Flavonoids from plants used in folk medicine- a review

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Flavonoids are natural compounds that possess therapeutic value is ethnobotany or ethnopharmacology. Anti-viral/bacterial, anti-inflammatory, cardioprotective, anti-diabetic, anti-cancer, anti-aging properties have long been received great attention and well supported by various studies. Their basic structures consist of C6-C3-C6 rings with different substitution patterns to produce a series of subclass compounds such as flavones, flavonols, flavanones, isoflavones, flavanols or catechins and anthocyanins. Many flavonoid compounds are shown to have an antioxidative activity, free radical scavenging capacity. This review includes selected flavonoids, their sources and various activities.

Key words: Traditional medicine, Flavonoids, Biological activity

Introduction

Flavonoids are a large group of naturally occurring phenolic compounds extensively distributed in the plant kingdom. (Nicole Cotelle, 2005).These aromatic compounds are found in almost every plant, and act as the primary chemical constituent in a variety of plant-based medicines. They have multiple biological activities, including vasodilatory, anticarcinogenic, anti-inflammatory, antibacterial, immune-stimulating, antiallergic, and antiviral effects(Gao, Huang, & Xu, 2001)

Traditional medicines have been effectively used for many generations in the Asian subcontinent, the majority of which are plant-based. It is now that research emerges, after phytochemical analysis of said plants and spices that the therapeutic nature of these medicines is governed by the various properties of the flavonic compounds present in them. There are currently hundreds of modern drugs based on active compounds isolated from plants (Zakaryan, Arabyan, Oo, & Zandi, 2017).

Based on the frequent and numerous uses of flavonoids in daily life, the potential risk of flavonoid -containing food/herb-drug interactions has been highly regarded (Fan *et al*., 2019).Flavonoids normally have a phenyl benzopyran structure (C6-C3-C6) and can be subdivided into different subgroups depending on the carbon of the C ring on which the B

Liquorice (*Glycyrrhizaglabra*),

Crotalaria prostrata,

Kava (*Piper methysticum*),

Chinese ginger(*Boesenbergia rotunda*),

Red ironwood (*Lophiraalata*),

Hops (*Humuluslupulus*)

ring is attached and the degree of unsaturation and oxidation of the C ring, namely isoflavones and neoflavanoids from B-C3 linkage and B-C4 linkages respectively. B-C2 linkages are further divided into subgroups like flavones, flavonols, flavanones, flavanonols, flavanols or catechins, anthocyanins and chalcones.(Panche, Diwan, & Chandra, 2016). They can exist in the free state or as glycosides.

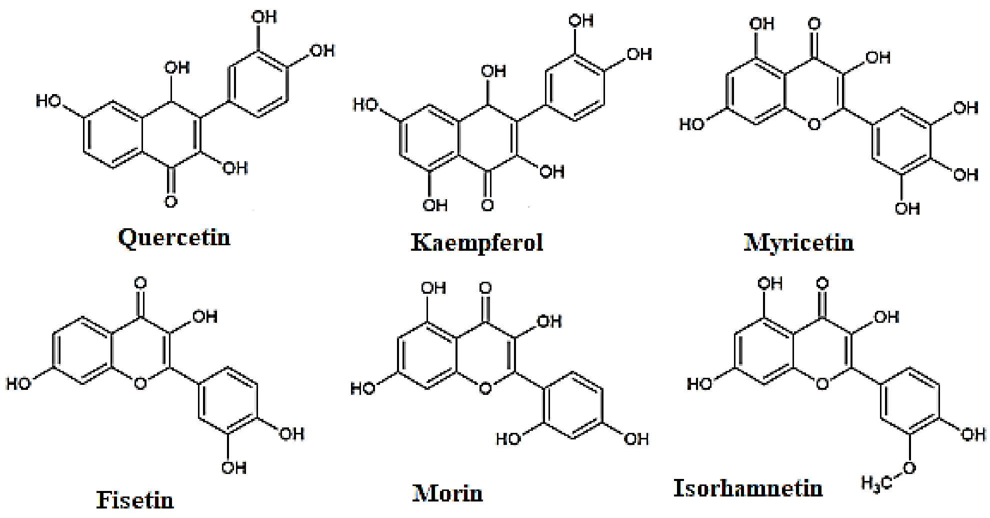
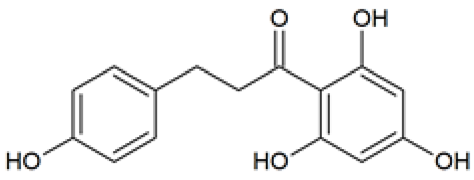


