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Protective effects of natural compounds against paraquat-induced pulmonary toxicity: the role of the Nrf2/ARE signaling pathway

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ABSTRACT

Paraquat (PQ) is a toxic herbicide to humans. Once absorbed, it accumulates in the lungs. PQ has been well documented that the generation of reactive oxygen species (ROS) is the main mechanism of its toxicity. Oxidative damage of PQ in lungs is represented as generation of cytotoxic and fibrotic mediators, interruption of epithelial and endothelial barriers, and inflammatory cell infiltration. No effective treatment for PQ toxicity is currently available. Several studies have shown that natural compounds (NCs) have the potential to alleviate PQ-induced pulmonary toxicity, due to their antioxidant and anti-inflammatory effects. NCs function as protective agents through stimulation of nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) signaling pathways. Elevation of Nrf2 levels leads to the expression of its downstream enzymes such as SOD, CAT, and HO-1. The hypothesized role of the Nrf2/ARE signaling pathway as the protective mechanism of NCs against PQ-induced pulmonary toxicity is reviewed.

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Herbicide; natural products; alleviative; lung; antioxidant

Introduction

Paraquat (PQ), or N, N′-dimethyl-4,4′-bipyridinium dichloride, is a prominent herbicide used for the control of grasses and weeds (Zhao et al. 2020; Zhang et al. 2021). Intentional or unintentional exposure to PQ can lead to severe toxic effects. Globally, PQ is attributed to approximately 20 deaths per million annually (Seok et al. 2009). Following oral intake, PQ is distributed throughout the body. In particular, PQ is toxic to the lungs, liver, and kidneys (Chen et al. 2016).

Upon entry into the cell, PQ undergoes reduction followed by re-oxidation, a process known as redox cycling. It has been established that redox cycling of PQ is a critical step for its toxicity (Dinis-Oliveira et al. 2008). Various enzymes are involved in the metabolization of PQ including NADPH-cytochrome P450 reductase, nitric oxide synthase, xanthine oxidase (XO), and NADH-ubiquinone oxidoreductase. Following cyclic reduction and re-oxidation of PQ, NADPH is rapidly oxidized. As a result, NADPH is consumed, leading to reactive oxygen species (ROS) generation. PQ also causes an increase in the permeability of the mitochondrial inner membrane, mitochondrial permeability transition. Subsequently, membrane depolarization, matrix swelling, and uncoupling occur. PQ

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disrupts the regulating role of endoplasmic reticulum (ER) Ca^{2+}, leading to increased intracellular Ca^{2+} levels along with cell death (Liu et al. 2022).

The production of reactive oxygen species (ROS) and consequently, pulmonary fibrosis has been reported following exposure to this pesticide (Park et al. 2010). Pulmonary fibrosis is a condition resulting in excessive mesenchymal cell proliferation with a parallel enhancement of the collagen level within the interstitial and alveolar regions of the lungs (Zhao et al. 2002).

Nuclear factor E2-related factor 2 (Nrf2), nuclear factor-kappa B (NF-κB), toll-like receptors (TLRs), peroxisome proliferator-activated receptor-γ (PPAR-γ), and mitogen-activated protein kinases (MAPKs) are several of the signaling pathways reported to be involved in PQ-induced pulmonary toxicity. (Subbiah and Tiwari 2021; Liu et al. 2022).

The Nrf2 signaling pathway is one of the most important endogenous antioxidant systems (He et al. 2012; Jeon et al. 2016). Nrf2 and Keap1 (Kelch ECH associating protein 1) are two key signaling proteins that are activated during oxidative stress. Nrf2 is a master regulator of redox homeostasis, involved in the regulation of more than 500 genes, including genes that regulate oxidative stress. Nrf2 is a member of the vertebrate Cap'n'Collar (CNC) transcription factor subfamily of basic leucine zipper (bZip) transcription factors (Audousset et al. 2021). Keap1 is a cysteine-rich protein containing a total of 27 cysteine residues. Three of these residues, C151, C273, and C288, have been shown to play a key role in the nuclear translocation of Nrf2 (Kansanen et al. 2013). Dimeric Keap1 is responsible for the recognition of Nrf2 through two key motifs in the Neh2 domain of Nrf2. The Kelch domain of each Keap1 binds to the "DLG" and "ETGE" motifs of Nrf2. The main feature of Nrf2 is its rapid mobilization and nuclear translocation which suggest the mechanisms that regulate its cytoplasmic free concentration (Audousset et al. 2021).

Under normal conditions, Nrf2 is continuously degraded through the Keap1/Cul3-Rbx1 complex (Kaspar et al. 2009). Keap1 functions as a substrate adaptor to link Nrf2 to Cullin 3 (Cul3) and Ring box protein 1 (Rbx1). There is an autoregulatory loop between Nrf2 and Cul3-Rbx1 that determines their cellular levels. Following activation, the level of Nrf2 rises, and nuclear Nrf2 heterodimerizes with one of the small Maf proteins. These Nrf2–Maf heterodimers recognize antioxidant response elements (AREs) and enhance the expression of antioxidant genes (Audousset et al. 2021).

