BIOACTIVE COMPOUNDS ASSOCIATED WITH CHRONIC DISEASE PREVENTION

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ABSTRACT

Chronic diseases such as cardiovascular disease, cancer, and type 2 diabetes are leading causes of mortality and disability worldwide nowadays. Preventive approaches focusing on dietary modifications, particularly the consumption of plant-based foods rich in bioactive compounds like phytochemicals, have shown promise in reducing the risk of these chronic diseases. Phenolics, flavonoids, carotenoids, stilbenes, and phytosterols are among the most studied bioactive compounds, recognized for their antioxidant, anti-inflammatory, and antiproliferative properties. Consuming a diverse range of fruits, vegetables, and whole grains, which provide these compounds, can enhance overall health, and prevent chronic diseases more effectively than isolated supplements. Epidemiological studies and clinical trials support the health benefits of bioactive compounds, suggesting that a varied diet rich in these natural substances is crucial for long-term health and disease prevention. This review underscores the importance of integrating bioactive compounds into dietary strategies to mitigate the growing burden of chronic diseases.

BIOGRAPHICAL SKETCH

Zhiruo Jin was born on January 27, 2001, in Tianjin, China. She earned her Bachelor of Science in Dietetics and Bachelor of Art in Zoology from Michigan State University in May 2023. Her academic achievements include being on the Dean's List, completing an Honor Option in Lifespan Human Development in Family, and graduating with a high cumulative GPA.

Currently, Zhiruo Jin is in Dr. Liu's lab, and pursuing her Master of Food Science at Cornell University, with an expected graduation date of May 2024. She has maintained a high academic standard, and her graduation thesis focuses on bioactive compounds associated with chronic diseases, showcasing her dedication to advancing knowledge in her field. Zhiruo's educational journey reflects her commitment to academic excellence and her passion for the sciences.

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Introduction

Chronic diseases — including forms of diabetes, cardiovascular diseases, and cancer — cause most of our health problems in the world today. They account for most deaths and cause most cases of disability worldwide. In the United States and the majority of industrialized nations, cardiovascular disease (CVD) and cancer rank as the primary causes of mortality (Liu, 2013). They result in impairment and poor quality of life, lead to enormous societal and economic costs. The United States spends more than $4 trillion a year on health care expenditures related to them (WHO Diet, 2003). The adverse effects of modern medical treatments put most conditions beyond mere treatment, not to mention cure. A huge and growing market thus exists for preventive approaches, with particular focus on dietary modifications that include suggesting people to consume more plant-based diet which full of fruits and vegetables that contains bioactive substances — especially phytochemicals — as the putative active and accessible ingredients. Consuming foods high in bioactive components or antioxidants can have positive health effects beyond merely fulfilling dietary requirements and can help prevent chronic illnesses (Liu, 2003).

According to the World Health Organization, chronic disease are responsible for more than 70 percent of all deaths worldwide, and furthermore are almost entirely modifiable i.e., due to our lifestyle choices (WHO, 2023). They are, as the Willett indicated, "preventable by a combination of promotion of healthy diets, regular physical activity, avoiding tobacco use, avoiding overweight, and moderate alcohol consumption" (Willett, 2002). With suitable food and lifestyle modifications, it is predicted that even over 30% of cancer-related deaths in the US might be prevented (Willett, 2002; Liu, 2013). Increasing volumes of chronic disease dictate that we need preventive approaches that mitigate disease, decreasing death in individuals and generating financial savings from less management- and treatment-related healthcare spending.

Because primary prevention of these kinds of chronic disease is more stable than treatment, the emphasis is shifting to diet – in particular, primary prevention of chronic disease through changes to diet. A diet that includes substantial amounts of processed, calorie-dense， salty, and saturated fats foods may be associated with an elevated risk of chronic disease, while a diet characterized by a wide variety of whole, minimally processed foods that include generous amounts of fruits, vegetables and fiber-rich grains is effective at preventing chronic disease (WHO Diet, 2003; Liu, 2003, 2013). In order to develop effective dietary prophylaxis, we need to identify what in food is providing the protective benefit.

Bioactive components of diet, especially those in plant-based foods – that is, fruits, vegetables, and whole grains – appear to have a role in human health and wellbeing that goes well beyond basic nutrition (Biesalski, et al., 2009). Many studies have shown strong relationships between dietary patterns including fruit, vegetable and whole-grain intake, and lowered risk of the two major causes of mortality and disability – cancer and cardiovascular disease – and this protection effect is believed to stem not only from traditional nutrients but also from plant chemicals phytochemicals (Liu, 2003, 2004, 2013). No phytochemicals are considered to be nutrients, they are called bioactive non-nutrients, but these chemicals are widely postulated to have the ability to reduce the risk of several major chronic diseases. Indeed, phytochemicals such as carotenoids, phenolics and flavonoids have been recognized for their potent antioxidant, anti-inflammatory and antiproliferative activities and are considered to be able to affect mechanisms that could help to prevent or at least lessen oxidative stress and DNA damage, which are contributors to disease formation (Liu, 2003, 2013, 2004, etc.). Moreover, there is evidence strongly indicates that the health benefits derived from consuming fruits and vegetables arise not from individual bioactive compounds consumed in isolation but from the collective and synergistic effects of the myriad phytochemicals they contain (Liu, 2004). This would imply that a diversity of whole plant foods seems the best strategy in order to maximize the benefit of fruit and vegetables for health.

There's great contemporary interest, by food science and nutritional science, in the ways in which bioactive compounds might potentially help in the prevention of chronic disease; we're increasingly interested in using them as a means toward achieving that; whether it's in finding them in new kinds of food sources, or in new ways that processing might help to increase their contribution to health, or through foods that have been fortified in ways that either enhance food or contribute to human health. Scientists are interested in how these compounds are digested, absorbed, and metabolized, as well as in how these compounds interact with other compounds present in foods or that are produced by our bodies.

This introduction sets the context for the central role of bioactive compounds in the prevention of chronic diseases, while later sections go on to clarify what kinds of bioactive compounds there are, where we can find them, how they work, and what the scientific literature says about their benefits, offering an overview of the potential for dietary interventions using these compounds to reduce chronic disease. In addition to drawing attention to the dynamics of diet in health maintenance, it also shed light on the interplay between food science and nutritional science in helping us to better understand and utilize these important bioactive compounds.

Bioactive compounds

Bioactive compounds are a type of chemicals that naturally occur in foods, playing a pivotal role beyond basic nutrition. The general consensus is that “bioactive compounds are essential and non-essential compounds (e.g., vitamins or polyphenols) that occur in nature, are part of the food chain, and can be shown to have an effect on human health” (Biesalski, et al., 2009). A wide variety of fruits and vegetables contain a mixture of bioactive compounds beyond macronutrients, such as dietary fibers, minerals, vitamins, and phytochemicals (Liu, 2004). They have lately gained increasing attention for their ability to support overall well-being and reduce the risk of chronic diseases.

Phytochemicals

The Greek root word phyto, which means plant, is combined with the word “chemical” to create the term “phytochemical” (Liu, 2013; Liu, 2004). Phytochemical are defined as “bioactive nonnutrient plant chemicals in fruits, vegetables, grains, and other plant foods that may provide desirable health benefits beyond basic nutrition to reduce the risk of major chronic diseases” (Liu, 2004). According to our present knowledge, there are more than 5,000 different types of phytochemicals, but a substantial portion of them are still unknown, and they may offer more advantages to humans than we now comprehend, warranting more investigation (Liu, 2013, 2004, 2003).

