Properties of free and microencapsulated quercetin: A literature review

https://doi.org/10.56238/sevened2023.007-024

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ABSTRACT
Quercetin is a bioactive compound classified as a polyphenolic flavonoid found in several plant sources, known for its antioxidant and anti-inflammatory properties, being able to modulate the expression of pro-inflammatory cytokines and transcription factors associated with inflammation. This is a literature review, with a search in scientific journals to provide a view of the therapeutic benefits of quercetin, especially for individuals with chronic diseases, in addition to presenting an innovative formulation such as microencapsulation, as an alternative to the free quercetin already used in supplementation, enabling the reduction of daily doses with considerably similar results. In the findings, it is highlighted that supplementation with bioactive compounds present in human food can significantly benefit individuals who have frailties, in addition, starting the discussion about pharmacological formulations that can reduce dosage and improve the site of absorption of these micronutrients, will make adherence to supplementation more effective, the importance of trained professionals for prescription with scientific basis and interest in Always keep up-to-date. Future research may add even more subsidies that corroborate the findings of this work.

Keywords: Quercetin, Antioxidant, Supplementatio, Microencapsulated.

1 INTRODUCTION

Quercetin is a polyphenolic flavonoid found in several plant sources, known for its antioxidant and anti-inflammatory properties (BATIHA et al., 2020). According to Uyanga (2021), quercetin can exert anti-inflammatory effects by modulating the expression of pro-inflammatory cytokines and transcription factors associated with inflammation, in addition to being related to the inhibition of

inflammatory signaling pathways, such as NF-kB. According to Snyder (2016), quercetin has shown potential to modulate gene expression involved in metabolic processes, suggesting benefits in the regulation of metabolism.

Modulations of the release of these compounds in the body is a challenge for researchers, the search for resolution and better use of the compounds in the body, led scholars to develop formulations with the use of microencapsulation, thus reducing doses and enabling the systemic effects of the antioxidant, as demonstrated in the research of Guazelli (2012).

The counterpoint lies in discussing a formulation that is accepted by the body and reduces the daily dosage of supplementation, but that maintains the benefits of the antioxidant.

Thus, the objective of this work is to demystify the use of daily quercetin supplementation as a valuable source of free radical scavenging substances and to present a formulation that can decrease the dosage to obtain the same results that the literature evidences in free quercetin.

2 MATERIALS AND METHODS

The present work was carried out through a bibliographic research, which consists of a review of the literature related to the theme addressed. To this end, journals, articles, Internet sites and other sources were used. According to Mejia (2021), bibliographic research seeks to solve a problem (hypothesis) through published theoretical frameworks, analyzing and discussing the various scientific contributions.

This type of research will provide subsidies for knowledge about the focus and perspectives, presenting subsidies contained in the scientific literature.

Thus, we seek to list researchers who corroborate the insertion of antioxidant supplementation, especially quercetin, in the daily lives of individuals with needs due to chronic diseases and thus enjoy the therapeutic benefits of this representative of the flavonoid class, remembering that it is a compound usually present in the human diet.

3 DEVELOPMENT

Antioxidants are compounds that play a crucial role in protecting the body from damage caused by unstable molecules known as free radicals. As evidenced by the literature (Chen et al., 2012; Pan et al., 2019), these free radicals are natural byproducts of cellular metabolism and can be induced by external factors such as exposure to ultraviolet radiation, environmental pollutants, and smoking, in turn, antioxidants act by neutralizing free radicals through electron donation, thus preventing oxidative damage to cells and biological molecules (Halliwell et al., 1995). reduced risk of several chronic diseases, including heart disease, cancer, and neurodegeneration. In addition, antioxidants demonstrate

the ability to modulate gene expression and regulate metabolic pathways, positively influencing cellular and systemic health (Sharifi-Rad, 2020).

In the human body, REs, both oxygen and nitrogen, ROS (reactive oxygen species) and ERN (reactive nitrogen species), respectively, are formed by several metabolic processes (LUSHCHAK, 2021) and/or by different environmental factors (TREVISAN et al., 2019). These molecules are electronically unstable, have an extremely short half-life, and are capable of reacting with numerous cellular components (EDGE; TRUSCOTT, 2021). Among the main REs, the following stand out: the superoxide anion (O2-.), hydrogen peroxide (H2O2) and the hydroxyl radical (OH.), for example, ROS and nitric oxide (NO) and peroxynitrite (NOO.), for example ERN (JAKUBCZYK et al., 2020)

To maintain oxidative balance, there are two antioxidant defense systems: one composed of endogenous elements, such as antioxidant enzymes and other antioxidant components, as well as those formed by exogenous factors, obtained by the diet (vitamins, phenolic compounds and carotenoids). The enzymatic antioxidant defense mechanism is due to the action of enzymes capable of converting REs into substances with less reactive potential. This is the case with the enzymes superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT). These enzymes are responsible for dismuting the superoxide anion into hydrogen peroxide, hydrogen peroxide into water, via reduced glutathione, and hydrogen peroxide into oxygen and water respectively (IGHODARO; AKINLOYE , 2018).