A battery of cytoprotective proteins supports cell survival following oxidative damage. These enzymes are responsible for the biotransformation of xenobiotics and drugs and include glutathione S-transferase (GST), NADPH quinone oxidoreductase 1 (NQO1), thioredoxin reductase (TrxR), and glutathione peroxidase (GPx) (Zhang et al. 2013; Niture et al. 2014).

Since the Nrf2 signaling pathway is the most important endogenous antioxidant system, the modulatory effect of natural compounds on this pathway has been investigated (He et al. 2012; Jeon et al. 2016). Nrf2 activators should be more precisely named "KEAP1 inhibitors" as their main target is KEAP1. Most Nrf2 activators are electrophilic compounds that covalently modify cysteine residues in the thiol-rich KEAP1 protein. One mechanism of KEAP1 inhibition is its sequestration in complexes with Nrf2 that cannot be ubiquitinated. Modification of cysteines in KEAP1 produces a closed form with both Neh2 motifs (DLG and ETGE) of Nrf2 interacting with the KEAP1 dimer but not leading to ubiquitination. As a result, free KEAP1 is not regenerated at an adequate rate, and recently synthesized Nrf2 has been shown to escape KEAP1-mediated ubiquitination. Curcumin, sulforaphane, and resveratrol are examples of NCs which affect KEAP1, owing to their electrophilic characteristic (Turpaev 2013; Robledinos-Antón et al. 2019).

Several natural compounds (NCs) exert their detoxifying effects by the activation of Nrf2. The role of Nrf2 in the protective effect of NCs has also been the subject of extensive research (Mascuch et al. 2017; Yan et al. 2018; Zhang and Chapman 2020). This article reviews the involvement of NCs against PQ-induced pulmonary toxicity through the induction of the Nrf2 signaling pathway (Figure 1).

