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The effect of berry consumption on cancer risk

Abstract

Berries have been consumed as part of the human diet for thousands of years. It is only recently, however, that their biological properties in relation to cancer inhibition and prevention have been realised. Original research by a number of sources has attributed these chemopreventative actions to the role of anthocyanin compounds in berries. A review of the literature surrounding the chemopreventative effects of berry consumption and cancer risk is explored here in order to summarise the existing evidence and to determine the future routes of research needed. This review concluded that the reliability of existing research in relation to human cancer risk is limited due to it being mainly in vitro and not enough conclusive evidence to show the application in humans. Future research should aim at understanding how berry compounds act on cancer in humans and investigations into why berry compounds are not being incorporated into effective methods for the treatment of cancer, one of the leading causes of death worldwide.

Keywords: berries, cancer, phytochemicals, anthocyanins, antioxidants

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Abbreviations: ACN, anthocyanins; ROS, reactive oxygen species; AA, antioxidant activity; LDL, low density lipoproteins; GAC, gastric adenocarcinoma; NDMA, n-nitrosodimethylamine; EA, ellagic acid; NBMA, n-nitrosobenzylmethylamine

Introduction

Berries have been part of the human diet for manyyears and only recently have their potential health benefits have been greatly understood. At present, there is a genuine consensus amongst most individuals, both academic and non-academic, that berries are good for an individual's health due to their phytochemical composition.[1] Research in pastyears has identified that berries contain a number of phytochemicals linked to good health. Phytochemicals include anthocyanins, flavonols, flavonoids and proanthocyanidins. These phytochemicals tend to be bioactive and as such have a wide range of biological properties such as they are; anti-carcinogenic, anti-mutagenic, antioxidants and cancer preventative.

For a number ofyears now, the general health benefits of fruit consumption has been widely established. In 1991 for example, Steinmetz and Potter[2] alluded to the fact that we as humans have adapted over time to a diet which regularly involves the consumption of fruit (including berries) and vegetables. Furthermore, it was hypothesised by Steinmetz and Potter[2] that a reduction in fruit and vegetable consumption could potentially lend itself to an increase in the likelihood of cancer development. It is only in recent years, however, that studies such as that by Neto[3] and Stoner et al.,[4] have begun to investigate the cancer preventative effects of these berry phytochemicals.

It is common knowledge that diet plays a key role in cancer risk both positively and negatively, for example negative effects include; the associations between cooking and the development of carcinogens, studies linking 'bad fats' with increased cancer prevalence and evidence to suggest excess meat consumption increases risk. On the other hand, positive effects include: the beneficial relationship of berry consumption and a lowered occurrence of cancer, the positive association of dietary fibre and reduced risk of colon cancer and some evidence to suggest that consumption of immune-boosting spices and herbs can lower certain types of cancers. This review focuses in particular on the effect of a diet rich in berries and the suggested beneficial link to cancer risk which has been the centre of attention in many recent cancer related studies.

To begin with, it is important to initially understand what cancer is and the possible mechanisms of cancer prevention associated with berry consumption. Cancer is defined by the National Cancer Institute[5] as 'diseases in which abnormal cells divide without control and are able to invade other tissues'. It is well known that there are a wide range of factors which directly cause cancer and/or contribute to the risk of developing cancer and its associated health issues. As cancer is a multi-factorial disease, understanding how berries and their components directly affect the risk of cancer is somewhat difficult. A number of possible mechanisms by which cancer is said to be prevented or by which the risk of developing a cancerous tumour is lowered have been identified in the past two decades. Increasing research into berries and cancer has lead to the identification of a number of beneficial mechanisms which are generally based around: vitamins, minerals, fibre and berry bioactives.

A review of the current literature surrounding the potential effects of berry consumption and the risk of developing cancer is addressed here. The review will aim at exploring and comparing the existing research behind three main berries:

i. Blueberry
ii. Cranberry
iii. Strawberry

These three berries are consumed regularly as part of the human diet and as such it is therefore important that the mechanisms of their benefits are further understood. If the relationship between these berries and cancer risk is understood in greater detail, then there may be the opportunity to develop more effective methods of cancer treatment and ultimately a cure. Current methods of cancer treatment are targeted at killing the cancerous cells, but these methods are invasive and are non-specific, in other words they don't just kill the cancerous cells, they kill healthy cells too.

Blueberry

Epidemiological studies suggest that the consumption of blueberries as part of a healthy balanced diet act as an inhibitory factor and reduces the risk of contracting certain types of human cancers. The blueberry is part of the genus *Vaccinium* species and is an extremely rich source of antioxidant phytochemicals in the human diet.[6] Phytochemicals are the non-essential nutrients mainly found in the chemical structure of fruits and vegetables. Blueberries, in particular, have an abundance of antioxidant acting phytochemicals, hence why they are regularly referred to as antioxidant super fruits. Blueberries contain a wide range of bioactive phytochemicals including; flavonoids (flavonols, anthocyanins and flavonols), phenolic acids, tannins (proanthocyanidins, ellagitannins and gallotannins), sterols, stilbenes (pterostilbene) and triterpenes.[7] All of these berry bioactives have been identified as beneficial to health and some in particular such as anthocyanins have been recognised specifically for their contributory effects in cancer prevention and suppression.

