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Review Article

Potential Application of *Rhododendron* Flavonoids' Anti-inflammatory and Antioxidant Activities in Animal Health Support and Protection

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Abstract

Rhododendron plants are abundant in flavonoid compounds, whose prominent antioxidant and anti-inflammatory physiological activities have attracted considerable attention. However, the application of related research in animal health maintenance and bodily protection, along with their underlying mechanisms, remains unclear. This ambiguity has constrained their translation into practical applications as physiological protective factors within animal husbandry. This study systematically reviewed relevant literature, identifying 17 *Rhododendron* flavonoids exhibiting significant antioxidant and anti-inflammatory activity. The antioxidant effects of these flavonoids are primarily achieved through multiple pathways: direct scavenging of free radicals, inhibition of oxidative enzymes (such as NADPH oxidase and xanthine oxidase), chelation of metal ions, supply of hydrogen ions, enhancement of the antioxidant system, and regulation of endogenous antioxidant capacity via the Keap1-Nrf2/ARE and MAPKs signaling pathways. Meanwhile, their anti-inflammatory effects are mediated through four main mechanisms: inhibition of inflammatory mediator production, modulation of cytokines and their receptors, scavenging of reactive oxygen species, and regulation of cell signaling pathways (including NF-κB and AP-1). To date, flavonoids have demonstrated significant efficacy in the treatment of various human diseases, including hypertension, atherosclerosis, cardiomyopathy, myocarditis, diabetes mellitus, and cancer. However, their potential in veterinary medicine has not been fully explored. This review summarizes recent advances in the antioxidant and anti-inflammatory physiological activities of *Rhododendron* flavonoids and their underlying mechanisms. It aims to provide scientific rationale for developing flavonoid-based physiological protective agents suitable for animals, thereby advancing their scientific application in animal health management and livestock production. This aligns with current priority areas in veterinary research.

Keywords: Antioxidant, Anti-inflammatory, Animal health support and protection, Flavonoids, *Rhododendron* plants

Introduction

Rhododendron belongs to the *Rhododendron* family, which is a large genus of *Rhododendron*, with common types such as Ying shan hong, Haunted Goat Flower, Zhao shan White, Goat Tramp, and so on, about 967 species, which are widely distributed in Asia, Europe, and North America, and are mainly native to East Asia and Southeast Asia [1]. About 700 species in China, except Xinjiang, Ningxia, everywhere, but in the southwest provinces and districts, mostly [2] The flowers, leaves and stems of *Rhododendron* plants are rich in flavonoids, which are high quality herbal medicines. Flavonoids have excellent antioxidant and anti-inflammatory activities and therefore also have many pharmacological effects such as anti-cancer, treatment of cardiovascular diseases and diabetes mellitus [3].

The development of many diseases is closely related to oxidative damage in the body, and reactive oxygen species (ROS) and reactive nitrogen species (RNS) free radicals are naturally produced during normal metabolism, and they play an important role in physiological activities. However, when the concentration of ROS/RNS is too high, they produce oxidative stress, a state that leads to tissue damage and has been linked to the development of a variety of diseases, including cancer, cardiovascular disease, neurodegenerative diseases, diabetes, respiratory infections, and others [4]. The high cost of treating related diseases caused by oxidative damage places a huge economic burden on the global community. Flavonoids

possess diverse physiological activities and low toxicity. Therefore, investigating their antioxidant and anti-inflammatory mechanisms to elucidate their protective effects in alleviating oxidative stress and mitigating cellular oxidative damage holds significant value for safeguarding animal organisms from injury, maintaining health homeostasis. Clarifying the antioxidant and anti-inflammatory mechanisms of these flavonoids may also facilitate the development of physiologically protective formulations, providing theoretical support for standardised animal health management [5].

Regarding the antioxidant and anti-inflammatory activities of flavonoid compounds, existing research has predominantly focused on their pharmacological effects in humans, while studies on their physiological support applications, pharmacokinetics, and safety in animals -particularly livestock and companion animals- remain fragmented and lack systematic integration. To address this research gap, this paper first provides a comprehensive review of studies concerning the antioxidant and anti-inflammatory physiological properties of flavonoids. It systematically outlines their mechanisms of action and applications in maintaining animal health and providing physiological protection, thereby establishing a foundational reference for subsequent research into the application of *Rhododendron* flavonoids in animal health management and livestock production. Subsequently, the focus shifts to the physiological protective value of *Rhododendron* flavonoids in veterinary health management. This involves systematically reviewing relevant domestic and international research findings, thoroughly elucidating their mechanisms of action, and examining their current applications in maintaining animal health and protecting against damage. This aims to establish a robust foundation for advancing research in this field, construct a standardised reference framework, and facilitate the translational application of flavonoids (particularly represented by *Rhododendron* flavonoids) in veterinary health management and livestock production.

Flavonoid Composition

In medicinal chemistry, a compound's chemical formula not only determines its physicochemical properties, but more crucially, the presence and positioning of specific functional groups within its structure directly dictate how it interacts with biological targets. This, in turn, influences its pharmacological activity and therapeutic applications. Consequently, understanding a compound's chemical formula forms the foundation for investigating its mode of action. The research on flavonoids of *Rhododendron* plants in China was first started in 1974, when the total flavonoid glycosides isolated from *Rhododendron* plants were acid-hydrolysed by the teaching and research group of pharmacology at Lanzhou Medical College, from which 3,5,7,8,3',4'-hexahydroxyflavonoids were isolated [6]. Nowadays, flavonoids are mainly detected and analysed by ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UHPLC-TOFMS) and various chromatographic methods [7]. To date, 17 flavonoid compounds with antioxidant or anti-inflammatory activity have been studied *(Table 1)*.

Antioxidant Mechanism of Action

Antioxidant and oxidative stress are inextricably linked to the occurrence of oxidative stress, which is a state in which excessive oxidative molecules (e.g. ROS) are produced or accumulated within an organism, exceeding the antioxidant capacity of the cells or tissues, resulting in oxidative damage to biomolecules (e.g. proteins, lipids, DNA, etc.) [20], and antioxidant refers to the process of scavenging oxygen free radicals, thereby protecting cells from oxidative stress. Therefore, as illustrated in *Fig. 1*, an understanding of the factors that induce oxidative stress in cells and the subsequent application of antioxidants to mitigate these triggers enables the attainment of effective antioxidant protection. Flavonoids, as an excellent antioxidant, can address oxidative stress through several pathways, such as stabilisation or reduction of reactive oxygen species (ROS), scavenging of free radicals, and modulation of endogenous antioxidant capacity are the three main pathways.

Stabilises or Reduces ROS, Scavenges Free Radicals

The two pathways, stabilisation or reduction of ROS and scavenging of free radicals, usually occur simultaneously in the process of flavonoids exerting antioxidant effects [21]. Thus, the two pathways are described together. The antioxidant modalities of both pathways are direct scavenging of free radicals, inhibition of oxidative enzymes (NADPH oxidase, xanthine oxidase), chelation of metal ions, provision of hydrogen ions and enhancement of the antioxidant system.

