REVIEW

A Comprehensive Review of Apples and Apple Components and Their Relationship to Human Health[1,2]

Dianne A. Hyson*

Department of Family and Consumer Sciences–Nutrition and Food/Dietetics, California State University, Sacramento, CA

ABSTRACT

There has been an increasing appreciation and understanding of the link between dietary fruit and vegetable intake and improved health in humans. The widespread and growing intake of apples and apple juice/products and their rich phytochemical profile suggest their important potential to affect the health of the populations consuming them. This review summarizes current clinical, in vitro, and in vivo data and builds upon earlier published reports that apple may reduce the risk of chronic disease by various mechanisms, including antioxidant, antiproliferative, and cell signaling effects. Exposure to apples and apple products has been associated with beneficial effects on risk, markers, and etiology of cancer, cardiovascular disease, asthma, and Alzheimer's disease. Recent work suggests that these products may also be associated with improved outcomes related to cognitive decline of normal aging, diabetes, weight management, bone health, pulmonary function, and gastrointestinal protection. *Adv. Nutr. 2: 408–420, 2011.*

There has been a growing appreciation and understanding of the link between fruit and vegetable consumption and improved health. Research has shown that biologically active components in plant-based foods, particularly phytochemicals, have important potential to modulate many processes in the development of diseases, including cancer, cardiovascular disease, diabetes, pulmonary disorders, Alzheimer's disease, and other degenerative disease states. Apples and AP[3], including juices and extracts, have been included in health-related studies around the world due to their rich content of varied phytochemicals. The potential of AP phytochemicals to reduce disease risk and improve health has caught the attention of scientists, practitioners, and the lay public.

A detailed report of apple phytochemicals and their health benefits was published by Boyer and Liu (1) in 2004. Their review included an overview of the positive association between AP and health benefits demonstrated in observational studies (1). In many of these studies, dietary intake was quantified using diet history or FFQ followed by tests for a statistical link between disease risk and defined strata of AP or AP-flavonoid consumption. Early work suggested a potential association between AP intake and reduced risk of coronary artery disease, lung cancer, asthma, and diabetes. AP consumption was also linked to beneficial effects on pulmonary function in healthy participants and those with diagnosed pulmonary disorders (1). Recent investigations have added to the earlier work as well as identified potential new health benefits of AP consumption.

The nature of the link between diet and disease is complex. Increasingly, research has moved toward studying compounds in individual foods to gain a greater understanding of their specific role(s) and the mechanisms involved in the prevention and reduction of disease in humans. A great deal of work has focused on dietary polyphenols, particularly the most abundant subclasses, including flavonoids (60% of all polyphenols) and phenolic acids (30% of total polyphenols) (2). More than 4000 flavonoids have been identified and all share a common carbon skeleton structure (C6-C3-C6). Flavonoids are further divided into different classes based on molecular structure, several of which are present in significant quantities in AP, including flavanols, flavonols, and anthocyanidins as well as dihydrochalcones and hydroxycinnamic acids (3). The chemical structures of several representative polyphenols present in AP are shown in **Fig. 1** (4).

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[3] Abbreviations used: AP, apple product; FRAP, ferric-reducing antioxidant potential; MDA, malondialdehyde; PKC, protein kinase C; ROS, reactive oxygen species; SOD, superoxide dismutase.

* To whom correspondence should be addressed. E-mail: dhyson@csus.edu.

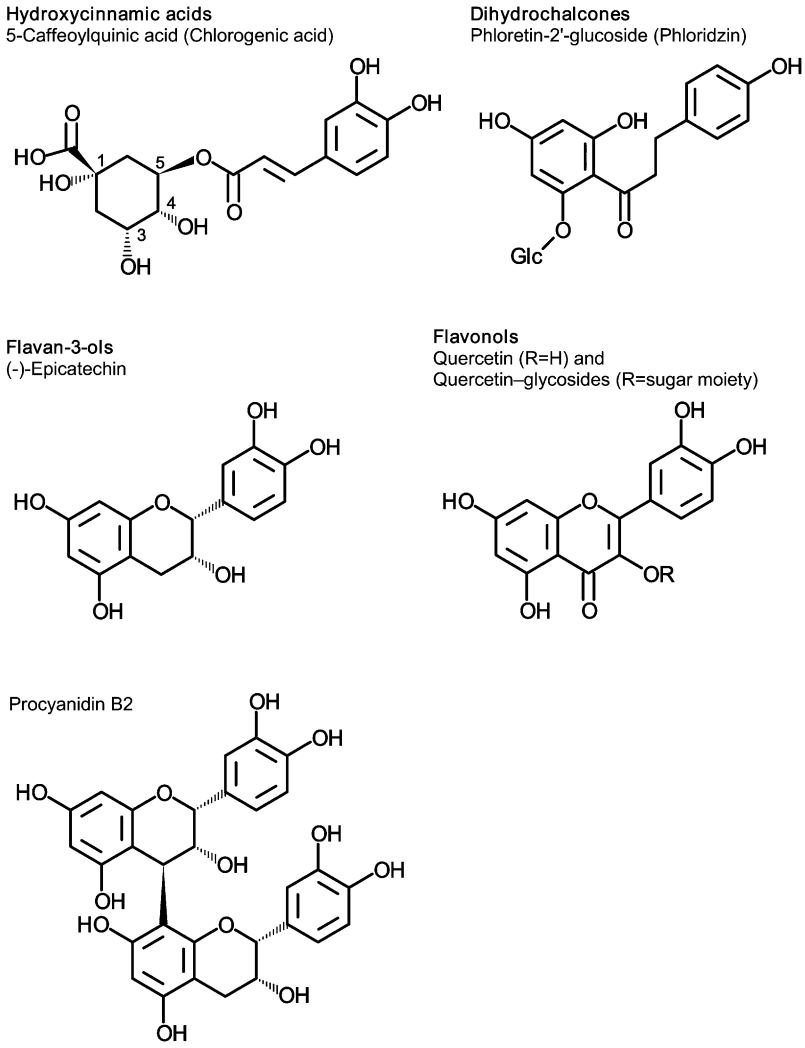

Figure 1 Selected polyphenols in apples and apple products. Adapted with permission from (4).

