

THE ROLE OF QUERCETIN IN HUMAN HEALTH

Doris Drmač^{1,2*}, Martin Kondža^{2,3}

¹Pharmaceutical Health Institution LUPRIV PHARM, Rodočkih branitelja bb, 88000 Mostar, Bosnia and Herzegovina

²University of Mostar, Faculty of Pharmacy, Matice hrvatske bb, 88000 Mostar, Bosnia and Herzegovina

³Josip Juraj Strossmayer University of Osijek, Faculty of Food Technology Osijek,
Franje Kuhača 18, 31000 Osijek, Croatia

review paper

Summary

Medical plants have become more popular in the last decades due to their low price, natural origin, and fewer side effects. Researchers are attributing quercetin as one of the well-known types of plants metabolites. It is found naturally in many fruits, vegetables, flowers, bark, and leaves, but is not made in the human body. Food sources with a high content of quercetin include onions and citrus. This review article highlights quercetin's potential health benefits, anti-inflammatory and neuroprotective properties. Quercetin is widely used for its health-promoting properties. When taken as a dietary supplement or in food, it is used to improve various health conditions such as cardiovascular disease, allergies, diabetes, high blood pressure, cancer, and to help boost the immune system. Most studies look at the impact of flavonoids such as quercetin within the diet rather than as a supplement. Quercetin is also an antioxidant, which means it helps fight off free radicals that can cause oxidative stress. According to these data, quercetin could play a significant role in the exacerbation period of these diseases and have a therapeutic effect in treating the symptoms of the diseases.

Keywords: quercetin, cancer, diabetes, blood pressure, allergy

Introduction

In recent times, there has been a significant increase in the utilization of natural bioactives for managing chronic ailments owing to their low toxicity and environmentally friendly characteristics. Quercetin (Figure 1), a bioactive molecule, has been the subject of extensive research due to its diverse pharmacological activities, including antioxidant, neuroprotective, immune-modulatory, and anticancer

activity with a low toxicity profile (Aghababaei et al., 2023). Quercetin (3,3',4',5,7-pentahydroxyflavone) is one of the most abundant dietary flavonoids and belongs to the flavonols subgroup. Flavonols (C6-C3-C6 polyphenols) have two hydroxylated benzene rings, A and B. Flavonols differ in the number and type of substitution in the B ring, where quercetin is dihydroxylated in positions 3' and 4'.

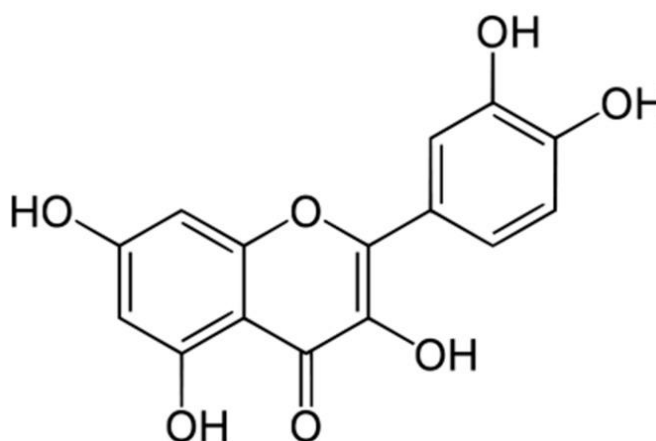


Figure 1. Chemical structure of quercetin

Quercetin is found in some fruits and vegetables, including onions, capers, apples, berries, tea, tomatoes, grapes, shallots, broccoli as well as pepper

and many nuts, seeds, barks, flowers, and leaves (Wiczowski et al., 2008). Quercetin has a broad pharmacological activity (Figure 2).

*Corresponding author: doris.drmac@farf.sum.ba

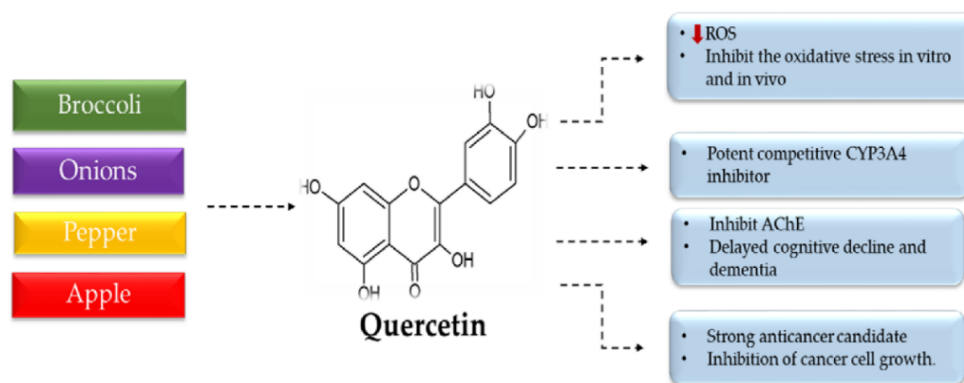


Figure 2. Pharmacological activity of quercetin (Salvamani et al., 2014)

