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Polyphenols, glucosinolates, dietary fibre and colon cancer: Understanding the potential of specific types of fruit and vegetables to reduce bowel cancer progression

Noura Eid, Gemma Walton, Adele Costabile, Gunter G.C. Kuhnle and Jeremy P.E. Spencer*
School of Chemistry, Food and Pharmacy, Department of Food and Nutritional Sciences, University of Reading, Reading, UK

Abstract. Colorectal cancer is the third most prevalent cancer worldwide and the most common diet-related cancer, influenced by diets rich in red meat, low in plant foods and high in saturated fats. Observational studies have shown that fruit and vegetable intake may reduce colorectal cancer risks, although the precise bioactive components remain unclear. This review will outline the evidence for the role of polyphenols, glucosinolates and fibres against cancer progression in the gastrointestinal tract. Those bioactive compounds are considered protective agents against colon cancer, with evidence taken from epidemiological, human clinical, animal and *in vitro* studies. Various mechanisms of action have been postulated, such as the potential of polyphenols and glucosinolates to inhibit cancer cell growth and the actions of insoluble fibres as prebiotics and the evidence for these actions are detailed within. In addition, recent evidence suggests that polyphenols also have the potential to shift the gut ecology in a beneficial manner. Such actions of both fibre and polyphenols in the gastrointestinal tract and through interaction with gut epithelial cells may act in an additive manner to help explain why certain fruits and vegetables, but not all, act to differing extents to inhibit cancer incidence and progression. Indeed, a focus on the individual actions of such fruit and vegetable components, in particular polyphenols, glucosinolates and fibres is necessary to help explain which components are active in reducing gastrointestinal cancer risk.

Keywords: Polyphenol, glucosinolate, fibre, fruit and vegetables, cancer, gut microbiota

1. Introduction

Cancer is one of the most widespread chronic diseases and one that is increasing in incidence in developing countries as a result of poor lifestyle choices [1–3]. Cancer is characterised by uncontrolled cellular growth that occurs as a consequence of alterations to, or the damage of genetic material [4] and it has been predicted that around 30 to 40% of various cancers may be modifiable by diet [5] in particular colorectal (CRC) [6, 7]. CRC is the 3rd most prevalent form of cancer (after lung and breast) and, as such, represents a major public health risk [3]. Colon carcinogenesis develops through a "multi-step" process, which starts with a period of abnormal epithelial proliferation, called 'hyperplasia', followed by a period of epithelial 'dysplasia' during which abnormal cell development occurs [8]. The abnormal colonocytes that result may lead to the formation of a "polyp" or "adenoma" at diverse sites along the surface of the colon and whilst these pedunculated, or sometimes sessile structures, are largely benign and asymptomatic, they may transform, over time, into malignant polyps marking the later stages of cancer development [9].

Various factors are associated with colon cancer development [10, 11], including genetic susceptibility

*Corresponding author: Jeremy P.E. Spencer, School of Chemistry, Food and Pharmacy, Department of Food and Nutritional Sciences, University of Reading, Reading RG6 6AP, UK. E-mail: j.p.e.spencer@reading.ac.uk.

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[12], gender [13], age [14, 15], socioeconomic status [16], race [17], excessive alcohol intake [18], smoking [19] and diet [6, 7, 20–25]. The sensitivity of the GI tract to diet in relation to cancer risk derives predominantly from the fact that the gut epithelium encounters, and interacts with, a vast array of nutrient and non-nutrient compounds, beneficial and detrimental, introduced through the diet. Dietary habits that correlate with the promotion of carcinogenesis include the intake of high amounts of haem iron present in processed and red meat [26–28], high fat consumption [29], and a low intake of plant-derived foods [30–32]. Amongst these, plant foods, which include, fruits and vegetables have also received much interest with regards to their anti-cancer potential [24, 32–38] and studies have identified that both fibres [30, 39] and phytochemicals [40–42] act as mediating protective components. This review will consider the latest evidence for the actions of fruit and vegetable intake and their constituent phytochemicals and fibres on cancer incidence and/or carcinogenesis in the GI tract. We will give an overview of the mechanisms by which constituent phytochemicals and fibres act to exert such beneficial activity, derived through observational data, animal models and *in vitro* work.

1.1. Diet and colorectal cancer

Colorectal cancer is the archetypal example of a diet-related cancer [3, 43, 44]. The classic 'western diet', rich in red meat, low in plant foods and high in saturated fat, is believed to play a major role in GI health and in the development of GI tract cancer [43]. In support of this, the adoption of a more 'Western diet' by Japanese migrants to the US and the UK has resulted in an increased incidence of CRC in this population [44]. Several hypotheses have been suggested to explain the association between meat consumption and CRC [26–28], including the high temperature formation of heterocyclic amines [27, 45], although this does not sufficiently explain the differences observed between red and white meat. An alternative hypothesis is the level of free [44] or haem bound iron, which itself genotoxic [46], but can also promote the formation of endogenous nitroso compounds that can result in the formation of mutagenic DNA adducts [47]. High meat consumption also displaces low-calorie dense plant foods, which may impact on cancer development in two ways. Firstly, red meat consumption will contribute to saturated fat intake, a factor known to increase CRC risk through the actions of fatty acids and secondary bile acids on the colonic mucosa [29]. Secondly, high red meat intake will potentially displace the intake of less calorie dense, phytochemicals and fibre containing plant foods, which have been postulated to possess cancer protective properties against epithelial cancer development in human [48, 49], animal [50, 51] and cell studies [52, 53]. Despite such data, the effects of plant foods on cancer development may be confounded by other dietary and lifestyle factors, with their intake closely associated with higher physical activity, higher mineral and vitamin intake, lower alcohol consumption, abstinence from cigarette smoking [16, 54–56], and human health factors, which include obesity [16, 57, 58] and aging [59–61].

There is an increasing interest in the role the gut microbiota play in modifying CRC risk [11]. The human gut harbours large numbers of bacterial species, each with unique metabolic capabilities [62, 63] and modification of these by non-digestible carbohydrates and fibres has been suggested to reduce CRC development indirectly [62, 64, 65]. Complex plant-derived polysaccharides that escape digestion in the upper gut, undergo saccharolytic metabolism in the large intestine, liberating short-chain fatty acids [65] and selectively affect the growth of the colonic microbiota, such as, bifidobacteria and lactobacilli that may favourably influence CRC risks, by the production of its metabolites [66], that were found to exert various anti-cancer effects [67]. Thus, research has been directed towards the consumption of plant foods, in particular fruit and vegetable intake, to reduce risks of CRC, however observational studies remain inconclusive (Table 1).

