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Biological activities of quercetin and other flavonols: A mini-review

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Abstract

There are countless benefits arising from the consumption of vegetables, which can present significant levels of compounds with bioactive properties, effectively acting in the promotion of human health. Bioactive compounds that play an antioxidant role have been widely studied since most of the diseases that affect humans can be derived from the presence of free radicals in the body, leading to a series of metabolic disorders. Quercetin has several pharmacological activities and antioxidant, anti-inflammatory, vasodilator, and anticancer effects. Despite the efficacy and safety of its consumption, the limited bioavailability of this phenol continues to be highlighted as a main concern, where factors such as solubility, absorption, and metabolism have a direct influence on this process and its beneficial effects. Among the compounds with antioxidant activity are flavonoids, such as quercetin, which have shown great effectiveness and are even associated with very positive responses against some types of tumor cells. Quercetin is shown to be a powerful ally in promoting health and a better quality of life. However, further studies are needed to be able to accurately state the benefits resulting from the consumption of this compound.

Keywords: flavonoids; antioxidant compounds; quercetin; health; secondary compounds.

Practical Application: Substances with bioactive properties found in plants present in native species can play essential roles in human metabolism, promoting health and well-being. Elucidating the action of these compounds and bringing to light the benefits they provide, in addition to acting in the preservation of biodiversity, can also be a way of using biodiversity in an intelligent way, promoting its preservation.

1 INTRODUCTION

The beneficial properties related to the daily consumption of fruits and vegetables are directly correlated with the bioactive compounds that these foods have, being considered extremely important in human metabolism. Bioactive compounds are essential or non-essential compounds that are naturally present in foods and that have different health-promoting properties, mainly related to their antioxidant power (Biesalski et al., 2009; Silva, E. P. et al., 2022). Among the compounds with bioactive properties present in plants, flavonoids deserve to be highlighted. According to Souza et al. (2022), flavonoids are of great interest to researchers because they promote the destruction or inactivation of free radicals through two main mechanisms of action: chain breaking, where a hydrogen atom is donated to the free radical, or by removing initiators from species that react to oxygen. Dietary flavonoids such as quercetin, kaempferol (KPF), and apigenin are considered to have stronger antioxidant activity in comparison to popular antioxidants, for example, vitamins C and E (Sokół-Łetowska et al., 2007). Furthermore, flavonols are phenolic compounds that belong to the subclass of flavonoids and are considered one of the most abundant phenolic compounds in the plant kingdom. Although the concentration and variety of flavonols in plants are quite high, they are largely absent from algae and fungi (Babu et al., 2013; Lobão et al., 2020). The main compounds in the class of flavonols are KPF, isorhamnetin, myricetin (MYR), and finally, quercetin (Crozier et al., 2009).

Aires et al. (2021) and E. P. Silva et al. (2022) reported that flavonol is the most active class of flavonoids, presenting a diversity of biological activities, including action in cardiovascular health, and therefore, is one of the most studied class of compounds. Around 1930, the first isolations of flavonoids from fruits were carried out, and these compounds were integrated into the group of vitamins, being named vitamin P (Aires et al., 2021; Silva, E. P. et al., 2022). There are 14 classes of flavonoids, which differ due to their carbonyl group at

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position 4, a hydroxyl group at position 3, and a double bond between positions 2 and 3, such as quercetin, MYR, and KPF (Silva, A. P. G., et al., 2022). These are products from the phenylpropanoid pathway, which converts phenylalanine to 4-coumaroyl-CoA and then to tetrahydroxyccone, in which 3-hydroxyflavone is the simplest flavonol and precursor of all other flavonols. These compounds also act as UV protectors, absorbing UV-A and UV-B wavelengths in plants (Flamini et al., 2013). According to Rana and Gulliya (2019), flavonoids, one of the major secondary metabolites present in medicinal plants, are foremost responsible for numerous pharmacological actions.

