

IMPACT OF FLAVONOIDS ON HUMAN HEALTH: A REVIEW

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ABSTRACT

Flavonoids are a group of plant derived chemical compounds with variable phenolic structures and functions. These secondary metabolites are known to have various health benefits and now are considered as an important part of a variety of pharmaceutical and nutraceutical application. This article attempts to focus on characterization and classification as well as highlight various biological activities and other therapeutic applications.

Keywords: Flavonoids, Antioxidants, Anti-Inflammatory, Anti-carcinogenic, Therapeutic, Anti-Microbial, Free Radicals.

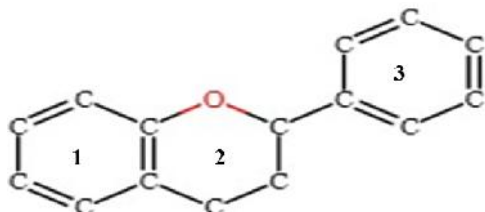
Introduction

Flavonoids are a group of organic molecules which are widely in trend and is research upon a lot these days due to its impact on human health. Flavonoids are benzo-gamma-pyrone derivative and are obtained from plant sources.¹ Basically these naturally derived organic compounds are a class polyphenolic compounds that are produces as secondary metabolites by plants. They are found in various fruits, vegetables, grains, flowers, bark etc. and are commonly consumed in diets. These natural products are known to have positive impact on human health and these compounds nowadays is an important constituent in a variety of medicinal, cosmetic, nutraceutical products worldwide.² The health promoting benefits present in these compounds are due to their anti-inflammatory, antioxidant, anti-carcinogenic and anti-mutagenic properties. This polyphenolic compound is known to modulate key cellular enzymatic functions and are known to be inhibitors of several enzymes like cyclo-oxygenase, xanthine oxidase, phosphoinositide 3-kinase and lipoxigenase.² These group of compounds are found in a variety of foods and beverages apart from fruits and vegetables like tea, wine and cocoa etc.

Flavonoids: Subclasses and Biological Sources

As mentioned before flavonoids belong to a group of compounds called polyphenols. These polyphenols are secondary metabolites which are involves in various plant processes like reproduction, pathogenic protection and pigmentation. Over the period of time the research in the flavonoid chemistry has increased for the search of various new compounds which are proposed to exert varied beneficial physiological properties.

These group of compounds more specifically contain a phenyl benzopyran functionally and so depending on the linkage position of the aromatic ring to this moiety, they can be divided into three categories namely the flavonoids (2-phenylbenzopyrans), isoflavonoids (3-benzopyrans), and the neoflavonoids (4-benzopyrans). All the three classes of compounds are biogenetically and structurally related as they have a common chalcone precursor.



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Flavonoids are subclassified into classes depending on the carbon of 2nd ring on which the 3rd ring is attached and the degree of unsaturation and oxidation of 2nd ring, the basic framework of which is shown below.² Sub groups of flavonoids are: flavonols, flavones, flavanones, flavanonols, flavanols or catechins, anthocyanins and chalcone. Other structurally related compounds include isoflavonoids and neoflavonoids.

Flavonoids with a ketone group are called Flavonols. These are found in abundances in various fruits and vegetables like tomatoes, kale, grapes, apple, berries etc and is an important constituent of proanthocyanin. The most studied compounds under this class include fisetin, myricetin, kaempferol and quercetin. They are associated with antioxidant properties as well as are known to reduce the risk of several vascular diseases. On the other hand, flavones are based on 2-phenyl-1-benzopyran-4-one. This is the class of increasing interest because of with biological activity both in-vitro and in-vivo. Major sources of flavones include red peppers, chamomile, mint, celery etc. flavones like Apegenin is present in chamomile tea, parsley etc. while olives are known to be the rich source of luteolin. The peel of various citrus fruits is known to contain polymethoxylated flavones.³

Anthocyanin is a class mainly comprising of pigments and is one of the crucial phytochemicals which are responsible for pigmentation in fruits and flowers. Outer layers of strawberries, cranberries, blueberries, merlot grapes contain these pigments abundantly. The colour imparted by anthocyanin varies according to the pH condition as well as methylation and acylation pattern within the compound. These are also found in tea, cocoa, cereal, honeys etc. these colourful group of phenols are highly studied due to its free radical scavenging and anti-oxidant capabilities. These compounds show protective action against DNA cleavage, lipid peroxidation, inflammation as well as fragility.⁴ Predominantly studied anthocyanins include cyanidin, malvidin, peonidin, delphinidin etc.

