



Anticancer Properties of Bioactive Compounds of Berry Fruits - A Review

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Authors' contributions

This work was carried out in collaboration between all authors. DSBC and AJT designed the study and wrote the first draft of the manuscript. DSB and AJT managed the literature search and analyses of the study. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

An overwhelming body of research has now firmly established that the dietary intake of berry fruits has a positive and profound impact on human health, performance, and disease. Evidence suggests that edible small and soft-fleshed berry fruits may have beneficial effects against several types of human cancers. Studies show that the anticancer effects of berry bioactives reduce and repair damage resulting from oxidative stress and inflammation. In addition, also regulate carcinogen and xenobiotic metabolizing enzymes, various transcriptions and growth factors, inflammatory cytokines, and subcellular signaling pathways of cancer cell proliferation, apoptosis and tumor angiogenesis. Berry phytochemicals may also potentially sensitize tumor cells to chemotherapeutic agents by inhibiting pathways that lead to treatment resistance, and consumption may provide protection from therapy-associated toxicities. This paper is a comprehensive review of the effects of phytochemicals present in berry fruits on cancer and encompasses the occurrence and bioavailability of these compounds evidences for their effects on the various mechanisms by which may exert their effects. These include effects on cellular differentiation and apoptosis; effects on proteins and enzymes that are involved in these processes

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at a molecular level, and other various effects through altered immune function and chemical metabolism.

Keywords: Anthocyanins; antioxidant; berry fruits; cancer; phytochemicals; anticancer properties.

1. INTRODUCTION

American blueberries include the lowbush or wild blueberry (*Vaccinium angustifolium* Aiton) and the highbush or cultivated blueberry (*Vaccinium corymbosum* L.), both of which have superior ranking among fruits and vegetables for their antioxidant capacity, mainly due to their high anthocyanin content. All these berries are known for having important health benefits [1,2].

Berries in general are rich in phenolic compounds, which are known for their high antioxidant capacity. Nutritional epidemiology provides some evidence regarding the anti-cancer effects, anti-neurodegenerative effects and anti-inflammatory effects. Because of these properties, many studies have been conducted to explore the potential relationship between the components found in blueberries and other berries and the prevention of chronic diseases [3].

Both genetic and environmental factors affect the production and accumulation of bioactive compounds (BC) in strawberry fruits. Differences in nutritional quality amongst strawberry cultivars are well known, even if only a few genotypes are well characterized for these important features. In addition to their nutritional quality, berries also display sensorial attributes (color, aroma, flavor) which are attractive and very important to the consumer and therefore must be maintained in successful new varieties.

One of the main chemical constituents found in berries are anthocyanins. Anthocyanins (Greek *antos*, flower and *kyanos*, blue) are part of the very large and widespread group of plant constituents known collectively as flavonoids. In fruits and vegetables there are six basic anthocyanin compounds [4].

Anthocyanins are the plant pigments responsible for red, blue or purple colors of berries, grapes, apples, purple cabbage and corn. They are water-soluble compounds occurring in plants primarily in the form of glycosidic polyhydroxyl and polymethoxyl derivatives of flavylium salts [5]. Anthocyanins are attached with one or more sugars such as glucose, galactose, arabinose,

xylose, rhamnose and glucuronid acid [6]. They differ in the number of hydroxyl and methoxyl groups, in the position of attachment of sugars and in a number of aliphatic or aromatic acids attached to sugars in the molecule (Fig. 1 and Table 1) [7].

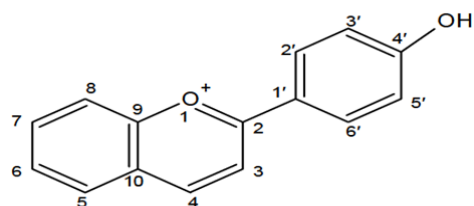


Fig. 1. Structure of Anthocyanins

In addition to using as food colorants, anthocyanins have demonstrated nutraceutical functions [8,9]. Due to naturally occurring high levels detected, berry anthocyanins have been extensively studied. It has been found that berry anthocyanins may prevent multiple chronic diseases such as cardiovascular disease [10], diabetes [11], cancer [12], and age-related neurodegenerative decline [13]. Studies conducted in animal models demonstrated that dietary berry anthocyanins might protect against carcinogen azoxymethane (AOM) induced colon carcinogenesis [14,15]. The potential mechanisms by which berry anthocyanins may prevent colorectal cancer may relate to apoptosis induction and cell-cycle arrest as well as inhibition of proliferation, inflammation, and angiogenesis [16,17].

During the past two decades an increasing number of studies have investigated the diverse protective effects elicited by polyphenolics present in various fruits and vegetables. These effects include antioxidant, anti-allergic, anti-inflammatory, anti-viral, anti-proliferative, anti-mutagenic, anti-microbial, anti-carcinogenic, protection from cardiovascular damage and allergy, microcirculation improvement, peripheral capillary fragility prevention, diabetes prevention, and vision improvement [18,19]. Polyphenolic research has recently intensified because of this increasing understanding and awareness of the potential beneficial human health effects.

2. STRUCTURE OF FOOD SOURCES

Edible berries constitute a very good source of several phytochemicals, such as phenolic acids, proanthocyanidins, anthocyanins and other flavonoids [19,20,21]. Much of the research on berries has focused on chemical composition, particularly on their flavonoid and phenolic acid contents. It has been reported that anthocyanins presents the health benefits in several fruits and berries, including apples [21,22], strawberries [23,24], blackberries [24], raspberries [25], blueberries [24,25,26], currants [24], chokeberries [24], cranberries [27,28] and cherries. Table 2 shown principals food sources and structure of bioactive compounds in berry fruits.

The pH differential method has been used extensively by food technologists and horticulturists to assess the quality of fresh and processed fruits and vegetables. The method can be used for the determination of total monomeric anthocyanin content, based on the structural change of the anthocyanin

chromophore between pH 1.0 and 4.5. The anticipated use of the method is in research and for quality control of anthocyanin-containing fruit juices, wines, natural colorants, and other beverages. The concept of determining the amount of anthocyanin present in a material by measuring the change in absorbance at 2 different pH values (3.4 and 2.0) was first introduced by Sondheimer and Kertesz in 1948. Since then, researchers have proposed using the pH values of 1.0 and 4.5 [29,30].