Polyphenolic compounds account for the color, flavor, taste, and metabolic activity of plant-based foods as well as the putative health benefits to humans. The concentration of polyphenols is influenced by the plant variety as well as environmental factors, including geographic region, growing season, and storage (3). The wide range of polyphenol content in whole apples and apple juice is depicted in **Table 1** (4,5). Typically, the greater values in the ranges shown for juices reflect the higher concentration of polyphenols in fresh juice prepared from cider apples and

TABLE 1 Polyphenolic concentration of whole apples (freeze dried) and apple juice

Polyphenolic compound	Whole apple (67 cultivars; n = 5 each), *mg/kg dry weight* (5)	Fresh juice (combined dessert and cider apples), *mg/L*[1]	Commercial juice (combined clear and cloudy juices), *mg/L*[1]
Hydroxycinnamic acids	50–3000	57–593	69–259
5-Caffeoylquinic acid (chlorogenic acid)	15–2960		
p-Coumaroylquinic acid	4–260		
Flavan-3-ols/procyanidins	4622–25,480	50–393	14–124
Procyanidins B2	69–2000		
Procyanidins C1	58–970		
(-) Epicatechin	69–2760		
(+) Epicatechin	10–720		
Oligomeric procyanidins	1374–19,850	n.d.	n.d.
Flavonols	80–1660	0.4–27	4–14
Dihydrochalcones	49–434	10–171	9–87
Anthocyanins (red peel)	10–551	n.d.	n.d.
Total polyphenols	5230–27,240	154–970	110–459

[1] Adapted with permission from (4).

commercial preparations of "cloudy" juice compared to lower quantities in fresh juice made with dessert apple varieties or commercial juices that are clear.

The estimated dietary intake of polyphenolic compounds varies widely depending upon methodology, consumption data, the combination of compounds (most commonly flavonoids) included in the analysis, and the food composition database used (6). In general, AP are among the top 3 or 4 dietary sources of total phenolics consumed in America and worldwide (7–9). Furthermore, AP are available on a year-round basis and the per capita utilization of apples and AP in the United States has been on the rise over the past several years (10). Thus, the study of AP is highly relevant and they have important potential to affect the health of the populations consuming them.

Oxidative stress, known to play a role in the pathogenesis of most diseases, has been the focus of many new studies to determine the effectiveness of AP in an antioxidant capacity. Other disease-related processes that are reportedly influenced by AP include cell proliferation and tumor production, inflammatory responses, apoptosis, cell differentiation (11), platelet aggregation, lipid metabolism, cell adhesion molecule expression, and endothelial function, among others (12). The purpose of the present review is to provide an updated summary and analysis of recent findings related to AP and associated compounds with a particular focus on their potential role(s) in disease risk and general human health. Studies are presented below, grouped by disease states and/or disease processes when applicable.

Cancer

It is estimated that one-third of all cancer deaths could be prevented by improved diet, particularly increased consumption of fruits, vegetables, and whole grains (13). There is convincing evidence that diets high in fruits and vegetables are associated with reduced cancer in the lung, oral cavity, esophagus, stomach, and colon (13). As reviewed by Boyer and Liu (1), there were several reports prior to 2004 demonstrating that AP intake was associated with reduced risk of cancer, particularly lung cancer in cohort and case-control studies. Recent trials have added data that suggest a protective effect of AP on risk of cancer.

Human trials

A hospital-based, case-control study published in 2005 included over 6000 participants from various regions in Italy and examined the association between fresh apple intake and risk of cancer (14). Data were based on FFQ (including interviews) of dietary intake in the 2 y prior to diagnosis. It was found that consuming one or more medium-sized apples (166 g)/d was associated with a reduction in risk of cancer compared to consumption of <1 apple/d. Significant risk reduction was observed in cancer at several sites (percent reduction in parentheses), including oral cavity and pharynx (18%), esophagus (22%), colorectal (30%), larynx (41%), breast (24%), ovary (24%), and prostate (7%). A similar pattern of beneficial association was present when the groups were stratified by age, energy intake, vegetable consumption, smoking, and BMI.

An updated analysis of fruit and vegetable consumption and lung cancer risk from the European Prospective Investigation into Cancer and Nutrition was published in 2007 (15). The data were based on dietary assessment questionnaires from a prospective cohort of 478,590 male and female participants in 23 centers from 10 European countries. Total daily intake (g/d) of "hard fruits" (apples and pears) was included in the analysis with a median follow-up time of 6.4 y. A comparison of the lowest quintile of intake (average 43 g/d) compared to the highest 2 quintiles (93.5 and 164.9 g/d, respectively) showed a significant inverse association between combined apple and pear intake and lung cancer in all participants and current smokers. There is no detailed breakdown of the relative proportion of apples compared to pears, but the authors noted that in general hard fruits were consumed in greater quantities than all other subgroups of fruit.

In addition to clinical data, recent animal feeding and in vitro studies have aimed to examine the potential protective link between AP and cancer. Colorectal or colon cancer, the 4th most common cancer and the 3rd most common cause of death in Western society (16), has been the focus of many investigations. There have also been several studies that examined the potential of AP to reduce breast cancer risk. As summarized below, recent studies demonstrate the potential of AP to mitigate many metabolic processes associated with the etiology of cancer at various stages. The data are presented in the context of colon cancer, followed by breast cancer and general studies.

Animal studies related to colon cancer

Barth et al. (17) used a well-established rat model of chemically induced colonic damage (using 1,2-dimethylhydrazine) to examine alterations associated with colon cancer and to test the effects of AP. Rats were fed 2 different preparations of apple juice pressed from a mixture of apples to determine if 7 wk of daily consumption protected the mucosa from 1,2-dimethylhydrazine–induced genotoxic damage. Because early lesions in the colon may progress to malignancy, the presence of premalignant hyperproliferative crypts and aberrant crypts are indicators of the potential pathogenesis of cancer in this model. Apple juice preparations, including a "cloudy" (higher procyanidin and pectin) and a clear juice preparation, reduced important markers, including DNA damage and hyperproliferation and lowered the number of large aberrant crypt foci in the distal colon. In follow-up studies, the same authors examined the effect of isolated fractions on the above markers and concluded that the juice fraction itself was more effective than individual components of juice, including polyphenolic-rich extracts (18). The findings of these investigators and many others suggest that the whole is greater than the sum of the parts in terms of a protective effect of AP on cancer.

A different study, using rats injected with the chemical carcinogen azoxymethane, known to cause a range of morphological changes including carcinoma, found protective

effects of an extract of apple procyanidins provided to the animals in their drinking water for 6 wk (19). There was a significant reduction of preneoplastic lesions in the animals exposed to the apple phytochemicals, including 50% fewer aberrant crypts. The authors estimated that the amount of procyanidin ingested would be comparable to humans consuming 2 apples/d (4–10 mg procyanidin/kg bodyweight).