Of the three flavonols mentioned, MYR is the flavonol that has the most potent antioxidant activity, followed by quercetin and, finally, KPF. Ascorbic acid enhances the antioxidant action of these flavonoids because, when combined with a flavonol, it causes a reduction of the flavonol and maintains its properties for a longer time. Quercetin has more potent antioxidant activity than vitamins E and C and, when combined with vitamin E, inhibits their photooxidation in the cell membrane of red blood cells, platelets, and leukocytes (Zanoni & Hermes-Uliana, 2015). The most well-known flavonols include (i) KMF, found in various foods and beverages such as spinach, beans, broccoli, and tea (Calderón-Montaño et al., 2011) and (ii) quercetin, present in many types of fruits, seeds, and vegetables such as capers, cabbage, and red onions (da Silva, 2021; Salehi et al., 2020). Quercetin intake varies by source, according to countries and their cuisine. For example, in Holland and Japan, the predominant source comes from tea; in Italy, it comes from wine, while in the USA, Finland, and Greece, it comes from onions and apples (Hertog et al., 1995). It is worth noting that onions are usually not consumed in large volumes; however, they have a high content of this flavonol. Conversely, apples, wines, and teas have high consumption and low content of quercetin. Moreover, the flavonoid content in foods can be influenced by genetic factors and environmental actions (Machado et al., 2005). Verma et al. (2021) related that quercetin and its oxidative products are potent antioxidants and play a very important role in oxidative stress-related processes. It is one of the strongest anti-carcinogenic compounds. It reduces the incidence of stomach cancer and cancer of the intestines and lungs, as well as other types of cancer. It is the most effective inhibitor of peroxidation of membrane lipids and thus can affect atherosclerosis (Hryniewicz et al., 2017; Semwal et al., 2016). Given the above, the present work aims to demonstrate the importance of flavonoids in promoting biological activities and aspects related to health, focusing mainly on quercetin, one of the most important bioactive compounds in this group.

2 METHODS

We performed a narrative and critical review of biomedical literature. PubMed/MEDLINE, Scielo, Scopus, Web of Science, googleacademic, capesperiodic, and Cochrane Library databases were searched for articles published in English, Spanish, French, and Portuguese in the last 5 years preferably.

3 RESULTS AND DISCUSSION

3.1 The flavonols group

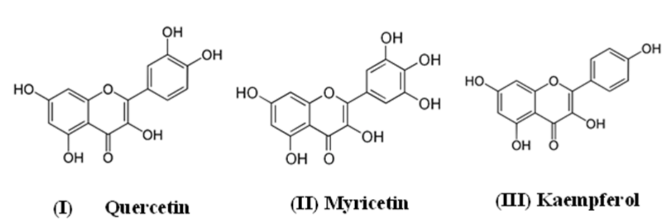
Among the classes of substances produced by plants that have great potential for application to the industrial sector, flavonoids stand out, which comprise an important group of structurally diverse secondary metabolites that have been the subject of considerable scientific interest due to their wide occurrence and therapeutic importance (Moraes et al., 2022). Flavonoids are antioxidant substances capable of nullifying the effects of free radicals from cellular metabolism and preventing lipid peroxidation. In addition to quercetin (Figure 1), which is the object of study in this article, other flavonoids such as KMF and MYR (Figure 1) also have some interesting functions within human metabolism. According to Dabeek and Marra (2019), quercetin and KMF compounds are widely found in fruits and vegetables, such as berries, spinach, and kale. These compounds display anti-inflammatory, anti-cancer, anti-allergic, and antiviral activities, among others (Ulusoy & Sanlier, 2020). Choi et al. (2009) reported that quercetin 7-rhamnoside (Q7R), a disaccharide glucoside, displays antiviral activities against the porcine endemic diarrhea virus.

3.2 Kaempferol

KPF is a flavonoid antioxidant found in fruits and vegetables. Many studies have described the beneficial effects of dietary KPF in reducing the risk of chronic diseases, especially cancer. Nevertheless, little is known about the cellular and molecular mechanisms underlying KPF actions in the central nervous system. Also, the relationship between KPF structural properties and their glycosylation and the biological benefits of these compounds is nuclear (Azevedo-Santos et al., 2021). KPF was shown to have higher antioxidant potential than its glycosylated derivatives. Two new KPF 3-O-glycosides (KPF 3-O-β-d-glucopyranosyl (1→2) β-d-xylopyranoside and KPF 3-O-α-l-arabinopyranosyl (1→2) β-d-galactopyranoside) obtained from *Solenostemma argel* are weaker than KPF aglycone, as shown by the 2,2-diphenyl-1-picrylhydrazyl (DPPH) method to evaluate free radical scavenging potential (Shafek et al., 2012). Similarly, Wang et al. (2018), using DPPH and 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) assays, showed that KPF had high free radical scavenging activity, while its glycoside derivatives showed no significant activity.

3.3 Myricetin

MYR is a flavonoid compound widely found in many natural plants, including bayberry (Song et al., 2021). So far, MYR has been proven to have multiple biological functions, and it is



Source: Vissiennon et al. (2012).