Phytochemicals encompass a variety of compounds, including “phenolics (flavonoids), alkaloids, nitrogen-containing compounds, organosulfur compounds, phytosterols, and carotenoids” (Liu, 2013, 2004), each with unique properties and effects. Phenolics and carotenoids are the most studied dietary phytochemical categories in relation to human health and well-being (Liu, 2013). The following content will introduce these different phytochemicals in sequence.

1. Phenolics

Among these most prevalent and influential natural bioactive compounds occurring in various fruits and vegetables, phenolics are one of the most studied groups due to their potent antioxidant activity that works against oxidative stress which contribute to heart diseases, diabetes, and cancer (Liu, 2013).

Phenolics– a class of secondary metabolites that have one or more aromatic rings and hydroxyl groups in the structures produced in plants encompassing a wide spectrum of different compounds, such as flavonoids and phenolic acids– have recently attracted significant interest as a promising new group of effective low-side effect preventative agents against chronic diseases (Liu, 2013). Phenolic acids constitute roughly one-third of the phenolics present in our food, whereas the remaining two-thirds are derived from flavonoids (Liu, 2004). Wild blueberry and blackberry are fruits that possess the highest total phenolic contents, while spinach has the highest total phenolic content among vegetables (Liu, 2013).

1) Flavonoids

Flavonoids which “consist of 2 aromatic rings linked by 3 carbons that are usually in an oxygenated heterocycle ring” are the most widespread group of phenolics and have been shown to reduce the risk of chronic diseases (Liu, 2013). Epidemiological studies have consistently demonstrated a negative correlation between high intake of flavonoid and a diminished risk of developing major chronic diseases (Liu, 2004). With over 4000 identified flavonoids, they are categorized into several types based on their chemical structure, including “flavonols, flavones, flavanols, flavanones, anthocyanidins, and isoflavonoids” (Liu, 2013). Each type has unique properties and can be found in different plant sources. The richest sources include “onion, apples, cider, grapes, wine, and tea”, although they are present in almost all vegetables and fruits (Perez-Vizcaino & Duarte, 2010).

Flavonols are the prominent subcategory of flavonoids in fruits and vegetables, include quercetin, kaempferol, and myricetin (Liu, 2013). Quercetin as the domination of flavonols, its levels are found in high concentrations in onions, kale, broccoli, beans, apples, blackcurrants, and tea (Hollman & Arts, 2000). Substantial evidence suggests that quercetin has antihypertensive and antiatherogenic effects and may prevent the most common cardiovascular diseases (Perez-Vizcaino & Duarte, 2010).

Flavones includes luteolin and apigenin, found high concentrations in foods like celery leaf, stalk, and red sweet peppers (Liu, 2013; Hollman & Arts, 2000).

Flavanols includes catechin and epicatechin, have been reported in tea (black tea), wine (red wine), fruits (apple, peach, plum, cherry), and legumes (Liu, 2013; Hollman & Arts, 2000).

Flavanones considered vasculoprotective include naringenin, hesperitin, and eriodictyol, commonly found in citrus fruits (Khan & Dangles, 2014). And interestingly, in contrast to the fleshy portion of citrus fruits, the peel contains the greatest concentrations of flavanones (Khan & Dangles, 2014).

Anthocyanidins includes cyanidin and malvidin, provides the vibrant blue, purple, red, and orange colors in many fruits and vegetables like berries, red grapes, and purple maize (Liu, 2013; de Pascual-Teresa & Sanchez-Ballesta, 2008). They have “antimicrobial, antioxidative, anti-inflammatory, and antimutagenic properties”, so are useful in the prevention and treatment of a wide range of chronic diseases, including cancer, metabolic disorders, cancer, and cardiovascular diseases (Lee, et al., 2017). Anthocyanidins consumption also improved glucose tolerance by lowering body weight and insulin resistance (Lee, et al., 2017).

Isoflavonoids includes genistein and daidzein, are found predominantly in soybean and soybean products (Liu, 2013; Křížová, et al., 2019). They are considered chemoprotective and can be utilized as an alternative treatment for a variety of hormonal problems, such as "breast and prostate cancer, cardiovascular diseases, osteoporosis, or menopausal symptoms" (Křížová, et al., 2019).

2) Phenolic acids

The other main sources of dietary phenolics is phenolic acids. Phenolic acids have been related with the "color, sensory qualities, and nutritional and antioxidant properties of foods" (Robbins, 2003). They are classified into two main groups based on their chemical structures, hydroxybenzoic acid derivatives and hydroxycinnamic acid derivatives (Liu, 2004).

Hydroxybenzoic acid derivatives (HBAs) include "*p*-hydroxybenzoic, gallic, protocatechuic, vanillic, and syringic acids" (Liu, 2013). They are commonly found in fruits, teas, and certain herbs and spices. All of the hydroxybenzoic acid derivatives are excellent antioxidants. Particularly, *p*-hydroxybenzoic acid is known for its effective antimicrobial properties against a wide range of bacteria and fungi, and commonly used as preservative and fungicide in foods (Jiang, et al., 2022).

Many edible berries, including blackberries, blackcurrants, and raspberries, contain *p*-hydroxybenzoic, protocatechuic, and gallic acids (Tomás-Barberán & Clifford, 2000). Herbs (dried basil herb), vegetables (horseradish leaf), and other fruits (strawberry) are also rich sources of *p*-hydroxybenzoic acids (Herrmann & Nagel, 1989; Tomás-Barberán & Clifford, 2000). Additionally, protocatechuic acids found in vegetables like onion peels and skin of potato tubers, and gallic acids are widely found in teas, especially green and black teas (Herrmann & Nagel, 1989; Tomás-Barberán & Clifford, 2000). Vanillic and syringic acids are commonly found in cereals (Canadian/American wheat flours, oats) and alcoholic beverages (wines) (Tomás-Barberán & Clifford, 2000).

Hydroxycinnamic acid derivatives include "*p*-coumaric, caffeic, ferulic, and sinapic acids" (Liu, 2013). They are abundant in coffee beans, whole grains, and certain fruits and vegetables such as apples, pears, and potatoes. They are found in a variety of common foods, making them an accessible antioxidant that can be easily incorporated into the diet to help fight oxidative stress and inflammation, enhance neurological health, and protect against microbial infections.

Caffeic acids are one of the most common hydroxycinnamic acids and is found abundantly in coffee beans, as well as in many fruits (apple, pears) and vegetables (olives, berries, potatoes, carrots) (Maity, et al., 2022). *p*-coumaric acids are one of the major phenolic acids in cereals (barley, wheat, oats, and maize), and is also widely found in fruits (apples, pears, grapes, berries) and vegetables (beans, potatoes, and onions) (Pei, et al., 2016; Boz, 2015). Ferulic acid is ubiquitous in plants, particularly in seeds and leaves where it is bound to cell wall polysaccharides and lignin (Liu, 2004). It is found in large quantities in grain foods including wheat, barley, maize, and oats, particularly in the bran of cereal (Chen & Ho, 1997; Boz, 2015). Sinapic acid is commonly found in various "fruits (lemon, Murcott oranges, strawberry), vegetables (cabbage, kale, leaf mustard, radish, broccoli), cereal grains (rye, rice, oat), oilseed crops (rapeseed and camelina), some spices and medicinal plants" (Nićiforović & Abramovič, 2014).

