Review Article

Flavonoids: The Future of Natural Remedies

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ABSTRACT

Fruits, vegetables, grains, bark, roots, stems, flowers, tea, and wine all contain flavonoids, a class of organic compounds with varying phenolic structures. The health benefits of these natural compounds are widely recognised, and attempts are being undertaken to separate the so-called flavonoids from the other constituents. In a wide range of nutraceutical, pharmacological, therapeutic, and cosmetic uses, flavonoids are increasingly seen as an essential component. This is explained by their ability to influence the activity of essential cellular enzymes as well as their anti-oxidative, anti-inflammatory, anti-mutagenic, and anti-carcinogenic capabilities. With the revelation of the low cardiovascular death rate and also CHD prevention, research on flavonoids gained an additional boost. Uncertainty still exists regarding the flavonoids' functioning processes. However, it has long been understood that products with a plant origin have a wide range of biological activities. The separation, characterization, identification, and functions of flavonoids, as well as their applications for improved health, are the current developments in flavonoid research and development. Molecular docking and bioinformatics expertise are increasingly being utilised to forecast prospective industrial uses and production. In this study, efforts have been made to examine current flavonoid research and development trends, flavonoid modes of action, flavonoid functions, and flavonoid applications. It has also been predicted that flavonoids may one day be used as medications to prevent chronic illnesses.

Keywords: Flavonoids, Biological activity, Bioflavonoids, Nutraceuticals, Pharmacological Potential.

INTRODUCTION

Plants include a class of natural substances known as flavonoids, which have varying phenolic structures. A novel chemical was extracted from oranges in 1930. It was given the name vitamin P at the time because it was thought to belong to a novel class of vitamins. Later, it was discovered that this component was a flavonoid (rutin), and as of today, more than 4000 different flavonoid variants have been discovered.

Plants are always containing flavonoids, which are a wide category of polyphenolic chemicals with a benzo-pyrone structure. By using the phenylpropanoid route, they are produced. The information that is now available suggests that flavonoids and other secondary phenolic metabolites are in charge of a wide range of pharmacological effects. Plants are known to produce flavonoids, which are hydroxylated phenolic compounds, in response to microbial infection[1]. Their actions are governed by structure. The structural class, level of hydroxylation, various substitutions and conjugations, and level of polymerization all affect the chemical makeup of flavonoids. The possible health advantages brought on by these polyphenolic compounds' antioxidant properties have sparked recent interest in these chemicals. Flavonoids' functional hydroxyl groups scavenge free radicals and/or chelate metal ions to exert their antioxidant properties. Chelation of metals may be essential for preventing the production of radicals that harm target biomolecules[2].

Flavonoids are believed to have health-promoting qualities as dietary components because of their strong antioxidant activity in both in vivo and in vitro systems. Flavonoids can activate the human body's defense-enhancing enzyme systems. Numerous studies have revealed that flavonoids have preventive properties against a variety of bacterial and viral infections as well as degenerative illnesses including cancer, cardiovascular disease, and other age-related illnesses.

This review includes different descriptions of the protective mechanisms that flavonoids offer. In plant tissues subjected to various abiotic and biotic stressors, flavonoids also function as a secondary antioxidant defence mechanism. Flavonoids are found in ROS production centres and the nuclei of mesophyll cells. They control plant growth factors like auxin as well. Several bacteria and fungi have integrated biosynthetic genes for improved flavonoid synthesis. The structural features of flavonoids and their preventive functions against a variety of human illnesses are covered in this study. Flavonoids' roles in plants and the microbes that produce them have also been discussed[3].

Chemistry of Flavonoids

Flavonoids have a fifteen-carbon skeleton made up of two benzene rings (A and B, as illustrated in Figure 1) connected by a heterocyclic pyrane ring (C), which gives them their chemical structure. These include flavones (such as flavone, apigenin, and luteolin), flavonols (such as quercetin, kaempferol, myricetin, and fisetin), flavanones (such as flavanone, hesperetin, and naringenin), and others. While individual compounds within a class differ in the pattern of substitution of the A and B rings, the many

classes of flavonoids vary in the amount of oxidation and pattern of substitution of the C ring.

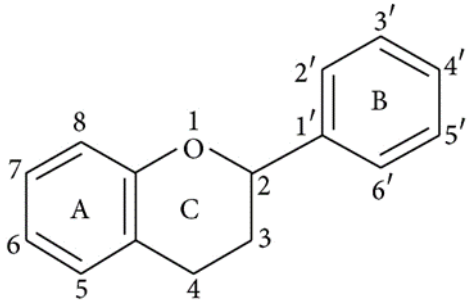

Figure 1: General backbone structure of Flavonoids[4]

Spectral Characteristics of Flavonoids

According to studies on flavonoids using spectroscopy, the majority of flavones and flavonols display two main absorption bands: Band I (320-385 nm) denotes the absorption of the B ring, whereas Band II (250-285 nm) denotes the absorption of the A ring. There may be a change in the wavelength of absorption due to functional groups connected to the flavonoid skeleton, such as from 367 nm for kaempferol to 371 nm for quercetin to 374 nm for myricetin (3,5,7,3′,4′,5′-hydroxyl groups). The difference between flavones and flavonols is the absence of a 3-hydroxyl group.

According to their UV spectral properties, flavanones contain a saturated heterocyclic C ring and no conjugation between the A and B rings. Flavanones show just a shoulder for Band I at 326 and 327 nm and a very significant Band II absorption maximum between 270 and 295 nm, namely 288 nm for naringenin and 285 nm for taxifolin. In compounds with a monosubstituted B ring, Band II shows one peak (270 nm), but when a di-, tri-, or o-substituted B ring is present, Band II shows two peaks or one peak (258 nm) with a shoulder (272 nm)[5]. The colour of anthocyanins varies with the quantity and location of the hydroxyl groups because they exhibit discrete Band I peaks in the 450–560 nm area owing to the hydroxyl cinnamoyl system of the B ring and Band II peaks in the 240–280 nm region due to the benzoyl system of the A ring.