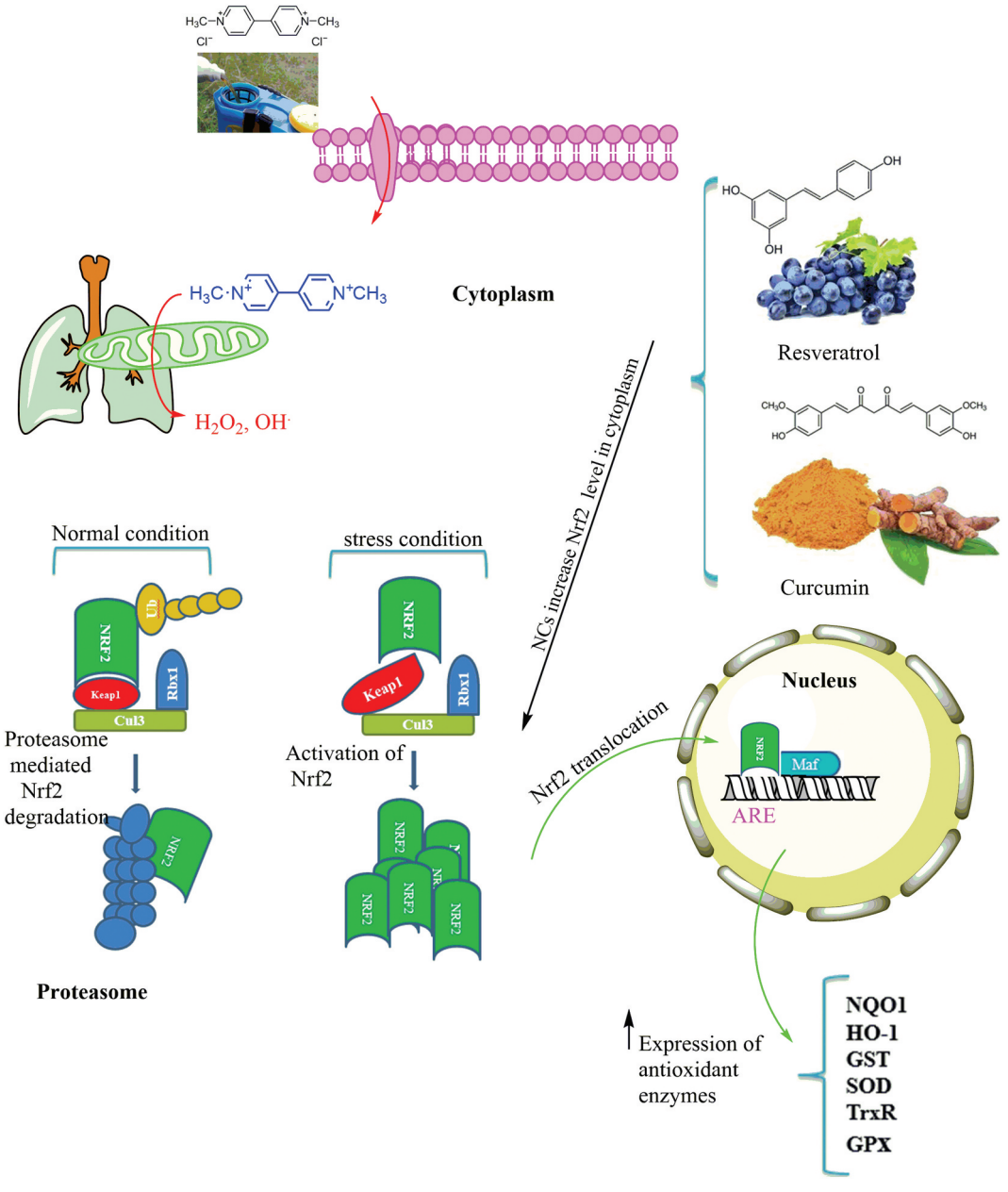

Figure 1. Paraquat (PQ) can enter the cell cytoplasm and produce oxidative damage. The Kelch-like ECH-associated protein 1 (Keap1), nuclear factor erythroid 2 (NFE2)-related factor 2 (Nrf2), and ubiquitin (Ub) proteasome pathways are shown in the figure. Ring box protein 1 (Rbx1) is the chief constituent of E3 ubiquitin ligases, which can affect different proteins for proteasome-mediated degradation. Cul3 and Rbx1 produce the ubiquitin ligase complex that is responsible for the ubiquitination and degradation of Nrf2. In the normal condition (basal state), Nrf2 is targeted by ubiquitin-proteasome complex and degraded. However, under stressed conditions, conformation changes in Keap1 will occur and will prevent the ubiquitination of Nrf2. Thus, oxidative damage can lead to Nrf2 dissociation from this complex. In the next step, Nrf2 is translocated from the cytoplasm to the nucleus where it attaches to small Maf (sMaf) proteins. This new complex can bind with antioxidant response elements (ARE). Subsequently, the expression of several antioxidant enzymes such as NQO1, HO-1, and GSTs will increase. NCs such as resveratrol and lipoic acid have been reported to alleviate the toxic effect of PQ in the lungs by activation of the Nrf2 pathway (Iranshahy et al. 2018; Molaei et al. 2021).

Methods

Scopus, PubMed, Web of Science, and Science Direct were searched for the terms lung or pulmonary, "Nrf2" or "nuclear factor erythroid 2 (NFE2)-related factor 2", "paraquat", "natural compounds" or "natural products", and "protective" until May 2022 (Figure 2). Review articles were excluded and only relevant *in vitro* and *in vivo* studies were selected.

In Scopus, PubMed, Web of Science, and Science Direct databases 46, 53, 40, and 115 articles were identified, respectively. We found 254 articles in the online databases, among which duplicated (64), nonrelevant (169), and non-English language (1) articles were excluded. The remaining 20 articles were carefully reviewed and included in the current review.

Results and discussion

Ncs that ameliorate PQ-induced pulmonary toxicity through the Nrf2/Keap1/ARE signaling pathway

Protective effects of active ingredients against pulmonary toxicity of PQ

Salvianolic acid B. Salvianolic acid B (SalB), a major component of *Salvia miltiorrhiza* roots and rhizomes, is a natural compound with antioxidant and radical scavenging properties (Peng et al.

