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BIOLOGICAL ACTIVITIES OF FLAVONOIDS: AN OVERVIEW

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ABSTRACT: Background: Plants and herbs consumed by humans are the rich sources of phytonutrients compounds synthesized in plants itself. Such bioactive substances are responsible for the plant's antioxidant and medicinal values. Flavonoids are an essential group of naturally occurring polyphenolic compounds, and its flavan nucleus characterizes it. It is one of the most common classes of compounds available in vegetables, fruits, and plant-derived beverages. Flavonoids are considered as health promoting and disease preventing dietary supplements. It is now considered as an indispensable component in a variety of nutraceutical, pharmaceutical, medicinal, cosmetic and other applications. **Objectives:** The main aim of this present review is to discuss the current trends of research and development on flavonoids, general working mechanisms of flavonoids, functions, and applications of flavonoids, prediction of flavonoids as potential drugs in preventing many chronic diseases and future research directions. **Discussion:** 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, cardioprotective, antidiabetic, anti-inflammatory, anti-allergic while some other flavonoid compounds exhibit potential antiviral activities. More recently flavonoids are proven to be the most effective as an anti-cancer agent, through apoptosis by induction of cell cycle arrest and inhibition of key enzymes involved in tumor promotion.

INTRODUCTION: Polyphenols are chemical compounds of the secondary plant metabolism that can accumulate in specific group of plant organs such as leaves, fruits, roots, and stems. As a large group of bioactive chemicals, they have diverse biological functions. Flavonoids are phenolic substances widely distributed in all vascular plants. They are a diverse group of phytonutrients (plant chemicals) ubiquitous in many fruits, vegetables and medicinal plants in which they occur as the free forms, glycosides, as well as methylated derivatives.

Flavonoids are the low molecular weight compound [1, 2] bioactive polyphenols [3] which play an essential role in photosynthesizing cells [4]. The original "flavonoid" research started in 1936, when Hungarian scientist Albert Szent-Gyorgi was uncovering a synergy between pure vitamin C and as yet unidentified cofactors from the peels of lemons, which he first called "citrin," and later it referred to as "vitamin P" [5].

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They display an extensive range of structures, and they are responsible for the significant organoleptic characteristics of plant-derived foods and beverages, particularly color and taste properties. They also contribute to the nutritional qualities of fruits and vegetables.

Flavonoids are hydroxylated phenolic substances and are synthesized by plants in response to microbial infection [6]. Flavonoids are a subdivision of a large group of polyphenolic compounds having a benzo-γ-pyrone structure, a versatile class of natural compounds that represent secondary metabolites. Flavonoids have aroused enormous interest in the preceding decade because of their multidimensional health effects on human and animal health, and omnipresence in the plant kingdom. They are called "functional ingredients" and "health promoting biomolecules" in recent literature due to their potential role in promoting health and preventing chronic degenerative diseases [7]. They have played significant roles in successful medical treatments in ancient as well as modern times.

Flavanoids having several biochemical and antioxidant effects associated with various diseases such as cancer, Alzheimer's disease (AD), atherosclerosis, *etc*. [8-10] Flavonoids are associated with a broad spectrum of health-promoting effects and are an indispensable component in a variety of nutraceutical, pharmaceutical, medicinal and cosmetic applications. This is because of their potent anti-oxidative, anti-inflammatory, anti-mutagenic, antimicrobial, anti-carcinogenic, vascular activities, free radical scavenging abilities, and other medicinal properties coupled with their capacity to modulate essential cellular enzyme functions. They are also known to be potent inhibitors for several enzymes, such as aldose reductase, Ca^{2+}- ATPase, xanthine oxidase (XO), cyclo-oxygenase (COX), lipoxygenase and phosphoinositide 3-kinase [11-13].