Classification

- **Flavonols**

Flavonoids with a ketone group are called flavonols. They serve as proanthocyanins' building components. 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. In addition to fruits and vegetables, other sources of flavonols include tea and red wine[6]. Consumption of flavonols has been linked to a number of health advantages, including antioxidant capacity and a decreased risk of vascular disease. When compared to flavones, flavonols have a third hydroxyl group on the C ring, which is also capable of being glycosylated. Given the many glycosylation patterns, flavonols, like flavones, have extremely variable methylation and hydroxylation patterns. They are also likely the most prevalent and biggest subclass of flavonoids in fruits and vegetables. For instance, quercetin may be found in many plant-based diets.

- **Neoflavonoids**

A subclass of polyphenolic chemicals are neoflavonoids. Neoflavonoids contain a 4-phenylchromen backbone with no substitution of the hydroxyl group at position 2, in contrast to flavonoids, which have a 2-phenylchromen-4-one backbone. Calophyllolide, a neoflavone found in seeds of the plant *Calophyllum inophyllum*, was the first one discovered in natural sources in 1951[7]. It can also be observed in the bark and wood of the unique shrub *Mesua thwaitesii* from Sri Lanka.

- **Flavan-3-ols, catechins, or flavanols**

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. The fruits and vegetables bananas, apples, blueberries, peaches, and pears are rich in flavanols[8].

- **Anthocyanins**

Anthocyanins are pigments that give plants, flowers, and fruits their hues. The anthocyanins that are most often researched are cyanidin, delphinidin, malvidin, pelargonidin, and peonidin. They are mostly found in the outer cell layers of a variety of fruits, including bilberries, blackberries, raspberries, strawberries, red grapes, black currants, and red and merlot grapes[9,10]. These chemicals' stability and health advantages make it possible for them to be employed in the food sector for a range of purposes. The pH and methylation or acylation at the hydroxyl groups on the A and B rings also affect the anthocyanin's hue.

- **Chalcones**

A subtype of flavonoids is chalcones. Their distinctive feature is the lack of "ring C" from the fundamental flavonoid skeleton structure seen in Fig. 1. As a result, they are also known as open-chain flavonoids. Phloridzin, arbutin, phloretin, and chalconaringenin are some prominent chalcone instances. Significant levels of chalcones may be found in tomatoes, pears, strawberries, bearberries, and some wheat products. Chalcones and their derivatives have drawn a lot of interest due to their multiple biological and nutritional advantages[11].

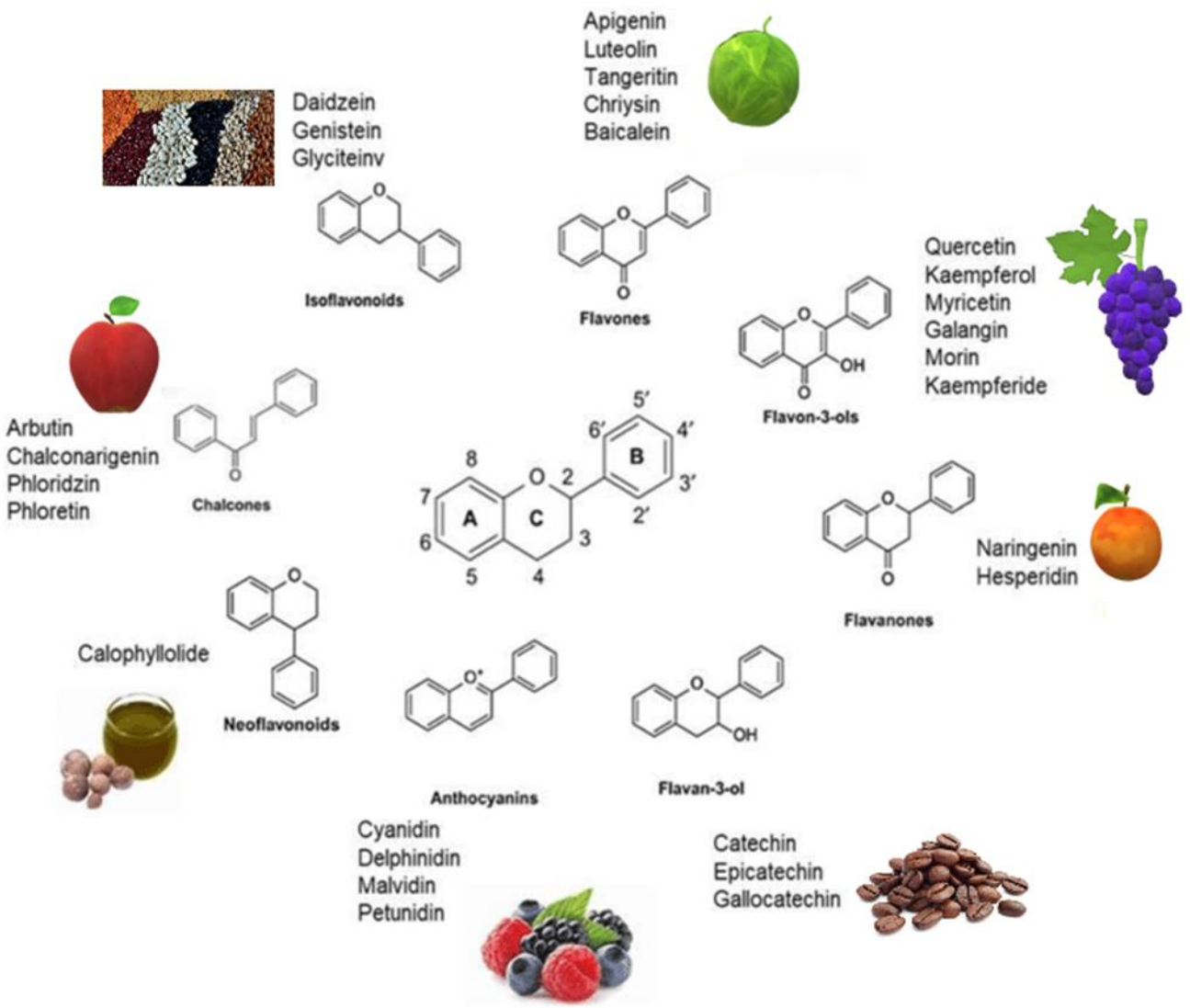

Figure 2: Classification of Flavonoids with their sources[12]

