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A REVIEW OF HIGHLY POTENTIAL ANTIOXIDANT INGREDIENT QUERCETIN: A BIOACTIVE FLAVONOID

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ABSTRACT

Antioxidants are chemicals that have the potential to shield cells from harm from unstable molecules like free radicals. Phenolic compounds called flavonoids are commonly present in fruits and vegetables. A naturally occurring polyphenolic molecule derived from plants, quercetin (3, 3′, 4′, 5, 7-pentahydroxyflavone) is a member of the flavonols subclass of flavonoids. Quercetin and other flavonoids usually accumulate as glycosides within plant cells; QUE-3-glucoside and rutin being the most prevalent types. Quercetin has been the subject of increased research interest in recent years. The most researched phytochemical and crucial flavonoid for scientific study is quercetin. *S. japonica L.*'s quercetin has numerous health-promoting qualities, including anti-inflammatory, anti-cancer, cardiovascular, and asthmatic effects. This makes it crucial to look at this molecule more thoroughly. **QuerciCure™** is developed by Biomed Ingredients, by using PAP sandwich technology to deliver the active ingredient. This product has greater DPPH activity, increased bioavailability and enhanced efficacy of active ingredients due to its other components such as piperine and phospholipids**.**

KEYWORDS: Quercetin, *S. japonica L.*, QuerciCure™, antioxidant, anti-inflammatory, ADME.

INTRODUCTION

Plants and their parts are used for their flavor, aroma, or medicinal qualities. The biological effects of the plant's extracts and phytoconstituents, including its antidiabetic, antihyperlipidemic, free-radical scavenging, and anti-inflammatory properties, have been demonstrated. Free radicals frequently have a significant impact on the emergence of metabolic diseases, which lowers quality of life. A pleasant and healthy existence can be achieved in a balanced environment provided by nature, which is a balanced system. Over the past few decades, there has been a rise in the quest for compounds with antioxidant action.[20]

A class of plant metabolites known as flavonoids is believed to have antioxidant properties and to improve cell signalling pathways. Numerous fruits and vegetables contain these compounds. Flavonoids are water-soluble polyphenolic compounds with fifteen carbon atoms. Their composition consists of a brief three-carbon chain joining two benzene rings. A third middle ring is created when one of the carbons in this chain directly or via an oxygen bridge connects to a carbon in one of the benzine rings. Chalcones, flavones, isoflavonoids, flavanones, anthoxanthins, and anthocyanins are the six main subtypes of flavonoids. A lot of these compounds, especially the anthoxanthins, are what give some petals their yellow color, while anthocyanins are frequently in charge of giving buds their red color and fall leaves their purple-red hue.[42] Quercetin is the most prevalent flavonoid in the diet. It can be found in a range of fruits and vegetables. One of the significant bioflavonoids found in over twenty plant materials is quercetin.[44,48]

Fruits and vegetables include the flavonoid quercetin, which has been shown to have positive effects on health.[24] Its biological activity is widely known. Among polyphenols, it is one of the most antioxidants.[18]

Quercetin mostly exists in confined forms in food, together with sugars, phenolic acids, alcohols, and other substances. Derivatives of quercetin are absorbed and metabolized after being hydrolyzed mostly in the gastrointestinal system following consumption.[45]

Quercetin is a yellow, crystalline substance with a bitter taste that is completely insoluble in cold water, soluble in lipids and alcohol, and very slightly soluble in hot water. It is an aglycone or aglycone without any carbohydrates in its composition, and it contributes vibrant hues to a variety of flowers.[17] Free radicals quickly react with other substances to take up their electrons and stabilize. A molecule that has been attacked loses an electron and becomes a free radical, which starts a chain of events that disrupts living cells.[4] According to published research, quercetin's antioxidant properties are mostly attributed to the hydroxyl groups located at positions 3, 5, 7, 30, and 40 of the A and B rings, the double bond that connects the second and third carbons, and the carbonyl group located on the fourth carbon.[36] Additionally, it shows promise as a range of exciting treatments for various health conditions, including anti-hyperuricemia and gouty arthritis[35], anticancer activity[39], antiallergic activity,[16] anti-diabetes activity[51], anti-obesity activity[37], and so on. The potential of quercetin to prevent the spread of some malignancies, such as those of the breast, cervical, lung, colon, prostate, and liver, is by far its most significant effect.[28] Bio-Med Ingredients develops **QuerciCure™**. This product's additional constituents, such as piperine and phospholipids, may contribute to its higher DPPH activity, increased bioavailability, and enhanced active ingredient performance. In Figure 1, the structure and characteristics of quercetin are displayed. The aforementioned anticancer effects are achieved through the ability to inhibit enzymes that activate carcinogens and various processes involving cellular signalling.[6]

