids and proteins of the tissue cells.[69] In septic lung injury, the lungs produce excessive ROS, disrupting the balance between oxidative and antioxidant systems. This leads to lipid peroxidation, mitochondrial DNA damage, pulmonary oedema, and irreversible lung injury.[70,71] Gerin et al established a septic lung injury model by cecum ligation and puncture in rats, showing that early administration of Quercetin reduced the levels of oxidative stress markers, such as xanthine oxidase (XO), nitric oxide (NO), and malondialdehyde (MDA), and increased the levels of antioxidant enzymes in lung tissues, leading to a reduction in oxidative stress and consequently reduced production of inflammatory factors in the lungs.[43] In a study by Sang et al using in vitro experiments with LPS-stimulated ML-12 cells, Quercetin was found to modulate the SIRT1/AMPK pathway to inhibit both endoplasmic reticulum stress and oxidative stress levels in cells, which was manifested by a decrease in the expression of PDI, CHOP, GPC78, ATF6, PERK, and IRE1A, together with enhanced mitochondrial function, and increased levels of matrix metalloproteinase (MMP) and superoxide dismutase (SOD) while reducing the production of ROS and MDA, which in turn reduced the release of inflammatory factors in the cells. In in vivo experiments, Quercetin could also regulate the SIRT1/AMPK pathway to reduce oxidative stress and inflammatory damage in mouse lungs, thus alleviating septic lung injury.[51] In a similar study, Quercetin reduced myeloperoxidase (MPO) activity and increased the levels of MDA in mouse lungs, thereby reversing oxidative stress; Quercetin also reduced the expression of COX-2, HMGB1, and iNOS expression and NF-κB p65 phosphorylation, inhibited the release of inflammatory factors (TNF-α, IL-6, NO), improved the permeability of the lungs, and reduced the levels of inflammatory cells in the BALF.[52] Thereby reducing the inflammatory response in the lungs and alleviating lung injury in the mice. In another in vivo experiment, Quercetin modulated the PTEN/β-catenin and AKT/GSK-3βpathways to reduce oxidative stress levels in the lungs, alleviating lung injury.[53] In conclusion, Quercetin can reduce oxidative stress and increase the activity of antioxidant enzymes during septic lung injury, thereby inhibiting lung injury.

Enhancement of Alveolar Macrophage Efferocytosis

When acute inflammation in the lungs subsides, alveolar macrophages can phagocytose the apoptotic inflammatory cells and, at the same time, promote the recovery of lung epithelial and endothelial function and the repair of lung tissue structure, a phenomenon known as efferocytosis. Efferocytosis of alveolar macrophages is essential for alleviating ALI as it prevents excessive inflammatory responses and assists in the reconstruction of lung tissue to attenuate lung injury.[72] The peroxisome proliferator-activated receptorγ(PPARγ)/liver X receptorα(LXR-α) signaling pathway is key to the regulation of inflammation and oxidative stress in vivo, and activation of this pathway can effectively inhibit the release of inflammatory mediators and ROS. Among them, the PPARγ-mediated pathway plays a vital role in expressing various cell burial-related factors and regulating efferocytosis.[73] In a study by Yang et al, it was found that Quercetin could enhance alveolar macrophage efferocytosis, reduce the serum levels of inflammatory factors, inhibit the development of a cytokine storm, and attenuate the inflammatory response in lung tissues and consequent pathological injury in an LPS-induced rat model of ALI, the mechanism of which was related to activation of the PPARγ/LXR-α signaling pathway.[45] Therefore, Quercetin can reduce septic lung injury by regulating the PPARγ/LXR-αaxis to increase lung tissue efferocytosis.

Inhibition of Cellular Pyroptosis

Cellular pyroptosis is an immune response triggered by pathogen detection, causing cell membrane rupture and the release of cytoplasmic contents and inflammatory mediators.[74] This in turn leads to inflammation and partial loss of tissue or organ function. NLRP3 inflammasome activation is an essential pathway in the occurrence of pyroptosis,[75] and its inhibition prevents the development of pyroptosis, as demonstrated by Shi et al. Inhibition of NLRP3 inflammasome pathway inhibited cellular pyroptosis, thereby attenuating PM2.5-induced lung injury.[76] NLRP3 inflammasome-mediated cellular pyroptosis also plays a key role in septic lung injury, making targeting NLRP3-cellular pyroptosis and its related signalling pathways critical. Quercetin inhibited the activation of NLRP3 inflammasome, reducing lactate production and lung pro-inflammatory factor release and ameliorating lung tissue injury, thus attenuating septic lung injury in mice.[47]

Quercetin in the Treatment of Radiological Lung Injury

Radiation-induced lung injury (RILI) is a common complication of radiotherapy for nasopharyngeal, cervical, and esophageal cancers, among others.[77] Inflammation and oxidative stress play essential roles in the pathogenic process of RILI.[78] The NF-κB and MAPK pathways are easily activated by ultraviolet light or radiation, leading to the expression of pro-inflammatory mediators, which promote the production of large amounts of inflammatory factors by macrophages.[79,80] In a mouse model of RILI, Quercetin was found to down-regulate expression of the NF-κB complex (NF-κB, p65, IκB-α) and MAPK (SAPK/JNK, P44/P42) pathway proteins, thereby inhibiting the release of inflammatory factors from the lungs and attenuating the pathological changes associated with lung injury. It can thus be concluded that Quercetin can inhibit the NF-κB and MAPK-mediated inflammatory pathways and, therefore, attenuate RILI in mice.[81] Further, Liu et al showed that early intervention using quercetin liposomes in RILI model mice reduced MDA contents in lung tissue, increased SOD and GSH-PX activities, and reduced the proportion of inflammatory cells and HP content in the BALF.Meanwhile, histological examination using HE staining showed suppression of the inflammatory response and reduced fibrosis scores in the lungs. This indicates that Quercetin can inhibit radiation-induced oxidative stress in the lungs, thereby reducing inflammation.[82] Furthermore, several network pharmacological analyses found that both *Houttuynia cordata* and *Scutellaria barbata* could reduce the radiation-induced inflammatory response and thus reduce lung injury; the main pharmaceutical component of these is Quercetin.[83,84] Therefore, Quercetin has an essential role in preventing and treating RILI.

Quercetin in the Treatment of Lung Ischemia-Reperfusion Injury

Lung ischemia-reperfusion injury (LIRI) frequently occurs following procedures such as pulmonary embolism extraction, cardiopulmonary bypass surgery, shock, and lower limb and trunk ischemia-reperfusion.[85] LIRI can result in pulmonary edema and pulmonary hemorrhage, both of which are closely linked to ARDS. LIRI is a complex condition characterized by a "sterile" inflammatory state. It involves the production of reactive oxygen and nitrogen species, which contribute to

endothelial damage. This damage triggers the activation of factors that attract neutrophils, leading to their infiltration. This process creates a vicious cycle that ultimately results in further endothelial and parenchymal damage, as well as fatal edema and impaired gas exchange.[86] The primary mechanisms associated with LIRI include inflammatory responses and oxidative stress, and targeting these pathways is crucial for LIRI mitigation.[87] In the study of Liu et al, it was found that quercetin could inhibit the expression of p-IκBα, p-PI3K, p-AKT/AKT, TNF-α, IL-6, IL-1β, and reduce the serum levels of TNF-α, IL-6, and IL-1β in lung tissues, through the establishment of a LIRI mouse model. At the same time, quercetin could also reduce the infiltration of large number of inflammatory cells in the alveolar lumen and lower the lung injury score. It can be concluded that quercetin can regulate the PI3K/AKT/NF-κB-mediated inflammatory pathway and thus inhibit lung injury.[88] Acid sphingomyelinase (aSMase) is a critical enzyme in sphingolipid biochemistry.[89] It can be activated during inflammatory conditions, converting sphingolipids to ceramide, a significant player in the inflammatory pathway.[90] Thus, inhibition of aSMase is beneficial in reducing inflammatory responses. In a rat model of LIRI induced by traumatic shock, Quercetin was observed to inhibit aSMase activation. This led to improved blood gas values, reduced IL-6 levels, and decreased MPO activity in the BALF, ultimately alleviating lung injury stemming from inflammation and oxidative stress.[91]