Flavonoids as a food nutrient

The most prevalent and extensively dispersed class of phenolic chemicals found in plants, flavonoids are mostly found in the cells of plants that are capable of photosynthesis. They play a significant role in blooming plants' colouring. Animal and human diets both include flavonoids. Flavonoids are phytochemicals that neither humans nor animals can synthesise. As a result, flavonoids in animals come from plants rather from being produced on-site through biosynthesis[13]. The majority of flavonoids found in food are flavonols. Food flavonoids are often responsible for colour, flavour, stopping fat from oxidising, and protecting vitamins and enzymes.

The soy isoflavones, flavonols, and flavones are the flavonoids that are present in the human diet in the greatest concentrations. Although catechins are present in most fruits and certain legumes, the quantities range from 4.5 to 610 mg/kg. a variety of the techniques utilised, food preparation and processing might reduce the amount of flavonoids present[14]. In a recent research, for instance, it was shown that orange juice had 81–200 mg/L of soluble flavanones, but cloud content was 206–644 mg/L, indicating that the flavanones are concentrated in the cloud during processing and storage. Because there are so many different types of flavonoids accessible, they are widely distributed in a variety of plants, and people consume them in a variety of ways, it is challenging to estimate the typical dietary intake of flavonoids.

The therapeutic potential of medicinal plants has recently attracted more attention, which may be attributed to their phenolic components, particularly flavonoids[15]. Since the beginning of human life on Earth, or for around 4 million years, people have ingested flavonoids. They possess a wide range of biological qualities that enhance human health and lower the risk of illness. It is believed that oxidative alteration of LDL cholesterol plays a crucial part in atherosclerosis[16].

The primary polyphenolic ingredient in *Glycyrrhiza glabra* (Fabaceae), isoflavan glabridin, which prevents LDL oxidation by scavenging free radicals. Drinking green or

black tea may decrease blood cholesterol levels and blood pressure, offering some protection against cardiovascular disease, according to a number of epidemiologic studies. By serving as flavorants, colourants, and antioxidants, flavonoids are also known to affect the quality and stability of food[17,18]. Berries' flavonoids may be effective in preventing Parkinson's disease and aiding the memory of elderly persons. In hypertensive rats, *Astragalus complanatus*' total flavonoid fraction had an antihypertensive effect. Consumption of antioxidant flavonoids has been found to be negatively correlated with the chance of developing dementia[19].

The solubility of flavonoids may be a significant factor in their medicinal effectiveness. With the exception of a very uncommon case of allergy, flavonoid ingestion does not cause immediate harmful effects in humans due to the poor solubility of flavonoid aglycones in water, short intestinal residence time, and low absorption. The limited solubility of flavonoids in water frequently hinders their use in medicine. As a result, the creation of semi-synthetic, water-soluble flavonoids such hydroxyethylrutosides and inositol-2-phosphatequercetin has been linked to the treatment of hypertension and microbleeding[20].

Flavonoid's role in plants

- **As a growth regulator**

Flavonoids have crucial functional functions in how plants interact with their environment. Flavonoids may control the transport and degradation of auxins (in the nanomolar range). Flavonoids' capacity to produce auxin gradients results in phenotypes with various morphoanatomical characteristics. In stress-induced morphogenic responses of plants, such as the flight strategy of sessile animals exposed to unfavourable circumstances, the influence of flavonoids on auxin transport may be of tremendous importance[21]. When compared to species rich in monohydroxy flavonoids, those rich in dihydroxy flavonoids have morphologies with phenotypical features that are noticeably different. In sunny situations, dwarf bushy phenotypes with few, tiny, and thick leaves are typically prevalent, shielding plants deep in the canopy from light-induced severe cellular homeostasis disruptions. Contrarily, shaded plants have long internodes, broad leaf lamina, and decreased leaf thickness[22]. They are also high in kaempferol and/or apigenin derivatives (with low quantities of quercetin derivatives).

Auxin is transported from cell to cell by PIN (pin formation) and MDR (multidrug resistance) glycoproteins, which are both efficiently inhibited by flavonoids at the plasma membrane. The presence of the catechol group in the B ring of the flavonoid skeleton is necessary for flavonoids to be able to block the action of the efflux facilitator PIN and MDR proteins. Additionally, based on their chemical makeup, flavonoids influence IAA-oxidase activity in a variety of distinct ways[23]. Flavonoids are capable of influencing the activity of proteins involved in cell development, according to recent research that suggests flavonoids (as well as enzymes of flavonoid production) are located in the nucleus. Therefore, flavonoids could control transcription.

- **Combating Oxidative Stress**

It has long been known that flavonoids have a variety of uses in plants. Different biotic and abiotic factors contribute to the production of ROS in plants, which causes oxidative stress. Oxidative stress nearly solely increases flavonoid production in plants. They are able to quench ROS after they have formed, suppress the production of ROS, and absorb the UV-B and UV-A wavelengths that are the most intense from the sun[24,25]. When early plants migrated from the water to the land for colonisation, flavonoids discharged their principal UV-B filtering capabilities. The kind of substitution on various rings of flavonoids determines the extent of antioxidant capability and UV-wavelength absorption. While their monohydroxy B ring substituted cousins are better at absorbing UV rays, dihydroxy B ring substituted flavonoids have more antioxidant capability.

In flavonoids, the most reactive hydroxyl groups—the 7-OH in flavones and the 3-OH in flavonols—are often glycosylated. Flavonoids may be transported from the endoplasmic reticulum to different cellular compartments and their secretion to the plasma membrane and cell wall thanks to glycosylation, which also enhances solubility in the aqueous cellular environment and guards the reactive hydroxyl groups against autooxidation. Recent research demonstrates that the chloroplast and the nucleus of mesophyll cells, which are ROS production hubs, contain antioxidant flavonoids[26]. Here, they may quickly extinguish singlet oxygen, the hydroxyl radical, and H_2O_2.