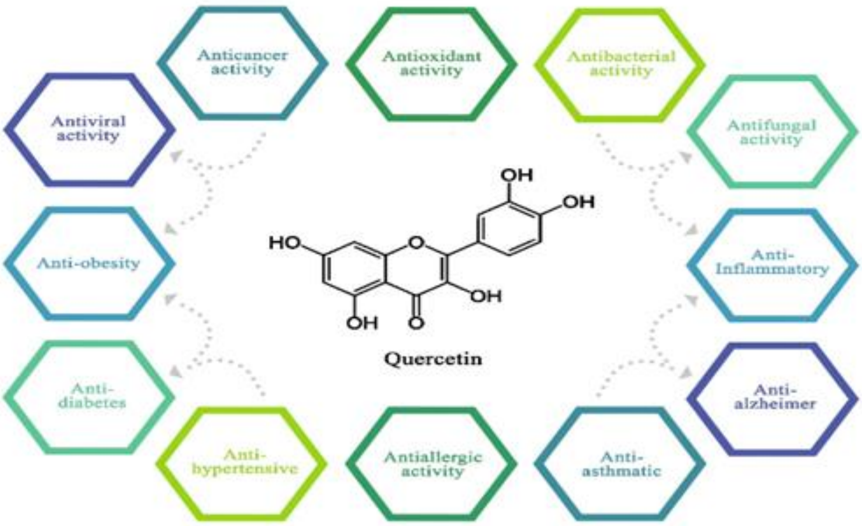

Figure 1: The structure and characteristics of quercetin.

Sources of Quercetin

Quercetin can be found in a wide range of plant-based foods. Okra has the highest concentration of quercetin and is found in capers, rocket, dill, coriander, fennel, juniper berries, corn poppy, and bee pollen, among other major plant sources.[47] Because localized habitats, customs, and other elements are complicated, there are differences between countries and regions in the diversified provenances of quercetin.[52] Furthermore, quercetin is present in more than twenty plant species, such as *Foeniculum vulgare, Santalum album, Mangifera indica, Emblica ofcinalis, Curcuma domestica valenton, Withania somnifera, and Cuscuta refexa.* Because quercetin has a wide spectrum of pharmacological effects, it is commonly used as a dietary supplement in powder and capsule form.[4] The amount of quercetin consumed each day can range from 50 to 800 mg, depending on the consumption of fruits, vegetables, and tea; different countries have reported different dietary intakes. Onions are the food that has been shown to possess the highest amount of quercetin (around 300 mg/kg) among those that have been studied.[36] Other plants, such broccoli and kale, also contained quercetin and kaempferol, although in much less concentrations. Tea, on the other hand, is low in quercetin flavonoid concentration but high in catechins. The color of fruits and vegetables indicates the amount of flavonoids present because anthocyanins, which include red grapes, cherries, and blueberries, are present in significant levels. The majority of these fruits also contain flavonoids, especially quercetin. Reports state that in countries like the USA, Spain, Japan, and China, the average daily consumption of quercetin is 9.75, 18.48, 16.2, and 18 mg.[26]

Chemistry of Quercetin

Structure

Quercetin is designated as 3,3',4',5,7-pentahydroxyflavanone (or) 3,3',4',5,7-pentahydroxy-2-phenylchromen-4-one in the International Union of Pure and Applied Chemistry (IUPAC) nomenclature, with a chemical formula of $C_{15}H_{10}O_7$. Pentamethyl derivatives are formed when quercetin molecules have five hydroxyl groups at positions 3, 5, 7, 3', and 4', as illustrated in Fig. 2. It is also referred to as meletin, sophretin, and quercetine.[8]

Other flavonoids can be built upon by quercetin. Food frequently contains quercetin as an aglycone. Quercitrin hydrolyzes in acid to produce quercetin and rhamnose.

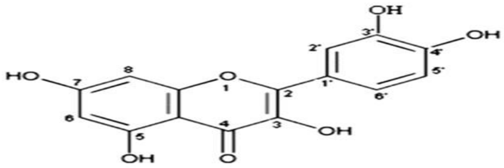

Figure 2: Structure of Quercetin.