Quercetin in Paraquat-Induced Toxic Lung Injury

The lungs are particularly susceptible to damage in cases of paraquat (PQ) poisoning, as PQ triggers a significant increase in ROS levels in lung tissues.[12] This surge in ROS results in secondary oxidative damage, ultimately leading to acute lung fibrosis. The toxic lung injury caused by PQ is closely linked to both oxidative stress and the development of fibrosis in the lungs. In a laboratory setting using PQ-exposed alveolar A549 cells, it was discovered that Quercetin activated the Nrf2/HO-1 pathway, leading to reduced ROS production and elevated GSH levels, consequently decreasing oxidative stress and ultimately enhancing the survival of alveolar cells damaged by PQ.[92] Pulmonary fibrosis involves the destruction of alveolar tissues, resulting in damage to the alveolar epithelium, increased fibroblast proliferation and collagen infiltration, and interstitial inflammation. Various cytokines are involved in alveolitis and pulmonary fibrosis, with TGF-β playing a central role.[69,93] Among them, TGF-β1 is the key cytokine in fibrogenesis[94] and is most closely associated with pulmonary fibrosis. Smad is the key downstream regulator of TGF-β1, and TGF-β1 positively regulates Smad to enhance its fibrogenic role.[95] Meanwhile, the Akt/mTOR signalling pathway is also crucial in TGF-β-mediated pulmonary fibrosis. Akt can stimulate mTOR to participate in pulmonary fibrosis through phosphorylation of the PH domain at the amino acid terminus.[96] Therefore, regulating TGF-β1/Smad and Akt/mTOR signalling pathways is essential for inhibiting pulmonary fibrosis. In an in vitro study of PQ-treated lung epithelial cells (MLE-12 cells), Quercetin was found to modulate the fibrotic process mediated by the TGF-β1/Smad and Akt/mTOR signaling pathways, altering the expression of markers of the epithelial-mesenchymal transition (EMT) and inhibiting the onset of fibrosis, resulting in improved cell survival.[97] A separate investigation into PQ-induced lung injury in rats revealed that Quercetin mitigated oxidative stress in the lungs by lowering MDA levels and enhancing GSH activity and total ROS-scavenging capacity via the up-regulation of HO-1 expression, consequently diminishing fibroblast distribution and collagen infiltration caused by PQ in the lungs.[98]

Quercetin for Treating Inhalation Lung Injury

Hyperoxic Acute Lung Injury

Oxygen therapy is a fundamental intervention for acute and critical patients in the ICU.[99] However, prolonged inhalation of elevated oxygen concentrations might precipitate hyperoxic acute lung damage (HALI), potentially resulting in bronchopulmonary dysplasia (BPD).[100] Oxidative stress and inflammation are intimately associated with the progression and severity of HALI. Maturu et al found that Quercetin reduced MDA protein adducts in mouse lungs and thus modulated hyperoxia-induced lung antioxidant solubilization by establishing a model of BPD in neonatal mice under hyperoxic conditions. Moreover, Quercetin also modulated the NF-κB pathway to reduce inflammatory cell infiltration in lung tissues and improve alveolarization and vascularized lung structures after hyperoxia exposure.[101] This indicates that Quercetin diminishes lung inflammation and enhances alveolization, thereby mitigating HALI and demonstrating efficacy in preventing BPD.Prostaglandin-endoperoxide synthase 2 (PTGS2) plays a crucial role in the synthesis of prostaglandins

under pathological conditions. It is recognized as a marker of ferroptosis and participates in the inflammatory cascade that enhances the release of inflammatory mediators. Therefore, targeting PTGS2 is essential for inhibiting ferroptosis.[102] Deng et al conducted a study employing network pharmacology and molecular docking, demonstrating that Quercetin inhibits ferroptosis, thereby reducing lung inflammatory responses. The MAPK/PTGS2 pathway mediated this action. The findings suggest that Quercetin aids in reducing hyperoxia-induced BPD and decelerates the progression of this condition.[103]

Smoke Inhalation Lung Injury

Smoke inhalation lung injury is common after exposure to fire in enclosed environments. The inhalation of smoke can trigger the production of significant amounts of inflammatory mediators, cytokines, and ROS in the lungs, leading to endothelial cell damage. This mechanism encourages the phospholipids and unsaturated fatty acids in the cell membrane to peroxide, which causes oxidative stress and an inflammatory reaction in the lungs, leading to pulmonary edema.[104] For example, quercetin was found to prevent and delay the progression of COPD lesions in an ex vivo model of cigarette smoke-induced COPD by inhibiting smoke-induced oxidative stress and mitigating the short-term changes in lung structure and function caused by cigarette smoke.[105] A recent review indicated that Quercetin can mitigate smoking-induced COPD due to its antioxidant, anti-inflammatory, and immunomodulatory properties. Two studies by Liu et al examined lung injury resulting from smoke inhalation. Quercetin was shown to reduce lung injury by lowering the production of inflammatory mediators and free radicals in the lungs of model mice. The effects were more pronounced with extended administration and earlier intervention.[106,107]

Seawater Inhalation Lung Injury

Seawater drowning often occurs in situations such as sailing, maritime operations, and naval warfare, and survivors usually suffer ALI induced by seawater inhalation.[108] The innate immune response mediated by lung macrophages plays an essential role in ALI, in which M1-type macrophages can stimulate oxidative damage and inflammatory responses in the lungs by releasing many pro-inflammatory factors and ROS, inducing lung injury.[109] Wang et al conducted a study utilizing a mouse model of seawater inhalation injury, demonstrating that Quercetin significantly decreased iNOS, TNF-α, and IL-1β levels in the lungs. Furthermore, it up-regulated mRNA expression of IL-4 and IL-10, mitigated M1-type macrophage polarization induced by seawater inhalation, reduced inflammatory factors associated with M1-type macrophages, improved arterial blood gases, and lessened interstitial and alveolar hemorrhage as well as structural alterations in lung tissues.[110] Therefore, Quercetin may improve gas exchange functions and reduce lung tissue damage caused by seawater inhalation by inhibiting M1-type macrophage polarization and its subsequent immune response.

Quercetin for Treating Hypoxic Lung Injury

The lung is recognized as vulnerable to hypoxia. Hypoxia increases oxidative stress, apoptosis, and inflammation in lung tissue, resulting in pulmonary edema and an increased risk of hypoxic lung injury.[111] Reducing oxidative stress, inflammation, and apoptosis alleviates hypoxic lung injury. In a rat model of hypoxic lung injury induced by sodium nitrite, Quercetin reduced the expression of immune-inflammatory mediators and heat shock proteins in the lungs. Furthermore, it reduced alveolar wall thickening and inflammatory cell infiltration in the alveolar mesenchyme. When quercetin and melatonin were combined, this protective effect was more evident.[112] In another in vivo investigation, quercetin attenuated lung damage brought on by apoptosis by downregulating the expression of Bax protein and up-regulating that of Bcl-2 in rat lungs exposed to hypoxia.[113] According to a study by Ankit Tripathi and associates, quercetin controls the expression of NF-κB and IKα/β that is triggered by hypoxia. This regulation decreased the levels of pro-inflammatory cytokines, such as TNF-α and INF-γ, while simultaneously increasing the levels of anti-inflammatory cytokines within the lungs, such as IL-4 and INF-γ. Furthermore, the study highlighted the role of Quercetin as an activator of Nrf-2, promoting GSH synthesis, enhancing GPX activity, and reducing MDA levels under hypoxic conditions. These effects collectively lowered oxidative stress in the lungs, thereby mitigating hypoxia-induced extravascular leakage and successfully combating hypoxia-induced pulmonary edema in the rat models.[114] An in vivo study demonstrated that hypoxia elevated free radical production in the body, leading to oxidative stress and the

inhibition of β2-AR signaling. Combining Quercetin and salbutamol reactivated β2-AR signaling under hypoxic conditions, enhancing the lungs' fluid clearance capacity. This was evidenced by the up-regulation of β2-AR, GPR-1, GPR-10, and GCS-α expression alongside increased lung cAMP content. Furthermore, there was a down-regulation of GRK-2 and NF-κB expression and a reduction in ROS production. It can be concluded that Quercetin can reduce lung inflammation and stimulate β2-AR to enhance AFC in rats, leading to therapeutic and protective effects in hypoxic lung injury.[115]

Quercetin for Severe Acute Pancreatitis-Associated Lung Injury

Severe acute pancreatitis-associated lung injury (SAP-LI) is one of the most critical complications of pancreatitis, and many of these cases are complicated by ARDS.[116] The development of SAP-LI is linked to a syndrome characterized by a systemic inflammatory response resulting from the excessive activation of inflammatory cells in the lungs, delayed apoptosis, and an overproduction of inflammatory mediators.[117] Xu et al conducted a study demonstrating that Quercetin mitigates lung injury in SAP model rats by up-regulating Bax expression, down-regulating Bcl-2, enhancing caspase-3 activity, and inducing apoptosis in alveolar neutrophils (PMN).[118] Xu's study demonstrated that Quercetin inhibits the TLR4/NF-κB pathway, effectively blocking the cascade of inflammatory factors while simultaneously inducing apoptosis in alveolar PMNs, thereby mitigating lung injury.[60]

