REVIEW

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# FLAVONOIDS AS BIOACTIVE COMPOUNDS: A SYSTEMATIC REVIEW

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**ABSTRACT**

In recent years, a high concentration has been paid on natural sources for the isolation of different secondary metabolites. Flavonoids are one such compound which are produced in several plant species with a strong therapeutic potential. Flavonoids are a naturally occurring organic compound which is biosynthesized in different parts of the plant such as fruits, vegetables, leaves, bark, roots etc. Some flavonoids are also known to impart the coloured pigmentation in fruits and flowers of higher plants (Anthocyanins). Their myriad health benefits, including anti-inflammatory, antiviral, cardio-protective, and anti-cancer properties, are seen in both human and animal bodies. They are highly used in the food, cosmeceutical, nutraceutical and pharmaceutical industries. However, the incorporation of flavonoids in pharmaceuticals requires highly pure and high-quality extraction methods. Numerous sustainable and high-yield flavonoid extraction techniques have been developed. This article provides a systematic review on sources, properties, classification, biosynthesis, identification of flavonoids and its application in enhancing the human health.

**KEYWORDS:** Flavonoids, Bioactive, Natural product, Properties, Biosynthesis, Application.

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## INTRODUCTION

Flavonoids are an important category of secondary metabolites which possesses the polyphenolic structure and are widely found in plant source. They are tremendously used in the food, cosmetics, nutraceutical and pharmaceutical industries. Flavonoids are compounds, known to be synthesised at specific locations in plants and are in charge of giving flowers their colour and scent [1]. Plants usually contain flavonoids in the form of glycosides bonded to sugar, and a single plant may have many glycosidic combinations of flavonoids. Due to this, it is usually preferable to focus on the aglycones found in hydrolysed plant extracts when analysing flavonoids rather than the potential complexity of glycosides found in the original extract.

Flavonoids are hydroxylated polyphenols having at least one aromatic hydroxyl group attached and two or more aromatic rings joined by heterocyclic pyran. The basic structure of flavonoid comprises a C15 carbon skeleton (C6-C3-C6) with two benzene rings [2]. These substances have a wide range of positive effects on human health due to their bioactive qualities, which include anti-inflammatory, anti-cancer, anti-aging, cardio-protective, neuroprotective, immunomodulatory, antidiabetic, antibacterial, antiparasitic, and antiviral effects [3]. The pigmentation in plants is attributed by different flavonoids as shown in Table 1 [4].

**Table: 1. Flavonoid compound and their pigmentation in plants.**

| Flavonoid Compound | Pigmentation in Plants |
|---|---|
| Anthocyanins | Red, Orange, Blue, Purple |
| Chalcones & Aurones | Yellow |
| Flavanols & Flavones | White, Pale Yellow |

Flavonoids are extensively used in daily life as food, dye and medicine. For example, Proanthocyanidin, an edible pigment enhances the taste in food and wine and it also has anti-inflammatory property that may help prevent cancer. The plant flavonoids may be administered to strengthen the activity of nervous, immune and reproductive system. They are often called as bioflavonoids [5,6].

### Occurrence and distribution

Flavonoids are widely distributed in plant kingdom, largely in vascular plants. The fruits, flowers, leaves, vegetables, roots, bark are found to be the major part of the plants to synthesize flavonoids. They act as growth enhancer and a defence against plaques in vegetables [7]. Table 2 shows some edible plant species containing flavonoids mainly quercetin, kaempferol, isorhamnetin, apigenin and luteolin [8].

**Table 2: Edible plant species containing flavonoid.**

| Common Name | Scientific Name | Parts |
|---|---|---|
| Amaranthus | *Amaranthus mangostanus* | Shoot |
| Amaranthus (Red) | *Amaranthus cruentus* | Shoot |
| Bamboo shoots | *Dendrocalamus latifloxus* | Root |
| Beet root | *Beta vulgaris* | Root |
| Cabbage | *Brassica oleracea* | Leaf |
| Coriander | *Coriandrum sativum* | Shoot |
| Tulsi/Basil | *Ocimum basilicum* | Shoot |
| Cucumber | *Momordica cochinchinensis* | Fruit / Shoot |
| Drumstick | *Moringa oleifera* | Leaf |
| Garden Chrysanthemum | *Glebionis coronaria* | Shoot |
| Lettuce | *Lactuca sativa* | Leaf |
| Nasturtium | *Tropaeolum majus* | Flower |
| Pumpkin / Water squash | *Cucurbita maxima* | Shoot/Bud/Fruit |
| Red pepper | *Capsicum annuum* | Shoot |
| Rosemary | *Rosmarinus officinalis* | Shoot |
| Sesame | *Sesamum indicum* | Shoot |
| Spider plant | *Cleome gynandra* | Shoot |
| Spinach (green stem) | *Spinacia oleracea* | Shoot |

