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Effects of Dietary Components on Cancer of the Digestive System

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Cancer is the second leading cause of death in developed countries and poor diet and physical inactivity are major risk factors in cancer-related deaths. Therefore, interventions to reduce levels of smoking, improve diet, and increase physical activity must become much higher priorities in the general population's health and health care systems. The consumption of fruit and vegetables exerts a preventive effect towards cancer and in recent years natural dietary agents have attracted great attention in the scientific community and among the general public. Foods, such as tomatoes, olive oil, broccoli, garlic, onions, berries, soy bean, honey, tea, aloe vera, grapes, rosemary, basil, chili peppers, carrots, pomegranate, and curcuma contain active components that can influence the initiation and the progression of carcinogenesis, acting on pathways implied in cell proliferation, apoptosis and metastasis. The present review illustrates the main foods and their active components, including their antioxidant, cytotoxic, and pro-apoptotic properties, with a particular focus on the evidence related to cancers of the digestive system.

Keywords Food, chemoprevention, neoplasia, digestive system cancer, apoptosis, oncogene, epigenetic

INTRODUCTION

Cancer is a major public health problem in many parts of the world (Siegel et al., 2012). According to World Health Organization (WHO), cancer is responsible for approximately 7.6 million (13%) of the 59 million deaths that occur each year and in 2030 deaths from cancer worldwide are expected to reach 11.8 million per year. Most cancer deaths are due to five leading behavioral and dietary risks, which include low fruit and vegetable intake. The evidence linking poor nutrition, overweight/obesity, and physical inactivity as risk factors for cancer continues to develop and a healthy diet is one of the most important lifestyle changes that a person can make to reduce his/her risk of cancer (Deng et al., 2009; Beaglehole et al., 2011; Kushi et al., 2012). WHO has graded the strength of the evidence for these lifestyle risk factors, in relation to a range of cancers, and estimated that around 1 million new cases could be prevented in the USA, UK, China, and Brazil alone, by merely correcting lifestyle behavior. Since most cancers are linked to lifestyle components and Western-type diet, knowledge of these causes should also lead to effective policies to prevent the export of a "Western pattern" of cancers in lower income countries such as in Africa (Wiseman, 2015).

Many herbs have traditionally been used for the treatment of tumors and during the 20th Century several molecules derived from natural substances were introduced as drugs. Dietary agents could be used alone or in combination with conventional chemotherapeutic agents, in order to prevent new cases of cancer and recent studies suggest that a Mediterranean diet decreases the risk of cancer (Visioli et al., 2005; Pelucchi et al., 2009). Cancer is a complex disease and an acquired knowledge of herbal and nutraceutical dietary components would favor an unexpected alliance between traditional pharmacology and "food-based" complementary approaches, thus developing public health recommendations for cancer prevention.

In recent years, epidemiological and basic research studies have shown that different components present in food, such as tomatoes, olive oil, broccoli, garlic, onions, berries, soy bean, honey, tea, aloe vera, grapes, rosemary, basil, chili peppers, carrots, pomegranate, and curcuma inhibit pro-proliferative signals implied in tumor progression and/or stimulate cancer

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cell apoptosis (Aggarwal and Shishodia, 2006); Ullah and Khan, 2008; Garavello et al., 2009; Kyle et al., 2010). A summary of these compounds with nutraceutical value and their dietary sources is reported in Table 1.

Therefore, considering the increasing interest in the role of dietary components in cancer biology, additional research could be developed to prospectively modify the cancer risk, through primary diet chemoprevention or by improving therapeutic results through multi-target approach therapies. In the present review, attention will focus on the epidemiological evidence of the dietary agents in cancer risk and the biological effects of the food compounds on pathways implied in cancer proliferation, apoptosis, and metastasis. The following sections illustrate the main foods of health interest with anti-cancer properties. Finally, the main cellular and molecular targets of specific compounds will be synthetically illustrated.

FOODS AND THEIR CHEMOPREVENTIVE AGENTS

Tomatoes

The tomato is a typical component of the Mediterranean diet and its consumption has been inversely related to the risk of developing cardiovascular diseases and cancer (Hwang and Bowen, 2002). Tomatoes are a plant species of the *Solanacae* family, native of South America, widely cultivated around the world. Several studies show that there is an inverse association between tomato intake and the risk of colorectal, gastric or pancreatic cancer although the U.S. Food and Drug Administration (FDA) found limited clinical evidence to support the beneficial effects of tomato consumption in cancer (Heber et al., 2001; Cohen, 2002; Müller et al., 2003; Davis et al., 2005; Jenab et al., 2005; Kavanaugh et al., 2007; Walfisch et al., 2007; Friedman et al., 2009; Polivkova et al., 2010; Shi et al., 2010; Lippi and Targher, 2011). Tomatoes contain substances with an in vitro tested anti-proliferative effect on cancer cells, such as lycopene and various polyphenols, at a concentration of 4–26 mg/100 g fresh food, in relation to plant varieties (Verhoeyen et al., 2002; Weisburger, 2002; Wang et al., 2003; Ferreres et al., 2010). Lycopene can function as an antioxidant because it reduces oxidative damage, preventing chronic diseases such as cancer and cardiovascular disease (Agarwal and Rao, 2000). Other proposed potential mechanisms of action for lycopene include regulation of gene function, communication via gap junctions, modulation of hormone and immune activity, as well as metabolism of carcinogens (Agarwal and Rao, 2000).

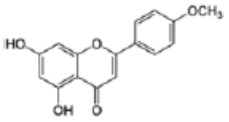
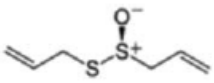
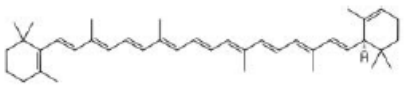
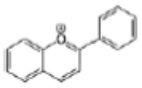
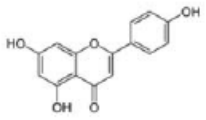
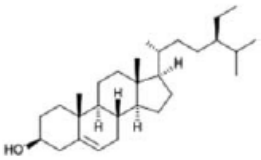
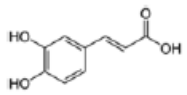
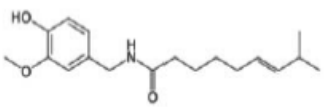
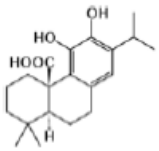
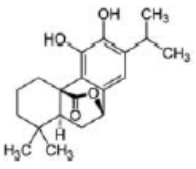
Olive Oil

Virgin olive oil consumption in populations with Mediterranean diet ranges from 25 to 50 ml per day (Corona et al., 2009). In a meta-analysis study, comparing 19 studies taking into account solely olive oil intake, people in the highest group of olive oil consumption had a 34% lower likelihood of having any type of cancer. More specifically, high olive oil consumption was associated with lower odds of developing cancer of the digestive system: odds ratio $= -0.36$, 95% Confidence Interval (CI) $= -0.50$ to -0.21 (Psaltopoulou et al., 2011). In vitro olive oil has an antiproliferative effect on colon cancer cell lines through the inhibition of fatty acid synthase, extracellular-signal-regulated kinases 1/2 (ERK 1/2) and cyclin D1 (Corona et al., 2009; Notarnicola et al., 2011). The main active components of olive oil include monounsaturated lipids (especially oleic acid), phenolic constituents (such as hydroxytyrosol, tyrosol, and oleuropein) and squalene (Omar, 2010). One of the major polyphenolic constituents of extra virgin olive oil is hydroxytyrosol that exerts strong antiproliferative effects against human colon adenocarcinoma cells, via the ability to induce a cell cycle block in G2/M phase, thanks to a strong inhibition of ERK1/2 phosphorylation and a downstream reduction of cyclin-D1 expression (Corona et al., 2009). Moreover, the action is mediated through the inhibition of fatty acid synthase, a key anabolic enzyme of biosynthesis of fatty acids that plays an important role in colon carcinoma development (Corona et al., 2009; Notarnicola et al., 2011).

Garlic and Onion

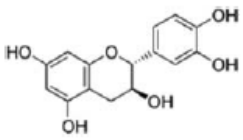
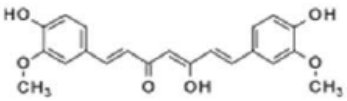
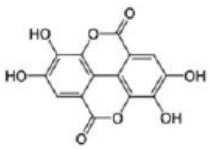
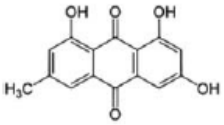
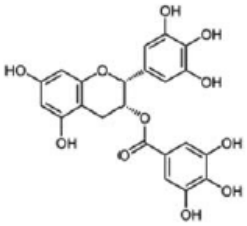
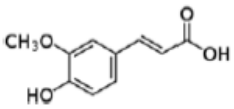
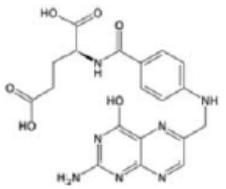
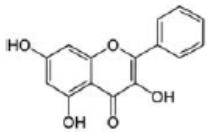
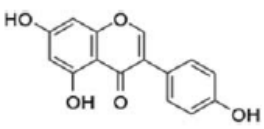
Garlic and onion are plants of the species *Allium*, named *Allium sativum* and *Allium cepa*, respectively, which are widely cultivated and consumed worldwide. The interest in their potential health benefits has its origins in antiquity and several epidemiologic investigations have suggested an inverse relation between intake of allium vegetables and stomach, colorectal and pancreatic cancer (Bianchini and Vainio, 2001; Chan et al., 2005; Galeone et al., 2006; Ngo et al., 2007; Pelucchi et al., 2009; Zhou et al., 2011). In a meta-analysis study, the consumption of large amounts of *Allium* vegetables reduced the risk for gastric cancer (odds ratio $= 0.54$, 95% CI $= 0.43$ to 0.65) (Zhou et al., 2011). Specific analyses for onion, garlic, leek, chinese chive, scallion, garlic stalk, and welsh onion yielded similar results, with the exception of onion leaf (Zhou et al., 2011). In a population-based case-control study, garlic and onion intake was inversely associated with the risk of pancreatic cancer; specifically when compared to the lowest intake quartile, the odds ratio for the highest quartile was 0.46 (95% CI, 0.33–0.63) (Chan et al., 2005). Evidence from several investigations suggests that the biological and medical functions of garlic and onions are mainly due to the high content of organo-sulphur compounds (such as allicin), and flavonoids (such as quercetin, the latter being abundant in onion but practically absent in garlic) (Dorai and Aggarwal, 2004; Russo et al., 2012). These compounds exert an anticarcinogenic effect through a number of mechanisms, such as increasing the detoxification enzymatic systems' activity of cytochrome p4502E1 and the DNA repair mechanisms,

Table 1 Food compounds with chemopreventive activity in cancer of gastrointestinal tract

