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Review

Role of Phytonutrients in the Prevention and Treatment of Chronic Diseases: A Concrete Review

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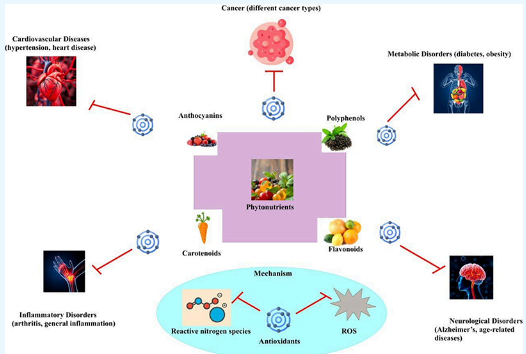
ABSTRACT: Delving into the intricate role of phytonutrients is paramount to effectively preventing and treating chronic diseases. Phytonutrients are "plant-based nutrients" that positively affect human health. Phytonutrients perform primary therapeutic functions in the management and treatment of various diseases. It is reported that different types of pathogenesis occur due to the excessive production of oxidants (reactive nitrogen species and reactive oxygen species). The literature shows that a higher intake of fruits, vegetables, and other plant-based food is inversely related to treating different chronic diseases. Due to many phytonutrients (antioxidants) in fruits, vegetables, and other medicinal plants, they are considered major therapeutic agents for various diseases. The main purpose of this review is to summarize the major phytonutrients involved in preventing and treating diseases. Fourteen major phytonutrients are discussed in this review, such as polyphenols, anthocyanin, resveratrol, phytosterol (stigmasterol), flavonoids, isoflavonoids, limonoids, terpenoids, carotenoids, lycopene, quercetin, phytoestrogens, glucosinolates, and probiotics, which are well-known for their beneficial effects on the human body and treatment of different pathological conditions. It is concluded that phytonutrients play a major role in the prevention and treatment of diabetes mellitus, obesity, hypertension, cardiovascular disorders, other types of cancers, neurological disorders, age-related diseases, and inflammatory disorders and are also involved in various biological activities.



■ INTRODUCTION

Chronic diseases are multifaceted challenges, but a promising solution lies in the realm of phytonutrients. These natural compounds, found abundantly in plants, play a pivotal role in preventing and treating chronic illnesses.[1,2] Phytonutrients encompass a diverse array of compounds, including flavonoids, carotenoids, polyphenols, and more, each with unique health benefits. Flavonoids, for instance, possess potent antioxidant properties that combat oxidative stress, reducing the risk of heart disease and cancer.[3] Carotenoids such as beta-carotene bolster immune function and promote eye health. Meanwhile, polyphenols found in foods like green tea and berries exhibit anti-inflammatory and anticancer properties.[4] Understanding the role of these phytonutrients is essential in crafting effective dietary and therapeutic strategies for chronic disease management. Incorporating a variety of plant-based foods into one's diet can provide a rich source of these compounds, offering a holistic approach to improving health and mitigating the burden of chronic diseases.[1]

Major nutrients present in food are macronutrients (protein, carbohydrate, and fats) and micronutrients (minerals and vitamins) that perform important functions in maintaining human health. Some biologically active components in the food, known as phytochemicals or phytonutrients, also play a necessary role in human health.[5] Phytonutrients are plant-based nutrients, also known as phytochemicals, which have important positive effects on human health. They support the health and regular functioning of the human body and increase life span. Phytonutrients perform major therapeutic functions in the management and treatment of various diseases. Various types of uninvestigated species of plants are also other sources of nutrients and biologically active phytochemicals with different healthful effects.[6,7] These plant-based phytochemicals work as an attractant for pollination and protect from pests and insects' assaults and also protect from different stresses like ultraviolet radiation.[8] Moreover, phytochemicals involved in the aroma, flavor, and color of the plants are also identified as having promising nutritional value and being good for human health. These phytochemicals are present in our daily diet by

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Table 1. Structures of Various Phytochemicals

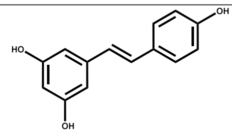
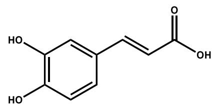
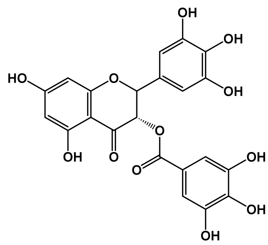
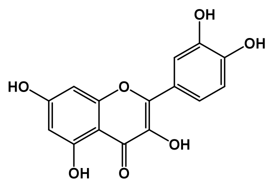
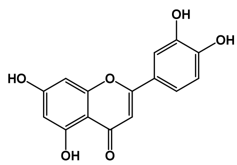
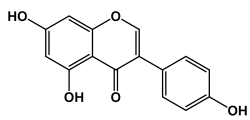
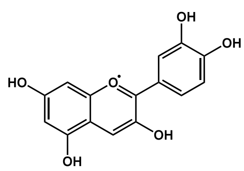
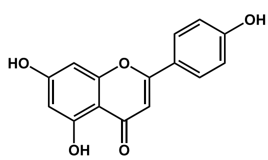
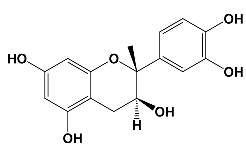
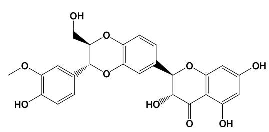
Category		Phytochemical	Structure	Reference
Polyphenols	Stilbene	Resveratrol		39
	Phenolic acid	Caffeic Acid		40
		Epigallocatechin-3-gallate		39
	Flavonoids	Quercetin (flavonols)		40
		Luteolin		39
		Genistein (Isoflavones)		41
		Cyanidin (Anthocyanin)		40
		Apigenin (Flavone)		40
		Catechin (Flavanols)		40
		Silymarin and Silibinim		39

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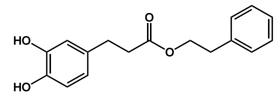
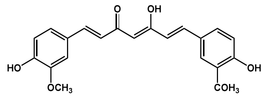
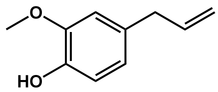
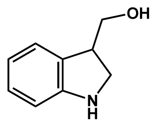
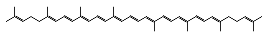
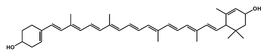
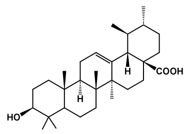
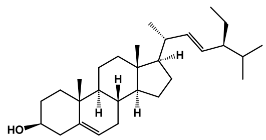
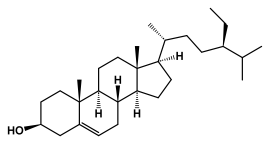
Table 1. continued

Category	Phytochemical	Structure	Reference
Phenolic compounds	Caffeic acid phenethyl ester		39
	Capsaicin		39
	Curcumin		39
	Eugenol		39
Organosulfur	Indole-3-carbinol		39
Carotenoids	Lycopene		40
	Lutein		40
Terpenoid	Ursolic acid		39
Phytosterol	Stigmasterol		14
	β- Sitosterol		14

consuming vegetables, fruits, grains, legumes, beans, nuts, tea, herbs and coffee.[9] Mainly, phytonutrients are terms that deal with different types of plant-based compounds or nutrients. They play important therapeutic functions, for example, antioxidative, anti-inflammatory, antimutagenic and anticarcinogenic activities.[10] The tradition of treating different disorders through various medicinal plants is older than civilization.[11] Multiple studies have demonstrated a clear correlation between the higher intake of plant-derived products and reduced risk of chronic diseases and mortality. Phytonutrients serve as antioxidants carrying out protective functions in the body.[12,13]

Phytonutrients are essential secondary metabolites, and these nutrients are also related to the different classes of the phytochemicals. Various major classes of phytochemicals have tremendous health benefits, for example, carotenoids, anthocyanins, flavonoids and isoflavonoids, lignins and neolignans, diarylalkanoids, polyphenols, tannins, phenolic acids and sterols.[14,15] However, phytonutrients such as polyphenols, phytoestrogen, glucosinolates, and carotenoids are not as essential as macro- and micronutrients. Still, they are beneficial for preventing and treating chronic diseases and keeping our body fit. Various highly nutritious fruits have many phytonutrients and micronutrients, such as grapes, guava, amla, and kokum. The health of young adults and antioxidant status can be improved through the usual intake of these fruit-based drinks.[16] The high variety of phytonutrient consumption depends mostly on the availability and affordability of healthful plant products. A research project has estimated that the balanced French diet contains 7 phytonutrients that effectively meet the requirements of both macronutrients and micronutrients. Furthermore, this diet is beneficial for maintaining optimal health.[17] More than 25,000 phytonutrients are determined from plant-based food products such as carotenoids, flavonoids, anthocyanins, phenolic acid, polyphenols, sterols, and terpenes. Phytonutrients' major beneficial functions stem from inherent antioxidative properties.[14,18] Polyphenols, flavonoids, isoflavones, carotenoids, phenolic acids, stilbenoids, coumarins, indoles, lignin, catechins, organosulfur, anthraquinones, procyanidins, isothiocyanates, ginsenosides, saponins, phenylpropanoids, etc. are the most common phytochemicals.[19,20]

The literature shows that a higher intake of fruits, vegetables and other plant-based food is inversely related to treating

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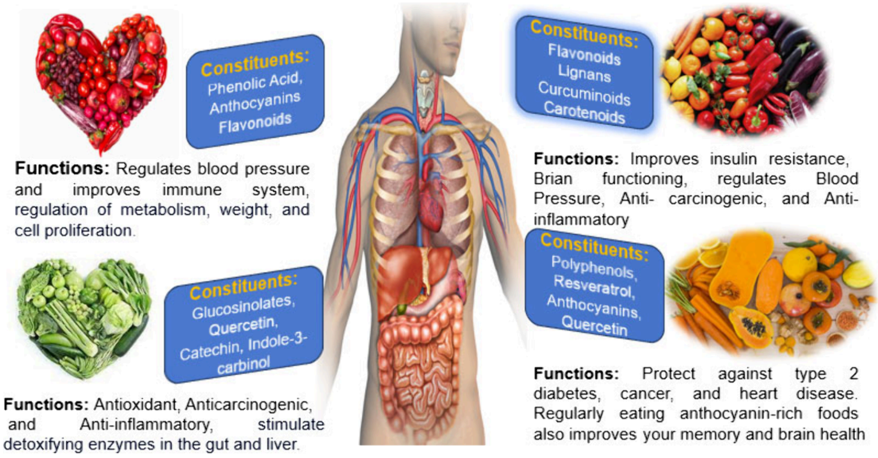

