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Review

Unravelling the Antioxidant Potential of Resveratrol and Quercetin in Animal Models: A Comprehensive Review

Ioana Craciun[1,*] and Florinel Gheorghe Brudașcă[1,]

[1] Department of Infectious Diseases, Faculty of Veterinary Medicine, University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Calea Mănăştur nr. 3-5, 400372 Cluj-Napoca, Romania. ioana.craciun@usamvcluj.ro, florinbrudasca@yahoo.com

Abstract: Resveratrol and quercetin are naturally occurring polyphenolic compounds widely studied for their potential health benefits, particularly their antioxidant properties. This abstract provides an overview of the extensive research conducted on resveratrol and quercetin as antioxidants in animal models, highlighting their mechanisms of action and therapeutic potential. Animal models, such as rodents, have been instrumental in elucidating the oxidative stress pathway and evaluating the efficacy of various antioxidants. Resveratrol and quercetin have demonstrated significant antioxidant effects in animal models through multiple mechanisms. These include direct scavenging of reactive oxygen species (ROS), upregulation of endogenous antioxidant enzymes, inhibition of lipid peroxidation, and modulation of oxidative stress-related signaling pathways.

Keywords: polyphenols; therapeutic implications; animal models

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1. Introduction

Resveratrol and quercetin supplementation has been found to reduce oxidative stress in a wide range of systems, including the liver [1], heart [2], brain [3], and kidneys [4] in animal models. It has been discovered that these antioxidants can reduce oxidative damage caused by disorders like ageing, inflammation, diabetes, neurological diseases, and cardiovascular conditions [1]. The adaptation of resveratrol and quercetin research to human applications faces several difficulties despite the encouraging results in animal studies [5]. To achieve efficient and secure therapeutic interventions, factors like bioavailability, metabolism, and dosage optimization need to be meticulously taken into consideration. Oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms, has been implicated in the pathogenesis of numerous diseases, including ageing, cardiovascular disorders, neurodegenerative diseases, and cancer [1]. Consequently, there is a growing interest in identifying natural compounds that possess potent antioxidant properties to counteract oxidative damage and promote overall health. Resveratrol and quercetin, two polyphenolic compounds abundantly found in various fruits, vegetables, and plant extracts, have garnered considerable attention for their potential as antioxidants in animal models [6].

The authors reported that quercetin treatment suppressed oxidative stress markers, including malondialdehyde (MDA) and protein carbonyl levels, while upregulating the expression of antioxidant enzymes, such as heme oxygenase-1 (HO-1).

Moreover, several mechanistic studies have shed light on the underlying antioxidant mechanisms of resveratrol and quercetin in animal models. For instance, in their comprehensive review, Han et al. (2007) summarized the multiple pathways through which resveratrol exerts its antioxidative effects, including ROS scavenging, activation of nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated antioxidant response, and modulation of signalling pathways like mitogen-activated protein kinases (MAPKs) and nuclear factor-kappa B (NF-κB)[11]. In a similar vein, Xu et al. (2019) elucidated the antioxidant mechanisms of quercetin, highlighting its ability to inhibit ROS generation, restore cellular redox balance, and activate antioxidant enzymes through Nrf2 signalling pathways in animal models. The evidence that resveratrol and quercetin have antioxidant functions in animal models is carefully increasing, and it includes the outcomes of this study in addition to a large number of additional studies. Understanding the processes by which these chemical compounds exert their effects is crucial for the development of effective medical therapies for oxidative disorders in individuals linked to stress. Additional research is required to bridge the gap between animal models and clinical trials. This will facilitate the development of safe and effective therapies for human health based on these findings.

2. Mechanism of Action of Resveratrol

Due to its extraordinary pharmacological potential, resveratrol, also known as 3,4′,5-trihydroxystilbene, is a nutraceutical that has attracted a lot of academic interest. It is a naturally occurring phytoalexin that is frequently found on numerous plants, notably berries, grapes, and peanuts. Resveratrol was initially extracted from the *Veratrum grandiflorum* plant, frequently referred to as white hellebore, in the 1940s, which is when it was first discovered [12, 13]. Red wine represents a processed plant product that is known to have a high resveratrol content. Due to its potential involvement in the "French paradox," which refers to the unusually low rate of heart disease among Southern French people despite their consumption of diets high in saturated fat, this substance has garnered interest. Red wine contains resveratrol, which has been proposed as a potential explanation for this phenomenon. Resveratrol concentrations in red wine can range from 0.1 to 14.3 mg/L [12, 14-16]. Numerous studies have elucidated the mechanisms through which resveratrol exerts its antioxidative effects [17, 18].

