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Review Article

An apple a day to prevent cancer formation: Reducing cancer risk with flavonoids

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ABSTRACT

The purpose of this review is to update and discuss key findings from *in vitro* and *in vivo* studies on apple and its biocompounds, with a special focus on its anticancer role. Several studies have proposed that apple and its extracts exhibit a variety of biological functions that may contribute to health benefits including beneficial effects against chronic heart and vascular disorders, respiratory and pulmonary dysfunction, diabetes, obesity, and cancer. In this review, we summarize the molecular mechanism(s) of various components in apple, as established in previous studies that indicated their growth-inhibitory effects in various cancer cell types. Moreover, an attempt is made to delineate the direction of future studies that could lead to the development of apple components as a potent chemopreventive/chemotherapeutic agent against cancer.

1. Introduction

Apples (*Malus* sp., Rosaceae) are common fruits consumed worldwide. Apples are a rich source of dietary phytochemicals such as flavonoids. They also contain high levels of polyphenols and other phytochemicals [1]. Polyphenols in apples and their extracts (juices) have been studied in several human studies that have shown promising results related to their beneficial effects [2]. For example, consumption of at least one apple a day was reported to reduce the risk of colorectal cancer (odds ratio = 0.65, 95% confidence interval, 0.39–1.09) [3]. The study also predicted that the risk of colorectal cancer reduced by approximately 50% upon consumption of more than one apple a day (odds ratio = 0.53, 95% confidence interval, 0.35–0.79). *In vitro* and *in vivo* anticancer effects of apple extracts have been

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evaluated in many studies, including those of phytochemical compounds in these extracts [4,5] and apple juice fractions [6]. In our previous studies, we have demonstrated that phloretin isolated from apple peels exhibits significant antihepatic tumor proliferation capacity through *in vivo* inhibition of type 2 glucose transporter (GLUT2) [5]. We have further demonstrated that phloretin significantly potentiates paclitaxel-induced DNA laddering effects in a human liver cancer cell model [4]. This observation indicated that phytochemical components in apples exhibit a beneficial effect on human health. In this review, we include an overview of the positive association between apple juice extract and health benefits demonstrated in observational studies. We also discuss the extract's basic antioxidant effects and mechanisms underlying cell growth cycle inhibition and cell death and its signaling.

For cancer chemoprevention, dietary nutrients should be more readily available. Many studies have demonstrated the chemopreventive effects of dietary polyphenols, especially the most abundant subclasses, including flavonoids (60% of all polyphenols) and phenolic acids (30% of total polyphenols) [7]. Flavonoids are divided into various groups based on their molecular structure, several of which are present in significant quantities in apple, including flavanols, flavonols, and anthocyanidins as well as dihydrochalcones and hydroxycinnamic acids [8,9]. The chemical structures of several representative polyphenols present in apple are shown in Figure 1 [1].

2. Antioxidant activity of apple polyphenols

Generation of oxygen radicals causes chronic diseases such as diabetes mellitus [10], retinal degeneration, neurodegenerative disorders, aging, and cancer. Several studies have demonstrated that apple polyphenols, including phloretin, exhibit promising antioxidants effects by playing a role in significant mechanisms responsible for the prevention of illnesses triggered by oxidative stress [11]. For example, in a previous study on Wistar rats, diabetes was induced by a single dose of streptozotocin. Rats in the diabetic group received either apple juice (15 mL/kg) or apple peel extract (1 g/kg) for 21 days. At the end of the study, lipid profile parameters were measured in serum samples and lipid peroxidation level, antioxidant enzyme activities, and level of inflammatory markers were evaluated in pancreatic tissue samples. The study concluded that supplementation with apple juice/extract may have protective effects against deleterious complications of diabetes mellitus due to its antioxidant effects [10]. In a different study on human participants, after 2 weeks of dietary intervention in 25 healthy individuals, the influence of apple and grape juices consumption on body antioxidant status was investigated. The results indicated that such a dietary consumption increased their plasma total antioxidant capacity and decreased their serum and plasma concentration of malondialdehyde [12].

3. Anticancer activity of apple polyphenols

3.1. *Apple polyphenol and cell proliferation*

In addition to its antioxidant activity, we [4,5,13] and others [14–16] have demonstrated that apple polyphenols have significant effects in affecting signaling pathways that control cell survival, growth, and proliferation both *in vitro* and *in vivo*. The results have shown that phloretin inhibited proliferation and induced apoptosis in nonsmall cell lung cancer cells (A549, Calu-1, H838, and H520) in a dose-dependent manner; phloretin also suppressed the invasion and migration of these cells [14]. In our group, we found that phloretin (50–150μM) significantly potentiates paclitaxel (10nM)-induced DNA laddering formation in human hepatoma (Hep G2) cells. The antitumor therapeutic efficacy of phloretin (10 mg/kg body

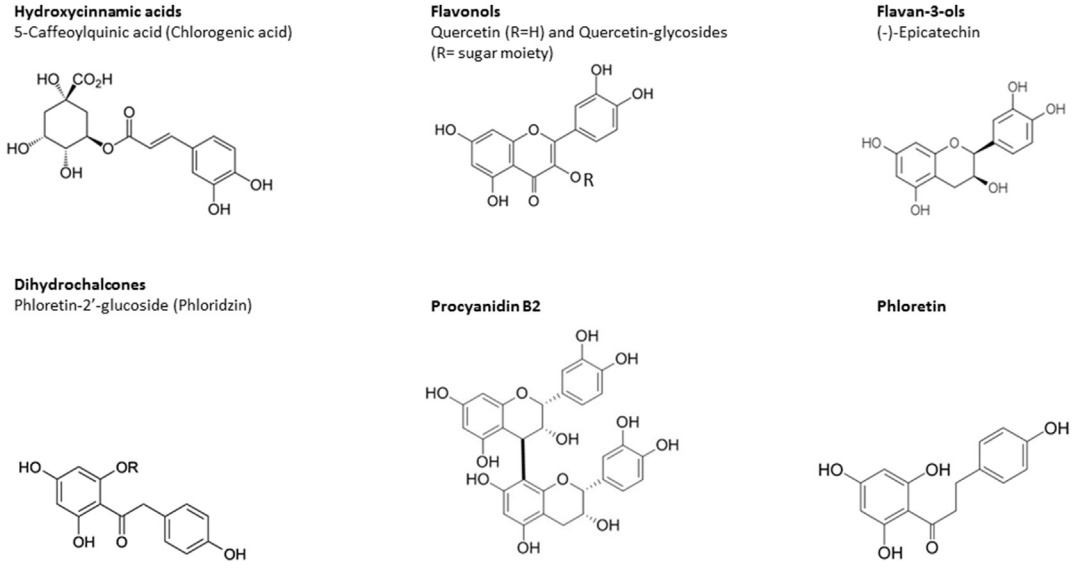

Figure 1 – Chemical structures of some selected typical biocompounds in apple juice belonging to the structural classes of hydroxycinnamic acids, dihydrochalcones, flavan-3-ols (catechins and procyanidins), flavonols (quercetin-glycosides), and triterpenoids.