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Review on Flavonoids

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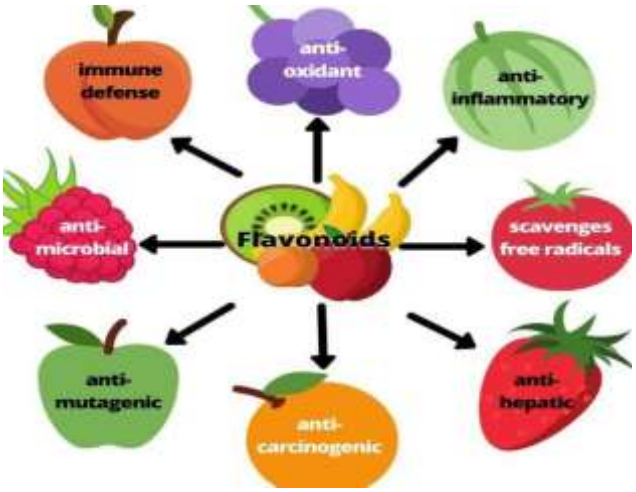
ABSTRACT:

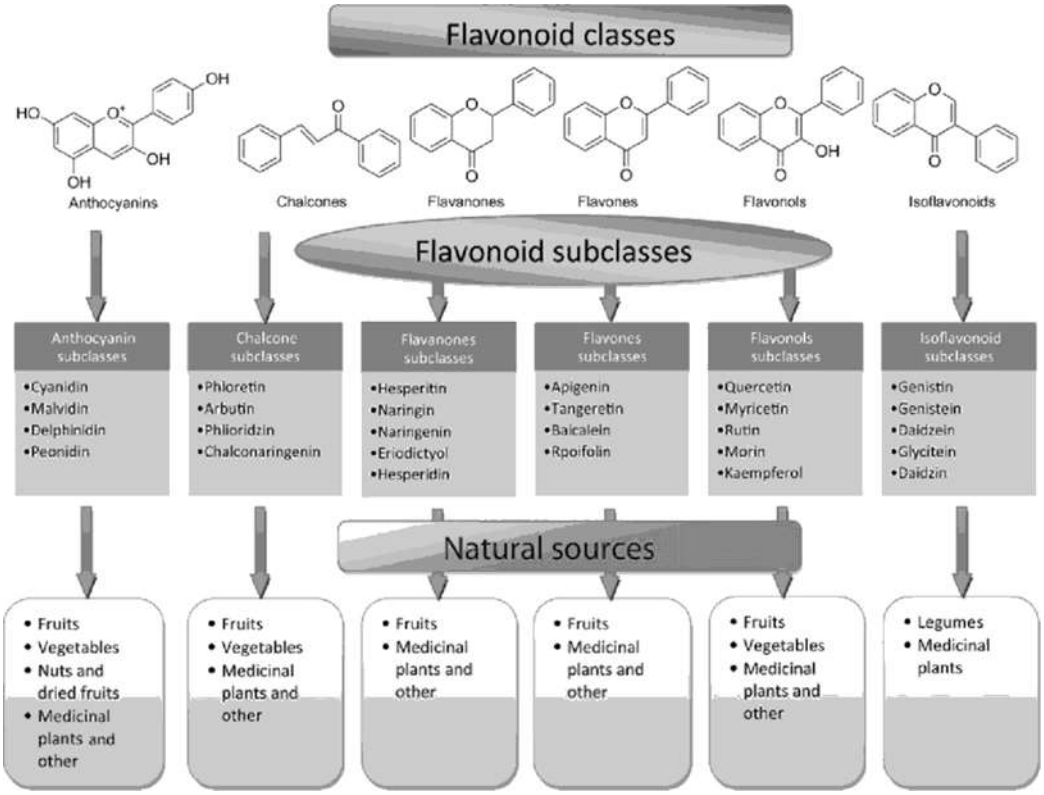
Flavonoids, a group of natural substances with variable phenolic structures, are found in fruits, vegetables, grains, bark, roots, stems, flowers, tea and wine. These natural products are well known for their beneficial effects on health and efforts are being made to isolate the ingredients so called flavonoids. Flavonoids are now considered as an indispensable component in a variety of nutraceutical, pharmaceutical, medicinal and cosmetic applications. Research on flavonoids received an added impulse with the discovery of the low cardiovascular mortality rate and also prevention of CHD. Information on the working mechanisms of flavonoids is still not understood properly. However, it has widely been known for centuries that derivatives of plant origin possess a broad spectrum of biological activity. Current trends of research and development activities on flavonoids relate to isolation, identification, characterisation and functions of flavonoids and finally their applications on health benefits. Molecular docking and knowledge of bioinformatics are also being used to predict potential applications and manufacturing by industry. In the present review, attempts have been made to discuss the current trends of research and development on flavonoids, working mechanisms of flavonoids, flavonoid functions and applications, prediction of flavonoids as potential drugs in preventing chronic diseases and future research directions.