2.1. Activation of Nrf2 Pathway

Resveratrol has been shown to activate the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, a crucial regulator of antioxidant defence systems. Nrf2 translocate into the nucleus upon activation, leading to the upregulation of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). For instance, Jia et al. (2019) demonstrated that resveratrol treatment increased the expression of Nrf2 and its target genes, resulting in reduced oxidative stress and liver injury in a rat model [9].

2.2. ROS Scavenging

Resveratrol exhibits direct scavenging properties against reactive oxygen species (ROS). By neutralizing ROS through electron transfer, resveratrol mitigates their damaging effects on cellular components. Aminjan et al. (2019) reported that resveratrol administration led to a decrease in ROS levels, contributing to the preservation of cellular redox balance and protection against oxidative stress-induced liver injury [19].

2.3.Modulation of Intracellular Signalling Pathways

Resveratrol modulates several intracellular signalling pathways associated with oxidative stress, such as mitogen-activated protein kinases (MAPKs) and nuclear factor-kappa B (NF-κB). Du et al. (2021) highlighted that resveratrol inhibits the activation of MAPKs, including ERK, JNK, and p38, thereby reducing oxidative stress-mediated cellular damage. By interfering with NF-κB signalling, resveratrol can suppress inflammation and oxidative stress-induced damage [20].

2.4. Activation of Sirtuins

Resveratrol activates sirtuins, a family of NAD+-dependent deacetylases, particularly the SIRT1 enzyme. SIRT1 activation has been associated with enhanced antioxidant defences and improved mitochondrial function [21]. Kaeberlein et al. (2021) emphasized that resveratrol-mediated SIRT1 activation contributes to cellular resilience against oxidative stress and overall cellular homeostasis [22].

3. Therapeutic Potential of Resveratrol

The mechanisms of action of resveratrol in animal models transfer into its potential medicinal applications for a variety of conditions linked to oxidative stress. Resveratrol, for instance, has been demonstrated to reduce renal oxidative stress, inflammation, and fibrosis in a mouse model of diabetic nephropathy[23]. Resveratrol appears to protect against myocardial ischemia/reperfusion injury in a rat model by reducing oxidative stress while improving cardiac function, according to Yu et al. (2021) [24]. Furthermore, Ibrahim et al. (2020) demonstrated that resveratrol reduced renal oxidative stress and inflammation, which attenuated cisplatin-induced nephrotoxicity[25]. Reservatrol was given to rats with chronic cerebral hypoperfusion in a study by Wang et al. (2014) [26]. According to the study's findings, resveratrol administration enhanced mental performance while lowering oxidative stress markers in the brain. In a study conducted by Wang et al. (2019), resveratrol was administered to rats with experimentally induced colitis [26]. Resveratrol treatment reduced oxidative stress preserved colonic tissue integrity, and ameliorated inflammation in the colon[27]. Wang et al. (2018) investigated the neuroprotective effects of resveratrol in a mouse model of Alzheimer's disease. They found that resveratrol supplementation improved cognitive function, reduced amyloid-beta plaque deposition, and alleviated oxidative stress in the brain [28]. In a study by Hu et al. (2020), resveratrol was administered to rats with acute lung injury induced by lipopolysaccharide (LPS)[29]. Resveratrol treatment attenuated lung injury, reduced oxidative stress markers, and inhibited inflammatory responses in the lung tissues. Aged mouse treatment with resveratrol was studied by Barger et al. (2008). According to their findings, resveratrol increased lifespan, lowered oxidative stress, and enhanced metabolic health in the treated mice compared to the control group [30]. Resveratrol's preventive properties were examined by Lan et al. (2022) in a rat model of renal ischemia-reperfusion injury. Administration of resveratrol reduced oxidative stress and inflammation in the renal tissues, improved renal function, and minimized kidney damage [31]. Resveratrol has been studied in a rat model of liver fibrosis induced on by carbon tetrachloride in a study by Abdu et al. (2017). By lowering oxidative stress, inflammation, and hepatic collagen deposition, resveratrol therapy improved liver fibrosis [32, 33]. These investigations collaboratively provide a spotlight on resveratrol's various medicinal benefits. Collectively, these studies have provide insight on the numerous therapeutic effects of resveratrol in animal models. They back up the idea that resveratrol has the potential to be an effective natural substance for both the prevention and treatment of many different oxidative illnesses associated with stress.