The effect of blueberry consumption on cancer risk has been studied in greater depths over recentyears, particularly through *in vitro* studies. However, there is still a relatively low number of *in vivo* human studies which conclusively show the link between consuming higher quantities of blueberries and a reduction in cancer risk. One human study which evaluates the anthocyanin components of blueberries was carried out in 2002 by Wu et al.[8] This study comprised of 6 healthy elderly women aged between 60-70years old. The study participants were given 189g of blueberry mixed in 315ml of water after fasting overnight. The mixture contained a total anthocyanin content of 690mg and participants gave urine and blood samples after consumption at regular intervals as deemed appropriate by the study organisers. Wu et al.,[8] was particularly focused at understanding the absorption and metabolism of anthocyanins and whether they would be present in the participants in significant amounts.

evidence from this study allowed the conclusion to be made that consumption of blueberries in the amount assessed does not provide for detection in blood samples. On the other hand, the study also provided results showing that anthocyanins were detected in the urine of the participants but the quantities present were relatively low. From the data provided in Figure 1, it can be seen that the level of absorption and metabolism of these anthocyanin compounds from blueberries is variable dependent on the type of anthocyanin consumed. Figure 1 highlights the differentiation between individual anthocyanins consumed at the same time. The graph shows the total anthocyanins (ACN) consumed compared to the average amount excreted in the urine of women. It is apparent that each ACN is absorbed and metabolised in different amounts in the body and thus it is important to further understand why this occurs.

Seeram et al.,[9] explored the biological properties of blueberry phytochemicals and their ability to inhibit proliferation and induce apoptosis in a range of site specific cancers. This study concluded that with increasing concentrations of blueberry extracts, cell propagation was suppressed at all cancer sites tested. In addition, it was further identified by Seeram et al. that blueberry extracts have the positive effect of inducing cell apoptosis. Apoptosis, also known as programmed cell death refers to the natural self-destruction of cells within the body.[10] Seeram et al.,[9] identified that berry extracts increase the prevalence of cell apoptosis and that this is an excellent method of inhibiting carcinogenesis. It was also recognised that inducing apoptosis aided the removal of damaged cells prior to the abnormal proliferation of cells known as neoplasia.

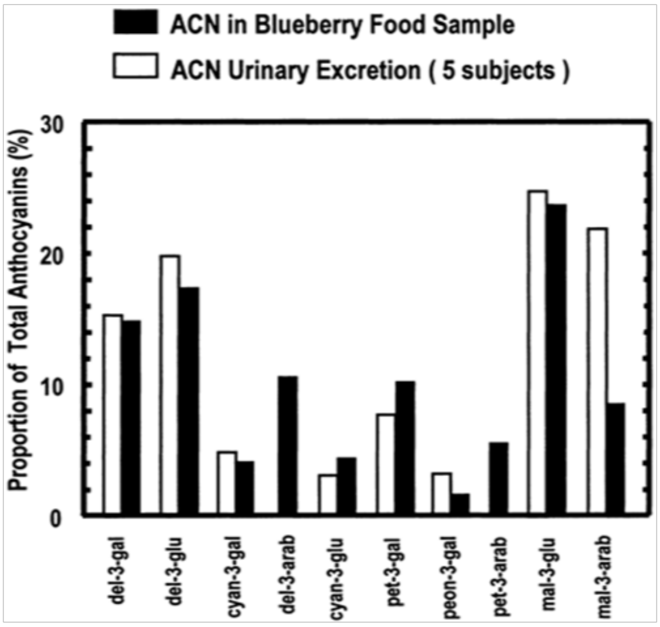

Figure 1 Absorption and metabolism of total anthocyanins by 6 healthy elderly women following consumption of 189g of blueberry.[10]

Reactive oxygen species (ROS) or free radicals have been known to scientist for their role in causing cell damage and their associated links to a number of diseases including cancer. According to past research in this area, if levels of these free radicals are increased to a point where they are in abundance in the body, then this will lead to oxidative stress. Once oxidative stress is achieved, it will lead to a cascade of physiological and biochemical lesions which have been associated with impaired metabolism.[11] This impairment of metabolism will then provide an opportunity for the oxidative damage to proteins, lipids and nucleic acids, and inevitably the subsequent occurrence of cell death.[12–14] Moreover, if there is an accumulation of oxidative damage to the cells in the body, then it is likely that there will be a greater incidence of diseases including certain cancers. Therefore, it is apparent that by consuming blueberries which are high in antioxidants, the effect of oxidative stress will not only be reduced, but may be prevented all together.

Furthermore, Stoner et al.,[4] carried out a review into a number of studies which focussed on the beneficial effects of the antioxidants in berries and berry extracts linked to ROS inhibition. In particular, this review was targeted at understanding how berry antioxidants reduce the effects linked to ROS formation and improve the antioxidants ability to scavenge ROS. Stoner et al.,[4] concluded that berry bioactives protect the body against oxidative DNA damage predominantly by the inhibition of carcinogen-induced DNA adducts and through the scavenging of ROS itself.