Figure 1. Bioactive constituents from different food sources and their functions in the human body.

different chronic diseases and is responsible for the health benefits.[21] In recent years, there has been a growing use of phytonutrients and nutraceuticals for the purpose of preserving immunological health.[22,23] It is observed that the parameters of antioxidant levels are reduced in patients with diabetes mellitus. According to different studies, phytochemicals are recommended to improve and overcome insulin sensitivity due to the phytochemical antioxidant level and free radical scavenging activities.[24,25] To address the complexities of diabetes, a range of photoactive substances such as flavonoids and propenylphenols are employed.[26,27] Phytonutrients are used for the antimicrobial effect, antioxidative effect, modulation of hormone metabolism and detoxification enzymes to reduce platelet aggregation and stimulation of the immune system.[28] Phytochemicals can detoxify substances that are carcinogenic, are antimutagenic, and have strong chemoprotective properties.[29,30]

The antioxidants and phytonutrient's dietary sources may positively and healthfully affect managing oxidative stress, neurological diseases, cardiovascular disorders, and cancer. Flavonoids, phenolic acids, and carotenoids are usually present in plant-based food items. These phytonutrients have powerful antioxidant characteristics and save cells from further harm, decreasing the hazard of CVD and Alzheimer's disease. Mostly obesity depends on physical inactivity and dietary intake, and the risk of obesity is reduced by using plant-derived dietary sources because it alters the lipid composition and metabolism.[31,32] Taking a healthy diet high in antioxidants and anti-inflammatory phytonutrients primarily prevents neurodegenerative disorders, which is one of the least expensive and most healthful solutions to overcome these kinds of problems.[33] Phytochemicals and polyunsaturated fatty acids obtained from walnuts have numerous health benefits and mainly play a role in the betterment of brain functioning.[34] Amaranth seeds and quinoa seeds have many health benefits, specifically in the reduction of oxidative stress-related problems such as cancer, diabetes, obesity, and cardiovascular disorders. The health benefits of amaranth and quinoa seed depend on the composition of their phytonutrients and the anti-inflammatory and antioxidant activities of the lipophilic (for example, fatty acids, carotenoids and tocopherols) and hydrophilic (for example, betacyanins and phenolic) nutrients.[35,36] Gastrointestinal disorders such as dyspepsia, irritable bowel syndrome, and functional constipation have been increasingly common in the past several years. Consuming biologically active dietary ingredients, such as phytochemicals and probiotics, has been shown in recent research to be effective in the treatment of the aforementioned conditions.[37,38] The objectives of this review are to comprehensively assess existing scientific literature on the role of phytonutrients in preventing and treating chronic diseases, evaluate the mechanisms by which phytonutrients impact health, assess their efficacy in lowering the risk of chronic diseases, and provide concrete recommendations for their incorporation into dietary and therapeutic strategies.

Major Phytonutrients and Their Health Benefits.

Polyphenols. The structures of various phytochemicals are presented in Table 1. Polyphenol is the most critical and very well-known phytonutrient.

It is a secondary metabolite with various unique bioactive characteristics that make it highly recommended for the positive health effects of plants and humans. Polyphenols are different compounds with respect to their structure but are necessary for the various functions in plants and provide the organoleptic and nutritional characteristics to plant-based foods. These polyphenols play a vital role in the betterment of the human body.[42,43] These are the naturally occurring components formed in plants with different chemical structures and features, eliciting powerful antioxidative properties. Polyphenols have two phenyl rings and one or more hydroxyl substituents.[44] The intake of Mediterranean or Asian diets has significant health effects due to the presence of many polyphenols in these diets. There is a relationship between the plant polyphenols and homeostatic systems of a cell which have protests, metabolic and redox equilibrium and inflammatory responses, establishing the different health effects.[45,46] Figure 1 presents the bioactive constituents from different food sources and their functions in the human body.

Polyphenols are a group of different phytonutrients with several health benefits. Other groups of polyphenols are divided according to the number of phenolic rings. Flavonoids are subclassified into many flavones, isoflavones, flavanols/catechins, flavonols/flavan 3 oil, anthocyanidins or anthocyanins, and chalcones. Non-flavonoids polyphenols are subclassified as stibenes, coumarins, tannins, benzophenones, diferuloylmethanes, secoriridoids and phenolic acids etc.[47,48] Polyphenols, including phenolic acids, can be found in a wide range of foods such as cereals, legumes, fruits, vegetables, chocolates, and beverages like tea, coffee, and wine, as well as in foods like artichokes, wheat flour, onions, apples, kiwis,

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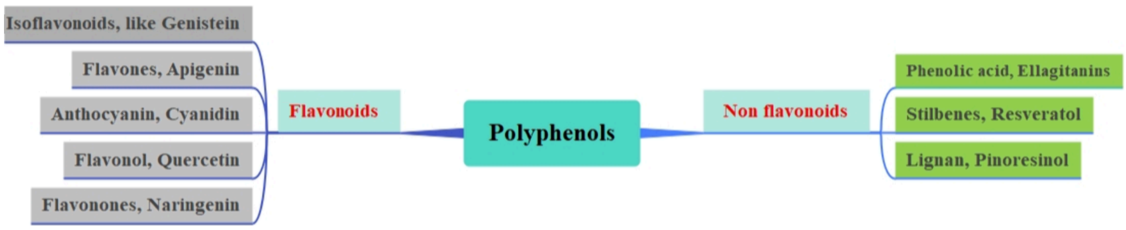

Figure 2. Classification of polyphenols phytonutrients.

berries, citrus fruits, and tropical fruits.[49−51] Polyphenols-rich foods and their extracts are useful and inversely related to the prevention and treatment of various diseases such as metabolic syndrome and some components, different types of cancers, cardiovascular disorders, and neurodegenerative diseases and are useful for their antioxidant and chemopreventive functions.[52,53] Different polyphenol compounds are utilized to prevent and stop the development and prognosis of cancer; for example, green tea has the polyphenols epigallocatechin 3 O gallate, resveratrol and curcumin.[54,55] Polyphenols also work as therapeutic agents in various autoimmune diseases.[56,57] The antioxidant and anti-inflammatory functions of polyphenols have advanced our knowledge in managing gut microbiota.[58] Various studies of plants and plant extracts have shown that polyphenols have powerful beneficial health effects in the prevention and management of several chronic diseases such as inflammation, CVDs, neurological diseases, and cancers.[59] As shown in Figure 2, polyphenols are classified into two groups: flavonoid and non-flavonoid molecules.[60]

Resveratrol. Resveratrol is a notable polyphenolic stilbene.[61] It plays positive health effects against different pathways such as angiogenesis, apoptosis, oxidative stress, inflammation and mitochondrial stress.[62,63] NADPH oxidase mediated formation of reactive oxygen species through lowering activities and oxidase expression is inhibited by resveratrol. Resveratrol decreases the generation of mitochondrial superoxide by stimulating the biogenesis of mitochondria. On the other hand, resveratrol also prevents or inhibits the production of superoxide from the uncoupled endothelial NO_2 synthase. It also increases the regulation of tetra-hydro biopterin synthesizing enzyme GTP cyclopyrrolone I (GTPCH-I).[64] Stilbene sources are grapes and wines. Dark chocolate, berries, apples, tomatoes, pistachios and peanuts also have minor amounts.[65] Other sources of resveratrol are jackfruits, cacao, blackberries, cranberries and grapes.[66] Various in vitro and animal studies also defined the role of resveratrol in the prevention of breast cancer, prostate cancer, colon cancer, and lung cancer. Resveratrol is also adopted as a therapeutic support in cancer treatments, for example, radiotherapy.[67] Resveratrol is a phytonutrient which works as an antioxidant, antiaging, antidiabetic, antiobesity, anticancer, neuroprotective, antiatherosclerotic and cardioprotective agent.[68] It also plays an effective role in inflammatory diseases and neurodegenerative diseases.[69] Resveratrol has enhanced exercise performance, increased insulin sensitivity, and mimicked the effects of calorie restriction. It also lowers body fat by upregulating the mobilization of lipids in adipose tissues and preventing abiogenesis.[70,71]

Flavonoids. Flavonoids make up one of the most prominent nutrient families known. From different studies, more than 6000 family members have been reported. The word flavonoids is derived from the Latin word flavus, which means yellow, because of their color-related properties. Flavonoid is a class of phytonutrients.[72] Flavonoids are naturally necessary polyphenolic compounds, and the flavan nucleus characterizes them. Most common phytonutrients are present in plant-based beverages, fruits, and vegetables. These are dietary compounds that help in the improvement of human health and prevent different disorders. Flavonoids are indispensable compounds used in cosmetics, pharmaceuticals, nutraceuticals, medicine, and other industries.[73] Flavonoids are the compound of polyphenols and are subclassified into six main groups such as flavanones, isoflavonoids, flavones, flavonols, flavanols, and anthocyanidins present in various plants. The main dietary sources of the flavonoids are plant-based foods like vegetables, fruits, plant-based drinks such as wine, green tea and cocoa-derived products.[74] These are biologically active compounds. Flavonoids-rich foods are grapes, berries, cherries, citrus fruits, artichokes, onions, cowpeas, soybeans, blackens, oregano, parsley and tea.[75] All of the bioactivities depend on the type of flavonoid, its bioavailability, and its mode of action. These medicinal phytonutrients have significant bioactivities and effects for several chronic diseases.[76,77] Flavonoids are the largest class of secondary metabolites that perform major beneficial healthful functions in humans, which include free radical scavenging abilities, antioxidative properties, antiatherosclerotic and anticancer activities, and hepatoprotective and cardiopreventive functions. Therefore, flavonoids are the center of attention in healthcare and pharmacological activity.[78] They play a healthy role as antidiabetic, antidegranulating, antiplatelet, anticoagulant, anti-inflammatory, antitumor, antibacterial, antifungal, antitubercular, antitrypanosomal, and immunomodulatory activities and aldehyde oxidase and influenza virus neuraminidase inhibition.[79] So, flavonoids are the best and most promising phytonutrients for effectively preventing and treating various diseases.[80]

