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Potential therapeutic interventions of plant–derived isoflavones against acute lung injury

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ABSTRACT

Acute lung injury (ALI) is a life-threatening syndrome that possibly leads to high morbidity and mortality as no therapy exists. Several natural ingredients with negligible adverse effects have recently been investigated to possibly inhibit the inflammatory pathways associated with ALI at the molecular level. Isoflavones, as phytoestrogenic compounds, are naturally occurring bioactive compounds that represent the most abundant category of plant polyphenols (*Leguminosae* family). A broad range of therapeutic activities of isoflavones, including antioxidants, chemopreventive, anti-inflammatory, antiallergic and antibacterial potentials, have been extensively documented in the literature. Our review exclusively focuses on the possible anti-inflammatory, antioxidant role of botanicals'-derived isoflavones against ALI and their immunomodulatory effect in experimentally induced ALI. Despite the limited scope covering their molecular mechanisms, isoflavones substantially contributed to protecting from ALI via inhibiting toll-like receptor 4 (TLR4)/Myd88/NF-κB pathway and subsequent cytokines, chemokines, and adherent proteins. Nonetheless, future research is suggested to fill the gap in elucidating the protective roles of isoflavones to alleviate ALI concerning antioxidant potentials, inhibition of the inflammatory pathways, and associated molecular mechanisms.

1. Introduction

Lung diseases are characterized by various abnormalities in the stroma and alveoli of the lungs which may eventually lead to death. There are many forms of lung diseases investigated over the past century including acute lung injury (ALI), acute respiratory distress syndrome

Abbreviations: AP-1, activator protein 1; AKT, protein kinase B; ALI, acute lung injury; Ang-1, angiopoietin 1; Ang-2, Angiopoietin 2; ARDS, acute respiratory distress syndrome; BALF, bronchoalveolar lavage fluid; CINC, cytokine-induced neutrophil chemoattractant; COX-2, cyclooxygenase-2; DES, deep eutectic solvent; ERK5, extracellular signal-regulated kinase 5; GR-α, glucocorticoid receptor-α; GR-β, glucocorticoid receptor-β; HDL, high density lipoprotein; HGF, hepatocyte growth factor; ICAM-1, intercellular adhesion molecule-1; IL-10, interleukin-10; IL-13, interleukin-13; IL-18, interleukin-18; IL-1Ra, interleukin 1 receptor antagonist; IL-1β, interleukin-1beta; IL-4, interleukin-4; IL-6, interleukin-6; IL-8, interleukin-8; iNOS, inducible nitric oxide synthase; KGF, keratinocyte growth factor; LPS, lipopolysaccharides; MMP-9, Matrix metalloproteinase-9; MPO, myeloperoxidase; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor-kappa B; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2; PAI-**1**, plasminogen activator inhibitor-1; PI3K, phosphoinositide 3-kinases; RAGE, Advanced glycation end-products; STAT, signal transduction and activator of transcription; sTNFr, soluble tumor necrosis factor receptors; TGFBBR, transforming growth factor beta receptor; TGF-β, transforming growth factor-beta; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-alpha; MD-2, myeloid Differentiation factor 2; TAK1, transforming growth factor beta-activated kinase 1; TIRAP, toll/interleukin-1 receptor domain-containing adapter protein; TLR2, toll-like receptor 2; TRAM, Translocating chain-associated membrane protein; TRIF, TIR-domain-containing adapter-inducing interferon-β; VEGF, Vascular endothelial growth factor; VWF, von Willebrand factor; p38MAPK, p38 mitogen-activated protein kinases; ICAM-1, Intercellular Adhesion Molecule 1; MIP-2, Macrophage inflammatory protein-2; HO-1, Heme oxygenase-1; PPAR-γ, Peroxisome proliferator-activated receptor gamma; BALF, blood and bronchoalveolar lavage fluid; IFN-γ, interferon gamma; Nrf2/HO-1, nuclear factor erythroid-2-related factor 2/ heme oxygenase-1.

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(ARDS), asthma, chronic obstructive pulmonary disease (COPD), ischaemia reperfusion injury (LIRI), lung sepsis, etc. ALI and ARDS are severe health problems that frequently occur in many countries and cause death, particularly in children [1]. The history of (ALI) and (ARDS) dates back to 1915 when the Canadian Forces attempted to treat a soldier who suffered from a "shock lung" after exposure to a poisonous gas [2,3]. Afterward, in 1994 the American-European Consensus Committee adopted a revised classification that acknowledged the variation in the seriousness of lung injury [4].

ALI and its serious form, ARDS, are considered serious respiratory diseases that are manifested by symptoms of less and more severe hypoxemia, alveolar permeability, and alveolar edema [5]. Hence, early diagnosis of ALI/ARDS builds a baseline understanding of subsequent development or complications of the disease. For instance, the ratio of partial pressure arterial oxygen to the fraction of inspired oxygen, static lung compliance, and the visible infiltration degree on chest x-rays and lung injury score are commonly used in clinical trials for the diagnostic evaluation of the seriousness of ARDS [5,6]. Despite the therapies releases and multiple attempts to track their molecular mechanisms, ALI/ARDS studies have reported an alarming mortality rate reached up to 40–60%[7,8]. The annual incidence of ALI was highly manifested in the USA (approximately ≈ 70 cases/100,000 people) and ≈ 17 cases/100,000 people in Northern Europe with an estimated 74,500 deaths/year [9].

Although there is no strategy to describe a precise therapeutic approach to ALI/ARDS, the treatment of ALI/ARDS is substantially supportive and therapeutically focuses on treating the underlying clinical condition and bedside manner, including artificial ventilation and corticosteroids administration [10]. Most recent research on ARDS pathogenicity and therapy deals with investigating the underlying reason and prognosis of the possible plasma and molecular mechanisms associated with ALI development and its progression to ARDS [2]. Despite the numerous therapeutic interventions, there are no therapeutic preparations that could effectively treat ALI or reduce the subsequent high mortality rates. Therefore, alternative natural products with their bioactive compounds have recently been examined *in vivo* and *in vitro* thanks to their anti-inflammatory activities.

