Journal of Food and Drug Analysis

Volume 25 | Issue 1 Article 1

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Review Article

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

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ARTICLE INFO

Article history:
Received 4 October 2016
Received in revised form
28 October 2016
Accepted 28 October 2016
Available online 5 December 2016

Keywords:
apple
cancer chemoprevention
phloretin
type 2 glucose transporter

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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http://dx.doi.org/10.1016/j.jfda.2016.10.016

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

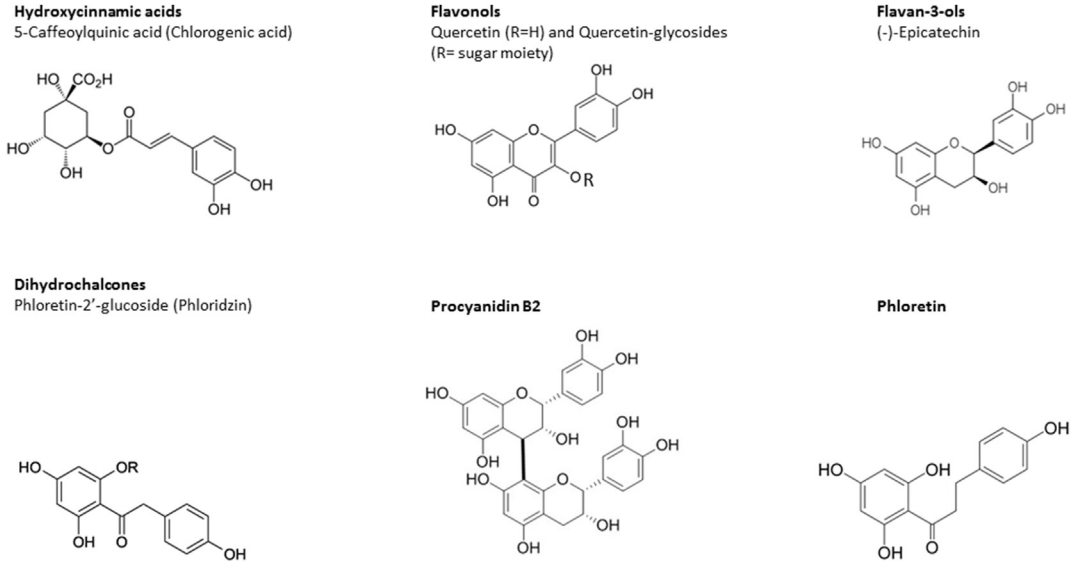

Figure 1 – Chemical structures of some selected typical biocompounds in apple juice belonging to the structural classes of hydroxycinnamic acids, dihydrochalcones, flavan-3-ols (catechins and procyanidins), flavonols (quercetin-glycosides), and triterpenoids.

weight) was determined by combined treatment of cells with antitumor drug (paclitaxel, 1 mg/kg body weight) in an SCID mouse model [4]. Recently [5,13], we have also further demonstrated that apple phloretin inhibits human colorectal cancer and liver cancer cells through inhibition of GLUT2 (Figure 2). These results further provide evidence to the hypothesis that glucose deprivation therapy has some important beneficial effects on human cancer therapy [17]. To test this hypothesis, another group evaluated the antiproliferative activity of apple juices *in vitro* in MCF-7 and MDA-MB-231 human breast cancer cells. The study results showed that Pelingo apple juice has promising effects to inhibit breast cancer cell proliferation [18]. It was demonstrated that 3-beta-*trans*-cinnamoyloxy-2alpha-hydroxy-urs-12-en-28-oic acid, which is one of the main components of apple peels, showed potent *in vitro* and *in vivo* antitumor activity against mammary tumor in a nude mouse xenograft model at a dose of 50 mg/kg/d without body weight loss and mortality [19].

3.2. *Apple polyphenols inhibit cell migration and invasion*

Antimetastasis effects of biocompounds in apple have been studied by our group. Our results have indicated that phloretin is an inhibitor of GLUT2 [4,5] and that targeting GLUT2 significantly inhibited COLO 205 colon cancer cell proliferation, migration, and invasion *in vitro* and *in vivo* [13]. In this study [13], p53-mediated signals were important. Inhibition of the wild-type p53 by dominant negative p53 will attenuate the phloretin-induced colon cancer migration and its related signals. In colorectal cancers, studies have demonstrated that the activation of nuclear factor-κB (NF-κB) occurs via lipopolysaccharide (LPS) binding to the Toll-like receptor 4 (TLR4). Modification of polysaccharide components in apple altered the LPS/TLR4/NF-κB pathway; consequently, supplementation of apple polysaccharide significantly inhibited the migratory ability *in vitro* on the LPS/TLR4/NF-κB pathway in colorectal cancer cells (HT-29 and SW620 cells) [20]. In a study on liver cancer cells, the effect of apple polyphenol extract on the proliferation and invasion of rat ascites hepatoma cell line (AH109A) was examined *in vitro*. The apple polyphenol extract suppressed both proliferation and invasion of the hepatoma cell line in a dose-dependent manner up to 200 μg/mL. In an *in vivo* study, apple polyphenol also reduced the growth and metastasis of solid hepatomas and significantly suppressed the serum lipid peroxide level in rats transplanted with AH109A [21].