Direct Scavenging of Free Radicals

Free radicals are atoms that exist in free form without pairs or free electrons, which can be produced by normal cellular metabolism [22]. Common types of free radicals include hydroxyl radicals (HO·), superoxide anion radicals (O_2^{-}·) and hydrogen peroxide radicals (HO_2·). Hydroxyl radicals (HO·) are the most active free radicals in the cell, which can react with lipids, proteins, and DNA, triggering the oxidation of unsaturated fatty acids and the formation of lipid peroxides (LPO), which can disrupt the membrane structure and lead to cell damage [23]. As illustrated in *Fig. 2-a*, quercetin, isoquercetin, rutin and other azalea plant flavonoids were able to directly scavenge HO· at concentrations up to 260 μM [24]. When

Table 1. *Flavonoid constituents of Rhododendron spp. with antioxidant and anti-inflammatory effects*

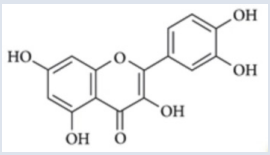
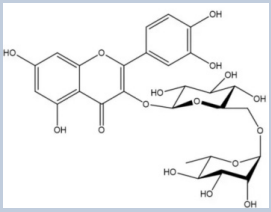
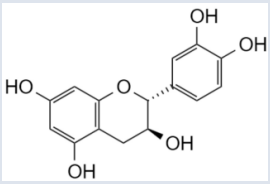
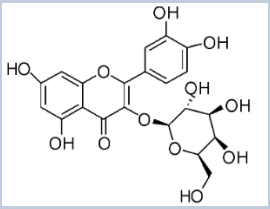
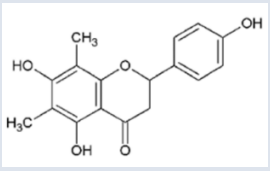
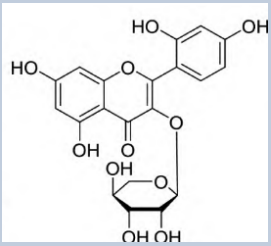
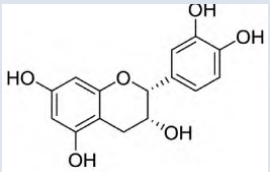
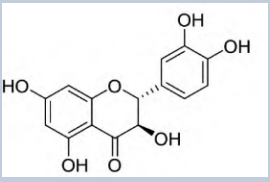
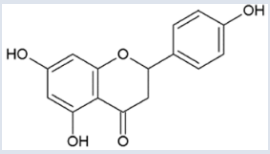
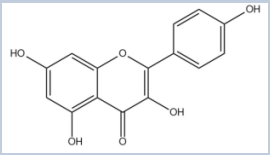
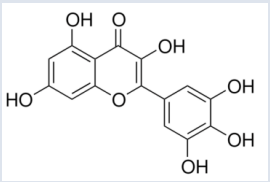
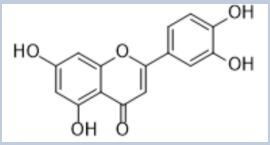
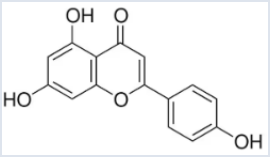
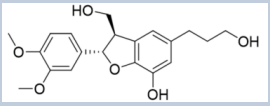
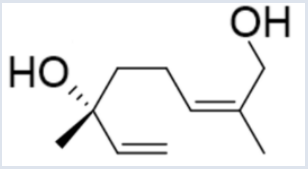
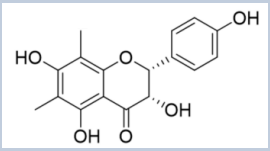
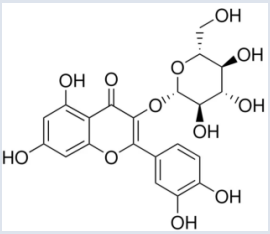
Serial Number	Phyto-Chemicals	Source Plant	Chemical Structure	Ref.
1	Quercetin	Almost all *Rhododendron* plants		[8]
2	Rutin	*Rhododendron arboreum*		[9]
3	Catechin	*Rhododendron nivale* Hook *Rhododendron dauricum* *Rhododendron wiltonii* Hemsl		[10,11]
4	Hyperin	Almost all *Rhododendron* plants		[8]
5	Farrerol	*Rhododendron primuliflorum* Bureau *Rhododendron dauricum*		[12,13]
6	Morin-3-O-β-L-lyxoside	*Rhododendron nivale* Hook		[10]
7	Epicatechin	*Rhododendron nivale* Hook		[10]
8	dihydroquercetin	*Rhododendron nivale* Hook		[10]

Table 1. *Continue*

Serial Number	Phyto-Chemicals	Source Plant	Chemical Structure	Ref.
9	Naringenin	*Rhododendron pachypodum* Balf		[14]
10	Kaempferol	*Rhododendron dauricum* *Rhododendron wiltonii* Hemsl		[11,13]
11	Myricetin	*Rhododendron dauricum* *Rhododendron anthopogon* D		[15]
12	Luteolin	*Rhododendron anthopogonoides* Maxim		[16,17]
13	Apigenin	*Rhododendron anthopogonoides* Maxim *Rhododendron amesiae* Rehder		[18]
14	4-O-Methylcedrin	*Rhododendron pachypodum* Balf		[14]
15	(2Z)-2,6 dimethyl-2,7-octadiene-1,6-diol	*Rhododendron pachypodum* Balf		[14]
16	6,8-di-C-methyldihydrokaempferol	Rhododendron pachypodum Balf		[14]
17	Isoquercitrin	*Rhododendron amesiae* Rehder		[19]

flavonoids bind to free radicals, the phenolic hydroxyl group of the flavonoid can provide an electron to the free radical, thus neutralising and deactivating it. When free radicals are scavenged, lipids, proteins, DNA and other biomolecules in the cell can exert their effects normally, reducing oxidative damage [25].

Inhibition of Oxidative Enzymes (NADPH Oxidase, Xanthine Oxidase)

Both NADPH oxidase and xanthine oxidase catalyse free radical generation. NADPH oxidase is a transmembrane enzyme complex consisting of several components such as NOX2, p22phox, p47phox, p67phox, etc., whose main function is the production of superoxide anion radicals ($O_2^{-}\cdot$). In phagocytes, such as neutrophils, NADPH oxidase is activated upon detection of pathogens, which, through the signalling pathway, leads to the production of cytokines (mainly p47phox) phosphorylation, prompting their transfer to membrane-bound NOX2 components and initiating the catalytic production of superoxide anion, the catalytic mechanism of which involves the transfer of electrons from NADPH to flavin adenine dinucleotide (FAD), then to proximal haemoglobin, rapidly to distal haemoglobin, and ultimately to molecular oxygen, to form superoxide anion [26]. Xanthine oxidase (XO), in catalysing the conversion of hypoxanthine to xanthine and further to uric acid, uses molecular oxygen as an electron acceptor to produce large amounts of uric acid and H_2O_2, of which H_2O_2 can be further decomposed to produce hydroxyl radicals (·OH), increasing the production of reactive oxygen species [27].

Both quercetin and lignans from the flavonoids of the genus *Rhododendron* showed inhibition of NADPH oxidase and xanthine oxidase. Quercetin inhibits NADPH oxidase activity and reduces ROS production, while it also inhibits xanthine oxidase activity, lowers serum uric acid levels and reduces H_2O_2 production [28]. Lignans also inhibit NADPH oxidase, reduce oxidative stress, and can reverse the elevation of xanthine oxidase activity induced by potassium oxonate, reduce serum and liver levels of uric acid and blood urea nitrogen, and reduce H_2O_2 production [29]. As illustrated in *Fig. 2-b*, populin acts on NADPH oxidase, and in silico predictions reveal a high docking score between populin and this enzyme, suggesting its potential to inhibit NADPH oxidase [30]. As illustrated in *Fig 2-c*, rutin and chrysin exert their primary inhibitory effects on xanthine oxidase; notably, rutin possesses diverse biological activities including antioxidant and anticancer properties, while chrysin inhibits xanthine oxidase activity via hydrogen bonding and van der Waals forces with the enzyme's catalytic active site, acting in a mixed competitive manner [31]. These flavonoids exert their antioxidant and protective effects by inhibiting the activity of oxidative enzymes and reducing oxidative stress and uric acid production.