Onions are thus qualitatively and quantitatively the most important source of quercetin. Among the investigated foods, it has been discovered that onions contain the highest amount of quercetin (approximately 300 mg/kg). According to the part of onions and shallots that is consumed, entirely various amounts and forms of quercetin are ingested. The quercetin forms of onion flesh include especially glucosides, with only minimal amounts of quercetin aglycone. Other vegetables, including broccoli, asparagus, green peppers, tomatoes, and red-leaf lettuce, could be great sources of ubiquitous quercetin, especially in the summer. Fruits (apples as well as berry crops, such as strawberries, red raspberries, blueberries, cranberries, and black currants), green tea, and wine could also be considered abundant dietary sources (Mlcek et al., 2016). In apples, another great quercetin source, there are well-studied antioxidant compounds such as quercetin-3-galactoside, quercetin-3-glucoside, and quercetin-3-arabinoside in the content range of 21–72 mg/kg; quercetin-3-rhamnoside; and quercetin-3-rutinoside. Quercetin conjugates are present entirely in the apple peels. Berry crops are rich in quercetin glycosides, with various types found across different berries. Strawberries and red raspberries contain quercetin-3-glucoside and quercetin-3-glucuronide, while these compounds, along with quercetin-3-rutinoside, are also present in blueberries. Additionally, quercetin-3-rhamnoside is found in red raspberries, black currants, blueberries, and cranberries, whereas quercetin-3-galactoside appears in blueberries, cranberries, and black currants, and quercetin-3-arabinose is specific to cranberries (Mlcek et al., 2016).

Flavonols present in red wine include aglycons, such as quercetin, myricetin, and kaempferol, as well as their glycosides (glucosides, galactosides, glucuronides and diglycosides). Quercetin is one of

the most abundant flavonoids present in red wines. Among the flavonoid groups, these compounds are recognized as the main active compounds due to their wide range of biological activities (Castaldo et al., 2019).

The antioxidant and antimicrobial capacity of polyphenols has attracted increasing interest. The primary phenolic compounds found in tomato by-products are flavonols and phenolic acids with quercetin, naringenin, and rutin being the predominant molecules. These compounds have the ability to scavenge free radicals and reactive oxygen species, which are known to be involved in the development of cardiovascular diseases and several cancers.

Quercetin: chemical properties and health benefits

Quercetin is one of the most potent antioxidants of plant origin and is one of the predominant flavonoids found more commonly in edible plants. It belongs to the flavonols class of flavonoids, representing a major class of polyphenols. The dietary intake of total flavonoids is estimated to be 200–350 mg/day, and the intake of quercetin is 10–16 mg/day. The recommended dosage of quercetin aglycone as a dietary supplement is 1 g/day (the absorption is up to 60%) (Kim et al., 2019).

Quercetin is largely metabolized in the intestine and liver. The plasma level of quercetin is normally in low ranges, but after consuming foods that are highly rich in it, the plasma level increases to different ranges (Lakhanpal et al., 2007).

Quercetin is a potent molecule that can be used to cure various health-related issues. It is known to be used in the treatment of cancer, allergic reactions, inflammation, skin disorders and cardiovascular disorders (Batiha et al., 2020).

Experiments show that quercetin intake also has a positive impact in preventing and treating the occurrence of diabetes mellitus (Zu et al., 2021).

Even though quercetin has low bioavailability, it can pass through the blood-brain barrier (BBB) due to its lipophilic nature and functions as a neuroprotective. Administration of quercetin has been shown to enhance learning and memory performance while also reducing acetylcholinesterase (AChE) (Amanzadeh et al., 2019).

Quercetin is known for its antioxidant activity through free radical scavenging and its anti-allergic properties. These properties include immune system stimulation, antiviral activity, inhibition of histamine release, decrease in pro-inflammatory cytokines, leukotriene production, and especially suppression of interleukin IL-4 production, so it can help with diseases such as allergic asthma, allergic rhinitis (AR), and atopic dermatitis (AD) (Mlcek et al., 2016).

Neuroprotective effects

Neuroprotection by quercetin has been reported in several *in vitro* studies.

Quercetin has been shown to have anti-inflammatory properties and has been studied in various neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and stroke. Some studies suggest that quercetin may have protective effects against neuroinflammation and potentially slow the progression of these diseases (Islam et al., 2021).