1.2. Fruit and vegetable intake and colon cancer

Fruit and vegetable consumption makes up an important part of the human diet and such foods deliver varying amounts of phytochemicals and fibre. Many fruits and vegetables are rich in an array of potentially bioactive components, including fibre [68], vitamin C [69], vitamin E [70], selenium [71], carotenoids [72], glucosinolates [73], and polyphenols (including phenolic acids, hydroxycinnamates and flavonoids) [41, 74–81], which have been linked with chemopreventive and anti-carcinogenic actions [82–84]. In 1997, the World Cancer Research Fund (WCRF) classified the evidence for a protective effect of dietary fibres in fruits and vegetables for different types of cancer,

Table 1
Diet & colorectal cancer

Trial	Duration	Type of food	Main results
Women from Nurses' Health Study and men from the Health Professionals Follow-Up Study [94]	10 year follow up for females and 4 years follow up for males	Fruits and vegetables	No association with reducing risks of colorectal cancers
Nested case-control study from the Alpha-Tocopherol Beta-Carotene Study cohort of male smokers [56]	5 to 8 years follow up	The main source of folate, was mostly green leafy vegetables	No association was observed between vegetable rich in folate and colorectal cancers
A case-control study [55]	3 years duration	Smoking and alcohol	Alcohol and smoking was associated with increasing the risks of colorectal cancer
The Adventists' Health Study [243]	6 years follow up	Salad and green vegetables	An inverse association between "salad" and "green vegetables" with colorectal cancer was seen
In the European Prospective Investigation into Cancer and Nutrition (EPIC), 2009 [32]	8 years follow up	Fruits and vegetables	An inverse association was seen
Cohort prospective study in Los Angeles, California [33]	8 years follow up	Fruits and vegetables, and fruits alone	An inverse association with colon cancer
Cancer prevention study II [34]	6 years follow up	Vegetables and grains	An inverse association was seen with vegetables and grains
The European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford) [235]	6 years follow up	Vegetarians	
The multiethnic Cohort study [244]	3 years follow up	Fruits, vegetable and grains	Association regarding fruits and colon cancer risk reduction was seen in men only
A prospective investigation on vegetarians and non vegetarians in the UK [245]	17 years follow up	Vegetarians and non-vegetarians	Vegetarians had reduced risks of colorectal cancers. It was also seen with fruits consumption, but not after adjusting alcohol and smoking
Population-based prospective mammography study of Swedish women [24]	9.6 years follow up	Fruits and vegetables	An inverse association with colon cancer and CRC, but not with rectal cancer whereas the association was much stronger with fruits, in particularly to rectal cancers.
The Western Australian Bowel Health Study [200]	2 years follow up	Fruits and vegetables; vegetable intake; fruits intakes	With regards to the proximal colon cancer, no association was observed, whereas distal colon cancer was reduced with apple and yellow vegetable intakes
Pooling Project of Prospective Studies of Diet and Cancer [246]	6 to 20 years	Fruits and vegetables	Reductions in distal colon cancer risks was seen with in comparison with other sites

including CRC, as "convincing", whereas in 2007, this was downgraded to "probable" [85]. Furthermore, global cancer statistics appear to indicate that fruit and vegetable consumption could reduce the incidence of disease by between 50 to 80 % [3, 86, 87], with several cohort and case-control studies indicating a potential reduction in CRC incidence [24, 32–38]. The consumption of fruits and vegetables is advised by the World Health Organization [88], the National Cancer Institute [89], the World Cancer Research Fund

(WCRF) [90] and the USDA (U.S. Department of Human Services, 2005) to be 3 servings (Austria), 5 servings (United Kingdom) or 9 servings (Greece), daily [91].

However, in 2012, the EPIC consortium indicated a strong relationship between the consumption of foods rich in fibre and phytochemicals, such as fruits, vegetables and cereals, and a reduction in the risk of CRC in non-smokers [92] and highly physical active participants [93]. In addition, other studies have failed to show such a relationship between fruit and vegetable consumption and CRC incidence [56, 94, 95]. This controversy in the literature is likely to reside in the fact that all fruits and vegetables are not equivalent in their ability to exert anti-cancer effects in humans, largely due to their differing content of both phytochemicals and/or fibre. As such, observational data calculated using general fruit and vegetable intake would be expected to yield only a small protective effect, as a majority of 'inactive' fruits and vegetables (with respect to cancer prevention) would 'dilute' the efficacy of the more active ones. Indeed, in studies concentrating on more specific fruit and vegetable intake, such as that of *Brassica* vegetables (leafy green vegetables, brussels sprouts, cabbage, and string beans), data have been more promising with regards to anti-cancer effects [96], probably due to their fibre, polyphenol and isothiocyanates content [97, 98]. As such, the population level approach to advising the intake of 5 portions of unspecified fruits and vegetable to prevent cancer is likely flawed. Rather, using evidence from intervention studies and well designed *in vivo* and *in vitro* investigations, one should strive to encourage the intake of 5 portions of the most effective cancer preventative fruits and vegetables, most likely those containing the highest levels of polyphenols and/or fibre. As previous epidemiological data does not take account of this, it is likely that previous calculations of the potency of fruits and vegetables to prevent CRC risk are underestimated.

As suggested above, the benefits of fruit and vegetable consumption against CRC development remains unclear, especially with regards to the following: 1) Are all fruits and vegetables equal in inducing cancer protection, and if not then which are the most potent; 2) what are the precise causal agents within fruits and vegetables that mediate cancer benefits, which exert the most powerful effects and via what mechanisms; 3) are direct interactions with the GI tract epithelium necessary for anti-cancer actions, or can individual components act indirectly via modulation of the gut microbiota. The remaining part of this review will strive to shed light on these questions and will strive to determine whether a broad, non-specific approach to fruit and vegetable intake at the population level is the most effective strategy for preventing CRC, or whether we should be attempting to target the increased intake of the most effective fruits and vegetables to effectively manage cancer prevention by diet.