3) Stilbenes

Stilbenes are phytoestrogens characterized by a structure comprising two aromatic rings linked by a methylene bridge, with each carbon atom of the trans-ethane double bond substituted by a phenyl group (Venugopal & Liu, 2012). The most well-known and studied stilbene is resveratrol, which is commonly found in grapes, red wine, peanuts, and some berries (Venugopal & Liu, 2012).

Resveratrol content significantly varies among different food sources, with peanuts containing roughly half the amount found in wines, and blueberries having twice the resveratrol of bilberries, displaying regional variations (Venugopal & Liu, 2012). The stability of resveratrol is compromised by heat, meaning that cooking or thermal processing can degrade its presence in these foods (Venugopal & Liu, 2012).

2. Carotenoids

Carotenoids constitute a family of more than 600 naturally occurring pigments synthesized by plants and are broadly classified into two main categories: xanthophylls, which contain oxygen, and carotenes, which are purely hydrocarbons and contain no oxygen (Liu, 2013). In nature, carotenoids exist predominantly in the all-trans configuration (Liu, 2013). These compounds are responsible for the vibrant red, yellow, and orange hues observed in many fruits, vegetables, whole grains, and other plants (Liu, 2013). Carotenoids are not only crucial for plant health but also provide significant health benefits such as provitamins and antioxidant effects when consumed by humans (Liu, 2013).

1) Xanthophylls

Xanthophylls, a subgroup of carotenoids, include astaxanthin, β-cryptoxanthin, lutein, and zeaxanthin (Rodriguez-Amaya, 2015). Each of these xanthophylls contributes uniquely to health, primarily through their roles as antioxidants and protectors against cellular damage.

Astaxanthin, a typical animal carotenoid, is naturally found in certain algae and responsible for the pink or red color in seafood such as salmon, trout, lobster, and cooked shrimp (Rodriguez-Amaya, 2015).

β-cryptoxanthin is present in fruits such as yellow- or orange-fleshed papayas, peach, and oranges (Rodriguez-Amaya, 2015). And this xanthophyll acts as a provitamin A source, enhancing immune function and reducing the risk of chronic diseases due to its antioxidant capability (Liu, 2013; Rodriguez-Amaya, 2015).

Lutein and zeaxanthin are found in the macular region, also known as the yellow spot, of the human retina, and are crucial for eye health, particularly in protecting against age-related macular degeneration and cataracts due to its ability to filter harmful blue light and act as an antioxidant (Liu, 2013; Rodriguez-Amaya, 2015). A diet abundant in lutein and zeaxanthin has been linked to a decreased likelihood of developing cataracts and macular degeneration (Liu, 2013). Lutein is predominantly found in green leafy vegetables, especially dark green leafy vegetables, such as spinach, kale, and broccoli, as well as in egg yolks and corn (Rodriguez-Amaya, 2015). Zeaxanthin is abundant in foods such as corn, orange bell peppers, honeydew, and also in green leafy vegetables alongside lutein (Rodriguez-Amaya, 2015). Furthermore, zeaxanthin and lutein are the primary carotenoids found in egg yolk and corn (Rodriguez-Amaya, 2015).

2) Carotenes

Carotenes, the other subgroup of carotenoids, include β-carotene, α-carotene, and lycopene (Rodriguez-Amaya, 2015).

β-carotene and α-carotene are two other carotenoids that contain provitamin A activity in addition to β-cryptoxanthin (Liu, 2013). β-carotene is the most famous carotene, known for giving carrots, sweet potatoes, and pumpkins their orange color. It is commonly found in orange and yellow vegetables and fruits, such as carrots, sweet potatoes, spinach, and red peppers (Liu, 2013; Rodriguez-Amaya, 2015). α-carotene is less well-known than β-carotene, found in similar foods but is especially concentrated in carrots and pumpkins (Rodriguez-Amaya, 2015).

Lycopene is a bright red carotene that provides the color for fruits and vegetables like tomatoes, watermelons, and red grapefruits (Rodriguez-Amaya, 2015). Tomatoes and tomato products are the most extensively studied and referenced food sources (Rodriguez-Amaya, 2015). Approximately 85% of lycopene consumption in the United States is derived from processed tomato products, including ketchup, tomato paste, and tomato soup (Liu, 2013). Unlike β-carotene and α-carotene, lycopene is not converted to vitamin A in the human body. However, it is valued for its potent antioxidant properties, which are believed to contribute to its role in preventing cardiovascular diseases, prostate cancer, and other types of cancer (Rodriguez-Amaya, 2015).

3. Phytosterols

Phytosterols, also known as plant sterols and stanols, are naturally occurring compounds found in the cell walls and membranes of plants, where they play a role similar to cholesterol in human cells (Sheng, Li, & Liu, 2018; Ostlund, 2002). Phytosterols are present in all plant-based foods, with the most abundant amounts found in vegetable oils (Ostlund, 2002). These substances are primarily recognized for their ability to reduce serum LDL and total cholesterol levels without affecting HDL cholesterol levels, as they compete with cholesterol for absorption in the digestive tract, thereby inhibiting the absorption of cholesterol (Sheng, Li, & Liu, 2018). This mechanism is beneficial for preventing cardiovascular diseases, especially coronary heart disease (Ostlund, 2002). In addition to vegetable oils, phytosterols are also present in nuts, seeds, whole grains, and legumes, with smaller amounts in fruits and vegetables (Siddiqui, et al., 2023; Ostlund, 2002; Chanioti, Katsouli & Tzia, 2021). Palm oil is an exception as it lacks phytosterols following the refining process for western markets (Ostlund, 2002).

The most common types of phytosterols include "β-sitosterol, campesterol, and stigmasterol" (Siddiqui, et al., 2023). β-sitosterol is predominantly found in a variety of plant-based foods. Key dietary sources include vegetable oils like canola, corn, and soybean oil, which are rich in this compound (Chanioti, Katsouli & Tzia, 2021). Olive oil, in particular, has the greatest concentration of β-sitosterol among all vegetable oils (Chanioti, Katsouli & Tzia, 2021). Nuts and seeds also provide significant amounts of β-sitosterol. Additionally, legumes like beans and peas, along with whole grains such as wheat germ and bran, are notable sources (Chanioti, Katsouli & Tzia, 2021).

Health Benefits: Antioxidant & Food Synergy

Thanks to the presence of these protective compounds, plants foods exhibit a wide array of pharmacological effects, such as antioxidant, anti-inflammatory, antiproliferative, anti-cancer, antimicrobial, antimutagenic, antihypertensive, and antiatherogenic properties (Liu, 2013, 2004, 2003; Robbins, 2003; Perez-Vizcaino & Duarte, 2010; Lee, et al., 2017).

Living organisms naturally produce reactive oxygen species (ROS) through normal cellular metabolism and external factors (Birben, et al., 2012). Oxidative stress occurs when there is an imbalance between the production of ROS and the body's ability to neutralize these harmful compounds or repair the resulting damage (Liu, 2004). Antioxidants play a crucial role in combating oxidative stress, which is associated with the development of many chronic diseases such as cardiovascular disease, diabetes, cancer, and neurodegenerative disorders (Liu, 2004; Birben, et al., 2012). These antioxidant compounds neutralize ROS, thus protecting cells and tissues from damage. Consuming foods rich in antioxidants regularly, like fruits and vegetables, can greatly enhance the body's capacity to repair and prevent the oxidative damage that contributes to chronic disease progression.