In vitro studies using cell lines related to colon cancer

Several investigations have used cultured colonic cells, both healthy and cancer-derived cells lines, representing various developmental stages, to examine the in vitro effects of AP on cancer-related processes. Antioxidant activity, including the scavenging of free radicals, is thought to reduce cell proliferation and induce detoxification enzymes and apoptosis. Schaefer et al. (20) crushed and extracted juice from cider and table apples harvested in Germany to prepare several polyphenolic mixtures, including one extract from apple pomace. Four preparations differing in relative percentages of 14 identified phytochemicals were compared for their effects on oxidative markers in cultured human colonic cell lines including HT29, an established cell line of colon adenocarcinoma, and Caco-2 cells (human colonic cells). All extracts significantly reduced oxidative damage and effectively reduced the presence of tert-butylhydroperoxide-induced ROS. Although there were observed differences in effectiveness and specificity between each extract preparation, the effective range was comparable to quantities of phytochemicals found in apple juice. In spite of the similar chemical composition between some extracts, the antioxidant capacity determined by Trolox equivalent antioxidant capacity differed, suggesting that there are unknown compounds accounting for the observed antioxidant effects of AP. Interestingly, prolonged exposure to AP resulted in even greater antioxidant capacity for some compounds, suggesting that metabolic products formed over a period of time may have differing antioxidant capacities than the parent phytochemicals and, in some cases, improved potential.

The effect of AP on cell proliferation has been the focus of many recent studies. HT29 cells, as well as a breast cancer cell line, MCF-7 were the models in a study of the effects of extracts of 10 fruits, including apple peel (*Malus domestica*) (21). An anthocyanidin-rich fraction from each of the fruit extracts was also tested. The apple peel extract was among the fruits that showed a significant dose-response reduction in cell proliferation in the HT29 but not the MCF-7 cells, the latter cell type being generally less responsive to extract exposure. There were also differential outcomes between cell lines in terms of the inhibitory effect of the anthocyanidin-rich fraction, with significant inhibition in the HT29 cells by apple anthocyanidins (compared to an actual increase in proliferation in response to this fraction in MCF-7 cells).

In a study of SW620, adenocarcinoma-derived metastatic cells of colon cancer, the goal was to determine whether polymeric apple phenols compared to monomeric forms were more effective in attenuating cell proliferation (19). The relevance of this study relates to the reduced ability of larger molecules in polymeric form to be absorbed in the upper segment of the intestine, resulting in a higher residual concentration in the colon. Incubating SW620 cells with an apple extract selected for procyanidins (mainly polymeric molecules) resulted in a dose-dependent inhibition of cell growth. There was a 50% inhibition at a concentration of 45 μg/mL and total inhibition at 70 μg/mL. In addition, the extract downregulated several signal pathways involved in cell proliferation and differentiation, including PKC and enzymes involved in polyamine biosynthesis. Polyamines, as regulators of cell function, have important potential in cancer by either promoting cell proliferation or cell death depending on the cell type. Flow cytometry demonstrated that the apple extract increased the number of apoptotic cells and also appeared to interfere with the cell cycle.

In a follow-up to the above study to examine mechanisms, it was found that apple procyanidins have a dual effect of downregulating polyamine biosynthesis concurrent with stimulating the catabolism or breakdown of these compounds (22). It was also found that the effect of apple procyanidins on apoptosis was enhanced by a known compound that inactivates polyamine oxidase, leading the authors to conclude that apple procyanidins might be considered as a chemopreventive agent for colon cancer by these mechanisms.

Other authors have described cell signaling and molecular mechanisms that respond to AP exposure. Kern et al. (23) recently reported that PKC activity was reduced by 50% in HT29 cells after 24-h exposure to apple extracts at a relatively high concentration (403 μg/mL). The longer exposure time suggests that apple extracts target signaling elements upstream of PKC and not PKC specifically. Individual compounds isolated from the apple extracts were not effective in altering any of the markers in this study, suggesting that the composite mixtures of components in the extracts were more important in mediating the observed effects than individual compounds, likely due to interaction/synergy between the different components.

The effects of AP on specific enzymes involved in colon carcinogenesis have been examined. Among the enzymes of interest in intestinal tissues is cytochrome P450 1A1, an enzyme known to activate chemical carcinogens. In a recent study using Caco-2 cells, it was found that an apple juice extract devoid of carbohydrates, acids, and other native compounds attenuated experimentally induced expression of cytochrome P450 1A1 and inhibited catalytic activity of the enzyme. Isolated fractions of the major phenolics in the juice (phloretin and quercetin and their 2 glucoside forms, phlorizin and rutin, respectively) were shown to account in part for the inhibitory effects.

Other enzymes related to cancer etiology are also favorably affected by AP (24). In one study, polyphenols were extracted from the juice of a variety of table and cider apples. In addition, a synthetic mixture developed to mimic the composition of the natural polyphenolic profile was formulated and tested on cultured HT29 cells. Incubation of these

cells with the apple juice extract for 24, 48, and 72 h reduced their growth. The synthetic mixture of polyphenols also inhibited growth, although less effectively, and isolated components were significantly less effective than either mixture. Treating the cells with apple juice extract increased the expression of several genes, including phase 2 enzymes associated with chemoprevention (sulfotransferases and glutathione *S*-transferases). Although further work needs to be done, it is intriguing that components in AP have the potential to modify genetic profiles in a potentially protective manner. These data support prior observations that complete mixtures of phytochemicals in AP are more effective than individual components tested alone.

Bioavailability and metabolism of AP related to colon cancer

Understanding and characterizing the bioavailability of AP in humans is important in examining their possible protective effects on colon cancer. A small study of absorption in ileostomy patients showed that 66.9–100% of ingested apple phenolics were absorbed or metabolized in the small intestine, implying that a range of 0–33% might reach the colon (25). Subsequent work by the same investigators provided a detailed analysis of the extent of metabolization of polyphenolic compounds after digestion and absorption. It was shown that extensive isomerization, cleavage, and conjugation of the native polyphenolic compounds occurred. Only 12.7% of the ingested compounds in cloudy apple juice reached the end of the intestine in unmetabolized form, whereas 22.3% were recovered as metabolites. These studies are among the few that highlight the importance of metabolized AP and emphasize the need to determine the biological activity of metabolites of phytochemicals in vivo. It is becoming apparent that native polyphenolic compounds are most commonly tested but due to extensive metabolic modification, the ingested compounds may be negligible or even absent in tissues under physiologic conditions.

Colonic microflora metabolize ingested polyphenols. Thus, it is important to consider the effects of potential breakdown products in the gut in addition to metabolites in the blood (12). To address this issue, a recent study by Veeriah et al. (11) in Germany used apple extracts fermented in vitro with human fecal flora to examine effects of the fermentation products on cultured HT29 and LT97 cells (the latter, a colon adenoma cell line representing early premalignant tumor development). Fecal fermentation resulted in a degradation of 99.9% of the parent polyphenols except for complex structures. There was also a 1.5-fold increase in SCFA in the fermented samples compared to nonfermented. Although the SCFA were not correlated with inhibition of growth in this study, it is known that SCFA can stimulate pathways of growth arrest, differentiation, and apoptosis. Fermented apple juice extract had an antiproliferative effect in both cell lines, particularly in the LT97 cells, suggesting a greater effect on precancerous than cancer cells. Unfermented apple juice extract also had potent antiproliferative effects.

