Nutrition 69 (2020) 110563

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review

# Targeting hallmarks of cancer with a food-system–based approach

James C. Lachance [a], Sridhar Radhakrishnan [b,c], Gaurav Madiwale [d], Stéphane Guerrier [e], Jairam K.P. Vanamala [b,f,*]

[a] Department of Environmental Science, Policy, and Management, University of California, Berkeley, Berkeley, California, USA
[b] Department of Food Science, The Pennsylvania State University, University Park, Pennsylvania, USA
[c] Research Diets, Inc., New Brunswick, New Jersey, USA
[d] Amazon.com, Inc., Seattle, Washington, USA
[e] Geneva School of Economics and Management & Faculty of Science, University of Geneva, Switzerland
[f] The Pennsylvania State Hershey Cancer Institute, Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania, USA

ARTICLE INFO

*Article History:*
Received 9 November 2018
Received in revised form 27 May 2019
Accepted 24 July 2019

*Keywords:*
Phytochemicals
Food processing
Farm-to-fork
Carotenoids
Glucosinolates
Polyphenols
Hallmarks of cancer

ABSTRACT

Although extensive resources are dedicated to the development and study of cancer drugs, the cancer burden is expected to rise by about 70% over the next 2 decade. This highlights a critical need to develop effective, evidence-based strategies for countering the global rise in cancer incidence. Except in high-risk populations, cancer drugs are not generally suitable for use in cancer prevention owing to potential side effects and substantial monetary costs (Sporn, 2011). There is overwhelming epidemiological and experimental evidence that the dietary bioactive compounds found in whole plant-based foods have significant anticancer and chemopreventative properties. These bioactive compounds often exert pleiotropic effects and act synergistically to simultaneously target multiple pathways of cancer. Common bioactive compounds in fruits and vegetables include carotenoids, glucosinolates, and polyphenols. These compounds have been shown to target multiple hallmarks of cancer in vitro and in vivo and potentially to address the diversity and heterogeneity of certain cancers. Although many studies have been conducted over the past 30 y, the scientific community has still not reached a consensus on exactly how the benefit of bioactive compounds in fruits and vegetables can be best harnessed to help reduce the risk for cancer. Different stages of the food processing system, from "farm-to-fork," can affect the retention of bioactive compounds and thus the chemopreventative properties of whole foods, and there are opportunities to improve handling of foods throughout the stages in order to best retain their chemopreventative properties. Potential target stages include, but are not limited to, pre- and postharvest management, storage, processing, and consumer practices. Therefore, there is a need for a comprehensive food-system–based approach that not only taking into account the effects of the food system on anticancer activity of whole foods, but also exploring solutions for consumers, policymakers, processors, and producers. Improved knowledge about this area of the food system can help us adjust farm-to-fork operations in order to consistently and predictably deliver desired bioactive compounds, thus better utilizing them as invaluable chemopreventative tools in the fight to reduce the growing burden of cancer worldwide.



## Introduction

### *Bioactive compounds: Linking the "hallmarks of cancer" and the food system*

This article focuses on how the hallmarks of cancer are affected by three classes of bioactive compounds: carotenoids, glucosinolates, and polyphenols (Table 1). How these compounds are affected by characteristics of five general stages of the food system, referred to herein as "farm-to-fork" stages, is considered here. The objective of this review is to foster discussion around integrative food system changes that might help reduce the growing cancer burden. This can be referred to as a "food-system–based approach" to cancer prevention. Implementing changes to everything from agricultural practices, to storage, processing, and consumer practices is a huge challenge. However, by exploring proposed shifts in the food system and integrating knowledge across disciplines of agricultural management, food science, and cancer biology, possibilities of better harnessing the anticancer activity of the food system exist, thus allowing further prevention and targeting of cancer. Additionally, this would enable us to

JCL and SR contributed equally to this work. The opinions expressed in this article are the authors and do not reflect the view of Amazon.com, Inc.

* Corresponding author: Tel.: +1 814 865 6842; Fax: +1 814 863 6132.
*E-mail address:* guthealth01@gmail.com (J.K.P. Vanamala).

https://doi.org/10.1016/j.nut.2019.110563
0899-9007/

**Table 1**
Plant bioactive compounds target the hallmarks of cancer

| Hallmarks | Compounds | References |
|---|---|---|
| Self-sufficiency in growth signals* | Polyphenols | Batra and Sharma (2013); Vanamala et al. (2011a); Radhakrishnan et al. (2011); Liu et al. (2014); Wang et al. (2003); Thangapazham et al. (2007). |
| | Carotenoids | Omenn et al. (1996a and 1996b); Nasri et al. (2014); Kotake-Nara et al. (2001); Hazuka et al. (1990); Levy et al. (1995); Onogi et al. (1998); Amir et al. (1999); Bolhassani (2015); Castro-Puyana et al. (2017). |
| | Glucosinolates | Wu et al. (2009); Lenzi et al. (2014); Wang et al. (2014); Li (2015). |
| Insensitivity to antigrowth signals* | Polyphenols | Wang et al. (2003); Charepalli et al. (2015); Vanamala et al. (2010); Ahmad et al. (2000); Gupta et al. (2000); Kao et al. (2015); Amatori et al. (2016). |
| | Carotenoids | Onogi et al. (1998); Murakoshi et al. (1992); Karas et al. (2000); Shao et al. (2016); Ivanov et al. (2007). |
| | Glucosinolates | Wu et al. (2009); Stan et al. (2014); Gamet-Payrastre et al. (2000); Traka (2016). |
| Evading apoptosis* | Polyphenols | Vanamala et al. (2011a); Thangapazham et al. (2007); Duthie (2007); Karna et al. (2011); Vanamala et al. (2006a and 2006b, 2008a and 2008b); Reddivari et al. (2010, 2007b); Massey et al. (2014); Madiwale et al. (2012, 2011). |
| | Carotenoids | Omenn et al. (1996a and 1996b); Nasri et al. (2014); Bertl et al. (2006); Schabath et al. (2004); Fernald and Kurokawa (2013); Niranjana et al. (2015). |
| | Glucosinolates | Wu et al. (2009); Ho et al. (2009); Kuang and Chen (2004); Jackson and Singletary (2004); Traka (2016). |
| Enabling replicative immortality* | Polyphenols | Jagetia and Aggarwal (2007); Lanzilli et al. (2006). |
| | Carotenoids | Tomita et al. (1987). |
| | Glucosinolates | Tsou et al. (2013); Meeran et al. (2010); Abbas et al. (2015). |
| Sustained angiogenesis* | Polyphenols | Garcia-Lafuente et al. (2009); Oak et al. (2003); Maeda et al. (2003); Martin et al. (2003); Favot et al. (2003); Kondo et al. (2002); Yoo et al. (2002); Bhandarkar and Arbiser (2007); Khan et al. (2013). |
| | Carotenoids | Kaulmann and Bohn (2014); Bertl et al. (2006); Wang et al. (2012); Ganesan et al. (2013); Umigai et al. (2012); Chen et al. (2012). |
| | Glucosinolates | Xu et al. (2005); Thejass and Kuttan (2007a); Xiao and Singh (2007). |
| Invasion and metastasis* | Polyphenols | Dihal et al. (2008); Menon et al. (1995); Baliga et al. (2005); Darvin et al. (2015); Hung et al. (2015); Amawi et al. (2017). |
| | Carotenoids | Arseneault et al. (2013); Chung et al. (2013); Huang et al. (2008); Niranjana et al. (2015). |
| | Glucosinolates | Hayes et al. (2008); Lenzi et al. (2014); Jeon et al. (2011); Conaway et al. (2005); Thejass and Kuttan (2006); Kim et al. (2015); Singh et al. (2009). |
| Genome instability and mutation† | Polyphenols | Cao et al. (2002); Hope Smith et al. (2004); Bub et al. (2003); Szeto et al. (2005). |
| | Carotenoids | Zu et al. (2014); Sharan et al. (2012); Stich et al. (1984); van Poppel et al. (1992); Russell (2004); Nordström et al. (2016). |
| | Glucosinolates | Asakage et al. (2006); Jiang et al. (2003); Singletary and MacDonald (2000); Bonnesen et al. (2001). |
| Tumor-promoting inflammation† | Polyphenols | Gatz and Wiesmuller (2008); Raso et al. (2001); Jung and Sung (2004); Lin et al. (2003); Udenigwe et al. (2008); Holmes-McNary and Baldwin (2000); Ellis et al. (2011). |
| | Carotenoids | Tanaka et al. (2012); Noureini and Wink (2012); Lu et al. (2006); Fedeles et al. (2015); Yasui et al. (2011); Kim (2011); Erkan et al. (2010); McMillan et al. (2002). |
| | Glucosinolates | Shay and Wright (2011); Farraye et al. (2010); Dey et al. (2010); Khor et al. (2006); Fuentes et al. (2015). |
| Reprogramming energy metabolism† | Polyphenols | Batra and Sharma (2013); Vanamala et al. (2012); Keijer et al. (2011); Fouad et al. (2013); de Boer et al. (2006); Dihal et al. (2006). |
| | Carotenoids | Sumantran et al. (2000); Kim et al. (2014); Bayley and Devilee (2012). |
| | Glucosinolates | Singh et al. (2004a and 2004b); Xiao et al. (2010); Amatoa et al. (2015). |
| Evading immune destruction† | Polyphenols | Okabe et al. (1997); Lin et al. (2009); Perez-Berezo et al. (2009); Ramiro-Puig and Castell (2009); Jung et al. (2012); Churchill et al. (2000); Bhaumik et al. (2000); Gomez-Cadena et al. (2016). |
| | Carotenoids | Tanaka et al. (2012); Stivala et al. (2000); Chew and Park (2004); Bendich (1989); Lin et al. (2015). |
| | Glucosinolates | Singh et al. (2004a and 2004b); Thejass and Kuttan (2007a); Amin and Shankar (2015). |

Adapted from Hanahan and Weinberg (2000, 2011)
*Original hallmark of cancer from Hanahan and Weinberg (2000).
†Additional hallmark of cancer included in Hanahan and Weinberg (2011).

develop a novel food-based framework that is built on a transdisciplinary approach, allowing for a deeper understanding of underlying mechanisms to develop safe, affordable, and effective measures to counter global epidemic of chronic diseases.

*The hallmarks of cancer*

As initially described by Hanahan and Weinberg (2000), the hallmarks of cancer are anticancer defense mechanisms that must be breached for a cell to become cancerous. This seminal paper concisely described this enormously complex disease in six fundamental principles, or hallmarks. These hallmarks are helpful in comprehensively understanding cancer, as there are >200 types of cancer that can each behave differently on a cellular level, a concept termed *tumor heterogeneity*. Hanahan and Weinberg (2011) proposed four new hallmarks, thus expanding the list to include 10 hallmarks of cancer (Table 1, column 1).

The hallmarks of cancer are important because they create a key framework for cancer research and analysis, and in a strict sense, are the targets of the food system–based approach. By better understanding the etiology of cancer, further insight into these hallmarks can be obtained. This deeper understanding of hallmarks can potentially help accelerate the development of targeted cancer therapies as well as the chemopreventive food-system–based approach highlighted in this review. A complete review of the hallmarks of cancer can be found in Hanahan and Weinberg (2000, 2011).

**Table 2**
The five farm-to-fork stages of the food system alter plant bioactive compounds

| Stages of food system | Compounds | References |
|---|---|---|
| Preharvest | Polyphenols | Khanizadeh et al. (2008); Tsao et al. (2003); Patil et al. (1995); Patil and Pike (1995); Islam et al. (2002, 2005); Massey et al. (2016); Lima et al. (2008); Stracke et al. (2009a and 2009b); Giovanelli and Buratti (2009). |
| | Carotenoids | Reddivari et al. (2007); Lima et al. (2005); De Rosso and Mercadante (2005); Oliveira et al. (2003); Marais et al. (1991); Stracke et al. (2009a and 2009b). |
| | Glucosinolates | Velasco et al. (2007); Cartea and Velasco (2007); Dal Pra et al. (2013); Kushad et al. (1999); Padilla et al. (2007); Farnham et al. (2004); Meyer and Adam (2007); Picchi et al. (2012); Pereira et al. (2002); Jeffery et al. (2003); Brown et al. (2002); Ciska et al. (2000); Verkerk et al. (2009); Robbins et al. (2005). |
| Postharvest | Polyphenols | Klimczak et al. (2007); Zhang et al. (2000); Hagen et al. (2009); Diaz-Mula et al. (2009). |
| | Carotenoids | Nhung et al. (2010); Dang et al. (2006). |
| | Glucosinolates | Verkerk et al. (2009); Robbins et al. (2005); Jones et al. (2006). |
| Processing | Polyphenols | Giovacchino et al. (1994); Vignoli et al. (2011); Spanos and Wrolstad (1990); Girennavar et al. (2008); Harbaum-Piayda et al. (2010); Oufedjikh et al. (1998). Zabetakis et al. (2000); Suthanthangjai et al. (2005); Patras et al. (2009a); Corrales et al. (2008); Xi et al. (2009); Casazza et al. (2012); Cai et al. (2012);. Kannan (2011); Suresh et al. (2007). |
| | Carotenoids | Marx et al. (2003); Sanchez-Moreno et al. (2006); Patras et al. (2009b); de Ancos et al. (2000); McInerney et al. (2007); Butz et al. (2002); Yildiz et al. (2010); Vallverdu-Queralt et al. (2013); Plaza et al. (2011); Roohinejad et al. (2014). |
| | Glucosinolates | Slominski and Campbell (1989); Vos and Blijleven (1988); Verkerk et al. (2001); Mandelova and Totusek (2007); Van Eylen et al. (2009). |
| Postprocessing | Polyphenols | Vanamala et al. (2005, 2006b); Aaby et al. (2007); Price et al. (1997). |
| | Carotenoids | Vasquez-Caicedo et al. (2006); Chen et al. (1996); Lin and Chen (2005); Vasquez-Caicedo et al. (2007). |
| | Glucosinolates | Johnson (2000); Vallejo et al. (2002). |
| Consumer practices | Polyphenols | Lombard et al. (2005); Suresh et al. (2008). |
| | Carotenoids | Pinheiro Sant'Ana et al. (1998); van Poppel et al. (1992); Plaza et al. (2011). |
| | Glucosinolates | Vallejo et al. (2002); Verkerk and Dekker (2004); Matusheski and Jeffery (2001); Matusheski et al. (2004); Sameer Khalil Ghawi (2013). |

*The agro-food system*

For the purpose of this review, the complex global agro-food system has been condensed into five unique "farm-to-fork" stages to facilitate understanding of the food system–based approach. These five stages include preharvest, postharvest, processing, postprocessing, and consumer practices, and build upon the understanding outlined in our previous work (Vanamala, 2015). These key stages are well studied and have been shown to have an effect on the content, composition, and availability of bioactive compounds, an abundance of which are shown to prevent cancer (Table 2). However, given the vast array of food system influences and research across many disciplines, it is important to understand that these five stages are not an exhaustive list of all possible food system effects on bioactive compounds. Instead, these stages can serve as an overarching structure for discussion.

Various classes of bioactive compounds, including carotenoids, glucosinolates, and polyphenols, which are highlighted in this review, are each susceptible to the effects of the food system. Therefore, the quality and quantity of each bioactive compound in foods can vary substantially by the time they reach consumers. However, advances have been made along these five stages—from cultivar selection to novel processing techniques—that provide an opportunity to retain and ultimately deliver the highest quantity of bioactive compounds, and therefore cancer-preventing properties, in fruits and vegetables. These advances are highlighted in our proposed food system–based approach to cancer prevention.

*Why bioactive compounds?*

Over the past 30 y, research has shown that many farm-to-fork operations affect bioactive compounds in foods, usually by either increasing or decreasing their content, or by altering their composition (Vanamala, 2017). Likewise, recent research of bioactive compounds in fruits and vegetables has shown how these compounds can target, both in vivo and in vitro, multiple hallmarks of cancer. Given the health benefits of bioactive compounds, and the effects of the food system on these compounds, it is important to understand how improvements can be made to retain and consistently deliver these compounds in fruits and vegetables.

Advantages of bioactive compounds include their ubiquity and accessibility as chemopreventive agents, as well as their synergy and low toxicity as compared with many modern anticancer drugs (Vanamala, 2017). Nevertheless, all bioactive compounds are not necessarily chemopreventive, safe for human consumption, or either, and in fact some can be toxic to humans at higher doses. For example, glycoalkaloids (found in Solanaceae crops like potatoes, tomatoes, eggplants, and peppers), as well as acrylamide (commonly found in chipped or fried potatoes, and some nut and cereal crops), and oxalates (found in spinach, rhubarb, and other Chenopodiaceae crops), can be toxic to humans and their toxicity can be influenced by cooking preparation (Gertz & Klostermann, 2002; Mottram et al., 2002; Prakash et al., 1993; Roswitha Siener, 2006; Rydberg et al., 2003). In addition to neurotoxicity, acrylamide is also a putative carcinogen, thus there is a growing interest in producing fried foods with low levels of acrylamide using novel processing methods such as vacuum frying.

*Why a food system–based approach?*

The key goal of this article is to summarize, interrogate, and integrate >30 y of bioactive compound and cancer research, and outline how a food system–based approach might be useful in cancer prevention and treatment. Moving forward, a better understanding of the effect of the food system on these bioactive compounds will help in drafting solutions for producers, the food-processing industry, policymakers, and consumers. Ultimately, this approach has the potential to enhance the delivery of

chemopreventive bioactive compounds through fruits and vegetables. In ancient times, foods were often thought of as medicines, and their consumption included delivery of bioactive compounds. How might the stages of the modern food system be adjusted to consistently and predictably deliver these same bioactive compounds, and what effect might this have on the growing cancer burden?

The rest of this review is organized as follows: The next section presents the three classes of bioactive compounds (i.e., carotenoids, glucosinolates, and polyphenols) considered in this review. Then the review will discuss how three classes of bioactive compounds target the hallmarks of cancer. Clinical studies on antiproliferating effects of plant bioactive compounds are then presented, followed by a section that introduces the whole food approach to targeting cancer hallmarks instead of individual compounds.

## Three classes of bioactive compounds

The following is an overview of carotenoids, glucosinolates, and polyphenols.

### *Carotenoids*

Carotenoids are natural pigments that provide bright coloration to plants and animals. They are commonly found in fruits and vegetables including tomatoes, carrots, papayas, and potatoes. Carotenoids such as β-carotene, α-carotene, lycopene, lutein, zeaxanthin, β-cryptoxanthin, fucoxanthin, canthaxanthin, and astaxanthin, are lipid-soluble bioactive compounds that have shown anticarcinogenic activity (Linnewiel-Hermoni et al., 2015; Tanaka et al., 2012). Preclinical studies have shown that some carotenoids have potent antitumor effects both in vitro and in vivo, suggesting potential preventive or therapeutic roles for the compound (Bolhassani, 2015; Nishino et al., 2002; Tanaka et al., 2012). The functional chemopreventive properties of carotenoids in fruits and vegetables are dependent on many factors, but epidemiological and in vivo literature generally suggest that they are beneficial to human health (Voutilainen et al., 2006). Although β-carotene intake as a high-dose supplement, found to be detrimental to health, (Omenn et al., 1996a and Omenn et al., 1996b) others highlighting the health benefits of carotenoids, such as for eye health and cancer prevention, also suggest further research to better understand their full effects on human health (Diplock et al., 1998; Johnson, 2002).

### *Glucosinolates*

Glucosinolates are sulfur-containing compounds that are primarily found in plants of the Brassicaceae family such as broccoli, cauliflower, and cabbage. Glucosinolate-containing plants contain the enzyme myrosinase, which, in the presence of water, cleaves off the glucose group from the glucosinolate to form an isothiocyanate, a nitrile, or a thiocyanate, the active substances that serve as defense for the plant (Fahey et al., 2001; Hayes et al., 2008; Murillo & Mehta, 2001). Glucotropaeolin, gluconasturtiin, glucoraphanin, and sinigrin are precursors to benzyl isothiocyanate (BITC), phenethyl isothiocyanate (PEITC), sulforaphane (SFN), and allyl isothiocyanate (AITC), respectively. Glucosinolates, as well as their breakdown products (e.g., indoles and isothiocyanates [ITCs]), possess health attributes, including fungicidal, bacteriocidal, detoxifying, and cancer chemopreventive properties (Fahey et al., 2001; Traka, 2016). Indoles (indole-3-carbinol) and ITCs (BITC, PEITC, and SFN) frequently have been examined for their anticancer effects and these studies are reviewed in Dinkova-Kostova and Kostov (2012).

### *Polyphenols*

Polyphenols are another ubiquitous group of bioactive compounds that have been shown to have chemopreventive properties, and their health benefits often are tied to the amount consumed and the varying bioavailability of the compound in different foods (Eberhardt et al., 2000; Gorzynik-Debicka et al., 2018; Huang & Ferraro, 1992; Knekt et al., 2002; Manach et al., 2004; Middleton et al., 2000; Tomás-Barberán et al., 2016). As summarized by Manach et al. (2004), the various types of polyphenols, hydroxybenzoic acids, hydroxycinnamic acids, anthocyanins, flavonols, flavones, flavanones, isoflavones, and monomeric flavanols are found in a variety of fruits and vegetables, from berries, citrus fruits, apples, and pears, to celery, parsley, chocolate, grains, and tea. The presence of polyphenols often results in strong pigmentation, and some plants and spices that contain flavonoids have been used in Eastern medicine for thousands of years (Middleton et al., 2000). Dietary polyphenols comprise >8000 aromatic ring compounds and are widely available antioxidants in the human diet (e.g., Lecour & Lamont, 2011, and the references therein). Polyphenols can be subdivided into five classes: flavonoids, phenolic acids, stilbenes, tannins, and diferuloylmethanes (Lin et al., 2016). Anthocyanins, which impart color to a variety of fruits, flowers, and vegetables, are flavonoids. Caffeic acid (found in many plant foods, including coffee, sunflower seeds, and some herbs and spices like thyme and cinnamon) and p-coumaric acid (found in foods such as peanuts, tomatoes, and garlic) are examples of phenolic acids. A common example of a stilbene is resveratrol, which is found in red grapes. Tannins include catechins, which are bitter, astringent compounds found in green tea. Curcumin, found in turmeric, is the most commonly known diferuoylmethane (Jatoi & Nguyen, 2008; Nasri et al., 2014).