Under circumstances that restrict the diffusion of CO2 to the carboxylation sites and the efficacy of carboxylation, oxidative stress brought on by an excess of excitation energy in the chloroplast may be worsened. Drought/salinity, low/high temperature, and nutrient shortage are some of the environmental factors that restrict the rate of CO2 absorption. Under these circumstances, the chloroplast's ROS detoxifying enzyme activity may be greatly reduced, which in turn triggers an increase in the manufacture of ROS-scavenging flavonoids[27]. In plants experiencing extreme stress, the lowering properties of flavonoids are crucial. The extremely high quantity of dihydroxy B ring substituted flavonoids coexists with these functional activities. In plant tissues subjected to various stressors, flavonoids have been proposed as a secondary antioxidant defence mechanism. Lipid peroxidation is a frequent result of oxidative stress, which compromises the integrity of the cell membrane. Rutin, a form of quercetin 3-O-rutinoside, may interact with phospholipid polar heads at the water-lipid interface, increasing membrane stiffness and so shielding membranes from oxidative damage[28].

Pharmacological effect

- **Anti-oxidant potential**

In the human body, reactive oxygen species (ROS) are mostly created as byproducts of the electron transport chain. They are necessary for the processes of immunity, differentiation, apoptosis, protein phosphorylation, and the beginning of various transcriptional factors. Nevertheless, when ROS interact with molecules like lipids, proteins, or nucleic acids, they also result in oxidative stress. ROS-induced lipid peroxidation damages cellular membranes[29] .With positive charges on the cell's outside and negative charges within, this membrane possesses an electrical potential. Damage to the membrane changes the cell's somotic pressure and membrane potential, ultimately leading to cell death. To combat endogenous increased ROS, the human defence system employs a variety of mechanisms and enzymes. Through four different mechanisms—namely, the inhibition of nitric-oxide synthase activity, the inhibition of xanthine oxidase activity, the modulation of channel pathways, or the interaction with other enzyme systems—flavonoids act as exogenous antioxidants and directly oxidise radicals to form less reactive species[30].

The location and total number of -OH groups in the molecule, conjugation and resonance effects, the environment surrounding the thermodynamically preferred antioxidant site, and the specific antioxidant mechanism for a compound are all factors that affect the antioxidant potential of flavonoids. Vitamins C and E are the two antioxidant supplements that are most often utilised[31]. Flavonoids have more antioxidant capacity than vitamins C and E. Consequently, it's crucial to consistently incorporate foods high in flavonoids, such as those fruits and vegetables, in your daily diet. For instance, flavonoids promote and are recognised for their anti-inflammatory and antioxidant effects, which benefit bone health. Flavonoids included in biomaterials have great promise for bone tissue engineering. This demonstrated the need for flavonoids to be added to the diets of older persons.

In its conjugated form, the antioxidant flavonoid quercetin enhances vascular health and lowers the risk of cardiovascular disease when it is present in the blood stream.Blood coagulation and the risk of stroke are both prevented by quercetin and its derivatives.Two flavonoids called hesperidin and hesperetin, which are found in citrus fruits and mushrooms, have been shown to have antioxidant, anti-inflammatory, antibacterial, and anticancer properties. Propolis is presently utilised in the pharmaceutical sector after years of usage as a folk remedy.It includes a variety of substances, including flavonoids, which are in charge of giving them their medicinal benefits, including their antioxidant, antibacterial, healing, and anti-proliferative qualities.A flavonol called rutin shown a variety of biological properties, such as cytoprotective, antioxidant, and anticancer properties.In vitro, sorghum has a strong antioxidant activity. The greatest antioxidants come from sorghums' flavonoids and tannins.

These findings demonstrated the need to promote sorghum grains and the products derived from them for use in meals. The small intestine absorbs sorghum flavonoids at a high rate. Although tannins render the grains unfit for human eating, alkaline boiling decreases the tannin content by 73%. It is crucial to genetically alter the sorghum's pathways for tannin synthesis in order to remove tannins from the grain. This crop may thrive in difficult climatic circumstances and is excellent for dry areas. The whole human population will have access to sorghum grains that are high in flavonoids in this way.

A group of polyphenols known as carotenoids have antioxidant properties. A flavonoid called fisetin (3, 3′, 4′, 7-tetrahydroxy flavone) exhibits both antioxidant and anti-inflammatory properties. *Eleutherine bulbosa* (Mill.) Urb. has aerial portions with a high flavonoid content and shown antioxidant action. The onion, *Allium cepa*. L, shown antioxidant properties. The medicinal aromatic herbs dill (*Anethum graveolens* L.) and parsley (*Petroselinum crispum* Mill.) contain phenolic and flavonoid compounds that make them potent antioxidants that can lower ROS species and fend against illnesses like cancer and cardiovascular problems that are caused by ROS[32,33]. Different processes, such as disintegrating peroxides and chelating metal ions that catalyse the oxidation process, may be responsible for these species' antioxidant activity. This antioxidant activity is correlated with the phenolic and flavonoid content (PC and FC); generally speaking, the higher the PC and FC, the higher the antioxidant activity displayed by the herbal plant. The addition of these herbs to everyday meals would enhance the nutritional content of food while also adding flavour and scent.