Chelating Metal Ions

The mechanism of action of flavonoids chelating metal ions to achieve antioxidant action mainly includes the following aspects. The first is that flavonoids form stable complexes through the formation of ligand bonds with metal ions (Fe, Gu, etc.) through specific functional groups such as hydroxyl (-OH) and carbonyl (C=O)

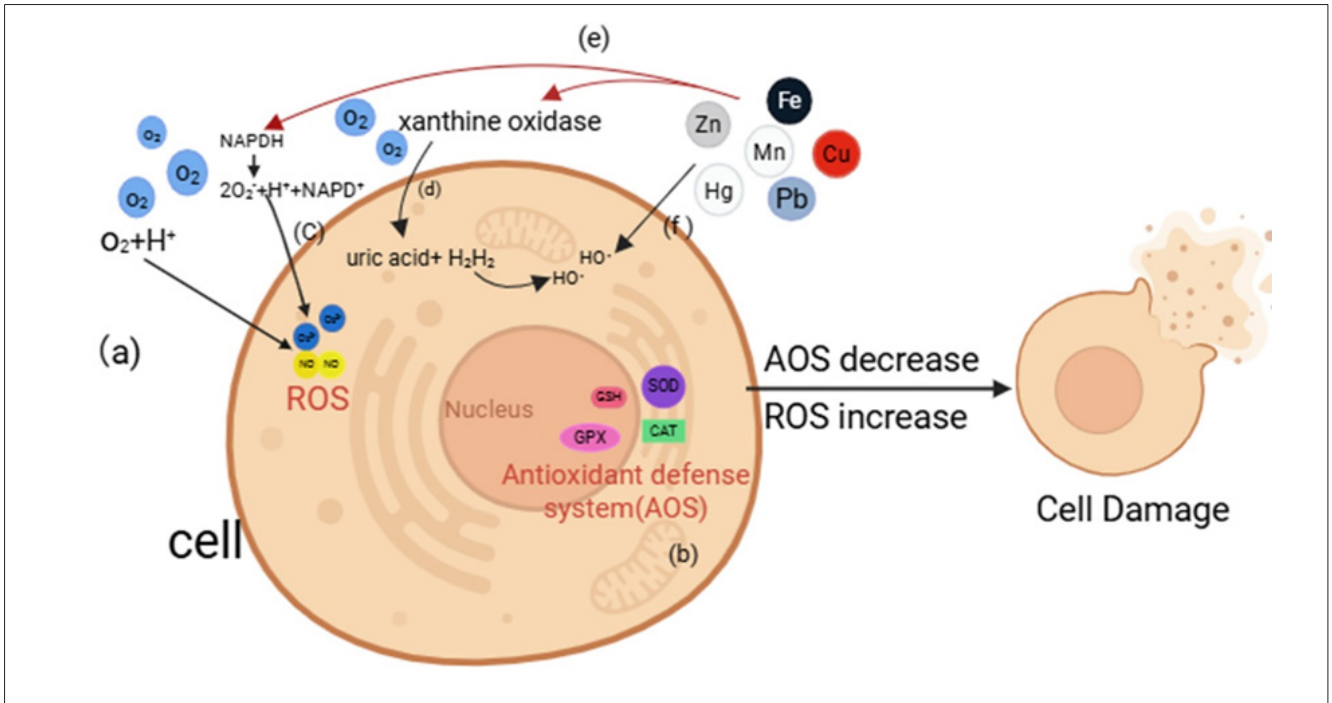


Fig 1. Several ways in which cells generate oxidative stress. (a) The reduction of oxygen to water produces ROS substances such as O_2^{2-} and NO, and the production of ROS causes oxidative damage to cells, (b) An imbalance in the antioxidant defence system increases ROS and swamps AOS, (c) Activation of NADPH oxidase leads to excessive ROS production, causing oxidative stress, (d) XOD catalyses the production of uric acid and H_2O_2 under aerobic conditions, and H_2O_2 is broken down to HO^{-}, loss of cells, (e) Metal ions catalyse the production of ROS by oxidative enzymes, (f) Metal ions such as iron and copper catalyse oxidative reactions that produce HO·, causing cell damage

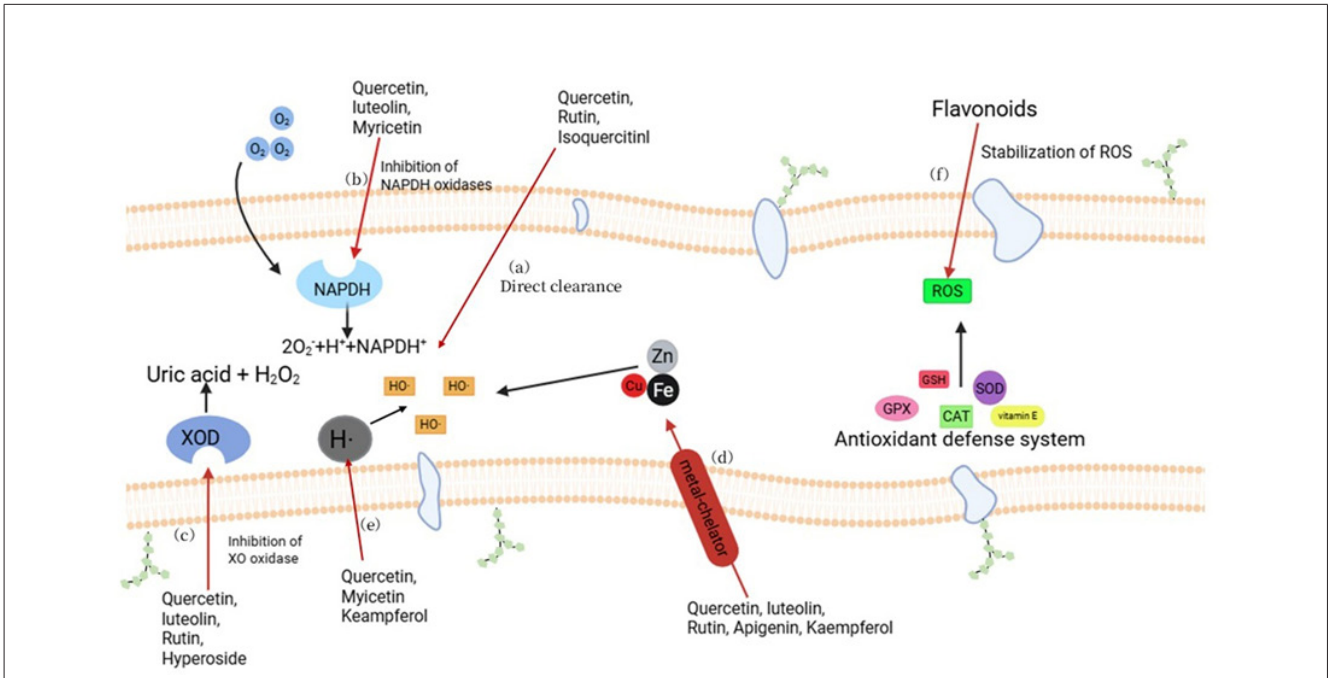


Fig 2. Azalea flavonoids as antioxidants through ROS stabilisation and free radical scavenging. (a) Quercetin, isoquercetin, and rutin directly scavenge HO·, (b) Quercetin, lignocerotin, and populin inhibit NADPH oxidase activity and reduce free radical production, (c) Quercetin, lignans, rutin, and chrysin inhibit xanthine oxidase activity and reduce free radical production, (d) Quercetin, lignans, rutin, apigenin and kaempferol chelate metal ions, reduce HO^- production and inhibit oxidase activity, (e) Quercetin, lignans, apigenin, and kaempferol provide hydrogen ions to scavenge HO-, (f) Flavonoids enhance the antioxidant capacity of the antioxidant system and stabilise ROS

groups in their molecular structure, and such complexes have stronger free radical scavenging ability than free flavonoids, in which metal ions can facilitate the transfer of electrons to enhance the capture of free radicals; finally, there may be synergistic antioxidant activity between flavonoids and metal ions in particular cases [32,33]. For example, complexes formed by flavonoids with copper ions show synergistic effects in scavenging superoxide anion $O_2^{-}\cdot$) and hydroxyl radical (OH·) [33].

