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**Review Article**

# QUERCETIN- A FLAVANOID

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**Abstract** Quercetin is the most abundant form of the flavonoids. It gain attention when quercetin was found to cause DNA mutations which can then contribute to cancer treatment. Quercitrin is present in the bark of Quercus tinctoria (American Oak). It is generally available in natural sources. In this article we have tried to simplify the basic understanding of quercetin, its synthesis, structure activity relationship, chemical reaction etc. It will help students to understand basic concept and chemistry of quercetin.

*Keywords:* Quercetin, flavones, flavonols, synthesis

## Introduction

Flavonoids occur either as free molecules or as glycosides. They have widespread occurrence in plant kingdom. They occur in families like compositae, leguminoceae, polygonaceae, rutaceae etc. contain a large number of flavonoids. Flavonoids have been reported in some green algae also. Chemically, flavonoids show a fifteen-carbon skeleton. Most of the flavonoids have a carbonyl function situated at one end of the bridge. Quercetin is the most abundant of the flavonoids. Plants containing various flavonoids have a long history of use in traditional medicines in many cultures, but the flavonoids themselves were not discovered until the 1930's. Quercetin first gained attention several decades ago when it was found to cause DNA mutations in bacteria, a possible sign that it might actually contribute to causing cancer.

Quercetin is 2-3,4-dihydroxyphenyl)-trihydroxy-4H-chromen-4-one with molecular weight of 302.24 and melting point of 316°C.(Fig.1) The common names of quercetin are quercetine, sophretin, meletin.[1]It occurs as the glycoside Quercitrin in the bark of Quercus tinctoria (American Oak). Good sources include apples, onions, teas, nuts, and red wines.it is also found in leafy vegetables, berries, cauliflower, cabbage and in herbs such as ginkgo and St. John's Wort.[2, 3]

Quercitrin appears to be the most widely distributed natural pigment. Quercitrin belongs to a group of plant pigments called Flavonoids, more specific, a Flavonol. Largely responsible for the colours of many fruits, flowers and vegetables.

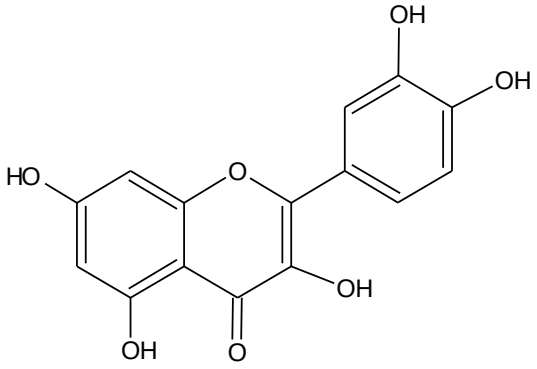


**Fig 1: Structure of Quercetin**

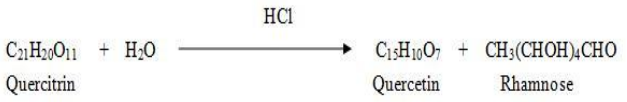


**Fig 2: Hydrolysis of Quercitrin**

Quercetin is also a building block for other flavonoids. Quercetin occurs in food as an aglycone. On hydrolysis with acid, quercitrin forms quercetin and one molecule of rhamnose.[4] (Fig.2) Quercetin belongs to the family of flavonoids and consists of 3 rings and 5 hydroxyl groups.[5] It is available in higher amounts in dietary supplements, usually in capsules or tablets ranging in doses from 50 milligrams (mg) to 500mg. There is no recommended standard dose for quercetin.

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## Isolation of Flavones and Flavonols

Plant material containing flavones or flavonol is extracted with boiling water and the tannins are removed as lead salts by means of lead acetate. Filtrate is diluted with water, acidified with hydrochloric acid and boiled for some hours when the sugar-free flavones or flavonols are precipitated.[1]They are crystalline compounds and soluble in water, dilute mineral acids, alcohol, alkalies etc. They give red brown colour with ferric chloride. Highly coloured in acidic medium than in bases, which contribute the colour, but this oxonium salt is unstable and is hydrolysed back to free State.