- **Cardiovascular effect**

The consumption of dietary flavonoids is positively correlated with a decline in cardiovascular illnesses. Numerous studies have shown that individuals who consume a lot of flavonoids had an 18% decreased chance of dying from cardiovascular illnesses. Numerous studies have demonstrated the chemoprotective, cardioprotective, and neuroprotective properties of flavonoids[34]. Tea has a lot of flavonoids, which lowers the risk of cardiovascular problems when consumed. Flavonoids like proanthocyanidin and anthocyanidin have been shown to be useful in treating heart conditions. Improved vascular health is provided by isoflavone, anthocyanins, and cocoa flavan-3-ols. The risk of cardiovascular illnesses is decreased by the reduction in arterial stiffness caused by high ingestion of these flavonoids. Flavonoids, one of the numerous chemicals found in the oils from the leaves and fruits of *Hippophae rhamnoides* (sea buckthorn), have been shown to have beneficial benefits on the cardiovascular system. Morin hydrate has strong biological action, including anti-inflammatory, anti-cancer, and cardiovascular disease prevention. Brazil nuts are abundant in flavonoids, which lower the risk of cancer and heart

disease. A flavone, chyrsin has positive benefits on epilepsy, depression, and neuroinflammation while also having neuroprotective properties[35].

The impact of *Primula veris* L. solid herbal extract (PVSHE) on myocontractile function was investigated for the goal of pre-clinical investigations on animal models. Purifying the chemicals using column chromatography allowed for the investigation of the phenolic compound extract composition. The content of all flavonoids was determined using differential UV spectrophotometry. NMR was then used to characterise the obtained compounds. Adult Wister rats participated in an experiment in which they were separated into control, intact, and experimental groups. *Primula veris* L. herbal extract was given to them, while a comparison medication was given to the second experimental group. Surgical techniques were used to detect cardiodynamic alterations, and computational methods were used to calculate myocardial contraction rate.

To identify CHF indicators, an ELISA (enzyme linked immune-sorption assay) was performed. Acting as biological markers for *Primula* L. were polymethoxylated flavonoids. The extract went through additional processing to acquire its components, including polymethoxylated flavonoids, flavonoid aglycons, and glycosides. The most likely cause of the lowered ROS generation and inhibited peroxide creation that result in the cardio-protective action of flavonoids is their presence. The results showed a greater rate of myocardial contraction and relaxation and a decreased frequency of animal fatalities. NMR spectroscopy has been used to characterise a number of flavonoids[36]. For instance, luteolin and its glycosylated version were shown to bind to the ATP binding region of the multidrug resistant transporter by saturation transfer difference (STD)-NMR. These flavonoids thus possess anticancer qualities. The ^{13}C-NMR and QSAR approaches can be used to access the antioxidant capabilities of flavonoids.

A bioflavonoid called morin has been shown through animal modelling to be a cardio-protective agent. Morin was provided orally and in dose-dependent fashion to the experimental group of rats after being separated into groups. The induction of myocardial necrosis revealed enhanced antioxidant effects and apoptosis.

- **Anti-cancer potential**

Hesperedin (Hsp) is an important flavonoid which displays efficient anticancer activity. Polylactic-co-glycolic acid (PLGA) nanoparticles were synthesized and loaded with Hsp to form hesperidin nanoparticles (HspNPs) to determine its potential application as an anticancer agent against C6 glioma cells. The encapsulated Hsp exhibited decreased in vitro cell viability against the C6 glioma cell line, and the controlled release of Hsp decreased the cytotoxicity of PLGA[37].

Aurone, a benzo-furanone, is another flavonoid that has been extensively used as an anticancer agent. Various analogues of aurone display different mechanisms against cancer cells because there are many possible targets. These targets include cyclin dependent kinase, histone deacetylase, the adenosine receptor, telomerase, sirtuins, and microtubules.

A naturally occurring flavonoid called quercetin is found in plants and popular foods including berries, green tea, and grains. The most successful use has been for colorectal cancer. Numerous mechanisms underlie the chemo-preventive actions of quercetin in colorectal cancer, including cell cycle arrest, a surge in apoptosis, antioxidant replication, manipulation of oestrogen receptors, control of signalling pathways, suppression of metastasis, and angiogenesis.

Natural flavonoid luteolin, which promotes apoptosis in hepatocellular carcinoma (HCC) cells, stops the growth of cancer cells in the G2/M stage. Using flotillin-1 as a direct target, luteolin was discovered to directly upregulate the miR-6809-5p, which is overexpressed in HCC.A natural flavanol called kaempferol can lower the chance of developing cancer[38]. It increases the body's antioxidant defences against the cancer-causing free radicals.

Myricetin is a significant flavonoid with anti-inflammatory and anti-cancer properties. It has antimitotic actions in liver cancer and targets many mitochondrial metabolic pathways that lead to cancer cell death. The flavonoid concentration of the *Matricaria recutita* L. (chamomile) flower is 157.9 ± 2.22 mg/g QE of dry extract. It demonstrated dose-dependently increased HepG2 cell death in HCC. A crucial mechanism called angiogenesis is perverted to advance cancer. Through VEGF receptors, vascular endothelial growth factor (VEGF) promotes angiogenesis, which promotes the development of blood vessels. Synthesised extract effectively inhibited VEGF expression in a dose-dependent manner, making it a potent anticancer agent.

Gastrocotyle hispida's aerial portions were air dried and utilised for extraction in one study. The extract contained 178 mg/g QE of flavonoids. The extract underwent an in vitro experiment to assess its anticancer potential against breast, liver, and kidney cancer cell lines[39]. According to several researches, the flavonoid anticancer effect is caused by the inhibition of protein kinases, which control cellular processes. Flavonoids and prenylated chalcone have structural similarities and are frequently regarded as structural equivalents.

In vitro research on prenylflavonoids' possible anticancer properties was conducted. Recently, the cytotoxicity of four prenylated flavonoids against the human breast cancer cell line T47D was examined. These flavonoids were extracted from the fruits of *Sinopodophyllum hexandrum*. The percentage of growth inhibition found indicated that the IC50 value was less than 10 mol L^{-1}. Apples contain a lot of flavonoids, which are directly linked to a healthier heart and lower the chance of developing asthma and Alzheimer's disease. Apple flavonoids are said to lower the risk of colorectal cancer. According to studies, eating one apple a

day can cut your risk of developing cancer by up to 50%. Female hop cones contain flavonoids that are highly valuable in medicine for their anti-carcinogenic and anti-microbial properties.