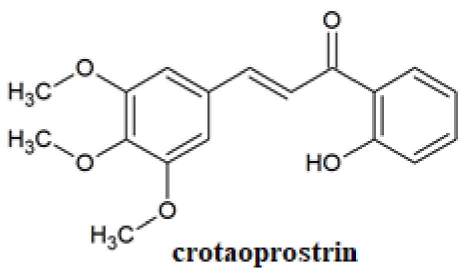
Fig 1: Flavonolsa) Backbone structure b) Important flavonols

Flavonols are found in Neem (*Azadirachtaindica*), Papaya (*Carica papaya*), Parsley (*Petroselinum crispum*), Radish (*Petroselinum crispum*), Fennel (Foeniculumvulgare), Cocoa(*Theobroma cacao*),Kale (*Brassica oleracea*), Spinach (*Spinaciaoleracea*), Tea (*Camiliasinensis*)

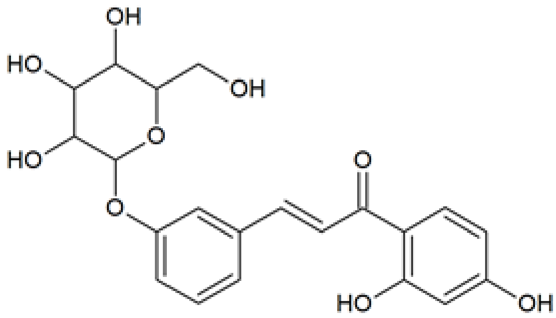
Chalcones are found in Apple (*Malusdomestica),*Liquorice (*Glycyrrhizaglabra*),*Crotalaria prostrata,*Kava (*Piper methysticum*),Chinese ginger(*Boesenbergia rotunda*), Red ironwood (*Lophiraalata*), Hops (*Humuluslupulus*)