## Basic Structure of Flavones and Flavonols

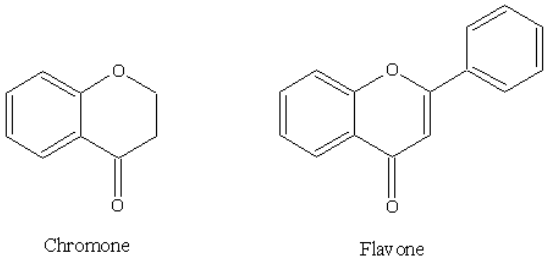


**Fig 3: Structure of Flavone**

Flavones also known as anthoxanthins, are yellow pigments which occur in the plant kingdom. They occur naturally in the free state, or as glycosides (the aglycon is the anthoxanthidin and the sugar is glucose, etc.). Flavones are hydroxylated derivatives of flavones (2-phenyl-4-chromone) which may be partially alkylated.(Fig.3) In almost all cases, positions 5 and 7 are hydroxylated, and frequently one or more of positions 3', 4' and 5'. Positions 5, 7 and 4' are generally unmethylated, but 3' and 5' are often methylated.[4]

## Chemistry of Quercetin

The molecular formula is $C_{15}H_{10}O_7$. It was found to contain five hydroxyl groups as it forms penta-acetyl and pentamethyl derivatives. It has no methoxyl group. On fusion with KOH, it gives phloroglucinol and protocatechuic acid indicating that Quercetin is 5,7,3',4',-tetrahydoxyflavonol or 3,5,7,3',4',-pentahydroxyflavone, I. (Fig.4) The structure I for quercetin is further proved by the fact that on boiling with alcoholic potash pentamethylquercetin gives 6-hydroxy-ω,2,4-trimethoxy acetophenone II and veratric acid III. (Fig.5) These results suggest that quercetin is 3,3',4',5,7-pentahydroxyflavone.[1] Finally, the structure for quercetin is proved by its synthesis. It can be synthesized by two methods, Kostanecki's Synthesis,[1] 2,4-dimethoxy-6-hydroxyacetophenone is condensed with 3,4-dimethoxybenzaldehyde in presence of NaOH.(Fig.6) The other method is Robinson et al. Synthesis.[4] It is a general method of synthesis for flavonols. ω-methoxyphloroacetophenone is condensed with veratric anhydride in the presence of the potassium salt of 3,4-dimethoxybenzoic acid (veratric acid).(Fig.7) The biogenetic relationship between flavonoids anthocyanidins and is explained in Fig.8

