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Review

The therapeutic potential of quercetin for cigarette smoking–induced chronic obstructive pulmonary disease: a narrative review

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***Abstract*:** Quercetin is a flavonoid with antioxidant and anti-inflammatory properties. Quercetin has potentially beneficial therapeutic effects for several diseases, including cigarette smoking–induced chronic obstructive pulmonary disease (CS-COPD). Many studies have shown that quercetin's antioxidant and anti-inflammatory properties have positive therapeutic potential for CS-COPD. In addition, quercetin's immunomodulatory, anti-cellular senescence, mitochondrial autophagy–modulating, and gut microbiota–modulating effects may also have therapeutic value for CS-COPD. However, there appears to be no review of the possible mechanisms of quercetin for treating CS-COPD. Moreover, the combination of quercetin with common therapeutic drugs for CS-COPD needs further refinement. Therefore, in this article, after introducing the definition and metabolism of quercetin, and its safety, we comprehensively presented the pathogenesis of CS-COPD related to oxidative stress, inflammation, immunity, cellular senescence, mitochondrial autophagy, and gut microbiota. We then reviewed quercetin's anti-CS-COPD effects, performed by influencing these mechanisms. Finally, we explored the possibility of using quercetin with commonly used drugs for treating CS-COPD, providing a basis for future screening of excellent drug combinations for treating CS-COPD. This review has provided meaningful information on quercetin's mechanisms and clinical use in treating CS-COPD.

Keywords: CS-COPD, drug combination, natural compound, quercetin, treatment mechanism

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Introduction

Chronic obstructive pulmonary disease (COPD) is a group of progressive lung diseases. It consists of chronic bronchitis, mild airflow obstruction, and emphysema. Its main characteristic is continuous and progressive airflow limitation.[1,2] The main symptoms of COPD are chronic cough, sputum production, shortness of breath, or dyspnea. As lung function deteriorates, it can become a severe disease and affect patients' quality of life.[3] COPD is often associated with advanced complications, such as right heart failure, respiratory failure, pulmonary encephalopathy, and spontaneous pneumothorax.[4–6] Its severe complications can worsen clinical symptoms and affect mortality.[7] COPD was the third leading cause of death worldwide, with an estimated 3.23 million deaths in 2019, according to the World Health Organization (WHO). Nearly 90% of COPD deaths below 70 years of age occurred in low- and middle-income countries.[8] It was associated with indoor and outdoor air pollution levels, diet, and other socioeconomic factors.[9] There will be more than 5.4 million deaths worldwide from COPD and related diseases by 2060 as the number of smokers in developed countries increases and the population ages.[8] The high incidence, disability, and mortality rates associated

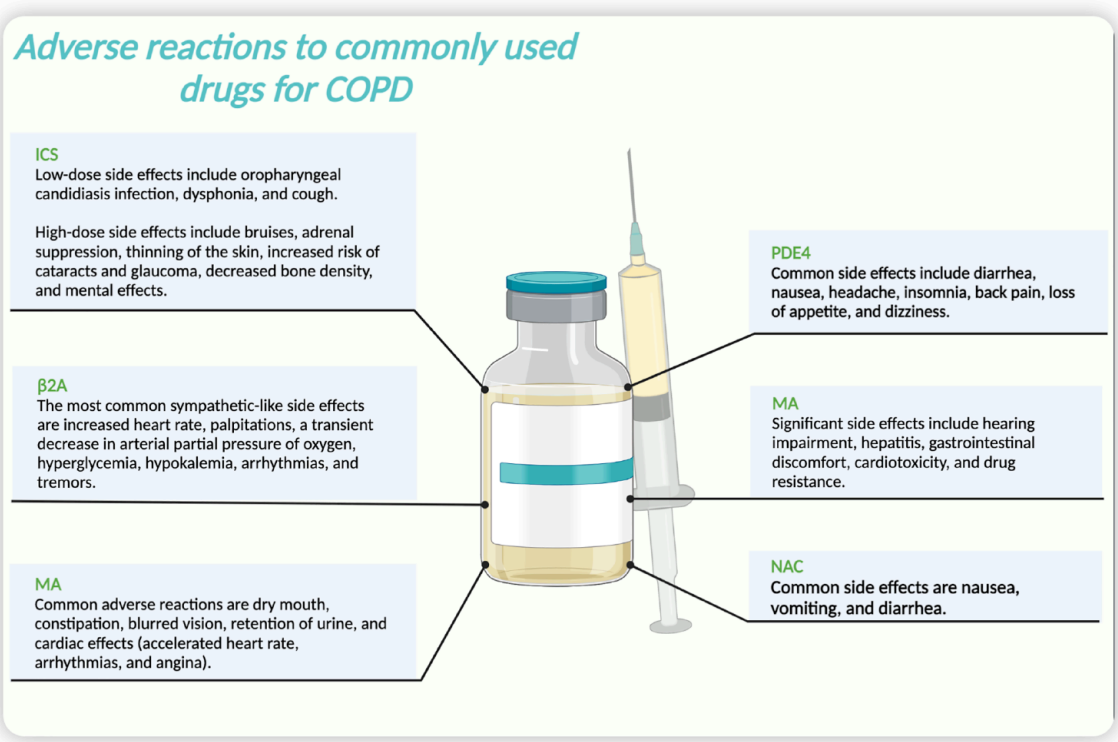

Figure 1. Adverse reactions to commonly used treatment drugs for CS-COPD.
ICS, inhaled glucocorticoids; MA, muscarinic antagonists; NAC, N-acetylcysteine; PDE4I, phosphodiesterase-4 inhibitors; β2A, β2 agonists.

with COPD will burden global healthcare and socioeconomic aspects.[10]

Pathological changes in COPD occur mainly in the airways, lung parenchyma, and pulmonary vasculature.[11] Pathological changes in the central airways include epithelial cell lesions, inflammatory cell infiltration, increased goblet cells, and increased mucus gland secretion. Pathologic changes in the small peripheral airways include shrinkage of the small peripheral airways and loss of short and terminal fine bronchioles. Pathological changes in the alveoli reduce the elasticity of the alveolar wall, resulting in dilated alveolar sacs.[12,13] Pathological changes in the pulmonary arteries were characterized by endothelial dysfunction, arterial smooth muscle hyperplasia, micro-thrombosis, and vessel wall thickening.[14] Smoking, occupational dust exposure, fuel smoke, air pollution, and respiratory infections are common environmental factors that trigger and promote pathological processes in COPD.[15,16] Cigarette smoke is a mixture of solid and liquid tar aerosols containing numerous toxic, carcinogenic, and teratogenic components, including nicotine, tar, carbon dioxide, formaldehyde, acrolein, acetone, ammonia, carbon monoxide, polycyclic aromatic hydrocarbons, and aromatic hydrocarbons.[17] Smoking is the most common and important cause of COPD.[9,18] According to current studies, the mechanism of cigarette smoking–induced chronic obstructive pulmonary disease (CS-COPD) involves oxidative stress (OS), inflammation, cellular senescence, mitochondrial autophagy, immunity, and gut microbiota.[19–22] Current clinical drug treatment strategies for CS-COPD include (1) bronchodilation: inhaled long-acting β2 agonists and long-acting muscarinic antagonists; (2) control airway inflammation: inhaled glucocorticoids, phosphodiesterase four inhibitors; (3) prevention of acute exacerbation of COPD (AECOPD) due to infection: macrolides; and (4) antioxidant stress: N-acetylcysteine (NAC). All these drugs have some side effects (Figure 1).[23–26] Recently, researchers have attempted to develop new drugs for the treatment of CS-COPD, but progress has yet to be satisfactory, limited by the singularity of drug-targeting pathways.[27,28] Therefore, finding new drugs and combinations with multi-target effects and fewer toxic side effects for CS-COPD is necessary.