Chemical and Physical Properties of Quercetin

It is difficult for quercetin to be available biologically due to its high molecular weight (302.24), melting point (316.5 °C), and limited water solubility. Quercetin is a lipophilic compound because it has five hydroxyl groups. The nature of derivatives of quercetin can vary depending on the kind of substituents included in the molecule, from hydrophilic to lipophilic. The prenyl, C-methyl, and O-methyl derivatives of quercetin are typically lipophilic in nature. The glands found on the surface of leaves, flowers, and fruits synthesize them. Plant tissue can be readily separated by submerging it in acetone.[9] At higher temperatures, quercetin undergoes structural breakdown and releases unpleasant fumes and an acrid smoke.[10]

Quercetin belongs to one of the six subclasses of flavonols, which are flavonoid compounds. In honor of Quercus, the term, which has been in use since 1857, is derived from quercetum, which is oak woods. It is a naturally occurring polar auxin transport inhibitor.[26]

International Union of Pure and Applied Chemistry (IUPAC) lists 3,30,40,5,7-pentahydroxyflvanone as the scientific name for quercetin, or by its synonym, 3,30,40,5,7-pentahydroxy-2-phenylchromen-4-one. This suggests that quercetin's OH groups are linked at positions 3, 5, 7, 30, and 40. Quercetin ($C_{15}H_{10}O_7$) is an aglycone without covalent sugar. A quercetin glycoside is produced by replacing one of the OH groups (usually at position 3) with a glycosyl group (rhamnose, a sugar like glucose or rutinose). The connected glycosyl group can affect the absorption, solubility, and in vivo actions. Because quercetin glycoside has a glycosyl group, it is generally more soluble in water than quercetin aglycone.[43] A quercetin glycoside is differentiated by its attached glycosyl group. In general terms, the term "quercetin" should only be used to describe the aglycone; however, the name is sometimes used to designate other quercetin-like substances, such as its glycosides, in research and the supplement industry.[26]

Mechanism of action

In the beginning, it was anticipated that quercetin is absorbed in the small intestine after human colonic microbiota breaks down the ß-glucoside linkage. However, subsequent research revealed that conjugation with glucose enhances quercetin absorption (Fig. 3). According to one theory, quercetin-3-glucoside combines with bacterial enzymes to generate quercetin, which then reacts with tissues and the colon to produce isorhamnetin and 3, 4-diOH-phenylacetic acid. Upon production, 3, 4-diOH-phenylacetic acid reacts with the colon and tissues to produce 3-OH-phenylacetic acid and fumes 5.4-OH-3-methoxy-phenylacetic acid; as a result, quercetin is eventually formed and absorbed from the small intestine to the colon.[6] According to a number of studies, between 0.07 and 17.4% of the quercetin that was eaten was eliminated as the compound or one of its conjugates. However, it has been found that the rat stomach absorbs quercetin in the form of glycosides. Walgren[49], et al. shown through his research using in vitro experiments on Caco-2 cells that the multi-drug resistance protein 2 transporters' efficient efflux is the main cause of the quercetin glucosides' lack of absorption. Later research including human participants found that bacterial enzymes in the small intestine hydrolyzed the quercetin glucosides.

According to a different study, quercetin and quercetin aglycone were absorbed at rates between 36 and 53 percent and 65 and 81 percent, respectively. In ileostomists, quercetin glucosides, rutinoside, and aglycone were reported to be absorbed at 52±5%, 17±15%, and 24±9%, respectively.[7,8,9,10,11,12]

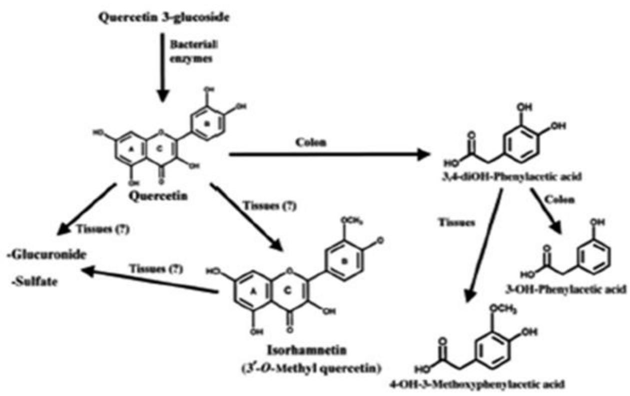

Figure 3: Mechanism of action of Quercetin.

Extraction of quercetin

The method used to generate the quercetin-containing flavonoid extract from ***S. japonica L*** as seen in figure 4. involved macerating and extracting flower buds that had been air-dried and thwarted three times in 80% ethanol (v/v) in a water bath at 70 °C for thirty minutes. After that, the mixture was filtered, and for 15 minutes, 15% of the initial plant mass was purified using charcoal. Following the combination of the extracts, the solvent was eliminated by rotary evaporation at 70 °C to 1/3 of the original volume. The concentrated solution was kept in a refrigerator without any preservatives after being diluted with hot water to its original amount. By filtering the settling residues and drying the retentate at 60 °C, the final extract (QFE) was obtained[25] seen as in Figure 5.

Figure 4: *S. japonica L* flowers from which Quercetin is extracted.

Figure 5: Quercetin extract.