Quercetin Treatment of Lung Injury Caused by Various Types of Pneumonia

Pneumonia is the predominant cause of acute lung damage, and severe pneumonia may advance to ARDS. Bacteria, fungi, and viruses are the predominant agents responsible for pneumonia. Pneumonia-induced ALI mainly involves inflammatory responses in the lungs. Quercetin has anti-inflammatory, antibacterial, and antiviral properties and thus can significantly affect pneumonia. For example, in an in vitro model of *Pseudomonas aeruginosa* infection of THP-1 macrophages, it was found that quercetin modulated activation of the MAPK pathway and the NLRP3 inflammasome, reducing the release of IL-1β from the cells, and thereby inhibiting the inflammatory response and consequently reducing the invasion of normal cells by pathogens.[119] Similar studies found that Quercetin modulated the PI3K/AKT/NF-κB pathway to attenuate *Pseudomonas aeruginosa*-induced inflammatory responses in the lungs, thereby reducing changes associated with lung damage.[120] In a mycoplasma-induced chicken pneumonia model, Quercetin regulated the AMPK/SIRT1/NF-κB pathway to suppress the release of inflammatory factors from the lungs, thus reducing inflammatory lung injury.[121] In a distinct study, Quercetin inhibited pneumococcal hemolysin (PLY) activity, thereby effectively obstructing pneumonia induced by Streptococcus pneumoniae. In in vitro experiments, quercetin treatment reduced PLY activity, consequently protecting alveolar epithelial cells from PLY-induced damage and enhancing cell survival. In vivo studies further showed that Quercetin reduced the dry-to-wet weight ratio of lung tissue, suppressed the release of inflammatory factors (IL-1β, TNF-α) in the BALF, and alleviated lung tissue edema, offering comprehensive defense against *Streptococcus pneumoniae* infection.[122] Network-based pharmacological and metabolomic investigations have demonstrated that Quercetin mitigates inflammatory lung injury induced by a respiratory syncytial virus (RSV) primarily by restoring mice metabolism changes resulting from RSV infection.[123] A study by Guimaraes' team demonstrated that the M2-1 protein of RSV, functioning as an anti-termination factor during transcription, is crucial in the premature dissociation of polymers, indicating its potential as a target for inhibitors of viral replication. This research synthesized quercetin tetraacetate and quercetin pentaacetate, acetylated quercetin derivatives, which interacted with the M2-1 RNA-binding site to inhibit viral replication. The findings highlight their potential therapeutic advantages in treating respiratory conditions, including pneumonia and bronchitis.[124]

Severe Acute Respiratory Syndrome SARS-CoV-2 was the virus responsible for COVID-19, a new coronavirus-associated pneumonia. COVID-19 was associated with the onset of concurrent ALI/ARDS and imposed a significant strain on the global economy and healthcare from its initial outbreak in 2019 and subsequent proliferation; a specific therapy for COVID-19 remains unknown.[125,126] Therefore, extensive research has been undertaken on the application of herbal medicine for the treatment of COVID-19; for instance, China and South Korea have established guidelines for the prevention and management of SARS-CoV-2 infections employing traditional medicines, with Quercetin identified as a potential therapeutic agent owing to its diverse bioactivities and pharmacological effects.[127,128] A clinical trial demonstrated that Quercetin is effective in treating SARS-CoV-2 infection.[129] A clinical prospective study has shown

the reliability of Quercetin in alleviating early symptoms and preventing progression to severe COVID-19.[130] The hydroxyl groups of Quercetin inhibit 85% of SARS-CoV 3CLpro expression by binding to the Gln189 site on 3CLpro, thereby preventing hydrolysis and blocking viral proliferation.[131–133] During viral infection, Quercetin was found to inhibit the virus-induced release of inflammatory factors, chemokines, and growth factors in macrophages via the calcium-STAT pathway, thereby attenuating virally induced inflammatory responses in the lungs and consequently mitigating lung injury.[134] Quercetin is also known for its extremely low cytotoxicity and can thus be used to prevent SARS-CoV invasion of host cells.[135] A review of Quercetin indicates that its combination with vitamin C demonstrates antiviral and immunomodulatory effects, enhancing therapeutic outcomes for COVID-19 and mitigating lung injury.[136] The results suggest that Quercetin may be an effective treatment for COVID-19.

Nano-Formulations of Quercetin for the Treatment of Acute Lung Injury

Numerous studies have shown that quercetin has a protective effect against numerous diseases. However, quercetin also has certain limitations in clinical applications, such as poor water solubility (< 7 μg/mL), low bioavailability (1–2%), high metabolic rate, poor absorption, and susceptibility to acidic environments[137] which have limited its use to the point where it has not yet been approved for clinical use. Thus, the finding of quercetin carriers is crucial. Currently, the hottest research is on nano-formulations, which can alter the solubility efficiency and improve the bioavailability of quercetin. Nano-formulations of quercetin include nanocrystals, nanoliposomes, polymeric micelles, nanocapsules, nano-emulsions, and nanoparticles (Figure 2).[138] Compared to conventional drugs, nano-formulations decrease particle size, enhance the absorption area, and improve solubility, thereby modifying pharmacokinetics and tissue distribution and increasing drug bioavailability.[138] Numerous studies indicate that quercetin nanoparticles exhibit protective effects on the

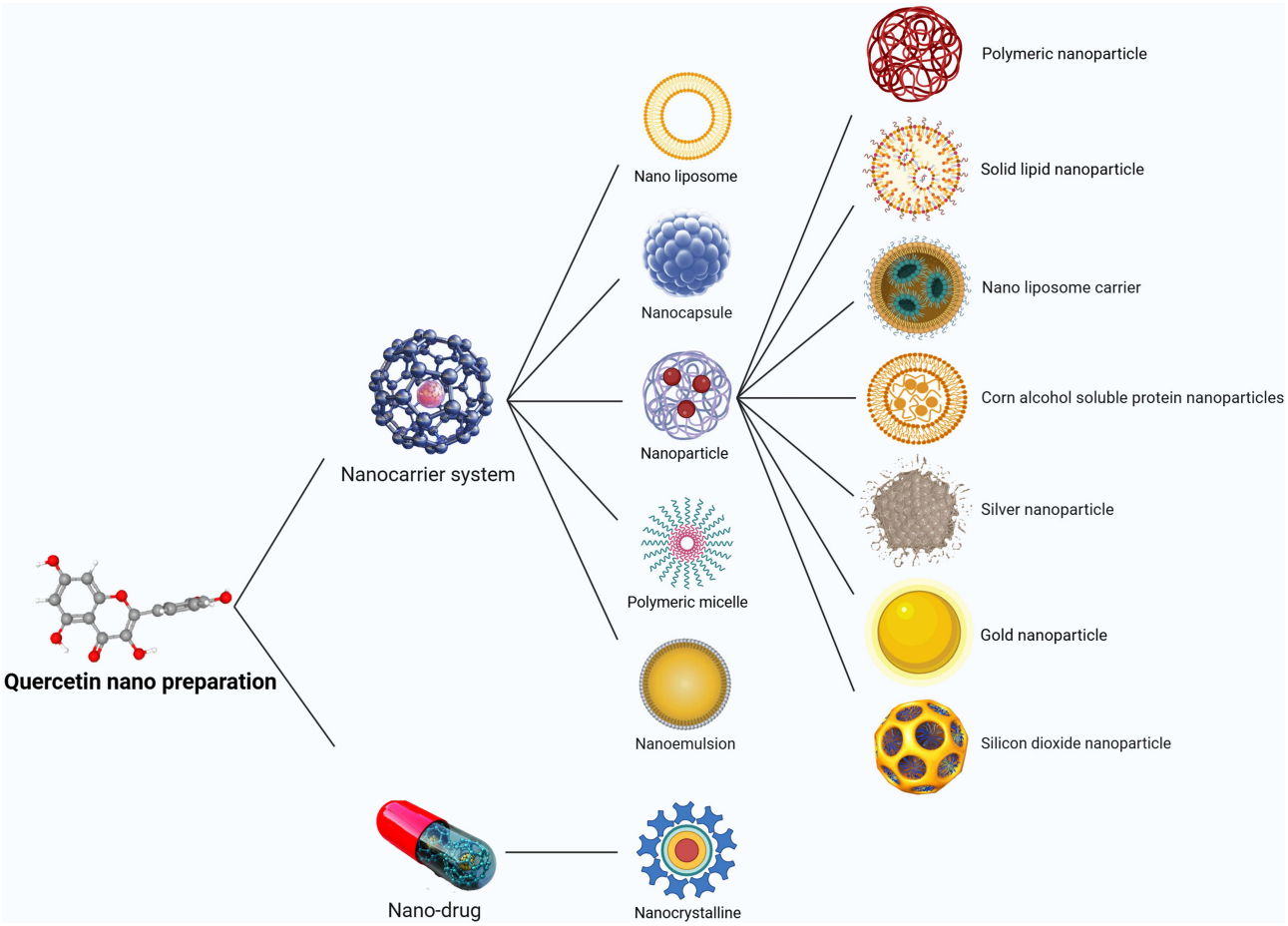


Figure 2 Classification of quercetin nano-formulations.

cardiovascular,[139] digestive,[140] urinary,[141] nervous,[142] and respiratory systems[143] and demonstrate antitumor[33] and anti-allergy properties.[144]

Patients with ALI/ARDS often suffer from poor metabolism, malabsorption, and disorders of the gastrointestinal environment, so there is a need to develop drugs that can be easily absorbed, and, although quercetin has a significant therapeutic effect on ALI, its low bioavailability limits its utilization. To address this problem, Chen et al developed an inhalable alginate quercetin nanogel (QU-Nanogel) based on alginate which is an FDA-approved polysaccharide with good biocompatibility. The QU-Nanogel had a uniform particle size distribution of less than 100 nm, facilitating the exposure of the active site on the surface, making it more readily absorbed and thus increasing the bioavailability of quercetin. It was also found that inhalation of the QU-Nanogel in model rats could reverse damage caused by oxidative stress and down-regulate the expression of inflammatory factors associated with ALI, reducing lung inflammation and preventing pulmonary fibrosis, thus mitigating lung injury[144] In addition, Liu et al found that quercetin liposomes could reduce radiation-induced oxidative stress in the lungs, alleviate acute pneumonitis, and delay the emergence of advanced fibrosis, thus effectively protecting mouse lung tissues from attack by the *Lepidoderma* slime mold.[82] Therefore, if quercetin is used in clinical applications, the use of quercetin nano-formulations would be preferred. Although quercetin nanoformulations have been found to be effective against ALI, the number of investigations is limited and research investment in this field needs to be strengthened.