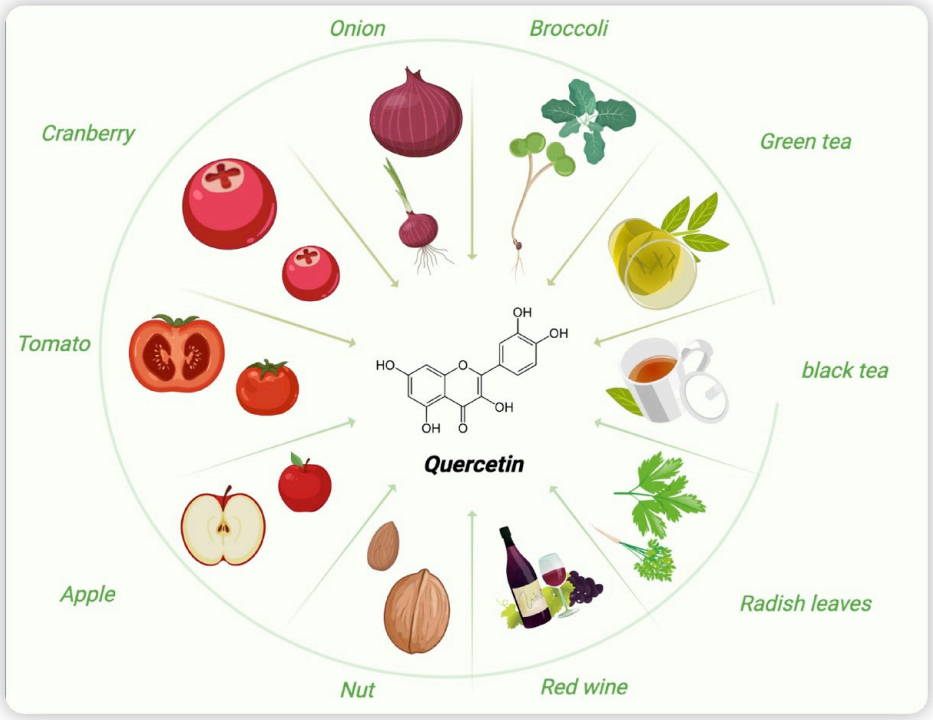

Figure 2. The main source of quercetin.

Flavonoids are naturally occurring polyphenolic compounds. In recent years, their antioxidant, anti-inflammatory, and immunomodulatory effects have received widespread attention for their potential therapeutic effects in CS-COPD.[29,30] Quercetin is a polyphenolic compound with antioxidant, anticoagulant, antibacterial, neuroprotective, and immune-enhancing properties.[31] Previous studies have demonstrated the protective effects of quercetin against OS and inflammation associated with CS-COPD.[32–34] Quercetin intake has no significant adverse effects on COPD patients.[35] In addition, quercetin may also prevent and treat CS-COPD through other potential pathways, such as anti-cellular senescence, immunomodulation, regulation of mitochondrial autophagy, and regulation of gut microbiota.[36–39] However, the protective effects and mechanisms of quercetin against CS-COPD regarding OS, inflammation, cellular senescence, immunity, mitochondrial autophagy, and gut microbiota have yet to be comprehensively discussed. Therefore, we reviewed and synthesized the relevant research. In addition, we sought to explore the potential of quercetin-containing drug combinations in the treatment of CS-COPD.

Definition and metabolism of quercetin

Quercetin is one of the most common flavonoids, with the molecular formula $C_{15}H_{10}O_7$, consisting of three rings and five hydroxyl groups.[40,41] Quercetin has vigorous antioxidant activity due to its structure's phenolic hydroxyl groups and a double bond.[42] It is found in tea, wine, onions, tomatoes, radish leaves, broccoli, lettuce, cranberries, apples, and nuts (Figure 2).[43,44] The intestine mainly absorbs quercetin, and the absorbed portion is transported through the portal vein to the liver, where it is tightly bound to albumin. Eventually, quercetin and its metabolites are excreted in the urine, bile, and feces. Intestinal enzymes and intestinal microbes convert the unabsorbed quercetin biosynthesis into metabolites.[45–47] The vast majority (93.3%) of quercetin is metabolized in the intestine and only a tiny fraction (3.1%) in the liver.[48,49] Quercetin metabolites include quercetin sulfate, quercetin glucosidic acid, quercetin glucosidic acid sulfate, phenolic acid, and short-chain fatty acids (SCFAs). Glycosides and sulfate complexes are more easily absorbed than quercetin.[50,51] Developing quercetin-related drugs has been challenging due to poor water solubility, low stability, and low bioavailability. The strategy of

encapsulation in colloidal particles to capture the active ingredients of quercetin improved its water solubility and chemical stability in food and the human intestine. By controlling quercetin's size and physical morphology, crystal engineering improved the bioavailability of quercetin.[52] In addition, quercetin loaded on polylactic acid–hydroxyacetic acid nanoparticles further enhanced its pharmacological activity.[53,54]

Safety of quercetin use in diseases

Currently, the safety of quercetin has been demonstrated in numerous phase I and II clinical trials (Table 1). A rigorous review of quercetin safety data indicates that its dietary intake is not associated with adverse health effects.[55] Quercetin is currently marketed primarily as free quercetin glycosides, typically at a daily dose of 1000 mg/day above the usual dietary intake. Safe and effective doses and forms of quercetin for various diseases need to be further investigated in numerous clinical trials.[56,57] One study found that cyclists who took 1000 mg of quercetin daily for 6 weeks had no side effects but no protection against exercise-induced OS and inflammation.[58] Regarding the safe intravenous use of quercetin, a phase I clinical trial recommended a push dose of 1400 mg/m^2 every 3 weeks or once a week.[59]

The efficacy and safety of quercetin have also been demonstrated in several respiratory diseases. Combining quercetin and polyvinyl alcohol pyrrolidone (QP) reduced resistance to the standard anti-tuberculosis quadruple therapy in primary destructive tuberculosis. There were no significant side effects of QP administration in primary destructive tuberculosis.[60] A randomized clinical trial determined that the maximum safely tolerated dose of quercetin in patients with mild-to-moderate COPD was 2000 mg/day.[35]

Quercetin is also safe and effective in the treatment of some cardiovascular diseases. A randomized, double-blind, placebo-controlled trial was the first to validate the hypotensive effect of quercetin. No adverse effects were observed during 28 days of treatment with 730 mg/day of quercetin.[69] An earlier clinical study using quercetin for cardiac protection found that a daily intake of 150 mg of quercetin for 6 weeks reduced systolic blood pressure and plasma-oxidized low-density lipoprotein concentrations in overweight patients with a high-risk phenotype for cardiovascular disease. Oral use of quercetin had no adverse effects on hepatic or renal function, hematology, or serum electrolytes.[61] A multicenter randomized clinical trial in Ukraine verified that intravenous administration of quercetin was safe and well tolerated to prevent reperfusion-induced limited infarct size and first anterior wall ST-segment elevation myocardial infarction.[62] Intravenous administration of 450 mg of quercetin was recommended and safer for reducing clinical severity in acute decompensated heart failure patients compared to 800 mg of quercetin over 5 days.[63]

Quercetin supplementation is safe and effective for two viral diseases – hepatitis C and coronavirus disease (COVID)-19. Quercetin up to 5 g/day was safe in some hepatitis C patients with antiviral activity.[64] Quercetin has a good antiviral effect, but its clinical application is limited by its low bioavailability. Quercetin conjugated from glucuronate enhances the total bioavailability of quercetin.[65] For 30 days, 1000 mg of Quercetin Phytosome per day improved symptoms in COVID outpatients, reducing hospitalization, readmission, and mortality, and was highly safe.[65] In addition, a randomized phase II clinical trial investigating the efficacy and safety of masitinib in combination with isoquercitrin for treating patients hospitalized with moderate and severe COVID-19 is in the enrollment phase (NCT Number: NCT04622865).