Pharmacokinetics

A recent study[22] examined the plasma concentrations of the flavonoids quercetin and apigenin as well as their impact on haemostasis in healthy adults. In a randomized, placebo-controlled, multiple crossover research, eighteen participants were given dietary supplements strong in flavonoids (like onions and parsley) or low in flavonoids (like a "placebo") for a week at a time. The parsley supplement provided 84 ± 6 mg (311 ± 22 µmol) of apigenin, the daily onion supplement contained 114 ± 3 mg (377 ± 10 µmol) of quercetin aglycone, and the placebo had 0.015 ± 0.004 mg (0.05 ± 0.01 µmol). At the conclusion of each research week, blood samples were collected, and post-column derivatization was used to measure the amounts of quercetin. The effects of apigenin, catechin, quercetin, and quercetin-3-glucoside on platelet aggregation were studied in a parallel in vitro experiment. Quercetin was found to have peak plasma concentrations of 447± 117 ng x mC1 (1.5 ± 0.4 µM, mean± SD) 90 minutes after onions were consumed. However, no effects were observed in vivo on thromboxane production, collagen-induced aggre-gation in whole blood and platelet-rich plasma, or other hemostatic variables. 27 participants in a related trial were given high dosages of flavonoids over the course of 28 days, including 1.0 g of quercetin/d, 1.0 g of bioflavonoids/d, 200 mg of rutin/d, and 200 mg of bromelain/d.[13] Samples of plasma were obtained on day 28 following a 10-hour fast. HPLC-UV was used to examine the samples after they had undergone acid and enzymatic hydrolysis. The content of quercetin in total plasma increased 14-fold (from 0.10 ± 0.09 to 1.5 ± 0.3 µM, or from 27.7 ± 25.7 to 427.1 ± 89.2 ng x ml-1), however there were no changes in the different cardiovascular disease risk variables. However, because glycosides and conjugates hydrolyze, total quercetin concentrations were determined in plasma in both investigations. Consequently, while considering quercetin aglycone as a molecule that may be active in vitro, it is important to measure its quantities in vivo. It is impossible to determine the true plasma concentration of free quercetin without first determining the ratio of conjugated to free fraction. Due to the likelihood of significantly lower free quercetin concentrations in plasma in vivo, it is challenging to match the effective in vitro concentrations of quercetin with the total quercetin concentrations in plasma. Despite the use of extremely sensitive techniques, the amounts of free quercetin in plasma before hydrolysis were too low for detection in other investigations, and the conjugated forms' antioxidant efficacy is lower than that of free quercetin.[31] Furthermore, it is highly improbable that the residual unbound concentration of free quercetin in plasma will have any pharmacologic effect in vivo provided the potent plasma protein binding of free quercetin.

Bioavailability of Quercetin

Bioavailability is the amount of a substance that gets to the desired site of action. However, when it comes to the absorption of polyphenols, bioavailability is defined as the amount in plasma. Furthermore, it is an evaluation of the dosage based on urine analysis of its constituent parts and metabolites. The pharmaceutical industry uses ADME, which stands for absorption, metabolism, disposal, and excretion, as a synonym.[2] Recent studies have looked at quercetin dosage and bioavailability from a variety of agricultural products.[14,23]

However, a number of factors limit its bioavailability, or the quantity of ingested chemical that enters the bloodstream. First, the small intestine finds it difficult to absorb quercetin due to its weak water solubility. Its bioavailability is reduced by its substantial metabolism in the liver and intestinal epithelium, which results in metabolites with reduced biological activity. Third, quercetin's bioavailability can be further complicated by the gut flora, which can potentially affect how the compound is absorbed and metabolized.[15]

The human body can only eat about 20 mg of quercetin per day, although quercetin-rich sources showed total plasma concentrations of 72 to 193 nmol/L of both free and conjugated quercetin after short-term intake. However, plasma buildup is not brought on by sustained food ingestion.[15] Oral bioavailability, which is thought to be 1% in humans, is also thought to have very low absorption in the gastrointestinal tract because of its poor solubility.[19]

Health Benefits of Quercetin

Antioxidant Action

The primary way that the antioxidant function of flavonoids neutralizes free radicals is by giving them hydrogen atoms. According to Pietta et al., it was difficult to link the flavonoid structure to their responsibility for radical scavenging.

Reactive oxygen species (ROS) production has been linked to heart failure, ischemic heart disease, hypertension, diabetes, and atherosclerosis. As the primary inhibitor of oxidative stress, quercetin functions as an antioxidant. The RNS scavenger ebselen was shown to be ten times less efficient against peroxynitrite than the flavonoids consisting of 3-OH and 3-, 4-catechol.[29]

The capacity of quercetin to bind transition metal ions and scavenge free radicals is what makes it as well-known as an antioxidant. To obtain a meaningful impact on the biomarkers/indices to be assessed, the ultimate effects of quercetin's antioxidant property on humans must be streamlined. A study found that eating a test meal consisting of fried onions considerably raised the levels of quercetin in the plasma. During the 48 hours that followed the consumption of the fried onions, there was little change in the oxidation of the plasma or isolated low-density lipoprotein (LDL), despite a rise in the plasma's overall antioxidant activity. It was observed that the two-week quercetin supplementation (150 mg/day) in healthy patients had no effect on plasma, alpha- or gamma-tocopherols, oxidized LDL, or the antioxidant capacity of the plasma.