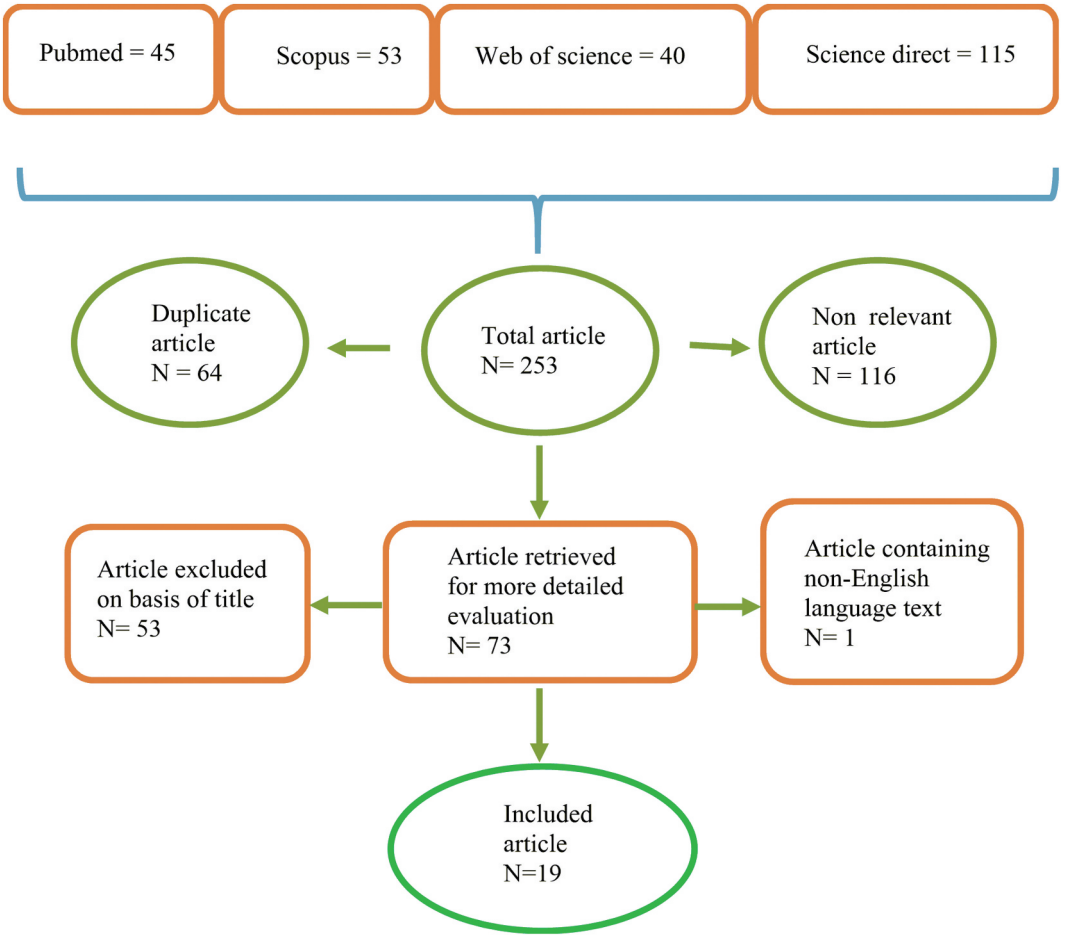

Figure 2. Flow diagram of narrative literature search representing the included and excluded studies.

Table 1. Summary of the protective effect of natural compounds (NCs) against paraquat (PQ)-induced pulmonary toxicity by activating the Nrf2 pathway.

Compound/extract	Animal/cell line	PQ dose/ route	NCs dose/route	Molecular tests	Reference
Silymarin	A549 cells	200 μM	25, 50,100 μg/ml	↑ Nrf2, HO-1, NQO, GPX ↓ LDH, MDA	(Podder et al. 2012)
Silymarin	Sprague-Dawley rats	30 mg/kg, i.p	200 mg/kg, i.p.	↑ Nrf2, HO-1, NQO, GPX,SOD, CAT ↓ TNF-a, IL-1b, IL-6 and TGF- β1	(Zhao et al. 2015)
Resveratrol	BEAS-2B	10 μM	10 μM	↑ Nrf2, HO-1, αSMA, collagen I ↓ TNFα, IL-6, TGFβ1	(He et al. 2012)
Resveratrol	Male mice	20 mg/kg, i.p	30 mg/kg, i.p.	↑ Nrf2, HO-1, SOD, CAT,GSH ↓ MDA	(Li et al. 2016)
Alpha-Lipoic Acid	BEAS-2B	0.2 mM	0.5 mM	↑ Nrf2, HO-1, CAT, GPX3,GPX4, NQO1	(Kim et al. 2013a)
Quercetin	A549	300 μM	5–40 μM	↑ Nrf2, HO-1, GSH, GPXs ↓ CAT, PRDXs	(Park et al. 2010)
Ellagic Acid	A549	100 μM	10 μM	↑ Nrf2, HO-1, NQO, GSH ↓ LDH, MDA	(Kim et al. 2013b)
Naringenin	BEAS-2B	0.2 mM	100 μM	↑ Nrf2, HO-1, NQO,GPX2, GPX3, GPX5, GPX7 ↓ LDH	(Podder et al. 2014)
Chlorogenic acid	A549	160 μM	100 μM	↑ Nrf2,GSH, SOD1, SOD2, GSH, Cytochrome c ↓ ROS, Caspase 3, Caspase9, Bax	(Kong et al. 2019)
Salvianolic acid B	Kunming male mice	300 mg/ kg, i.g.	200 mg/kg, 400 mg/kg/ gavage	↑ Nrf2, HO-1, collagen I, collagen III,GSH, αSMA ↓ p-smad3, TNFα, IL-17, TGFβ1, NOX4, MDA	(Liu et al. 2016)
Curcumin	Wistar rats	5 mg/kg, gavage	30 mg/kg/day, gavage	↑ Nrf2, HO-1, NQO1 ↓ KEAP1, hydroxyproline,	(Hosseini et al. 2019)
Ligustrazin	female C57BL/6 mice	10 mg/kg, i.p	30 mg/kg, tail vein injection	↑ Nrf2, miR-193a ↓ TGF-β1, Collagen I, Collagen III	(Liu et al. 2019)
Ginkgolide C	male SD rats	30 mg/kg, gavage	8, 16, 32 mg/kg, i. p.	↑ Nrf2, SOD, GSH ↓ TNF-a, IL-1b, IL-6, CK,LDH, MDA, CAT, NADPH	(Zhang et al. 2022)
Diterpene ginkgolides meglumine injection (DGMI)	male SD rats	20 mg/kg, i.p.	1.25, 2.5, 5 mg/kg, i.p.	↑ Nrf2, HO-1, SOD ↓ TNF-a, IL-1b, IL-6	(Li et al. 2018)
Methanolic extract of *Hippophae rhamnoides* L.	A549	200 μM	25–200 μg/ml	↑ Nrf2, HO-1, NQO, GPX1,SOD, GSR ↓ LDH, MDA	(Podder et al. 2013)
Makgeolli Lees	A549	0.2 mM	0.1 mg/ml	↑ Nrf2, HO-1, NQO1, GPXs, SOD1, CAT, PRDX3,PRDX4	(Jeon et al. 2016)
Methanolic extract of Xuebijing	Sprague-Dawley rats	30 mg/kg, i.p	8 mL/kg, injection into the tail vein	↑ Nrf2, IkB ↓ p38 MAPK, NF-κB65, HIF-1α, Nrf2, TGF-β1	(Liu et al. 2014)
Ethanolic extract of *Radix puerariae*	C57BL/6J (B6) mice	10 mg/kg, i.p.	30 mg/kg, i.p.	↑ Nrf2, HO-1, NQO, GSH and GSSG, SOD, collagen I, collagen III,GSH ↓ MDA, hydroxyproline	(Liu et al. 2015)
Water extract of Licorice	Kunming male mice	45 mg/kg, i.g.	40 μg/kg	↑ Nrf2, SOD ↓ MDA	(Liu et al. 2019)
Ethanolic extract of *Arenaria kansuensis*	C57BL mice	20 mg/kg, i.p	170, 350, 700 mg/ kg/i.g.	↑ Nrf2, collagen I, collagen III,GSH, SOD, αSMA ↓ p-smad2, p-smad3, TNFα, IL-1β, IL-6, TGFβ1, NOX4	(Cui et al. 2021)