Except for cardiovascular, respiratory, and viral diseases, the safety of quercetin has been demonstrated in treating several other diseases. Patients with rheumatoid arthritis who received 500 mg of quercetin daily (for 8 weeks) significantly improved clinical symptoms and disease activity.[66] The same 500 mg daily dose of quercetin (taken for 4 weeks) had a safe uric acid-lowering effect.[67] A clinical trial showed that quercetin was a promising and safe drug to prevent contrast nephropathy.[68] In addition, two randomized controlled studies are in the enrollment phase to validate the safety of quercetin supplementation for Alzheimer's disease and age-related macular degeneration (NCT Numbers: NCT05422885; NCT05062486), respectively. Currently, preliminary evidence supports that quercetin supplementation and intravenous administration are safe in healthy individuals and some disease states. However, optimal dose selection of quercetin for specific diseases still requires more future

Table 1. Summary of clinical studies evaluating the safety of quercetin.

Duration of intervention	Results	Reference
1 week	One patient reported mild adverse events, including gastroesophageal reflux disease, which was observed in both the placebo and quercetin groups.	Han *et al.*[35]
10 days	Quercetin in patients with NDTB does not cause side effects.	Butov *et al.*[60]
6 weeks	Quercetin supplementation did not affect nutritional status. Blood parameters of liver and kidney function, hematology, and serum electrolytes did not show any adverse consequences of quercetin.	Egert *et al.*[61]
3 months	Intravenous quercetin therapy is safe and well tolerated.	Parkhomenko *et al.*[62]
5 days	Intravenous quercetin treatment is safe without any serious adverse events.	Kozhukhov[63]
28 days	Quercetin was well tolerated at high doses with no adverse events or signs of toxicity. CBC, complete metabolome, cholesterol, and coagulation studies did not change significantly from baseline to week 2 and 4 measurements.	Lu *et al.*[64]
30 days	The results confirmed quercetin's very high safety profile and hinted at possible anti-fatigue and appetite-stimulating properties.	DI Pierro *et al.*[65]
8 weeks	During the study, there was no change in drug dosage or physical activity. No side effects were reported except for stomach pain in one patient in the placebo group, who was excluded from the study.	Javadi *et al.*[66]
4 weeks	According to the lifestyle maintenance questionnaire, there were no significant changes in lifestyle or medication during the study period, and no adverse events were reported after receiving quercetin or a placebo.	Shi and Williamson[67]
3–5 days	Quercetin at a dose of 500 mg every 8 h produced no adverse effects for 3–5 days, with only 3% of patients reporting moderate gastrointestinal pain.	Vicente-Vicente *et al.*[68]

CBC, complete blood count; NDTB, newly diagnosed destructive pulmonary tuberculosis.

information from large samples of phase III trials.

CS disrupts the oxidation/antioxidation balance in the lungs

As the introduction mentions, CS is the most common and important cause of COPD. Its mechanisms include OS and inflammation, cellular senescence, immune dysregulation, mitochondrial autophagy, and gut microbiota dysbiosis (Figure 3).[19–22] Among these pathological mechanisms of CS-COPD, OS is the initial and most crucial pathological mechanism.[70] CS could cause an imbalance of the oxidation/antioxidation system in the lungs, resulting in OS. Free radicals are chemical substances that contain single or multiple unpaired electrons in their external orbit and are generally strongly reactive to cellular and subcellular structures.[71] Free radicals can be divided into endogenous and exogenous free radicals. CS is an essential source of exogenous free radicals in humans. Inhaled tobacco smoke includes gas and tar phases containing high amounts of free radicals. Due to their high reactivity, they cause damage to cellular structures or molecules (e.g. proteins, nucleic acids, lipids), a process that involves electron uptake.[72] CS-related oxidative damage caused the accumulation of inflammatory cells (e.g. macrophages and neutrophils) in the lung, causing an increase in endogenous reactive oxygen species (ROS).[73] In addition, CS induced endogenous ROS production in airway epithelial cells and smooth muscle cells. The activity of ROS-producing enzymes (NADPH-oxidases, xanthine/xanthine oxidase system, and neutrophil-driven myeloperoxidase) increased in the bronchial lavage fluid of the CS-COPD population. These endogenous ROS persisted after smoking cessation.[74] CS decreased antioxidant enzyme activity (catalase and superoxide dismutase) and antioxidants (glutathione

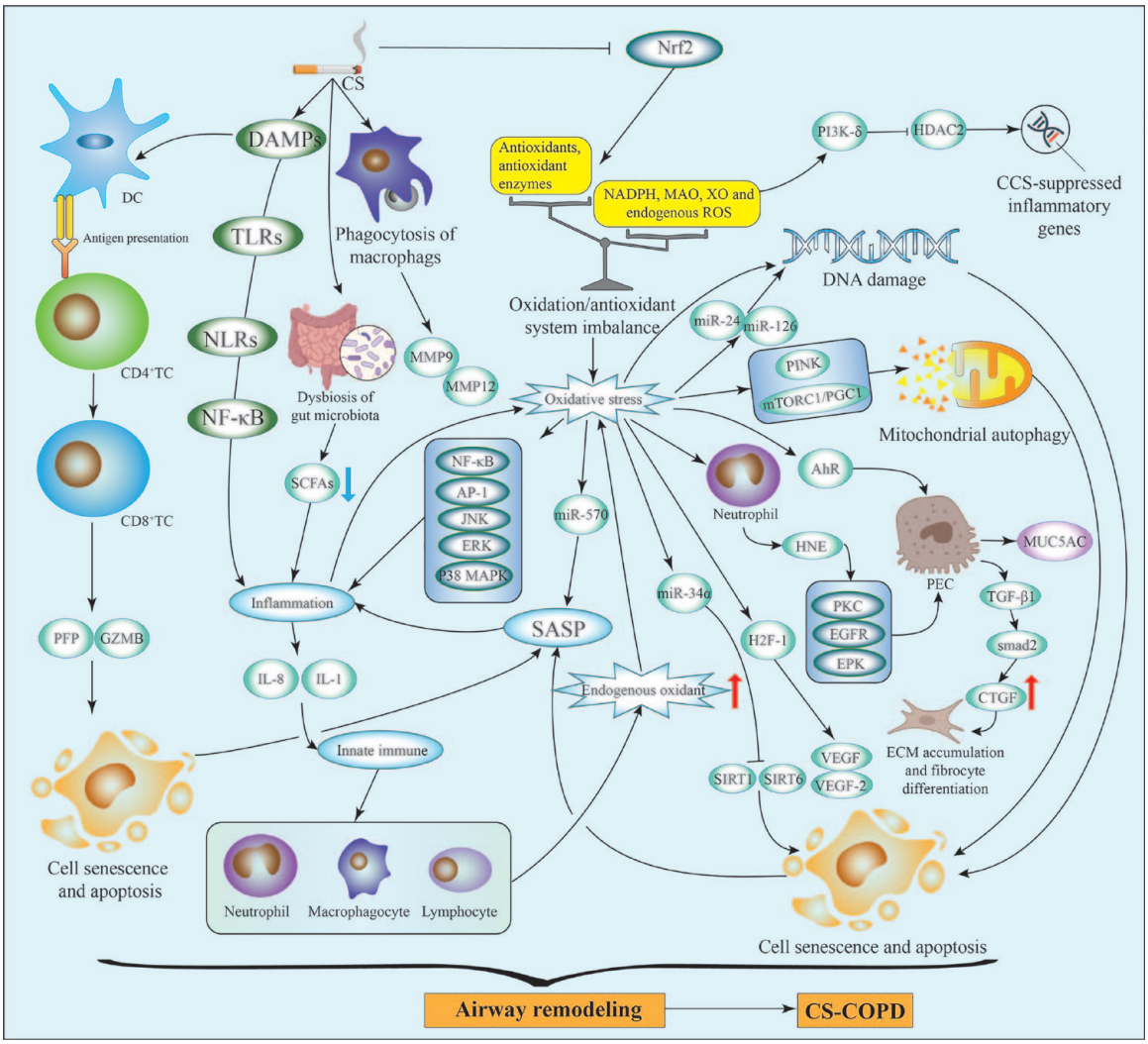

Figure 3. Multiple mechanisms are involved in CS-COPD. Among them, OS and inflammation are the initiators and the core, and immune dysregulation, cellular senescence, mitochondrial autophagy, and gut microbiota dysbiosis are also involved.