| | | |
|---|---|---|
| Sweet potato | *Ipomoea batatas* | Shoot |
| Tomato | *Solanum esculentum* | Fruit |
| Vegetable Soybean | *Glycine max* | Seed |
| Water cress | *Nasturtium officinale* | Shoot |
| Water mint | *Mentha aquatica* | Shoot |
| Wild Turmeric | *Curcuma aromatica* | Stem |

*Figure 1. Edible flavonoid containing plants*

**Properties of flavonoids**

**General properties**

- They are non- nitrogenous universal plant pigment.
- They are biosynthesized by phenylpropanoid pathway, against microbial infection in plants.
- They are the largest group of naturally occurring polyphenols.
- They are mostly yellow in colour.
- Widely distributed in vascular plants.
- Intensity of yellow colour depends upon the number of hydroxyl groups.
- Free flavonoids are soluble in ethanol, methanol, ethyl acetate, chloroform and other organic solvents.

**Physical Properties**

- Flavonoids are low molecular weight secondary metabolites.
- Most of them are crystalline solid except flavone glycosides (amorphous). Example: apigenin in chamomile.
- They are optically active.
- They are mainly water soluble.
- They can change their colour when treated with base or ammonia.
- Anthocyanins are intensely coloured water-soluble pigments.

**Chemical Properties:**

- It is a phenolic compound consisting of $C_6$-$C_3$-$C_6$ carbon skeleton together with a heterocyclic benzopyran ring.
- They are structurally derived from flavone as shown in Figure 1.
- They occur in glycosidic combination.
- Most flavonoids are acidic in nature due to presence of phenolic hydroxyl groups [9-11].

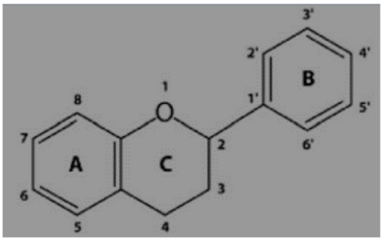


*Figure 2. Structure of Flavonoid*

**Classification [1, 12-14]**

Flavonoids are among many phenolic plant components in which the carbon atoms are arranged in two benzene rings, generally referred to as A and B, which are joined by a pyrene ring (C) that contains an oxygen. Depending upon the attachment of B ring in the carbon of C ring, flavonoids can be categorised into different sub groups such as isoflavones, flavones, flavonols, flavanones, flavanonols, catechin, anthocyanins and chalcones.

**1. Isoflavones**

They are an important class of flavonoids. Legumes, particularly soy, are the principal source of isoflavones. Other legumes such as split peas,

chickpeas, black beans, lima beans, sunflower seeds, clover sprouts, and green split peas have been reported to contain isoflavones. In isoflavone, the B ring is attached to carbon 3 of C ring such as in the structure of Genistein and Daidzein (major isoflavones in human diet) as shown in the Figure 2.a & 2.b. These compounds have the promising effect in prevention of breast cancer and cardiovascular disorders. Cassidy A. et al has found that the soy isoflavone influences the hormonal status in women and helps regulation of menstrual cycle.

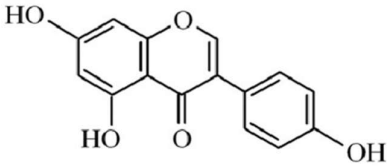

*Figure 2.a. Genistein*

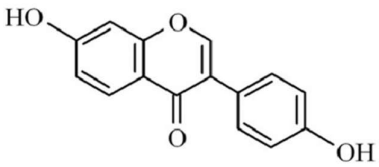

*Figure 2.b. Daidzein*

**2. Flavones**

These are one of the important sub groups of flavonoids mainly found in the flowers, fruits, leaves of various plant species such as ginkgo biloba, mint, celery, chamomile etc. They have a double bond between position 2 and 3 and a ketone group in position 4 of C ring Figure 3. luteolin, apigenin, tangeretin, nobiletin are major flavones. It has been reported that the apigenin possess antibacterial, anticancer, anti-inflammatory, antispasmodic and antioxidant effects. The luteolin enriched plants are used in Chinese system of medicine for prevention and treatment of hypertension, cancer, inflammatory disease. The induction of apoptosis, DNA damage, redox modulation, protein kinases, prevention of cell metastasis, proliferation, and angiogenesis are all associated with its anticancer activities.