Summary and Outlook

With a high safety profile and minimal side effects, quercetin is a naturally occurring flavonoid that is extensively distributed in nature and exhibits a variety of biological activities and pharmacological effects. In ALI cases, it can suppress oxidative stress, inflammatory reactions, cell death, apoptosis, fibrosis, and bacterial and viral infections by targeting various pathways and signaling processes. This versatility indicates its potential to mitigate the different forms of ALI. This study presents a systematic classification of ALI based on existing research findings.

Quercetin has demonstrated encouraging therapeutic effects on acute lung damage and other conditions. Quercetin protects the neurological system and can improve the prognosis and clinical symptoms of neurodegenerative disorders, stroke, Parkinson's disease, and Alzheimer's disease.[86,145] Quercetin mitigates cardiovascular diseases by regulating blood pressure, inhibiting ventricular remodeling, improving cardiac function, and protecting against myocardial damage caused by diabetes and hyperthyroidism.[146,147] It also exhibits antiarrhythmic properties and potential therapeutic effects in infective endocarditis.[148] Quercetin has a therapeutic effect on acute kidney injury caused by various reasons and shows potential as an anti-kidney injury agent.[149] It also displays a hepatoprotective effect by reducing bile acid reabsorption, inhibiting the NTCP transporter expression, and controlling hepatic lipid metabolism.[150,151] Quercetin acts as an antitumor agent by preventing tumor cell proliferation, migration, invasion, and other mechanisms. It also improves the effects of some chemotherapeutic drugs, reduces multidrug resistance, and improves patient quality of life.[152,153] The therapeutic applications of Quercetin for various disorders have been briefly discussed above; different diseases could benefit from quercetin in both research and practical applications, highlighting its broad therapeutic potential. Therefore, Quercetin is a very promising therapeutic candidate molecule for drug development.

Despite the evident therapeutic effects of Quercetin on ALI, this review presents several limitations. The current research on Quercetin for treating ALI reveals two important shortcomings in the discussion. The current research on applying Quercetin in the treatment of ALI lacks comprehensiveness. Topics such as lung injuries induced by trauma, drugs, transfusion, mechanical ventilation, thermal radiation, phosgene inhalation, gastric contents inhalation, acute organophosphorus poisoning, meconium inhalation, and dust inhalation have not been addressed. There are no relevant reports on these clinically prevalent forms of ALI. Further research on the application of quercetin in various types of lung injury is essential to enhance the accessibility of its treatment.Several experimental cases assessing quercetin's efficacy in treating ALI can be broadened by conducting studies that incorporate quercetin interventions informed by newly identified mechanisms associated with ALI. In investigating fundamental concepts and mechanisms, it is crucial to consider the relationships and functions of each mechanism. Limitations in experimental conditions, expertise, and financial resources render a complete understanding of all relevant mechanisms of action impractical, thereby necessitating comprehensive review articles to synthesize the findings. The second limitation is that most studies investigating

Quercetin's efficacy in treating ALI have predominantly focused on basic experimental approaches. The lack of clinical trials necessitates the incorporation of findings from basic research to investigate the clinical effectiveness of this treatment further. Thirdly, Quercetin may cause several side effects. Users have reported experiencing nausea, vomiting, diarrhea, abdominal pain, headaches, and a tingling sensation in the limbs, along with other discomforts. In some cases, severe complications such as acute hepatic and renal insufficiency can occur. Additionally, when quercetin is taken with medications that are metabolized by the cytochrome P450 enzyme, the likelihood of side effects increases significantly.[154] Research on the adverse side effects of Quercetin is limited, and it remains unclear whether other deleterious consequences exist. Therefore, researchers should focus on the side effects of Quercetin to alleviate potential risks in future studies on Quercetin and lung injury.

Quercetin has been extensively studied in the medical field due to its well-established therapeutic mechanisms, high safety profile, and minimal side effects. However, its low bioavailability remains a significant barrier to the advancement of Quercetin as a therapeutic agent. This issue necessitates solutions involving drug delivery carriers, developing quercetin precursors, and synthesizing quercetin analogs and derivatives, among other approaches. Despite the existing research, the advancement of Quercetin into clinical applications remains a significant challenge.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by grants from 2024 Guizhou Moutai Hospital Research and Talent Training Funding Project (grant number: MTy2024-27), the Science and Technology Projects of Guizhou Province (grant number: LC [2024]077).

Disclosure

All authors declare that they have no known conflicts of interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Meyer NJ, Gattinoni L, Calfee CS. Acute respiratory distress syndrome. *Lancet*. 2021;398(10300):622–637. doi:10.1016/s0140-6736(21)00439-6
2. Máca J, Jor O, Holub M, et al. Past and present ARDS mortality rates: a systematic review. *Respir Care*. 2017;62(1):113–122. doi:10.4187/respcare.04716
3. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *N Engl J Med*. 2005;353(16):1685–1693. doi:10.1056/NEJMoa050333
4. Matthay MA, Arabi Y, Arroliga AC, et al. A new global definition of acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2024;209(1):37–47. doi:10.1164/rccm.202303-0558WS
5. Mokrá D. Acute lung injury - from pathophysiology to treatment. *Physiol Res*. 2020;69(Suppl 3):S353–s366. doi:10.33549/physiolres.934602
6. Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. *J Clin Invest*. 2012;122(8):2731–2740. doi:10.1172/jci60331
7. Spadaro S, Park M, Turrini C, et al. Biomarkers for acute respiratory distress syndrome and prospects for personalised medicine. *J Inflamm*. 2019;161. doi:10.1186/s12950-018-0202-y
8. Huppert LA, Matthay MA, Ware LB. Pathogenesis of acute respiratory distress syndrome. *Semin Respir Crit Care Med*. 2019;40(1):31–39. doi:10.1055/s-0039-1683996
9. Tang Z, Yang Z, Feng H, et al. Attenuation of the severity of acute respiratory distress syndrome by Pomiferin through Blocking inflammation and oxidative stress in an AKT/Foxo1 pathway-dependent manner. *Oxid Med Cell Longev*. 2022;20225236908. doi:10.1155/2022/5236908
10. Wang C, Liu T, Tong Y, et al. Ulinastatin protects against acetaminophen-induced liver injury by alleviating ferroptosis via the SIRT1/NRF2/HO-1 pathway. *Am J Transl Res*. 2021;13(6):6031–6042.
11. Wang Y, Wu Y, Shen F, et al. [[Impact and mechanism of NEMO binding domain peptide on pulmonary inflammation and apoptosis of lung tissues in mice with acute respiratory distress syndrome]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*. 2021;33(4):410–415. Chinese. doi:10.3760/cma.j.cn121430-20201106-00704
12. Elenga N, Merlin C, Le Guern R, et al. Clinical features and prognosis of paraquat poisoning in French Guiana: a review of 62 cases. *Medicine*. 2018;97(15):e9621. doi:10.1097/md.0000000000009621

