Apple Bioactive Compounds

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Population studies have associated a diet high in fruits to lower incidence of cancer. Specifically, research shows that secondary plant metabolites known as phytochemicals, which are commonly found in fruits, have onco-preventive and chemo-protective effects. Apple is a commonly consumed fruit worldwide that is available all year round and is a rich source of phytochemicals. The health benefits of apples are thought to be mainly due to their phytochemical composition. Additionally, apple consumption is associated with lower incidence of some cancers based on animal and cell culture studies.

fruit apple phytochemicals cancer phenolics

1. Introduction

Chronic diseases including cancer continues to remain a public health burden globally [1][2][3][4][5]. In 2020, cancer was the second leading chronic illness following cardiovascular disease, with an estimate of 19 million new cases and accounting for 10 million deaths per year, globally [6][7]. Data from GLOBOCAN [7] show that cancers of the breast are the most commonly diagnosed followed by cancers of the lung, colorectal and prostate.

To reduce cancer's global health burden, it is necessary to promote both cancer treatment as well as cancer prevention.

There is growing evidence that diet, especially phytochemicals found in vegetables and fruits, play a major role in cancer aetiology and prevention. One fruit that is a rich and important source of bioactive phytochemicals in western diet, is apple [8][9][10][11]. Apples are globally consumed due to their year-round availability, their cultivar diversity, low price, and easy storage [8][12].

2. Apple Phytochemical Profile and Bioavailability

To better understand the health benefits of apples, in this section we provide a comprehensive review of the main phytochemical patterns observed in apples and their potential health benefits depending on variety, and part consumed (skin/peel versus the flesh of the apple).

Apples contain a wide variety of phytochemicals, including triterpenoids, organic acids, fatty acids and apple phenolic compounds (Figure 1) [13]. Triterpenoids are components mainly of apple waxes [14]. The main triterpenoids found in apples are oleanolic, betulinic and ursolic acid and their derivates such as maslinic, corosolic, euscaphic, pomaceic and pomolic acids [15].

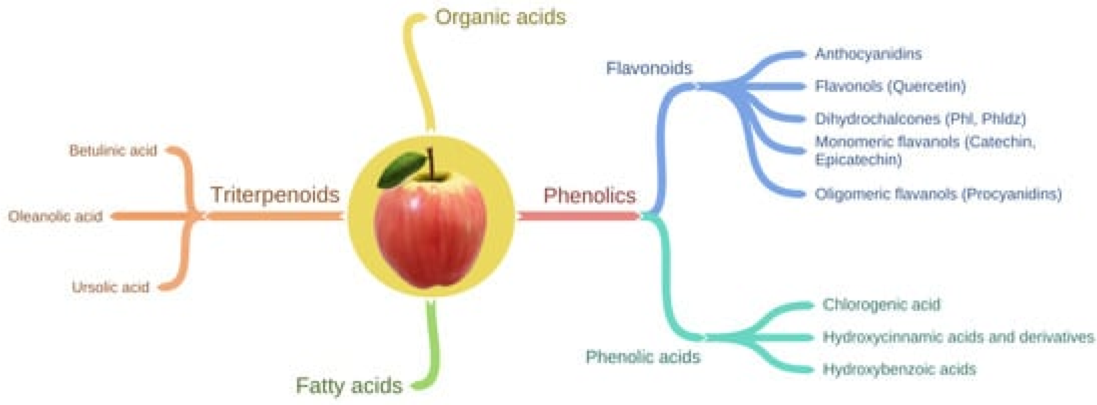

Figure 1. Schematic showing the classification of phytochemicals present in apple.

The most well-studied group of apple phytochemicals for their health benefits are phenolic compounds [16]. Studies show that apples are an important source of phenolic compounds in our diet contributing to 22% of phenolic intake [17][18]. Most of the phenolic compounds in the fruit are usually present in the conjugated form such as glycosides or esterified carboxylic acids. However, compared to other fruit, apples contain more of the readily bioavailable free forms of phenolic compounds [19][20][21]. For instance, the 'Red Delicious' apple had the highest levels of free forms of phenolic compounds compared to pear, plums, kiwifruit and peach [22].