Neurological Effects

It has been demonstrated that quercetin is both neurotoxic and neuroprotective. When combined with fish oil. Joseph[34], et al. found to have neuroprotective effects in the rat brain, protecting against neurodegenerative illnesses (e.g., Alzheimer's disease). Choi[11], along with others, demonstrated inhibitory effects on acetylcholinesterase. It has been observed that quercetin reduced the oxidative stress caused by 6-hydroxydopamine in the rat striatal brain neurons.[40] Another study found that quercetin administration reduced intracellular glutathione levels, which in turn impaired nervous system function.[30]

Antiviral Activity

It has been observed that quercetin is effective against viruses, indicating that it has antiviral activity against enveloped viruses such Sindbis, parainfluenza type 3, respiratory syncytial, and herpes simplex type I. Additionally, it was demonstrated to be resistant to the cardiac virus.[31] Quercetin's capacity to attach to viral coat protein and polymerases, as well as to damage DNA, is what gave rise to its antiviral activity. It has been discovered that quercetin's capacity to impose or prevent damage to DNA is linked to its mutagenic, carcinogenic, and anti-carcinogenic properties. According to a paper, ascorbate stabilizes quercetin, enhancing its antiviral action. This effect is comparable to the improved antiproliferative effect of ascorbate on squamous cell carcinoma.[32] It has also been demonstrated that quercetin increased the antiviral activity of drugs like 5°ethyl-2'-deoxyuridine and interferon.

Anticancer Agent

Fruits and vegetables are rich sources of quercetin and other flavonoids, which are thought to have a protective effect against cancer. Numerous investigations have been conducted to assess the anti-carcinogenic properties of quercetin in cell cultures. These studies have revealed that quercetin inhibits the growth of cancer cells and promotes apoptosis. It has been demonstrated that a crucial first step in the creation of a novel anticancer medication is the stimulation of apoptosis in cancer cells.[33] Quercetin may help prevent some malignancies, particularly colon cancer, according to some research done on animals.[34]

Canker Sores

Canker sores, sometimes called aphthous ulcers, are tiny, shallow lesions that develop on the soft tissues of the mouth or at the gum line. Quercetin has been shown by Sharma[46], et al. to decrease the incidence of mouth sores and to provide minor symptomatic relief.

Cardiovascular Properties

In affluent nations, heart disorders have been found to be the main and most common cause of death. Oxidative stress and inflammation have been shown to be important factors in the development of heart disease, even though the precise etiology and mechanism of the condition are still unknown. The potential use of quercetin as a secure substitute for anti-inflammatory and antioxidant medications for ailments including cardiovascular disease has been studied. According to research, quercetin significantly lowered blood pressure and cytokine-induced C-reactive protein (CRP) production, two risk factors linked to heart disease, in both preclinical and clinical investigations. It was additionally discovered to be a potent vasodilator.[34]

Anti-inflammatory

Inflammation is the normal biological reaction to trauma, microbial infection, intoxication, and chemical irritation. It had been assumed that immune cells migrating from blood vessels to the wounded or infected location and mediators being released to fight the injury or infection were what caused inflammation.[25]

It is commonly recognized that quercetin has anti-inflammatory properties. When rats were given a combination of quercetin and polysorbate 80 during an in vivo investigation by Lin[27], et al., the rats' paw edema was prevented. Because of its poor absorption value, quercetin glycoside treatments applied topically were found to be unsuccessful in reducing inflammation. The rat skin route absorbed a significant amount of the quercetin pentamethylether formulation, which demonstrated its robust anti-inflammatory properties by effectively reducing inflammation.[26]

Asthma

Breathing becomes difficult due to the swelling and narrowing of the airways caused by asthma, a chronic lung illness. It has been discovered that quercetin reduces asthma symptoms. It was discovered to ease the smooth muscle of the airways, reduce the quantity and activation of inflammatory immune cells, and cut off the level of histamine. Compared to steroid inhalers that lessen airflow resistance and typical asthma maintenance drugs, Rigolin[41], et al. observed that quercetin was beneficial against asthma even at the lowest dose.