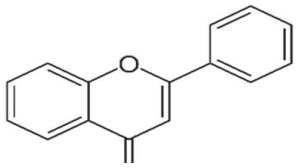

*Figure 3. Structure of Flavone*

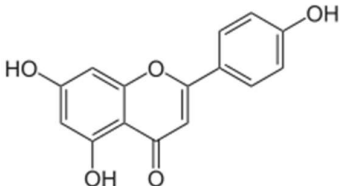

*Figure 3.a Apigenin*

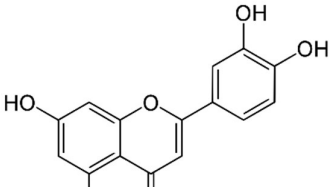

*Figure 3.b Luteolin*

**3. Flavonols**

Flavonols are widely distributed in leaves and petals of higher plants as pigments. They occur frequently in combination with glycosides. Kaempferol, quercetin, myricetin are common flavonols. They have a hydroxyl group in position 3 of the C ring. The onion. Kale, tomatoes, apples berries are the fruits enriched with flavonols. The pictures of common flavonols are presented below in Figure 4. These compound shows plentiful health benefits. The intake of flavonols leads to reduce risk of cardiovascular disease.

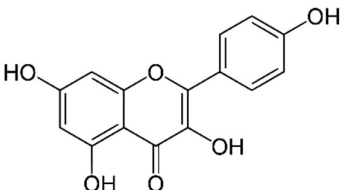

*Figure 4. Kaempferol*

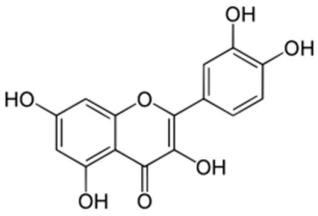

*Figure 4.a Quercetin*

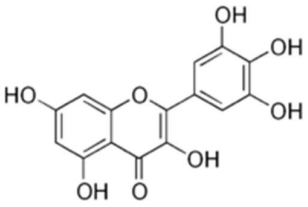

*Figure 4.b Myricetin*

**4. Flavanones**

Another significant class of flavonoids is flavanones, which are found practically in all citrus fruits, including lemons, oranges, grapes, and members of the plant families *Leguminosae*, *Rutaceae*, and *Compositae*. The flavonones in citrus peels give them their bitter flavour. They are also referred to as dihydroflavones, that has the saturated C ring. [15]. The naturally occurring flavanones are optically active and they are linked to sugars in the form of 7-O- glycosides. The double bond in position 2 and 3 of C ring is saturated which makes the structural difference between the flavanones and flavones. Naringenin (5,7,4'- trihydroxy flavanone) and Hesperitin (4' – methoxy- 5,7,3'-trihydroxyflavanone) are two commonly known flavanones. Naringenin supplementation at a nutritionally relevant level was shown in the experiments to reduce atherosclerosis in mice fed with high-fat, high-cholesterol diet [16]. The other potential pharmacological activity of flavanone includes anticancer, antiviral and anti-inflammatory [12].

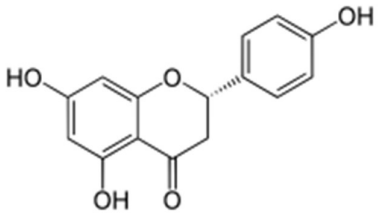


*Figure 5.a Naringenin*

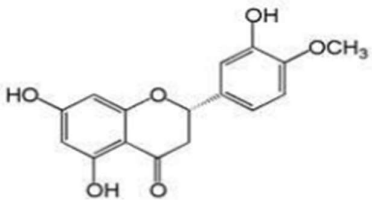


*Figure 5.b Hesperitin*

**5. Flavanonols**

The flavanonols are the most abundant subclass of flavonoid, and are commonly known as flavanols, flavan-3-ols or catechin. So far, common foods such as cereals, legumes, fruits, vegetables, hops, beers, red wine, tea, chocolate, grapes, and apples have been found to contain flavanols. It is confirmed that the flavanols or catechins are the main phenolic constituents of tea leaves. For instance, the catechin level of Darjeeling black tea exceeds 10% [17]. The primary structural distinction of flavanols from other flavonoids is the lack of a C4 carbonyl in ring C and a double bond between C2 and C3.