As illustrated in *Fig. 2-d*, quercetin, rutin, apigenin, lignans, and kaempferol in the flavonoids of the genus *Rhododendron* can form complexes with metal ions and exhibit antioxidant activity [34].

Hydrogen Atom

Flavonoids provide hydrogen ions to scavenge free radicals in two main ways. The first is that the antioxidant activity of flavonoids interrupts the chain reaction mainly through the reaction of their phenolic hydroxyl groups with oxygen radicals to form resonance-stabilised semiquinone radicals. In this process, hydrogen atoms on the phenolic hydroxyl groups of flavonoids can combine with peroxyl radicals to form flavonoid radicals, which in turn react with other radicals, thus terminating the free radical chain reaction. The second is that intramolecular hydrogen bonding in flavonoids reduces the antioxidant activity of hydroxyl groups that act as hydrogen bond donors (e.g., 5-OH, 3-OH, and 3'-OH) while enhancing the antioxidant activity of hydroxyl groups that act as hydrogen bond acceptors (e.g., 4'-OH) [35].

As illustrated in *Fig. 2-e*, quercetin, populin and kaempferol among the flavonoids of the genus Azalea exhibit antioxidant activity by providing hydrogen atoms to scavenge free radicals [24].and the antioxidant activities of populin and kaempferol were also positively correlated with the number of phenolic hydroxyl groups on the B-ring [36].

Antioxidant Defence System

The antioxidant system is mainly composed of a number of antioxidant enzymes, non-enzymatic antioxidants, and low molecular weight antioxidants [37]. Antioxidant enzymes are the first-line defence mechanisms of the antioxidant defence system, including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), etc. These enzymes are able to scavenge reactive oxygen species, such as superoxide radicals and hydrogen peroxide, to prevent them from causing cellular damage [37]. Non-enzymatic antioxidants, including reduced glutathione (GSH), coenzyme Q (CoQ), lipoic acid, uric acid, and various proteins (e.g. ferritin, transferrin, cuprocyanin, and albumin), which are able to directly neutralise free radicals and protect cells from oxidative damage [38]. Low molecular weight antioxidants such as vitamin C, vitamin E, polyphenols, coenzyme Q or the metabolic compound urate, which scavenge free radicals and reduce oxidative stress [37].

As illustrated in *Fig. 2-f*, flavonoids reduce oxidative stress by modulating the antioxidant enzyme system, enhancing the activity of antioxidant enzymes and the antioxidant capacity of the AsA-GSH cycle, and are also able to stimulate the ascorbic acid biosynthetic pathway and its upstream glycolytic metabolic pathway, leading to an increased accumulation of flavonoids, which act as one of the antioxidants in the non-enzymatic system, providing hydroxyl radicals to scavenge excess reactive oxygen species [39]. It can also act synergistically with vitamin E, partially regenerating in the presence of combined antioxidants, driving the regeneration process by the scavenging of semiquinone radicals in a synergistic reaction, and also by interactions with glutathione and ascorbic acid, in which oxidised flavonoids can be re-reduced by glutathione and ascorbic acid to continue to exert their antioxidant effects [40].

Modulates Endogenous Antioxidant Capacity

Azalea flavonoids regulate endogenous antioxidant capacity and enhance antioxidant capacity mainly through activation of Keap1-Nrf2/ARE and $MAPK_S$ signalling pathways [10].

Antioxidant of Keap1-Nrf2/ARE Signalling Pathway

Nuclear transcription factor E2-related factor 2 (Nrf2) is a member of the Cap'n'collar (CNC) family of regulatory proteins, and is a transcription factor with a basic leucine zip structure, which is widely found in various organs of the body, and is mainly responsible for regulating cellular redox reactions [41]. Keap1 is a Cullin3 (Cul3)-dependent substrate articulating protein of the E3 ubiquitin ligase complex that assembles with CuI3 and Rbx1 to form a functional E3 ubiquitin ligase complex (Keap1-Cul3-E3), which in turn regulates Nrf2 [42]. As illustrated in *Fig. 3-a*, under normal physiological conditions, Nrf2 binds to its endogenous inhibitor Kelch ECH-related protein 1 (Keap1), exists in an inactive state in the cytosol and is rapidly degraded via the ubiquitin proteasome pathway in order to maintain the low transcriptional activity of Nrf2 under physiological conditions [43]. As illustrated in *Fig. 3-b*, upon stimulation of cells by reactive oxygen species (ROS) or other nucleophiles, Nrf2 dissociates from Keap1, undergoes activation and translocates into the nucleus. In the nucleus, Nrf2 binds to Maf proteins to form heterodimers, which then recognize and bind to antioxidant response elements (AREs)-enhancer sequences located in the regulatory regions of Nrf2 target genes that are critical for the recruitment of transcriptionally essential factors [44]. In this way, the Nrf2-Maf heterodimer activates the expression of target genes and regulates the transcriptional activity of phase II metabolic enzymes, antioxidant enzymes or drug transporters, thus exerting antioxidant damage and counteracting the effects of oxidative stress [45].

Flavonoids, as antioxidants, can act as antioxidant damages and restore cellular homeostasis by activating the Keap1-Nrf2/ARE signalling pathway and modulating the transcriptional activity of antioxidant enzymes or drug transporters. This signalling pathway plays a key role in cellular resistance to external oxidative stress and is an important defence system against oxidative damage [46]. As illustrated in *Fig. 3-c*, quercetin and apigenin in the