Abbreviations Human bronchial epithelial cells (BEAS-2B), Human lung carcinoma cell line (A549), Nuclear factor-erythroid factor 2-related factor 2 (Nrf2), Heme oxygenase 1 (HO-1), Catalase (CAT), Glutathione peroxidase (GPX), Peroxiredoxin 3 (PRDX3), Peroxiredoxin 4 (PRDX4), α-Smooth muscle actin (αSMA), Glutathione (GSH), Tumor necrosis factor (TNFα), Interleukin-17 (IL-17), Transforming growth factor β1 (TGF β1), Malondialdehyde (MDA), Lactate Dehydrogenase (LDH), Micro RNA-21 (miR-21), Bcl-2-associated X protein (Bax), Follistatin-like 1 (FSTL1), p38 mitogen-activated protein kinases (p38MAPKs), Nuclear factor kappa B 65 (NF-κB 65), Metalloproteinase 9 (MMP-9), Lactate dehydrogenase (LDH), Malondialdehyde (MDA), Inhibitor of nuclear factor kappa B (IkB), Hypoxia-inducible factor 1-alpha (HIF-1α), intragastricl (i.g), intraperitoneal (i.p.).

2021). PQ was administrated to mice to induce a lung fibrotic model. A single dose of PQ led to structure alteration, collagen deposition, extreme inflammatory infiltration, cytokine release, and oxidative injuries in lung tissue. The administration of SalB in PQ-treated mice significantly alleviated these effects and lead to the enhancement of the transforming growth factor-β (TGF-β) and Nrf2 levels (Liu et al. 2016). However, the generation of NOX4 was inhibited in the SalB-treated animals. NADPH oxidases (NOX) are a class of plasma membrane enzymes that play a central role in the generation of O_2- and H_2O_2 (Ma et al. 2018). Several NOX isoforms including NOX1, NOX2, and NOX4 are expressed in the airway and alveolar epithelial cells (Barangi et al. 2018; Yousefian et al. 2019). NOX4 is overexpressed in the case of pulmonary fibrosis (van der Vliet 2015). SalB prevented myofibroblast transdifferentiation in experimental pulmonary fibrosis through the up-regulation of Nrf2 (Liu et al. 2018) (Table 1).

Alpha lipoic acid. Alpha lipoic acid (LA), a naturally occurring organosulfur compound with potent antioxidant properties, is present in plants, animals, and humans (Szeląg et al. 2012). The ameliorative effect of this active component was observed in PQ-induced oxidative injuries in bronchial epithelial cells grown in culture (Iles et al. 2005). LA reduced the elevated levels of ROS, LDH, and malondialdehyde (MDA) in BEAS-2B cells. LA up-regulated the expression of Nrf2 and its downstream targets including HO-1, CAT, GPXs, and NQO1 in PQ-treated cells. The cytoprotective effect of HO-1 in pulmonary cells has also been reported (Iles et al. 2005). Due to its catalytic activity, NQO1 protects cells against the harmful effects of quinones and their metabolic precursors (Kim et al. 2013). The Keap1/Nrf2/ARE complex controls the expression of NQO1. Dinkova-Kostova and Talalay have demonstrated that induction of NQO1 is correlated with the reduction of susceptibilities to oxidative damage (Dinkova-Kostova and Talalay 2010).