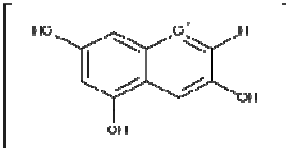
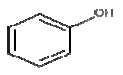
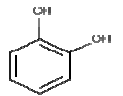
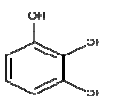
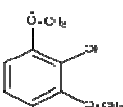
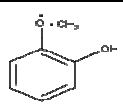
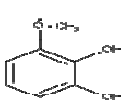
Monomeric anthocyanins undergo a reversible structural transformation as a function of pH (colored oxonium form at pH 1.0 and colorless hemiketal form at pH 4.5; Fig. 2). Thus, the difference in absorbance at the $\lambda_{vis-max}$ (ca 520 nm) of the pigment is proportional to the concentration of pigment. Degraded anthocyanins in the polymeric form are resistant to color change with change in pH. Therefore, polymerized anthocyanin pigments are not measured by this method because they absorb both at pH 4.5 and 1.0.

Table 1. Naturally occurring anthocyanidins

Name	Position of Substitution						Some of the produced colors
	3	5	6	7	3'	5'	
Common basic structures							
Pelargonidin	OH	OH	H	OH	H	H	Orange
Cyanidin	OH	OH	H	OH	OH	H	Orange-red
Delphinidin	OH	OH	H	OH	OH	OH	Bluish-red
Common methylated structures							
Peonidin	OH	OH	H	OH	OMe	H	Orange-red
Petunidin	OH	OH	H	OH	OMe	OH	Bluish-red
Malvidin	OH	OH	H	OH	OMe	OMe	Bluish-red
3-deoxy structures							
Apigeninidin	H	OH	H	OH	H	H	Orange
Luteolinidin	H	OH	H	OH	OH	H	Orange
Tricetinidin	H	OH	H	OH	OH	OH	Red
Rare hydroxylated structures							
Aurantidin	OH	OH	OH	OH	H	H	Orange
6-Hydroxycyanidin	OH	OH	OH	OH	OH	H	Red
6-Hydroxydelphinidin	OH	OH	OH	OH	OH	OH	Bluish-red
Rare methylated structures							
Capensinidin	OH	OMe	H	OH	OMe	OMe	Bluish-red
Europinidin	OH	OMe	H	OH	OMe	OH	Bluish-red
Hirsutidin	OH	OH	H	OMe	OMe	OMe	Bluish-red
7-O-methylapigeninidin	H	OH	H	OMe	H	H	Orange-red
5-Methylcyanidin	OH	OMe	H	OH	OH	H	Orange-red
Pulchellidin	OH	OMe	H	OH	OH	OH	Bluish-red
Rosinidin	OH	OH	H	OMe	OMe	H	Red

Updated from Strack, D. & Wray, V. [7]

Table 2. Structure and main food sources of anthocyanins

Structure of the cation <i>flavilium</i>	Structure	Name	Food sources
		Pelargonidin	Strawberry
		Cyanidin	Blemish, fig, plum, blackberry
		Delphinidin	Eggplant, pomegranate, passion fruit
		Malvidin	Grape, beans
		Peonidin	Grape, cherry
		Petunidin	Various fruits

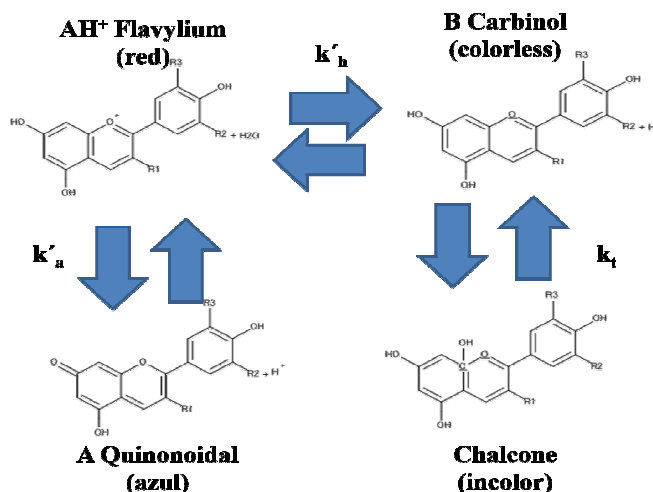


Fig. 2. Predominant anthocyanin structural forms present at different pH levels

The anthocyanins have also been classified in agreement with the amount of sugar molecules that constitute their molecules (i.e., monosides, besides, triosides) and, interestingly, the number of probable compounds is greatly increased by taking into account the sugar diversity and all the possible structural points of glycosylation, although the order of sugar occurrence in natural

anthocyanins is glucose, rhamnose, xylose, galactose, arabinose, and fructose. Additionally, many anthocyanins have shown in their structures ester bonds between sugars and organic acids i.e., acylated anthocyanins), and in nature the most common acyl groups are coumaric, caffeic, ferulic, *p*-hydroxy benzoic, synaptic, malonic, acetic, succinic, oxalic, and

malic [31]. Moreover, the substitution of hydroxyl and methoxyl groups influences the color of anthocyanins. Increments in the number of hydroxyl groups tend to deepen the color to a more bluish shade. On the other hand, increments in the number of methoxyl groups increase redness. With all of these facts in mind, it must be not difficult to understand the gamut of colors observed in nature that is produced from a single structure.

3. ANTIOXIDANT ACTIVITY OF BERRY FRUITS

Numerous epidemiologic studies have shown that high consumption of fruits and vegetables are associated with the lower risk of chronic diseases, such as cancer, cardiovascular diseases, cataracts, and hypertension. Vegetables and fruits probably protect against a range of cancers, including mouth, pharynx, larynx, esophagus, stomach, lung, pancreas and prostate. Because it contains vitamins and minerals and are good sources of phytochemicals. These are biologically active compounds that may help protect body cells from damage that can lead to cancer (Fig. 3).

Overproduction of reactive oxygen species (ROS), such as superoxide anion, hydrogen peroxide and peroxy radicals, and reactive nitrogen species (RNS), such as nitric oxide and peroxy nitrite radicals, could lead to oxidative

stress and nitrosative stress, respectively. These reactive species can damage proteins, lipids and DNA, leading to lipid peroxidation, altered signal transduction pathways, and the destruction of membranes and organelles that could be responsible for the development of several disorders, including cancer, cardiovascular disease, diabetes and neurodegeneration [32,33]. The brain is particularly susceptible to oxidative stress pertaining to its high oxygen demand, as well as due to the fact that it is enriched with polyunsaturated fatty acids. Moreover, a high iron concentration and low levels of antioxidants are also factors responsible for overproduction of ROS and RNS in brain cells [32,33]. It has been reported by several researchers that excessive production of oxidative and nitrosative compounds is associated with brain aging and neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases [33,34]. The balance between ROS and antioxidants in biological systems is referred to as redox homeostasis, which is essential for normal cell function [35]. In order to combat oxidative stress, there are several types of endogenous enzymatic antioxidants such as superoxide dismutase, catalase and glutathione peroxidase, as well as non-enzymatic glutathione; and there are also several non-enzymatic antioxidants that are obtained primarily in the diet, including tocopherol, ascorbate, carotenoids and various polyphenolic compounds [32].

