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Dietary flavonoids with diverse anticancer properties: literature review and meta analysis

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Abstract

Free radicals are responsible for oxidative stress in cells and cause degenerative diseases such as cancer. The use of herbal substances to prevent cancer has increased significantly in recent decades. The consumption of antioxidants seems to be necessary due to their preventive effect. Polyphenols are powerful antioxidants with healthy effects on humans. These compounds exert their effects through various mechanisms and prevent chronic diseases (such as cancer) in humans. Polyphenols are free aglycones glycosidic esters flavonoids and non-flavonoid compounds. The anticancer potential of polyphenols depends on their structures. This review discusses the current status of studies on anti-cancer and the antioxidative effects of these compounds.

Keywords: Free radicals, Phytochemicals, Cancer, Flavonoid compounds, Antioxidant effects.

1- Introduction

Free radicals cause oxidative stress in various human cell molecules (such as nucleic acids, lipids, and proteins), and cause some degenerative diseases such as cancer, diabetes, asthma, and cardiovascular diseases. To promote health, the consumption of antioxidants seems necessary due to their preventive effects. These phytochemicals can inhibit oxidative stress by some scavenging mechanisms [1].

Cancer involves the uncontrolled growth of cells that can attack other parts of the body. Under normal conditions, the body's immune system can recognize and remove cancer cells. However, some specific mechanisms can protect these cells from attack by the body's immune system and cause them to be distributed in different tissues. Dietary habits are the most important cause of cancer. Other factors that can increase the risk of cancer are exposure to harmful chemicals, pollution, smoking, radiation, alcoholic beverages, and stress. However, changes in the genome of the cells can lead to the development of different

types of cancer. The possibility of metastasis in advanced cancers makes treatment a complex procedure. Diet and lifestyle are two major factors that influence the onset and development of many types of cancer. Several studies have shown that a healthy and balanced diet with a high proportion of fruit and vegetables can reduce cancer risk. Phytochemicals are found in plants, such as fruits, vegetables, oilseeds, and grains. Bioactive components are the phytochemicals that protect human health against chronic degenerative diseases. Polyphenols are polyphenolic substances in the form of glycosidic esters or free aglycones, that are widely distributed in plants, such as fruit, vegetables, tea, nuts, and wine, and can prevent chronic diseases. The amounts of polyphenols in fruit and vegetables are around 200-300 mg per 100 g fresh weight [2-12]. The primary objective of this review is to comprehensively examine the anticancer properties and chemistry of dietary flavonoids, elucidating their mechanisms of action and potential applications. This study also aims to systematically analyze existing literature to identify and categorize the various types of flavonoids, their sources, and their bioactive compounds. Furthermore, the current review seeks to evaluate the antioxidative and the anticancer effects of these compounds, through meta-analysis, providing a consolidated understanding of their efficacy in cancer prevention and therapy. By exploring the structure-activity relationships of flavonoids and their interactions within biological systems, this review intends to highlight the therapeutic potential of these natural compounds in the context of cancer, thereby contributing to the development of effective dietary strategies for cancer prevention and management. Diet and lifestyle are two key effective factors in the progression of cancer. This literature focuses on the categories, structures, and plant sources of polyphenols and their positive effects on cancer therapy.

2- Anticancer and antioxidant effect of bioactive compounds

Natural bioactive agents from plants are gaining wide attention for their anticancer activities. Several studies have found that natural plant-based bioactive compounds can **enhance the efficacy of chemotherapy**, and in some cases ameliorate some of the side-effects of drugs used as chemotherapeutic agents. One of the most important categories of natural bioactive compounds is polyphenols. Dietary flavonoids, a diverse group of phytonutrients found abundantly in fruits, vegetables, tea, and wine, have garnered significant attention for their potent antioxidative properties [13-16]. These compounds, play a crucial role in neutralizing free radicals, thereby mitigating oxidative stress—a key factor in the pathogenesis of chronic diseases such as cardiovascular diseases, cancer, and neurodegenerative disorders [17]. The antioxidative mechanism of flavonoids involves several pathways: direct scavenging of reactive oxygen species (ROS), chelation of metal ions that catalyze ROS production, and upregulation of endogenous antioxidant defenses by activating transcription factors like Nrf2 [18]. Additionally, flavonoids modulate cell signaling pathways related to apoptosis, inflammation, and gene expression, further contributing to their protective effects [19]. Emerging evidence from both in-vitro and in-vivo studies underscores the potential of dietary flavonoids to enhance cellular antioxidant

capacity, suggesting that their regular consumption could be a viable strategy for the prevention of oxidative stress-related conditions [20].