Alzheimer's disease

Alzheimer's disease (AD) contributes to 60–80% of total dementia cases, and it mostly affects elderly people (65 years of age or older). The pathogenesis of AD is typically associated with the accumulation of amyloid- β (A β) aggregates and the hyperphosphorylation of tau proteins, leading to neurofibrillary tangles (NFTs) and synaptic dysfunction. It has been shown that quercetin protects neurons from oxidative damage while reducing lipid peroxidation. In addition to its antioxidant properties, it inhibits the fibril formation of amyloid- β proteins, counteracting cell lyses and inflammatory cascade pathways (Khan et al., 2019).

Quercetin has also shown therapeutic efficacy, improving learning, memory, and cognitive functions in AD. Khan et al. (2009) and Shimmyo et al. (2008) concluded that quercetin administration resulted in the inhibition of AChE and secretase enzymes using *in vitro* models, thus preventing the degradation of acetylcholine, and decreasing A β production, respectively.

Parkinson's disease

Quercetin has been shown to have potentially beneficial effects on Parkinson's disease (PD) by targeting various mechanisms involved in the pathogenesis of the disease (Jung et al., 2018).

Here are some of the results and molecular mechanisms of quercetin in PD. Quercetin has been shown to have anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines and other inflammatory molecules. Chronic inflammation in the brain is believed to contribute to the development and progression of PD, and reducing inflammation may help slow down the disease (Table 1). Alpha-synuclein is a protein that forms aggregates in the brains of individuals with PD. Quercetin has been shown to inhibit alpha-synuclein aggregation and reduce the formation of these aggregates, which may help slow down the progression of the disease. It has been shown to have neuroprotective effects by protecting against neuronal damage and death in the brain. This may help slow the progression of PD and improve motor function (Chiang et al., 2023).

Inflammation plays a crucial role in the development and progression of a stroke, and reducing inflammation may help protect against neuronal damage. Guo et al. showed that quercetin has anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines and other inflammatory molecules in stroke (Guo et al., 2022).

These studies have shown that quercetin has potent anti-inflammatory and antioxidant properties, making it a potential candidate for neuroprotection and neuroinflammation.

Anti-allergic effects

Allergic rhinitis

Allergic rhinitis (AR) is a chronic disease with high prevalence worldwide, resulting in a huge health and economic burden. AR usually occurs in combination with asthma, conjunctivitis, and sinusitis (Bousquet et al., 2020).

The imbalance of innate and adaptive immunity is an important pathogenesis that induces AR, involving antigen-presenting cells, lymphocytes, and specific T cells. The imbalance between type 1 helper T (Th1) and Th2 cells is the immunological basis of AR. Th2 cells are the drivers of IgE-mediated allergic reactions that facilitate the release of IgE, IL-4, and IL-5. In addition, the dysfunction of regulatory T cells (Treg)/Th17 cells is also involved in the pathogenesis of AR (Table 1). Th17 cells regulate the pro-

inflammatory response, while Treg regulates the anti-inflammatory response (Ke et al., 2023).

Ke et al. (2023) considered quercetin to attenuate the inflammatory reactions of AR by improving the imbalance of Th1/Th2 and Treg/Th17 and inhibiting the increase of inflammatory cells, including epithelial cells, eosinophils, neutrophils, lymphocytes, and macrophages. They established the AR mice model and used multiple differentiations of quercetin to treat it. First, the nasal symptoms were assessed. The results illustrated that quercetin reduced the number of rubbing and sneezing in mice in a dose-dependent way.

Asthma

Asthma is a disease of the airways with various clinical and pathophysiological features, such as increased mucus secretion, reversible bronchial obstruction, airway hyperresponsiveness and narrowing, goblet cell hyperplasia, and inflammation. About 315 million people worldwide have asthma. This rate increases by 50% every decade and negatively affects public health (Huang et al., 2020). CD4⁺ T cells play a central role in mediating immune responses in allergic asthma. T helper (Th) 1 and Th17 cells contribute to the recruitment of neutrophils and are linked to more severe forms of asthma that may not respond to steroids. Th9 cells play roles in stimulating mucus secretion, attracting mast cells, and enhancing IgE levels. Other immune cells like CD8⁺ T cells, NKT cells and gamma delta T cells also influence inflammation and airway hyperresponsiveness (AHR) in asthma. On the other hand, regulatory T (Treg) cells work to reduce both innate and adaptive immune activity, thereby lowering inflammation. While research has expanded our understanding of various T cell subsets in asthma, Th2-type immune responses remain the most closely tied to the asthma's underlying mechanisms (Lloyd et al., 2010).