Chalcones are characterised by the absence of the 2nd ring in their skeletal framework and so they are also referred as open chain flavonoids. Their derivatives find application in artificial sweeteners, scintillators etc apart from other therapeutic applications. These compounds present a very broad spectrum of therapeutic application like antimicrobial properties including protection from various parasites, antilipidemic, anti-angiogenic, free radical scavenging as well as neuroprotective properties. Major example of chalcones are Rubone, auretiacin A, mixtecacin, Pedicin, fissionin and isofissionin etc. these are majorly found in medicinal plants like *Dydimocarpus aurentica*, *Myrica gale*, fruits of *Mallotus philippinensis*, stem of *Angelica keiskei*, leaves of *Desmos cochinchinensis* etc.⁵

Isoflavonoids is another large and very important group of flavonoids which are found in soyabeans, peanuts and other plants of Leguminosae family. They are derived from the phenylpropanoid pathway and are found to be associated with many biological properties like anti-cancer properties, reduction in cardiovascular diseases as well reduce other conditions like osteoporosis. According to various studies isoflavonoids are found to show beneficial effects against various diseases. Certain simplex and complex isoflavonoids acts as phytoestrogen. They are also known for their antifungal and insecticidal properties. Apart from that compounds like Daidzein possess hepatoprotective while genistin show anti-cancer property. In mice, genistein which is found in soyabean has demonstrated to inhibit UV induced tumorigenesis thereby exhibiting antioxidant properties. Commonly known isoflavonoids are Biochanin, Glycitein, Formononetin, Genistein, Olibergin, Puerarin, Scanderone, Senegalensin etc. As mentioned previously they found in various legumes like kidney beans, green gram, black gram, peas, chickpeas, dry cowpea etc. but they are also found in non-legumes like aloe vera, *Arabidopsis thaliana*.⁶

Similarly, Neoflavonoids is another class of polyphenolic compounds found in plants. These compounds have a limited taxonomic distribution and are found in plants of Papilionoideae, Guttiferae, Rubiaceae, Passifloraceae etc.⁷ According to study these compounds exhibit chemoprotective role in carcinogenesis by suppression of NF- κ B activation, inhibition of aromatase enzyme as well QR1 induction. These compounds apart from anti-cancer properties are studied to show other therapeutic application like antidiabetic, antimalarial, anti-allergic as well as anti-fungal properties. These 4-phenylchromen-4-one backbones containing compounds include Calophyllolide, Nivetin, Dalbergin, Coutareagenin. The first neoflavonoid containing compound was isolated from seeds of *Calophyllum inophyllum* was calophyllolide.²

Biological Effects of Flavonoids: Impact on Human Health

Flavonoids being naturally occurring and derived from plant sources are actively consumed as a part of our regular diet. These compounds are also found in various medicinal plants and are known have many health benefits. They are well known to exhibit various protective properties including Anti-inflammatory, anti-oxidant and radical scavenging activity, anti-cholinesterase, anti-microbial properties and many others.