Exogenous antioxidants include vitamin E, vitamin C, glutathione, β-carotene, flavonoids, polyphenols, among others. These substances act mainly by donating an electron to REs, making them less reactive and preventing the reaction with biomolecules (lipids, proteins, nucleic acids), thus preventing the formation of cell damage (FARAONE et al., 2023). Lipids constitute one of the classes of molecules most vulnerable to oxidation, due to the membranes of some cells being formed mainly by unsaturated fatty acids, resulting in lipid peroxidation (FAROUX et al., 2020). Increased oxidative stress, associated with lipid peroxidation in endothelial cells, may be one of the major causes of diabetic complications triggered by hyperglycemia (PAPACHRISTOFOROU, 2020). One of the most important consequences of oxidative stress in relation to metabolic abnormalities in diabetes is the overproduction of mitochondrial superoxide in endothelial cells (KIRAC et al., 2021). This increased superoxide production results in the activation of pathways involved in the pathogenesis of diabetic complications, such as increased intracellular production of advanced glycation end products, leading to inflammation and endothelial dysfunction (LUC et al., 2019). Oxidative stress, in which the production of ROS and ERN overwhelms antioxidant defenses, is a feature of many neurological and neurodegenerative diseases. In addition, oxidative stress also activates mechanisms that result in a glia-mediated inflammation that also causes secondary neuronal damage. Recent research on oxidative stress in diabetes has identified that different populations of sympathetic neurons differ in their

susceptibility to neuropathy, which in turn is due to a greater vulnerability to oxidative stress (HASSAN et al., 2022).

Multiple therapeutic strategies have shown that treatment with antioxidants prevents and/or neutralizes the formation of radical species resulting from oxidative stress, minimizing or avoiding the neurological complications of DM (KALSON et al., 2023).

Drugs that reduce oxidative stress may play a relevant role in the treatment of chronic complications in humans, some natural products with antioxidant activity may be useful in helping the endogenous protective system, and can be used as nutraceuticals. From this perspective, the antioxidants present in our diet assume great importance as possible protective agents that help the human body reduce oxidative damage (WHITNEY et al., 2019).

A group of polyphenols with important antioxidant activity has been highlighted in the literature, the flavonoids (BHUYAN; HANDIQUE, 2022). The antioxidant activity of flavonoids refers to the fact that they are metal chelators, free radical scavengers, including OH•, and neutralize singlet oxygen (O2) (SPEISKY et al. 2022), currently, the structure of flavonoids and the antioxidant action is studied (SINGH et al., 2023), in the human diet we find these compounds in fruits, vegetables, grains, flowers, green tea and wine.

Quercetin (3,5,7,3',4'-pentahydroxyflavone) is the main flavonoid present in the human diet and its estimated daily consumption in Western populations varies between 20-50 mg/day (SCOTT et al., 2007), being the main representative of the flavonol subclass of the flavonoid family. These antioxidant phenolic compounds are found widely in vegetables, especially fruits and leaves. Onions, broccoli, apples, cherries and beverages such as green tea and red wine have relevant concentrations of these compounds, among the different types of flavonoids present in plants, the flavonol quercetin is the most abundant (MEENA, 2017).

The chemical structure of flavonoids is represented by three rings (A, B and C) with a carbonic backbone C6 – C3 – C6. The "A" ring is aromatic. The "C" ring is a heterocyclic ring attached to an oxygen and connected, through a C-C bond, to the aromatic "B" ring (GĂLĂŢANU; PANŢUROIU; SANDULOVICI, 2022). The basic structure of flavonoids allows for the possibility of substitutions in benzene rings A and B by hydroxylation, glycosylation, methylation, sulfation, and glucuronidation (CHEN et al., 2022).

In the diet, quercetin is most often found as a β-glucoside, i.e. with a sugar attached at position 3 of the "C" ring (MICHALA; PRITSA, 2022). However, quercetin can be found without the sugar molecule attached, and in this case, it is referred to as aglycone.

By definition, quercetin is an aglycone, lacking a sugar attached. It is a bright lemon yellow color and is completely insoluble in cold water, weakly soluble in hot water, but quite soluble in alcohol (PARASURAMAN; ANAND DAVID; ARULMOLI, 2016). The nature of glycosylation is known to

influence the efficiency of its absorption. When glycosylated quercetin is ingested, glycosyl groups can be released during chewing, digestion, and absorption, due to the action of enzymes in the mouth and intestine, which can hydrolyze quercetin glycosides into aglycones.

There is evidence that there is a contribution of bacteria in the mouth and intestine to this enzymatic hydrolysis (KAWABATA; YOSHIOKA; TERAH, 2019). In rodents, quercetin in the aglycone form is partially absorbed from the stomach, whereas glycosylated quercetin, such as isoquercitrin and rutin, are not (WANG et al., 2020). Quercetin aglycone is considered lipophilic, so presumably it should be able to cross enterocyte membranes through simple diffusion, resulting in better absorption than the glycosylated forms that reach the intact gut (NASCIMENTO et al., 2018).