peroxidase, glutathione transferase, and total glutathione).[72,75] The oxidative/antioxidant balance disruption caused by active additional endogenous ROS could create the conditions for generating OS.[76] Prolonged OS in the lung resulted in impaired protease/antiprotease homeostasis, defective tissue repair mechanisms, accelerated apoptosis, and enhanced autophagy in lung cells.[77] CS also affected antioxidant signaling and antioxidant protein expression. Many cellular antioxidant and detoxification enzymes were regulated by nuclear factor erythroid 2-related factor 2 (Nrf2).[74] There was evidence that the loss of protective antioxidant responses mediated by the Nrf2 pathway in patients with advanced CS-COPD was a critical factor in the pathophysiological progression of emphysema.[78] The antioxidant protein, sestrin-2 (SESN2), could serve as a potential marker of airway remodeling and a therapeutic target. Mutant inactivation of SESN2 prevented the development of CS-induced emphysema by selectively accumulating intracellular superoxide anion ($O_2(-)$) and upregulating platelet-derived growth factor receptor beta (PDGFRβ) expression, suggesting a SESN2-PDGFRβ role in the pathogenesis of COPD-negative correlation.[79] In contrast, SESN2 showed overexpression in CS-COPD mice, reducing alveolar maintenance.[79]

In addition, ROS exacerbated airway remodeling by affecting mucin secretion and the protease/antiprotease balance. ROS increased neutrophil

elastase activity by inactivating α1-antitrypsin and secretory leukocyte protease inhibitors through oxidation.[80] Enhanced neutrophil elastase activity exacerbated the protease/antiprotease imbalance in the lung. Moreover, neutrophil elastase–induced mucin 5AC (MUC5AC) expression was seen in human airway epithelial cells exposed to ROS via the protein kinase C/epidermal growth factor receptor/extracellular-regulated kinase pathway.[81] ROS-mediated aromatic hydrocarbon receptors in respiratory epithelial cells promoted MUC5AC secretion by respiratory epithelial cells.[82] CS polarized macrophages to M1 and M2 phenotypes and increased matrix metalloproteinases 9 (MMP9) and MMP12 expression.[83]

Furthermore, CS-associated ROS also contributed to the exacerbation of airway remodeling by upregulating the expression of several cytokines. ROS in the lung tissue of COPD patients with chronic bronchitis upregulated vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor-2 (VEGFR-2) expression through induction of hypoxia-inducible factor 1.[84,85] VEGF and VEGFR-2 stimulated proliferation, pulmonary vascular remodeling, and airway remodeling.[86] ROS-induced transforming growth factor (TGF) expression is also involved in CS-COPD. VEGF and VEGFR-2 damaged epithelial cells, and the damaged epithelial cells released TGF-β. CS activated the smad2 (TGF-1/Smad2) pathway, upregulating connective tissue growth factor (CTGF) gene expression in epithelial and mesenchymal cells through an oxidative mechanism, leading to the release of active TGF-1.[87] CTGF promoted lung extracellular matrix accumulation and fibroblast differentiation.[88] TGF-β1 expression played a crucial role in airway remodeling in COPD, promoting epithelial-to-mesenchymal transition. Interestingly, intervention with an estrogen receptor antagonist (tamoxifen) attenuated OS in female mice after smoking, suggesting that estrogen is involved in airway remodeling associated with OS.[89] TGF-β1 also inhibits Nrf2, attenuating endogenous antioxidant protection.[90]

Mechanisms of the effects of CS on inflammation and immune activation in COPD

CS exacerbates the inflammatory response in COPD by activating intrinsic immunity and OS-inflammation-related signaling pathways. CS could activate damage-associated molecular patterns (DAMPs), toll-like receptors, and nucleotide oligomerization domain (NOD)-like receptors. Those receptors and CS-associated ROS sequentially activated nuclear factor kappa B (NF-κB) and Caspase 1 to generate the chemokines IL-1 and IL-8.[91] These chemokines activated intrinsic immunity and recruited more neutrophils, macrophages, and lymphocytes.[91] Activated neutrophils and macrophages could produce oxidants that promote inflammatory responses.[92,93] CS also decreased corticosteroid sensitivity in COPD patients. The potential mechanism was that ROS promoted Histone deacetylase 2 inactivations by activating phosphatidylinositol-3-kinase (PI3K)-δ impairment, which prevented corticosteroids from shutting down activated inflammatory genes, activating the intrinsic immune response and thus exacerbating inflammation.[94] In addition, CS-induced OS could also increase the inflammatory response by regulating redox-sensitive transcription factors, such as NF-κB and activator protein 1 (AP-1), c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), and p38 mitogen-activated protein kinase (p38MAPK) pathways.[77,93] CS-mediated endogenous immune pathways activated epithelial cells and alveolar macrophages. These cells secreted chemotactic molecules and pro-inflammatory factors and recruited more inflammatory cells into the lung.[77,93] These mechanisms perpetuate OS in the lung, creating a vicious OS inflammation cycle.

CS initiates adaptive immunity in COPD and reduces the phagocytosis of pathogens by phagocytes and neutrophils. When tolerance mechanisms fail, certain DAMPs (e.g. galectin, cathepsin, heat shock protein, and high mobility group box-1) induce dendritic cells to mature and deliver antigens to helper T cells to activate adaptive immunity.[95] CD4+ T cells activate antibody-producing B cells that produce IgG autoantibodies to mediate autoimmunity in CS-COPD. CD4+ cells also promote the survival of CD8+ cells, which cause cell death and apoptosis in CS-COPD pathology by secreting cytotoxic perforin and granzyme B.[96] Infection with respiratory pathogens exacerbates inflammation in COPD. CS-related ROS is closely related to the clearance of COPD pathogens and their degree of pathogenicity. Cigarette smoke and lipid peroxidation

product-modified matrix proteins reduce macrophage phagocytosis of apoptotic neutrophils containing bacteria.[97] Oxidants from cigarette burning drive the carbonylation of alveolar macrophages and affect their phagocytosis.[98] There is evidence that OS is associated with rhinovirus-induced deterioration of COPD.[99] In addition, targeted inhibition of endosomal ROS production reduces the pathogenicity of the influenza A virus.[100] In conclusion, attenuation of CS-related OS is protective against CS-COPD progression and severe damage from persistent infection.

CS-COPD and cellular senescence, mitochondrial autophagy-regulating

Abnormal RNA gene expression, DNA damage, inflammation, mitochondrial dysfunction, and structure in CS-COPD promote cellular senescence.[101,102] Aberrant expression of long-stranded non-coding RNA and mRNA is present in lung tissue of chronic CS-COPD mouse models.[103] CS and its associated ROS regulate cellular senescence sensitivity by altering miRNA expression. miR-34a expression activated by ROS downregulates sirtuin 1 (SIRT1) and SIRT6 expression, thereby promoting cellular senescence. miR-570 activated by ROS promotes cellular senescence and senescence-associated secretory phenotype (SASP) factor secretion. miR-24 and miR-126 on CS-COPD DNA inhibition of repair were also associated with cellular senescence.[102] The role of long-stranded non-coding RNA and its potential encoded protein genes in CS-COPD cell senescence must be further explored. CS-associated OS regulates COPD airway remodeling and cellular senescence by affecting the nuclear red lineage P45-Nrf2 pathway leading to aberrant DNA methylation in small airway epithelial cells.[104] CS-associated OS-induced methylation of the glutamylcysteine synthetase catalytic subunit gene promoter contributes to cellular senescence.[105] In addition, CS-associated OS exacerbates inflammation, increases ROS, and leads to DNA double-strand breaks.[106,107] The DNA damage response exacerbates cellular senescence and apoptosis and activates the SASP. SASP, in turn, exacerbates inflammation. A vicious cycle of inflammation-ROS-induced cellular senescence and SASP is formed.[108] The interaction of ROS with organelles, such as mitochondria and endoplasmic reticulum, may disrupt the metabolic homeostasis of cells.[109] Chronic exposure to CS alters cellular metabolism in primary human respiratory smooth muscle cells, replacing glucose oxidative phosphorylation with aerobic glycolysis and affecting functional mitochondrial energy metabolic pathways.[110] CS-induced mitochondrial damage and ROS production are associated with promoting bronchial epithelial cell senescence.[111]