2. Polyphenols and colon cancer prevention

2.1. Structure and metabolism

Phenolic compounds are ubiquitous in the plant kingdom acting as catalysts for photosynthesis [99] and are involved in protecting plants from pathogens, harmful insects' effects and oxidative damage from UV and sunlight [100]. Polyphenols arise in plants from two synthetic pathways "shikimate pathway and the acetate pathway" [81, 101] and can be subdivided into several subclasses depending on chemical structures [102], which include, flavonoid and non-flavonoid compounds. Flavonoids, a major class of phenolics in the human diet and can be divided into six major subgroups (Fig. 1) [103]: flavonols (quercetin and kaempferol), found mostly in onions, leeks, broccoli and blueberries; flavones (luteolin and apigenin) found mainly in celery and parsley; flavanones (hesperetin and naringenin) are rich in oranges and grapefruits respectively; isoflavones, found mainly in soya and legumes; flavanols (catechin and proanthocyanidins) are rich in chocolate and tea, and (epigallocatechin and epigallocatechin gallate) are mainly in grapes; proanthocyanidins are rich in peaches, pears, apples and berries; anthocyanins (cyanidin, petunidin, pelargonidin and malvidin). Phenolic acids, on the other hand consist of the benzoic derivatives (hydroxybenzoic acids, gallic acids and tannins) and are found widely in fruits and vegetables as well as nuts, whereas cinnamic derivatives (coumaric, ferulic, sinapic caffeic and chlorogenic acid) are found at great concentrations in coffee [81, 101].

The intake of flavonoids in the human diet has been the subject of much discussion and has been estimated to be 2 mg/daily in the US and UK in 1976 [104], although more recently this has been increased to between 1 to 20 mg/daily [105]. Several factors affect polyphenol intake, including harvest time, UV exposure, ripening time and storage [101, 106, 107], in

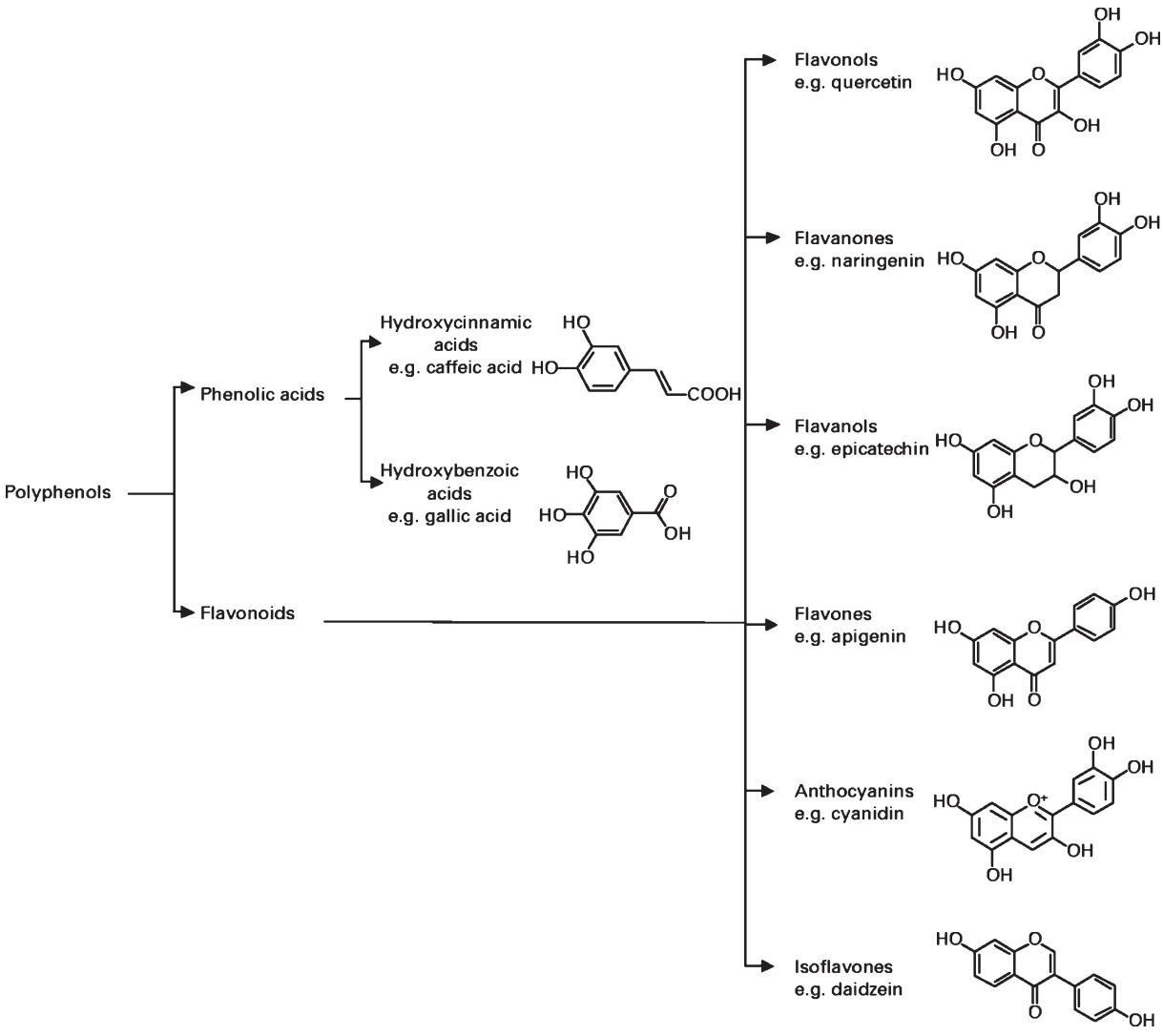

Fig. 1. Polyphenol classification.

addition to the intake of fruits and vegetables a person consumes. With regards to the latter, the complexity associated with assessing population intakes may lead to under-or over-estimates of overall intake [108]. The bioavailability and metabolism of those compounds varies according to its structure [109–111]. The colon is considered the 'primary' site of polyphenol exposure in the human body, as only between 10 and 40% of polyphenols are absorbed in the small intestine, with the majority passing to the large intestine [112–114] where they may be metabolised by the colonic microbiota [113] leading to potential protective effects [100, 115, 116].

2.2. *In vivo and in vitro studies*

Observational data have indicated that flavanol [117] isoflavone, flavonol and anthocyanin [118], procyanidin [119] and flavanone [42] intake are associated with an reduction in CRC risk. Furthermore, a significant reduction in cancer recurrence in resected colon cancer patients has been observed after consumption of a mixture of apigenin and epigallocatechin [120]. *In vivo* studies measuring cancer protection have been conducted in animals [121] and in humans, although data with regards the latter remain inconclusive (Table 2), perhaps dues to low levels of intake

