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REVIEW ON FLAVONOID QUERCETIN

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ABSTRACT

Quercetin (3,3',4',5,7-pentahydroxyflavone) is one type of flavonoid that is commonly found in a wide range of foods, including fruits and vegetables. Quercetin has many health benefits, such as improving cardiovascular health, treating allergy disorders, relieving pain from arthritis, and having anti-inflammatory and anti-cancer properties. The main objective of this review is to understand the physiochemical behavior of quercetin as well as its pharmacokinetic and biosynthetic mechanisms and therapeutic applications.

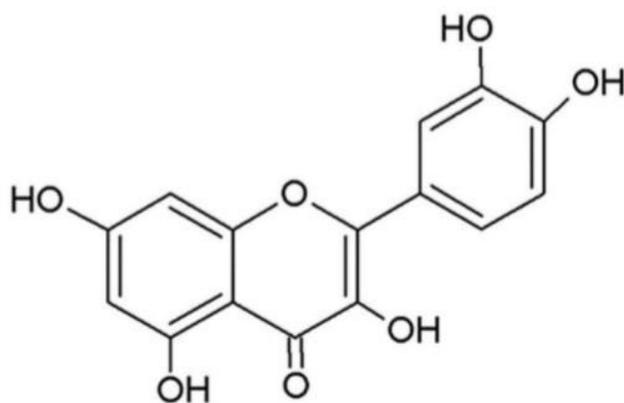
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INTRODUCTION

Researchers have spent a lot of effort researching quercetin, a unique bioflavonoid, over the past 30 years. 1930 saw the earliest discovery of bioflavonoids by Nobel Prize winner Albert Szent Gyorgyi. Flavonoids are a class of chemical substances with varying phenolic structures that can be found in fruits, vegetables, cereals, bark, roots, stems, flowers, tea, and wine [1].

These natural compounds were well known for their health benefits even before flavonoids were discovered to be the active constituents. More than 4000 different types of flavonoids exist, and many of them are responsible for the eye-catching colors of flowers, fruits, and leaves [2].

The most common flavonoid, quercetin, is found in abundance in onions, broccoli, apples, and berries (the word comes from the Latin - quercetum, meaning oak forest, quercus oak).



Quercetin has three rings and five hydroxyl groups (Figure 1).
Figure 1: Structure of Quercetin

GENERAL OCCURANCE OF QUERCETIN

Quercetin is a yellow, crystalline, bitter-tasting chemical that is soluble in aqueous alkaline solutions, glacial acetic acid, and alcohol acid but insoluble in water [3].

Quercetin is a flavonoid found in many plant-based foods, including fruits, vegetables, cereals, and herbs. Some of the most well-liked food sources of quercetin are as follows: Berries and fruits, such as apples, onions, raspberries, cranberries, and blueberries Wine, grapes, and citrus fruits (such lemons, oranges, and grapefruit) Broccoli, tomatoes, red and black beans, and leafy greens (such as spinach and kale), Tea, especially the green kind [4]. Furthermore, quercetin is a dietary supplement that is often taken in conjunction with other antioxidants or flavonoids. However, it is usually advisable to obtain nutrients through

a balanced diet rather than depending on supplements.

BIOSYNTHESIS OF QUERCETIN [5]

Quercetin is a flavonoid, or type of polyphenol, that is present in many fruits, vegetables, and grains. Plants manufacture quercetin by a series of enzyme reactions that convert simple precursor molecules into the end product.

The creation of quercetin starts with the shikimate pathway, which also produces aromatic amino acids like phenylalanine and tyrosine. Cinnamic acid and p-coumaric acid are the products of the conversion of these amino acids by phenylalanine ammonia-lyase (PAL) and tyrosine ammonia-lyase (TAL), respectively. These two acids are then converted into the crucial intermediate compound naringenin by the enzymes 4-coumarate CoA ligase (4CL) and cinnamoyl 4-hydroxylase (C4H).

The enzyme flavanone 3-hydroxylase (F3H) then transforms naringenin into dihydrokaempferol, which is then changed into dihydroquercetin by the enzyme flavonoid 3'-hydroxylase (F3'H). Finally, the flavonol synthase (FLS) enzyme transforms dihydroquercetin into querdisepri.

The complex biosynthesis of quercetin is comprised of a succession of intricate enzyme steps that start with simple precursor molecules and end with the production of the final quercetin molecule.

MECHANISM OF ACTION

I. Antioxidative action

The most well-described property of quercetin is its capacity to act as an antioxidant. For protecting the organism from reactive oxygen species, which are produced either naturally during oxygen metabolism or as a result of external damage, the flavonoid quercetin seems to be the most effective [6].