Autophagy can prevent cellular senescence by removing CS-induced mitochondrial damage. Overexpression of Parkin RBR E3 Ubiquitin Protein Ligase (PRKN) protein can reduce oxidative modifications and mitochondrial damage that accelerate cellular senescence by limiting the rate of phosphatase and tensin homolog-induced putative protein kinase 1 (PINK1)-PRKN-mediated mitochondrial autophagy.[112] PINK1-PARK2-mediated mitochondrial autophagy is essential for CS-induced bronchial epithelial cells' ROS production and cellular senescence.[111] However, inappropriate PINK1-PARK2-mediated mitochondrial autophagy leads to CS-COPD myofibroblast differentiation.[113] In the SIRT1-deficient CS mouse model, cellular senescence is accelerated by a mechanism that may involve reduced autophagy associated with the FOX03/PINK1 signaling pathway.[114] Deletion of NLRP3 upregulates the PINK1-Parkin pathway and is protective against inflammation and mitochondrial ROS.[115] The mTORC1/PGC-1 axis activation disrupts dynamic mitochondrial homeostasis and increases cellular senescence.[116] The exploration of the ROS-mitochondria-associated signaling pathway for cellular senescence and autophagy needs to be completed and needs further studies to be refined. Necrotic prolapse triggered by CS-induced mitochondrial autophagy is a programmed cell death involving more humid and inflammatory responses. Mitochondrial dysfunction and mitochondrial ROS production due to mitochondrial ferrous iron overload associated with chronic smoke ingestion lead to mitochondrial iron accumulation, which may promote necroptosis.[117,118]

Gut microbiota and CS-COPD

There is an exciting link between gut microbiota and pulmonary, called the gut–lung axis. CS can indirectly affect the composition and distribution of gut microbiota by altering immune homeostasis and the microbial 'microenvironment' (including oxygen, pH, and acid production).[119] Smoking reduced the diversity of gut microbiota, downregulating the abundance of Firmicutes and

Proteobacteria and upregulating the abundance of Bacteroidetes and Actinobacteria on an overall level.[19] In turn, some gut microbiotas and their metabolites can indirectly influence the inflammatory and immune response in CS-COPD through the gut–lung axis.

Specific gut microbiota and their metabolites could influence the inflammatory response in CS-COPD by modulating inflammatory signaling. Parabacteroides Goldsteinii (PG), a commensal bacterium, can inhibit pulmonary inflammation in CS-COPD mice. The anti-inflammatory effect may be related to the antagonistic effect of PG-lipopolysaccharide extracted from it on the TLR4 signaling pathway.[120] The results of an *in vitro* experiment showed that rhamnose and short bacilli inhibited CS-induced NF-κB and downregulated inflammatory mediators, such as IL-1β, IL-6, IL-10, IL-23, TNFα, and CXCL-8 released by CS-activated human macrophages.[121] The oral intervention of *Lactobacillus rhamnosus* in CS-COPD reduced the expression of TLR2, TLR4, TLR9, STAT3, and NF-κB in lung tissue and induced an anti-inflammatory environment in the lung.[122] *Bifidobacterium breve* or *L. rhamnosus* reduced macrophage aggregation.[123] CS-related OS causes damage to the gastrointestinal epithelium, given the evidence that CS induces numerous gastrointestinal mucosal diseases.[124] Phosphorylcholine-containing bacteria can be partially transferred to the lungs via intestinal injury. They bind to the platelet-activating factor receptor to activate the NLRP3 inflammasome, causing downstream inflammation and neutrophil recruitment.[125] SCFAs can reduce the NLRP3 inflammasome through their protective effect on the intestinal barrier.[19]

Some gut microbiota and their beneficial metabolites can modulate the immune response within CS-COPD. Lactobacillus Casei Shirota intake positively correlates with NK cell activity and CD16+ cell counts, enhancing intrinsic human immunity.[126] Remodeling of the gut microbiota can maintain Th17/Treg homeostasis and improve COPD.[127] Currently, there are limited studies on oral probiotics modulating immunity to COPD. The mechanisms involved need to be further investigated.[128] Some gut microbiota metabolites are similarly involved in the immune regulation of CS-COPD. SCFAs reduce the innate immune response to smoking by inhibiting the activity of the enzyme 3-hydroxy-3-methyl-glutaryl coenzyme A, an enzyme that can help reduce lung inflammation and airway remodeling.[129] SCFAs and lipopolysaccharides regulate the immune tone and cellular metabolism of IL-1β, FFAR2, and FFAR3 expression in lung tissue.[130]

Clinical evidence for improvement of CS-COPD with quercetin

The existence of an association between dietary flavonoid intake and CS-COPD has been reported in several studies. A 4-year Dutch population-based epidemiological survey showed that a high intake of apples (which contain quercetin) was beneficial for CS-COPD and was positively associated with improved FEV_1 and respiratory symptoms.[131] More recently, the Danish MORGEN study, a prospective cohort with a sample size of 55,143 aged above 23 years, found a negative correlation between flavonoid intake and CS-COPD, with quercetin included in the flavonoid intake.[132] Currently, Some *in vivo* and *ex vivo* evidence suggests that quercetin has promising anti-CS-COPD effects, which may be related to its antioxidant, anti-inflammatory, immunomodulatory, mitochondrial autophagy-regulating, anti-aging, and gut microbiota-regulating mechanisms (Figure 4). Therefore, in the next section, we highlight quercetin's therapeutic mechanisms and effects on CS-COPD.

Quercetin ameliorates OS and oxidative damage in CS-COPD

Quercetin counteracts OS in CS-COPD by modulating the Nrf2, TGF-β1/Smad 2/3 signaling pathway, quercetin ameliorates OS-related injury in CS-COPD. Quercetin is a natural antioxidant, and as mentioned before, the phenolic hydroxyl groups and double bonds in its structure confer its potent oxidative activity.[42] Quercetin can counteract OS through several pathways, such as direct scavenging free radicals, inhibiting lipid oxidation, and modulator enzyme activity in free radical production.[29] Quercetin increased superoxide dismutase (SOD), catalase, and GSH activities, decreased protein carbonylation, and reduced ROS and nitric oxide (NO) production in alveolar macrophages in CS-treated mice.[34] Quercetin can potentially prevent oxidative damage in CS-COPD by modulating the relevant pathways involved in OS. Quercetin enhances the antioxidant response and reduces the production of pro-inflammatory factors by activating Nrf2,