Isoflavonoids. Isoflavones are natural flavonoids mainly present in the diet of the East Asian population. Their structure can exert nonsteroidal estrogen activities on the cells of humans. According to researchers worldwide, positive results are found in clinical and epidemiological studies.[81] These phytonutrients are present in various food products, such as vegetables and legumes, such as red and white clover, soy, beans, and alfalfa. The most significantly known isoflavone dietary sources in humans are soy and different soy-based products.[82] For some years, various evidence-based researchers have claimed that isoflavonoids either are dietary or come from medicinal plants. They perform a major role in managing type 2 diabetes mellitus because their various metabolically positive health effects are also associated with diabetes. Bioflavonoids have the ability down-regulate the progression of long run diabetic complications such as neuropathy, nephropathy, retinopathy and cardiovascular disorders.[83,84] Daidzein,

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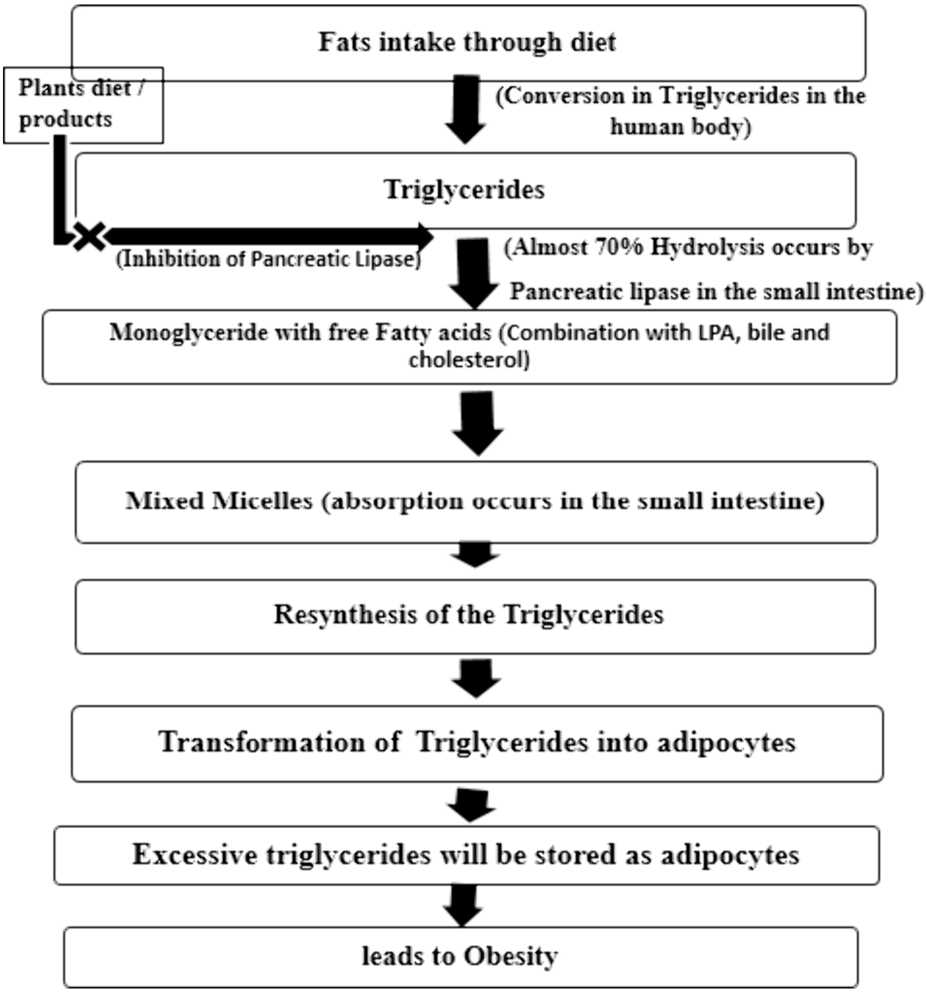

Figure 3. Mechanism of action of phytonutrients to prevent and inhibit obesity.

glycitein, and genistein are soybean isoflavones and have exceptional health benefits. Isoflavonoids are also good anti-inflammatory agents. They also inhibit cell division in *Staphylococcus aureus* and helps in the treatment of salivary gland problems, which occurred due to estrogen deficiency. The mineral content of bones increases due to daidzein and genistein, so they protect from bone loss. For neck and head cancer, genistein is the preventive chemical agent.[85] As an alternative therapy for hormonal disorders, isoflavones act as chemoprotective agents. They are also therapeutic for different types of cancers, such as prostate and breast cancer, and they play beneficial functions in treating cardiovascular disorders, menopausal symptoms and osteoporosis.[86]

Anthocyanins. Anthocyanins are a class of water-soluble flavonoids and a secondary metabolite.[87] Anthocyanin and proanthocyanins play important biological activities like antioxidative activities. These are also widely spread in the plant kingdom.[88] These compounds are found in several different color plants, such as purple, blue and red grains, vegetables and fruits.[89] Anthocyanin is a natural pigment responsible for the blue and red colors of various vegetables, fruits, and grains. Due to its large distribution in plant-based foods, the dietary intake of anthocyanins is higher than that of other flavonoids.[90] The properties of anthocyanins and their color stability depend on the temperature, solvent, pH, and other environmental factors. These are the bioactive components and anthocyanin intake benefits to human health due to their antioxidant properties.[91] The antioxidative properties of anthocyanins in food are good.[92,93] Studies show that blueberries are rich in anthocyanins, which will decrease the peak postprandial glucose level in humans.[94] To prevent and treat different chronic disorders, anthocyanins are consumed because of their antioxidative, antiapoptotic, and anti-inflammatory effects. Anthocyanins are the most commonly known nutraceuticals for enhancing health benefits by managing oxidative stress, inflammatory diseases and age-related problems.[95] Several findings indicate anthocyanin's properties in treating different types of cancer, allergies and osteoporosis.[96,97] Moreover, they also target different molecules in the signaling transduction and management of metabolic syndrome-related disorders like cardiovascular diseases, obesity, diabetes and fatty liver disorders, as mentioned in Figure 3.[98] Anthocyanins also have healthful effects like antimicrobial activities, regulating blood pressure, decreasing cancer cell proliferation, and preventing tumor cell formation.[99] Oral blackcurrant intake has a promising impact on patients of open-angle glaucoma and is also effective for antiglaucoma drugs. On the other hand, anthocyanins-rich bilberry extracts have beneficial effects on vision during retinal inflammation.[100,101]

Quercetin. Quercetin belongs to the class of flavonols. It is a very important flavonoid. Bioactive compounds are useful in

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the most important flavonoid pharmaceutical industries and medicine. It is found in many food items, for example black tea, green tea, red wine, onions and broccoli.[102] Apples, wines, and onions have a rich amount of quercetin. It is also present in different plant species, e.g., pepper, reddish, fennel, coriander, and tea. Quercetin has health-promoting properties against several disorders, such as cancer, diabetes, obesity, cardiovascular disorders, neurological disorders, asthma, allergies and atopic diseases.[103] This class of flavonoids is an active compound for managing hypertension, vascular diseases, and inflammatory problems. Quercetin also treats major heart-related disorders such as the endothelium independent vasodilator effect, inhibition of LDL oxidation, and decreasing adhesion molecules and other inflammatory markers. It has a beneficial effect on NO_2 and endothelial function in conditions of oxidative stress and is also protective against neuronal inflammatory and oxidative damage and platelet antiaggregate effects.[104] It is a dietary compound that gives potential health benefits and is an alternative medicine for breast cancer.[105] Quercetin is also used to treat atherosclerotic cardiovascular disorders, as it has antioxidant and anti-inflammatory characteristics and involves lowering lipids in the blood and also affects endothelium-dependent vasodilation.[106]

Carotenoids. Carotenoids are broadly found as natural phytonutrients. Various studies were conducted on compounds like lutein, beta-carotene and lycopene, which are involved in the management of human health and beta-carotene, lutein, violaxanthin, spermidine and zeaxanthin in the photosynthetic processes of plants and bacteria.[107] Many researchers' classification of carotenoids and their effect on human health are also explained. The most known carotenoids are zeaxanthin, lutein, lycopene, canthaxanthin, astaxanthin and beta carotene.[108] In the leaves of all plants, neoxanthin, lutein, violaxanthin, and beta carotene are present. Carotenoids are also present in the petals of flowers and fruits containing specific chloroplast carotenoids and other derivative compounds, such as lycopene and capsanthin. The dietary sources of the carotenoids are green leafy vegetables like broccoli, spinach, brussels sprouts, kale, arugula, and lettuce. Moreover, these compounds are also present in carrots, tomatoes, squash, peppers, sweet potatoes, citrus fruits, seeds, mushrooms, and other plants. They are also found in herbs like basil and parsley.[109−111] The mechanism of action of the carotenoids is not well-defined, but it has been linked with the antioxidative capacity of carotenoids. It works against reactive oxygen species, inhibiting free radicals and carotenoids and also modulating gene expression. These dietary components accumulate in the liver and other organs.[112] Retinoids and carotenoids have different bioactive properties, such as downregulating tumor cells' growth, induction of apoptosis and antioxidative properties.[113] Primarily giving an antioxidants effect, individual carotenoids also work through different mechanisms; for example, lutein or zeaxanthin has macular eye pigment, and beta carotene has the function of pro-vitamin A. Lutein gives a beneficial effect on age-related macular eye disorders and cataracts. Foods rich in lutein have adequate consumption recommendations, which will help promote awareness in the local public. Different evidence is also available about the carotenoids' healthful effects on the eyes. They also help promote cognitive abilities and help prevent cancer and cardiovascular disorders.[114] Carotenoids play an essential role in the treatment of Alzheimer's disorders and other neurodegenerative problems.[115]

Lycopene. Lycopene is a naturally present pigment of carotenoids. Its dietary consumption is recommended throughout life due to its health-promoting characteristics. Lycopene plays different beneficial roles in human health, as it involves stimulation to modulate the growth of cells and expression of connexin 43. Lycopene also provides protection to DNA, lipids and proteins from oxidative damage, IGF1 or IGF binding protein blood levels also intermediate in the inflammatory and immune processes.[116] Lycopene is a carotenoid noncyclic component present in tomatoes. It is the most responsive in vitro free radical scavenger of all of the carotenoids. Lycopene enhances the levels of glutathione and enhances the activities of the antioxidative enzymes, for example, glutathione peroxidases, catalase, and superoxide dismutase. Lycopene protects lipids, DNA and other macromolecules due to its antioxidative characteristics.[117] Dietary lycopene and its supplementation are helpful in the prevention and management of different chronic disorders such as cardiovascular disease, asthma and cancers.[118] It also effectively treats oxidative-stress-mediated malfunctions, diabetes (T2DM), cardiovascular-related complications, and inflammatory problems. Lycopene gives good results in managing skin and bone diseases and neural, hepatic, and reproductive disorders. It is majorly present in tomatoes and tomato-derived food products.[119] Guava, pink grapefruits, and melons are all natural sources of lycopene. Its bioavailability is affected due to cooking. Its bioavailability is high in heat treated in comparison to natural products.[120] Most consumed are tomatoes, watermelons, papaya, guava and grapefruit.[121,122]