Phytoestrogens e.g., botanicals'– derived-bioactive compounds have attracted growing attention due to their ability to exhibit various biological functions e.g., anti-inflammation, antiaging, and anticancer when consumed in considerable amounts [11]. Isoflavones are bioactive compounds characterized by B ring with hydroxyl groups which show structural similarity to the human estrogen and accordingly function as phytoestrogens [12]. Genistein, daidzein, formononetin, biochanin A, and puerarin are the main isoflavones present in botanicals. These naturally occurring compounds exert various therapeutic functions such as anti-inflammatory, antioxidant, anti-oxidative stress, and immunomodulatory functions. Owing to their anti-inflammatory potentials, botanicals'-derived-isoflavones could be possibly utilized as a potential drug to alleviate the ALI [13,14]. According to the best of our knowledge, no previous published scoping reviews paid attention to identifying and analyzing the data linked to the potential role of isoflavones in treating ALI. This research may build a baseline understanding of the mechanisms of action of isoflavones as estrogenic receptors in the treatment of lung injury. As a sequence, our current review outlined the evidence of the previously published data regarding relevant potential anti-inflammatory, antioxidant activities of botanicals'-derived-isoflavones, immunomodulatory effect and highlighted their inflammatory inhibitory pathways and possible molecular mechanisms.

This review extensively navigated the relative published articles, papers, and books indexed in Scopus, Web of Science, PubMed databases. The investigations reported using the keywords mentioned above were approximately 515, out of which 332 were excluded and 183 studies met the eligibility criteria. The present findings diversely comprise review papers and articles from preclinical studies.

2. Etiology of ALI

The causes of ALI may be due to genetic factors, trauma (chest trauma), inhalation (aspiration of gastric contents), chemical and physical agents, or several microbial agents such as viruses and bacteria [15,16]. ALI incidence could also be due to indirect causes such as burns, sepsis, pancreatitis, near drowning or fat embolism and hyperoxia [17,18].

Acute viral pneumonia is considered a major cause of ALI [19]. Over the past two decades, the incidence of coronavirus has led to a variety of significant health events that consequently resulted in abrupt far-reaching epidemics such as Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), and coronavirus disease 2019 (COVID-19) [20]. Also, pandemic infection with the 2009 H1N1 influenza virus can lead to pneumonia and acute respiratory failure, often complicated by bacterial coinfection [21]. Other viral pathogens, such as rhinovirus, respiratory syncytial virus, and human metapneumovirus, may also cause lung injury through direct or indirect pneumonia [22].

A bacterial agent such as *Pseudomonas aeruginosa* is another cause of microbial lung infection; it is a Gram-negative pathogen that may cause a severe lung infection, resulting in significant lung injury and mortality in susceptible patients [23]. *Staphylococcus aureus* has also been recorded as the leading cause of community-acquired pneumonia [22]. In addition, *Escherichia coli* lipopolysaccharide and the bacteria themselves cause extreme ALI and rapid accumulation of inflammatory cells, leading to serious inflammation, lung vascular permeability, and pulmonary edema development [24]. Generally, individuals who experience multiple chronicity, chronic alcohol abuse, intensive care medicine, or chronic lung infections are highly susceptible to develop ALI [25–27].

3. Pathophysiology and biomarker of ALI

ALI is defined as an acute inflammatory disorder that promotes the disturbance in endothelial and epithelial lung cells. This could be the core concept of the pathogenesis of ALI, which involves multiple relevant symptoms such as losing the durability of the alveolocapillary membrane, uncontrolled transepithelial migration of neutrophils, and activated secretion of various cytotoxic and proinflammatory mediators [28,29]. Microvascular endothelial damage may result in decreased permeability of the capillaries. This permeability modification enables the release of protein-rich edema fluid into the peribronchovascular connective tissue (interstitium) and eventually passively moves through the epithelial barrier into the distal airspaces of the lung [30]. Various studies have reported that the increased expression of signaling pathways of von Willebrand factor (vWF) is associated with ALI [31,32] and upregulation of genes targeting the intracellular adhesion molecule-1 (ICAM-1) [33,34].

While inflammation is a significant barrier against infection and essential for tissue homeostasis, uncontrolled inflammation may reveal severe inflammatory conditions particularly in ALI [35,36]. Transepithelial neutrophil migration is considered a potential contributor to ALI since neutrophils are the key inflammatory mediators. Excessive or inappropriate prolonged activation of neutrophils was revealed to break down the alveolar basement membrane and hyperpermeability of the alveolocapillary barrier [37]. Neutrophils also were reported to trigger the release of harmful proinflammatory and proapoptotic tissue mediators, which may harm or cause injury or ulcerative lesions to the adjacent cells [37,38].

However, ALI could be further developing, even with a lack of invading neutrophils, suggesting that independent pathways of neutrophils may also result in respiratory manifestation [39]. Upregulation of chemokines and proinflammatory circulating cytokines occurs as a direct response after an infection or traumatic injury and is also considered a key marker of ongoing cellular damage and consequently, acute hypoxemic respiratory failure [40]. There are different

mechanisms involved in the pathophysiology of ALI, but the most common mechanisms and markers were listed in Table 1.

4. Pharmaceutical natural ingredients (PNIs) with potentials against ALI

Currently, supportive and pharmacological therapeutic interventions are considered the main two strategies for alleviating the symptoms of ALI [61]. Pharmacological therapy as anti-inflammatory and physiological therapies were reported to induce severe side effects which minimize their wide applications. Therefore, there is an urgent demand to discover novel therapeutic agents with minor toxicity. A variety of herbal preparations, PNIs and their potential derivatives in *in vivo* and *in vitro* studies have been contributed to prevent or alleviate the symptoms of ALI. In this regard, herbal Chinese medicines have been extensively proposed to make a fundamental contribution to treat ALI-associated-COVID-19 [62]. Therefore, plant-derived bioactive compounds have been recently utilized to prevent lung tissue from the progression of ALI. Besides, the treatment with PNIs was found to effectively target the inflammatory pathways associated with ALI and promote the regeneration of lung tissue [63]. Moreover, PNIs have been used to exert a potential role as immunomodulatory and anti-oxidative stress [64,65]. Furthermore, PNIs may act as a suppressive agent to the activation of NLRP3 inflammasome and GRP78/IRE1α/JNK pathway induced by lung injury [66,67]. For instance, flavonoids, alkaloids, terpenoids, polyphenols, coumarins and saponins were widely demonstrated to exert anti-ALI via multiple mechanisms [68,69]. Among flavonoids, isoflavones have been found to exhibit anti-inflammatory and immunomodulatory effects and prevent oxidative stress in both clinical and preclinical investigations [70]. Hence, the current discourse around herbal extracts and their isolated PNIs has shown encouraging results to modulate the expressions of different inflammatory mediators in ALI. Our current review reveals a high number of potentially relevant reports that highlighted the therapeutic interventions of plant-derived isoflavones against ALI.

