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THE ROLE OF PHYTOCHEMICALS IN THE MANAGEMENT OF LIFESTYLE DISORDERS

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ABSTRACT: *Phytochemicals are natural chemical constituents or bioactive compounds found in medicinal plants, aromatic plants, vegetables, fruits, leaves, flowers and roots which work in conjunction with nutrients and dietary fibers to act as defense against diseases and to slow the aging process. The medicinal values of plants lie in the abilities of these phytochemicals to produce definite physiological action on the human body. A variety of phytochemicals such as polyphenols, terpenoids, flavonoids, tannins, saponins, glycosides and steroids present in plants and their products are key factors in the treatment of several disorders including lifestyle disorders. Lifestyle disorders, also known as non-communicable diseases, are conditions associated with the way people live and behave. According to the World Health Organization (WHO) fact sheets, lifestyle disorders like obesity, diabetes, cancer, cardiovascular diseases, respiratory and gastrointestinal diseases account for 59 percent of the 56.5 million deaths annually and 45.9 percent of the global burden of disease (WHO, 2021). This review introduced and identified various phytochemicals reported with beneficial effects or roles and their functional classification or subclasses that have been identified to help prevent diseases associated with lifestyle changes.*

KEYWORDS: Cardiovascular diseases, Medicinal plants, Lifestyle disorders, Obesity, Phytochemicals.

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INTRODUCTION

Plants represent an enormous reservoir of biologically active compounds used in the treatment of various ailments from times immemorial. These plant constituents are divided into two groups: primary and secondary constituents, based on their functions in plant metabolism. The primary constituents are common sugars, amino acids, proteins and chlorophyll, while the secondary constituents, which are referred to as phytochemicals, are alkaloids, terpenoids, flavonoids, tannins, phenolic compounds, saponins, cardiac glycosides and many more (Adeyemi et al., 2023).

Phytochemicals are natural chemical constituents or bioactive compounds found in medicinal plants, aromatic plants, vegetables, fruits, leaves, flowers and roots which work in conjunction with nutrients and dietary fibers to act as a defense against diseases and to slow the aging process (Adeyemi et al., 2023). The medicinal values of plants lie in these phytochemicals which produce definite physiological action on the human body. A variety of phytochemicals such as polyphenols, alkaloids, terpenoids, flavonoids, tannins, saponins, glycosides, steroids and proteins present in plants and their products are key factors in the treatment of several disorders including lifestyle disorders. The emergence of phytochemicals with health benefits offers an excellent opportunity to improve health and disease conditions and has received much attention in recent years from scientific community, consumers and health care providers as they are being identified and characterized with scientific evidence to support their concept of health promotion.

Lifestyle disorders, also known as non-communicable diseases, are conditions associated with the way people live and behave. As opposed to infectious diseases, they are caused by lack of physical activity, unhealthy eating, alcohol, substance use disorders and smoking tobacco, which can lead to heart disease, stroke, obesity, type II diabetes, and lung cancer (Mathur et al., 2019). According to the World Health Organization (WHO) fact sheets, lifestyle disorders such as diabetes, obesity, cardiovascular diseases, cancer, osteoporosis, respiratory diseases and gastrointestinal diseases account for 59 percent of the 56.5 million deaths annually and 45.9 percent of the global burden of disease (WHO, 2021). Lifestyle and diet are major factors thought to influence susceptibility to many diseases. Other factors such as drug abuse, tobacco smoking and alcohol drinking as well as lack of exercise are associated with risk of developing certain diseases especially at later life. Lifestyle disorder arising from changes in lifestyle, such as increased affluence and urbanization, is associated with increased onset of chronic diseases such as obesity and cardiovascular disease (Farhud, 2015).

