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QUERCETIN IN HEALTH AND DISEASE

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Abstract

For the vast majority of the population, natural medicine still continues to show its dominant role in the health system and this is especially true in developing countries. The foundations of modern medicine lie in antiquity, in the discoveries of ancient human civilizations regarding the plant world. Flavonoids, an important group of natural substances with variable structures, belong to a class of secondary metabolites of plants and are widely found in fruits, vegetables, grains, roots, stems, flowers, tea and wine. These natural sources are well known for their beneficial effects on health and efforts are currently being made to isolate and extract plant compounds. Quercetin, a flavonoid found in fruits and vegetables, has unique biological properties that can improve mental / physical performance. These properties are formed based on the potential benefits for general health and disease resistance, including anti-carcinogens, anti-inflammatory, antiviral, antioxidant and psychostimulant activities, as well as the ability to inhibit lipid peroxidation, platelet aggregation and capillary permeability and mitochondrial stimulation of biogenesis.

Keywords: FLAVONOIDS, QUERCETIN, GENERAL HEALTH.

1. INTRODUCTION

Flavonoids, an important group of natural substances with variable structures, belong to a class of secondary metabolites of plants and are widely found in fruits, vegetables, grains, roots, stems, flowers, tea and wine. These natural sources are well known for their beneficial effects on health and efforts are currently being made to isolate and extract plant compounds. Quercetin, a flavonoid found in fruits and vegetables, has unique biological properties that can improve mental / physical performance. These properties are formed based on the potential benefits for general health and disease resistance, including anti-carcinogens, anti-inflammatory, antiviral, antioxidant and psychostimulant activities, as well as the ability to inhibit lipid peroxidation, platelet aggregation and capillary permeability and mitochondrial stimulation of biogenesis.

Quercetin ($C_{15}H_{10}O_7$) is an aglycone (Figure 1), part of a glucoside without

carbohydrate content. The residue that remains after the substitution of a glycosidic group in a glucoside with a hydrogen atom is called an aglycone or genine. Quercetin is completely insoluble in cold water, poorly soluble in hot water, but quite soluble in alcohol and lipids.

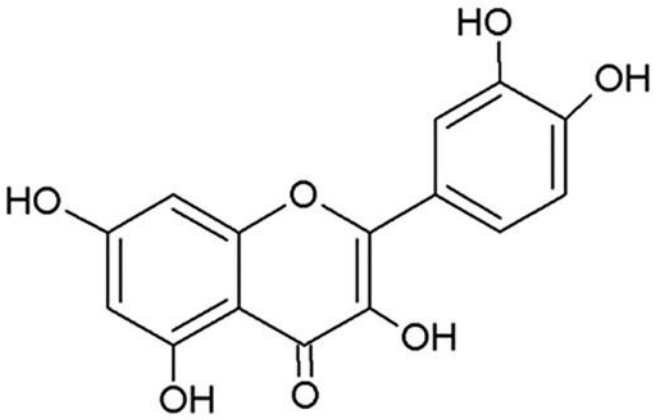

Figure 1. The chemical structure of quercetin

Quercetin was first isolated in 1854, and in 1899 its chemical structure was discovered by hydrolysis reactions. This not only promoted the study of the chemical structure of flavonoids, but also allowed their synthesis.

As a pure substance, quercetin is rare, but the glycosylated form is very common in plants, pollen, flowers, leaves and bark [1]. Quercetin and its derivatives usually exist in the form of yellow powder or crystals.

Quercetin undergoes many chemical changes, such as oxidation, during the formation of the food bolus and gastric chyme. The chemical stability of quercetin is influenced by oxygen concentration, pH value, temperature, concentration of other antioxidants, and the presence of metal ions.

The in vivo absorption, distribution, metabolism and bioavailability of quercetin have been widely studied in animal models and in humans. Figure 2 illustrates the mechanisms of absorption and metabolism of quercetin [2].

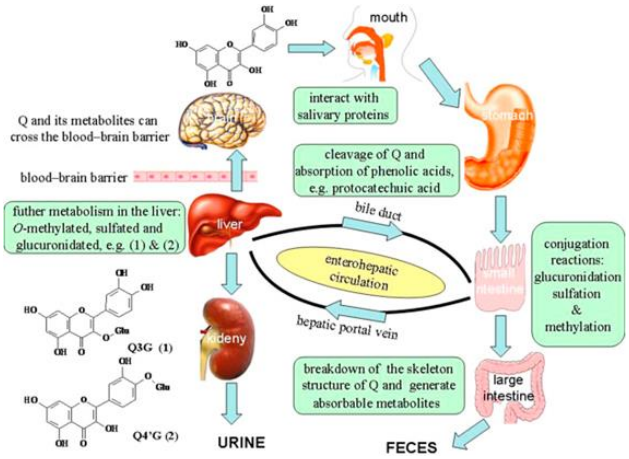

Figure 2. Schematic illustration of the absorption and metabolism of quercetin in the human body, Q represents quercetin (Wang et. Al, 2016)