Figure 1. Chemical structure of quercetin, myricetin, and kaempferol, respectively.

a natural compound with promising research and development prospects. MYR (3, 5, 7, 3', 4', 5'-hexahydroxyflavonol, MYR) was originally isolated from the bark of the tree *Myrica rubra* (Lour.). It is a polyhydroxyflavonol compound composed of light yellow crystals and is easily soluble in methanol, acetonitrile, ethanol, and other polar solvents. Its chemical formula is C15H10O8, and its relative molecular mass is 318.24. It is widely distributed in natural plants of several families, including Myricaceae, Vitaceae, Leguminosae, and Rosaceae. According to Deepak et al. (2016) and Nardini and Garaguso (2020), its activity can be associated with regulation of Hippo, MAPK, GSK-3β, PI3K/AKT/mTOR, STAT3, TLR, IκB/NF-κB, Nrf2/HO-1, ACE, eNOS/NO, AChE, and BrdU/NeuN expression. MYR also enhances immunomodulatory functions, suppresses cytokine storms, improves cardiac dysfunction, possesses antiviral potential, and is a potential adjuvant treatment against cancer, cardiovascular injury, and nervous system diseases, as well as a drug against COVID-19 and other viral infections.

3.4 Quercetin-3-rutinoside: Rutin

Rutin, first classified as vitamin P, is the most ingested flavonol in the human diet (about 95%). It is present in onions, apples, broccoli, wines, and citrus fruits (Singla et al., 2019). Its production results from the combination of two pathways, shikimate and acetate, that is, a mixed biosynthesis, which is hydrolyzed by glycosidases in the body, producing quercetin-3-glycosidic (Q3G) and quercetin aglycone (Somerville et al., 2016).

The absorption of rutin is hampered by the presence of the disaccharide dimer in its structure, where hydrolysis facilitates this process. However, Q3G is more easily absorbed than quercetin aglycone, as it binds to sodium-dependent glucose transporters (SGLT-1) in epithelial cells (Hollman et al., 1995); that is, quercetin in the aglycone form has lower solubility than quercetin with the presence of a glycosidic group (Chen et al., 2010; Di Petrillo et al., 2022).

3.5 Bioactive properties of quercetin

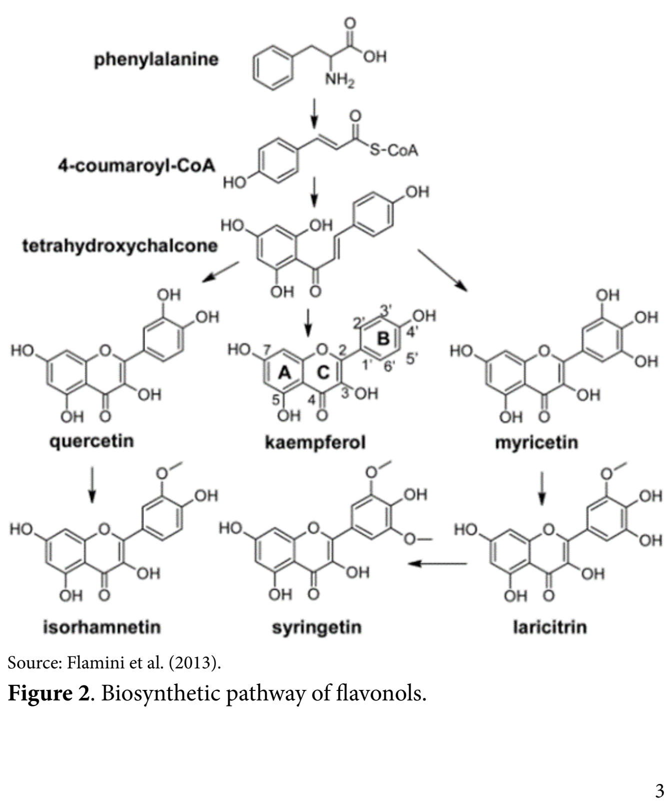
Quercetin is the most abundant polyphenolic flavonoid (flavonol subclass) in vegetal foods and medicinal plants. This dietary chemopreventive agent has drawn significant interest for its multiple beneficial health effects ("polypharmacology"), largely associated with the well-documented antioxidant properties (Guo et al., 2022). It has antioxidant properties that inhibit lipid peroxidation, one of the causes of atherosclerotic plaque formation, and also anticancer properties, being obtained through the hydrolysis of rutin, present in fruits, seeds, and plants (Di Petrillo et al., 2022; Satyendra et al., 2012). The glycosidic variety is the most widespread, the most common of which is quercetin-3-rutinoside (rutin).