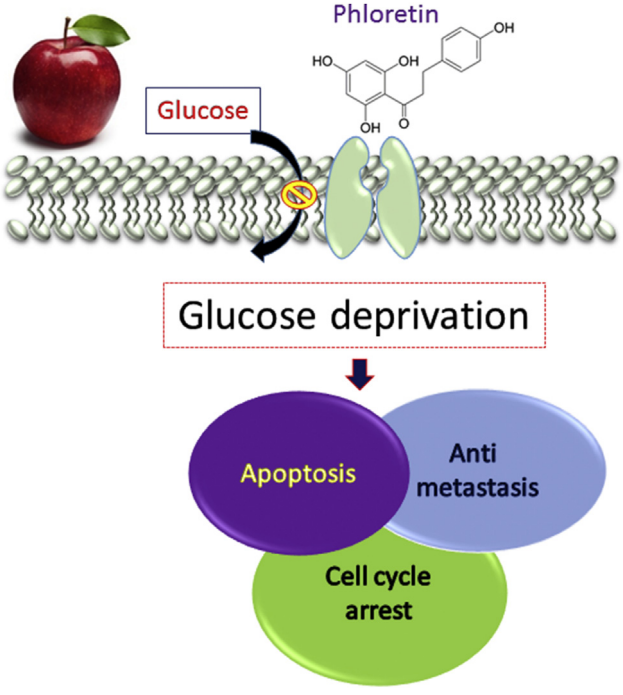

Figure 2 – Apple polyphenol phloretin inhibits growth of cancer cells through inhibition of type 2 glucose transporter. Our groups have demonstrated that phloretin can induce growth arrest of cells in the G_0/G_1 phase, induce apoptotic cell death, and inhibit tumor cells migration and metastasis. All these effects can be attributed to the phloretin-induced intracellular glucose deprivation.

3.3. *Apple polyphenols induced apoptotic cancer cell death*

Our previous results demonstrate that apple polyphenol phloretin (50–150μM) significantly potentiates paclitaxel (10nM)-induced DNA laddering formation in Hep G2 cells. We have also demonstrated that the caspases 3, 8, and 9 were involved in apoptosis, as evidenced by activity assays [4]. Previous studies in this area have also demonstrated that phloretin inhibited leukemia cell growth [22] and induced apoptosis of melanoma cells through deprivation of glucose uptake by inhibition of glucose transmembrane transport [23]. Using ^{18}F-fluorodeoxyglucose micropositron emission tomography the effects of phloretin-induced suppression of liver tumor growth were demonstrated to involve regulation of glucose transportation [5]. The ^{18}F-fluorodeoxyglucose uptake in the phloretin-treated Hep G2 tumor-bearing mice was significantly suppressed as compared with the control mice. Effects of phloretin on glioblastoma cancer cells have been investigated via induction of apoptosis and cells' growth cycle arrest. The identified mechanisms demonstrated increased expression of p27 and decreased expression of cdk2, cdk4, cdk6, cyclin D, and cyclin E. Moreover, the phosphatidylinositol-3-kinase/Akt and the mammalian target of rapamycin (PI3K/Akt/mTOR) signaling cascades were suppressed by phloretin in a dose-dependent manner [24]. Phloretin-based combination treatment enhanced the anticancer effects of cisplatin on nonsmall cell lung cancer cell lines by suppressing the expression of Bcl-2, increasing the protein expression of cleaved caspases 3 and 9, and deregulating the expression of matrix metalloproteinase-2 and metalloproteinase-9 on gene and protein levels [14]. The results suggest that inhibition of intracellular glucose uptake was the most important mechanism responsible for the cancer cell killing effects. Because many cancer cells rely on aerobic glycolysis for energy production, Xintaropoulou et al [15] targeted this pathway as a potential strategy to inhibit cancer cell growth. In that study, inhibition of five glycolysis pathway molecules (GLUT1, HKII (hexokinase II), PFKFB3 (6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3), PDHK1 (pyruvate dehydrogenase kinase I), and LDH (lactate dehydrogenase)) using nine inhibitors (phloretin, quercetin, STF31 (Glut1 inhibitor),

WZB117 (Glut1 inhibitor), 3PO (3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one, glycolytic inhibitor), 3-bromopyruvate, dichloroacetate, oxamic acid, NHI-1 (lactate dehydrogenase A inhibitor)) was investigated in panels of breast and ovarian cancer cell line models. Their results indicated that growth of breast and ovarian cancer cell lines was more sensitive to the glycolytic pathway, with increased sensitivity to the inhibitors under normoxic conditions [15].

