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Review Article

Application Potential of Luteolin in the Treatment of Viral Pneumonia

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Aim of the Review. This study aims to summarize the therapeutic effect of luteolin on the pathogenesis of viral pneumonia, explore its absorption and metabolism in the human body, evaluate the possibility of luteolin as a drug to treat viral pneumonia, and provide a reference for future research. *Materials and Methods*. We searched MEDLINE/PubMed, Web of Science, China National Knowledge Infrastructure, and Google Scholar and collected research on luteolin in the treatment of viral pneumonia and related diseases since 2003. Then, we summarized the efficacy and potential of luteolin in directly inhibiting viral activity, limiting inflammatory storms, reducing pulmonary inflammation, and treating pneumonia complications. *Results and Conclusion*. Luteolin has the potential to treat viral pneumonia in multiple ways. Luteolin has a direct inhibitory effect on coronavirus, influenza virus, and respiratory syncytial virus. Luteolin can alleviate the inflammatory factor storm induced by multiple factors by inhibiting the function of macrophages or mast cells. Luteolin can reduce pulmonary inflammation, pulmonary edema, or pulmonary fibrosis induced by multiple factors. In addition, viral pneumonia may cause multisystem complications, while luteolin has extensive protective effects on the gastrointestinal system, cardiovascular system, and nervous system. However, due to the first-pass metabolism mediated by phase II enzymes, the bioavailability of oral luteolin is low. The bioavailability of luteolin can be improved, and its potential value can be further developed by changing the dosage form or route of administration.

1. Introduction

Pneumonia is one of the leading causes of morbidity and mortality worldwide. Before 2019, about 450 million cases of pneumonia were diagnosed per year, and 3 to 4 million people died as a result [1]. Pneumonia is also the leading cause of death among children under 5 years old globally. In 2015 alone, pneumonia caused nearly one million deaths among children [2]. It is worth noting that COVID-19 pneumonia, which has been raging around the world since 2019, has caused 621 million confirmed cases and 6.5 million deaths by 16th October 2022 [3], and the economic losses caused are difficult to estimate. Viruses are the main pathogen of community-acquired pneumonia. There are about 200 million cases of viral pneumonia each year, and half of them are children [4]. A case-control study of 1769 pneumonia children with positive chest X-rays from 7 countries in Asia and Africa showed that viruses are the cause of pneumonia in 61.4% of study subjects, including respiratory syncytial viruses (31.1%), human rhinovirus, human metapneumovirus (hMPV) A or B, and human parainfluenza virus [5]. In addition, coronavirus, influenza A virus, and adenovirus are also common causes of viral pneumonia [4].

Luteolin (3′, 4′, 5, 7-tetrahydroxyflavone), a natural flavonoid, and its derivatives are found in a variety of herbs, vegetables, and fruits, including apple skins, broccoli,

cabbages, carrots, onion leaves, and peppers [6, 7]. Structurally, like all flavonoids, luteolin has a diphenylpropane structure (c6-c3-c6) and is linked with a hydroxyl group (-OH) at 3′-, 4′-, 5-, and 7- positions. Derivatives of luteolin are defined as luteolin compounds in which the hydroxyl group (-OH) is replaced by other groups at 3′-, 4′-, 5-, or 7 positions. Luteolin and its derivatives may exist as aglycone or combine with one or several sugars as glycoside in nature [8]. After organism metabolism, luteolin can also exist in the form of glucuronide, monoglucoside, monoglucuride, or sulfate etc. The chemical structural formula of luteolin and some of its derivatives are shown in Figure 1.

Luteolin and its derivatives have shown a variety of biological activities in vivo, in vitro, and in silico studies [6], including anti-inflammatory, antiviral, antiallergic, and immunomodulatory effects [9–13]. This article aims to give an overview of the possible efficacy of luteolin and its derivatives in the treatment of viral pneumonia and explore the possibility of developing this flavonoid as a drug for the prevention and treatment of viral pneumonia. The mechanism of pathological damage caused by viral pneumonia is shown in Figure 2.

2. Direct Antiviral Effect of Luteolin

2.1. Coronaviruses. Coronaviruses are a family of enveloped, positive sense, and single-strand RNA viruses. Before the outbreak of SARS-CoV-2 in 2019, the SARS-CoV reported in 2003 and the MERS-CoV reported in 2012 caused a huge negative impact on human society [14]. SARS-CoV-2 contains a single-stranded RNA of about 26000–32000 bases, which is 80% similar to SARS-CoV and 50% similar to MERS-CoV [15]. The genomes of coronavirus are composed of 6–11 open reading frames (ORFs), with the first ORF (ORF1a/b) containing 67% of the viral RNA and encoding two large replicase polyproteins, pp1a and pp1ab. These polyproteins are further processed to 16 nonstructural proteins (NSPs) by virally encoded chymotrypsin-like proteases (3CLpro) or main proteases (Mpro) and one or two papain-like proteases (PLpro) [16, 17], which are required for viral genome replication and transcription. The other ORFs code for 4 structural proteins (spike, envelope, membrane, and nucleocapsid) and accessory proteins [14].

Similar to SARS-CoV, the cellular entry of SARS-CoV-2 depends on the binding of viral spike (s) proteins to the SARS-CoV receptor ACE2 (angiotensin converting enzyme 2) [18], and luteolin showed a binding ability to both viral protein and the ACE2 receptor. Yi et al. found that luteolin could bind to the S protein from SARS-CoV and prevent the virus from infecting Vero E6 cells (EC50 = 10.6 μM and CC50 = 155 μM), with significant antiviral activity [19]. Yu et al. found that luteolin may form 4H-bonds with residues GLN-965, SER-968, and ASN-969 of SARS-COV-2 S protein and π-cation interaction with residues PHE-970, but the binding energy is low [20]. Based on a relaxed complex scheme, Shadrack et al. found that luteolin strongly binds to the anchor residues TYR453, TYR505, and GLY496 of the virus, as well as residues HIS34, LYS353, ASP38, and GLN35 from the ACE2 receptor of the host cell, showing binding energy of about 36.82 KJ/mol [21]. Besides, Halil Ibrahim Guler found that luteolin can bind Tyr127, Ser128, Thr129, and other groups of ACE2 receptors with a binding energy of −7.29 kcal/mol [22].

3CLpro is also essential for virus replication. The 3CLpro inhibitor can inhibit the replication of SARS-CoV-2 in primary human airway epithelial cells cultured in vitro [23]. In the mouse model of MERS-CoV infection, the 3CLpro inhibitor increased the survival rate of mice, reduced the pulmonary virus titer, and alleviated lung tissue damage. Ran Yu screened the binding sites between luteolin and the crystal structure of 3CLpro by molecular docking technology; luteolin forms 5 hydrogen bonds with residues GLN-189, LEU-4, ASN-142, and THR-26 and forms hydrophobic interaction with MET-49 and VAL-3 [20]. Ryu et al. found that luteolin inhibited 3CL protein activity (IC50 = 20.2 μM) by using fluorescence resonance energy transfer (FRET) technology, which may be related to the C-3′-substituted hydroxy group of luteolin [24].

2.2. Respiratory Syncytial Virus. Saisai Wang found that luteolin significantly inhibited RSV replication in a dose-dependent manner in vitro. In mice, luteolin reduced the viral titer in the lungs and alleviated the pathological damage of lung tissues [25]. The anti-RSV effect of luteolin may be achieved by inducing the expression of miRNA-155 in host cells. The high expression of miRNA-155 can down-regulate the expression of SOCS1, which is a negative regulator of STAT1, and promote the upregulation of ISG expression to produce an anti-RSV effect [26]. Ooi et al. found that luteolin-7-O-glucoside inhibited the cytotoxicity of RSV in Hep-2 cells through cytopathic effect reduction assay and that its antiviral activity was equivalent to that of ribavirin [27]. It is worth noting that after using 3 kinds of 6-C-monoglycosides of luteolin to intervene Hep-2 cells, Ying Wang observed the same RSV inhibitory effect [28].

2.3. Influenza Virus. After influenza virus infection, the viral polymerase-RNA complex is transported to host cells and plays an important role in viral replication and transcription. Influenza RNA polymerase is a heterotrimeric enzyme, which contains three subunits: PA (polymerase acidic protein), PB1 (polymerase basic protein 1), and PB2 (polymerase basic protein 2) [29]. The virus cannot synthesize the 5′-mRNA cap, which is necessary for eukaryotic cell translation, and the primer needs to be obtained through the "cap sequencing" mechanism [30]. In this process, PB2 first binds 5′-cap (m7GTP) of host pre mRNA, then PA cleaves about 10–13 nucleotides downstream of 5′-cap as primers, and finally, PB1 uses this as a template for viral gene synthesis [31–33]. RNA-dependent RNA polymerase is highly conservative in all influenza virus strains, and the "cap sequencing" mechanism has been observed in all influenza viruses [34]. Therefore, drugs targeting RNA polymerase may be able to inhibit influenza virus replication.

A structural biology study found that luteolin and its C-glucoside orientin inhibit the PA N-terminal domain (PA-Nter) of influenza RNA-dependent RNA polymerase with endonuclease activity [35]. The most effective inhibitors are luteolin (IC50 = 73 ± 3 nM) and its 8-C-

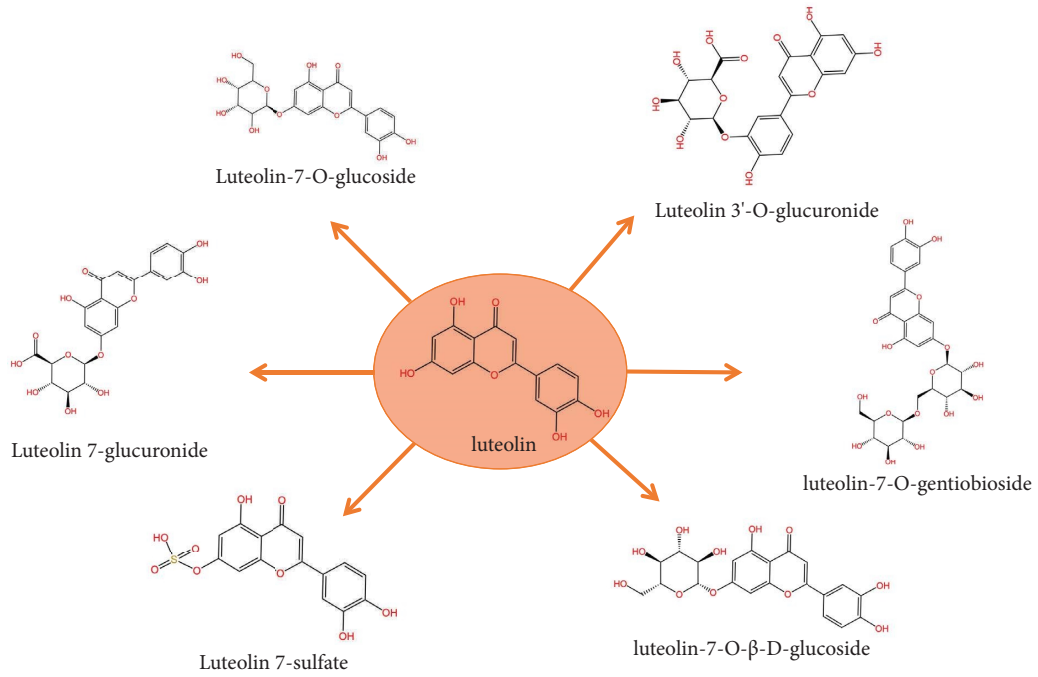

Figure 1: Luteolin and its derivatives.

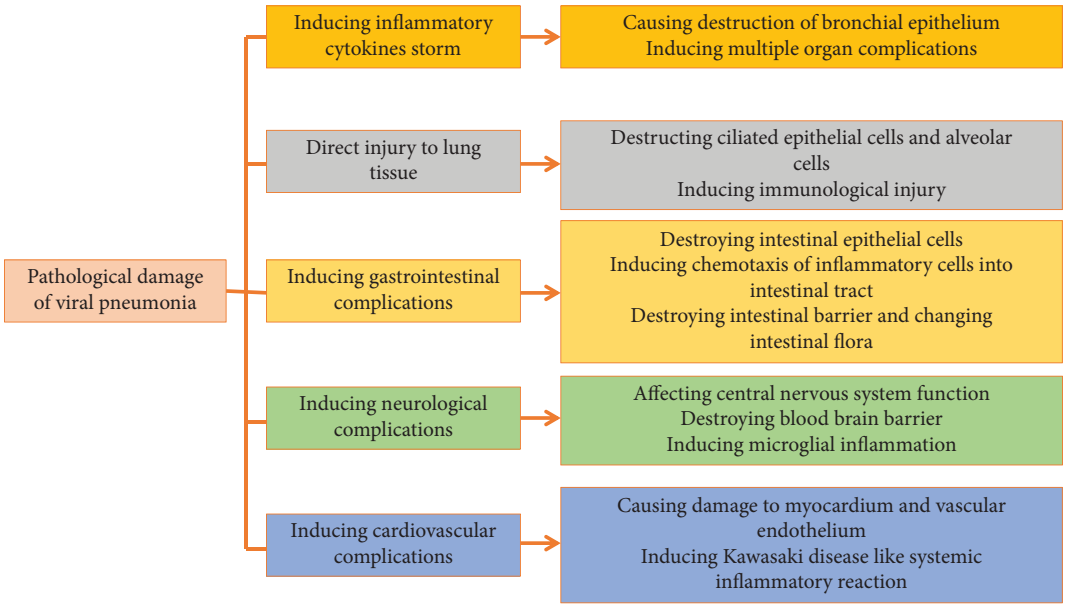

Figure 2: Pathological damage of viral pneumonia.

glucoside orientin (IC50 = 42 ± 2 nM) [35]. The endonuclease active site of PA-Nter is a negatively charged pocket, which is composed of His-41 and Lys-134 as well as a triad of acid residues and can combine with $Mg2^{+}$ or $Mn2^{+}$ ions [36, 37]. Through X-ray crystallography, Václav Zima found that 3′, 4′-dihydroxyphenyl moiety of luteolin can combine with the active site of endonuclease through coordination with manganese ion and form a strong hydrogen bonding network to eliminate the biological activity of endonuclease [37].