13. Yastrebov K, Kapalli T, Manganas C. Semiquantification of Systemic Venous Admixture During Venovenous Extracorporeal Oxygenation Via Bicaval Double-Lumen Cannula in Critically Ill Patients. *Asaio*. 2020;66(1):23–31. doi:10.1097/mat.0000000000000943
14. Hazafa A, Rehman KU, Jahan N, et al. The role of polyphenol (Flavonoids) compounds in the treatment of cancer cells. *Nutr Cancer*. 2020;72 (3):386–397. doi:10.1080/01635581.2019.1637006
15. Kumar M, Barbhai MD, Hasan M, et al. Onion (Allium cepa L.) peels: a review on bioactive compounds and biomedical activities. *Biomed Pharmacother*. 2022;146112498. doi:10.1016/j.biopha.2021.112498
16. Li Y, Yao J, Han C, et al. Quercetin, inflammation and immunity. *Nutrients*. 2016;8(3):167. doi:10.3390/nu8030167
17. Yi H, Peng H, Wu X, et al. The therapeutic effects and mechanisms of quercetin on metabolic diseases: pharmacological data and clinical evidence. *Oxid Med Cell Longev*. 2021;20216678662. doi:10.1155/2021/6678662
18. Spagnuolo C, Moccia S, Russo GL. Anti-inflammatory effects of flavonoids in neurodegenerative disorders. *Eur J Med Chem*. 2018;153105–-153115. doi:10.1016/j.ejmech.2017.09.001
19. Nam JS, Sharma AR, Nguyen LT, et al. Application of bioactive quercetin in oncotherapy: from nutrition to nanomedicine. *Molecules*. 2016;21 (1):E108. doi:10.3390/molecules21010108
20. Rajesh RU, Sangeetha D. Therapeutic potentials and targeting strategies of quercetin on cancer cells: challenges and future prospects. *Phytomedicine*. 2024;133155902. doi:10.1016/j.phymed.2024.155902
21. Zhou J, Feng S, Feng YL, et al. Research progress of quercetin ester derivatives. *Chemical Bulletin*. 2023;86(10):1240–1249. doi:10.14159/j.cnki.0441-3776.2023.10.006
22. Olewnik-Kruszkowska E, Ferri M, Cardeira MC, et al. Comparison of polylactide-based active films containing berberine and quercetin as systems for maintaining the quality and safety of blueberries. *Polymers (Basel)*. 2024;16(11):1577. doi:10.3390/polym16111577
23. Chen H, Lii YC, Wang DL, et al. Study on acute and subacute toxicity of quercetin extract. *Proceedings of the 11th Member Congress and 13th Symposium of the Chinese Society of Animal Husbandry and Veterinary Pharmacology and Toxicology Branch and the 5th Symposium of the Professional Committee of Veterinary Toxicology of the Chinese Society of Toxicology*. 2015.
24. Lu NT, Crespi CM, Liu NM, et al. A Phase I dose escalation study demonstrates quercetin safety and explores potential for bioflavonoid antivirals in patients with chronic Hepatitis C. *Phytother Res*. 2016;30(1):160–168. doi:10.1002/ptr.5518
25. Kandeel M, Kitade Y, Almubarak A. Repurposing FDA-approved phytomedicines, natural products, antivirals and cell protectives against SARS-CoV-2 (COVID-19) RNA-dependent RNA polymerase. *PeerJ*. 2020;8e10480. doi:10.7717/peerj.10480
26. Roy S, Ezati P, Khan A, et al. New opportunities and advances in quercetin-added functional packaging films for sustainable packaging applications: a mini-review. *Crit Rev Food Sci Nutr*. 2024;64:8464–8479; doi:10.1080/10408398.2023.2200553
27. Ding K, Jiang W, Zhan W, et al. The therapeutic potential of quercetin for cigarette smoking-induced chronic obstructive pulmonary disease: a narrative review. *Ther Adv Respir Dis*. 2023;17175346662311708000. doi:10.1177/17534666231170800
28. Valko M, Jomova K, Rhodes CJ, et al. Redox- and non-redox-metal-induced formation of free radicals and their role in human disease. *Arch Toxicol*. 2016;90(1):1–37. doi:10.1007/s00204-015-1579-5
29. Jiang YH, Jiang LY, Wang YC, et al. Quercetin attenuates atherosclerosis via modulating oxidized LDL-induced endothelial cellular senescence. *Front Pharmacol*. 2020;11512. doi:10.3389/fphar.2020.00512
30. Ali I, Khan SN, Chatzicharalampous C, et al. Catalase prevents myeloperoxidase self-destruction in response to oxidative stress. *J Inorg Biochem*. 2019;197110706. doi:10.1016/j.jinorgbio.2019.110706
31. Nutmakul T. A review on benefits of quercetin in hyperuricemia and gouty arthritis. *Saudi Pharm J*. 2022;30(7):918–926. doi:10.1016/j.jsps.2022.04.013
32. Yang L, Wang YQ, Huang X, Yang, ZM, et al. [Quercetin for the treatment of prostate cancer: Progress in studies]. *Zhonghua Nan Ke Xue*. 2021;27(7):654–658. Chinese.
33. Mu D, Zhou L, Shi L, et al. Quercetin-crosslinked chitosan nanoparticles: a potential treatment for allergic rhinitis. *Sci Rep*. 2024;14(1):4021. doi:10.1038/s41598-024-54501-2
34. Yardim A, Kandemir FM, Ozdemir S, et al. Quercetin provides protection against the peripheral nerve damage caused by vincristine in rats by suppressing caspase 3, NF-κB, ATF-6 pathways and activating Nrf2, Akt pathways. *Neurotoxicology*. 2020;81137–81146. doi:10.1016/j.neuro.2020.10.001
35. Aghababaei F, Hadidi M. Recent advances in potential health benefits of quercetin. *Pharmaceuticals*. 2023;16(7):1020. doi:10.3390/ph16071020
36. Massi A, Bortolini O, Ragno D, et al. Research progress in the modification of quercetin leading to anticancer agents. *Molecules*. 2017;22 (8):1270. doi:10.3390/molecules22081270
37. Chen YF, Qiu Q, Wang L, et al. Quercetin ameliorates myocardial injury in diabetic rats by regulating autophagy and apoptosis through AMPK/mTOR signaling pathway. *Am J Chin Med*. 2024;52(3):841–864. doi:10.1142/s0192415x24500344
38. Yuan M, Sun T, Zhang Y, et al. Quercetin alleviates insulin resistance and repairs intestinal barrier in db/db mice by modulating gut microbiota. *Nutrients*. 2024;16(12):1870. doi:10.3390/nu16121870
39. Rathi V, Sagi SSK, Yadav AK, et al. Quercetin prophylaxis protects the kidneys by modulating the renin-angiotensin-aldosterone axis under acute hypobaric hypoxic stress. *Sci Rep*. 2024;14(1):7617. doi:10.1038/s41598-024-58134-3
40. Li X, Niu C, Yi G, et al. Quercetin inhibits the epithelial-mesenchymal transition and reverses CDK4/6 inhibitor resistance in breast cancer by regulating circHIAT1/miR-19a-3p/CADM2 axis. *PLoS One*. 2024;19(7):e0305612. doi:10.1371/journal.pone.0305612
41. Sun P, Yang Y, Yang L, et al. Quercetin protects blood-brain barrier integrity via the PI3K/Akt/Erk signaling pathway in a mouse model of meningitis induced by Glaesserella parasuis. *Biomolecules*. 2024;14(6):696. doi:10.3390/biom14060696
42. Zhuang M, Rao L, Chen Y, et al. Controlled SPION-exosomes loaded with quercetin preserves pancreatic beta cell survival and function in Type 2 diabetes mellitus. *Int J Nanomedicine*. 2023;185733–185748. doi:10.2147/ijn.S422416
43. Gerin F, Sener U, Erman H, et al. The effects of quercetin on acute lung injury and biomarkers of inflammation and oxidative stress in the rat model of sepsis. *Inflammation*. 2016;39(2):700–705. doi:10.1007/s10753-015-0296-9
44. Wang XF, Song SD, Li YJ, et al. Protective effect of quercetin in LPS-induced murine acute lung injury mediated by cAMP-Epac pathway. *Inflammation*. 2018;41(3):1093–1103. doi:10.1007/s10753-018-0761-3