Phytochemicals and Lifestyle Disorders

Phytochemicals for Diabetes

Phytochemicals derived from plants have been used ethno-medicinally for the prevention and/or treatment of diabetes due to the extended belief of their therapeutic properties and safety (Bacanli et al., 2019). Diabetes mellitus is a chronic metabolic disease characterized by elevated levels of blood glucose, insufficiency in production and action of insulin. It is reported that approximately 80% of diabetic patients rely on herbal medicine for successive treatment (Kifle, 2021). Diabetes mellitus is associated with increased formation of free radicals and decreased antioxidant potential (Gaikwad et al., 2014) and the seventh leading cause of death worldwide (Bacanli et al., 2019; Thent & Latiff, 2018). Medicinal plants' phytochemicals are

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used alone or in combination with antidiabetic drugs (Ezuruike & Prieto, 2014) and these phytochemicals present an exciting opportunity for the development of new types of therapeutics for diabetes mellitus (Gaikwad et al., 2019; Krawczyk et al., 2023). Phytochemicals which can exert antioxidant and free radical scavenging activities are suggested to improve the insulin sensitivity. Studies (Chanwitheesuk et al., 2005; Bacanli et al., 2019) have shown that phytochemicals showed protective effects against oxidative stress mediated diseases including diabetes and can prevent the formation of Advanced Glycation End-Products (AGEs) and other diabetic complications associated with high oxidative stress conditions (Rahimi et al., 2005). Antioxidant phytochemicals such as allicin, cinnamic acids, coumarins, diterpenes, flavonoids, lignans, monoterpenes, phenylpropanoids, tannins and triterpenes can be found in all parts of plants like wood, bark, stems, pods, leaves, fruit, roots, flowers, pollen and seeds in high concentrations (Table 1, Figure 1).

Table 1: Main phytochemicals, their plants of origin and major health effects (Ban Canli et al., 2019)

Phytochemicals	Plants of Origin	Health Effects
Quercetin	Onion Apple Berries Many nuts Brassica *Piper sarmentosum* *Ficus racemose*	Antihyperglycemic effects Antioxidant effects Ameliorative effects on diabetic complications
Kaempferol	*Ficus racemose*	Antihyperglycemic effects Antioxidant effects
Naringenin	*Ficus racemose*	Antihyperglycemic effects Antioxidant effects
Baicalein	*Ficus racemose*	Antihyperglycemic effects Antioxidants effects
Glabridin	*Glycyrrhiza spp*	Antihyperglycemic effects Antioxidants effects
Magniferi	Mango	Antidiabetic effects Anticancer effects Antiviral effects Antiaging effects Antioxidant effects
Momorcharins Momordin Charantin Goyasaponins	*Momordica charantia*	Antihyperglycemic effects Antioxidant effects Ameliorative effects on diabetic complication
Ginsenosides	*Panax ginseng*	Antidiabetic effects
Oleanolic acid	*Olea europaea*	Antihyperglycemic effects
Limonene	*Citrus* plants	Antihyperglycemic effects Antioxidant effects Ameliorative effects on diabetic complications
Ursolic acid	*Malus pumila*	Antihyperglycemic effects

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	Ocimum basilicum *Vaccinium spp* *Vaccinium macrocarpon* *Olea europaea* *Origanum vulgare* *Rosmarinus officinalis* *Salvia spp* *Thymus spp.*	Antioxidant effects Ameliorative effects on diabetic complications
Cinnamic acid	Blueberry Kiwi Cherry Plum Apple Pear Chicory Artichoke Coffee *Cinnamonum cassia*	Antihyperglycemic effects Antioxidant effects Ameliorative effects on diabetic complications
Cinnamaldehyde	*Cinnamomum cassia*	Antihyperglycemic effects Ameliorative effects on diabetic complications
Curcumin	*Curcuma longa*	Antihyperglycemic effects Antioxidant effects Ameliorative effects on diabetic complications
Resveratrol	Grapes Cranberries Blueberries	Antihyperglcemic effects Antioxidant effects Ameliorative effects on diabetic complications
Naringin	Tomatoes Grapefruits *Citrus* plants	Antihyperglycemic effects Antioxidant effects Ameliorative effects on diabetic complications
Catechins	Cocoa	Antihyperglycemic effects Antioxidant effects Ameliorative effects on diabetic complications