A follow-up mechanistic study using a similar approach with polyphenol-rich apple extract was conducted to examine the effect of fermentation-generated SCFA on inhibition of histone deacetylase in 2 colon cancer cell lines, including HT29 and Caco-2 (26). Histone deacylation inhibition is associated with reduced colon carcinogenesis. The fermentation products of the apple juice extract in combination with pectin included acetate, propionate, and butyrate, the latter of which was most significantly correlated with histone deacylation inhibition. This work proposes a potential mechanism by which AP, particularly metabolites related to AP exposure, might exert anticarcinogenic effects in the colon.

Animal studies related to breast cancer

Animal feeding and in vitro studies have shown the potential of AP in breast cancer reduction. Liu et al. (27) treated rats with a carcinogenic agent (7,12-dimethylbenz[a]anthracene) to induce mammary tumors and then fed extracts of whole apples by gavage to the animals. Daily administration of the apple extract (~272 mg of phenolics/100 g of apples) for 24 wk resulted in a significant dose-dependent reduction in the number and onset of mammary tumors compared to control rats. Increasingly protective effects were observed in rats fed extract doses equivalent to 1, 3, or 6 apples/d with reductions in tumor incidence of 17, 39, and 44%, respectively. After 24 wk, cumulative tumor numbers in groups receiving low, medium, or high doses of the extract were reduced by 25, 25, and 61%, respectively, and there was a dose-dependent delay in tumor onset.

Follow-up work with this model to further characterize the effects of the fresh apple extract demonstrated dose-dependent inhibition of markers of cell proliferation (proliferating cell nuclear antigen) and down regulation of the cell cycle in mammary tumor cells (cyclin D1 protein expression) (28). There was a concurrent and dose-dependent increase in expression of Bax, a proapoptotic protein and downward expression of Bcl-2, an antiapoptotic protein. Histological analysis showed that consumption of the apple extract also reduced the proportion of highly malignant adenocarcinoma in a dose-dependent manner from 81.3% in the control group to ~57, 50, and 23% in the low, middle, and high doses of apple extracts, respectively, over 24 wk.

In vitro studies using cell lines related to breast cancer

In vitro studies from the above laboratory examined the potential mechanisms by which AP may cause reduction in mammary tumors (29). Their work focused on NF-κB, a transcription factor involved in regulation of inflammation, immunity, apoptosis, cell proliferation, and differentiation. Several extracellular stimuli, including oxidative stress, bacteria, viruses, inflammatory cytokines, and others, are known to activate NF-κB by release of an inhibitory protein, Iκ-Bα. In this study, human breast cancer cells (MCF-7) were exposed to TNFα (10 μg/L) to activate NF-κB. Subsequent tests were conducted to determine if apple extracts (peel and flesh) and selected phytochemicals could attenuate

this activation. It was found that cell proliferation was reduced in cells exposed to apple extracts in a dose-dependent manner with a median EC_{50} of 65.1 g/L. The apple extracts and curcumin, but not other phytochemicals, significantly reduced the TNFα-induced activation of NF-κB by reducing proteasome activity, a known target in regulation of NF-κB.

In another study, the same investigators used 2 breast cancer cell lines, including the MCF-7 cells as an estrogen-responsive model and MDA-MB-231 as an estrogen-negative model (30). The cells were exposed to apple extracts, prepared from fresh fruit (assayed for total phenolic and flavonoid content) across several ranges from 0 to 60 g/L. The apple extract significantly inhibited cell proliferation and downregulated cell cycle protein expression. The estrogen-negative cells exhibited a greater sensitivity to the apple extracts than the estrogen-responsive model. The in vitro findings align with the results of animal studies, demonstrating that apple extracts modulate the cell cycle, an important mechanistic explanation of the observed effects of AP on mammary tumor inhibition.

Effect of AP on mechanisms related to cancer

An effect of AP on NF-κB activity was observed in another cell line in a recent study by Davis et al. (31). An extract isolated from a mixture of 4 apple varieties was incubated for 24 h with cultured human umbilical vein endothelial cells to test the effect of AP on NF-κB response to TNFα stimulation. It was found that high concentrations of the extract (200–2000 nmol/L) for longer incubation periods with TNFα (3–6 h) resulted in reduced NF-κB activity, likely mediated via inhibited phosphorylation of IκBα. The reduction in NF-κB activity observed in these studies aligns with the suppression of cell proliferation by AP reported in many investigations.

There are ongoing attempts to elucidate other bioactive compounds, beyond flavonoids, that might account for the observed effects of AP on cancer risk. One recent investigation focused on isolating and identifying bioactive compounds in apple peel associated with antiproliferative activity (32). Thirteen pure compounds were identified as triterpenoids and tested for antiproliferative activity against human liver cancer cells (HepG2), as well as human breast cancer and colon cancer cells (MCF-7 and Caco-2, respectively). Every triterpenoid significantly suppressed cancer cell proliferation; some were highly potent and reduced cell growth by 50% at relatively low concentrations (~10–17 μmol/L). The authors concluded that these compounds could be partially responsible for the anticancer activities associated with AP.

In vitro work has demonstrated that several important pathways and processes involved in carcinogenesis are affected by AP and phytochemicals in AP. Although further work is needed to extrapolate these findings to clinical outcomes, it is promising that there are multiple plausible mechanisms by which AP intake might reduce the risk of cancer in humans.

One widely studied mechanism related to cancer is oxidation. Many investigations have assessed the potential antioxidant effects of AP. These are described in the following section in the context of cardiovascular disease, although it is recognized that antioxidant effects are likely important in chemoprevention as well.

Cardiovascular disease

It is estimated that over 80 million American adults (1 in 3 and particularly adults older than 60 y) have one or more types of cardiovascular disease. These include the diet-related conditions of hypertension, coronary artery disease, myocardial infarction, angina, heart failure, and stroke (33). As such, there is considerable interest in foods and dietary patterns that might be cardioprotective.

As summarized by Boyer and Liu (1), early reports showed an inverse association between AP and AP-flavonoid intake and coronary mortality. A group of Finnish women consuming >71 g of apple/d experienced a 43% reduction in coronary mortality compared to women who did not eat apples. In men, the risk reduction was 19% in the group consuming >54 g compared to no apple intake (34). These findings were consistent with prior data showing reduced coronary mortality in elderly Dutch men (65–84 y) who consumed apples (average 69 g/d) compared to men who had little or no apple intake (35). Collectively, these studies indicate that a relatively modest intake of apple is associated with reduced risk of cardiovascular disease and associated mortality.

Recent work in humans has moved toward a greater emphasis on examining mechanisms and biomarkers related to cardiovascular risk, in particular, oxidation and lipid metabolism. Overproduction and/or overexposure to oxidants in the body can result in an imbalance leading to cellular damage. Oxidative damage appears to be an initiating factor in several chronic diseases, including cardiovascular disease, due to disruptions in DNA, protein, lipids, and other cellular components by ROS. Dietary antioxidants are of interest, because they add to the endogenous potential of the body to scavenge ROS and nitrogen-free radicals and directly counteract lipid peroxidation reactions.