Influenza neuraminidase (NA) is also a key enzyme in the replication and transmission of the influenza virus. NA is a glycoprotein on the surface of influenza virus particles, which can recognize the carbohydrate structures and bind to the terminal sialic acid on the surface of host cells [38]. NA acts together with another key glycoprotein, hemagglutinin, to regulate the separation and binding of viruses and host cells and affect the movement of viruses in the respiratory tract [38]. A molecular docking study shows that luteolin can bind to the NA site of the influenza virus with a binding

energy of −7.1 Kcal/mol (binding energy of oseltamivir: −5.8 Kcal/mol) [39]. In-Kyoung Lee found that luteolin effectively inhibited the NA activity of H1N1, H3N2, and H5N1 influenza viruses in a dose-dependent manner, and CPE reduction assay results showed that luteolin reduced the cell injury of MDCK cells (Madin Darby cancer kidney cells) induced by influenza viruses [40].

In addition, Haiyan Yan infected multiple cell lines with two subtypes of influenza A virus and found that the replication of the virus can be inhibited by luteolin [40]. At the same time, luteolin can down-regulate viral endocytosis β-COP protein, which prevents the absorption and internalization of viruses [41]. Yu et al. found that luteolin, as an effective component of Moslea Herba flavonoids, can target NOX4 to inhibit the NF-κB/MLCK pathway to reduce the release of cytokines induced by influenza virus and the damage of pulmonary microvascular endothelial cells and protect the pulmonary endothelial barrier [42].

3. Regulate Immune Response and Inhibit Inflammatory Cytokines Storm

Cytokine storm or cytokine release syndrome is a life-threatening systemic inflammatory syndrome characterized by elevated circulating cytokine levels and hyperactivity of immune cells, which can be induced by a variety of pathogens, cancers, autoimmune diseases, single-gene diseases, and so on [43]. Viral infection, including viral pneumonia, is one of the causes of cytokine storms. In patients with SARS-CoV-2 pneumonia, cytokine storms can cause serious complications, including acute respiratory distress syndrome, sepsis, and multiple organ failure, increasing the risk of death [44]. In viral pneumonia, cytokines are first produced by alveolar cells or activated endothelial cells due to virus replication in lung tissue cells [45, 46]. Subsequently, activated macrophages and dendritic cells trigger further immune responses and produce a large number of cytokines [47]. In viral pneumonia, mast cells are also an important source of cytokines [48].

3.1. Macrophage Signaling Pathways. Macrophages can not only phagocytose pathogens directly, induce other immune cells to release cytokines, and activate downstream immune responses but can also cause cytokine storms to damage normal tissues [49]. Evangelos J Giamerellos-Bourboulis observed 54 patients with SARS-CoV-2 pneumonia, 28 of whom had severe respiratory failure (SRF). All SRF patients showed macrophage activation syndrome accompanied by excessive release of TNF-α and IL-6 and substantial reduction of CD4 lymphocytes, CD19 lymphocytes, and natural killer (NK) cells [50]. The autopsy and pathological investigations of 2 deceased cases with COVID-19 showed that the S protein of COVID-19 could directly bind to the ACE2 receptor expressed by alveolar macrophages. The researchers also found that IL-6 in the blood of these 2 cases increased, indicating that abnormal activation of macrophages may exist among COVID-19 patients [25]. The influenza virus can also replicate efficiently in alveolar macrophages [51]. Upon influenza virus infection, macrophages can induce TNF related apoptosis inducing light (TRAIL) expression by releasing IFN-β, causing damage to alveolar epithelial cells [52].

Alveolar macrophages can interact with T cells to continuously drive persistent alveolar inflammation during virus infection [13]. Grant et al. collected bronchial lavage fluid from 88 patients with respiratory failure secondary to COVID-19 infection and found that there were a large number of $CD4^+$, $CD8^+$T cells, and monocytes in their alveoli [13]. Bulk and single-cell transcription profiling results showed that T cells secrete a large amount of IFN-γ and induce alveolar macrophages to release inflammatory cytokines [13].

Macrophages are extremely plastic and can be divided into classically activated (or inflammatory) macrophages (M1) and alternatively activated (or wound-healing) macrophages (M2) [53]. M1 macrophages promote inflammation, while M2 macrophages repair damaged tissues [54]. The M1/M2 macrophage balance is often destroyed in severe infection [54].

Luteolin can regulate macrophage polarization. Luteolin can inhibit the production of reactive oxygen species in RAW264.7 murine macrophage cells stimulated by lipopolysaccharide (LPS), reduce the activation of the NLRP3 inflammasome complex, and promote the polarization of macrophages from M1 into M2 [55]. Shuxia Wang also observed the same phenomenon: luteolin prevented LPS-induced polarization of RAW264.7 cells towards M1 and reduced IL-6 and TNF-α by down-regulating p-STAT3 and up-regulating p-STAT6 [56]. Xiumei Chen isolated macrophages from the peripheral blood of BALB/c mice and found that luteolin promotes macrophage M2 polarization by up-regulating the expression of arginase and mannose receptor C type 1 [57].

In addition, luteolin can reduce the aggregation and activation of macrophages in white adipose tissue of obese mice induced by a high-fat diet and alleviate chronic inflammatory reactions [58]. Luteolin can also reduce the activity of mouse macrophage ANA-1 cells in vitro and induce apoptosis and autophagy of ANA-1 cells by activating Akt and MAPK signaling pathways [59].

3.2. Mast Cell Pathway. Mast cells (MCs) can participate in a variety of severe inflammatory syndromes including severe COVID-19 pneumonia by releasing mediators that promote inflammation, fibrosis, and thrombosis [48]. Mast cells are widely distributed throughout the body, especially on the mucosal surface. Upon viral invasion, mast cells first contact with pathogens and produce complex reactions [60], synthesizing and releasing histamine, tryptase, TNF, β-hex (β-hexosaminidase), IL-6, IL-8, CCL2 (chemokine ligand 2), and other inflammatory factors [61, 62].

Luteolin and its novel structural analog 3′, 4′, 5, 7-tetramethoxyluteolin can inhibit mast cell function [63]. In human cultured LAD2 mast cells stimulated by substance P (SP), degranulation was significantly inhibited by luteolin or methoxyluteolin, and the synthesis and release of

cytokines such as IL-1β and TNF were inhibited [64]. In human cord-blood-derived MCs stimulated by IgE/anti-IgE, the release of β-hex, histamine, TNF, and CCL2 was inhibited [63]. Luteolin and methoxyluteolin may inhibit the degranulation of mast cells by reducing intracellular calcium ions [65, 66] while inhibiting the release of inflammatory factors throughout the NF-κB signal pathway [63]. Luteolin and methlut can inhibit intranuclear phosphorylation of IκBα and the DNA-binding activity of NF-κB p65, while reducing the mRNA expression of NFKB1 and RELA and blocking NF-κB activation at both the gene and protein levels [63]. Luteolin or methoxyluteolin can inhibit IL-31, CCL2, and CCL5 released by IL-33 stimulated mast cells, while ERK, JNK, p38 MAPK, and NF-κB p65 activation are also inhibited [9, 67].

In addition, luteolin can inhibit mast cell activation stimulated by hormones or neuropeptides [68]. The corticotropin-releasing hormone can induce mast cells to express the IgE receptor, FcεRI. Luteolin can reduce the expression of the IgE receptor and inhibit the ability of mast cells to release the vascular endothelial growth factor (VEGF) when stimulated by IgE/anti-IgE [68]. Mast cells can produce inflammatory mediators TNF, CXCL8, and VEGF in response to neuropeptide stimulation; this phenomenon can be inhibited by luteolin by preventing mTOR activation [69]. Luteolin can also inhibit the interaction between mast cells and T cells [70]. Compared with incubation alone, Jurkat cells activated by anti-CD3/anti-CD28 increase IL-2 release by 30-fold when incubated with mast cells, and luteolin can inhibit not only myelin basic protein-induced human mast cell activation but also mast cell-dependent stimulation of Jurkat T cells [70].

4. Attenuate Pulmonary Inflammation

Respiratory viruses can target ciliated epithelial cells, alveolar cells, or lung immune cells to directly cause lung tissue damage, and they can also destroy the balance between the elimination of viruses and the protection of normal tissues in the immune system, thus mediating immune damage [45]. CT findings indicate that the characteristics of viral pneumonia include consolidation or ground-glass infiltrates of lung tissue, necrosis and exfoliation of bronchial epithelium, thickening of the bronchial wall, alveolar edema, and fibrin exudation, and so on [71, 72]. Luteolin not only directly inhibits viruses and prevents cytokine storms but also has extensive protective and immune regulatory effects on lung tissues.

In animal models, luteolin has protective effects on acute lung injury induced by surgery [73–75], drugs (bleomycin) [76],and small molecular substances such as LPS, mercuric chloride, or cadmium [10, 77–79].

Sepsis can be induced by pathogens that invade the circulation and produce systemic inflammatory response syndrome, which can affect almost all organs. Luteolin can reduce inflammatory factors IL-6, IL-1α, IL-1β, IL-6, IL-17A, and TNF-α in lung tissue of sepsis mouse models, reduce the damage of lung tissue [73–75], mitigate oxidative stress [73, 75], and prevent cell apoptosis [75]. It is worth noting that the protective effect of luteolin may be achieved by regulating the differentiation of helper T cells. Luteolin contributes to the expression of $CD4^+CD25^+FOXP3^+$ Tregs and the release of IL-10 and induces macrophages to polarize toward M2 [74]. If Treg cells are depleted, the lung tissue protective effect of luteolin will disappear, while the use of antibodies combined with IL-10 will aggravate cell pyroptosis [75].

LPS is the main component of the cell wall of gram-negative bacteria, which can be recognized by pattern recognition receptors and trigger a series of immune reactions, hence causing lung damage. Luteolin can diminish lung inflammation induced by LSP and reduce the release of inflammatory factors such as TNF-α, IL-6, IL-1β, iNOS, and COX-2 [80–82]. At the same time, luteolin can alleviate pulmonary edema by reducing vascular injury and neutrophil infiltration [78, 81] and decreasing apoptosis of bronchial epithelial cells [82]. Luteolin blocks the NF-κB pathway to exert protection on lung tissue stimulated by LPS. Luteolin can inhibit NF-κB DNA-binding activity in macrophages and block IκB degradation and nuclear accumulation of the NF-κB P65 subunit [80]. Besides, luteolin can also reduce the activation of neutrophils by blocking the PI3K/Akt pathway [78, 81].

Last but not least, luteolin can also reduce bleomycin-induced lung injury and pulmonary fibrosis, prevent alveolar epithelial cells from transforming into mesenchymal cells with a myofibroblast-like phenotype, and inhibit fibroblast proliferation [76]. By up-regulating Nrf2 and down-regulating NF-κB, luteolin alleviates lung injury caused by mercury chloride or cadmium [10, 79]. Luteolin can induce helper T cells to differentiate into $CD4^+CD25^+FOXP3^+$ Tregs and promote the release of IL-10, which also exists in OVA-sensitized asthma mouse models [83]. At the same time, luteolin can also attenuate airway allergic inflammation, reduce mucus hypersecretion in the airway, and reduce goblet cell hyperplasia and collagen deposition [84, 85]. The direct protective effect of luteolin on lung tissue is shown in Table 1.

5. Control Systemic Complications

5.1. Gastrointestinal Complications. Gastrointestinal symptoms are the most common complications of viral infection. Existing epidemiological studies show that the highest proportion of COVID-19-infected patients with diarrhea and anorexia symptoms is 49.5% and 26.8%, respectively [86, 87]. Xiao et al. analyzed 73 hospitalized COVID-19 pneumonia patients and found that 39 patients (53.42%) had positive RT-PCR results for COVID-19 in their feces, and 17 patients (23.29%) continued to have positive results in feces after showing negative results in respiratory samples [88]. The positive staining of ACE2 and COVID-19 could also be observed in the gastrointestinal epithelium of these patients [88]. Qian et al. found that RNA and virus particles appeared in surgically-resected rectal specimens of COVID-19-infected patients, accompanied by the infiltration of a large number of lymphocytes and macrophages [89]. Besides, virus RNA can also be detected in the feces of influenza virus-infected individuals [90].

Table 1: Luteolin can directly reduce lung tissue damage.

Signal pathways involved in the effect of luteolin	Pharmacological effects of luteolin	Reference
Unclear	Reducing the infiltration of neutrophils in bronchial lavage fluid, alleviating bleomycin-induced lung injury and pulmonary fibrosis, preventing alveolar epithelial cells from transforming into mesenchymal cells with a myofibroblast-like phenotype, and inhibiting fibroblast proliferation	[76]
Inhibiting the gamma-aminobutyric acid pathway	Reducing the excessive secretion of airway mucus and goblet cell proliferation induced by OVA and reducing the release of IL-4/5/13	[84]
Inhibiting MEK/ERK and PI3K/Akt pathways	Alleviating lipopolysaccharide-induced lung injury and reducing the increase of vascular permeability and neutrophil exudation	[78]
Inhibiting the NF-κB pathway and the iNOS pathway	Alleviating pulmonary edema and protein exudation, reducing IL-6 and IL-1β and TNF-α in lung tissue, and reducing adhesion molecule ICAM-1	[73]
Activating the AKT/Nrf2 pathway and inhibiting NF-κB active	Reducing the oxidative stress in cells, reducing the release of inflammatory factors, reducing the activation of neutrophils, reducing the pathological changes of lung tissues, and reducing cell apoptosis	[79]
Activating the AKT pathway and inhibiting NF-κB active	Reducing lung tissue damage, reducing pulmonary edema and permeability, and reducing the production of inflammatory factors such as TNF-α, IL-6 iNOS, and COX-2	[81]
Inhibiting the MAPK/NF-κB pathway	Reducing lung tissue lesions (hemorrhage, interstitial edema, and polymorphous neutrophil infiltration), improving lung function, reducing lung tissue oxidative damage and lipid peroxidation, and reducing the secretion of inflammatory factors	[77]
Down-regulating the expression of microRNA-132 to reduce NF-κB activation	Reducing the apoptosis of human bronchial epithelial cells and the expression of inflammatory factors, IL-1β, IL-6, and TNF-α, and increasing cell activity	[82]
Activating the AKT/Nrf2 pathway	Inhibiting the damage of bronchial epithelial cells caused by cadmium, reducing cell apoptosis, and reducing the level of intracellular oxidative stress	[10]
Unclear	Inhibiting the airway inflammation induced by OVA, reducing the levels of IL-4, IL-5, IL-13, and eosinophil chemokines, and increasing IL-10, IFN-γ, and TGF-β1	[83]
Unclear	Reducing lung inflammatory damage and down-regulating IL-17A, MPO, and NF-κB, up-regulating the level of IL-10 in serum and bronchoalveolar lavage fluid, up-regulating M2 macrophages, and down-regulating M1 macrophages	[74]
Activating the PI3K/Akt/mTOR pathway	Inhibiting OVA-induced airway inflammation, reducing cell autophagy, reducing inflammatory factors IL-4/5/13 and IgE, and reducing the number of inflammatory cells and collagen deposition	[85]
Unclear	Inducing T cells to differentiate into Treg cells, reducing cell pyroptosis, and reducing the levels of IL-6, TNF-α, IL-17A, IL-1α, IL-1β, and intracellular oxidative stress	[75]
Unclear	Reducing the inflammatory response of alveolar macrophages induced by LPS and inhibiting the expression of TNF-α, IL-6, iNOS, and COX-2 at the transcriptional level	[80]

In addition to directly binding to intestinal cells [91], viruses can also induce the migration of inflammatory cells, causing intestinal immune damage [92]. After influenza virus infection, lung-derived $CD4^+$T cells will enter the small intestine mediated by chemokines, CCL25 and CCR9, work together with the gut microbiota to promote the polarization of Th17 cells, and cause immune damage [92].