In 2017, the effects of several herbs were investigated by Luo et al. (2018). The study shows that quercetin could be used to develop new bronchodilators to treat obstructive lung diseases such as asthma and chronic obstructive pulmonary disease. Different effects of quercetin, such as inhibitory effect on mast cell activation, eosinophil activation, relaxation of tracheal ring, reduction in IL-4 and IgE serum, blocking airway epithelial cell IL-8 and MCP-1 expression, suggest a valuable role of quercetin for allergic asthma. It is also suggested that quercetin might be a therapeutic candidate for allergic asthma and provide new insight into the immunopharmacological role of quercetin.

Oliveira et al. (2015) investigated the effect of onion extract and quercetin on cytokines and on smooth

muscle contraction *in vitro* and its effectiveness in a murine model of asthma. After a treatment with onion extract or quercetin, they examined a decrease in pro-inflammatory cytokines creation, a release of tracheal rings, and a lowering of cell quantity in bronchoalveolar lavage and eosinophil peroxidase in the lungs.

As the plant-derived flavonoid quercetin is part of many foods and seems to be safe despite long-term use in animals and humans, therefore, its microemulsion would form an interesting and practical formulation to increase its oral bioavailability and, in turn, to evaluate its potential clinical advantage for treating certain inflammatory and allergic diseases (Rogerio et al., 2010).

Skin benefits

Because of its beneficial health effects and the fact that it is easily available from plants and food industry byproducts, quercetin has the potential to be used in medicine, particularly in the treatment of skin diseases.

The presented studies focus on the role of quercetin in the prevention and treatment of dermatological diseases analyzing its effect at a molecular level, its signal transduction, and metabolism. Aspects of quercetin's potential for skin treatment include protection against anti-aging and UV radiation, wound healing stimulation, and therapeutic effects on atopic dermatitis (Zaborowski et al., 2024).

Atopic dermatitis

The number of atopic dermatitis (AD) patients has been increasing steadily worldwide. AD is a dangerous disorder because it not only causes chronic inflammation but also leads to bacterial and viral skin infections. Quercetin has a therapeutic effect on AD through suppression of angiogenesis and Th2-related cytokine expression, including TSLP and TARC, in an AD-like Nc/Nga mouse model. Jung et al. suggest that quercetin might be an effective and improved therapeutic strategy that should be investigated further for the treatment of AD (Jung et al., 2010).

The results of testing the anti-inflammatory effects of quercetin in a mouse model showed that quercetin reduced the severity of dermatitis, mast cell infiltration, and epidermis thickness. Quercetin can also reduce the expression levels of TNF- α , CCL17, CCL22, IFN- γ , IL-4, and IL-6 (Hou et al., 2019).

UV radiation

When it comes to UV radiation, quercetin prevents the degradation of collagen due to UV radiation in human skin and inhibits MMP-1 and COX-2 expression. Quercetin inhibits UV-induced AP-1 activity and NF- κ B. Additionally, quercetin may reduce phosphorylation of ERK, JNK, and AKT, and STAT3. Kinase assays using purified protein demonstrated quercetin's ability to directly inhibit the activity of PKC δ and JAK2. This suggests its possible direct interaction with PKC δ and JAK2 in the skin, counteracting UV-induced aging (Shin et al., 2019). Research by Vicentini et al. (2011) confirmed reduction in skin irritation due to UV radiation by inhibition of NF- κ B and such inflammatory cytokines as IL-1 β , IL-6, IL-8, and TNF- α . Kim et al. (2020) point to the fact that quercetin in propolis reduces PDK-1 and AKT phosphorylation, which suggests its efficacy in preventing UV-induced photoaging. Furthermore, when combined with caffeic acid ester and apigenin, quercetin reduces PI3K activity, further enhancing its protective effect. Conversely, studies by Chondrogianni et al. (2010) on quercetin and its derivative, quercetin caprylate, showed that both compounds induce changes in the physiological characteristics of cells, including a localized whitening effect.

Wound healing

Wound healing is a natural restorative response that involves cell migration in tissue damage. Quercetin can accelerate wound healing by downregulating pro-inflammatory cytokines and supporting antioxidant capacity. The mechanism of quercetin impact on the improvement in wound healing quality was investigated by Baken et al. (2020). They performed a cell migration assay to investigate the effect of quercetin on tissue repair. AD-stimulating agents significantly delayed wound closure compared to the control group, indicating that tissue repair is impaired in AD. On the contrary, the single application of quercetin or its coadministration with AD-inducing agents was significantly effective in closing the wound gap.