2-1- Polyphenols

Polyphenols are a large group of phytochemicals present in many fruits and vegetables. These phytochemicals have antioxidant properties and health benefits. Polyphenols are found in the outer layers of the tissues and seeds of plants and protect these organs from environmental factors. Polyphenols include two main groups flavonoids and non-flavonoids [21].

Flavonoids

Flavonoids make up about two-thirds of the polyphenols in plants. However, more than 4000 flavonoids have been isolated from plant materials. Onions, leeks, and broccoli are the main sources of flavonoids. The general structure of flavonoids is C6-C3-C6, consisting of two benzene rings. They are categorized into different groups including flavonols, flavones, flavanols, flavanones, and anthocyanins, which differ in the oxidation state of the central carbon [6, 22- 24].

- *Flavonols*

Flavan-3-ols (flavonols) such as kaempferol, myricetin, quercetin, and their glycosides are relatively common substances in various plant materials**,** such as fruits, vegetables, and cereals [25]. The glycone portion of these compounds includes arabinose, rutinose, and rhamnose [26]. The basic structure of flavonols is shown in Figure 1. Fruits, vegetables, and grains, such as apples, raspberries, oranges, kale, broccoli, cereals, oats, etc. are rich sources of flavonols. The generative mechanisms of flavonols are activated by sunlight in the fruit. The content of these compounds in the different parts of the fruit varies according to the degree of exposure to sunlight. Quercetin and kaempferol are the most important compounds in this group [13, 25].

- *Flavones*

Flavones are a class of flavonoids that have a similar structure to flavonoids. Chrysin, apigenin, and luteolin are the most important flavones, which exhibit high antioxidant and anti-cancer properties even at low concentrations. Chrysin and apigenin, have been shown to have anxiolytic and sedative properties [27-29]. Fabbro et al. [30] investigated the effects and mechanism of action of chrysin against the toxicity of zearalenone in male mice. The results showed that this compound is an effective preventive treatment against the destructive effect of zearalenone. Flavones have a C6–C3–C6 structure, known as the B-ring, C-ring, and A-ring. These compounds are soluble under alkaline conditions and have a yellow color, while they are uncolored at other pH values [31-33]. Flavones are usually found in some herbs, such as mint, thyme, parsley, carrots and apples peel, red pepper, cabbage, celery, onion leaves, and broccoli [32]. Chrysin is found in many plant extracts, medicinal herbs, and flowers [30]. Plants such as celery, parsley, oregano, and carrots, are

the main sources of apigenin [34, 35]. The main sources of luteolin include thyme, celery, clover flowers, dandelion, ragweed pollen, and chamomile [36].

- *Flavanols*

Flavanols (flavan-3-ols) can be divided into proanthocyanidins and catechins, which are found in polymeric and monomeric forms. There are two groups of proanthocyanidins including prodelphinidin and procyanidin. In contrast to the flavonoids, which have a glycoside form, flavanols have been found in the aglycone form. The esters of flavanols and gallic acid form various structures, including epigallocatechin (EGC), epicatechin gallate (ECG), and epigallocatechin gallate (EGCG). EGCG is the most important polyphenol as it can inhibit the production of malondialdehyde (MDA), which causes DNA mutagenesis. This bioactive compound has been shown to have anti-cancer properties, inhibiting breast, colon, prostate, leukemia, and lung cancer [37-46]. Borutinskaitė et al. showed the ability of EGCG to inhibit the apoptosis of promyelocytic leukemia cells [47]. In the next study conducted 4 years later by Ferrari et al. it was observed that this compound can promote cytotoxic autophagy and induce apoptosis. In contrast to flavonoids, flavanols do not have a double bond between C_2 and C_3. Two important isomeric configurations of this group are catechin, which has a trans structure, and epicatechin, which has a sis configuration (Figure 1). The main sources of flavanols are the tea leaves (*Camellia sinensis*), cocoa beans, and the skins of apples, grapes, and blueberries [39, 48-49].
Flavanones