Respiratory viruses can also damage the barrier function of the intestinal tract, alter the microbiota of the gastrointestinal tract, and affect its function [93, 94]. The expression of genes involved in the construction of the intestinal barrier in influenza A virus-infected mice was significantly down-regulated, while the expression of inflammation-related genes in the liver was significantly up-regulated [95]. In patients with high infectivity of COVID-19, the gut microbiota is characterized by loss of salutary bacteria and increased functional capacity for nucleotide, amino acid biosynthesis, and carbohydrate metabolism [94]. The damage to gut microbiota caused by viruses will weaken the pulmonary immune function, resulting in double-infection of respiratory viruses and bacteria [96].

Luteolin can alleviate intestinal inflammation through multiple pathways. In the intestinal inflammation mouse model induced by dextran sulfate sodium (DSS), luteolin reduces the release of inflammatory factors and alleviates inflammatory damage through down-regulating NF-κB [97]. By up-regulating PPAR-γ, luteolin can increase the transporter OCTN2 and reduce cytokines IL-1β and IL-6 to alleviate intestinal inflammation [98]. Luteolin can activate the Nrf2/HO-1/NQO1 pathway, reduce inflammatory factors such as iNOS, MDA, TNF-α, and IL-6, increase the activities of catalase and superoxide dismutase, and reduce oxidative damage [99, 100]. Apart from that, luteolin can also activate the ERK1/2 pathway, reduce the apoptosis and autophagy of intestinal epithelial cells induced by inflammation, and promote crypt cell proliferation [101].

Luteolin can protect intestinal barrier function. Through the SHP-1/STAT3 pathway, luteolin can reverse TNF-α and IFN-γ induced increase in permeability of Caco-2 cells and increase tight junction proteins such as OCLN, CLDN1, and ZO1 [102]. The protective effect of luteolin on intestinal barrier function is also reflected in the rat model of the nonalcoholic fatty liver. Luteolin maintains the integrity of intestinal barrier function by increasing the level of intestinal tight junction protein [103, 104]. At the same time, luteolin reduces liver steatosis by inhibiting the TLR4/NF-κB signal pathway, reduces IL-1β, IL-6, and TNF-α in the liver, and reduces liver inflammatory damage [103].

The inhibitory effect of luteolin on intestinal inflammation and the protective function of the intestinal barrier is beneficial to the regulation of gut microbiota under inflammatory conditions. The KEGG enrichment analysis of intestinal inflammation and gut microbiomes after luteolin administration showed that the affected gut microbiomes were related to DNA repair, protein recombination, purine, pyrimidine, ribosome, and peptidase metabolism [97]. Luteolin can regulate the relative abundance of certain microbiota in the model of metabolic disorder and non-alcoholic fatty liver induced by a high-fat diet. At the level of phylum, firmicutes and bacteroides predominate in the intestine, and the ratio of Firmicutes and Bacteroides (F/B) will increase in rats on a high-fat diet [103]. Luteolin can down-regulate F/B [12, 103] at the level of genus, and luteolin increases the relative abundance of Lactobacillus, Bifidobacterium, Desulfovibrio, Parvibacter, Faecalitaleq, and Allobaculum [103, 104]. At the level of the family, luteolin increases the abundance of Lachnospiraceae, Helicobacteraceae, Marinifilaceae, and Peptococcaceae [12]. The gastrointestinal protective effect of luteolin is shown in Table 2.

5.2. Neurological Complications. Nervous system damage is an insidious and dangerous complication of viral pneumonia. Before the COVID-19 pandemic, the outbreak of influenza A (H1N1) in 2009 gave us a glimpse of the neurological complications of viral infection. Compared with common influenza, H1N1 influenza causes more serious damage to the nervous system [106]. There are reports of severe neurological complications leading to disability and death worldwide [107].

The nervous system may be affected in the early stage of COVID-19 infection. A study of 417 mild or moderate COVID-19 pneumonia patients from 12 hospitals showed that 85.6% and 88.0% of the patients had olfactory and taste disorders, respectively, and there was a significant correlation between these two symptoms [108]. A retrospective study of 214 patients with COVID-19 showed that 78 patients (36.4%) had neurological symptoms, and those with severe infection had a higher proportion suffering severe neurological diseases such as acute cerebrovascular diseases, disturbance of consciousness, and seizures [109]. Notably, children with viral infections are more likely to suffer from serious neurological complications [110]. A retrospective study showed that 7.5% of children (23 in 307) infected with H1N1 influenza will suffer from nervous system complications, 65% of these children will require intensive care monitoring, and 13% will die as a result [111]. During the H1N1 influenza pandemic in Texas from 2009 to 2010, about 2/3 of the children with central nervous system complications required admission to intensive care, and about half of them required mechanical ventilation [112].

Viruses can damage the nervous system in multiple ways. Viruses may enter the central nervous system from peripheral organs through the peripheral nervous system or directly enter the central nervous system from the olfactory nerve or nasal mucosa epithelium through the intranasal route [113]. SARS-CoV antigen and RNA can be found in the brain neurons of patients who died from SARS [114]. Xu et al. isolated the SARS coronavirus strain from the brain tissue specimens of SARS patients with severe central nervous system symptoms [115]. Moreover, the lungs of mice infected with MERS-CoV were shown to contain MERS titers and RNA four days after infection [116].

Virus infection can damage blood brain barrier function (BBB). A cohort study of 102 COVID-19 patients showed that 24 (23.5%) patients had severe neurological involvement [117] including cerebral ischemia, intracerebral

Table 2: Luteolin can reduce gastrointestinal complications.

Signal pathways involved in the effect of luteolin	Pharmacological effects of luteolin	Reference
Unclear	Reducing IL-17 and IL-23 in the intestinal tract, increasing PPAR-γ, and adjusting intestinal flora	[97]
Inhibiting the SHP-1/STAT3 pathway	Reducing intestinal cell permeability, increasing tight junction proteins such as OCLN, CLDN1, and ZO1, reducing CLDN2, and relieving symptoms of ulcerative colitis	[102]
Unclear	Reducing liver steatosis and inflammatory damage, maintaining the integrity of intestinal mucosa, reducing intestinal permeability, up-regulating tight junction proteins such as OCLN, CLDN1, and ZO1, and increasing the diversity of intestinal flora	[103]
Inhibiting the TLR4/NF-κB pathway	Improving liver fat accumulation and inflammation, adjusting intestinal flora, reducing intestinal permeability, and reducing plasma LPS	[104]
Activating the Nrf2 pathway	Reducing intestinal iNOS, TNF-α, and IL-6 levels and reducing oxidative damage in the colon	[105]
Inhibiting the NF-κB pathway	Alleviating intestinal damage and down-regulating SOD, MPO, MDA, PGE2, TNF-α, IL-1β, and CRP	[100]
Inhibiting the PPAR-γ/RXRα pathway	Reducing intestinal damage and the levels of IL-1β and IL-6, and increasing the level of OCTN2 in the colon	[98]
Activating the ERK1/2 pathway	Reducing intestinal TNF-α and COX-2 expression, reducing autophagy and apoptosis of intestinal epithelial cells, and promoting the proliferation of crypt cells	[101]

hemorrhage, seizures, and encephalitis, of which 8 severe patients had BBB injury with elevated cytokines such as IL-6, IL-8, and TNF-α in cerebrospinal fluid [117].

Additionally, the immune response caused by the virus is also an important cause of neurological complications. The degranulation of mast cells can occur in the dura matter [118, 119]. Once mast cells are activated in brain tissue, microglia will also be activated, thus releasing a large number of cytokines [120], which indicates that mast cell-mediated inflammatory storms may occur in the brain [121]. In cerebrospinal fluid and serum samples of 2 children who died of an influenza-related acute encephalopathy, IL-6 and TNF-α significantly increased [122]. One case also had vasogenic cerebral edema and systemic vasculopathy, indicating immune damage to vascular endothelium [122].

Luteolin has extensive protective effects on the nervous system. A randomized controlled trial showed that palmitoylethanolamide combined with luteolin can improve the olfactory impairment of COVID-19 patients and promote the recovery of olfactory, which was more effective in patients with long-term olfactory dysfunction [123].

Luteolin can inhibit the activation of microglia and reduce the neuroinflammation induced by microglia. In the rat model of acute intracerebral hemorrhage, luteolin reverses the TLR4/TRAF6/NF-κB signal pathway by inhibiting the ubiquitination of TRAF6 and blocking NF-κB p65 nuclear translocation, thereby reducing inflammatory factors IL-6, IL-1β, and TNF-α to protect neurons [124]. In another study, luteolin alleviated LSP-induced inflammation of BV2 microglia and inhibited the release of inflammatory factors such as TNF-α and IL-1β in the hippocampus and cerebral cortex of mice [125]. In the rat model of chronic cerebral hypoperfusion (CCH), luteolin inhibits the hyperactivation of microglia, reduces the number of astrocytes in the hippocampus and cerebral cortex, and reduces the mRNA and protein levels of TNF-α, IL-1β, and IL-6 [126]. At the same time, luteolin also improved CCH-induced learning, memory impairments, and white matter injury and increased presynaptic transmitter release in rats [126].

Luteolin has a protective effect on BBB. Zhang used coculturing human brain microvascular endothelial cells (hBMECs) and human astrocytes (hAs) to build a BBB model in vitro and found that luteolin can protect vascular endothelial function under fAβ1–40 stimulation, maintain BBB function, and reduce inflammatory factors such as COX-2, TNF-α, IL-6, IL-8, and IL-1β [127].

Luteolin can effectively alleviate oxidative damage to the nervous system. Luteolin decreases the inflammatory and oxidative stress damage in the spinal cord of spinal cord ischemia-reperfusion injury (SCII) rats [11]. At the same time, luteolin reduces the level of MDA, XO, and other oxides, improves the activities of antioxidant enzymes SOD and GSH-Px, and protects mitochondrial function [11]. The protective effect of luteolin on spinal neurons involves the upregulation of Nrf2 and down-regulation of NLRP3 [128]. In the model of secondary brain injury (SBI) after intracerebral hemorrhage, luteolin can increase the nuclear displacement of Nrf2, inhibit the ubiquitination of Nrf2, activate the p62-Keap1-Nrf2 pathway, increase the levels of antioxidant proteins such as HO-1, NADPH, and NQO1, and reduce the production of superoxide in neurons [129]. The neuroprotective effect of luteolin is shown in Table 3.

5.3. Cardiovascular Complications. Cardiovascular complications are also important extrapulmonary manifestations of severe pneumonia. Pneumonia patients may have a series of cardiovascular complications, including the decreased function of the left ventricle, myocardial injury, arrhythmia, and vascular endothelial lesions [130]. Once cardiovascular complications occur in patients admitted for community-acquired pneumonia, the short-term or long-term risk of

Table 3: Neuroprotective effects of luteolin.

Signal pathways involved in the effect of luteolin	Pharmacological effects of luteolin	Reference
Inhibiting the TLR4/TRAF6/NF-κB pathway	Preventing microglia activation, reducing the release of inflammatory factors such as IL-1β, IL-6, and TNF-α, and alleviating stress-induced cerebral inflammation	[124]
Unclear	Improving the olfactory disorder	[123]
Inhibiting the p38MAPK pathway	Reducing the production of COX-2, TNF-α, IL-1β, IL-6, and IL-8, maintaining the trans-endothelial electric resistance, and protecting the blood brain barrier	[127]
Activating the Nrf2 pathway and inhibiting the NLRP3 pathway	Increasing the survival of neurons after spinal surgery, inhibiting cell apoptosis, reducing intracellular reactive oxidative species such as MDA and XO, and enhancing the activity of antioxidant enzymes such as GSH and SOD	[128]
Activating the p62/Keap1/Nrf2 pathway	Inhibiting the production of superoxide in neurons and increasing the levels of downstream antioxidant proteins such as HO-1, NADPH, and NQO1	[129]
Activating the Nrf2/GCLc/GCLm pathway	Down-regulating inflammatory factors such as TNF-α and IL-1β, inhibiting cell apoptosis, reducing intracellular reactive oxidative species such as MDA and XO, and enhancing the activity of antioxidant enzymes such as GSH and SOD	[11]
Unclear	Reducing neuronal damage and inflammatory reaction in the hippocampus and cortex and reducing the level of inflammatory mediators such as NO, TNF-α, and IL-1β	[125]
Unclear	Preventing the release of inflammatory factors induced by chronic cerebral hypoperfusion, improving the activities of antioxidant enzymes such as SOD and GSH, inhibiting the over-activation of microglia and astrocyte proliferation, and improving learning and short-term memory dysfunction	[126]

death increases [131, 132]. Many pathogens of viral pneumonia, including influenza virus, respiratory syncytial virus, and adenovirus, can also cause myocarditis [130, 133, 134]. In COVID-19 pneumonia patients, the incidence of myocardial injury characterized by elevated cardiac troponin I varies from 7.2% to 27.8% [135]. Compared with the surviving patients, patients who died from COVID-19 had a higher probability of cardiovascular diseases [136].