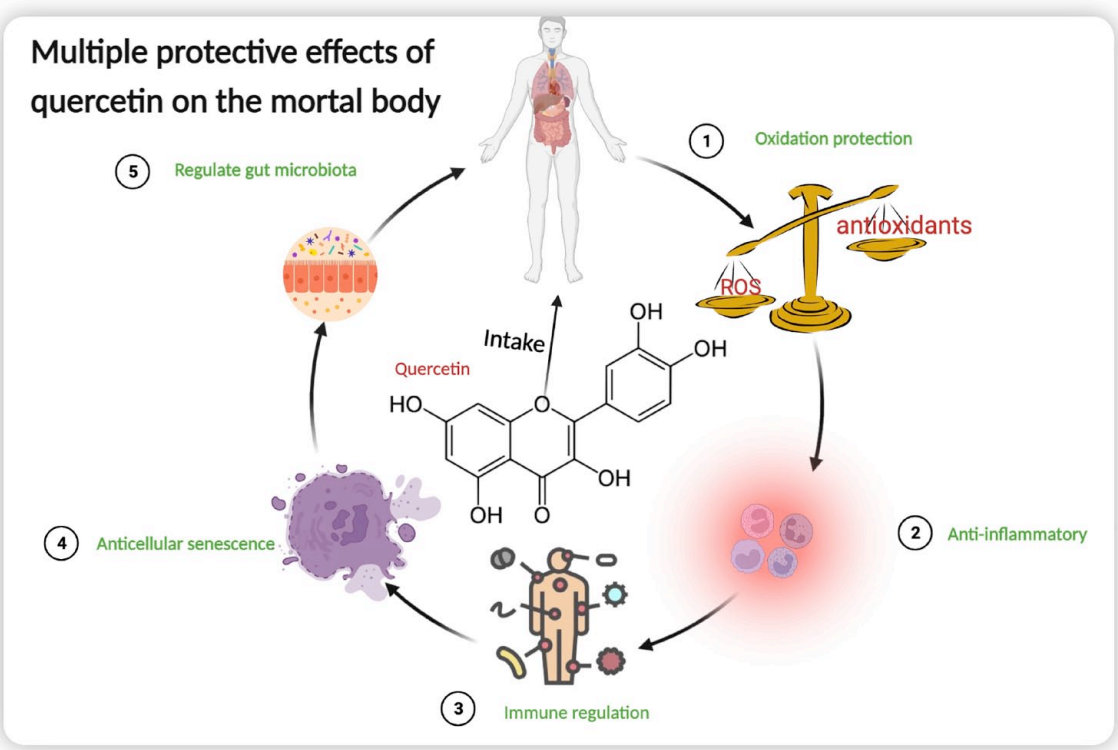

Figure 4. The multiple beneficial effects of quercetin on the human body.

an essential pathway for antioxidant protection in CS-COPD.[133] In addition, including quercetin in Qiwei Putao powder reduced the inflammatory factors IL-1β and TNF-α, increased SOD activity, and reduced oxidative damage in the lungs of CS-COPD mice by activating the Nrf2 pathway.[134] Furthermore, *in vitro*, quercetin upregulates Nrf2 expression via activated AMPK in CS-COPD.[135] The ROS-activated TGF-β1/Smad2/3 pathway is also closely associated with airway remodeling. Quercetin inhibits the activation of the TGF-β1/Smad2/3 signaling pathway. However, the exact mechanism and role of quercetin inhibition of this pathway in CS-COPD airway remodeling need to be explored.[136]

Quercetin reduces the inflammatory response and modulates the intrinsic immunity in CS-COPD

Quercetin can reduce the inflammatory response in CS-COPD and slow the progression of airway remodeling by blocking multiple inflammatory pathways. An animal study found that, possibly through inhibition of the NF-κB pathway and EGFR phosphorylation, quercetin attenuated the inhibition of OS and inflammatory responses and reduced MUC5AC synthesis induced in CS-treated rats.[137] Quercetin may also attenuate the inflammatory response by inhibiting the redox-sensitive transcription factor-related pathways discussed in the previous section, such as JNK and p38 MAPK.[138,139] In addition, CS can stimulate excessive ROS production by alveolar macrophages and lung epithelial cells, recruiting MMP produced by inflammatory cells and epithelial cells, which can lyse the alveolar wall and thus exacerbate emphysema development. Quercetin delays emphysema by reducing OS, lung inflammation, and the expression of MMP9 and MMP12.[140] Quercetin inhibits PDE4 in converging neutrophils and increases cAMP expression, indirectly reducing the inflammatory response.[141] An interesting finding was the induction of macrophages, neutrophils, and inflammatory factors, including IL-1β and TNF-α, in the lungs of CS-treated mice. The recruitment of inflammatory cells and the increase in inflammatory factors appear to be associated with increased expression of 5-HTR2A and 5-HTR2B. However, the mechanisms involved are unclear, and 5-HTR appears to be associated

with the mitogen-activated protein kinase pathway.[142] This effect is inhibited by the 5-HT receptor inhibitor quercetin, which attenuates the thickening and collagen deposition around the small airways.[142] Quercetin decreased the inflammatory factors IL-10, IL-13, and IL-22 in the CS-COPD mouse model, which were associated with the progression of airway remodeling. Among them, IL-13 and IL-22 were produced by Th2 cells and Th17 cells, respectively.

Quercetin may also exert an indirect anti-inflammatory effect by modulating intrinsic immunity.[32] Infections caused by microorganisms in the lungs are an essential factor in the increased inflammation of COPD. CS causes dysfunction of some intrinsic immune cells, increasing the likelihood of infection. Quercetin may play a role in preventing infection in CS-COPD by restoring the phagocytosis of neutrophils and lung macrophages. For example, the ability of neutrophils to take up the respiratory pathogen *Staphylococcus aureus* is reduced in smokers. β-carotene and quercetin enhance the phagocytosis of neutrophils after CS exposure.[143] In addition, quercetin has been found to protect the phagocytosis of virus-suppressed lung macrophages.[144]

Potential regulatory effects and mechanisms of quercetin on cellular senescence and mitochondrial autophagy in CS-COPD

Quercetin affects the regulation of cellular senescence and mitochondrial autophagy in CS-COPD. It has been shown previously that DNA damage and mitochondrial morphological damage promote cellular senescence in CS-COPD. Bulk and nanoforms of quercetin protect against DNA damage in the lymphocytes of COPD patients exposed to food mutagens.[145] In addition, vitamin C and quercetin inhibit the damage of mitochondrial structure and function in human bronchial epithelial cells by PM2.5.[146] Therefore, it is reasonable to speculate that quercetin may exert anti-cellular senescence effects by protecting DNA and mitochondrial integrity in CS-COPD. Furthermore, quercetin reduces emphysema manifestations and SASP in mice by activating AMPK.[147] Activation of AMPK promotes Nrf2 signaling and contributes to oxidative/antioxidant homeostasis. Thus, reducing OS pathways may be another mechanism by which quercetin exerts its anti-aging effects on cells. Enhanced mitochondrial autophagy clears mitochondrial damage and avoids progression to cellular senescence. PINK1/Parkin is a critical pathway involved in mitochondrial autophagy, and quercetin has potential regulatory effects on this pathway. Quercetin produces mitochondrial autophagy by activating PINK1/Parkin and SIRT1/PINK1/Parkin, exerting anti-cellular senescence effects.[148,149] Combining quercetin and dasatinib has been used to treat several aging-related diseases.[150,151] Whether quercetin modulation of PINK1/Parkin-dependent mitochondrial autophagy has a retarding effect on CS-COPD, cell senescence needs to be explored in future studies.

Beneficial effects and mechanisms of quercetin regulation of gut microbiota and gut microbiota metabolites on CS-COPD

By modulating gut microbiota and SCFAs, quercetin modulates inflammation and immunity in CS-COPD. *In vitro*, quercetin inhibited *S. aureus, Pseudomonas aeruginosa*, and *Escherichia coli*.[152] It can enhance the abundance of probiotics, such as *Bifidobacterium* and *Lactobacillus*.[153] The abundance of *Bifidobacterium* and *Lactobacillus* decreased after CS exposure.[19] In addition, quercetin may also affect gut microbiota metabolites. Quercetin increased SCFAs in mouse offspring after maternal PM 2.5 exposure.[154] This effect may be achieved by quercetin restoring probiotic bacteria after PM 2.5 exposure.[155,156] Quercetin ameliorated the CS-induced decrease in the abundance of *Bifidobacterium* and *Lactobacillus*. *Bifidobacterium* and *Lactobacillus* could metabolize dietary fiber to produce SCFAs.[19] Therefore, it is highly likely that quercetin also promotes the production of SCFAs in CS-COPD. SCFAs regulate inflammation and immunity in CS-COPD by reducing NLRP3 inflammatory vesicles and modulating the mevalonate pathway as follows.[19] Butyrate, one of the SCFAs, is associated with the expression of tight junction proteins, maintaining the integrity of the intestinal mucosa.[157] In addition, quercetin itself regulates the expression of occludin and zonula occludens-1 with protective effects against disruption of epithelial integrity.[158] The integrity of the intestinal mucosal epithelium prevents the colonization of the lungs by some live bacteria or proteins from dead bacteria.[19]

It is well known that gut microbiota and their metabolites influence inflammatory and immune responses in the lung via the pulmonary–intestinal

axis. Modifying gut microbiota and their metabolites with natural compounds to treat CS-COPD is a promising approach. However, there are no studies on quercetin modulation of CS-COPD-related gut microbiota changes. In addition, there are no studies on the regulatory effects of quercetin on some specific gut microbiota. Some gut microbiotas were beneficial in alleviating CS-COPD, such as *B. breve*, *L. rhamnosus*, and PG.