- **Anti-inflammatory Property:** Protection against inflammation is among the crucial properties shown by flavonoids. The molecular mechanisms involved in prevention from inflammation involves inhibition of inflammation promoting enzymes like lipoxygenase, inducible NO synthase, Cyclooxygenase-2, MAPK etc. According to some studies it was observed that in mice model, COX-2 can be inhibited by quercetin and kaempferol in peritoneal macrophages while Catechin was inhibiting the same at very high concentration. It was also observed that lipoxygenase can be inhibited by flavonols rather than flavones like kaempferol, morin, quercetin etc. unlike flavonones which were found to be ineffective. Inhibition of NO production in Lipopolysaccharide/Cytokine treated macrophages, to a large extent was shown by apigenin, luteolin and quercetin.⁸

Isoflavones which is a well-known phytochemical is also known to possess anti-inflammatory characteristics. According to some studies these are found to be beneficial for the patients with cardiovascular diseases, osteoporosis and cancer. In mouse, they reduce inflammation by affecting granulocytes, monocytes and lymphocytes as well. Similarly, they prevent inflammation by manganese superoxide dismutase and also modulate the action of inflammatory cytokine IL-6, IL-1, TNF- α , Prostaglandin E2. Puerarin, an isoflavone have neuroprotective effect from ischemic damage by reducing COX-2 expression in microglial and astrocytes.⁹ On the same grounds, Neoflavonoids extracted from plant sources were found to show cytotoxic effects and prevent inflammation.

- **Antioxidant Property:** It is well known that flavonoids are known to exhibit antioxidant property but according to some studies they also act as pro-oxidants. An antioxidant is any substance that reduces, protects or removes damage due to oxidation to a target molecule. Studies show that consumption of red wine could be beneficial as they stimulating platelet inhibition by downregulating the PECAM-1 receptor. In-vitro studies in various cell lines show that these polyphenolic compounds tend to show higher antioxidant properties than vitamin E and C. Molecular mechanism which can prevent injury caused due to free radicals include upregulation and expression of antioxidant enzymes while downregulation of various oxidases; increasing metal chelating activity; scavenging the reactive oxygen species directly; preventing oxidative stress due to NO; and by reducing concentration of α -tocopheryl radicals. These naturally derived enzymes are capable of inducing the expression of detoxifying enzymes like glutathione S-transferase. These enzymes are found to play important role against electrophilic toxicants. Cytoprotective effect of flavonoids like quercetin and catechin against hydrogen peroxide cytotoxicity has also been investigated in rat liver cell lines which exhibit increased expression of glutathione peroxidase present in cytoplasm. Cocoa flavonoids are also known to cause activation and increase in activity of enzymes like glutathione reductase and glutathione peroxidase.¹⁰
- **Anti-carcinogenic Property:** Flavonols present in plant sources like green tea, celery, cocoa, chocolate, apple is observed to have ability to fight against human rectal, prostate and oral cancers. Similarly, anthocyanins also have potential to fight against colorectal cancer. Brussel sprouts, acai palm, kale, cherries, lemon juice are naturally occurring plant products known to have ability to combat against breast, thyroid, stomach, laryngeal as well as colon cancer. Studies done in in vitro tumor models shows that flavonoids like apigenin scavenges free radicals and promotes metal chelating property thereby showing protective properties against skin as well as colon cancer. Apigenin plays a role in inhibiting expression of casein kinase in both breast and prostate cancer models. It downregulates expression of HIF-1 and VEGF via PI3K/Akt/p70S6K1 and HDM2/p53 pathways in ovarian cancer cells. Kaempferol also act as chemoprotective agent by curbing the growth of various carcinomas like lung, glioblastoma, osteosarcoma, breast adenocarcinoma etc. by arresting cell cycle in actively proliferating cancer cells. These are found to quite effective against angiogenesis as well. Consumption of citrus fruits which contain flavones like diosmin shows beneficial effects by inhibiting proliferation of cancer cells. The mechanism underlying this cancer chemo-preventive property includes cell cycle arrest, tyrosine kinase inactivation, heat shock protein and Ras protein downregulation. These organic polyphenol containing compounds are found to possess anti-tumor and anti-cancer activities by acting as cell cycle inhibitors, preventing cell proliferation, angiogenesis and oxidative stress.¹¹
- **Anti-microbial Property:** There are various studies that have evaluated inhibitory effect of flavonoids against various bacteria, fungi, parasites as well as viruses. Some of the molecular mechanism involved in antibacterial activity of these compounds include formation of complex with the components present in cell wall and then preventing formation of adhesions as well as