## The hallmarks of cancer and three bioactive compounds

The hallmarks of cancer, as reviewed by Hanahan and Weinberg (2000, 2011), are biological properties that cancer cells have or acquire during the multistep development of human tumors. They are characteristics present in most tumors and have been the targets of many pharmacologic approaches. Table 1 lists the 10 main hallmarks of cancer. The distinct features of cancer provide an interesting avenue for treatment. Because many cancers show similar characteristics, drugs targeting the hallmarks of cancer often are expected to be “silver bullet” treatments; accordingly, recently developed cancer drugs specifically target unique hallmarks, with several of them currently in preclinical and clinical trials (Hanahan & Weinberg, 2011). However, as most pharmacologic approaches are based on focused drug design (Sporn, 2011), they only target one or two hallmarks. This might explain part of the reason for certain drugs failing in clinical trials or potentially being associated with cancer relapse. In some cases, pharmaceutical approaches to treat cancer also can be associated with serious side effects (Jatoi & Nguyen, 2008; Nasri et al., 2014). Conversely, bioactive compounds such as carotenoids, glucosinolates, and polyphenols are found in many foods, have multiple targets, and often have complementary effects. Increasing evidence suggests that these bioactive compounds in food can target most, if not all, of the hallmarks of cancer and their deliberate integration into diets is therefore key to modern cancer prevention and treatment strategies (Bolhassani, 2015). This might explain why the same compounds might have potent efficacy against multiple cancers alone or when combined with radio/chemotherapy, even with biologic drugs that target specific molecular events. Furthermore, a majority of studies suggest that food-based bioactive compounds are

generally non-toxic and well tolerated in humans, with minimal concern for side effects. Studies on the effects of carotenoids, glucosinolates, and polyphenols on the hallmarks of cancer in different models, including human, in vivo, and in vitro studies, are summarized in the following sections.

### Carotenoids

#### Sustained proliferation

Carotenoids have shown to inhibit the growth and proliferation of several cancer cell lines (Bolhassani, 2015), including prostate (Kotake-Nara et al., 2001), melanoma (Hazuka et al., 1990), lung (Levy et al., 1995), medulloblastoma (World Academy of Science, 2017), mammary (Levy et al., 1995), colon (Castro-Puyana et al., 2017; Onogi et al., 1998), and leukemia cancer cells (Amir et al., 1999). Carotenoids also have shown suppression of tumor growth in in vivo models. In a skin tumorigenesis experiment by Murakoshi et al., the incidence of tumor-bearing mice in the positive control group (initiator: 7,12-dimethylbenz[a]anthracene; promoter: 12-*O*-tetradecanoylphorbol-13-acetate), was 69%, whereas those in the groups treated with β- and α-carotene were 13% and 25%, respectively (Murakoshi et al., 1992). In the same study, where lung carcinogenesis was initiated in the mouse model by 4-nitroquinoline 1-oxide and promoted by glycerol, the average multiplicity of lung tumors was significantly reduced in the carotene-treated group with a reported average of 1.33 per mouse compared with the positive control group, having an empirical average of 4.06 per mouse (Murakoshi et al., 1992).

#### Evading growth suppressors

In a study on MCF-7 mammary carcinoma cells, treatment with lycopene, a carotenoid commonly found in tomato, watermelon, carrots, cabbage, asparagus, and mango, showed slower insulin-like growth factor (IGF)-1–stimulated cell cycle progression that was not accompanied by either apoptotic or necrotic cell death (Karas et al., 2000). Lycopene-induced delay in gap 1 phase (G1) and S phase progression also has been observed in other human cancer cell lines (leukemia and cancers of endometrium, lung and prostate; Amir et al., 1999). Likewise, in another study, β-carotene was found to induce a cell cycle delay in the G1 phase in normal human fibroblasts (Stivala et al., 2000). A staxanthin was shown to inhibit proliferation and induce apoptosis and cell cycle arrest in mice H22 hepatoma cells in vitro and in vivo (Shao et al., 2016). Ivanov et al. (2007) reported that cell cycle arrest in prostate cancer cells at the gap 0 phase (G0)/G1 phase by lycopene is mediated by a decreased level of cyclins D1 and E, and cyclin-dependent kinase 4 (cdk4) along with retinoblastoma protein phosphorylation.

#### Immune system evasion

Carotenoids also have been shown to improve immune responses that could aid in recognition and destruction of cancer cells (Bendich, 1989; Chew & Park, 2004; Tanaka et al., 2012). Tomita et al. (1987) showed that β-carotene enhanced the tumor immunity of mice. Oral administration of β-carotene to BALB/c mice inoculated with syngeneic BALB/c Meth A fibrosarcoma cells (Meth A) led to a remarkable rejection against Meth A upon rechallenge. Furthermore, this effect was dose-dependent. In another experiment, the lymph nodes from tumor-bearing mice fed either a control diet or β-carotene–supplemented diets were mixed with fresh tumor cells. The cell mixture was injected into healthy mice. Tumors that developed in the carotenoid group were one-seventh as large as those in the mice fed the control diet, suggesting improved anticancer efficacy. Tomita et al.'s (1987) laboratory replicated these studies using canthaxanthin and astaxanthin in the same model and showed that the two carotenoids reduced tumor burden and enhanced cytotoxic T-cell activity. In another study, astaxanthin was shown to modulate lymphocytic immune responses in vitro. Furthermore, the researchers showed that it partly exerted its ex vivo immunomodulatory effects by increasing interferon-γ and interleukin (IL)-2 production (Lin et al., 2015). This could potentially be linked to its anticancer activity. However, more studies are needed to confirm whether genetic background, age, and sex of the mouse can affect the immunomodulatory effects, and in turn the anti-ancer activity of carotenoids.

#### Replicative immortality

Cancer cells also are armed with limitless replicative potential. A study using crocin, a carotenoid from saffron, has shown that crocin can suppress this replicative immortality (Noureini & Wink, 2012). The researchers showed that telomerase activity in 0.5 μg protein extract of HepG2 cells treated with 3 mg/mL crocin was reduced to about 51% compared with untreated control cells. The relative expression level of the catalytic subunit of human telomerase reverse transcriptase (*hTERT*) gene showed a 60% decrease compared with untreated control cells. There is, however, only limited information on the effect of carotenoids on telomerase activity during carcionogenesis.

#### Chronic low-grade inflammation

Chronic inflammation is a backbone for cancer development in multiple tissues, including in the colon (Lu et al., 2006). A recently published article also demonstrated a mechanistic link between inflammation and cancer, suggesting inflammation not only promotes, but also induces cancer (Fedeles et al., 2015). Carotenoids have shown antioxidant and anti-inflammatory properties in multiple studies (Tanaka et al., 2012). Astaxanthin has been shown to suppress the expression of inflammatory cytokines and the master regulator transcription factor nuclear factor κ-light chain enhancer of activated B cells (NF-κB), and inhibited inflammation-associated colon carcinogenesis in mice (Yasui et al., 2011). Lycopene is also reported to inhibit pancreatitis (Kim, 2011). Chronic pancreatitis is believed to increase the risk for pancreatic cancer (Erkan et al., 2010). A human study consisting of 30 controls and 15 patients for both breast and prostate and 11 patients with colorectal cancer showed that concentrations of C-reactive protein (CRP), an acute-phase inflammatory marker, were significantly higher and vitamins and antioxidants were lower in the patients with cancer. In controls and cancer patients, C-reactive protein concentrations presented pairwise significant correlation with circulating concentrations of lutein, lycopene, α-carotene, and β-carotene. Moreover, these relationships appeared to be independent of the presence and type of cancer (McMillan et al., 2002). Anti-inflammatory properties of carotenoids in both in vitro and in vivo studies have been summarized by Kaulmann and Bohn (2014).

#### Angiogenesis

Angiogenesis is a physiologic process relevant for tissue growth, remodeling, and wound healing that is also a prerequisite for tumor growth and metastasis (Bertl et al., 2006). Carotenoids also have been linked to suppression of angiogenesis. Wang et al. (2012) showed that fucoxanthin significantly decreased the expression of vascular endothelial growth factor (VEGF) in sarcoma 180 (S180) of xenograft-bearing mice. Ganesan et al. (2013) demonstrated fucoxanthin and siphonaxanthin downregulates signal transduction by fibroblast growth factor (FGF)-2 and its receptors fibroblast growth factor receptor-1 to exert their anti-angiogenic effects. Although research clearly shows that fucoxanthin has

promising effects against cancer angiogenesis, it is possible that plant-derived carotenoids, in combination with other bioactive compounds, may produce similar results. Indeed, there are reports on the anti-angiogenic activity of crocetin in in vitro studies (Umigai et al., 2012). However, the role of lycopene in prevention of prostate cancer still remains controversial (Zu et al., 2014). The study by Chen et al. (2012) demonstrated, using the in vivo Matrigel assay, that lycopene downregulates the activity of matrix metalloproteinase (MMP)-2, urokinase-type plasminogen activator, and protein expression of ras-related C3 botulinum toxin substrate 1, and upregulates the expression of metallopeptidase inhibitor-2 and plasminogen activator inhibitor-1 and this was mediated via VEGF receptor-2 mediated phosphoinositide 3-kinase protein kinase B; also known as Akt (PKB) and ERK/p38 signaling pathways. This was one of the studies that explained detailed mechanism of how lycopene inhibits angiogenesis in vivo. Furthermore, higher lycopene intake was associated with lesser degree of angiogenesis in the tumor in the ongoing prospective Health Professionals Follow-up Study. However, the role of lycopene in prevention of prostate cancer still remains controversial (Zu et al., 2014), whereas there is general consensus that increased tomato consumption is inversely associated with prostate cancer risk, emphasizing the importance of whole food approach to cancer prevention (Rowles et al., 2018).

*Genome instability*

Carotenoids have been shown to reduce genetic damage associated with carcinogens as demonstrated by the study on betel chewers in Philippines. Chewing betel, which is the leaf plant in the Piperaceae family, is linked to oral cancer and the World Health Organization classifies betel as a carcinogen (Sharan et al., 2012). It is commonly chewed throughout South and Southeast Asia. Ingestion of 30 mg of a β-carotene and retinol supplement twice per week for 3 mo decreased the proportion of buccal mucosal cells with micronuclei to one-third, whereas an unsupplemented control group showed no change (Stich et al., 1984). A similar approach was used by van Poppel et al. (1992). Supplementation of heavy smokers with 20 mg/d of β-carotene for 14 wk was associated with a 27% decrease in the frequency of micronuclei in exfoliated lung cells in sputum, relative to a placebo group. However, in the U.S. CARET (Carotene and Retinol efficacy Trial) study of >18,000 male and female smokers and male asbestos workers, 30 mg β-carotene supplements over 4 y were linked to a 28% higher risk for lung cancer and a 17% higher risk for deaths from all causes compared with smokers taking a placebo (Omenn et al., 1996a and Omenn et al., 1996b). Accumulating evidence suggests that high-dose β-carotene in smoke-exposed mammals can give rise to a variety of transient oxidative metabolites that enhance cell proliferation. Additionally, eccentric cleavage of β-carotene metabolites aid in the binding of smoke-derived carcinogens to DNA (Russell, 2004). In patients with bladder cancer, baseline and mutagen-induced DNA damage was significantly higher than in controls and when analyzed jointly with carotenoid intake, high DNA damage and low carotenoid intake were associated with the highest risk, suggesting a preventive role for carotenoids in bladder cancer (Schabath et al., 2004). In another study, circulating carotenoids at diagnosis, particularly among men carrying specific somatic variations, were inversely associated with risk for high-grade prostate cancer. In exploratory analyses, higher lycopene level was associated with less genomic instability among men with low-grade disease (Nordström et al., 2016). These results suggest that it may be beneficial to obtain fat-soluble carotenoids that accumulate in the body via whole food consumption instead of supplements. Whole foods such as carrots and pumpkins contain a variety of carotenoids and xanthophylls and thus, typically none of them reach pro-oxidant level.

*Avoiding cell death*

Apoptosis, or programmed cell death, is the process by which the body removes unwanted cells. Cancer cells elevate anti-apoptotic machinery to prevent cell death (Fernald & Kurokawa, 2013). Neoxanthin- and fucoxanthin-treated prostate cancer cells demonstrated reduced cell viability through apoptosis induction, a process of programmed cell death that efficiently eliminate dysfunctional cells (Kotake-Nara et al., 2001). Lutein has been shown to induce apoptosis in transformed cancer cells but not in normal human mammary cells. Furthermore, lutein protected normal cells from apoptosis induced in cell culture (Sumantran et al., 2000). Fucoxanthin effectively induced apoptosis by the downregulation of anti-apoptotic proteins and upregulation of the pro-apoptotic caspase pathway in S180 xenograft-bearing mice (Wang et al., 2012). These data suggest that carotenoids can induce apoptosis both in vitro and in vivo. Mechanisms of apoptosis-inducing effects of carotenoids are summarized by Niranjana et al. (2015).

*Cell energetics*

Not many studies have linked carotenoids with changes in energy metabolism in cancer cells or tissue. Both crocetin and crocin reduced the protein expression of lactate dehydrogenase A (LDHA), one of the targets for chemoprevention in cancer cells, by 34.2% and 10.5%, respectively, compared with the control in HeLa, a well-known cervical cancer cell line (Kim et al., 2014). Cancer cells have been shown to preferentially use anaerobic glycolysis even in the presence of oxygen to fulfill cellular metabolic demands, called the Warburg effect (Bayley & Devilee, 2012). This unique metabolism is thought to protect cancer cells from reactive oxygen species (ROS) produced in the mitochondria. Knockdown of LDHA, a mediator of aerobic glycolysis, was reported to elevate mitochondrial ROS production and resulted in a concomitant decrease in cell proliferation (Arseneault et al., 2013), suggesting a mechanism for how carotenoids may effect cell energetics to prevent cancer.

*Invasion and metastasis*

Carotenoids have been shown to protect against invasive and metastatic properties of cancer cells. The inhibitory effect of lycopene on tumor metastasis was studied in vivo using athymic nude mice injected with human hepatoma cells. The results revealed that lycopene decreased the protein expressions of VEGF, proliferating cell nuclear antigen (PCNA), and MMP-9, and increased the expression of an anti-metastatic gene, *Nm23-H1* (Huang et al., 2008). Chung et al. (2013) studied the effect of fucoxanthin on B16-F10 cells (metastatic murine melanoma) MMP-2 and MMP-9 (Chung et al., 2013). These MMPs are expressed in cancer cells and degrade type IV collagen during cancer invasion. Fucoxanthin treatment resulted in decreased expression and secretion levels of MMP-9. Moreover, the numbers of invaded B16-F10 cells were also decreased. Furthermore, daily oral administration of astaxanthin (1 mg/kg by mouth for 14 d) markedly attenuated the promotion of hepatic metastasis induced by restraint stress (Kurihara et al., 2002). The molecular mechanisms underlying the antimetastatic effects of carotenoids are summarized in (Niranjana et al., 2015). These results suggested that carotenoids might improve antitumor immune responses by inhibiting invasion and metastatic pathways.

*Inconclusive studies*

Randomized controlled trials of β-carotene were unable to show a significant reduction in the risk for lung cancer in smokers (Hennekens et al., 1996). Although β-carotene may be a marker for the intake of fruits and vegetables, it may have detrimental effect in isolated pharmacologic doses (Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group, 1994; Omenn et al., 1996a and Omenn et al., 1996b).

*Glucosinolates*

*Sustained proliferation*

Glucosinolates have shown antiproliferative effects in a variety of in vitro and in vivo models (Lenzi et al., 2014; Wu et al., 2009). PEITC was shown to attenuate proliferation of $CD44^{hi}/+/CD24^{low}/$, stem-like, sphere-forming subpopulations of cancer stem cells (CSCs) in a concentration- and time-dependent manner that was comparable to the CSC antagonist salinomycin (Li, 2015; Wang et al., 2014). In the same study, PEITC pretreatment reduced tumors in xenograft of CSC in a mice model. In another study, PEITC inhibited the growth of pancreatic cancer cells in vitro and in a MIA-Paca2 xenograft animal model. Exposure to PEITC inhibited pancreatic cancer cell growth in a dose-dependent manner, with an IC50 of ~7 μM (Stan et al., 2014). Antiproliferative effects of SFN and other ITCs in in vitro and in vivo models have been reviewed in many studies (Lenzi et al., 2014; Wu et al., 2009).

*Evading growth suppressors*

SFN, found in cruciferous vegetables such as broccoli, Brussels sprouts, and cabbage, was shown to induce cell cycle arrest and subsequent cell death in a dose-dependent manner in HT-29 colon cancer cells. SFN-induced cell cycle arrest correlated with an increased expression of cyclins A and B1 (Gamet-Payrastre et al., 2000). In another study in prostate cancer cells, SFN induced a G1 arrest in androgen-dependent LnCaP cells and androgen-independent DU-145 cells. Although the studies with LnCaP and DU-145 cells reported a G1 arrest, SFN caused an gap 2 phase/mitotic phase arrest in PC-3 cells (Singh et al., 2004a and Singh et al., 2004b). SFN-mediated cell cycle arrest has been reported in several other cell lines (Lenzi et al., 2014). In vitro studies on glucosinolates and cell cycle arrest are summarized in Traka (2016).

*Immune system evasion*

SFN administration significantly enhanced natural killer (NK) cell activity in B16F-10 melanoma-induced metastasis-bearing C57BL/6 mice. Moreover, antibody-dependent cellular cytotoxicity also was enhanced significantly in metastatic tumor-bearing animals after SFN administration compared with untreated control tumor-bearing animals (Thejass & Kuttan, 2007b). Another study involving WEHI-3 leukemia cell xenografts in BALB/c mice showed that PEITC increased the level of cluster of differentiation 3 (CD3) and decreased the levels of CD3 and Mac-3, suggesting that the differentiation of the precursor of macrophages and T cells was inhibited, but the differentiation of the precursor of B cells was promoted in mice with leukemia. PEITC enhanced phagocytosis by monocytes and macrophages from peripheral blood mononuclear cells and the peritoneal cavity and also promoted the NK cell cytotoxic activity in comparison with the control group of leukemia mice (Tsou et al., 2013). In another study, SFN was shown to upregulate NK group 2, member D ligands and modulate the susceptibility of tumor cells (MCF7, A549, MDA-MB-231, and U937 cells) to NK cell-mediated killing (Amin & Shankar, 2015). These observations suggest that SFN and PEITC can promote immune responses to enhance killing of cancer cells, thus preventing immune system evasion.

*Replicative immortality*

Inhibition of telomerase has received considerable attention because of its high expression in cancer cells and extremely low level of expression in normal cells (Meeran et al., 2010; Shay & Wright, 2011). SFN treatment caused dose- and time-dependent inhibition of *hTERT*, the catalytic regulatory subunit of telomerase, in both MCF-7 and MDA-MB-231 human breast cancer cells. DNA methyltransferases (DNMTs), especially DNA (cytosine-5)-methyltransferase 1 (DNMT1) and DNA (cytosine-5)-methyltransferase 3a (DNMT3a), were also decreased in SFN-treated breast cancer cells, suggesting that SFN may repress *hTERT* by affecting epigenetic pathways. Additionally, downregulation of *hTERT* expression facilitated the induction of cellular apoptosis in human breast cancer cells (Meeran et al., 2010). In a recent study, SFN was shown to inhibit the expression and activity of *hTERT*, which was correlated with SFN-induced changes in chromatin structure and composition. This ability of SFN to modify chromatin composition and structure associated with target gene expression provides a new model by which dietary phytochemicals may exert their chemoprevention activity (Abbas et al., 2015).

*Inflammation*

The risk for colorectal cancer is increased in ulcerative colitis, as inflammation is presumed to provide a conducive environment for cancer to develop (Farraye et al., 2010). Orally administered PEITC reduced the acute and chronic symptoms of ulcerative colitis in mice, leading to improvements in body weight and stool consistency and decreased intestinal bleeding, mucosal inflammation, depletion of goblet cells, and infiltration of inflammatory cells (Dey et al., 2010). Another study found that cyclooxygenase-2 activity was lower in polyps of $Apc^{min/+}$ mice fed SFN. SFN also inhibited activation of transcription factor NF-κB, the expression of proinflammatory mediators, and reduced the number of activated macrophages (Dinkova-Kostova & Kostov, 2012; Khor et al., 2006). Both SFN and PEITC were shown to inhibit NF-κB transcriptional activation as well as NF-κB–regulated VEGF, cyclin D1, and *Bcl-X (L)* gene expression mediated through the inhibition of IKKβ phosphorylation, IκBα phosphorylation and degradation, and the decrease of nuclear translocation of p65 in PC-3 cells (Xu et al., 2005). Anti-inflammatory effects of dietary glucosinolates SFN, PEITC, indole-3-carbinol (I3C) in the context of cancer has been reviewed in Fuentes et al. (2015).

*Angiogenesis*

In vivo anti-angiogenic activity of glucosinolates was studied using B16F-10 melanoma cell-induced capillary formation in C57BL/6 mice. Intraperitoneal administration of AITC and PEITC at a concentration of 25 μg/dose per animal significantly inhibited tumor-directed capillary formation. Treatment with AITC and PEITC significantly downregulated serum nitric oxide and tumor necrosis factor-α levels in angiogenesis-induced animals compared with untreated control animals (Thejass & Kuttan, 2007a). The in vitro anti-angiogenic study, using the rat aortic ring assay, showed that both AITC and PEITC at non-toxic concentrations inhibited the production of proangiogenic factors from B16F-10 melanoma cells, which was evident with the inhibition of microvessel outgrowth from aortic rings (Thejass & Kuttan, 2007a). In another study using human umbilical vein endothelial cells as a model of angiogenesis, SFN inhibited tube formation on Matrigel and caused a decrease in the proliferation of endothelial cells. SFN also caused a dose-dependent decrease in the proliferative activity of endothelial cells by elevating apoptosis (Asakage et al., 2006). PEITC also was shown to have antiangiogenic effect in vitro and ex vivo in prostate cancer models (Xiao & Singh, 2007). These results

demonstrate that glucosinolates target tumor-specific angiogenesis to aid in anticancer efficacy.

*Genome instability*

There are multiple studies on the effects of glucosinolates on genome instability in cancer. Cotreatment of human hepatoma HepG2 cells and human hepatocytes with micromolar concentrations of SFN plus 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), a mutagen and carcinogen, reduced the level of PhIP, DNA adducts (Jiang et al., 2003). In the human mammary epithelial MCF-10F cell line, SFN inhibited DNA adduct formation by benzo [a]pyrene (B[a]P) and 1,6-dinitropyrene by 63% to 81% and by 30% to 56%, respectively (Singletary & MacDonald, 2000). It is important to note that significant protection was observed at concentrations as low as 0.1 μM SFN. SFN was also shown to protect against B[a] P-induced single-strand DNA breaks in the comet assay, with concentrations as low as 5 μM (Bonnesen et al., 2001). SFN was also shown to inhibit histone deacetylase activity in human colorectal and prostate cancer cells (Ho et al., 2009).