Table 1 compares the scavenging capacities of five different berry species in relation to four different ROS radicals. From the data it is apparent that blackberries showed the highest capacity for O_2.-, H_2O_2 and OH. inhibition. Whereas, although blueberries demonstrated a

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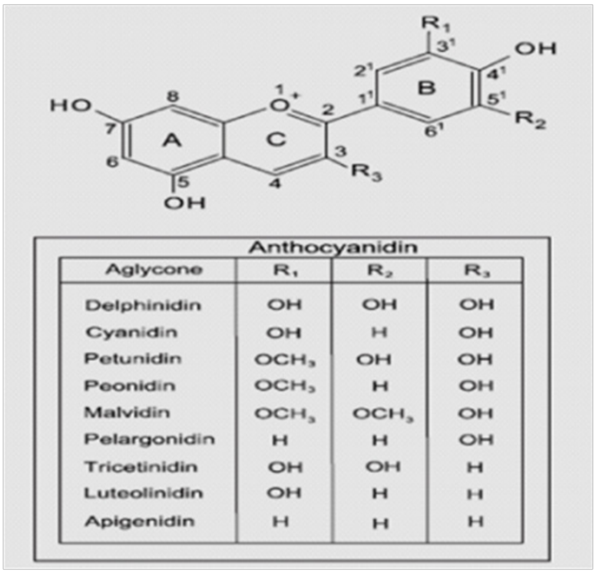
relatively strong ability to inhibit O_2.- and H_2O_2, they also showed the lowest inhibition of OH. and 'O_2. From this evidence, it can be concluded that the inhibitory capacities of different species of berries varies due to berry type and cultivar but blueberries are particularly proactive scavengers of O_2.- and H_2O_2. Additionally, it has been suggested by a number of studies that the direct scavenging of ROS by berry bioactive compounds is also greatly affected by the number of antioxidant enzymes in berries. Accumulating evidence suggests that the ability of berry bioactives to scavenge free radicals is more prominent and effective when the levels of antioxidant enzymes are higher.[4,9] However, the effectiveness of this synergistic relationship in mammals is yet to be determined and requires further research as a result. The research lead by Stoner[4] highlighted that whether these enzymes retain their functional capabilities when in the GI tract is unknown. Therefore the functionality of blueberries to impart their beneficial effects onto the body is determined in part by their absorption levels in the body, and this supports what Wu et al.[8]

Table 1 Scavenging capacities of five berry species related to four different free radicals[8]

Cultivar	% Inhibition[a]			
	$O_2^{\cdot-}$	H_2O_2	$OH^{\cdot}$	'O_2
Blackberry[b]	64.3	66.3	72.0	12.4
Blueberry	60.1	61.2	58.7	7.71
Cranberry	59.0	59.8	64.2	8.64
Raspberry	57.3	60.9	66.9	8.88
Strawberry	64.2	65.3	68.6	15.41
LDS 0.05	3.02	2.33	1.79	1.16
Significant Cultivar[c]	**	**	**	**

Shown in Figure 2 is a common anthocyanidin structure and the consequent specific aglycone forms and their respective R groups. A thesis presented by Kay[15] provided an association between a greater number of hydroxyls and a greater anthocyanin capacity. It is noteworthy, therefore, to conclude that the structural characteristics of berry anthocyanins are vitally important to the effectiveness of the antioxidants in anthocyanin rich berries such as blueberries. The thesis put forward by Kay[15] showed that the basic structural orientation of polyphenolics is a predominant factor in the antioxidant capacities in berries. Prior to the thesis by Kay,[15] there was a study by Lien et al.,[16] which demonstrated a slightly more in depth look at the physicochemical influences of structure on the antioxidant capacity of flavonoids. The evidence put forward by Lien et al.,[16] provided a strong and reliable basis on which the following conclusion was made. Lien et al.,[16] concluded that a higher antioxidant capacity of flavonoids is dependant primarily on the number of free phenolic OH groups. So an assumption can be made from the evidence put forward[15,16] that there is a positive linear relationship between increasing numbers of OH groups and an increase in the capacity of antioxidants.

This linear relationship is further supported in recent work carried out by Wang et al.[17] This study focussed on 42 different blueberry cultivars and their total antioxidant activity (AA). The study included 36 cultivars from the rabbiteye blueberry (*Vaccinium ashei*), 3 cultivars from *Vaccinium ashei* hybrids and 3 from the highbush blueberry species. The concluding results found that the rabbit eye cultivars provided the highest mean values of antioxidant activity. The results were then correlated against eight antioxidant enzymes and 2 non-enzyme components in order to identify the level of correlation. These correlations were positive in all eight cases and subsequently showed that a high antioxidant activity is linked to a high incidence of antioxidant enzymes within blueberries (Table 2).



Anthocyanidin			
Aglycone	R1	R2	R3
Delphinidin	OH	OH	OH
Cyanidin	OH	H	OH
Petunidin	OCH3	OH	OH
Peonidin	OCH3	H	OH
Malvidin	OCH3	OCH3	OH
Pelargonidin	H	H	OH
Tricetinidin	OH	OH	H
Luteolinidin	OH	H	H
Apigenidin	H	H	H

Figure 2 A common anthocyanidin structure showing the interchangeable aglycone forms and their 'R' positions.[4]

In addition to the number of free OH groups in the anthocyanin structure, there has also been convincing evidence from a number of sources which attribute high antioxidant capacities to the conjugation of the anthocyanin ring. For example; in literature from Middleton et al.,[18] Zheng & Wang,[19] there is a commonly identified link between a number of structural features and their high ability to impart effective free radical scavenging. A summary of the structural characteristics which have been identified for leading to the most successful scavenging of free radicals by flavonoids in blueberries can be seen in Table 3.