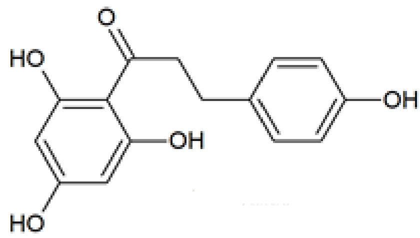
Phloretin



crotaoprostrin

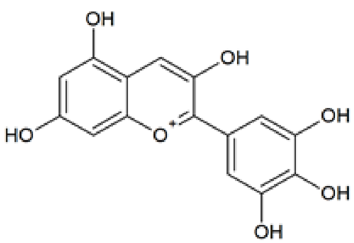


Isoliquiritin

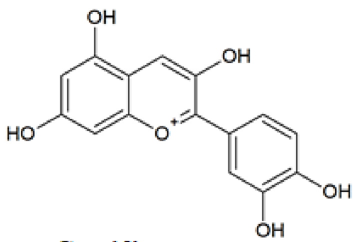


Chalconaringenin

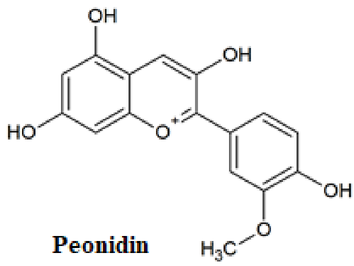
Fig 2:Chalcones



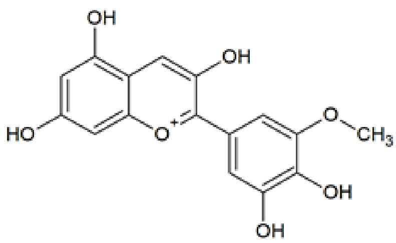
Delphinidin



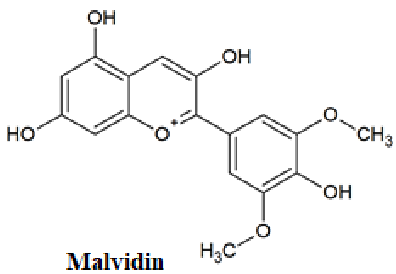
Cyanidin



Peonidin



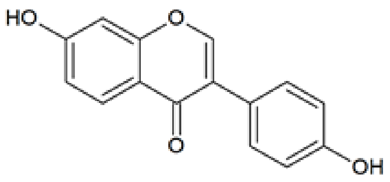
Petunidin



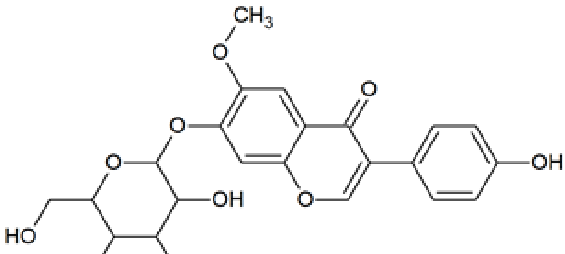
Malvidin

Fig 3: Anthocyanins

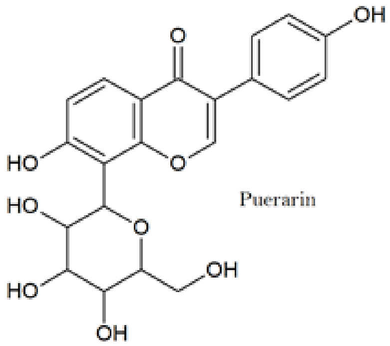
Anthocyanins are found inPurple sweet potato (*Ipomoea batatas* L.),Beetroot (*Beta vulgaris)*,Indian blackberry (*Syzygiumcumini*)Blueberry (*Vaccinium sp.)*,Plums (*Prunus sp.)*,Red grapes *(Vitisvinifera*), Raisins, Blue,red,purple flowers



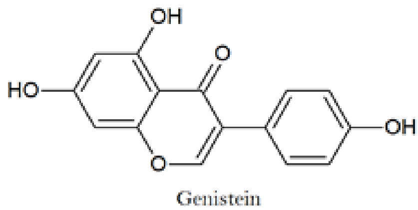
Daidzein



Glycitin

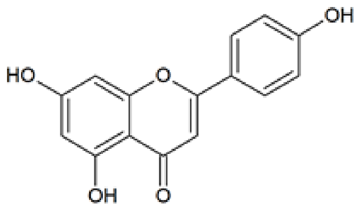


Puerarin

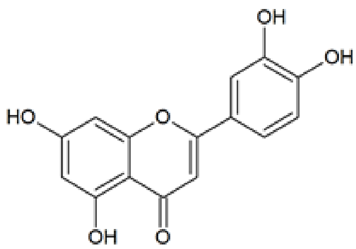


Genistein

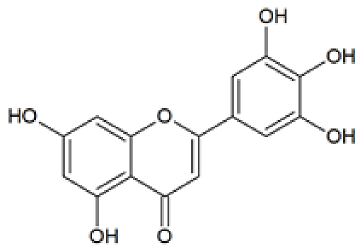
Fig 4: Isoflavones



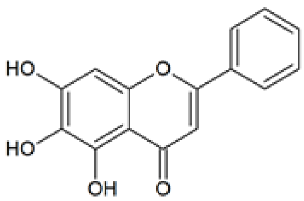
Apigenin



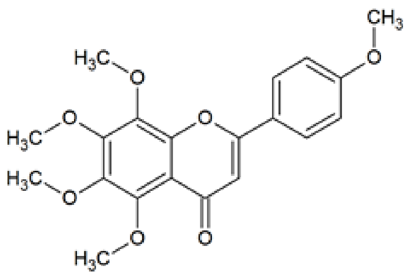
Luteolin



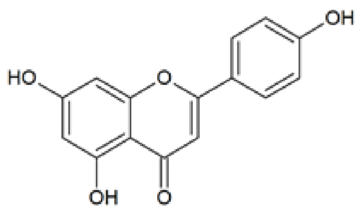
Myricetin



Baicalein



Tangeretin



Chrysin

Fig 5: Flavones

Isoflavones are found in Babooltree*(Acacia Arabica*),Barley (*Hordeumvulgare*), *Puerariatuberosa*, legumes like Soya (*Glycine max)*, Tofu, Fava beans (*Viciafaba*)Pistachios (*Pistaciavera*), Sunflower seeds (*Helianthus)*,

