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Mini-review

Apigenin: A dietary flavonoid with diverse anticancer properties

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ABSTRACT

Apigenin is a natural flavonoid found in several dietary plant foods such as vegetables and fruits. A large number of studies conducted over the past years have shown that this particular natural compound has potential antioxidant, anti-inflammatory, and anticancer properties. Therefore, apigenin has generated a great deal of interest as a possible chemotherapeutic modality due to its low intrinsic toxicity and remarkable effects on normal versus cancerous cells, compared with other structurally related flavonoids. Here, we review its role in anticancer research, as well as several cancer signalling pathways, including MAPK, PI3K/Akt and NF-κB pathways, and their specific role in different cancer types. Based on the available literature, the beneficial effects of apigenin as a future anticancer modality are promising but they require further *in vitro* and *in vivo* studies to enable its translation from bench to bedside.

1. Introduction

Cancer is nowadays one of the most serious life-threating diseases, affecting people of all ages and is considered one of the leading causes of mortality and morbidity worldwide. Statistics show it is the second most common cause of death after cardiovascular diseases in developed countries [1]. Cancer cells are characterized by mutations and genetic instabilities which consequently lead to impaired regulation of cell cycle, uncontrolled proliferation and overcoming of apoptosis and similar checkpoint mechanisms [2]. Anticancer treatments usually use compounds that target fast-dividing cells. This approach, regrettably, has a negative side effect because normal, fast-dividing cells such as hair follicles and epithelial cells in the digestive system are also affected. Furthermore, one of the aggravating circumstances is that many cancer cells gradually develop resistance to conventional forms of therapy [3]. Therefore, many studies in the last few years have focused on the development of an effective anticancer therapy which would have little or no effect on normal cells.

In this regard, natural compounds from plants are proving to be suitable candidates for such a therapy [4]. Interfering with the process of carcinogenesis through diet or by the added digestion of natural compounds has been termed “chemoprevention” [5]. An increasing importance is being given today to alternative medicine and dietary approach in prevention and treatment of cancer. A large number of epidemiological, *in vitro*, *in vivo* and clinical studies demonstrated growing evidence linking increased consumption of a plant-based diet with a reduced risk of chronic diseases such as cancer, as well as neurodegenerative, metabolic and heart diseases [6–11]. It should be noted that many epidemiological studies reported inconsistent results. This can be partly explained by the fact that those studies are based on food questionnaires, which are not always an exact source of information. Furthermore, within an abundant number of plant species, only 10% of them have been analysed as pharmacology agents. Therefore, both *in vitro* and *in vivo* research present a better way to elucidate the beneficial effect of plant phytochemicals. Accordingly, many researchers have dedicated their studies to analyse a possible anticancer effect of natural compounds from vegetables and fruits.

There are many categories of plant bioactive compounds, such as alkaloids, glycosides, polyphenols, tannins, gums, resins and oils, and many of these phytochemicals have been shown to possess low intrinsic toxicity and exert prominent effects on cancerous versus normal cells. An encouraging fact is that, in the last few decades,

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nearly 70% of all anticancer drugs originated from natural sources or are derivatives of natural products [12].

The most extensively studied group of plant secondary metabolites are polyphenols, characterized by their structure of multiple phenol (benzene) rings [13]. Polyphenols, ranging in their structure from small molecules to highly complex compounds, are widely distributed in various vegetables, fruits, legumes, coffee, wine, beer, spices and nuts [4,10]. Polyphenols are further divided into flavonoids, phenolic acids, stilbenes, lignans and other polyphenols. Their structural variance is the reason why polyphenols possess many different biological functions; most importantly anticancer activity. This activity is dependent on their structure, concentration and the type of cancer.

Flavonoids, a group representing 60% of all natural polyphenols, are present in all parts of plants, especially in flowers and leaves. Based on their structure, flavonoids can be classified into distinct sub-groups including anthoxanthins (flavones and flavonols), flavanones, flavanols, isoflavonoids and anthocyanidins. They exert their anticancer activity through the induction of apoptosis in cancer cells. Studies have shown that high dietary intake of flavonoids is associated with reduced occurrence of many types of cancer [12,13], but there is still insufficient data on the precise mechanisms of flavonoid anticancer effects. Apart from the anticancer activity, flavonoid-mediated health benefits include antioxidant activity through the removal of free radicals, which are capable of damaging lipids, proteins and DNA [14], anti-inflammatory, neuroprotective and antiproliferative activity, as well as an ability to modulate signalling pathways involved in central cell processes.