*Avoiding cell death*

ITCs and SFN have been shown to induce apoptosis in a variety of cancer models both in vitro and in vivo (Lenzi et al., 2014; Wu et al., 2009). Glucosinolate derivatives including PEITC, BITC, and I3C induced apoptosis in human non-small cell lung carcinoma A549 cells in a concentration-dependent manner (Kuang & Chen, 2004). Flow cytometric analyses and annexin V staining showed that induction of apoptosis occurred at low concentrations of PEITC and BITC ($\leq$10 μM) and that necrosis occurred at higher concentrations of PEITC and BITC (25 μM); however, apoptosis was not the major pathway for the antiproliferative effects of I3C. The mechanisms by which ITCs induce apoptosis have been extensively explored with cell models, and several key processes within the apoptotic pathways have been shown to be affected by ITCs, such as induction of caspases, disruption of mitochondrial integrity through induction of the proapoptotic members of the Bcl-2 family, and release of mitochondrial proteins cytochrome c, Smac/DIABLO and AIF (reviewed in Traka, 2016). Apoptotic markers have also been observed with SFN in xenograft models. In BALB/c mice implanted with murine mammary carcinoma cells and subsequently given 15 nmol SFN for 13 d by intravenous injection, there was a 60% decrease in tumor mass and an increase in cleaved poly [ADP-ribose] polymerase 1. Oral administration of SFN (5.6 μmol, 3 times/wk) also significantly inhibited growth of PC-3 xenografts in nude mice, with a reduction typically >50% in tumor volume. Apoptosis induction in tumors of SFN-treated mice was associated with an increase in TUNEL staining, and increases in the expression of proapoptotic proteins such as Bax and Bid (Singh et al., 2004a and Singh et al., 2004b).

*Cell energetics*

PEITC-induced cell death in LNCaP and PC-3 human prostate cancer cells was initiated by production of ROS due to inhibition of oxidative phosphorylation (Xiao et al., 2010). Exposure of LNCaP and PC-3 cells to pharmacologic concentrations of PEITC resulted in ROS production, which correlated with inhibition of complex III activity, suppression of oxidative phosphorylation, and ATP depletion. These effects were not observed in a representative normal human prostate epithelial cell line (Amatoa et al., 2015; Xiao et al., 2010), suggesting specificity of PEITC for cancer cells. In another study, SFN induced apoptosis in human hepatic cancer cells through inhibition of 6-phosphofructo-2-kinase/fructose-2 and 6-biphosphatase 4, both mediated by the hypoxia inducible factor-1-dependent pathway (Jeon et al., 2011), suggesting that dietary glucosinolates modulate cellular energetic pathways for preventing cancer.

*Invasion and metastasis*

In a study with human cervical CSC, lung metastasis was observed only in the cervical CSC-injected group in vivo that did not receive PEITC pretreatment suggesting anti-metastatic efficacy of PEITC (Wang et al., 2014). The ability of SFN to inhibit malignant progression of lung adenomas induced by tobacco carcinogens was demonstrated in A/J mice treated for 8 wk with the carcinogens 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and B[a]P. Twenty weeks after the beginning of carcinogen administration, mice were fed diets containing SFN during weeks 21 to 42. Histopathologic examination of tumors demonstrated a significant reduction in malignant lung tumor multiplicity (Conaway et al., 2005). The inhibitory effects of SFN were associated with an increase in the fraction of apoptotic cells (TUNEL-positive and caspase-3-positive cells) and a reduction of cell proliferation in the lung. In another study, SFN inhibited lung metastasis induced by B16F-10 melanoma cells in C57BL/6 mice. In this study, SFN also significantly increased the life span of metastatic tumor-bearing animals (Kim et al., 2015). Oral gavage of SFN was also effective in reducing pulmonary metastasis incidence and multiplicity in TRAMP mice, a model of prostate cancer progression associated with immune modulation (Singh et al., 2009). Other glucosinolates have also demonstrated anti-metastatic effects (Dinkova-Kostova & Kostov, 2012; Meadows, 2012).

*Inconclusive data*

Glucosinolates have shown potent anticancer effects in many experimental studies. However, cohort studies in the Netherlands (Schuurman et al., 1998), United States (Giovannucci et al., 2003), and Europe (Key et al., 2004) have examined a wide range of daily cruciferous vegetable intake and found no significant associations with risk for prostate cancer. However, some case−control studies have found that individuals who ate larger amounts of cruciferous vegetables had a lower risk for prostate cancer (Jain et al., 1999; Kolonel et al., 2000). Similar results have been observed for cancers in the colon (Voorrips et al., 2000), lungs (Feskanich et al., 2000), and in the breast (Terry et al., 2001). Although laboratory studies show a clear benefit of glucosinolates, there seem to be conflicting results of anticancer efficacy of glucosinolates in many epidemiological studies.

*Polyphenols*

Polyphenols are secondary metabolites of plants involved in the defense against different types of stress. Of late, researchers and food manufacturers have become increasingly interested in polyphenols owing to recognition of their antioxidant and anti-inflammatory properties, their dietary abundance, and their role in the prevention of various diseases including cancer (Kampa et al., 2007; Manach et al., 2004; Scalbert et al., 2005). Polyphenols have been shown to induce tumor cell death and interfere with carcinogenesis, tumor growth, and dissemination (Batra & Sharma, 2013; Dashwood, 2007; Kampa et al., 2007; Zhou et al., 2016). The class of polyphenols is very large and consists of a variety of subclasses including phenolic acids, flavonoids, stilbenes, and lignans (Manach et al., 2004). The following sections briefly review the anticancer properties of some of the most commonly consumed polyphenols.

*Sustained proliferation*

We previously showed that the stilbenoid resveratrol (100−150 μM) exhibited antiproliferative properties in HT-29 cells, even after insulin-like growth factor (IGF)-1 exposure, by suppressing insulin-like growth factor receptor (IGFR) protein levels and concurrently attenuating the downstream PKB/wingless-type MMTV integration site family (Wnt) signaling pathways that play a critical

role in cell proliferation (Vanamala et al., 2011a). Other studies have demonstrated antiproliferative effects of resveratrol in colon cancer cells HCT-116 (Radhakrishnan et al., 2011) and Caco-2 (Liu et al., 2014). In another study, polyphenols from tomatoes and soy (genistein, quercetin, kaempferol, biochanin A, daidzein and rutin) demonstrated antiproliferative effects against IGF-1a, induced AT6.3 rat prostate cancer cell line. These effects were in part owing to inhibition of multiple intracellular signaling pathways involving tyrosine kinase activity (Wang et al., 2003). In another study involving nude mice inoculated with human breast cancer MDA-MB-231 cells (Thangapazham et al., 2007), green tea polyphenols and epigallocatechin gallate (EGCG) treatment were effective in delaying the tumor incidence and reducing the tumor burden when compared with the water-fed and similarly handled control. Green tea polyphenols and EGCG treatment were also found to inhibit tumor proliferation (PCNA) when the tumor tissue sections were examined by immunohistochemistry. We recently showed that purple potato anthocyanins suppressed colon cancer stem cell number in vitro and in mice with azoxymethane-induced colon tumorigenesis (Charepalli et al., 2015).

*Evading growth suppressors*

A previous study of HT-29 colon cancer cells showed that resveratrol also induced G1 phase arrest and suppressed cyclin D1 protein levels (Vanamala et al., 2010). In nude mice inoculated with human breast cancer MDA-MB-231 cells (Thangapazham et al., 2007), green tea polyphenols and EGCG treatment induced cell cycle arrest at G1 phase. The expression of cyclin D, cyclin E, CDK 4, and CDK 1 were downregulated in green tea polyphenol- and EGCG-treated groups, compared with the controls suggesting G1 phase block. In another study, EGCG treatment of A431 cells resulted in significant dose- and time-dependent.

- upregulation of WAF1/p21, KIP1/p27, p16 and p18;
- downregulation of cyclin D1, cyclin dependent kinase 4 (cdk4) and cyclin dependent kinase 6 (cdk6); and
- inhibition of the kinase activities associated with cyclin E, cyclin D1, cdk2, cdk4 and cdk6 (Ahmad et al., 2000).

EGCG-induced gap 0 phase (G0)/G1-phase arrest in this study, resulting in elevated apoptosis. In another work, polyphenol-rich strawberry extract suppressed the number of A17 cells, a highly invasive breast cancer cell line, inducing the accumulation of cells in G1 phase. Polyphenols also have caused cell cycle arrest in models of prostate, lung, and bladder cancers and these have been reviewed in Gupta et al. (2000); Kao et al. (2015); Okabe et al. (1997).

*Immune system evasion*

Polyphenols have been shown to have immunomodulatory activities. Rutin, a flavonoid, has been shown to promote immune response in vivo in a murine model of leukemia (Lin et al., 2009). High-dose intake of cocoa, rich in epicatechin, catechin, and procyanidins, improved the Th1 response in young rats and increased intestinal δT lymphocyte count (Perez-Berezo et al., 2009). In another study, cocoa regulated the secretion of inflammatory mediators from macrophages and other leucocytes in vitro (Ramiro-Puig & Castell, 2009). Splenocyte proliferation, which was diminished after irradiation, was enhanced significantly by quercetin supplementation after 30 d of irradiation (Jung et al., 2012). Curcumin treatment in APCMin/+ mice produced increases in mucosal CD4+ T and B cells in animals treated with curcumin. This suggests that curcumin improved lymphocyte-mediated immune functions (Churchill et al., 2000). Curcumin also increased the activation of T cells, B cells, macrophages, neutrophils, NK cells, and dendritic cells in some studies (Bhaumik et al., 2000; Churchill et al., 2000). Low-dose curcumin also enhanced antibody responses (Jagetia & Aggarwal, 2007). In another work, gallotannin-rich fraction, obtained from *Caesalpinia spinosa*, mediated anti-tumor effects predominantly by the endogenous immune response. Tumor cells (breast carcinoma and melanoma) treated with this extract were highly immunogenic in vaccinated mice and induced immune system activation shown by the generation of interferon-γ producing CD8+ T cells. Additionally, tumor-protective effects were abolished in immunodeficient mice, and partially lost after CD4 and CD8 depletion, demonstrating that the immune system is essential for the anti-tumor activity (Gomez-Cadena et al., 2016). These and other studies indicate that the immunomodulatory activities of polyphenols may be responsible for their anticancer effects.

*Replicative immortality*

A recent study presented clear in vitro and in vivo evidence that the inhibition of the cancer-associated enzyme telomerase is a key mechanism involved in cancer inhibition by EGCG (Naasani et al., 2003). The researchers demonstrated in a nude mice model bearing both telomerase-dependent and -independent xenograft tumors cloned from a single human cancer progeny, that only the telomerase-dependent tumors responded to prolonged oral administration of EGCG. In another study involving drug-sensitive (H69) and drug-resistant (H69VP) small cell lung carcinoma cells, EGCG at 70 μM for 24 h resulted in 50% to 60% reduced telomerase activity (Sadava et al., 2007). In MCF-7 cells, resveratrol treatment also downregulated telomerase activity and nuclear levels of *hTERT* (Lanzilli et al., 2006). Resveratrol effects on telomerase are hypothesized to be indirect via inhibition of PKC, PKB, and NF-κB pathways, which play a role in regulating *hTERT* through phosphorylation and nuclear shuttling, respectively (Gatz & Wiesmuller, 2008). These data suggest that polyphenols significantly reduce the progression of cancer probably by targeting telomerase activity.

*Inflammation*

Polyphenols are potent anti-inflammatory agents. Downregulation of cyclooxygenase-2 expression by apigenin and quercetin has been demonstrated in lipopolysaccharide-stimulated J774A.1 cells (Raso et al., 2001). Quercetin and nobiletin in mouse macrophages (Jung & Sung, 2004) and in human synovial fibroblasts (Lin et al., 2003), respectively, produced a similar effect. Resveratrol elicited potent anti-inflammatory effects in multiple studies both in vitro and in vivo (Udenigwe et al., 2008). Resveratrol is a potent inhibitor of both NF-κB activation and NF-κB–dependent gene expression through its ability to inhibit IκB kinase activity, the key regulator in NF-κB activation (Holmes-McNary & Baldwin, 2000). Green tea polyphenol EGCG has been shown to suppresses melanoma growth by suppressing inflammasome (NACHT, LRR, and PYD domains-containing protein 3 [NLRP3] signaling) and IL-1β secretion/NF-κB signaling (Ellis et al., 2011). Several mechanisms explaining the anti-inflammatory activity of flavonoids, a major class of polyphenols, have been described (Garcia-Lafuente et al., 2009), including the following:

- Antioxidant and radical scavenging activities,
- Regulation of cellular activities of inflammatory cells,
- modulation of the activities of enzymes involved in arachidonic acid metabolism and nitric oxide synthase, and
- Modulation of the production of proinflammatory molecules by affecting gene expression.

*Angiogenesis*

Polyphenols from wine and green tea have been shown to inhibit growth factors such as thrombin and platelet-derived growth facor, involved in angiogenesis (Maeda et al., 2003; Oak et al., 2003). Delphinidin, an anthocyanin, strongly inhibited endothelial cell proliferation and migration by cyclin D1- and cyclin A-dependent pathways in response to VEGF (Favot et al., 2003; Martin et al., 2003). EGCG suppressed endothelial cell proliferation and migration by inducing apoptosis through mitochondrial depolarization, activation of caspase-3 and reduction of binding of VEGF to its receptors in human endothelial cells (Kondo et al., 2002; Yoo et al., 2002). Curcumin is a direct inhibitor of angiogenesis and also downregulates various proangiogenic proteins like VEGF and basic FGF. Curcumin's antiangiogenic effect is due, in part, to its inhibitory effect on signal transduction pathways, including those involving protein kinase C and the transcription factors NF-κB and AP-1 (Bhandarkar & Arbiser, 2007). In a prostate cancer xenograft model, chitosan-based nanoformulated EGCG, a green tea polyphenol, reduced the expression of CD31 and VEGF-positive cells in the tumor tissues demonstrating anti-angiogenic activity in vivo (Khan et al., 2013). The anti-angiogenic effects of polyphenols are summarized in Cao et al. (2002) and Diniz et al. (2017).

*Genome instability*

Juice from strawberries, blueberries, and raspberries, all rich in polyphenols, were shown to strongly inhibit mutagenesis caused by the alkylating agent methylmethanesulfonate (MMS) and the procarcinogen B[a]P (Hope Smith et al., 2004). In this study, strawberry juice suppressed MMS mutagenesis by 37% and B[a]P carcinogenesis by 76%. In another study, consumption of Aronia, blueberry, and boysenberry juice, rich in anthocyanins and other polyphenols, for 5 wk significantly decreased oxidative DNA damage in blood cells isolated from human volunteers (Bub et al., 2003). Consumption of wolfberries, which contain significant levels of ellagic acid, carotenoids, and vitamin C, reduced DNA strand breakage in buccal cell scrapings from a small group of individuals compared with controls (Szeto et al., 2005). Although these foods are very high in polyphenols, it is impossible to ascertain which are the most bioactive phytochemicals. The effect of berries on genome stability in cancer is reviewed by Duthie (2007).

*Avoiding cell death*

We previously have shown that resveratrol induced apoptosis in HT-29 and SW-480 colon cancer cell lines and that it potentiated grape seed extract (GSE)-induced apoptosis (Radhakrishnan et al., 2011; Vanamala et al., 2010). Resveratrol-induced apoptosis was found to be independent of cellular p53 status. Studies in our laboratory suggested that resveratrol and GSE act in concert in potentiating their anticancer properties at suboptimal doses. In this study, we showed that resveratrol (~25 μM) potentiated GSE-induced (≤35 μg/mL) colon cancer cell apoptosis via activation of p53-dependent pathways. Elevation of apoptosis was much more pronounced in p53 +/+ cells than in p53 −/− cells. Apoptosis was strongly correlated with p53 levels and Bax to Bcl-2 ratio, both of which are key players in the mitochondrial apoptotic pathway. Caspase-3 inhibition and ROS suppression attenuated apoptosis induced by the combination (Radhakrishnan et al., 2011). Moreover, sweet potato green extract (SPGE) was shown to modulate apoptotic regulatory molecules, and induced apoptosis in human prostate cancer PC-3 cells both in vitro and in vivo (Karna et al., 2011). Oral administration of 400 mg/kg SPGE remarkably inhibited growth and progression of prostate tumor xenografts by ~69% in nude mice, as shown by tumor volume measurements and non-invasive real-time bioluminescent imaging. Our laboratory has shown apoptotic effects of plant polyphenols in different in vitro models of cancer (Charepalli et al., 2015; Madiwale et al., 2011; Madiwale et al., 2012; Massey et al., 2014; Reddivari et al., 2007a and Reddivari et al., 2007b; Reddivari et al., 2010; Vanamala et al., 2006a and Vanamala et al., 2006b; Vanamala et al., 2008a and Vanamala et al., 2008b). Recently, we reviewed the apoptotic mechanisms of anthocyanins, a class of polyphenols (Vanamala et al., 2012).

*Cell energetics*

In addition to antioxidant and anti-inflammatory effects, polyphenols have been shown to regulate energy metabolism (Keijer et al., 2011). We have shown previously that the pentose phosphate pathway (PPP), a key pathway that produces reducing equivalents for cancer cells, was suppressed by resveratrol in the HT-29 colon cancer cell line (Vanamala et al., 2011b). Enzymatic assays confirmed that resveratrol suppressed glucose-6 phosphate dehydrogenase (rate limiting) and transketolase, key enzymes of the PPP. In Fouad et al. (2013), resveratrol (100 μM) significantly decreased the glycolytic enzymes pyruvate kinase and lactate dehydrogenase in Caco-2 cells, whereas an increase in citrate synthase activity and a decrease in glucose consumption were observed in Caco-2 and HCT-116 cell lines. Quercetin, a polyphenol present in apples, onions, tea, and wine, is known to affect energy metabolism (de Boer et al., 2006) and was able to inhibit azoxymethane-induced colon carcinogenesis in rats (Dihal et al., 2006). This was accompanied with lower expression of glycolytic enzymes, suggestive of inhibition of glycolytic metabolism (Dihal et al., 2008).

*Invasion and metastasis*

Oral administration of polyphenols such as curcumin and catechin at concentrations of 200 nmol/kg body weight of mice were found to inhibit lung metastasis of B16F10 melanoma cells as observed by a reduction in the number of lung tumor nodules (80%; Menon et al., 1995). Other polyphenols that inhibited lung tumor nodule formation in this study included rutin (71.2%), epicatechin (61%), naringin (27.2%), and naringenin (26.1%). The life span of animals treated with polyphenols also was increased. Curcumin (143.85%), catechin (80.81%), and rutin (63.59%) produced the highest increase in life span. The results indicate a possible use of these compounds in arresting the metastatic growth of tumor cells (Menon et al., 1995). Additionally, treatment of BALB/c mice bearing 4T1 breast cancer cell tumors with EGCG-rich green tea polyphenols in drinking water resulted in reduced tumor growth and PCNA and activation of caspase 3 in the tumors. Metastasis of tumor cells to lungs was inhibited and survival period of animals was increased after green tea treatment (Baliga et al., 2005). Sorghum polyphenols were shown to suppress the growth as well as metastasis of colon cancer xenografts (to lung) through co-targeting janus kinase 2/signal transducer and activator of transcription 3 and phosphoinositide 3-kinase /PKB/mammalian target of rapamycin pathways (Darvin et al., 2015). Antimetastatic effects also have been investigated for apple polyphenols (Hung et al., 2015). These and other studies (reviewed in Amawi et al., 2017; Weng & Yen, 2012) suggest that polyphenolic compounds alter metastatic pathways to inhibit cancer progression and improve life span.

*Inconclusive data*

Many of the polyphenolic compounds have properties including antioxidant, antimutagenic, antiestrogenic, anticarcinogenic and anti-inflammatory effects that might potentially be beneficial in preventing cancer. However, not all polyphenols and not all actions of individual polyphenols are necessarily beneficial. Some have mutagenic and/or pro-oxidant effects, as well as interference with essential biochemical pathways, including topoisomerase enzyme activities, prostanoid biosynthesis, and signal transduction

(Ferguson, 2001). There is a very large amount of in vitro data available, but far fewer animal studies, and these are not necessarily predictive of human effects because of differences in bacterial and hepatic metabolism of polyphenols between species (Russo et al., 2017). Some epidemiological studies present no significant correlation(s) between polyphenol intake and reduced risk for cancer (Arts & Hollman, 2005). Generally, in vitro and some animal experiments have provided strong positive evidence, whereas evidence from in vivo and human epidemiological studies is not conclusive (Wang & Wang, 2015). However, accumulating epidemiological evidence of a reduction in cancer risk from case–control and cohort studies assessing polyphenol intake emphasizing the need for further investigation of polyphenols and their anticancer activity.

*Gut microbial metabolism*

We have presented a variety of mechanisms by which these bioactive compounds could target cancerous cells in vitro and in vivo. Given that many of these compounds have low bioavailability in vivo, their health benefits are mediated through their interaction with the gut microbes and microbial metabolism. Many of these bioactive compounds are broken down by the gut microbiota into smaller, more functional metabolites (for e.g., equol from soy foods; Davis & Milner, 2009; Nussbaumer et al., 2011) that elicit the desired anticancer effect. Bioactive compounds also can modulate the content and composition of the gut microbiota (Davis & Milner, 2009). Therefore, the intestinal microbiota is both a target for bioactive intervention and a factor influencing the biological activity of these functional compounds consumed through the diet. Through increased knowledge of the mechanisms involved in the interactions between the bioactive compounds, microbiota and its host, we will be in a better position to develop better treatments for cancer.

## Clinical trials

The major treatments currently used to treat cancer include chemotherapy, radiotherapy, and surgery. Some of the commonly used chemotherapeutics include antimetabolites (e.g., methotrexate), DNA-interactive agents (e.g., cisplatin, doxorubicin), antitubulin agents (taxanes), hormones, and molecular targeting agents (Nussbaumer et al., 2011). However, as mentioned earlier, these compounds have severe side effects. Although most of the studies outlined in this review are preclinical studies, and data on anticancer effects of bioactive compounds in humans is limited, many clinical trials are in the pipeline and recent publications in this area are promising. Curcumin, a polyphenol, is already in multiple clinical trials both alone and in combination with drugs/other phytochemicals in the prevention of oral, colon, and prostate cancers as well as cancers of multiple other organ sites (Carroll et al., 2011; Maru et al., 2016). Other phytochemicals that show beneficial effects in clinical trials include resveratrol in colon cancer, including in patients with hepatic metastasis as well as green tea on multiple cancer sites (Howells et al., 2011; Patel et al., 2010). Berry phytochemicals have been widely studied in clinical trials and have shown protection against cancers at various sites (summarized by Bishayee et al., 2016) by targeting multiple hallmarks of cancer. Black raspberry was shown to reduce cancer cell proliferation significantly in 20 patients with cancer—6 with colon cancer and 14 with rectal cancer (Pan et al., 2015). Black raspberry treatment modified genetic and epigenetic markers positively in colorectal adenocarcinomas and adjacent normal tissues, especially in genes in the Wnt signaling pathway that regulates intestinal cell proliferation. In addition to Wnt pathway, black raspberry modified protectively expression of genes related to proliferation, apoptosis, and angiogenesis. In a subsequent study, inflammatory markers, plasma IL-8 was suppressed and granulocyte macrophage colony-stimulating factor was elevated in 24 patients with cancer receiving the same black raspberry treatment, suggesting inflammatory signaling pathways were also targeted (Mentor-Marcel et al., 2012). In Knobloch et al. (2016), black raspberry-rich troches were shown to be tolerated well and phytochemicals were detected in the oral squamous cell carcinoma tissues in patients. Furthermore, raspberry consumption reduced the expression of antiapoptotic and proinflammatory genes that were overexpressed in the cancer tissues (Knobloch et al., 2016). Albeit these positive signs, there have been many negative results demonstrating little to no effect of bioactives in clinical trials particularly when in isolated form (Poulsen et al., 2013). A putative reason could be the dosage because several clinical trials found that administration of dietary phytochemicals resulted in low or undetectable levels in blood. Potential factors contributing to low bioavailability suggest the following:

- low aqueous solubility (polarity, poor dissolution rate) of compounds;
- poor absorption (lipophilic nature)
- extensive metabolic conversion to conjugates/metabolites; and
- metabolism by gut bacteria (Maru et al., 2016).