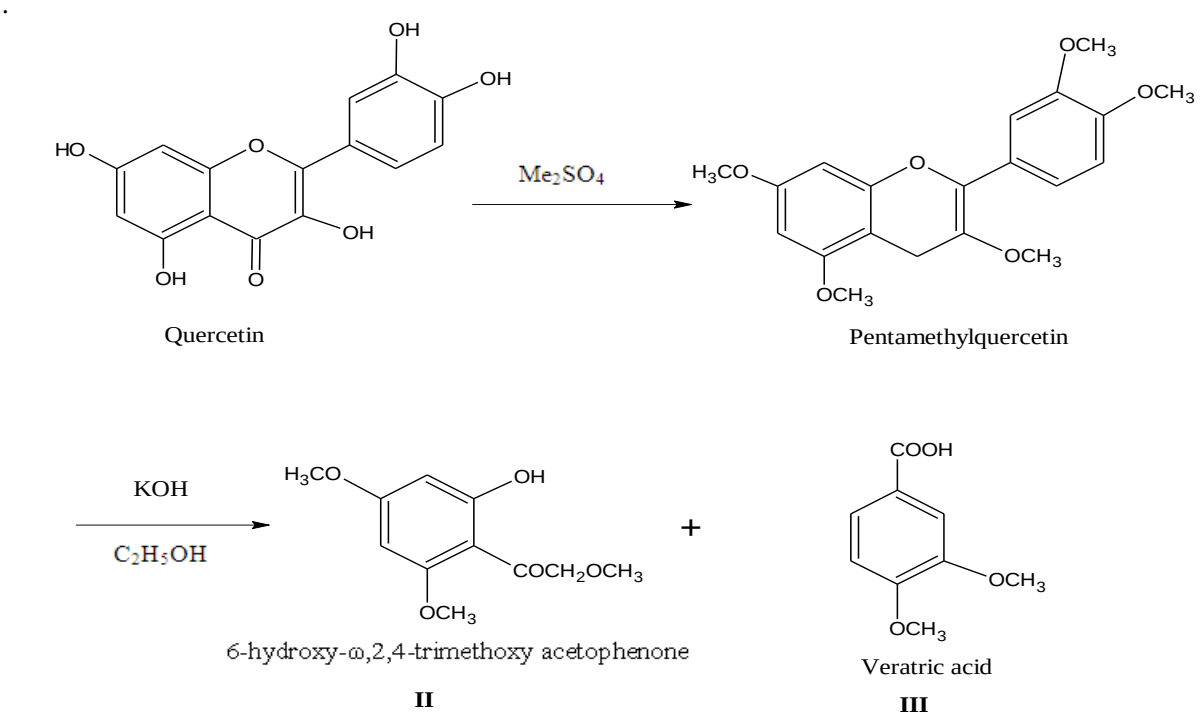


**Fig 5: Structural proves of quercetin**

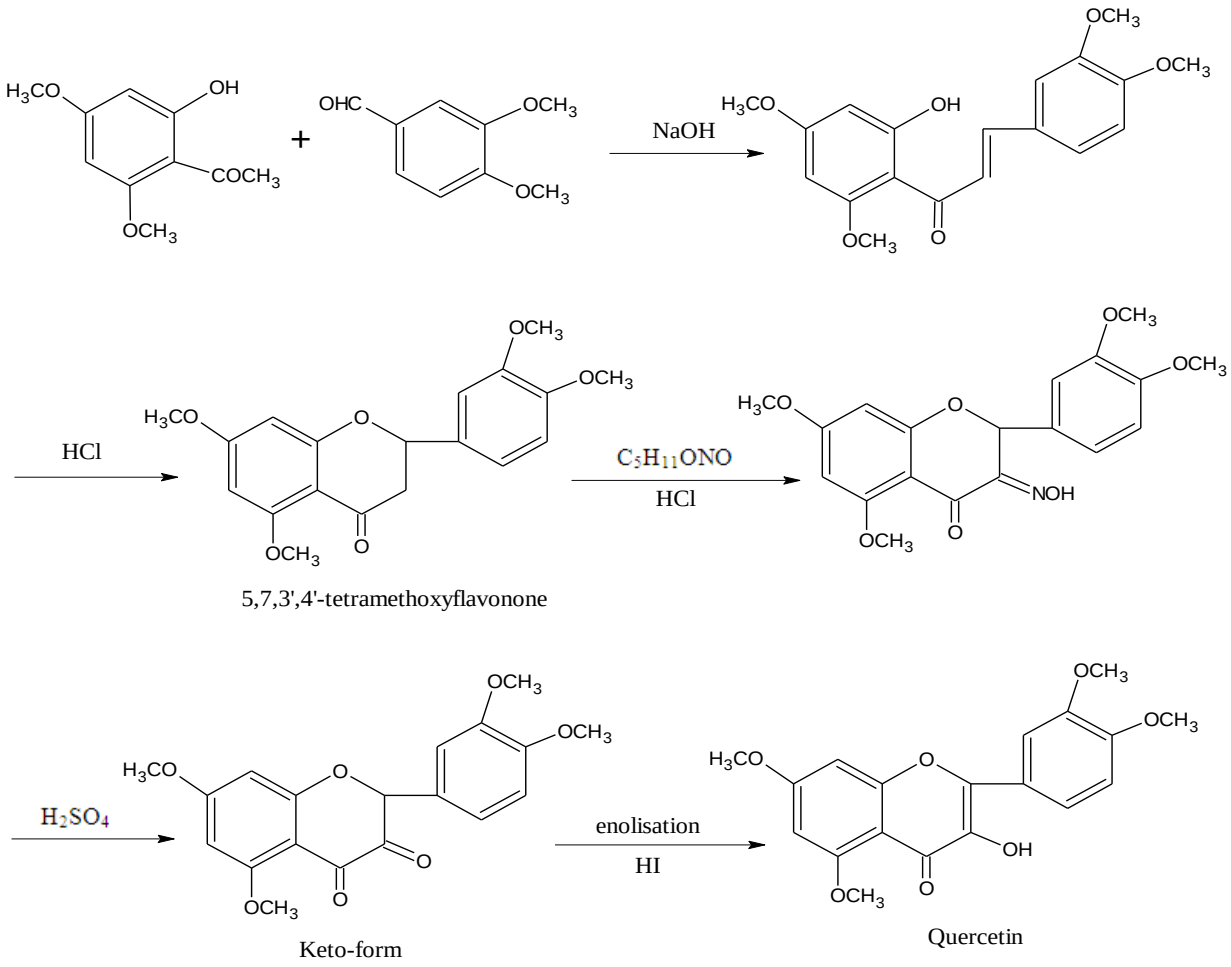


**Fig 6: Kostanecki's Synthesis**

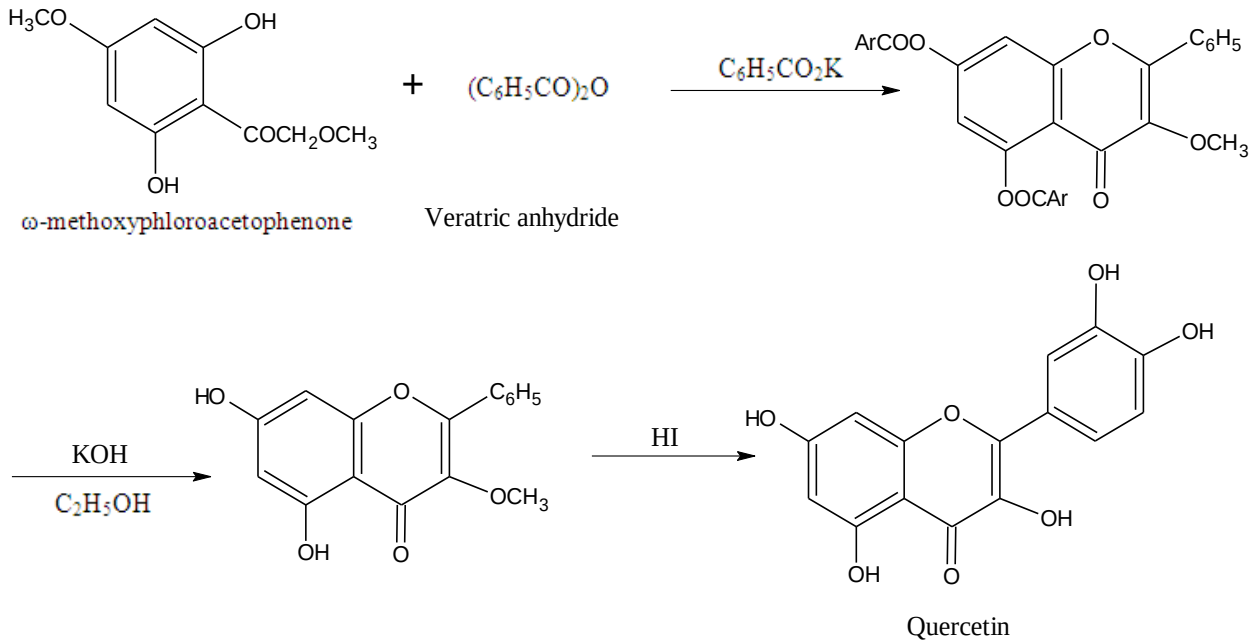


**Fig 7: Robinson et al. Synthesis**

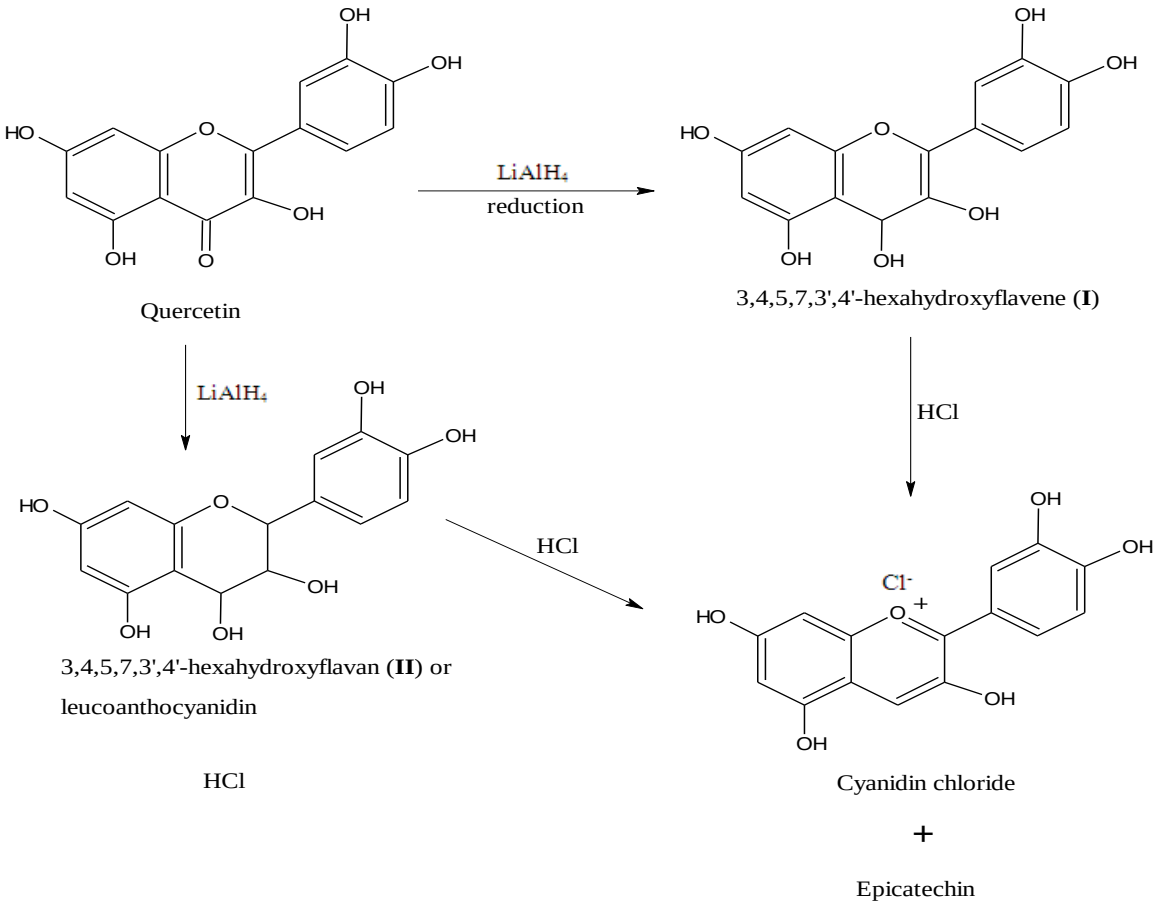