One of the most abundant and most studied flavonoid is 4′,5,7-trihydroxyflavone, commonly referred to as apigenin, with molecular structure $C_{15}H_{10}O_5$ and molecular mass 270.24 g mol^{-1} (Fig. 1). Apigenin is found in significant quantities in a variety of vegetables and fruits such as parsley, celery, chamomile, oranges, thyme, onions, honey and spices, as well as beverages derived from plants; tea, beer and wine [4,15]. The name “apigenin” comes from *Apium* genus in Apiaceae family, a group of mostly aromatic flowering plants including celery, carrot and parsley [13]. It is a secondary plant metabolite, usually found in nature in glycosylated form, more soluble than its pure form which is unstable and quite insoluble in water and organic solvents [9,15]. The first reference of apigenin in science literature comes from the 1950s at what time Spicak and Subrt [16] analysed its effect on histamine release. It was not until the 1980s that apigenin was associated with the process of carcinogenesis when Birt et al. [17] reported its effective anti-mutagenic and anti-promotion properties. Since then, apigenin has been investigated in many studies as a potential cancer chemopreventive agent against a wide selection of different cancer types.

Interest in apigenin, as a beneficial and health promoting agent, has grown in recent years because of its low intrinsic toxicity and remarkable effects on normal *vs* cancerous cells [18,19]. There is also very little evidence that suggests that apigenin promotes adverse metabolic reactions *in vivo* when consumed as part of a normal diet. Moreover, apigenin has been increasingly recognized as a cancer chemopreventive agent in a series of studies done both *in vitro* and *in vivo*. This interest could be largely attributed to its potent antioxidant and anti-inflammatory activities [19]. Indirect support to this hypothesis is provided by a study where consumption of flavonoid free diets by healthy human volunteers has reportedly led to a decrease in the oxidative stress markers such as antioxidant vitamins and superoxide dismutase (SOD) activities, which are commonly associated with enhanced disease risk and progression [20].

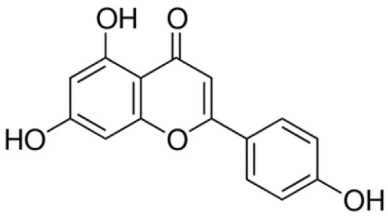

Fig. 1. . Chemical structure of dietary flavonoid apigenin.

A variety of biological effects of apigenin in a number of mammalian systems *in vitro* as well as *in vivo* are mainly related to its antioxidant effects and its role in free radical scavenging. Besides, apigenin exhibits anti-mutagenic, anti-inflammatory and antiviral effects [21]. The actions of apigenin in inhibiting the cell cycle, diminishing oxidative stress, improving the efficacy of detoxification enzymes, inducing apoptosis, and stimulating the immune system are also known [21–23]. One human study demonstrated that apigenin was absorbed systemically by a subject fed a diet rich in parsley. Results showed that this subject had elevated levels of the antioxidant enzymes glutathione reductase and SOD [24], while the activities of catalase and glutathione peroxidase were found to be unchanged. Other biological effects induced by flavonoids include the reduction of plasma levels of low-density lipoproteins, inhibition of platelet aggregation, and reduction of cell proliferation [21–23,25]. This is also apparent from another cross-sectional study conducted in Japan in which the total intake of flavonoids among women was found to be inversely correlated with plasma total cholesterol and low-density lipoprotein concentration, after adjustment for age, body mass index, and total energy intake [26]. Moreover, the effects of flavonoids on the hematologic systems were also performed in a 7-day study of 18 healthy men and women examining the effects of a daily dietary supplement, providing apigenin from parsley, on platelet aggregation and other haemostatic variables. The authors of that study observed no significant changes in collagen- or ADP-induced platelet number, factor VII, plasminogen, and PAI-1 activity or fibrinogen concentrations [27]. These specific properties categorise apigenin as part of a class of beneficial compounds which possess health-promoting and disease-preventing dietary effects.

In the following chapters, including Tables and Figures, we present a summary of apigenin anticancer activities including dose ranges used in both *in vitro* and *in vivo* studies that exerted beneficial effects against cancer growth and development.

2. Apigenin effects in cancers

2.1. Head and neck cancer

Several studies have evaluated the effect of apigenin on head and neck cancers. Apigenin was shown to inhibit proliferation in human head and neck squamous carcinoma cells which was followed with G2/M cell cycle arrest and increase in intracellular reactive oxygen species (ROS) levels. Growth inhibition was accompanied by apoptosis through the up-regulation of both tumour necrosis factor receptor (TNF-R) and TNF-related apoptosis-inducing ligand receptor (TRAIL-R) signalling pathways [28]. A study by Chakrabarti et al. [29] investigated the synergistic effect of human telomerase reverse transcriptase (hTERT) knockdown and apigenin treatment in human malignant neuroblastoma cells. This combination therapy led to cell proliferation with the inhibition of invasion and induced apoptosis characterized by down-regulation of MMP-2 and -9, N-Myc, PCNA, CDK-2, CDK-4 and cyclin D1. In the next study, same authors showed that