5. Chemistry and occurrence of isoflavones

Isoflavones are flavones with an aromatic B ring attached to C-3 instead of C-2. These structural properties allow isoflavones to mimic the functions of phytoestrogens, which exhibit mild estrogenic activity compared to estrogen [71]. Isoflavones are phytochemicals that exist mainly in various plants and are widely distributed in many species belonging to the *Leguminosae* family [72]. These phytochemicals, including aglycones and glycosides, are considered the most remarkable compounds of the botanical sources, e.g., soybean, red clover, and kudzu. Besides, these botanicals contain a considerably large quantity of phytochemicals (flavonoids and non-flavonoids). Each group of these plants constitutes a unique isoflavone profile. The structural form isoflavones occur predominantly as glycosides forms and are rarely found in nature as aglycons [73–75]. Although different forms exist in the plant-based products ingested, the fate of isoflavones in our body is greatly different [76]. It was stated that aglycones are superior to glucosides in different biological activities due to the fast absorption through the intestinal enterocytes [77].

The current discourse around incorporating the plant-derived bioactive natural ingredients (secondary metabolites) both individually or in combinations has successfully been implemented and exhibited various pharmacological activities. Within this context, botanicals' derived isoflavones have demonstrated significant implications to be used for the treatment of lung injury especially ALI [78–80]. However, the complete understanding of the protective effects of structure-associated isoflavones against ALI remains obscure.

There are four main molecules of aglycone isoflavones in soybean isoflavones: daidzein, genistein, and quite low quantity of glycitin and coumestrol (isoflavone aglycones). Also, they exist as their

Table 1
Common mechanisms and biomarkers of acute lung injury (ALI).

Mechanisms	Sample sources	Pathogenesis role	References
Pro-inflammatory	Plasma	Neutrophil recruitment and activation Cofactor for lymphocyte differentiation and activation	[41]
	Plasma BALF	↑ the alveolar barrier permeability Overexpression of inflammatory cytokines and chemokines Inflammatory and immune cells recruitment Pro-fibrotic effect Fusion and repair of epithelium	[41]
	Plasma	Enhanced adherence of neutrophils Enhanced adherence of macrophages	[42]
	Plasma BALF	Activation and differentiation of B and T lymphocytes Monocyte-macrophage activation Repair of damaged epithelium and cyto-protection of endothelial cells	[42,43]
	Plasma BALF	Recruitment of inflammatory mediators Activated neutrophils Upregulated expression of adhesion molecules	[43,44]
	Plasma BALF	Enhancement of IL-6 effects	[45]
	Plasma BALF	Overexpression of inflammatory cytokines and chemokines Inflammatory mediators Recruitment Indirect promotion of pulmonary edema	[46,47]
Anti-inflammatory	Plasma BALF	Anti-inflammatory and IL-1 β receptor antagonist	[48]
	Plasma	↓ TH expression or differentiation ↓ chemokine and cytokine efflux Suppression by neutrophils	[49]
	Plasma BALF	Repair of Epithelium ↓ pro-inflammatory cytokines synthesis ↑ release of IL-1Ra Pulmonary fibrotic effect	[50]
	Plasma BALF	Modulates TNF-α activity	[51]
Pleiotropic	Plasma	↓ pro-inflammatory cytokine stimulation ↑ release of IL-1Ra	[52]
	Plasma	↓ expression and regulation of pro-inflammatory adhesion molecules	[52]
Coagulation	Plasma BALF	Regulation of fibrinolysis and fibrin clots dissolution	[42]
	Plasma	Activator of endogenous anticoagulation Improves endothelial permeability Suppresses pro-inflammatory cytokines	[42]
	BALF	↓ deposition of fibrin ↓ accumulation of leukocyte ↓ permeability pulmonary edema	[42]
Growth factor	Plasma	Promotes endothelial and epithelial apoptosis Causes barrier dysfunction	[53]
	BALF	Mitogen for alveolar epithelial cells Repair of Epithelial cells	[54,55]
	BALF	Mitogen for alveolar epithelial cells Repair of Epithelial cells	[56]
	Plasma BALF	↑ vascular permeability ↑ endothelial cell survival and proliferation	[57]
Epithelial cell -type II marker	Plasma BALF	↓ surface tension Grant innate immunity	[58,59]
Epithelial cell-type I marker	Plasma BALF	Release of pro-inflammatory cytokines, ROS, and protease optimization	[60]
Endothelial cell marker	Plasma BALF	Hemostasis and platelet function	[59]

Ang-1; angiopoietin 1, **HGF**; hepatocyte growth factor, **ICAM-1**; intercellular adhesion molecule 1, **IL-18**; interleukin-18, **IL-1Ra**; interleukin 1 receptor antagonist, **KGF**; keratinocyte growth factor, **PAI-1**; plasminogen activator inhibitor 1, **RAGE**; advanced glycation end-products, **sTNFr**; soluble tumor

necrosis factor receptors, **TGF-*β*;** transforming growth factor-beta, **VEGF**; vascular endothelial growth factor, **VWF**; von Willebrand factor

corresponding glycosides (daidzin, genistin, and glycitin) [81]. Most of the isoflavones in foods as glycoside conjugates, which could be attributed to the extraction conditions were fully reviewed elsewhere [82]. The naturally occurring glycosylated and derived forms are usually maintained by extracts obtained from soybean. Previous literature attempted to sulfonate genistein in order to improve its bioavailability. This was a significant step towards synthesizing a comparatively more hydrophilic compound, namely genistein-3′-sodium sulfonate (GSS) [3].

In red clover, the methoxy derivative isoflavones, which differ from those that exist in soy products, are formononetin and biochanin A, the latter being present in the form of aglycone. The formononetin glycosylated form is called ononin [83]. In kudzu (*Pueraria* genus*)*, puerarin was reported to be the most prominent isoflavone [84]. Other available isoflavones include (chickpeas, peas, shell beans, lentils, mungo beans, and alfalfa sprouts) which comprise a quite lower quantity of isoflavones but still not negligible. Food and Agriculture Organization (FAO) of the United Nations estimated the annual needs of kudzu and soybeans between 50 and 217.6 million tons, respectively [85,86]. Notably, FDA claimed that the threshold consumption level of soy protein to exhibit health benefits is 25 g [87].

The health benefits of isoflavones are complex and largely driven by the source, active ingredients, and bioactive compounds. Hence, the physicochemical properties of isoflavones promoted a substantial contribution to bioavailability *in vivo* and *in vitro*. Therefore, synthesizing isoflavone derivatives, e.g., genistein-3′-sodium sulfonate, revealed many potentially relevant and influential pharmaceutical functions [88]. The most abundant representative aglycones and glycoside chemotypes are presented in Table 2.

6. Potentials of isoflavones as an alternative treatment

Although several researchers have potentially contributed to understanding the ALI development at the molecular level, no therapeutic preparations have knocked out its treatment [95]. Moreover, corticosteroids have been utilized for many years to alleviate ALI symptoms [96,97]. Therefore, developing new bioactive compounds that potentially contribute to treating life-threatening diseases such as ALI is essential. This approach is fundamentally necessary to reduce the adverse effects resulting from the administration of corticosteroids. Therefore, naturally occurring bioactive agents were potentially overviewed to make a significant transition from the currently available medicines to therapeutic substitutes or complementary treatments to existing therapies that could be the starting point to release a new drug to the market [98–100].