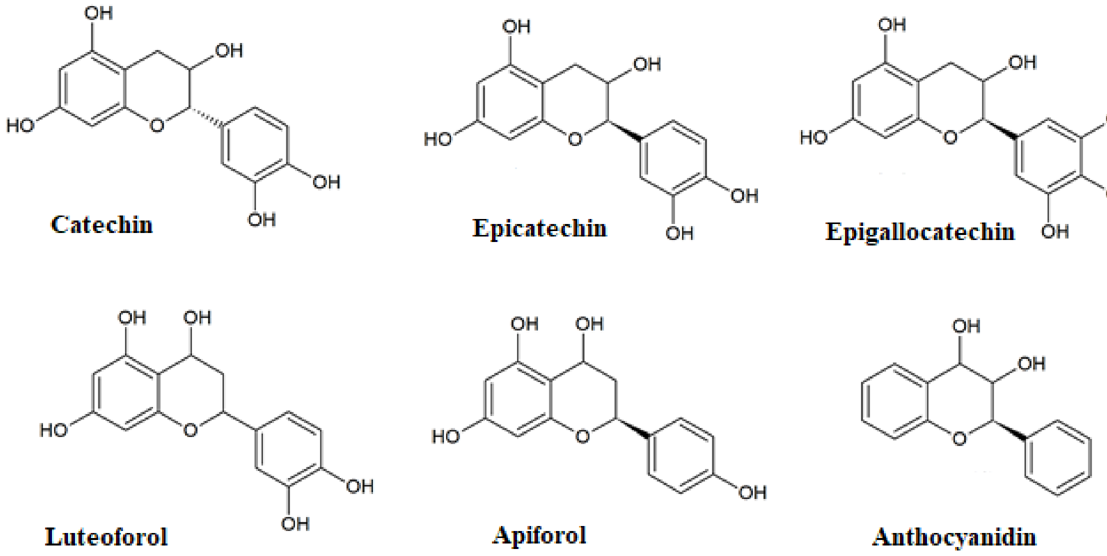


Fig 6: Flavans

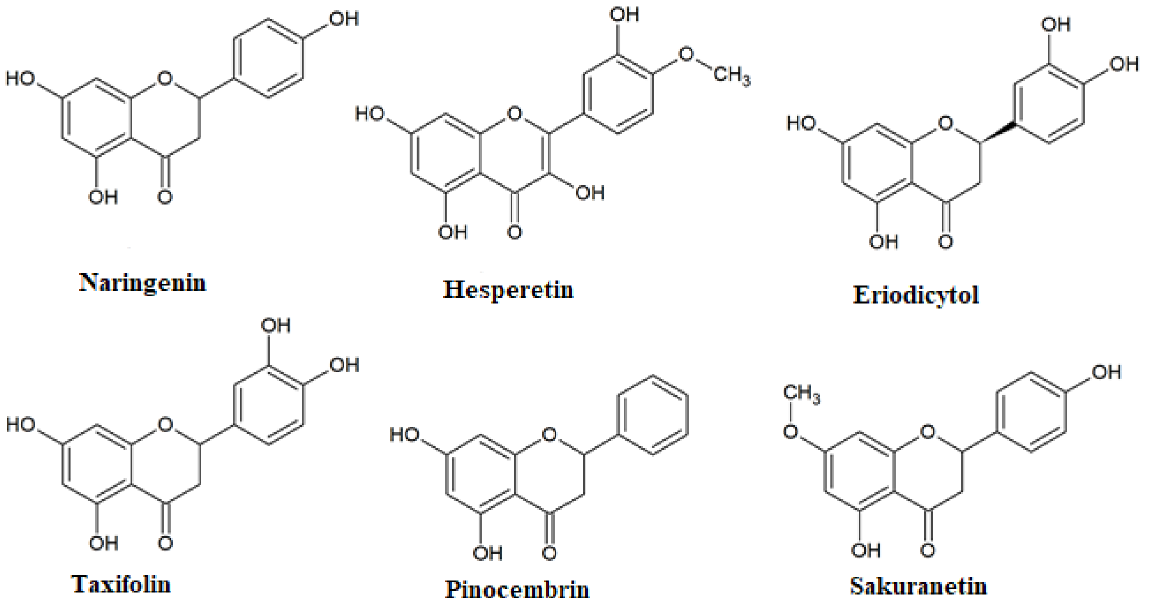


Fig 7: Flavanones

Flavones are found in Tulsi (*Ocimumtenuiflorum*),Thyme (*Thymus vulgaris*), Eucalyptus (*Eucalyptus macrorhincha)*,Liquorice (*Glycyrrhizaglabra*),*Aloe vera*, Brahmi (*Bacopamonnieri)*,Parsley (*Petroselinum crispum*). Flavans are found in Cocoa, Green, black tea (*Camellia sinensis)*, apples, berries,Lychee (*Litchi chinensis),Carallia brachiate*,*Mammealongifolia.*