Terpenoids. Terpenoids are the natural phytonutrients in different green plants and food products. Various preclinical and clinical studies suggest that these phytonutrients have important pharmacological activities.[123] Some natural sources of terpenes are ethanol extract and oregano essential oil.[124] Terpenoids were used in pharmaceuticals, cosmetics, and the food industry as a raw material. Terpenoids are used as antibacterial, antimalarial, antitumor, antiviral, and anti-inflammatory agents. They also increase transdermal absorption and manage diabetes and cardiovascular diseases.[125] Terpenoids also have some other therapeutic characteristics that make them important in the medical field, such as antimicrobial, chemotherapeutic and immune modulatory effects.[126] A detailed review is also available, which concluded the industrially best antimicrobial bioactivities and mechanism of action for three types of nutraceutical plants: terpenoids, for example, carnosic acid; thiols, for example, allicin; and polyphenols, for example, quercetin. These are the important constituents of plants' essential oils with positive antimicrobial effects. The mentioned phytochemicals are mainly present in vegetables and fruits and, importantly, are used in food preservation as microbial growth inhibitors.[127]

Limonoids. These compounds are the group of oxygenated triterpenoids in the plant families of Meliaceae and Rutaceae. Limonoids attracted people's attention and were considered problematic for the citrus fruit industries because of their bitter properties, through the biochemical transformation of the tasteless limonoid aglycone precursor into the bitter one.[128,129] Citrus fruit limonoids are tetranortriterpenoid phytonutrients present in lemons, grapefruits, oranges, and all other citrus fruits. These phytonutrients have antioxidative, anti-inflammatory, antitumor, antineurological diseases, immune-modulatory, antibacterial, anti-insect, antiviral, etc activities.[130] Limonoids are the smaller number of plant families, exhibiting

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Table 2. Food Sources and Health Benefits of Major Phytonutrients

Phytonutrients	Dietary Sources	Health Benefits	References
Polyphenols	Wheat flours	Antioxidant	49,152
	Cereals	Chemopreventive	153
	Vegetables	Anti-inflammatory	52
	Dry legumes	Antidiabetic	58
	Chocolate	Antihyperlipidemia	154
	Beverages such as coffee, tea and wine	Managing autoimmune disorders	56
	Onions	Manage cardiovascular diseases	59
	Kiwis	Manage Neurodegenerative diseases	155
	Berries	Antiviral	156
	Apples	Antiobesity	
	Citrus fruits		
	Tropical fruits		
Terpenoids	Green Foods	Antitumor	124
	Fruits	Anti-inflammatory	127
	Vegetables	Antibacterial	125
	Grains	Antiviral	126
	Oregano essential oil	Antimalarial	
		Antimicrobial	
		Promote transdermal absorption	
		Manage cardiovascular diseases	
		Hypoglycemic activities	
		Immunomodulatory	
		Chemotherapeutic	
Resveratrol	Peanuts	Antioxidant	65
	Pistachios	Neuroprotective	66
	Grapes	Cardioprotective	68
	Blackberries	Antiaging	69
	Cranberries and all other Berries,	Antiatherosclerosis	67
	Jake fruit	Antidiabetic	
	Tomatoes	Anti-inflammatory	
	Apples	Antiobesity	
	Dark chocolate	Anticancer in the colon, prostate, breast and lungs	
Flavonoids	Vegetables	Antioxidant	75
	Fruits	Antidiabetes	73
	Plant-based beverages	Anti-inflammation	74
	Green tea	Antibacterial	78
	Cocoa-based products	Antifungal	79
	Berries	Anticancer	
	Citrus fruits	Antiplatelet	
	Grapes	Anticoagulant	
	Cherries	Antidegranulating activity	
	Onions	Antitrypanosomal activity	
	Artichokes	Aldehyde oxidase inhibition	
	Soybeans	Immune-modulatory	
	Cowpeas	Antiatherosclerotic	
	Black beans	Hepatoprotective	
	Parsley		
	Oregano		
Isoflavones	Legumes such as soy, white and red clover	Nonsteroidal estrogen activity	82
	Alfalfa	Antidiabetic	86
	Beans	Manage cardiovascular disease	81
		Manage Nephropathy	83
		Manage Neuropathy	
		Manage Retinopathy	
		Anti-inflammatory	
		Helps breast cancer and prostate cancer treatment	
		Osteoporosis	
		Reduce menopausal symptoms	
Anthocyanins	Cereals	Antioxidant	93
	Grains	Anti-inflammatory	90
	Wines	Antiapoptotic effects	89

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Table 2. continued

Phytonutrients	Dietary Sources	Health Benefits	References
	Juices	Age-related diseases	99
	Jams	Manage some types of cancers	95
	Vegetables	Manage Allergies	98
	Eggplant	Treat osteoporosis	96
	Red onion	Treat Metabolic syndrome related disease such as obesity, CVD, diabetes	
	Red cabbage	Manage fatty liver disease	
	Black rice	Antiproliferative	
	Strawberries	Antimicrobial	
	Raspberries		
	Blackberries		
	Blueberries		
	Cranberries		
	Cherries		
	Apples		
	Plums		
	Purple carrots		
Quercetin	Onion	Antioxidant	102
	Black tea	Neuroprotective	103
	Broccoli	Antiobesity	104
	Red wine	Antiallergy	106
	Green tea	Antiasthmatic	103
	Apples	Antihypertensive	
	Pepper	Anti-inflammation	
	Coriander	Antidiabetes	
	Fennel	Cardioprotective	
	Reddish	Reduction of adhesion molecules and other inflammatory markers	
Carotenoids	Carrots	Antioxidant	109−111
	Spinach	Inhibits malignant tumor growth and induction of apoptosis	113
	Tomatoes	Beneficial effects on eye health	114
	Herbs like parsley and basil	Improve cognitive function	115
	Leafy greens such as lettuce and arugula, broccoli, kale, brussels sprouts	Improve cardiovascular health	
	Squash	Prevent from some cancer	
	Sweet potato	Treat Alzheimer's disease	
	Peppers	Treat neurodegenerative disorder	
	Citrus fruits		
	Seeds		
	Mushrooms		
Lycopene	Tomatoes and tomatoes related products	Prevent cancer	117
	Melon	Prevent asthma	120
	Watermelon	Manage cardiovascular disorders	121
	Grapefruit	Good in diabetes mellitus	118
	Guava	Anti-inflammatory	119
	Papaya	Skin and bone diseases	
		Manage hepatic	
		Manage neural	
		Treat reproductive disorders	
Limonoid	Oranges	Antitumor	130
	Lemons	Antioxidative	
	Grapefruits and all other fruits of Citrus	Anti-inflammatory	
		Antineurological	
		Immune-modulatory	
		Anti-insect	
		Antibacteria	
		Antiviral activities	
Stigmasterol (Phytosterol)	Plant based and fortified in different foods	Antidiabetic	135
		Anti-inflammatory	134
		Cholesterol lowering effects	133
		Cardiovascular disease prevention	
Phytoestrogens	Soy and soy-based foods	Antiestrogenic	139

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Table 2. continued

Phytonutrients	Dietary Sources	Health Benefits	References
	Legumes	Lowered risk of menopausal symptoms like hot flushes and osteoporosis	140
	Flaxseed	Lowered risks of cardiovascular disease, obesity, metabolic syndrome and type 2 diabetes	137
	Chickpeas	Manage brain disorders	
	Green beans	Breast and prostate cancer treatment	
	Dairy products	Manage bowel cancer and other cancers.	
Glucosinolates	Crucifer plants such as Broccoli, cabbage, cauliflower	Anticancer	143
	Oilseed crops like rapeseed	Protective effects against cardiovascular disease	144
	Condiments such as mustard seed	Antidiabetes	146
	Herbage such as Brassica kale	Treat neurodegenerative disorder	
		Several inflammatory disorders	
Probiotics	Dairy products	Enhance the beneficial gut microflora	149
	Fermented fruits	Improving lactose metabolism	151
	Fermented vegetable	Antimicrobial activities	147
		Lower gastrointestinal infection	
		Controlling serum cholesterol	
		Anticarcinogenic	
		Antidiarrheal properties	
		Improve inflammatory bowel diseases.	

a larger range of health-promoting, disease preventing and medicinal properties.[131]

Stigmasterol (Phytosterol). Phytosterols play a prominent role in pharmaceuticals, nutrition, food and cosmetics.[132] Phytosterols are natural plant cell membranes and have great value in the food industry because they lower the level of low-density lipoproteins and cholesterol in human blood. These are plant-derived bioactive metabolites and act as anti-inflammatory and antidiabetic agents and have cholesterol-lowering abilities.[133] In different studies, the effect of foods rich in sterols or stanols and the effect of sterol or stanol supplements on the management of the serum concentration of LDL are very well characterized. On the other hand, they also show beneficial and useful effects on nonlipid problems, such as inflammatory and coagulation parameters, endothelial role and oxidative stress markers, etc. All these functions of phytosterols and stanols make them more attractive and an alternative for dietary intake to prevent the CVDs, mainly in low- or medium-risk populations.[134] Nowadays, phytosterols are also used to fortify and enrich various food products. Phytosterols are easily oxidized as unsaturated fatty acids and cholesterol. To overcome the drawbacks which are associated with the use of phytosterols, microencapsulation is beneficial for food fortification.[135]