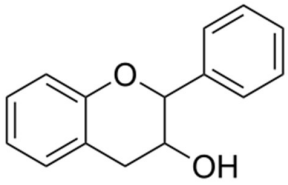


*Figure 6. Flavanonols*

**6. Anthocyanins**

Anthocyanins are phenolic compound that imparts red, blue and purple pigments in plants specially to tubers, flowers and fruits. These are water soluble pigments found mostly in the form of glycoside. It is a derivative of flavonol and has the basic structure of flavylium ion. The basic structure of anthocyanin is shown in figure 7 [18].

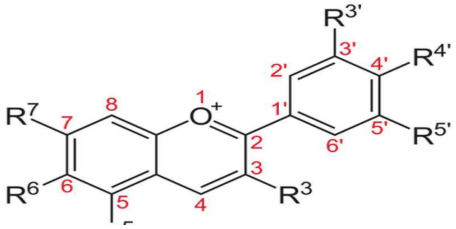


*Figure 7. Basic structure of anthocyanin*

### 7. Chalcones

Chalcones are polyphenolic flavonoid compound derived from plant source. Chalcones are typically α, β-unsaturated ketones made up of a three-carbon alkenone unit connecting two aromatic rings (rings A and B). Figure 8 shows the general structure of Chalcone [19]. Licochalcone A, licochalcone D, and morachalcone A are among the several chalcone chemicals that are reported to be present in plants [20]. Production of these substances is carried out by the type III polyketide synthase enzyme chalcone synthase. All the vascular plants and a number of non-vascular plants contain this enzyme. It has been demonstrated that chalcone derivatives have a number of bioactivities, such as anti-inflammatory, antifungal, antimalarial, and antituberculosis properties. Additionally, chalcones have significant capacity for radical scavenging [19].

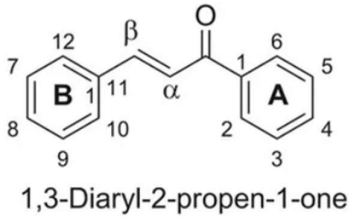


*Figure 8. General structure of Chalcone*

**Biosynthesis of flavonoids**

Flavonoids are the broad class of naturally occurring chemical compounds found mainly in the seeds, roots, bark, flowers, leaves and fruits of the plants. They have been shown to support UV protection and floral colour in plants [21]. The diverse plant species used the shikimic acid and phenylpropanoid pathways to synthesize the various types of flavonoids.

***Shikimic acid pathway***

The shikimic acid pathway plays a crucial role in biosynthesis of flavonoids and involves several enzymes such as DAHP Synthase (first enzyme in this pathway), 3- Dehydroquinate synthase, 3-Dehydroquinate dehydratase, Shikimate dehydrogenase, Shikimate kinase, EPSP Synthase and Chorismate synthase [22].

This pathway starts with the aldol condensation of phosphor-enol pyruvate and D-erythrose-4-phosphate to produce 3-deoxy-D-arabino-heptulosonate −7-phosphate (DAHP) in the presence of enzyme DAHP synthase. In the presence of DHQ synthase enzymes, the intramolecular cyclisation reaction converts the DAHP to 3-dehydroquinic acid (DHQ). The DHQ converts into 3-dehydroshikimic acid (DHS) by losing a water molecule [23]. Further, 3-dehydroshikimic acid is transformed into Shikimic acid in the presence of shikimate dehydrogenase enzyme. The formation of shikimic acid leads to the biosynthesis of Phenylalanine with various enzymatic activity in between as shown in figure 9.