Table 2
Polyphenols and colorectal cancer

Trial	Duration	Type of food	Main results
Iowa Women's health study [117]	12 years follow up	Catechin from fruits and from tea	Catechin from fruits was associated with lowering risks of the upper digestive tract. Whereas catechin from tea was associated with lowering risks of rectal cancers
Italian case-control study [118]	4 years follow up	a. Isoflavones, anthocyanidins, flavones and flavonols b. flavan-3-ols, flavanones and total flavonoids	With a) there was a significant correlation with reducing colon cancer, whereas with b) there was not
A national prospective case-control study in Scotland [119]	1 year before diagnosis	Flavonols, quercetin, catechin, and epicatechin from fruit and vegetable or from other flavonoid sources.	The significant dose-dependent reductions in colorectal cancer risk that were associated
Women from Nurses' Health Study and men from the Health Professionals Follow-Up Study [247]	10 years follow up	Quercetin, Kaempferol Myricetin from tea, onions, apples, broccoli and tomatoes	In this study there was no association between flavonoid intakes and colorectal cancers
A prospective study on patients with a history of resected colon cancer and others with polypectomized patients [120]	3 to 4 years follow up	flavonoid mixture (20 mg apigenin and 20 mg epigallocatechin-gallate daily)	Patients with resected colon cancer where treated with flavonoids, and no occurrence of cancer was seen
Case-control study [42]	10 years follow up	a. Tea flavonoids; flavonol, procyanidin and flavon-3-ol b. Non-tea flavonoids; quercetin c. Dietary flavonoids; in fruits and vegetable	The only association with lowering risks of colon cancer was seen with non-tea drinkers
Study cohort of the Alpha-Tocopherol, Beta-Carotene Cancer prevention (ATBC) in Finland [248]	6.1 years follow up	Flavonol and flavones intake	There was no association with reducing risks of colon cancer
Prospective study from the Women's health Study [16]	11.5 years follow up	• Total flavonoids • Individual flavonols (quercetin, kaempferol, and myricetin) and flavones (apigenin and luteolin) • Flavonoid-rich foods (tea, apple, broccoli, onion, and tofu)	With a), b) and c) there was no association with reducing risks of colorectal cancers
A human trial on patients with advanced stage of colon cancer [212]	Received every 14 days for 4 weeks	Flavopiridol, a synthetic flavone that inhibits cell cycle progression	Treatment with Flavopiridol did not show any changes in the colon cancer proliferation
A human trial on Familial adenomatous polyposis (FAP) [249]	6 month treatment (3 times per day)	Curcumin and quercetin	Treatments have successfully reduced the number of adenomas in colon
The Colorectal Adenoma Study in Tokyo (CAST) [250]	1 year duration	Isoflavones	There was a significant association in reducing colorectal cancer risks in both Japanese male and females

relative to those used *in vitro* experiments [122]. Human trials with respect to colorectal cancer have predominantly been designed to assess the impact of fruits and vegetables on colon health by assessment of transit time, beneficial bacterial growth and the presence of anti-cancer agents, rather than by assessment if specific cancer endpoints. Unlike those trials assessing cardiovascular risk, where blood pressure, vascular function and LDL cholesterol may be assessed non-evasively, assessment of cancer reduction in the GI tract requires surgical intervention due to a distinct lack of prognostic biomarkers of cancer status. As such, most work in this area has been conducted using animal models, which have been largely positive in terms of detecting significant inhibition of cancer development afforded to ferulic acid, quercetin, resveratrol and anthocyanins [50, 123–129]. However, caution with respect to the dose of polyphenol exposure should be expressed here with some animal trials indicating an increase in tumour lesions rather than decreasing, when polyphenols, such as quercetin were used at high doses [130, 131]. Indeed, *in vitro* data suggest that specific polyphenols are less cytotoxic than others and dose dependency has been observed with anthocyanins [132, 133].

In support of these animal studies, a large number of *in vitro* studies have indicated that the effects of polyphenol rich extracts and individual polyphenols induce apoptosis of gut epithelial adenocarcinoma cells [52, 122, 134–144], thus suggesting that these compounds may reduce tumour size in the large gut. These data are supported by other studies that indicate many specific apoptotic markers are induced following exposure of colon cancer cells to polyphenols [138, 139, 145, 146]. Alternatively, they have been shown to inhibit the proliferation of cancer cells [52], which may be mediated by a number of mechanisms, including their potential to inhibit the cell cycle to interfere with cell signalling [138, 147] and down regulate specific MAPK kinase and transcription factors [10, 52, 148–150]. This is significant as several members of the MAPK signalling pathway, including ERK and JNK are involved in cellular apoptosis and proliferation, as well as tumour invasion and metastasis [151]. The inhibitory effects of polyphenols against colon cancer may also be related to their potential to influence inflammatory status [152] observed with cocoa polyphenols, that have inhibited inflammatory-induced colon cancer in rat models, via modulating pro-inflammatory enzymes, such as, cyclo-oxygenase-2 (COX-2) and NO synthase (iNOS) [153].

With regards to epidemiological observations, there is still a lack of evidence to link polyphenols found in specific fruits and vegetables to a reduction in colorectal cancer risk. However, evidence from studies with tea flavanols, onions and apples [119], anthocyanidins [118] and isoflavones in soya [154] have all provided data suggesting that these polyphenol-rich foods are effective. In addition, experiments with quercetin and curcumin have been shown to be effective in treating patients suffering from colon cancer [64] and apigenin/epigallocatechin-gallate are effective in those with a history of polypectomized tumours [120], similar to that observed *in vitro* work [52]. These studies highlight that flavonoids, flavonoid rich foods and/or other polyphenols may act as effective anti-cancer agents to reduce the adenomas and the recurrence of cancer [64, 120].

2.3. Impact on the microbiota

The specific actions of polyphenols on the gut microbiota have been initially focussed on its metabolites actions [155] their antimicrobial effects towards pathogenic bacteria [156, 157], and their potential to reduce intestinal inflammation [158, 159]. However, more recently, there has been increasing focus on the potential to specifically modify the growth of favourable gut bacteria to achieve 'healthy' gut ecology [64, 115, 160–162]. For example, it has been demonstrated that polyphenols rich foods and polyphenol extracts may exhibit prebiotic effects in human trials (Table 3) and in pH-controlled batch culture experiments [155]. The potential to shift the gut ecology and increasing specific bacterial species, such as beneficial bacteria and butyrate-producing microbes might have the potential to reduce colorectal cancer risk [163]. With regards to human studies, high cocoa-flavanol intervention (494 mg/day) has been shown to induce a significant increase in both bifidobacteria and lactobacilli and a decrease in clostridia species [164]. These data are in agreement with previous *in vitro* data, which also indicated the ability of flavanols to positively shift the microbiota [155]. Whole grain breakfast cereals have also been shown to induce a positive influence of microbial growth in human volunteers, with ferulic acid postulated to be involved in these effects in addition to fibres [165].