Resveratrol. Resveratrol (Res) is a phytoalexin polyphenol that is found in a variety of plants (Neumann et al. 2009). Res has anticancer, antiobesity, and cardioprotective properties (Alamolhodaei et al. 2017; Tabeshpour et al. 2018; Ahmadi et al. 2021). Under the stimulation of pro-fibrogenic elements such as PQ, myofibroblasts are activated. Alpha smooth muscle actin (αSMA) is generated during myofibroblast activation (Tang et al. 2014; Staloch et al. 2015; Xie et al. 2016). Extensive disruption of cell-cell contact can stimulate (TGF)-β1-induced epithelial-mesenchymal transition (EMT) and the myofibroblast marker αSMA (O'Connor et al. 2016; Zhuang et al. 2019). Neumann and co-workers showed that PQ induced the generation of αSMA, TGF β1, and inflammatory cytokines in BEAS- 2B cells (Neumann et al. 2009). It was observed that Res inhibited the fibrogenic response and oxidative damage resulting from PQ exposure in these cells. In comparison to cells treated with PQ, TNF-α, IL-6, TGF β1, αSMA, and collagen I levels were significantly lower in cells also treated with Res (Neumann et al. 2009). A similar result was reported by He and co-workers (He et al. 2012). They showed that Res can inhibit the effect of PQ on inflammatory and profibrogenic factors (He et al. 2012).

Another group has reported that intraperitoneal administration of Res in mice enhanced the expression of Sirtuin 1 (SIRT1). Increased SIRT1 expression has been correlated with a high level of Nrf2. The activity of CAT, HO-1, and SOD was also enhanced after the administration of Res in PQ-treated mice (Li et al. 2016).

Chlorogenic acid. Chlorogenic acid (CA) is an active component that can be isolated from plants such as sunflowers and strawberries. It has cardioprotective, antimicrobial, and anticancer properties. The protective effect of CA was investigated in A549 cells exposed to PQ (Kong et al. 2019). CA alleviated the apoptotic effect of PQ by enhancing the expression of SIRT1 (Kong et al. 2019). It is known that the enzyme, deacetylase, efficiently protects cells against oxidative stress (Nogueiras et al. 2012; Hong et al. 2018). *In vitro* findings have shown that SIRT1 mediated the deacetylation of Nrf2 and enhanced the nuclear accumulation of Nrf2 (Huang et al. 2013, 2015). CA also enhanced

the levels of Nrf2, SOD1, SOD2, and cytochrome c in cells treated with PQ, while, ROS, Caspase 3, Caspase 9, and Bax levels were reduced.

Curcumin. Curcumin is the active ingredient of turmeric that is obtained from the roots of *Curcuma longa* (Hewlings and Kalman 2017; Valokola et al. 2019). It has major biological effects including antioxidant, hepatoprotective, and immune-modulatory action (Hosseinzadeh et al. 2011; Shakeri et al. 2019). The ameliorating effects of curcumin and nanocurcumin were demonstrated in PQ-induced lung injury (Hosseini et al. 2019). In this study, the expression of Keap1 diminished in animals; however, the levels of Nrf2, HO-1, and NQO1 were enhanced. The negative regulator, Keap1, if detached from Nrf2 will activate Nrf2 and its downstream pathway. The administration of this antioxidant has been reported to reduce the severity of pulmonary fibrosis (collagen deposition) in rats (Hosseini et al. 2019).

Quercetin. Quercetin is a plant pigment found in many fruits, vegetables, and seeds (Ternaux and Portalier 2002). In recent years, its neuroprotective, antioxidant, and antidiabetic effects have been documented (Mahmoud et al. 2013; Kanter et al. 2016; Miltonprabu et al. 2017). The protective effect of this pigment was demonstrated in A549 cells. Quercetin attenuated the cytotoxicity of PQ through the expression of protective enzymes such as GPx and Catalase. In addition, quercetin has been shown to enhance the expression of Nrf2 and HO-1 in PQ-treated cells (Zerin et al. 2013).

Naringenin. Naringenin (NG) is an active herbal ingredient that can be obtained from cocoa, cherries, and tomatoes (Al-Rejaie et al. 2013). It has exhibited multiple pharmacologic activities such as antitumor, antiviral, and anti-inflammatory properties (Salehi et al. 2019). Podder and his colleagues have shown that NG efficiently alleviates PQ-induced cytotoxicity in BEAS-2B cells by the Nrf2-regulated antioxidant defense pathway. NG not only enhanced the nuclear translocation of Nrf2 but increased the induction of GPXs. NG also diminished the intracellular level of ROS in PQ-exposed cells (Podder et al. 2014).