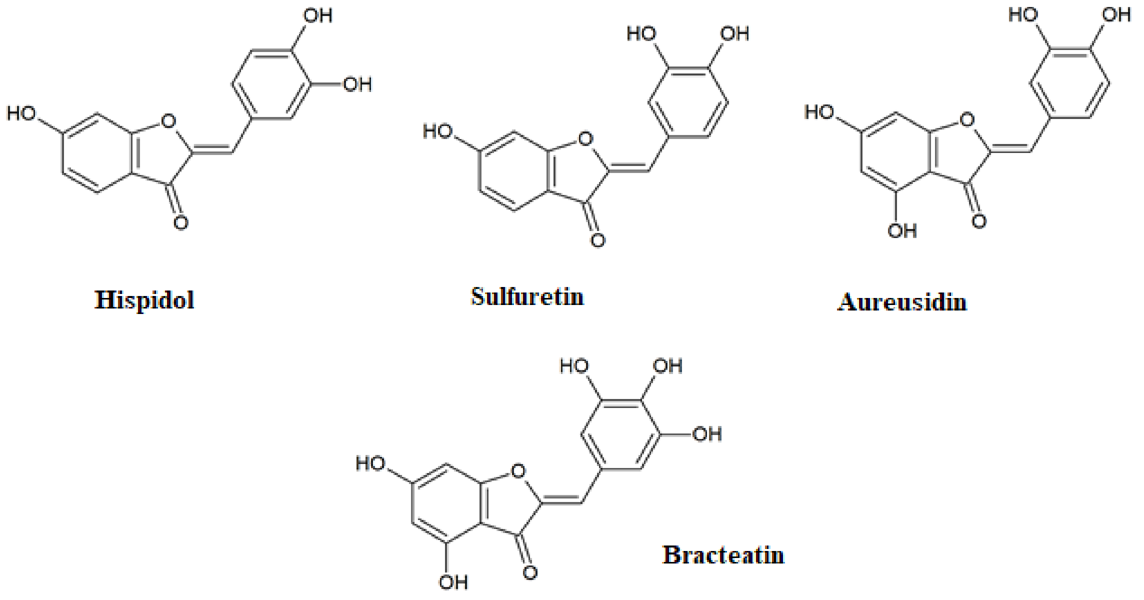


Fig 8: Aurones

Flavanones are found in Mandarin orange (*Citrus reticulata*)Tulsi (*Ocimumtenuiflorum*), *Scutellariabaicalensis*Liquorice *(Glycyrrhizaglabra)*, Selfheal herb (*Prunella vulgaris*), Grapefruit (*Citrusparadisi*), grapes, Lemon *(Citrus limon*). Aurones are found in Soya (*Glycine max*),Snapdragon (*Antirrhinum sp.*),Tickseed (*Coreopsis grandiflora*)

Indian medicinal plants will be used to elucidate the various sources of these phenolic compounds. *Azadirachtaindica*, a common medicinal plant in the Indian subcontinent, is a well-documented source of flavonols like Quercetin and Kaempferol. Leaves of *Carica papaya* also showed abundance in these compounds and their derivatives. The holy basil *Ocimumtenuiflorum*(Tulsi) is an abundant source of flavanones like Naringin, flavones such as Luteolin and Apigenin**(Biology, 2014)**

Eucalyptus macrorhincha is a good source of the O-glycoside polyphenol- Rutin. Flavones like myricetin and triacetin can also be extracted. Citrus fruits like *Citrus limon*are known to contain hesperidin and tangeritin. Anthocyanins are generally obtained from red, purple or blue coloured flowers and fruits like berries and beetroots. Isoflavones are abundantly found in fruits of leguminous plants like nuts and beans. Aurones can be found in yellowish-orangish pigmented flowers like Snapdragon

Biosynthesis of flavonoids

Flavonoids can be produced as a response to biotic or abiotic stresses. The latter usually includes factors like Co2 and O3 levels, UV radiation etc**. (Bidart-bouzat & Imeh-nathaniel, 2008) .** The type of the soil, light exposure rainfall, culture methods, and fruit yield per tree etc. also have ab impact on their biosynthesis **(Hussain *et al*., 2016).** The synthesis of flavonoids can be tied to enzymes which are products of the MYB gene family. The overexpression of MYB12 confers the resistance to insect attack in tobacco and the tolerance to salt and drought in Arabidopsis **(B. Li *et al*., 2019).** This relatively diverse family of aromatic molecules is derived from Phenylalanine and malonyl-coenzyme A (CoA; via the fatty acid pathway **(Winkel-shirley, 2001)** . The biosynthesis occurs by the Phenylpropanoid pathway where phenylalanine is transformed into 4-coumaroyl-CoA which then enters the flavonoid biosynthesis pathway **((Casati, 2012)**