Compound	Molecular formula	Chemical structure	Compound Identification (CID) Number	Foods and vegetables*	References
Acacetin	$C_{16}H_{12}O_5$		5280442	Honey	Jaganathan and Mandal (2009)
Allicin	$C_6H_{10}OS_2$		65036	Garlic	Khanum et al. (2004)
Alpha-carotene	$C_{40}H_{56}$		4369188	Berries, carrots	Stoner et al. (2006)
Anthocyanin	$C_{15}H_{11}O^+$		145858	Berries, grapes	Kaur et al. (2009)
Apigenin	$C_{15}H_{10}O_5$		5280443	Honey	Jaganathan and Mandal (2009)
Beta-carotene	$C_{40}H_{56}$		5280489	Berries, carrots	Stahl and Sies (2005); Stoner et al. (2006)
Beta-sitosterol	$C_{29}H_{50}O$		222284	Berries	Stoner et al. (2006)
Caffeic acid	$C_9H_8O_4$		689043	Honey	Jaganathan and Mandal (2009)
Capsaicin	$C_{18}H_{27}NO_3$		1548943	Chili peppers	Norton (1998)
Carnosic acid	$C_{20}H_{28}O_4$		65126	Rosemary	Ngo et al. (2011)
Carnosol	$C_{20}H_{26}O_4$		442009	Rosemary	Ngo et al. (2011)

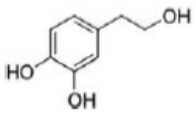
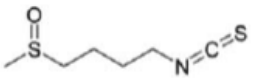
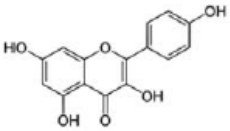
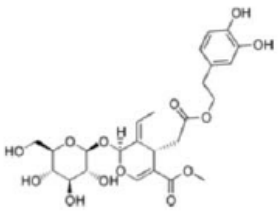
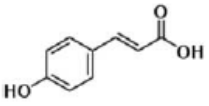
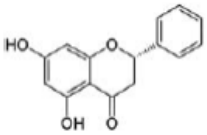
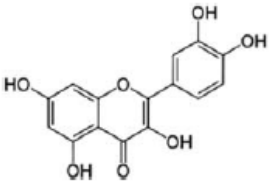
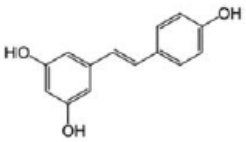
(Continued on next page)

Table 1 Food compounds with chemopreventive activity in cancer of gastrointestinal tract *(Continued)*

Compound	Molecular formula	Chemical structure	Compound Identification (CID) Number	Foods and vegetables*	References
Catechin	$C_{15}H_{14}O_6$		9064	Grapes, tea	Kaur et al. (2009); Chow and Hakim (2011)
Curcumin	$C_{21}H_{20}O_6$		969516	Curcuma	Lu et al. (2008)
Ellagic acid	$C_{14}H_6O_8$		5281855	Berries, pomegranate	Stoner et al. (2006); Bell and Hawthorne (2008)
Emodin	$C_{15}H_{10}O_5$		3220	Aloe vera	Akev et al. (2007)
Epigallo catechin 3-gallate (EGCG)	$C_{22}H_{18}O_{11}$		65064	Green tea	Chow and Hakim (2011)
Ferulic acid	$C_{10}H_{10}O_4$		445858	Berries	Stoner et al. (2006)
Folic acid	$C_{19}H_{19}N_7O_6$		6037	Berries	Stoner et al. (2006)
Galangin	$C_{15}H_{10}O_5$		5281616	Honey	Jaganathan and Mandal (2009)
Genistein	$C_{15}H_{10}O_5$		5280961	Soy beans	Xiao (2008)

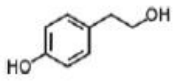
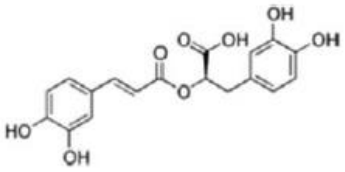
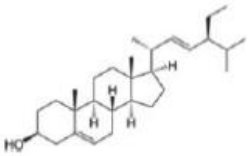
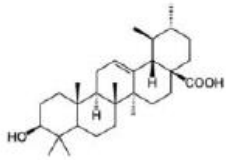
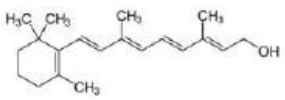
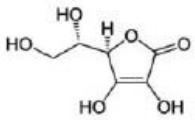
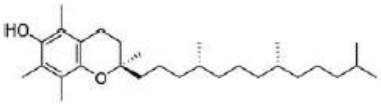
(Continued on next page)

Table 1 Food compounds with chemopreventive activity in cancer of gastrointestinal tract *(Continued)*

Compound	Molecular formula	Chemical structure	Compound Identification (CID) Number	Foods and vegetables*	References
Hydroxytyrosol	$C_8H_{10}O_3$		82755	Olive	Omar (2010)
Isothiocyanates, (sulforaphane)	$C_6H_{11}NOS_2$		9577379	Broccoli	Herr and Buchler (2010);
Kaempferol	$C_{15}H_{10}O_6$		5280863	Berries, honey	Stoner et al. (2006); Jaganathan and Mandal (2009)
Lutein	$C_{40}H_{56}O_2$		6433159	Berries, grapes	Stoner et al. (2006); Kaur et al. (2009)
Lycopene	$C_{40}H_{56}$		446925	Tomatoes, grapes	Agarwal and Rao (2000)
Oleuropein	$C_{25}H_{32}O_{13}$		5281544	Olive	Omar (2010)
p-coumaric acid	$C_9H_8O_3$		637542	Berries	Stoner et al. (2006)
Pinocembrin	$C_{15}H_{12}O_4$		68071	Honey	Jaganathan and Mandal (2009)
Quercetin	$C_{15}H_{10}O_7$		5280343	Onion, berries, honey, grapes	Stoner et al. (2006); Jaganathan and Mandal (2009); Kaur et al. (2009); Russo et al. (2012)
Resveratrol	$C_{14}H_{12}O_3$		445154	Grapes	Jang et al. (1997)

(Continued on next page)

Table 1 Food compounds with chemopreventive activity in cancer of gastrointestinal tract *(Continued)*

Compound	Molecular formula	Chemical structure	Compound Identification (CID) Number	Foods and vegetables*	References
Tyrosol	$C_8H_{10}O_2$		10393	Olive	Omar (2010)
Rosmarinic acid	$C_{18}H_{16}O_8$		5281792	Rosemary	Ngo et al. (2011);
Squalene	$C_{30}H_{50}$		638072	Olive	Omar (2010)
Stigmasterol	$C_{29}H_{48}O$		5280794	Berries	Stoner et al. (2006)
Ursolic acid	$C_{30}H_{48}O_3$		64945	Rosemary, basil	Ngo et al. (2011)
Vitamin A	$C_{20}H_{30}O$		445354	Berries, carrots	Stoner et al. (2006)
Vitamin C	$C_6H_8O_6$		5785	Berries	Stoner et al. (2006)
Vitamin E (Alpha-tocopherol)	$C_{29}H_{50}O_2$		2116	Berries	Stoner et al. (2006)

Chemical structure is from Wikipedia, available under the Creative License, molecular formula and CID number from U.S. NLM website http://pubchem.ncbi.nlm.nih.gov/.

*Only the foods and vegetables described in this review are reported in this column.

thus preventing chromosomal damage (Khanum et al., 2004), and an inhibition of cellular proliferation by induction of apoptosis and inhibition of cell division (Rose et al., 2005). Low doses of quercetin (0.1–10 μg/ml) exert complex stimulus-dependent anti-inflammatory and immunomodulatory effects on human blood basophils (Chirumbolo et al., 2010). The doses acting in vitro are within the range of quercetin plasma concentration, which has been found to be attained during intervention trials in humans (Manach et al., 2005; Egert et al., 2008; Moon et al., 2008).

Berries

Berry fruits most commonly consumed include blackberries (*Rubus spp.*), black raspberries (*Rubus occidentalis*), blueberries (*Vaccinium corymbosum*), cranberries (*Vaccinium macrocarpon*), red raspberries (*Rubus idaeus*), and strawberries (*Fragaria* × *ananassa*) (Seeram, 2008). Several phase IIa clinical trials are underway in patients at high risk for esophagus and colon cancer, i.e., Barrett's esophagus (BE), esophageal dysplasia and colonic polyps, to determine if berries modulate various

histological and molecular biomarkers for these diseases. BE is a premalignant esophageal condition that confers a 30- to 40-fold increased risk for the development of esophageal adenocarcinoma. A pilot study investigating the effect of the administration of 32 or 45 g lyophilized black raspberries (LBRs) for 10 BE patients (female and male, respectively), showed that daily consumption of LBRs promotes a reduction in the urinary excretion of two markers for oxidative stress, 8-epi-prostaglandin F2alpha and, to a lesser extent, 8-hydroxy-2′-deoxyguanosine (Kresty et al., 2006). Results from a toxicity study indicate that freeze-dried black raspberries are well tolerated in humans. Berries contain a wide range of phytochemicals with antioxidant, anticancer, anti-neurodegenerative, and anti-inflammatory properties. Chemopreventive agents present in berries include vitamins A, C and E, folic acid, calcium, selenium, beta-carotene, alpha carotene, lutein, polyphenols, such as ellagic acid, ferulic acid, p-coumaric acid, anthocyanins, quercetin, and several phytosterols such as beta-sitosterol, stigmasterol, and kaempferol. Anthocyanins are glucosides of anthocyanidins, common plant pigments based on the 2-phenylchromenylium cation (Table 1). Berry extracts added to cell cultures significantly inhibit cancer-associated processes and dietary freeze-dried berries were shown to inhibit esophagus and colon chemically induced cancer in rodents from 30 to 80%. Prevention trials in humans have been planned (Stoner et al., 2006). A raspberry ethanol extract suppresses cell proliferation in human squamous cell carcinoma without modifying the cell viability, inhibits translation of the angiogenic cytokine vascular endothelial growth factor (VEGF), suppresses nitric oxide synthase activity and induces both apoptosis and terminal differentiation (Rodrigo et al., 2006). This data implies that this extract is a promising candidate for use as a chemopreventive agent in persons with oral epithelial dysplasia. On a molecular level, berries modulate the expression of genes involved in proliferation, apoptosis, inflammation, and angiogenesis, such as nuclear factor kappa B (NF-kB), activator protein-1 (AP-1) and PI-3K/Akt, leading to effects on downstream genes, such as cyclooxigenase-2 (COX-2), VEGF and inducible NOS (iNOS) (Stoner et al., 2007).