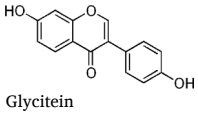
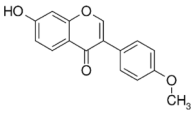
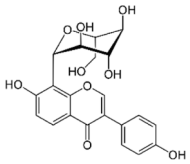
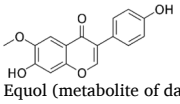
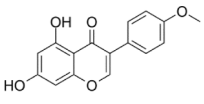
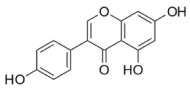
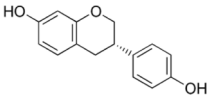
Isoflavones, in general, are involved in protection against ultraviolet radiation, mechanical damage, or environmental attack via electron transport during photosynthesis [101]. The similarity of isoflavones to β-estradiol has demonstrated protection against age-related and hormone-dependent diseases. In the same context, isoflavones were reported to possibly exhibit estrogen-agonist and estrogen-antagonist activities [102].

Substantial shreds of evidence confirmed the health benefits of the consumption of these isoflavones. In addition, previous studies have shown various pharmacological potentials of isoflavones, e.g. antioxidant, anti-inflammatory, anti-metastatic, and anticancer activities [88]. Moreover, it was reported that isoflavones may possibly alleviate the postmenopausal symptoms in women [103–105]. Thus, Japan has declared a recommended daily dietary dose of isoflavones allowance of 15 – 22 mg supplementation/day for a 60-kg man [106,107]. Consequently, it is technologically and economically valuable to recover isoflavones from plant sources for various pharmacological purposes [85,108].

In many *in vivo* experiments, potential health benefits of phytoestrogens present in the food sources were reported to show possible biological activities such as antidiabetic, antihypertension, antiosteoporosis, and skin aging [109–111]. Additionally, a metabolite of daidzein named “equol”, a metabolic product that results from the action of intestinal microflora, has been found to possibly demonstrate higher estrogenic potency, antioxidative and antiandrogenic properties [112]. Due to the limited scope covering the pharmaceutical potentials of botanical sources, a pressing challenge exists to investigate the effect of their active ingredients “isoflavones” on lung diseases particularly ALI.

The mechanisms of action of isoflavones as phytoestrogen are primarily based on their binding to the α or β estrogenic receptors (ERs). The selective activity of isoflavones as agonists or antagonists is exclusively dependent on their binding activity [113,114]. Therefore, regardless of the common structural similarities to the human hormone estrogen, isoflavones exhibit different biological activities in the body dependant on their binding affinity to either ERα or Erβ. At the same time, the effect of isoflavones administration is largely complex and driven by the source, active compound sex, dose, and administration period.

Table 2
Description of the botanical sources of isoflavones in some potential plants [89–91]

Variables	Soybean	Red clover	kudzu
Botanical family	*Fabaceae / Leguminosae – Pea family*	*Fabaceae / Leguminosae – Pea family*	*Fabaceae / Leguminosae – Pea family*
Scientific name (species)	*Glycine* max	*Trifolium pratense*	*Pueraria* spp.
Major isoflavones	Daidzein, genistein and glycitein	Formononetin and biochanin A	Puerarin, daidzein and genistein
Chemical structure	Daidzein	Formononetin	Puerarin
	 Glycitein	 Biochanin A	 Genistein
	 Equol (metabolite of daidzein)		
			
Isoflavone content	0.01 % – 3 % [92]	0.14 % – 1.2 % [93]	1.8 % – 12 % [94]

For instance, isoflavones (daidzein and genistein) were addressed to modulate the protective response against ALI via activating the expression of NO and improving the expression of inducible nitric oxide synthase (iNOS) by ERα pathway [115]. In another study, it was reported that ER pathway was involved in inhibiting the pulmonary arterial hypertension (PAH) induced hypoxia. Similarly, ERβ was documented to restore the lung inflammation and fibrosis in PAH after the administration of genistein [116]. This could be explained by the fundamental role of these isoflavones to act against oxidative stress and enhance cell regeneration. In this regard, previous research has revealed the ability of soy isoflavones to upregulate the ERβ and Bcl-2/Bax expression and modulate PI3K pathway induced by oxidative stress [117]. Despite attempting to understand the mechanisms of action, the full role of isoflavones as binding agents to estrogenic receptors in modulating ALI was poorly investigated and requires further refinement and scrutiny.

Interestingly, male mice are more susceptible to ALI than females' counterparts [118]. Clinically, isoflavones administration has shown different interactions among women and men. It has been observed that women demonstrated higher values of IL-6 values after soy diets high in isoflavones. Similarly, in preclinical studies, it has been declared that the effect of isoflavones intake is sex dependant. Consumption of isoflavones or diet-containing isoflavones may stimulate bone formation in male mice and the opposite action in females' counterparts [119]. In other contradicting studies, it has been claimed that isoflavones may possibly affect the development of reproductive system and puberty in both males and females [120]. Despite the fact that there is no consensus about their effect as estrogenic receptors, nobody can deny the beneficial therapeutic potentials of isoflavone, particularly in ALI.

7. Role of isoflavones against lung injury

Lung injuries involve acute and chronic inflammation that comes up as a response to repair the damaged lung tissues and, at the same time, is associated with lung dysfunction. Isoflavones, in this regard, were documented to possess prospective anti-inflammatory and antioxidant properties that can alleviate the symptoms of lung diseases.

Recently, the protective mechanisms of glabridin, a type of isoflavones, were evaluated in lipopolysaccharide (LPS)-induced ARDS in rats. The lung injury was alleviated via inhibiting the p38MAPK and ERK signaling pathway, enhancing the antioxidant enzymes and reducing the inflammatory biomarkers [121,122]. Additionally, the combination of puerarin with edaravone was investigated against black gunpowder smog-induced lung injury. The author stated that this combination could be a prospective drug treatment against ALI/ARDS. The combined treatment was demonstrated to significantly reduce the lung MPO activity, prevent the increase in IL-6 and TNF-α and total protein in BALF, and improve the inflammatory exudates in lung tissues [123].