**Fig 8: The biogenetic relationship between flavonoids, anthocyanidins and catechins**

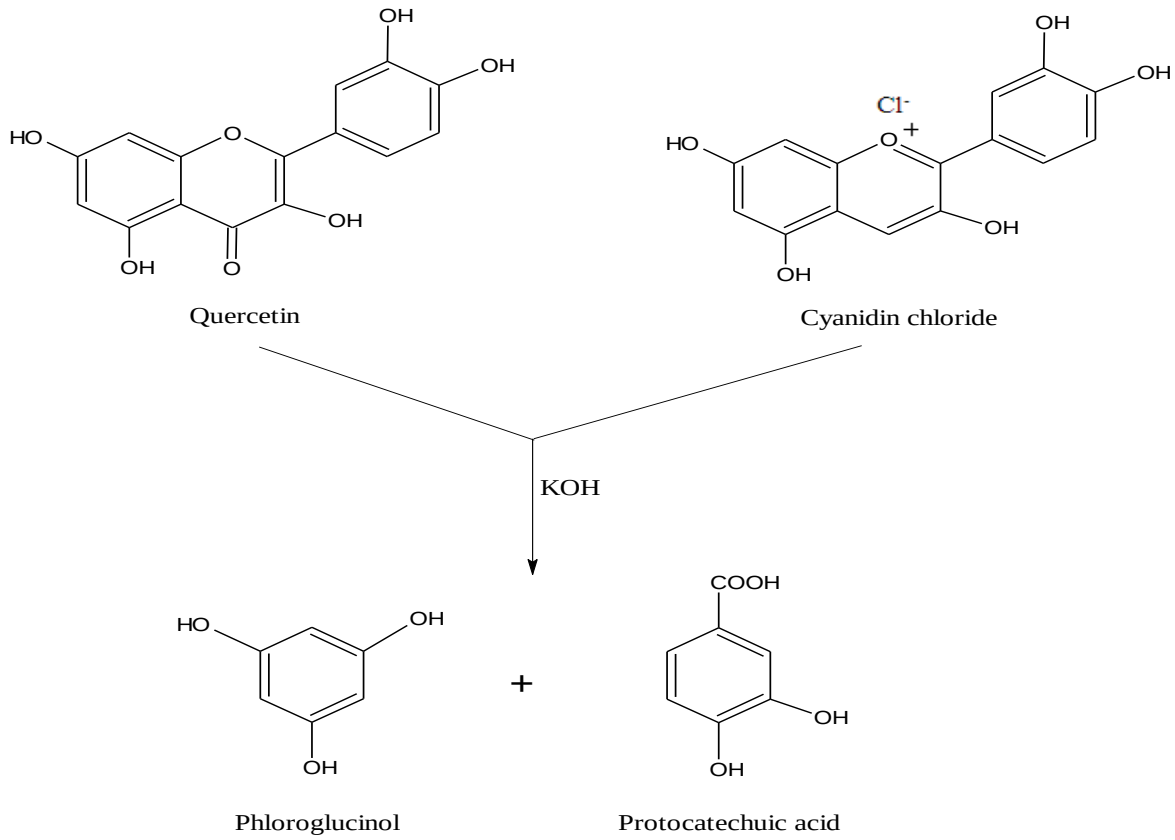


**Fig 9: Structural Relationship between Flavonoids (Quercetin), Anthocyanidins and Catechins- On fusion with alkali**

## Identification test for Flavonoids

***Test 1:***
Prepare an aqueous filtrate of powdered drug, and take a portion of filtrate in a test tube, add 5ml of dilute ammonia followed by addition of few drops of concentrated sulfuric acid. A yellow coloration confirms the presence of flavonoid. Upon further standing, the yellow coloration disappears.

***Test 2:***
Take a small amount of powdered drug in a test tube, add 10 ml ethyl acetate and heat it over a steam bath for 3 minutes then filter the mixture, take 4 ml of the filtrate with 1ml of dilute ammonia solution. Observe the formation of yellow coloration. It is the indication of flavonoid compounds present in the drug.