Broccoli

Broccoli is a member of the cruciferous plant family. Flowers and leaves of this family are attracting increasing attention as healthy foods because of their content in glucosinolates, the degradation products of which include isothiocyanates that possess cancer preventive and therapeutic properties. The majority of glucosinolates present in broccoli correspond to glucoraphanin and the degradation product sulforaphane is one of the most powerful isothiocyanates against cancer (Herr and Buchler, 2010). Several epidemiological studies in humans demonstrate a correlation between a high intake of cruciferous plants and a reduced risk in different cancer types. An extensive review of epidemiologic studies published prior to 1996 reported that the majority (67%) of 87 case-control studies found an inverse association between cruciferous vegetable intake and cancer risk (Verhoeven et al., 1996; Higdon et al., 2007; Hayes et al., 2008). At the present time, there is little epidemiological evidence to support a role for cruciferous vegetables as chemopreventive agents against lung, colorectal, breast, prostate and pancreatic cancer. In the case of gastric cancer, a high consumption of cruciferous vegetables tends to exert a protective action, although in the published studies the individual risk estimate is not statistically significant. Possible mechanisms of anti-carcinogenic action of sulforaphane are various and involve the direct detoxification of carcinogens through the cytochrome p450 system (Shishu et al., 2003), the elimination of reactive oxidant species (ROS) and the improvement of antioxidative cellular activity (Zhang al., 2005). Sulforaphane induces cell cycle arrest and apoptosis in cancer cells through the inhibition of histone deacetylase (Clarke et al., 2008), reduces the NF-kB activity (Myzak and Dashwood, 2006), inhibits transcription factors such as hypoxia inducible factor-1α (HIF-1α) and c-myc, reduces the production of matrix metallo-proteinase-2 (MMP-2) and the endothelial cell proliferation (Bertl et al., 2006; Juge et al., 2007). Furthermore, experimental data points to the targeted elimination of tumorigenic pancreatic cancer stem cells by sulforaphane through downregulation of NF-kB activity, a major mediator of the pronounced resistance of pancreatic cancer cells to therapy (Kallifatidis et al., 2009).

Soy Bean

During the past 20 years, a remarkable amount of research into the health effects of soy consumption has been carried out which in large part can be attributed to the presence of isoflavones in the soybean. Around the 1990s the role of soy foods in disease prevention began to receive widespread attention, largely because of research sponsored by the U.S. National Cancer Institute. Epidemiological studies suggest that soy consumption is associated, at least in part, with lower incidence of a number of chronic diseases such as cancer, with the inhibition of bone loss and hot flashes in postmenopausal women and with the ability to reduce serum lipoprotein (Anderson et al., 1995; Omoni and Aluko, 2005; Kang et al., 2010; Messina, 2010; Anderson and Bush, 2011). In the past few decades, extensive efforts have been made towards identifying bioactive components in soy that are responsible for health benefits. Isoflavones, such as genistein and soy proteins, are the two major groups of components that have received the most attention (Xiao, 2008). Isoflavones belong to a broad group of plant-derived compounds that have structural and functional similarities to estrogens and this has led to the term phytoestrogens. The mixture of soy isoflavones and other bioactive components in soybean are more powerful when combined in soy extracts rather than as individual molecules. Genistein modulates key regulatory proteins such as Akt and NF-kB (Banerjee et al., 2008; Pavese et al., 2010), inhibits cytochrome p450 (Chun

et al., 2005) and induces apoptosis (Ramos, 2007) by both caspase-mediated and caspase-independent mechanisms in pancreatic cell lines (Saif et al., 2009). The addition of a derivative of the isoflavone genisten to gemcitabine is synergistic in cellular and animal models of pancreatic cancer and could represent a novel combination of drugs for pancreatic cancer patients (Saif et al., 2009). Prior research has demonstrated that specific isoflavones derived from soy may exhibit antitumor effects against many cancers, including oral cancer. Administration of whole soy protein significantly inhibited oral cancer growth in vitro and exerted these effects at lower concentrations compared to pure flavonoids (proanthocyanidins), suggesting a synergistic action of several components (Kingsley et al., 2011).

Honey

Honey is a naturally sweet, viscous liquid made by honeybees from the nectar of flowers. Worldwide production is now estimated to be worth at least 1.7 billion dollars annually. The harvesting of honey featured in rock paintings more than 6,000 years ago and its healing medicinal properties were even recognized in ancient Egypt (Ratcliffe et al., 2011). Honey is used for both domestic and medicinal purposes, but recently its nutraceutical properties against several diseases including cancer, coronary heart disease, inflammatory diseases and neurological degeneration have been the subject of a renewed interest (Jaganathan and Mandal, 2009). The mechanism of the anti-cancer activity of honey as chemopreventive and therapeutic agent include its apoptotic, antiproliferative, antioxidant, anti-inflammatory, estrogenic and immunomodulatory activities (Ahmed and Othman, 2013). In this context, honey is studied as a source of phenolic compounds and other antioxidants such as ascorbic acid. Several subtypes of polyphenols found in honey, including caffeic acid, galangin, quercetin, kaempferol, acacetin, pinocembrin, and apigenin, may be considered as promising complementary agents in the prevention and treatment of cancer (Jaganathan and Mandal, 2009). Honey induces apoptosis in human colon cancer cells, associated with the arrest of the cells at subG1 phase, with caspase-3 activation and poly-ADP-ribose polymerase (PARP) cleavage (Jaganathan and Mandal, 2009; Jaganathan et al., 2011). Moreover, honey is a potent inhibitor of *Helicobacter pylori*, the main causing agent of peptic ulcers and gastritis that precedes the development of gastric cancer (Bogdanov et al., 2008). In rat models of induced gastric ulcers, the substance exerts antioxidant properties, reducing the ulcer index, microvascular permeability, and myeloperoxidase activity (Ali al., 1997; Gharzouli et al., 1999; Gharzouli et al., 2002).

Tea

Tea, the most consumed beverage in the world after water, is derived from the infusion of leaves of *Camellia Sinensis*, a species of the Theaceae family, processed in different ways in different parts of the world. Green tea and its major polyphenol constituents tea catechins, such as (−)-epicatechin (EC), (−)-epicatechin-3-gallate (ECG), (−)-epigallocatechin (EGC), and (−)-epigallocatechin-3-gallate (EGCG), have been shown to have many health benefits, including cancer prevention. Tea catechins and tea catechin metabolites/catabolites are bioavailable in the systemic circulation after oral intake of green tea or green tea catechins (Chow and Hakim, 2011). A typical tea beverage usually contains 620–880 mg of water-extractable solids; tea catechins usually account for 30–42% of them and 2–5% consist of caffeine (Sang et al., 2011). Green tea has been shown to be linked to a lower rate of several digestive tract cancers (Gao et al., 1994; Ji et al., 1996; Ji et al., 1997). In particular, the association between green tea consumption and colorectal cancer (CRC) risk was evaluated in a large prospective cohort study involving 69,710 Chinese women and regular consumption was associated with a significantly reduced risk of CRC (risk ratio 0.63; 95% CI 0.45–0.88) (Yang et al., 2007). Inhibition of tumorigenesis by green tea extracts and tea polyphenols has been studied in different animal models, including those for cancers of the oral cavity, esophagus, stomach, small intestine, colon, liver, and pancreas (Yang et al., 2002; Yang et al., 2011a). In vitro models have demonstrated the modulation of signal transduction and metabolic pathways by EGCG, the most abundant and active polyphenol in green tea. These molecular events can result in cellular changes, such as enhancement of apoptosis, suppression of cell proliferation and inhibition of angiogenesis (Yang et al., 2009). In a mouse model of intestinal tumorigenesis, oral administration of EGCG significantly decreased small intestinal tumor formation resulted in increased levels of E-cadherin and decreased levels of nuclear β-catenin, c-myc, phospho-Akt, and phospho-ERK1/2 whereas caffeine was not effective in inhibiting tumorigenesis in this animal model (Ju et al., 2005).

Grapes

Grapes and grape-based products are a class of dietary products that have shown cancer chemopreventive potential and are also known to improve overall human health (Kaur et al., 2009). Grapes contain over 1,600 compounds, including anthocyanins, catechins, ellagic acid, lutein, lycopene, quercetin, and other potent antioxidants, such as the intensively studied constituent resveratrol, a non-flavonoid phenol, of which the grape skin of black grapes are particularly endowed. Since the first publication in *Science* describing cancer chemopreventive potential (Jang et al., 1997), many beneficial properties have been ascribed to resveratrol, such as the capacity to positively influence risk factors associated with cardiovascular health, neurodegenerative disease, and age-related cognitive decline (Pezzuto, 2008; Vislocky and Fernandez, 2010). The anti-carcinogenic effects of resveratrol seem to be closely

related to the interaction with multiple molecular targets involved in cancer growth. In contrast, a minimizing toxicity has been shown in normal tissues. Resveratrol can inhibit COX, hydroperoxidase, protein kinase C (PKC), Bcl-2 phosphorylation, Akt, focal adhesion kinase (FAK), NF-kB, matrix metalloproteinases-9 (MMP-9) and cell cycle regulators (Liu et al., 2007). An anti-tumor activity has also been attributed to white grapes without resveratrol; compounds in the form of proanthocyanidins have been found in the seeds of grapes, the antioxidant capacity of which has been shown to be greater than other known antioxidants, such as vitamins C and E (Hudson et al., 2007; Kaur et al., 2009).

Rosemary

Rosemary (*Rosmarinus officinalis*) is a plant typical to the Mediterranean region, widespread in many parts of the world as a common household plant used for many purposes including food flavoring, beverages, as well as cosmetic uses. Rosemary is a member of the mint family *Lamiaceae*, which includes many other herbs and is one of the two species in the genus *Rosmarinus*. The leaves of *Rosmarinus officinalis* contain several active compounds including carnosol, carnosic acid, ursolic acid, and rosmarinic acid. Traditionally, rosemary has been reported to have potential therapeutic effects in the treatment and/or prevention of several health conditions including renal colic, dysmenorrhea and respiratory disorders. In addition, phenolic constituents have been found to exert protective effects on colon cancer and other types of cancer through several mechanisms (Ngo et al., 2011). Extracts of rosemary have been applied to human cancer liver cell lines. The extracts exerted cytotoxic effects against various cell lines at relatively low doses (between 12 and 47 μg/ml). The activity of the detoxification enzymes glutathione-*S*-transferase and quinone reductase is increased in the liver and stomach of animals fed with diets containing rosemary extract (Singletary and Rokusek, 1997).

Basil

Basil *(Ocimum basilicum)* is an aromatic plant of the *Lamiaceae* family, belonging to the genus *Ocimum*. Originally from India, it is widely used in Italian cuisine, considering it as a typical food of the Mediterranean diet. The most active component of basil is ursolic acid, a triterpenoid, also derived from rosemary, whose antitumoral activity has recently been investigated (Sultana, 2011). Ursolic acid acts as an antitumor-promoting agent, inhibiting inflammation produced by tumor promoters and suppressing the expression of c-jun and c-fos oncogenes (Liu, 1995). One of the most critical targets of these chemopreventive ingredients involves NF-kB that regulates the expression of a whole variety of genes, including cyclin D1, MMP-9, and COX-2, responsible for inflammation and implicated in malignant transformation. The suppression of Nf-kB by basil is mediated through the inhibition of IkB kinase (Aggarwal and Shishodia, 2004). Moreover, ursolic acid can sensitize a wide variety of cancer cell types, including colon cancer cells, to TNF-related apoptosis-inducing ligand (TRAIL), and is thus considered a promising candidate as a new anti-cancer drug. Its potential use in combination with TRAIL should be further explored (Prasad et al., 2011).