Thus, currently there has been considerable focus on evaluating the usage of combination therapy or whole food approaches to harness the anti-inflammatory and anticancer activity. Further well-designed clinical studies are essential for the development of effective whole food approaches to primary and secondary prevention of cancer.

## Significance of whole foods in the food-system–based approach

Consumption of fruits and vegetables has been associated with a significant decrease in cancer incidence (Farvid et al., 2019) and cardiovascular disease (Badimon et al., 2019). As a result, numerous bioactive compounds have been isolated and identified, and their potential health-promoting effects have been evaluated extensively, both in vitro and in vivo. However, it should be understood that purified phytochemicals may not necessarily exert the same beneficial health effect as phytochemicals found in the food matrix and among other bioactive compounds. Therefore, because the anticancer efficacy of phytochemicals relies in part on consumption of whole foods and not purified phytochemicals, it is important to realize the overall significance of food system–based approaches. Growing evidence suggests that phytochemicals administered as dietary supplements do not provide the same health benefits as phytochemicals administered through diets rich in fruits, vegetables, and whole grains (Kok et al., 2008). Although relatively high doses of single bioactive agents may show potent anticarcinogenic effects, the synergistic interactions between different dietary ingredients that potentiate the activities of any single constituent better explain the observed benefits of whole foods and diets in many epidemiological studies (Kok et al., 2008; Liu, 2004). In a recent study that compared GSE-induced anticancer effects to the effects of its individual components, the researchers found that GSE is significantly more potent to inhibited growth than its individual components, epigallocatechin and procyanidins (Dinicola et al., 2012). Thus, it is possible that the beneficial effects of fruit/vegetable consumption may arise from the combination of different compounds. Additionally, bioactive compounds may have pleiotropic effects that in combination reduce the risk for chronic

disease. Different compounds might target different pathways to better suppress cancer cell growth (Kris-Etherton et al., 2002; Majumdar et al., 2009). As illustrated in this review, these bioactive compounds simultaneously act on different pathways at the same time. Recently, there have been many studies on bioactive components and their synergistic anticancer effects (Aggarwal et al., 2004; Chuang & McIntosh, 2011; Follo-Martinez et al., 2015; Mertens-Talcott et al., 2003; Mertens-Talcott & Percival, 2005; Vanamala et al., 2008a and Vanamala et al., 2008b; Yang & Liu, 2009). As a result, although this review discussed the aspect of anticancer effects of bioactive compounds from the three classes of carotenoids, glucosinolates, and polyphenols, we stress the importance of assessing the whole foods that contain them and how farm-to-fork stages affect the composition and content of these bioactive compounds.

## Carotenoids

### Pre- and postharvest

Much of the future carotenoid content of fruits and vegetables is accounted for in the effect of genotype, making cultivar selection of great importance in the ultimate delivery of carotenoids. In a recent study of 25 potato genotypes, where various carotenoids including lutein, violaxanthin, and β-carotene were analyzed, plant genotype was the most significant preharvest parameter in determining total carotenoid content (Reddivari et al., 2007a and Reddivari et al., 2007b). Similarly, in Lima et al.'s (2005) study of acerola fruit, a common Brazilian export because of its high carotenoid and anthocyanin content, genotype selection and maturity at harvest both played a significant role in the level of bioactive compounds as well as the overall performance of the fruit in terms of its bioactive compound content, with a single genotype out-performing in terms of polyphenol and carotenoid content. Another study evaluated levels of four types of carotenoids (β-carotene, β-cryptoxanthin, α-carotene, and lutein) found in two commonly cultivated acerola genotypes. One cultivar exhibited significantly higher levels of β-carotene, β-cryptoxanthin, and α-carotene, whereas the second cultivar was higher in lutein. This study also suggested that annual variation in sunlight exposure altered carotenoid biosynthesis across acerola cultivars (De Rosso & Mercadante, 2005). In addition to genotype, other related preharvest factors including soil type, climate, farm management type, and maturity at harvest have been shown to significantly affect carotenoid levels. Both of the aforementioned acerola studies also found that climate and seasonality affected carotenoid synthesis and content. Similarly, in studies of grapes, soil characteristics and irrigation played an important role in determining carotenoid content (Oliveira et al., 2003). Additionally, lutein and β-carotene concentrations have been found to be higher in grapes from warmer regions (Marais et al., 1991).

Farm management type, although not yet well understood, can further affect carotenoids, and there is much public interest surrounding the influence of organic versus conventional management practices (Stracke et al., 2009a and Stracke et al., 2009b). A study of tomatoes under organic and conventional management showed organically managed tomatoes had higher levels of lycopene (+14%) and β-carotene (+42%) when analyzed as fresh matter, yet these differences decreased when analyzed as dry matter, with lycopene differences nonsignificant and β-carotene levels at +25% (Caris-Veyrat et al., 2004). This study found the higher level of carotenoids in organic tomatoes to be consistent with their higher red color value, and also found that the differences between levels of lycopene and β-carotene in fresh versus dry matter analyses to be due to higher levels of dry matter content in organic tomatoes. Another study found no significant difference between organic and conventionally produced carrots as manifested in the carotenoid levels of plasma of men when analyzed after consumption (Stracke et al., 2009a and Stracke et al., 2009b).

Beyond comparisons of organic versus conventional management practices, general management considerations such as maturity at harvest, as well as climate and weather, can affect bioactive compounds. Maturity at harvest can affect carotenoid levels and might vary by species, as Marais et al. (1991) showed in their study of grapes where overall carotenoid concentrations significantly decreased with fruit maturity, whereas in the previously mentioned study of acerola, and in another study of mango cultivars, levels of violaxanthin and β-carotene increased with fruit maturity (Mercadante & Rodriguez-Amaya, 1998). Lutein and β-carotene levels in grapes were higher when grown in hot rather than cool regions (Marais et al., 1991).

Similar to preharvest practices, certain postharvest practices also affect carotenoid content. For example, storage time and type has shown to affect gac, a common fruit in Vietnam, with carotenoid levels declining in the second week of storage (Nhung et al., 2010). A study of mangoes also showed that harvesting at the sprung stage, instead of at the mature green stage, and then keeping the mangoes in controlled atmosphere storage for 3 or 5 wk resulted in significantly higher carotenoid content than the same storage for mature green stage mangoes (Dang et al., 2006). However, many of these studies did not take total water content into account and future studies should present bioactive compound levels on a dry weight basis.

### Processing and postprocessing

Processing and postprocessing techniques also can significantly alter carotenoid content (Cilla et al., 2018). High temperatures during processing degrade β-carotene and visual color in pumpkin puree, as well as affect the *trans-cis* form of carotenoids, with the visual color change a direct representation of the change in β-carotene values (Marx et al., 2003). high-pressure processing (HPP) is a relatively new method of food preservation that employs high isostatic pressure ranging from 300 to 600 MPa, causing inactivation of micro-organisms and enzymes. Sanchez-Moreno et al. (2006) demonstrated that HPP tomato puree retains the highest overall carotenoids compared with high-temperature pasteurization, low-temperature pressurization, freezing, and high-pressure pasteurization plus freezing, whereas Patras et al. (2009a and 2009b) showed significant increase in the carotenoid content of HPP-treated tomato and carrot purees. However, there are numerous studies reporting mixed results for several combinations of individual carotenoids and specific fruit or vegetable matrices, implying that HPP has a case-specific effect on individual carotenoids (de Ancos et al., 2000; McInerney et al., 2007; Sanchez-Moreno et al., 2006). Butz et al. (2002) reported no change in the carotenoid content of carrots, broccoli, and tomatoes. In general, when compared with other methods, HPP is effective at retaining carotenoids and other phytonutrients.

Ohmic and pulsed-electric field (PEF) processing are two new methods that uniformly apply electric current to food matrices, causing localized heating that destroys micro-organisms and enzymes. Yildiz et al. (2010) studied the effect of four different voltage gradients in the range of 1040 V/cm at various temperatures and holding times. They observed that β-carotene content of spinach significantly increased with holding time at 30 V/cm field strength. Vallverdu-Queralt et al. (2013) reported an increase in carotenoid content of tomato juice using both medium and high PEF methods. Plaza et al. (2011) reported no significant change in the carotenoid content of orange juice subjected to PEF (35 kV cm 1/750 μs). Roohinejad et al. (2014) indicated that the extractability of carotenoids is dependent on the frequency and strength of the

electric field applied. They reported that carotenoids were more easily extracted from carrots until 10 Hz at 1 kV cm 1, after which extraction plateaued.

In addition to these novel processing techniques, postprocessing methods of removing oxygen from packaging and keeping produce out of light are well-understood and standard practices to prevent oxidation, and are two key steps to maintaining high levels of β-carotene (Vasquez-Caicedo et al., 2006). In a study of carrot juice that was acidified, pasteurized, and then stored in light or dark conditions, Chen et al. (1996) found that amounts of lutein, α-carotene, β-carotene, and vitamin A significantly decreased as storage temperature increased or as the product was exposed to light. Duration of postprocessing storage also caused *trans*-lutein and its *cis* isomers to break down in tomato juice, light again facilitating this degradation (Lin & Chen, 2005). A study of β-carotene in a mango matrix also showed that time and temperature affect *trans-cis*-isomerisation of β-carotene, although the authors suggested that this degradation might be offset by improved availability and release of β-carotene as a result of the pureeing (Vasquez-Caicedo et al., 2007).

*Consumer practices*

Once food reaches the consumer, individual food preparation methods can significantly affect content and composition as well as bioactivity of bioactive compound (Murador et al., 2018; Rothwell et al., 2015). A study comparing different preparation practices found different losses of total carotenoids for each preparation method, reporting that water cooking without pressure best retains carotenoids in carrots (Pinheiro Sant'Ana et al., 1998). Another study found traditional sun drying and ambient ventilated storage of amaranth, cowpea, peanut, pumpkin, and sweet potato leaves significantly decreased carotenoid levels, whereas a combination of blanching, shade drying, and airtight storage showed potential to improve carotenoid retention and availability (Stich et al., 1984). Plaza et al.'s (2011) study of carotenoids in orange juice showed that carotenoid content decreased by ~11% after 20 d of refrigerated (4°C) storage.

*Glucosinolates*

*Pre- and postharvest*

Much like with carotenoids, pre- and postharvest processing has been shown to affect glucosinolate content and composition. Velasco et al. (2007) showed that plant age and development stage are important factors in glucosinolate levels at harvest, with preharvest insect damage by lepidopterous pests on kale (Brassica oleraceaasephala group) decreasing glucosinolate content in the damaged leaves. They found that overall glucosinolate levels in kale leaves increased from the seedling to early flowering stages, at which point glucosinolate concentration shifted from the leaves to the buds. Velasco et al. also suggested that soil properties and temperature appear to significantly influence glucosinolate content, but encouraged further research on the topic. In a related study, Cartea and Velasco (2007) looked at >150 varieties of kale and cabbage to determine glucosinolate content as it relates to seasonal variation. They found that of these cultivars, four kale varieties had the highest sinigrin or glucobrassicin contents, and that two specific cabbage varieties had both high glucosinolate content and yields suggesting these cultivars are valuable for future breeding research. Furthermore, they found that the type of glucosinolates present in cabbages varied by season, with spring planted cabbages containing high amounts of glucobrassicin and glucoiberin, and fall planted cabbages containing high amounts of glucoiberin. In their review of the glucosinolate-myrosinase system, Dal Pra et al. (2103) found that climate, soil type, genotype, and seasonal variation can all affect glucosinolate content, and they suggested that cultivar selection should be tailored at each individual growing site to optimize glucosinolate production. Recent studies have shown significant variation in glucosinolate content across various species of *Brassicaciae* family vegetables, suggesting that the health-promoting properties of different cultivars might vary, and that certain cultivars might be best to focus on within breeding programs because of their dual performance in both yield and glucosinolate content (Kushad et al., 1999; Padilla et al., 2007). In Farnham et al. (2004), the broccoli genotype affected glucosinolate levels more than environmental factors, suggesting that a broccoli cultivar can be developed that is specifically designed for maximum chemoprotective potential.

For glucosinolates, the effect of farm management type is not well understood and results vary across studies. For example, in a study comparing various glucosinolate levels in organic and conventional broccoli and red cabbage in the European Union, significant differences were found in the content of glucosinolates in each cultivar group. The organic broccoli and cabbage cultivars had higher levels of glucobrassicin than conventional ones, although the conventional red cabbage had higher gluconapin, and no difference was found in glucoraphanin in either group (Meyer & Adam, 2007). It is possible that various glucosinolates respond differently to organic and conventional management, as is also reflected in a study on glucosinolate and phytochemical levels in another member of the brassica family, cauliflower (Picchi et al., 2012). In addition to differences in farm management regimes, maturity at harvest has been shown to influence glucosinolate levels, with younger harvested broccoli having the highest levels of glucosinolates (Pereira et al., 2002).

Glucosinolate content and the content of its breakdown compounds also varies with plant genotype, and thus can affect the chemopreventive properties of commonly consumed glucosinolate-containing vegetables, such as broccoli (Jeffery et al., 2003). This complicates recommendations of fruit and vegetable intake as well as cultivar selection, as much research of cultivars and their bioactive compound and chemopreventive properties is ongoing (Brown et al., 2002). Much like carotenoids, the effect of cultivar is also influenced by environment, and temperature also has been shown to significantly affect glucosinolate levels in broccoli (Pereira et al., 2002). A study using several brassica species revealed that glucosinolates levels of different cultivars are significantly influenced by climatic conditions and showed that dry and hot conditions were most conducive for production of glucosinolates (Ciska et al., 2000). As summarized by Verkerk et al. (2009), water stress has been shown to increase glucosinolate content in certain species including water cress, cabbage, and red cabbage, although, as they point out, Robbins et al. (2005) found that water stress actually reduced glucosinolate content, highlighting that other environmental factors are likely influencing glucosinolates. The effect of postharvest storage time and conditions can further affect glucosinolate content, with relative humidity and continuous cooling being effective in retaining glucosinolates (Verkerk et al., 2009). Similarly, in their review of the effects of postharvest treatments on broccoli, Jones et al. (2006) found that retaining the cellular integrity of broccoli, and thus preventing the interaction of glucosinolates with myrosinase, is best achieved through low temperature (<4°C) and high relative humidity.

*Processing and postprocessing*

The processing of vegetables within the Brassicaceae family can affect the chemopreventive properties that are available in the consumption of their raw versus processed form. Many types of

processing, but especially thermal processing of glucosinolate-containing vegetables, generally leads to loss of glucosinolates or breakdown of myrosinase, and/or their leaching into cooking water (Lafarga et al., 2018; Slominski & Campbell, 1989). Vos and Blijleven (1988) found that cooking reduces glucosinolate levels by ~30% to 60%, fermenting gradually degrades all glucosinolates, and pulping of brassicas will completely breakdown glucosinolates through autolysis. Slominski and Campbell (1989) found that heat by steaming (10 min) or cooking (40 min) significantly decomposed several indole glucosinolate levels. Conversely, Verkerk et al. (2001) found an unexpected increase in certain individual glucosinolate levels after chopping of broccoli, with some indolyl glucosinolates being induced by mechanical damage of chopping, thus suggesting that the generally understood decrease in total glucosinolate levels with processing does not acknowledge the potential stress-induced increase of individual breakdown glucosinolates. This potential stress-induced increase in glucosinolates is linked to myrosinase activity and the breakdown of glucosinolates into active forms. Although a review of environment and process parameters on glucosinolate-myrosinase activity by Dal Pra et al. (2013) suggests that both thermal and HPP can disrupt this process, work by Van Eylen et al. (2009) suggests that myrosinase activation can be facilitated through novel processing techniques. For example, Van Eylen et al. suggest that mild levels of HPP can actually be used to stimulate myrosinase activity, which thermal treatments cannot likewise achieve.

Glucosinolate levels have benefited from novel processing techniques in other ways. Mandelova and Totusek (2007) reported that a 14-d administration of broccoli juice treated with 500 MPa pressure for 10 min showed significant antimutagenic activity in mice. They also reported similar activity of broccoli juice treated by freezing, yet untreated broccoli juice (as a control treatment) did not have an antimutagenic effect. This suggests that HPP may enhance the anticarcinogenic activity of Brassicaceae vegetable juices by keeping glucosinolates and their derivatives stable, although there is a knowledge gap regarding the lack of antimutagenic effect from the control. It is worth noting that HPP is an effective processing technique that helps retain the bioactivity of phytonutrients. In another study, Van Eylen et al. (2009) published similar results from their study of the effects of temperature/pressure on glucosinolate conversion in broccoli. They suggested that HPP can induce the formation of glucosinolates into ITCs, which have potential health-benefiting properties. Another novel processing technique—PEF—has been studied for use with glucosinolate containing vegetables, but has not had the same promising results. Broccoli puree treated with PEF displayed significant increase in cell membrane permeability at 20 kV/cm and significantly inactivated myrosinase at 35 kV/cm. The authors observed that most of the glucosinolates degraded during pureeing as a result of autolysis but the degradation was furthered by PEF (Meeran et al., 2010). This result suggests that PEF may not be an effective method to retain phytonutrients in broccoli. However, this warrants an investigation into finding appropriate sample preparation methods and testing a range of electric field strengths.

Postprocessing practices also can affect the chemopreventive properties of glucosinolate-containing vegetables, with degradation often occurring by thermal or mechanical disruption. Song and Thornalley (2007) found that storage of intact broccoli, Brussels sprouts, cauliflower, and green cabbage under refrigeration did not lead to large losses of glucosinolates, but that levels in shredded vegetables declined ~75% over 6 h. Freezing of broccoli, a common practice, best retains glucosinolates if the broccoli is blanched before freezing to inactivate myrosinase; otherwise, once thawed, myrosinase will break down the remaining glucosinolates (Johnson, 2000).

*Consumer practices*

Cooking methods of glucosinolate-containing vegetables are important to consider, especially because of the potential for cooking to affect the enzyme myrosinase, which is responsible for breaking down glucosinolates in to various chemopreventive agents. Song and Thornalley (2007) also found that the cooking method greatly affected retention of glucosinolates, with steaming, microwaving and stir-frying retaining the most glucosinolates, as detected by liquid chromatography-tandem mass spectrometry analysis. Vallejo et al. (2002) also suggested that steaming has minimal effects on the glucosinolates in broccoli, but found that microwaving or either high-pressure or conventional boiling could have greater losses, with microwaving losing 74% of total glucosinolates, and high-pressure and conventional boiling losing 33% and 55% of glucosinolates, respectively. Other cooking practices, such as shredding and boiling, led to ~75% to 90% of the glucosinolates leaching into cooking water (Song & Thornalley, 2007). In another study of glucosinolates in red cabbage, microwave cooking led to an increase in glucosinolate content compared with untreated red cabbage (Verkerk & Dekker, 2004), which contradicts broccoli findings and suggests that effect of cooking method with respect to bioactive compounds could vary across species. The level of increase also appeared to be significantly dependent on the energy input. Myrosinase activity was retained at low (24 min, 180 W) and intermediate (8 min, 540 W) microwave powers; however, a high power (4.8 min, 900 W) inactivated the enzyme. In an in vivo study in rats, sulforaphane had substantially more potent anticarcinogenic activity than sulforaphane nitrile, a similarly formed product of glucoraphanin hydrolysis (Matusheski & Jeffery, 2001). Myrosinase activity as a driver of sulforaphane production in broccoli also increased if fresh broccoli florets and sprouts were heated to 60°C before homogenization instead of 70°C; this also decreased formation of sulforaphane nitrile (Matusheski et al., 2004). As an alternative to lower temperature heat treatment to retain sulforaphane, and as a possibility for enhancing the bioactive compound content of boiled (and thus inactivated myrosinase) broccoli, research by Sameer Khalil Ghawi (2013) demosntrated that the addition of powdered mustard seeds to heat processed (e.g., boiled) broccoli can increase the formation of sulforaphane, suggesting that myrosinase of certain crops can tolerate different temperatures before inactivation, and that it can still be responsible for formation of sulforaphane if combined with other glucosinolate-containing crops.

*Polyphenols*

*Pre- and postharvest*

Pre and postharvest management of fruits and vegetables can significantly alter levels of polyphenols. Cultivar selection is an important determinant in polyphenol level, with Tsao et al.'s (2003) and Khanizadeh et al.'s (2008) studies, each of eight distinct apple cultivars, showing significant differences between cultivars as well as differences in polyphenol concentration in apple flesh versus skin. In potatoes, cultivar selection has been shown to be the most important factor in determining phenolic content (Reddivari et al., 2007a and Reddivari et al., 2007b). Onions are another commonly consumed source of polyphenols, as they are a potent source of quercetin, the content of which varies both with onion bulb color and in the different layers of onions (Patil et al., 1995; Patil & Pike, 1995). A study of 75 cultivars of onions found that although yellow, pink, and red onions had higher levels of quercetin than white onions, the potential also exists to breed for quercetin content that is independent of the color of the onion (Patil et al., 1995). A study of sweet potatoes showed that different

parts of the plant have different levels of polyphenols, that the leaves have the highest levels of polyphenols, and that levels of polyphenols in sweet potato leaves vary significantly by genotype (cultivar; Islam et al., 2002). We demonstrated that sweet sorghum components also differed in their levels of polyphenols, with leaf and seed head having highest levels of polyphenols compared to dermal and pith layer (Massey et al., 2016). A study of sweet potato leaves found that temperature and shading of cultivars affected the accumulation of anthocyanins in the leaves, with the highest levels of anthocyanins accumulating under moderate (20°C) conditions and without shading (Islam et al., 2005). In a study of phenols and flavonoids in commonly discarded parts of vegetables to analyze their possible use as an alternative nutritional source, Lima et al. (2008) found a tendency for organically produced foods to show higher polyamine and total phenol contents, but lower flavonoid contents in whole foods. In a 3-y study of golden delicious apples under organic and conventional production practices, polyphenol levels significantly varied in one of the 3 y, with higher levels in the organic apples, and the study determined that annual climate generally had a higher affect on polyphenol content (Stracke et al., 2009a and Stracke et al., 2009b). Phenolic content has also been found to be higher in wild blueberries than in commonly cultivated varieties (Giovanelli & Buratti, 2009). Similarly, in a study of strawberries, organically managed strawberries were found to have significantly higher antioxidant and phenol concentrations than conventionally managed strawberries (Jackson & Singletary, 2004).

