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The impact of flavonoids on health and disease: comprehensive review of their biological properties

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Abstract: Flavonoids are a category of natural compounds distinguished by their varied phenolic structures, found in numerous sources such as bark, wines, fruits and vegetables. These compounds are closely associated with human nutrition and health, necessitating an assessment of the relationships between their structure and function. This extensive group of phenolic plant constituents can be categorized into several classes, including flavonols, flavones, isoflavones, flavanones, anthocyanins and chalcones. Flavonoids interacts with great number of cellular targets such as anti-cancer, anti-viral, anti-inflammatory, cardiovascular properties. Flavonoids are regarded as essential elements in numerous applications across nutraceutical, pharmaceutical, medicinal, and cosmetic fields. Flavonoids have significant industrial potential but face challenges related to bioavailability and stability. To overcome these issues, various cutaneous delivery systems have been explored. Encapsulating flavonoids in lipid or polymer-based nanoparticles shows promise for skin applications due to effective encapsulation and low toxicity. This review discusses the classes of flavonoids relevant to skin use, their challenges, future prospects, and their roles as therapeutic and preventive agents.

Keywords: Biological activity, Flavonoids, Novel Technology, Bioavailability.

1. Introduction

Flavonoids are a class of phenolic compounds present in a wide range of vegetables, plants, and fruits characterized by a carbon skeleton of C6-C3-C6. These compounds are widely consumed in the human diet and have attracted considerable scientific interest owing to their various reported benefits, which encompass antibacterial [1], antimicrobial[2], anticancer[3], anti-inflammatory[4], and antiviral effect[5].They are synthesized in plants via shikimic pathways utilizing acetic acids or phenylalanine as secondary metabolites [6].Flavonoids, despite their health-promoting properties, exhibit poor stability when exposed Factors related to the environment, such as heat, light, oxidation, and pH levels. Additionally, their low solubility in water and limited bioavailability following oral intake further constrain their potential applications and health advantages
[7,8,9]

Flavonoids exhibit biological activity across a range of organisms, including animals, bacteria and plants. In the plant kingdom, these compounds are recognized for their synthesis in specific locations, contributing to the coloration and fragrance of flowers. Additionally, in fruits, flavonoids serve to attract pollinators, thereby facilitating fruit dispersal, which is essential for the germination of seeds and spores, as well as the growth and development of seedlings [10]. Flavonoids serve to safeguard plants against various biotic and abiotic stresses, functioning as distinctive UV filters. They also act as signaling molecules, antimicrobial defence substances, allelopathic compounds, detoxifying agents [11]. At present, extensive research is underway to explore the therapeutic advantages of flavonoids for a range of skin conditions. These compounds have demonstrated the ability to absorb ultraviolet radiation and influence signaling pathways associated with cancer and inflammation. This review examines the ongoing studies regarding the use of flavonoids in skin diseases, including the prevention of premature photoaging, The prevention and management of skin cancer, along with the improvement of skin wound healing [12].

2. Classification of Flavonoids

Flavonoids predominantly reside in the vacuoles of plant cells, existing primarily as C-glycosides [13]. The fundamental molecular architecture of flavonoids is determined by their core C6–C3–C6 framework. These compounds are categorized into seven subclasses, as illustrated in figure 1, according to the alterations made to their fundamental structures [14,15].