Aloe Vera

Aloe vera, a succulent plant from the *Aloeacee* family, is a tropical plant that is easily grown in hot and dry climates and widely distributed in Asia, Africa, and other tropical areas. *Aloe vera* is a popular remedy for a variety of conditions, mainly related to inflammatory skin diseases (dermatitis), used to treat burns and promotes wound healing. The components of *Aloe vera*, in particular emodin, may well inhibit tumor growth, reduce tumor mass and inhibit metastasis (Akev et al., 2007; He et al., 2008). Some studies suggest an antiproliferative effect on cancer cells in vitro (El-Shemy et al., 2010) but evidence from clinical trials is currently lacking. Aloe emodin inhibited cell proliferation of a human colon carcinoma cell line by arresting the cell cycle at the G2/M phase and inhibiting cyclin B1. Moreover, emodin induces apoptosis specifically through the activation of caspase-6 (Suboj et al., 2012). Furthermore, the use of aloe as a prophylactic agent in cancer prevention has been suggested, since the best inhibitory effect on tumor growth was observed when aloe extract was given prophylactically before tumor implantation in mice (Akev et al., 2007). Aloe mixed with honey was partially effective in treating tumor growth in rats (Tomasin and Gomes-Marcondes, 2011).

Chili Peppers

Chili peppers are the pungent fruits of various species of the genus *Capsicum* and members of the *Solanaceae* family. Chili is a spice used as basic ingredient in a great variety of cuisines all over the world. It is also the most heavily and frequently consumed spice, used as a flavoring or coloring agent and adds taste to the otherwise insipid food (Kothari et al., 2010). Capsaicin is the major biologically active ingredient of chili peppers. Traditionally, capsaicin has been used for topical application including treatment for pain and burning of arthralgias, plantar warts, pharyngitis, diabetic neuralgia and hemodialysis-related pruritus (Norton, 1998). Extensive studies suggest that capsaicin is also a cancer-suppressing agent through its antioxidant and anti-inflammatory activities, by blocking several signal transduction pathways, including Nf-kB and AP-1 (Surh et al., 1998; Surh 2002; Bai et al., 2011). In the context of chronic pancreatitis, capsaicin demonstrates strong activities against inflammation and proliferation and

can inhibit progression of murine Pancreatic Intraepithelial Neoplasia (mPanIN) lesions and carcinogenesis, by blocking phospho-ERK and Hedgehog/GLI pathway activation. Capsaicin has been proposed as a very promising agent for inhibiting chronic pancreatitis and mPanINs formation and ultimately pancreatic carcinogenesis (Bai et al., 2011). Moreover, in several instances it has been demonstrated that capsaicin modulates microsomal cytochrome P450-dependent monooxygenase, thereby affecting metabolism of carcinogens and other xenobiotics (Surh et al., 1998).

Carrots

Carrot (*Daucus Carota*) is a plant species of the *Apiaceae* that is widely cultivated for its edible yellow-orange root. The plant has finely divided leaves and flat clusters of small white flowers. Carrots are one of the chief dietary sources of β-carotene, the dominating carotenoid in human blood and tissues. Carotenoids exhibit specific antioxidant activity but also influence signaling and gene expression at the cellular level (Stahl and Sies, 2005; Stahl and Sies, 2012). The effect of β-carotene supplementation on cancer incidence has been investigated in several randomized controlled trials. β-carotene has been proven to have anti-carcinogenic activity in several tissues, although high doses of β-carotene as dietary supplements failed to exhibit chemopreventive activity in clinical trials (Druesne-Pecollo et al., 2010). Data on a subsample of women in the Women's Health Initiative indicates that a relatively high serum level of β-carotene was inversely associated with risk of colon and colorectal cancer in postmenopausal women (Kabat et al., 2011).

Pomegranate

Pomegranate (*Punica granatum*) is a fruit-bearing deciduous shrub that, while native to Iran, grows throughout the Mediterranean region and the USA. The pomegranate has been of health-related interest since 1999 when Israeli researchers demonstrated the antioxidant potency of pomegranates (Schubert et al., 1999), which has been attributed to hundreds of phytochemicals in particular to ellagic acid, the main polyphenol in pomegranate (Bell and Hawthorne, 2008). It is interesting to note that many studies have observed the extract or the juice to be more beneficial compared to the individual or purified ingredient. Also in this instance, this suggests the existence of a chemical synergy when using an extract (Adhami et al., 2009). The use of juice, peel and oil has been shown to possess anticancer activities, including interference with tumor cell proliferation, cell cycle, invasion and angiogenesis (Adhami et al., 2009). These may be associated with plant based anti-inflammatory effects. Only a few well controlled clinical trials have been completed, despite the impressive amount of preclinical work indicating cancer preventive or therapeutic efficacy with limited toxicity (Lansky and Newman, 2007). Pomegranate juice and its ellagitannins inhibited proliferation and induced apoptosis in colon cancer cells inhibiting COX-2, Akt, and NF-kB (Adams et al., 2006). Moreover, both the lipid and aqueous pomegranate fractions appear to possess selective apoptotic potential down-regulating cyclins A and B1 and upregulating cyclin E, resulting in cell-cycle arrest in S phase and apoptosis, via an intrinsic pathway mediated by the release of cytochrome c from mitochondria into the cytosol (Lansky and Newman, 2007). The *in vitro* and *in vivo* effects of the pomegranate juice in colon cancer prevention have been recently reviewed (Jaganathan et al., 2014).

Curcuma

Radix curcumae, commonly known as turmeric, is a Chinese medicinal herb commonly used as food flavoring worldwide, to which a role is attributed in the treatment of malignancy and several other diseases such as liver cirrhosis, chronic renal disease, chronic obstructive lung disease, diabetes (Bengmark et al., 2009). The major active principle, curcumin (diferuloylmethane), is nontoxic and has a variety of therapeutic properties including anti-oxidant, analgesic, anti-inflammatory, and antiseptic activity. Extract solution from *radix curcumae* has a chemopreventive effect on gastric cancer induced by *N*-Methyl-*N'*-Nitro-*N*-Nitrosoguanidine in rats (Lu et al., 2008). Curcumin has been found to possess anti-cancer activities via its effect on a variety of biological pathways involved in mutagenesis, oncogene expression, cell cycle regulation, apoptosis, tumorigenesis and metastasis. Curcumin has shown anti-proliferative effects in head and neck cancers (Wilken et al., 2011) and is an inhibitor of the NF-kB transcription factor and downstream gene products including c-myc, Bcl-2, COX-2, NOS, cyclin D1, tumor necrosis factor alpha (TNF-α), interleukins, and MMP-9. The emergence of multidrug resistance (MDR) is a big challenge to cancer chemotherapy. Interestingly, it has been shown that fractionated extracts of curcuma (variety *wenyujin*) exhibited significant effects in sensitization of resistant cancer cells at non-toxic concentration to doxorubicin and docetaxel. All these fractions could enhance the apoptosis induced by doxorubicin in MDR cells (Yang et al., 2011b). Combining curcumin and various anti-cancer drugs has been suggested as a novel strategy to establish more efficient and less toxic treatment modalities (Troselj and Kujundzic, 2014).

CELLULAR ALTERATIONS AND MOLECULAR TARGETS

Cancer is a complex disease initiated by genetic mutations and carried out by continuous cell deregulation at many levels. Unrestrained cell proliferation and defective apoptosis are hallmarks of oncogenic transformation. Oncogenes and tumor suppressor genes are implied in cancer transformation and

food components are a source of important molecules with biological activities acting on neoplastic progression. Since genetic and epigenetic abnormalities have been shown to be both causative and contributing factors in cancer initiation and/or progression, natural compounds that are regulators of the epigenome constitute an excellent approach in cancer prevention and potentially in anti-cancer therapy. Several nutrients have been shown to affect DNA methylation, target histone modification and regulate oncogenic and tumor suppressor micro-RNAs (Stefanska et al., 2012).

Oncogenes are genes that promote cell cycle and cell proliferation and allow escaping from apoptosis, acting in a dominant fashion as a single alteration in one copy, inducing neoplastic growth. Since molecular analyses allow identification of specific pathways which are dysregulated in cancer cells, agents which epigenetically down-regulate the action of one or more oncogene-related proteins are potential candidates for individualized tumor prevention and therapy. Figure 1 describes some molecular targets of natural compounds derived from foods and herbs on the signal transduction pathways and oncogenes that are involved in cell proliferation as is in turn stimulatedtriggered by EGF.

Tumor suppressor genes are genes that negatively regulate cell cycle and cell proliferation, promoting apoptosis, and differentiation. Tumor suppressor genes are involved in repairing DNA damage and both copies need to be inactivated, in order to promote cancer development, as Knudson's "two-hits" theory says. Conversely, agents that enhance the activity of defective oncogenes and/or stimulate apoptosis may slow down cell cancer growth. Apoptosis is controlled by two diverse pathways, the intrinsic or mitochondrial-mediated pathway and the extrinsic or death receptor-mediated pathway. A long list of dietary constituents is known to induce apoptosis of cancer cells without affecting normal cells (Khan et al., 2008). Figure 2 illustrates the major activation pathways, molecular steps and control systems of cell apoptosis, with indications of the demonstrated targets of several compounds described in this review.

DISCUSSION AND CONCLUSIONS

During the past several decades, there has been growing interest in natural products for the cure and prevention of cancer. The concept of disease prevention is becoming more and more attractive as healthcare costs continue to escalate. Strongest data, pointing to cancer chemoprevention by food components, is currently coming from epidemiological studies