Postharvest storage practices also can affect polyphenols. In a study of orange juice under different storage regimes, the stability of certain polyphenols varied, with hydroxycinnamic acids the most sensitive and easily degraded, whereas flavanones were only slightly affected (Klimczak et al., 2007). Similarly, polyphenols in litchi fruit under refrigerated and ambient storage had significant degradation over 7 d, suggesting the sensitivity of polyphenols to common storage techniques (Zhang et al., 2000). Alternatively, several studies suggest that postharvest storage has no significant effect, or can even increase, the polyphenol levels in some fruits and vegetables, including studies on oranges, kale, and fresh plums (Diaz-Mula et al., 2009; Hagen et al., 2009; Plaza et al., 2011). In another study, controlled atmospheric storage at 4.4°C was shown to retain higher amounts of quercetin in onions than storage at 5°C, 24°C, and 30°C (Patil et al., 1995). In a study of white, yellow, and purple potatoes, Madiwale et al. (2011) found that after 90 d of storage, all three potato types had increased antioxidant activity, yet only the purple-fleshed potatoes had an increase in total phenolic content. But perhaps more importantly, Madiwale et al. also found that although total phenolic and antioxidant activity increased, the storage time suppressed apoptosis induction of colon cancer cells compared with fresh potatoes, suggesting that analysis of phenolic and antioxidant activity must be used alongside in vitro or in vivo analyses.

*Processing and postprocessing*

Processing techniques, especially water-based processing, can affect the content of phenolic compounds, as they are generally water soluble (Pinhero et al., 2016). From the point of processing stability, anthocyanins, phenolic acids, and tannins are the most extensively studied polyphenols. Resveratrol is gaining importance due to potential anticancer properties, but there is limited data available on curcumin stability. In olive oil processing, a pressure and centrifugal system with warm water extraction leads to an olive oil with lower amounts of phenols than if a percolation system is used (Giovacchino et al., 1994). Similarly, in the processing of coffee beans for soluble coffee, a commonly consumed product in eastern Europe, Asia/Pacific, and Australia, the conditions and methods of both roasting and extraction can affect antioxidant activity and capacity. Vignoli et al. (2011) found that robusta coffee had higher antioxidant activity than Arabica coffee, as a result of its higher caffeine levels. All soluble coffee products they studied had high antioxidant potential from the combination of caffeine, phenolic compounds, and melanoidins. Roasting had a nonsignificant effect on overall antioxidant activity probably because of a balance of degraded and formed antioxidant compounds that occurs with roasting. Instead, antioxidant activity is more a result of coffee composition than roasting (Vignoli et al., 2011).

Processing of grape juice showed different effects on phenolic acid levels from sulfar dioxide or non-sulfar dioxide addition during processing, although this did not affect quercetin glycosides. In the same study, storage of grape juice at 25°C for 9 mo caused extensive oxidation and total loss of cyanidins and quercetin glycosides (Spanos & Wrolstad, 1990). Irradiation of some fruits and vegetables, like grapefruit, has been shown to induce higher flavonoid levels (Girennavar et al., 2008; Harbaum-Piayda et al., 2010; Oufedjikh et al., 1998), although our work has shown that irradiated grapefruit pulp does not suppress high multiplicity aberrant crypt foci, a biomarker for colon cancer, whereas non-irradiated grapefruit did suppress the marker (Vanamala et al., 2006a and Vanamala et al., 2006b). Our work also has shown that irradiation, freeze drying, and storage can affect different bioactive compounds uniquely (Vanamala et al., 2005), and that price has no significant correlation to flavonoid content in a comparison of made-from-concentrate and not-from-concentrate orange and grapefruit juices in the United States (Vanamala et al., 2006a and Vanamala et al., 2006b).

Polyphenol levels are susceptible to degradation under different storage practices. For example, in a study of strawberries that examined the phenolic content of different parts of the fruit, it was found that purees of strawberry that contained the achenes (the small seeds on the flesh with comparatively high phenolic content) increased overall phenolic compound levels and stability under storage regimes (Aaby et al., 2007). Regarding the processing of onions (Allium cepa), Price et al. (1997) found that the curing and 6-mo storage of onions, a standard commercial practice, leads to a 50% reduction in quercetin levels. They also found that subsequent preparation by boiling or frying leads to the loss of another 25% of overall quercetin. Storage of apples under specific in-package modified atmosphere had a negative effect on anthocyanin levels in the skins of Starkrimson apples compared with unpackaged apples (Lin et al., 1989). In a study of thornless blackberries, it was found that various ozone storage regimens helped to retain initial anthocyanin levels through 12 d of storage (Barth et al., 1995).

HPP (200–800 MPa) caused moderate losses in anthocyanin content of strawberries and raspberries. In both cases, low temperature ~4°C was found to be a good condition to mitigate the losses in anthocyanins content observed due to HPP. Compared with untreated samples, anthocyanin degradation seemed to be influenced by the amount of pressure applied and days of storage (Suthanthangjai et al., 2005; Zabetakis et al., 2000). Patras et al. (2009a and 2009b) reported no change in anthocyanin content of strawberry and blackberry purees subjected to 400 to 600 MPa pressure compared with untreated samples. In fact, they observed a significant increase in the total phenolic content post-HPP, leading to an increase in the antioxidant activity of samples. The authors attributed this to increased extractability of phenolic compounds due to high pressure (Patras et al., 2009a and Patras et al., 2009b). Corrales et al. (2008) compared the effect of ultrasonics, HPP, and PEF on extraction of anthocyanins from grape by-products. Compared with untreated samples, ultrasonic-extracted samples had twice the levels of anthocyanins, HPP samples three times the levels, and PEF-treated samples four times the levels of

anthocyanins. HPP led to a 30% increase in the extractability of polyphenolics from green tea leaves when compared with traditional heat reflux extraction (Xi et al., 2009). Casazza et al. (2012) used a high-pressure, high-temperature technique to extract phenolic compounds from grape skins. They reported high yields of gallic acid, 5-hydroxymethylfurfural, protocatechuic acid, catechin, vanillic acid, syringic acid, coumaric acid, trans-resveratrol, and quercetin with retained antioxidant activity. Plant suspension cultures of *Vitis vinifera* subjected to a combined treatment of PEF and ethephon, a plant growth regulator, showed significantly higher levels of phenolic acids and 3-*O*-glycosyl-resveratrol. PEF alone was also effective in increasing levels of these compounds. The effect, however, was strongly accentuated in the presence of ethephon (Cai et al., 2012). PEF treatments were also effective in enhancing the extraction of phenolic compounds, including anthocyanins, from whole red cabbage (Kannan, 2011).

From a processing standpoint, curcumin is one of the least studied bioactives. To the best of our knowledge, there are no available data on the effect of HPP or PEF or any novel processing technique on curcumin. Suresh et al. (2007) subjected dried turmeric, a very rich source of curcumin, to thermal treatments such as boiling and pressure cooking. They reported losses in curcumin ranging from 27% to 53%. However, the losses were lessened by 12% to 30% in the presence of tamarind, which is used as a household acidulant in Indian cooking.

*Consumer practices*

In-home preparation of foods also can significantly affect polyphenol content of fruits and vegetables. For example, a study of five types of onions prepared by sauting, baking, and boiling found that baking and sauting led to a 7% to 25% increase in quercetin concentration, whereas boiling led to an 18% decrease in quercetin concentration, with results being consistent across all five cultivars (Lombard et al., 2005). Heat treatment (as in cooking) readily degrades curcumin (Suresh et al., 2008); therefore, consumer practices involving cooking turmeric can cause considerable decrease in its concentration of curcumin.

## Conclusions

Increased knowledge of the hallmarks of cancer has paved the way for new therapies, with each of the hallmarks now being targeted by drug therapies. However, such approaches have a narrow scope and might explain why many drugs fail during clinical trials or are associated with relapse. Furthermore, cells within the same tumor can show distinct morphological and phenotypic profiles (including cellular morphology, gene expression, metabolism, motility, proliferation, and metastatic potential), which introduces significant challenges in designing effective cancer treatment strategies. Another concern is the development of drug resistant and aggressive tumors. As suggested by “Hallmarks of Cancer” coauthor Hanahan, perhaps a better way to target cancer and to better combat the worldwide cancer epidemic would be to develop drugs (or drug combinations) that can target multiple hallmarks at the same time or more specifically, that target multiple molecular biomarkers associated with the each of the hallmarks of cancer (NCRI Conference, 2015).

This need to target multiple hallmarks is one of the major reasons why, in the context of cancer research, there are many proponents of investigating plant foods as they can deliver a cocktail of bioactive compounds. Many plant food components have demonstrated anticancer properties via targeting enzymes, cell surface molecules, intracellular receptors, and by influencing gene expression, among other actions (Kris-Etherton et al., 2002; Kris-Etherton et al., 2004). Mounting evidence suggests that bioactive compounds in whole foods can target most, if not all, of the hallmarks of cancer (Kris-Etherton et al., 2002; Liu, 2013). Moreover, they fit the characteristics of an ideal chemopreventive agent, as these compounds are selective to cancerous or precancerous cells and have low (or zero) toxicity concerns (Almeida et al., 2009; Biesalski et al., 2009), target most types of cancers, can be consumed as a part of a daily diet, are already broadly delivered throughout many stages of the food system, and are relatively inexpensive in cost (Kaur et al., 2009). Related research has already shown that following vegetarian and vegan diets results in lower cancer rates, with the suggestion that the anticancer effects of the vegan diet may primarily be attributed to proportionally higher consumption of plant-based foods containing bioactive compounds (Tantamango-Bartley et al., 2013). Similar results have also been seen in the China study, where plant-rich diets were shown to reduce the risk for coronary heart disease and other chronic diseases (Campbell et al., 1998). Furthermore, their results also suggested that there is not a clear threshold when the benefits from a plant-rich diet diminish.

Building upon the content of this review, an opportunity exists to further integrate and expand the role of bioactive compounds in cancer prevention by using food system–based approaches best suited to local conditions. Moreover, recent work suggests our modern agro-food system is implicated in larger public health problems, with cancer being only one example in the midst of rising incidence of obesity and cardiovascular disease (Anand et al., 2015; Reganold et al., 2011). Many strategies exist in combating the rise in the incidence of food system-related diseases. As we have demonstrated in this review, much current research focuses on the potential of various genetic and management-related approaches to improving bioactive compound delivery, ranging from organic management and investigation of diverse landrace varieties, to related research into biofortification, which combines conventional breeding with various new technologies (King & Gershoff, 1987; Pfeiffer & McClafferty, 2007; Reganold et al., 2015). As authors of this review, we are not proponents of any single approach. Instead, we advocate for a broader food system–based approach that integrates many methods across the stages of the food system, while recognizing that a key challenge in targeting such diseases with a food system–based approach is to apply the findings in practical, accessible solutions for consumers, policymakers, processors, producers, researchers and health care providers. However, as a starting point, critical points in the staple crops food system practices that greatly alter the content (Fig. 1) and composition of putative anticancer compounds (Madiwale et al., 2012) as well as in vivo anti-inflammatory/anticancer studies of foods should be assessed using human-relevant animal models (Sido et al., 2017). Furthermore, emerging evidence suggests that there is a reciprocal interaction between plant bioactive compounds and gut bacteria (Hidalgo et al., 2012). For example, anthocyanins, a class of flavonoids, elevate beneficial gut bacterial abundance such as *Bifidobacterium* and the gut bacterial anthocyanin metabolites are more active in suppressing a well-known proinflammatory cytokine IL-6, a crucial regulator of chronic colonic inflammation as well as colon carcinogenesis, than the parent compound (Amini et al., 2018; Sido et al., 2017).

These food system stakeholders must find ways to better collaborate to create a directed food system–based approach with the focus on farm-to-fork to function; this is a grand and complex challenge that can perhaps be best realized through targeted solutions, especially because the needs of stakeholders vary so greatly, and the agro-food system has such complex political, economic, and public dimensions. Indeed, a recent publication from Willett et al. (2019) strongly recommended doubling the consumption of

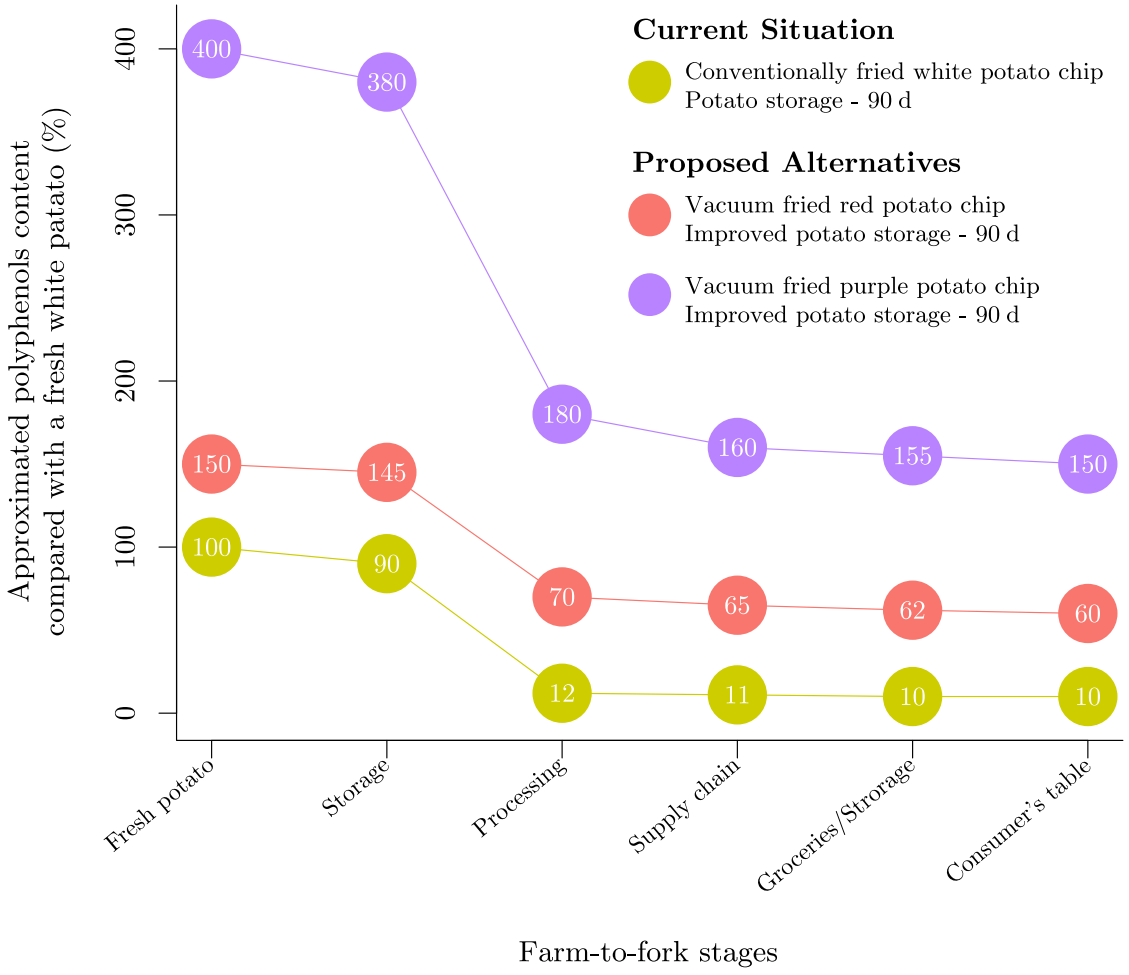


**Fig. 1.** Harnessing the anticancer potential of staple crops, using potato as an example. By selecting the color-fleshed potato cultivars, reducing storage time (potatoes can be grown in different geographical locations through the year) and by adopting novel alternative frying technologies like vacuum frying, antiproliferative polyphenolic compounds levels could be elevated in the human diet. Additionally, vacuum frying is also shown to reduce acrylamide, a putative carcinogen, in plant food products compared with conventional countertop frying methods. Thus, even minimal changes to food systems at critical control points can improve the anticancer activity of whole foods.

plant-based food at the expense of meat intake to promote both health of humans and our planet. To better harness the health benefits of plant-based food, future studies should particularly focus on the following:

- Servings of fruits and vegetables to meet the required health benefits.
- Whether alterations in the content and composition of phytochemicals due to the food systems processes, in turn alter the potent gut bacteria derived metabolite levels.
- Interindividual variability in terms of absorption, distribution, metabolism, and excretion of bioactive phytochemicals and their gut bacteria derived metabolites, preferably using isogenic lines (cultivars with or without that specific class/individual phytochemical).

However, some of the phytochemicals that are poorly bioavailable can exert anti-inflammatory and anticancer effects as their gut microbiome-derived metabolites can be absorbed and can be more potent anti-inflammatory compounds than the poorly available parent compounds.

As was a review, we can only begin to outline exploratory considerations for the food system–based approach, but we believe that recognition, understanding, and integration of this approach can enhance the ongoing conversation about the role of the food system in public *health* and that it is of the utmost importance in decreasing the global cancer burden.

## Acknowledgments

The authors acknowledge Gary D. Stoner and A. Catharine Ross for their constructive feedback. They also acknowledge Cara Boothroyd, Kaitlyn Shondelmyer, Yuming Zhang, and Menaka Suri for the edits and comments. Finally, they acknowledge Robert B. Beelman for his insightful discussions and critical edits.

## References

Aaby K, Wrolstad RE, Ekeberg D, Skrede G. Polyphenol Composition and Antioxidant Activity in Strawberry Purees; Impact of Achene Level and Storage. Journal of Agricultural and Food Chemistry 2007;55:5156–66.

Abbas A, Hall JA, Patterson WL III, Ho E, Hsu A, Al-Mulla F, Georgel PT. Sulforaphane modulates telomerase activity via epigenetic regulation in prostate cancer cell lines. Biochemistry and Cell Biology 2015;94(1):71–81.

Aggarwal B, Bhardwaj A, Aggarwal R, Seeram N, Shishodia S, Takada Y. Role of Resveratrol in Prevention and Therapy of Cancer: Preclinical and Clinical Studies. Anticancer Research 2004;24:2783–840.