The antimicrobial properties of flavonoids were proposed for both the development of new food preservatives and development of therapies. It is used for the treatment of various microbial infections, considering the increase in microbial resistance against antibiotic treatment. Nowadays, about 70% of the bacteria that cause infections in hospitals are resistant to at least one of the drugs most commonly used for treatment. Some organisms are immune to all approved antibiotics and can only are treated with experimental and potentially toxic drugs.

The main aim of this review was to highlights the overview of the research in the field of flavonoids. The potential valuable physiological and antimicrobial actions of flavonoids are discussed. In the last part of this review article, the critical clinical applications of flavonoids in human body system were discussed.

Chemistry of Flavonoid: Flavonoids are part of the polyphenol class of phytonutrients. Polyphenols have historically been used in Chinese and Ayurvedic medicine. According to the Global Healing Center, they are associated with skin protection, brain function, blood sugar, and blood pressure regulation, in addition to antioxidant and anti-inflammatory activity. In 1930 a new substance was isolated from oranges. At that time it was believed to be a member of a new class of vitamins and was designated as vitamin P. Later on it became clear that this substance was a flavonoid (rutin) and till now more than 4000 varieties of flavonoids have been identified [14].

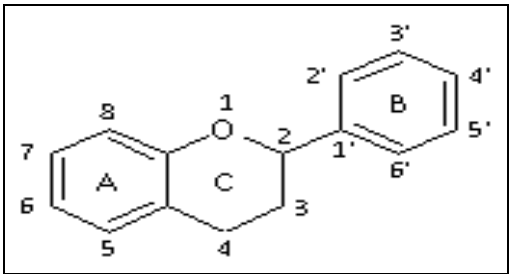

FIG. 1: BASIC STRUCTURE OF FLAVONOID

Flavonoids occur as aglycones, glycosides and methylated derivatives [15]. In plants, flavonoids aglycones (*i.e.*, flavonoids without attached sugar) occur in a variety of structural forms. The basic chemical structure of flavonoid is a skeleton of diphenyl propane, contain fifteen carbon atoms in their primary nucleus: two six-membered rings linked with a three carbon unit which may or may not be a part of a third ring [16]. Mainly two benzene rings (ring A and B) are linked together through third heterocyclic oxygen-containing pyrene ring [17]. So, this structure is also referred to as C6-C3-C6 labeled A, B, and C [18-19] **Fig. 1**.

Flavonoids can be subdivided into different subgroups depending on the carbon of the C ring on which B ring is attached and the degree of unsaturation and oxidation of the C ring [20]. Flavonoids in which B ring is linked in position 3 of the ring C are called isoflavones; those in which B ring is linked in position 4, neoflavonoids, while those in which the B ring is linked in position 2 can be further subdivided into several subgroups on the basis of the structural features of the C ring. This subgroup is flavones, flavonols, flavanones, flavanonols, flavanols or catechins, and anthocyanins [21-22] **Fig. 2**. Finally, flavonoids with open C ring are called chalcones.