Gopalakrishnan et al. (2016) also emphasized the significant role of TGF- β 1 and VEGF activation by quercetin in the wound healing acceleration process. Two groups of rats: a control group and a Que-treated group were subject to evaluation for 14 days. The quercetin-treated group exhibited a faster rate of wound closure compared to the control group. In addition to activating the above-mentioned compounds, quercetin significantly attenuated TNF- α

activity, supported fibroblast proliferation processes and collagen activity, and induced IL-10 levels.

Cardiovascular protection

More and more studies have found that quercetin has great potential utilization value in cardiovascular diseases (CVD), such as antioxidant, antiplatelet aggregation, antibacterial, cholesterol lowering, endothelial cell protection, etc.

With the accelerating global population aging, the prevalence of hypertension in developing countries is also increasing each year, and most cases are of unknown etiology. Hypertension is a chronic disease associated with endothelial dysfunction, smooth muscle cell contraction, and hyperlipidemia.

Kim et al. (2018) found that quercetin can inhibit the contraction of vascular smooth muscle through AMPK signaling pathway, thereby playing a role in reducing blood pressure (Table 1).

Another randomized, double-blind, crossover clinical study found that 41 hypertensive patients had a significant decrease in blood pressure after 28 days of continuous administration of 730 mg quercetin (Edwards et al., 2007).

Quercetin (25mg/kg) can inhibit myocardial fibrosis by modulating the TGF- β /Smads pathway, thereby helping to treat arrhythmia (Wang et al., 2021).

There is also evidence that quercetin suppresses the progression of atherosclerosis in animal studies, and several anti-atherosclerotic mechanisms have been proposed (Garelnabi et al., 2014).

Diabetes mellitus

Natural substances are inexpensive and easily obtained. Therefore, they can be used as an alternative to treat diabetes and other pathologies. Quercetin, due to its antioxidant, anti-inflammatory, hypoglycemic, and hypolipidemic activities, is known to be involved in the treatment of type 2 diabetes mellitus. Quercetin reduces blood glucose levels and preserves both the function of islets cells and the number of β cells in model rats and mice with diabetes (Table 1). Experiments show that quercetin intake has a positive effect on preventing and treating diabetes mellitus (Hosseini et al., 2021).

Quercetin is regarded as a very important flavonoid with beneficiary metabolic functions. Studies performed by Mahabady et al. (2021) showed that the oral administration of 75 mg/kg of quercetin to diabetic rats reduced the number of placental glycogen cells as compared to the control group. The plant compound acts as an oxygen scavenger and is known to protect against lipid peroxidation when present in

circulation. The antioxidant property of quercetin prevents the *in vivo* and *in vitro* oxidation of biomolecules. Quercetin is known to prevent embryonic malformations in pregnant diabetic mice (Mahabady et al., 2021).

Cancer

Quercetin is a potent flavonoid known for its chemoprotective activities in various *in vivo* and *in vitro* models. The various anti-cancerous properties such as reduced proliferation, the ability for induction of apoptosis, inhibition of mitotic events, causing cell cycle arrest makes it a reliable molecule in the therapy for cancer. Quercetin can be used as a potent therapeutic but it has poor solubility, poor permeability, and low bioavailability.

Treatment with appropriate dose makes quercetin non-toxic and shows inhibitory effects on the formation of tumors. Various *in vivo* and *in vitro* studies show that quercetin promotes apoptosis, inhibits metastasis, and

regulates the cell cycle. In colorectal cancer quercetin arrests the cell cycle, modulates receptors of estrogen, regulates signaling pathways, and hence exhibits its chemo-protective functions (Ullah et al., 2020).

It has been studied that in leukemia in the case of humans, quercetin arrests the cell cycle at G2. Quercetin is also known to regulate p53 related pathways in cancerous cells. It regulates the release of p53 and hence inhibits the activities of cyclin A, cyclin B, CDK2, and therefore stagnates the MCF-7 cells of breast cancer in the S phase of the cell cycle. Quercetin affects the apoptotic pathways of the cancerous cells and therefore induces the death of cancer cells (Table 1). Treatment with an appropriate dose of quercetin increases the apoptosis-inducing protein expression and reduces the expression of the apoptosis-inhibiting protein. Studies on human metastatic ovarian cancer PA-1 cell lines show that quercetin induces the apoptotic pathway that is mitochondrial-mediated and thus inhibits the growth of metastatic ovarian cancer cells (Yang et al., 2020).