Likewise, daidzein and genistein were found to show an ameliorative effect against chronic obstructive pulmonary disease (COPD) in cigarette smoke-induced emphysema in a murine model. The experimental group administrated with isoflavones showed a significant attenuation in inflammatory cells and gene expression of TNF-α and CXCL2 (MIP-2) [124]. Another preclinical research conducted on experimental rats suffered from COPD concluded that animals administrated with daidzin revealed an improvement in the lung injury by declining Caveolin-1 and via Wnt/β-catenin signaling pathway [125]. Needless to say, that COPD is a fatal disease affecting over 100 million people and is mainly caused by the inhalation of cigarette smoke and environmental pollutants [126].

Based on the literature review, several researchers paid attention to the contribution of isoflavones in the treatment of asthma. Asthma is a chronic airway inflammatory disorder characterized by difficulty in breathing and episodes of coughing, chest tightness, and obstruction in the lung airflow. It affects the lower mucosa of the respiratory tract through increased production of IL–4, IL–13, IL–5 and IL–9 [127]. In a recent study, it was reported that, biochanin A effectively ameliorated the markers associated with airway inflammation in ovalbumin (OVA)-induced asthma in a mouse model. Further, they demonstrated that anti-inflammatory actions of biochanin A are mediated through a nuclear receptor PPARγ [128]. Similarly, Tectorigenin was also recorded to be a promising therapy against asthma through TGF-β1/Smad signaling pathway and TLR4/NF-κB signalling pathway [129]. Moreover, it was reported the potential effect of puerarin against OVA-induced asthma in mice via inhibiting eotaxin-3 [130]. Besides, puerarin was found to decrease the oxidative stress by regulating the secretion of interleukin (IL)-4, IL-5, IL-13 levels and increasing the level of interferon gamma (IFN-γ) in bronchoalveolar lavage fluid. Not only do isoflavones serve as bioactive therapeutic compounds but also a diet enriched with isoflavones (genistin and daidzin) have been investigated to reduce the pulmonary antigen-induced eosinophilia of asthma model in guinea pig [131].

Isoflavones also have made a substantial contribution to the treatment of lung ischaemia–reperfusion injury (LIRI). LIRI is a severe clinical disease affecting the patient after lung transportation in which a restriction of blood supply to lung tissues is visible. Zheng et. al. has utilized puerarin (30 mg/kg) to protect against pulmonary ischemia and reperfusion injury in rabbits. The results demonstrated that puerarin was efficient to alleviate the pulmonary changes via decreasing pulmonary cell apoptosis and inhibiting Fas/FasL mRNA expression in rabbits [132]. However, it is clear from the literature that a limited number of reports covered the effect of isoflavones on LIRI.

Also, few numbers of studies focused on the effect of isoflavones on sepsis-induced lung injury. Genistein-3′-sodium sulphonate (1 and 10 mmol L^{-1}) was shown to protect against sepsis-induced ALI through regulating Myd88/NF-κB/BCL-2 signaling or decreasing the expression of TNF-α and IL-6 via the Myd88/NF-κB signaling pathway [88,133]. Another study revealed that daidzein (1 mg/kg b. wt.) relieved the lung injury symptoms by reducing inflammatory enzyme activities and increasing the survival time in septic mice [134].

To conclude, although a high number of potentially relevant and influential studies have revealed that different types of isoflavones are beneficial in controlling lung diseases, the complete understanding of their mechanism of action is yet obscure.

8. Isoflavones and ALI

8.1. Effect of isoflavones against ALI

8.1.1. Anti-inflammatory effect of isoflavones against ALI

The naturally occurring bioactive compounds have been revealed to contribute to treating inflammation and other relevant disorders substantially. This could importantly provide an opportunity for releasing novel drugs to treat various inflammatory manifestations. The ability of these compounds to reduce inflammation in the lungs has been explored in cell cultures and animal models [135]. Several significant findings have highlighted the molecular mechanisms of these bioactive substances with relevance to the inhibition of NF-κB, which in turn inhibit Toll-like receptors (TLRs) signaling pathways [14,88,133,136–139] as represented in Table 3 and Fig. 1. Inhibition of NF-κB consequently inhibits cytokines, chemokines, and adhesion molecules that attenuate ALI inflammatory process.

The MEK5/ERK5 (mitogen-activated protein kinase 5/extracellular signal-regulated kinase 5) and NF-κB signaling pathways are closely related to ALI induction. Xue et al. [136] studied the MEK5/ERK5 and NF-κB signaling pathways in adenocarcinoma human alveolar basal epithelial (A549) cells exposed to ambient fine particulate matter (PM2.5). Injured A549 cells showed upregulations in MEK5/ERK5 and NF-κB pathways. On the contrary, A549 cells treated with biochanin A significantly reduce MEK5, ERK5, and NF-κB expression. Similarly, biochanin A inhibited lipopolysaccharide (LPS)-induced nitric oxide

Table 3
Possible protective mechanism of actions of isoflavones against ALI.

Bioactive compounds	Animal/cell	Mechanism of action	ALI induction method	References
Biochanin A	Adenocarcinoma human alveolar basal epithelial cells (A549 cells)	↓MEK5/ERK5 expression ↓NF-κB activation	Ambient fine particulate matter (PM2.5)	[136]
Daidzein	Rat/ A549 cells	↓MPO activity ↓TLR4 ↓MyD88 protein and ↓NF-κB activation in lung	LPS	[14]
	Mice	↓TNF-α ↓MPO activity ↓iNOS ↓GR-α, and GR-β genes in lung	Cecal ligation and puncture	[14]
Genistein	Rat	↓CINC ↓MMP-9 ↓NF-κB	LPS	[137]
	Rat	↓MMP-9 ↓NF-κB ↓NO	LPS	[138]
	Rat	↓MPO activity in cell-free BALF ↓ICAM-1 expression in lung	LPS	[146]
	Mice	↓COX-2 expression ↓TGFBR1 and TGFBR2 expressions	Radiation	[150]
	A549 cells	↓MEK5/ ERK5/NF-κB signaling pathway	Particulate matter (PM2.5)	[136]
	Mouse lung epithelial (MLE)-12 cells	↓TNF-α, ↓IL-6, and ↓IL-1β ↓NF-κB	LPS	[139]
Genistein-3′-sodium sulfonate	Lung vascular endothelial cell (EC)	↓TNF-α and ↓IL-6 ↓Myd88/NF-κB signaling pathway	LPS	[88]
	Mice	↓TNF-α and ↓IL-6 in the lung and serum ↓Myd88/NF-κB signaling pathway	LPS	[133]
Formononetin	Mice	Reduction of hyperoxia-induced ALI Nrf2/HO-1-mediated antioxidant and anti-inflammatory potentials	Hyperoxic ALI	[152]
	Mice	↓ BALF ↑ PPAR-γ gene expression ↑ SOD	LPS	[153]

CINC; cytokine-induced neutrophil chemoattractant, **COX-2**; cyclooxygenase-2, **ERK5**; extracellular signal-regulated kinase 5, **GR-α**; glucocorticoid receptor-α, **GR-β**; glucocorticoid receptor-β, **ICAM-1**; intercellular adhesion molecule-1, **IL-1β**; interleukin-1beta, **IL-6**; interleukin-6, **iNOS**; inducible nitric oxide synthase, **LPS**; lipopolysaccharides, **MMP-9**; matrix metalloproteinase-9, **MPO**; myeloperoxidase, **MyD88**; myeloid differentiation factor 88, **NF-κB**; nuclear factor-kappa B, **NO**; nitric oxide, **TGFBR**; transforming growth factor beta receptor, **TLR4**; toll-like receptor 4, **TNF-α**; tumor necrosis factor-alpha, **SOD**; superoxidase dismutase, ↓ refers to downregulation or decrease

(NO) production in macrophage (BV2 microglia) [140], RAW264.7 cells [141] and myocardial ischemia/ reperfusion injury in rats [142] through downregulation of NF-κB.