INTRODUCTION:

Flavonoids are the natural compound widely distributed in plant kingdom, it is responsible for the various colors exhibited by bark, leaves, flowers, fruits and seeds of plants. They are the secondary metabolites of plant with significant antioxidant properties. Flavonoids have antioxidant, sedative, antidepressant, anticonvulsant, antiproliferative, anti-inflammatory, anti-microbial, anticancer, cardioprotective, antihypertensive, antiulcerogenic, antidiabetic and hepatoprotective activity. Many researchers have revealed that the above mentioned pharmacological actions are mainly due to its antioxidant property. Flavonoids have effect on mammalian enzymes like protein kinases, alpha- glucosidase and aldose reductase, thereby regulate multiple cellular signaling pathway that were altered during disease conditions. Various researches on flavonoids are in progress due to its versatile health benefits. En number of flavonoids are available in the market as pharmaceutical products because of its cost effective bulk production and health benefits. The present review is focused on the classification, metabolism, pharmacological and biological actions and flavonoid supplement available in market.



CLASSIFICATION OF FLAVONOIDE-



LITERATURE SURVEY

- **Flavones**

One of the crucial subgroups of flavonoids are flavones. As glucosides, flavones are abundantly distributed in leaves, flowers, and fruits. Major sources of flavones include celery, parsley, red peppers, chamomile, mint, and ginkgo biloba. This subclass of flavonoids includes luteolin, apigenin, and tangeritin. The polymethoxylated flavones tageretin, nobiletin, and sinensetin are abundant in citrus fruit peels (1).They have a ketone in the fourth position of the C ring and a double bond between positions 2 and 3. According to the taxonomic categorization of the specific vegetable or fruit, hydroxylation in other places, such as position 7 of the A ring or 3′ and 4′ of the B ring, may vary. The majority of flavones in vegetables and fruits have a hydroxyl group in position 5 of the A ring.

- **Flavonols**

Flavonoids with a ketone group are called flavonols. They serve as proanthocyanins' building blocks. Flavonols are widely distributed across a range of fruits and vegetables. The flavonols kaempferol, quercetin, myricetin, and fisetin have undergone the greatest research. Flavonols are abundant in foods including onions, kale, lettuce, tomatoes, apples, grapes, and berries. Tea and red wine are additional sources of flavonols in addition to fruits and vegetables. Consumption of flavonols has been linked to a number of health advantages, including antioxidant potential and a decreased risk of vascular disease.

- **Flavanones**

Another significant class, flavanones, are typically found in all citrus fruits, including oranges, lemons, and grapes. Examples of this group of flavonoids include hesperitin, naringenin, and eriodictyol. Flavonones are related with a multitude of health advantages because of their free radicalscavenging effects. Citrus fruit peel and juice both have a bitter flavour because of these substances. Intriguing pharmacological properties of citrus flavonoids as antioxidants, anti-inflammatory, blood lipid-lowering, and cholesterol-lowering agents. The main structural difference between the two subgroups of flavonoids is that the double bond between positions 2 and 3 is saturated in flavanones, also known as dihydroflavones, but it is not in flavones. The quantity of flavanones has dramatically increased over the previous 15 years.

- **Isoflavonoids**

A sizable and highly distinctive subset of flavonoids is called isoflavonoids. Isoflavonoids are mostly found in soybeans and other leguminous plants and have a very restricted distribution in the plant kingdom. Microbes have also reportedly been found to contain certain isoflavonoids (2). They are also discovered to have a significant function as phytoalexin precursors during plant-microbe interactions (2,3). Isoflavonoids have amazing potential to treat many ailments. Due to their oestrogenic action in some animal models, isoflavones like genistein and daidzein are frequently considered to be phyto-oestrogens. Szkudelska and Nogowski examined how genistein causes hormonal and metabolic alterations that have the potential to affect a number of disease pathways..

- **Flavanols, flavan-3-ols or catechins-**

The 3-hydroxy derivatives of flavanones are known as dihydroflavonols or catechins. They are a subgroup with a wide range of substitutions. Because the hydroxyl group is always attached to position 3 of the C ring, flavanols are also known as flavan-3-ols. There is no double bond between positions 2 and 3, unlike many other flavonoids. Bananas, apples, blueberries, peaches, and pears are loaded with flavanols.

- **Anthocyanins-**

Anthocyanins are pigments that give plants, flowers, and fruits their colours. The anthocyanins that are most frequently researched are cyanidin, delphinidin, malvidin, pelargonidin, and peonidin. They occur largely in the outer cell layers of numerous fruits such as cranberries, black currants, red grapes, merlot grapes, raspberries, strawberries, blueberries, bilberries and blackberries. These chemicals' stability and health advantages make it possible for them to be used in the food sector for a range of purposes (4). The pH and methylation or acylation at the hydroxyl groups on the A and B rings also affect the anthocyanin's colour.