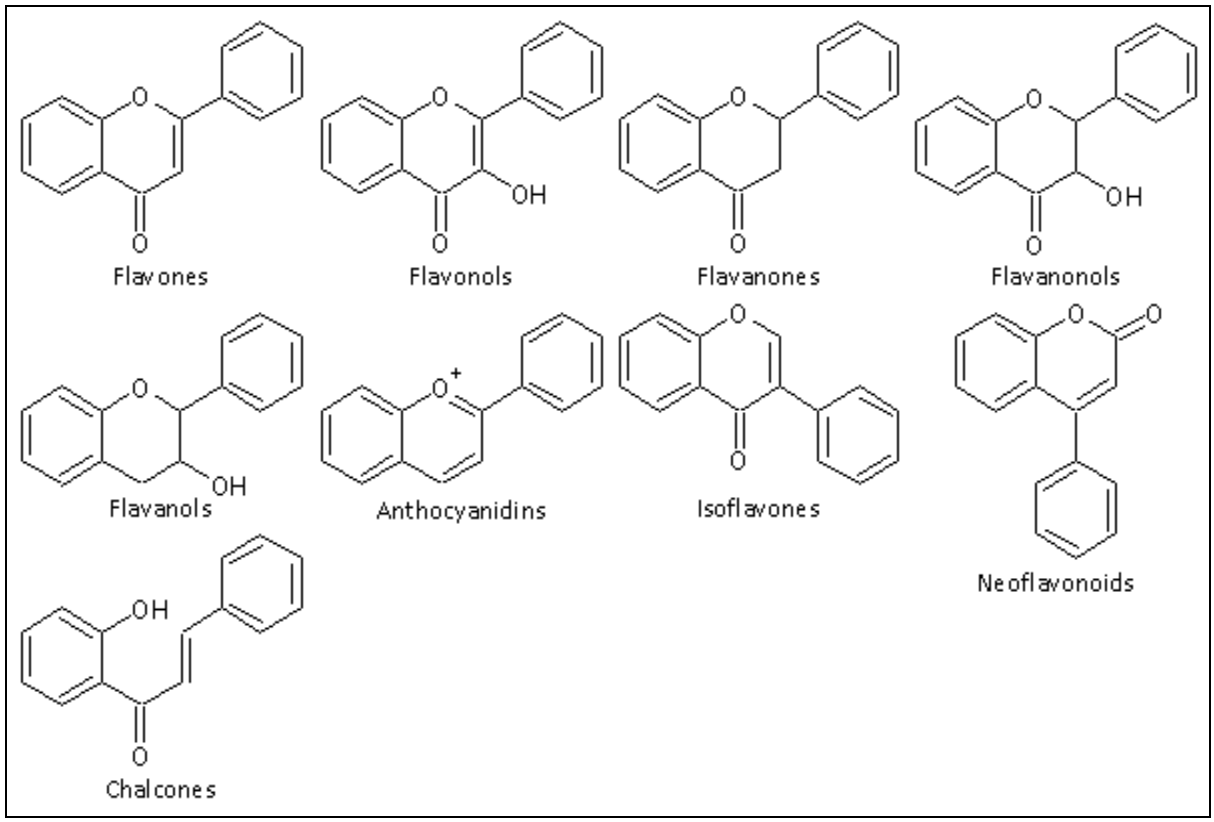

FIG. 2: DIFFERENT TYPES OF FLAVONOID AND THEIR CHEMICAL STRUCTURE

Some food sources containing different classes of flavonoids are given in **Table 1**. Being phytochemicals, flavonoids cannot be synthesized by humans and animals. Flavonoids are found in the highest amounts in the human diet include the soy isoflavones, flavonols, and the flavones. **Table 2** summarizes some of the medicinal plants rich in flavonoid contents.

TABLE 1: SUBCLASSES OF FLAVONOIDS AND THEIR OCCURRENCE IN FOODS [23-25]

S. no.	Flavonoid subclass	Examples of compounds	Food source	References
1	Flavonol	Kaempferol, quercetin, myricetin and tamarixetin	Onion, red wine, kale, olive oil, broccoli apples, cherries, berries, and grapefruit and tea	26
2	Flavones	Chrysin, apigenin Rutin, luteolin, and glucosidestangeretin	Fruit skins, red wine, buckwheat, red pepper, tomato skin, Parsley, Thyme	27-30
3	Flavonones	Naringin, naringenin, taxifolin, and hesperidin	Citrus fruits, grapefruits, lemons, and oranges	31-32
4	Flavanol	Catechin, epicatechin, epigallocatechin, glausan-3-epicatechin, proanthocyanidins	Apple, tea	26
5	Anthocyanidins	Apigenidin, cyaniding, delphinidin, pelargonidin, malvidin	Cherries, easberry, strawberry, and Grapes	26 & 30
6	Isoflavones	Genistein, daidzein	Soya beans, Legumes	33, 34