2. THE NUTRITIONAL IMPORTANCE OF QUERCETIN

2.1. The antioxidant action of quercetin

The antioxidant activity of quercetin is mainly manifested by its effect on glutathione (GSH), enzymatic activities, signal transduction pathways and reactive oxygen species caused by environmental and toxicological factors. Quercetin has a strong antioxidant activity mainly by maintaining the oxidative balance [3]. Quercetin increases the body's antioxidant capacity by regulating GSH levels. This is because once oxygen free radicals are generated in the body, superoxide dismutase (SOD) quickly captures O_2- and converts it to H_2O_2. This enzyme further catalyzes the breakdown of H_2O_2 into non-toxic H_2O. This reaction requires GSH as a hydrogen donor. Animal studies and cell lines have shown that quercetin induces GSH synthesis [4].

The -OH groups of quercetin are related to important amino acid residues at the active site of two enzymes. In this way, it has a stronger inhibitory effect against key enzymes, acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), which are associated with oxidative properties [5]. Quercetin attenuates the decline in manganese-induced antioxidant enzyme activity, increased AChE activity, hydrogen peroxide generation, and increased lipid peroxidation in rats, thus preventing manganese intoxication [6].

2.2. Anti-inflammatory action

The anti-inflammatory action of quercetin is due to the inhibitory power of enzymes, such as lipoxygenase (an enzyme with inflammatory action to convert arachidonic acid into derivatives that will give rise to leukotrienes, substances with a strong chemotactic effect on neutrophils, eosinophils, body, aggravates the symptoms

of diseases such as cardiovascular or osteoarticular), and inhibition of inflammatory mediators. Quercetin also inhibits the release of histamine, which causes congestion, from basophils and mast cells [7].

2.3.Antineoplastic action

Quercetin can prevent cancer induced by oxidative stress due to its antioxidant activity and the suppression of many kinases involved in cancer cell growth, proliferation and metastasis. It has also been observed that it could induce receptor-mediated apoptosis in ascites cells of Dalton lymphoma-carrying rats [7]. Moreover, quercetin restricted the activity of protein kinase C in another study, which contributes to cancer progression [8].

2.4.Improving sports performance

Quercetin is part of a broad group of natural polyphenolic flavonoids that are being researched for their widespread benefits for health and athletic performance. As many studies are being conducted to show that natural flavonoids, such as quercetin, can increase mitochondrial biogenesis through intracellular signaling pathways. Quercetin can also improve endurance through a caffeine-like psychostimulating effect. Quercetin is also a competitive antagonist of type A1 adenosine receptors, at least in vitro, and the delay in fatigue results at least in part from its ability to block adenosine receptors in the brain.

3. IMPLICATIONS IN THE PATHOLOGY OF QUERCETIN

3.1. Obesity

Quercetin is the most common flavonoid found in vegetables, fruits and tea. Although it remains a matter of debate, flavonoids, including quercetin, appear to play an important role in preventing cardiovascular and other lifestyle-related diseases by eliminating free radicals, inhibiting lipid peroxidation and other antioxidant actions. Unlike catechins in tea, there are few studies in humans to determine the effects of quercetin on obesity and overweight.

However, the suppressive effects of quercetin on obesity and metabolic syndrome are gradually elucidated in animal studies. In recent years, it has been suggested that quercetin and other polyphenols are able to ameliorate obesity through various molecular pathways. It is necessary to make a clear distinction between the anti-obesity effects of quercetin when administered as a pure aglycone as opposed to when it is present in polyphenolic extracts. However, focusing on the "direct" effects of quercetin administration may help to better hypothesize its potential mechanism of action [9].

The effects of quercetin against obesity have been widely studied in laboratory animals and cell lines, but it should be emphasized that there are a limited number of interventional studies in human subjects. In his review, Kobori reported a list of studies on the effect of quercetin on obesity in mice and rats [10]. In short, a Western diet containing 0.05–0.25% quercetin significantly reduced body weight gain and accumulation of visceral and liver fat, as well as improved hyperglycemia,

hyperinsulinemia, and dyslipidemia in mice after 20 weeks of feeding.

In another investigation, rats, which followed a high diet in fat and sucrose and supplemented with 30 mg/kg body weight/day of quercetin, did not show any significant reduction in body weight or tissue adipose size and no changes in the activity of lipogenic enzymes or lipoprotein lipase were observed. However, quercetin has significantly reduced glucose and insulin levels, suggesting a more effective role as an anti-diabetic than as an anti-obesity factor [11].

3.2. Diabetes

Because quercetin has been reported to have a positive effect on blood glucose, many studies have focused on its hypoglycemic properties in different models of diabetic laboratory animals. Among them, rats are the most used laboratory animals to study the effect of quercetin. Oral administration of various doses of quercetin may reduce blood glucose, hemoglobin (Hb) and glycosylated hemoglobin (HbA1C) levels and prevent in vivo body weight loss.