The flavonoids in Emblica officinalis have a variety of pharmacological effects, including anticancer, antioxidant, anti-inflammatory, and immunomodulatory effects. Esophageal cancer is prevented by berry flavonoids. The methoxy-flavone shown chemopreventive abilities against cancer[40]. Together with their anti-inflammatory and antioxidant properties, cocoa polyphenols have anticancer properties. Epicatechin, proanthocyanidin B2, and proanthocyanidin B4—flavonoids derived from litchi—have demonstrated anti-breast cancer action. Prostate cancer is actively inhibited by soy isoflavons. Lung cancer risk is decreased by the flavonoids present in tea and other foods high in flavonoids, such as apple, onion, and others.

The effects of flavonoid modified drugs (FMD) on lung cancer cell lines A549 and L929 are much superior. Wild onions known as Allium flavum and Allium carinatum are edible and high in rutin, quercetin 3-O-glucoside, and kaempferol 3-O-glucoside, all of which are flavonoids. These are powerful anticancer agents in addition to having proven antioxidant activity. They upregulate angiogenic factor against human hepatoma (HepG2) and lung cancer (A549) cell lines when coupled with doxorubicin.

The structure of these isolated flavonoids from plant leaves was later determined using spectroscopic analysis. The isolated substance demonstrated enzyme inhibition and has potential as a cancer treatment. Over three hundred flavonoids are found in licorice (the roots of *Glycyrrhiza uralensis*), which is used to ease coughing, phlegm, and stomach pain. Recent studies demonstrate that it demonstrates a variety of pharmacological properties, including antiviral, anticancer, and antibacterial effects[41]. Baicalein and baicalin are phytochemicals that suppress tumour development in vivo and are both cytotoxic and cytostatic to a variety of human tumour cells.

The *Peganum* genus has a few plants that have been used medicinally in China for a very long period. Numerous alkaloids, flavonoids, etc. are included in this species. It has a wide range of biological effects, including anti-inflammatory, anti-tumor, anticoagulant, and anti-parasitic qualities. *Ouratea* and other genera of the Ochnaceae family include flavonoids and bioflavonoids that have significant biological effects such DNA topoisomerase inhibition, anti-tumor, antibacterial, and antiviral properties.

- **Effect on nervous system**

Particularly dementia, Parkinson's, and Alzheimer's disease, flavonoids protect against age-related neurological disorders. Numerous neurological illnesses are influenced by the ROS and nitrogen species (NOCs). Citrus fruit flavonoid tangeretin protects against ROS and NOCs species and works as an antioxidant in neurodegenerative diseases like Parkinson's disease[42].

Two flavonoids, hesperetin (Hst) and hesperidin (Hsd), are recognised for their neuro-pharmacological properties, including neuroprotection, antidepressant, and memory-enhancing actions. Berries include a variety of naturally occurring flavonoids, including polyphenolic substances like stilbene and anthocyanins. These flavonoids are said to work well as anti-mutagenic, anti-neurodegenerative, and antibacterial agents. The analogue 3-O-methyl epicatechin of the antioxidant flavonoid epicatechin, which is prevalent in wood plant life, prevents neurotoxicity in vitro. The polyphenolic luteolin flavonoid exhibits both neuroprotective and anti-age-related neurodegenerative properties. *Forsythia suspensa* is a dried fruit and a traditional Chinese medicine plant having anti-infective properties, antioxidant activity, and neuroprotective properties.

Alcoholism causes a number of health issues and has a harmful impact on the brain. When exposed with low concentrations of ethanol, the acetylpectolinarin (ACP) flavonoid found in *Linaria vulgaris* Mill. has been shown to reduce hangover symptoms by improving the spontaneous network activity of cultured hippocampus neurons[43]. Through the agonistic activity of the SK potassium channel, it affects GABAergic synapses.

Hyperalgesia, an intensified pain perception brought on by peripheral nerve degeneration, is frequently seen in diabetes patients. Combining quercetin and salt can reduce diabetic complications by acting as antinociceptives. The antioxidant 6-methoxyflavone can help lessen the hyperalgesia caused by cisplatin.

- **Anti-malarial potential**

The parasite Plasmodium species is the primary cause of malaria. The conventional antimalarial medications like chloroquine are no longer effective against Plasmodium falciparum and other species, and this resistance is spreading to artemisinin and its variants. To treat Plasmodium strains that are treatment resistant, new medications are needed. Plant extracts rich in chemicals including flavonoids, chalcones, terpenes, quinones, and xanthones have been shown to have antimalarial properties in the ongoing endeavour to synthesise antimalarial drugs. Prosopis is a genus of plants that has been used medicinally for a long time. Flavonoids, tannins, and alkaloids are only a few of its constituents. These bioactive substances have antimalarial, ulcer-healing, and antibacterial properties.

Psiadia species extract includes terpenoids, phenylpropanoids, coumarins, and flavonoids. It displays pharmacological effects as antibacterial, antiviral, anti-inflammatory, and antimalarial ones. Some plant extracts, like those from *Psiadia dentata* and *Psiadia arguta*, stop Plasmodium falciparum from growing[44]. Extract from Waltheria indica (also known as *Waltheria americana*) contains flavonoids, epicatechin, kaempferol, quercetin, and other compounds. It is used to cure inflammation, reduce oxidative stress, and treat infectious disorders such malaria and bacterial lung infections caused by *Klebsiella*

pneumoniae and Escherichia coli. *Artocarpus styracifolius* bark-derived prenylated flavonoids have antiplasmodial and antitrypanosomal properties. Silymarin has been extracted and refined from *Silybum marianum*. Silymarin, a polyphenolic flavonoid with anti-plasmodial properties, prevents the transformation of poisonous free heme into crystalline non-toxic heamozoid by forming the silymarin-heme complex. The leaf extract of *Indigofera oblongifolia* is effective against malaria and defends the liver against damage brought on by *P. chabaudi* by acting as an antioxidant and an anti-inflammatory[45].