Flavanones are colorless ketone flavones. Naringin, hesperetin, eriodictyol, isosakuranetin, prunin, and their glycosides are important flavanones. These compounds have become increasingly important due to their ability to scavenge radicals, their antioxidant activity, and their anti-cancer and anti-inflammatory effects. Naringenin and hesperetin have been tested in in-vitro and in-vivo studies to determine the anti-cancer effects of these compounds in somatic cells and tissues [17, 26, 50, 51]. The unique substitution patterns of flavanones, such as furanoflavanones, prenylatedflavanones, pyranoflavanones, and benzylated flavanones give this subgroup many substituted derivatives [52]. Flavanones are isolated from citrus fruits, tomatoes, and aromatic plants such as mint. The content of flavanones in the rigid and enveloping parts of fruits is 5 times higher than in juices [53].

- *Anthocyanins*

Anthocyanins are water-soluble pigments found in some plants. More than 600 anthocyanins have been extracted from plants, which are derived from 6 anthocyanidins, including cyanidin, delphinidin, pelargonidin, peonidin, petunidin, and malvidin [54]. Several studies have demonstrated the anti-cancer properties of anthocyanins. Abdelrahman et al. [55] have shown that anthocyanins from pomegranate peels, chili pepper fruits, and *bougainvillea* flowers have strong anti-cancer and antioxidant properties.

Anthocyanidins are the primary structure of these compounds, with the sugar part placed at the C_3, C_5, or C_7 in the A-ring (Figure 1) [56]. Anthocyanins are hydrophilic polyphenolic pigments, responsible for the red, blue, or purple color of fruits and

vegetables, but their color can be affected by pH variation. Fruits such as blueberries, bilberries, and cranberries are the most important sources of anthocyanins. The aglycone part is formed by anthocyanidins which are the base of these glycosides [57].

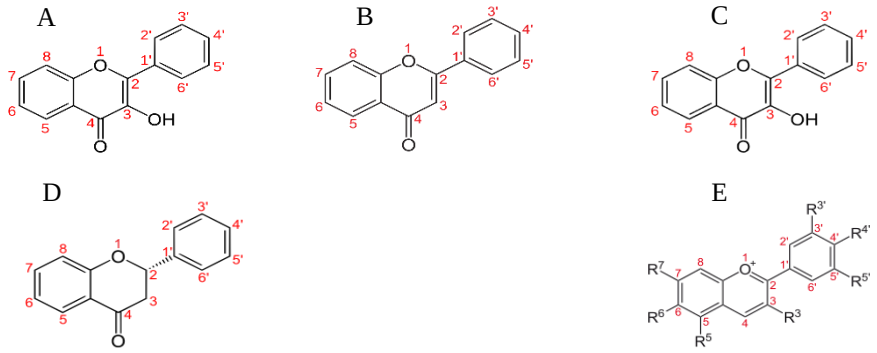

Figure 1. Chemical structures of Flavonol (A), Flavone (B), Flavanol (C), Flavanone (D), Anthocyanin (E)

3- Conclusions

This review highlights the significant anticancer properties and diverse mechanisms of action of dietary flavonoids, showcasing their potential as natural agents in cancer prevention and therapy. Our comprehensive analysis reveals several novel findings: specific flavonoids exhibit potent anticancer activities through apoptosis induction, cell cycle arrest, and inhibition of angiogenesis and metastasis. The meta-analysis demonstrates that these flavonoids can selectively target cancer cells while sparing normal cells, suggesting a favorable therapeutic index. These insights underscore the necessity for further clinical trials to validate the efficacy and safety of flavonoid-based interventions in cancer patients. Overall, the findings of this review provide a compelling case for the inclusion of flavonoid-rich foods in dietary regimens as a strategic approach to combat cancer.

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