Table 1. The various properties and the mechanism of action of quercetin

No.	Properties	Mechanism of Action	References
1	Neuroprotective effects	reduces neuronal oxidative damage and neuroinflammation by inhibiting the production of pro-inflammatory cytokines	Chiang et al. (2023)
2	Anti-allergic effects	improves the imbalance of Th1/Th2 and Treg/Th17 and inhibits the increase of epithelial cells, eosinophils, neutrophils, lymphocytes, and macrophages	Ke et al. (2023)
3	Skin benefits	reduces the expression levels of TNF- α , CCL17, CCL22, IFN- γ , IL-4, IL-6	Hou et al. (2019)
4	Cardiovascular protection	inhibits the contraction of vascular smooth muscle through the AMPK signaling pathway and modulates the TGF- β /Smads pathway	Kim et al. (2018) Wang et al. (2021)
5	Anti-diabetic effects	reduces the number of placental glycogen cells and protects against lipid peroxidation	Hosseini et al. (2021)
6	Anti-cancer effects	promotes apoptosis, inhibits metastasis and mitotic events causing cell arrest	Ullah et al. (2020)

Conclusion

Flavonoid polyphenols are most beneficial for down-regulating or suppressing inflammatory pathways and functions. Quercetin is considered one of the most widely distributed and well-known naturally derived flavonols, showing strong effects on immunity and inflammation mediated by leukocytes and other intracellular signals. Quercetin can play a significant role in different diseases. This flavonoid has various biological activities, which are mainly related to its ability to inhibit enzymes and its effects on immune responses. Quercetin is known to possess antioxidant properties and has a protective function against aging. It exerts a protective role against neurodegeneration.

The molecule is known to lower blood glucose levels and preserve the function of β cells in diabetic rats and mice. It shows a positive impact on treating and preventing diabetes. Various *in vitro* and *in vivo* studies have shown that quercetin has anti-cancerous activities and can be a reliable drug in cancer therapy. It has been shown that quercetin has anti-inflammatory and neuroprotective effects, partly through its ability to modulate the activity of specific signaling pathways. All this explains why many experts recommend regularly consuming food sources that contain quercetin.