## Structural Relationship between Flavonoids (Quercetin), Anthocyanidins and Catechins:

1. On fusion with alkali, they give the same products, viz., phloroglucinol and protocatechuic acid in the following manner. (Fig.9)
2. Quercetin on reduction with lithium aluminium hydride followed by treatment with HCl produces cyaniding (Anthocyanidin) which on catalytic reduction gives epicatechin (catechin). (Fig.10)

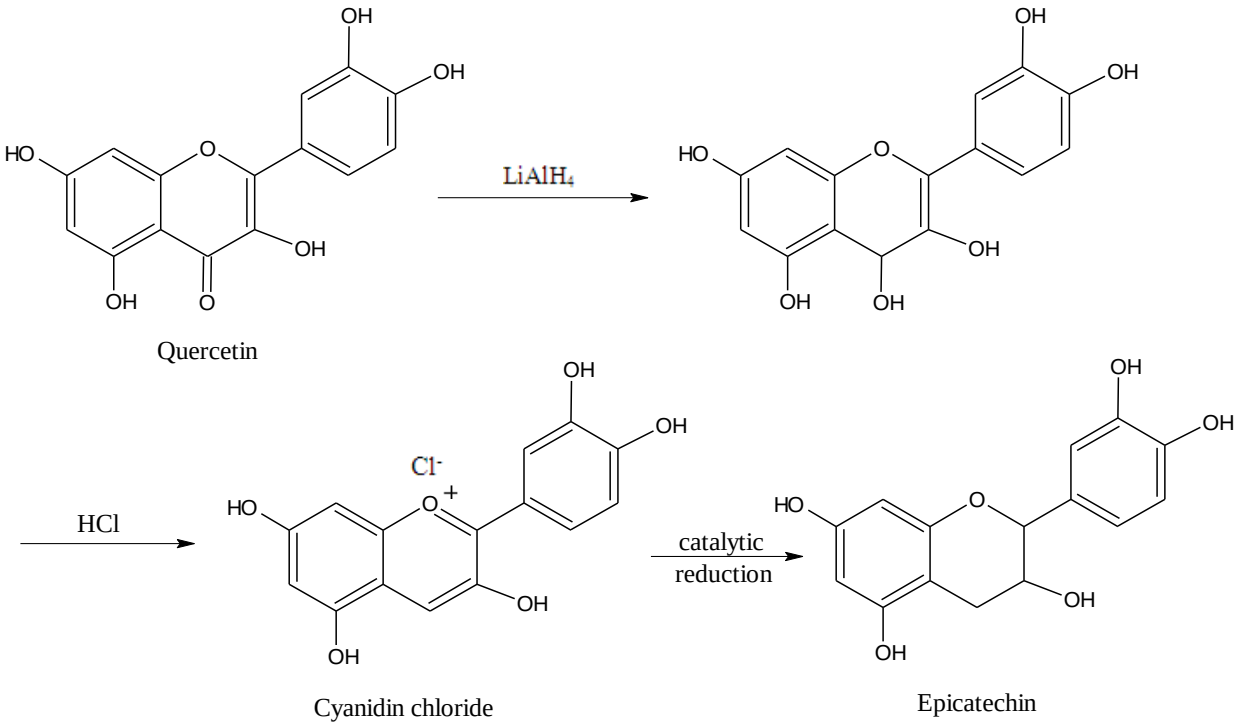


**Fig 10: Structural Relationship between Flavonoids (Quercetin), Anthocyanidins and Catechins on reduction with lithium aluminium hydride**

## Uses of Qurcetin

***Anti-Inflammatory:*** Quercetin has demonstrated significant anti-inflammatory activity because of the direct inhibition of several initial processes of inflammation. It inhibits both the production and release of histamine and other allergic/inflammatory mediators.

***Asthma and Arthritis:*** Quercetin's antihistaminic action may help to relieve both allergic and asthma symptoms. The anti-inflammatory properties may help to reduce pain from disorders such as arthritis. The anti-inflammatory action of quercetin is caused by the inhibition of enzymes, such as lipoxygenase and cyclooxygenase, and the inhibition of inflammatory mediators, including leukotrienes and prostaglandins.[6] Quercetin also inhibits the release of histamine, which causes congestion, by basophils and mast cells. Studies have shown an improved lung function and lower risk of certain respiratory diseases (asthma and bronchitis) for people with high apple (rich in quercetin) intake.

***Anti-Viral Activity:*** Quercetin exerts antiviral activity against reverse transcriptase of HIV and other retroviruses, and was shown to reduce the infectivity and cellular replication of Herpes simplex virus etc.