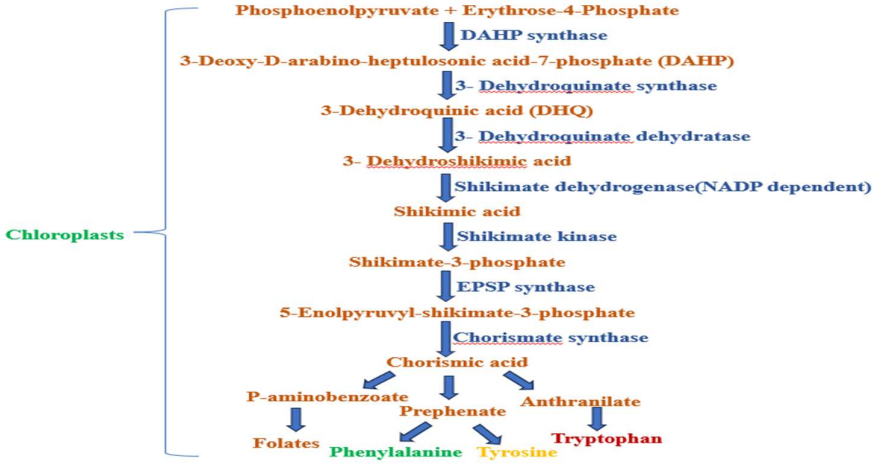


*Figure 9. Shikimic acid pathway in biosynthesis of flavonoid*

***Phenylpropanoid pathway***

The shikimic acid pathway plays a crucial role in flavonoid biosynthesis by providing an important amino acid phenylalanine. The phenylalanine ammonia lyase enzyme is the first enzyme involved in phenylpropanoid pathway. By using amino acid phenylalanine, the plant produces 4-coumaroyl-CoA, which can be coupled with malonyl-CoA to produce chalcones, a class of molecules having two phenyl rings that constitute the real backbone of flavonoids [24]. The phenylpropanoid pathway for biosynthesis of flavonoid is summarised in figure 10.

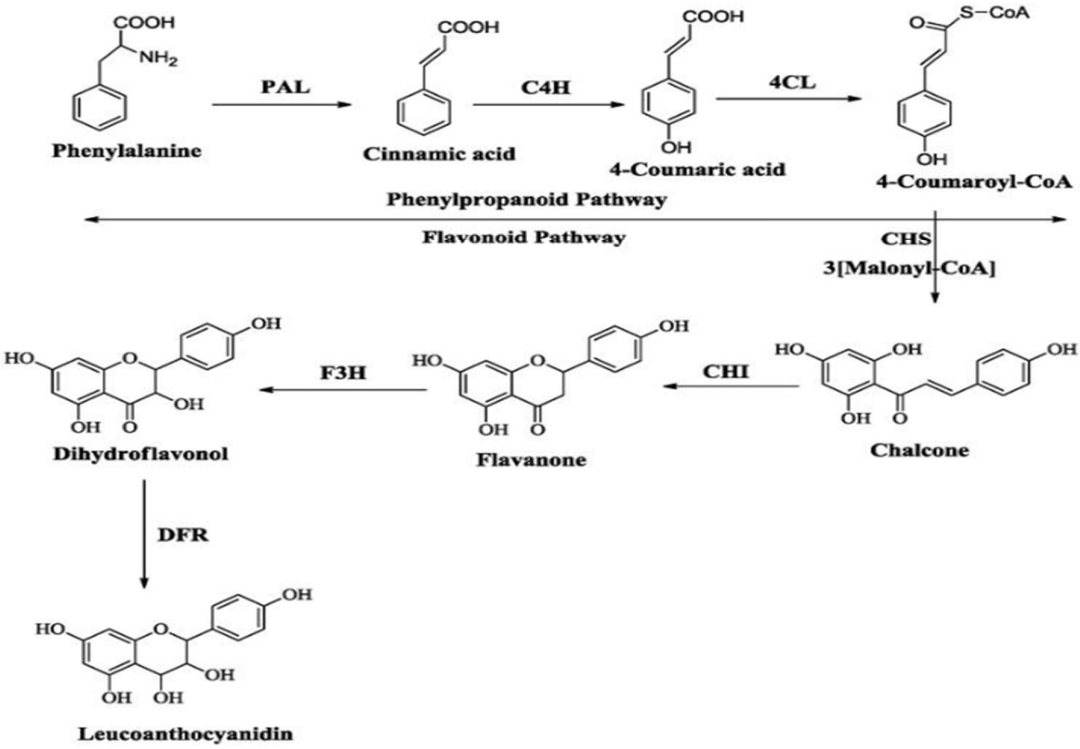


*Figure 10. Phenylpropanoid pathway for biosynthesis of flavonoid*

**Medical application of flavonoids**

1. **Anticancer:** About 9.6 million fatalities worldwide are attributed to cancer, making it a serious health issue and a leading cause of mortality. Research has shown that flavonoids can stop the growth of tumour cells by preventing the production of reactive oxygen species (ROS) and suppressing the enzymes xanthine oxidase, cyclooxygenase-2, and 5-lipoxygenase, all of which are crucial for the emergence and development of tumours [25].