microbial growth; inhibition of bacterial enzymes; inhibition of the bacterial efflux pump; by increase in the susceptibility of existing antibiotics. Flavonols like quercetin are observed to exhibit antibacterial activity against certain strains of bacteria like *S. aureus*, MRSA, *P. gingivalis*, *S. epidermidis*, *B. subtilis*. Whereas myricetrin-3-O-rhamnoside was found to exhibit potent activity against *E. coli*, *S. aureus*, *K.pneumoniae*. Researcher have reported that compounds like chalcones were found to show activity against bacterial strains in combination with antibiotics. Apart from this chalcones were also found to exhibit biofilm inhibition. Lupinifolin which is an example of flavane 3-ol compounds is found to show bioactivity against *P. aeruginosa*, *E. coli*, *S. aureus* and *B. subtilis*. While flavanone compounds like Pinocembrin was found to be effective against *M. tuberculosis* and 7-Hydroxyflavanone were found effective against *S. pneumoniae*.¹²

Some studies show that these phytochemicals have ability to inhibit spore germination. A flavanone recently extracted from *Eysenhardtia texana* has been found to show potency against *C. albicans*. Some flavonoids exhibit high antifungal property against *A. flavus*, *P. digitatum* and *Cladosporium spp.* as well.¹⁵

Flavones and flavonols show synergistic effects against HSV. These polyphenols also show synergy with other antiviral agents like Quercetin and acyclovir works efficiently against HSV and pseudorabies infection. Compounds like quercetin, morin, rutin, leucocyanidin, pelargonidin chloride and catechin possess activity against various virus including herpes simplex virus (HSV), respiratory syncytial virus, poliovirus and Sindbis virus.^{13,14} Some ongoing studies are focussing on inhibitory effects of certain flavonoids against HIV enzymes¹⁵

- **Anticholinesterase and Neuroprotective Property:** As mentioned above flavonoids also possess anti-cholinesterase property which can help in combating Alzheimer's disease. Increasing the concentration of acetyl choline in the central nervous system by lowering the expression of cholinesterase could help in symptomatic relief of mild to moderate Alzheimer's. Therefore, flavonoids like quercetin, rutin, kaempferol 3-O- -D-galactoside and macluraxanthone tend to inhibit this enzyme out of which quercetin and macluraxanthone possess concentration dependent inhibition capacity to minimize acetylcholinesterase as well as butyrylcholinesterase. Docking analysis for macluraxanthone shows the that it gets bound to the enzyme more tightly than quercetin thereby acting as a potent cholinesterase inhibitor.²

The recent studies on these plant derivatives show that they may have a key role in enzyme and receptor systems of the brain therefore heling in combating multiple neurodegenerative disorders like Alzheimer's and Parkinson's disease. Flavonoids possess ability to inhibit action of various enzymes like COX, Xanthine oxidase and Ca⁺² ATPase.² Apart from these flavonoids also protect neurons from injury due to neurotoxins a therefore suppressing neuroinflammation and also promote learning, memory and may prevent cognitive losses.¹⁶

Apart from the above-mentioned properties, flavonoids play role in various other important bioactivities like: reducing ischemia-reperfusion injury, atherosclerosis prevention, act as promotor and activator of insulin receptor, anti-platelet functions as well anti mutagenic property.

Conclusion

Flavonoids are one of common, ubiquitously present phytochemical commonly found in fruits, leaves, nuts, stem, honey as well as flowers. This mini-review deal with various bioactivities and health promoting properties of these chemicals. These naturally occurring chemicals play an important role in chemotherapeutics as well as helps in fighting various health problems. They have received much attention in recent research studies as well literature in the last 15 years due to the potential health benefits mentioned above. Controlled intake of flavonoids in diet could help in improving human health but still there are certain grey areas that has to be studied in depth. Therefore, there is need of research programme involving various *in-vivo* studies which will help in getting an insight and safe picture for the future.

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