In recentyears, there have been new developments and research into the beneficial activity of a specific flavonoid, quercetin, which is found in blueberries and has been linked with a potentially positive role in cancer prevention. Spagnuolo et al.,[20] reviewed the possible use of quercetin for the sensitisation of cancer cell lines in leukaemia. The conclusions of this study suggested that quercetin could be combined with other therapeutic treatments to reduce the proliferation of leukaemia in particular. It was also found by Spagnuolo et al.,[20] that quercetin works on cancer cells by enhancing apoptosis and sensitising cell death in malignant cell lines. Therefore, if the benefits of this flavonoid receive greater investigation then it may be possible that in the future, clinicians will begin to incorporate quercetin into pre-existing cancer treatments. Thus reducing the negative effects of chemotherapy but at the same time promoting the beneficial effects of the antioxidant activity from quercetin.

In conclusion, the literature which has been reviewed would suggest that there is a positive effect of blueberry consumption on cancer risk. The current identified links between the berry bioactive components of blueberries and their proposed antioxidant, anti-carcinogenic and anti-mutagenic are well established. These links have been proven on a number of occasions in numerous studies to be vital in the scavenging of free radicals as well as reducing other potential cancer proliferation mechanisms.[4,11] There is a general agreement in this field that although blueberries contain a number of chemopreventative agents such as anthocyanins, quercetin and flavonoids, but the actual absorption of these compounds into the bloodstream is low however. It is therefore fair to conclude that further research into how absorption and metabolism can be increased is vital. Moreover, the development of blueberries with very high levels of antioxidants and anthocyanins through specific breeding of different cultivars would be a potential route for future advances in this field. Inevitably, the production of a specific blueberry species which contains high levels of chemopreventative agents which are readily available for absorption in the body would epitomise the advances which have already been made.

Table 2 Scavenging capacities of five berry species related to four different free radicals[8]

	AA[b]	ASA[c]	GSH[c]	CAT[d]	ASA-POD[d]	GR[d]	GSH-POD[d]	SOD[d]	HAR[d]	DAR[d]	GPOD[d]
AA	I										
ASA	0.94	I									
GSH	0.92	0.88	I								
CAT	0.91	0.89	0.90	I							
ASA-POD	0.90	0.84	0.88	0.89	I						
GR	0.90	0.81	0.82	0.78	0.86	I					
GSH-POD	0.90	0.85	0.87	0.87	0.88	0.82	I				
SOD	0.91	0.85	0.83	0.77	0.82	0.86	0.87	I			
DHAR	0.91	0.84	0.91	0.87	0.90	0.86	0.85	0.79	I		
MDAR	0.91	0.83	0.85	0.86	0.90	0.83	0.91	0.86	0.88	I	
G-POD	0.90	0.80	0.84	0.85	0.89	0.81	0.89	0.87	0.82	0.92	I

Table 3 Scavenging capacities of five berry species related to four different free radicals[8]

- The catechol (O-dihydroxy) group in the B ring confers great scavenging, with exception such as those described by Ratty and Das (1983), who thought it did not contribute towards lipid peroxidation in rat brain mitochondria.
- A pyrogallol (trihydroxy) group in ring B of a catechol, as in myricetin, produces even higher activity.The C2-C3 double bond of the C ring appears to increase scavenger activity because it confers stability to the phenoxy radicals produced.
- The 4-oxo (Keto double bond at position 4 of ring), especially in association with the C2-C3 double bond, increases scavenging activity by delocalizing electrons from the B ring.
- The 3-OH group on the C ring generates an extremely active scavenger, in fact, the combination of C2-C3 double bond and 4-oxo group to be the best combination on top of the catechol group.
- The 5-OH and 7-OH groups may also add scavenging potential in certain cases.

Cranberry

For a number ofyears now, research into the effect of cranberry consumption and the associated anti-cancer activity has been governed by the evidence suggesting cranberries exhibit powerful antioxidant effects. Recent research however, has begun to further understand how these antioxidants actually reduce the proliferation of cancer cells and also their role in stopping cancer cells from initially developing. Originally native to North America, the cranberry (*Vaccinium macrocarpon*) has been the centre of a number of research papers aimed at further understanding their antioxidant and anti-cancer properties.