The concept that polyphenols might beneficially modify the microbiota towards a state that is anti-

Table 3
Polyphenols and the gut microbiota

Trial	Duration	Type of food	Main results
A randomized, controlled, double-blind, crossover intervention study [164]	4 weeks treatment	Cocoa-derived flavanols	Significant increase in bifidobacteria and lactobacilli, and a decrease in clostridia
A randomized, controlled, double-blind, crossover intervention study [174]	6 weeks treatment	Wild blueberry drink	Significant increase in total Eubacterium and Bifidobacteria, whereas lactobacilli have increased by the treatment and the placebo
A randomized, controlled, double-blind, crossover intervention study [65]	4 weeks treatment	Red wine	Significant increase in bifidobacteria, enterecocci, prevotella, Bacteroides, Bacteroides uniformis, and Blautia coccoides-Eubacterium rectale

carcinogenic is related to two factors. Firstly, the reduced growth of certain species of E. Coli and some clostridium species will prevent carcinogen production (via bacterial β-glucuronidase and β-nitroreductase activity) in the presence of amines, bile acids and following high consumption of meat [166]. As such, certain types of clostridium species have been implicated in the progression of colon cancer and inflammatory bowel syndrome [167], whereas other types of colonic bacteria, such as bifidobacteria and lactobacilli are believed to be protective due to their low activity of mutagen generating enzymes [166]. The beneficial shift in microbial levels will also be accompanied by increased bacterial end-products, such as phenolic acids [100]. Butyrate, which is known to be involved in reducing cell apoptosis and differentiation [67, 168–172] and mainly produced by Rosburia faeces and *Eubacterium rectale* group [163, 173], was seen to be increased with flavanol supplementation [164].

In addition, it is possible that microbial metabolites of polyphenols may act directly on gut epithelial cancer cells to restrict their growth/proliferation [64] For example, intestinal metabolites of quercetin, chlorogenic and caffeic acids have been shown to interfere with enzymes involved in colon carcinogenesis, reducing COX-2, preventing DNA damage and by enhancing GSTT2 in colon cancer cell lines [138, 139, 145, 146]. The modification of the gut microbiota by polyphenols is likely to be a realistic way in bringing about reductions in cancer cell proliferation in the large gut although at present very few trials have been conducted to specifically test this, with only cocoa [164], blueberry [174] and wine [65] shown to induce a bifidogenic effect. Future trials testing the potential of fruits/fruit extracts to act as prebiotics are warranted and require focus on the growth of other bacteria known to be involved in colon cancer prevention [163, 173].

3. Glucosinolates and colon cancer prevention

3.1. Structure and importance

Glucosinolates are sulphur-rich compounds consisting of a β-D-glucopyranose residue attached via a sulphur group to a (*Z*)-*N*-hydroximinosulfate ester, with a side chain containing an amino acid [175]. More than 120 types of glucosinolates have been reported, and they may constitute around 10% of the seed weight. The main characteristics of these compounds reside in their odour and bitter taste and they are involved in microbial defence in plants [176]. With regards to human consumption, they are predominantly found as glycosides in Brassica vegetables, such as cabbage, Brussels sprouts, kale, broccoli, and cauliflower, whereas in Japan, radishes are considered the richest source of glucosinolates. Glucosinolates levels vary in different vegetables, with glucobrassicin and glucoraphanin found at high amounts in broccoli but to a lesser degree in cabbage, brussels sprouts and cauliflower [177], although levels are affected by climate, cultivar and soil conditions. Whilst glucosinolates are largely biologically inactive, active compounds may be generated via the release of myrosinase enzymes, during bruising, handling and mastication. The active components include nitriles, isothiocyanates and thiocyanates: notably sulforaphane and sulforaphane nitrile as a result of glucoraphanin hydrolysis, phenethyl isothiocyanates as a result of gluconasturtiin hydrolysis and indole-3-carbinol as a result of glucobrassicin hydrolysis [178]. Many of these have been suggested to hold significant

Table 4
Glucosinolates and colorectal cancers

Trial	Duration	Type of food	Main results
The Singapore Chinese health study [251]	5 years follow up	Cruciferous vegetables	There was an inverse association with colorectal cancer risks
The Netherlands Cohort Study on Diet and Cancer [35]	6.3 years follow up	*Brassica* vegetables and cooked leafy vegetables, Brussels sprouts, cabbage, and string beans	An inverse association was demonstrated in both genders with distal colon cancer
The Western Australian Bowel Health Study [200]	2 years follow up	Brassica vegetables	An inverse association was related with the proximal colon cancer
Epidemiological study on patients from Buffalo and Kenmore [252]	6 years follow up	cabbage, brussels sprouts, and broccoli	A decrease in the risk of colon cancer

chemopreventive actions against colon cancer progression [98, 179–181].

Studies have demonstrated a strong association between the consumption of cruciferous vegetables and the reduction in colorectal cancer risks (Table 4). For example, glutathione S-transferase (GST) activity has been observed to be significantly elevated in human plasma following brussels sprouts consumption [182]. GST is known to detoxify carcinogens and to suppress colon carcinogenesis [183–186]. *In vitro* work has supported such observations, showing that glucosinolates present in Brassica spp., such as, isothiocyanates, sulforaphane and indoles interfere with carcinogenesis [187], whilst sulforaphane is known to induce detoxification enzymes and phase II enzymes related with the metabolism and excretion of xenobiotics [188]. Furthermore, they have been observed to inhibit cell growth and a stimulate apoptosis in colon cancer cells, via the triggering increased expression of the tumour suppressor protein p-53 and an activation of the cell death programme inducers, capcase-3 [189] capcase-9 and Bcl-2 proteins [190]. The consumption of Brassica vegetables may reduce risks of colon cancer due to its anti-cancer mechanisms [180] However, recent research on the gut microbiota must be also directed towards such types of vegetables.

4. Dietary fibre and colon cancer prevention

4.1. Type, intake and metabolism

The American Association of Cereal Chemists (AACC) defines dietary fibres as "the edible parts of plants or analogous carbohydrates that are resistant to digestion and absorption in the human small intestine but undergo complete or partial fermentation in the large intestine" [191]. Dietary fibre, which includes polysaccharides, oligosaccharides, lignin, and associated substances, are well known to promote beneficial physiological effects including laxation and/or blood cholesterol attenuation and/or blood glucose attenuation [192, 193]. Fibres are divided into soluble and insoluble according to their physiochemical properties. Insoluble fibres, including resistant starch, escape small intestinal digestion and absorption and pass to the colon where they are fermented by the gut microbiota. Resistant oligosaccharides, which include fructo-oligosaccharides FOS, found in onions and artichoke, inulin and galacto oligosaccharides GOS exhibit a prebiotic potential by inducing selective growth of the microbiota [63, 194, 195]. Soluble types of fibres (polysaccharides) have also been linked with changing the gut ecology, although they are more effective in lowering blood cholesterol, due to their potential to alter fat absorption [196].