TABLE 2: SOME COMMON MEDICINAL PLANTS RICH IN FLAVONOIDS

Plant	Flavonoid	References
Aloe vera	Luteolin	35
Bacopa moneirra	Luteolin	35
Acalypha indica	Kaempferol glycosides	35
Azadirachta indica	Quercetin	36
Betula pendula	Quercetin	37
Butea monospermea	Genistein	38
Brysonima crassa	(+)-catechin	39
Cannabis sativa	Quercetin	36
Clitoria ternatea	Kaempferol-3-neohesperidoside	40
Mimosa pudica	Isoquercetin	41
Oroxylum indicum	Chrysin	41
Pongamia pinnata	Pongaflavonol	42

Special Characteristics of Flavonoids: Flavonoids are one of the most essential non-nitrogenous plant pigments. It is responsible for flower coloration by producing yellow or red/blue pigmentation in shoots, leaves, buds, petals, and fruits. This pigmentation is to attract pollinators to the flowers. In some types of plants, flavonoids are involved in UV filtration, symbiotic nitrogen fixation and floral pigmentation.

Different studies on flavonoids by spectroscopy analysis have revealed that most flavones and flavonols exhibit two major absorption bands. The band I (320-385) nm represents the flavan B ring absorption, while Band II (250-285) nm corresponds to the flavan A ring absorption **Fig. 3**.

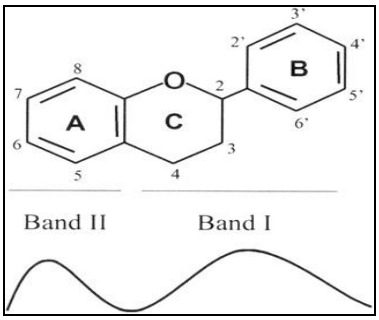

FIG. 3: DIFFERENT SPECTRUM OF SPECTROSCOPIC ABSORPTION OF FLAVAN NUCLEUS

Different functional groups attached to the flavonoid structure which may cause a shift in spectroscopic absorption from 367 nm in kaempferol (3,5,7,4′-hydroxyl groups) to 371 nm in quercetin (3,5,7,3′,4′-hydroxyl groups) and 374 nm in myricetin (3,5,7,3′,4′,5′-hydroxyl groups) [43] **Fig. 4**. Flavanones also have a saturated heterocyclic C ring, with no conjugation between the A and B rings, as determined by their UV spectral characteristics [44].

Flavanones exhibit a very strong Band II absorption maximum range between 270 and 295 nm, namely 288 nm (naringenin) and 285 nm (taxifolin) and only a shoulder for Band I at 326 and 327 nm. Band II appears as one peak (270 nm) in compounds with a mono-substituted B ring, but as two peaks or one peak (258 nm) with a shoulder (272 nm) when a di-, tri-, or O-substituted B ring is present. As anthocyanins show distinctive B and I peak in the 450-560 nm region due to 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, the colour of the anthocyanins varies with the number and position of the hydroxyl groups [45].

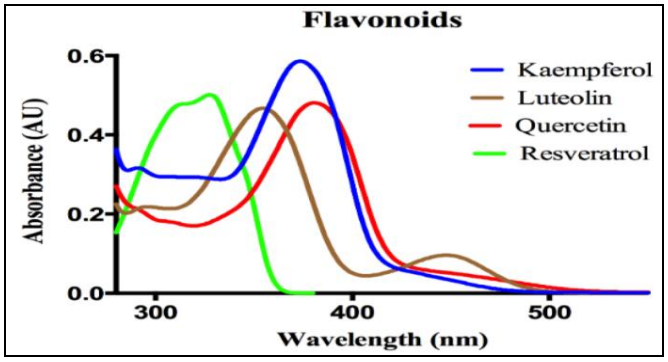

FIG. 4: UV SPECTRAL CHARACTERISTICS OF DIFFERENT FLAVONOIDS

Biological Activities of Flavonoids: Besides the main antioxidant property, flavonoids also possess many diverse biological activities that owe to the health aspects of human [46-47]. These activities are, for instance, anti-inflammatory, antiulcer, antiviral, anti-cancer, anti-diabetic and cytotoxic, *etc*.