An *in vivo* human study by Duthie et al.,[21] produced results which where contradictory to *in vitro* studies in this same field. The study by Duthie et al.,[21] assessed cranberry juice for its anthocyanin bioavailability and its capacity for antioxidant related behaviour in healthy human candidates. This study compromised of 20 healthy female adults aged between 18 and 40 who took part in a placebo intervention study in which each group of volunteers (2 groups) received either a cranberry juice drink or a placebo drink of flavoured water. The results obtained in the recent study by Duthie et al. found that in the case of the subjects who consumed the cranberry juice drink 3 times a day, the levels of anthocyanins and catechins detected in the blood and urine were zero. The participants consumed the cranberry juice in nutritionally significant doses (3 x 250ml per day) which would lead to the hypothesis that the anthocyanins in the juice were not significantly absorbed during the digestion process. However, an alternative finding from this study showed that although the anthocyanin content in blood and urine was not increased, the vitamin C levels were increased significantly. This differentiation in results between anthocyanins and vitamin C levels could potentially be attributed to the variation in absorption efficiency of vitamin C. Further conclusions were made by Duthie et al.[21] for example; the volunteers who consumed the cranberry juice did not exhibit any increase in antioxidant enzyme activity nor was there any change in their lipid profile. It was therefore concluded by Duthie et al.,[21] that the anthocyanin compounds present in cranberries in the amounts consumed in the human diet may not be as effective chemopreventative agents as previously proposed. In addition, results that show the ability of berry anthocyanins to inhibit and reduce the occurrence of carcinogenesis and oxidative stress *in vivo*, are limited in numbers.

Alternatively to *in vivo* studies, a number of *in vitro* reviews and experiments have provided us with a greater understanding to how cranberry phytochemicals specifically act towards cancer cells. An *in vitro* study by Sun et al.,[22] provided evidence for the proposed links between cranberry consumption and its relative anti-cancer characteristics. The study recognised that the cranberry has the highest total phenolic content when compared to a number of other commonly consumed fruits. As well as identifying the total phenolic content, the cranberry was also further accredited for containing the highest total antioxidant activity. Sun et al.,[22] also focussed on identifying the anti-proliferative activity of a number of common fruits. It was found that the cranberry exhibited the highest inhibitory effect when used *in vitro* on human liver cancer cells.

Figure 3 shows the results that were obtained by Sun et al.,[22] and it is evident from this data that not only do cranberries contain the highest phenolic content; the phenolic compounds are present in soluble free form. It was suggested by Sun and colleagues that the form in which phytochemicals are present in fruits is influential to their capability at targeting specific cancers. For example; it was concluded that bound phytochemicals are not digested by enzymes as effectively and as early in the digestion process. Thus, it is reasonable to expect that as cranberry phytochemicals are present in the soluble free form, their digestion and absorption occurs earlier in the digestion process. Hence, cranberries may be more effective in targeting cancers such as stomach cancer as opposed to colon cancer due to their absorption in close proximity to the site. In comparison, this claim is supported by evidence from Sun et al. that would suggest that fruits such as pineapples contain the majority of their phytochemicals in the bound form. As a result, it is interesting to note that these phytochemicals are able to travel through the stomach and small intestine without being digested. Conclusively, it is therefore fair to say that the phytochemicals in pineapple would be more effective in treating colon cancer due to their retained anti-cancer properties at the colon site. Similarly, cranberries are therefore more successful in the prevention and anti-proliferation of stomach cancer cells. Ayear prior to the study by Sun et al.,[22] Vinson et al.,[23] carried out a research project to identify the quality and quantity of free or bound forms of phenol antioxidants in a number of fruits. The study identified the free and total phenol content of a number of fruits via their ability to limit the oxidation of low density lipoproteins (LDL's). It was found that cranberries were in particular excellent sources of high quality phenol antioxidants and that they were extremely important in protecting LDL's from oxidation. Increasing evidence has been provided by a number of studies which show a positive correlation between intakes of cranberry and the resulting reduced effect on certain cancers. A study by Sun et al.,[22] showed conclusive evidence of the anti-cancer and anti-proliferative effect of cranberry consumption. In particular, the results provided by Sun et al.,[22] show a dose dependant suppression of human breast cancer cells after treatment with cranberry extracts (Figure 4). It is interesting to note the doses that were used in this study, for example; at a dose of 5mg/mL the observed rate of cancer cell inhibition was calculated at around 10%. A 30mg/mL dose provided the inhibitory result of approximately 52% on the proliferation of breast cancer cells. From the data collated by Sun and Liu, an average effective dose of 28.6mg/mL was established for the partial inhibition of human breast cancer cells (MCF-7).

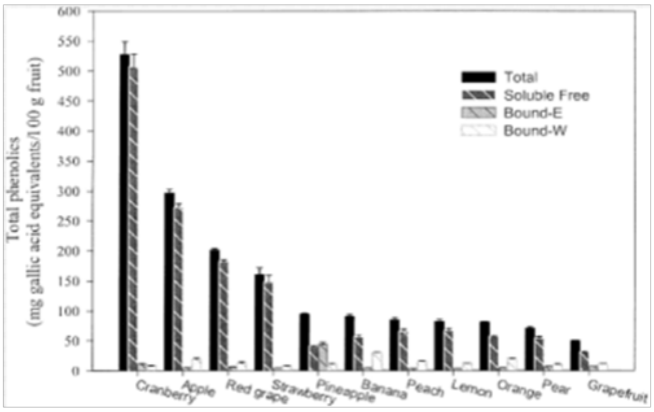


Figure 3 Total phenolic content and respective forms found in a range of common fruits.[10]