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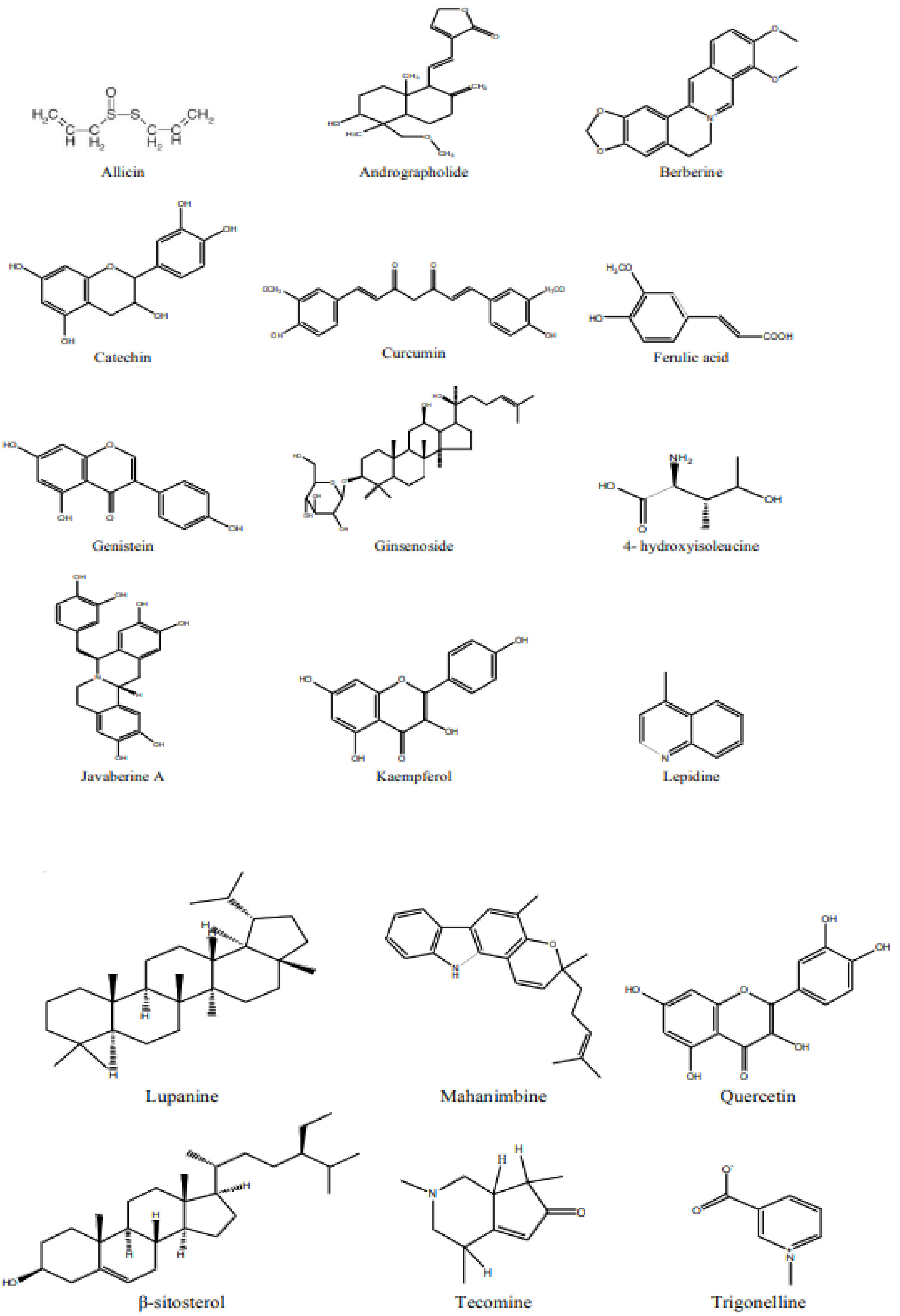

Figure 1: Structures of Important phytochemicals for diabetes management (Gaikwad et al., 2014)

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Phytochemicals for Obesity

Obesity termed as the "New World Syndrome" (Nammi et al., 2004) is considered a global problem by the World Health Organization (WHO, 2014) that over 1.4 billion adults aged twenty and older were overweight, among whom almost 300 million women and more than 200 million men were obese (Seyedan et al., 2015). Also, it is estimated that 58% of the world population will become obese by 2030 (Tremmel et al., 2017). Obesity is increased energy intake than energy expenditure resulting in fat deposition and weight gain to an extent where health may be impaired (Muller et al., 2021; WHO, 2014). Many medications have been employed in the treatment and management of obesity over the years. However, despite the unescapable progression of these disease and the promising results of some drugs on lowering body weight and adjustment of numerous cardio-metabolic factors in the past few years, most of the approved anti-obesity drugs have been withdrawn from the market due to serious side effects (Seyedan et al., 2015; Kang & Park, 2012).