Phytoestrogens. Phytoestrogens are a plant-based compound, and their structure is similar to that of 17 beta-estradiol. Majorly, four phenolic components are characterized as phytoestrogens: stilbene, lignin, coumestan, and isoflavones. Some certain types of functional food are known as phytoestrogens and nonsteroidal compounds. These compounds are derived from the metabolic activities of precursors present in plants. These secondary metabolites produce biological responses by mimicry/modulating the action of endogenous estrogen.[136,17] Beta estrogen is a basic female sex hormone structurally similar to E2 and allows the phytoestrogens to produce anti-oestrogenic effects through binding with the estrogen receptors. Decreasing the hazard of menopausal symptoms, such as osteoporosis and hot flashes, also reduces the risk of diabetes, obesity, CVDs, metabolic disorders, neurological disorders, and different types of cancers, like breast cancer, bowel cancer, prostate cancer and other cancers.[137] Generally, phytoestrogen is considered weak estrogen compared to estradiol, and phytoestrogen is needed in higher amounts than estradiol to give similar biological activities. Polyphenolic phytoestrogens include compounds known as isoflavones, which occur as glucoconjugates of daidzein, glycitein, and genistein. All the phytoestrogens and metabolites have a minimum of one aromatic ring.[138] All over the world, soy and soy products plus legumes are considered a part of a healthy lifestyle. So, phytoestrogens are a regular part of daily life. Phytoestrogens' activities depend on the microbiome. Their metabolites have powerful estrogenic functions compared to the naturally occurring substances and due to the differences in the microbiomes. There is more difference in the useful effects of phytoestrogens in individuals.[139] Dietary estrogens are consumed from plants, such as green beans, chickpeas, soy, flaxseeds, etc., or plant-derived food products, such as soy-based food, dairy products, etc.[140]

Glucosinolates. Glucosinolates are bioactive secondary metabolites with various nutritional benefits.[141,142] Glucosinolates are compounds from the *brassicaceae* plant family, such as mustard, horse radish, cabbage, broccoli, cauliflower and rapeseeds.[143] Naturally found glucosinolates are also known as thioglucosides in cruciferous plants like cabbage, oil seed crops, herbage like brassica kale, and condiments like mustard seeds.[144] More than 120 types of glucosinolates are present in cruciferous plants. The content and chemical structure may affect the beneficial nutritional effects on human health. There are also some cases in which GSLs are associated with toxic effects. Mainly, toxic effects are related to hypertrophy of the thyroid glands and induction of goiter. GSLs are biologically active compounds with important health effects on the different types of cancers and carcinogenesis activities and in the intact form after its enzymatic or nonenzymatic transformation in the indole and isothiocyanates compounds.[145] Glucosinolates (GSLs) protect from neurodegenerative diseases, diabetes mellitus, CVDs, and various inflammatory problems.[146]

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Probiotics. Probiotics are a live microbial culture; they increase the useful effects of the gut microflora to enhance the quality of the health of humans. They are an emerging field of interest with high growth potential in the dairy food industry. Food supplements of probiotics also have great interest in the field. Several yeasts, molds, and bacteria can be used as a probiotic. A commonly used microorganism is lactic acid bacteria. These lactic acid bacteria are involved in the fermentation of different dairy products, foods and beverages and produce lactic acid as an end product of fermentation.[147,148] Fermented vegetables and fermented fruits are known as prebiotics and are among the sources of probiotics. They are rich in antioxidative properties and give beneficial health effects to humans.[149] From the perspective of cholesterol in dairy product probiotics in developed countries and due to the economic condition of developing countries, research is now diverted to nondairy probiotics. From the research, rapidly emerging nondairy probiotics-based food products are legumes, cereals, vegetables, and fruits. All of these alternative dairy probiotic sources are cheap and have increased phytochemicals or phytonutrients. Alternative nondairy sources also decrease the hazard of cholesterol diseases in lactose-intolerant persons.[150] Fermented potatoes and their beverages are advantageous for vegetarians who have allergies to dairy products. Probiotics are also involved in the management of the metabolism of hosts. Probiotics are good to use due to their antimicrobial properties. They also reduce GIT infection, improve the metabolism of lactose intolerant people, control serum cholesterol, have antidiarrheal activities and improve IBS symptoms, and have anticarcinogenic properties.[151] The major phytonutrients, their food sources, and their health benefits are presented in Table 2.

Phytonutrients Involved in the Prevention and Treatment of Various Diseases. *Antidiabetic Phytonutrients.* Diabetes Mellitus is a metabolic disorder in which a continuous increase in the blood glucose level occurs, known as "hyperglycemia".[157] Diabetes mellitus is classified into two main types: type 1 diabetes mellitus and type 2 diabetes mellitus. Type 2 diabetes mellitus has the highest prevalence rate (>85%). Diabetes mellitus can cause both microvascular end-point complications, such as neuropathy, nephropathy and retinopathy, and macrovascular end point complications, which are peripheral vascular disorders, ischemic heart disorders and stroke. Type 1 diabetes mellitus etiology is not completely understood. According to the studies, the prevalence of diabetes mellitus in 2017 was 435 million people globally, and it is expected that the prevalence of diabetes will rise to 629 million people by 2045.[158] Type 2 diabetes mellitus is rapidly increasing in developing countries, and its prevalence rate depends on the degree of urbanization and is according to the urban and rural habitat. In a few ethnic groups, such as South Asians and other Asian plus Africans, they may develop diabetes earlier and at a lower BMI as compared to whites. They had abdominal obesity and also leading diabetes phase from the prediabetes.[159,160]

Phytochemicals can act as an antidiabetic and must be utilized according to their recommended dosages. Some diabetes-treated phytonutrients include resveratrol, lycopene, quercetin, thymoquinone, and biguanides. But the proper formulation and clinical trials of these phytochemicals are still in progress. Most determined findings focus on the specific aspect of different biochemical pathways including antioxidation, increasing glucose utilization, antiglycation, induction of insulin production, etc. Detailed research on the biochemical, functional and immunological factors of phytonutrients indicating their safety and efficacy in managing diabetes is reported.[161] The mediterranean diet's components (vegetables, fruits, olive oil, tree nuts, and fatty fish) serve as functional foods due to their nutraceutical contents such as terpenoids, polyphenols, flavonoids, sterol, pigments, alkaloids, and unsaturated fatty acids. Studies in diabetic and high-risk patients using polyphenols in the Mediterranean diet, which is rich in herbages, for example, green tea, coffee, black tea and yerba mate, show well know clinical positive effects on the management of metabolic conditions, microvascular activities, cholesterol-lowering, fasting glucose lowering, antioxidative activities, and anti-inflammatory activities.[162]

According to a study, diabetes mellitus type 2 depends on the person's lifestyle. Intake of vegetables may prevent diabetes, and this is dependent on the selection of vegetables and the consumed amount of phytonutrients, minerals, vitamins and dietary fibers.[163] Flavonoid is a biologically active compound with antidiabetic effects and various health benefits in all citrus fruits. There have been in vivo and in vitro studies on the potential antidiabetic action molecular mechanism of citrus fruit flavonoids. Flavonoids involve the relation of the biomarkers of glucose control, renal and hepatic functions, lipid profile, and antioxidant enzymes and also modulate the signaling pathways in association with glucose intake and insulin sensitivity, which mainly contribute to the pathogenesis of diabetes.[164,165]

Large amounts of phytochemicals, peptides, and proteins are present in legumes. Biologically active components are found to lower the risk of noncommunicable diseases like diabetes and obesity.[166,167] Polyphenols are antidiabetic phytonutrients in dietary sources such as tea, coffee, red wine, cocoa, guava, whortleberry, grapes, propolis, olive oil, and chocolates. These food sources have positive effects by increasing glucose metabolism, decreasing insulin resistance and HbA1c level, and improving vascular functions in diabetic patients.[168] Polyphenols are also present in plant-based beverages, mainly apples, citrus fruits, plums, berries, and broccoli. Flavanones such as hesperidin in citrus fruits, flavonols (quercetin in the apple, tea, and onions), flavanols in tea, cocoa, broad beans and apples, anthocyanins in berries, and hydroxycinnamates (coffee and many fruits) are common polyphenols. Despite extensive research, the exact mechanism of action of polyphenols in humans is not well-known. However, some important evidence was also found that they are involved in carbohydrate digestion and nitric oxide metabolism, and oxidative enzymes are good for healing effects.[169] Various human and animal studies have been reported, indicating that polyphenols are involved in reducing hyperglycemia and improving insulin sensitivity and its secretions. Different emerging evidence also shows that polyphenols from the diet influence blood glucose at various levels to manage diabetic complications.[42,170]

Different studies and clinical trials indicate that resveratrol also benefits diabetes mellitus patients.[171] Resveratrol's food sources are grapes, berries, peanuts, and wine. But it is more abundantly present in the grape's skin and seeds. Resveratrol is considered a well-tolerated and well-known phytonutrient that helps in the prevention of diabetes and related complications. It also is involved in inflammation, oxidative stress, neurodegeneration, aging, cancers and glycation.[69] This bioactive nutrient, through the intake of fruits and vegetables, has