Ahmad N, Cheng P, Mukhtar H. Cell cycle dysregulation by green tea polyphenol epigallocatechin-3-gallate. Biochemical and Biophysical Research Communications 2000;275:328–34.
Almeida L, et al. Pharmacokinetic and safety profile of trans-resveratrol in a rising multiple-dose study in healthy volunteers. Molecular Nutrition and Food Research 2009;53(Suppl 1):S7–15.
Amatoa L, Ritschardb J, Sprechera I, Lacroixa C, Schupplerb M, Meilea L. Effect of packaging materials, environmental factors and rRNA transcriptional activity of surface microflora on red-smear cheese defect development. International Dairy Journal 2015;41:50–7.
Amatori S, Mazzoni L, Alvarez-Suarez JM, Giampieri F, Gasparrini M, Forbes-Hernandez TY, Afrin S, Provenzano AE, Persico G, Mezzetti B, et al. Polyphenol-rich strawberry extract (prse) shows in vitro and in vivo biological activity against invasive breast cancer cells. Scientific reports 2016;6:30917.
Amawi H, Ashby CR, Samuel T, Peraman R, Tiwari AK. Polyphenolic nutrients in cancer chemoprevention and metastasis: Role of the epithelial-to-mesenchymal (emt) pathway. Nutrients 2017;9(8):911.
Amin PJ, Shankar BS. Sulforaphane induces ros mediated induction of nkg2d ligands in human cancer cell lines and enhances susceptibility to nk cell mediated lysis. Life sciences 2015;126:19–27.
Amini AM, Spencer JP, Yaqoob P. Effects of pelargonidin-3-o-glucoside and its metabolites on lipopolysaccharide-stimulated cytokine production by thp-1 monocytes and macrophages. Cytokine 2018;103:29–33.
Amir H, Karas M, Giat J, Danilenko M, Levy R, Yermiahu T, Levy J, Sharoni Y. Lycopene and 1,25-Dihydroxyvitamin D3 Cooperate in the Inhibition of Cell Cycle Progression and Induction of Differentiation in HL-60 Leukemic Cells. Nutrition and Cancer 1999;33:105–12.
Anand SS, et al. Food Consumption and its Impact on Cardiovascular Disease: Importance of Solutions Focused on the Globalized Food System: A Report From the-Workshop Convened by theWorld Heart Federation. Journal of the American College of Cardiology 2015;66:1590–614.
Arseneault R, Chien A, Newington J, Rappon T, Harris R, Cumming R. Attenuation of LDHA expression in cancer cells leads to redox-dependent alterations in cytoskeletal structure and cell migration. Cancer Letters 2013;338:255–66.
Arts IC, Hollman PC. Polyphenols and disease risk in epidemiologic studies. The American Journal of Clinical Nutrition 2005;81:317s–25s.
Asakage M, Tsuno N, Kitayama J, Tsuchiya T, Yoneyama S, Yamada J, Okaji Y, Kaisaki S, Osada T, Takahashi K, Nagawa H. Sulforaphane induces inhibition of human umbilical vein endothelial cells proliferation by apoptosis. Angiogenesis 2006;9:83–91.
Badimon L, Chagas P, Chiva-Blanch G. Diet and cardiovascular disease: effects of foods and nutrients in classical and emerging cardiovascular risk factors. Current medicinal chemistry 2019.
Baliga MS, Meleth S, Katiyar SK. Growth inhibitory and antimetastatic effect of green tea polyphenols on metastasis-specific mouse mammary carcinoma 4T1 cells in vitro and in vivo systems. Clinical Cancer Research 2005;11:1918–27.
Barth MM, Zhou C, Mercier J, Payne FA. Ozone Storage Effects on Anthocyanin Content and Fungal Growth in Blackberries. Journal of Food Science 1995;60:1286–8.
Batra P, Sharma A. Anti-cancer potential of flavonoids: recent trends and future perspectives. 3 Biotech 2013;3:439–59.
Bayley JP, Devilee P. The Warburg effect in 2012. Current Opinion in Oncology 2012;24:627.
Bendich A. Carotenoids and the Immune Response. Journal of Nutrition 1989;119:112–5.
Bertl E, Bartsch H, Gerhauser C. Inhibition of Angiogenesis and Endothelial Cell Functions are Novel Sulforaphane-mediated Mechanisms in Chemoprevention. Molecular Cancer Therapeutics 2006;5:575–85.
Bhandarkar SS, Arbiser JL. Curcumin as an inhibitor of angiogenesis. Advances in Experimental Medicine and Biology 2007;595:185–95.
Bhaumik S, Jyothi MD, Khar A. Differential modulation of nitric oxide production by curcumin in host macrophages and NK cells. FEBS Letters 2000;483: 78–82.
Biesalski H, et al. Bioactive compounds: Safety and efficacy. Nutrition 2009;25:1206–11.
Bishayee A, et al. Potential Benefits of Edible Berries in the Management of Aerodigestive and Gastrointestinal Tract Cancers: Preclinical and Clinical Evidence. Critical Reviews in Food Science and Nutrition 2016;56:1753–75.
Bolhassani A. Cancer Chemoprevention by Natural Carotenoids as an Efficient Strategy. Anti-Cancer Agents in Medicinal Chemistry 2015;15(8):1026–31.
Bonnesen C, Eggleston IM, Hayes JD. Dietary indoles and isothiocyanates that are generated from cruciferous vegetables can both stimulate apoptosis and confer protection against DNA damage in human colon cell lines. Cancer Research 2001;61:6120–30.
Brown AF, et al. Glucosinolate Profiles in Broccoli: Variation in Levels and Implications in Breeding for Cancer Chemoprotection. Journal of the American Society for Horticultural Science 2002;127:807–13.
Bub A, et al. Fruit juice consumption modulates antioxidative status, immune status and DNA damage. Journal of Nutritional Biochemistry 2003;14:90–8.
Butz P, et al. Changes in functional properties of vegetables induced by high pressure treatment. Food Research International 2002;35:295–300.
Cai Z, Kastell A, Knorr D, Smetanska I. Exudation: an expanding technique for continuous production and release of secondary metabolites from plant cell suspension and hairy root cultures. Plant Cell Reports 2012;31:461–77.
Campbell TC, Parpia B, Chen J. Diet, lifestyle, and the etiology of coronary artery disease: the Cornell China study. American Journal of Cardiology 1998;82:18T–21T.
Cao Y, Cao R, Brakenhielm E. Antiangiogenic mechanisms of diet-derived polyphenols. Journal of Nutritional Biochemistry 2002;13:380–90.
Caris-Veyrat C, et al. Influence of Organic versus Conventional Agricultural Practice on the Antioxidant Microconstituent Content of Tomatoes and Derived Purees; Consequences on Antioxidant Plasma Status in Humans. Journal of Agricultural and Food Chemistry 2004;52:6503–9.
Carroll RE, et al. Phase IIa clinical trial of curcumin for the prevention of colorectal neoplasia. Cancer Prevention Research Phila. Pa 2011;4:354–64.
Cartea ME, Velasco P. Glucosinolates in Brassica foods: bioavailability in food and significance for human health. Phytochemistry Reviews 2007;7:213–29.
Casazza AA, Aliakbarian B, Sannita E, Perego P. Highpressure hightemperature extraction of phenolic compounds from grape skins. International Journal of Food Science and Technology 2012;47:399–405.
Castro-Puyana M, Perez-Sanchez A, Valdes A, Ibrahim O, Suarez-Alvarez S, Ferragut J, Micol V, Cifuentes A, Ibanez E, Garcia-Canas V. Pressurized liquid extraction of neochloris oleoabundans for the recovery of bioactive carotenoids with antiproliferative activity against human colon cancer cells. Food Research International 2017;99:1048–55.
Charepalli V, et al. Anthocyanin-containing purple-fleshed potatoes suppress colon tumorigenesis via elimination of colon cancer stem cells. Journal of Nutritional Biochemistry 2015;26:1641–9.
Chen HE, Peng HY, Chen BH. Stability of carotenoids and vitamin A during storage of carrot juice. Food Chemistry 1996;57:497–503.
Chen M-L, Lin Y-H, Yang C-M, Hu M-L. Lycopene inhibits angiogenesis both in vitro and in vivo by inhibiting mmp-2/upa system through vegfr2-mediated pi3k-akt and erk/p38 signaling pathways. Molecular nutrition & food research 2012;56(6):889–99.
Chew BP, Park JS. Carotenoid Action on the Immune Response. Journal of Nutrition 2004;134:257s–61s.
Chuang CC, McIntosh MK. Potential Mechanisms by Which Polyphenol-Rich Grapes Prevent Obesity-Mediated Inflammation and Metabolic Diseases. Annual Review of Nutrition 2011;31:155–76.
Chung T, Choi H, Lee J, Jeong H, Kim C, Joo M, Choi J, Han C, Kim S, Choi J, Ha K. Marine algal fucoxanthin inhibits the metastatic potential of cancer cells. Biochemical and Biophysical Research Communications 2013;439:580–5.
Churchill M, Chadburn A, Bilinski RT, Bertagnolli MM. Inhibition of intestinal tumors by curcumin is associated with changes in the intestinal immune cell profile. Journal of Surgical Research 2000;89:169–75.
Cilla A, Bosch L, Barberá R, Alegría A. Effect of processing on the bioaccessibility of bioactive compounds—a review focusing on carotenoids, minerals, ascorbic acid, tocopherols and polyphenols. Journal of Food Composition and Analysis 2018;68:3–15.
Ciska E, Martyniak-Przybyszewska B, Kozlowska H. Content of Glucosinolates in Cruciferous Vegetables Grown at the Same Site for Two Years under Different Climatic Conditions. Journal of Agricultural and Food Chemistry 2000;48:2862–7.
Conaway C, Wang C, Pittman B, Yang Y, Schwartz J, Tian D, McIntee E, Hecht S, Chung F. Phenethyl isothiocyanate and sulforaphane and their N-acetylcysteine conjugates inhibit malignant progression of lung adenomas induced by tobacco carcinogens in A/J mice. Cancer Research 2005;65:8548–57.
Corrales M, Toepfl S, Butz P, Knorr D, Tauscher B. Extraction of anthocyanins from grape by-products assisted by ultrasonics, high hydrostatic pressure or pulsed electric fields: a comparison. Innovative Food Science and Emerging Technologies 2008;9:85–91.
Dal Pra V, et al. A review of influence of environment and process parameters on glucosinolatemyrosinase system. Journal of Applied Pharmaceutical Science 2013;3:39543959.
Dang KT, Singh Z, Tan SC. Influences of maturity stage at harvest and ethylene application on colour and quality of controlled atmosphere-stored mango fruit. XXVII International Horticultural Congress-IHC2006: International Symposium on The Role of Postharvest Technology 2006;768:209–16.
Darvin P, Joung YH, Nipin S, Kang DY, Byun HJ, Hwang DY, Cho KH, Do Park K, Lee HK, Yang YM. Sorghum polyphenol suppresses the growth as well as metastasis of colon cancer xenografts through co-targeting jak2/stat3 and pi3k/akt/mtor pathways. Journal of Functional Foods 2015;15:193–206.
Dashwood RH. Frontiers in Polyphenols and Cancer Prevention. Journal of Nutrition 2007;137:267S–9S.
Davis CD, Milner JA. Gastrointestinal microflora, food components and colon cancer prevention. Journal of Nutritional Biochemistry 2009;20:743–52.
de Ancos B, Gonzalez E, Cano MP. Effect of high-pressure treatment on the carotenoid composition and the radical scavenging activity of persimmon fruit purees. Journal of Agricultural and Food Chemistry 2000;48:3542–8.
de Boer VC, et al. Chronic quercetin exposure affects fatty acid catabolism in rat lung. Cellular and Molecular Life Sciences 2006;63:2847–58.
De Rosso VV, Mercadante AZ. Carotenoid composition of two Brazilian genotypes of acerola (Malpighia punicifolia L.) from two harvests. Food Research International 2005;38:1073–7.
Dey M, Kuhn P, Ribnicky D, Premkumar V, Reuhl K, Raskin I. Dietary phenethylisothiocyanate attenuates bowel inflammation in mice. BMC Chemical Biology 2010;10:4.
Diaz-Mula HM, et al. Changes in hydrophilic and lipophilic antioxidant activity and related bioactive compounds during postharvest storage of yellow and purple plum cultivars. Postharvest Biology and Technology 2009;51:354–63.

Dihal AA, et al. Quercetin, but not its glycosidated conjugate rutin, inhibits azoxymethaneinduced colorectal carcinogenesis in F344 rats. Journal of Nutrition 2006;136:2862–7.
Dihal AA, et al. Transcriptome and proteome profiling of colon mucosa from quercetin fed F344 rats point to tumor preventive mechanisms, increased mitochondrial fatty acid degradation and decreased glycolysis. Proteomics 2008;8:45–61.
Dinicola S, et al. Antiproliferative and Apoptotic Effects Triggered by Grape Seed Extract (GSE) versus Epigallocatechin and Procyanidins on Colon Cancer Cell Lines. International Journal of Molecular Sciences 2012;13:651–64.
Diniz C, Sulibursk a J, Ferreira IM. New insights into the antiangiogenic and proangiogenic properties of dietary polyphenols. Molecular nutrition & food research 2017;61(6):1600912.
Dinkova-Kostova AT, Kostov RV. Glucosinolates and Isothiocyanates in Health and Disease. Trends in Molecular Medicine 2012;18:337–47.
Diplock A, Charleux J, Crozier-Willi G, Kok F, Rice-Evans C, Roberfroid M, Stahl W, Vina-Ribes J. Functional Food Science and Defence Against Reactive Oxidative Species. British Journal of Nutrition 1998;80(1):77–112.
Duthie SJ. Berry phytochemicals, genomic stability and cancer: Evidence for chemoprotection at several stages in the carcinogenic process. Molecular Nutrition & Food Research 2007;51:665–74.
Eberhardt MV, Lee CY, Liu RH. Nutrition: Antioxidant Activity of Fresh Apples. Nature 2000;405:903–4.
Ellis LZ, Liu W, Luo Y, Okamoto M, Qu D, Dunn JH, Fujita M. Green tea polyphenol epigallocatechin-3-gallate suppresses melanoma growth by inhibiting inflammasome and il-1_ secretion. Biochemical and biophysical research communications 2011;414(3):551–6.
Erkan M, Reiser-Erkan C, Michalski CW, Kleeff J. Tumor Microenvironment and Progression of Pancreatic Cancer. Experimental Oncology 2010;32:128–31.
Fahey JW, Zalcmann AT, Talalay P. The Chemical Diversity and Distribution of Glucosinolates and Isothiocyanates among Plants. Phytochemistry 2001;56:5–51.
Farnham MW, Wilson PE, Stephenson KK, Fahey JW. Genetic and environmental effects on glucosinolate content and chemoprotective potency of broccoli. Plant Breeding 2004;123:60–5.
Farraye FA, Odze RD, Eaden J, Itzkowitz SH. AGA technical review on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. Gastroenterology 2010;138:746–74. 774–4–3.
Farvid MS, Chen WY, Rosner BA, Tamimi RM, Willett WC, Eliassen AH. Fruit and vegetable consumption and breast cancer incidence: Repeated measures over 30 years of follow-up. International journal of cancer 2019;144(7):1496–510.
Favot L, Martin S, Keravis T, Andriantsitohaina R, Lugnier C. Involvement of cyclin-dependent pathway in the inhibitory effect of delphinidin on angiogenesis. Cardiovascular Research 2003;59:479–87.
Fedeles B, Freudenthal B, Yau E, Singh V, Chang S, Li D, Delaney J, Wilson S, Essigmann J. Intrinsic Mutagenic Properties of 5-Chlorocytosine: A Mechanistic Connection between Chronic Inflammation and Cancer. Proceedings of the National Academy of Sciences of the United States of America 2015;112:E4571–80.
Ferguson LR. Role of plant polyphenols in genomic stability. Mutation Research 2001;475:89–111.
Fernald K, Kurokawa M. Evading apoptosis in cancer. Trends Cell Biology 2013;23:620–33.
Feskanich D, Ziegler RG, Michaud DS, Giovannucci EL, Speizer FE, Willett W, Colditz G. Prospective study of fruit and vegetable consumption and risk of lung cancer among men and women. Journal of the National Cancer Institute 2000;92:1812–23.
Follo-Martinez AD, Banerjee N, Li X, Safe S, Mertens-Talcott S. Resveratrol and Quercetin in Combination Have Anticancer Activity in Colon Cancer Cells and Repress Oncogenic microRNA-27a. Nutrition and Cancer 2015;65:494–504.
Fouad MA, Agha AM, Merzabani MM, Shouman SA. Resveratrol inhibits proliferation, angiogenesis and induces apoptosis in colon cancer cells: calorie restriction is the force to the cytotoxicity. Human and Experimental Toxicology 2013;32:1067–80.
Fuentes F, Paredes-Gonzalez X, Kong A-NT. Dietary glucosinolates sulforaphane, phenethyl isothiocyanate, indole-3-carbinol/3, 3-diindolylmethane: Antioxidative stress/inflammation, nrf2, epigenetics/epigenomics and in vivo cancer chemopreventive efficacy. Current pharmacology reports 2015;1(3):179–96.
Gamet-Payrastre L, Li P, Lumeau S, Cassar G, Dupont M, Chevolleau S, Gasc N, Tulliez J, Terce F. Sulforaphane, a naturally occurring isothiocyanate, induces cell cycle arrest and apoptosis in HT29 human colon cancer cells. Cancer Research 2000;60:1426–33.
Ganesan P, Matsubara K, Sugawara T, Hirata T. Marine algal carotenoids inhibit angiogenesis by down-regulating FGF-2-mediated intracellular signals in vascular endothelial cells. Molecular and Cellular Biochemistry 2013;380:1–9.
Garcia-Lafuente A, Guillamon E, Villares A, Rostagno MA, Martinez JA. Flavonoids as anti-inflammatory agents: implications in cancer and cardiovascular disease. Inflammation Research 2009;58:537–52.
Gatz SA, Wiesmuller L. Take a break - resveratrol in action on DNA. Carcinogenesis 2008;29:321–32.
Gertz C, Klostermann S. Analysis of Acrylamide and Mechanisms of its Formation in Deep-Fried Products. European Journal of Lipid Science and Technology 2002;104:762–71.
Giovacchino LD, Solinas M, Miccoli M. Effect of extraction systems on the quality of virgin olive oil. Journal of the American Oil Chemists' Society 1994;71:1189–94.
Giovanelli G, Buratti S. Comparison of polyphenolic composition and antioxidant activity of wild Italian blueberries and some cultivated varieties. Food Chemistry 2009;112:903–8.
Giovannucci E, Rimm EB, Liu Y, Stampfer MJ, Willett WC. A prospective study of cruciferous vegetables and prostate cancer. Cancer Epidemiology, Biomarkers and Prevention 2003;12:1403–9.
Girennavar B, et al. Grapefruit juice and its furocoumarins inhibits autoinducer signaling and biofilm formation in bacteria. International Journal of Food Microbiology 2008;125:204–8.
Gomez-Cadena A, Urue~na C, Prieto K, Martinez-Usatorre A, Donda A, Barreto A, Romero P, Fiorentino S. Immune-system-dependent anti-tumor activity of a plant-derived polyphenol rich fraction in a melanoma mouse model. Cell death & disease 2016;7(6):e2243.
Gorzynik-Debicka M, Przychodzen P, Cappello F, Kuban-Jankowska A, Marino Gammazza A, Knap N, Wozniak M, Gorska-Ponikowska M. Potential health benefits of olive oil and plant polyphenols. International journal of molecular sciences 2018;19(3):686.
Gupta S, Ahmad N, Nieminen A, Mukhtar H. Growth Inhibition, Cell-Cycle Dysregulation, and Induction of Apoptosis by Green Tea Constituent (-)-Epigallocatechin-3-gallate in Androgen-Sensitive and Androgen-Insensitive Human Prostate Carcinoma Cells. Toxicology and Applied Pharmacology 2000;164:82–90.
Hagen SF, Borge GIA, Solhaug KA, Bengtsson GB. Effect of cold storage and harvest date on bioactive compounds in curly kale (Brassica oleracea L. var. acephala). Postharvest Biology and Technology 2009;51:36–42.
Hanahan D, Weinberg RA. The Hallmarks of Cancer. Cell 2000;100:57–70.
Hanahan D, Weinberg RA. Hallmarks of Cancer: The Next Generation. Cell 2011;144:646–74.
Harbaum-Piayda B, et al. Influence of pre-harvest UV-B irradiation and normal or controlled atmosphere storage on flavonoid and hydroxycinnamic acid contents of pak choi (Brassica campestris L. ssp. chinensis var. communis). Postharvest Biology and Technology 2010;56:202–8.
Hayes JD, Kelleher MO, Eggleston IM. The Cancer Chemopreventive Actions of Phytochemicals derived from Glucosinolates. European Journal of Nutrition 2008;47(2):73–88.
Hazuka MB, Edwards-Prasad J, Newman F, Kinzie JJ, Prasad KN. Beta-Carotene induces Morphological Differentiation and Decreases Adenylate Cyclase Activity in Melanoma Cells in Culture. Journal of the American College of Nutrition 1990;9:143–9.
Hennekens C, Buring J, Manson J, Stampfer M, Rosner B, Cook N, Belanger C, LaMotte F, Gaziano J, Ridker P, Willett W, Peto R. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. The New England Journal of Medicine 1996;334:1145–9.
Hidalgo M, Oruna-Concha MJ, Kolida S, Walton GE, Kallithraka S, Spencer JP, de Pascual-Teresa S. Metabolism of anthocyanins by human gut microflora and their influence on gut bacterial growth. Journal of Agricultural and Food Chemistry 2012;60(15):3882–90.
Ho E, Clarke JD, Dashwood RH. Dietary Sulforaphane, a Histone Deacetylase Inhibitor for Cancer Prevention. Journal of Nutrition 2009;139:2393–6.
Holmes-McNary M, Baldwin AS. Chemopreventive Properties of trans-Resveratrol Are Associated with Inhibition of Activation of the IkB Kinase. Cancer Research 2000;60:3477–83.
Hope Smith S, et al. Antimutagenic activity of berry extracts. Journal of Medicinal Food 2004;7:450–5.
Howells LM, et al. Phase I randomized, double-blind pilot study of micronized resveratrol (SRT501) in patients with hepatic metastases–safety, pharmacokinetics, and pharmacodynamics. Cancer Prevention Research Phila. Pa 2011;4:1419–25.
Huang C-S, Liao J-W, Hu M-L. Lycopene inhibits experimental metastasis of human hepatoma sk-hep-1 cells in athymic nude mice. The Journal of nutrition 2008;138(3):538–43.
Huang MT, Ferraro T. Phenolic Compounds in Food and Cancer Prevention. ACS Symposium Series, USA 1992;507:834.
Hung C-H, Huang C-C, Hsu L-S, Kao S-H, Wang C-J. Apple polyphenol inhibits colon carcinoma metastasis via disrupting snail binding to focal adhesion kinase. Journal of Functional Foods 2015;12:80–91.
Islam MS, et al. Identification and Characterization of Foliar Polyphenolic Composition in Sweetpotato (Ipomoea batatas L.) Genotypes. Journal of Agricultural and Food Chemistry 2002;50:3718–22.
Islam MS, Jalaluddin M, Garner JO, Yoshimoto M, Yamakawa O. Artificial Shading and Temperature Influence on Anthocyanin Compositions in Sweetpotato Leaves. American Society for Horticultural Science 2005;40:176–80.
Ivanov NI, Cowell SP, Brown P, Rennie PS, Guns ES, Cox ME. Lycopene differentially induces quiescence and apoptosis in androgen-responsive and-independent prostate cancer cell lines. Clinical Nutrition 2007;26(2):252–63.
Jackson SJ, Singletary KW. Sulforaphane: a naturally occurring mammary carcinoma mitotic inhibitor, which disrupts tubulin polymerization. Carcinogenesis 2004;25:219–27.
Jagetia GC, Aggarwal BB. 'Spicing up' of the immune system by curcumin. Journal of Clinical Immunology 2007;27:19–35.
Jain MG, Hislop GT, Howe GR, Ghadirian P. Plant foods, antioxidants, and prostate cancer risk: findings from case-control studies in Canada. Nutrition and Cancer 1999;34:173–84.