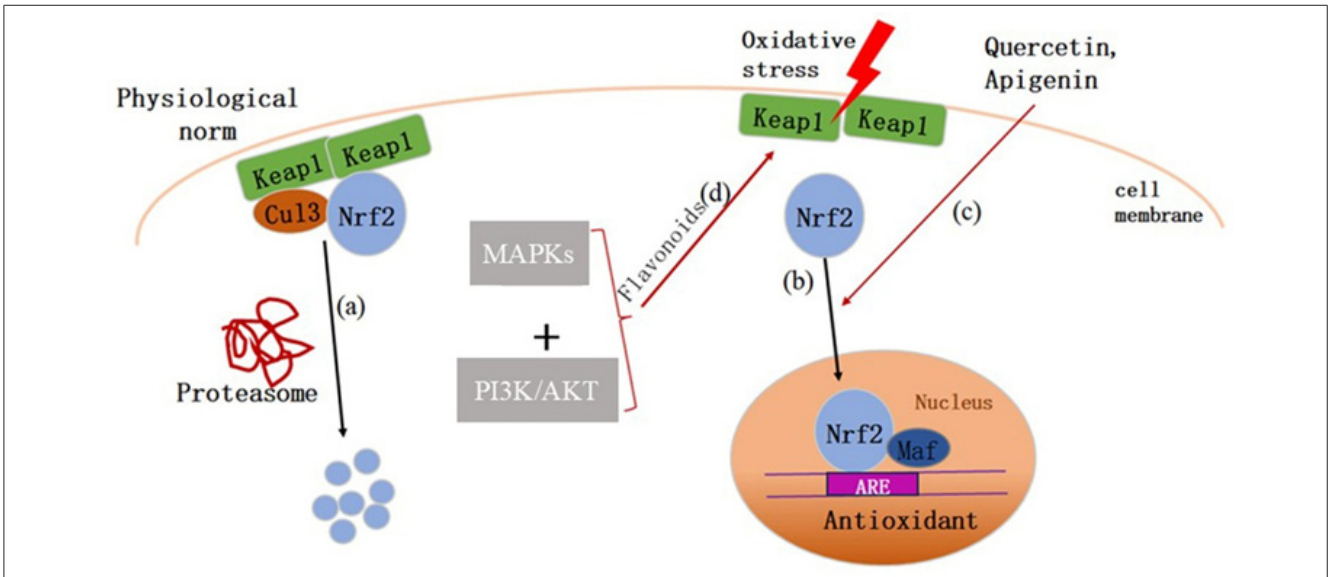


Fig 3. Flavonoids of Azalea plants are antioxidant by regulating Keap1-Nrf2 and MAPKS signalling pathways. (a) Under normal conditions, Keap1-Nrf2 signalling pathway, Nrf2 signalling molecules are degraded, (b) Suffering from oxidative stress, Nrf2 signalling molecules are released into the nucleus to bind with Maf proteins to form heterodimers and exert antioxidant effects, (c) Quercetin and apigenin promote Nrf2 translocation into the nucleus and increase the level of Nrf2 in the nucleus, (d) Flavonoids activate Nrf2 through MAPKs and PI3K/AKT signalling pathways, which in turn enhance the antioxidant response

flavonoids of genus Azalea can inhibit the degradation of Nrf2, promote the translocation of Nrf2 into the nucleus, and increase the level of Nrf2 in the nucleus as a means of up-regulating the endogenous antioxidant capacity of cells [47,48].

Antioxidant MAPK$_s$ Signalling Pathway

The mitogen-activated protein kinase (MAPK$_s$) signalling pathway consists of three major signalling pathways, JNK, ERK and p38, which play an important role in cellular responses to external stimuli (e.g. oxidative stress) [49]. It has been shown that ROS activate Nrf2 through MAPKs and phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT) cell signalling pathways in response to cellular damage caused by oxidative stress [50].

As illustrated in *Fig. 3-d*, flavonoids activate Nrf2 via MAPKs signalling pathway in conjunction with PI3K/AKT signalling pathway and thus enhance the antioxidant response.

Mechanism of Action of Anti-Inflammatory

The anti-inflammatory properties of flavonoids from the genus Azalea are achieved through four main areas: inhibition of the production of inflammatory mediators, modulation of cytokines and receptors, scavenging of oxygen free radicals and cell signalling pathways.

Inhibition of the Production of Inflammatory Mediators

Prostaglandin E2 (PGE2) and NO are the two main pro-inflammatory mediators. Arachidonic acid (AA) produces PGE2 via the cyclooxygenase pathway, which contributes to inflammation by increasing vascular permeability and vasodilation causing redness, swelling, stiffness and pain [51]. Cyclooxygenase 2 (COX-2) mainly catalyses the production of large amounts of PGE2, which is involved in the inflammatory response, and inducible NO synthase (iNOS) catalyses the production of large amounts of NO from L-arginine, resulting in cellular damage [52]. Thus, inhibition of COX-2 and iNOS expression reduces cellular inflammation and alleviates cellular damage.

As illustrated in *Fig. 4-a*, quercetin and lignans in the flavonoids of *Rhododendron* can inhibit the expression of iNOS and COX-2 at the mRNA and protein levels to reduce the production of NO and PGE2 and exert their anti-inflammatory effects [52,53].

Regulation of Cytokines and Receptors

In the inflammatory response, proliferating cells such as macrophages, neutrophils, eosinophils and epithelial cells can synthesise and release a variety of cytokines such as interleukin 1β (IL-1β)), interleukin 6 (IL-6), interleukin 8 (IL-8), and tumour necrosis factor (TNF-α), etc. Flavonoids can be used to inhibit these inflammatory cytokines by inhibiting their production and hindering

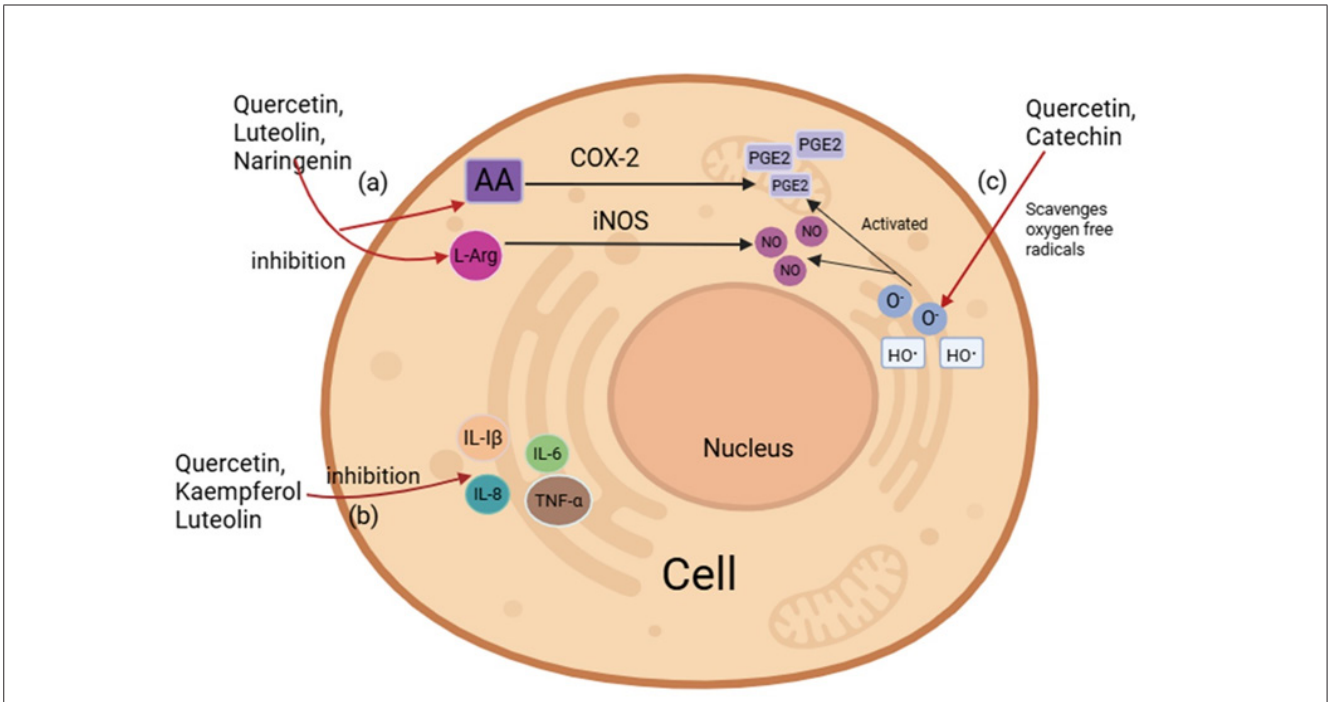


Fig 4. Azalea flavonoids are anti-inflammatory by inhibiting the production of inflammatory mediators, modulating cytokines and receptors and scavenging oxygen radicals. (a) Quercetin and lignans inhibit the expression of iNOS and COX-2 and reduce NO and PGE2 production, (b) Kaempferol, quercetin and lignans regulate cytokines and exert anti-inflammatory effects, (c) Quercetin and catechin scavenge oxygen free radicals and inhibit the activation of inflammatory mediators by oxygen free radicals

their association with the Receptor binding, play an anti-inflammatory role [54].