- **Anti-fungal potential**

According to the emergence of resistance and unfavourable side effects, the currently existing antifungal medications are not totally effective, necessitating the development of new antifungal medicines. *Aquilaria* leaves contain a variety of bioactive substances, including flavonoids that give them their antiviral, antifungal, and anticancer properties. Sacriflavone A and Sacriflavone B, two flavonoids found in *Artemisia sacrorum* extract, both exhibit potent antifungal properties. Additionally, the prenyl flavonoid 2′,4′-dihydroxy-5′-(1‴,1‴-dimethylallyl)-8-prenylpinocembrin (8PP) was isolated from *Dalea elegans* and has antifungal properties against *Candida albicans* biofilms.

- **Anti-diabetic potential**

Cranberry flavonoids have been demonstrated to lower blood glucose levels and improve insulin sensitivity in mice. Anthocyanins reduce obesity, which helps to avoid type 2 diabetes as a result. Chrysin is a natural flavone with several health advantages, including impacts on diabetes, allergies, cancer, and tumours[46]. Numerous flavonoids alleviate hyperglycemia, decrease insulin resistance, enhance skeletal muscle absorption of glucose, and increase insulin production, all of which are anti-diabetic effects. In healthy patients, chocolate high in flavonoids improves insulin sensitivity and lowers insulin resistance. Onion flesh and skin are abundant in quercetin derivatives, have inhibitory effect against protein tyrosine phosphatase 1B (PTP1B), reduce the expression of PTP1B, and improve glucose absorption, making them promising anti-oxidants and anti-diabetic drugs.

In the digestive system, flavonoids play a number of critical roles, including lipid metabolism and glucose regulation. Black bean anthocyanins offer anti-diabetic properties. O-prenylated flavonoids found in the extract of Melicope lunuankenda leaves have antidiabetic action against type 2 diabetes. Black carrots (Daucus carota) contain flavonoids that can treat diabetes and obesity. Citrus fruits contain naringenin and its glycosides, which have antioxidant and anti-diabetic properties. Numerous naturally occurring substances, such as flavonoids and polyphenols with antibacterial and anti-diabetic properties, are found in the genus Sterculia.

A naturally occurring flavonoid called kaempferol functions as an anti-diabetic drug by preventing cell division, lowering the expression of PI3K, P63, and SREBP-1, and phosphorylating the substrates of insulin resistance [47].

The plant Warionia saharae is high in flavonoids. Animal models were utilised to demonstrate its extract's antidiabetic effects. Diabetes was produced in rats using the drug treptotocin (STZ), while healthy rats served as the control group. After 15 days of oral treatment of the extract, a liver histological examination and a glucose tolerance test were conducted. The test group rats' liver and pancreas were found to be in better condition, and the treatment showed promise as both an effective antioxidant and antidiabetic. New methods should be developed to maximise the absorption of flavonoids in order to address the problems with their absorption and bioavailability.

In one of these studies, glycosylated hydrophilic flavonoid baicalin was placed into nano-structured lipid carriers. These baicalin-containing medications were tested on diabetic rats, and it was shown that they significantly reduced blood sugar levels via preventing lipid peroxidation.

Although several research using murine models have demonstrated that hesperidin regulates blood glucose levels, human clinical trials have not produced the same results. Therefore, the vast majority of clinical investigations suggest that hesperidin did not affect insulin or the enzymes involved in the metabolism of glucose. These clinical studies' hesperidin absorption-related limitations do exist.

Methylglyoxal is a metabolite whose blood content rises when a person has diabetes. It induces atherogenesis (a disease in which artery blockages are brought on by artheromatous plaque development) and damages nerves by attaching to nerve endings[48]. While epicatechin had no discernible benefit, clinical studies on quercetin showed a reduction in the plasma level of methylglyoxal.

- **Anti-viral potential**

Cordata Houttuynia A plant native to Eastern Asia called thumb exhibits promise antiviral properties in vitro against enveloped viruses including the influenza virus, herpes simplex virus type 1, and human immunodeficiency virus type 1. Flavonoids, both natural and synthetic, have the potential to treat a wide range of illnesses, including HIV. The flavonoids glabranine and 7-O-methyl-glabranine were taken from the Tephrosia madrensis plant in Mexico. These isolates have antiviral properties that prevent dengue virus multiplication, according to the results of the plaque assay. Spectroscopic analysis was used to determine the structures of the isolates, and [3H]-thymidine test was used to analyse the stoichiometry and cytotoxicity[49]. Glabranine suppressed the reproduction of the dengue virus by 76.9% at a concentration of 25 M, whereas 7-O-methyl-glabranine did so by 75%.

Chikungunya virus is actively inhibited by the antioxidants baicalein, quercetin, and fisetin. Murine norovirus is lessened by epicatechin 3-gallate, fisetin, quercetin, and

daidzein, while feline calicivirus is lessened by kaempferol. Four flavonoids that were isolated from the Mosla scabra plant (5-hydroxy-7,8-dimethoxyflavone, 5-hydroxy-6,7-dimethoxyflavone, acacetin, and apigenin) have antiviral action against influenza viruses. *Castanea crenata*'s burs (involucre) are thought to contain a variety of bioactive phytoconstituents, including flavonoids, tannins, phenolic acids, coumarins, phenylpropanoids, and steroids. The SRB technique was used to assess the extract's antiviral activity utilising the cytopathic effect (CPE) reduction test in HeLa or Vero cells. With regard to HRV1B, CVB3, and PR8, the isolated flavonoid kaempferol exhibited improved antiviral activities. Flavonoid analogues are also discovered to be effective against H1N1 virus neuraminidase using molecular docking and simulation studies.

Due to the presence of flavonoid, a bioactive component, in the roots of Scutellaria baicalensis, a member of the Lamiaceae family plant, which has been used as a medicinal herb for generations, it has positive health effects. Utilising an animal model, the root extract was given after the influenza virus had been inhaled for two hours. The histopathology showed considerable suppression of IAV-infected mice with a higher survival rate and a decrease of oxidative stress by reducing NO generation[50].