After 30 min intratracheal instillation of LPS (5 mg/kg), daidzein was intraperitoneally injected by doses of 2, 4, 8 mg/kg in rats [14]. The authors stated that daidzein treatment remarkably improved the pulmonary histology and significantly inhibited macrophages and neutrophils infiltration of lung tissues along with inhibition of MPO activity. Moreover, daidzein effectively reduced the inflammatory cytokines in BALF in response to inhibition of LPS-induced TLR4 and MyD88 protein overexpression and NF-κB activation in lung tissues due to LPS. These data indicate that the anti-inflammatory effects of daidzein against LPS-induced ALI were exhibited via inhibiting TLR4-MyD88-NF-κB pathway suggesting the potential therapeutic effect of daidzein against LPS-induced ALI. Also, a potential impact was stated when daidzein was subcutaneously pre-treated at a dose of 1 mg/kg body weight for a week after observing the improvement of survival time of septic mice. Daidzein was also documented to decrease the risk of bacterial invasion in the blood, lungs, peritoneal fluid, and plasma level of TNF-α. Furthermore, the glucocorticoid receptor α (GR-α), associated mRNA expressions of iNOS, and glucocorticoid receptor β (GR-β) genes were reported to be restored following the administration of daidzein in septic lungs [134]. Consequently, downregulation of iNOS reduced NO production, resulting in alleviating the inflammation [143].

8-Hydroxydaidzein (8-HD) is a daidzein metabolite isolated from soybeans that diminish the gene expressions of iNOS, COX-2, and TNF-α in macrophage-like RAW264.7 cells by regulating the transcriptional activities of NF-κB and activator protein 1 (AP-1), suggesting the potential use of 8-HD as an anti-inflammatory drug [144].

Myeloperoxidase (MPO) activity was reported to be abundantly expressed, particularly in neutrophil granulocytes. The hypohalous acids produced by the action of MPO contribute to exhibiting their antimicrobial activity. Still, apolipoprotein A-I (apoA-I) undergoes oxidation by MPO that subsequently reduces the high-density lipoprotein (HDL)-mediated inhibitory mechanisms of apoptosis and inflammation, thereby minimizing the inflammation progress [145]. Daidzein and genistein successfully inhibited MPO activity and controlled the inflammatory process in ALI [14,134,146].

Genistein as an isoflavone abundantly found in soy plays an important role in preventing various chronic diseases including cancer [147]. It may serve as a potential supplement in preventing hepatic and renal inflammatory diseases [148,149]. Furthermore, genistein induced significant decreases in NF-κB, leading to reduction of cytokine-induced neutrophil chemoattractant (CINC), NO, matrix metalloproteinase-9 (MMP-9), cyclooxygenase-2 (COX-2), TNF-α, IL-6, IL-1β, transforming growth factor-beta receptor (TGFBR)-1, and (TGFBR)-2 [136–138,146,150]. Moreover, genistein-3′-sodium sulfonate significantly inhibited MyD88 /NF-κB, leading to a potential impact in reducing TNF-α and IL-6 expression, alleviating the risk of inflammation in pulmonary vascular endothelial cell (EC) [88] and mice models [133]. Generally, genistein and genistein-3′-sodium sulfonate are considered promising natural bioactive compounds of anti-inflammatory effect.

Formononetin has exhibited a variety of pharmacologic activities including anti-inflammatory effects, particularly in respiratory diseases. Formononetin treatments appeared to inhibit the activation of NF-κB dramatically and significantly elevated the expression of HO-1 [151]. The pretreatment using formononetin has demonstrated a reduction in hyperoxia-induced ALI through the antioxidant and anti-inflammatory effects mediated by Nrf2/HO-1 [152]. In addition, other research outlined that the formononetin has contributed to decreasing BALF, enhancing PPAR-γ gene expression and SOD activity with a prominent improvement in the pulmonary histological properties [153].