Anti-obesity drugs may operate through catecholamine releasing agents such as amphetamine, phentermine, and related substituted amphetamines (e.g., bupropion) which act as appetite suppressants, increasing body metabolism, interfering with the ability of the body to absorb specific nutrients in food and inhibiting enzymes involved in fat absorption. Development of nutrient digestion and absorption of enzyme inhibitors are considered important strategies in the effort to decrease energy intake via gastrointestinal mechanism. Due to these adverse effects of anti-obesity drugs, it is crucial to discover novel inhibitors derived from natural sources (Birari & Bhutani, 2007; Mohammed et al., 2014), particularly plants containing phytochemicals that are not associated with side effects (Sharma & Kanwar, 2018). The potential sites targeted by these phytochemicals include the brain to alter neural signals related to hunger, the gastrointestinal tract involved in nutrient absorption and adipose tissue that plays a vital role in fat storage and degradation. Dietary phytochemicals have been reported to target different stages of the adipocytes (fat cells) life cycle (Williams et al., 2013). These dietary phytochemicals such as polyphenols acts by inducing apoptosis of fat cells, lipolysis and inhibition of inflammation. Based on the possible mode of action to combat obesity, phytochemicals are classified into six major types: (1) lipase inhibitors, (2) appetite suppressants, (3) energy expenditure regulators (thermogenesis), (4) lipid metabolism regulators, (5) adipocyte differentiation regulators and (6) other phytogenic compounds (Balaji et al., 2015) (Figure 2).

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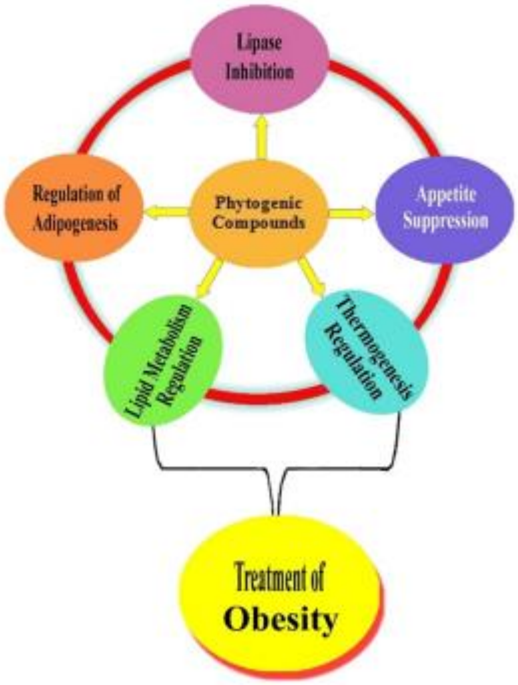

Figure 2: Phytochemicals and the major possible target to contain obesity (Balaji et al., 2015)

Phytochemicals for body weight control strategies could be outlined as: i) inhibition of food intake, by inhibiting orexigenic signals or enhancing anorexigenic signals, and limiting the bioavailability of macronutrients, ii) decrease in the caloric content of foods, by substituting sugar or fat less caloric or less digestible substances, iii) stimulation of energy expenditure (thermogenesis), iv) regulation of nutrient partition between tissues and not favoring the efficiency of fat deposition processes. (Manjula & Suneetha, 2011).

Phytochemicals with Anti-obesity Potential

Phytochemicals that have been found in plants and appeared to possess anti-obesity properties as depicted in Figure 2 are:

Flavonoids

Flavonoids are a group of plant metabolites containing 15 carbon (C) atoms. Flavonoids are gaining interest because of their potential role in the prevention of diseases such as obesity, cancer, gastrointestinal, cardiovascular and neurodegenerative diseases (Fernandes et al., 2017). Flavonoids such as quercetin show anti-lipase activity by preventing adipogenesis and inducing cell death in mouse pre-adipocytes (Fang et al., 2008; Zheng et al., 2010); Kaempferol extracted from *Bauhinia sp* leaves reduces hyperglycemia (Jorge et al., 2004); and Isorhamnetin found in *Ginkgo biloba, Hippophae sp, Oenanthe javanica* and *Opuntia ficus-indica* possess anti-obesity activities (Rodriguez-Rodriguez et al., 2015).