Additionally, it has been found that quercetin lessens the diseases associated with asthma, including airway hyperactivity, eosinophil and neutrophil enrollment, bronchial epithelial cell activation, and mucus and collagen synthesis. It has been found that the amount of quercetin consumed through food affects asthma symptoms. Clinical research has demonstrated that quercetin may be used to treat or prevent asthma in people.[43]

CONCLUSION

The pharmaceutical industry is expected to undergo a revolution as a multifaceted therapeutic agent due to the remarkable flavonoid known as quercetin. Extensive research on quercetin has revealed a multitude of health benefits, offering a promising outlook for various medical conditions. As science and technology continue to advance, the precise mechanisms underlying quercetin's effects are becoming clearer. The future of quercetin in pharmaceuticals is undoubtedly bright, as its versatile properties as an antioxidant, anti-inflammatory, antiviral, anticancer, and cardiovascular agent make it a beacon of hope in the quest for improved healthcare and disease management.The active ingredient in QuerciCure^{TM} is delivered by PAP sandwich technology, has been developed by Biomed Ingredients. Due to its additional constituents, which include phospholipids and piperine, this product has higher DPPH activity, increased bioavailability, and improved efficacy of active substances.

REFERENCES

1. Aherne, S.A.; O'Brien, N.M. Dietary flavonols: chemistry, food content, and metabolism. Nutrition, 2002; 18(1): 75-81.
2. Almeida, A.F.; Borge, G.I.A.; Piskula, M.; Tudose, A.; Tudoreanu, L.; Valentová, K.; Williamson, G.; Santos, C.N. Bioavailability of Quercetin in Humans with a Focus on Interindividual Variation. Compr. Rev. Food Sci. Food Saf; 2018, 17: 714–731. [CrossRef].
3. Aramwit, P.; Bang, N. & Srichana, T. The properties and stability of anthocyanins in mulberry fruits. Food Res. Int; 2010; 43: 1093-1097.
4. Azeem, M.; Hanif, M.; Mahmood, K.; Ameer, N.; Chughtai, F.R.S.; Abid, U. An Insight into Anticancer, Antioxidant, Antimicrobial, Antidiabetic and Anti-Inflammatory Effects of Quercetin: A Review. Polym. Bull, 2023; 80: 241–262.
5. Azuma, K.; Ippoushi, K & Terao, J. Evaluation of tolerable levels of dietary quercetin for exerting its antioxidative effect in high cholesterol-fed rats. Food Chem. Toxicol, 2010; 48: 1117-1122.