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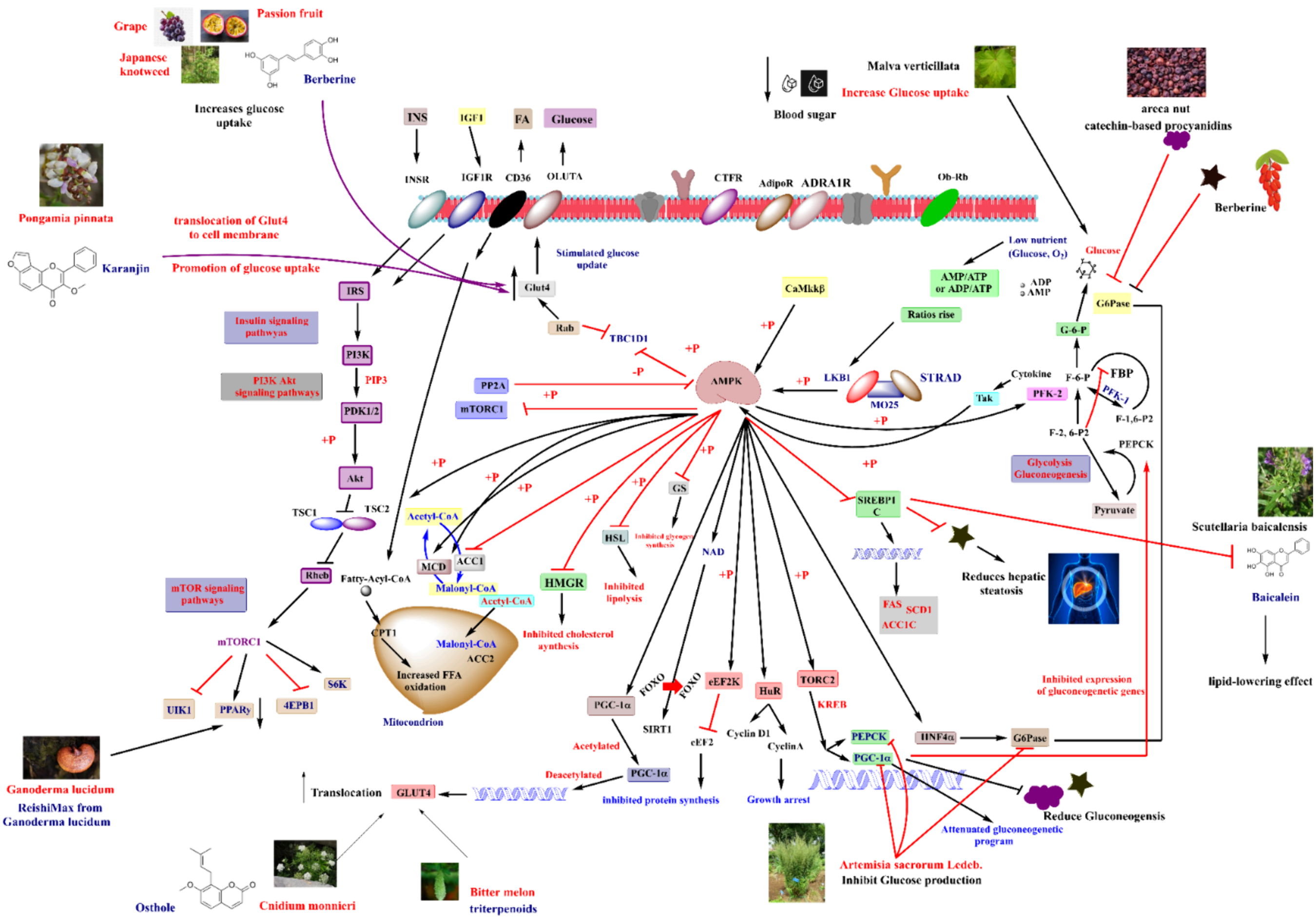

Figure 4. Influence of phytonutrients on AMPK activation. Phytonutrients from medicinal plants stimulate AMPK, promoting glucose uptake, enhancing fatty acid oxidation, and boosting mitochondrial biogenesis.[177]

positive effects such as anti-inflammatory, antioxidant, and electrolyte properties. It also has functional properties, for example, low glycemic load and energy density.[172] Intake of lycopene is directly related to the peripheral antioxidant level among type 3 diabetes patients. Fasting plasma glucose and HbA1c level are reduced due to the increase in the consumption of lycopene. Lycopene is involved in managing the pathophysiology of diabetes and oxidative stress.[173] Oxidative stress in the liver due to diabetes is controlled by enhancing the managed hepatic malondialdehyde, plasma alpha-tocopherol levels, and erythrocyte superoxide dismutase. On the other hand, this diabetes-induced oxidative stress is manifested by decreasing the hepatic glutathione level and catalase activity. Intake of soybeans and whole wheat both have positive effects on the intake treatment of oxidative stress.[174] Intake of legumes and beans is associated with reducing noncommunicable diseases because legumes or pulses contain large amounts of antioxidants, dietary fibers, minerals and phenolics.[44,175]

Among the critical pathways involved in diabetes management, AMP-activated protein kinase (AMPK) plays a pivotal role in regulating the energy balance and glucose metabolism, especially during physical activity. When cellular energy levels are depleted, AMPK is activated, initiating processes that help restore energy equilibrium, such as enhancing glucose uptake and promoting fatty acid breakdown. Unlike the insulin signaling pathway—which relies on insulin secretion to activate a cascade of molecular events leading to increased glucose absorption—AMPK functions independently of insulin, offering an alternative mechanism to improve glucose tolerance and overall metabolic function.[176] Exercise serves as a significant activator of AMPK, further contributing to its importance in diabetes management. Muscle contractions during physical activity stimulate AMPK, which improves insulin sensitivity and glucose uptake by facilitating the movement of the glucose transporter type 4 (Glut4) to the cell surface. This also stimulates mitochondrial biogenesis, enhancing energy production and further supporting metabolic regulation. Moreover, elevated calcium levels during muscle contraction activate additional pathways, such as calcium- and calmodulin-dependent protein kinases (CaMKs), which further amplify glucose metabolism. A key downstream effect of AMPK activation is the regulation of the peroxisome proliferator-activated receptor gamma coactivator (PGC)-1α, which is essential for mitochondrial biogenesis and energy metabolism. PGC-1α interacts with various transcription factors to support muscle fiber adaptation, shifting energy production from glycolysis to more efficient oxidative processes (Figure 4).

Antiobesity Phytonutrients. In the contemporary world, appropriate food choices and physical inactivity are the leading preconditions for abnormal weight gain or obesity.[178] Obesity is a chronic disorder and the main public health problem. Mediocre inflammation is a major underlying cause of obesity

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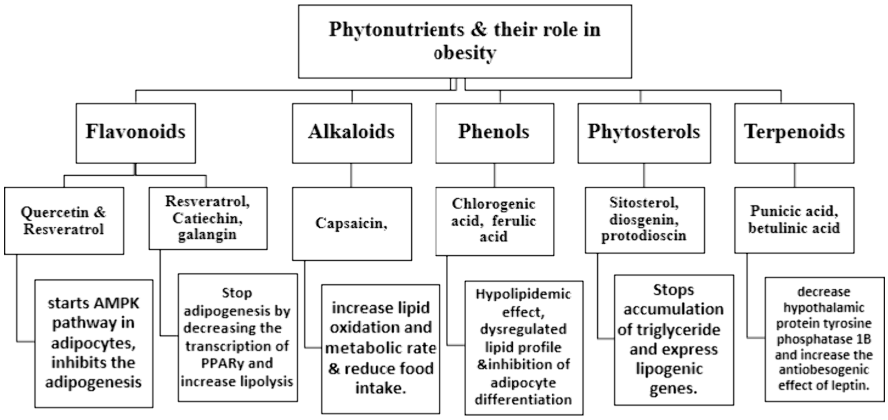

Figure 5. Regulation of various pathways mediates antiobesity effects of phytonutrients.

and obesity-related metabolic diseases. Majorly, adipose tissues are involved in systematic inflammation. According to different studies, inflammation related to obesity commonly starts from gut problems such as changes in the microbiome profile and intestinal bacteria.[179] Irrespective of ethnicity, socioeconomic status, or geographical locality, the rate of obesity is higher in both genders and all ages. The prevalence rate of obesity is high in women and the older population. In epidemiological studies, BMI is commonly used to characterize overweight and obesity levels.[180] According to the research of the World Health Advisory Group, overweight and obesity are a worldwide common public health problem. The overweight and obese population is more than the underweight population. According to a study in 2016, 40% females and 39% males aged 18 years and above, accounting for almost 2 billion adults, were overweight. There were 15% females and 11% males, more than 1/2 billion people, who were obese globally. Over the past 4 decades, both obesity and overweight have shown a remarkable increase.

Severe epidemic burden obesity is related to several disorders, for example, diabetes, cardiovascular disease, metabolic-related fatty liver disorder and even COVID-19.[181] Obesity/overweight increases the risk of associated disorders like dyslipidemia, T2DM, arterial hypertension, coronary heart disease, gallbladder lithiasis, ovarian polcytosis, arthropathy, cerebral vasculopathy, sleep apnea syndrome and some neoplasms.[182] Figure 3 shows the mechanism of action of phytonutrients to prevent obesity. In the normal mechanism, dietary lipids convert into triglycerides after entering the human body, and then up to 70% hydrolysis occurs by the pancreatic lipase in the small intestine, and then it is converted into the MGs and FFAs. Then due to mixed micelles, resynthesis of TGs occurs, and again, adipose cells are synthesized and stored in the body and cause obesity. So, to prevent obesity, phytonutrients are used (plant products) to inhibit pancreatic lipase activity.[183]

Intake of fats and lipids is directly related to obesity and associated disorders. According to different in vivo and in vitro studies, various biologically active phytonutrients in different fats and oils (phytosterol, phenolic compounds, and tocopherols) are significant in obesity management. Due to this reason, this present review focuses on biologically active components found in oils and their involvement in obesity management.[184] Resveratrol is another phytonutrient that helps in anti-inflammatory and antioxidant action and gives beneficial effects in the prevention and development of many disorders, including obesity. Quercetin is abundant in flavonoids in different fruits, vegetables, tea and wine.[185] It is a main representative of the flavonoid subclass of flavonols.[186] Quercetin is a flavonol present in red onions, apples, green tea, etc.[187]

Phytonutrients having antiobesity effects are carotenoids, anthocyanins, chlorophyll, etc. It is also evidenced that states or nations consuming the lowest fruits and vegetables have the highest rate of obesity. Higher phytonutrient consumption and improved body composition are strongly correlated. Overall dietary quality makes more difference, but the phytonutrients or phytochemicals give key benefits.[188] According to human trials, obesity and polyphenols such as curcumin, quercetin, resveratrol, and some polyphenolic extracts are interlinked. The healthful and positive effects of polyphenols are dependent on their bioavailability and amount consumed. Polyphenols involve inhibiting adipose cell differentiation, stimulating beta-oxidation and counteracting oxidative stress.[156] Tea, coffee, cocoa, onions, broccoli, apples, berries, plums, and citrus fruits have plant polyphenols. Chlorogenic acid, quercetin, resveratrol, curcumin, and epigallocatechin 3 gallate are polyphenols that are extensively studied because of their health benefits. Tea is a beverage that is most extensively consumed and prepared from the leaves of *Camellia sinensis*. Tea contains different alkaloids, flavonoids, theanine and phenolics, which have antioxidative properties, are beneficial for health, and have antiobesity properties.[189]

Anthocyanins are natural phytonutrients found in foods which play an important part in attenuating obesity and decreasing the adipose tissues and weight.[190] Anthocyanin is involved in antiobesity functions by several mechanisms, and biosynthesis of anthocyanins in various microorganisms also has extensive uses as mentioned in Figure 3. Various mechanisms involved in regulating lipid metabolism also inhibit the absorption of lipids/fats, enhancing energy expenditure, decreasing intake of food and regulating gut microbiota.[191] Anthocyanins have healthy effects on obesity-associated inflammation and metabolic disorders. A variety of anthocyanins such as delphinidins, pelargonidins, cyanidins, malvidins, petunidin, and peonidins are present in different food items, for example, blueberry, mulberry, cherry, chokeberry, black elderberry, black currant, jaboticaba peel, black soybeans, and red cabbage micro green. All these are reported to change both inflammatory and metabolic markers in human and animal cells.[192] Different research confirms that the intake of foods rich in anthocyanins improved obesity, which is