4. Signaling molecules and disease protection effects of phloretin

As described earlier, apple polyphenols induced anticancer activity mainly through their antioxidant activity. Such results have been confirmed by basic *in vitro* studies. Moreover, phloretin-induced cell cycle arrest was associated with increased expression of p27 and decreased expression of cdk2, cdk4, cdk6, cyclin D, and cyclin E [24]. Inhibition of intracellular signaling pathways as well as the PI3K/Akt/mTOR and ERK/Nrf2 signaling cascades was suppressed by phloretin in a dose-dependent manner [25]. In addition, many previous studies have also proposed that phloretin triggered the mitochondrial apoptosis pathway [26–28] and generated reactive oxygen species (ROS) [29]. Most of these studies were accompanied by induction of cell growth arrest and apoptosis through upregulation of proapoptotic molecules such as Bax, Bak, and poly (ADP-ribose (adenosine diphosphate-ribose)) polymerase (cleaved) and downregulation of Bcl-2. The antioxidant agents N-acetyl-L-cysteine and glutathione weakened the effect of phloretin on glioblastoma cells. In conclusion, these results demonstrate that phloretin exerts a potent chemopreventive activity in human glioblastoma cells through the generation of ROS. Such effects may have some potential applications for clinical patients. For example, in acute hepatitis patients, liver damage is induced by several damaging factors, among which viral exposure, alcohol consumption, and drug and immune system issues are most popular [30]. In addition to antioxidant effects, phloretin is also able to modulate inflammatory responses. A previous study demonstrated that phloretin suppressed the activation and function of mouse dendritic cells [31]. The study results showed that phloretin disturbed the multiple intracellular signaling pathways in dendritic cells induced by the TLR4 agonist LPS, including ROS, mitogen-activated protein kinases (extracellular signal-regulated kinase, c-Jun N-terminal kinase, p38 mitogen-activated protein kinase), and NF-κB, thus reducing the production of inflammatory cytokines and chemokine [31].

5. Apple polyphenol-induced anticancer effects in animal model

The anticancer activity of biocompounds in apple has also been documented in animal models. We further examined the antitumor effect of phloretin *in vivo* by treating SCID mice bearing COLO 205 and Hep G2 tumor xenografts [5,13]. We have demonstrated that phloretin has significant effects on the inhibition of type 2 glucose 2 transporter as evidenced by micro-positron emission tomography imaging assay. The chemopreventive potential of apple extract following medium-term oral carcinogenesis assay induced by 4-nitroquinoline 1-oxide has been studied by histopathological analysis and gene expression of antioxidant enzymes and it was shown that the apple extract is able to modulate medium-term oral carcinogenesis assay due to its antioxidant ability [32]. Recently, a model of human microbiota-associated rats has been developed, where mice were fed with a human-type diet and injected with 1,2-dimethylhydrazine to induce colorectal tumor. The study results demonstrated that the number and size of 1,2-dimethylhydrazine-induced aberrant crypt foci were significantly higher in human microbiota-associated rats than in germ-free or conventional rats. Interestingly, the authors used this model to assess the protective effect of an apple proanthocyanidin-rich extract (APE) on colon carcinogenesis. In this model, aberrant crypt foci number and multiplicity were not reduced by APE at 0.001% and 0.01% concentration in drinking water. Such results provide evidence that the cross-talk between human microbiota and the colon epithelium should be considered in carcinogenesis models and that it is necessary to pay increased attention prior to using proanthocyanidin extracts as dietary supplements for humans [33]. Moreover, *in vivo* studies have shown the cancer prevention potential of apple extracts based on their ability to protect genotoxicity and inhibit the development of aberrant crypt foci experimentally induced in a rat model using dimethylhydrazine [34,35]. Using a pure compound isolated from apple peels, 3beta-trans-cinnamoyloxy-2alpha-hydroxy-urs-12-en-28-oic acid, another study showed potent *in vitro* antitumor activity against human tumor cells. *In vivo* experiments further demonstrated that 3beta-trans-cinnamoyloxy-2alpha-hydroxy-urs-12-en-28-oic acid significantly inhibited the growth of mammary tumor in a nude mouse xenograft model at a dose of 50 mg/kg/d without body weight loss and mortality [19]. Apple polyphenol extracts were also evaluated for their *in vivo* effects on the growth and metastasis of rat ascites hepatoma cell line (AH109A) and the results were promising [21].

6. Summary and conclusion

This review provides a summary of recent studies suggesting an association between apple polyphenols and reduced risk of carcinogenesis and indicating multiple plausible mechanisms by which apple polyphenols might be protective in humans. Recent studies have demonstrated multiple beneficial effects of apple polyphenols, including antiproliferative, apoptotic, and antioxidative effects. These data suggest that apple polyphenol might have the potential to reduce the risk of several forms of cancer formation and metastasis. The identified antioxidant mechanisms have important implications to better understand the protective effect of apple polyphenols on cancer formation. Although these are preliminary results, the obtained results are intriguing, as they clearly demonstrate the potential of apple polyphenols to modulate some of these processes in animal models. The observations that apple intake might be associated with reduced risk of cancer have led to an expanded field of animal and *in vitro* research studies using cell models that mimic phases in the initiation, promotion, and progression of cancer.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgments

Part of the study results reported in this review were supported by the Health and Welfare Surcharge on tobacco products (MOHW105-TDU-B-212-134001) to Dr Y.-S.H.

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