6. Beecher, G.R. Overview of dietary flavonoids: nomenclature, occurrence and intake. Journal Nutrition, 2003; 10: 3248S-3254S.
7. Buchner, N.; Krumbein, A.; Rhon, S. & Kroh, L.W. Effect of thermal processing on the flavonols rutin and quercetin. Rapid Commun. Mass Spectro, 2006; 20: 3229-3235. doi: 10.1002/rcm.2720.
8. Cao, X.G.; Li, X.X. & Bao, Y.Z. Responses of human lens epithelial cells to quercetin and DMSO. Invest Ophthalmol Vis Sci; 2007; 48: 3714-3718. doi: 10.1167/iovs.06-1304.
9. Carlsen, C. & Stapelfeldt, H. Light sensitivity of elderberry extract. Quantum yields for photodegradation in aqueous solution. Food Chemistry, 1997; 60: 383-387. doi: 10.1016/S0308-8146(96)00356-1.
10. Chandrasekara, N. & Shahidi, F. Effect of roasting on phenolic content and antioxidant activities of whole cashew nuts, kernels and testa. J. Agr. Food Chem; 2011; 59: 5006-5014.
11. Choi, G. N.; Kim, J. H.; Kwak, J. H.; Jeong, C.H.; Jeong, H. R.; Lee, U. & Heo, H. J. Effect of quercetin on learning and memory performance in ICR mice under neurotoxic trimethyltin exposure. Food Chemistry, 2012; 132: 1019- 1024.
12. Cisneros-Zevallos, L. The use of controlled postharvest abiotic stresses as a tool for enhancing the nutraceutical content and adding-value of fresh fruits and vegetables. J. Food Sci; 2003; 68(5): 1560–1564.
13. Conquer JA, Maiani G, Azzini E, Raguzzini A, Holub BJ 1998 Supplementation with quercetin markedly in- creases plasma quercetin concentration without ef-fect on selected risk factors for heart disease in healthy subjects. J Nutr; 1998; 128: 593-597.
14. Dabeek, W.M.; Marra, M.V. Dietary Quercetin and Kaempferol: Bioavailability and Potential Cardiovascular-Related Bioactivity in Humans. Nutrients, 2019; 11: 2288. [CrossRef].
15. Degroote, J.; Vergauwen, H.; Van Noten, N.; Wang, W.; De Smet, S.; Van Ginneken, C.; Michiels, J. The Effect of Dietary Quercetin on the Glutathione Redox System and Small Intestinal Functionality of Weaned Piglets. Antioxidants, 2019; 8: 312. [CrossRef].
16. Ding, Y.; Li, C.; Zhang, Y.; Ma, P.; Zhao, T.; Che, D.; Cao, J.; Wang, J.; Liu, R.; Zhang, T.; et al. Quercetin as a Lyn Kinase Inhibitor Inhibits IgE-Mediated Allergic Conjunctivitis. Food Chem. Toxicol, 2020; 135: 110924.
17. El-Saber Batiha, G.; Beshbishy, A.M.; Ikram, M.; Mulla, Z.S.; Abd El-Hack, M.E.; Taha, A.E.; Algammal, A.M.; Ali Elewa, Y.H. The Pharmacological Activity, Biochemical Properties, and Pharmacokinetics of the Major Natural Polyphenolic Flavonoid: Quercetin. Foods, 2020; 9: 374.
18. Formica J.F., Regelson W., Review of the biology of quercetin and related bioflavonoids. Food Chem.Tox, 1995; 33: 1061–1080.
19. Fujimori, M.; Kadota, K.; Shimono, K.; Shirakawa, Y.; Sato, H.; Tozuka, Y. Enhanced Solubility of Quercetin by Forming Composite Particles with Transglycosylated Materials. J. Food Eng; 2015; 149: 248–254. [CrossRef].
20. Gupta M, Mazumder UK, Gomathi P, Selvan VT. Antiinflammatory evaluation of leaves of Plumeria acuminata. BMC Complement Altern Med; 2006; 6: 36.
21. Hovenier R, Hollman PCH, Katan MB 1998 Effects of the flavonoids quercetin and apigenin on the he-mostasis in healthy volunteers: results from an in vitro an dietary supplement study. Am J Clin Nutr; 1998; 67: 255-262.
22. Janssen PLTMK, Mensink RP, Cox FJJ, Harryvan JL, Joseph, D.; Muralidhara, K.M. Enhanced neuroprotective effect of fish oil in combination with quercetin against 3-nitropropionic acid induced oxidative stress in rat brain. Prog. Neuro-Psychopharmacol. Biol Psychiatry, 2013; 40: 83-92.
23. Kasikci, M.B.; Bagdatlioglu, N. Bioavailability of Quercetin. Curr. Res. Nutr. Food Sci; 2016; 4: 146–151. [CrossRef].
24. Kaur Ch., Kapoor H. C., Antioxidants in fruits and vegetables – the millennium’s health. Int. J. Food Sci. Technol, 2001; 36: 703–725.
25. Koleva B, Stanchev V, Spasova D, Bahchevanska S. Investigation of the process of maceration of flowers from Sophora japonica. Food Science, Engineering and Technologies. Scientific works. Plovdiv: UFT; 2005; 380-385.
26. Li, Y.; Yao, J.; Han, C.; Yang, J.; Chaudhry, M.T.; Wang, S.; Liu, H.; Yin, Y. Quercetin, Inflammation and Immunity. Alzheimer’s Dis; 2016; 8: 167.
27. Lin, C.F.; Leu, Y.L.; Al-Suwayeh, S.A.; Ku, M.C.; Hwang, T.L & Fang, J.Y. Anti-inflammatory activity and percutaneous absorption of quercetin and its polymethoxylated compound and glycosides: the relationships to chemical structures. Eur. J. Pharm Sci; 2012; 47: 857-864.
28. Liu, Y.; Tang, Z.G.; Lin, Y.; Qu, X.G.; Lv, W.; Wang, G.-B.; Li, C.L. Effects of Quercetin on Proliferation and Migration of Human Glioblastoma U251 Cells. Biomed. Pharmacother, 2017; 92: 33–38.
29. Lombard, K.; Peffley, E.; Geoffriau, E.; Thompson, L. & Herring, A. Quercetin in onion (Allium cepa L.) after heat-treatment simulating home preparation. J. Food Composition Anal, 2005; 18: 571-581. doi: 10.1016/j.jfca.2004.03.027.
30. Małgorzata, Materska. Quercetin and its derivatives: chemical structure and bioactivity-A review. Pol. J. Food Nutr. Sci; 2008; 58(4): 407-413.
31. Manach, C., Morand, C., Crespy, V., Demigné, C., Texier, O., Régérat, F., & Rémésy, C. (1998). Quercetin is recovered in human plasma as conjugated derivatives which retain antioxidant