The flavonoids of the genus *Rhododendron*, including kaempferol, quercetin and lignans, can all have anti-inflammatory effects by modulating cytokines. Kaempferol and quercetin can rapidly scavenge DPPH and ABTS free radicals, and can effectively inhibit the secretion of IL-6, IL-1β and TNF-α [55]. A dose of quercetin (10-25 mol/L) reduces NO and TNF-α in lipopolysaccharide (LBS)-induced mouse glioma cells [56]. As illustrated in *Fig. 4-b,* mucuna pruriens has a highly significant inhibitory effect on both TNF-α and IL-6 [57].

Radical Scavenging

Oxygen free radicals are non-specific damage factors widely present in phagocytes of the body and are one of the important pathological mechanisms of inflammation. When the body is stimulated by inflammation, macrophages will produce a large number of oxygen free radicals, disrupting the dynamic balance in the body; at the same time, oxygen free radicals will also activate inflammatory factors, exacerbating the inflammatory response. Therefore, elimination of oxygen free radicals can slow down the inflammatory response [58]. The chemical structure of flavonoids, especially those with a catechol structure, tends to have a large number of phenolic hydroxyl groups, a structural advantage that gives them good free radical scavenging properties [35].

As illustrated in *Fig. 4-c,* quercetin and catechin in the flavonoids of *Rhododendron* contain o-diphenol hydroxyl structure, which can effectively scavenge oxygen free radicals [59].

Cell Signalling Pathways

NF-KB Signalling Pathway: NF-κB is a dimer consisting of five monopeptide proteins, P50 (also known as NF-κB1), p52 (also known as NF-κB2), RelA (also known as p65), RelB and c-Rel [60]. It is also a widely distributed and functional eukaryotic transcription factor. Functional NF-κB binding sequences are present in promoters and enhancers of genes, so NF-κB can bind to fixed nucleotide sequences in the promoter regions of many genes to initiate gene transcription, and control a variety of targets such as cytokines, adhesion factors, growth factors, enzymes (COX-2, iNOS), neuropeptides, and so on.It plays an important role in immune response, inflammation and cell growth regulation [61]. Flavonoids inhibit IKk (IK kinase) production and increase IkB (inhibitory factor) expression by preventing NF-κB from entering the nucleus for transcription. The anti-inflammatory effects of these compounds are exerted in three ways: by preventing NF-κB from entering the nucleus for transcription, by inhibiting IKk (IK kinase) production and by increasing IkB expression [58].

Quercetin inhibits the activation of the NF-κB signalling pathway and prevents the entry of NF-κB into the nucleus

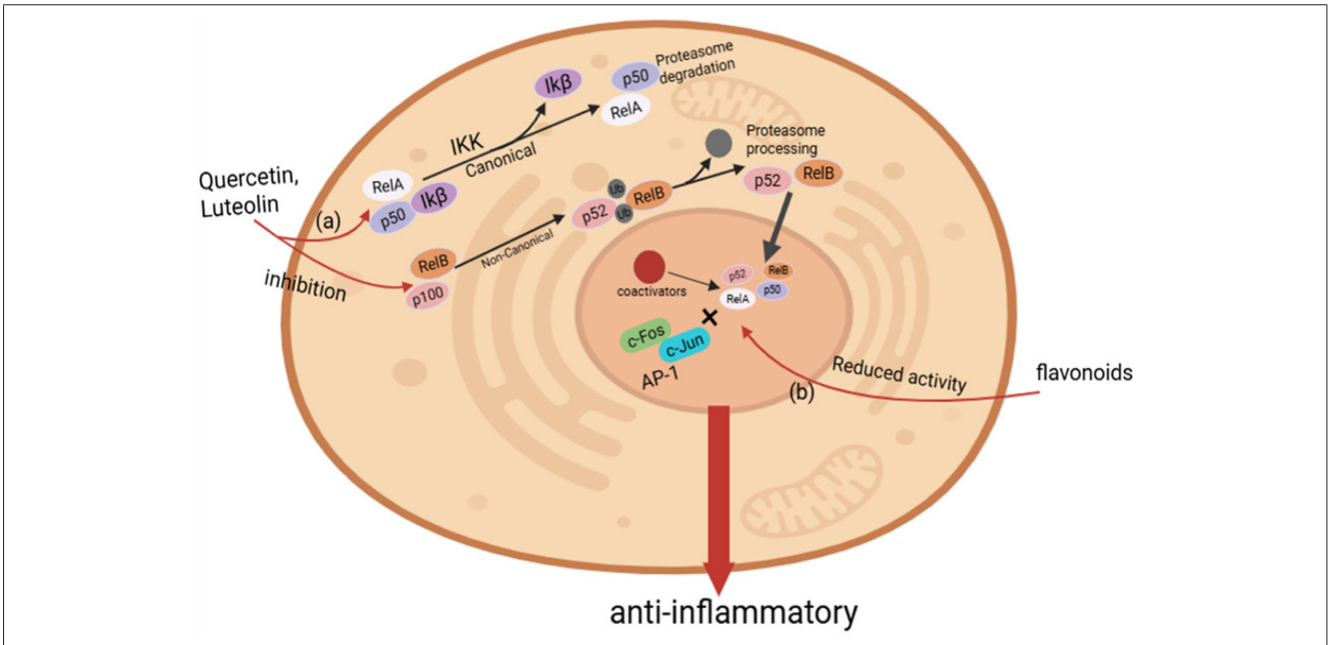


Fig 5. Flavonoids of the genus Azalea are antioxidants through the signalling pathway. NF-κB regulates the inflammatory response through both classical and non-classical pathways. The classical pathway is dependent on the activation of the IκB kinase complex (IKK), which leads to the phosphorylation of the IκB protein, which in turn triggers ubiquitination and proteasomal degradation of IκB, and after IκB degradation, the dimer of p50/RelA is released and enters the nucleus. The non-classical pathway is dependent on NF-κB-inducible kinase (NIK), activation of which leads to partial degradation of p100 into p52, which forms a dimer with RelB and enters the nucleus. (a) Quercetin and lignans inhibit the NF-κB signalling pathway and prevent its dimerisation into the nucleus, (b) Flavonoids reduce the activity of NF-κB dimer and AP-1 in the nucleus of the cell nucleus to achieve cellular anti-inflammation

for transcription, thereby reducing the inflammatory response [62]. As illustrated in *Fig. 5-a*, lignans can significantly inhibit the phosphorylation of IkKβ and IkBα in inflammatory cells, reduce the expression of P65 in the nucleus, and then better inhibit the NF-κB signalling pathway to exert anti-inflammatory activity [57].

Transcription Factor Activator Protein 1 (AP-1): AP-1 is an intracellular transcriptional activator that is a heterodimer of c-Fos and c-Jun. Often works with NF-κB to regulate the expression of inflammatory factors in mediating inflammatory responses [63]. NF-KB is mainly involved in the regulation of cytokine expression and other inflammatory mediators, whereas AP-1 is involved in the synthesis of innate immune effector molecules and cytokine responses [64]. As illustrated in *Fig. 5-b*, quercetin Significantly Reduces High Glucose-Induced NF-κB and AP-1 Activity [65].

Applications of *Rhododendron* Flavonoids

Maintain Blood Pressure Homeostasis

Flavonoids exert anti- MAPKs inflammatory and antioxidant effects by modulating the Keap1-Nrf2/ARE, NF-κB, and AP-1 signalling pathways, playing a significant role in maintaining cardiovascular homeostasis and tissue protection in animals. Research indicates that flavonoids may assist in maintaining blood pressure homeostasis, mitigate abnormal vascular lipid deposition, and safeguard myocardial structural and functional integrity, thereby demonstrating positive physiological protective effects on the cardiovascular system in animals [3].