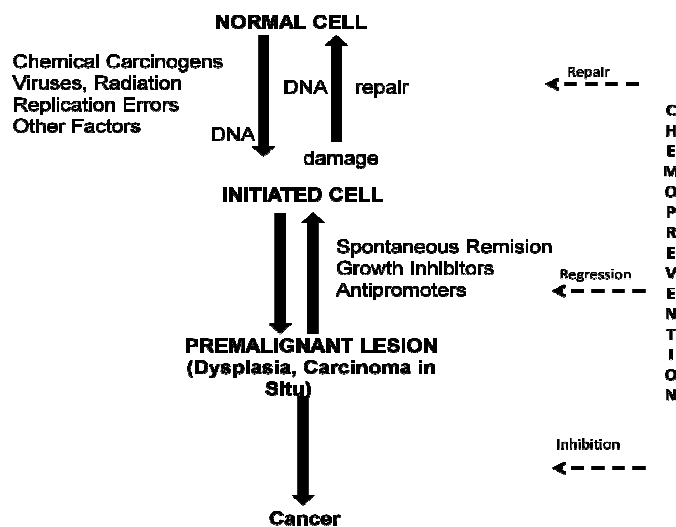


Fig. 3. A multistep carcinogenesis model

Polyphenols are a large class of natural compounds that have high antioxidant capacity and potential beneficial effects including cardio- and neuro-protective effects, anti-carcinogenic benefits, anti-inflammatory properties and anti-microbial activities [36]. These classes of compounds also appear to have positive effects on the cardiovascular system, which may be due to their ability to act as free radical scavengers or by other mechanisms [37]. Polyphenols are abundant in plants, especially vegetables and fruits. Berry crops are very rich sources of polyphenolic antioxidants, particularly flavonoid compounds [38]. Since plant derived supplements are considered as natural and hence potentially safer than synthetic drugs, there has been an increasing demand of 'nutraceuticals' [39]. The term nutraceutical was originally defined by Dr. Stephen DeFelice as daily nutritional supplements like food or a part of food, which have beneficial effects in treating or preventing diseases [40]. Berries have been reported to have diverse health promoting phytochemicals and are very rich sources of polyphenolics especially flavonoids, anthocyanins, and proanthocyanidins. An enormous body of research has been published suggesting that the dietary consumption of berries has positive effects on human health and diseases [41,4]. The health promoting properties of berries are gaining continued interest in the berry market not only as antioxidants, but also because of their bioactive properties *in vivo* [41,42]. The use of phytochemicals as dietary supplements is growing. However, many of these dietary supplements have been developed based on the results from chemical analysis, *in vitro* studies and animal experiments. For a thorough understanding of the efficacy and long-term safety of many dietary supplements, further investigation is needed. What dose of a single antioxidant should be used as a dietary supplement? Natural phytochemicals at the low levels present in fruit and vegetables offer health benefits, but these compounds may not be effective or safe when consumed at higher doses, even in a pure dietary supplement form. Generally speaking, taking higher doses increases the risk of toxicity. In the case of antioxidant nutrients, the proper physiologic dose should follow the recommended dietary allowance (RDA) [34]. The pharmacologic dose is not equal to the physiologic dose and in some cases can be toxic. In a human study, 30 healthy individuals whose diets were supplemented with 500 mg vitamin C/d showed an increase of oxidative damage in the DNA isolated from

lymphocytes [35]. This study suggests that vitamin C at a high dose (500 mg) may act as a prooxidant in the body. We do not have an RDA for phytochemicals. Therefore, it is not wise to take megadoses of purified phytochemicals as supplements before strong scientific evidence supports doing so.

In particular, the potential of berries and their constituents to protect the brain from aging and neurodegenerative disease has gained increased attention in recent years. For example, dietary supplementation with polyphenol containing fruits can decrease age-related behavioral deficits in rats [43]. In a recent study conducted with a mouse model of Alzheimer's disease, treatment with berries rich in polyphenols decreased the extent of behavioral abnormalities associated with the disease [44]. Other experimental studies have shown that rats fed a diet enriched with blueberries can protect the brain against oxidative stress and associated learning deficits [45]. Surprisingly, a diet enriched with blueberries has been demonstrated to later protect animals from the damage induced by ischemic stroke [46]. Berries constitute one of the most important sources of potential health supporting phytochemicals in the human diet. They are a rich source of ascorbic acid and phenolic compounds, particularly phenolic acids, anthocyanins, proanthocyanidins and other flavonoids. These compounds provide the pigmentation of fruits and prove beneficial to human health. Their biological activities include: protection against the incidence and mortality rates of cancer, protection against ischemic heart disease mortality and as well as they have antitumorigenic, antimicrobial, antiinflammatory-allergic and antimutagenic properties.

The berry fruits have high antioxidant activity due to the presence of bioactive compounds, including are anthocyanins. Anthocyanins are potent antioxidant superior to classical antioxidants such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and α -tocopherol [47,48]. Glycosylation of an anthocyanin decreases radical scavenger activity compared with the aglycone, as it reduces the ability of the anthocyanin radical to delocalize electrons. In accordance with this, Fukumoto and Mazza [48], reported increased antioxidant activity to increase in the hydroxyl groups and decreased antioxidant activity with glycosylation of anthocyanidins (Table 3).

4. BIOAVAILABILITY OF BERRY BIO-ACTIVES

The bioavailability and metabolism of phenolics, the predominant phytochemicals present in berry fruits, have been reviewed [49,50] and therefore will not be discussed in detail in this paper. It is noteworthy that the bioavailability of phenolics, the predominant phytochemicals present in berry fruits, is widely accepted by the scientific community to be poor on the basis of their relative "low" levels detected in circulation. However, these compounds are extensively metabolized in the body's tissues and by the colonic microflora. When the gut microflora is involved, the efficiency of absorption is often reduced because the flora also degrades the aglycons that it releases and produces various simple phenolic and aromatic acids in the process. During the course of absorption, phenolics are conjugated (usually methylated, sulfated, and glucuronidated) in the small intestine and later in the liver, a metabolic detoxification process that facilitates biliary and urinary elimination. Many of these metabolites are still largely unknown and not accounted for, and knowledge of their tissue disposition is scarce. In addition, there are also large variations in polyphenol bioavailability observed among individuals due to nutrigenetic and nutrigenomic effects. Therefore, it is critical that these aforementioned factors be taken into consideration for a complete evaluation of the impact of the bioavailability and metabolism of berry phenolics on cancer prevention.