- **Chalcones-**

Chalcones are a subclass of flavonoids. They are characterised by the absence of ‘ring C’ of the basic flavonoid skeleton structure. Hence, they can also be referred to as open- chain flavonoids. Major examples of chalcones include phloridzin, arbutin, phloretin and chalconaringenin. Chalcones occur in significant amounts in tomatoes, pears, strawberries, bearberries and certain wheat products. Chalcones and their derivatives have garnered considerable attention because of numerous nutritional and biological benefits. Table 1 describes the food sources of all dietary flavonoids discussed throughout the article for their bioactivity and research trends (4,5) . The intake of flavonoids through food sources could be the simplest and safest way to combat diseases as well as modulate activities.

MECHANISM OF ACTION OF FLAVONOID

One of the important underlying mechanisms of action of dietary favonoid and related polyphenols is associated with their inhibition of oxidative stress and related downstream responses including infammatory diseases. Flavonoids scavenge free radicals and their subsequent damage by forming relatively stable phenoxy radicals and also by metal chelation [6]. In addition, favonoid interact with multiple gene products to inhibit their specifc actions and thereby directly modulate a limited response or for kinase inhibition, the interaction could impact multiple downstream pathways.

- **Flavonoid as kinase inhibitors**

Although favonoid directly bind many proteins and modulate their activities, their interactions with multiple kinases and subsequent effects on downstream kinases- dependent signaling have been extensively investigated (6). Genistein was among the first favonoid identified as a receptor tyrosine kinase (RTK) inhibitor [6] and inhibited autophosphorylation of the epidermal growth factor receptor (EGFR) and it actsas a non- competitive inhibitor of histone H2B [7]. Subsequent studies show the genisteinand many other favonoid inhibit a diverse spectrum of kinases by direct interactions with these proteins and a few structure–activity studies have identified favonoid with optimal activities.

- **Flavonoid effects on membrane-bound receptors-**

Several studies demonstrate that favonoid modulate expression or activity of multiple RTKs including EGFRs, cMET, insulin-like growth factor receptor (IGFR), vascular endothelial growth factor receptors (VEGFRs) and platelet-derived growth factor receptors [6,8]. Many publications show that favonoid inhibit the function of RTKs and block downstream signaling pathways, however, there is limited data on the mechanisms of favonoid-RTK interactions. There is evidence that favonoid mimic ATP and interact with ATP binding sites of RTKs [5] and this is also observed for kinases.

- **Flavonoid effects on G-protein coupled receptor-**

G-protein—coupled receptors (GPCR) are seven transmembrane receptors and there are over 800 GPCRs that play diverse roles in vision, taste, smell, behavior, immune responses and the nervous system. summarizes some of the GPCRs that are modulated by favonoids [9,10] and demonstrates that these phytochemicals can potentially influencethe large class of cell membrane receptors.

- **Flavonoid and the Aryl Hydrocarbon Receptor (AhR)-**

The AhR is a basic-helix-loop-helix transcription factor that forms an active nuclear heterodimer with the AhR nuclear translocator (Arnt) protein to activate gene expression [11]. The AhR was initially discovered as the intracellular receptor that mediates the biochemical and toxic effects induced by 2,3,7,8-tetrachlorodinezo-p-dioxin (TCDD) and structurally related halogenated aromatics.

CONCLUSION

1. Flavonoids are groups of various compounds found naturally in many plants, such as fruits and vegetables, along with plant products such as coffee, chocolate, and tea.
2. It had been repeatedly reported that flavonoids possess a wide range of health benefits. For example, flavonoids are rich in antioxidants, providing our body with natural immune protections from daily environmental and endogenous toxins.
3. Different classes of flavonoids are so far isolated with several significant biological activities such as anticancer, antibacterial, antifungal, anti-diabetic, antimalarial, neuroprotective, cardio-protective, anti-inflammatory.
4. Thus, including different types of flavonoids in daily diet is highly recommended to stay healthy and to reduce the risk of serval life threatening diseases such as diabetes mellitus, cancer as well as lowering the risk of having stroke and heart attack.
5. The therapeutic effects of flavonoids have been proved in majority of pre-clinical studies in murine models. Different approaches should be used in clinical trials so that the absorption and bioavailability of flavonoids are not compromised.
6. Their production should be increased through expression of their biosynthetic pathway enzymes in other plants and species with rapid growth.
7. The funding agencies should facilitate research on flavonoids due to their versatile role in health and wellness. Further, the conjugates of flavonoids with other important drugs may enhance the potency of those compounds. Decisively, more research work is needed to resolve more the structures of more flavonoids and to investigate their therapeutic applications.
8. Flavonoids structures will always inspire research for the design and synthesis of new