The importance of assessing the health potential of bioactive compounds in food cannot be overstated. These compounds often work synergistically within the complex matrix of whole foods, which means that the health benefits cannot be fully replicated by consuming individual compounds in isolation, such as in supplements (Liu, 2004, 2013). The food synergy hypothesis suggests that the interplay between different phytochemicals in whole foods results in combined effects that are greater than the sum of their parts. Furthermore, consuming higher doses of bioactive compounds in supplement form may increase toxicity risks (Liu, 2013, 2004). These are why a varied diet rich in fruits, vegetables, and whole grains is consistently recommended over dietary supplements for preventing chronic diseases.

Bioactive compounds in the prevention of cardiovascular disease

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality globally, despite a decline in death rates over the previous three decades, accountable for around 47% of female deaths and 39% of male deaths, imposing significant health, economic, and developmental challenges (Li, et al., 2022; Birger, et al., 2021; Mensah, et al., 2023). The global burden of CVDs continues to rise, influenced by both demographic changes and risk factor proliferation (Birger, et al., 2021). According to recent data published in the Journal of the American College of Cardiology, CVDs accounted for approximately 17.9 million deaths annually, making up a third of all global deaths (Mensah, et al., 2023). As a result, primary cardiovascular diseases prevention is a top public health target.

The interplay between dietary intake and the incidence of cardiovascular diseases is a critical area of study in medical and nutritional science, particularly focusing on the role of bioactive compounds in modulating disease risk and outcomes. Phytochemicals present in a diverse range of fruits and vegetables are increasingly recognized for their potential in mitigating cardiovascular risk factors and improving heart health through various biological mechanisms (Liu, 2013).

Many epidemiological studies underscore the benefits of consumption higher amounts of fruits and vegetables is consistently associated with reduced mortality from coronary heart disease (CHD) and myocardial infarction (Liu, 2013). A cohort study was mostly conducted in North America, involving a total of 91,379 men, 129,701 women, and 5,007 cases of coronary heart disease (CHD) events, showing that each additional serving per day of fruit and vegetable intake reduced the risk of CHD by 4%, while fruit intake alone reduced the risk by 7% (Dauchet, et al., 2006). The findings of this current meta-analysis of cohort studies suggest that there is a negative relationship between the consumption of fruits and vegetables and the occurrence of coronary heart disease (CHD) (Dauchet, et al., 2006). High fruits and vegetables intake like more than 4 servings per day was linked to a 20% to 30% decrease in the risk of cardiovascular disease (CVD), according to estimates (Liu, 2013). Another meta-analysis of prospective cohort studies has shown that increasing the consumption of fruits and vegetables from less than 3 servings per day to more than 5 servings per day is linked to a 17% decrease in the risk of coronary heart disease (CHD) (He, et al., 2007). The results strongly endorse the advice to consume more than 5 servings per day of fruits and vegetables (He, et al., 2007). Also, there was a NHANES Epidemiologic Follow-up Study indicated by Liu's article, shown that individuals who consumed fruits and vegetables at least three times per day had a 27% decreased risk of cardiovascular disease mortality compared to those who consumed them just once per day (Liu, 2013).

Flavonoids contained in vegetables and fruits play a vital role in reducing cardiovascular disease (Liu, 2013; Perez-Vizcaino & Duarte, 2010). Increased dietary intake of flavonoids in general and more specifically to flavonols (quercetin) correlates with lower LDL cholesterol and total cholesterol levels, which are significant risk factors for CVD (Liu, 2013; Perez-Vizcaino & Duarte, 2010). Flavonols such as quercetin have been demonstrated to exert vasodilator effects independent of the endothelium, directly influencing vascular smooth muscle cells. These effects are critical in maintaining vascular health under oxidative stress conditions, where flavonols protect nitric oxide (NO) integrity, enhancing endothelial function (Perez-Vizcaino & Duarte, 2010).

Dietary flavonols are also linked with antioxidant, anti-inflammatory, and antihypertensive effects. The antioxidative properties of flavonols help in scavenging harmful free radicals and inhibit low-density lipoprotein (LDL) oxidation, and they also modulate inflammatory pathways by reducing the expression of adhesion molecules and other inflammatory markers, crucial for preventing inflammatory processes within blood vessels (Perez-Vizcaino & Duarte, 2010). Human intervention trials have shown that flavonols can reduce blood pressure, a major risk factor for CVD. The antihypertensive effects are believed to arise from the direct cardiovascular actions of these compounds, including their role in modulating vascular reactivity and reducing arterial stiffness (Perez-Vizcaino & Duarte, 2010). Flavonols additionally impact platelet aggregation, an essential factor in thrombosis and cardiovascular events like myocardial infarction. They demonstrate platelet antiaggregant effects by interfering with the platelet activation pathways, thus reducing the potential for clot formation (Perez-Vizcaino & Duarte, 2010).

A small cohort study on men and women aged 30-69 years old without any presence of heart diseases, shown that the beneficial impact of flavonoids was linked to a diet characterized by a significant consumption of apples and onions, especially in women (Knekt, et al., 1996). Apples are widely consumed in the human diet and are rich in flavonoids, which are mostly found in the apple's skin (Toh, et al., 2013). The consumption of apples accounted for around 10% of the total ingested flavonoids (Boyer & Liu, 2004). Individuals with very limited consumption of flavonoids are more susceptible to developing cardiovascular disease. (Knekt, et al., 1996). Women who consumed the greatest quantities of flavonoids observed a 35% decrease in the likelihood of experiencing cardiovascular events (Sesso, et al., 2003; Boyer & Liu, 2004). In addition, those who consumed larger amounts of quercetin had a reduced risk of death from ischemic heart disease (Knekt, et al., 2002).

Multiple clinical research have shown that carotenoids possess the ability to decrease the likelihood of gaining cardiovascular diseases (Milani, et al., 2017). Carotenoids have the potential to reduce the risk of cardiovascular diseases (CVDs) through various mechanisms, including: "(a) lowering blood pressure, (b) reducing pro-inflammatory cytokines, (c) decreasing markers of inflammation such as C-reactive protein, and (d) improving insulin sensitivity in the liver, muscle, and adipose tissues" (Milani, et al., 2017). More specific, there is a correlation between β-carotene and the reduced risk of cardiovascular diseases, such as coronary heart disease (Milani, et al., 2017; Rodriguez-Amaya, 2015). There is a study investigated the connection between congestive heart failure, a major cause of cardiovascular mortality and illness in Western countries, in a group of 1,031 Finnish males aged 45–65 years (Karppi, et al., 2013). Men in the lowest quartile of β-carotene had a nearly 3-fold increased risk of congestive heart failure (Karppi, et al., 2013). However, "serum concentrations of lycopene and α-carotene were not associated with the risk of congestive heart failure" (Karppi, et al., 2013).