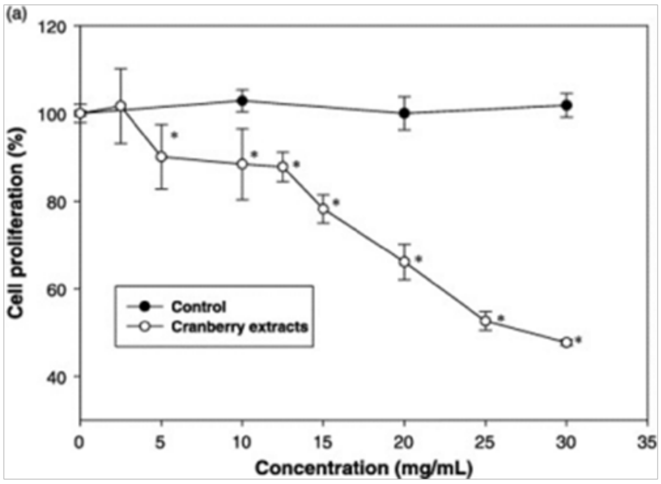


Figure 4 Dose dependant inhibition of human breast cancer cell proliferation by cranberry extracts.[10]

Research lead by Yan et al.,[24] explored the antioxidant activities of cranberry extracts by antitumor screening. This study was based around the antitumor potential of cranberry extracts to scavenge free radicals when tested on seven different tumour cell lines. Furthermore, assay-guided fractionation of whole cranberries was used by Yan et al.,[24] in order to separate individual glycosides so that a greater understanding of how phenolic compounds in cranberries act on cancer could be readily observed. Specific glycoside forms of quercetin and myricetin were isolated from the flavonoids in cranberries as well as one anthocyanin glycoside called cyanidin 3-galactoside. Yan et al.,[24] discovered that the glycoside forms of myricetin and quercetin were more active in their ability to scavenge free radicals and inhibit the oxidation of lipoproteins. It was further noted by Yan et al.,[24] that in the case of the glycoside forms, this chemopreventative effect was still apparent event at micromolar concentrations. From this study, Yan et al.,[24] concluded that it was in fact the anthocyanin cyanidin 3-galactoside which was most effective in the prevention of LDL oxidation and more prominent in its ability to scavenge free radicals when compared with the other flavonol glycosides also analysed.

Additionally, studies such as that by Shih et al.,[25] show a definite relationship between specific cancers and the effect of anthocyanins found in cranberries. This study examines the effect of anthocyanins on gastric cancer, specifically human gastric adenocarcinoma (GAC). The study was aimed at gaining an understanding as to whether or not anthocyanins could be used for the prevention of the GAC carcinogenesis process. The conclusion of this study on nine kinds of anthocyanins and anthocyanidins was that malvidin, an anthocyanin, acted more effectively in the anti-proliferation of gastric adenocarcinoma cells. This study was also the first to identify that an acidic environment, such as that found in the stomach, contributes significantly to the stabilisation of anthocyanins.

Twoyears later, Shih et al.,[25] published another study linking anthocyanins to the activation of phase II enzymes (antioxidant and detoxifying enzymes) and subsequently the detoxification of carcinogens present in the body. The study assessed the efficiency of anthocyanins to activate phase II antioxidant and detoxifying enzymes in hepatocytes. The results of the experiment allowed the conclusion to be made that four specific anthocyanins corresponded to an increase in the activation of phase II enzymes. The four anthocyanins accredited with this increase in activation were malvidin, cyanidin, kuromanin and delphinidin. Based on these conclusions, it is acceptable to state that the chemopreventative benefits of anthocyanins are also achieved through the activation of phase II enzymes and thus consumption of cranberries which are high in anthocyanins can greatly reduce the risk of carcinogenesis.

A summary of the literature behind the effect of cranberry consumption on cancer risk has been reviewed here. The review has recognised a number of studies for providing strong evidence towards the anti-cancer properties of cranberries, as well as the identification of a number of chemopreventative mechanisms.[22,23,26] Cranberries have been proven useful for the effective prevention of cancer proliferation and progression both *in vitro* and *in vivo* (mainly animal studies). However, epidemiological studies involving human participants have failed to provide consistent and clear evidence for the associated links of anthocyanins and their proposed anti-cancer properties. On the other hand, a number of studies have recognised the mechanisms by which phytochemicals act in the prevention and suppression of cancer.[27]

The most common chemopreventative methods acknowledged in recent studies are as follow: induction of pro-apoptic effects, activation of phase II enzymes, anti-cell proliferation and their high aptitude for scavenging ROS. Further research is needed in order to explore in greater detail why the constituents of cranberries linked to cancer prevention are not quantifiable in humans. Perhaps the answers to this challenge may lie with how humans absorb, metabolise and process these compounds in the body, or it could be to do with the food matrix composition which ultimately determines the effectiveness of these compounds when in our body. Whatever the reasoning is behind this problem, it needs to be identified as soon as possible in order for humans to gain the most from the chemopreventative agents of cranberries in the future.