The nature of its sugars and its food matrix directly influence the bioavailability of the quercetin derivative. Onion glycosides, for example, are a better source compared to aglycone isolated as a pure compound. However, when compared to a source rich in aglycone, the latter has an advantage (Perez-Vizcaino & Duarte, 2010), that is, its food matrix is a fundamental factor defining its bioavailability.

Quercetin is synthesized from the amino acid phenylalanine (1) via the phenylpropanoid pathway, consisting of a flavone core of two benzene rings linked by heterocyclic pyran (Chirumbolo, 2010; Dabeek & Marra, 2019). The steps of formation of this flavonol are basically conversions of substances, starting with the addition of 4-coumaroyl-CoA (2) to three molecules of malonyl-CoA (3), followed by 7,2-dihydroxy, 4-methoxy isoflavanol, resulting in tetrahydroxychalcone (4). Through chalcone isomerase, tetrahydroxychalcone is converted to naringenin (5), which is converted to eriodictiol (6) through the flavonoid 3-hydroxylase, which is converted to dihydro-quercetin (7) and finally to quercetin, using flavonol synthase (Figure 2).

When the flavonol quercetin reacts with a free radical, it donates a proton and ends up becoming a radical. However, its unpaired electron undergoes resonance, decreasing its energy and making the radical less reactive (Di Petrillo et al., 2022; Mariani et al., 2008).

In addition to the antioxidant effect, quercetin has several pharmacological activities, such as anti-inflammatory, vasodilatory, and anticancer *in vitro*. It is important to note that it does not produce adverse health effects in the diet (D'Andrea, 2015; Michala & Pritsa, 2022). Table 1 shows some studies related to the action of quercetin in the body and its main implications for health promotion, showing extremely important results from the supplementation of this compound. As suggested by Guo et al. (2022), controversies in the literature may be due to its dual anti-/pro-oxidant character and poor stability/bioavailability but multifaceted bioactivities, leaving uncertainties about its exact roles *in vivo*. Increasing evidence indicates that a prior oxidation of quercetin to generate an array of chemically diverse products with redox-active/electrophilic moieties is emerging as a new linkage to its versatile actions.



Source: Flamini et al. (2013).

Figure 2. Biosynthetic pathway of flavonols.

Table 1. Human studies on the relationship between quercetin and health.

SEARCH GROUP	DOSE mg/day	OBJECTIVES	RESULTS	REFERENCES
Twenty-two patients (5 men and 17 women) with classically documented interstitial cystitis (IC)	Received one capsule of Cysta-Q complex (equivalent to 500 mg of quercetin) twice a day for 4 weeks.	Quercetin-based supplement in patients with clinically proven interstitial cystitis (IC).	The mean problem index improved from 11.3 to 5.1, the mean symptom index improved from 11.9 to 4.5, and the mean global assessment score improved from 8.2 to 3.5.	Katske et al. (2001)
Men and women with prehypertension (*n* = 19) and stage 1 hypertension (*n* = 22)	730 mg quercetin/d for 28 days.	The hypothesis is that quercetin supplementation reduces blood pressure in hypertensive patients.	Blood pressure was not altered in prehypertensive patients after quercetin supplementation.	Edwards et al. (2007)
35 Healthy volunteers	50,100 and 150 mg/d of quercetin for 2 weeks	Investigate the effects of oral supplementation with quercetin.	Quercetin supplementation significantly increased plasma concentrations by 178, 359, and 570%, respectively.	Egert et al. (2008)
Healthy individuals	500 mg three times daily.	The purpose of this study was to examine the pharmacokinetics of quercetin aglycone as well as its conjugated metabolites and to develop a population pharmacokinetic model for quercetin that incorporates enterohepatic recirculation.	Increased oral clearance with an average terminal half-life of 3.5 h for quercetin.	Moon et al. (2008)
Female subjects (*n* = 120)	Three groups, 500 mg quercetin/d (n 38), 1000 mg quercetin/d (n 40) or placebo (n 42), 12-week study period	The study was to investigate the effects of long-term quercetin supplementation on innate immune function and inflammation in human subjects.	Increased plasma levels of quercetin but had no influence on measures of innate immune function or inflammation.	Heinz et al. (2010)
The study was conducted on 40 Japanese subjects with symptomatic knee osteoarthritis (OA).	GCQ supplement (1200 mg of glucosamine hydrochloride, 60 mg of chondroitin sulfate, and 45 mg of quercetin glycosides per day).	This clinical study was aimed at investigating the potential of a dietary supplement containing glucosamine and chondroitin sulfate in combination with derivatives of quercetin, a naturally occurring flavonoid (GCQ supplement), for knee OA care for 16 weeks.	The results of the symptomatic efficacy assessment showed that scores for two of the four symptom/function subscales, as well as the aggregate scores, were significantly improved at week 16 or earlier in the GCQ group.	Kanzaki et al. (2011)
Study with two groups of non-smoking, untreated sarcoidosis patients, matched for age and gender.	One group was given 4×500 mg quercetin (n=12) orally within 24 h; the other one placebo (n=6).	The aim is to examine the effect of quercetin supplementation on markers of oxidative stress and inflammation in sarcoidosis.	Quercetin supplementation improved the antioxidant defense as indicated by the increased total plasma antioxidant capacity. Moreover, quercetin supplementation also reduced markers of oxidative stress and inflammation in the blood of sarcoidosis patients.	Boots et al. (2011)
Healthy persons with dyslipidemia. The study was designed as a double-blind, randomized study with two hundred patients in each arm, and the total duration of the study was 2 months.	–	Evaluate the effects of regular consumption of quercetin on blood lipid values among healthy persons with dyslipidemia.	The test group has demonstrated a decrease in cholesterol, triglyceride, and LDL values with a parallel increase in HDL. Average cholesterol values at the end of the study were 5.09 mmol/l, whereas HDL and LDL values changed to 1.29 mmol/L and 2.91 mmol/L, respectively.	Talirevic and Jelena (2012)
Dietary quercetin and kaempferol (KMF): bioavailability and potential cardiovascular-related bioactivity in humans	500 mg of the aglycone form	This article reviewed the current literature on the bioavailability of quercetin and KMF from food sources and evaluated the potential cardiovascular effects in humans. Foods with the highest concentrations of quercetin and KMF in plants are not necessarily the most bioavailable sources.	The optimal effective dose of quercetin reported to have the beneficial effect of lowering blood pressure and inflammation is 500 mg of the aglycone form. Few clinical studies have examined the potential cardiovascular effects of high intakes of quercetin- and KMF-rich plants. However, it is possible that a lower dosage from plant sources could be effective due to its higher bioavailability compared to the aglycone form.	Dabeek and Marra (2019)