Role of Flavonoids in Plants

- **Combating Oxidative Stress**

It has long been known that flavonoids have a variety of uses in plants. Different biotic and abiotic factors contribute to the production of ROS in plants, which causes oxidative stress. Oxidative stress nearly solely increases flavonoid production in plants. They are able to quench ROS after they have formed, suppress the production of ROS, and absorb the UV-B and UV-A wavelengths that are the most intense from the sun. When early plants migrated from the water to the land for colonisation, flavonoids discharged their principal UV-B filtering capabilities. The kind of substitution on various rings of flavonoids determines the extent of antioxidant capability and UV-wavelength absorption. While their monohydroxy B ring substituted cousins are better at absorbing UV rays, dihydroxy B ring substituted flavonoids have a stronger potential as antioxidants.

In flavonoids, the most reactive hydroxyl groups—the 7-OH in flavones and the 3-OH in flavonols—are often glycosylated. Flavonoids may be transported from the endoplasmic reticulum to different cellular compartments and their secretion to the plasma membrane and cell wall thanks to glycosylation, which also enhances solubility in the aqueous cellular environment and guards the reactive hydroxyl groups against autooxidation[51-55]. Recent research demonstrates that the chloroplast and the nucleus of mesophyll cells, which are ROS production hubs, contain antioxidant flavonoids. Here, they may quickly extinguish singlet oxygen, the hydroxyl radical, and H_2O_2.

Under circumstances that restrict the diffusion of CO2 to the carboxylation sites and the efficacy of carboxylation, oxidative stress brought on by an excess of excitation energy in the chloroplast may be worsened. Drought/salinity, low/high temperature, and nutrient shortage are some of the environmental factors that restrict the rate of CO2 absorption. Under these circumstances, the chloroplast's ROS detoxifying enzyme activity may be greatly reduced, and this in turn triggers an increase in the manufacture of ROS-scavenging flavonoids[56,57]. In plants experiencing extreme stress, the lowering properties of flavonoids are crucial. The extremely high quantity of dihydroxy B ring substituted flavonoids coexists with these functional activities. In plant tissues subjected to various stressors, flavonoids have been proposed as a secondary antioxidant defence mechanism. Lipid peroxidation is a frequent result of oxidative stress, which compromises the integrity of the cell membrane. Rutin, a form of quercetin 3-O-rutinoside, may interact with phospholipid polar heads at the water-lipid interface, increasing membrane stiffness and so shielding membranes from oxidative damage[58,59].

- **As Growth Regulator**

Flavonoids have crucial functional functions in how plants interact with their environment. Flavonoids may control the transport and degradation of auxins (in the nanomolar range). Flavonoids' capacity to produce auxin gradients results in phenotypes with various morphoanatomical characteristics. In stress-induced morphogenic responses of plants, including the flight strategy of sessile animals exposed to unfavourable circumstances, the influence of flavonoids on auxin transport may be of tremendous importance. When compared to species rich in monohydroxy flavonoids, those rich in dihydroxy flavonoids have morphologies with phenotypical features that are noticeably different[60]. In sunny situations, dwarf bushy phenotypes with few, tiny, and thick leaves are typically prevalent, shielding plants deep in the canopy from light-induced severe cellular homeostasis disruptions. Contrarily, shaded plants have long internodes, broad leaf lamina, and decreased leaf thickness. They are also high in kaempferol and/or apigenin derivatives (with low quantities of quercetin derivatives).

Auxin is transported from cell to cell by PIN (pin formation) and MDR (multidrug resistance) glycoproteins, which are both efficiently inhibited by flavonoids at the plasma membrane. The presence of the catechol group in the B ring of the flavonoid skeleton is necessary for flavonoids to be able to block the action of the efflux facilitator PIN and MDR proteins. Additionally, based on their chemical makeup, flavonoids influence IAA-oxidase activity in a variety of distinct ways[61]. Flavonoids are capable of influencing the activity of proteins involved in cell development, according to recent research that suggests flavonoids (as well as enzymes of flavonoid production) are located in the nucleus. Therefore, flavonoids could serve as transcriptional regulators.

Future perspective and developments

Over the past ten years, flavonoids have attracted a lot of interest in the literature, and a number of possible positive benefits have been clarified. However, some investigations that were conducted included in vitro and in silico research. Therefore, more research is required to increase the value of flavonoids in the diet and promote human health. Due to the variety of the many molecular structures and the lack of information on bioavailability, studying flavonoids is difficult. Additionally, it is difficult to evaluate objective end goals because there aren't enough tools available to assess oxidative damage in vivo. To enable the gathering of additional information on absorption and excretion, analytical procedures must be improved. Particularly less information exists on the long-term effects of chronic flavonoid use. Numerous investigations have stressed the need for molecular docking studies to find new flavonoid compounds for use in treating a range of illnesses in the human health system. Future study should focus on how flavonoids interact with receptor molecules to treat both acute and chronic illnesses[62]. To replace the usage of synthetic medications that are damaging to the body, further study is required to find new flavonoids from the richness of nature. Research and development initiatives incorporating in vivo investigations are required in this situation in order to provide a positive and secure outlook on the future. Currently, the intake of fruit, vegetables and beverages containing flavonoids is recommended, although it is too early to make recommendations on daily flavonoid intakes.

CONCLUSION

It is generally recognised that phytochemicals, particularly flavonoids, can be used to prevent and treat illness. Flavonoids can be found naturally in fruits and vegetables. Different flavonoids that may be found in nature each have unique physical, chemical, and physiological characteristics. Flavonoids' structure-function link is a prime example of important biological functions. Numerous flavonoids have a well-established history of use in medicine as antibacterial, hepatoprotective, anti-inflammatory, anticancer, and antiviral medicines. These drugs are used more often in underdeveloped nations. Specific biochemical assays must be used to confirm the therapeutic usage of novel substances. It is now feasible to generate flavonoids on a big scale via genetic changes. Additional developments will offer fresher perspectives and undoubtedly usher in a new era of pharmacological agents based on flavonoids for the treatment of several infectious and degenerative disorders.

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