BIOLOGICAL ACTIVITY

Antibacterial activity

A lot of flavonoids possess antibacterial tendencies against a myriad of bacteria in a variety of mechanisms ranging from wall disruption (Apigenin) to inhibition of various metabolic enzymes (kaempferol and quercetin)(Górniak, Bartoszewski, & Króliczewski, 2019)

They are found to be effective against (atleast) *P. vulgaris, P. mirabilis, S. aureus, S. albus B. cereus, MRSA, S. typhimurium, B. subtillis, L. monocytogenes, S.epidermidis. M. LuteusEnterococcus spp, P. aeruginosa, K. pneumoniae, C. freundii, E. cloacae, M. tuberculosis,S. maltophilia*etc**(Cushnie& Lamb, 2005)**

Antiviral activity

Similarly, antimycotic activity has been reported against (and not restricted to)

Candida albicans, C. krusei(Orhan, Özçelik, Özgen, & Ergun, 2010), *Aspergillus ochraceus*(Júnior et al., 2014), *Aspergillus flavus, Aspergillus tamarii, Aspergillus fumigatus, Aspergillus niger, Cladosporiumherbarum, Cladosporiumsphaerospermum*(Cushnie & Lamb, 2005), *Penicilliumdigitatum, Penicilliumcitrii, Penicilliumglabrum, Penicilliumitalicum, Alternariaalternata (Fr.) Keissler, Macrophominaphaseolina*(Kanwal, Hussain, Siddiqui, & Javaid, 2010)

Dengue, spread by the various serotypes of the DEN virus is one of the leading causes death in the tropics and subtropics of the Indian subcontinent and China. Traditional medicine systems of India like Ayurveda and Siddha prescribe the use of extracts of *Vitexnegundo*, *Andrographispaniculata*, *Justiciaadhatoda* and*Carica papaya*, among few others. Phytochemical analysis of these plants confirms the presence of phenolic compounds like Luteolin, Kaempferol and Vitegnoside from *Vitexnegundo*(Sathiamoorthy *et al*., 2007), Apigenin, quercetin, kaempferol and vitexin from *Justiciaadhatoda*(Kumar Singh Scholar *et al*., 2017) and daidzein, prunin, naringenin, genistein, apigenin etc. from *Andrographispaniculata.*(Y. Li *et al*., 2019)

Flavones like Baicalein ,extracted from the roots of *Scutellariabaicalensis* is effective against a variety of viruses like **i**nfluenza H5N1 virus, H1N1 virus, HIV-1,chikungunya virus (CHIKV),severe acute respiratory syndrome coronavirus (SARS-CoV), rhesus rotavirus, CHIKV and Japanese encephalitis virus (JEV)(Zakaryan, Arabyan, Oo, & Zandi, 2017b).

Flavanols like Quercetin and its derivatives also demonstrated a dose-dependent antiviral activity against poliovirus type 1, HSV-1, HSV-2, respiratory syncytial virus (RSV) ,HSV, Newcastle disease virus (NDV), vesicular stomatitis virus (VSV) in vitro, as well as influenza A subtypes (H1N1, H5N2,H7N3 and H9N2) in vivo. (State, 2015; Zakaryan *et al*., 2017).

OXIDATIVE STRESS AND ANTI INFLAMMATORY EFFECTS

In healthy organisms, ROS production is counterbalanced by the antioxidant defence system to maintain an appropriate redox balance (Chen *et al*., 2010; Kruidenier & Verspaget, 2002). Oxidative stress occurs when the cellular redox balance is altered, disrupting redox signalling and regulation. It can occur through the generation and action of reactive species such as superoxide anion, hydrogen peroxide, peroxynitrite, and other reactive products that can alter thiol redox circuits(Hahn, Timme-laragy, Karchner, & Stegeman, 2015).