Among the main bioactive compounds present on berry fruits are anthocyanins. Basing on the data review by Galvano et al. [51], the results of a literature survey since 2002 on cyanidin and glycosides bioavailability in humans are presented in Table 4. The studies were reported, single doses of 188-3570 mg total glycosides were given to the volunteers, most often in the form of berries, berry extracts, or juices. After such intakes, maximal plasma anthocyanin concentrations were very low, on the order of 2.3-96 nmol/L. The mean time to reach these concentrations was around 1.5 hours. Most studies reported very low relative anthocyanin urinary excretions, ranging from 0.018 to 0.37%. Maximal urinary cyanidin excretion is usually achieved in less than 4 h. The most striking features of these surveys are thus that glycosides

are very quickly absorbed and urinary excreted and that the fraction of orally administered cyanidin excreted in urine is very low.

Many studies have only detected unchanged anthocyanin glycosides in both plasma and urine [57]. However, these last years, methylated derivatives, anthocyanidin glucuronide conjugates as well as anthocyanin glycoside glucuronides have been identified in urine or plasma by the use of HPLC combined with mass spectrometry [58]. Kay et al. [59] have also identified an oxidized derivative of anthocyanins.

Methylation at the 3'-OH moiety of various cyaniding glycosides (glucoside, galactoside, xyloside, sambubioside) has been largely reported [52,58-60]. Tian et al. [60] observed that methylation potentially occurred at both the 3- or 4'-hydroxyl position of a triglycoside anthocyanin (Cy 3-xylosylrutinoside) whereas mono- or diglycosides gave rise to only one methylated derivative.

Formation of monoglucuronides of Cy and its methylated derivative peonidin has been observed after various berry anthocyanin feeding [52,58,61]. After blackberry consumption, two monoglucuronconjugates of cyanidin have been identified [61]. Moreover, a cyaniding diglucuronide has been identified in urine [61].

Wu et al. [52] have also identified a cyanidin 3-glucoside glucuronide in urine from elderly women after consumption of an elderberry concentrate. The exact sites of cyaniding glucuronidation are still unknown. Two possible pathways could explain the formation of monoglucuronides of cyanidin and glycosides. A possible pathway is that glycosides were hydrolyzed to aglycones then rapidly glucuronidated by an UDP-glucuronosyltransferase in the intestine. On the other hand, another possible pathway is that glycosides could serve as a substrate for UDP-glucose dehydrogenase to form cyanidin glucuronides. Indeed, such an enzyme is present in both the small intestine and liver [62]. This last hypothesis does not require hydrolysis to aglycones, which are unstable at physiological pH. Therefore, it could be regarded as a principal glucuronidation pathway and could thus result in the formation of the major metabolites.

Table 3. Antioxidant and prooxidant activity of selected anthocyanins (adapted from: Fukumoto and Mazza [48])

Compound	Current study				Selected results from literature ORAC assay ¹ ORAC slope ⁶
	β -carotene method Initial slope ²	DPPH method Antiradical activity ³	HPLC method		
			Antioxidant activity ⁴ (μ M of compound added)	Prooxidant activity ⁵	
Cyanidin	836 \pm 69	-7.40 \pm 0.15	200-300	+	2.239 \pm 0.029
Cyanidin-3-glucoside	278 \pm 32	- 6.81 \pm 0.30	300-400	+	3.491 \pm 0.011
Cyanidin-3,5-diglucoside	220 \pm 39	-3.32 \pm 0.07	500-1000	+	1.689 \pm 0.052
Delphinidin	897 \pm 147	-8.86 \pm 0.28	500-1000	+	1.809 \pm 0.068
Malvidin	288 \pm 34	-4.49 \pm 0.28	1500-2000	+	2.009 \pm 0.167
Malvidin-3-glucoside	448 \pm 40	-4.29 \pm 0.42	500-1000	+	1.404 \pm 0.052
Malvidin-3,5-diglucoside	266 \pm 27	-2.56 \pm 0.10	2000-2500	+	1.550 \pm 0.062
Pelargonidin	Nc	-4.63 \pm 0.25	1500-2000	+	1.540 \pm 0.033
Pelargonidin-3-glucoside	444 \pm 94	-3.95 \pm 0.22	2000-2500	+	1.560 \pm 0.145
Pelargonidin-3,5-diglucoside	Nc	-2.04 \pm 0.10	2000-2500	+	1.067 \pm 0.043
Peonidin	169 \pm 22	-4.05 \pm 0.17	1500-2000	+	1.693 \pm 0.035
Peonidin-3-glucoside	251 \pm 4	-3.38 \pm 0.15	2500-3000	+	1.805 \pm 0.014
Standards					
Ascorbic acid	Nc	-1.83 \pm 0.07	>4000	+	
A-Tocopherol	870 \pm 21	-1.95 \pm 0.07	2000-2500 (50%)	Nd	
BHA	835 \pm 50	-2.61 \pm 0.01	1000-1500	Nd	
BHT	864 \pm 76	-3.17 \pm 0.07	200-300	Nd	

¹The oxygen radical absorbing capacity (ORAC) assay measuring reaction with peroxyl radicals expressed as μ M of Trolox equivalent per μ M of compound. Results for anthocyanidins/anthocyanins were taken from Wang et al. [47].

²Values are means of slope coefficients calculated by linear regression \pm standard deviations ($n=3$) in A450 nm after 90 minutes of incubation in the dark/ μ M of compound added.

³Values are means of slope coefficients calculated by linear regression \pm standard deviations ($n=3$) in μ M of DPPH/ μ M of compound.

⁴Antioxidant activity was defined by the concentration range of compound added needed to reach 0% malonaldehyde of the control.

⁵Prooxidant activity was positive (+) if the % malonaldehyde of the control was >100% in the concentration range tested.

⁶Values are slope coefficients calculated by linear regression \pm standard error.

nc: not calculated since linear regression $r^2 < 0.800$.

nd: not detected.

Table 4. Human studies of cyanidins bioavailability

Source	Cy and Cyg	Ingested amount (mg)	Plasma C _{max} (nmol/L)	Plasma T _{max} (h)	Urinary excretion (% of intake)	Urine Tmax (h)	Duration of urinary collection (h)	References
Elderberry extract	Cy-3-samb,Cy-3-glc	720			0,077		4	[52]
Blackcurrant juice	Cy-3-rut	716-1239		-0,75	0,048-0,072		4	[53]
Blackcurrant concentrate	Cy-3-rut, Cy-3-glc	188			0,064	-2	7	[54]
Boysenberry concentrate	Cy-3-glc, Cy-3-soph	344			0,029	-2	7	[54]
Elderberry juice concentrate	Cy-3-samb, Cy-3-glc	3570			0,053	-1	5	[55]
Elderberry extract	Cy-3-samb, Cy-3-glc	147	-27	1,5	0,37	1,5	7	[56]
Blackcurrant juice	Cy-3-rut	145	-5,7	1	0,04	1,5	7	[56]

Cy: cyaniding a: depending on the cyaniding considered in the mixture.