Alkaloids

Alkaloids are a class of naturally occurring secondary metabolites with more than 2000 known compounds, mostly containing basic nitrogen atoms. Alkaloids such as synephrine from *citrus aurantium*; piperine from *Piper nigrum*; piperlongumine from *Piper longum*; and liensinine,

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isoliensinine, neferine and nuciferine from *Nelumbo nucifera* have shown potential effects on obesity (Acharya & Shrivastava, 2008). Caffeine and chlorogenic acid are the principal constituents of green coffee bean extract which causes reduction in body mass and body fat due to decrease in the absorption of glucose. Decrease in glucose absorption eventually causes an increase in the utilization of fats reserves, due to the reduced availability of glucose as an energy source (Tajik et al., 2017).

Phenols

Phenols such as p-coumaric, cafferic, ferulic, cinnamic, ellagic and p-hydroxybenzoic acids have been shown to modulate physiological and molecular pathways that are involved in energy metabolism, adiposity and obesity (Son et al., 2010; Krawczyk et al., 2023). Simple phenolic acids are non-flavonoid phenolic compounds which conjugate with other phytochemicals such as flavonoids, alcohols, hydroxy fatty acids, sterols, and glucosides. Ferulic acid has hypocholesteremic and hypoglycemic effects, and thus, it could be effective in lowering the risk of high fat diet-induced obesity (de Melo et al., 2017; Jin Son et al., 2010). Chlorogenic acid and coumaric acid cause significant inhibition of cell growth and enhance apoptosis.

Phytosterols

Phytosterols are structurally similar to mammalian cell-derived cholesterol (Gupta et al., 2011). Phytosterols exist in both esterified and free alcohol forms. Phytosterols that appear to reduce obesity include diosgenin, campesterol, brassicasterol, sitosterol, stigmasterol and guggulsterone. High intakes of these compounds decrease low density lipoprotein-cholesterol levels. In the intestinal lumen, phytosterols compete with cholesterol for micelle formation and thus effectively inhibit cholesterol absorption (Izar et al., 2011). Their influence on intestinal genes and transcription factors make phytosterols the key regulators in metabolism and cholesterol transport in the expression of liver genes (Jesch et al., 2008).

Terpenoids

Terpenoids (isoprenoids) are chemically modified terpenes and comprise more than 40,000 compounds of both primary and secondary metabolites. Terpenoids such as gymnemic acid from *Gymnerma sylvestre*, oleanolic acid from *Panax ginseng* and corosolic acid from *Lagestroemia speciose* have potential therapeutic effects on obesity (Osman et al., 2010). Peroxisome Proliferator-Activated Receptors (PPAR) activation attenuates obesity and type-2 diabetes. Geranylgeraniol, farnesol and geraniol terpenoids are ligands with the potential to activate PPAR and dietary lipid sensors that control energy homeostasis, as well as lipid and carbohydrate disorders (Goto et al., 2010).

Phytochemicals as Pancreatic Lipase Inhibitors

One of the strategies used to combat obesity is by interfering at the gastrointestinal level through the inhibition of specific enzymes like lipase and amylase. Lipase is a digestive enzyme, a subclass of the esterases (triacylglycerol hydrolase E.C. 3.1.1.3) that catalyzes the hydrolysis of ester bonds in water-insoluble lipid substrates. Lipase performs essential roles in digestion, and processing of dietary lipids (e.g., triacylglycerols, fats and oils) to monoglycerides and free fatty acids in humans. The decreased digestion and absorption of ingested fats leads to overall decreased caloric absorption leading to decreased obesity (Tsujita

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et al., 2006; Balaji et al., 2015). Currently, there are few drugs which can interact with lipases and inhibit their action. Orlistat's lipase inhibitory activity occurs through a covalent bond at the lipase's active site (serine) and has been associated with serious side effects. Therefore, focus on screening novel side effects-free lipase inhibitors derived from plants and other natural sources are essential. Plant phytochemicals provide pancreatic lipase inhibitors with potential for development into clinical products (Table 2).