8.1.2. Effect of isoflavones against oxidative stress in ALI

Oxidative stress is defined as an increase in the intracellular reactive

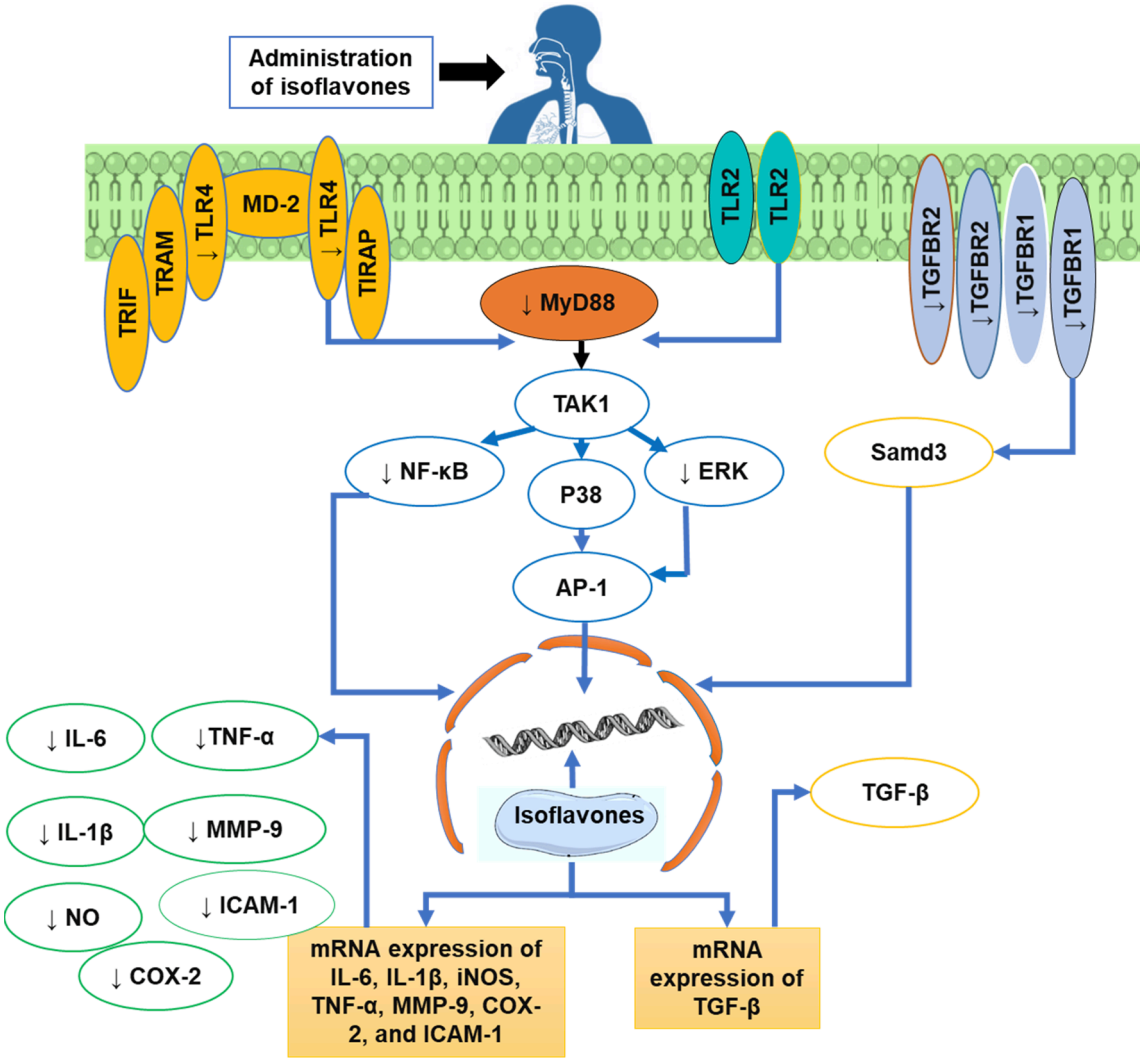


Fig 1. Effect of some major isoflavones on NF-κB and cytokines (designated for this review). **AP-1**; activator protein 1, **COX-2**; cyclooxygenase-2, **ERK**; extracellular signal-regulated kinase, **ICAM-1**; intercellular adhesion molecule-1, **IL-1*β***; interleukin-1beta, **IL-6**; interleukin-6, **iNOS**; inducible nitric oxide synthase, **MMP-9**; matrix metalloproteinase-9, **MyD88**; myeloid differentiation factor 88, **NF-κB**; nuclear factor-kappa B, **NO**; nitric oxide, **MD-2**; myeloid Differentiation factor 2, **TAK1**; transforming growth factor beta-activated kinase 1, **TGFBR**; transforming growth factor beta receptor, **TIRAP**; toll/interleukin-1 receptor domain-containing adapter protein, **TLR2**; toll-like receptor 2, **TLR4**; toll-like receptor 4, **TNF-*α***; tumor necrosis factor-alpha, **TRAM**; Translocating chain-associated membrane protein, **TRIF**; TIR-domain-containing adapter-inducing interferon-*β*. ↓ Refers to downregulation or decrease.

oxygen species (ROS) such as malondialdehyde (MDA), H_2O_2, superoxide, hydroxyl radical that lead to an increase the interleukins and inflammatory mediators [154]. Isoflavones are well-recognized bioactive compounds that exert antioxidant activities, decreasing oxidative stress and inflammation in ALI. Generally, isoflavones are secreted in plants to play a significant role in scavenging ROS derived from hazardous environmental conditions.

The antioxidant activity of non-glycosylated flavonoids is exhibited due to the number of hydroxyl groups in the molecule [155]. In ALI, intraperitoneal injection of formononetin (100 mg/kg b. wt) was revealed to exhibit antioxidant activity by reducing hyperoxia-induced ALI via enhancing Nrf2/HO-1 expression [152]. According to Ying et. al, (12.5 ~ 50 μM), iridine, a natural type of isoflavones, efficiently minimized glucose uptake, lactate production. In addition, iridine was recorded to exert antioxidant activities, inhibit ROS production and release of MCP-1 and TNF-α in a dose-dependent manner [156]. As stated by Zhang et al., glabridin (30 mg/kg orally) played a significant role in inhibiting inflammatory markers and suppressing the activation of the p38MAPK and ERK signaling pathway in LPS-induced ARDS. Moreover, glabridin mediated the inhibition of inflammatory protein expressions and lowered surfactant protein A in lung tissues [121,122].

Soy isoflavones administration in experimental animals were documented to enhance the activation of antioxidant enzymes after treadmill exercise for 30 mins e.g., SOD, glutathione peroxidase, and catalase [157]. Soy isoflavones were also found effective to reduce the infiltration of neutrophils after the irradiation of the lungs. It was suggested that isoflavones that exist in soy showed potential protection to the lung parenchyma after irradiation from the infiltration and activation of macrophages and neutrophils [158].

Similarly, tephrosin is a rotenoid isoflavonoid that is recognized for its ability to reduce inflammatory lymphocytes in mice and also decrease oxidative stress and cytokine production [159]. Yang et al. highlighted the potential effect of tephrosin (60 mg/kg) in attenuating ALI via reducing the ICAM-1 and MIP-2 in the lung tissues [160].

According to Chen et al. the administration of puerarin has protected the rabbits from acute pulmonary thromboembolism. Puerarin was documented to significantly decline the plasma malondialdehyde content and increase the plasma superoxide dismutase level. The conclusion found was that puerarin has potentially played an antioxidant role against the development of acute pulmonary thromboembolism. Other

evidence suggested that formononetin may reduce oxidative stress via enhancing the activity of superoxide dismutase and regulating the expression of HO-1 [152]. In another study, pre-treatment of hyperoxia-induced ALI using formononetin was revealed to decrease hypoxia symptoms via Nrf2/HO-1-mediated antioxidant and anti-inflammatory activities [161].

Additionally, genistein (200 mg/kg) has shown significant protection against ALI. The antioxidant, free radical scavenging properties of genistein assisted in ameliorating both the acute effect of ionizing radiation via preventing fibrosis and the decline in TGF beta receptor 1 (TGFβRI) [150]. Overall, thanks to their ability to hinder tissue oxidation, isoflavones have been widely examined in many studies. However, there is still limited research conducted for understanding their complete mechanisms of action as anti-oxidative stress.