Silymarin. Silymarin is a natural flavonoid that can be extracted from *Silybum marianum*. Its protective effects have been investigated in PQ-induced pulmonary injury in male rats. Silymarin abated the histopathologic changes and decreased the inflammatory cell infiltration in PQ-treated animals (Podder et al. 2012). Silymarin enhanced the generation of Nrf2 and its target enzymes including SOD, CAT, GPXs, NQO1, and HO-1. This active ingredient effectively alleviated the toxic effects of PQ on the lungs of animals (Zhao et al. 2015). In another study, the protective effect of silymarin against PQ-induced oxidative damage on the A549 adenocarcinoma cell line was investigated. The expression of defensive agents including Nrf2, NQO1, and HO-1was rapidly induced (Podder et al. 2012).

Ellagic acid. Ellagic acid (EA) is an organic antioxidant that occurs naturally in nuts, grapes, raspberries, and strawberries. The ameliorative effect of EA against PQ-induced toxicity in the A549 cell line was investigated. EA exerted its alleviating effect by activation of the Nrf2 pathway and the target cytoprotective enzymes, HO-1 and NQO1. In addition, EA decreased the levels of intracellular ROS, lipid peroxidation, and LDH in cells treated with both compounds (Kim et al. 2013).

Ligustrazin. Ligustrazin is an active ingredient of *Ligusticum chuanxiong* Hort (Liu et al. 2019). It is extracted from roots and stems and has a cardioprotective effect through the inhibition of free radical formation and lipid peroxidation (Liu et al. 2019). The ameliorative property of ligustrazin was shown in a murine model of PQ-induced lung fibrosis. It was shown that long-term PQ exposure can decrease miR-193a level and increase TGF-β1 and collagen I and III. Ligustrazin increases lung cell autophagy and improves paraquat-induced pulmonary fibrosis by blocking PI3K/Akt/mTOR signaling pathways (Liu et al. 2019).

Ginkgolide C. *Ginkgo biloba* has been used as a traditional herbal remedy for many years in China. The anticancer and cardioprotective effects of this herbal plant have been reported (Gao et al. 2016; Zhou et al. 2022). Ginkgolide C (GC) is a member of the structurally unique family of diterpenoids extracted from *Ginkgo biloba* leaf (Vogensen et al. 2003). The effect of GC on acute lung injury (ALI) induced by PQ has been demonstrated by Zhang et al. (2022). GC significantly inhibited polymorphonuclear neutrophil (PMN) infiltration after PQ poisoning. In addition, histopathological damage, ultrastructural changes, and hypoactivity of lung tissue induced by PQ were ameliorated. The results also suggested that GC-activated Nrf2-based cytoprotective enzymes such as CAT and SOD (Zhang et al. 2022).

Diterpene ginkgolides meglumine. Diterpene ginkgolides meglumine injection (DGMI) is an extract of *Ginkgo biloba* L, which has been used for the treatment of stroke and related complications (XX et al. 2021). The protective effect of DGMI was demonstrated in PQ-induced pulmonary fibrosis in rats (Li et al. 2018). DGMI decreased the levels of inflammatory cytokines including IL-1β, IL-6, and TNF-α in PQ-treated animals. The anti-oxidative and anti-inflammatory response of DGMI was suggested to have been achieved through activation of the Akt-Nrf-2 pathway (Li et al. 2018).

Extracts of NCs that have protective effects against pulmonary toxicity of PQ

Ethanolic extract of Arenaria kansuensis. *Arenaria kansuensis* is a herbal plant found in different areas of China. The anti-inflammatory, antihypoxic and antioxidative effects of *A. kansuensis* are well known (Cui et al. 2017, 2018). Recently, the antifibrotic property of an *A. kansuensis* ethanol extract (AE) was investigated in C57BL mice exposed to PQ (Cui et al. 2021). The collagen deposition in the lung tissue of PQ-exposed mice was enhanced. The degree of the destruction of lung tissue, body weight, and survival rate of mice improved in animals treated with both AE and PQ. In addition, the AE extract reduced the collagen deposition in lung tissue. Although PQ increased the expression of TGF-β1, NOX4, and NF-kB, the ethanolic extract of *Arenaria kansuensis* ameliorated or at least reduced the toxicity of this pesticide (Cui et al. 2021).

Ethanolic extract of Radix puerariae. *Radix puerariae* is a traditional Chinese herbal medicine prescribed for alcoholism. Puerarin is a bioactive component that is extracted from the root of *R. puerariae* (Liu et al. 2015). Follistatin-like protein 1 (FSTL1) is a 306-amino acid that is produced by fibroblasts, osteocytes, myocytes, and endothelial cells (Chaly et al. 2012). FSTL1 is involved in numerous pathophysiological processes. This glycoprotein plays a role in the central nervous system and lung development (Chaly et al. 2012; Li et al. 2020). Interestingly, inhibition of miR-21 attenuated lung fibrosis in mice (Liu et al. 2015). PQ is a profibrogenic agent that induces lung fibrosis through the TGF-β1/Smad signaling pathway (Jin et al. 2018). It was observed that *Radix puerariae* extracts (RPEs) alleviated or at least reduced PQ-induced pulmonary fibrosis by inhibition of the FSTL1 and Nrf2 signaling pathways. RPEs also reduced several pathological features of lung fibrosis by the inhibition of oxidative stress through decreased micro RNA-21 (miR-21) expression (Liu et al. 2015). miR-21 is a key target that is upregulated during fibrogenesis. TGF-β1 has been shown to stimulate the expression of this marker in the lungs of mice. It was observed that the expression of miR-21 increased in the lungs of patients with idiopathic pulmonary fibrosis (IPF) (Yamada et al. 2013).