The respiratory virus can directly infect the myocardium or cause myocardial injury through an immune response. Guido Tavazzi performed a myocardial biopsy on a COVID-19 patient with acute myocardial injury and found viral particles in the endocardium [137]. Chonyang L Albert found viral RNA in the myocardium of another COVID-19 patient with cardiogenic shock, making it clear that COVID-19 can infect the myocardium [138].

In the autopsy of patients who died from COVID-19, researchers found that endothelial inflammation and small vessel lesions in the lungs and other organs were one of the main characteristics of pathological damage [139, 140], often accompanied by thrombosis and inflammatory cell infiltration [139, 141]. Valentina O. Puntmann conducted a cardiac magnetic resonance study on 100 patients who had recently recovered from COVID-19. 78% of the patients had abnormal results, and 60% had ongoing myocardial inflammation, which was characterized by active lymphocyte inflammation [142]. In addition, COVID-19 infection can also induce Kawasaki-like systemic inflammatory syndrome in children, which is characterized by conjunctivitis, hand-foot edema, lymphopenia, thrombocytopenia, and complement consumption [143].

Luteolin has been identified to provide cardioprotective effects [144]. In the mouse model of myocardial ischemia-reperfusion (IR), luteolin can up-regulate the expression of Bcl-2, reduce the ratio of Bax to Bcl-2, reduce cardiomyocyte apoptosis, and reduce the infarct size [145–148]. By down-regulating TLR4, NLRP3, MyD88, and NF-κB-related receptors, luteolin can reduce the levels of AST, CK-MB, and LDH in the serum of myocardial IR rats, reduce myocardial damage, and inhibit the secretion of IL-1β, IL-18, and TNF-α by H9c2 cells in vitro [149]. By inhibiting p38 MAPK and NF-κB pathway activation, luteolin can reduce the levels of LDH, MDA, and ROS in cardiomyocytes, increase the activity of superoxide dismutase (SOD), stabilize the mitochondrial membrane potential [150], and reduce IR myocardial oxidative damage [150, 151].

Luteolin can also enhance myocardial contractility. Luteolin can promote the expression of SERCA2a through multiple pathways [152–155], thus promoting calcium ion transport, enhancing myocardial contractility, and improving left ventricular function [152–154].

Last but not least, luteolin also has a protective effect on vascular endothelium. Luteolin can significantly inhibit TNF-α induced adhesion of monocytes to EA. Hy 926 cells, and inhibits the secretion of MCP-1, ICAM-1, and VCAM-1 in vitro [34, 156]. Fan Xia pretreated human umbilical vein endothelial cells with luteolin and found that TNF-α-induced oxidative damage was alleviated and intracellular ROS, as well as the expression of Nox4, p22phox, ICAM-1, and VCAM-1, were down-regulated [157]. Using luteolin-7-O-glucoside to intervene in endothelial cells in vitro can inhibit endothelial cell proliferation and reduce the expression of inflammation-related genes [158]. Analysis of cell metabolites showed that cholesterol-hydroxylated substances in endothelial cells were significantly reduced after luteolin-7-O-glucoside treatment [158]. The cardiovascular protective effect of luteolin is shown in Table 4.

6. Absorption and Metabolism of Luteolin

6.1. Absorption of Luteolin. Luteolin usually appears as glycosylated protein forms [159], and absorption of luteolin requires transportation across the intestinal epithelial barrier, whether from vegetables, fruits, or herbal water solvents. The small intestine is the main site for the absorption of flavonoid glucosides, and beta-glucosidases-mediated deglycosylation is the key to absorption [159]. Kayoko Shimoi studied the absorption of luteolin and luteolin 7-O-β-glucoside in rats and human intestines [160]. The results of the everted intestine absorption experiment in rats showed that luteolin 7-O-β-glucoside was difficult to pass through the bowel wall and was barely detectable in rat plasma, so Kayoko Shimoi speculated that luteolin glycosides need to be deglycosylated to aglycones by gut microbiota before being absorbed [160]. On the other hand, using LC/MS analysis, Kayoko Shimoi detected free luteolin and monoglucuronide of unchangeable luteolin in the plasma of rats taking luteolin orally and obtained the same results in humans [160]. This suggests that monoglucuronide may be the main metabolite of luteolin and may be related to the antioxidant activity of the hydroxyl group of luteolin on 3′-, 4′-, 5-, and 7-positions [160].

Intravenous injection can ensure that luteolin glycosides enter the circulation. Ran Yin studied the pharmacokinetics of three luteolin glycosides in beagle dogs [161], The calibration curves of luteolin-7-O-gentiobioside, luteolin-7-O-β-D-glucoside, and luteolin-7-O-β-D-glucuronide show good linearity in the concentration ranges of 1.0–250 ng/ml, 1.0–250 ng/ml, and 4.0–1000 ng/ml, respectively [161]. The extraction recoveries of all luteolin glycosides in blood were over 75% [161]. The blood drug concentrations of three luteolin decreased rapidly after intravenous administration, and the average half-elimination time was between 1.10 h and 1.33 h [161].

Wittermer et al. studied the metabolic process of artichoke leaf extract containing luteolin-7-O-glucoside in the human body [162]. Researchers gave 14 healthy volunteers two different extracts containing luteolin glycosides equivalent to 14.4 or 35.2 mg of luteolin, respectively. After taking the two extracts, luteolin-7-O-glucoside could not be detected in the plasma and urine samples of volunteers. Analysis of blood and urine by HPLC showed that luteolin administered orally in the form of glucoside would exist in the body as sulfate or glucuronide after metabolism [162]. The peak plasma concentration of the two groups of volunteers appeared 30–40 minutes after administration (59.08 and 156.58 ng/mL), and its elimination half-life was 2-3 h [162]. The rapid absorption of luteolin indicates that its

Table 4: Cardiovascular protective effects of luteolin.

Signal pathways involved in the effect of luteolin	Pharmacological effects of luteolin	Reference
Inhibiting the IKK/IκBα/NF-κB pathway	Suppressing TNF-α mediated vascular inflammation and the expression of MCP-1, ICAM-1, and VCAM-1	[156]
Inhibiting the JAK/STAT3 pathway	Promoting endothelial differentiation and proliferation, widely reducing the expression of inflammatory factors, and reducing the accumulation of ROS-related cholesterol-hydroxylated substances	[158]
Unclear	Modulating SERCA2a via Sp1 upregulation to attenuate myocardial ischemia	[153]
Activating the ERK/PP1a/PLB/SERCA2a pathway	Enhancing the contractile function of myocardial cells, reducing the infarct size, reducing the release of lactate dehydrogenase, and reducing cell apoptosis	[154]
Activating the PI3K/Akt pathway	Improving the level of SERCA2a and ATPase activity, reducing apoptosis, and enhancing heart function as well as reducing fibrosis of the heart muscle in the heart failure model	[152]
Unclear	Alleviating ischemia-reperfusion injury, reducing cell apoptosis, and improving cardiac function	[148]
Inhibiting the p38MAPK pathway	Increasing the contractile function of myocardial cells, reducing cell apoptosis, and promoting the excitation-contraction coupling of myocardial cells	[155]
Inhibiting the p38MAPK pathway	Reducing the level of cellular oxidative stress, promoting the recovery of myocardial cells, reducing the level of LDH, enhancing the activity of antioxidant enzymes such as SOD, and reducing the production of ROS and MDA in cells	[150]
Activating the PI3K/Akt pathway	Restoring heart function, reducing infarct size, reducing the lactate LDH level, and reducing the cell apoptosis rate	[146]
Inhibiting the SHP-1/STAT3 pathway	Reducing the myocardial infarction area, increasing left ventricular ejection fraction, reducing cell death and serum proinflammatory cytokines, and reducing inflammatory reaction	[147]
Inhibiting the p38MAPK/NF-κB pathway	Inhibiting the level of intracellular oxidative stress, reducing the increase of the intracellular calcium level caused by oxidative stress, protecting mitochondrial function, and reducing apoptosis	[151]
Inhibiting Nox4/ROS-NF-κB and p38MAPK pathways	Reducing TNF-α induced oxidative stress and inflammation	[157]
Unclear	Suppressing the adhesion of monocytes to vascular endothelial cells mediated by TNF-α, reducing the release of VCAM-1 and MCP-1, and reducing aortic inflammation	[33]
Unclear	Reducing the expression level of miR-208b-3p and myocardial cell apoptosis after myocardial ischemia-reperfusion injury	[145]
Inhibiting the TLR4/NF-κB/NLRP3 pathway	Alleviating myocardial ischemia/reperfusion injury, reducing the release of inflammatory factors, and improving cardiac function	[149]

absorption site may be in the upper digestive tract, and the short elimination half-life indicates that luteolin may be rapidly metabolized once in circulation.

Zhou et al. found that the effective permeability and the absorption rate constant of pure luteolin (5.0 microg/mL) in the duodenum and jejunum of rats were significantly higher than those in the colon and ileum [163]. It is worth noting that the peak concentration and the area under the curve of luteolin in the form of peanut shell extract in rat plasma are significantly higher than those of pure luteolin, suggesting that the bioavailability of luteolin in the form of peanut shell extract is significantly higher than that of pure luteolin [163].

Compared with luteolin aglycone and luteolin-7-O-glucoside in pure solution, luteolin in the form of a plant extract is more easily absorbed by intestinal epithelial Caco-2 cells [164]. Mukinda et al. incubated intestinal epithelial Caco-2 cells with luteolin aglycone, luteolin-7-O-glucoside, and unhydrolyzed or acid-hydrolyzed Artemisia afra extracts and collected samples on the basolateral and apical sides of Caco-2 cells for HPLC and LC-MS analyses [164]. The results showed that the apical-to-basolateral permeability coefficients of luteolin and luteolin-7-O-glucoside in the extract were 1.6–2 times higher than those of the nonplant solution. At the same time, researchers also found that glucuronidation is an important form of luteolin absorption [164].

Michiko Torii Yasuda studied the absorption and metabolism of luteolin and its glycosides in chrysanthemum extract in rats and Caco-2 cells. After oral administration of chrysanthemum extract (equivalent to luteolin 22.8 μmol/kg and luteolin-7-O-glucoside 58.3 μmol/kg), luteolin, luteolin monoglucoside, and luteolin monoglucuronide can be quickly measured in the blood of rats. The plasma concentration of luteolin reached the first peak after 1 hour and the second peak after 6 hours [165]. The reason for the second peak may be that luteolin glycosides are converted to aglycones in the intestine after enterohepatic circulation; its aglycone is metabolized into conjugates and absorbed [165]. On the other hand, after the administration of chrysanthemum extract on the apical side of cells, luteolin was also rapidly detected in the basolateral side of Caco-2 cells [165].

6.2. Metabolism of Luteolin. The first step of flavonoid metabolism in the human body is the hydrolysis of flavonoid glycosides mediated by lactase pyrorizin hydrolase (LPH) and human intestinal flora. After intestinal absorption and transportation by the portal system, phase II metabolic enzymes including UDP-glucuronosyltransfers (UGTs), catechol-O-methyltransferases (COMTs), and sulfotransferases (SULTs) dominate the metabolism of flavonoids [166], and cytochrome P450 enzyme mediated phase I metabolism has little effect on luteolin metabolism [167]. It is because of the first-pass metabolism mediated by phase II enzymes that the bioavailability of luteolin is limited [168].

Glucuronidation is the main pathway of luteolin metabolism. Natsumi Hayasaka found that no matter what form of luteolin (extracted from green pepper leaves, including glycosides or aglycones) was given to rats, luteolin glucuronide could be measured in their plasma and organs [169]. If human beings take luteolin aglycone orally, the most abundant luteolin metabolite in plasma is luteolin-3′-O-sulfate, which indicates that there are differences in luteolin metabolism among species [169]. On the other hand, luteolin glucuronide can also be metabolized into aglycone by RAW264.7 cells in vitro [169].

UGTs-mediated glucuronylation may interact with COMTs-mediated methylation [170]. Liping Wang used rat liver S9 fractions to study the metabolism of luteolin in vitro and found two main metabolic pathways. (1) A part of luteolin is first methylated by COMTs to glutathione and diosgenin, and then glutathione and diosgenin are glucuronidated with the remaining luteolin by UGTs. (2) Luteolin is first catalyzed by UGTs to luteolin-7-glucuronide (Lut-7-G), Lut-4′-G, and Lut-3′-G, and some Lut-7-G is further methylated by COMTs [170]. The above results indicate that the metabolism of luteolin in the human body requires the joint effect of UGTs and COMTs. If the effect of COMTs is inhibited, the luteolin methylation products in plasma will be significantly reduced, while the other metabolite concentrations will increase [171].

After giving luteolin orally to rats, Changrui Deng collected plasma, urine, bile, feces, and multiple organ tissues for analysis, and the results show that luteolin-3′-O-β-D-glucuronide has the highest content in rat plasma and most tissues. Compared with other organs, luteolin and its metabolites have the highest content in the stomach, small intestine, and liver, followed by the lung and kidneys [172]. After oral administration of luteolin (20 μ mol/kg) 48 hours later, the cumulative recoveries of luteolin and its metabolites in bile, urine, and feces were 54.8%, 5.9%, and 5.8%, respectively. This indicates that bile excretion is the main metabolic pathway of luteolin taken orally [172].

6.3. Attempts to Improve the Bioavailability of Luteolin. As the first-pass metabolism mediated by phase II enzymes limits the bioavailability of luteolin, researchers have carried out relevant research to improve the efficiency of luteolin use.