Small amounts of sulfoconjugates of cyanidin have been identified in urine [61]. Cyanidin sulfoconjugate formation requires hydrolysis of glucoside to the aglycone and then sulfoconjugation of the aglycone by sulfotransferases present in numerous tissues, including the intestine and liver [63]. Furthermore, aglycone (cyanidin) has been detected in urine samples analyzed immediately after their collection [61]. Given that aglycone is very unstable at physiological pH, it is unlikely that it all arise from the small intestine. Small amounts of aglycone could thus be released from conjugates by β -glucuronidases and sulfatases present in both kidney and urine [64,65].

The proportion of metabolites (methylated and/or glucuronides) related to total anthocyanins excreted in urine was estimated at around 6% [56], 25% [52], 68% [58] or higher than 85% [61]. Some of these discrepancies could arise from sample conservation, extraction procedures as well as the sensitivity and resolution of HPLC methods.

The glycoside moiety may have an influence on the absorption of glycosides. Indeed, Nielsen et al. [53] have found a higher plasma concentration and urinary excretion of cyanidin rutinosides than of cyanidin glucosides in relation to dose.

Overall, studies indicate that ACNs are mainly absorbed in their intact forms as glycosides. However, the absorption mechanism involved has not been identified yet. Within the intestinal cells, ACNs are partly metabolized via methylation and/or glucuronidation. In the liver and kidneys further metabolism takes place, and ACNs are excreted in the urine either as the intact glycosides, or as methylated or glucuronidated forms. Fig. 4 represents possible pathways of ACNs during their absorption, metabolism and excretion. All animal and human studies on ACN absorption agree on the extremely low bioavailability of these compounds. In addition, the review of the literature on ACN bioavailability shows, that there is a large variability in the reported dose-plasma concentration ratios, which is most likely due to the different applied methods for measuring ACN concentration in plasma. To date there is no general validated assay for the extraction of ACNs in plasma or urine samples. It is therefore questionable if the reported low plasma concentrations are sufficient enough for ACNs to exert health-related effects *in vivo*. If it is possible

to maximize ACN absorption into the human body, the resulting ACN concentrations in the blood circulation may be sufficient enough to provide target tissues with adequate amounts to perform health-related effects.

5. ANTI-CANCER PROPERTIES OF ANTHOCYANINS

This group of polyphenols has been demonstrated to have biological functions such as anti-inflammatory and anti-oxidant activities, chemoprevention, and apoptosis induction, as well as is associated with a lower risk of cardiovascular disease. Furthermore, *in vitro* and *in vivo* anti-cancer activities of anthocyanins have been reported regarding anti-angiogenesis and cancer invasion [66,67].

Peonidin 3-glucoside and cyanidin 3-glucoside, extracted from black rice (*Oryza sativa L. indica*), inhibited the invasion and motility of SKHep-1 and Huh-7 cells, which resulted from the suppression of MMP-9, uPA, and AP-1 [68]. Anthocyanins isolated from meoru (*Vitis coignetiae Pulliat*) inhibited the migratory and invasive activity on Hep3B cells by downregulating MMP-2/MMP-9 expression and partially inhibiting NF- κ B activation [69]. Furthermore, peonidin 3-glucoside and cyanidin 3-glucoside also inhibited cell invasion via repressions of MMP-2 or u-PA expression in various cancer cells, such as SCC-4, Huh-7, and HeLa cells [68].

Cyanidin 3-glucoside and cyaniding 3-rutinoside isolated from mulberry exhibited an inhibitory effect on the migration and invasion of an A549 human lung cancer cell line via decreased productions of MMP-2 and u-PA [70]. Cyanidin 3-glucoside and peonidin 3-glucoside could significantly reduce the expression of MMP-9 and u-PA in SKHep-1 cells. Recent studies have shown that NF- κ B and AP-1 play significant roles in the activation of MMP-2, and -9 [71] while u-PA is also responsible for the migration and regulation of MMPs activation through NF- κ B and AP-1 pathways [72,73]. The cyaniding 3-glucoside or peonidin 3-glucoside could reduce the binding of AP-1 to DNA in their DNA-binding domains, which was accompanied by the inhibition of nuclear expression of this factor. -In breast cancer, delphinidin can inhibit HGF-induced early biochemical effects, such as receptor tyrosine phosphorylation and upregulation, activation of the major signaling pathways, as well as delayed biological

responses, namely block of proliferation and cell migration [67]. Recent studies reveal the possible benefits of delphinidin in preventing tumor development and malignant progression through inhibition of several major pathways involved in breast oncogenesis. Cyanidin 3-glucoside inhibits ethanol-mediated migration/invasion in cells expressing high levels of ErbB2 and inhibited ethanol stimulated phosphorylation of ErbB2, cSrc, FAK, and p130^{Cas} in breast cancer BT474, MDA-MB-231, and MCF-7 cells [74]. Anthocyanin-enriched and proanthocyanidin-enriched fractions from blueberry (*Vaccinium angustifolium*) downregulated the activity of MMP-2 and MMP-9 and increased the activity of TIMP-1 and TIMP-2 in prostate cancer cells in prostate cancer DU-145 cells by modulating PKC and MAPK pathways [75].

Anthocyanins isolated from *V. coignetiae* Pulliat inhibited the invasion of colon cancer HT-29 cells by suppressing MMP-2/MMP-9 though the inhibition of NF- κ B activation [76]. Anthocyanins induced apoptosis in human colon cancer HCT-116 cells partly through activation of p38-MAPK and suppression of p-Akt. [77].

Delphinidin inhibited the invasion in fibrosarcoma HT-1080 cells by inhibiting the activities of MMP-2/MMP-9 [78]. Lamy et al. [79] revealed that the anthocyanins present in fruits, such as cyanidin, delphinidin, and petunidin, act as potent inhibitors for the migration of glioblastoma U-87 cells. The treatment with these compounds decreased the expression of uPAR and PAI-1 but uPA was increased. At the same time, the uPA-dependent conversion of plasminogen to plasmin was decreased. This finding indicates that the induction of plasminolytic activity might be not associated with the upregulation of uPA by these compounds. The proposed target proteins and mechanisms of the above-mentioned compounds on the inhibition of cancer invasion in vitro are summarized in Table 5.

The inhibitory effect of anthocyanins in carcinogenesis and tumor growth may be through two main mechanisms: redox status modification and interference with basic cellular functions (cell cycle, apoptosis, inflammation, angiogenesis, invasion and metastasis).