45. Yang XR, Fan MR, Yang B. To investigate the effect of quercetin on alveolar macrophages in acute lung injury based on PPARγ/LXR-α signaling pathway. *Journal of Modern Chinese and Western Integrative Medicine*. 2024;33(02):147–154+161.
46. Jia YJ, Xiong S, Yao M, et al. HMGB1 inhibition blocks ferroptosis and oxidative stress to ameliorate sepsis-induced acute lung injury by activating the Nrf2 pathway. *Kaohsiung J Med Sci*. 2024;40:710–721. doi:10.1002/kjm2.12851
47. Chen LL, Song C, Zhang Y, et al. Quercetin protects against LPS-induced lung injury in mice via SIRT1-mediated suppression of PKM2 nuclear accumulation. *Eur J Pharmacol*. 2022;936175352. doi:10.1016/j.ejphar.2022.175352
48. Takashima K, Matsushima M, Hashimoto K, et al. Protective effects of intratracheally administered quercetin on lipopolysaccharide-induced acute lung injury. *Respir Res*. 2014;15(1):150. doi:10.1186/s12931-014-0150-x
49. Deng S, Li J, Li L, et al. Quercetin alleviates lipopolysaccharide-induced acute lung injury by inhibiting ferroptosis via the Sirt1/Nrf2/Gpx4 pathway. *Int J Mol Med*. 2023;52(6). doi:10.3892/ijmm.2023.5321
50. Kerins MJ, Ooi A. The roles of NRF2 in modulating cellular iron homeostasis. *Antioxid Redox Signal*. 2018;29(17):1756–1773. doi:10.1089/ars.2017.7176
51. Sang A, Wang Y, Wang S, et al. Quercetin attenuates sepsis-induced acute lung injury via suppressing oxidative stress-mediated ER stress through activation of SIRT1/AMPK pathways. *Cell Signal*. 2022;96110363. doi:10.1016/j.cellsig.2022.110363
52. Sul OJ, Ra SW. Quercetin prevents LPS-induced oxidative stress and inflammation by modulating NOX2/ROS/NF-kB in lung epithelial cells. *Molecules*. 2021;26(22). doi:10.3390/molecules26226949
53. Yuan HN, He XY, Li ZF, et al. Effects of quercetin on acute lung injury, inflammation and oxidative stress in sepsis rats. *Chinese Journal of Immunology*. 2024;40(04):780–785.
54. Li GR, Shen CY, Wei D, et al. Quercetin inhibits LPS-induced acute lung injury and proinflammatory phenotype of macrophages in rats. *Ningxia Medical Journal*. 2023;45389–392+384. doi:10.13621/j.1001-5949.2023.05.0389
55. Jing HK. Quercetin alleviates the effects of lipopolysaccharids-induced acute lung injury through the SCAP/SREBP2/NLRP3 pathway. *Journal of Chongqing Medical University*. 2023. doi:10.27674/d.cnki.gcyku.2023.000142
56. Lu P, Lu N, Xu CR. The TLR4/Myd88 signaling pathway mediates quercetin to inhibit lung damage in septic shock rats. *Adv Anat Sci*. 2019;25(02):186–189. doi:10.16695/j.cnki.1006-2947.2019.02.020
57. Liu SW. Protective effect of quercetin on lipopolysaccharids-induced acute lung injury in rats and effect of Nrf-2/ARE signaling pathway. *J Zunyi Med Univ*. 2019.
58. Zaccolo M, Zerio A, Lobo MJ. Subcellular organization of the cAMP signaling pathway. *Pharmacol Rev*. 2021;73(1):278–309. doi:10.1124/pharmrev.120.000086
59. de Rooij J, Zwartkruis FJ, Verheijen MH, et al. Epac is a Rap1 guanine-nucleotide-exchange factor directly activated by cyclic AMP. *Nature*. 1998;396(6710):474–477. doi:10.1038/24884
60. Wang X, Song S, Hu Z, et al. Activation of Epac alleviates inflammation and vascular leakage in LPS-induced acute murine lung injury. *Biomed Pharmacother*. 2017;961127–961136. doi:10.1016/j.biopha.2017.11.110
61. Frankenstein H, Robak J, Lewandowska U, et al. Sirtuina 1 jako potencjalny cel molekularny resweratrolu w wybranych chorobach [Sirtuin 1 as a potential molecular target of resveratrol in selected diseases]. *Postepy Biochem*. 2024;69(4):264–273. Danish. doi:10.18388/pb.2021_499
62. Hardeland R. Melatonin and inflammation-story of a double-edged blade. *J Pineal Res*. 2018;65(4):e12525. doi:10.1111/jpi.12525
63. Zhong WJ, Yang HH, Guan XX, et al. Inhibition of glycolysis alleviates lipopolysaccharide-induced acute lung injury in a mouse model. *J Cell Physiol*. 2019;234(4):4641–4654. doi:10.1002/jcp.27261
64. Wagener FA, Volk HD, Willis D, et al. Different faces of the heme-heme oxygenase system in inflammation. *Pharmacol Rev*. 2003;55(3):551–571. doi:10.1124/pr.55.3.5
65. Wang Y, Chen D, Xie H, et al. AUF1 protects against ferroptosis to alleviate sepsis-induced acute lung injury by regulating NRF2 and ATF3. *Cell Mol Life Sci*. 2022;79(5):228. doi:10.1007/s00018-022-04248-8
66. Xie Y, Hou W, Song X, et al. Ferroptosis: process and function. *Cell Death Differ*. 2016;23(3):369–379. doi:10.1038/cdd.2015.158
67. Andres S, Pevny S, Ziegenhagen R, et al. Safety aspects of the use of quercetin as a dietary supplement. *Mol Nutr Food Res*. 2018;62(1). doi:10.1002/mnfr.201700447
68. Xue L, Bo L, Lei M. Observation of lung tissue injury, inflammation/oxidative stress, iron death and activation of Nrf2/HO-1 signaling pathway in quercetin pretreated ALI rats. *Shandong Medicine*. 2024;64(15):13–18.
69. Geiser T. Idiopathic pulmonary fibrosis--A disorder of alveolar wound repair? *Swiss Med Wkly*. 2003;133(29–30):405–411. doi:10.4414/smw.2003.09986
70. Hu M, Yang J, Xu Y. Effect of α-tocopherol in alleviating the lipopolysaccharide-induced acute lung injury via inhibiting nuclear factor kappa-B signaling pathways. *Bioengineered*. 2022;13(2):3958–3968. doi:10.1080/21655979.2022.2031399
71. McVey MJ, Kapur R, Cserti-Gazdewich C, et al. Transfusion-related acute lung injury in the perioperative patient. *Anesthesiology*. 2019;131(3):693–715. doi:10.1097/aln.0000000000002687
72. Zhang J, Zhang M, Huo XK, et al. Macrophage inactivation by small molecule Wedelolactone via targeting sEH for the treatment of LPS-induced acute lung injury. *ACS Cent Sci*. 2023;9(3):440–456. doi:10.1021/acscentsci.2c01424
73. Zhang F, Liu P, He Z, et al. Crocin ameliorates atherosclerosis by promoting the reverse cholesterol transport and inhibiting the foam cell formation via regulating PPARγ/LXR-α. *Cell Cycle*. 2022;21(2):202–218. doi:10.1080/15384101.2021.2015669
74. Paik S, Kim JK, Silwal P, et al. An update on the regulatory mechanisms of NLRP3 inflammasome activation. *Cell Mol Immunol*. 2021;18(5):1141–1160. doi:10.1038/s41423-021-00670-3
75. Gaul S, Leszczynska A, Alegre F, et al. Hepatocyte pyroptosis and release of inflammasome particles induce stellate cell activation and liver fibrosis. *J Hepatol*. 2021;74(1):156–167. doi:10.1016/j.jhep.2020.07.041
76. Shi S, Huang D, Wu Y, et al. Salidroside pretreatment alleviates PM(2.5) caused lung injury via inhibition of apoptosis and pyroptosis through regulating NLRP3 Inflammasome. *Food Chem Toxicol*. 2023;177113858. doi:10.1016/j.fct.2023.113858
77. Hanania AN, Mainwaring W, Ghebre YT, et al. Radiation-induced lung injury: assessment and management. *Chest*. 2019;156(1):150–162. doi:10.1016/j.chest.2019.03.033
78. Arroyo-Hernández M, Maldonado F, Lozano-Ruiz F, et al. Radiation-induced lung injury: current evidence. *BMC Pulm Med*. 2021;21(1):9. doi:10.1186/s12890-020-01376-4