Because of the diverse chemical structures of flavonoids and their metabolites, they can have hydrophilic or relatively lipophilic properties and may interact with plasma proteins as well as the polar surface region of phospholipid bilayers in lipoproteins and cell membranes and hence protect against free radical attacks in both lipid and aqueous environments**.** (O’Byrne, Devaraj, Grundy, & Jialal, 2002)The antioxidant capabilities of these polyphenols, as reported in a few articles, surpass that of alpha-tocopherol (Vitamin E). The presence of a catechol group in the B ring is an essential feature for the antioxidant activity, whereas the hydroxyl group at C-6 in the pyrogallol group of the A ring is not crucial for activity, since its blockade by methoxylation has no effect and the introduction of a glucuronide moiety at C-7 has a weak influence.(Sanz*et al*., 1994)

Polyphenols have some anti-inflammatory and antibiotic properties and may, in addition, activate the transcription factor Nrf2(Hussain *et al*., 2016). Nrf2 plays a crucial role in cellular protection against oxidative stress as it regulates the expression of antioxidant genes like HO-1.

There are three central kinase cascades that are involved in the Nrf-2 translocation , ERK, JNK, and p38 MAPK (Johnson & Lapadat, 2002) . Quercetin induces Nrf2 nuclear translocation and HO- 1 upregulation via the ERK/MAPK and p38/MAPK Spathway. (Yao *et al*., 2007).Hesperidin has been found to facilitate the phosphorylation of ERK1/2 and contributes to HO-1 expression and Nrf2 nuclear translocation.Other flavonoids such as Myricetin and Fisetin also inactivate the NF-κB, mTOR and Aktpathways , which inhibits the production of inflammatory mediators induced by TNF-α. (Adhami, Syed, Khan, & Mukhtar, 2012; Lee & Lee, 2016)

'Respiratory burst' of neutrophils, a common phenomenon in which superoxide radicals and other reactive oxygen species are generated by neutrophils, with microbicidal intent. However, this mechanism consequently leads to damage to surrounding host tissue. Inhibition of Respiratory burst by flavonoids like quercetin and kaempferol involves prevention of generation of ROS in the NADPH oxidase pathway by a multienzyme complex of the same name (Ciz *et al*., 2012)

Citrus extracts were found toprevent oxidative stress in human adipocytes and retard free radical-induced hemolysis of erythrocytes(Ramful *et al*., 2010). Other citrus fruits have also shown promising activity. Low concentrations of juice extracts from *Citrus bergamia* reduce the LPS-induced inflammatory response in THP-1 monocytes through SIRT1-mediated NF-kB inhibition and exert an anti-inflammatory effect in vivo.

Epicatechin, a flavan-3-ol found in cocoa bean stimulates the antioxidant defence response by activating redox-regulated transcription factors, and a phenolic cocoa extract protects against oxidative stress by modulating the antioxidant enzyme activities through Extracellular Regulated Kinase (ERK) pathways in hepatic cells. (Cordero-Herrera, Martín, Goya, & Ramos, 2015).

MOLECULAR MECHANISMS

Flavonoids like quercetin, luteolin and apigenin were found to cause wild type p53 accumulation in non-cancerous cells, causing arrest of cell cycle at G2/M phase,and subsequently undergoing apoptosis(Plaumann, Fritsche, Rimpler, Brandner, & Hess, 1996).

Immune response

Flavanols like quercetin and epicatechin act as anti-inflammatory molecules by preventing the formation of inflammatory mediators like Leukotriene B4 (LTB4) by inhibiting human 5-LOX, an enzymatic component of LTB4(Xiao *et al*., 2011). They are also known to stimulate T cell production of the cytokine IFN-γ, which brings about various immune responses against tumours and pathogens.

Quercetin is an effective inhibitor of phospholipase A2 (PLA2), hence protecting Skeletal and motor nerve membrane phospholipid hydrolysis by phospholipase A2 (PLA2), a potent component of snake venom. Other phospholipases like PLA2-IIA and PLA2-IB are also inhibited. This property can be attributed to the C-ring-2,3-double bond.(Kim, Son, Chang, & Kang, 2004)

Glucose metabolism

Quercetin, on its own, is known to decrease blood glucose levels after treatment of 9-10 days. In complex with Vanadium, it is shown to enhance insulin produced by Streptozotocin damaged β-pancreatic cells. (SZT-diabetes). Isoflavonoids like puerarin, decrease plasma glucose concentration in general, hence ameliorating hyperglycaemic and SZT-diabetic conditions in murine models(Cazarolli *et al*., 2008)

Cognition and memory

Flavonoids have been studied for their effects on neuronal protection and cognition and have shown promising results, which are still yet to be fully comprehended. Their activity is linked with either of five different pathways (PKA,PKB, PKC, ,CaMKIV or ERK) finally resulting in activation of CREB (cAMP-response element-binding protein), which is responsible for the promotion of many genes coding for synapse reshaping proteins and those linked with an increase in synaptic plasticity (Spencer, Vauzour, & Rendeiro, 2009).