Flavonoids exert a blood pressure-stabilising regulatory effect, with quercetin exerting a significant influence on blood pressure by reducing diastolic pressure in hypertensive animal models and systolic pressure in normotensive animal models [66]. Nitric oxide (NO), as the primary vasodilator, plays a crucial role in blood pressure regulation. In rat models, kaempferol administered orally at 10 mg kg^{-1} day^{-1} for 6 weeks significantly enhanced aortic eNOS expression, elevated serum NO levels, and reduced systolic blood pressure (approximately ↓18 mmHg) in a dose-dependent manner [67]. In spontaneously hypertensive rat models, the *Rhododendron*-derived flavonoid falarone (at doses of 10-40 mg kg^{-1} over 8 weeks) reduced systolic blood pressure in a dose-dependent manner by inhibiting angiotensin II-mediated NADPH oxidase activation. This alleviated vascular oxidative stress, restored endothelium-dependent relaxation in the aorta, and reduced intimal hypertrophy [68]. In dogs, intravenous administration of rhoifolin (5 mM/kg) and vitexin significantly reduced mean aortic pressure (by 8%), arterial and pulmonary capillary pressures, and heart rate through vasodilation and negative inotropic effects. Oral administration of Elsholtzia blanda total flavonoids (25-100 mg/kg) dose-dependently reduced myocardial infarction area (from 19.42% to 8.87%), decreased serum creatine kinase-MB (CK-MB) and malondialdehyde (MDA) levels, and inhibited lipid peroxidation in a coronary artery occlusion model [69,70]. In horses, administration of 50-75 mg horse chestnut seed extract (containing 2% aescin and flavonoids) every 12 h improved venous tone, reduced transcapillary filtration, and enhanced venous return, with clinical application in chronic venous insufficiency [71].

Lowering blood lipid levels is the optimal approach for preventing and treating atherosclerotic diseases, whilst flavonoids counteract atherosclerosis by inhibiting inflammation in adipose tissue, enhancing cholesterol reverse transport, and reducing blood lipid levels. In a high-fat diet rat model, continuous oral administration of *Rhododendron* methanolic extract (dose: 300-200 mg/kg·d) for 63 days reduced plasma total cholesterol by approximately 28%, triglycerides by approximately 32%, and low-density lipoprotein cholesterol by approximately 35%, while increasing high-density lipoprotein cholesterol by approximately 25%. Its efficacy in reducing the atherosclerosis index surpassed that of lovastatin (10 mg/kg), with no significant toxic reactions observed [72]. In a study by Shubhi Agarwal and colleagues on a high-cholesterol New Zealand rabbit model, continuous oral administration of *Rhododendron* extract reduced serum total cholesterol, triglycerides, and low-density lipoprotein cholesterol levels, increased high-density lipoprotein cholesterol, and decreased the atherosclerosis index [73].

Restriction of cardiac contraction and relaxation constitutes a common clinical manifestation of cardiomyopathy. Calcium ions represent a primary factor in cardiac contraction whilst flavonoid compounds can inhibit Ca^{2+}-sensitivity dysregulation induced by troponin I phosphorylation [74,75]. In isolated rat hearts and cardiomyocytes, total *Rhododendron* flavonoids (5-20 μg/mL) inhibited potassium-induced calcium influx and sarcoplasmic reticulum calcium release, thereby reducing intracellular Ca^{2+} levels. This mitigated hypoxia-induced injury and diminished infarct size, revealing a calcium-regulated cardioprotective mechanism [76]. In an autoimmune myocarditis rat model, green tea catechins (400 mg/kg·d administered for 4 consecutive weeks) mitigated left ventricular dysfunction, reduced inflammatory cell infiltration and myocardial fibrosis, and shifted the cytokine profile towards anti-inflammatory characteristics. This demonstrates that tea flavonoids can simultaneously alleviate inflammatory responses and adverse remodelling in experimental myocarditis [77].

Anticancer

Flavonoids, as natural radiosensitising agents and chemo-

therapeutic sensitising agents, can be integrated into comprehensive cancer management across four levels: primary prevention, synergistic radiotherapy, overcoming drug resistance, and secondary chemoprevention. They demonstrate significant potential particularly in enhancing radiotherapy sensitivity, improving the efficacy of chemotherapeutic drugs, and reversing tumour multidrug resistance [78].

Regarding radiotherapy sensitisation, multiple studies provide clear dose-response evidence. In colon cancer models, 24 h pretreatment of HT-29 and DLD-1 cells with 50 μM quercetin significantly increased sensitivity to 6 Gy X-rays by downregulating the Notch-1 signalling pathway, reducing colony survival rates by approximately 40% [79]. In mouse solid tumour studies, daily intraperitoneal administration of 25 mg/kg apigenin combined with 10 mg/kg cryptotanshinone for 14 consecutive days, alongside 2 Gy local irradiation, achieved a tumour volume suppression rate of 78% in Ehrlich tumours. This effect markedly exceeded the 44% observed in the radiotherapy-alone group, fully demonstrating the advantages of flavonoid compounds in synergising radiotherapy [80].

Flavonoids also demonstrate remarkable efficacy in enhancing chemotherapy outcomes. In a prostate cancer xenograft model, daily oral administration of 50 mg/kg quercetin concurrently with weekly docetaxel (5 mg/kg) over four weeks elevated tumour weight inhibition to 72%, substantially surpassing the 38% achieved by docetaxel monotherapy. Its mechanism of action is associated with downregulating P-glycoprotein (P-gp) expression, inhibiting the PI3K/Akt signalling pathway, and modulating androgen receptor signalling [81]. In the hormone-refractory PC-3 prostate cancer model, combining 40 mg/kg quercetin with 10 mg/kg paclitaxel (administered every 3 days for 5 consecutive cycles) prolonged tumour doubling time by 1.8-fold through inducing endoplasmic reticulum (ER) stress and reactive oxygen species (ROS) bursts, offering novel insights for enhancing chemotherapy efficacy [81]. In addition to synergising with chemotherapeutic agents, certain flavonoid compounds themselves exhibit distinct *in vivo* antitumour activity. For instance, research by Ma et al.[82] on the *in vivo* antitumour evaluation of *Rhododendron* decorum flavonoids demonstrated that in a Kunming mouse model transplanted with S180 sarcoma, oral administration of total flavonoids from *Rhododendron* grandiflorum (at doses of 50, 100, 200 mg/kg/d) via oral gavage for 10 consecutive days. The 200 mg/kg group achieved a tumour volume inhibition rate of 54.7% ($P<0.01$). Mechanistic studies revealed that this dose significantly elevated serum interleukin-2 (IL-2) and TNF-α levels while reducing VEGF levels, suggesting a synergistic anticancer effect through immune enhancement and anti-angiogenesis. No hepatotoxicity, nephrotoxicity, or abnormal body weight changes were observed during the experiment. Consequently, it is proposed that *Rhododendron* decorum flavonoids exert a dose-dependent antitumour effect in animals via a dual immune-antiangiogenic mechanism.

In the field of reversing tumour multidrug resistance (MDR), the efficacy of flavonoid compounds has also been demonstrated. In a colon cancer model resistant to 5-fluorouracil (5-FU), co-treatment with 20 μM kaempferol and 5 μM 5-FU for 48 hours produced a significant synergistic inhibitory effect on LS174-Resistant cells (combination index CI≈0.6), elevating apoptosis rates to 3.7 times that of monotherapy. primarily through inhibiting ABCB1 transporter function and inducing G_2/M phase arrest in the cell cycle [81]; In the HL-60/NB4 acute myeloid leukaemia resistance model, 40 μM kaempferol effectively restored cell sensitivity to doxorubicin by downregulating ABCB1 and ABCC1 transporter expression alongside Akt and BCL2 signalling molecules, reducing the resistance index from 8.2 to 2.1 [83].