79. Cowley S, Paterson H, Kemp P, et al. Activation of MAP kinase kinase is necessary and sufficient for PC12 differentiation and for transformation of NIH 3T3 cells. *Cell*. 1994;77(6):841–852. doi:10.1016/0092-8674(94)90133-3
80. Vile GF, Tanew-Ilitschew A, Tyrrell RM. Activation of NF-kappa B in human skin fibroblasts by the oxidative stress generated by UVA radiation. *Photochem Photobiol*. 1995;62(3):463–468. doi:10.1111/j.1751-1097.1995.tb02369.x
81. Wang J, Zhang YY, Cheng J, et al. Preventive and therapeutic effects of quercetin on experimental radiation induced lung injury in mice. *Asian Pac J Cancer Prev*. 2015;16(7):2909–2914. doi:10.7314/apjcp.2015.16.7.2909
82. Liu H, Xue JX, Li X, et al. Quercetin liposomes protect against radiation-induced pulmonary injury in a murine model. *Oncol Lett*. 2013;6(2):453–459. doi:10.3892/ol.2013.1365
83. Sun PY, Wang AS, Zhang ZF, et al. Network pharmacology-based strategy to investigate the active ingredients and molecular mechanisms of Scutellaria Barbata D. Don against radiation pneumonitis. *Medicine (Baltimore)*. 2021;100(47):e27957. doi:10.1097/md.0000000000027957
84. Lai GH, Wang F, Nie DR, et al. Identifying active substances and the pharmacological mechanism of Houttuynia cordata thunb. in treating radiation-induced lung injury based on network pharmacology and molecular docking verification. *Evid Based Complement Alternat Med*. 2022;20223776340. doi:10.1155/2022/3776340
85. Beckers PAJ, Gielis JF, Van Schil PE, et al. Lung ischemia reperfusion injury: the therapeutic role of dipeptidyl peptidase 4 inhibition. *Ann Transl Med*. 2017;5(6):129. doi:10.21037/atm.2017.01.41
86. Fiser SM, Tribble CG, Long SM, et al. Lung transplant reperfusion injury involves pulmonary macrophages and circulating leukocytes in a biphasic response. *J Thorac Cardiovasc Surg*. 2001;121(6):1069–1075. doi:10.1067/mtc.2001.113603
87. Saito M, Chen-Yoshikawa TF, Suetsugu K, et al. Pirfenidone alleviates lung ischemia-reperfusion injury in a rat model. *J Thorac Cardiovasc Surg*. 2019;158(1):289–296. doi:10.1016/j.jtcvs.2018.08.098
88. Liu W, Kang K, Zhang JN, et al. Protective effect and mechanism of quercetin on lung ischemia-reperfusion injury in mice. *J North Sichuan Med College*. 2021;36(07).
89. Uhlig S, Gulbins E. Sphingolipids in the lungs. *Am J Respir Crit Care Med*. 2008;178(11):1100–1114. doi:10.1164/rccm.200804-595SO
90. Frazziano G, Moreno L, Moral-Sanz J, et al. Neutral sphingomyelinase, NADPH oxidase and reactive oxygen species. Role in acute hypoxic pulmonary vasoconstriction. *J Cell Physiol*. 2011;226(10):2633–2640. doi:10.1002/jcp.22611
91. Chamorro V, Pandolfi R, Moreno L, et al. Effects of quercetin in a rat model of hemorrhagic traumatic shock and reperfusion. *Molecules*. 2016;21(12). doi:10.3390/molecules21121739
92. Zerin T, Kim YS, Hong SY, et al. Quercetin reduces oxidative damage induced by paraquat via modulating expression of antioxidant genes in A549 cells. *J Appl Toxicol*. 2013;33(12):1460–1467. doi:10.1002/jat.2812
93. Meng XM, Nikolic-Paterson DJ, Lan HY. TGF-β: the master regulator of fibrosis. *Nat Rev Nephrol*. 2016;12(6):325–338. doi:10.1038/nrneph.2016.48
94. Willis BC, Borok Z. TGF-beta-induced EMT: mechanisms and implications for fibrotic lung disease. *Am J Physiol Lung Cell Mol Physiol*. 2007;293(3):L525–534. doi:10.1152/ajplung.00163.2007
95. Wang F, Zhang ZF, He YR, et al. Effects of dipeptidyl peptidase-4 inhibitors on transforming growth factor-β1 signal transduction pathways in the ovarian fibrosis of polycystic ovary syndrome rats. *J Obstet Gynaecol Res*. 2019;45(3):600–608. doi:10.1111/jog.13847
96. Abdalla M, Sabbineni H, Prakash R, et al. The Akt inhibitor, triciribine, ameliorates chronic hypoxia-induced vascular pruning and TGFβ-induced pulmonary fibrosis. *Br J Pharmacol*. 2015;172(16):4173–4188. doi:10.1111/bph.13203
97. Zhang JW, Su YW, Ma WY, et al. Effect of quercetin on the survival rate of paraquat infected lung epithelial cells and markers of epithelial interstitial transformation. *Occupational Health and Emergency Rescue*. 2021;39(04):388–393+475. doi:10.16369/j.oher.issn.1007-1326.2021.04.005
98. Park HK, Kim SJ, Kwon DY, et al. Protective effect of quercetin against paraquat-induced lung injury in rats. *Life Sci*. 2010;87(5–6):181–186. doi:10.1016/j.lfs.2010.06.011
99. Cox R Jr, Phillips O, Fukumoto J, et al. Enhanced resolution of hyperoxic acute lung injury as a result of aspirin triggered resolvin D1 treatment. *Am J Respir Cell Mol Biol*. 2015;53(3):422–435. doi:10.1165/rcmb.2014-0339OC
100. Vaidya R, Zambrano R, Hummler JK, et al. Recombinant CCN1 prevents hyperoxia-induced lung injury in neonatal rats. *Pediatr Res*. 2017;82(5):863–871. doi:10.1038/pr.2017.160
101. Maturu P, Wei-Liang Y, Androutsopoulos VP, et al. Quercetin attenuates the hyperoxic lung injury in neonatal mice: implications for Bronchopulmonary dysplasia (BPD). *Food Chem Toxicol*. 2018;11423–11433. doi:10.1016/j.fct.2018.02.026
102. Li D, Liu X, Pi W, et al. Fisetin attenuates doxorubicin-induced cardiomyopathy in vivo and in vitro by inhibiting ferroptosis through SIRT1/Nrf2 signaling pathway activation. *Front Pharmacol*. 2021;12808480. doi:10.3389/fphar.2021.808480
103. Deng X, Chen D, Xie A, et al. Quercetin alleviates hyperoxia-induced bronchopulmonary dysplasia by inhibiting ferroptosis through the MAPK/PTGS2 pathway: insights from network pharmacology, molecular docking, and experimental evaluations. *Chem Biol Drug Des*. 2024;103(4):e14520. doi:10.1111/cbdd.14520
104. Hamahata A, Enkhbaatar P, Lange M, et al. Administration of a peroxynitrite decomposition catalyst into the bronchial artery attenuates pulmonary dysfunction after smoke inhalation and burn injury in sheep. *Shock*. 2012;38(5):543–548. doi:10.1097/SHK.0b013e31826e9c54
105. da Silva Araújo NP, de Matos NA, Leticia Antunes Mota S, et al. Quercetin attenuates acute lung injury caused by cigarette smoke both in vitro and in vivo. *COPD*. 2020;17(2):205–214. doi:10.1080/15412555.2020.1749253
106. Liu YP, Zhang JM, Liu Q, et al. Effect of prophylactic quercetin on lung therapy in rats with inhalation injury. *Journal of Tianjin Medical University*. 2013;19(2):104–106+169.
107. Liu YP, Zhang JM, Liu Q, et al. Experimental study on the therapeutic effect of quercetin on lung injury induced by smoke inhalation. *Chinese Journal of Injury and Repair*. 2012;7(06):600–604.
108. Diao M, Zhang S, Wu L, et al. Hydrogen gas inhalation attenuates seawater instillation-induced acute lung injury via the Nrf2 pathway in rabbits. *Inflammation*. 2016;39(6):2029–2039. doi:10.1007/s10753-016-0440-1
109. Ying H, Kang Y, Zhang H, et al. MiR-127 modulates macrophage polarization and promotes lung inflammation and injury by activating the JNK pathway. *J Immunol*. 2015;194(3):1239–1251. doi:10.4049/jimmunol.1402088
110. Wang BJ, Mao X. Quercetin alleviates acute lung injury induced by seawater inhalation in mice by inhibiting M1 polarization of lung macrophages. *Journal of Cellular and Molecular Immunology*. 2017;33(06):751–755. doi:10.13423/j.cnki.cjcmi.008159