II. Xanthine Oxidase inhibitory action

The xanthine oxidase pathway has been recognized as a crucial component in the oxidative damage to tissues, particularly after ischemia-reperfusion [7]. The enzymes xanthine oxidase and dehydrogenase are involved in the conversion of xanthine to uric acid. The enzyme is present as xanthine dehydrogenase under normal circumstances, but ischemia and oxidative stress lead it to change into xanthine oxidase. By preventing

xanthine oxidase from functioning, quercetin seems to lessen oxidative damage [8].

III. Decreasing Leukocyte immobilisation

Leukocyte immobilisation and strong adhesions to the endothelium wall are yet another important mechanism that not only creation of free radicals originating from oxygen, but also for the discharge of cytotoxic oxidants and inflammatory mediators, as well as for additional complement system activation. In a healthy state, leukocytes can easily travel along the walls of the endothelium. However, a variety of chemicals, mainly mediators released by the endothelium and complement factors, may cause the leukocytes to cling to the endothelial walls during ischemia and inflammation, immobilizing them and triggering neutrophil degranulation. This leads to the production of inflammatory mediators and oxidants, which harm tissue. Oral administration of a pure micronized flavonoid fraction has been demonstrated to lower the quantity of immobilized leukocytes after reperfusion, a finding that may be related to its anti-inflammatory characteristics [9].

Apart from the previously mentioned benefits, quercetin also demonstrates the following actions:

- Excessive scavenging behavior

-inhibition of the production of inducible nitric oxide

-Control of the expression of genes

-relationships to other systems of enzymes.

IV. FREE-RADICAL AND HEALTH

The production of physiological amount (low or moderate concentrations) of free-radical is essential to fight against an unfavorable environment. Indeed, phagocytes release free radicals to destroy pathogenic microbes. The free radicals such as nitric oxide (NO), superoxide anion, and related reactive oxygen species (ROS) play an important role as regulatory mediators in signaling processes. In higher organisms, NO and ROS regulate vascular tone, oxygen tension in control of ventilation, and erythropoietin production [10]. Both enzymatic and nonenzymatic processes can result in the production of free radicals. Oxygen starts the nonenzymatic reactions, while the respiratory chain, phagocytosis, prostaglandin synthesis, and the cytochrome P450 system are all involved in the enzymatic reactions that produce free radicals [11]. Reactive nitrogen species, or ROS, can be produced by exogenous sources like heavy metals, transition metals, alcohol, cigarettes smoke, water pollution, air pollution, cancer, aging, immune cell activation, inflammation, mental stress, excessive exercise, ischemia, infection, and radiation, or by endogenous sources like air

pollution, water pollution, cigarette smoke, and radiation [12]. Overproduction of free radicals modifies cellular processes and leads to degenerative and chronic illnesses.

V. DIETRY SOURCES

Quercetin is mostly found in fruits and vegetables, particularly in citrus fruits, apples, onions, parsley, tea, and red wine. Dark cherries, blueberries, bilberries, olive oil, and grapes are other foods high in quercetin-rich flavonoids.

62 edible tropical plants, including myricetin, quercetin, kaempferol, luteolin, and apigenin, were studied for their flavonoid content. The highest total flavonoid concentrations were found in onion leaves, semambu leaves, bird chillies, black tea, papaya shoots, and guava, with 1497 mg/kg of quercetin, 391 mg/kg of luteolin, and 832 mg/kg of kaempferol per kilogramme. The main flavonoid found in these plant extracts is quercetin, which is followed by myricetin and kaempferol. Vegetables are primarily composed of quercetin, but they also contain glycosides of kaempferol, luteolin, and apigenin. Quercetin glycosides are primarily found in fruits, although myricetin and kaempferol glycosides are sporadically seen [13]. A range of dietary items' respective quantities of quercetin, myricetin, and kaempferol are displayed in (Table 1).