The Mediterranean diet is closely associated with cardiovascular disease (CVD) prevention, characterized by high intakes of fruits, vegetables, whole grains, nuts, seeds, olive oil, and fish, which provide a diverse array of bioactive compounds including flavonoids, phenolic acids, and fiber (Widmer, et al., 2015; Liu, 2013). Epidemiological studies have robustly linked the Mediterranean diet with a reduced incidence of major cardiovascular events (Liu, 2013). The original Seven Countries Study has shown the favorable effects of the Mediterranean diet in terms of protecting the heart, measuring indicators for cardiovascular disease, and reducing overall morbidity and mortality (Widmer, et al., 2015). A study of 22043 adults in Greece were pointed out in Liu's article, indicated individuals who strictly follow the Mediterranean diet, observe a significant 25% decrease in overall mortality and a 33% decrease in mortality specifically related to coronary heart disease (CHD) (Liu, 2013). The Lyon Heart Study, a randomized controlled trial (RCT), provides significant evidence supporting the effectiveness of the Mediterranean diet in reducing cardiovascular disease events and death. The study showed that individuals who were assigned to follow the Mediterranean diet experienced a reduction in composite endpoints of cardiovascular disease events and death for a period of up to 4 years after an initial event. This finding establishes the Mediterranean diet as a crucial component in secondary prevention (Widmer, et al., 2015). Another meta-analysis using a sample size of 2650 individuals demonstrated that the Mediterranean diet yielded a more substantial decrease in risk factors for cardiovascular disease and signs of inflammation (Nordmann, et al., 2011).

Bioactive compounds in the prevention of cancer

Cancer is a significant global public health issue. It ranks as the second most common cause of death in the United States and the "leading cause among people younger than 85 years old" (Siegel, Miller, & Jemal, 2019; Siegel, Giaquinto, & Jemal, 2024). It involves the uncontrolled growth and spread of cells that can affect virtually any part of the body. Lung, breast, colorectal, prostate, and stomach cancers are the five most common cancers globally (Chen & Liu, 2018). Prostate cancer is the most common kind of cancer in males, and breast cancer is the most common kind of cancer in females, each one of them representing 28% of all diagnosed cases. Lung cancer is the second most common kind of cancer, accounting for 15% in males and 14% in females (Venugopal & Liu, 2012).

Approximately "30% of all cancer related deaths in the United States" could be prevented by making suitable changes to one's diet (Liu, 2004, 2013). There are a lot of evidence shown that a diet rich in fruits and vegetables can lower the risk of cancer development by impacting these critical cellular processes (Liu, 2004). Increasing dietary intake of bioactive compounds and antioxidants found in "fruits, vegetables, whole grains, and other plant-based foods" may help prevent or mitigate DNA oxidation and influence cellular mechanisms governing cell growth and programmed cell death (Liu, 2004).

Consuming at least 28 servings of vegetables weekly reduces the risk of prostate cancer by 35%, while high fruit and vegetable intake is inversely associated with the risks of pancreatic, colon, and colorectal cancers (Liu, 2013; Cohen, Kristal, & Stanford, 2000). Specifically, consuming five or more servings of fruits per day is linked to a decreased risk of colorectal adenomas compared to those consuming one serving or less (Liu, 2013; Michels, et al., 2006). Additionally, a daily intake of about 5.8 servings of fruits and vegetables significantly lowers the risk of cancers of the oral cavity, pharynx, and larynx (Liu, 2013; Freedman, et al., 2008). Overall, a 200g daily increase in fruits and vegetables can slightly reduce overall cancer risk, underscoring the protective effects of these foods against various malignancies (Liu, 2013; Boffetta, et al., 2010).

1. **Lung cancer**

Multiple studies provide evidence that high amounts of bioactive substances, including flavonoids such as quercetin found in onions and apples are significantly associated with a decreased likelihood of developing lung cancer (Liu, 2004; Le Marchand, et al., 2000; Muller, et al., 2019). A comprehensive research conducted in Finland, which followed approximately 10,000 individuals over a period of 24 years, revealed a significant correlation between a high consumption of flavonoids and a 50% decrease in the chance of developing lung cancer (Knekt, et al., 1997; Liu, 2004). Moreover, the intake of onions has been shown to be particularly beneficial in safeguarding against squamous-cell cancer (Liu, 2004). Furthermore, another study conducted by Boyle et al. has demonstrated that the consumption of onions enhances the ability of DNA to withstand damage and lowers the presence of oxidative metabolites in urine (Boyle, et al., 2000; Liu, 2004). Additionally, a higher intake of isoflavones, primarily from soy products, was associated with a reduced risk of lung cancer. There is a study in Japan, highlight a significant inverse associated between high isoflavone intake and lung cancer risk among men who never smoked (Shimazu, et al., 2010). This protective effect was not observed in men who were current or former smokers.

Carotenoids have been extensively studied to determine their involvement in the prevention of lung cancer. The available information, however, portrays an intricate scenario, mostly contingent on the specific carotenoid, the quantity administered, and the risk factors prevalent in the community. β-carotene has been extensively researched, was previously seen as a potential candidate for the prevention of lung cancer, based on observational epidemiological studies (Rodriguez-Amaya, 2015). These investigations indicated that consuming larger amounts of β-carotene in the diet was linked to a lower occurrence of lung cancer. Nevertheless, later clinical studies conducted on high-risk populations, such as smokers and workers with asbestos exposure, yielded unexpected and worrisome findings. For example, in trials such as the ATBC and CARET investigations, the administration of large amounts of β-carotene as a supplement led to a rise in the occurrence of lung cancer among the participants. The ATBC research documented an 18% increase in lung cancer rates, and CARET research which prompted the trial to be terminated prematurely due to a significant 28% spike in lung cancer incidence among the group receiving the supplements (Rodriguez-Amaya, 2015). The data suggest that the supplementation of β-carotene, especially at high levels, might provide a danger to persons with a high susceptibility to lung cancer. In contrast, some varieties of carotenoids have had more encouraging outcomes. For instance, a comprehensive research conducted in Singapore with a substantial sample size of over 63,000 Chinese individuals revealed that consuming significant amounts of β-cryptoxanthin via food was linked to a decreased likelihood of developing lung cancer (Yuan, et al., 2003; Rodriguez-Amaya, 2015). It indicates that although β-carotene may increase the risk of lung cancer in some circumstances, other carotenoids such as β-cryptoxanthin may have preventive advantages. Significantly, these results advise against the use of high-dose carotenoid supplements, especially for persons with a higher chance of developing lung cancer. Instead, it is recommended to receive these phytochemicals naturally by following a well-balanced diet that includes a variety of fruits and vegetables. This method guarantees the consumption of a diverse range of carotenoids, as well as other advantageous phytochemicals, which may work together in a mutually beneficial way to promote general health and prevent diseases.

2. Breast cancer and prostate cancer

β-sitosterol, a prevalent phytosterol, has shown favorable outcomes in the prevention of breast and prostate cancer (Saeidnia, et al., 2014; Awad, et al., 2007; Muti, et al., 2003). *β*-sitosterol inhibits the growth of cancer cells, specifically hormone-dependent forms such as MCF-7, and triggers programmed cell death in the context of breast cancer prevention (Saeidnia, et al., 2014; Awad, et al., 2007). It enhances caspase activity, resulting in programmed cell death, and diminishes estrogen-induced tumor development in animal models, indicating its potential efficacy in regulating hormone-related growth factors in breast cancer (Saeidnia, et al., 2014). *β*-sitosterol inhibits cell proliferation and promotes programmed cell death (apoptosis) in prostate cancer cell lines by activating the sphingomyelin cycle, which modulates cellular signaling pathways involved in growth and death (Saeidnia, et al., 2014). *β*-sitosterol has been shown in clinical tests to enhance urinary symptoms related to benign prostatic hyperplasia (BPH), a disease that might potentially develop into prostate cancer if not treated. While it does not decrease the size of the prostate, it improves the flow of urine and relieves discomfort (Saeidnia, et al., 2014).