111. Sarada S, Himadri P, Mishra C, et al. Role of oxidative stress and NFkB in hypoxia-induced pulmonary edema. *Exp Biol Med*. 2008;233(9):1088–1098. doi:10.3181/0712-rm-337
112. Al-Rasheed NM, Fadda L, Attia HA, et al. Original research paper. Pulmonary prophylactic impact of melatonin and/or quercetin: a novel therapy for inflammatory hypoxic stress in rats. *Acta Pharm*. 2017;67(1):125–135. doi:10.1515/acph-2017-0010
113. Al-Rasheed NM, Fadda LM, Attia HA, et al. Quercetin inhibits sodium nitrite-induced inflammation and apoptosis in different rats organs by suppressing Bax, HIF1-α, TGF-β, Smad-2, and AKT pathways. *J Biochem Mol Toxicol*. 2017;31(5). doi:10.1002/jbt.21883
114. Tripathi A, Kumar B, Sagi SSK. Prophylactic efficacy of quercetin in ameliorating the hypoxia induced vascular leakage in lungs of rats. *PLoS One*. 2019;14(6):e0219075. doi:10.1371/journal.pone.0219075
115. Tripathi A, Kumar M, Kaur P, et al. Efficacy of quercetin as a potent sensitizer of β2-AR in combating the impairment of fluid clearance in lungs of rats under hypoxia. *Respir Physiol Neurobiol*. 2020;273103334. doi:10.1016/j.resp.2019.103334
116. Elder AS, Saccone GT, Dixon DL. Lung injury in acute pancreatitis: mechanisms underlying augmented secondary injury. *Pancreatology*. 2012;12(1):49–56. doi:10.1016/j.pan.2011.12.012
117. Nolan B, Kim R, Duffy A, et al. Inhibited neutrophil apoptosis: proteasome dependent NF-kappaB translocation is required for TRAF-1 synthesis. *Shock*. 2000;14(3):290–294. doi:10.1097/00024382-200014030-00008
118. Xu XW, Yang XM, Jin ZX, et al. Effect of quercetin on apoptosis of alveolar neutrophils in rats with severe acute pancreatitis. *Chinese Journal of Pathophysiology*. 2013;29(03):499–503.
119. Chanjitwiriya K, Roytrakul S, Kunthalert D. Quercetin negatively regulates IL-1β production in Pseudomonas aeruginosa-infected human macrophages through the inhibition of MAPK/NLRP3 inflammasome pathways. *PLoS One*. 2020;15(8):e0237752. doi:10.1371/journal.pone.0237752
120. Jia X, Gu M, Dai J, et al. Quercetin attenuates Pseudomonas aeruginosa-induced acute lung inflammation by inhibiting PI3K/AKT/NF-κB signaling pathway. *Inflammopharmacology*. 2024;32(2):1059–1076. doi:10.1007/s10787-023-01416-5
121. Lu Z, Wang H, Ishfaq M, et al. Quercetin and AMPK: a dynamic duo in alleviating MG-induced inflammation via the AMPK/SIRT1/NF-κB pathway. *Molecules*. 2023;28(21):7388. doi:10.3390/molecules28217388
122. Lv Q, Zhang P, Quan P, et al. Quercetin, a pneumolysin inhibitor, protects mice against Streptococcus pneumoniae infection. *Microb Pathog*. 2020;140103934. doi:10.1016/j.micpath.2019.103934
123. Sun YL, Zhao PP, Zhu CB, et al. Integrating metabolomics and network pharmacology to assess the effects of quercetin on lung inflammatory injury induced by human respiratory syncytial virus. *Sci Rep*. 2023;13(1):8051. doi:10.1038/s41598-023-35272-8
124. Guimarães GC, Piva HRM, Araújo GC, et al. Binding investigation between M2-1protein from hRSV and acetylated quercetin derivatives: (1)H NMR, fluorescence spectroscopy, and molecular docking. *Int J Biol Macromol*. 2018;11133–11138. doi:10.1016/j.ijbiomac.2017.12.141
125. Zaim S, Chong JH, Sankaranarayanan V, et al. COVID-19 and multiorgan response. *Curr Probl Cardiol*. 2020;45(8):100618. doi:10.1016/j.cpcardiol.2020.100618
126. Fauci AS, Lane HC, Redfield RR. Covid-19 - navigating the uncharted. *N Engl J Med*. 2020;382(13):1268–1269. doi:10.1056/NEJMe2002387
127. Ren JL, Zhang AH, Wang XJ. Traditional Chinese medicine for COVID-19 treatment. *Pharmacol Res*. 2020;155104743. doi:10.1016/j.phrs.2020.104743
128. Ang L, Lee HW, Choi JY, et al. Herbal medicine and pattern identification for treating COVID-19: a rapid review of guidelines. *Integr Med Res*. 2020;9(2):100407. doi:10.1016/j.imr.2020.100407
129. Di Pierro F, Derosa G, Maffioli P, et al. Possible therapeutic effects of adjuvant quercetin supplementation against early-stage COVID-19 infection: a prospective, randomized, controlled, and open-label study. *Int J Gen Med*. 2021;142359–142366. doi:10.2147/ijgm.S318720
130. Di Pierro F, Iqtadar S, Khan A, et al. Potential clinical benefits of quercetin in the early stage of COVID-19: results of a second, pilot, randomized, controlled and open-label clinical trial. *Int J Gen Med*. 2021;142807–142816. doi:10.2147/ijgm.S318949
131. Nguyen TT, Woo HJ, Kang HK, et al. Flavonoid-mediated inhibition of SARS coronavirus 3C-like protease expressed in Pichia pastoris. *Biotechnol Lett*. 2012;34(5):831–838. doi:10.1007/s10529-011-0845-8
132. Chen L, Li J, Luo C, et al. Binding interaction of quercetin-3-beta-galactoside and its synthetic derivatives with SARS-CoV 3CL(pro): structure-activity relationship studies reveal salient pharmacophore features. *Bioorg Med Chem*. 2006;14(24):8295–8306. doi:10.1016/j.bmc.2006.09.014
133. Yao C, Xi C, Hu K, et al. Inhibition of enterovirus 71 replication and viral 3C protease by quercetin. *Virol J*. 2018;15(1):116. doi:10.1186/s12985-018-1023-6
134. Kim YJ, Park W. Anti-inflammatory effect of quercetin on RAW 264.7 mouse macrophages induced with polyinosinic-polycytidylic acid. *Molecules*. 2016;21(4):450. doi:10.3390/molecules21040450
135. Yi L, Li Z, Yuan K, et al. Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. *J Virol*. 2004;78(20):11334–11339. doi:10.1128/jvi.78.20.11334-11339.2004
136. Colunga Biancatelli RML, Berrill M, Catravas JD, et al. Quercetin and Vitamin C: an experimental, synergistic therapy for the prevention and treatment of SARS-CoV-2 related disease (COVID-19). *Front Immunol*. 2020;111451. doi:10.3389/fimmu.2020.01451
137. Jiang W, Zhang H, Wu J, et al. CuS@MOF-based well-designed quercetin delivery system for chemo-photothermal therapy. *ACS Appl Mater Interfaces*. 2018;10(40):34513–34523. doi:10.1021/acsami.8b13487
138. Ma J, Li H. Safety evaluation of nanomedicine. *Chinese Journal of Pharmacology and Toxicology*. 2013;27(03):452–453.
139. Ahmed OAA, Hassan NA, Azhar AS, et al. A nano-pharmaceutical formula of quercetin protects from cardiovascular complications associated with metabolic syndrome. *Front Pharmacol*. 2021;12696981. doi:10.3389/fphar.2021.696981
140. Shang J, Liang T, Wei D, et al. Quercetin-loaded PLGA nanoparticles coating with macrophage membranes for targeted delivery in acute liver injury. *Nanotechnology*. 2023;35(11). doi:10.1088/1361-6528/ad1440
141. Abdelrahman FAF, El-Sayed SA, Abuel-Atta AA, et al. Nephrotoxicity induced by different diameters of sphere gold nanoparticles with special emphasis on the nephroprotective role of quercetin. *Open Vet J*. 2023;13(6):723–731. doi:10.5455/OVJ.2023.v13.i6.7
142. Mohammed HA, Sulaiman GM, Anwar SS, et al. Quercetin against MCF7 and CAL51 breast cancer cell lines: apoptosis, gene expression and cytotoxicity of nano-quercetin. *Nanomedicine*. 2021;16(22):1937–1961. doi:10.2217/nnm-2021-0070
143. Abdelrahman SA, El-Shal AS, Abdelrahman AA, et al. Neuroprotective effects of quercetin on the cerebellum of zinc oxide nanoparticles (ZnoNps)-exposed rats. *Tissue Barriers*. 2023;11(3):2115273. doi:10.1080/21688370.2022.2115273

144. Yao J, Li Y, Meng F, et al. Enhancement of suppression oxidative stress and inflammation of quercetin by nano-decoration for ameliorating silica-induced pulmonary fibrosis. *Environ Toxicol*. 2023;38(7):1494–1508. doi:10.1002/tox.23781
145. Ossola B, Kääriäinen TM, Männistö PT. The multiple faces of quercetin in neuroprotection. *Expert Opin Drug Saf*. 2009;8(4):397–409. doi:10.1517/14740330903026944
146. Russo M, Spagnuolo C, Tedesco I, et al. The flavonoid quercetin in disease prevention and therapy: facts and fancies. *Biochem Pharmacol*. 2012;83(1):6–15. doi:10.1016/j.bcp.2011.08.010
147. Larson AJ, Symons JD, Jalili T. Therapeutic potential of quercetin to decrease blood pressure: review of efficacy and mechanisms. *Adv Nutr*. 2012;3(1):39–46. doi:10.3945/an.111.001271
148. Bombardi Duarte AC, Santana MG, Di Camilo Orfali G, et al. Literature evidence and ARRIVE assessment on neuroprotective effects of flavonols in neurodegenerative diseases' models. *CNS Neurol Disord Drug Targets*. 2018;17(1):34–42. doi:10.2174/1871527317666171221110139
149. Shoskes DA. Effect of bioflavonoids quercetin and curcumin on ischemic renal injury: a new class of renoprotective agents. *Transplantation*. 1998;66(2):147–152. doi:10.1097/00007890-199807270-00001
150. Li Y, Chen M, Xu Y, et al. Iron-mediated lysosomal membrane permeabilization in ethanol-induced hepatic oxidative damage and apoptosis: protective effects of quercetin. *Oxid Med Cell Longev*. 2016;20164147610. doi:10.1155/2016/4147610
151. Miltonprabu S, Tomczyk M, Skalicka-Woźniak K, et al. Hepatoprotective effect of quercetin: from chemistry to medicine. *Food Chem Toxicol*. 2017;108(Pt B):365–374. doi:10.1016/j.fct.2016.08.034
152. Pan HC, Jiang Q, Yu Y, et al. Quercetin promotes cell apoptosis and inhibits the expression of MMP-9 and fibronectin via the AKT and ERK signalling pathways in human glioma cells. *Neurochem Int*. 2015;8060–8071. doi:10.1016/j.neuint.2014.12.001
153. Brito AF, Ribeiro M, Abrantes AM, et al. Quercetin in cancer treatment, alone or in combination with conventional therapeutics? *Curr Med Chem*. 2015;22(26):3025–3039. doi:10.2174/0929867322666150812145435
154. Tang SM, Deng XT, Zhou J, et al. Pharmacological basis and new insights of quercetin action in respect to its anti-cancer effects. *Biomed Pharmacother*. 2020;121109604. doi:10.1016/j.biopha.2019.109604