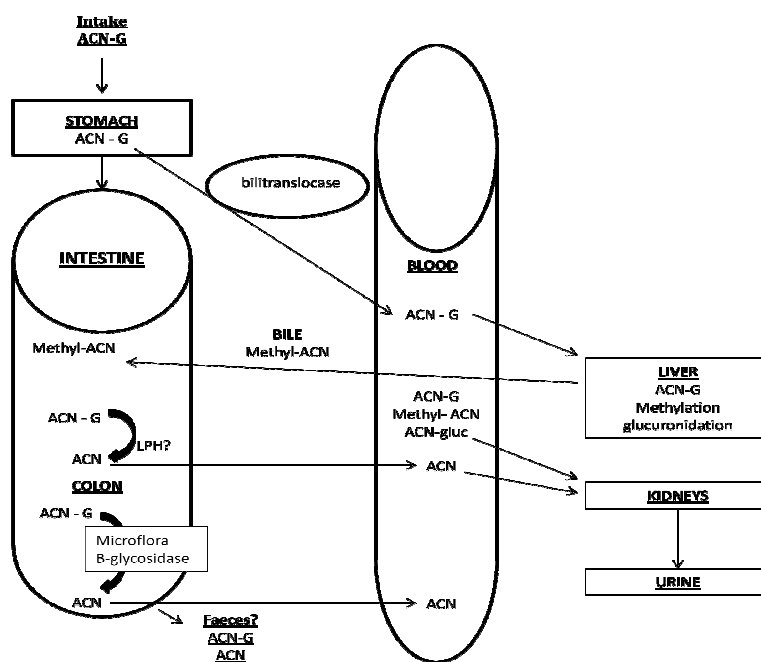


Fig. 4. Possible pathways of ACN absorption, metabolism, and excretion in the animal/human body. ACN (ACN aglycone), ACN-G (ACN-glucoside), methyl- ACN (methylated ACNs), ACN-gluc (glucuronidated ACNs), SGLT₁ (sodium-dependent glucose transporter), LPH (lactase phloridzin hydrolase)

Table 5. The proposed molecular targets on the inhibition of cancer invasion of anthocyanins in culture cell models and animal model

Cancer type	Cell/animal model	Biological effects	Molecular targets	References
Hepatoma	Hep3B/HepG2/SK-Hep-1/HSC	↓ invasion; migration; cell-matrix adhesion; MMP-9/MMP-2; MT1-MMP;MUC1	↓ ERK	[80,81,82,83]
Lung cancer	95-D/BZR bronchial tumor cells	↓ invasion; migration; MMP-2/MMP-9	↓ NF κβ	[84,85]
Breast cancer	MDAMB231/MCF-7/ MCF-7/HGF-induced MCF10A / EGF and HGR -inducedMCF-7/	↓ invasion; migration; cell-matrix, adhesion; fibronectin; vitronectin; uPA; snail; β-catenin; VASP; EGFR; ErbB2/ErbB3; Met; VEGF; α5-, β1-, αv-, β3-integrin receptors , MMP-9 and MT1-MMP ↑: TIMP-1/TIMP-2; E-cadherin; γ-catenin; MTA3	↓ NF-κβ ERK; FAK; Akt; AP-1; Rac1; ↑: FOXO3; ERα	[86,87,88,89, 90,91,92]
Prostate cancer	DU-145/LNCAp/PSA-triggered DU-145 and LNCAp/ FCM-induced DU-145	↓ invasion; migration; uPA; MMP-9/MMP-2/MMP-3; PSA; VEGF; ↓:↑: TIMP-1	↓ ERK;p38; AP-1; NF-κβ	[93,94, 95]
Colorectal cancer	HCT116/	↓ invasion; Met	↓ ERK; Akt	[96,97]
Oral cancer	OC2/HSC3/HSC4/CC9/SCC25/S GT	↓ invasion; migration; ↓ uPA; β1-integrin MMP-9; ↑ RECK	↓ FAK;ERK;Akt	[98,99,100,101]
Fibrosarcoma	HT-1080	↓ invasion; MMP-2; MT-1-MMP	↓ ERK; p38	[102,103,104]
Hepatoma	SKHep-1/Huh-7/Hep3B	↓ invasion; migration;	↓ AP-1; NF-κβ	[68, 69]
Lung cancer	A-549/H1299	↓ MMP-2/MMP-9; uPA;	↓ ERK; AP-1; NF-κβ	[70]
Breast cancer	HGF-mediated MCF-10A/ethanol-mediated BT474, MDA-MB231, MCF-7 ^{ERB2}	↓ invasion; migration; cell-matrix adhesion; ErbB2; Met	↓ FAK/cSrc/p130 ^{CAS} , paxillin/Gab-1/GRB-2; Ras/ERK;P13K/Akt/mTOR/p70S6K;PKC;STAT3; NF- κβ	[73]
Prostate cancer	DU145	↓ MMP-9/MMP-2 ↑ TIMP-1	↓ PKC; MAPK	[74]
Colon cancer	HCT116 HT-29	↓ migration; MMP-2; u-PA	↓ p38;P13K/Akt; NF-κβ	[75,76]
Oral cancer	SCC-4	↓ invasion; MMP-2; u-PA	-	[68]
Cervical cancer	HeLa	↓ invasion; MMP-2;u-PA	-	[68]
Fibrosarcoma	HT-1080	↓ invasion; MMP-2/MMP-9	-	[77]
Glioblastoma	U-87	↓ invasion; uPA; plamin activation	-	[78]

HRG heregulin –β1, FCM fibroblast conditioned medium; Updated from Weng, C.J. & Yen, G.C. [105].

5.1 Cellular Redox Status Modification by Anthocyanins

Reactive oxygen species from both endogenous and exogenous sources may be involved in the etiology of diverse human diseases, such as coronary artery disease, stroke, rheumatoid arthritis, and cancer [106]. Anthocyanins can exert a major chemopreventive activity due to their antioxidant property [107]. Antioxidants function as inhibitors at both initiation and promotion/propagation/transformation stages of tumor promotion/carcinogenesis, and protect cells against oxidative damage. Antioxidants are potent scavengers of free radicals and serve as inhibitors of neoplastic processes. Antioxidant activity of phenolics is mainly due to their redox potential which allows them to act as reducing agents, hydrogen donors, singlet oxygen quenchers and metal chelators [108].

5.2 Free Radical Scavenging Activity of Anthocyanins

Flavonoids have shown potential health benefits arising from the antioxidative effects of these phytochemicals, whose properties are attributed to the phenolic hydroxyl groups attached to the flavonoid structure. This is due to the ease with which an H-atom from an aromatic hydroxyl group of polyphenols can be donated to a free radical, and the ability of the aromatic group to then support the unpaired electron via delocalization around the π -electron system [109]. Antioxidative properties of anthocyanins arise from their high reactivity as hydrogen or electron donors, from the ability of the polyphenol-derived radicals to stabilize and delocalize the unpaired electron, and from their ability to chelate transition metal ions (termination of the Fenton reaction) [110]. Thus, anthocyanins may play a role as antioxidants.