properties. *FEBS Letters*, 1998; *426*(3), 331–336. https://doi.org/10.1016/s0014-5793 (98)00367-6.
32. Marco, P.H.; Poppi, R.J.; Scarmino, I.S. & Tauler, R. Investigation of the pH effect and UV radiation on kinetic degradation of anthocyanin mixtures extracted from Hibiscus acetosella. Food Chemistry, 2011; 125: 1020-1027.
33. Morand, C.; Crespy, V.; Manach, C.; Besson, C.; Demigne, C.; & Remesy, C. Plasma metabolites of quercetin and their antioxidant properties. Am. J. Physiol, 1998; 275: R212-219.
34. Murakami, M.; Yamaguchi. T.; Takamura, H. & Matoba, T. Effects of thermal treatment on radical-scavenging activity of single and mixed polyphenolics compounds. Food Chem. Toxicol, 2004; 69: FCT 7-10.
35. Nutmakul, T. A Review on Benefits of Quercetin in Hyperuricemia and Gouty Arthritis. Saudi Pharm. J; 2022; 30: 918–926.
36. Ozgen, S.; Kilinc, O.K.; Selamoglu, Z. Antioxidant Activity of Quercetin: A Mechanistic Review Kuersetinin Antioksidan Aktivitesi: Mekanik Bir Derleme. Turk. J. Agric.-Food Sci. Technol, 2016; 4: 1134–1138.
37. Perdicaro, D.J.; Rodriguez Lanzi, C.; Gambarte Tudela, J.; Miatello, R.M.; Oteiza, P.I.; Vazquez Prieto, M.A. Quercetin Attenuates Adipose Hypertrophy, in Part through Activation of Adipogenesis in Rats Fed a High-Fat Diet. J. Nutr. Biochem, 2020; 79: 108352.
38. Pietta, P.G. Flavonoids as antioxidants. J. Natural Products, 2000; 63(7): 1035-1042.
39. Rauf, A.; Imran, M.; Khan, I.A.; ur-Rehman, M.; Gilani, S.A.; Mehmood, Z.; Mubarak, M.S. Anticancer Potential of Quercetin: A Comprehensive Review. Phytother. Res; 2018; 32: 2109–2130.
40. Rietveld, A. & Wiseman, S. Antioxidant effect of tea: evidence from human clinical trials. Journal Nutrition, 2003; 133(10): 3285S-3292S.
41. Rigolin, L.; Fortunato Freitas, D.C.; Alves Martins, M.; Teixeira P. & Rogerio, A. Quercetin: A flavonoid with the potential to treat asthma. Braz. J. Pharm. Sci; 2012; 48(4): 589-599.
42. Robertson, S. (2022, Nov 4). Retrieved from https://www.news-medical.net/health/What-are-Flavonoids.aspx
43. Ross, J.A.; Kasum, C.M. Dietary Flavonoids: Bioavailability, Metabolic Effects, and Safety. Annu. Rev. Nutr; 2002; 22: 19–34.
44. Salvamani S, Gunasekaran B, Shaharuddin NA, Ahmad SA, Shukor MY. Antiartherosclerotic effects of plant flavonoids. Biomed Res Int; 2014; 2014: 480258.
45. Scalbert A., Williamson G., Dietary intake and bioavailability of polyphenols. J. Nutr; 2000; 130: 2073–2085.
46. Sharma, P. & Gujral, H.S. Effect of sand roasting and microwave cooking on antioxidant activity of barley. Food Res. Int; 2011; 44: 235-240.
47. Suganthy, N.; Devi, K.P.; Nabavi, S.F.; Braidy, N.; Nabavi, S.M. Bioactive Effects of Quercetin in the Central Nervous System: Focusing on the Mechanisms of Actions. Biomed. Pharmacother, 2016; 84: 892–908.
48. Sultana B, Anwar F. Flavonols (Kaempeferol, quercetin, myricetin) contents of selected fruits, vegetables and medicinal plants. Food Chem; 2008; 108: 879‑84.
49. Walgren, R.A.; Lin, J.T. & Kinne, R.K. Cellular uptake of dietary flavonoids quercetin-4-beta-glucoside by sodium dependant glucoside transporter SGLTI. J. Pharmacol. Exp. Ther, 2000; 294: 837-843.
50. Wang, W.; Sun, C.; Mao, L.; Ma, P.; Liu, F.; Yang, J.; Gao, Y. The Biological Activities, Chemical Stability, Metabolism and Delivery Systems of Quercetin: A Review. Trends Food Sci. Technol, 2016; 56: 21–38.
51. Yao, Z.; Gu, Y.; Zhang, Q.; Liu, L.; Meng, G.; Wu, H.; Xia, Y.; Bao, X.; Shi, H.; Sun, S.; et al. Estimated Daily Quercetin Intake and Association with the Prevalence of Type 2 Diabetes Mellitus in Chinese Adults. Eur. J. Nutr, 2019; 58: 819–830.
52. Yi, H.; Peng, H.; Wu, X.; Xu, X.; Kuang, T.; Zhang, J.; Du, L.; Fan, G. The Therapeutic Effects and Mechanisms of Quercetin on Metabolic Diseases: Pharmacological Data and Clinical Evidence. Oxid. Med. Cell. Longev, 2021; 2021: 6678662.