Worldwide, recommendations on fibre-intake differ markedly, perhaps reflecting a lack of detailed knowledge regarding their health activity. In the UK, the recommended intake is 18 g/d, in Germany 30 g/d and in the USA 38 g/d, for men aged 20–50 years, whilst for women an amount of 26 g/d is recommended in the USA [197]. As with most macro- and micro-nutrients, the intake of fibre varies within populations according to age and education [195], as well as due to differences in the definition of fibre and disparity in socioeconomic status [198]. Despite variations in intake, an increase in the intake of high-fibre foods is widely recommended to prevent chronic disease [63, 193].

Table 5
Dietary fibres and colorectal cancers

Trial	Duration	Type of food	Main results
The European prospective investigation into cancer and nutrition (EPIC) [253]	11 years follow up	Dietary fibres from cereals, fruits and vegetables	An inverse association between fibre intake and colon cancer was seen
The European Prospective Investigation into Cancer and Nutrition (EPIC), 2003 [39]	4.5 years follow up	Dietary fibres; Cereals were the main sources of fibre in the Netherlands, Germany, Sweden, and Denmark, whereas vegetables were most important in France and the UK. Fruit was an important source of fibre in Italy and Spain. Legumes and potatoes contributed small amounts and were more important in Spain, the Netherlands, and Denmark.	An inverse association was mostly seen in the colon rather than the rectum
Case-control studies conducted in northern Italy [68]	18 years follow up	Dietary fibres	There was an inverse association with colon cancer
Population-based study in Murcia in Spain and Copenhagen in the Denmark [254]	5 years follow up	Fibre intake	Fibre intake in Spanish population was 31% higher than Denmark populations, which was mainly from non-starch polysaccharides. A reduction of colon cancer in Murcia was also observed
Population-based prospective mammography study of Swedish women [24]	9.6 years follow up	Fibre intake	No association was found with cereal fibres
The prospective Scandinavian HELGA cohort [255]	11.3 years follow up	Fibre intake in vegetables, fruits, potatoes, and cereals	There was a significant association in reducing risk of colon cancer but not rectal cancers with total fibre intake and cereal fibres in particularly
A prospective study on women with no history of colon cancer [211]	16 year follow up	Fibre intake	There was no association with colon cancer

4.2. In vivo and in vitro studies

Strong observation data have demonstrated that dietary fibre intake may reduce the risk of CRC in various populations (Table 5), which was also been seen in relation to fruit and vegetable consumption (Table 1). Early reports that highlighted dietary fibre as having beneficial actions in the large gut also suggested that there may be significant reductions possible in CRC risk [30, 192]. Insoluble fibre are well reported to increase the faecal bulk and to reduce transit time, resulting in the dilution of toxin concentrations and the duration of potential carcinogen exposure to the colonic epithelial mucosa [193]. Indeed, dietary fibre has been shown to have a laxative potential in constipated patients [199]. Furthermore, fibre intake has been shown to reduce DNA damage and genotoxic components in healthy volunteers [200] and in polypectomized and CRC patients [201–203]. In addition, resistant starch consumption reduces secondary bile acids concentration in the gut in patients with colonic lesions [196, 204]. As discussed earlier, dietary choices will greatly influence fibre intake and thus its potential protective effects. For example, consuming less meat usually correlates with increased fibre intake [30, 205].

With regards to prebiotics (xylooligosaccharides & fructooligosaccharides) and synbiotics (bifidobacterium longum and lactulose), significant declines in aberrant crypt foci (ACF) numbers in animal models have been observed [49, 206, 207]. Similar outcomes have been observed with diets containing different types of fibres, such as resistant starch [208] and wheat bran [209], where reductions in tumour mass has been observed [51]. Cell studies with fibres are perhaps more difficult to interpret, as the addition of unfermented fibres to cells in culture has limited physiological significance. However, *in vitro* data suggest different mechanisms of action for the inhibitory effects of fibres on the growth of colon cancer cells, with reductions in colonocytes DNA damage [22, 170, 207] thought to be involved. There are other biomarkers, involved in CRC progression which also need to be considered, including bile acids, n-nitroso-compounds and calcium [210]. However, to date intervention studies regarding the effects of fruit and vegetable fibres on CRC risk are scarce [211, 212], with almost all studies conducted using broad fruit and vegetable intake and very few looking at the effects of specific fibre-rich ones, such as Jerusalem artichoke rich which is rich in fructo-oligosaccharides [213]. Therefore, future trials should be directed at the use of specific high fibre fruits and vegetables and/or specific fibre interventions to shed further light on their specific anti-cancer potential.

4.3. Impact of shifting the bacterial population favourably on cancer risk

There have been many investigations into the influence diets rich in fibres or prebiotics have on the selective growth of the microbiota (Table 6), including FOS, inulin, lactulose, oligofructose, resistant starch and different types of whole grains, all of which exert significant increases in the growth of bifidobacteria and lactobacilli and smaller changes in *Bacteroides*, *Clostridium* subgroups, *Eubacterium*, enterecocci, and ruminococcus [165, 213–217]. Such human data is supported by animal studies [218] and in pH-controlled batch culture experiments [219–223]. In such trials, other bacterial fermentation biomarkers were also investigated, including stool weight and breath-hydrogen excretion, which alter due to alterations in the microbial ecology and/or resultant carbohydrate fermentation [154, 224]. Some studies suggest that the fermentation of fibre found in fruits and vegetables is significantly quicker and more extensive than that found in grains [159, 166], suggesting that the consumption of fruits and vegetables may have at least as good a potential to modulate the gut microbiota in a favourable way.

There is still a debate as to whether dietary fibre is involved in preventing CRC [211, 212], even though fibres intake has been implicated in reducing CRC risks by around 25% [39]. The saccharolytic fermentation of carbohydrates by the microbiota results in the formation of short chain fatty acids (SCFAs), such as acetate, propionate and butyrate, which were found to exert various anti-cancer effects in transformed/initiated cells *in vitro* [67, 168–172]. They have been postulated to do this through their ability to down regulate enzymes involved in carcinogenesis, such as glutathione S-transferases (GST) [171] and alkaline phosphatase (AP), to interfere with the cancer cell proliferation [225] and to induce apoptosis in colon cancer cell lines [22, 67, 226–229]. Such observations have been detected using butyrate and propionate at less than 2 mM, which are considered to be physiologically relevant [230]. Elsewhere, *in vitro* data indicate that butyrate down regulate cyclin B1 CB1 and increasing *p*-21 cell-cycle inhibitor, which all resulted in cell apoptosis [169, 231]. With regards to the MAPK kinases, butyrate was shown to inhibit the JNK MAKP, rather than the p38 pathway, in colon cancer cell lines [172].