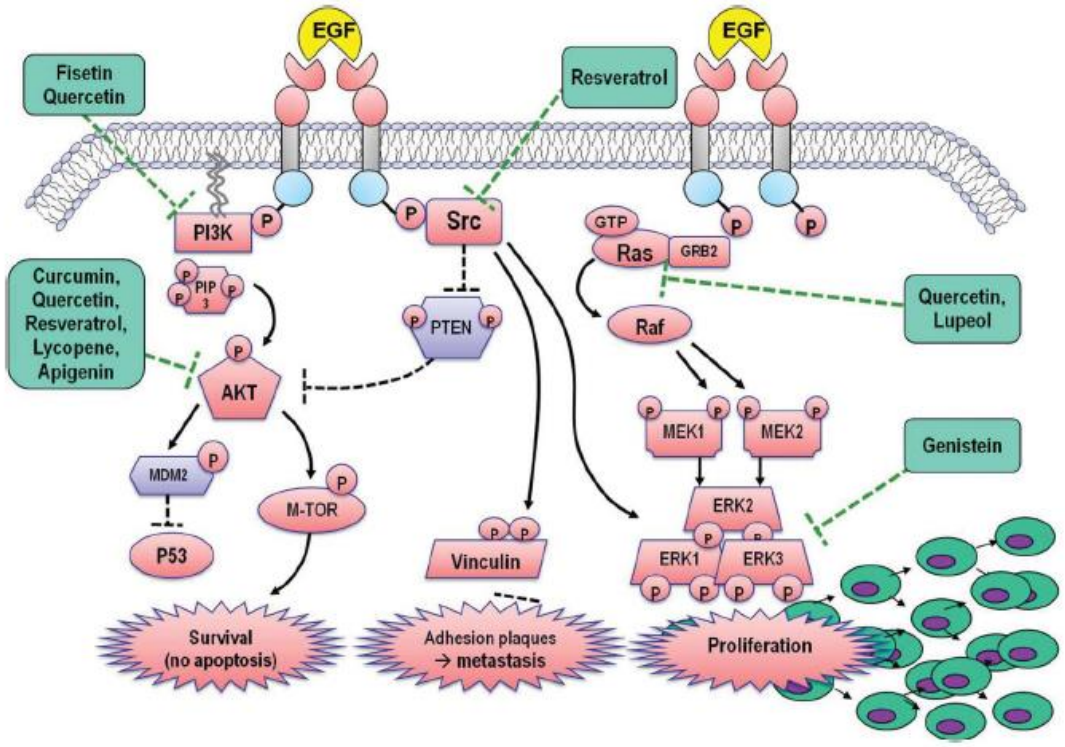


Figure 1 Schematic drawing of signal transduction pathways of EGF and targets of some natural compounds with regulatory activity. Abbreviations: PI3K = phospatidylinositol-3-kinase; PIP3 = Phosphatidylinositol (3,4,5)-triphosphate; Src = sarcoma; Ras = rat sarcoma; Raf = Rapidly accelerated fibrosarcoma; AKT (also called protein kinase B) = AK strain Transforming; PTEN = Phosphatase and Tensin homolog; BAD = Bcl-xL/Bcl-2-Associated Death promoter; MEK = Mitogen activated kinase (MEK1 and MEK2, also called MAP kinase kinases n. 1 and n. 2); ERK = Extracellular signal-Regulated Kinase (also called MAPK 3,4,5); MDM2 = Murine Double Minute2; mTOR = mammalian Target Of Rapamycin; GRB2 = Growth factor Receptor-Bound protein 2.

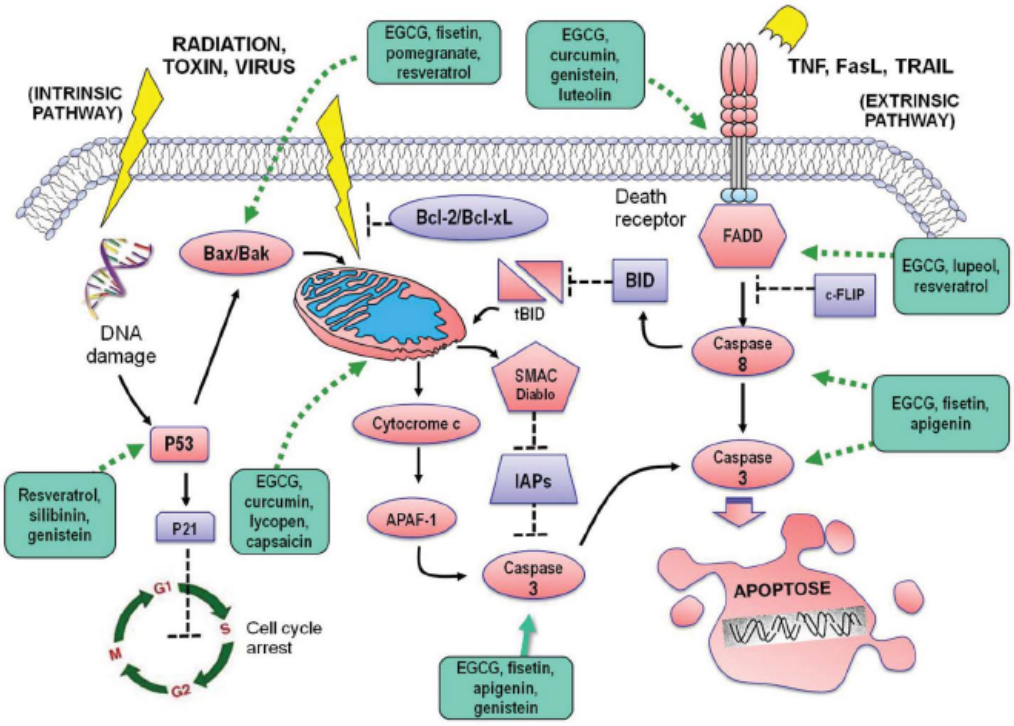


Figure 2 Schematic drawing of signal transduction pathways of apoptotic signals and targets of some natural compounds with stimulating activity. Abbreviations: TNF = Tumor Necrosis Factor; FAS = Fragment Apoptosis Stimulant; TRAIL = Tumor-necrosis-factor Related Apoptosis Inducing Ligand; APAF-1 = Apoptosis Activator Factor-1; Bcl-2 = B-cell lymphoma 2; Bax = Bcl-2-associated X protein; Bak = Bcl-2 homologous antagonist killer; SMAC = Second Mitocondrial Activator of Caspase; IAPs = Inhibiting Apoptosis Proteins; FADD = Fas-Associated protein with Death Domains; cFLIP = cellular caspase 8 (FLICE)-Inhibitory Protein; FLICE (also called caspase 8) = Fas-associated protein with death domain-Like IL-1β-Converting Enzyme-inhibitory protein; BID = BH3 (Bcl-2 Homology-3)-Interacting Domain death agonist; tBID = Truncated BID.

and from in vitro cell cultures, whereas the clinical evidence from intervention trials remains scanty. A large number of epidemiological observations have established links between diet and disease prevention, a number of biologically active compounds have been identified and a few plants used in folk and traditional medicine have been scientifically explored (Mukherjee et al., 2001). Recent studies have shown that conventional cancer therapies, such as chemotherapy, radiotherapy and surgery, could be administered in association with co-adjuvant therapies. Together, these can improve the prognosis and the quality of life for cancer patients. As a result, there is major interest in developing adjuvant chemotherapies to augment currently available treatment protocols, which may allow for decreased side effects and toxicity, without compromising therapeutic efficacy.

Fruit, vegetables, herbs and spices comprise a plethora of opportunities for drug discovery. Unfortunately, at this time none of the completed trials have produced forceful evidence to justify the use of traditional antioxidant-related vitamins or minerals for cancer prevention. At the present time, acquired knowledge in the nutritional science shows that specific antioxidant activity is not the only mechanism of action for vitamins and minerals. Antioxidants and other components contained in foods act in synergy, with the consequence that the use of single substances at high doses could exert a paradoxical effect. The lack of success may be explained by a variety of factors that need to be considered for the next generation research. These factors include the following: a lack of good biological rationale for selecting specific agents of interest; a limited number of agents clinically tested; the use of pharmacological, rather than dietary doses and an insufficient duration of intervention and follow-up. These results are consistent with the hypothesis that the effects of antioxidant use may only be detectable at a subclinical (molecular) level, whereas a reduction in risk of clinically detectable disease requires prolonged exposures that may not be achievable in a traditional cancer prevention trial. Moreover, it is necessary to highlight that it is not possible to directly deduce a safe clinical effectiveness from in vitro models alone, since cell lines are not necessarily representative of complex tissue and organic systems that one would want to treat in human cancer (Goodman et al., 2011).

There is also the problem of the biphasic effects, a phenomenon also called "hormesis" (Calabrese, 2010) and consequently the selection of an appropriate dosage becomes a critical issue. For example, although genistein has many potentially therapeutic actions, its biphasic activity (cytotoxic

at higher concentrations and vitalizing at low concentrations) requires caution in determining the therapeutic dose (Ravindranath et al., 2004). Similarly, resveratrol induces hormesis-like biphasic dose responses in a wide range of human tumor cell lines affecting breast, prostate, colon, lung, uterine and leukemia (Calabrese et al., 2010): this compound at low doses acts as an anti-apoptotic agent while at higher doses it acts as a pro-apoptotic compound, inducing apoptosis in cancer cells, by exerting a death signal. (Mukherjee et al., 2010). Quercetin is a powerful dietary polyphenol that can exert hormetic dose-responses on cells, depending on its concentration and on the agonist receptors used (Vargas and Burd, 2010; Chirumbolo et al., 2010).

Another example of these complexities is given by folic acid or folate (the form naturally occurring in the body). Some investigations have proposed that diets high in folate may be related to a lower risk of colorectal cancer (Sanjoaquin et al., 2005). However); however, folate is important for cells and tissues that rapidly divide; many cancer cells have a high requirement for folic acid and overexpress the folic acid receptor and drugs that interfere with folate receptors or metabolism are used to treat cancer. Likewise, it has been suggested excess folate may promote tumor initiation (Kim, 2004). In addition, folic acid could even be contraindicated in patients affected by cancer or precancerous conditions. So, the benefits of folic acid against cancer may depend on dosage, type of dietary source or supplementation and individual conditions. It is reassuring that in a meta-analysis of 8 trials of folic acid supplementation there was no significant effect on overall cancer or mortality in the populations studied (Clarke et. al., 2010).

Cancer progression includes derangement or disruption of cellular and systemic networks that cause sustained proliferative signaling, evasion of growth suppressors, resistance of cell death and replicative immortality, angiogenesis, invasion and metastasis, immune suppression and deregulation of cellular energetics. These cancer cell properties are facilitated or inhibited by the pro-inflammatory components of the tumor microenvironment. Therefore, multidisciplinary approaches are needed and the use of an extract, rather than a purified compound, could explain the inhibition of multiple targets observed in many studies and thus the greater likelihood for producing cancer chemopreventive effects in humans. This may account for the synergistic preventive and/or anti-cancer effects and the approach could be explored in laboratory, animal, clinical and epidemiological studies in the future. It is anticipated that in-depth research into the anticancer activities of naturally occurring compounds would one day enable the development of a cocktail of such molecules for effective prevention (Adhami et al., 2009).

This study may help to explain why diets rich in fruit, vegetables and soy protein are associated with protection against the development and progression of digestive system cancers, although further studies of the best formulations and dosages are needed to develop specific public health recommendations for treatment and prevention of cancer.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

REFERENCES

Adams, L. S., Seeram, N. P., Aggarwal, B. B., Takada, Y., Sand, D. and Heber, D. (2006). Pomegranate juice, total pomegranate ellagitannins, and punicalagin suppress inflammatory cell signaling in colon cancer cells. *J. Agric. Food Chem.* **54**:980–985.

Adhami, V. M., Khan, N. and Mukhtar, H. (2009). Cancer chemoprevention by pomegranate: Laboratory and clinical evidence. *Nutr. Cancer* **61**:811–815.

Agarwal, S. and Rao, A. V. (2000). Tomato lycopene and its role in human health and chronic diseases. *CMAJ* **163**:739–744.

Aggarwal, B. B. and Shishodia, S. (2004). Suppression of the nuclear factor-kappaB activation pathway by spice-derived phytochemicals: Reasoning for seasoning. *Ann. N. Y. Acad. Sci.* **1030**:434–441.

Aggarwal, B. B. and Shishodia, S. (2006). Molecular targets of dietary agents for prevention and therapy of cancer. *Biochem. Pharmacol.* **71**:1397–1421.