Jatoi A, Nguyen PL. Side Effects and Pharmaceutical Company Bias: Adverse Event Reporting in Cancer Supportive and Palliative Care Trials. Expert Opinion on Investigational Drugs 2008;17:1787–90.
Jeffery EH, et al. Variation in content of bioactive components in broccoli. Journal of Food Composition and Analysis 2003;16:323–30.
Jeon YK, Yoo DR, Jang YH, Jang SY, Nam MJ. Sulforaphane induces apoptosis in human hepatic cancer cells through inhibition of 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase4, mediated by hypoxia inducible factor-1-dependent pathway. Biochimica et Biophysica Acta 2011;1814:1340–8.
Jiang ZQ, Chen C, Yang B, Hebbar V, Kong AN. Differential responses from seven mammalian cell lines to the treatments of detoxifying enzyme inducers. Life Sciences 2003;72:2243–53.
Johnson EJ. The Role of Carotenoids in Human Health. Nutrition in Clinical Care: an Official Publication of Tufts University 2002;5:56–65.
Johnson I. Brassica vegetables and human health: glucosinolates in the food chain. In: III International Symposium on Brassicas and XII Crucifer Genetics Workshop, 539; 2000. p. 39–44.
Jones RB, Faragher JD, Winkler S. A review of the influence of postharvest treatments on quality and glucosinolate content in broccoli (Brassica oleracea var. italica) heads. Postharvest Biology and Technology 2006;41:1–8.
Jung JH, Kang JI, Kim HS. Effect of quercetin on impaired immune function in mice exposed to irradiation. Nutrition Research and Practice 2012;6:301–7.
Jung WJ, Sung MK. Effects of major dietary antioxidants on inflammatory markers of RAW 264.7 macrophages. Biofactors 2004;21:113–7.
Kampa M, Nifli AP, Notas G, Castanas E. Polyphenols and cancer cell growth. Reviews of Physiology, Biochemistry and Pharmacology 2007;159:79–113.
Kannan V. Extraction of bioactive compounds from whole red cabbage and beetroot using pulsed electric fields and evaluation of their functionality 5, Master's thesis. University of Nebraska; 2011.
Kao Y, et al. Apple polyphenol induces cell apoptosis, cell cycle arrest at G2/M phase, and mitotic catastrophe in human bladder transitional carcinoma cells. Journal of Functional Foods 2015;14:384–94.
Karas M, Amir H, Fishman D, Danilenko M, Segal S, Nahum A, Koifmann A, Giat Y, Levy J, Sharoni Y. Lycopene Interferes with Cell Cycle Progression and Insulin-like Growth Factor I Signaling in Mammary Cancer Cells. Nutrition and Cancer 2000;36:101–11.
Karna P, et al. Polyphenol-rich sweet potato greens extract inhibits proliferation and induces apoptosis in prostate cancer cells in vitro and in vivo. Carcinogenesis 2011;32:1872–80.
Kaulmann A, Bohn T. Carotenoids, Inflammation, and Oxidative Stress - Implications of Cellular Signaling Pathways and Relation to Chronic Disease Prevention. Nutrition Research 2014;34:907–29.
Kaur M, Agarwal C, Agarwal R. Anticancer and Cancer Chemopreventive Potential of Grape Seed Extract and Other Grape-Based Products. Journal of Nutrition 2009;139:1806S–12S.
Keijer J, Bekkenkamp-Grovenstein M, Venema D, Dommels YEM. Bioactive food components, cancer cell growth limitation and reversal of glycolytic metabolism. Biochimica et Biophysica Acta 2011;1807:697–706.
Key TJ, Allen N, Appleby P, Overvad K, Tjønneland A, Miller A, Boeing H, Karalis D, Psaltopoulou T, Berrino F. Fruits and vegetables and prostate cancer: no association among 1104 cases in a prospective study of 130544 men in the European Prospective Investigation into Cancer and Nutrition (EPIC). International Journal of Cancer 2004;109:119–24.
Khan N, Bharali DJ, Adhami VM, Siddiqui IA, Cui H, Shabana SM, Mousa SA, Mukhtar H. Oral administration of naturally occurring chitosan-based nanoformulated green tea polyphenol egcg effectively inhibits prostate cancer cell growth in a xenograft model. Carcinogenesis 2013;35(2):415–23.
Khanizadeh S, et al. Polyphenol composition and total antioxidant capacity of selected apple genotypes for processing. Journal of Food Composition and Analysis 2008;21:396–401.
Khor T, Hu R, Shen G, Jeong W, Hebbar V, Chen C, Xu C, Nair S, Reddy B, Chada K, Kong A. Pharmacogenomics of cancer chemopreventive isothiocyanate compound sulforaphane in the intestinal polyps of ApcMin/+ mice. Biopharmaceutics and Drug Disposition 2006;27:407–20.
Kim H. Inhibitory Mechanism of Lycopene on Cytokine Expression in Experimental Pancreatitis. Annals of the New York Academy of Sciences 2011;1229:99–102.
Kim M, Cho HJ, Kwon GT, Kang Y-H, Kwon S-H, Her S, Park T, Kim Y, Kee Y, Park JHY. Benzyl isothiocyanate suppresses high-fat diet-stimulated mammary tumor progression via the alteration of tumor microenvironments in obesity-resistant balb/c mice. Molecular carcinogenesis 2015;54(1):72–82.
Kim SH, Lee JM, Kim SC, Park CB, Lee PC. Proposed cytotoxic mechanisms of the saffron carotenoids crocin and crocetin on cancer cell lines. Biochemistry and Cell Biology 2014;92:105–11.
King SR, Gershoff SN. Nutritional evaluation of three underexploited andean tubers: Oxalis tuberosa (Oxalidaceae),Ullucus tuberosus (Basellaceae), and Tropaeolum tuberosum (Tropaeolaceae). Economic Botany 1987;41:503–11.
Klimczak I, Matecka M, Szlachta M, Gliszczynska-Swigto A. Effect of storage on the content of polyphenols, vitamin C and the antioxidant activity of orange juices. Journal of Food Composition and Analysis 2007;20:313–22.
Knekt P, Kumpulainen J, Jarvinen R, Rissanen H, Heliovaara M, Reunanen A, Hakulinen T, Aromaa A. Flavonoid Intake and Risk of Chronic Diseases. The American Journal of Clinical Nutrition 2002;76:560–8.
Knobloch TJ, et al. Suppression of Proinflammatory and Prosurvival Biomarkers in Oral Cancer Patients Consuming a Black Raspberry Phytochemical-Rich Troche. Cancer Prevention Research Phila. Pa 2016;9:159–71.
Kok TMd, Breda SGv, Manson MM. Mechanisms of combined action of different chemopreventive dietary compounds. European Journal of Nutrition 2008;47:51–9.
Kolonel L, Hankin J, Whittemore A, Wu A, Gallagher RP, Wilkens L, John E, Howe GR, Dreon D, West DW. Vegetables, fruits, legumes and prostate cancer: a multiethnic case-control study. Cancer Epidemiology, Biomarkers and Prevention 2000;9:795–804.
Kondo T, Ohta T, Igura K, Hara Y, Kaji K. Tea catechins inhibit angiogenesis in vitro, measured by human endothelial cell growth, migration and tube formation, through inhibition of VEGF receptor binding. Cancer Letters 2002;180:139–44.
Kotake-Nara E, Kushiro M, Zhang H, Sugawara T, Miyashita K, Nagao A. Carotenoids Affect Proliferation of Human Prostate Cancer Cells. Journal of Nutrition 2001;131:3303–6.
Kris-Etherton P, Lefevre M, Beecher G, Gross M, Keen C, Etherton T. Bioactive compounds in nutrition and health-research methodologies for establishing biological function: the antioxidant and anti-inflammatory effects of flavonoids on atherosclerosis. Annual Review of Nutrition 2004;24:511–38.
Kris-Etherton PM, et al. Bioactive compounds in foods: their role in the prevention of cardiovascular disease and cancer. The American Journal of Medicine 2002;113:71–88.
Kuang YF, Chen YH. Induction of apoptosis in a non-small cell human lung cancer cell line by isothiocyanates is associated with P53 and P21. Food and Chemical Toxicology 2004;42:1711–8.
Kurihara H, Koda H, Asami S, Kiso Y, Tanaka T. Contribution of the antioxidative property of astaxanthin to its protective effect on the promotion of cancer metastasis in mice treated with restraint stress. Life Sciences 2002;70:2509–20.
Kushad MM, et al. Variation of Glucosinolates in Vegetable Crops of Brassica oleracea. Journal of Agricultural and Food Chemistry 1999;47:1541–8.
Lafarga T, Bobo G, Vi~nas I, Collazo C, Aguilo-Aguayo I. Effects of thermal and non-thermal processing of cruciferous vegetables on glucosinolates and its derived forms. Journal of food science and technology 2018;55(6):1973–81.
Lanzilli G, Fuggetta MP, Tricarico M, Cottarelli A, Serafino A, Falchetti R, Ravagnan G, Turriziani M, Adamo R, Franzese O. Resveratrol down-regulates the growth and telomerase activity of breast cancer cells in vitro. International Journal of Oncology 2006;28:641–8.
Lecour S, Lamont KT. Natural polyphenols and cardioprotection. Mini reviews in medicinal chemistry 2011;11(14):1191–9.
Lenzi M, Fimognari C, Hrelia P. Sulforaphane as a promising molecule for fighting cancer. Cancer Treatment and Research 2014;159:207–23.
Levy J, Bosin E, Feldman B, Giat Y, Miinster A, Danilenko M, Sharoni Y. Lycopene is a more Potent Inhibitor of Human Cancer Cell Proliferation than either Alpha-Carotene or Beta-Carotene. Nutrition and Cancer 1995;24:257–66.
Li X. Parents' and children's acceptance of skim Ccocolate milks sweetened by monk fruit and stevia leaf extracts. Journal of Food Science 2015;80(5):1083–92.
Lima GPP, Da Rocha SA, Takaki M, Ramos PRR, Ono EO. Comparison of polyamine, phenol and flavonoid contents in plants grown under conventional and organic methods. International Journal of Food Science and Technology 2008;43:1838–43.
Lima VLAG, et al. Total phenolic and carotenoid contents in acerola genotypes harvested at three ripening stages. Food Chemistry 2005;90:565–8.
Lin CH, Chen BH. Stability of carotenoids in tomato juice during storage. Food Chemistry 2005;90:837–46.
Lin D, Xiao M, Zhao J, Li Z, Xing B, Li X, Kong M, Li L, Zhang Q, Liu Y, et al. An overview of plant phenolic compounds and their importance in human nutrition and management of type 2 diabetes. Molecules 2016;21(10):1374.
Lin JP, et al. Rutin inhibits the proliferation of murine leukemia WEHI-3 cells in vivo and promotes immune response in vivo. Leukemia Research 2009;33:823–8.
Lin K-H, Lin K-C, Lu W-J, Thomas P-A, Jayakumar T, Sheu J-R. Astaxanthin, a carotenoid, stimulates immune responses by enhancing INF- and IL-2 secretion in primary cultured lymphocytes in vitro and ex vivo. International journal of molecular sciences 2015;17(1):44.
Lin N, et al. Novel anti-inflammatory actions of nobiletin, a citrus polymethoxy flavonoid, on human synovial fibroblasts and mouse macrophages. Biochemical Pharmacology 2003;65:2065–71.
Lin TY, Koehler PE, Shewfelt RL. Stability of Anthocyanins in the Skin of Starkrimson Apples Stored Unpackaged, Under Heat Shrinkable Wrap and In-Package Modified Atmosphere. Journal of Food Science 1989;54:405–7.
Linnewiel-Hermoni K, Khanin M, Danilenko M, Zango G, Amosi Y, Levy J, Sharoni Y. The Anti-Cancer Effects of Carotenoids and other Phytonutrients Resides in their Combined Activity. Archives of Biochemistry and Biophysics 2015;572:28–35.
Liu BIN, et al. Resveratrol inhibits proliferation in human colorectal carcinoma cells by inducing G(1)/S-phase cell cycle arrest and apoptosis through caspase/cyclin-CDK pathways. Molecular Medicine Reports 2014;10:1697–702.
Liu RH. Potential Synergy of Phytochemicals in Cancer Prevention: Mechanism of Action. Journal of Nutrition 2004;134:3479S–85S.
Liu RH. Dietary Bioactive Compounds and Their Health Implications. Journal of Food Science 2013;78:A18–25.
Lombard K, Peffley E, Geoffriau E, Thompson L, Herring A. Quercetin in onion (Allium cepa L.) after heat-treatment simulating home preparation. Journal of Food Composition and Analysis 2005;18:571–81.
Lu H, Ouyang W, Huang C. Inflammation, a Key Event in Cancer Development. Molecular Cancer Research 2006;4:221–33.

Madiwale GP, Reddivari L, Holm DG, Vanamala J. Storage elevates phenolic content and antioxidant activity but suppresses antiproliferative and pro-apoptotic properties of colored-flesh potatoes against human colon cancer cell lines. Journal of Agricultural and Food Chemistry 2011;59:815566.
Madiwale GP, Reddivari L, Stone M, Holm DG, Vanamala J. Combined effects of storage and processing on the bioactive compounds and pro-apoptotic properties of color-fleshed potatoes in human colon cancer cells. Journal of Agricultural and Food Chemistry 2012;60:11088–96.
Maeda K, et al. Green tea catechins inhibit the cultured smooth muscle cell invasion through the basement barrier. Atherosclerosis 2003;166:23–30.
Majumdar APN, et al. Curcumin SynergizesWith Resveratrol to Inhibit Colon Cancer. Nutrition and Cancer 2009;61:544–53.
Manach C, Scalbert A, Morand C, Remesy C, Jimenez L. Polyphenols: Food Sources and Bioavailability. The American Journal of Clinical Nutrition 2004;79:727–47.
Mandelova L, Totusek J. Broccoli juice treated by high pressure: chemoprotective effects of sulforaphane and indole-3-carbinol. High Pressure Research 2007;27:151–6.
Marais J, Van Wyk C, Rapp A. Carotenoid levels in maturing grapes as affected by climatic regions, sunlight and shade. South African Journal of Enology and Viticulture 1991;12:64–9.
Martin S, Favot L, Matz R, Lugnier C, Andriantsitohaina R. Delphinidin inhibits endothelial cell proliferation and cell cycle progression through a transient activation of ERK-1/-2. Biochemical Pharmacology 2003;65:669–75.
Maru GB, Hudlikar RR, Kumar G, Gandhi K, Mahimkar MB. Understanding the molecular mechanisms of cancer prevention by dietary phytochemicals: From experimental models to clinical trials. World Journal of Biological Chemistry 2016;7:88–99.
Marx M, Stuparic M, Schieber A, Carle R. Effects of thermal processing on transcisisomerization of -carotene in carrot juices and carotene-containing preparations. Food Chemistry 2003;83:609–17.
Massey AR, et al. Pro-apoptotic activity against cancer stem cells differs between different parts of sweet sorghum. Journal of Functional Foods 2016;23:601–13.
Massey AR, Reddivari L, Vanamala J. The dermal layer of sweet sorghum (sorghum bicolor) stalk, a byproduct of biofuel production and source of unique 3-deoxyanthocyanidins, has more antiproliferative and proapoptotic activity than the pith in p53 variants of hct116 and colon cancer stem cells. Journal of Agricultural and Food Chemistry 2014;62(14):3150–9.
Matusheski NV, Jeffery EH. Comparison of the Bioactivity of Two Glucoraphanin Hydrolysis Products Found in Broccoli, Sulforaphane and Sulforaphane Nitrile. Journal of Agricultural and Food Chemistry 2001;49:5743–9.
Matusheski NV, Juvik JA, Jeffery EH. Heating decreases epithiospecifier protein activity and increases sulforaphane formation in broccoli. Phytochemistry 2004;65:1273–81.
McInerney JK, Seccafien CA, Stewart CM, Bird AR. Effects of high pressure processing on antioxidant activity, and total carotenoid content and availability, in vegetables. Innovative Food Science and Emerging Technologies 2007;8:543–8.
McMillan D, Talwar D, Sattar N, Underwood M, O'Reilly D, McArdle C. The Relationship between Reduced Vitamin Antioxidant Concentrations and the Systemic Inflammatory Response in Patients with Common Solid Tumours. Clinical Nutrition 2002;21:161–4.
Meadows GG. Diet, nutrients, phytochemicals, and cancer metastasis suppressor genes. Cancer and Metastasis Reviews 2012;31:441–54.
Meeran SM, Patel SN, Tollefsbol TO. Sulforaphane causes epigenetic repression of hTERT expression in human breast cancer cell lines. PLOS ONE 2010;5:e11457.
Menon LG, Kuttan R, Kuttan G. Inhibition of lung metastasis in mice induced by B16F10 melanoma cells by polyphenolic compounds. Cancer Letters 1995;95:221–5.
Mentor-Marcel RA, et al. Plasma cytokines as potential response indicators to dietary freeze-dried black raspberries in colorectal cancer patients. Nutrition and Cancer 2012;64:820–5.
Mercadante AZ, Rodriguez-Amaya DB. Effects of Ripening, Cultivar Differences, and Processing on the Carotenoid Composition of Mango. Journal of Agricultural and Food Chemistry 1998;46:128–30.
Mertens-Talcott SU, Percival SS. Ellagic acid and quercetin interact synergistically with resveratrol in the induction of apoptosis and cause transient cell cycle arrest in human leukemia cells. Cancer Letters 2005;218:141–51.
Mertens-Talcott SU, Talcott ST, Percival SS. Low Concentrations of Quercetin and Ellagic Acid Synergistically Influence Proliferation, Cytotoxicity and Apoptosis in MOLT-4 Human Leukemia Cells. Journal of Nutrition 2003;133:2669–74.
Meyer M, Adam ST. Comparison of glucosinolate levels in commercial broccoli and red cabbage from conventional and ecological farming. European Food Research and Technology 2007;226:1429–37.
Middleton E, Kandaswami C, Theoharides TC. The Effects of Plant Flavonoids on Mammalian Cells: Implications for Inflammation, Heart Disease, and Cancer. Pharmacological Reviews 2000;52:673–751.
Mottram DS, L.Wedzicha B, Dodson AT. Acrylamide is Formed in the Maillard Reaction. Nature 2002;419:448–9.
Murador D, Braga AR, Da Cunha D, De Rosso V. Alterations in phenolic compound levels and antioxidant activity in response to cooking technique effects: A meta-analytic investigation. Critical reviews in food science and nutrition 2018;58(2):169–77.
Murakoshi M, Nishino H, Satomi Y, Takayasu J, Hasegawa T, Tokuda H, Iwashima A, Okuzumi J, Okabe H, Kitano H. Potent Preventive Action of Alpha-Carotene against Carcinogenesis: Spontaneous Liver Carcinogenesis and Promoting stage of Lung and Skin Carcinogenesis in Mice are Suppressed more Effectively by Alpha-Carotene than by Beta-Carotene. Cancer Research 1992;52:6583–7.
Murillo G, Mehta RG. Cruciferous Vegetables and Cancer Prevention. Nutrition and cancer 2001;41(1-2):17–28.
Naasani I, et al. Blocking telomerase by dietary polyphenols is a major mechanism for limiting the growth of human cancer cells in vitro and in vivo. Cancer Researchy 2003;63:824–30.
Nasri H, Baradaran A, Shirzad H, Rafieian-Kopaei M. New Concepts in Nutraceuticals as Alternative for Pharmaceuticals. International Journal of Preventive Medicine 2014;5:1487–99.
NCRI Conference (2015). The Hallmarks of Cancer - Cancer Research UK. http://scienceblog.cancerresearchuk.org/2010/11/10/ncri-conference-the-hallmarks-of-cancer/. Accessed: 2018-02-13.
Nhung DTT, Bung PN, Ha NT, Phong TK. Changes in lycopene and beta carotene contents in aril and oil of gac fruit during storage. Food Chemistry 2010;121:326–31.
Niranjana R, Gayathri R, Mol SN, Sugawara T, Hirata T, Miyashita K, Ganesan P. Carotenoids modulate the hallmarks of cancer cells. Journal of Functional Foods 2015;18:968–85.
Nishino H, Murakosh M, Li T, Takemura M, Kuchide M, Kanazawa M, Mou X, Wada S, Masuda M, Ohsaka Y, Yogosawa S, Satomi Y, Jinno K. Carotenoids in Cancer Chemoprevention. Cancer Metastasis Reviews 2002;21:257–64.
Nordström T, Van Blarigan EL, Ngo V, Roy R, Weinberg V, Song X, Simko J, Carroll PR, Chan JM, Paris PL. Associations between circulating carotenoids, genomic instability and the risk of high-grade prostate cancer. The Prostate 2016;76(4):339–48.
Noureini SK, Wink M. Antiproliferative Effects of Crocin in HepG2 cells by Telomerase Inhibition and *hTERT* Down-Regulation. Asian Pacific Journal of Cancer Prevention 2012;13:2305–9.
Nussbaumer S, Bonnabry P, Veuthey J, Fleury-Souverain S. Analysis of anticancer drugs: a review. Talanta 2011;85:2265–89.
Oak MH, Bedoui JE, Schini-Kerth VB. Thrombin induces the expression of pro-MMP-2 and its conversion to MMP-2 in vascular smooth muscle cells: both responses are inhibited by red wine polyphenols. Journal of Thrombosis and Haemostasis 2003;:(Supp 1):682.
Okabe S, et al. Mechanisms of growth inhibition of human lung cancer cell line, PC-9, by tea polyphenols. Japanese Journal of Cancer Research 1997;88:639–43.
Oliveira C, et al. Carotenoid Compounds in Grapes and Their Relationship to Plant Water Status. Journal of Agricultural and Food Chemistry 2003;51:5967–71.
Omenn G, Goodman G, Thornquist M, Balmes J, Cullen M, Glass A, Keogh J, Meyskens F, Valanis B, Williams J, Barnhart S, Hammar S. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. The New England Journal of Medicine 1996a;334:1150–5.
Omenn G, Goodman G, Thornquist M, Balmes J, Cullen M, Glass A, Keogh J, Meyskens FJ, Valanis B, Williams JJ, Barnhart S, Cherniack M, Brodkin C, Hammar S. Risk Factors for Lung Cancer and for Intervention Effects in CARET, the Beta-Carotene and Retinol Efficacy Trial. Journal of the National Cancer Institute 1996b;88:1550–9.
Onogi N, Okuno M, Matsushima-Nishiwaki R, Fukutomi Y, Moriwaki H, Muto Y, Kojima S. Antiproliferative Effect of Carotenoids on Human Colon Cancer Cells Without Conversion to Retinoic Acid. Nutrition and Cancer 1998;32:20–4.
Oufedjikh H, Mahrouz M, Lacroix M, Amiot MJ, Taccini M. The influence of gamma irradiation on flavonods content during storage of irradiated clementina. Radiation Physics and Chemistry 1998;52:107–12.
Padilla G, Cartea ME, Velasco P, de Haro A, Ordas A. Variation of glucosinolates in vegetable crops of Brassica rapa. Phytochemistry 2007;68:536–45.
Pan P, et al. Beneficial Regulation of Metabolic Profiles by Black Raspberries in Human Colorectal Cancer Patients. Cancer Prevention Research Phila. Pa 2015;8:743–50.
Patel KR, et al. Clinical pharmacology of resveratrol and its metabolites in colorectal cancer patients. Cancer Research 2010;70:7392–9.
Patil BS, Pike LM. Distribution of quercetin content in different rings of various coloured onion (Allium cepa L.) cultivars. Journal of Horticultural Science 1995;70 (4):643–50.
Patil BS, Pike LM, Yoo KS. Variation in the quercetin content in different colored onions (allium cepa l.). Journal of the American Society for Horticultural Science 1995;120:909–13.
Patras A, Brunton N, Da Pieve S, Butler F, Downey G. Effect of thermal and high pressure processing on antioxidant activity and instrumental colour of tomato and carrot purees. Innovative Food Science and Emerging Technologies 2009a;10:16–22.
Patras A, Brunton NP, Da Pieve S, Butler F. Impact of high pressure processing on total antioxidant activity, phenolic, ascorbic acid, anthocyanin content and colour of strawberry and blackberry purees. Innovative Food Science and Emerging Technologies 2009b;10:308–13.
Pereira FMV, et al. Influence of Temperature and Ontogeny on the Levels of Glucosinolates in Broccoli (Brassica oleracea Var. italica) Sprouts and Their Effect on the Induction of Mammalian Phase 2 Enzymes. Journal of Agricultural and Food Chemistry 2002;50:6239–44.
Perez-Berezo T, et al. Influence of a cocoa-enriched diet on specific immune response in ovalbumin-sensitized rats. Molecular Nutrition and Food Research 2009;53:389–97.
Pfeiffer WH, McClafferty B. HarvestPlus: Breeding Crops for Better Nutrition. Crop Science 2007;47. S–88–S–105.