Methanolic extract of Hippophae rhamnoides L. *Hippophae rhamnoides* L. or sea buckthorn belongs to the family of Elaeagnaceae. Cytoprotective, antioxidant, antidiabetic, and cardioprotective effects of sea buckthorn have been reported (Xiao et al. 2021). A sea buckthorn extract (SBT) was reported to reduce the untoward effects of PQ-exposed A549 cells through induction of Nrf2 and its targets including CAT, NQO1, GPXs, and glutathione reductase (Podder et al. 2013). Nrf2 nuclear translocation and its downstream enzyme activation have been observed in SBT-treated cells (Podder et al. 2013).

Methanolic extract of Xuebijing. Xuebijing injection is a Chinese herbal medicine consisting of a mixture of Chuanxiong, Chishao, Danshen, and Honghua (Liu et al. 2014). PQ increased MAPK expression and stimulated the production of TNF-α and IL-1β in the lungs of rats (Liu et al. 2014). p38 Mitogen-activated protein kinases (MAPK) are key mediators of cellular stressors such as inflammatory cytokines. MAPK indirectly decreased the Nrf2 level (Liu et al. 2014). Liu et al. investigated the protective effect of Xuebijing in an animal model. Their findings suggested that this herbal mixture decreased IL-6, TNF-α, IL-1β, IL-10, and TGF-β1 levels in PQ-treated animals. Although the levels of Nrf2 and GSH were increased in the lungs, Xuebijing was reported to protect rats against PQ lung-induced toxicity through the down-regulation of MAPK (Liu et al. 2014).

Aqueous extract of licorice. Licorice is derived from the rhizomes and roots of *Glycyrrhiza inflate*, *G. glabra*, and *G. uralensis* (Liu et al. 2019). Licorice is comprised of several active components including triterpenoids, polysaccharides, and polyphenols (Wang and Nixon 2001). Licorice has antioxidative, anti-inflammatory, and hepatoprotective activity (Zhang and Ye 2009). Under both *in vivo* and *in vitro* test conditions, the detoxification property of licorice against PQ-induced toxicity was investigated. Licorice increased SOD activity and decrease MDA levels. In addition, licorice alleviated pulmonary fibrosis and edema in PQ-treated mice apparently through induction of Nrf2 expression (Liu et al. 2019).

Makgeolli lees. Makgeolli is a Korean alcoholic beverage made from rice. It has various ingredients such as vitamins, organic acids, and proteins (Jung et al. 2014). *Makgeolli* lees (ML) is extracted from Makgeolli during the fermentation process. It was reported that ML elevated Nrf2 expression in a human lung carcinoma cell line (A549) that was exposed to PQ. A marked increase in the expressions of cytoprotective enzymes i.e. GPXs, SOD1, CAT, and Prdxs was observed in the ML-treated cells (Jeon et al. 2016).

Conclusion and future prospective

PQ is highly toxic to humans. After oral or skin absorption, it is distributed throughout the body, concentrating in the lungs. It has been demonstrated that the generation of ROS is the main mechanism of PQ toxicity. Currently, no effective treatment for PQ toxicity is available.

The Nrf2/ARE signaling pathway is the most important endogenous antioxidant system. NCs such as silymarin, resveratrol, and curcumin have been reported to have a significant protective effect against PQ-induced pulmonary toxicity through the Nrf2/ARE signaling pathway. Elevation of Nrf2 levels leads to the expression of its downstream enzymes such as SOD, CAT, GPXs, NQO1, and HO-1. We have reviewed several NCs that may have a protective effect against PQ-induced pulmonary toxicity via induction of the Nrf2 signaling system. Additional nonclinical studies are needed to support appropriate clinical trials that will be able to assess the efficacy and safety of these NCs in humans.

Abbreviations

ARE	Antioxidant response element
Keap1	Kelch-like ECH-associated protein 1
GST	Glutathione S-transferase
NQO1	NAD(P)H quinone oxidoreductase 1
Nrf2	Nuclear factor erythroid 2 (NFE2)-related factor 2
HO-1	Heme oxygenase-1
GPx	Glutathione peroxidase
XO	xanthine oxidase
SOD	Superoxide dismutase
NF-κB	Nuclear factor-κB

NC	Natural compounds
PQ	Paraquat
TRX1	Thioredoxin-1
NCs	Natural compounds
TLRs	Toll like receptors
PPAR-γ	Peroxisome proliferator-activated receptor-γ
MAPKs	Mitogen-activated protein kinases
CAT	Catalase
PRDX3	Peroxiredoxin 3
PRDX4	Peroxiredoxin 4

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