One way to increase the application efficiency is to increase the solubility of luteolin, and lipid delivery technology is the most common choice [173]. Liu et al. prepared luteolin in the form of nanostructured lipid carriers and microemulsions. Compared with luteolin suspension, the bioavailability of luteolin in the form of nanostructured lipid carriers or microemulsions is higher than that of luteolin suspension in vivo and in vitro [174]. Wu et al. found that luteolin encapsulated with liposome has a better anti-CT26 colon cancer effect than free luteolin. Pharmacokinetics showed that the concentration of luteolin encapsulated in liposome in plasma was 10 times that of free luteolin two hours after injection [175]. Li et al. found that liposome-coated luteolin has stronger anti-A549 cancer cell abilities in vivo and in vitro than free luteolin and can remain in circulation for a longer time [99].

In addition to lipid encapsulation technology, Parichat Tawornchat synthesized polymerized luteolin nanoparticles by one-pot synthesis, which not only have a concentration-dependent anti-inflammatory activity but also have no cytotoxicity at high concentrations [176]. Yan et al. prepared luteolin-loaded long-circulating micelles, which not only have a long circulation time in vivo but also have a strong anticancer effect on A549 cells and mild cytotoxicity against normal cells [177]. Garbinato et al. used micronization technology to prepare the micronized luteolin, of which the average particle diameter is one-tenth that of wild luteolin, and the bioavailability in zebrafish is also higher than that of wild luteolin [178].

Besides, researchers have explored the possibility of transdermal administration of luteolin. Altamimi et al. prepared luteolin-loaded cationic nanoemulsions, which can enhance the transdermal ability of luteolin and increase the local drug concentration [179]. Luteolin-loaded elastic liposomes can also penetrate the skin and are compared with the luteolin standard. Luteolin-loaded elastic liposomes showed much more obvious growth inhibition on human breast cancer cells (MCF-7) in vitro [180]. Luteolin micelles can not only penetrate the skin more easily but also penetrate the BBB efficiently. In the rat model of cerebral IR injury, luteolin micelles are more prone to accumulate in damaged brain tissue [181].

7. Conclusion

Luteolin has great potential to improve the treatment of viral pneumonia. Luteolin not only has a direct antiviral effect but also can reduce pulmonary inflammation and effectively prevent or treat multiple system complications. Luteolin exerts antiviral effects by inhibiting viral entry and replication. Moreover, luteolin can prevent the aberrant release of cytokines and prevent inflammation storms by regulating the macrophage and mast cell pathways. In addition to reducing lung inflammation, luteolin also has protective effects on the gastrointestinal, cardiovascular, and nervous systems, which indicates that luteolin can be used for adjuvant therapy or prevention of severe pneumonia. The key molecules in the signal pathway involved in the therapeutic effect of luteolin include NF-κB, PI3K/Akt, Nrf2, and ERK1/2, and exploring the correlation between various action pathways of luteolin can be the direction for future research.

The COVID-19 pandemic reminds us that there is still a lack of drugs that can effectively control viral pneumonia, and luteolin may be a good choice. However, the problem of low oral bioavailability of luteolin has not been solved, which limits its clinical application. Interestingly, compared with pure luteolin, luteolin mixed with other plant ingredients is more easily absorbed, which suggests that the form of water decoction may be more conducive to the use of natural plant drugs. To further develop the potential value of luteolin, further research is needed to improve its absorption and bioavailability.

Abbreviations

ACE2: Angiotensin converting enzyme 2
SARS-CoV: Severe acute respiratory syndrome coronavirus
SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2
MERS-CoV: Middle East Respiratory Syndrome Coronavirus
ORF: Open reading frames
NSPs: Nonstructural proteins
3CLpro: Chymotrypsin-like proteases
Mpro: Main proteases
PLpro: Papain-like protease
EC50: Concentration for 50% of maximal effect
CC50: Concentration of cytotoxicity 50%
FRET: Fluorescence resonance energy transfer
RSV: Respiratory syncytial virus
MEFs: Mouse embryonic fibroblasts
HPAEpiC: Human pulmonary alveolar epithelial cells
SOCS1: Suppressors of cytokine signaling
STAT1/3: Signal transducer and activator of transcription 1/3
ISG: Interferon-stimulated gene
Hep-2: Human hepatocellular carcinomas-2
SHL: Shuang huang lian
KEGG: Kyoto Encyclopedia of Genes and Genomes
PA: Polymerase acidic protein
PB1: Polymerase basic protein 1
PB2: Polymerase basic protein 2
PA-Nter: PA N-terminal domain
NA: Influenza neuraminidase
CPE: Cytopathogenic efficiency
MDCK: Madin-darby canine kidney
β-COP: β-coat protein
NOX4: NADPH oxidase 4
NF-κB: Nuclear factor kappa-B
MLCK: Myosin light chain kinase
SRF: Severe respiratory failure
TNF-α: Tumor necrosis factor-α
IL-6: Interleukin-6
CD4/25: Cluster of differentiation 4/25
NK: Natural killer
COVID-19: Corona virus disease 2019
TRAIL: TNF related apoptosis inducing light
M1: Classically activated macrophages
M2: Alternatively activated macrophages
NLRP3: NOD-like receptor thermal protein domain associated protein 3
MC: Mast cell
LPS: Lipopolysaccharide
β-hex: β-hexosaminidase
CCL2/5/25: Chemokine ligand 2/5/25
FOXP3: Forkhead transcription factor3
SP: Substance P
LAD2: Laboratory of allergic diseases 2
IκBα: Inhibitor of NF-κB α

ERK: Extracellular regulated protein kinases
JNK: c-Jun N-terminal kinase
FcεRI: Fc epsilon RI
VEGF: Vascular endothelial growth factor
CXCL8: C-X-C motif chemokine 8
CT: Computed tomography
ICAM-1: Intercellular cell adhesion molecule-1
iNOS: Inducible nitric oxide synthase
COX-2: Cyclooxygenase-2
CCR9: C–C motif chemokine receptor 9
DSS: Dextran sulfate sodium
OCTN2: Organic cation transporter 2
MDA: Malonaldehyde
Nrf2: Nuclear factor erythroid 2-related factor 2
HO-1: Heme oxygenase-1
NQO1: Quinone oxidoreductase-1
SHP-1: Src homology region 2 domain-containing phosphatase 1
IFN-γ: Interferon-γ
CLDN1: Claudin-1
TRAF6: TNF receptor associated factor 6
CCH: Chronic cerebral hypoperfusion
hBMECs: Coculturing human brain microvascular endothelial cells
hAs: Human astrocytes
SCII: Spinal cord ischemia-reperfusion injury
SOD: Superoxide dismutase
GSH-Px: Glutathione peroxidase
SBI: Secondary brain injury
Keap1: Kelch-like ech-associated protein 1
NADPH: Nicotinamide adenine dinucleotide phosphate
Bax: B-cell lymphoma-2 associated X protein
Bcl-2: B-cell lymphoma-2
IR: Ischemia-reperfusion
MyD88: Myeloid differentiation factor 88
AST: Aspartate transaminase
CK-MB: Creatine kinase MB isoenzyme
LDH: Lactate dehydrogenase
SOD: Superoxide dismutase
MCP-1: Monocyte chemotactic protein 1
VCAM-1: Vascular cell adhesion molecule-1
HPLC: High performance liquid chromatography
LC-MS: Liquid chromatograph mass spectrometer
LPH: Lactase-phlorizin hydrolase
UGT: UDP-glucuronosyltransferase
COMT: Catechol-O-methyltransferase
SULT: Sulfotransferase
Lut-7-G: Luteolin-7-glucuronide
MCF-7: Human breast cancer cells.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interests.

Authors' Contributions

Yuan Bin and Tao Jia-Lei designed the work and provided financial support. Li Wei-Feng, Wang Xuan, and Wang Tian-Han carried out the collection of the relevant literature. Wang Tian-Han, Ding Ya-li, and Wang Meng-Xi sorted out the literature. Li Wei-Feng and Wang Xuan wrote the manuscript, and Yuan Bin reviewed the manuscript. All authors discussed and approved the final manuscript. Li Wei-Feng and Wang Xuan contributed equally to this work.

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References

[1] O. Ruuskanen, E. Lahti, L. C. Jennings, and D. R. Murdoch, "Viral pneumonia," *The Lancet*, vol. 377, no. 9773, pp. 1264–1275, 2011.
[2] L. Liu, S. Oza, D. Hogan et al., "Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals," *The Lancet*, vol. 388, no. 10063, pp. 3027–3035, 2016.
[3] World Health Organization, "Weekly epidemiological update on COVID-19-19 October 2022," 2022, https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19--19-october-2022.
[4] J. M. Galván, O. Rajas, and J. Aspa, "Review of non-bacterial infections in respiratory medicine: viral pneumonia," *Archivos de Bronconeumología*, vol. 51, no. 11, pp. 590–597, 2015.
[5] K. L. O'Brien, H. C. Baggett, W. A. Brooks et al., "Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study," *The Lancet*, vol. 394, no. 10200, pp. 757–779, 2019.
[6] N. Aziz, M. Y. Kim, and J. Y. Cho, "Anti-inflammatory effects of luteolin: a review of in vitro, in vivo, and in silico studies," *Journal of Ethnopharmacology*, vol. 225, pp. 342–358, 2018.
[7] M. Lopez-Lazaro, "Distribution and biological activities of the flavonoid luteolin," *Mini-Reviews in Medicinal Chemistry*, vol. 9, no. 1, pp. 31–59, 2009.
[8] Y. Taheri, J. Sharifi-Rad, G. Antika et al., "Paving luteolin therapeutic potentialities and agro-food-pharma applications: emphasis on in vivo pharmacological effects and bioavailability traits," *Oxidative Medicine and Cellular Longevity*, vol. 2021, Article ID 1987588, 20 pages, 2021.
[9] D. N. Che, J. Y. Shin, H. J. Kang, B. O. Cho, Y. S. Kim, and S. I. Jang, "Luteolin suppresses IL-31 production in IL-

33-stimulated mast cells through MAPK and NF-κB signaling pathways," *International Immunopharmacology*, vol. 83, Article ID 106403, 2020.

[10] N. Chu, X. Zhang, S. Chen, Q. Zhen, and Y. Wang, "Luteolin has a significant protective effect against cadmium-induced injury in lung epithelial Beas-2B cells," *Nan Fang Yi Ke Da Xue Xue Bao*, vol. 41, no. 5, pp. 729–735, 2021.

[11] J. Fu, W. Xu, Y. Zhang, H. Sun, and J. Zhao, "Luteolin modulates the NF-E2-Related factor 2/glutamate-cysteine ligase pathway in rats with spinal cord injury," *Journal of Medicinal Food*, vol. 24, no. 3, pp. 218–225, 2021.

[12] X. Ge, C. Wang, H. Chen et al., "Luteolin cooperated with metformin hydrochloride alleviates lipid metabolism disorders and optimizes intestinal flora compositions of high-fat diet mice," *Food and Function*, vol. 11, no. 11, pp. 10033–10046, 2020.

[13] R. A. Grant, L. Morales-Nebreda, N. S. Markov et al., "Circuits between infected macrophages and T cells in SARS-CoV-2 pneumonia," *Nature*, vol. 590, no. 7847, pp. 635–641, 2021.

[14] M. Russo, S. Moccia, C. Spagnuolo, I. Tedesco, and G. L. Russo, "Roles of flavonoids against coronavirus infection," *Chemico-Biological Interactions*, vol. 328, Article ID 109211, 2020.

[15] M. A. Shereen, S. Khan, A. Kazmi, N. Bashir, and R. Siddique, "COVID-19 infection: e," *Journal of Advanced Research*, vol. 24, pp. 91–98, 2020.

[16] A. Grottesi, N. Besker, A. Emerson et al., "Computational studies of SARS-CoV-2 3CLpro: insights from MD simulations," *International Journal of Molecular Sciences*, vol. 21, no. 15, 2020.

[17] Q. Li and C. Kang, "Progress in developing inhibitors of SARS-CoV-2 3C-like protease," *Microorganisms*, vol. 8, no. 8, p. 1250, 2020.

[18] Y. Sun, L. Liu, and X. Pan, "Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus S proteins," *Journal of Mirobiology*, vol. 24, no. 4, pp. 25–30, 2004.

[19] L. Yi, Z. Li, K. Yuan et al., "Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells," *Journal of Virology*, vol. 78, no. 20, pp. 11334–11339, 2004.

[20] R. Yu, L. Chen, R. Lan, R. Shen, and P. Li, "Computational screening of antagonists against the SARS-CoV-2 (COVID-19) coronavirus by molecular docking," *International Journal of Antimicrobial Agents*, vol. 56, no. 2, Article ID 106012, 2020.

[21] D. M. Shadrack, G. Deogratias, L. W. Kiruri et al., "Luteolin: a blocker of SARS-CoV-2 cell entry based on relaxed complex scheme, molecular dynamics simulation, and metadynamics," *Journal of Molecular Modeling*, vol. 27, no. 8, p. 221, 2021.

[22] H. I. Guler, G. Tatar, O. Yildiz, A. O. Belduz, and S. Kolayli, "Investigation of potential inhibitor properties of ethanolic propolis extracts against ACE-II receptors for COVID-19 treatment by molecular docking study," *Archives of Microbiology*, vol. 203, no. 6, pp. 3557–3564, 2021.

[23] A. D. Rathnayake, J. Zheng, Y. Kim et al., "3C-like protease inhibitors block coronavirus replication in vitro and improve survival in MERS-CoV-infected mice," *Science Translational Medicine*, vol. 12, no. 557, 2020.

[24] Y. B. Ryu, H. J. Jeong, J. H. Kim et al., "Biflavonoids from Torreya nucifera displaying SARS-CoV 3CL(pro) inhibition," *Bioorganic and Medicinal Chemistry*, vol. 18, no. 22, pp. 7940–7947, 2010.

[25] C. Wang, J. Xie, L. Zhao et al., "Alveolar macrophage dysfunction and cytokine storm in the pathogenesis of two severe COVID-19 patients," *EBioMedicine*, vol. 57, Article ID 102833, 2020.

[26] S. Wang, Y. Ling, Y. Yao, G. Zheng, and W. Chen, "Luteolin inhibits respiratory syncytial virus replication by regulating the MiR-155/SOCS1/STAT1 signaling pathway," *Virology Journal*, vol. 17, no. 1, p. 187, 2020.

[27] L. S. Ooi, H. Wang, Z. He, and V. E. Ooi, "Antiviral activities of purified compounds from Youngia japonica (L.) DC (Asteraceae, Compositae)," *Journal of Ethnopharmacology*, vol. 106, no. 2, pp. 187–191, 2006.