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related to the disposition of the gut microbiota and inflammation in the adipose tissues. Anthocyanin intake prevents healthy humans from obesity, helps in the maintenance or decreasing of the body weight of obese person, also promotes metabolism and improves energy balance.[193]

BMI (body mass index) and waist circumference are decreased through the intake of green tea and coffee due to catechins.[194] Most of the published data shows that foods and food fortification with natural polyphenols and phenolic acid compounds are healthy and good for maintaining lack of obesity.[195] The healthy dietary pattern of a Mediterranean-style diet is encouraged due to its antioxidant nutraceuticals, such as polyphenols. Quercetin, oleuropein, resveratrol, hydroxytyrosol, and hydroxycinnamic derivatives are well-known due to their anti-inflammatory and antioxidative activities. It also exerts antiobesity properties. Dietary polyphenols in the Mediterranean diet involve deregulation of NADPH, metabolic inflammation and oxidase (NOX) and NF-κB-mediated oxidative stress.[196]

Flavonoids are the natural, biologically active antiobesity compounds which may perform any effect in functional food or antiobesity drugs without side effects. Flavonoids directly stop weight gain through their bioactive metabolites with the help of different pathways.[197] The antiobesity effects of phytonutrients are started by the regulation of different mechanisms or pathways such as lipid intake, absorption, and expenditure of energy, decreased lipogenesis and increasing lipolysis, and proliferation and differentiation of preadipocytes, as shown in Figure 5.[198]

Studies indicate that the consumption of flavonoids plays an essential part in protection against oxidative damage and also helps with biochemical and pharmacological functions in managing human health.[199] Some other research reports also tell us that citrus fruits' flavonoids, nobiletin and naringenin protect humans against obesity and metabolic disorders.[200] Flavonoids reduce the fat mass and body weight of the body, lowering the plasma triglycerides or cholesterol levels. This process can be observed through various pathways or mechanisms such as decreasing the food intake and absorption of fats or lipids, modulation of lipid metabolism, and enhancing the energy expenditure or regulation of the gut microbiota profile.[201] Some medication-based analyses have also determined that the gut microbiome mediates the positive effect of stilbene and flavonoids, approximately 11%, for preventing obesity.[202] Pomegranate juice has more antioxidant capacity, polyphenols, flavonoids, tannins, and anthocyanins. Healthful phytonutrients in pomegranate juice are directly related to good human health.[203]

Phytonutrients Involved in Managing Hypertension. Hypertension is a very common disease. Approximately 1 billion adults are affected worldwide.[204] Hypertension is a very significant risk factor for diseases such as stroke, ischemic heart disease, other cardiovascular diseases, dementia, and chronic kidney disorder. According to the studies, in 2015, almost 8.5 million deaths were reported due to systolic blood pressure >115 mmHg; from this, 88% of the population was from low-income and middle-income countries.[205] Some variations in the levels of different risk factors, such as low potassium, increased sodium intake, obesity, physical inactivity, alcohol intake and unhealthy diet, were involved in the prevalence.[206] There is a higher risk of developing hypertension and cardiovascular diseases depending on a diet high in sodium, refined carbohydrates, fat content, energy-dense foods, and added sugars and a diet low in vegetables and fruits.[207]

High blood pressure is a more prevalent problem in Pakistan. 18% of adults under the age of 45 and 33% above the age of 45 are the targeted population of hypertension. Watermelon seed has a sufficient amount of phytonutrients (saponins, polyphenols, flavonoids, and alkaloids) and cations (calcium, potassium, and magnesium). It has an antihypertensive effect because of its antioxidant, vasodilatory and antiangiotensin converting enzyme properties.[208] Recently, phytonutrient food sources have been good for treating high blood pressure. The endothelium is a key compound that modulates the contractility of vessels and thus affects the basal tone and blood pressure.[209] According to epidemiological studies, the Mediterranean diet is related to a great quality of life because the presence of a higher number of vegetables and fruits in the MD has a high number of polyphenols. Rich food sources of polyphenols are grapes and grape-derived products. Pomegranate, tomatoes, soy, tea and cocoa are involved in lowering blood pressure in hypertension patients.[210] Some polyphenols are good for hypertension: isoflavones, flavones, flavanones, flavonols, flavan-3-ols, anthocyanins, and proanthocyanin's. Dietary consumption of polyphenols-rich foods, beverages and herbs helps improve vascular health and decrease the risk of high blood pressure.[211] Another study is found in which it is stated that polyphenol foods, including cocoa and green tea rich in flavan-3-ols, berries rich in anthocyanins, soy products rich in isoflavones, and almond and pistachios rich in the hydroxycinnamic acids, also are beneficial for the improvement of hypertension.[212] Increased polyphenol chocolate is also beneficial for treating the triglyceride levels in patients with hypertension and diabetes. It also lowers the blood pressure and fasting blood sugar without affecting inflammatory markers, weight and insulin resistance/glycemic control.[213] Flavonols, flavanols, flavones, and flavanones help modulate the blood pressure by restoring endothelium functions directly by (NOS) affecting the nitric oxide levels and indirectly by another mechanism. In animal and human studies, quercetin has the most appropriate blood pressure lowering effect irrespective of duration, dose and disease status.[214] Resveratrol is also a polyphenol and acts as an antioxidant and antihypertensive.[215]

Phytonutrients Involved in Managing Cardiovascular Diseases. The cardiovascular system contains the heart and its blood vessels. Various types of problems arise within the Cardiovascular system, such as conduction abnormalities, rheumatic heart diseases, and endocarditis. Cardiovascular disorders are also recognized as heart diseases. These 4 entities are named: cerebrovascular disease, coronary artery disease, coronary heart disease, aortic atherosclerosis, and peripheral artery disease. Coronary artery diseases occur due to the reduction in myocardial perfusion, which causes angina due to ischemia and leads to myocardial infarction or heart failure.[216] Modifiable cardiovascular risk factors are diabetes mellitus, cigarette smoking, hypertension, and lipid/fat abnormalities, these risk factor hypertension are mainly related to the strong evidence of cause and high prevalence of exposure. Different studies also reported that higher blood pressure is a significant risk for atrial fibrillation, heart failure, aortic syndrome, heart valve diseases, coronary heart disease, stroke, dementia and chronic kidney disorder.[217]

There is a complex relationship between diet and health, and some strategies to prevent or treat chronic disorders. Globally

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CVD is also a major cause of death and different disabilities. Several studies suggest the Mediterranean dietary pattern, which is rich in vegetables and fruits and acts as a cardioprotective due to the presence of a higher number of phytonutrients and biologically active compounds, for example, vitamins, minerals, unsaturated fatty acids, fiber, phytosterols, and polyphenols. All these mentioned substances act as an anti-inflammatory, antithrombotic and antioxidative effect.[218] All plant-based food products are very healthful, for example, vegetables, fruits, nuts, flaxseeds, beans, dietary fiber, whole grains, peas, and the vegan diet are involved in the management of cardiovascular health. Plant based foods decrease LDL-C levels and also reduce the risk of cardiovascular disorders. Cardiovascular risk markers are triglyceride, total cholesterol and LDL cholesterol.[219]

According to an experiment, dietary quinoa's effect is positive after intake for 30 days in 22 students of 18 to 45 years. 42.2% were found to have low blood pressure and a 40.7% decrease in weight. Amarnath oil is also helpful for reducing triglyceride, total cholesterol, low-density lipoprotein, and VLDL in humans, when taking 18 mL/day for almost 3 weeks.[36] Quinoa seeds mainly have beta carotene, and amaranth seeds have carotenoids, commonly lutein and zeaxanthin. Both these seeds also contain good-quality lutein, tocopherols and polyunsaturated fatty acids,[41] Vitamin A, B, E, and K, minerals including phosphorus, magnesium, and potassium, phenolic acids and flavonoids, plant sterol, and other phytonutrients such as lignin's and bound phytochemicals present in all the types of corns. Different types of corn consist of different phytonutrient levels like flavonoids and carotenoids. Yellow corn is rich in carotenoids, with more than 823 μg per 100 g of DW corn having beta carotene 4%, beta-cryptoxanthin 3%, lutein 50%, zeaxanthin 40%, and alpha-carotene 2%. Purple, blue, and red corn increased the anthocyanidins' concentration of more than 325 mg/100 g DW corn, including peonidin derivatives of 15 to 20%, cyaniding derivatives 75−90% and pelargonidin derivatives 5 to 10%. Amylose corn is rich in amylose and has more than 70% of all carbohydrates.[220,221]

Beetroot phytonutrients such as polyphenols, organic acids, batnin, and saponins can inhibit or reduce gastrointestinal digestion, and also a hypothesis is rising that beetroot has a cardioprotective effect due to the combination of nitrite or nitrate and biologically active substances, which will reduce the production of the (ROS) reactive oxygen species and modulation of gene expression. In vivo, in vitro and clinical trials reported that beetroot nitrate and its phytonutrients have excellent and supportive therapeutic effects on cardiovascular diseases.[222] Another study is conducted in which bitter apricot seeds were consumed for 42 days daily to check their effect on the cardiac system. Bitter apricot seeds also have a large number of phytonutrients in them. The focus of this study was to check the LDL cholesterol levels in CVDs patients. In the results, it is declared that it effects positively the modified lipoprotein profile in the group of elevated cholesterol.[223]

Phytonutrients are also present in whole-grain barley. The phytonutrients in whole-grain barley are flavonoids, phenolic acids, folate, phytosterols, tocols, and lignans. The mentioned phytochemicals are helpful due to their cholesterol-reducing abilities, their antiproliferative and antioxidant activities, and their effectiveness in reducing the risk of certain disorders. So, we can say that a large amount of barley is good for health.[224] Oxidative stress is involved in the pathogenesis of atherosclerosis. Due to the consumption of food rich in dietary antioxidants, for example, different types of nuts are involved improving the biomarkers associated with oxidative stress and participating in the management of atherosclerosis. Nuts also have phytonutrients such as polyphenols and vitamin E, which prevent primary and secondary cardiovascular disorders.[225] Different biologically active dietary products have phytonutrients, specifically carotenoids, which play antioxidative effects and decrease the markers of oxidative stress. Carotenoids are very healthful and beneficial for preventing chronic disorders like cardiovascular problems by lowering inflammatory responses.[226] Some studies demonstrate that cardiovascular diseases are inversely related to the blood concentration of antioxidants (carotenoids, vitamin C and vitamin E).[12]