Phenolic compounds in apple can be sub-divided into two main groups (Table 1, Figure 1) known as flavonoids and phenolic acids. Flavonoids can be further divided into four structural subclasses including anthocyanidins, flavonols, dihydrochalcones and flavan-3-ols (flavanols) which can exist in the monomeric and oligomeric form [23][24] (Table 1). Phenolic acids include chlorogenic acid, hydroxycinnamic acid and hydroxybenzoic acid [23][24]. In general, chlorogenic acid, monomeric and polymeric flavanols are the major phenolic compounds, whereas anthocyanins and dihydrochalcones are minor phenolic compounds of apples [25]. Moreover, anthocyanidins are responsible for the apple redness [26][27]. Therefore, anthocyanidins are abundant in the apple cultivars with red skin (e.g. 'Red Delicious') and are not present or present in low concentrations in the green skinned apple cultivars (e.g. 'Granny Smith') [27][28].

Table 1. Classification of apple phenolics.

Phenolics Group	Phenolic Subgroup	Phenolic Compounds
Flavonoids	Anthocyanidins	Cyanidin 3-O-arabinoside
		Cyanidin 3-O-galactoside
		Cyanidin 3-O-xyloside
		Cyanidin 3-O-xylgalactoside

Phenolics Group	Phenolic Subgroup	Phenolic Compounds
		Quercetin
		Quercetin 3-arabinopyranoside
		Quercetin-3-arabinofuranoside
	Flavonols	Quercetin 3-galactoside
		Quercetin 3-glucoside
		Quercetin 3-rhamnoside
		Quercetin 3-rutinoside
		Quercetin 3-xyloside
	Dihydrochalcones	Phloretin
		Phloretin-2′-O-xyloglucoside
		Phloridzin
		3-hydroxyphloridzin
	Flavan-3-ols	Monomeric
		(+)-Catechin
		(−)-Epicatechin
		Oligomeric (Procyanidins)
		Procyanidin B1
		Procyanidin B2
		Procyanidin B5
		Procyanidin B7
		Procyanidin C1
Phenolic acids		Chlorogenic acid Hydroxy benzoic acid Hydroxy cinnamic acid

There are differences in the distribution and type of phenolic compounds within various parts of an apple such as peel, flesh, core, and seeds. The phenolic compounds distribution and concentration in the peel and flesh of apples vary greatly due to genetic diversity, maturity stage, growing conditions and geographical location, harvest, and storage conditions [21][29][30][31][32][33]. However, studies have highlighted that there is a similar phenolics distribution pattern for most apple cultivars (**Figure 2**).

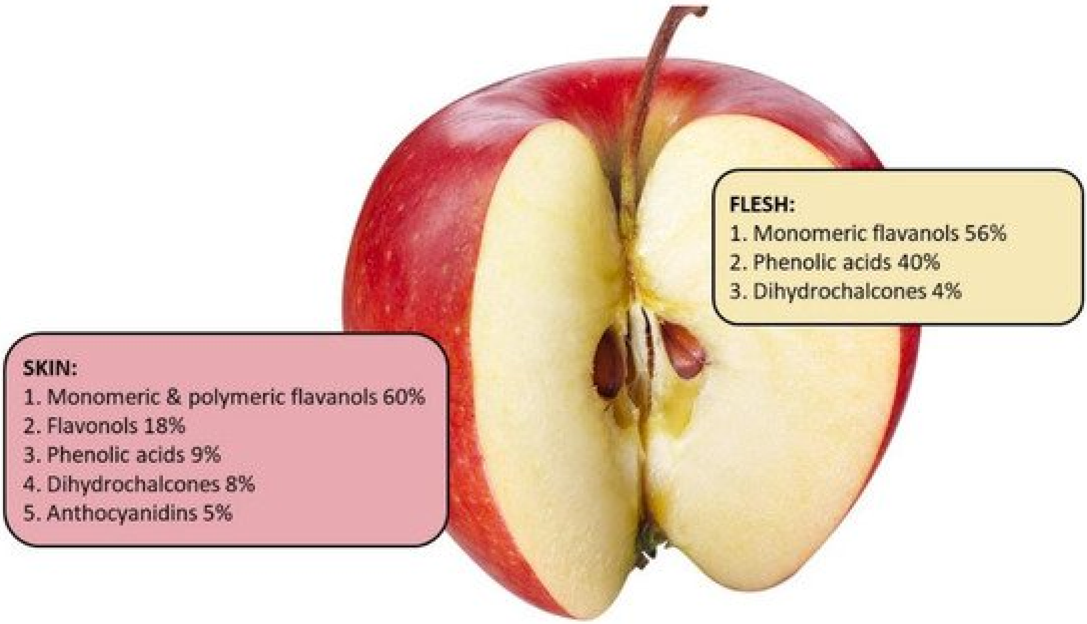

Figure 2. Phenolics distribution pattern in the skin and flesh of an average apple based on the data from Lata, *et al.* [34], Tsao*, et al.* [35], Lata [36], McGhie, *et al.* [25].