[28] Y. Wang, M. Chen, J. Zhang et al., "Flavone C-glycosides from the leaves of Lophatherum gracile and their in vitro antiviral activity," *Planta Medica*, vol. 78, no. 01, pp. 46–51, 2012.

[29] P. Yuan, M. Bartlam, Z. Lou et al., "Crystal structure of an avian influenza polymerase PA(N) reveals an endonuclease active site," *Nature*, vol. 458, no. 7240, pp. 909–913, 2009.

[30] D. Koppstein, J. Ashour, and D. P. Bartel, "Sequencing the cap-snatching repertoire of H1N1 influenza provides insight into the mechanism of viral transcription initiation," *Nucleic Acids Research*, vol. 43, no. 10, pp. 5052–5064, 2015.

[31] A. Dias, D. Bouvier, T. Crepin et al., "The cap-snatching endonuclease of influenza virus polymerase resides in the PA subunit," *Nature*, vol. 458, no. 7240, pp. 914–918, 2009.

[32] F. G. Hayden and N. Shindo, "Influenza virus polymerase inhibitors in clinical development," *Current Opinion in Infectious Diseases*, vol. 32, no. 2, pp. 176–186, 2019.

[33] J. Zhang, Y. Hu, R. Musharrafieh, H. Yin, and J. Wang, "Focusing on the influenza virus polymerase complex: recent progress in drug discovery and assay development," *Current Medicinal Chemistry*, vol. 26, no. 13, pp. 2243–2263, 2019.

[34] L. Zhang, X. Wang, L. Zhang, C. Virgous, and H. Si, "Combination of curcumin and luteolin synergistically inhibits TNF-alpha-induced vascular inflammation in human vascular cells and mice," *The Journal of Nutritional Biochemistry*, vol. 73, Article ID 108222, 2019.

[35] R. Reiberger, K. Radilova, M. Kral et al., J. Konvalinka, Synthesis and in vitro evaluation of C-7 and C-8 luteolin derivatives as influenza endonuclease inhibitors," *International Journal of Molecular Sciences*, vol. 22, no. 14, p. 7735, 2021.

[36] E. Kowalinski, C. Zubieta, A. Wolkerstorfer, O. H. J. Szolar, R. W. H. Ruigrok, and S. Cusack, "Structural analysis of specific metal chelating inhibitor binding to the endonuclease domain of influenza pH1N1(2009) polymerase," *PLoS Pathogens*, vol. 8, no. 8, Article ID e1002831, 2012.

[37] V. Zima, K. Radilova, M. Kozisek et al., "Unraveling the anti-influenza effect of flavonoids: experimental validation of luteolin and its congeners as potent influenza endonuclease inhibitors," *European Journal of Medicinal Chemistry*, vol. 208, Article ID 112754, 2020.

[38] U. Grienke, M. Schmidtke, S. von Grafenstein, J. Kirchmair, K. R. Liedl, and J. M. Rollinger, "Influenza neuraminidase: a druggable target for natural products," *Natural Product Reports*, vol. 29, no. 1, pp. 11–36, 2012.

[39] S. M. Sadati, N. Gheibi, S. Ranjbar, and M. S. Hashemzadeh, "Docking study of flavonoid derivatives as potent inhibitors of influenza H1N1 virus neuraminidase," *Biomed Reports*, vol. 10, no. 1, pp. 33–38, 2019.

[40] I. K. Lee, B. S. Hwang, D. W. Kim et al., "Characterization of neuraminidase inhibitors in Korean papaver rhoeas bee

pollen contributing to anti-influenza activities in vitro," *Planta Medica*, vol. 82, no. 06, pp. 524–529, 2016.

[41] H. Yan, L. Ma, H. Wang et al., "Luteolin decreases the yield of influenza A virus in vitro by interfering with the coat protein I complex expression," *Journal of Natural Medicines*, vol. 73, no. 3, pp. 487–496, 2019.

[42] W. Y. Yu, L. Li, F. Wu et al., "Moslea Herba flavonoids alleviated influenza A virus-induced pulmonary endothelial barrier disruption via suppressing NOX4/NF-κB/MLCK pathway," *Journal of Ethnopharmacology*, vol. 253, p. 112641, 2020.

[43] C. Storm, *New England Journal of Medicine*, NEJM Group, Waltham, MA, USA, 2021.

[44] A. E. Peter, B. V. Sandeep, B. G. Rao, and V. L. Kalpana, "Calming the storm: natural immunosuppressants as adjuvants to target the cytokine storm in COVID-19," *Frontiers in Pharmacology*, vol. 11, Article ID 583777, 2020.

[45] N. Clementi, S. Ghosh, M. De Santis et al., "Viral respiratory pathogens and lung injury," *Clinical Microbiology Reviews*, vol. 34, no. 3, Article ID e00103-20, 2021.

[46] K. R. Short, T. Kuiken, and D. Van Riel, "Role of endothelial cells in the pathogenesis of influenza in humans," *The Journal of Infectious Diseases*, vol. 220, no. 11, pp. 1859-1860, 2019.

[47] Q. Liu, Y. H. Zhou, and Z. Q. Yang, "The cytokine storm of severe influenza and development of immunomodulatory therapy," *Cellular and Molecular Immunology*, vol. 13, no. 1, pp. 3–10, 2016.

[48] T. C. Theoharides, "Potential association of mast cells with coronavirus disease 2019," *Annals of Allergy, Asthma, and Immunology*, vol. 126, no. 3, pp. 217-218, 2021.

[49] M. Dukhinova, E. Kokinos, P. Kuchur, A. Komissarov, and A. Shtro, "Macrophage-derived cytokines in pneumonia: linking cellular immunology and genetics," *Cytokine and Growth Factor Reviews*, vol. 59, pp. 46–61, 2021.

[50] E. J. Giamarellos-Bourboulis, M. G. Netea, N. Rovina et al., "Complex immune dysregulation in COVID-19 patients with severe respiratory failure," *Cell Host and Microbe*, vol. 27, no. 6, pp. 992–1000.e3, 2020.

[51] W. C. L. Yu, R. W. Y. Chan, J. Wang et al., "Viral replication and innate host responses in primary human alveolar epithelial cells and alveolar macrophages infected with influenza H5N1 and H1N1 viruses," *Journal of Virology*, vol. 85, no. 14, pp. 6844–6855, 2011.

[52] K. Hogner, T. Wolff, S. Pleschka et al., "Macrophage-expressed IFN-beta contributes to apoptotic alveolar epithelial cell injury in severe influenza virus pneumonia," *PLoS Pathogens*, vol. 9, no. 2, Article ID e1003188, 2013.

[53] S. C. Funes, M. Rios, J. Escobar-Vera, and A. M. Kalergis, "Implications of macrophage polarization in autoimmunity," *Immunology*, vol. 154, no. 2, pp. 186–195, 2018.

[54] C. Atri, F. Z. Guerfali, and D. Laouini, "Role of human macrophage polarization in inflammation during infectious diseases," *International Journal of Molecular Sciences*, vol. 19, no. 6, p. 1801, 2018.

[55] B.-C. Zhang, Z. Li, W. Xu, C.-H. Xiang, and Y.-F. Ma, "Luteolin alleviates NLRP3 inflammasome activation and directs macrophage polarization in lipopolysaccharide-stimulated RAW264.7 cells," *American Journal of Tourism Research*, vol. 10, no. 1, pp. 265–273, 2018.

[56] S. Wang, M. Cao, S. Xu et al., "Luteolin alters macrophage polarization to inhibit inflammation," *Inflammation*, vol. 43, no. 1, pp. 95–108, 2020.

[57] X. Chen, Y. Lai, X. Song et al., "Polysaccharides from Citrus grandis associate with luteolin relieves chronic pharyngitis by anti-inflammatory via suppressing NF-κB pathway and the polarization of M1 macrophages," *International Journal of Immunopathology and Pharmacology*, vol. 32, Article ID 2058738418780593, 2018.

[58] E. Y. Kwon and M. S. Choi, "Luteolin targets the toll-like receptor signaling pathway in prevention of hepatic and adipocyte fibrosis and insulin resistance in diet-induced obese mice," *Nutrients*, vol. 10, no. 10, p. 1415, 2018.

[59] Y. Liao, Y. Xu, M. Cao et al., "Luteolin induces apoptosis and autophagy in mouse macrophage ANA-1 cells via the bcl-2 pathway," *Journal of Immunology Research*, vol. 2018, Article ID 4623919, 9 pages, 2018.

[60] J. S. Marshall, L. Portales-Cervantes, and E. Leong, "Mast cell responses to viruses and pathogen products," *International Journal of Molecular Sciences*, vol. 20, no. 17, p. 4241, 2019.

[61] S. Eglite, J. M. Morin, and H. Metzger, "Synthesis and secretion of monocyte chemotactic protein-1 stimulated by the high affinity receptor for IgE," *The Journal of Immunology*, vol. 170, no. 5, pp. 2680–2687, 2003.

[62] D. Kempuraj, M. Huang, K. Kandere-Grzybowska et al., "Azelastine inhibits secretion of IL-6, TNF-α and IL-8 as well as NF-κB activation and intracellular calcium ion levels in normal human mast cells," *International Archives of Allergy and Immunology*, vol. 132, no. 3, pp. 231–239, 2003.

[63] Z. Weng, A. B. Patel, S. Panagiotidou, and T. C. Theoharides, "The novel flavone tetramethoxyluteolin is a potent inhibitor of human mast cells," *The Journal of Allergy and Clinical Immunology*, vol. 135, no. 4, pp. 1044–1052.e5, 2015.

[64] A. Taracanova, I. Tsilioni, P. Conti, E. R. Norwitz, S. E. Leeman, and T. C. Theoharides, "Substance P and IL-33 administered together stimulate a marked secretion of IL-1β from human mast cells, inhibited by methoxyluteolin," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 115, no. 40, pp. E9381–E9390, 2018.

[65] D. Kempuraj, B. Madhappan, S. Christodoulou et al., "Flavonols inhibit proinflammatory mediator release, intracellular calcium ion levels and protein kinase C theta phosphorylation in human mast cells," *British Journal of Pharmacology*, vol. 145, no. 7, pp. 934–944, 2005.

[66] M. Kimata, M. Shichijo, T. Miura, I. Serizawa, N. Inagaki, and H. Nagai, "Effects of luteolin, quercetin and baicalein on immunoglobulin E-mediated mediator release from human cultured mast cells," *Clinical and Experimental Allergy*, vol. 30, no. 4, pp. 501–508, 2000.

[67] M. A. Bawazeer and T. C. Theoharides, "IL-33 stimulates human mast cell release of CCL5 and CCL2 via MAPK and NF-κB, inhibited by methoxyluteolin," *European Journal of Pharmacology*, vol. 865, Article ID 172760, 2019.

[68] S. Asadi and T. C. Theoharides, "Corticotropin-releasing hormone and extracellular mitochondria augment IgE-stimulated human mast-cell vascular endothelial growth factor release, which is inhibited by luteolin," *Journal of Neuroinflammation*, vol. 9, no. 1, Article ID 571, 2012.

[69] A. B. Patel and T. C. Theoharides, "Methoxyluteolin inhibits neuropeptide-stimulated proinflammatory mediator release via mTOR activation from human mast cells," *Journal of Pharmacology and Experimental Therapeutics*, vol. 361, no. 3, pp. 462–471, 2017.

[70] D. Kempuraj, M. Tagen, B. P. Iliopoulou et al., "Luteolin inhibits myelin basic protein-induced human mast cell activation and mast cell-dependent stimulation of Jurkat T cells," *British Journal of Pharmacology*, vol. 155, no. 7, pp. 1076–1084, 2008.

[71] H. J. Koo, S. Lim, J. Choe, S. H. Choi, H. Sung, and K. H. Do, "Radiographic and CT features of viral pneumonia," *RadioGraphics*, vol. 38, no. 3, pp. 719–739, 2018.

[72] K. Stefanidis, E. Konstantelou, G. T. Yusuf et al., "Radiological, epidemiological and clinical patterns of pulmonary viral infections," *European Journal of Radiology*, vol. 136, Article ID 109548, 2021.

[73] S. Rungsung, T. U. Singh, D. J. Rabha et al., "Luteolin attenuates acute lung injury in experimental mouse model of sepsis," *Cytokine*, vol. 110, pp. 333–343, 2018.

[74] K. Xie, Y. S. Chai, S. H. Lin, F. Xu, and C. J. Wang, "Luteolin regulates the differentiation of regulatory T cells and activates IL-10-dependent macrophage polarization against acute lung injury," *Journal of Immunology Research*, vol. 2021, Article ID 8883962, 12 pages, 2021.

[75] Z. T. Zhang, D. Y. Zhang, K. Xie, C. J. Wang, and F. Xu, "Luteolin activates Tregs to promote IL-10 expression and alleviating caspase-11-dependent pyroptosis in sepsis-induced lung injury," *International Immunopharmacology*, vol. 99, Article ID 107914, 2021.

[76] C. Y. Chen, W. H. Peng, L. C. Wu, C. C. Wu, and S. L. Hsu, "Luteolin ameliorates experimental lung fibrosis both in vivo and in vitro: implications for therapy of lung fibrosis," *Journal of Agricultural and Food Chemistry*, vol. 58, no. 22, pp. 11653–11661, 2010.

[77] M. Y. Kuo, M. F. Liao, F. L. Chen et al., "Luteolin attenuates the pulmonary inflammatory response involves abilities of antioxidation and inhibition of MAPK and NFκB pathways in mice with endotoxin-induced acute lung injury," *Food and Chemical Toxicology*, vol. 49, no. 10, pp. 2660–2666, 2011.

[78] J. P. Lee, Y. C. Li, H. Y. Chen et al., "Protective effects of luteolin against lipopolysaccharide-induced acute lung injury involves inhibition of MEK/ERK and PI3K/Akt pathways in neutrophils," *Acta Pharmacologica Sinica*, vol. 31, no. 7, pp. 831–838, 2010.

[79] B. Liu, H. Yu, R. Baiyun et al., "Protective effects of dietary luteolin against mercuric chloride-induced lung injury in mice: involvement of AKT/Nrf2 and NF-κB pathways," *Food and Chemical Toxicology*, vol. 113, pp. 296–302, 2018.