Antioxidant effects

Diet trials in humans

Several recent intervention studies have examined the effect of fresh apple consumption on oxidative markers in humans. A study conducted in Turkey included 15 elderly participants (mean age 72 y; 8 female, 7 male) who ate fresh apples at a daily dose of 2 g/kg for 1 mo (36). Pre- and post-study values were compared to assess antioxidant activity in the participants' erythrocytes and plasma. It was found that apple consumption increased antioxidant enzymes, including SOD and glutathione peroxidase, in erythrocytes and overall antioxidant potential in plasma. The upregulation of these enzymes suggests that regular apple consumption might promote a favorable milieu to reduce oxidation. Although total daily apple intake was not reported in this small study, it is estimated that the average intake would not be much more than 1 small apple/d (149 g) based on a conservative speculated average bodyweight range of 60–70 kg.

Another study examining oxidation in humans involved providing 150 mL of apple juice, prepared from homogenized apple flesh, to 10 healthy young male participants in Japan and testing their blood at periodic intervals using a fluorescent probe (2,7-dichlorofluorescin) as an indicator of ROS formation and oxidative stress (37). Apple juice was among 8 fresh fruit juices that exhibited an antioxidant effect within 30 min postconsumption that was sustained for up to 90 min. Although this was a small study, the moderate amount of apple juice and the prolonged antioxidant effect are positive indicators of AP potential to mitigate oxidation.

A crossover study of ex vivo data examined the effect of a bolus of apple (600 g of homogenized unpeeled apples) in a small group of young healthy males in Italy ($n = 6$) (38). The men were fed a restrictive, antioxidant-poor diet for 48 h followed by the apple challenge. Apple intake increased plasma total antioxidant activity by 64% at 3 and 6 h postconsumption compared to a water control, with resumption to baseline by 24 h after the test. Apple also decreased the presence of ROS generated by hydrogen peroxide exposure in lymphocytes isolated from each participant at 3 and 6 h after the apple test meal. The investigators tested for the ability of apple to protect against DNA damage in cultured lymphocytes isolated after apple exposure and found a significant protective effect at 3 h with a gradual loss of protection 24 h postconsumption.

A study in Oregon involved testing 6 healthy participants (3 men and 3 women) after they consumed 5 apples (flesh and skin, 1037 $\pm$ 38 g) (39). Blood sampled at 1, 2, 3, and 6 h postconsumption was assayed for FRAP and plasma ascorbate and urate levels. After apple consumption, FRAP increased significantly by 12% at 1 h and plasma levels of ascorbate and urate also increased. Interestingly, a subsequent analysis of this work showed that urate, but not ascorbate, levels were correlated with the increase in FRAP (39). This led the investigators to feed a fructose solution to the study participants to mimic the content in 5 apples (64 g fructose). They observed an increase in FRAP and a correlated increase in plasma urate levels, leading them to speculate that fructose-mediated urate production might account for their observations.

Animal feeding studies

A recent animal study indicated that AP are potentially important in counteracting dietary prooxidants. Dietary fat, including high PUFA intake, is associated with increased lipid peroxidation resulting in DNA damage (40). Pigs were fed a prooxidant diet, high in PUFA (linseed oil) with or without concurrent fresh apples for 22 d and then tested for several markers of oxidative damage. Apple feeding significantly reduced the concentration of the oxidative marker MDA in urine to levels lower than those in healthy control animals. Apple intake also reduced DNA damage in mononuclear blood cells, an effect the investigators proposed was likely mediated by antioxidant mechanisms.

Feeding trials are important in illustrating in vivo effects of AP and there are convincing data that AP intake is associated with improved antioxidant capacity in plasma and other tissues. However, it is still not fully understood which components mediate the observed effects. Whereas it has been argued that the low bioavailability of most flavonoids results in plasma concentrations that are well below the levels needed to exert antioxidant effects (41), others attribute the antioxidant capacity of fruit, including AP, to the flavonoid content, particularly the high procyanidin levels. Several studies, summarized below, have attempted to elucidate specific antioxidant components in AP using in vitro assays.

In vitro studies of oxidation

An extensive analysis of phytochemical metabolites in apple was reported by Cefarelli et al. (42). The investigators isolated 43 components from an organic extract of apple and tested each for antioxidant/free radical scavenging activity using 5 different in vitro methods. All of the isolated compounds, including newly characterized triterpenes, had antioxidant activity at various levels. The authors provided a detailed analysis of the association between compound structure and related antioxidant potential using TBARS, autooxidation of methyl linoleate, and scavenging of radicals including 2,2-diphenyl-2-picrylhydrazyl hydrate, H_2O_2, and NO.

Others have worked to characterize the effects of individual compounds known to be present in AP. Individual phytochemicals, including rutin, chlorogenic acid, and caffeic acid, were all effective, with some reconstituted mixtures being more effective than the original, in terms of antioxidant capacity and reducing DNA damage (43). The most effective compounds on all antioxidative parameters included quercetin and phloretin.

In a follow-up study, the above investigators developed reconstituted mixtures including 5 major apple-derived compounds to determine the relative antioxidant contribution of selected polyphenolics (20). The range of the isolated compounds with demonstrated activity was comparable to levels observed in human plasma in feeding trials. It has been suggested that the aglycone form of flavonoids (i.e. no attached saccharide residue) may be better taken up by cells and may have higher reactivity/antioxidant capacity. This is of importance, because many flavonoids and dihydrocalchones are present in intact plant foods as glycosides with saccharide residues, but during processing and storage hydrolysis occurs, leading to the aglycone form. However, the authors suggest that more work remains to fully understand the effects of hydrolysis on antioxidant capacity in AP.

A variety of in vitro systems have been used to test AP extracts for potential antioxidant capacity and the results of these studies have been variable. It has been proposed that assessment of total oxidant scavenging activity might overcome the inconsistencies observed in other assays. Lichtenthaler et al. (44) suggested that their use of total oxidant scavenging activity would be an effective test against 3 physiologically relevant ROS in realistic conditions. Their

experiments tested for the effectiveness of various fruits in inhibiting ROS-induced production of ethylene from α-keto-γ-methiolbutyric acid. Commercial apple juice in Germany was tested among other fruit juices. The results showed that apple juice was a fairly effective antioxidant compared to other juices against some ROS (peroxyl and hydroxyl radicals) but less effective against peroxynitrite. The authors are among the few to address the potential importance of pH in flavonoid-mediated activity.