References

- Aghababaei, F., Hadidi, M. (2023): Recent Advances in Potential Health Benefits of Quercetin, *Pharmaceuticals* 16(7), 1020.
- Amanzadeh, E., Esmaili, A., Rahgozar, S., Nourbakhshnia, M. (2019): Application of quercetin in neurological disorders: From nutrition to nanomedicine, *Rev Neurosci* 30(5), 555-572.
- Batiha, G. E., Beshbishy, A. M., Ikram, M., Mulla, Z. S., El-Hack, M. E. A., Taha, A. E., Algammal, A. M., Elewa, Y. H. A. (2020): The Pharmacological Activity, Biochemical Properties, and Pharmacokinetics of the Major Natural Polyphenolic Flavonoid: Quercetin, *Foods* 9(3), 374.
- Beken, B., Serttas, R., Yazicioglu, M., Turkecul, K., Erdogan, S. (2020): Quercetin Improves Inflammation, Oxidative Stress, and Impaired Wound Healing in Atopic Dermatitis Model of Human Keratinocytes, *Pediatr Allergy Immunol Pulmonol* 33(2), 69-79.
- Bousquet, J., Anto, J. M., Bachert, C., Baiardini, I., Bosnic-Anticevich, S., Canonica, G. W., Melén, E., Palomares, O., K Scadding, G. K., Togias, A., Toppila-Salmi, S. (2020): Allergic rhinitis, *Nat Rev Dis Primers* 6(1), 95.
- Castaldo, L., Narváez, A., Izzo, L., Graziani, G., Gaspari, A., Di Minno, G., Ritieni, A. (2019): Red Wine Consumption and Cardiovascular Health, *Molecules* 24(19), 3626.
- Chiang, M. C., Tsai, T. Y., Wang, C. J. The Potential Benefits of Quercetin for Brain Health: A Review of Anti-Inflammatory and Neuroprotective Mechanisms, *Int J Mol Sci* 24(7), 6328.
- Chondrogianni, N., Kapeta, S., Chinou, I., Vassilatou, K., Papassideri, I., Gonos, E.S. (2010): Anti-Ageing and Rejuvenating Effects of Quercetin, *Exp. Gerontol* 45, 763-771.
- Edwards, R. L., Lyon, T., Litwin, S. E., Rabovsky, A., Symons, J. D., Jalili, T. (2007): Quercetin reduces blood pressure in hypertensive subjects, *J Nutr* 137(11), 2405-11.
- Garelnabi, M., Mahini, H., Wilson, T. (2014): Quercetin intake with exercise modulates lipoprotein metabolism and reduces atherosclerosis plaque formation, *J Int Soc Sports Nutr* 11, 22.
- Gopalakrishnan, A., Ram, M., Kumawat, S., Tandan, S., Kumar, D. (2016): Quercetin accelerated cutaneous wound healing in rats by increasing levels of VEGF and TGF- β 1, *Indian J Exp Biol* 54(3), 187-95.
- Guo, C., Wang, W. J., Liao, Y. C., Zhao, C., Yin, Y., Yao, M. N., Ding, Y., Wang, J. W. (2022): Effect and Mechanisms of Quercetin for Experimental Focal Cerebral Ischemia: A Systematic Review and Meta-Analysis. *Oxidative Med. Cell. Longev* 2022, 9749461.
- Hosseini, A., Razavi, B. M., Banach, M., Hosseinzadeh, H. (2021): Quercetin and metabolic syndrome: A review, *Phytother Res* 35(10), 5352-5364.
- Hou, D. D., Zhang, W., Gao, Y. L., Sun, Y. Z., Wang, H. X., Qi, R. Q., Chen, H. D., Gao, X. H. (2019): Anti-inflammatory effects of quercetin in a mouse model of MC903-induced atopic dermatitis, *Int Immunopharmacol* 74, 105676.
- Huang, W-C., Fang, L-W., Liou, C-J. (2020): Corrigendum: Phloretin Attenuates Allergic Airway Inflammation and Oxidative Stress in Asthmatic Mice, *Front Immunol* 11:582838.
- Islam, M. S., Quispe, C., Hossain, R., Islam, M. T., Al-Harrasi, A., Al-Rawahi, A., Martorell, M., Mamurova, A., Seilkhan, A., Altybaeva, N., Abdullayeva, B., Docea, A. O., Calina, D., Sharifi-Rad, J. (2021): Neuropharmacological Effects of Quercetin: A Literature-Based Review, *Front. Pharmacol* 12:665031.
- Jung, M. K., Hur, D. Y., Song, S. B., Park, Y., Kim, T. S., Bang, S. I., Kim, S., Song, H. K., Park, H., Cho, D. H. (2010): Tannic acid and quercetin display a therapeutic effect in atopic dermatitis via suppression of angiogenesis and TARC expression in Nc/Nga mice, *J Invest Dermatol* 130(5), 1459-63.
- Jung, U. J., Kim, S. R. (2018): Beneficial Effects of Flavonoids Against Parkinson's Disease, *J. Med. Food* 21(5), 421-432.
- Ke, X., Chen, Z., Wang, X., Kang, H., Hong, S. (2023): Quercetin improves the imbalance of Th1/Th2 cells and Treg/Th17 cells to attenuate allergic rhinitis, *Autoimmunity* 56(1), 2189133.
- Khan, H., Ullah, H., Aschner, M., Cheang, W. S., Akkol, E. K. (2019): Neuroprotective Effects of Quercetin in Alzheimer's Disease, *Biomolecules* 10(1), 59.
- Khan, M. T. H., Orhan, I., Şenol, F., Kartal, M., Şener, B., Dvorská, M., Šmejkal, K., Šlapetová, T. (2009): Cholinesterase inhibitory activities of some flavonoid derivatives and chosen xanthone and their molecular docking studies, *Chem. Biol. Interact* 181(3), 383-9.
- Kim, D. H., Auh, J. H., Oh, J., Hong, S., Choi, S., Shin, E. J., Woo, S. O., Lim, T. G., Byun, S. (2020): Propolis Suppresses UV-Induced Photoaging in Human Skin through Directly Targeting Phosphoinositide 3-Kinase, *Nutrients* 12(12), 3790.
- Kim, D. H., Khan, H., Ullah, H., Hassan, S. T. S., Šmejkal, K., Efferth, T., Mahomoodally, M. F., Xu, S., Habtemariam, S., Filosa, R., Lagoa, R., Rengasamy, K. R. (2019): MicroRNA targeting by quercetin in cancer treatment and chemoprotection, *Pharmacol Res.* 147, 104346.
- Kim, S. G., Kim, J. R., Choi, H. C. (2018): Quercetin-Induced AMP-Activated Protein Kinase Activation Attenuates Vasoconstriction Through LKB1-AMPK Signaling Pathway, *J Med Food* 21(2), 146-153.
- Lakhanpal, P., Rai, D. K. (2007): Quercetin: a versatile flavonoid, *Internet J Med Update* 2(2), 22-37.
- Lloyd, C. M., Hessel, E. M. (2010): Functions of T cells in asthma: more than just T(H)2 cells, *Nat Rev Immunol* 10(12), 838-48.
- Luo, X., Xue, L., Xu, H., Zhao, Q. Y., Wang, Q., She, Y. S., Zang, D. A., Shen, J., Peng, Y. B., Zhao, P., Yu, M. F., Chen, W., Ma, L. Q., Chen, S., Chen, S., Fu, X., Hu, S., Nie, X., Shen, C., Zou, C., Qin, G., Dai, J., Ji, G., Su, Y., Hu, S., Chen, J., Liu, Q. H. (2018): *Polygonum aviculare* L. extract and quercetin attenuate contraction in airway smooth muscle, *Sci Rep* 8(1), 3114.