Ahmed, S. and Othman., N. H. (2013). Honey as a potential natural anticancer agent: a review of its mechanisms. *Evid Based Complement Alternat. Med.* **2013**:829070.

Akev, N., Turkay, G., Can, A., Gurel, A., Yildiz, F., Yardibi, H., Ekiz, E. E. and Uzun, H. (2007). Effect of Aloe vera leaf pulp extract on Ehrlich ascites tumours in mice. *Eur. J. Cancer Prev.* **16**:151–157.

Ali, A. T., al-Swayeh, O. A., al-Humayyd, M. S., Mustafa, A. A., al-Rashed, R. S. and al-Tuwaijiri, A. S. (1997). Natural honey prevents ischaemia-reperfusion-induced gastric mucosal lesions and increased vascular permeability in rats. *Eur. J. Gastroenterol. Hepatol.* **9**:1101–1107.

Anderson, J. W. and Bush, H. M. (2011). Soy protein effects on serum lipoproteins: A quality assessment and meta-analysis of randomized, controlled studies. *J. Am. Coll. Nutr.* **30**:79–91.

Anderson, J. W., Johnstone, B. M. and Cook-Newell, M. E. (1995). Meta-analysis of the effects of soy protein intake on serum lipids. *N. Engl. J. Med.* **333**:276–282.

Bai, H., Li, H., Zhang, W., Matkowskyj, K. A., Liao, J., Srivastava, S. K. and Yang, G. Y. (2011). Inhibition of chronic pancreatitis and pancreatic intraepithelial neoplasia (PanIN) by capsaicin in LSL-KrasG12D/Pdx1-Cre mice. *Carcinogenesis* **32**:1689–1696.

Banerjee, S., Li, Y., Wang, Z. and Sarkar, F. H. (2008). Multi-targeted therapy of cancer by genistein. *Cancer Lett.* **269**:226–242.

Beaglehole, R., Bonita, R. and Magnusson, R (2011). Global cancer prevention: An important pathway to global health and development. *Public Health* **125**:821–831.

Bell, C. and Hawthorne, S. (2008). Ellagic acid, pomegranate and prostate cancer–a mini review. *J. Pharm. Pharmacol.* **60**:139–144.

Bengmark, S., Mesa, M. D. and Gil, A. (2009). Plant-derived health: The effects of turmeric and curcuminoids. *Nutr. Hosp.* **24**:273–281.

Bertl, E., Bartsch, H. and Gerhäuser, C. (2006). Inhibition of angiogenesis and endothelial cell functions are novel sulforaphane-mediated mechanisms in chemoprevention. *Mol. Cancer Ther.* **5**:575–585.

Bianchini, F. and Vainio, H. (2001). Allium vegetables and organosulfur compounds: Do they help prevent cancer? *Environ. Health Perspect.* **109**: 893–902.

Bogdanov, S., Jurendic, T., Sieber, R. and Gallmann, P. (2008). Honey for nutrition and health: A review. *J. Am. Coll. Nutr.* **27**:677–689.

Calabrese, E. J. (2010). Hormesis and medicine. *Br. J. Clin. Pharmacol.* **66**:594–617.

Calabrese, E. J., Mattson, M. P. and Calabrese, V. (2010). Resveratrol commonly displays hormesis: Occurrence and biomedical significance. *Hum. Exp. Toxicol.* **29**:980–1015.

Chan, J. M., Wang, F. and Holly, E. A. (2005). Vegetable and fruit intake and pancreatic cancer in a population-based case-control study in the San Francisco bay area. *Cancer Epidemiol. Biomarkers Prev.* **14**:2093–2097.

Chirumbolo, S., Marzotto, M., Conforti, A., Vella, A., Ortolani, R. and Bellavite, P. (2010). Bimodal action of the flavonoid quercetin on basophil function: An investigation of the putative biochemical targets. *Clin. Mol. Allergy* **8**:13.

Chow, H. H. and Hakim, I. A. (2011). Pharmacokinetic and chemoprevention studies on tea in humans. *Pharmacol. Res.* **64**:105–112.

Chun, H. S., Chang, H. J., Choi, E. H., Kim, H. J. and Ku, K. H. (2005). Molecular and absorption properties of 12 soy isoflavones and their structure-activity relationship with selected biological activities. *Biotechnol. Lett.* **27**:1105–1111.

Clarke, J. D., Dashwood, R. H. and Ho, E. (2008). Multi-targeted prevention of cancer by sulforaphane. *Cancer Lett.* **269**:291–304.

Clarke, R., Halsey, J., Lewington, S., Lonn, E., Armitage, J., Manson, J. E., Bønaa, K. H., Spence, J. D., Nygård, O., Jamison, R., Gaziano, J. M., Guarino, P., Bennett, D., Mir, F., Peto, R., Collins, R.; B-Vitamin Treatment Trialists' Collaboration. (2010). Effects of lowering homocysteine levels with B vitamins on cardiovascular disease, cancer, and cause-specific mortality meta-analysis of 8 randomized trials involving 37485 individuals. *Arch. Intern. Med.* **170**:1622–1631.

Cohen, L. A. (2002). A review of animal model studies of tomato carotenoids, lycopene, and cancer chemoprevention. *Exp. Biol. Med. (Maywood)* **227**:864–868.

Corona, G., Deiana, M., Incani, A., Vauzour, D., Dessì, M. A. and Spencer, J. P. (2009). Hydroxytyrosol inhibits the proliferation of human colon adenocarcinoma cells through inhibition of ERK1/2 and cyclin D1. *Mol. Nutr. Food Res.* **53**:897–903.

Corona, G., Spencer, J. P. and Dessì, M. A. (2009). Extra virgin olive oil phenolics: Absorption, metabolism, and biological activities in the GI tract. *Toxicol. Ind. Health* **25**:285–293.

Davis, C. D., Clevidence, B., Swanson, C. A., Ziegler, R. G., Dwyer, J. T. and Milner, J. A. (2005). A research agenda for lycopene/tomato supplementation and cancer prevention. *J. Nutr.* **135**:2074S.

Deng, G. E., Frenkel, M., Cohen, L., Cassileth, B. R., Abrams, D. I., Capodice, J. L., Courneya, K. S., Dryden, T., Hanser, S., Kumar, N., Labriola, D., Wardell, D. W. and Sagar, S.; Society for Integrative Oncology. (2009). Evidence-based clinical practice guidelines for integrative oncology: Complementary therapies and botanicals. *J. Soc. Integr. Oncol.* **7**:85–120.

Dorai, T. and Aggarwal, B. B. (2004). Role of chemopreventive agents in cancer therapy. *Cancer Lett.* **215**:129–140.

Druesne-Pecollo, N., Latino-Martel, P., Norat, T., Barrandon, E., Bertrais, S., Galan, P. and Hercberg, S. (2010). Beta-carotene supplementation and cancer risk: A systematic review and metaanalysis of randomized controlled trials. *Int. J. Cancer* **127**:172–184.

Egert, S., Wolffram, S., Bosy-Westphal, A., Boesch-Saadatmandi, C., Wagner, A. E., Frank, J., Rimbach, G. and Mueller, M. J. (2008). Daily quercetin supplementation dose-dependently increases plasma quercetin concentrations in healthy humans. *J. Nutr.* **138**:1615–1621.

El-Shemy, H. A., Aboul-Soud, M. A., Nassr-Allah, A. A., Aboul-Enein, K. M., Kabash, A. and Yagi, A. (2010). Antitumor properties and modulation of antioxidant enzymes' activity by Aloe vera leaf active principles isolated via supercritical carbon dioxide extraction. *Curr. Med. Chem.* **17**:129–138.

Ferreres, F., Taveira, M., Pereira, D. M., Valentão, P. and Andrade, P. B. (2010). Tomato (Lycopersicon esculentum) seeds: New flavonols and cytotoxic effect. *J. Agric. Food Chem.* **58**:2854–2861.

Friedman, M., Levin, C. E., Lee, S. U., Kim, H. J., Lee, I. S., Byun, J. O. and Kozukue, N. (2009). Tomatine-containing green tomato extracts inhibit growth of human breast, colon, liver, and stomach cancer cells. *J. Agric. Food Chem.* **57**:5727–5733.

Galeone, C., Pelucchi, C., Levi, F., Negri, E., Franceschi, S., Talamini, R., Giacosa, A., and La Vecchia, C. (2006). Onion and garlic use and human cancer. *Am. J. Clin. Nutr.* **84**:1027–1032.

Gao, Y. T., McLaughlin, J. K., Blot, W. J., Ji, B. T., Dai, Q. and Fraumeni, J. F. (1994). Reduced risk of esophageal cancer associated with green tea consumption. *J. Natl. Cancer Inst.* **86**:855–858.

Garavello, W., Lucenteforte, E., Bosetti, C. and La Vecchia, C. (2009). The role of foods and nutrients on oral and pharyngeal cancer risk. *Minerva Stomatol.* **58**:25–34.

Gharzouli, K., Amira, S., Gharzouli, A. and Khennouf, S. (1999). Prevention of ethanol-induced gastric lesions in rats by natural honey and glucose-fructose-sucrose-maltose mixture. *Pharmacol. Res.* **39**:151–156.

Gharzouli, K., Amira, S., Gharzouli, A. and Khennouf, S. (2002). Gastroprotective effects of honey and glucose-fructose-sucrose-maltose mixture against ethanol-, indomethacin-, and acidified aspirin-induced lesions in the rat. *Exp. Toxicol. Pathol.* **54**:217–221.

Goodman, M., Bostick, R. M., Kucuk, O. and Jones, D. P. (2011). Clinical trials of antioxidants as cancer prevention agents: Past, present, and future. *Free Radic. Biol. Med.* **51**:1068–1084.

Hayes, J. D., Kelleher, M. O. and Eggleston, I. M. (2008). The cancer chemopreventive actions of phytochemicals derived from glucosinolates. *Eur. J. Nutr.* **47**(Suppl 2):73–88.

He, T. P., Yan, W. H., Mo, L. E. and Liang, N. C. (2008). Inhibitory effect of aloe-emodin on metastasis potential in HO-8910PM cell line. *J. Asian Nat. Prod. Res.* **10**:383–390.

Heber, D., Lu, Q. Y. and Go, V. L. (2001). Role of tomatoes, tomato products and lycopene in cancer prevention. *Adv. Exp. Med. Biol.* **492**:29–37.

Herr, I. and Buchler, M. W. (2010). Dietary constituents of broccoli and other cruciferous vegetables: Implications for prevention and therapy of cancer. *Cancer Treat. Rev.* **36**:377–383.

Higdon, J. V., Delage, B., Williams, D. E. and Dashwood, R. H. (2007). Cruciferous vegetables and human cancer risk: Epidemiologic evidence and mechanistic basis. *Pharmacol. Res.* **55**:224–236.

Hudson, T. S., Hartle, D. K., Hursting, S. D., Nunez, N. P., Wang, T. T., Young, H. A., Arany, P. and Green, J. E. (2007). Inhibition of prostate cancer growth by muscadine grape skin extract and resveratrol through distinct mechanisms. *Cancer Res.* **67**:8396–8405.