Recent study has emphasized the potential anticancer effects of quercetin, a bioactive polyphenolic flavone. Quercetin has been shown to promote apoptotic cell death in breast cancer (BC) therapy by regulating several signaling pathways (Ezzati, et al., 2020). Research has repeatedly shown a positive association between consuming a diet high in flavonoids and a decreased likelihood of developing breast cancer (Ezzati, et al., 2020). Experiments conducted on rats have shown that phytochemical extracts from whole apples may effectively hinder the formation of breast cancer (Liu, Liu, & Chen, 2005). This implies that including apples into one's diet might be an effective approach for preventing cancer. Moreover, a study examining the interactions between apple phytochemicals discovered that the combination of apple phytochemical extracts and quercetin 3-β-d-glucoside had a synergistic impact on suppressing the growth of MCF-7 human breast cancer cells (Yang & Liu, 2009). This suggests that combining treatments could potentially enhance the effectiveness of the treatment.

Another phytochemical associated with breast cancer prevention is the resveratrol. Resveratrol has been identified as a potent anti-proliferative agent against breast cancer cells (Venugopal & Liu, 2012). Studies reveal that resveratrol can inhibit cancer cell proliferation and induce apoptosis, particularly in breast cancer cell lines such as MCF-7, KPL-1, and MKL-F (Venugopal & Liu, 2012).

3. Other cancers

Research shows that quercetin can effectively inhibit colon cancer cells growth. It effectively induces apoptosis in HT-29 colon cancer cells by activating AMP-activated protein kinase (AMPK) and up-regulating p53-dependent apoptotic pathways, leading to increased cell cycle arrest and decreased cell viability in a dose-dependent manner (Kim, et al., 2010). Meanwhile, apple extracts, particularly those containing the peel, also demonstrate substantial anti-tumor properties, inhibiting colon cancer cell proliferation by up to 43%, indicating the significant role of phytochemicals in apple peels in cancer prevention (Eberhardt, Lee, & Liu, 2000).

Anthocyanins in colored corn, particularly those found in purple corn such as cyanidin 3-O-β-D-glucoside, show promising health benefits in the context of colon cancer prevention and digestive health (Sheng, Li & Liu, 2018; Tsuda, et al., 2003). Anthocyanins derived from purple sweet potatoes, red cabbage, and purple corn, when included in the diet at a concentration of 5%, shown a substantial reduction in colorectal carcinogenesis by 48%, 63%, and 89%, respectively (Wang & Stoner, 2008). A twelve-week animal study demonstrated that dietary anthocyanins could reduce colon cancer risk by increasing fecal butyric acid content and significantly reducing body weight by 16.6% at a dosage of 200 mg/kg (Wu et al., 2017; Sheng, Li & Liu, 2018).

Consumption of fruits was found to specifically reduce the risk of cancers affecting the esophagus, oral cavity, and larynx (Liu, 2004). Lycopene intake is broadly protective against various cancer types, with the most significant reduction observed in esophageal carcinoma ((De Stefani, et al., 2000)). Interestingly, the study noted that, except for laryngeal carcinoma, raw tomatoes offered greater cancer protection than foods rich in tomato sauce (De Stefani, et al., 2000).

Bioactive compounds in the prevention of type 2 diabetes

Type 2 diabetes is a persistent metabolic condition characterized by elevated blood sugar levels, resistance to insulin, and a relative deficiency of insulin. The International Diabetes Federation reported that there were roughly 463 million persons worldwide living with diabetes in 2019, indicating a substantial global health concern (International Diabetes Federation, 2019). Approximately 90% of all instances of diabetes are classified as type 2 diabetes, which is largely caused by an excessive amount of body weight and a lack of physical exercise (International Diabetes Federation, 2019). The potential of dietary bioactive substances for reducing type 2 diabetes has received significant interest.

Research on distinct bioactive compounds, such as resveratrol, which is included in red wine and berries, shows encouraging outcomes in enhancing glycemic control among individuals with type 2 diabetes (Venugopal & Liu, 2012; Bhatt, Thomas, & Nanjan, 2012). Recent study further emphasizes the advantages of consuming soy foods and isoflavones in decreasing the likelihood of developing type 2 diabetes. A meta-analysis of three US cohorts revealed a substantial correlation between the intake of isoflavones (including daidzein and genistein) in soy products and a reduced likelihood of acquiring type 2 diabetes (Ding, et al., 2016). Furthermore, dietary anthocyanins, prevalent in berries and other deeply colored fruits, have been studied for their roles against obesity and inflammation, which are key components in the prevention and management of type 2 diabetes (Lee, et al., 2017).

Conclusion

The research underscores the pivotal role of bioactive compounds in preventing chronic diseases such as cardiovascular diseases, cancer, and type 2 diabetes. The evidence highlights that a diet rich in fruits, vegetables, and whole grains, which are abundant in bioactive compounds like phenolics, flavonoids, carotenoids, stilbenes, and phytosterols, can significantly reduce the risk of these conditions. These compounds exhibit potent antioxidant, anti-inflammatory, and antiproliferative properties, contributing to their health benefits. However, it is emphasized that these benefits are best achieved through whole food consumption rather than isolated supplements, due to the synergistic effects of the compounds within their natural food matrices. While the consumption of dietary supplements is on the rise, especially among certain demographics, the potential risks associated with high doses of isolated bioactive compounds warrant caution. Further research is needed to fully understand the efficacy and long-term safety of dietary supplements. The findings advocate for dietary interventions that incorporate a wide variety of plant-based foods as an effective strategy for chronic disease prevention, promoting overall health and reducing the burden of these pervasive conditions.

REFERENCES

Liu, R. H. (2013). Dietary bioactive compounds and their health implications. *Journal of food science*, *78*(s1), A18-A25.

Liu, R. H. (2013). Health-promoting components of fruits and vegetables in the diet. *Advances in nutrition*, *4*(3), 384S-392S.

WHO Diet. (2003). Chronic Diseases. *Geneva: World Health Organization*.

Liu, R. H. (2003). Health benefits of fruit and vegetables are from additive and synergistic combinations of phytochemicals. *The American journal of clinical nutrition*, *78*(3), 517S-520S.

World Health Organization. (2023). Noncommunicable diseases. https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases

Willett, W. C. (2002). Balancing life-style and genomics research for disease prevention. *Science*, *296*(5568), 695-698.

Liu, R. H. (2004). Potential synergy of phytochemicals in cancer prevention: mechanism of action. *The Journal of nutrition*, *134*(12), 3479S-3485S.

Biesalski, H. K., Dragsted, L. O., Elmadfa, I., Grossklaus, R., Müller, M., Schrenk, D., ... & Weber, P. (2009). Bioactive compounds: Definition and assessment of activity. *Nutrition*, *25*(11-12), 1202-1205.