In conclusion, quercetin may exert anti-CS-COPD effects by affecting CS-related OS and inflammation, cellular senescence, mitochondrial autophagy, immune dysregulation, and gut microbiota (Figure 5). Quercetin may act as a natural compound with multi-targeted effects against CS-COPD. As mentioned above, conventional therapeutic agents for CS-COPD are associated with specific adverse effects, and the efficacy achieved is limited by the singularity of the targeted pathways and mechanisms, leaving room for improvement. Therefore, in the next section, we explored the possibility of synergizing quercetin with some existing drugs to treat CS-COPD.

The potential of quercetin in combination with conventional drugs for the treatment of CS-COPD

Quercetin's bronchodilating, anti-inflammatory, anti-infective, and antiviral drug efficacy is of value in preventing and treating COPD. Quercetin may synergize with β-agonists and M-receptor antagonists, corticosteroids and roflumilast, antibiotics, and NAC to increase efficacy in treating CS-COPD (Table 2).

Quercetin nebulized inhalation doubly inhibits PDE4 and phospholipase C-β. It increases the 50% effective concentration of the β-agonist isoprenaline. Quercetin has a synergistic effect with isoprenaline, producing greater airway relaxation when used in combination. Quercetin alone or combined with short-acting beta-agonists can be used in asthma and COPD.[165] In using this combination, lower doses of β-agonists can be considered to avoid the adverse effects of their high-dose use. *In vitro*, quercetin concentration dependently inhibited tracheal constriction induced by electric field stimulation and carbachol in mice, a process involving antagonism of postsynaptic muscarinic receptors and presynaptic NO production in airway smooth muscle cells.[159] The results indicate that the mechanisms of action of quercetin and musk muscarinic receptor antagonists may overlap. The combination of the two may have synergistic effects on diastolic smooth muscle. In addition, quercetin's mAChR pathway-mediated defecation effect may alleviate some muscarinic receptor antagonist-induced constipation.[166] Suppression of inflammation is the main focus in preventing the progression of COPD, and steroid hormones clinically induce remission of AECOPD. However, patients with hormone-insensitive COPD may require high doses of steroid hormones to control symptoms, with an increased risk of concomitant adverse effects. Quercetin reverses CS-induced corticosteroid hypersensitivity by activating AMPK-induced Nrf2 expression.[135] Quercetin inhibits IL-8 expression in CS-COPD airway epithelial cells through the activity of EGFR and Akt.[33] Roflumilast is another anti-inflammatory agent that blocks inflammatory response signaling by selectively inhibiting PDE4. As mentioned earlier, quercetin can reduce inflammation by inhibiting PDE4. Quercetin and Roflumilast have the same target site, and their combination may have additional anti-inflammatory potency. Several clinical studies have combined quercetin and roflumilast to intervene in COPD-related cardiovascular disease. In a clinical study, combining roflumilast and quercetin effectively reduced systemic inflammation in patients with COPD stage III complicated by ischemic heart disease and improved immunity. It reduced the incidence of cardiovascular complications in patients.[167] In addition, the combination of quercetin and roflumilast is feasible and effective in treating patients with severe COPD exacerbation with coronary heart disease.[160]

Bacterial infections are a significant cause of COPD progression. Therefore, it is essential to find a better antimicrobial combination. Nontypeable Haemophilus influenzae (NTHi) and *Streptococcus pneumoniae* are susceptible bacteria in COPD patients.[168] Quercetin has a good bactericidal effect on NTHi. In addition to the direct bactericidal effect, quercetin reduced NTHi-induced expression of pro-inflammatory factors IL-8, CXCL-1, IL-6, PDE4b, and TNF-α by inhibiting Akt phosphorylation, and therefore modulating the immune response.[161] Quercetin reduces the risk of *S. pneumoniae* infection by inhibiting *S. pneumoniae* hemolysin activity and sortase A, a transpeptidase associated with

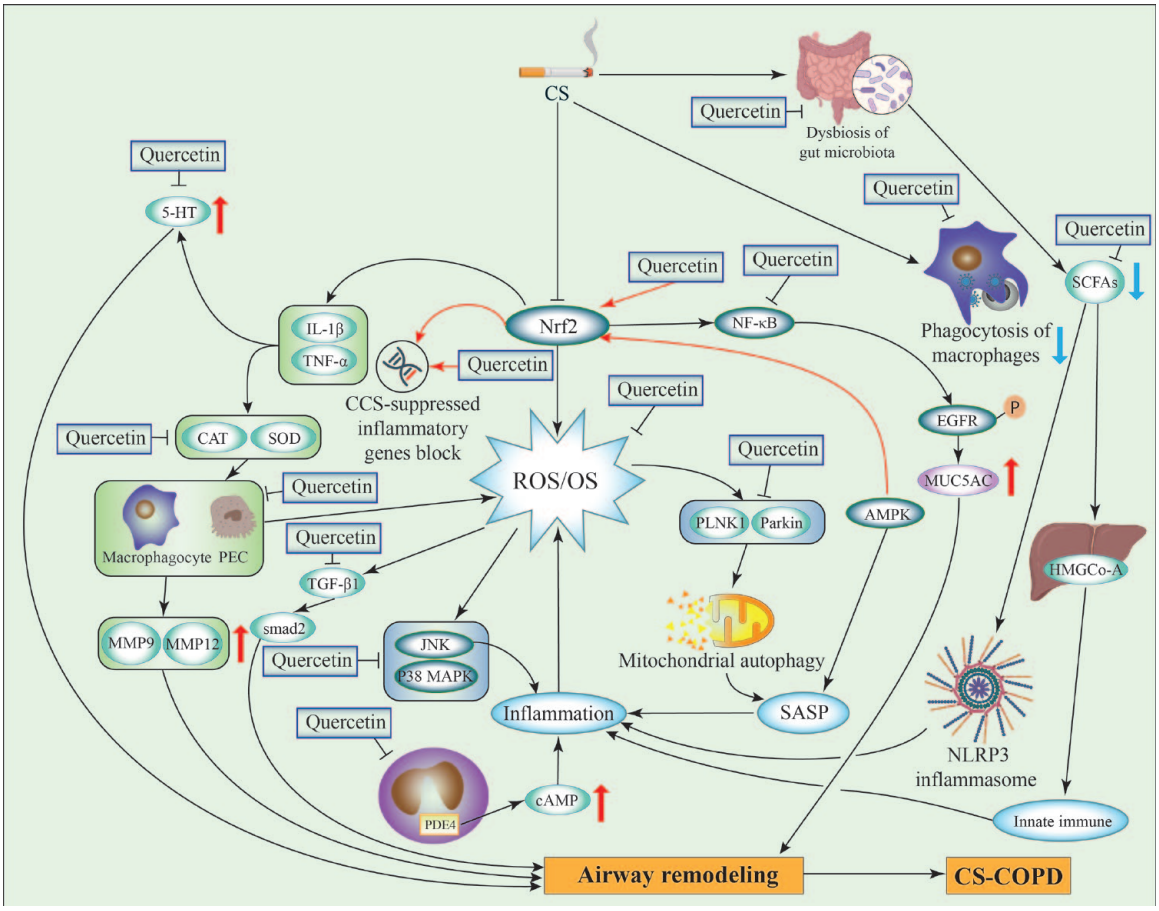

Figure 5. The anti-CS-COPD mechanism of quercetin involves antioxidant, anti-inflammatory, immunomodulatory, anti-cellular senescence, mitochondrial autophagy modulation, and regulation of gut microbiota.