[80] C. Y. Chen, W. H. Peng, K. D. Tsai, and S. L. Hsu, "Luteolin suppresses inflammation-associated gene expression by blocking NF-κB and AP-1 activation pathway in mouse alveolar macrophages," *Life Sciences*, vol. 81, no. 23-24, pp. 1602–1614, 2007.

[81] Y. C. Li, C. H. Yeh, M. L. Yang, and Y. H. Kuan, "Luteolin suppresses inflammatory mediator expression by blocking the akt/nf?b pathway in acute lung injury induced by lipopolysaccharide in mice," *Evidence-Based Complementary and Alternative Medicine*, vol. 2012, 8 pages, Article ID 383608, 2012.

[82] X. Liu and J. Meng, "Luteolin alleviates LPS-induced bronchopneumonia injury in vitro and in vivo by down-regulating microRNA-132 expression," *Biomedicine and Pharmacotherapy*, vol. 106, pp. 1641–1649, 2018.

[83] S. H. Kim, E. Saba, B. K. Kim et al., "Luteolin attenuates airway inflammation by inducing the transition of CD4(+) CD25(-) to CD4(+)CD25(+) regulatory T cells," *European Journal of Pharmacology*, vol. 820, pp. 53–64, 2018.

[84] M. L. Shen, C. H. Wang, C. H. Lin, N. Zhou, S. T. Kao, and D. C. Wu, "Luteolin attenuates airway mucus overproduction via inhibition of the GABAergic system," *Scientific Reports*, vol. 6, no. 1, Article ID 32756, 2016.

[85] S. Wang, T. Wuniqiemu, W. Tang et al., "Luteolin inhibits autophagy in allergic asthma by activating PI3K/Akt/mTOR signaling and inhibiting Beclin-1-PI3KC3 complex," *International Immunopharmacology*, vol. 94, Article ID 107460, 2021.

[86] M. Galanopoulos, F. Gkeros, A. Doukatas et al., "COVID-19 pandemic: pathophysiology and manifestations from the gastrointestinal tract," *World Journal of Gastroenterology*, vol. 26, no. 31, pp. 4579–4588, 2020.

[87] A. Sirinawasatien, T. Chantarojanasiri, S. Ekpanyapong, N. Tivatunsakul, and V. Luvira, "Coronavirus disease 2019 gastrointestinal and liver manifestations in adults: a review," *JGH Open*, vol. 5, no. 11, pp. 1257–1265, 2021.

[88] F. Xiao, M. Tang, X. Zheng, Y. Liu, X. Li, and H. Shan, "Evidence for gastrointestinal infection of SARS-CoV-2," *Gastroenterology*, vol. 158, no. 6, pp. 1831–1833.e3, 2020.

[89] Q. Qian, L. Fan, W. Liu et al., "Direct evidence of active SARS-CoV-2 replication in the intestine," *Clinical Infectious Diseases*, vol. 73, no. 3, pp. 361–366, 2021.

[90] M. C. Chan, N. Lee, P. K. Chan, T. F. Leung, and J. J. Sung, "Fecal detection of influenza A virus in patients with concurrent respiratory and gastrointestinal symptoms," *Journal of Clinical Virology*, vol. 45, no. 3, pp. 208–211, 2009.

[91] R. Zang, M. F. Gomez Castro, B. T. McCune et al., "TMPRSS2 and TMPRSS4 promote SARS-CoV-2 infection of human small intestinal enterocytes," *Science Immunology*, vol. 5, no. 47, Article ID eabc3582, 2020.

[92] J. Wang, F. Li, H. Wei, Z. X. Lian, R. Sun, and Z. Tian, "Respiratory influenza virus infection induces intestinal immune injury via microbiota-mediated Th17 cell-dependent inflammation," *Journal of Experimental Medicine*, vol. 211, no. 12, pp. 2397–2410, 2014.

[93] L. C. Gierse, A. Meene, D. Schultz et al., "Influenza A H1N1 induced disturbance of the respiratory and fecal microbiome of German landrace pigs - a multi-omics characterization," *Microbiology Spectrum*, vol. 9, no. 2, Article ID e0018221, 2021.

[94] T. Zuo, Q. Liu, F. Zhang et al., "Depicting SARS-CoV-2 faecal viral activity in association with gut microbiota composition in patients with COVID-19," *Gut*, vol. 70, no. 2, pp. 276–284, 2021.

[95] V. Sencio, A. Gallerand, M. Gomes Machado et al., e0073420, Influenza virus infection impairs the gut's barrier properties and favors secondary enteric bacterial infection through reduced production of short-chain fatty acids," *Infection and Immunity*, vol. 89, no. 9, 2021.

[96] V. Sencio, A. Barthelemy, L. P. Tavares et al., "Gut dysbiosis during influenza contributes to pulmonary pneumococcal superinfection through altered short-chain fatty acid production," *Cell Reports*, vol. 30, no. 9, pp. 2934–2947.e6, 2020.

[97] B. Li, P. Du, Y. Du et al., "Luteolin alleviates inflammation and modulates gut microbiota in ulcerative colitis rats," *Life Sciences*, vol. 269, Article ID 119008, 2021a.

[98] P. Li, Y. Wang, J. Luo et al., "Downregulation of OCTN2 by cytokines plays an important role in the progression of inflammatory bowel disease," *Biochemical Pharmacology*, vol. 178, Article ID 114115, 2020.

[99] J. Li, X. Cheng, Y. Chen et al., "Vitamin E TPGS modified liposomes enhance cellular uptake and targeted delivery of luteolin: an in vivo/in vitro evaluation," *International Journal of Pharmaceutics*, vol. 512, no. 1, pp. 262–272, 2016c.

[100] D. Liu, X. Yu, H. Sun, W. Zhang, G. Liu, and L. Zhu, "Flos lonicerae flavonoids attenuate experimental ulcerative colitis in rats via suppression of NF-κB signaling pathway," *Naunyn-Schmiedeberg's Archives of Pharmacology*, vol. 393, no. 12, pp. 2481–2494, 2020.

[101] I. Vukelic, D. Detel, L. Baticic, I. Potocnjak, and R. Domitrovic, "Luteolin ameliorates experimental colitis in mice through ERK-mediated suppression of inflammation, apoptosis and autophagy," *Food and Chemical Toxicology*, vol. 145, Article ID 111680, 2020.

[102] B. L. Li, D. Y. Zhao, P. L. Du, X. T. Wang, Q. Yang, and Y. R. Cai, "Luteolin alleviates ulcerative colitis through SHP-1/STAT3 pathway," *Inflammation Research*, vol. 70, no. 6, pp. 705–717, 2021.

[103] X. Liu, R. Sun, Z. Li et al., "Luteolin alleviates non-alcoholic fatty liver disease in rats via restoration of intestinal mucosal barrier damage and microbiota imbalance involving in gut-liver axis," *Archives of Biochemistry and Biophysics*, vol. 711, Article ID 109019, 2021.

[104] W. L. Sun, J. W. Yang, H. Y. Dou et al., "Anti-inflammatory effect of luteolin is related to the changes in the gut microbiota and contributes to preventing the progression from simple steatosis to nonalcoholic steatohepatitis," *Bioorganic Chemistry*, vol. 112, Article ID 104966, 2021.

[105] Y. Li, L. Shen, and H. Luo, "Luteolin ameliorates dextran sulfate sodium-induced colitis in mice possibly through activation of the Nrf2 signaling pathway," *International Immunopharmacology*, vol. 40, pp. 24–31, 2016b.

[106] J. J. Ekstrand, A. Herbener, J. Rawlings et al., "Heightened neurologic complications in children with pandemic H1N1 influenza," *Annals of Neurology*, vol. 68, no. 5, pp. 762–766, 2010.

[107] S. Lochindarat and T. Bunnag, "Clinical presentations of pandemic 2009 influenza A (H1N1) virus infection in hospitalized Thai children," *Journal of the Medical Association of Thailand = Chotmaihet thangphaet*, vol. 3, no. 94, pp. S107–S112, 2011.

[108] J. R. Lechien, C. M. Chiesa-Estomba, D. R. De Siati et al., "Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study," *European Archives of Oto-Rhino-Laryngology*, vol. 277, no. 8, pp. 2251–2261, 2020.

[109] L. Mao, H. Jin, M. Wang et al., "Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in wuhan, China," *JAMA Neurology*, vol. 77, no. 6, pp. 683–690, 2020.

[110] A. Prerna, J. Y. Lim, N. W. Tan et al., "Neurology of the H1N1 pandemic in Singapore: a nationwide case series of children and adults," *Joural of Neurovirol*, vol. 21, no. 5, pp. 491–499, 2015.

[111] S. Kedia, B. Stroud, J. Parsons et al., "Pediatric neurological complications of 2009 pandemic influenza A (H1N1)," *Archives of Neurology*, vol. 68, no. 4, pp. 455–462, 2011.

[112] A. N. Wilking, E. Elliott, M. N. Garcia, K. O. Murray, and F. M. Munoz, "Central nervous system manifestations in pediatric patients with influenza A H1N1 infection during the 2009 pandemic," *Pediatric Neurology*, vol. 51, no. 3, pp. 370–376, 2014.

[113] K. Bohmwald, N. M. S. Galvez, M. Rios, and A. M. Kalergis, "Neurologic alterations due to respiratory virus infections," *Frontiers in Cellular Neuroscience*, vol. 12, p. 386, 2018.

[114] Y. Ding, L. He, Q. Zhang et al., "Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways," *The Journal of Pathology*, vol. 203, no. 2, pp. 622–630, 2004.

[115] J. Xu, S. Q. Zhong, J. H. Liu et al., "Detection of severe acute respiratory syndrome coronavirus in the brain: potential role of the chemokine mig in pathogenesis," *Clinical Infectious Diseases*, vol. 41, no. 8, pp. 1089–1096, 2005.

[116] K. Li, C. Wohlford-Lenane, S. Perlman et al., "Middle East respiratory syndrome coronavirus causes multiple organ damage and lethal disease in mice transgenic for human dipeptidyl peptidase 4," *The Journal of Infectious Diseases*, vol. 213, no. 5, pp. 712–722, 2016.

[117] M. Fleischer, M. Kohrmann, S. Dolff et al., "Observational cohort study of neurological involvement among patients with SARS-CoV-2 infection," *Therapeutic Advances in Neurological Disorders*, vol. 14, Article ID 175628642199370, 2021.

[118] J. J. Rozniecki, V. Dimitriadou, M. Lambracht-Hall, X. Pang, and T. C. Theoharides, "Morphological and functional demonstration of rat dura mater mast cell-neuron interactions in vitro and in vivo," *Brain Research*, vol. 849, no. 1-2, pp. 1–15, 1999.

[119] T. C. Theoharides, J. Donelan, K. Kandere-Grzybowska, and A. Konstantinidou, "The role of mast cells in migraine pathophysiology," *Brain Research Reviews*, vol. 49, no. 1, pp. 65–76, 2005.

[120] T. C. Theoharides, "Ways to address perinatal mast cell activation and focal brain inflammation, including response to SARS-CoV-2, in autism spectrum disorder," *Journal of Personalized Medicine*, vol. 11, no. 9, 2021.

[121] T. C. Theoharides, C. Cholevas, K. Polyzoidis, and A. Politis, "Long-COVID syndrome-associated brain fog and chemofog: luteolin to the rescue," *BioFactors*, vol. 47, no. 2, pp. 232–241, 2021.

[122] T. Togashi, Y. Matsuzono, M. Narita, and T. Morishima, "Influenza-associated acute encephalopathy in Japanese children in 1994-2002," *Virus Research*, vol. 103, no. 1-2, pp. 75–78, 2004.

[123] L. D'Ascanio, F. Vitelli, C. Cingolani, M. Maranzano, M. J. Brenner, and A. Di Stadio, "Randomized clinical trial "olfactory dysfunction after COVID-19: olfactory rehabilitation therapy vs. intervention treatment with Palmitoylethanolamide and Luteolin": preliminary results," *European Review for Medical and Pharmacological Sciences*, vol. 25, no. 11, pp. 4156–4162, 2021.

[124] Y. Yang, X. Tan, J. Xu et al., "Luteolin alleviates neuroinflammation via downregulating the TLR4/TRAF6/NF-κB pathway after intracerebral hemorrhage," *Biomedicine and Pharmacotherapy*, vol. 126, Article ID 110044, 2020.

[125] W. Zhou, M. Hu, J. Hu, Z. Du, Q. Su, and Z. Xiang, "Luteolin suppresses microglia neuroinflammatory responses and relieves inflammation-induced cognitive impairments," *Neurotoxicity Research*, vol. 39, no. 6, pp. 1800–1811, 2021.

[126] Z. H. Yao, X. L. Yao, Y. Zhang, S. F. Zhang, and J. C. Hu, "Luteolin could improve cognitive dysfunction by inhibiting neuroinflammation," *Neurochemical Research*, vol. 43, no. 4, pp. 806–820, 2018.

[127] J. X. Zhang, J. G. Xing, L. L. Wang, H. L. Jiang, S. L. Guo, and R. Liu, "Luteolin inhibits fibrillary beta-amyloid1-40-induced inflammation in a human blood-brain barrier model by suppressing the p38 MAPK-mediated NF-kappaB signaling pathways," *Molecules*, vol. 22, no. 3, 2017.

[128] J. Fu, H. Sun, Y. Zhang et al., "Neuroprotective effects of luteolin against spinal cord ischemia-reperfusion injury by attenuation of oxidative stress, inflammation, and apoptosis," *Journal of Medicinal Food*, vol. 21, no. 1, pp. 13–20, 2018.

[129] X. Tan, Y. Yang, J. Xu et al., "Luteolin exerts neuroprotection via modulation of the p62/keap1/nrf2 pathway in

intracerebral hemorrhage," *Frontiers in Pharmacology*, vol. 10, p. 1551, 2019.

[130] V. F. Corrales-Medina, D. M. Musher, S. Shachkina, and J. A. Chirinos, "Acute pneumonia and the cardiovascular system," *The Lancet*, vol. 381, no. 9865, pp. 496–505, 2013.