Anti-oxidant Activity: Different studies have revealed broad nutritional effects of flavonoids to anti-oxidant activity. Most anti-oxidant chemical assays are showing to free radical scavenging mechanisms [48]. Antioxidants are reactive chemical compounds that protect human, animal and plant cells against the damaging effects of ROS. Flavonoids are one of the best phytochemicals that act as antioxidants and thus inhibit the factors of disease-causing. Antioxidant activity depends on the arrangement of functional groups in the flavan nucleus [49-50].

The configuration, substitution and total number of –OH groups substantially influence several mechanisms of antioxidant activity such as radical scavenging, activation of antioxidant enzymes [51], reduction of α-tocopheryl radicals [52-53], inhibition of oxidases [53-54], mitigation of oxidative stress caused by nitric oxide [55], metal ion chelation ability [56] and increase in antioxidant properties of low molecular antioxidants [57]. The flavan nucleus B ring -OH configuration is the most significant determinant of scavenging of ROS and RNS because it donates hydrogen and an electron to hydroxyl, peroxyl and peroxynitrite radicals, stabilizing them and giving rise to a relatively stable flavonoids radical [58]. Flavonoids are also protecting the cell membranes which are damaged due to lipid peroxidation. Thus, the flavonoids contribute as antioxidants, in the prevention of many diseases caused due to oxidative stress [59].

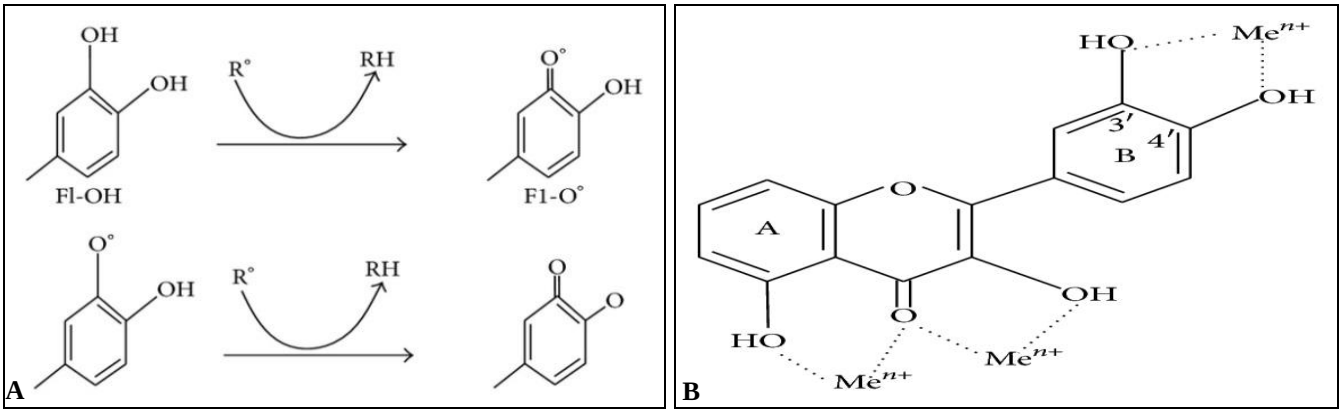

FIG. 5: (A) SCAVENGING OF ROS (R°) BY FLAVONOIDS (Fl-OH); (B) BINDING SITES FOR TRACE METALS WHERE Me^{n+} INDICATES METAL IONS