Hwang, E. S. and Bowen, P. E. (2002). Can the consumption of tomatoes or lycopene reduce cancer risk? *Integr. Cancer Ther.* **1**:121–132.

Jaganathan, S. K. and Mandal, M. (2009). Antiproliferative effects of honey and of its polyphenols: A review. *J. Biomed. Biotechnol.* **2009**:830616.

Jaganathan, S. K., Mazumdar, A., Mondhe, D. and Mandal, M. (2011). Apoptotic effect of eugenol in human colon cancer cell lines. *Cell. Biol. Int.* **35**:607–615.

Jaganathan,S. K., Vellayappan, M. V., Narasimhan,G. and Supriyanto, E. (2014) Role of pomegranate and citrus fruit juices in colon cancer prevention. *World J. Gastroenterol.* **20**:4618–4625.

Jang, M., Cai, L., Udeani, G. O., Slowing, K. V., Thomas, C. F., Beecher, C. W., Fong, H. H., Farnsworth, N. R., Kinghorn, A. D., Mehta, R. G., Moon, R. C. and Pezzuto, J. M. (1997). Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science* **275**:218–220.

Jenab, M., Ferrari, P., Mazuir, M., Tjonneland, A., Clavel-Chapelon, F., Linseisen, J., Trichopoulou, A., Tumino, R., Bueno-de-Mesquita, H. B., Lund, E., Gonzalez, C. A., Johansson, G., Key, T. J. and Riboli, E.; European Prospective Investigation into Cancer and Nutrition (EPIC) study. (2005). Variations in lycopene blood levels and tomato consumption across European countries based on the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *J. Nutr.* **135**:2032S–2036S.

Ji, B. T., Chow, W. H., Hsing, A. W., McLaughlin, J. K., Dai, Q., Gao, Y. T., Blot, W. J. and Fraumeni, J. F. Jr. (1997). Green tea consumption and the risk of pancreatic and colorectal cancers. *Int. J. Cancer* **70**:255–258.

Ji, B. T., Chow, W. H., Yang, G., McLaughlin, J. K., Gao, R. N., Zheng, W., Shu, X. O., Jin, F., Fraumeni, J. F. Jr. and Gao, Y. T. (1996). The influence of cigarette smoking, alcohol, and green tea consumption on the risk of carcinoma of the cardia and distal stomach in Shanghai, China. *Cancer* 77:2449–2457.

Ju, J., Hong, J., Zhou, J. N., Pan, Z., Bose, M., Liao, J., Yang, G. Y., Liu, Y. Y., Hou, Z., Lin, Y., Ma, J., Shih, W. J., Carothers, A. M. and Yang, C. S. (2005). Inhibition of intestinal tumorigenesis in Apcmin/+ mice by (-)-epigallocatechin-3-gallate, the major catechin in green tea. *Cancer Res.* **65**:10623–10631.

Juge, N., Mithen, R. F. and Traka, M. (2007). Molecular basis for chemoprevention by sulforaphane: A comprehensive review. *Cell. Mol. Life Sci.* **64**:1105–1127.

Kabat, G. C., Kim, M. Y., Sarto, G. E., Shikany, J. M. and Rohan, T. E. (2011). Repeated measurements of serum carotenoid, retinol and tocopherol levels in relation to colorectal cancer risk in the Women's Health Initiative. *Eur. J. Clin. Nutr.* **66**:549–554

Kallifatidis, G., Rausch, V., Baumann, B., Apel, A., Beckermann, B. M., Groth, A., Mattern, J., Li, Z., Kolb, A., Moldenhauer, G., Altevogt, P., Wirth, T., Werner, J., Schemmer, P., Büchler, M. W., Salnikov, A. V. and Herr, I. (2009). Sulforaphane targets pancreatic tumour-initiating cells by NF-kappaB-induced antiapoptotic signalling. *Gut* **58**:949–963.

Kang, J., Badger, T. M., Ronis, M. J. and Wu, X. (2010). Non-isoflavone phytochemicals in soy and their health effects. *J. Agric. Food Chem.* **58**: 8119–8133.

Kaur, M., Agarwal, C. and Agarwal, R. (2009). Anticancer and cancer chemopreventive potential of grape seed extract and other grape-based products. *J. Nutr.* **139**:1806S–1812S.

Kavanaugh, C. J., Trumbo, P. R. and Ellwood, K. C. (2007). The U.S. Food and Drug Administration's evidence-based review for qualified health claims: Tomatoes, lycopene, and cancer. *J. Natl. Cancer Inst.* **99**: 1074–1085.

Khan, N., Adhami, V. M. and Mukhtar, H. (2008). Apoptosis by dietary agents for prevention and treatment of cancer. *Biochem. Pharmacol.* **76**: 1333–1339.

Khanum, F., Anilakumar, K. R. and Viswanathan, K. R. (2004). Anticarcinogenic properties of garlic: A review. *Crit. Rev. Food Sci. Nutr.* **44**:479–488.

Kim, Y. I. (2004). Will mandatory folic acid fortification prevent or promote cancer? *Am. J. Clin. Nutr.* **80**:1123–1128.

Kingsley, K., Truong, K., Low, E., Hill, C. K., Chokshi, S. B., Phipps, D., West, M. A., Keiserman, M. A. and Bergman, C. J. (2011). Soy Protein Extract (SPE) exhibits differential in vitro cell proliferation effects in oral cancer and normal cell lines. *J. Diet. Suppl.* **8**:169–188.

Kothari, S. L., Joshi, A., Kachhwaha, S. and Ochoa-Alejo, N. (2010). Chili peppers–a review on tissue culture and transgenesis. *Biotechnol. Adv.* **28**:35–48.

Kresty, L. A., Frankel, W. L., Hammond, C. D., Baird, M. E., Mele, J. M., Stoner, G. D. and Fromkes, J. J. (2006). Transitioning from preclinical to clinical chemopreventive assessments of lyophilized black raspberries: Interim results show berries modulate markers of oxidative stress in Barrett's esophagus patients. *Nutr. Cancer* **54**:148–156.

Kushi, L. H., Doyle, C., McCullough, M., Rock, C. L., Demark-Wahnefried, W., Bandera, E. V., Gapstur, S., Patel, A. V., Andrews, K. and Gansler, T.; American Cancer Society 2010 Nutrition and Physical Activity Guidelines Advisory Committee. (2012). American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: Reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J. Clin.* **62**:30–67.

Kyle, J. A., Sharp, L., Little, J., Duthie, G. G. and McNeill, G (2010). Dietary flavonoid intake and colorectal cancer: A case-control study. *Br. J. Nutr.* **103**:429–436.

Lansky, E. P. and Newman, R. A. (2007). Punica granatum (pomegranate) and its potential for prevention and treatment of inflammation and cancer. *J. Ethnopharmacol.* **109**:177–206.

Lippi, G. and Targher, G. (2011). Tomatoes, lycopene-containing foods and cancer risk. *Br. J. Cancer* **104**:1234–1235.

Liu, J. (1995). Pharmacology of oleanolic acid and ursolic acid. *J. Ethnopharmacol.* **49**:57–68.

Liu, B. L., Zhang, X., Zhang, W. and Zhen, H. N. (2007). New enlightenment of French Paradox: Resveratrol's potential for cancer chemoprevention and anti-cancer therapy. *Cancer Biol. Ther.* **6**:1833–1836.

Lu, B., Xu, L., Yu, L. and Zhang, L. (2008). Extract of radix curcumae prevents gastric cancer in rats. *Digestion* **77**:87–91.

Manach, C., Williamson, G., Morand, C., Scalbert, A. and Remesy, C. (2005). Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am. J. Clin. Nutr.* **81**:230S–242S.

Messina, M. (2010). A brief historical overview of the past two decades of soy and isoflavone research. *J. Nutr.* **140**:1350S–1354S.

Moon, Y. J., Wang, L., Di Cenzo, R. and Morris, M. E. (2008). Quercetin pharmacokinetics in humans. *Biopharm. Drug Dispos.* **29**:205–217.

Mukherjee, A. K., Basu, S., Sarkar, N. and Ghosh, A. C. (2001). Advances in cancer therapy with plant based natural products. *Curr. Med. Chem.* **8**:1467–1486.

Mukherjee, S., Dudley, J. I. and Das, D. K. (2010). Dose-dependency of resveratrol in providing health benefits. *Dose Response* **8**:478–500.

Müller, N., Alteheld, B. and Stehle, P. (2003). Tomato products and lycopene supplements: Mandatory components in nutritional treatment of cancer patients? *Curr. Opin. Clin. Nutr. Metab. Care* **6**:657–660.

Myzak, M. C. and Dashwood, R. H. (2006). Chemoprotection by sulforaphane: Keep one eye beyond Keap1. *Cancer Lett.* **233**:208–218.

Ngo, S. N., Williams, D. B., Cobiac, L. and Head, R. J. (2007). Does garlic reduce risk of colorectal cancer? A systematic review. *J. Nutr.* **137**:2264–2269.

Ngo, S. N., Williams, D. B. and Head, R. J. (2011). Rosemary and cancer prevention: Preclinical perspectives. *Crit. Rev. Food Sci. Nutr.* **51**:946–954.

Norton, S. A. (1998). Useful plants of dermatology. V. Capsicum and capsaicin. *J. Am. Acad. Dermatol.* **39**:626–628.

Notarnicola, M., Pisanti, S., Tutino, V., Bocale, D., Rotelli, M. T., Gentile, A., Memeo, V., Bifulco, M., Perri, E. and Caruso, M. G. (2011). Effects of olive oil polyphenols on fatty acid synthase gene expression and activity in human colorectal cancer cells. *Genes Nutr.* **6**:63–69.

Omar, S. H. (2010). Oleuropein in olive and its pharmacological effects. *Sci. Pharm.* **78**:133–154.

Omoni, A. O. and Aluko, R. E. (2005). Soybean foods and their benefits: Potential mechanisms of action. *Nutr. Rev.* **63**:272–283.

Pavese, J. M., Farmer, R. L. and Bergan, R. C. (2010). Inhibition of cancer cell invasion and metastasis by genistein. *Cancer Metastasis Rev.* **29**:465–482.

Pelucchi, C., Bosetti, C., Rossi, M., Negri, E. and La Vecchia, C. (2009). Selected aspects of Mediterranean diet and cancer risk. *Nutr. Cancer* **61**:756–766.

Pezzuto, J. M. (2008). Grapes and human health: A perspective. *J. Agric. Food Chem.* **56**:6777–6784.

Polívková, Z., Šmerák, P., Demová, H. and Houška, M. (2010). Antimutagenic effects of lycopene and tomato puree. *J. Med. Food* **13**:1443–1450.

Prasad, S., Yadav, V. R., Kannappan, R. and Aggarwal, B. B. (2011). Ursolic acid, a pentacyclin triterpene, potentiates TRAIL-induced apoptosis through p53-independent up-regulation of death receptors: Evidence for the role of reactive oxygen species and JNK. *J. Biol. Chem.* **286**:5546–5557.