5.3 Anthocyanins as Metal Chelators

As an alternative antioxidant property, some phenolic compounds with dihydroxy groups can conjugate transition metals, preventing metal-induced free radical formation. The redox active metal ions such as Cu^+ or Fe^{2+} interact with hydrogen peroxide (H_2O_2) through Fenton chemistry (as shown in reaction 3 below) to form hydroxyl radicals ($\cdot\text{OH}$), which is the most reactive ROS known, being able to initiate free radical chain reactions by abstracting hydrogen from almost any molecule. Phenolic compounds

with catecholate and gallate groups can inhibit metal-induced oxygen radical formation either by coordination with Fe^{2+} and enhancing autoxidation of Fe^{2+} (as shown in reaction 4 below), or the formation of inactive complex with Cu^{2+} , Fe^{2+} , or Cu^+ with relatively weaker interaction [111]. The attachment of metal ions to the flavonoid molecule can be 3',4'-o-diphenolic groups in the B ring, 3,4 or 3,5-o-diphenolic groups, and the ketol structures 4-keto,3-hydroxy or 4-keto,5-hydroxy groups in the C ring [112]. It was also proposed that optimum metal-binding and antioxidant activity is associated with the structures which contain hydroxy-keto group (a 3-OH or 5-OH plus a 4-C = O), as well as a large number of catechol/gallol groups [112,113].

5.4 Interference of Basic Cellular Functions by Anthocyanins

Pure anthocyanins and anthocyanin-rich extracts from fruits and vegetables have exhibited anti-proliferative activity towards multiple cancer cell types in vitro [114,115]. Anthocyanins have an important role in the prevention against mutagenesis and carcinogenesis mediating some physiological functions related to cancer suppression [116]. Anthocyanins show inhibitory effects on the growth of some cancer cells [117] and also inhibit cell transformation [118]. Anthocyanins have also been widely reported to inhibit the growth of some human, mice and rat cancer cells [119], and to induce apoptosis in different human cancer cell lines [120] and in Jurkat T cells in which p53 and bax protein expression is modulated.

Cell proliferation was inhibited by the ability of anthocyanins to block various stages of the cell cycle via effects on cell cycle regulator proteins (e.g., p53, p21, p27, cyclin D1, cyclin A, etc.). Anthocyanin rich extracts induce apoptosis through both intrinsic (mitochondrial) and extrinsic (FAS) pathways [121,122]. In the intrinsic pathway or mitochondrial mediated mechanism, anthocyanin treatment of cancer cells results in an increase in mitochondrial membrane potential, cytochrome c release and modulation of caspase-dependent anti- and pro-apoptotic proteins. In the extrinsic pathway or death-receptor mediated mechanism (e.g., tumor necrosis factor (TNF) receptor, TNF related apoptosis-inducing ligand and Fas), anthocyanins modulate the expression of FAS and FASL (FAS ligand) in cancer cells resulting in apoptosis. In addition, treatment of cancer cells, but not normal cells, with anthocyanins

leads to an accumulation of ROS (reactive oxygen species) and subsequent apoptosis, suggesting that the ROS-mediated mitochondrial caspase-independent pathway is important for anthocyanin-induced apoptosis [123]. The chemopreventive mechanisms of anthocyanins include scavenging reactive oxygen species, (which might have the potential to damage cell components, such as DNA, proteins, and lipids) reducing cell proliferation, up-regulating/inducing apoptosis and modulating mitogen-activated protein kinase (MAPK) activities [124]. Oxidative damage might be involved in initiating events in cancer, and free radicals may help to induce the initiation of apoptosis [125]. Anthocyanins and their aglycones such as cyanidin, delphinidin, malvidin, pelargonidin and peonidin exhibit antiproliferative and proapoptotic properties in gastric adenocarcinoma [126], HT-29 and Caco-2 (colon cancer) [127] and bovine aortic endothelial cells [124], and also protect against esophageal cancer in rodents [128].

The over-expression of inducible cyclooxygenases (COX-2) is believed to be associated with colon, lung, breast and prostate carcinogenesis. Cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) are enzymes involved in both inflammatory processes and tumor development [129]. Cranberry anthocyanins inhibited COX-1 and COX-2 activity by approximately the same degree, reducing activity by ~10% at 125 mg/L. Pure cyanidin was more effective in this assay, showing greater inhibition of COX-2 (47%) than COX-1 (37%) [130]. Mixed anthocyanin-rich extracts inhibited the induction of vascular endothelial growth factor by both hydrogen peroxide and tumor necrosis factor (TNF- α) and also resulted in decreased hemangioma formation and tumor growth [131]. This suggests that the antioxidant and anti-inflammatory properties of these compounds may limit angiogenesis. Anti-angiogenic approaches to prevent and treat cancer represent a priority area in investigative tumor biology [132]. Vascular endothelial growth factor (VEGF) expression has been detected in a large variety of malignant human tumours, and it has been concluded that VEGF has an important role in the process of tumour angiogenesis [133]. Berry extracts (wild blueberry, bilberry, cranberry, elderberry, raspberry seed, and strawberry) demonstrated significant inhibition of both H₂O₂ as well as TNF- α (Tumor Necrosis Factor-alpha)-induced VEGF expression by human keratinocytes [134]. Proanthocyanidins and other flavonoids from

cranberries and blueberries demonstrate some promise toward limiting processes involved in tumor invasion and metastasis, including blocking the expression of matrix metalloproteinases (MMPs), which are involved in remodeling of the extracellular matrix [135]. Anthocyanin extracts, from different berry types, has inhibition were found to inhibit cancer cell invasion through reducing the expression of MMP and urokinase-plasminogen activator (u-PA). A recent study shown that whole cranberry polyphenolic extract at 100 μ g/mL inhibits the expression of matrix metalloproteinases MMP-2 and MMP-9 in the DU-145 prostate tumor cell line [136].

6. ROLE OF ANTHOCYANIN ON DIFFERENT CANCER CELLS

6.1 *In vivo* Studies in Animals

6.1.1 Esophageal cancer

The most commonly used preclinical animal model for esophageal squamous cell carcinoma is the Fischer 344 rat in which esophageal papillomas are induced by the nitrosamine carcinogen, *N*-nitrosomethylbenzylamine. NMBA is administered repeatedly, after which esophageal tumors appear in all treated animals within 20–25 weeks [137]. Studies [128,138] have demonstrated the ability of lyophilized berries to prevent the development of NMBA-induced esophageal tumors and determined their mechanism(s) of action [128]. In a recent study, indicated that diets rich in anthocyanins preventing the development of esophageal tumors, reducing tumor numbers by 42–47%, suggesting that the anthocyanins in lyophilized berries are important for their chemopreventive activity [139]. The role of these anthocyanins in the prevention of esophageal tumors *in vivo*, however, has not been determined.