Quercetin exerts significant hypoglycemic activity and thus promotes glycogen synthesis, inhibiting α-glucosidase activity and improving insulin resistance. It can also reduce islet cell deficiency, increase β-cell insulin secretion, and prevent diabetes by reducing oxidative stress in diabetic patients. Quercetin has many pharmacological effects and satisfactory results in the treatment of diabetes.

3.3. Neurological diseases

Quercetin, by purifying direct free radicals and the chelating activity of heavy metals, can effectively inhibit the neuronal damage caused by oxidative stress. Despite its direct antioxidant activity, quercetin can also alleviate oxidative stress by effectively inhibiting the enzymes xanthine oxidase and nitric oxide synthetase [12]. Quercetin appears to potentiate the process of learning and improving memory, as shown in tests performed on laboratory mice in Alzheimer's disease, especially when administered as nanoparticles [13-15].

In another study, this molecule was found to improve short-term and long-term memory in mice exposed to chronic stress by using older mice [16,17]. In the same vein, Mohammadi et al., in 2014 [18], reported how quercetin attenuated the harmful effects of chronic stress on learning in rats, thus improving their cognitive deficit by suppressing oxidative stress.

Several in vitro studies using neural cell lines and neurons in the cerebral cortex illustrated the role of quercetin in increasing the resistance of cells to oxidative stress induced by oxidants such as oxygen peroxide, hydroperoxide and neurotoxicity molecules such as beta-amyloid peptide, 6-hydroxy-dopamine, either by its direct or indirect antioxidant activity [19,20].

3.4. Cardiovascular disease

One of the first studies in humans in 1993 to investigate the potential of quercetin in medical practice showed that older men consuming 25.9 mg / day of quercetin had a significantly reduced risk of developing coronary heart disease [21]. These important studies indicate that quercetin has a

clinically important impact on many cardiovascular diseases. In recent years, many research groups have investigated the potential systemic, cellular, and molecular mechanisms involved in cardiovascular protection attributed to quercetin. Most results indicate proven efficacy in reducing cardiac hypertrophy, heart attack area, oxidative stress and inflammatory conditions in animal models of human cardiovascular disease.

Considerable attention has been paid to polyphenols, such as quercetin, due to their anti-inflammatory and antioxidant properties. Several mechanisms have been described and attributed to the anti-atherogenic effects of exercise and quercetin. It is universally accepted that moderate exercise is an important component of a healthy lifestyle, which helps prevent or delay the onset of cardiovascular disease. These beneficial effects are lost when subjects become sedentary. Quercetin has been shown to act through various mechanisms related mainly to reducing inflammation and the level of oxidative stress, the main culprits of atherosclerotic pathogenesis.

In a study conducted in 2014, it was found that mice supplemented with quercetin during exercise sessions had a 78% reduction in atherosclerotic plaque compared to mice in the control group and a 40% lower chance of developing an atherosclerotic plaque compared to the control group [22]. Thus. the intake of quercetin, associated or not, with exercise has an important role in preventing the formation of atherosclerotic plaques. It is thought that these changes may have resulted from the modulation of lipid metabolism.

CONCLUSION

In conclusion, current knowledge about the protective effects of quercetin against obesity seems to correlate with its ability to suppress the increase in oxidative stress and anti-inflammatory effect on fat cells. Quercetin acts as an effective therapeutic agent against various neurodegenerative diseases by suppressing oxidative stress, inflammation and improving neurogenesis. Therefore, quercetin can be considered a potent nutrient with limited toxicity.

There is now an increasingly confirmed certainty that natural products, such as phytochemicals, can be used as supplements or even for the prevention and treatment of pathologies. Evidence has been provided that certain foods lower blood pressure, influence the immune system, improve cognitive function, inhibit the development of cancer cells, protect against cardiovascular disease, diabetes, obesity.

Despite the multitude of studies present to identify, describe and demonstrate the effects of quercetin and its derivatives, it is not yet possible to establish exact dietary recommendations as to the amount and form in which they should be consumed, given that few studies have been performed in human subjects and the adverse effects and how to counteract them are not yet known. The huge variability of its derivatives, chemical structure and natural distribution in food are major factors of error in reporting the types or quantities consumed, as well as incomplete knowledge of their properties if

we refer to the idea of interventional studies in a clinical setting.

Since many of the previously described studies on the therapeutic applications of quercetin have been performed either in vitro, using cell cultures, or in vivo, using laboratory animals, additional data will certainly be obtained from studies in human subjects. Thus, it is hoped that in the near future there will be such clinical trials in both healthy individuals and patients to confirm the properties of quercetin mentioned and previously confirmed by experiments, to determine the optimal doses and forms under which they should be administered and to assess the risks and possible side effects.

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