- Mahabady, M. K., Shamsi, M. M., Ranjbar, R., Tabandeh, M. R., Khazaeel, K. (2021): Quercetin improved histological structure and upregulated adiponectin and adiponectin receptors in the placenta of rats with gestational diabetes mellitus, *Placenta* 106, 49-57.
- Mlcek, J., Jurikova, T., Skrovankova, S., Sochor, J. (2016): Quercetin and Its Anti-Allergic Immune Response, *Molecules* 21(5), 623.
- Oliveira, T. T., Campos, K. M., Cerqueira-Lima, A. T., Cana Brasil Carneiro, T., da Silva Velozo, E., Ribeiro Melo, I. C., Figueiredo, E. A., de Jesus Oliveira, E., de Vasconcelos, D. F., Pontes-de-Carvalho, L. C., Alcântara-Neves, N. M., Figueiredo, C. A. (2015): Potential therapeutic effect of *Allium cepa* L. and quercetin in a murine model of *Blomia tropicalis* induced asthma, *Daru* 23(1), 18.
- Rogério, A. P., Dora, C. L., Andrade, E. L., Chaves, J. S., Silva, L. F., Lemos-Senna, E., Calixto, J. B. (2010): Anti-inflammatory effect of quercetin-loaded microemulsion in the airways allergic inflammatory model in mice, *Pharmacol Res* 61(4), 288-97.
- Salvamani, S., Gunasekaran, B., Shaharuddin, N. A., Ahmad, S. A., Shukor, M. Y. (2014): Antiatherosclerotic effects of plant flavonoids, *Biomed Res Int*. 480258.
- Shimmyo, Y., Kihara, T., Akaike, A., Niidome, T., Sugimoto, H. (2008): Flavonols and flavones as BACE-1 inhibitors: Structure–activity relationship in cell-free, cell-based and in silico studies reveal novel pharmacophore features, *Biochim. Et Biophys. Acta* 1780(5), 819-25.
- Shin, E. J., Lee, J. S., Hong, S., Lim, T. G., Byun, S. (2019): Quercetin Directly Targets JAK2 and PKC δ and Prevents UV-Induced Photoaging in Human Skin, *Int J Mol Sci* 20(21), 5262.
- Szabo, K., Mitrea, L., Călinoiu, L. F., Teleky, B. E., Martău, G. A., Plamada, D., Pascuta, M. S., Nemeş, S. A., Varvara, R. A., Vodnar, D. C. (2022): Natural Polyphenol Recovery from Apple-, Cereal-, and Tomato-Processing By-Products and Related Health-Promoting Properties, *Molecules* 27(22), 7977.
- Ullah, A., Munir, S., Badshah, S. L., Khan, N., Ghani, L., Poulson, B. G., Emwas, A. H., Jaremko, M. (2020): Important Flavonoids and Their Role as a Therapeutic Agent, *Molecules* 25(22), 5243.
- Vicentini, F. T., He, T., Shao, Y., Fonseca, M. J., Verri, W. A. Jr., Fisher, G. J., Xu, Y. (2011): Quercetin inhibits UV irradiation-induced inflammatory cytokine production in primary human keratinocytes by suppressing NF- κ B pathway, *J Dermatol Sci*. 61(3), 162-8.
- Wang, H., Jiang, W., Hu, Y., Wan, Z., Bai, H., Yang, Q., Zheng, Q. (2021): Quercetin improves atrial fibrillation through inhibiting TGF- β /Smads pathway via promoting MiR-135b expression, *Phytomedicine* 93, 153774.
- Wiczkowski, W., Romaszko, Jerzy., Bucinski, A., Szawara-Nowak, D., Honke, J., Zielinski, H., Piskula, M. K. (2008): Quercetin from shallots (*Allium cepa* L. var. *aggregatum*) is more bioavailable than its glucosides, *J Nutr*. 138(5), 885–8.
- Yang, D., Wang, T., Long, M., Li, P. (2020): Quercetin: Its Main Pharmacological Activity and Potential Application in Clinical Medicine, *Oxid Med Cell Longev*, 8825387.
- Zaborowski, M. K., Długosz, A., Błaszak, B., Szulc, J., Leis, K. (2024): The Role of Quercetin as a Plant-Derived Bioactive Agent in Preventive Medicine and Treatment in Skin Disorders, *Molecules* 29(13), 3206.
- Zu, G., Sun, K., Li, L., Zu, X., Han, T., Huang, H. (2021): Mechanism of quercetin therapeutic targets for Alzheimer disease and type 2 diabetes mellitus, *Sci Rep* 11(1), 22959.