6.1.2 Colon cancer

Anthocyanin-rich foods and anthocyanin pigments have been suggested as potential agents to reduce the risk of colon cancer by inhibiting proliferation of human colon cancer cells *in vitro* [140]. Katsube et al. [67] found that the ethanol extract significantly inhibited proliferation of HL60 human promyelocytic leukemia cells and HCT116 human colon carcinoma cells in the range from 2 to 6 mg/mL. *In vitro*, HCT116 colon cancer cells were inhibited by anthocyanin-containing berry

extracts including cowberry, strawberry, blueberry, and bilberry extracts [67]. In vivo, anthocyanin-rich tart cherry extract added to the drinking water was associated with fewer and smaller tumors in the cecum of APCMin mice [119], suggesting that anthocyanin-rich extracts may reduce the risk of intestinal cancer. Freeze-dried black raspberries and purple corn have been shown to inhibit nitrosamine-induced initiation and postinitiation events in the F344 rat esophagus. Recently, it was demonstrated that an antioxidant, 1-O-hexyl-2,3,5-trimethylhydroquinone (HTHQ), can inhibit colon tumor development driven by PhIP as a second stage carcinogen, in male F344 rats [141]. In the azoxymethane (AOM)-induced model of colon cancer in F344 rats, diets containing lyophilized black raspberries significantly decreased total tumors (adenomas and adenocarcinomas) [13]. Raspberry ellagitannins have also been found to be inhibitory against TPA-induced ornithine decarboxylase activity, TPA-stimulated hydroperoxide production and TPA-stimulated DNA synthesis. Freeze-dried strawberries inhibit NMBA-induced esophageal tumorigenesis in the F344 rat model [142]. Phytochemicals from berries, berry fractions and purified anthocyanins have antiproliferative effects on colon cancer cells *in vitro* [143]. There is also evidence that polyphenols present in fruit can prevent metastases and invasion of cancer cells *in vitro* [144].

6.1.3 Skin cancer

Polyphenols act as a sunscreen. This ability of natural polyphenols to act as sunscreens can reduce inflammation, oxidative stress and DNA damaging effects of UV radiation in the skin and, thus, on topical application the photoprotective effects of polyphenols are due in part to this sunscreen effect. Anthocyanins have also been shown to prevent skin cancer in rodents. Topical application of anthocyanin-containing pomegranate extract elicited a delay in onset and decrease in incidence and burden of skin tumours [145].

A variety of edible berry extracts have been demonstrated to exhibit a broad spectrum of benefits including cardiovascular, neurological, urinary tract, and ocular protection as well as antioxidant, anti-diabetic, skin health, and antiaging properties. The effects of UVB radiation resulting in damaged DNA can initiate photocarcinogenesis. In addition, UV radiation produces reactive oxygen species (ROS) that

can also damage DNA molecules and other lipid components, ultimately leading to carcinogenesis [146].

6.1.4 Lung cancer

Anthocyanins have been shown to inhibit the development of tumors induced in mice following the subcutaneous injection of lung tumor cells. Isoliquiritigenin is a simple chalcone derivative and found in licorice, often used in Chinese medicine, and vegetables such as shallot and bean sprouts. The isoliquiritigenin inhibited cell proliferation in the A549 human lung cancer cell line and induced cell cycle arrest at the G2/M phase, and this induction was associated with the enhanced expression of p21CIP1/WAF1. These results suggest that isoliquiritigenin will be a promising agent for use in chemopreventive or therapeutics against lung cancer [147].

In a case-control study in Hawaii, found inverse associations of lung cancer with total intakes of vegetables and subgroups of vegetables particularly rich in other phytochemicals (dark green vegetables, cruciferous vegetables, tomatoes, carrots) that were stronger than that with beta-carotene [148].

6.2 Human Studies

Anthocyanins have been shown to have some positive therapeutic effects including in the treatment of diabetic retinopathy, in fibrocystic disease of the breast in human, and on vision [149]. Two case-control studies examining potential beneficial links between flavonoid intake and development of colorectal cancer. In a case-control study conducted in Italy [150] found reduced risk of developing colorectal cancer with increasing isoflavone, anthocyanin, flavone and flavanol intakes, but not with catechin or flavanone intake. A Scottish case-control study [151] also observed reduced colorectal cancer risk with higher intakes of flavonols, catechins and procyanidins.

In a case-control study in Hawaii found inverse associations of lung cancer with total intakes of vegetables and subgroups of vegetables particularly rich in other phytochemicals (dark green vegetables, cruciferous vegetables, tomatoes, carrots) [148].

A study in Germany showed that individuals who consumed an anthocyanin/polyphenolic-rich fruit juice had reduced oxidative DNA damage. In a

cross-over study, mixed fruit juices, one especially rich in anthocyanins and the other rich in flavanols, similarly decreased the level of Endo III (endonuclease III) sensitive sites during the second treatment period [152]. The Endo III sensitive sites returned to baseline levels 13 weeks after the treatment period. The result may indicate delayed effect of polyphenol-rich juices on DNA damage in lymphocytes. Studies show that black raspberry powder (which contains anthocyanins and ellagitannins) acts in the prevention of oral, oesophageal and colon cancer [153]. The anthocyanins cyanidin-3-glucoside and cyanidin-3,5-diglucoside have been reported to be incorporated into human plasma with their structures maintained [154]. Berries containing a large amount of anthocyanins are likely to suppress cancer through the induction of apoptosis and/or inhibition of cancer cell growth in vivo.

7. CONCLUSION

With a rising number of new cases of all types of cancers worldwide, novel agents that could cure or prevent cancers are still very much needed. Most anticancer agents act by induction of apoptosis, cell cycle arrest, as well as an inhibition and proliferation of cell growth. This review indicates that many of the phenolic contents of fruits and vegetables, mainly berry fruits, have been shown to have anticancer activities and that they exert their effects through one of the aforementioned mechanisms. It is expected that the effects of polyphenols on cell cycle, cell growth and proliferation, as well as induction of apoptosis in cancer cells, will provide clues for the prediction of novel agents that may be useful in cancer chemoprevention or chemotherapy. However, while the combination of some polyphenols enhances the anticancer activity of some agents, other reports indicate that such combinations are not always beneficial in terms of potentiating the action of other anticancer agents. Moreover, the concentrations of different polyphenols in fruits and vegetables and the interactions between them have yet to be fully elucidated; therefore, more information is needed with regards to the possible role of fruits and vegetables in cancer prevention and therapy.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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