Studies aimed at ranking in vitro antioxidant capacity of AP have been inconsistent as have those of other fruits and vegetables; some investigations rank antioxidant capacity as relatively poor, whereas others report good antioxidant activity compared to other fruits (45). There is also inconsistency in the correlation between in vitro outcomes and in vivo antioxidant activity mediated by AP. The variability might be attributed in part to the many types of apples and apple components studied in addition to varied reaction conditions, including pH, concentration, types of ROS, and other study conditions. It has been proposed that an integrated approach incorporating antioxidant capacity values from several different assays in a validated statistical model might provide a more accurate assessment of the relative antioxidant capacity of foods (46). Several ranking studies have been completed and the pros and cons of chemical methods used to assess in vitro antioxidant activity of fruits and vegetables have been debated and will not be reviewed here. Further investigation of the in vivo effects of AP as well as other sources of antioxidants relative to antioxidant status is relevant and warranted.

Lipids and lipid metabolism

Elevated lipids and aberrations in lipid metabolism are well-established risk factors for many types of cardiovascular disease. Research in animals allows for detailed analyses of the effect of AP on lipid parameters beyond simply measuring lipid levels in plasma. A recent study in hamsters evaluated the effects of adding daily apples and apple juice (pressed from fresh apples) to an atherogenic diet on lipids, oxidative markers, and early aortic lesions (47). Hamsters were provided with apples to approximate human intake of 600 g/d (~2.5 large apples) or 500 mL of juice/d. The calculated intake of phenols was comparable to dietary intake in humans (930 mg in apple group; 1100 mg in apple juice group). After 12 wk, it was found that both apples and apple juice significantly reduced total cholesterol (11 and 24%, respectively) and lowered the ratio of total cholesterol:HDL (25 and 38%). Both products also reduced the percentage of aortic surface area covered by foam cells (aortic fatty streak lesion area) by 48% in the apple group and 60% in the apple juice group compared to controls. Favorable effects on antioxidant enzymes in liver including SOD, GSHPx, and general markers of oxidation (hepatic TBARS) were significantly reduced by 47–52%.

Ogino et al. (48) studied the potential of 2 doses of procyanidin-rich apple polyphenol extract to attenuate disruptions in lipid membranes and lipid metabolism resulting from exposure to dietary cholesterol oxidation products. Feeding the extract to rats for 3 wk resulted in significant dose-dependent reductions in several markers of lipid metabolism including reduced lipoperoxides (measured by TBARS) in serum and liver, lowered SOD activity in RBC, lower hepatic Δ6 desaturase activity, altered fecal excretion patterns, and reduced levels of oxidized cholesterol products in serum and liver. Plasma levels of HDL cholesterol increased and liver TG content decreased, although plasma TG levels were somewhat higher. The authors concluded that the high procyanidin content and metabolites in the apple extract might directly interfere with cholesterol absorption in addition to modulating lipids and lipid-related processes.

In vitro work in cultured human intestinal cells suggested that AP may directly alter lipid absorption and metabolism (49). Caco-2/TC7 cells were exposed to apple extract, including a polyphenolic concentration equivalent to the consumption of 3 apples/d. It was found that the accumulation of esterified cholesterol decreased and the secretion of apo-B (B-48 and B-100) containing lipoproteins was reduced. Similar results were found in cells exposed to an enriched extract of procyanidins (flavanols, catechin, and epicatechin). If these findings are applicable to the in vivo situation, altered intestinal lipid secretion might account for the lipid-lowering effect of AP observed in some studies and suggest one possible mechanism for reduced risk of cardiovascular disease.

Asthma and pulmonary function

The prevalence of pulmonary disorders, particularly asthma, has been increasing over the past several decades worldwide (50). It is speculated that environmental and lifestyle factors, such as reduced intake of dietary antioxidants, are contributing to the rise (51). It is thought that lungs are particularly susceptible to oxidative damage due to high and continual exposure to oxygen. Oxidant stress also activates inflammatory mediators that induce asthma in experimental models and appears to be important in the etiology of asthma in humans (51). AP might be protective because of their antioxidant potential and phytochemical content.

Early research described an inverse association between AP consumption and asthma and chronic obstructive pulmonary disease, including bronchitis and emphysema, as well as a general benefit to ventilatory function in healthy individuals as reviewed in (1). Recent data support these findings, particularly those related to asthma.

A new report using data from the French branch of the European Prospective Investigation into Cancer and Nutrition trial provided evidence of a link between apple intake and reduced asthma prevalence in a sample of 68,535 adult women, mostly teachers, enrolled in a national health insurance plan (52). Validated FFQ including 208 food items and photographic prompts were used to determine dietary intake and categorize food into quartiles. Diagnosed asthma, on the basis of self-reported data using validated questionnaires, was present in 3.1% of the cohort. Women in the highest quartile of apple intake compared to the lowest

quartile had a significantly lower incidence of asthma. Apple intake of >31.2 g/d (i.e. >15% of a large apple) was associated with a 10% risk reduction. Although this effect was less robust after adjustment for intake of other fruits and vegetables, the association remained.

Other reports have indicated that apple intake is associated with reduced risk of asthma and related symptoms. Investigators in the laboratory of Shaheen et al. (53) recently published a follow-up analysis of an earlier study in which they demonstrated a protective effect of apple consumption on asthma (54). The goal of the follow-up study was to determine if flavonoid content of apples accounted for the observed improvement in outcomes related to asthma. More than 1400 adult participants in a case-control study of dietary antioxidants and asthma in the UK completed FFQ for assessment of daily intake of 3 major classes of flavonoids, including flavonols, flavones, and catechins. There was no statistical association between reduced asthma or asthma severity and any of the flavonoids examined, inferring that compounds other than those studied must be attributed to the observed reduction in risk of asthma. Several investigators have proposed that unknown compounds beyond those currently examined and characterized in AP might account for improved health and be linked to reduced risk of disease.

In a separate study, Shaheen et al. (55) examined the effect of AP on the presence of asthma diagnosis and symptoms (defined as "wheeze") in children in the UK. Parents/caregivers reported apple and apple juice intake and health data of over 2600 children aged 5–11 y. It was found that apple juice from concentrate was significantly and dose-dependently associated with reduced wheeze (juice ranging from 1 serving/mo to 1 serving/d) but not with reduced presence of asthma. Fresh apple intake (2–6/wk) tended to be protective but was not significant for a dose-response relationship.

An intriguing report published in 2007 involved studying the association between maternal diet and the presence of asthma and respiratory symptoms in offspring 5 y later (56). A self-administered FFQ was used to assess maternal diet at 32 wk of gestation. It was shown that in maternal groups with progressively greater apple intake ranging from 0–1/wk to 1–4/wk to >4/wk, there was a significant and linear reduction in diagnosed asthma as well as reduced reports of ever having wheezed or ever having asthma among the nearly 1200 5-y olds in the study. The association persisted even after correction for other factors, including childhood diet and lifestyle variables. Among the various foods studied, apples were the only individual fruit associated with the protective association.