It continues...

Table 1. Continuation.

SEARCH GROUP	DOSE mg/day	OBJECTIVES	RESULTS	REFERENCES
Comparative analysis of molecular properties and reactions with oxidants for quercetin, catechin, and naringenin		The present study addressed the evaluation of the electronic properties of some flavonoids belonging to different classes, such as quercetin (flavonols), catechin (flavonols), and naringenin (flavanones), and their interactions with oxidants in model systems of DPPH reduction, flavonoid autoxidation, and chlorination.	The best antioxidant quercetin had the highest value of HOMO energy, a planar structure, and optimal electron orbital delocalization on all the phenolic rings due to the C2=C3 double bond in the C ring (absent in catechin and naringenin).	Veiko et al. (2021)
Quercetin: A molecule of great biochemical and clinical value and its beneficial effect on diabetes and cancer.	The daily intake of quercetin in the diet ranges from 10 to 500 mg	The aim of this review is to present a recent bibliography on the mechanisms of quercetin absorption and metabolism, bioavailability, and antioxidants and their clinical effects in diabetes and cancer.	This review highlights that quercetin is a valuable dietary antioxidant, although a specific daily recommended intake for this substance has not yet been determined and further studies are required to decide a beneficial concentration threshold.	Michala and Pritsa (2022)

GCQ: combination supplement containing glucosamine hydrochloride, chondroitin sulfate and quercetin glycosides; LDL: low-density lipoproteins; HDL: high-density lipoproteins; HOMO: Highest Occupied Molecular Orbital; MAPK: mitogen-activated protein kinase.
Source: adapted from Cai et al. (2013) and Ulusoy and Sanlier (2020).

4 CONCLUSIONS

Quercetin flavonol, of natural origin, is of great interest to researchers due to its antioxidative character, helping to prevent diseases caused by free radicals, as well as the inhibition of lipid oxidation, one of the causes of the emergence of neurodegenerative diseases, tumors, and the formation of atherosclerotic plaques. Studies have shown that quercetin has several pharmacological activities and antioxidant, anti-inflammatory, vasodilator, and anticancer effects. Despite the efficacy and safety of its consumption, the limited bioavailability of this phenol continues to be highlighted as a main concern, where factors such as solubility, absorption, and metabolism have a direct influence on this process and its beneficial effects. More research is needed that focuses on the health aspects after consumption of products fortified with these compounds or in natura, and especially on the regulation of the intestinal microbiota, which is associated with several health benefits, in addition to the effectiveness of *in vitro*, *ex vivo*, and *in vivo* test protocols.

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