In general, the apple peel contains about 2-4 times higher levels of phenolics, and higher levels of total procyanidins and total flavonoids, compared to flesh [34]. In general, evidence from multiple studies comparing various cultivars of apples, have shown that apple peel contains all groups of phenolic compounds and has greater concentrations of procyanidins, and total flavonoids compared to the flesh [21][35][36][37]. On the other hand, chlorogenic acid can be found in both flesh and peel but tends to be higher in the flesh [21][32]. Taken together these data suggest that apple peel of most apple varieties contain more phenolics than the flesh. More information on the phytochemicals patterns in different cultivars is provided in the review article linked to this entry.

It is important to consider that apple peel contributes only up to 10% of the weight of the whole fruit, therefore the intake of some phenolic compounds from the peel after consumption of a whole apple might not be as significant as the intake from the flesh. Only a few studies have reported on the phenolic compounds content relative to the weight of the peel compared to the whole apple [25][34]. McGhie, *et al.* [25] demonstrated that peel of ‘Braeburn’, ‘Royal Gala’ and ‘Red Delicious’ contributed 55%, 50% and 52% respectively of the apple’s total phenolics. Data from New Zealand heritage apple cultivar ‘Monty’s Surprise’ and the commercial varieties ‘Braeburn’ and ‘Red Delicious’ (Table 2) showed that the contribution of total phenolics was lower from the peel compared to the flesh. However, anthocyanidins were only present in the peel and flavonols were found only in small quantities in the flesh. Taken together, a combination of unpublished data from New Zealand (Table 2) and other published studies suggests that for most apple varieties the peel is a significant source of phenolic compounds. Therefore, discarding the peel during production of some traditional apple products, such as apple sauce [38] may decrease the health potential of the apples.

Table 2. Estimated apple peel contribution to the total phenolics content in whole apple. Phenolic compounds were measured using Liquid chromatography-Mass Spectrometry (LC-MS, Dionex Ultimate RS3000 UHPL and a Bruker micrOTOF-QII) in 2019, Plant and Food research, for 3 apple varieties-Monty's surprise, Braeburn and Red Delicious. Each compound concentration was quantified by comparison with an authentic standard where possible or as equivalents to standard compounds. Each phenolic compound in the table is presented as a percentage of total concentration measured using LC-MS. Percentage total phenolics was calculated based on the average weight of whole apple (180 g) where apple skin contributed 18 g.

	Monomeric Flavanols		Procyanidins		Flavonols		Dihydrochalcones		Chlorogenic acid		Anthocyanins		Total Phenolics	
Cultivar	**Skin (%)**	**Flesh (%)**	**Skin (%)**	**Flesh (%)**	**Skin (%)**	**Flesh (%)**	**Skin (%)**	**Flesh (%)**	**Skin (%)**	**Flesh (%)**	**Skin (%)**	**Flesh (%)**	**Skin (%)**	**Flesh (%)**
Monty's Surprise	33	67	[39] 29	71	94	6	42	58	10	90	100	n.e.	37	63
Braeburn	19	81	21	79	99	1	8	92	1	99 [40][41][42]	100	n.e.	31	69
Red Delicious	37	63	36	64	94	6	40	60	2	98	100 [42]	n.e.	46	54

* Monty's Surprise – New Zealand's heritage apple variety.

* n.e. - not evaluated (Anthocyanins were not evaluated in the flesh as they are not present.)

...tribution ... available ... olubility, ... olics are released in and absorbed from the large intestine, with aid from gut microbiota [41][43][44]. The gut microbiota is capable of transforming complex phenolic compounds into metabolites that are more easily absorbed [45]. It was demonstrated that once absorbed phenolic compounds can be detected in human plasma and urine after consumption of apple [46], apple juice [47], and apple cider [48]. Bioavailability of the main apple phytochemicals is described in section 5.2 of the main review article linked to this entry.