Table 1: Amount of Quercetin in selected foods [14, 15]

Sr. No.	Food	Quercetin (mg/100g)
1	Broccoli, Raw	2.8
2	Carrot, Raw	0.4
3	Celery, Raw	3.5
4	Cocoa powder, Unsweetened	20.1
5	Onions, Raw	22.6
6	Tomatoes, Raw	0.5
7	Apples	4-20
8	Oysters	10-50
9	Berries	2-59
10	Citrus fruits	1-35
11	Leafy greens	4-30
12	Tomatoes	1-10
13	Red wine	0.1-14
14	Coriander leaves, Raw	52.9
15	Juniper berries, Raw	46.6
16	Dill weed, fresh	55.1
17	Carob fibre	58.1
18	Loose leaf	2.0
19	Red grapes	1.38
20	Green tea	1.99

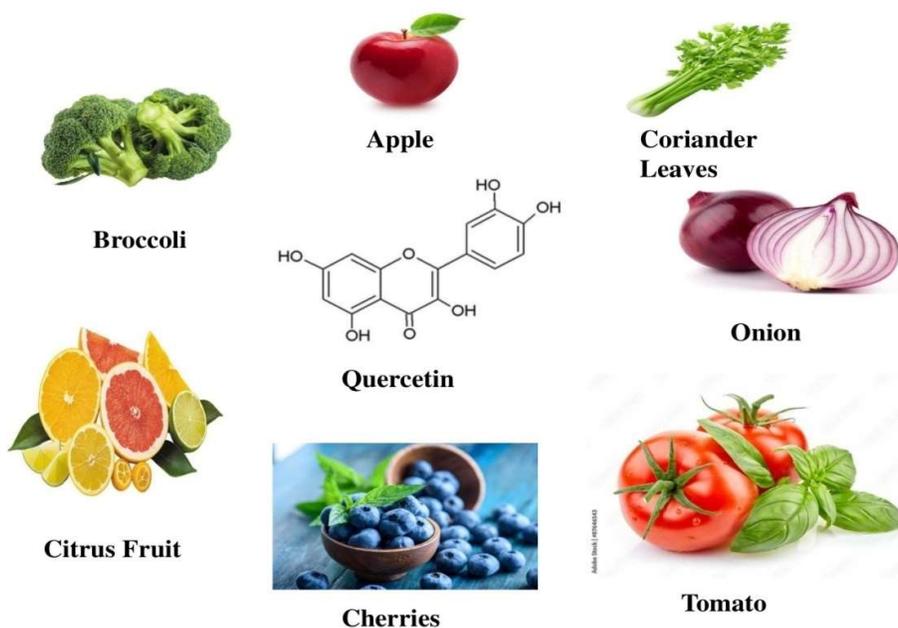


Figure 2: Natural Source of Quercetin

THERAPEUTIC USES

Among the many possible therapeutic applications for quercetin are the prevention and treatment of the diseases mentioned below. Quercetin seems to work even better

when paired with the pineapple-derived digestive enzyme bromelain.

A. Cancer

Even though there are many potential contributing factors to cancer (such as nutrition, genetics, and environment),

reactive oxygen and nitrogen species (ROS/RNS) are well known to be important in the pathophysiological process. ROS/RON have been shown to be carcinogenic in addition to causing damage to DNA, changing cell signaling pathways (MAPK, NFκB, AP-1, PLA, and ASK-1), and modifying gene expression (proto-oncogene, tumour suppressor gene). Clinical trials, epidemiological studies, in vitro and in vivo laboratory investigations, and other research have demonstrated the preventative effects of plant-based diets against a number of malignancies. Indeed, it has been shown that diets high in fruits and vegetables may reduce the incidence of 7–31% of cancer cases [16].

B. Gout

Quercetin prevents the production of uric acid, thereby reducing gout symptoms since it inhibits xanthine oxidase [17].

C. Antibacterial activity

Quercetin appears to have antibacterial activity against almost all types of bacteria known to cause respiratory, gastrointestinal, cutaneous, and urinary issues [18].

D. Coronary heart disease

Oxidized low-density lipoprotein (bad cholesterol) causes coronary heart disease (CHD), which can be avoided by consuming antioxidant quercetin. Frequent ingestion of flavonoids from food may reduce the incidence of CHD-related mortality in older men, according to Hertog *et al* [19].

Furthermore, a Japanese study discovered a negative correlation between total plasma cholesterol levels and quercetin ingestion. Quercetin has also been shown to effectively inhibit platelet aggregation in dogs and primates. The main antiplatelet aggregating effect is caused by the reduction of thromboxane A2 [20]. Quercetin inhibits platelet aggregation, mitogen-activated protein kinase phosphorylation, and proliferation and migration of aortic smooth muscle cells. These findings provide new insights and a foundation for quercetin's potential use in the management of cardiovascular diseases in the future.