In humans, studies suggest that quercetin glucoside is efficiently hydrolyzed in the small intestine by beta glucosidases to the aglycone form, much of which is then absorbed (TANAKA; SHINOKI; HARA, 2016). However, studies suggest that, in humans, quercetin aglycone may be more bioavailable, or at least more reliably bioavailable, than its glycosylated form (KANDEMIR et al., 2022).

Supplementation with 500 and 1,000 mg/day for 12 weeks resulted in an increase in plasma liquid concentration of quercetin during overnight fasting of 332 and 516 mcg/L, respectively (NIEMAN, 2010). Regarding the distribution of quercetin, both quercetin and its metabolites are widely distributed in tissues, with higher concentrations observed in the lungs, and lower concentrations in the brain, yellow adipose tissue, and spleen (LI et al., 2016). After quercetin is absorbed, the subsequent step of its metabolization is conjugation. Quercetin can combine with glucuronic acid. This process improves the solubility of quercetin in water, which can facilitate its elimination.

In addition to conjugation, quercetin can also be extensively methylated in the liver by the action of O-methyltransferase (Mullen et al., 2006). The extensive methylation of quercetin, in addition to other conjugation reactions to form glucuronides and sulfates, may be the main cause for the lack of toxicity of these compounds (LI et al., 2016).

Studies in humans are in agreement that the percentage of quercetin metabolites excreted in the urine after an oral dose is small (RAHAL et al., 2014). A large amount of absorbed quercetin is extensively metabolized and eventually eliminated by the lungs (Kaushik et al., 2012).

In the last 3 decades, several studies have shown that quercetin has pharmacological properties that make it act beneficially on biological systems, the effects of quercetin have also been researched in conditions of chronic diseases and their complications caused by oxidative stress. In rodents with streptozotocin-induced diabetes (STZ), treatment with quercetin reversed the concentration of oxidized glutathione in the brain and the activity of hepatic glutathione peroxidase (VERAS et al., 2011), which corroborates the satisfactory transposition of its use to humans.

In addition, quercetin sequesters oxygen radicals such as (•OH and O2-) inhibits xanthine oxidase and lipid peroxidation. The hydroxyl radical and the superoxide anion promote tissue damage by initiating lipid peroxidation. Thus, quercetin may have a protective action against factors that induce oxidative stress (KELLY, 2011).

Thus, the search for therapeutic formulations that can control the dose effect and favor the daily use of this antioxidant in a supplementary way has become a challenge for researchers and studies can contribute a lot in this process, to change the site of release of the supplement in the intestine and assist in the maintenance of the intestinal immune barrier.

An innovative formulation in the administration of quercetin in animal experiments is the microencapsulated system for modified drug release (SLF), which allowed to predict and control the rate of drug release, thus prolonging the therapeutic activity and/or providing site-specific release (ZALFEN, 2008).

The advances in research in SLF are due to the recognition of clinical and therapeutic advantages, as well as to economic factors such as the possibility of patent protection. The rational planning of the LFS is a crucial step for the modulation of drug release, appropriate to the clinical and pharmacokinetic needs and to the absorption sites (MONTEIRO et al. 2007).

Some strategies are employed to enable the modified release, aiming at the colonic release of drugs, among them the delivery of the drug in a polymeric matrix (FIGUEIREDO, 2008; KARROUT et al., 2009), chemical bonding to ion exchange resins, incorporation into an osmotic pump, and use of monolithic or multiparticulate coatings (HEINRICH; SCHUSTER, 2012). Microcapsules are multi-particulate systems that have the advantage of greater reproducibility in intestinal transit time compared to monolithic ones, helping to minimize sites of high concentration, reducing and even avoiding irritation and ulceration (ASGHAR; CHANDRAN, 2006), in addition to reducing inter- and intra-individual variation in treatment response (REDIGUIERI, 2008).

The pectin/casein polymer complex is a promising alternative in the constitution of modified release systems aiming at colonic release of the drug (RIBAS BARRETO, 2015) since pectin is a polysaccharide capable of resisting the action of proteases and amylases present in the upper gastrointestinal tract (GIT), but it can be digested by pectinases present in the intestine (GUAZELLI, 2012).

However, we need to emphasize the importance of new studies and the constant search to update the theoretical frameworks that can contribute to improving the quality of life of chronic degenerative patients, and not least, that they are accompanied by professionals qualified to prescribe supplementation according to individual needs and with a holistic character and in a planned manner.

4 FINAL THOUGHTS

At the end of the present work, it is possible to conclude that supplementation with bioactive compounds present in the human diet can greatly benefit individuals who have frailties such as chronic diseases and an increase in free radicals due to their disease.

In the same way, initiating the discussion about pharmacological formulations that can reduce dosage and improve the absorption site of these micronutrients will make adherence to supplementation more effective. This is reflected in the acceptance of nutritional therapy by professionals qualified to prescribe such conducts

In this sense, special attention is needed, seeking to identify the conditioning factors for the use of the compounds and the benefits that can be added to conservative therapy, being an adjuvant to pharmacological treatments and have a synergistic action in improving the cellular stress caused by the disease and effectively, in the long term, improve the general picture of complications caused by chronic diseases in general.

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