Picchi V, et al. Phytochemical content in organic and conventionally grown Italian cauliflower. Food Chemistry 2012;130:501–9.
Pinheiro Sant'Ana HM, Stringheta PC, Cardoso Brandao SC, Cordeiro de Azeredo RM. Carotenoid retention and vitamin A value in carrot (Daucus carota L.) prepared by food service. Food Chemistry 1998;61:145–51.
Pinhero RG, Tsao R, Liu Q, Sullivan JA, Bizimungu B, Yada RY. Protein and phenolic contents and antioxidant activities of 14 early maturing potatoes as affected by processing. American Journal of Plant Sciences 2016;7(01):69.
Plaza L, et al. Impact of minimal processing on orange bioactive compounds during refrigerated storage. Food Chemistry 2011;124:646–51.
Poulsen MM, Vestergaard PF, Clasen BF, Radko Y, Christensen LP, Stødkilde-Jørgensen H, Møller N, Jessen N, Pedersen SB, Jørgensen JOL. An investigator-initiated, randomized, placebo-controlled clinical trial of substrate metabolism, insulin sensitivity, and body composition. Diabetes 2013;62(4):1186–95.
Prakash D, Nath P, Pal M. Composition, Variation of Nutritional Contents in Leaves, Seed Protein, Fat and Fatty Acid Profile of Chenopodium Species. Journal of the Science of Food and Agriculture 1993;62:203–5.
Price KR, Bacon JR, Rhodes MJC. Effect of Storage and Domestic Processing on the Content and Composition of Flavonol Glucosides in Onion (Allium cepa). Journal of Agricultural and Food Chemistry 1997;45:938–42.
Radhakrishnan S, Reddivari L, Sclafani R, Das UN, Vanamala J. Resveratrol potentiates grape seed extract induced human colon cancer cell apoptosis. Frontiers in bioscience (Elite edition) 2011;3:1509–23.
Ramiro-Puig E, Castell M. Cocoa: antioxidant and immunomodulator. British Journal of Nutrition 2009;101:931–40.
Raso GM, Meli R, Di Carlo G, Pacilio M, Di Carlo R. Inhibition of inducible nitric oxide synthase and cyclooxygenase-2 expression by flavonoids in macrophage J774A.1. Life Sciences 2001;68:921–31.
Reddivari L, Hale AL, Miller JC. Genotype, Location, and Year Influence Antioxidant Activity, Carotenoid Content, Phenolic Content, and Composition in Specialty Potatoes. Journal of Agricultural and Food Chemistry 2007a;55:8073–9.
Reddivari L, Vanamala J, Chintharlapalli S, Safe SH, Miller JC Jr. Anthocyanin fraction from potato extracts is cytotoxic to prostate cancer cells through activation of caspase-dependent and caspase-independent pathways. Carcinogenesis 2007b;28:2227–35.
Reddivari L, Vanamala J, Safe SH, Miller JC Jr. The bioactive compounds alpha-chaconine and gallic acid in potato extracts decrease survival and induce apoptosis in LNCaP and PC3 prostate cancer cells. Nutrition and Cancer 2010;62:601–10.
Reganold, et al., et al. Fruit and Soil Quality of Organic and Conventional Strawberry Agroecosystems. PLOS ONE 2015;5(9):1–14.
Reganold JP, et al. Transforming US agriculture. Science 2011;332:670–1.
Robbins RJ, Keck A, Banuelos G, Finley JW. Cultivation conditions and selenium fertilization alter the phenolic profile, glucosinolate, and sulforaphane content of broccoli. Journal of Medicinal Food 2005;8:204–14.
Roohinejad S, Everett DW, Oey I. Effect of pulsed electric field processing on carotenoid extractability of carrot puree. International Journal of Food Science and Technology 2014;49:2120–7.
Roswitha Siener RH. Oxalate Contents of Species of the Polygonaceae, Amaranthaceae and Chenopodiaceae Families. Food Chemistry 2006;98:220–4.
Rothwell JA, Medina-Remón A, Pérez-Jiménez J, Neveu V, Knaze V, Slimani N, Scalbert A. Effects of food processing on polyphenol contents: A systematic analysis using phenol-explorer data. Molecular nutrition & food research 2015;59(1):160–70.
Rowles JL, Ranard KM, Applegate CC, Jeon S, An R, Erdman JW. Processed and raw tomato consumption and risk of prostate cancer: a systematic review and dose–response meta-analysis. Prostate cancer and prostatic diseases 2018;3(21):319–36.
Russell RM. The enigma of beta-carotene in carcinogenesis: what can be learned from animal studies. Journal of Nutrition 2004;134:262S–8S.
Russo GL, Tedesco I, Spagnuolo C, Russo M. Antioxidant polyphenols in cancer treatment: Friend, foe or foil? Seminars in cancer biology. Elsevier; 2017.
Rydberg P, Eriksson S, Tareke E, Karlsson P, Ehrenberg L, Tornqvist M. Investigations of Factors that Influence the Acrylamide Content of Heated Foodstuffs. Journal of Agricultural and Food Chemistry 2003;51:7012–8.
Sadava D, Whitlock E, Kane SE. The green tea polyphenol, epigallocatechin-3-gallate inhibits telomerase and induces apoptosis in drug-resistant lung cancer cells. Biochemical and Biophysical Research Communications 2007;360:233–7.
Sameer Khalil Ghawi LM. The potential to intensify sulforaphane formation in cooked broccoli (Brassica oleracea var. italica) using mustard seeds (Sinapis alba). Food Chemistry 2013;138:1734–41.
Sanchez-Moreno C, Plaza L, de Ancos B, Cano MP. Impact of high-pressure and traditional thermal processing of tomato puree on carotenoids, vitamin C and antioxidant activity. Journal of the Science of Food and Agriculture 2006;86:171–9.
Scalbert A, Johnson IT, Saltmarsh M. Polyphenols: antioxidants and beyond. The American Journal of Clinical Nutrition 2005;81:215S–7S.
Schabath M, Grossman H, Delclos G, Hernandez L, Day R, Davis B, Lerner S, Spitz M, Wu X. Dietary carotenoids and genetic instability modify bladder cancer risk. Journal of Nutrition 2004;134:3362–9.
Schuurman AG, Goldbohm RA, Dorant E, van den Brandt PA. Vegetable and fruit consumption and prostate cancer risk: a cohort study in The Netherlands. Cancer Epidemiology, Biomarkers and Prevention 1998;7:673–80.
Shao Y, Ni Y, Yang J, Lin X, Li J, Zhang L. Astaxanthin inhibits proliferation and induces apoptosis and cell cycle arrest of mice h22 hepatoma cells. Medical science monitor: international medical journal of experimental and clinical research 2016;22:2152.
Sharan RN, Mehrotra R, Choudhury Y, Asotra K. Association of Betel Nut with Carcinogenesis: Revisit with a Clinical Perspective. PLOS ONE 2012;7:e42759.
Shay JW, Wright WE. Role of telomeres and telomerase in cancer. Seminar in Cancer Biology 2011;21:349–53.
Sido A, Radhakrishnan S, Kim SW, Eriksson E, Shen F, Li Q, Bhat V, Reddivari L, Vanamala JK. A food-based approach that targets interleukin-6, a key regulator of chronic intestinal inflammation and colon carcinogenesis. The Journal of nutritional biochemistry 2017;43:11–7.
Singh AV, Xiao D, Lew KL, Dhir R, Singh SV. Sulforaphane induces caspase-mediated apoptosis in cultured PC-3 human prostate cancer cells and retards growth of PC-3 xenografts in vivo. Carcinogenesis 2004a;25:83–90.
Singh S, Herman-Antosiewicz A, Singh A, Lew K, Srivastava S, Kamath R, Brown K, Zhang L, Baskaran R. Sulforaphane-induced G2/M phase cell cycle arrest involves checkpoint kinase 2-mediated phosphorylation of cell division cycle 25C. Journal of Biological Chemistry 2004b;279:25813–22.
Singh SV, Warin R, Xiao D, Powolny AA, Stan SD, Arlotti JA, Zeng Y, Hahm E-R, Marynowski SW, Bommareddy A, et al. Sulforaphane inhibits prostate carcinogenesis and pulmonary metastasis in tramp mice in association with increased cytotoxicity of natural killer cells. Cancer research 2009;69(5):2117–25.
Singletary K, MacDonald C. Inhibition of benzo[a]pyrene- and 1,6-dinitropyrene-DNA adduct formation in human mammary epithelial cells bydibenzoylmethane and sulforaphane. Cancer Letters 2000;155:47–54.
Slominski BA, Campbell LD. Formation of indole glucosinolate breakdown products in autolyzed, steamed, and cooked Brassica vegetables. Journal of Agricultural and Food Chemistry 1989;37:1297–302.
Song L, Thornalley PJ. Effect of storage, processing and cooking on glucosinolate content of Brassica vegetables. Food and Chemical Toxicology 2007;45:216–24.
Spanos GA, Wrolstad RE. Influence of processing and storage on the phenolic composition of Thompson Seedless grape juice. Journal of Agricultural and Food Chemistry 1990;38:1565–71.
Sporn MB. Perspective: The Big C - for Chemoprevention. Nature 2011;471:S10–1.
Stan SD, Singh SV, Whitcomb DC, Brand RE. Phenethyl isothiocyanate inhibits proliferation and induces apoptosis in pancreatic cancer cells in vitro and in a MIA-Paca2 xenograft animal model. Nutrition and Cancer 2014;66:747–55.
Stich HF, Rosin MP, Vallejera MO. Reduction with vitamin A and beta-carotene administration of proportion of micronucleated buccal mucosal cells in Asian betal nut and tobacco chewers. The Lancet 1984;1:1204–6.
Stivala L, Savio M, Quarta S, Scotti C, Cazzalini O, Rossi L, Scovassi I, Pizzala R, Melli R, Bianchi L, Vannini V, Prosperi E. The Antiproliferative Effect of Beta-Carotene requires p21waf1/cip1 in Normal Human Fibroblasts. European Journal of Biochemistry 2000;267:2290–6.
Stracke BA, et al. Bioavailability and nutritional effects of carotenoids from organically and conventionally produced carrots in healthy men. British Journal of Nutrition 2009a;101:1664–72.
Stracke BA, Rufer CE, Weibel FP, Bub A, Watzl B. Three-Year Comparison of the Polyphenol Contents and Antioxidant Capacities in Organically and Conventionally Produced Apples (Malus domestica Bork. Cultivar 'Golden Delicious'). Journal of Agricultural and Food Chemistry 2009b;57:4598–605.
Sumantran VN, Zhang R, Lee DS, Wicha MS. Differential regulation of apoptosis in normal versus transformed mammary epithelium by lutein and retinoic acid. Cancer Epidemiology, Biomarkers and Prevention 2000;9:257–63.
Suresh D, Gurudutt KN, Srinivasan K. Degradation of bioactive spice compound: curcumin during domestic cooking. European Food Research and Technology 2008;228:807–12.
Suresh D, Manjunatha H, Srinivasan K. Effect of heat processing of spices on the concentrations of their bioactive principles: Turmeric (Curcuma longa), red pepper (Capsicum annuum) and black pepper (Piper nigrum). Journal of Food Composition and Analysis 2007;20:346–51.
Suthanthangjai W, Kajda P, Zabetakis I. The effect of high hydrostatic pressure on the anthocyanins of raspberry (Rubus idaeus). Food Chemistry 2005;90:193–7.
Szeto YT, et al. A buccal cell model comet assay: development and evaluation for human biomonitoring and nutritional studies. Mutation Research 2005;578:371–81.
Tanaka T, Shnimizu M, Moriwaki H. Cancer Chemoprevention by Carotenoids. Molecules 2012;17:3202–42.
Tantamango-Bartley Y, Jaceldo-Siegl K, Fan J, Fraser G. Vegetarian Diets and the Incidence of Cancer in a Low-risk Population. Cancer Epidemiology, Biomarkers and Prevention 2013;22:286–94.
Terry P, Wolk A, Persson I, Magnusson C. Brassica vegetables and breast cancer risk. The Journal of the American Medical Association 2001;285:2975–7.
Thangapazham RL, et al. Green tea polyphenols and its constituent epigallocatechin gallate inhibits proliferation of human breast cancer cells in vitro and in vivo. Cancer Letters 2007;245:232–41.
The Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group. The Effect of Vitamin E and Beta Carotene on the Incidence of Lung Cancer and other Cancers in Male Smokers. The New England Journal of Medicine 1994;330:1029–35.
Thejass P, Kuttan G. Antimetastatic activity of Sulforaphane. Life Sciences 2006;78:3043–50.
Thejass P, Kuttan G. Allyl isothiocyanate (AITC) and phenyl isothiocyanate (PITC) inhibit tumour-specific angiogenesis by downregulating nitric oxide (NO) and tumour necrosis factor-alpha (TNF-alpha) production. Nitric Oxide 2007a;16:247–57.
Thejass P, Kuttan G. Modulation of cell-mediated immune response in B16F-10 melanomainduced metastatic tumor-bearing C57BL/6 mice by sulforaphane. Immunopharmacology and Immunotoxicology 2007b;29:173–86.

Tomás-Barberán FA, Selma MV, Espín JC. Interactions of gut microbiota with dietary polyphenols and consequences to human health. Current Opinion in Clinical Nutrition & Metabolic Care 2016;19(6):471–6.
Tomita Y, Himeno K, Nomoto K, Endo H, Hirohata T. Augmentation of Tumor Immunity Against Syngeneic Tumors in Mice by Beta-Carotene. Journal of the National Cancer Institute 1987;78:679–81.
Traka MH. Health benefits of glucosinolates. Advances in Botanical Research, 80. Elsevier; 2016. p. 247–79.
Tsao R, Yang R, Young JC, Zhu H. Polyphenolic Profiles in Eight Apple Cultivars Using High-Performance Liquid Chromatography (HPLC). Journal of Agricultural and Food Chemistry 2003;51:6347–53.
Tsou M, Tien N, Lu C, Chiang J, Yang J, Lin J, Fan M, Lu J, Yeh S, Chung J. Phenethyl isothiocyanate promotes immune responses in normal BALB/c mice, inhibits murine leukemia WEHI-3 cells, and stimulates immunomodulations in vivo. Environmental Toxicology 2013;28:127–36.
Udenigwe CC, Ramprasath VR, Aluko RE, Jones PJ. Potential of resveratrol in anticancer and anti-inflammatory therapy. Nutrition Reviews 2008;66:445–54.
Umigai N, Tanaka J, Tsuruma K, Shimazawa M, Hara H. Crocetin, a carotenoid derivative, inhibits VEGF-induced angiogenesis via suppression of p38 phosphorylation. Current Neurovascular Research 2012;9:102–9.
Vallejo F, Tomas-Barberan F, Garcia-Viguera C. Glucosinolates and vitamin C content in edible parts of broccoli florets after domestic cooking. European Food Research and Technology 2002;215:310–6.
Vallverdu-Queralt A, et al. Impact of high-intensity pulsed electric fields on carotenoids profile of tomato juice made of moderate-intensity pulsed electric field-treated tomatoes. Food Chemistry 2013;141:3131–8.
Van Eylen D, et al. Influence of pressure/temperature treatments on glucosinolate conversion in broccoli (Brassica oleraceae L. cv Italica) heads. Food Chemistry 2009;112:646–53.
van Poppel G, Kok FJ, Hermus RJ. Beta-carotene supplementation in smokers reduces the frequency of micronuclei in sputum. British Journal of Cancer 1992;66:1164–8.
Vanamala J. Food Systems Approach to Cancer Prevention. Critical Reviews in Food Science and Nutrition 2015;57(12):2573–88.
Vanamala J. Food systems approach to cancer prevention. Critical reviews in food science and nutrition 2017;57(12):2573–88.
Vanamala J, et al. Bioactive compounds of grapefruit (Citrus paradisi Cv. Rio Red) respond differently to postharvest irradiation, storage, and freeze drying. Journal of Agricultural and Food Chemistry 2005;53:3980–5.
Vanamala J, et al. Suppression of colon carcinogenesis by bioactive compounds in grapefruit. Carcinogenesis 2006a;27:1257–65.
Vanamala J, et al. Dietary fish oil and pectin enhance colonocyte apoptosis in part through suppression of PPARdelta/PGE2 and elevation of PGE3. Carcinogenesis 2008a;29:790–6.
Vanamala J, Radhakrishnan S, Reddivari L, Bhat VB, Ptitsyn A. Resveratrol suppresses human colon cancer cell proliferation and induces apoptosis via targeting the pentose phosphate and the talin-FAK signaling pathways-A proteomic approach. Proteome Science 2011a;9:49.
Vanamala J, Radhakrishnan S, Reddivari L, Bhat VB, Ptitsyn A. Resveratrol suppresses human colon cancer cell proliferation and induces apoptosis via targeting the pentose phosphate and the talin-fak signaling pathways-a proteomic approach. Proteome science 2011b;9(1):49.
Vanamala J, Radhakrishnan S, Reddivari L, Massey A. Anthocyanins as apoptotic regulators. Novel Apoptotic Regulators in Carcinogenesis. Springer; 2012. p. 93–122.
Vanamala J, Reddivari L, Radhakrishnan S, Tarver C. Resveratrol suppresses IGF-1 induced human colon cancer cell proliferation and elevates apoptosis via suppression of IGF-1R/Wnt and activation of p53 signaling pathways. BMC Cancer 2010;10:238.
Vanamala J, et al. Suppression of colon carcinogenesis by bioactive compounds in grapefruit. Carcinogenesis 2006b;27:1257–65.
Vanamala J, Tarver CC, Murano PS. Obesity-enhanced colon cancer: functional food compounds and their mechanisms of action. Current Cancer Drug Targets 2008b;8:611–33.
Vasquez-Caicedo AL, Schilling S, Carle R, Neidhart S. Impact of packaging and storage conditions on colour and _-carotene retention of pasteurised mango puree. European Food Research and Technology 2006;224:581–90.
Vasquez-Caicedo AL, Schilling S, Carle R, Neidhart S. Effects of thermal processing and fruit matrix on _-carotene stability and enzyme inactivation during transformation of mangoes into puree and nectar. Food Chemistry 2007;102:1172–86.
Velasco P, Cartea ME, Gonzalez C, Vilar M, Ordas A. actors Affecting the Glucosinolate Content of Kale (Brassica oleracea acephala Group). Journal of Agricultural and Food Chemistry 2007;55:955–62.
Verkerk R, et al. Glucosinolates in Brassica vegetables: The influence of the food supply chain on intake, bioavailability and human health. Molecular Nutrition and Food Research 2009;53:S219.
Verkerk R, Dekker M. Glucosinolates and myrosinase activity in red cabbage. Brassica Oleracea 2004;52(24):7318–23.
Verkerk R, Dekker M, Jongen WMF. Post-harvest increase of indolyl glucosinolates in response to chopping and storage of Brassica vegetables. Journal of the Science of Food and Agriculture 2001;81:953–8.
Vignoli JA, Bassoli DG, Benassi MT. Antioxidant activity, polyphenols, caffeine and melanoidins in soluble coffee: The influence of processing conditions and raw material. Food Chemistry 2011;124:863–8.
Voorrips LE, Goldbohm RA, van Poppel G, Sturmans F, Hermus R, Van Den Brandt PA. Vegetable and fruit consumption and risks of colon and rectal cancer in a prospective cohort study: The Netherlands Cohort Study on Diet and Cancer. American Journal of Epidemiology 2000;152:1081–92.
Vos RHd, Blijleven WGH. The effect of processing conditions on glucosinolates in cruciferous vegetables. Z Lebensm Unters Forsch 1988;187:525–9.
Voutilainen S, Nurmi T, Mursu J, Rissanen TH. Carotenoids and Cardiovascular Health. The American Journal of Clinical Nutrition 2006;83:1265–71.
Wang D, Upadhyaya B, Liu Y, Knudsen D, Dey M. Phenethyl isothiocyanate upregulates death receptors 4 and 5 and inhibits proliferation in human cancer stem-like cells. BMC Cancer 2014;14:591.
Wang J, Chen S, Xu S, Yu X, Ma D, Hu X, Cao X. In vivo induction of apoptosis by fucoxanthin, a marine carotenoid, associated with down-regulating STAT3/EGFR signaling in sarcoma 180 (S180) xenografts-bearing mice. Marine Drugs 2012;10:2055–68.
Wang S, DeGroff VL, Clinton SK. 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. Journal of Nutrition 2003;133:2367–76.
Wang JTL, Wang J. Biomarkers of Dietary Polyphenols in Cancer Studies: Current Evidence and Beyond. Oxidative Medicine and Cellular Longevity 2015;2015:1–14.
Weng CJ, Yen GC. Flavonoids, a ubiquitous dietary phenolic subclass, exert extensive in vitro anti-invasive and in vivo anti-metastatic activities. Cancer and Metastasis Reviews 2012;31:323–51.
Willett W, Rockström J, Loken B, Springmann M, Lang T, Vermeulen S, Garnett T, Tilman D, De-Clerck F, Wood A, et al. Food in the anthropocene: the eat–lancet commission on healthy diets from sustainable food systems. The Lancet 2019;393(10170):447–92.
World Academy of Science, Engineering and Technology, International Journal of Medical and Health Sciences (2017). *Inhibitory Effects of Crocin from Crocus Sativus L. on Cell Proliferation of a Medulloblastoma Human Cell Line*, Number 12. World Academy of Science, Engineering and Technology, International Journal of Medical and Health Sciences.
Wu X, Zhou Q, Xu K. Are isothiocyanates potential anti-cancer drugs? Acta Pharmacologica Sinica 2009;30:501–12.
Xi J, et al. Characterization of polyphenols from green tea leaves using a high hydrostatic pressure extraction. International Journal of Pharmaceutics 2009;382:139–43.
Xiao D, Powolny A, Moura M, Kelley E, Bommareddy A, Kim S, Hahm E, Normolle D, Van H, Singh S. Phenethyl isothiocyanate inhibits oxidative phosphorylation to trigger reactive oxygen species-mediated death of human prostate cancer cells. Journal of Biological Chemistry 2010;285:26558–69.
Xiao D, Singh SV. Phenethyl isothiocyanate inhibits angiogenesis in vitro and ex vivo. Cancer research 2007;67(5):2239–46.
Xu C, Shen G, Chen C, Gelinas C, Kong AN. Suppression of NF-kappaB and NF-kappaBregulated gene expression by sulforaphane and PEITC through IkappaBalpha, IKK pathway in human prostate cancer PC-3 cells. Oncogene 2005;24:4486–95.
Yang J, Liu RH. Synergistic effect of apple extracts and quercetin 3-beta-d-glucoside combination on antiproliferative activity in MCF-7 human breast cancer cells in vitro. Journal of Agricultural and Food Chemistry 2009;57:8581–6.
Yasui Y, Hosokawa M, Mikami N, Miyashita K, Tanaka T. Dietary Astaxanthin Inhibits Colitis and Colitis-associated Colon Carcinogenesis in Mice via Modulation of the Inflammatory Cytokines. Chemico-Biological Interactions 2011;193:79–87.
Yildiz H, Icier F, Baysal T. Changes in-Carotene, chloroplyll and color of spinach puree during ohmic heating. Journal of Food Process Engineering 2010;33:763–79.
Yoo HG, et al. Induction of apoptosis by the green tea flavonol (-)-epigallocatechin-3-gallate in human endothelial ECV 304 cells. Anticancer Research 2002;22:3373–8.
Zabetakis I, Leclerc D, Kajda P. The effect of high hydrostatic pressure on the strawberry anthocyanins. Journal of Agricultural and Food Chemistry 2000;48:2749–54.
Zhang D, Quantick PC, Grigor JM. Changes in phenolic compounds in Litchi (Litchi chinensis Sonn.) fruit during postharvest storage. Postharvest Biology and Technology 2000;19:165–72.
Zhou Y, Zheng J, Li Y, Xu D-P, Li S, Chen Y-M, Li H-B. Natural polyphenols for prevention and treatment of cancer. Nutrients 2016;8(8):515.
Zu K, Mucci L, Rosner B, Clinton S, Loda M, Stampfer M, Giovannucci E. Dietary Lycopene, Angiogenesis, and Prostate Cancer: A Prospective Study in the Prostate-Specific Antigen Era. Journal of the National Cancer Institute 2014;106(2):1–10.