[131] R. Cangemi, C. Calvieri, M. Falcone et al., "Relation of cardiac complications in the early phase of community-acquired pneumonia to long-term mortality and cardiovascular events," *The American Journal of Cardiology*, vol. 116, no. 4, pp. 647–651, 2015.

[132] F. Violi, R. Cangemi, M. Falcone et al., "Cardiovascular complications and short-term mortality risk in community-acquired pneumonia," *Clinical Infectious Diseases*, vol. 64, no. 11, pp. 1486–1493, 2017.

[133] R. Dennert, H. J. Crijns, and S. Heymans, "Acute viral myocarditis," *European Heart Journal*, vol. 29, no. 17, pp. 2073–2082, 2008.

[134] S. H. Rezkalla and R. A. Kloner, "Viral myocarditis: 1917-2020: from the Influenza A to the COVID-19 pandemics," *Trends in Cardiovascular Medicine*, vol. 31, no. 3, pp. 163–169, 2021.

[135] L. Ma, K. Song, and Y. Huang, "Coronavirus disease-2019 (COVID-19) and cardiovascular complications," *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 35, no. 6, pp. 1860–1865, 2021.

[136] M. Madjid, P. Safavi-Naeini, S. D. Solomon, and O. Vardeny, "Potential effects of coronaviruses on the cardiovascular system: a review," *JAMA Cardiol*, vol. 5, no. 7, pp. 831–840, 2020.

[137] G. Tavazzi, C. Pellegrini, M. Maurelli et al., "Myocardial localization of coronavirus in COVID-19 cardiogenic shock," *European Journal of Heart Failure*, vol. 22, no. 5, pp. 911–915, 2020.

[138] C. L. Albert, A. E. Carmona-Rubio, A. J. Weiss, G. G. Procop, R. C. Starling, and E. R. Rodriguez, "The enemy within sudden-onset reversible cardiogenic shock with biopsy-proven cardiac myocyte infection by severe acute respiratory syndrome coronavirus 2," *Circulation*, vol. 142, no. 19, pp. 1865–1870, 2020.

[139] S. E. Fox, A. Akmatbekov, J. L. Harbert, G. Li, J. Quincy Brown, and R. S. Vander Heide, "Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans," *The Lancet Respiratory Medicine*, vol. 8, no. 7, pp. 681–686, 2020.

[140] S. E. Fox, F. S. Lameira, E. B. Rinker, and R. S. Vander Heide, "Cardiac endotheliitis and multisystem inflammatory syndrome after COVID-19," *Annals of Internal Medicine*, vol. 173, no. 12, pp. 1025–1027, 2020.

[141] B. Schurink, E. Roos, T. Radonic et al., "Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study," *The Lancet Microbe*, vol. 1, no. 7, pp. e290–e299, 2020.

[142] V. O. Puntmann, M. L. Carerj, I. Wieters et al., "Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19)," *JAMA Cardiol*, vol. 5, no. 11, pp. 1265–1273, 2020.

[143] F. Licciardi, G. Pruccoli, M. Denina et al., "SARS-CoV-2-Induced kawasaki-like hyperinflammatory syndrome: a novel covid phenotype in children," *Pediatrics*, vol. 146, no. 2, Article ID e20201711, 2020.

[144] Y. Luo, P. Shang, and D. Li, "Luteolin: a flavonoid that has multiple cardio-protective effects and its molecular mechanisms," *Frontiers in Pharmacology*, vol. 8, p. 692, 2017.

[145] C. Bian, T. Xu, H. Zhu et al., "Luteolin inhibits ischemia/reperfusion-induced myocardial injury in rats via down-regulation of microRNA-208b-3p," *PLoS One*, vol. 10, no. 12, Article ID e0144877, 2015.

[146] F. Fang, D. Li, H. Pan et al., "Luteolin inhibits apoptosis and improves cardiomyocyte contractile function through the PI3K/Akt pathway in simulated ischemia/reperfusion," *Pharmacology*, vol. 88, no. 3-4, pp. 149–158, 2011.

[147] D. Liu, H. Luo, and C. Qiao, "SHP-1/STAT3 interaction is related to luteolin-induced myocardial ischemia protection," *Inflammation*, vol. 45, no. 1, pp. 88–99, 2021.

[148] L. Qi, H. Pan, D. Li, F. Fang, D. Chen, and H. Sun, "Luteolin improves contractile function and attenuates apoptosis following ischemia-reperfusion in adult rat cardiomyocytes," *European Journal of Pharmacology*, vol. 668, no. 1-2, pp. 201–207, 2011.

[149] X. Zhang, Q. Du, Y. Yang et al., "The protective effect of Luteolin on myocardial ischemia/reperfusion (I/R) injury through TLR4/NF-κB/NLRP3 inflammasome pathway," *Biomedicine and Pharmacotherapy*, vol. 91, pp. 1042–1052, 2017.

[150] R. Q. Zhang, D. Y. Li, T. D. Xu et al., "Antioxidative effect of luteolin pretreatment on simulated ischemia/reperfusion injury in cardiomyocyte and perfused rat heart," *Chinese Journal of Integrative Medicine*, vol. 23, no. 7, pp. 518–527, 2017.

[151] H. I. Chen, W. S. Hu, M. Y. Hung et al., "Protective effects of luteolin against oxidative stress and mitochondrial dysfunction in endothelial cells," *Nutrition, Metabolism, and Cardiovascular Diseases*, vol. 30, no. 6, pp. 1032–1043, 2020.

[152] W. Hu, T. Xu, P. Wu et al., "Luteolin improves cardiac dysfunction in heart failure rats by regulating sarcoplasmic reticulum Ca2+-ATPase 2a," *Scientific Reports*, vol. 7, no. 1, Article ID 41017, 2017.

[153] Y. Hu, C. Zhang, H. Zhu et al., "Luteolin modulates SERCA2a via Sp1 upregulation to attenuate myocardial ischemia/reperfusion injury in mice," *Scientific Reports*, vol. 10, no. 1, Article ID 15407, 2020.

[154] X. Wu, T. Xu, D. Li et al., "ERK/PP1a/PLB/SERCA2a and JNK pathways are involved in luteolin-mediated protection of rat hearts and cardiomyocytes following ischemia/reperfusion," *PLoS One*, vol. 8, no. 12, Article ID e82957, 2013.

[155] S. Zhu, T. Xu, Y. Luo et al., "Luteolin enhances sarcoplasmic reticulum Ca2+-ATPase activity through p38 MAPK signaling thus improving rat cardiac function after ischemia/reperfusion," *Cellular Physiology and Biochemistry*, vol. 41, no. 3, pp. 999–1010, 2017.

[156] Z. Jia, P. Nallasamy, D. Liu et al., "Luteolin protects against vascular inflammation in mice and TNF-alpha-induced monocyte adhesion to endothelial cells via suppressing IKBα/NF-κB signaling pathway," *The Journal of Nutritional Biochemistry*, vol. 26, no. 3, pp. 293–302, 2015.

[157] F. Xia, C. Wang, Y. Jin et al., "Luteolin protects HUVECs from TNF-alpha-induced oxidative stress and inflammation via its effects on the nox4/ROS-NF-kappa B and MAPK pathways," *Journal of Atherosclerosis and Thrombosis*, vol. 21, no. 8, pp. 768–783, 2014.

[158] A. De Stefano, S. Caporali, N. Di Daniele et al., "Anti-inflammatory and proliferative properties of luteolin-7-O-glucoside," *International Journal of Molecular Sciences*, vol. 22, no. 3, p. 1321, 2021.

[159] K. Meth, G. W. Plumb, J. G. Berrin et al., "Deglycosylation by small intestinal epithelial cell beta-glucosidases is a critical

step in the absorption and metabolism of dietary flavonoid glycosides in humans," *European Journal of Nutrition*, vol. 42, no. 1, pp. 29–42, 2003.

[160] K. Shimoi, H. Okada, M. Furugori et al., "Intestinal absorption of luteolin and luteolin 7-O-beta-glucoside in rats and humans," *FEBS Letters*, vol. 438, no. 3, pp. 220–224, 1998.

[161] R. Yin, F. Han, Z. Tang et al., "UFLC–MS/MS method for simultaneous determination of luteolin-7-O-gentiobioside, luteolin-7-O-β-d-glucoside and luteolin-7-O-β-d-glucuronide in beagle dog plasma and its application to a pharmacokinetic study after administration of traditional Chinese medicinal preparation: kudiezi injection," *Journal of Pharmaceutical and Biomedical Analysis*, vol. 72, pp. 127–133, 2013.

[162] S. M. Wittemer, M. Ploch, T. Windeck et al., "Bioavailability and pharmacokinetics of caffeoylquinic acids and flavonoids after oral administration of Artichoke leaf extracts in humans," *Phytomedicine*, vol. 12, no. 1-2, pp. 28–38, 2005.

[163] P. Zhou, L.-P. Li, S.-Q. Luo, H.-D. Jiang, and S. Zeng, "Intestinal absorption of luteolin from peanut hull extract is more efficient than that from individual pure luteolin," *Journal of Agricultural and Food Chemistry*, vol. 56, no. 1, pp. 296–300, 2008.

[164] J. T. Mukinda, J. A. Syce, D. Fisher, and M. Meyer, "Effect of the plant matrix on the uptake of luteolin derivatives-containing Artemisia afra aqueous-extract in Caco-2 cells," *Journal of Ethnopharmacology*, vol. 130, no. 3, pp. 439–449, 2010.

[165] M. T. Yasuda, K. Fujita, T. Hosoya, S. Imai, and K. Shimoi, "Absorption and metabolism of luteolin and its glycosides from the extract of Chrysanthemum morifolium flowers in rats and caco-2 cells," *Journal of Agricultural and Food Chemistry*, vol. 63, no. 35, pp. 7693–7699, 2015.

[166] K. Murota, Y. Nakamura, and M. Uehara, "Flavonoid metabolism: the interaction of metabolites and gut microbiota," *Bioscience, Biotechnology, and Biochemistry*, vol. 82, no. 4, pp. 600–610, 2018.

[167] Z. Chen, S. Zheng, L. Li, and H. Jiang, "Metabolism of flavonoids in human: a comprehensive review," *Current Drug Metabolism*, vol. 15, no. 1, pp. 48–61, 2014.

[168] L. Wu, J. Liu, W. Han et al., "Time-dependent metabolism of luteolin by human UDP-glucuronosyltransferases and its intestinal first-pass glucuronidation in mice," *Journal of Agricultural and Food Chemistry*, vol. 63, no. 39, pp. 8722–8733, 2015.

[169] N. Hayasaka, N. Shimizu, T. Komoda et al., "Absorption and metabolism of luteolin in rats and humans in relation to in vitro anti-inflammatory effects," *Journal of Agricultural and Food Chemistry*, vol. 66, no. 43, pp. 11320–11329, 2018.

[170] L. Wang, Q. Chen, L. Zhu et al., "Metabolic disposition of luteolin is mediated by the interplay of UDP-glucuronosyltransferases and catechol-O-methyltransferases in rats," *Drug Metabolism and Disposition*, vol. 45, no. 3, pp. 306–315, 2017.

[171] Z. Chen, M. Chen, H. Pan et al., "Role of catechol-O-methyltransferase in the disposition of luteolin in rats," *Drug Metabolism and Disposition*, vol. 39, no. 4, pp. 667–674, 2011.

[172] C. Deng, C. Gao, X. Tian et al., "Pharmacokinetics, tissue distribution and excretion of luteolin and its major metabolites in rats: metabolites predominate in blood, tissues and are mainly excreted via bile," *Journal of Functional Foods*, vol. 35, pp. 332–340, 2017.

[173] M. Huang, E. Su, F. Zheng, and C. Tan, "Encapsulation of flavonoids in liposomal delivery systems: the case of quercetin, kaempferol and luteolin," *Food and Function*, vol. 8, no. 9, pp. 3198–3208, 2017.

[174] Y. Liu, L. Wang, Y. Zhao et al., "Nanostructured lipid carriers versus microemulsions for delivery of the poorly water-soluble drug luteolin," *International Journal of Pharmaceutics*, vol. 476, no. 1-2, pp. 169–177, 2014.

[175] G. Wu, J. Li, J. Yue, S. Zhang, and K. Yunusi, "Liposome encapsulated luteolin showed enhanced antitumor efficacy to colorectal carcinoma," *Molecular Medicine Reports*, vol. 17, no. 2, pp. 2456–2464, 2018.

[176] P. Tawornchat, T. Pattarakankul, T. Palaga, V. Intasanta, and S. Wanichwecharungruang, "Polymerized luteolin nanoparticles: synthesis, structure elucidation, and anti-inflammatory activity," *ACS Omega*, vol. 6, no. 4, pp. 2846–2855, 2021.

[177] H. Yan, P. Wei, J. Song, X. Jia, and Z. Zhang, "Enhanced anticancer activity in vitro and in vivo of luteolin incorporated into long-circulating micelles based on DSPE-PEG2000 and TPGS," *Journal of Pharmacy and Pharmacology*, vol. 68, no. 10, pp. 1290–1298, 2016.

[178] C. Garbinato, C. A. Lima-Rezende, S. E. Schneider et al., "Investigation on the anticonvulsant potential of luteolin and micronized luteolin in adult zebrafish (Danio rerio)," *Neurochemical Research*, vol. 46, no. 11, pp. 3025–3034, 2021.

[179] M. A. Altamimi, A. Hussain, M. AlRajhi, S. Alshehri, S. S. Imam, and W. Qamar, "Luteolin-loaded elastic liposomes for transdermal delivery to control breast cancer: in vitro and ex vivo evaluations," *Pharmaceuticals*, vol. 14, no. 11, p. 1143, 2021a.

[180] M. A. Altamimi, A. Hussain, S. Alshehri, S. S. Imam, and U. A. Alnemer, "Development and evaluations of transdermally delivered luteolin loaded cationic nanoemulsion: in vitro and ex vivo evaluations," *Pharmaceutics*, vol. 13, no. 8, p. 1218, 2021b.

[181] L. Tan, C. Liang, Y. Wang, Y. Jiang, S. Zeng, and R. Tan, "Pharmacodynamic effect of luteolin micelles on alleviating cerebral ischemia reperfusion injury," *Pharmaceutics*, vol. 10, no. 4, p. 248, 2018.