Although data relating AP intake to reduced risk of asthma are provocative, there are some inconsistent reports. One study published by a different group in 2006 did not find an association between fruit intake (reported in a semiquantitative FFQ) and several endpoints related to diagnosed asthma in Dutch children (57). A case-control study from the UK also did not show a protective effect of apples on risk of developing asthma (58). In this study, 515 adults with diagnosed asthma were compared to 515 controls using dietary assessment by a 6-d food diary and 24-h recall. Although apples and citrus were collectively associated with reduced risk of diagnosed asthma, adjustment for citrus eliminated the significance of the effect of apples.

Aging and cognitive processes

There is growing evidence that dietary variables may be related to cognitive decline in normal aging and also influence the risk and course of neurodegenerative diseases of aging. A series of recent studies from the laboratory of Shea et al. (59–65) have provided novel data on the potential of apple juice concentrate to modulate processes associated with the risk of Alzheimer's disease. This group developed a standardized mouse model of neurodegeneration in which aged mice exhibit impaired cognitive performance and increased oxidative parameters in brain tissue when subjected to a prooxidant diet (deficient in vitamin E and folate; high in iron). However, when these mice received apple juice concentrate diluted in drinking water (0.5%) for 1 mo (equivalent to human consumption of 2–3 eight-ounce glasses of apple juice/d), there was a significant improvement in cognitive-related performance and reduced prooxidative status compared to controls (59).

Additional work from this laboratory using mice with genetically induced oxidative stress (an ApoE-deficient strain) showed that 1 mo of apple juice concentrate intake reduced the accumulation of ROS in brain tissue and attenuated cognitive impairment (60,61). Further examination demonstrated that apple juice intake reduced a compensatory increase in the endogenous antioxidant glutathione, suggesting that the antioxidant activity of apple juice accounts in part for the observed protective effects in animals subject to dietary and genetic oxidative stress and a potential neuroprotective effect of AP under these conditions (59).

Investigations with this model have provided important clues that mechanisms of neuroprotection may extend beyond antioxidant effects. In particular, apple juice concentrate prevents the characteristic decline in acetylcholine associated with aging and oxidative stress (62). Because cholinergic depletion is associated with impaired memory and reduced cognitive performance, and acetylcholine reduction in particular is associated with Alzheimer's disease, there is potential importance in the ability of apple juice to maintain levels of this neurotransmitter.

Apple juice concentrate may work by other mechanisms, including the ability to suppress overexpression of presenilin-1, which is linked to the production of amyloid β peptide, a hallmark of Alzheimer's disease (63,64). Apple juice also attenuated the neurotoxicity of amyloid β peptide in vitro (65). Shea et al. (65) propose that the content of *S*-adenosyl methionine in apple juice concentrate might account in part for these effects, because comparable effects were observed with *S*-adenosyl methionine alone.

A research group in Italy studied the effects of 10 wk of fresh apple intake in aged rats (66). They found that apple

consumption reduced anxious behavior in rats in elevated maze tests and restored synaptic function (long-term potentiation) to the level of younger animals. In addition, apple intake was associated with reduction in SOD elevation in the hippocampus of aged rats, suggesting that apples provide antioxidant protection that mitigates the predicted compensatory elevation of enzymes associated with aging. These data support the potential of antioxidant activity to improve markers related to behavioral changes associated with the aging process.

Diabetes

The incidence of diabetes, chiefly type 2 diabetes, has increased dramatically and is the subject of intensive study around the world. New data have suggested a possible link between AP consumption and reduced risk of diabetes. In a large ongoing trial, the Women's Health Study, semiquantitative FFQ were analyzed to determine if dietary flavonoid intake was associated with risk of diabetes and related markers of insulin resistance and inflammation (67). Apples were identified as the only flavonoid-rich food that might be protective. There was a 27 and 28% lower risk of type 2 diabetes associated with the consumption of 2–6 apples/wk or 1 apple/d, respectively, compared to no apple consumption. The highest quartile of intake was > 47 g of apple/d, which approximates one-third of a medium-sized apple. Inflammatory markers and insulin resistance were not affected by any dietary components.

The authors of this study also searched for an association between total flavonol and flavone intake and a limited number of subtypes of these flavonoids (5 total) and reduced risk. The protective effect of AP was not associated with any of these, leading the authors to speculate that other unrecognized compounds, including catechins, may have accounted for the link. Mechanistically, it is feasible that catechins or other polyphenolic components in AP may be inversely related to the risk of type 2 diabetes, possibly by preserving pancreatic β-cell function via reduced oxidative stress-induced tissue damage. It has also been proposed that dihydrochalcones, particularly phloretin-2′-0-glucoside present in relatively high amounts in AP, inhibit sodium-dependent glucose transporters in the intestinal lumen, therefore potentially reducing postprandial glucose response (68,69). It is not known whether this is important under physiologic conditions, but it is an interesting mechanism by which AP might be related to glucose control in diabetes.

Weight loss

Current guidelines recommend daily consumption of foods that are a good source of dietary fiber and low in energy density to promote healthy weight maintenance or weight loss. Based on this premise, a study was conducted in Brazil on 49 overweight women with high blood cholesterol levels to determine the effect of fruit intake on blood lipids and body weight (70). The women were randomized to 1 of 3 diet groups for 10 wk including a daily intake of 300 g of apple (~1.5 large size), daily intake of a similar quantity of pear, or 60 g of oat cookies. All 3 groups were matched for the additional dietary fiber provided by each of the treatments. Each group was provided guidelines for a moderate hypocaloric diet designed to reduce body weight at a rate of 1 kg/mo (deficit of 250 kcal/d). Results of the study were presented in 2 reports, the most recent in 2008. The addition of apples as part of an average daily caloric intake of 2401 $\pm$ 389 kcal resulted in a significant weight loss of 1.32 kg after 10 wk. The authors proposed that the weight loss was due in part to the significant decrease in energy density of the diet due to the addition of apples compared to the oat cookies in spite of the comparable fiber content of the two.

The strengths of this diet study included the use of whole fruits rather than extracts in addition to the easily achievable energy level of the weight loss regime and the involvement of a registered dietitian to implement the diet. However, the study had several limitations including a high attrition rate (29%) resulting in unequal sample sizes between groups (50% fewer in the oat cookie than either the apple or pear group) and a slight but significant difference in age between study groups (41.6 vs. 46.2 y in apple vs. cookie, respectively). As such, it would be inaccurate to conclusively state that apples alone induce weight loss on the basis of this study. However, it is plausible that the low-energy density and fiber content of apples make them effective in weight reduction diets. Thus, apples may be potentially important in weight-related disorders.