Strawberry

For manyyears now strawberries have been consumed as a regular part of the human diet, especially during summer months when they are in abundance and of particularly high quality but yet relatively low in cost. The strawberry (*Fragaria xananassa*) is not classed as a botanical berry as such, but due to its popularity and regularity of consumption amongst the general population it is considered a berry. A number of studies have elucidated to the potential of the strawberry to provide beneficial effects towards cancer prevention and inhibition. Furthermore, there are a wide variety of different strawberry genotypes which all differ in their nutritional composition, but overall it is generally accepted that all the cultivars of strawberries are on average high in antioxidants phytochemicals.[24]

One *in vivo* study by Chung et al.,[28] focused on identifying whether the consumption of whole strawberries could show an ability to inhibit the endogenous development of N-nitrosodimethylamine (NDMA), a known genotoxic carcinogen. The study encompassed 40 healthy participants (23 male and 17 female) who were all non-smokers and aged between 17 and 30years old. Chung et al. devised this *in vivo* study in order to understand the chemopreventative effect that strawberries could possibly have on the formation of NDMA. The study aimed at combining the consumption of whole strawberries into a high amine diet which contained a number of nitrosatable precursors with nitrate. It was a four day trial in which the first three days involved following a controlled diet which excluded the consumption of high nitrate, NDMA and various other compounds from the diet. The fourth day of the trial was an experimental day in which participants provided a 5ml sample of saliva twohours after eating dinner and an 18hour urine collection sample. These samples where then tested and Chung et al. published a set of results showing that by incorporating the consumption of whole strawberries into a high amine diet, there can be a significant decline in the excretion of NDMA, and thus consequently a reduction in cancer risk.

Alternatively, a recent *in vitro* study by Zhang et al.,[29] was aimed at separating and identifying the phenolic compounds in strawberries and understanding their anti-proliferative and antioxidant interactions when used on human cancer cells. Zhang et al.,[29] identified 10 pure compounds in strawberries and then investigated the extent to which these compounds were able to inhibit the proliferation of human oral, prostate and colon cancer cells. Comparisons of the ten compounds and their inhibitory effects on colon cancer cell proliferation can be seen in Figure 5. It is evident from Figure 5,[29] that the pure compounds analysed showed differing levels of effectiveness on the propagation of colon cancer cells and the reasons for this may be due to different absorption and metabolism efficiencies between compounds.

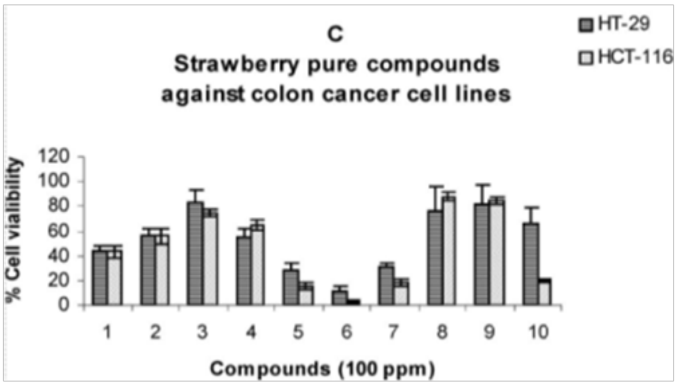


Figure 5 Inhibition of colon cancer cell line proliferation by pure compounds extracted from strawberry.[38]

A study of six healthy adults (3 male and 3 females) analysed the bioavailability of the anthocyanins present in strawberries in order to identify the efficiency of the absorption and metabolism process in the body.[30] The participants avoided products high in polyphenols for 24hours prior to and during the experiment so that reliable results could be obtained. After the 24hour overnight fast, the volunteers consumed a breakfast consisting of 200g strawberries, 15g sugar, 10g butter and 60g bread. In addition, urine samples were collected at appropriate intervals both previous to the study as well as after consumption of the breakfast. Following urinary analysis, Felgines et al.,[30] concluded that the anthocyanins in strawberries are more bio-available when they are in the glucuro- and sulfo- conjugated forms. Furthermore, the metabolite mono-glucuronide of pelargonidin was also found to be the main anthocyanin detected in the urine samples and thus indicates that its absorption and metabolism is the most efficient in the body. Possible assumptions can therefore be made based on these findings, that the anthocyanin, pelargonidin in strawberries, may have the greatest positive effects on cancer inhibition and prevention due to it having a higher bioavailability in the body.

Strawberries consist of a vast number of compounds that have been investigated for their potential to act as chemopreventative agents in cancer formation. One compound present in strawberries which has received a great deal of research in recentyears is ellagic acid. Ellagic acid is a phenolic acid which is of particular interest in cancer prevention due to its associated links with preventing, inhibiting and reducing the mechanisms of cancer formation.[26] A study as early as 1991 identified the potential for ellagic acid (EA) to act as a chemopreventative agent, particularly in oesophageal cancer. The study[5] evaluated the inhibitory effect of EA on oesophageal tumorigenesis in rats after treatment with the carcinogen N-nitrosobenzylmethylamine (NBMA) The rats were split into two groups, both being fed on a controlled diet, but one group receiving NBMA and the other receiving NBMA + EA.