E. Eye disorders

Free radicals are thought to contribute to the onset of several illnesses, including cataracts and macular degeneration. Through the elimination of these free radicals, quercetin helps to prevent and treat a number of eye conditions. In a research involving 3,072 individuals with indications of macular degeneration, moderate red wine consumption—a source of quercetin—offered modest protection against the onset and progression of the illness [21]. Consuming dark berries helps to stave against macular degeneration [22].

Other medical conditions for which quercetin is used as a treatment include allergies, asthma, hay fever, hives, arthritis, viral infections, osteoporosis, diabetic complications, prostatitis,

neurodegenerative disorders, peptic ulcers, cardiovascular disease, inflammation, injury, and pain; sleep; gastroprotective and oral mucosa effects; metabolic syndrome traits; sport nutrition; antioxidant; hypertension; mood disorders; and infection.

F. Anti-inflammatory

An inflammatory biological response occurs when sections of the human body are subjected to damaging or irritating stimuli. This response aids in self-defense by attempting to eliminate pathogens, damaged cells, or other toxic stimuli while also initiating the healing process. It's not always the case that inflammation equals infection. Most of the time, a virus, bacteria, or fungus causes an infection, whereas the body's attempt to cure itself is what causes inflammation. The modulation of inflammation is one of quercetin's most notable core capabilities. Quercetin reduces pro-inflammatory mediators such as prostaglandins and leukotrienes by inhibiting the inflammatory enzymes lipooxygenase and cyclooxygenase (COX) [23, 24].

Nutrition specialists at Michigan State University explored the influence of dietary flavonoids such as quercetin in their overall roles as systemic anti-inflammatory agents [25]. High levels of C-reactive protein (CRP) have been linked to a number of disease conditions, including lupus, heart

disease, and obesity. This study has shown that eating particular meals can reduce the levels of the inflammatory risk factor (CRP). Quercetin significantly decreased the levels of inflammatory mediators in human hepatocyte-derived cell line, including NO synthase, COX-2, and CRP, in preclinical in vitro investigations [26]. Rats treated with a comparable amount of quercetin (80 mg) had considerable antiarthritic effect against adjuvant-induced arthritis, as well as inhibition of both acute and chronic inflammation [27, 28].

Askari *et al*. studied the effect of 2-month flavonoid quercetin (500 mg) supplementation in healthy male nonprofessional athletes with regular exercise, and the study results showed a significant decrease in the levels of CRP [29]. However, in a pathological condition, quercetin did not show any significant alteration in the levels of CRP in women with rheumatoid arthritis (RA). The study was conducted for 8 weeks, and the RA patients were administered with quercetin 500 mg/day [30]. In addition to that, quercetin having the ability to inhibit xanthine oxidase prevents the accumulation of uric acid, which may help the subjects who are suffering from gout [31].

G. Ulcer and gastritis

According to research, quercetin functions as a gastroprotective agent by preventing the production of stomach acid and lipid

peroxidation in gastric cells. Infection with *Helicobacter pylori* is also inhibited [32]. In rats that were given ethanol to cause gastric mucosal injury, Suzuki *et al.* investigated the antioxidant and antiulcer properties of quercetin at doses of 50 and 100 mg/kg. Their findings indicate that quercetin has excellent anti-ulcer activity. Because quercetin increases the synthesis of stomach mucus or has the ability to scavenge free radicals, it has anti-ulcer qualities [33, 34].

H. Allergies, asthma, hay fever, and hives

Quercetin exerts anti-allergy effects by inhibiting the release of histamine from mast cells and other allergic substance thus acting as a natural antihistamine. Quercetin's ability to prevent allergic effects has tremendous implications for the treatment and prevention of asthma and bronchitis. The cell membranes of mast cells which have been known to be an immune gateway to the brain as well as the environment and emotional stress [35].

CONTRAINDICATIONS AND PRECAUTIONS

Despite the general consensus that quercetin is safe, there are a few cautions and limitations to be aware of:

- At this point, there is insufficient information to tell whether quercetin is safe to use while pregnant or breast feeding. It is advised to stay away from quercetin-containing supplements during these periods.

- Blood-thinning medications: Quercetin may increase the risk of bleeding when used with medications that thin the blood, such as warfarin or aspirin.

- People with renal illness may experience negative effects from quercetin accumulation in their kidneys.

- Quercetin has the ability to increase liver enzyme levels, which may exacerbate liver illness.

- Some people may experience adverse reactions to quercetin, particularly if they have hay fever or are allergic to other flavonoids.

- Medication interactions: Quercetin may have an effect on how certain pharmaceuticals, like antibiotics and chemotherapeutic treatments, are metabolised. If you are taking any drugs, it is advised that you speak with your doctor before using quercetin supplements.