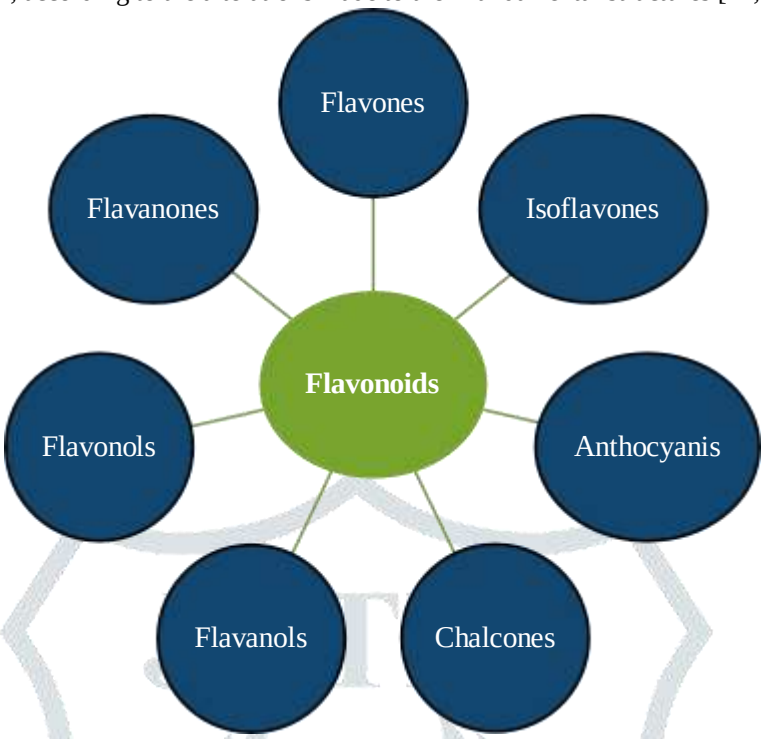

Fig. (1) Classification of Flavonoids

2.1 Flavones

Flavones are a major category of flavonoids with a structure and a phenyl group at the second position. These compounds are predominantly occurred glycosides and are found in plants [16,17,18]. In glycosylated variants included flavones [19]. Apigenin has the capacity to counteract free radicals and regulate the function of antioxidant enzymes. Furthermore, it has demonstrated efficacy in diminishing inflammation [20,21].

2.2 Flavonols

Flavonols, known scientifically as 3-hydroxy flavone, are characterized by distinct substitutions in their A- and B-rings, which are linked by a three-carbon chain [22]. These compounds feature is predominantly found in epidermal cells, serving to safeguard DNA from damage caused by ultraviolet radiation [23]. Four primary types of flavanol compounds are commonly found in various vegetables and fruits [24].

2.3 Flavanones

Flavanones are defined by saturated C ring [25], with key differences from the other flavonoids being the A fully saturated double bond exists between the second and third positions of the C-ring. They are mainly found in citrus fruits like oranges, lemons, and limes [26]. Naringenin and hesperetin, which are the primary dietary flavanones, are predominantly found in citrus fruits. Naringin has the potential to boost the activity of antioxidant enzymes and strengthen the immune system [26,27].

2.4 Isoflavones

Isoflavones are characterized by a B-ring located at the C3 position of the heterocyclic C-ring within the diphenyl propane framework, which distinguishes them chemically from other flavonoids [28]. The main sources of isoflavones are leguminous plants belonging to the Leguminosae family. Other notable sources include red wine,and linseed with red clover containing the highest levels of phytoestrogens. Notable examples of isoflavones include genistein, daidzein. [29,30].

2.5 Flavonols

Flavanols, commonly referred to as catechins, are distinguished by the presence of a hydroxyl group at the third position of the ring [31]. Notably, flavanols do not possess a double bond between the second and third positions within the ring [32]. A variety of flavanols, which are prevalent in numerous fruits, including banana, apple and blueberries [33,34]. Furthermore, flavanols have been shown to enhance the nitric oxide content in blood vessels, thereby providing protective effects against tobacco-related damage to blood vessels.

2.6 Anthocyanins

Anthocyanins are glycosylated polyphenolic compounds known for their solubility as pigments in vacuoles, exhibiting a spectrum of colours. The observed is influenced by the pH levels in the micro-environment of fruits, vegetative tissues, flowers and seeds [35]. These compounds are primarily found in the outer cell layers of various fruits and vegetables [36,37]. Anthocyanins play a crucial role in reducing the risk of cardiovascular disease in human, enhancing visual acuity, aiding in cholesterol breakdown [38,39]. Additionally, they are commonly used as colorants in food products.

2.7 Chalcones

Chalcones are natural flavonoids which are Found in plant families like Zingiberaceae, Moraceae and Cannabaceae [40]. These bioactive compounds exhibit various biological properties, including antiviral, anticancer, antiulcer and antioxidant activities [41].

3. Biological Properties of Flavonoids

Flavonoids, in addition to their primary antioxidant characteristics, exhibit a wide range of biological activities that contribute to human health [42,43]. These activities include, but are not limited to, anticancer, antiviral, antibacterial, anti-inflammatory and cardiovascular properties.

3.1 Antioxidant Property

Numerous antioxidant chemical assays suggest the presence of mechanisms that facilitate the scavenging of free radicals and chemical assays suggest the presence of mechanisms that facilitate the scavenging of free radicals. [44]. Antioxidants are active chemical compounds that protect the cells of humans, animals, and plants from the detrimental impacts of reactive oxygen species (ROS). Flavonoids represent some of the most potent phytochemicals that act as antioxidants, thereby mitigating the elements that contribute to disease. The efficacy of their antioxidant properties is influenced by the configuration of functional groups within the flavin nucleus [45,46].