The aforementioned studies consistently demonstrate that flavonoid compounds such as quercetin, kaempferol, and total flavonoids from *Rhododendron* anthopogon, within the dose range of 20-200 μM *(in vitro)* or 25-200 mg/kg *(in vivo),* can significantly enhance radiotherapy/chemotherapy efficacy, reverse ABC transporter-mediated resistance, or exert direct antitumour effects through diverse mechanisms. These well-defined dose-response relationships in preclinical studies provide a foundation for incorporating flavonoid compounds into clinical anticancer combination therapies or for their standalone use. chemotherapy efficacy, reverse ABC transporter-mediated resistance, or exert direct antitumour effects. This clear dose-response relationship in preclinical evidence provides substantial support for the clinical application of flavonoids in combined anticancer therapies or as monotherapy.

Animal Diabetes Mellitus

Flavonoids intervene in type 2 diabetes mellitus (T2DM) and its microvascular and macrovascular complications by lowering blood glucose, improving insulin sensitivity, and preventing complications. Regarding hypoglycaemic effects and insulin resistance improvement, high-dose quercetin (≥100 mg/kg/day via gastric lavage in db/db mice for 8 weeks) inhibits protein tyrosine phosphatase 1B (PTP1B), elevates insulin receptor substrate 2 (IRS-2) phosphorylation, and markedly reduces fasting blood glucose. administered via gastric lavage to db/db mice for 8 weeks) inhibits protein tyrosine phosphatase 1B (PTP1B), elevates insulin receptor substrate 2 phosphorylation levels, significantly reduces fasting blood glucose, and

improves oral glucose tolerance. At equivalent doses, kaempferol mitigated inflammatory insulin resistance by blocking IKKβ/NF-κB signalling, thereby downregulating inflammatory mediators such as IL-6 and TNF-α [84].

Flavonoids exert effects by promoting insulin secretion and modulating the intestinal-pancreatic axis. In a C57BL/6 high-fat diet model, 50 μmol/L quercetin or 25 μmol/L kaempferol effectively stimulated L-cell secretion of glucagon-like peptide-1 (GLP-1) in the ileum. inhibiting dipeptidyl peptidase-4 (DPP-4) activity and elevating total GLP-1 levels by 1.8-fold, thereby enhancing glucose-dependent insulin release [85]. In preventing diabetic complications, flavonoids exhibit multi-target protective effects: For retinopathy, quercetin at 50 mg/kg/d (intraperitoneal injection, STZ-induced rats, 12 weeks) suppressed retinal vascular endothelial growth factor (VEGF) and intercellular adhesion molecule-1 (ICAM-1) expression, reducing blood-retinal barrier leakage; For diabetic nephropathy, kaempferol at 75 mg/kg/day (oral administration, db/db mice for 16 weeks) reduced urinary albumin excretion and fibronectin deposition, a mechanism associated with inhibition of the TGF-β1/Smad3 signalling pathway; For cardiomyopathy and osteoporosis, quercetin alleviates myocardial oxidative stress by activating the Nrf2/HO-1 pathway and protects the bone matrix by inhibiting receptor for advanced glycation end-products (RAGE) expression [86].

Conclusion

In this paper, we review the past research progress on the mechanism and clinical application of antioxidant and anti-inflammatory activities of flavonoids from *Rhododendron* plants. We have identified 17 flavonoids in *Rhododendron* plants with significant antioxidant and anti-inflammatory activities. These compounds act through a variety of mechanisms, including direct scavenging of free radicals, inhibition of oxidative enzymes (e.g. NADPH oxidase and xanthine oxidase), chelation of metal ions, provision of hydrogen ions and enhancement of the antioxidant system to stabilise or reduce reactive oxygen species (ROS) and scavenging of free radicals, as well as modulation of the endogenous antioxidant capacity by the Keap1-Nrf2/ARE and $MAPK_S$ signalling pathways. The antioxidant is achieved by means of the Keap1-Nrf2/ARE and $MAPK_S$ signalling pathways. Its anti-inflammatory effects are achieved by inhibiting the production of inflammatory mediators, modulating cytokines and receptors, scavenging oxygen free radicals, and affecting cell signalling pathways such as NF-κB and AP-1. At present, it has become a prevailing trend to study the antioxidant and anti-inflammatory properties of flavonoids at home and abroad. *Rhododendron* is found all over the world and is rich in flavonoids, so isolating the specific composition and structure of flavonoids from *Rhododendron* will help to design and develop more effective natural antioxidant protective agents and animal health supplements [87]. An in-depth elucidation of its antioxidant and anti-inflammatory mechanisms holds promise for advancing the development of novel natural antioxidants for protecting animal organisms against oxidative damage and maintaining health homeostasis [88].

In terms of clinical applications, flavonoids have been shown to have potential therapeutic effects on cardiovascular diseases such as hypertension, atherosclerosis, cardiomyopathy and myocarditis [3]. It also shows great therapeutic potential in the fields of diabetes and anticancer [78,86]. A deeper understanding of their antioxidant and anti-inflammatory mechanisms will advance research into the application of flavonoids in animal health management, thereby fully harnessing their physiological protective and supportive efficacy.

Flavonoids and terpenoids can act synergistically to enhance each other's pharmacological activities, especially in the fight against cancer. Terpenoids modulate caspase-3 activity and flavonoid circuit affects enzyme activity [89]. Flavonoids and terpenoids collectively influence the regulation of ATP-binding cassette (ABC) transporter protein efflux function, and semi-synthetic nitrogen-containing flavonoids and terpenoids derivatives possess potential as multidrug resistance (MDR) reversal agents designed to be effective in cancer [90]. Azalea plants are rich in flavonoids and terpenoids, the study of Azalea plants can not only study flavonoids and terpenoids, but also study the synergistic effect of the two, the development of new anti-cancer drugs.

Although some progress has been made on the antioxidant and anti-inflammatory activities of flavonoids in the genus *Rhododendron*, there are still some limitations, such as the absence of systematic studies on their mechanistic mechanisms, small sample sizes, and geographical bias. Future studies need to consider a wider range of samples and different geographical regions to validate the existing findings and further systematically explore the pharmacological mechanisms of action of flavonoids [10]. Moreover, in-depth research into flavonoids holds promise for providing further scientific rationale for developing novel approaches to maintaining and safeguarding animal health, particularly demonstrating significant research and application value in antioxidant and anti-inflammatory physiological protection.

In conclusion, significant progress has been made in research concerning the antioxidant and anti-inflammatory physiological activities of flavonoids from *Rhododendron* species. This has laid a solid foundation for subsequent development of natural physiological

protective agents and their application in animal health management. Future studies should continue to explore the physiological protective and supportive potential of these compounds, overcome existing research limitations, and further expand their application scenarios in safeguarding animal organisms and maintaining health.

Declarations

Availability of Data and Materials: The data and materials used to support the findings of this study are available from the first author (Z.Z.) and the primary corresponding author (Z.C.) upon reasonable request. All relevant data have been properly curated and can be provided to facilitate reproducibility of the research results.

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Conflict of Interest: The authors declare no conflicts of interest.

Declaration on Generative Artificial Intelligence (AI): Generative artificial intelligence was only used for language polishing in this study; it was not involved in any other aspects of the research. All authors have reviewed the final content and take full responsibility for its authenticity and scientificity.

Author Contributions: All authors made substantial contributions to this study. Ziqin Zhang was responsible for conceptualization, methodology and original draft writing; Sheng Kang and Hailong Dong engaged in data curation and formal analysis; Meixue Ni and Xiaoqing Guo participated in investigation, resources collection and validation. As corresponding authors, Qingxia Wu was in charge of supervision, funding acquisition and manuscript review & editing; Zhenyu Chang, the primary corresponding author, undertook supervision, conceptualization, methodology and manuscript review & editing.

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