Table 2: Medicinal plants and their active components with lipase inhibitory activity

Plant	Used parts	Active components	References
Salix masudama	Leaf	Polyphenol fraction	Han et al., 2003
Aesculus turbinata	Seed	Aesin/escin	Kimura et al., 2006
Coffea canephora		Caffeine, chlorogenic acid, neochlorogenic acid, feruloylqurinic acid	Shimoda et al., 2006
Xylopia aethiopica	Fruit	Aqueous extract	Etoundi et al., 2010
Scorodophloeus zenkeri	Husk, Seed	Aqueous extract	Etoundi et al., 2010
Baccharis trimera	Stem	Methanolic extract	Souza et al., 2011
Murraya koenigii (L.)	Spreng leaves	Mahanimbine	Rahul et al., 2010
Aronia melanocarpa (L.)	Water extract	Anthocyanidin	Worsztynowicz et al., 2014
Black berry	Stem bark	Ellagic acid	Lei et al., 2007
Pomegranate leaf		Platicodin saponins	Xu et al., 2005
Platycodi radix	Bark	Ethanolic extract	Kim & Kang 2005
Juniperus communis	Wood	Water extract	
Illicium religiosum	Rhizomes	Chikusetsu saponins	Han et al., 2005
Panax japonicas	Bark, Seed	Ethanolic extract	Sharma et al., 2005; Moreno et al., 2006
Vitis vinifera	Leaves	Ethanolic extract	Sharma et al., 2005
Cudrania tricuspidata	Seeds	Methanolic extract	Jo et al., 2017
Eisenia bicyclis	Brown algae	Phloroglucinol derivatives	Eom et al., 2013
Opuntia ficus-indica	Fructus	Aqueous extract	Padilla-Camberos et al., 2015
N. nucifera petal	Petals	Methanol extract	Ono et al., 2006
Aframomum melegueta, Spilanthes acmella	-	Crude ethanolic extract	Ekanem et al., 2007
Camellia sinensis, Theaceae	Tea	EGCG	Groove et al., 2012
Salacia reticulate	Nut	(-).4-O-methylepigallocatechin	Kishino et al., 2006
Millettia pinnata	Bark	Aqueous extract	Hari et al., 2013

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Terminatia paniculata	Bark	Ethanolic extract	Mopuri & Meriga, 2014
Oolong tea	Leaves		Zhu et al., 2015
Phragmanthera incana	Leaves	Methanolic extracts	Adeyemi, 2023; 2024

Phytochemicals and Cardiovascular Disease

Cardiovascular disease accounts for roughly 20% of all deaths per year worldwide in both developed and developing countries (Vasanthi et al., 2012). Lifestyle factors including a diet high in saturated fat, energy and in cholesterol, have a crucial part in the onset of Cardiovascular Disease (CVD) risk. Epidemiological studies examining CVD risks in different populations have observed a positive correlation between elevated levels of low density lipoprotein-cholesterol and development of CVD as well as low levels of high density lipoprotein-cholesterol and CVD (Liu et al., 2023; Hsu et al., 2019; Wen et al., 2019; Saito et al., 2020; Al-Shoabi et al., 2023; Razavi et al., 2024; Ren & Wang, 2023). Consuming a diet rich in natural antioxidants has been associated with prevention from and/or treatment of CVD. Bioactive components of food, which are of special interest, include Vitamins E and C, polyphenols, carotenoids (mainly lycopene and β-carotene), and coenzyme Q10, featured by their antioxidant properties. (Islam et al., 2021). A number of bioactive compounds generally obtained from plants, such as icariin, isoflavones, diosgenin, resveratrol, quercetin, catechin, sulforaphane, tocotrienols and carotenoids, are proven to reduce the risk of cardiovascular diseases and aid cardioprotection (Zheng et al., 2022; Guan et al., 2021). The cardioprotective effects of the various phytochemicals are perhaps due to their antioxidative, antihypercholesterolemic, antiangiogenic, anti-ischemic, inhibition of platelet aggregation and anti-inflammatory activities that reduce the risk of cardiovascular disorders (Al-Shoabi et al., 2023; Vasanthi et al., 2012; Islam et al., 2021; Zeng et al., 2022).