3.2 Anti-Inflammatory Property

Inflammation is a complex biological response of tissues to harmful stimuli, such as irritants, pathogen and cellular damage. This process involves the activation of blood vessels, a range of molecular meditators and immune cells. It begins with the movement of immune cells and the secretion of chemical mediators at the location of the injury. Flavonoids play a significant role in the management of diseases associated with inflammation, such as leukaemia, asthma, and rheumatoid arthritis. The inflammatory response mobilizes cells that generate reactive oxygen and nitrogen species, along with pro-inflammatory cytokines, to fight off pathogens and facilitate tissue repair. Although inflammation typically occurs rapidly and resolves on its own, inadequate resolution may result in chronic conditions [47]. Compounds such as Hesperidin, Luteolin, and Quercetin demonstrate antiinflammatory properties by modulating enzyme systems and inhibiting phosphodiesterase's that are engaged in the process of cell activation.

3.3 Anti-Bacterial Property

Flavonoids produced by plant as a defence against microbial infections, making them effective antimicrobial agents. Studies show that extracts from flavonoid-rich plants possess significant antibacterial properties [48-51]. Compounds like apigenin, galanin, and flavanol glycosides demonstrate strong antimicrobial efficacy [52], likely

by deactivating microbial adhesins, enzymes, and transport proteins. flavonoids have the potential to interfere with membrane of bacteria [53,54].

3.4 Antiviral Property

Naturally occurring flavonoids possess significant antiviral properties. These compounds play a crucial role in inhibiting various enzymes that are integral to the viral life cycle. Research has revealed a structural and functional correlation between flavonoids and their ability to inhibit enzyme activity. Notably, in selectively inhibiting immunodeficiency viruses [55]. Additionally, other studies indicate that hesperetin, naringin, and quercetin exhibit anti-dengue effect [56].

3.5 Anticancer Property

Cancer is a complex disease characterized by multiple stages and influenced by a variety of factors, including chemicals, physical, environmental all of which significantly contribute to the onset and progression of the disease. Numerous flavonoids compounds exhibit a wide range of biological effects, particularly in their anticancer properties [57,58]. Research indicates that these compounds can disrupt cancer by modulating various enzymes and receptors involved in signal transduction pathways associated with cellular processes such as apoptosis, inflammation, proliferation, metastasis. They function through mechanisms such as modulation of Ras protein expression, cell-cycle arrest, inhibition of several cancer-promoting enzymes, and in addition to exhibiting antioxidant properties and also antibacterial, anti-inflammatory, antiviral and particularly anti-cancer effects.

3.6 Cardivascular Disease

Numerous cohort studies have investigated the association between dietary flavonoid consumption and the risk of cardiovascular disease, yielding compelling evidence. It was first identified in Zutphen, in 1993 due to over consumption of Flavonoids [59] and also demonstrated that higher dietary levels of flavanols and flavones are associated with lower mortality rates from cardiovascular disease [60]. A review of the existing indicates that one study specifically highlights a relation between the consumption of tea

flavonoids and cardiovascular disease [61]. The biological function of the flavonoids; anti-inflammatory, antiulcer, antiviral, anticancer, antidiabetics, cardiovascular disease, antibacterial, antioxidant (shown in figure2).