While apple is a rich source of nutrients and phytochemicals, there is evidence to suggest that the apple food matrix (non-nutrient component) plays an important role in the absorption and bioavailability of apple phytochemicals. Aprikain, *et al.* [44] demonstrated that ingestion of phenolics rich apple extract and apple pectin together had greater effect on gut microbiota metabolism in the large intestine and lipid metabolism than ingestion of the phenolics-rich apple extract alone, suggesting a beneficial interaction between fibre and phenolics [44].

3. Health Benefits of Apple Phytochemicals: Cancer

Current research attributes the health benefits of apples mainly to the phenolic compounds which exhibit several biological functions beneficial for human health [16]. Apple phenolic compounds are believed to lower incidence of chronic conditions such as cardiovascular disease, cancer, asthma and pulmonary disease, diabetes, and obesity [24][49][8][9][10][11][12][50].

Apple phytochemicals are suggested to have many chemo-preventive and chemo-protective effects (Figure 3) against various types of cancer. Apple phytochemicals were reported to have significant effects on inhibiting multiple 'hallmarks of cancer' which are important in growth and progression of cancer [51].

These effects include regulation of proliferation, cell cycle, apoptosis, reactive oxygen species (ROS) and anti-inflammatory activities [45][52][53][54][55]. In this section we discuss health benefits of apple phytochemicals in relation to cancer from epidemiological studies, their ability to alter ROS in cancer cells and impact on cancer biology from *in vitro* and *in vivo* studies.

Phenolic compounds from different apple cultivars were positively associated with the higher degree of inhibition of breast cancer cell proliferation [56][57][58] and induction of cell cycle arrest [57][59]. Additionally, apple extracts inhibited growth of prostate [59] and lung [60] cancer cells. Extracts of phenolics from apple pomace of different apple cultivars were reported to inhibit proliferation of oral [61] and colon cancer cells [20]. In addition to *in vitro* studies, apple polyphenol extracts also inhibited *ex vivo* proliferation of a hepatoma cell line [62].

Multiple studies have demonstrated that apple phytochemicals can inhibit the activity of p21, growth factors, pyruvate dehydrogenase kinases (PDKs), cyclin-dependent kinases (CDKs) and extracellular protein kinases (ERKs) essential for cell cycle progression [58][63][64][65]. Furthermore, apple phytochemicals can also prevent cell cycle progression by activation of maspin, a tumour suppressor gene [59]. Changes in the key molecules essential for regulating cell cycle by apple phytochemicals leads to cancer cells arrest [57][59]. Apple extracts were reported to inhibit apoptosis in breast cancer cells [56][60]. Apple phenolic compounds were shown to regulate pro-apoptotic genes such as p53, p21, Bax, Bcl-2 [66]. In addition to inhibiting cell proliferation and promoting apoptosis, apple phytochemicals have also been implicated in inhibiting angiogenesis by regulating VEGF [51]; and inhibiting invasion and metastasis [20][62] by regulating matrix metalloproteinases-2,-9 (MMP-2,-9), cadherins and integrins [51] and regulating COX-2 a marker of inflammation [51]. Additionally, the ability of apple phytochemicals to inhibit cell proliferation and in turn reduce incidence of cancer was also observed in rats, where rats fed one human apple equivalent, had reduced appearance of different precancerous markers (ACF, MDF, genes and proteins related to colorectal cancer progression) [67]. Similarly, the incidence of mammary tumours in rats was reduced after two weeks of oral administration of 3.3, 10 and 20 g of apple extract/kg of body weight, which correspond to the human consumption one (200 g), three, and six apples per day [68].

There is evidence that anticancer properties of apples are due to the synergistic effects between apple phytochemicals and between apple phytochemicals and food matrix [69][70][71][72]. Veeriah, et al. [69] demonstrated that the order of inhibition against a colon cancer cells treated with an apple extract (extract from a mixture of different apples) reduced cell proliferation to a greater extend compared to a synthetic apple extract composed of eight apple phenolics or individual apple phenolic compounds [69]. Results from this study indicate the importance of the apple food matrix, which may contain other bioactive compounds present in the apple extract but not in the synthetic mixture.

Taken together, evidence from *in vitro*, *ex vivo* and *in vivo* studies suggest that apple phytochemicals work synergistically, to inhibit multiple ‘hallmarks of cancer’, which in turn can influence cancer incidence and improve outcomes to chemotherapeutic treatments.

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