They play an essential role in cognition, dementia and dementia-like diseases such as Alzheimers Disease (AD), by preventing the accumulation of beta-amyloid (Aβ), produced by the degradation of the amyloid precursor protein (APP)(Flanagan, Müller, Hornberger, & Vauzour, 2018).The mechanisms to achieve this include metal ion chelation, modulation of metalloproteinase domain-containing protein 10 (ADAM10) and A disintegrin(Obregon *et al*., 2006), which in result in enhanced cleavage of APP and hence preventing the formation of Aβ.

DNA interactions

The mechanism by which flavonoids bind with DNA is significantly dependent on the substituent to the standard 15 carbon backbone. These include base pair intercalation, loop, minor groove binding etc. in various forms of DNA such as ct-DNA, ds DNA and quadruplex forms. The base intercalation has been further confirmed by the fact that certain polyhydroxy substituted flavonoids get displaced by Ethidium bromide, which is known to intercalate. (Sengupta, 2019)

They can bind to phosphates or the base pairs, and stabilise the duplex or cause a transformation from B to A type DNA at higher concentrations (Kanakis, Tarantilis, Polissiou, Diamantoglou, & Tajmir-Riahi, 2005)

Table 1:Cell lines used to study the benefits of flavonoids

Type/Source organ	Name
Prostrate epithelial	RWPE-1, WPE1-NA22, WPE1-NB14, WPE1-NB11 and WPE1-NB26 (Sak, 2014)
Brain	Microglial cells from cerebral cortices of C57BL/6 mice Neurons from Tg2576 mice Human neuroblastoma SH-SY5Y cells (Gao *et al*., 2001) Swedish mutant human APP (SweAPP. N2a cells) (Obregon *et al*., 2006)
Colon cancer	HT15, HT116, HT29 (Adhami*et al*., 2012)
Melanoma cells	A375, (Liu-Smith & Meyskens, 2016) SK-Mel-28, B16F10, SK-Mel-1 (Rodriguez *et al*., 2002)
Lung carcinoma	H441,H520,H460, H461
Breast cancer	MDA-MB-231, (Trivedi, Ahmad, Sahabjada, & Misra, 2018) MDA-MB-435, MDA-MB-453, BT549 (Boadi, Myles, & Garcia, 2019)
Glioblastoma	U251, TG1, GL-15 (da Silva *et al*., 2019)
Hepatic	L02 (Chen *et al*., 2010), HepG2 (Sun, Tao, Huang, Ye, & Sun, 2019)

Uterine	HeLa, RL95‑ 2, SiHa
Ovary	A2780, OVCAR‑ 5, SK‑ OV3 (Sak, 2014)
Others	HaCaT cells (Lee & Lee, 2016), Phenochromocytoma cells (PC12) (Velmurugan, Rathinasamy, Lohanathan, Thiyagarajan, & Weng, 2018) human first trimester trophoblast cell line HTR-8/SVneo, (Ebegboni, Dickenson, & Sivasubramaniam, 2019) Sarcoma-180 cell line (Raja, Mathuram, & Kumanan, 2018) human monocytic THP-1 cell line, normal fibroblast C-12352 cell lines(Vergara Barragán *et al*., 2019) human adipocyte cell SW872, (Ramful *et al*., 2010) Human kidney cancer cell HEK293 (Boadi *et al*., 2019)

Discussion and Conclusion

This review reflects on the different sources of flavonoids which are widely used in traditional or folk medicine. It is evident that these plants are continuously being screened for their pharmacological properties. Usage and study of crude extracts have led to the isolation of new compounds. However some of the folk medicines are understudied. Flavonoids are such phytochemicals exhibit many biological properties which are beneficial for human health. They are rich sources of natural antioxidants in human diets. Flavonoids counterbalance the harmful effects of free radicals in the best of ways and thus help in the prevention of many diseases. They interact with a great number of cellular targets such as anti-oxidant, free-radical scavenger activities and also the anti-inflammatory, antibacterial, antiviral, anti-aging and especially anti-cancer properties.Their applications in industry are beyond the limit of nutraceuticals and drug candidate molecules.

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Conflicts

None

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