***Prostate Health:*** Men who are concerned about prostate problems would also benefit from quercetin[3]. In addition, preliminary laboratory studies indicate that quercetin may inhibit the growth of prostate cancer cells in test tubes. How this will ultimately translate to prevention or treatment of prostate cancer in men is unknown at this time.[7]

***Anti-Oxidant Activity:*** It exerts potent anti-oxidant activity and vitamin-C sparing action.[8] It will help to combat free radicals molecules, which can damage cells.

***High Cholesterol:*** Quercetin prevents the oxidation of LDL (bad) cholesterol. Red wine or orange juice may lower cholesterol levels.

***Platelet Aggregation:*** quercetin has inhibitory properties of blood platelet aggregation (clumping). [9]

***Eye Disorders:*** Free radicals are thought to contribute to the development of certain eye disorders including cataracts and macular degeneration (a disorder that leads to lens damage and possibly blindness). Flavonoids, such as quercetin, neutralize free radicals and may play a role in the prevention and/or treatment of these eye conditions. Quercetin is a strong inhibitor of human lens aldose reductase. [6]

***Fibromyalgia:*** People with fibromyalgia who switched from a typical western diet to a vegan diet high in flavonoids such as quercetin experienced improvement in their symptoms. [7]

***Cancer:*** Quercetin and other flavonoids from fruits and vegetables have long been considered important substances to possibly help prevent cancer. Studies done in cell cultures in the lab have shown that quercetin has activity against some types of cancer cells. Recent studies suggest that quercetin can slow the growth of cancer cells and can help foster apoptosis, a form of natural cell death that doesn't happen in most cancer cells. Some studies in animals have shown that quercetin may help protect against certain cancers, particularly colon cancer. [2]

***Heart Disease:*** Quercetin has many health promoting effects, including improvement of cardiovascular health, reducing risk for cancer.

***Canker Sores:*** Quercetin may reduce the frequency of mouth sores and produce mild symptomatic relief. [7]

***Skin Treatment:*** Quercetin is also an effective treatment for inflammatory conditions that affect the skin. It increases the production of both collagen and fibronectin, two substances necessary to keep the joints and skin healthy. This makes quercetin helpful to both arthritis sufferers and those wishing to treat or prevent wrinkles. Quercetin is an active ingredient in more and more cosmetic products that claim to help diminish signs of aging. Quercetin may also help speed wound healing; studies have also shown that quercetin helps repair damage to nerve tissues in skin wounds. [10]

***Others:*** Quercetin also seems to reduce the production of uric acid, by inhibiting the xanthine oxidase, thereby easing gout symptoms. Quercetin may also help reduce symptoms like fatigue, depression and anxiety. [3] Quercetin shows anti-tumor activity.

## Side Effects

Quercetin is contraindicated with antibiotics; it may interact with fluoroquinolones (a type of medicinal antibiotic), as quercetin competitively binds to bacterial DNA gyrase. Whether this inhibits or enhances the effect of fluoroquinolones is not entirely clear.[11]
Quercetin is also a potent inhibitor of CYP3A4, an enzyme that breaks down most drugs in the body. As such, quercetin would be expected to increase serum levels, and therefore effects, of drugs metabolized by this enzyme.
Drug Interaction The bioavailibility of diltiazem in the rabbits pretreated with quercetin is increased significantly[12].
Quercetin has been shown to cause chromosomal mutations in certain bacteria in test tube studies.[13] Although the significance of this finding for humans is not clear, some doctors are concerned about the possibility that birth defects could occur in the offspring of people supplementing with quercetin at the time of conception or during pregnancy.[14]

## Quercetin Products

***Quercetin Bromelain:*** Bromelain is an enzyme complex derived from the pineapple stem. Bromelain may assist the absorption of quercetin in the G.I.tract. Quercetin and Bromelain both have inhibitory properties of blood platelet aggregation.[12]

***Activated Quercetin:*** It is a blend of quercetin, magnesium ascorbate, and bromelain.[12]

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