2. **Antioxidant:** Reactive Oxygen Species are produced in the human body both endogenously and exogenously. Endogenously, it is produced as a result of immune cell activation, inflammation, infection, excess stress to the body and aging. The exogenous ROS may be produced due to environmental pollutants, heavy metals, solvents, radiation etc. When these exogenous compounds entered the body, they undergo degradation and the ROS are produced as byproduct [26]. The ROS or free radical plays a crucial role in regulating growth, development and metabolic activity in organisms. On the other hand, an excess of ROS oxidises organic materials and damages cells due to oxidative stress [27].
Flavonoids work as antioxidants by scavenging ROS, inhibiting the enzyme that generates them, chelating the trace elements involved in their synthesis, or upregulating or protecting antioxidant defences [28].

3. **Antimicrobial activity:** Antibacterial qualities of flavonoids such apigenin, galangin, flavone glycosidase, and chalcone have been proved by Cushnie and lamb [29]. Numerous flavonoids in a wide range of therapeutic nonflowering plants

and flowering plants exhibit antibacterial action. Gliricidin 7-O-hexoside is found in *Asplenium nidus nidus L.*, and quercetin-7-O-rutinoside is a fern that protects against three pathogens: *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Proteus vulgaris* [25].

4. **Neuroprotective:** Neurodegenerative and mood disorders are a growing medical and societal concerns, mainly caused by oxidative stress, neuroinflammation, change in neurotransmitter metabolism, and certain lipid/carbohydrate balance disruptions. Flavonoids, including flavonols, flavones, flavonones, flavanols, and isoflavonoids, have been linked to neuroprotection by reducing pro-inflammatory cytokines via the NF-κB pathway. Their other common method of action is the activation of the Nrf2 pathway, which stimulates antioxidative enzymes such as catalase, superoxide dismutase, GST, and HO-1[30]. The flavonoid metabolites of *Syzygium aromaticum* including quercetin, kaempferol, myricetin, kumatakenin has shown to induce neuronal survival and decrease cognitive impairment [31].

5. **UV protective:** Flavonoids have anti-oxidant, anti-inflammatory and anticarcinogenic properties that help with photo-protection [32]. Moreover, nanoparticles infused with flavonoids have been examined for their potential to enhance the safety and efficacy of topical sunscreens, suggesting improved photo-protection and a possible decrease in dependence on traditional UV filters [33].

6. **Anti-inflammation:** Plant flavonoids are known for their anti-inflammatory effects as well. *Oroxylum indicum*, a highly used medicinal plant in Sikkim Himalaya has been emerged as the notable source of bioactive flavonoids, with immunomodulatory and anti-inflammatory properties. The flavonoid content of plant specially from its grilled fruit demonstrate significant anti-inflammatory effects in Lipopolysaccharide and Urban dust-stimulated RAW 264.7 macrophages by dose dependently inhibiting nitric oxide generation without inducing cytotoxicity [34].

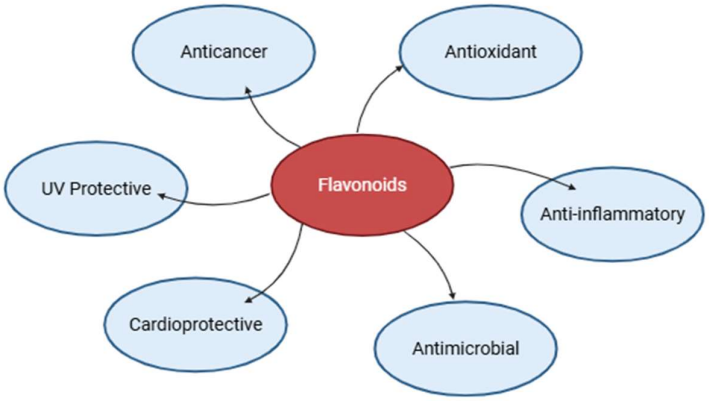


*Figure 11. Therapeutic activity of flavonoids*

**Conclusion**

Flavonoids are secondary metabolites produced by plants. They have been shown to provide numerous health benefits. Traditional medicine and medicinal plant species, particularly in Asia, contain many flavonoids and polyphenols. However, authenticating, validating, and standardising natural sources is important key steps for developing phytopharmaceutical products and medical uses. Since flavonoids have a wide range of health-promoting effects, plant tissue culture technique may be used to create flavonoid compounds more quickly than naturally grown plants. It allows for the development of a desired plant or secondary metabolites in a shorter amount of time or findings of these studies can be used by governments to establish agricultural policies that will incentivise locals to farm these plants or create traditional medicinal recipes using best practices and quality control. In addition to helping the medical and phytopharmaceutical sectors, this will raise the income of the local population, improving their quality of life and sustainability.

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