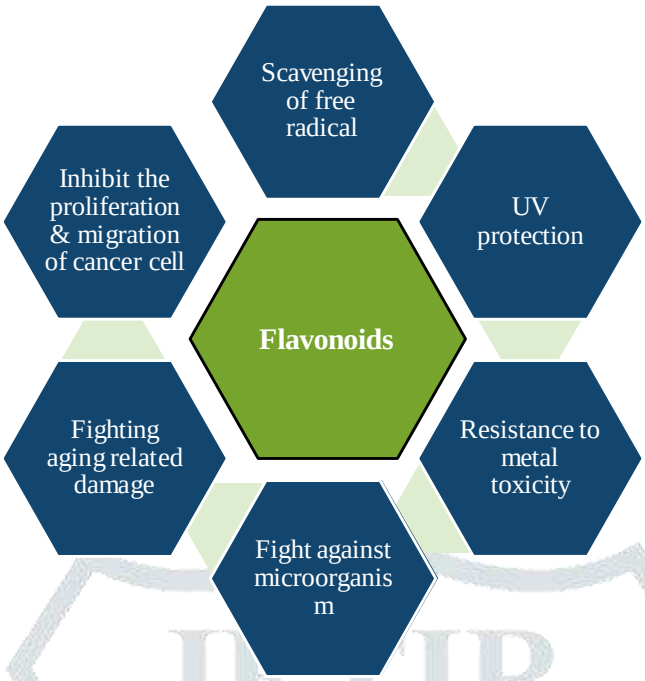

Fig. (2) Biological Function of Flavonoids

4. Innovations in delivery system

4.1 Nanoformulation

The skin's impermeability hinders effective drug delivery, often leading to sub optimal therapeutic outcomes with standard dosages. To address this delivery systems for flavonoids are needed to improve bioavailability, site specific delivery and solubility. Currently, gels dominate topical administration, but alternative systems such as polymeric nanoparticles and transferosomes are also being explored. These carriers can be formulated into creams and gels to enhance patient adherence [62]. Innovative drug delivery systems can significantly improve the efficacy and safety of compounds with poor physicochemical properties. Nanotechnology applications include micro and nanodevices which can penetrate the skin barrier and release drugs directly at the target site, reducing toxicity and prolong releasing [64,65]. Utilizing nanocarriers can enhance key drug characteristics, including diffusivity, solubility, blood circulation half-life.

In conclusion, the benefits of utilizing nanocarriers for transdermal drug delivery encompass the following aspects:

(1) Targeted delivery that enhances efficacy while reducing systemic side effects

(2) Controlled release of the drug

(3) Extended half-life within the systemic circulation

(4) Enhanced patient adherence

(5) Increased solubility and permeability of the drug

(6) Safeguarding against the degradation of antioxidants

(7) Administration of multiple drugs to achieve a synergistic effect

(8) Enhanced biocompatibility [66,67,68,69]

4.2 Encapsulation system

Flavonoids are recognized for their potential health benefits; however, their limited stability and poor solubility present significant challenges for their integration into food products. Additionally, these compounds are susceptible to degradation in the highly acidic environment of gastric juice, leading to reduced bioavailability and absorption [70]. Consequently, encapsulation emerges as a promising strategy for safeguarding these compounds. Various techniques and coating materials are employed for the encapsulation of such components. These techniques can be categorized into chemical methods, physicochemical methods and physical methods [71,72].

Encapsulation approaches applied for flavonoids.

(1) Spray drying

(2) Molecular complexes

(3) Polymer nanoparticles

(4) Liposome's entrapment

5. Challenges of Flavonoids

The previous discussions emphasized the potential of the PC in a range of applications across different industry sectors. However, to apply these molecules effectively, several challenges must be overcome.

1. The minimal levels of these compounds detected in plant tissues may limit their availability to meet the high industrial demand.
2. Furthermore, their vulnerability Exposure to light and heat can degrade environmental factors, reducing their bioactivities.

3. In addition, to maximize their effectiveness as therapeutic and functional agents, it is crucial to gain a deeper understanding of and improve their bioavailability characteristics.

5.1 Stability of Flavonoids compounds

Encapsulation is most widely employed techniques for safeguarding flavonoid compounds from degradation. Various methods, including complex coacervation, spray drying and freeze drying have been utilized to achieve encapsulated phytochemicals [73,74]. Among these, spray drying and freeze drying are the predominant techniques for encapsulating phytochemicals derived from plant materials. Spray drying is particularly advantageous due to its rapid processing, ease of scalability and continuous production capabilities. Conversely, freeze drying is also a straightforward method that operates at low temperatures and in the absence of air, which minimizes oxidative degradation and structural alterations of the compounds [75,76]. These techniques function under markedly different conditions, resulting in encapsulation systems with unique characteristics [73,75].

Encapsulation techniques not only enhance the stability and resistance of functional compounds to various factors but also help to conceal certain sensory alterations, including changes in taste, which may arise into food matrix due to incorporation of compounds [77,79]. Furthermore, these technologies have been successful in improving the bioavailability of these molecules [80,81,82,83,84]. The intricate nature of each phytochemical, in conjunction with the chosen wall material and their interactions with other substances, necessitates a careful and individualized approach to selecting the most suitable encapsulation technique. Research indicates that freeze-drying demonstrates greater efficiency compared to spray-drying [85]. Similar findings were observed in studies involving the encapsulation of bioactive compounds derived from Hibiscus acetosella Welw [86].