4. Mechanism of Action of Quercetin

The chemical compound 3,5,7-trihydroxy-2-(3,4-dihydroxy phenyl)-4Hchromen-4-one, typically known as quercetin, is a dietary flavonoid that exists in a variety of plant sources, including capers, black chokeberries, onions, tomatoes, and lettuce [34]. Quercetin can be identified in plants in a conjugated state, paired with phenolic acids, sugars, ethers, and other substances. The precise forms of quercetin derivatives can affect how quickly they are absorbed in the stomach and small intestine [35]. The mechanism of action of quercetin involves its interactions with multiple cellular targets, leading to its diverse pharmacological effects. Quercetin is an excellent free radical scavenging antioxidant [36]. Consuming foods that contain flavonoids lowers the chance of developing long-term illnesses including diabetes, coronary heart disease, and stroke that are brought on by oxidative stress [36–38]. The flavonoid quercetin, which can be discovered in fruits and vegetables, has unique biological properties that could enhance cognition and physical performance while reducing the risk of illness [8]. The foundation for possible benefits to general health and disease resistance is established by these characteristics, which include the ability to suppress lipid peroxidation, platelet aggregation, and capillary permeability as well as the capacity to induce mitochondrial biogenesis [39]. It additionally possesses anti-inflammatory, antiviral, anti-inflammatory, antioxidant, and stimulant effects.

4.1 Antioxidant Activity

One of the primary mechanisms through which quercetin exerts its effects is its potent antioxidant activity. Quercetin acts as a free radical scavenger, effectively neutralizing reactive oxygen species (ROS) and inhibiting lipid peroxidation. It also enhances the activities of endogenous antioxidant enzymes, such as superoxide dismutase (SOD) and catalase (CAT), thereby augmenting the cellular defence against oxidative stress [40, 41].

4.2 Anti-Inflammatory Effects

Quercetin demonstrates notable anti-inflammatory properties by modulating various inflammatory signalling pathways. It inhibits the production and release of pro-inflammatory mediators, including cytokines (such as tumour necrosis factor-alpha and interleukins) and inflammatory enzymes (such as cyclooxygenase-2 and inducible nitric oxide synthase). Quercetin achieves this by suppressing the activation of nuclear factor-kappa B (NF-κB), a key transcription factor involved in the inflammation [41, 42].

4.3 Modulation of Cellular Signalling Pathways

Quercetin influences several cellular signalling pathways involved in cellular homeostasis and disease processes. It activates the adenosine monophosphate-activated protein kinase (AMPK) pathway, which plays a critical role in cellular energy metabolism and oxidative stress response. Quercetin-mediated activation of AMPK promotes cellular antioxidant defences and inhibits oxidative stress-induced damage [43, 44].

4.4 Epigenetic Modifications

Quercetin has been shown to exert epigenetic modifications, particularly through its influence on DNA methylation and histone acetylation. It can alter the expression of genes involved in various physiological processes, including antioxidant defence, inflammation, and cell cycle regulation [45]. By modulating epigenetic mechanisms, quercetin may exert long-term effects on cellular function and disease development [46]. These mechanisms collectively contribute to the pharmacological effects of quercetin, including its antioxidant, anti-inflammatory, and cytoprotective properties.