Phytochemicals and Cancer

Cancer is a condition where the body cells multiply in an uncontrollable manner, one of the leading causes of death worldwide, killing approximately 9.6 million people annually despite significant advancements in its treatment over the past decades (Khatoon et al., 2022). Dietary factors are thought to account for about 30% of cancers as diet is second only to tobacco as a potentially preventable cause of cancer (Zam & Hassan, 2019). The contribution of diet to risk of cancer in developing countries is lower around 20% (Padala et al., 2020). Dietary antimutagens which may provide a means of slowing progression towards cancer have been identified such as certain types of dietary fibers, certain probiotics or dietary phytochemicals acting as antioxidants, which include curcumin, ascorbic acid, vitamin E, various polyphenols and carotenoids (George et al., 2021; Xiao & Bai, 2019). Phytochemicals such as curcumin, resveratrol, tocotrienol, and quercetin have emerged as potential chemosensitizing agents in cancer cells due to their less toxic and multitargeted properties. Preclinical and clinical studies enumerated their potential to prevent drug resistance and sensitize cancer cells to chemotherapeutic agents by modulating several genes/proteins or pathways that regulate the key factors during the growth and progression of tumors such as inhibition of anti-apoptotic proteins, activation of pro-apoptotic proteins, reduced expression of different transcription factors, chemokines, enzymes, cell adhesion molecules, protein tyrosine kinases, and cell cycle regulators (George et al., 2021; Khatoon et al., 2022).

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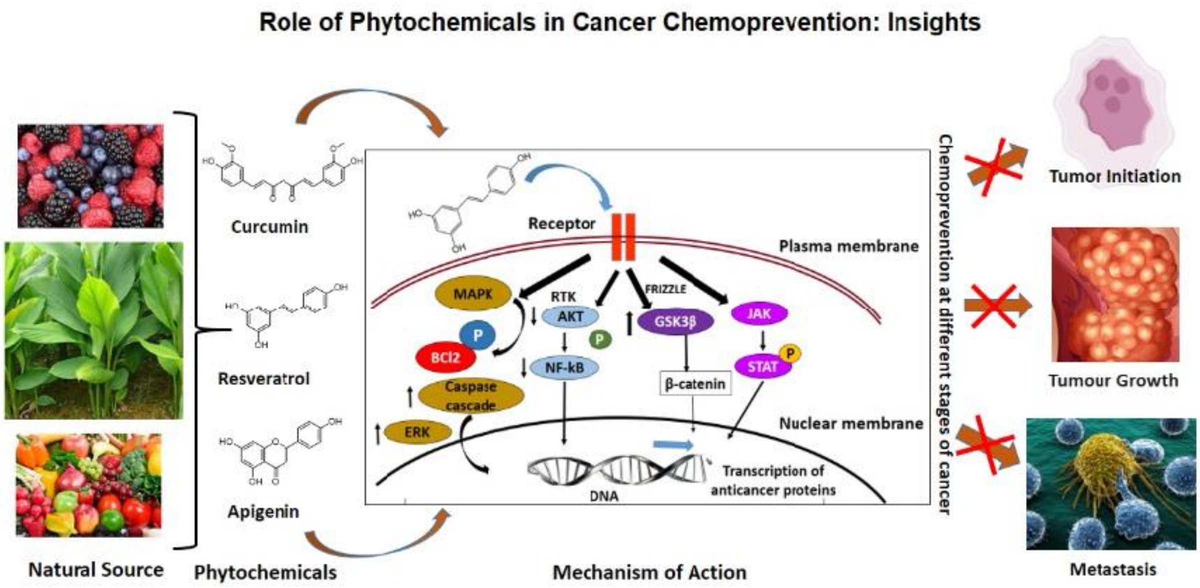

Figure 3: Role of phytochemicals in cancer chemoprevention: Insights (George et al., 2021)

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