Despite the wealth of positive data which suggest an anti-cancer effect, some studies are less positive, possibly due to variability in the diets administered [232, 233] and age of participants [234]. In addition, human data are required in order to fully assess the anti-cancer potential of fibre-rich foods *in vivo*. There is little doubt that dietary fibre has the potential to positively alter the colonic microbiota and metabolite levels in a way that should enhance the gut health. Indeed, good data have been observed with lactulose [217], oligofructose and inulin [235]. Other studies have shown the prebiotic potential of fibres supplemented into biscuits [214] and bars [216]. However, although not specifically tested, the consumption of fibre-containing fruits and vegetables may also be effective, with blueberry having a significant impact in modulating the gut ecology into a healthier one [174] and Jerusalem artichoke and chicory intake shown to have bifidogenic ability [216]. Ideally, the selection of a natural food source that contains fibres (with identification of a prebiotic potential) and polyphenols will be interesting to test in

Table 6
Dietary fibres and the gut microbiota

Trial	Duration	Type of food	Main results
A randomized, controlled, double-blind, crossover intervention study [165]	3 weeks treatment	Whole grain cereals WG Whole bran cereals WB	Significant increase in bifidobacteria and lactobacilli, was seen more with WG than WB
A randomized, controlled, double-blind, crossover intervention study [173]	3 weeks treatment	Polydextrose PDX	Significant increase in ruminococcus intestinalis and some clostridium clusters, and a decrease in lactobacillus–enterococcus species
A randomized, controlled, double-blind, crossover intervention study [214]	3 weeks treatments	Partially hydrolysed guar gum PHGG biscuit Fructo-oligosaccharides FOS biscuit	Significant increase was seen in bifidobacteria with PHGG and FOS biscuits
A randomized, controlled, double-blind, crossover intervention study [256]	Between 26 to 33 days	Lactulose powder	Significant increase in bifidobacteria and lactobacilli, and a decrease in clostridia was seen
A randomized, controlled, double-blind, crossover intervention study [217]	6 weeks treatment	Lactulose	Significant increase in bifidobacteria
A randomized, controlled, double-blind, crossover intervention study [215]	7 days treatment	Non digestible carbohydrates NDCHs, such as, short-chain fructooligosaccharides, soybean oligosaccharides, galacto-oligosaccharides, and type III resistant starch, lactulose, long-chain inulin, and isomaltooligosaccharides	Significant increase in bifidobacteria was only seen with short-chain fructooligosaccharides, soybean oligosaccharides, galactooligosaccharides, and type III resistant
A randomized, controlled, double-blind, crossover intervention study [218]	45 days treatment	Oligofructose and inulin	Significant increase in bifidobacteria was seen by both oligofructose and inulin. However inulin have decreased gram-positive bacteria and oligofructose have reduced counts of clostridia, and fusobacteria
A randomized, controlled, double-blind, crossover intervention study [254]	21 days treatment	Maize-derived whole grain cereal WGM	Significant increase in bifidobacteria was seen by WGM
A randomized, controlled, double-blind, crossover intervention study [216]	3 weeks	a. snack bars without supplementation of inulin (placebo) b. snack bars with CH chicory inulin c. snack bars with JA Jerusalem artichoke	Significant increase in bifidobacteria was been by both bars with CH and JA, but no changes in SCFAs was seen
A randomized, controlled, double-blind, crossover intervention study [257]	3 weeks	Shots of pear-carrot-sea buckthorn (PCS) or plum-pear-beetroot (PPB), containing Jerusalem artichoke (JA) inulin	Significant increases in both bifidobacteria and lactobacillus were seen
A randomized, controlled, double-blind crossover intervention study [258]	3 weeks	Wheat/rye bread with or without Arabinoxylan oligosaccharides (AXOS)	Significant increase in bifidobacteria
A randomized, controlled, double-blind crossover intervention study [259]	3 weeks	Bread enriched with Arabinoxylan oligosaccharides (AXOS)	Limited changes were seen with AXOS-breads, whereas bifidobacteria elevated following control breads consumption

human trials and such an approach may be required in future.

5. Summary and future perspectives

The intake of at least 5 different 80 g portions of fruits and vegetables a day is encouraged for the prevention of cancer. However, on-going observational studies have concluded that the link between fruit and vegetable intake and colorectal cancer incidence in weaker than originally thought. Why is this? As food intake assessment has improved, the fruit and vegetable intake data available in such studies has become more extensive and included a wider range of individual items. However, rather than being a good thing, we suggest that the weakening association between the intake of fruits and vegetables and cancer may lie in the notion that all fruits and vegetables are not equal in their anti-cancer potential, notably due to their widely different levels of fibre and/or polyphenols. The inclusion of certain 'inactive' fruits and vegetables in calculations relating to a reduction in cancer risk would be expected to weaken such an association. We suggest that there are specific fruits and vegetables that have specific potency with regards to preventing colorectal cell initiation and progression and that this potential is underpinned by their fibre and polyphenol content and the effects these have on gut epithelial cells and the microbiota. In other words, population level advice to increase fruit and vegetable intake generally is likely to be less effective in bringing about a reduction in GI tract cancer than an approach which targets those fruits and vegetables which contain the highest levels of fibre/polyphenols and which have been demonstrated to exert anti-cancer effects in various systems.

It seems likely that fruits and vegetables capable of delivering high amounts of fibres, such as, pears, apples, and berries [236], or high levels of polyphenols, such as, blueberries, strawberries and grapes [119] and dried fruits, such as date fruits [237], figs, and plums [199], or indeed high levels of both [238], such as apples [203, 204], oranges [239], date fruits [237, 240], and *Brassica* vegetables [96] might have the greatest potential to induce reductions in colon cancer development/progression. We predict that the inclusion of such foods in clinical trials aimed at investigating the impact of fruits and vegetables intake on bowel cancer development is likely to yield a stronger inverse relationship between these two factors relative to that observed following board, non-descriptive fruit and vegetable intake supplementation. The concentration of polyphenols and fibres found within these specific fruits and vegetables, will deliver high levels of bioactive compounds to the intestinal epithelium where they may act to inhibit cancer cell proliferation and induce cancer cell apoptosis.