Hollman, P. C. H., & Arts, I. C. W. (2000). Flavonols, flavones and flavanols–nature, occurrence and dietary burden. *Journal of the Science of Food and Agriculture*, *80*(7), 1081-1093.

Khan, M. K., & Dangles, O. (2014). A comprehensive review on flavanones, the major citrus polyphenols. *Journal of food composition and analysis*, *33*(1), 85-104.

de Pascual-Teresa, S., & Sanchez-Ballesta, M. T. (2008). Anthocyanins: from plant to health. *Phytochemistry reviews*, *7*, 281-299.

Křížová, L., Dadáková, K., Kašparovská, J., & Kašparovský, T. (2019). Isoflavones. *Molecules*, *24*(6), 1076.

Perez-Vizcaino, F., & Duarte, J. (2010). Flavonols and cardiovascular disease. *Molecular aspects of medicine*, *31*(6), 478-494.

Lee, Y. M., Yoon, Y., Yoon, H., Park, H. M., Song, S., & Yeum, K. J. (2017). Dietary anthocyanins against obesity and inflammation. *Nutrients*, *9*(10), 1089.

Robbins, R. J. (2003). Phenolic acids in foods: an overview of analytical methodology. *Journal of agricultural and food chemistry*, *51*(10), 2866-2887.

Herrmann, K., & Nagel, C. W. (1989). Occurrence and content of hydroxycinnamic and hydroxybenzoic acid compounds in foods. *Critical reviews in food science & nutrition*, *28*(4), 315-347.

Tomás-Barberán, F. A., & Clifford, M. N. (2000). Dietary hydroxybenzoic acid derivatives–nature, occurrence and dietary burden. *Journal of the Science of Food and Agriculture*, *80*(7), 1024-1032.

Jiang, Z., Wang, J., Xiang, D., & Zhang, Z. (2022). Functional properties and preservative effect of P-hydroxybenzoic acid grafted chitosan films on fresh-cut jackfruit. *Foods*, *11*(9), 1360.

Pei, K., Ou, J., Huang, J., & Ou, S. (2016). p-Coumaric acid and its conjugates: dietary sources, pharmacokinetic properties and biological activities. *Journal of the Science of Food and Agriculture*, *96*(9), 2952-2962.

Boz, H. (2015). p-Coumaric acid in cereals: presence, antioxidant, and antimicrobial effects. *International Journal of Food Science & Technology*, *50*(11), 2323-2328.

Maity, S., Kinra, M., Nampoothiri, M., Arora, D., Pai, K. S. R., & Mudgal, J. (2022). Caffeic acid, a dietary polyphenol, as a promising candidate for combination therapy. *Chemical Papers*, 1-13.

Chen, J. H., & Ho, C. T. (1997). Antioxidant activities of caffeic acid and its related hydroxycinnamic acid compounds. *Journal of agricultural and food chemistry*, *45*(7), 2374-2378.

Boz, H. (2015). Ferulic Acid in Cereals--a Review. *Czech Journal of Food Sciences*, *33*(1).

Nićiforović, N., & Abramovič, H. (2014). Sinapic acid and its derivatives: natural sources and bioactivity. *Comprehensive reviews in food science and food safety*, *13*(1), 34-51.

Rodriguez-Amaya, D. B. (2015). Carotenes and xanthophylls as antioxidants. In *Handbook of antioxidants for food preservation* (pp. 17-50). Woodhead Publishing.

Sheng, S., Li, T., & Liu, R. (2018). Corn phytochemicals and their health benefits. *Food Science and Human Wellness*, *7*(3), 185-195.

Ostlund Jr, R. E. (2002). Phytosterols in human nutrition. *Annual review of nutrition*, *22*(1), 533-549.

Siddiqui, S. A., Khan, S., Mehdizadeh, M., Bahmid, N. A., Adli, D. N., Walker, T. R., ... & Câmara, J. S. (2023). Phytochemicals and bioactive constituents in food packaging: A systematic review. *Heliyon*.

Chanioti, S., Katsouli, M., & Tzia, C. (2021). β-Sitosterol as a functional bioactive. In *A centum of valuable plant bioactives* (pp. 193-212). Academic Press.

Birger, M., Kaldjian, A. S., Roth, G. A., Moran, A. E., Dieleman, J. L., & Bellows, B. K. (2021). Spending on cardiovascular disease and cardiovascular risk factors in the United States: 1996 to 2016. *Circulation*, *144*(4), 271-282.

Mensah, G. A., Roth, G. A., & Fuster, V. (2019). The global burden of cardiovascular diseases and risk factors: 2020 and beyond. *Journal of the American College of Cardiology*, *74*(20), 2529-2532.

Li, Y., Li, T., & Liu, R. H. (2022). Bioactive compounds of highland barley and their health benefits. *Journal of Cereal Science*, *103*, 103366.

Dauchet, L., Amouyel, P., Hercberg, S., & Dallongeville, J. (2006). Fruit and vegetable consumption and risk of coronary heart disease: a meta-analysis of cohort studies. *The Journal of nutrition*, *136*(10), 2588-2593.

He, F. J., Nowson, C. A., Lucas, M., & MacGregor, G. A. (2007). Increased consumption of fruit and vegetables is related to a reduced risk of coronary heart disease: meta-analysis of cohort studies. *Journal of human hypertension*, *21*(9), 717-728.

Knekt, P., Jarvinen, R., Reunanen, A., & Maatela, J. (1996). Flavonoid intake and coronary mortality in Finland: a cohort study. *Bmj*, *312*(7029), 478-481.

Sesso, H. D., Gaziano, J. M., Liu, S., & Buring, J. E. (2003). Flavonoid intake and the risk of cardiovascular disease in women. *The American journal of clinical nutrition*, *77*(6), 1400-1408.

Boyer, J., & Liu, R. H. (2004). Apple phytochemicals and their health benefits. *Nutrition journal*, *3*, 1-15.

Toh, J. Y., Tan, V. M., Lim, P. C., Lim, S. T., & Chong, M. F. (2013). Flavonoids from fruit and vegetables: a focus on cardiovascular risk factors. *Current atherosclerosis reports*, *15*, 1-7.

Knekt, P., Kumpulainen, J., Järvinen, R., Rissanen, H., Heliövaara, M., Reunanen, A., ... & Aromaa, A. (2002). Flavonoid intake and risk of chronic diseases. *The American journal of clinical nutrition*, *76*(3), 560-568.

Widmer, R. J., Flammer, A. J., Lerman, L. O., & Lerman, A. (2015). The Mediterranean diet, its components, and cardiovascular disease. *The American journal of medicine*, *128*(3), 229-238.

Nordmann, A. J., Suter-Zimmermann, K., Bucher, H. C., Shai, I., Tuttle, K. R., Estruch, R., & Briel, M. (2011). Meta-analysis comparing Mediterranean to low-fat diets for modification of cardiovascular risk factors. *The American journal of medicine*, *124*(9), 841-851.

Milani, A., Basirnejad, M., Shahbazi, S., & Bolhassani, A. (2017). Carotenoids: biochemistry, pharmacology and treatment. *British journal of pharmacology*, *174*(11), 1290-1324.

Karppi, J., Kurl, S., Mäkikallio, T. H., Ronkainen, K., & Laukkanen, J. A. (2013). Serum β-carotene concentrations and the risk of congestive heart failure in men: a population-based study. *International journal of cardiology*, *168*(3), 1841-1846.