Bone health

The loss of bone mass is associated with osteoporosis and is viewed by some as a global epidemic. An estimated 10 million Americans over age 50 y have osteoporosis and another 34 million are at risk (71). It is estimated that 1.5 million people will suffer an osteoporotic-related fracture each year. Fruits and vegetables provide nutrients that are thought to be associated with improved bone health (vitamin C, potassium, magnesium, and vitamin K) in addition to producing alkaline metabolites that might improve bone health by reducing calcium excretion (72). Intake of fruits and vegetables is associated with improvement in bone mineral density and other bone markers in epidemiologic studies (73). Only a few studies have examined AP but preliminary observations suggest that AP may have a positive impact on markers related to bone health.

In a cross-over study, 15 healthy female participants 19–50 y (mean 24.6 y) old each consumed a 500-kcal test meal on 3 different occasions consisting of either fresh peeled apples, unsweetened canned apple sauce, or candy. The test meals were adjusted to provide comparable macronutrients. The fresh peeled apple meal included 311 g of unpeeled apple plus a protein drink and 53 g of candy; the applesauce test meal included 877.5 g of unsweetened canned applesauce and a protein drink and the control meal included just the candy (108 g) and the protein drink. An analysis of urinary samples collected postconsumption at 1.5, 3, and 4.5 h demonstrated that the fresh and processed apple meals each

decreased 3-h net acid excretion and attenuated calcium loss to a similar extent compared to the control meal (73).

Another study of AP was conducted in ovariectomized rats subjected to inflammation as a physiologic model of the postmenopausal state in humans (74). It has been shown that the estrogen decline associated with menopause is linked to increased production of inflammatory mediators within the bone microenvironment. The rats were provided phloridzin, a flavonoid isolated from apple wood in this study but also present in apples, particularly the peel. The quantity of phloridzin the rats consumed represented ~6 apples/d, depending on variety. After 80 d of treatment, it was found that phloridzin intake improved femoral bone mineral density and markers of bone turnover. An indirect outcome of inflammation (splenomegaly) was also reduced in the groups taking the phloridzin. This study focused on a single concentration of one isolated compound; an expansion of work with this model using a wider range of concentrations and varied phytochemicals would be of interest.

Gastrointestinal protection from drug injury

A few studies have evaluated the potential of AP to prevent or reduce injury to gastric mucosa by drugs (75). In a combined investigation using cell and animal models to mimic nonsteroidal antiinflammatory drug injury, cultured gastric epithelial cells (MKN 28 from a human gastric tubular adenocarcinoma) were exposed to oxidative stress via 2- to 3-h exposure to xanthine oxidase and live rats were subjected to indomethacin, each with or without treatment with phenolic-rich extracts of freeze-dried apple (flesh only). The apple protected cells from oxidative damage, particularly the extract that was highest in chlorogenic acid (10^{-4} mmol/L). The fraction highest in catechin also protected cells from oxidative damage in a dose-dependent manner with a maximal protective effect at 3 h. The protective effect was associated with a corresponding increase in antioxidant activity and reduced lipid peroxidation per measurement of MDA. In the living rats, drinking the apple extract in water for 10 d or 1 h prior to indomethacin-induced injury prevented macroscopic injury and partial microscopic damage by ~40–45% (75).

Very preliminary in vitro evidence indicates that compounds from AP could be protective against gastric ulcer. Carotenoid extracts from apple peel were effective against *H. pylori* in an in vitro medium (76). Another in vitro study with AP demonstrated that there may be other beneficial effects to gastrointestinal health by an alternate mechanism of reducing risk of mutagenesis in gastric cancer (77). Extracts of apple pulp were shown to release NO from human saliva under acidic conditions, prompting the authors to propose a possible gastroprotective role of AP in mediating and scavenging of nitrogen oxides. The effect was mediated by apple phenolics but particularly chlorogenic acid and (+)-catechin (5 μmol/L).

Summary and conclusion

The current report focused on studies published since the last review of AP and health in 2004 (1). The reviewed studies do not prove cause and effect and further work remains to be done. However, there are convincing data suggesting an association between AP and reduced risk of major diseases and indicating multiple plausible mechanisms by which AP might be protective in humans. Many recent studies demonstrate a beneficial effect of AP on critical processes in the etiology of disease at the metabolic and cellular level. There are current data suggesting that AP might be linked to reduced risk of several forms of cancer, cardiovascular disease, and asthma. AP may also have beneficial effects on outcomes related to Alzheimer's disease, cognitive decline of normal aging, diabetes, weight management, bone health, and gastrointestinal protection from drug injury.

The antioxidant mechanisms described in many studies have important implications for a protective effect of AP on not only cancer but also cardiovascular disease, Alzheimer's disease, asthma, and potentially diabetes. However, there are provocative data suggesting that mechanisms beyond antioxidant effects are important, including suppression of neurotoxic mediators in Alzheimer's disease. The processes associated with aging and amplified in neurodegenerative diseases of aging are complex and not completely understood. The available data show preliminary but intriguing potential of AP to modulate some of these processes in animal models.

The observations that AP intake might be associated with reduced risk of cancer have led to an expanded field of animal and in vitro work with cell models that mimic phases in the initiation, promotion, and progression of cancer. Several studies demonstrate that AP reduce cell proliferation, alter markers of the cell cycle, increase apoptotic mechanisms, and modulate signal transduction pathways. Although further work is needed to extrapolate these findings to clinical outcomes, it is promising that there are multiple plausible mechanisms by which AP intake might reduce the risk of cancer in humans.

Evidence relating AP to lung health was summarized in the review of Boyer and Liu (1) and newer studies have built upon earlier work that implicated AP in reduced risk of asthma. Many investigators have taken great care to control for confounding variables known to affect lung health, but it is likely that unknown dietary and lifestyle factors have important effects. There is clearly a need for controlled clinical intervention studies using AP to further examine the potential association between AP and asthma.

Preliminary observations show the potential of a link between AP intake and possible risk reduction for osteoporosis and diabetes, but the work on potential mechanisms needs to be expanded. Given the increasing incidence of these 2 conditions, further study of the effect of AP on osteoporosis and diabetes is important to consider.

Ongoing research is providing more detailed data on specific components and/or combinations of components in AP that might be protective. Although there is a trend toward studying polyphenol-enriched extracts or isolated constituents and fewer clinical studies since the last review of AP and health, several investigators note that native AP and extracts

are often more effective than individual compounds or synthetic mixtures of compounds. There are several thousand phytochemicals present in whole foods and there is still limited characterization of the bioavailability and metabolism of these compounds in AP. Even less is known about the complex interactions between isolated constituents, but it is speculated that the synergistic interactions and balance of nutrients in native AP are difficult to duplicate experimentally (27).

In conclusion, the data related to AP and disease risk reduction are provocative and varied. The combined phytochemical and nutrient profiles in AP suggests their potential to be powerful in the prevention of several chronic conditions in humans. Ongoing work continues to further delineate multiple mechanisms by which AP might be protective and suggests great promise. Future studies, including well-conducted clinical trials using whole apple preparations and juice, are clearly warranted.

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