It is apparent from Figure 6,[31] that ellagic acid was significantly effective in reducing the multiplication of tumours in the rats induced with NBMA. More importantly this study also indicates that ellagic acid is more effective when not working synergistically with the CRA. It is worth noting therefore, that this negative synergism is for that reason undesired and by consuming both EA and CRA together may negatively impact on the inhibitory effects on cancer which have been attributed to ellagic acid.[31] Further findings of this study quantified the actual percentage inhibition exhibited by ellagic acid on NBMA induced oesophageal papillomas to be 60% on average. This number is significant in the case of the rats tested but whether this number is transferrable when in humans would warrant further *in vivo* human studies. The digestion, absorption and metabolism methods and rates in rats and humans are different and as such the links to potential cancer benefits of ellagic acid from strawberries on human health needs further investigation.

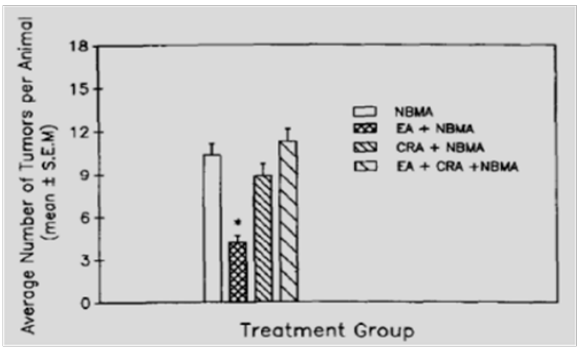


Figure 6 Multiplication of tumours in rats after treatment with various combinations of NBMA, ellagic acid and another chemopreventative agent 13-cis-retinoic acid (CRA).[5]

Literature surrounding the topic of strawberry consumption and cancer risk has provided a number of mechanisms by which the compounds in strawberries work on preventing cancer. However, the majority of work and findings in this field have been the results of either *in vitro* tests or *in vivo* animal tests, as opposed to human studies.[29,31] Future research needs to further investigate the effect of strawberry on cancer i*n vivo* human studies in particular. Some possible routes for future research opportunities may include analysing the effect of strawberry compounds on specified mechanisms of cancer promotion, i.e. how strawberry components can reduce oxidative damage and reduce cell proliferation. Not only are additional human studies vital, but they will hopefully lead to a greater understanding of the bioavailability of strawberry chemopreventative compounds.[32]

Furthermore, future research will hopefully identify a number of techniques by which individuals can increase the absorption of these chemopreventative compounds in the body, thus increasing the associated benefits on cancer. Overall, the interest of strawberry consumption and cancer risk has grown in recentyears and it is undoubted that further investigations into how we can maximise these positive natural compounds warrants the time and effort associated with human studies.[33–35]

Conclusion

Literature surrounding the topic of berry consumption and its associated effect on cancer risk has been reviewed here. It is important that current research is collated, understood and then used to identify areas in which further research is worthy of investigation. Currently, there is a general consensus amongst academics in this field that consuming berries, particularly ones high in anthocyanins, have positive associations with reducing cancer risk.[2–4] However, there have been several research studies that failed to identify the positive effects of berry consumption and cancer risk when assessed through *in vivo* human studies.[21] Furthermore, mechanisms such as reducing oxidative stress, inducing apoptosis and scavenging free radicals have all been attributed to being part of the chemopreventative features of berries.[9,4] Although the basis of cancer prevention and inhibition is understood, there are still potential areas for future research. Some prospective areas that warrant further investigation include; research into how berry compounds can be incorporated into effective methods for the treatment of cancer, the development of specific berries that contain very high anthocyanin content, perhaps through breeding and genetic modification. Finally, in order for the chemopreventative properties of berries to be harnessed and used effectively in the treatment and prevention of cancer, there is a drastic need for human trials. Berries have been an integral part of the human diet for thousands of years and it is now time that we, as humans, understand their full potential to prevent and treat chronic diseases such as cancer.[36–38]

Research strategy

The information obtained in this review is principally taken from primary sources such as journals, and it is thus acceptable to recognise any conclusions discussed from primary sources as reliable. Some journals which have been reviewed here include:

i. Journal of Nutrition
ii. Journal of Agricultural and Food Chemistry
iii. Journal of Food Chemistry
iv. The American Journal of Medicine
v. European Journal of Nutrition
vi. Journal of Food and Chemical Toxicology

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Previous to beginning this review into the effect of berry consumption on cancer risk, I developed a plan which allowed me to separate this topic area into three areas each having sub-topics of their own. Background research into three main berries (Blueberry, Cranberry and Strawberry) was carried out through the exploration of databases containing relevant journal articles such as; Web of Science, Medline and Scopus. These databases contained thousands of topic specific articles and journals which provided an understanding of the existing research, current viewpoints and the proposed future requirements within the field. Once a general understanding of the topic area had been established, it was then important to collate a good number of journals in which the most relevant and topic specifc articles were present. This allowed for the most accurate and specific information and it was on this information that this literature review was based on.

The list above shows a number of journals which were investigated thoroughly due to their specificity to the topic area and thus allowed for the most up to date review of past and present literature. Once the most relevant journals had been identified, searching within them included the use of their search engines and the input of specific key words that would ultimately provide the most topic specific articles and research papers. Finally, once sufficient numbers of articles providing accurate and reliable data had been gathered for each berry, it was then time to cross-examine the different points of view with the aim of summarising current agreements, trends and disputes within the field.

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Conflict of interest

Author declares that there is no conflict of interest.

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