5. Therapeutic Potential of Quercetin

The diverse mechanisms of action of quercetin in animal models translate into its potential therapeutic applications for various conditions. Neuroprotection: quercetin has shown neuroprotective effects in animal models of diabetic neuropathy, Alzheimer's disease, and ischemic brain injury. Its antioxidant and anti-inflammatory properties contribute to the preservation of neuronal function and protection against neurodegeneration [47, 48]. Hepatoprotection, animal studies have demonstrated that quercetin can attenuate liver injury, fibrosis, and inflammation in models of liver fibrosis and hepatotoxicity. Its antioxidant and anti-inflammatory actions contribute to the preservation of liver function and the reduction of liver damage [49-51]. Cardiovascular Health: quercetin supplementation has shown cardioprotective effects in animal models of myocardial ischemia-reperfusion injury. It reduces oxidative stress, suppresses inflammation, and improves cardiac function, suggesting its potential in preventing cardiovascular diseases [52-54]. Anti-Inflammatory Effects: Quercetin exhibits anti-inflammatory effects in animal models of colitis and other inflammatory conditions. It mitigates inflammation, preserves tissue integrity, and reduces oxidative stress, highlighting its potential as an adjunct therapy for inflammatory bowel diseases [54, 55].

6. Discussions

In the field of both human and veterinary medicine, various studies using animal models have provided important light on the mechanisms of action and therapeutic potential of quercetin and resveratrol. The results of these investigations are all featured in this review. The review of quercetin and resveratrol's mechanisms of action and therapeutic potential in both veterinary and human medicine delivers important insights into the potential applications of these organic compounds as therapeutic agents. Although preliminary evidence is provided through animal research, it is crucial to take into account the parallels and discrepancies between animal models and human patients to ensure the reliability and practicality of the results. The variation in species and their physiological peculiarities are an important factor that must be taken into consideration. The pharmacokinetics and therapeutic response to quercetin and resveratrol can vary amongst individuals and animals based on individual metabolism, organ structure, and genetics. In light of this, extreme caution should be taken when extrapolating findings from animal studies to human patients, and their findings should be confirmed more thoroughly in meticulously planned clinical trials. The effectiveness and safety of quercetin and resveratrol in both veterinary and human medicine are significantly affected by factors other than the biodiversity of species, particularly dosage, formulation, and method of administration. Understanding the optimal dosages and delivery methods for each species is essential to achieve desired therapeutic outcomes. Furthermore, the bioavailability and metabolism of these compounds may differ between animals and humans, emphasizing the need for further research to establish appropriate dosing regimens in clinical practice. Long-term safety and potential drug interactions are important considerations in both veterinary and human medicine. While animal studies provide insights into short-term effects, long-term studies are necessary to evaluate any potential adverse effects or interactions with other medications commonly used in clinical practice. Rigorous monitoring and assessment of safety profiles are required to ensure the well-being of patients. In both veterinary and human medicine, quercetin and resveratrol have the potential for alleviating an extensive spectrum of diseases. These chemicals have demonstrated promise in animal models for the treatment of neurological conditions, liver diseases, cardiovascular problems, and metabolic disorders. Similar to animal research, there is growing evidence that indicates

antioxidants could have a role in the management and prevention of chronic illnesses like cancer, cardiovascular disease, and neurodegenerative disorders. However, more clinical studies are required to confirm these results and determine accurate characteristics of patients, optimal dosages, and lengths of treatment. Research on the application of quercetin and resveratrol for veterinary and human medicine should be expanded by cooperation between scientists, doctors, and pharmaceutical companies. For researchers to provide accurate information regarding safety, efficacy, and optimal methods of treatment, well-designed clinical trials taking into consideration species-specific features and involving a variety of patients must be conducted. These investigations may additionally look at potential interactions with currently administered pharmaceuticals, establish early warning signs or contraindications, and contribute to developing clinical practice guidelines.

7. Conclusion

The research conducted with animal models provides significant insights into the therapeutic potential of resveratrol and quercetin in both human and veterinary medicine. While the findings from animal studies are promising, caution should be exercised when translating these results to human applications, considering species differences and variations in pharmacokinetics. Further research, including well-designed clinical trials, is necessary to establish the optimal dosages, safety profiles, and efficacy of these compounds in both veterinary and human patients. Collaboration among researchers, clinicians, and pharmaceutical companies will play a crucial role in advancing the research and application of quercetin and resveratrol, ultimately improving the health outcomes of both animals and humans.

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