Anti-Inflammatory Activity: Inflammation is a complex biological response of body tissues to harmful stimuli, such as pathogen infection, damaged cells, tissue injury, and chemical irritation. It is a protective response involving immune cells, blood vessels, and molecular mediators. This is initiated by the migration of immune cells from blood vessels and the release of chemical mediators at the site of tissue damage. Generally, the essential role of flavonoids on inflammation involved diseases such as leukemia, sepsis, asthma, sclerosis, atherosclerosis, psoriasis, allergic rhinitis, ileitis/ colitis, rheumatoid arthritis, etc. has been proposed. This process is followed by recruitment of inflammatory cells, the release of ROS, RNS, and proinflammatory cytokines to eliminate foreign pathogens and repair injured tissues. In general, normal inflammation is rapid and self-limiting, but the aberrant resolution and prolonged inflammation cause various chronic disorders [60]. Hesperidin, Luteolin and Quercetin are known to possess such type of anti-inflammatory property. They mainly affect the enzyme systems involved in the generation of inflammatory processes. Flavonoids also inhibit phospho-di-esterases involved in cell activation.

Anti-Bacterial Activity: Plants can synthesize flavonoids in response to microbial infection and hence they are very effective antimicrobial substances against a wide variety of micro-organisms. The different study shows the flavonoid-rich plant extracts from different plants possess antibacterial activity [61-64]. Apigenin, galangin, flavone and flavonol glycosides, isoflavones, flavanones, and chalcones have been proved to possess potent antimicrobial activity [65]. The mode of antimicrobial action may be related to their ability to inactivate microbial adhesins, enzymes, cell envelope transport proteins, and so forth. Lipophilic flavonoids may also disrupt bacterial membranes [66-67].

Antiviral Activity: Since the 1940s and many reports show that naturally occurring flavonoids exhibit a remarkable anti-viral activity. They help in the inhibition of various enzymes associated with the life cycle of viruses. The structural and functional relationship between flavonoids and their enzyme inhibitory activity has been observed. Flavon-3-ol was found to be more effective than flavones and flavonones in selective inhibition of HIV-1 & HIV-2 and similar immunodeficiency

virus causing infections [68]. The different study shows that quercetin, hesperetin, and naringin also possess anti-dengue activity [69].

Anti-Cancer Activity: Cancer is a multistep disease incorporating physical, environmental, metabolic, chemical and genetic factors, which play an important role in the induction and deterioration of cancers. Many polyphenolic compounds such as flavonoids, phenolic acids, anthocyanidins, and tannins possess a broad spectrum of pharmacological activity including anti-cancer activities [70-71]. They have been reported to interfere in the initiation, promotion, and progression of cancer by modulating different enzymes and receptors in signal transduction pathways related to cellular proliferation, differentiation, apoptosis, inflammation, angiogenesis, metastasis and reversal of multidrug resistance.

Due to their multiple molecular mechanisms of action, flavonoids have been proved for their potential applications in anti-cancer therapies. Flavonoids greatly influence the cascade of immunological events associated with the development and progression of cancer. They have the potential of modulating many biological events in cancer such as apoptosis, vascularization, cell differentiation, cell proliferation, etc. A strong correlation persists between flavonoid-induced modulation of kinases with apoptosis, cell proliferation and tumor cell invasive behavior *in-vitro*. Flavonoids mainly stimulate the initiation and promotion stages of the carcinogenicity, along with influences on development and hormonal activity. They also act by cell-cycle arrest, down-regulation of mutant p53 protein, inhibition of many cancer-triggering enzymes and expression of Ras proteins.

CONCLUSION: Prevention and cure of diseases by using phytochemicals compounds especially flavonoids are well known. Fruits and vegetables are natural sources of flavonoids. 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 neutralize 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.

This review highlights the dietary sources and various important biological activities of flavonoids that attributes to their beneficial roles in human health. Their applications in industry are beyond the limit of nutraceuticals and drug candidate molecules.

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CONFLICT OF INTEREST: The authors declare that they have no conflict of interests.

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