8.1.3. Immunomodulatory effect of isoflavones against ALI

There have been observed potential outcomes for the beneficial effect of isoflavones on the immune system *in vitro* or *in vivo* studies. Isoflavones exert immuno-modulator functions by reducing the inflammatory markers and declining oxidative stress [154]. For instance, soy isoflavones at the dose of 1 mg per day were demonstrated to be associated with increasing Arginase-1 expression in radiation-induced lung injury. The findings stated that soy isoflavones contributed to the protection of Arginase–1-positive expression by Myeloid-derived suppressor cells, which in turn, aid to inhibit the development of radiation-induced NF-κB and inflammatory cytokines [162].

TNF-α, IL-1β, and IL-6 are proinflammatory cytokines in the development of ALI which play a major role against innate immunity. The study investigated by Hu et al. suggested that biochanin A may inhibit the activation of TLR4/NF-κB and promote the expression of PPAR-γ in ALI that in turn will enhance the innate immune system [163]. Additionally, after the supplementation of soybean diet (1,500 mg total soy-derived isoflavones) to pig meals, immunological health benefits against porcine reproductive and respiratory syndrome virus were observed in young pigs. The results of this research demonstrated a reduction of neutrophilia and improvement of cytotoxic-to-helper T-cell ratios, which significantly assisted in the activation of the immune system [164,165]. Recently, sophoricoside, an isoflavone glycosidic extract from *Sophora japonica* seeds, was examined against LPS-induced ALI. The extract was believed to have anticancer, anti-inflammatory, antioxidant activities and immunomodulatory activities [166,167]. The study found out that administration of sophoricoside at the level of 20 mg/kg intraperitoneally (i.p.) after injection of LPS has significantly attenuated pathological damage, tissue permeability, neutrophil infiltration. Moreover, the mouse pre-treatment with sophoricoside reduced proinflammatory cytokines (TNF-α, IL-1β and IL-6) and mediators (iNOS, NO) in LPS-induced RAW264.7 cells and BMDMs [168]. In a preclinical tumor study, soy isoflavones exhibited radioprotective via inhibiting the immune-inflammatory cytokines in lung tissue [169]. Another study similarly concluded soy isoflavones concluded that soy isoflavones substantially contributed to promoting arginase −1-expressing granulocytic-MDSCs that may downregulate the immune-inflammatory cells and enhance lung radioprotection [170]. Furthermore, genistein was elucidated to significantly alleviate the lung damage induced by radiation in Sprague-Dawley rats. The immune-modulatory activity was investigated to be due to the contribution of genistein to diminish IL-1β and TNF-α and TNF-α levels [171]. Another compound, formononetin, was examined to exert immunomodulatory function via exhibiting antioxidant and anti-inflammatory potentials by abolishing Nrf2/HO-1 expression in mice [161]. Besides, puerarin was reported to promote T-helper cell type-1 (Th1) immunity and diminish Th2 and Th17 inflammatory responses in ALI induced by gunpowder smog. These findings also highlighted the role of puerarin to reduce the pathological degeneration in lung tissues e.g., inflammatory cells infiltration and vascular leakage [172].

Generally, isoflavones exert immunomodulatory regulatory actions and directly enhances the immune response by increasing the proliferation and maturation of natural killer cells, monocytes, granulocytes and T and B lymphocytes. However, the full understanding of immune-modulatory effect involved in mitigating the immune response of ALI is still obscure and requires further experimental research.

9. Effects of isoflavones against other inflammatory-related diseases

In recent decades, there have been extensive experimental studies that indicated the beneficial role of isoflavones as anti-inflammatory agents [13]. Notwithstanding the broad range of biological potentials against ALI, isoflavones originally were speculated to exert anti-inflammatory actions against other inflammatory-related diseases. Autoimmune diseases are autoinflammatory health concerns in which the immune system activates against self-antigens and results in possible severe inflammatory reactions e.g., type 1 diabetes mellitus (TI-DM) systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD) with its subtypes, Crohn's disease and ulcerative colitis (UC), rheumatoid arthritis (RA), experimental autoimmune encephalomyelitis (EAE) and multiple sclerosis (MS). The anti-inflammatory activities of isoflavones are organically speculated due to their ability to down-regulate cytokines-induced signaling pathways in the immune cells [173]. Recently, soy protein isolates revealed anti-inflammatory functions in experimental animals with RA via inhibiting TNF-α, MMP-9, anticyclic citrullinated peptide and MDA [174]. Similarly, soy isoflavones were examined to reduce IFN-γ secretion and alleviate the symptoms of lupus through their binding affinity to ERβ than Erα [175,176]. In other *in vivo* experiments, isoflavone administration was efficient enough to alleviate EAE through the reduction of both IFN-γ and IL-12 secretions and lymphocyte proliferation (daidzein,300 mg/kg) as well as modulating the gut microbiome [177,178].

In addition, isoflavones (genistein and daidzein) exhibited their anti-inflammatory properties in IBD through negative regulation of neural stem/progenitor cell maintenance and minimizing wound-repair reaction [179–181]. At the same time, isoflavones were stated to be a potential replacement therapy to diminish the complication of diabetes mellitus [182]. For example, soy dietary isoflavones were concluded to repress oxidative stress and reduce the lipid peroxidation and hinder the progression of diabetic nephropathy [183]. We conclude that isoflavones are promising potential natural substitutes that withstand to balance the inflammatory immune cells and cytokines/chemokines of various inflammatory diseases. Also, there are, notwithstanding, some health concerns regarding the safe consumption of isoflavones as anti-inflammatory agents. Nonetheless, extensive scientific examinations are still warranted to investigate the exact mechanisms of action and respond to the safety worry [13].

10. Conclusion

ALI is characterized by diffuse alveolar damage caused by multiple lung injuries which may result in acute hypoxemic respiratory failure. Plasma and bronchoalveolar lavage biomarkers have previously been associated with the severity of ALI. The most promising biomarkers for the early detection of ALI include the proinflammatory TNF-α, IL-1β, IL-6, IL-8, and IL-18, promoting the oxidative stress. Owing to their structural similarity to 17-β estradiol, isoflavones, as phytoestrogenic compounds, represent an opportunity for agonistic and antagonist actions on estrogen. As a sequence, the review outlined the therapeutic potentials of several isoflavones in experimentally-induced ALI. Biochanin A, daidzein, genistein, and genistein-3′-sodium sulfonate, and formononetin and other members of isoflavones exhibited protection against ALI's inflammatory process mainly through inhibition of TLR4/NF-κB pathway and the subsequent release of cytokines, chemokines, and adhesion proteins. Nevertheless, other isoflavones' protective effects, either *in vitro* or *in vivo*, are highly recommended to be put on the

upcoming research agenda. Based on that, we suggest more future investigations for understanding the protective role of isoflavones against ALI through studying their mechanisms of action.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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