biofilm formation of *S. pneumoniae*.[162,163] This evidence demonstrates quercetin's potential for controlling and preventing bacterial infections in the lower respiratory tract in COPD. For existing antibiotic regimens in COPD, quercetin may provide an additional complement. NAC is an antioxidant used to treat sputum thickening in COPD patients. A new nebulized combination, Quercinex (nebulized quercetin-NAC), significantly improved the symptoms of dyspnea in some COVID-19 patients without leaving lung scarring, suggesting that this combination may have good antiviral and anti-inflammatory utility.[164] The combination could also be tried to induce remission of viral infection-associated AECOPD. In addition, quercetin-crowned NAC liposome is a novel oral combination formulation with improved bioavailability. Its pharmacokinetics, drug interactions, and bioavailability *in vivo* need further investigation.[169]

Given the results of the previous review of the toxicity and safety of quercetin, quercetin has a high safety profile for use. A randomized clinical trial determined COPD patients can safely tolerate 2000 mg/day of quercetin intake.[35] Therefore, observational studies on the efficacy of quercetin supplementation in combination with beta-agonists and M-receptor antagonists, corticosteroids and roflumilast, antibiotics, and NAC in CS-COPD are recommended. However, due to the low oral bioavailability of quercetin, some novel drug delivery modalities need to be considered when developing combination drug use.

Conclusion and future direction

Quercetin is a class of natural flavonoids with various biological functions which prevent and treat various diseases. Safety is a prerequisite for drug use. According to the available clinical

Table 2. Summary of studies exploring the potential synergistic effect and mechanism between the routine treatment of COPD and quercetin.

The experimental type	The experimental type	Delivery way	Results of the study	Pharmacodynamic interaction	Mechanism	Conclusion	Reference
Quercetin	*In vitro*	Solution	Quercetin treatment reduced IL-8 levels in AEC in COPD patients.	Not applicable	EGFR/PI 3-kinase /Akt activity was regulated to restore nuclear FOXO3A	Quercetin therapy reduces inflammation in COPD.	Ganesan *et al.*[33]
Quercetin	*In vitro*	Solution	Quercetin reversed reduced corticosteroid sensitivity in PBMC.	Not applicable	Increased AMPK activity and Nrf2 protein expression	Quercetin restores sensitivity to corticosteroids and maybe a new treatment for COPD in combination with corticosteroids.	Mitani *et al.*[135]
Quercetin	*In vitro*	Solution	Quercetin inhibited tracheal constriction induced by electric field stimulation and carbacholine in a concentration-dependent manner in mice.	Not applicable	NO production and MA receptor antagonism	Quercetin inhibits tracheal contractility in rats through presynaptic and postsynaptic sites of action.	Capasso *et al.*[159]
Quercetin and roflumilast	Clinical research	Oral	Combining roflumilast and quercetin as part of the primary treatment of COPD and IHD improved clinical symptoms, reduced C-reactive protein levels, increased plasma α2-macroglobulin levels, and reduced the incidence of cardiovascular events.	Synergy	Not applicable	By reducing systemic inflammatory activation and improving immune defenses, combination therapy significantly improves clinical outcomes in AECOPD patients with IHD and reduces the incidence of cardiovascular complications.	Herych and Iatsyshyn[160]
Quercetin	Animal study	Solution	Quercetin administration in a zebrafish model of sepsis infection during NTHi infection resulted in bacterial clearance without signs of host toxicity.	Not applicable	Inhibition of Akt phosphorylation, NTHi airway epithelial invasion reduction, and bacterial-induced expression of the pro-inflammatory markers IL-8, CXCL-1, IL-6, PDE4B, and TNF α	Quercetin has the potential for anti-NTHi infection.	Fernández-Calvet *et al.*[161]
Quercetin	Animal study	Solution	Quercetin treatment reduced PLY-mediated cell damage, improved the survival rate of mice infected with a lethal dose of *Streptococcus pneumoniae*, alleviated pathological damage to lung tissue, and inhibited the release of cytokines (IL-1β and TNF-α) in bronchoalveolar lavage fluid.	Not applicable	Inhibited the formation of oligomers	Quercetin can fight *S. pneumoniae* infection	Lv *et al.*[162]
Quercetin	*In vitro*	Solution	Quercetin inhibited biofilm formation by affecting sialic acid production.	Not applicable	Inhibition of Sortase A transpeptidase associated with biofilm formation in *S. pneumoniae*	The inhibition of quercetin on Sortase A is helpful for the prevention and treatment of *S. pneumoniae* infection	Wang *et al.*[163]
Quercinex	Clinical research	Atomization inhalation	Quercinex significantly improved the symptoms of dyspnea in some COVID-19 patients without remaining lung scarring.	Synergy	Not applicable	Quercinex formulation helps alleviate COVID-19 and possibly other viral lung diseases through its anti-inflammatory and antiviral effects.	Schettig *et al.*[164]

AEC, alveolar epithelial cell; AMPK, adenosine 5′ monophosphate-activated protein kinase; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease-19; CXCL, chemokine (C-X-C motif) ligand; EC50, 50% effective concentration; EGFR, endothelial growth factor receptor-2; IHD, ischemic heart disease; IL, interleukin; MA, muscarinic; NO, nitric oxide; NTHi, nontypeable *Haemophilus influenzae*; PBMC, peripheral blood mononuclear cells; PDE4I, phosphodiesterase-4 inhibitors; PI, phosphatidylinositol; PLY, pneumolysin; TNF, tumor necrosis factor.

studies, the intake of quercetin in the range of 500–2000 mg/day has a high safety level for disease intervention. The therapeutic effect of quercetin in modulating multiple targets and biological signaling tracks has been widely explored in various disease prevention and treatment strategies. Since quercetin is a highly potent antioxidant, we explored the possibility of quercetin against CS-COPD by linking it to a disease whose pathogenesis is closely related to OS. The review results suggest quercetin has multiple and comprehensive protective effects against CS-COPD. Quercetin prevents CS-COPD and counteracts airway remodeling through antioxidant, anti-inflammatory, immunomodulatory, anti-cellular senescence, mitochondrial autophagy modulation, and gut microbiota regulation. In particular, we reviewed the interactions between quercetin and some drugs commonly used in CS-COPD, hoping to provide potential potentiating or mitigating combinations of drugs. The results of this review suggest that quercetin has potential synergistic effects with beta-agonists and M-receptor antagonists, corticosteroids and roflumilast, antibiotics, and NAC, respectively, in exerting bronchodilatory, anti-inflammatory, antibacterial, and antiviral effects.

In conclusion, quercetin is a safe, natural compound with great potential for treating CS-COPD. However, there are some challenges to overcome to realize this potential. First, in clinical studies correlating CS-COPD with quercetin intake, quercetin supplementation has been chiefly provided in quercetin-containing diets. There needs to be more direct evidence that quercetin monomeric components are involved in improving CS-COPD. Furthermore, the anti-CS-COPD mechanism of quercetin needs further elucidation. For example, studies on the effect of quercetin on CS-COPD via TGF-β1/Smad and PINK1/Parkin pathways need to be added. In addition, there is a paucity of studies on the modulatory effects of quercetin on CS-COPD-related dysbiosis. Some specific intestinal genera and their metabolites have immunomodulatory and anti-inflammatory effects on CS-COPD via the pulmonary–intestinal axis, such as *B. breve, L. rhamnosus*, and PG. Finally, studies exploring the synergistic effects of quercetin with common CS-COPD drugs are still in their early stages. Excellent and safe drug combinations require more evidence and support from *in vitro*, animal, and clinical studies.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors unanimously approved the publication of this manuscript.

Author contributions

Kaixi Ding: Conceptualization; Methodology; Writing – original draft; Writing – review & editing.

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