5.2 Bioavailability of Flavonoids compounds

Flavonoid compounds are processed by the body similarly to xenobiotics, undergoing metabolism that facilitates their rapid excretion. Flavonoid compounds must be circulated through the bloodstream [87]; the extent to which this occurs is referred to as bioavailability. Generally, Flavonoid compounds exhibit less bioavailability, with the absorption rate of certain compounds estimated to range [88,87]. Additionally, when a Flavonoid compound is consumed, another important factor known as bioaccessibilitiy must be taken into account. Bioaccessibilitiy refers to the proportion of a compound that is released into the gastrointestinal tract from the food matrix, thereby becoming available for absorption [87]. Various factors can influence the bioaccessibilitiy of these compounds, including their food processing methods, dietary intake, interactions with other substances, chemical structure and water solubility [87]. Nanocarriers which are lipid based in nature and have demonstrated potential in enhancing the bioaccessibilitiy of flavonoids compounds due to their ability to improve and maintain the stability and solubility under gastric conditions, and facilitate controlled release of these compounds [89]. A significant limitation of flavonoids in various applications is their restricted bioavailability. Current strategies to enhance their bioavailability include the development which containing flavonoids such as microemulsion, microcapsules [90,91]. Address the challenges of inadequate bioactivity and solubility, [92] researchers have created formulations that incorporate one or many flavonoids utilizing the biocompatible Surface-active ionic liquid known as choline oleate They have also examined how changes in dosage forms affect the food preservation properties.

A) Quercetins traditional oral delivery relies on non-covalent interactions [93,94], which are unstable in the acidic gastrointestinal tract due to their sensitivity to ions. Effective intestinal targeting is challenging, as most carriers lack acid resistance and stability, leading to short resistance times.
B) Intestinal inflammation generates reactive oxygen species that can oxidize quercetin into inactive quinone, raising concerns about its efficacy post-release. Research shows that sulfhydrylated carriers can form disulfide bonds with mucins in intestinal mucus [94] and helping to scavenge reactive oxygen species [95].

The main factor contributing to the adverse side effects of flavonoids in clinical applications, especially those associated with flavonoid injections are strongly bind of this charged complex, which complicates extraction through standard separation methods. Although numerous flavonoids have been successfully synthesized using microorganisms, the challenge of low production efficiency persists in the manufacturing of many flavonoids.

6. Prospective Inshights on Flavonoids

Research on the pharmacological properties of flavonoids is rapidly expanding, with ongoing investigations into their effects and mechanisms. Future studies will focus on developing new drug delivery systems and modifying flavonoid chemical structures.

The modification of the chemical structure of flavonoid compounds is a significant approach in the development of new pharmaceuticals [96]. Notably, the alteration in ring of flavonoids, along with the targeted introduction of

functional groups, are essential techniques for generating compounds with potent biological properties. These methods are under extensive research.

The development of biological metabolic pathways and the improvement of cellular synthesis methods are essential approaches for addressing the challenge of limited material sources for flavonoid compounds [97].

Advancements in design and engineering of metabolic pathways are greatly aided by rapid developments in metabolomics and genomics. This progress will improve the identification of gene clusters for flavonoid production and allow for the modularization of essential gene components into standardized "production parts" using techniques like gene editing. Additionally, the antimicrobial properties of flavonoids have received significant research attention in past few decades [98]. The formulation of oral dosage forms containing flavonoids presents significant challenges due to their generally low solubility in water and their rapid degradation and metabolism within the body. These issues have prompted the creation of nano-formulations and various delivery methods aimed at enhancing the solubility of flavonoids. The encapsulation of flavonoids within nano formulations markedly improves their pharmacokinetics and safety profile. Additionally, dermal administration facilitates the penetration of flavonoids through the skin barrier, thereby mitigating their adverse effects. Flavonoids possess outstanding encapsulation capabilities and exhibit low toxicity, allowing for their effective delivery to the skin when integrated into medicines. The utilization of nanoscale formulations improves drug delivery by targeting specific locations and showcases impressive physical and chemical characteristics [99].

Future research on flavonoids will focus on innovative delivery systems and the interactions between flavonoids and receptor molecules for treating acute and chronic diseases [100]. In this context, research and development efforts that include in vivo studies are essential to ensure a promising and safe perspective for the future.

Conclusion

Phytochemical compounds, especially flavonoids, are recognized or their role in disease prevention and treatment. Fruits and vegetables are rich in flavonoids. Flavonoids interact with multitude cellular targets. This review discusses encapsulation systems that improve the stability and bioavailability of flavonoids, highlighting their dietary sources and significant biological activities that positively impact on human health.

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