- Reduced blood pressure: Research indicates that quercetin reduces blood pressure. If a person has low blood pressure, they should use caution when taking quercetin supplements.

- Surgery: Quercetin may increase the risk of bleeding both during and after the procedure. It is recommended to stop using quercetin-containing supplements at least two weeks before to surgery.

DRUG INTERACTIONS

Quercetin has been shown to provide a number of health benefits, including

antiviral, anti-inflammatory, and antioxidant properties. The way that one medication interacts with another can affect its effectiveness, metabolism, or absorption.

Quercetin interactions have been reported with the following medications: [36, 37].

- Blood thinners: Quercetin may raise the risk of bleeding when combined with blood thinners such as aspirin, warfarin, or clopidogrel.

- Drugs used in chemotherapy: Combining quercetin with some chemotherapy drugs, such as doxorubicin, vincristine, and etoposide, may cause side effects.

- Antibiotics: Quercetin may reduce the effectiveness and impair the absorption of antibiotics such as norfloxacin and ciprofloxacin.

- Immunosuppressants: Quercetin may change how the body processes drugs that suppress the immune system, such as cyclosporine, which may lessen their efficacy.

- Antidepressants: Quercetin with antidepressants such as fluoxetine and sertraline may have unfavorable interactions.

- By changing how the body absorbs corticosteroid drugs like prednisone, quercetin may reduce their effectiveness.

DOSAGE

People who take doses as low as 150 mg/day had significantly higher plasma quercetin concentrations, suggesting a biological

activity. The most common dosage used in investigations was 1,000 mg/day, usually given in two doses that were evenly spaced apart.

SIDE EFFECT AND TOXICITY DATA

Although quercetin is known to be mutagenic according to the Ames test, most in vivo animal studies indicate that it is non carcinogenic. In 1999, the International Agency for Research on Cancer (IARC) determined that quercetin was not carcinogenic to humans [38, 39].

However, studies conducted in vitro suggest that quercetin may offer protection against harmful substances as well as potentially adverse effects on embryonic development. Quercetin's potential teratogenic effects on embryonic development are not supported by any solid data [40]. In mice lacking in DNA repair, prenatal exposure to quercetin led to a slight increase in the incidence of cancers in the offspring [41].

Rats fed more than 314 mg and 157 mg of quercetin/kg body weight/day, respectively, exhibited significantly greater liver and kidney weight ratios to body weight over the course of a four-week study. At doses higher than 157 mg quercetin/kg body weight/day, a prooxidant impact was also observed [42].

In human trials, quercetin has generally been well tolerated. Blood tests evaluating liver and kidney function have not shown any harmful effects from haematology, serum

electrolytes, or dosages up to 1,000 mg/day over several months.

Given the lethal outcomes that this combination produced in a single pig study, the co-administration of high quercetin dosages along with digoxin is currently the most dangerous scenario. For those on digoxin, it is probably preferable to stay away from quercetin until further information about acceptable dosage ranges becomes available [43].

ADVERSE DRUG REACTION

Quercetin is typically considered safe when consumed in moderation from food sources, but consuming excessive amounts of quercetin in supplements may have unfavorable effects.

Many adverse drug reactions have been connected to supplemental quercetin, including: [44, 45, 46, 47].

- Digestive distress: Excessive doses of quercetin may cause upset stomach, vomiting, diarrhoea, and nausea.
- Headaches: People who take supplements containing quercetin sometimes report having headaches.
- Quercetin allergy reactions are possible in certain people, particularly in those who are allergic to other plant compounds or have a history of allergies.
- Quercetin-containing supplements may increase the risk of bleeding and interact with a number of medications, including blood thinners.

- Kidney risk: Excessive supplementation with quercetin may, in rare cases, result in renal damage.

CONCLUSION

Several plant-based foods, including fruits, vegetables, and grains, contain the flavonoid quercetin. It has been investigated for its potential to have anti-inflammatory, immune-modulating, and antioxidant properties. It has also been demonstrated to have potential antiviral, anticancer, and neuroprotective effects. Although the data for quercetin is encouraging, additional research is required to ascertain its efficacy and safety in treating or preventing a variety of illnesses. Quercetin may interfere with several medications, according to some research, and there isn't much data on how safe it is over the long run. More research is necessary to ascertain whether quercetin is safe and effective for treating or preventing a variety of disorders, even though the evidence for it is encouraging. There is also a lack of information regarding quercetin's long-term safety, and some studies indicate that it may interact with other medications.

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