Siegel, R. L., Miller, K. D., & Jemal, A. (2019). Cancer statistics, 2019. *CA: a cancer journal for clinicians*, *69*(1), 7-34.

Siegel, R. L., Giaquinto, A. N., & Jemal, A. (2024). Cancer statistics, 2024. *CA: a cancer journal for clinicians*, *74*(1), 12-49.

Venugopal, R., & Liu, R. H. (2012). Phytochemicals in diets for breast cancer prevention: The importance of resveratrol and ursolic acid. *Food Science and Human Wellness*, *1*(1), 1-13.

Chen, H., & Liu, R. H. (2018). Potential mechanisms of action of dietary phytochemicals for cancer prevention by targeting cellular signaling transduction pathways. *Journal of agricultural and food chemistry*, *66*(13), 3260-3276.

Knekt, P., Järvinen, R., Seppänen, R., Heliövaara, M., Teppo, L., Pukkala, E., & Aromaa, A. (1997). Dietary flavonoids and the risk of lung cancer and other malignant neoplasms. *American journal of epidemiology*, *146*(3), 223-230.

Le Marchand, L., Murphy, S. P., Hankin, J. H., Wilkens, L. R., & Kolonel, L. N. (2000). Intake of flavonoids and lung cancer. *Journal of the National Cancer Institute*, *92*(2), 154-160.

Muller, A. G., Sarker, S. D., Saleem, I. Y., & Hutcheon, G. A. (2019). Delivery of natural phenolic compounds for the potential treatment of lung cancer. *DARU Journal of Pharmaceutical Sciences*, *27*, 433-449.

Boyle, S. P., Dobson, V. L., Duthie, S. J., Kyle, J. A. M., & Collins, A. R. (2000). Absorption and DNA protective effects of flavonoid glycosides from an onion meal. *European Journal of Nutrition*, *39*, 213-223.

Yuan, J. M., Stram, D. O., Arakawa, K., Lee, H. P., & Yu, M. C. (2003). Dietary cryptoxanthin and reduced risk of lung cancer: the Singapore Chinese Health Study. *Cancer Epidemiology Biomarkers & Prevention*, *12*(9), 890-898.

Shimazu, T., Inoue, M., Sasazuki, S., Iwasaki, M., Sawada, N., Yamaji, T., ... & Japan Public Health Center–based Prospective Study Group. (2010). Isoflavone intake and risk of lung cancer: a prospective cohort study in Japan. *The American journal of clinical nutrition*, *91*(3), 722-728.

Yang, J., & Liu, R. H. (2009). Synergistic effect of apple extracts and quercetin 3-β-D-glucoside combination on antiproliferative activity in MCF-7 human breast cancer cells in vitro. *Journal of agricultural and food chemistry*, *57*(18), 8581-8586.

Saeidnia, S., Manayi, A., Gohari, A. R., & Abdollahi, M. (2014). The story of beta-sitosterol-a review.
Awad, A. B., Chinnam, M. F. C. S., Fink, C. S., & Bradford, P. G. (2007). β-Sitosterol activates Fas signaling in human breast cancer cells. *Phytomedicine*, *14*(11), 747-754.
Muti, P., Awad, A. B., Schünemann, H., Fink, C. S., Hovey, K., Freudenheim, J. L., ... & Berrino, F. (2003). A plant food–based diet modifies the serum β-sitosterol concentration in hyperandrogenic postmenopausal women. *The Journal of nutrition*, *133*(12), 4252-4255.
Birben, E., Sahiner, U. M., Sackesen, C., Erzurum, S., & Kalayci, O. (2012). Oxidative stress and antioxidant defense. *World allergy organization journal*, *5*, 9-19.
Ezzati, M., Yousefi, B., Velaei, K., & Safa, A. (2020). A review on anti-cancer properties of Quercetin in breast cancer. *Life sciences*, *248*, 117463.
Liu, R. H., Liu, J., & Chen, B. (2005). Apples prevent mammary tumors in rats. *Journal of Agricultural and Food Chemistry*, *53*(6), 2341-2343.
Kim, H. J., Kim, S. K., Kim, B. S., Lee, S. H., Park, Y. S., Park, B. K., ... & Jung, J. Y. (2010). Apoptotic effect of quercetin on HT-29 colon cancer cells via the AMPK signaling pathway. *Journal of agricultural and food chemistry*, *58*(15), 8643-8650.
Eberhardt, M. V., Lee, C. Y., & Liu, R. H. (2000). Antioxidant activity of fresh apples. *Nature*, *405*(6789), 903-904.
Cohen, J. H., Kristal, A. R., & Stanford, J. L. (2000). Fruit and vegetable intakes and prostate cancer risk. *Journal of the National Cancer Institute*, *92*(1), 61-68.
Michels, K. B., Giovannucci, E., Chan, A. T., Singhania, R., Fuchs, C. S., & Willett, W. C. (2006). Fruit and vegetable consumption and colorectal adenomas in the Nurses' Health Study. *Cancer Research*, *66*(7), 3942-3953.
Freedman, N. D., Park, Y., Subar, A. F., Hollenbeck, A. R., Leitzmann, M. F., Schatzkin, A., & Abnet, C. C. (2008). Fruit and vegetable intake and head and neck cancer risk in a large United States prospective cohort study. *International journal of cancer*, *122*(10), 2330-2336.
Boffetta, P., Couto, E., Wichmann, J., Ferrari, P., Trichopoulos, D., Bueno-de-Mesquita, H. B., ... & Trichopoulou, A. (2010). Fruit and vegetable intake and overall cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Journal of the National Cancer Institute*, *102*(8), 529-537.
Tsuda, T., Horio, F., Uchida, K., Aoki, H., & Osawa, T. (2003). Dietary cyanidin 3-O-β-D-glucoside-rich purple corn color prevents obesity and ameliorates hyperglycemia in mice. *The Journal of nutrition*, *133*(7), 2125-2130.
Wu, T., Guo, X., Zhang, M., Yang, L., Liu, R., & Yin, J. (2017). Anthocyanins in black rice, soybean and purple corn increase fecal butyric acid and prevent liver inflammation in high fat diet-induced obese mice. *Food & function*, *8*(9), 3178-3186.
Wang, L. S., & Stoner, G. D. (2008). Anthocyanins and their role in cancer prevention. *Cancer letters*, *269*(2), 281-290.
De Stefani, E., Oreggia, F., Boffetta, P., Deneo-Pellegrini, H., Ronco, A., & Mendilaharsu, M. (2000). Tomatoes, tomato-rich foods, lycopene and cancer of the upper aerodigestive tract: a case-control in Uruguay. *Oral oncology*, *36*(1), 47-53.
International Diabetes Federation. (2019). IDF diabetes atlas, 9th edn. Brussels. *Belgium2015 [Available from: http://www. diabetesatlas. org*.

Bhatt, J. K., Thomas, S., & Nanjan, M. J. (2012). Resveratrol supplementation improves glycemic control in type 2 diabetes mellitus. *Nutrition research*, *32*(7), 537-541.

Ding, M., Pan, A., Manson, J. E., Willett, W. C., Malik, V., Rosner, B., ... & Sun, Q. (2016). Consumption of soy foods and isoflavones and risk of type 2 diabetes: a pooled analysis of three US cohorts. *European journal of clinical nutrition*, *70*(12), 1381-1387.