Psaltopoulou, T., Kosti, R. I., Haidopoulos, D., Dimopoulos, M. and Panagiotakos, D. B. (2011). Olive oil intake is inversely related to cancer prevalence: A systematic review and a meta-analysis of 13,800 patients and 23,340 controls in 19 observational studies. *Lipids Health Dis.* **10**:127.

Ramos, S. (2007). Effects of dietary flavonoids on apoptotic pathways related to cancer chemoprevention. *J. Nutr. Biochem.* **18**:427–442.

Ratcliffe, N. A., Mello, C. B., Garcia, E. S., Butt, T. M. and Azambuja, P. (2011). Insect natural products and processes: New treatments for human disease. *Insect Biochem. Mol. Biol.* **41**:747–769.

Ravindranath, M. H., Muthugounder, S., Presser, N. and Viswanathan, S. (2004). Anticancer therapeutic potential of soy isoflavone, genistein. *Adv. Exp. Med. Biol.* **546**:121–165.

Rodrigo, K. A., Rawal, Y., Renner, R. J., Schwartz, S. J., Tian, Q., Larsen, P. E. and Mallery, S. R. (2006). Suppression of the tumorigenic phenotype in human oral squamous cell carcinoma cells by an ethanol extract derived from freeze-dried black raspberries. *Nutr. Cancer* **54**:58–68.

Rose, P., Whiteman, M., Moore, P. K. and Zhu, Y. Z. (2005). Bioactive S-alk (en)yl cysteine sulfoxide metabolites in the genus Allium: The chemistry of potential therapeutic agents. *Nat. Prod. Rep.* **22**:351–368.

Russo, M., Spagnuolo, C., Tedesco, I., Bilotto, S. and Russo, G. L. (2012) The flavonoid quercetin in disease prevention and therapy: Facts and fancies. *Biochem. Pharmacol.* **83**:6–15.

Saif, M. W., Tytler, E., Lansigan, F., Brown, D. M. and Husband, A. J. (2009). Flavonoids, phenoxodiol, and a novel agent, triphendiol, for the treatment of pancreaticobiliary cancers. *Expert Opin. Investig. Drugs* **18**:469–479.

Sang, S., Lambert, J. D., Ho, C. T. and Yang, C. S. (2011). The chemistry and biotransformation of tea constituents. *Pharmacol Res.* **64**:87–99.

Sanjoaquin, M. A., Allen, N., Couto, E., Roddam, A. W. and Key, T. J. (2005). Folate intake and colorectal cancer risk: A meta-analytical approach. *Int. J. Cancer* **113**:825–828.

Schubert, S. Y., Lansky, E. P. and Neeman, I. (1999). Antioxidant and eicosanoid enzyme inhibition properties of pomegranate seed oil and fermented juice flavonoids. *J. Ethnopharmacol.* **66**:11–17.

Seeram, N. P. (2008). Berry fruits for cancer prevention: Current status and future prospects. *J. Agric. Food Chem.* **56**:630–635.

Shi, J., Yang, B., Feng, P., Li, D. and Zhu, J. (2010). Induction of apoptosis by tomato using space mutation breeding in human colon cancer SW480 and HT-29 cells. *J. Sci. Food Agric.* **90**:615–621.

Shishu, Singla, A. K. and Kaur, I. P. (2003). Inhibition of mutagenicity of food-derived heterocyclic amines by sulphoraphene–an isothiocyanate isolated from radish. *Planta Med.* **69**:184–186.

Siegel, R., Naishadham, D. and Jemal, A. (2012). Cancer statistics, 2012. *CA Cancer J. Clin.* **62**:10–29.

Singletary, K. W. and Rokusek, J. T. (1997). Tissue-specific enhancement of xenobiotic detoxification enzymes in mice by dietary rosemary extract. *Plant Foods Hum. Nutr.* **50**:47–53.

Stahl, W. and Sies, H. (2005). Bioactivity and protective effects of natural carotenoids. *Biochim. Biophys. Acta* **1740**:101–107.

Stahl, W. and Sies, H. (2012). Photoprotection by dietary carotenoids: Concept, mechanisms, evidence and future development. *Mol. Nutr. Food Res.* **56**:287–295.

Stefanska, B., Karlic, H., Varga, F., Fabianowska-Majewska, K. and Haslberger, A. G. (2012). Epigenetic mechanisms in anti-cancer actions of bioactive food components-the implications in cancer prevention. *Br. J. Pharmacol.* **167**:279–297."

Stoner, G. D., Chen, T., Kresty, L. A., Aziz, R. M., Reinemann, T. and Nines, R. (2006). Protection against esophageal cancer in rodents with lyophilized berries: Potential mechanisms. *Nutr. Cancer* **54**:33–46.

Stoner, G. D., Wang, L. S., Zikri, N., Chen, T., Hecht, S. S., Huang, C., Sardo, C. and Lechner, J. F. (2007). Cancer prevention with freeze-dried berries and berry components. *Semin. Cancer Biol.* **17**:403–410.

Suboj, P., Babykutty, S., Srinivas, P. and Gopala, S. (2012). Aloe emodin induces G2/M cell cycle arrest and apoptosis via activation of caspase-6 in human colon cancer cells. *Pharmacology* **89**:91–98.

Sultana, N. (2011). Clinically useful anticancer, antitumor, and antiwrinkle agent, ursolic acid and related derivatives as medicinally important natural product. *J. Enzyme Inhib. Med. Chem.* **26**:616–642.

Surh, Y. J. (2002). Anti-tumor promoting potential of selected spice ingredients with antioxidative and anti-inflammatory activities: A short review. *Food Chem. Toxicol.* **40**:1091–1097.

Surh, Y. J., Lee, E. and Lee, J. M. (1998). Chemoprotective properties of some pungent ingredients present in red pepper and ginger. *Mutat. Res.* **402**:259–267.

Tomasin, R. and Gomes-Marcondes, M. C. (2011). Oral administration of Aloe vera and honey reduces Walker tumour growth by decreasing cell proliferation and increasing apoptosis in tumour tissue. *Phytother. Res.* **25**:619–623.

Troselj, K. G. and Kujundzic, R. N. (2014) Curcumin in combined cancer therapy. *Curr. Pharm. Des.* **20**:6682–6696.

Tse, G. and Eslick, G. D. (2014) Cruciferous vegetables and risk of colorectal neoplasms: a systematic review and meta-ana.ysis. *Nutr. Cancer* **66**:128–139.

Ullah, M. F. and Khan, M. W. (2008). Food as medicine: Potential therapeutic tendencies of plant derived polyphenolic compounds. *Asian Pac. J. Cancer Prev.* **9**:187–195.

Vargas, A. J. and Burd, R. (2010). Hormesis and synergy: Pathways and mechanisms of quercetin in cancer prevention and management. *Nutr. Rev.* **68**:418–428.

Verhoeyen, M. E., Bovy, A., Collins, G., Muir, S., Robinson, S., de Vos, C. H. and Colliver, S. (2002). Increasing antioxidant levels in tomatoes through modification of the flavonoid biosynthetic pathway. *J. Exp. Bot.* **53**: 2099–2106.

Verhoeven, D. T., Goldbohm, R. A., van Poppel, G., Verhagen, H. and van den Brandt, P. A. (1996). Epidemiological studies on brassica vegetables and cancer risk. *Cancer Epidemiol. Biomarkers Prev.* **5**:733–748.

Visioli, F., Bogani, P., Grande, S. and Galli, C. (2005). Mediterranean food and health: Building human evidence. *J. Physiol. Pharmacol.* **56** (Suppl. 1):37–49.

Vislocky, L. M. and Fernandez, M. L. (2010). Biomedical effects of grape products. *Nutr. Rev.* **68**:656–670.

Walfisch, S., Walfisch, Y., Kirilov, E., Linde, N., Mnitentag, H., Agbaria, R., Sharoni, Y. and Levy, J. (2007). Tomato lycopene extract supplementation decreases insulin-like growth factor-I levels in colon cancer patients. *Eur. J. Cancer Prev.* **16**:298–303.

Wang, S., DeGroff, V. L. and Clinton, S. K. (2003). Tomato and soy polyphenols reduce insulin-like growth factor-I-stimulated rat prostate cancer cell proliferation and apoptotic resistance in vitro via inhibition of intracellular signaling pathways involving tyrosine kinase. *J. Nutr.* **133**: 2367–2376.

Weisburger, J. H. (2002). Lycopene and tomato products in health promotion. *Exp. Biol. Med. (Maywood)* **227**:924–927.

Wilken, R., Veena, M. S., Wang, M. B. and Srivatsan, E. S. (2011). Curcumin: A review of anti-cancer properties and therapeutic activity in head and neck squamous cell carcinoma. *Mol. Cancer* **10**:12.

Wiseman, M. J. (2015) Nutrition and cancer – global and African perspectives: a focused update. *Proc. Nutr. Soc.* Published online Jan 22:1–4. DOI:http://dx.doi.org/10.1017/S0029665114001761.

Wu, Q. J., Yang, Y., Wang, J. Han, L.H. and Xiang, Y. B. (2013) Cruciferous vegetable consumption and gastric cancer risk: a meta-analysis of epidemiological studies. *Cancer Sci.* **104**:1067–1073.

Xiao, C. W. (2008). Health effects of soy protein and isoflavones in humans. *J. Nutr.* **138**:1244S–1249S.

Yang, C. S., Maliakal, P. and Meng, X. (2002). Inhibition of carcinogenesis by tea. *Annu. Rev. Pharmacol. Toxicol.* **42**:25–54.

Zhang, Y., Li, J. and Tang, L. (2005). Cancer-preventive isothiocyanates: Dichotomous modulators of oxidative stress. *Free Radic. Biol. Med.* **38**: 70–77.

Yang, G., Shu, X. O., Li, H., Chow, W. H., Ji, B. T., Zhang, X., Gao, Y. T. and Zheng, W. (2007). Prospective cohort study of green tea consumption and colorectal cancer risk in women. *Cancer Epidemiol. Biomarkers Prev.* **16**:1219–1223.

Yang, C. S., Wang, H., Li, G. X., Yang, Z., Guan, F. and Jin, H. (2011a). Cancer prevention by tea: Evidence from laboratory studies. *Pharmacol. Res.* **64**:113–122.

Yang, C. S., Wang, X., Lu, G. and Picinich, S. C. (2009). "Cancer prevention by tea: Animal studies, molecular mechanisms and human relevance." *Nat. Rev. Cancer* **9**:429–439.

Yang, L., Wei, D. D., Chen, Z., Wang, J. S. and Kong, L. Y. (2011b). Reversal of multidrug resistance in human breast cancer cells by Curcuma wenyujin and Chrysanthemum indicum. *Phytomedicine* **18**:710–718.

Zhou, Y., Zhuang, W., Hu, W., Liu, G. J., Wu, T. X. and Wu, X. T. (2011). Consumption of large amounts of Allium vegetables reduces risk for gastric cancer in a meta-analysis. *Gastroenterology* **141**:80–89.