With regards to future avenues of investigation, there is certainly a lack of data regarding the effects of specific polyphenols and/or polyphenol-rich foods on the specific growth of the microbiota? Therefore, studies aimed at understanding the influences of polyphenols on the microbiota should be undertaken both in mixed, pH controlled culture vessels and in human clinical studies. Furthermore, whilst it is reasonably well understood how polyphenols are metabolised by the microbiota to produce smaller phenolic acids [115] (akin to SCFAs if carbohydrates are used as substrates), to date, few, if any, studies have considered the positive effects of such metabolites on cancer cell fate and related mechanisms of action. In the course of such experiments, and particularly with relation to *in vitro* batch culture studies, one should give thought to the realistic amounts of polyphenols (delivered by foods) that reach the large intestine. In this respect, analytical methods to measure polyphenol metabolites (including the application metabonomics and metabolomics) in the circulation have greatly improved and such methodology should be applied to the measurement of phenolic metabolites formed in the large gut.

Regarding the actions of polyphenols on cancer cells in the large intestine, the data are also quite unclear. Whilst there have been various investigations of the influence of polyphenols on the proliferation of colonic cancer cells and their potential to induce apoptosis, few of these have considered whether such activity is modified by the metabolism of these compounds by the resident bacteria. This is critical, as polyphenols entering the large intestine will be subject to rapid degradation meaning that large intestinal epithelial cells will rarely, if ever, be exposed to native polyphenol compounds. Rather the smaller phenolic acid metabolic products are expected to dominate in the small intestine and it is within these that the anti-cancer potential should be assessed [241]. With regards to dietary fibre, although the impact of these on the gut microbiota is well established, the persistence of these effects is unclear. In addition, the combined actions of both dietary fibres and polyphenols on colon health are unknown at present. As both are found at reasonable

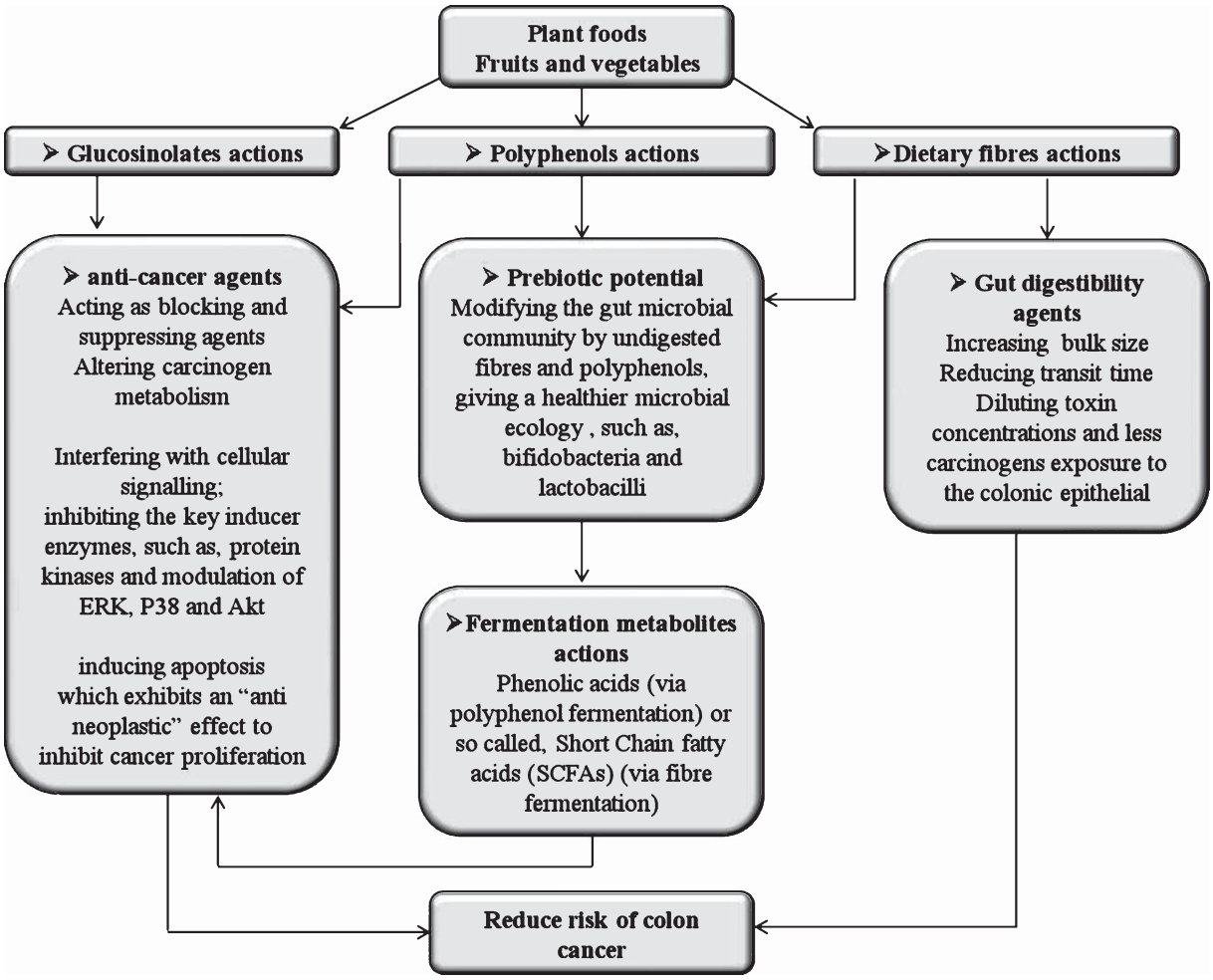

Fig. 2. Fruits, vegetables and colon cancer prevention.

quantities in the foods we have outlined in this review (apple and other stone fruits, orange and other citrus fruits, dates, raisons and other dried fruits and *Brassica* vegetables), future human trials to assess the influence of such foods on anti-cancer activities at the cellular and microbiological level are warranted.

Additionally, nutrigenomics may also be an important factor when assessing the potential reaction of humans towards specific diets or dietary agents [242]. Recent research has highlighted many potential risk factors for colorectal cancers, including that of obesity [16]. *In vitro* data suggest that obesity hormones such as leptin may enhance colon cancer progression [57], something also observed in animal models [58]. Such factors may influence the potential benefits of polyphenol/fibre rich fruits and vegetables in human populations, along with a host of other genetic factors associated with cancer development. As such, the degree of protection afforded by polyphenol/fibre-rich diets may be altered either favourably or unfavourably when combined with such genetic and/or lifestyle factors. Finally, aging is one of the strongest risks factors for cancer progression, with over than 90% of people diagnosed with colorectal cancer being over 50 years of age. Such a statistic is likely associated DNA oxidation/methylation, processes which is directly involved in cancer development [59]. Therefore, it would be of interest to compare the influence of fruit and vegetable interventions on individuals of different ages, most notably above and below 50, where modulation of early DNA damage may have real potential to prevent mutagenesis and progression to cancer cell phenotypes.

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