Findings indicate that the catechins, proanthocyanins, and anthocyanins present in cocoa are effective for lowering blood pressure. And monacolins or red yeast rice also act positively to lower cholesterol.[194] Seaweed also has polyphenols, and it performs the key role in managing different cardiovascular diseases.[227] Polyphenols are commonly found in fruits, vegetables, and beverages, and all of these sources are good for cardiac fibrosis and other cardiovascular disorders. Different studies show that polyphenol produces antifibrotic and (MI) myocardial protective effects through regulating the oxidative stress, inflammation and fibrotic molecular signals.[228] Another example is apple due to the presence of different polyphenols in it. Apple's polyphenols are related to the reduction of cardiovascular diseases. Quantification and phenolic profile analysis indicate that the polyphenolic extract of apple peels has an increased quantity of total flavonoids and phenolic compared to the polyphenol apple fleshes.[229]

Polyphenolics antioxidative ability prevents atherosclerosis, LDL oxidation, vascular smooth muscle cell proliferation, endothelial dysfunction, macrophages/T lymphocytes, inflammatory processes by the monocytes, and platelet aggregation. Polyphenols decrease reactive oxygen species' generation by inhibiting the oxidases. This involves suppressing VSMC proliferation and migration, lowering the generation of the superoxide, and stopping OxLDL formation. They also decrease platelet aggregation and help to improve mitochondrial oxidative stress. Through the intake of polyphenol phytonutrients, diabetes, high blood pressure, and obesity and hyperlipidemia development become reduced.[230] To maintain human health, a vegetable diet has preventive effects. Majorly brassica vegetables play a role in reducing the risk of chronic disorders, mainly cardiovascular diseases. Glucosinolates and isothiocyanates are phytonutrients that are mostly present in the cruciferous family of vegetables. These are the antioxidants mainly contributing to the cardiovascular system protection.[231] Phytosterols are non-nutritive components and are good for health due to their cholesterol-lowering properties, mainly present in plant-based food items. They are classified into two groups, plant stanols and plant sterols. Various clinical trials indicate that 2 g phytosterols/day gives the LDL-C lowering efficacy 8−10%. Various studies also determine that the phytosterols are inversely related to the LDL-C reduction.[232]

Phytonutrients Involved in Managing Different Types of Cancer. The condition of abnormal growth of cells with the power to invade and metastasize into other parts of the body is recognized as cancer. Various factors are involved in the initiation of cancer cells. Cancer cell initiation includes gene alterations that mediate the body's normal

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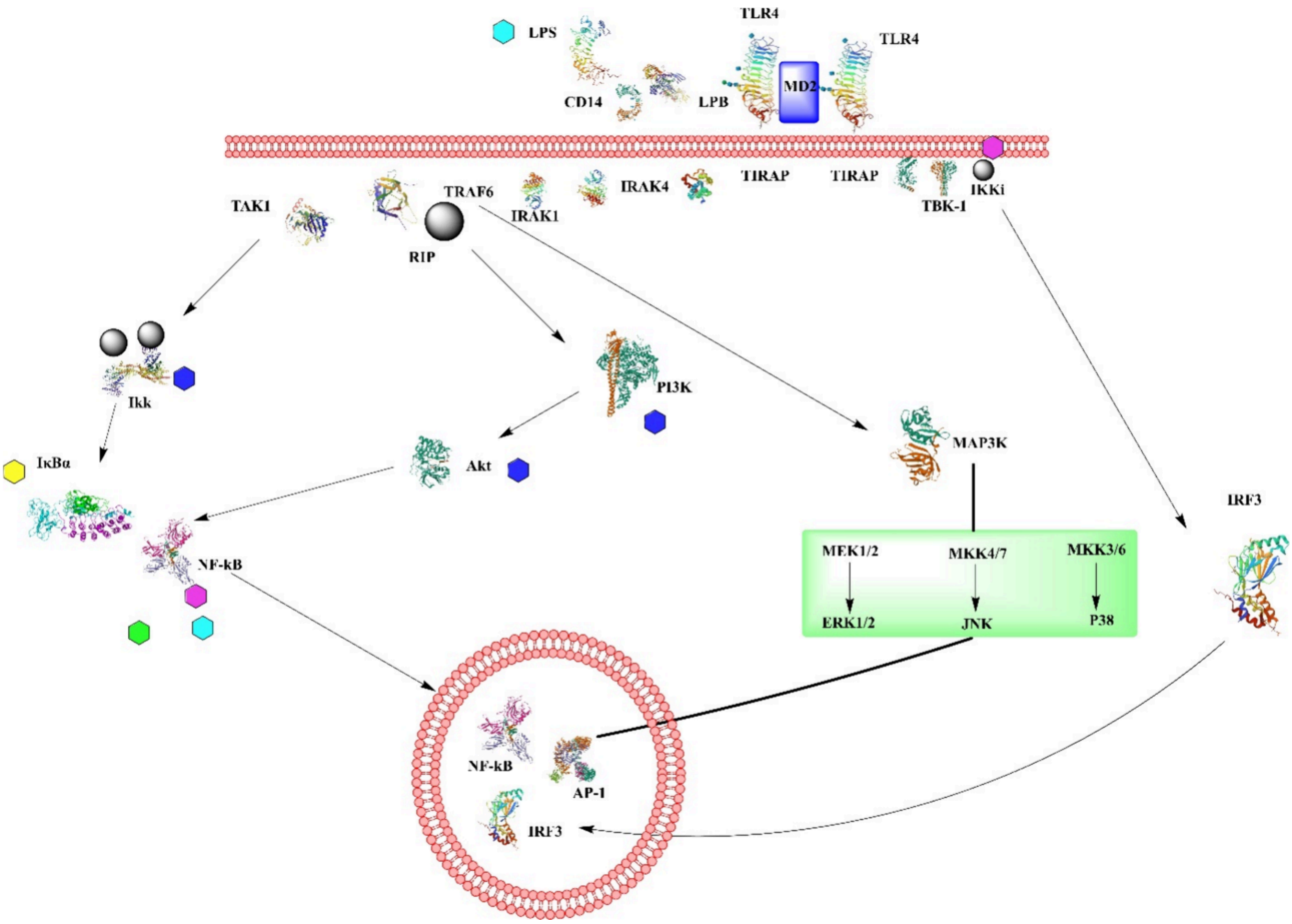

Figure 6. Schematic of selected phytochemical affection on Nf-kB singling pathways: Apigenin, purple hexagon; Curcumin, yellow hexagon; Epigallocatechin gallat, light blue hexagon; Genistein, green hexagon; Macranthoin G, blue hexagon.

function to reverse/suppress the initiation phase of carcinogenesis and to prevent the invasion of the premalignant cells through natural, biological and synthetic chemo-preventive agents.[233] Several epidemiological studies demonstrate that dietary food rich in biologically active components is associated with a lower incidence of various cancer types. Research about the effect of biologically active compounds on the epigenome is spreading widely, with the target of regulation of epigenetic gene expression mechanisms like genomic DNA methylation.[234] It is evident that the different phytonutrients we can eat from plant products can inhibit specific carcinogenesis stages. Various findings also reported that phytonutrients can act as a chemopreventive for human cancers. Phytonutrients are chemopreventive for the infection of the cell cycle and initiation, proliferation, and inhibition of apoptosis. Daily intake of phytonutrients is very helpful as a chemopreventive.[235]

The risk of cancer and other chronic disorders is decreased due to the consumption of a higher number of fruits, vegetables, and whole grains. Plant-derived food product's anticancer activities are associated with the action of phytonutrients. A potential anticancer mechanism of phytonutrients is the regulation of cellular signal transduction pathways, and that is why they affect the behavior of cancer cells like invasion, apoptosis, and proliferation. Due to their anticancer capacity, phytonutrients focus on the various cell signaling pathways at several levels, such as protein activation, intercellular messaging, and transcriptional/post-transcription regulation.[236] By 2030, it is expected that there will be an increase in the number of 23.6 million new cases of cancers, according to the statistics of the American Cancer Society. It is necessary to evaluate different cancer preventive measures due to the higher risk of severity. Studies also show that dietary polyphenols and other phytonutrients have the characteristics of modifying epigenetic mechanisms, which involve the modulation of expression of the genes and resultantly lead to cancer regulation.[237] Natural phytochemicals, such as polyphenols, are organic chemicals that have phenol units in their structures. Polyphenols have antitumor characteristics, but under the in vivo conditions, the half-life of polyphenols is short and they have very low bioavailability. This natural chemical means phytochemicals are very helpful for chemoprevention and oncotherapy.[238]

The meta-analysis of 143 prospective studies indicates that isoflavones and flavonoids are significantly related to lower risk of stomach, lung, breast, and colorectal cancers. Case-control studies also revealed that the individual or the total classes of flavonoids are related to breast cancer, lung cancer, aerodigestive tract cancer and colorectal cancer and isoflavones are associated with lung cancer, breast cancer, ovarian cancer, endometrial cancer and colorectal cancer.[239] Flavonoid is the most researched subclass of flavonoids with cancer hazards. Studies also demonstrate that flavonoid consumption is rarely linked to lowering cancer risk. Still, isoflavones in soy and soy-

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based foods can decrease the danger of prostate, breast, and colorectal cancers in Asian peoples. Results are dependent on the assessment of polyphenol consumption, and the food frequency questionnaire and polyphenol food composition can measure it. Sometimes nutritional biomarkers have been used to estimate the relation between polyphenol consumption and cancer.[240] Another article also demonstrates that isoflavonoids such as genistein, glycitein and daidzein are the most studied, showing good anticancer properties and activities focusing on invasion-associated proteins such as MMP-9, MMP-2 and EMT. That is why the isoflavonoids are used in invasive cancer as chemotherapeutics.[241] Phytonutrients present in foods give a chemo-preventive effect on colon and rectum cancers through the regulation of various markers and signaling pathways, and the gut microbiome also performs a role as an effect in colorectal cancer onset and progression. So, any dietary change in it may be involved in colorectal cancer occurrence. Various studies have displayed the key function of growth factors and their signaling process in colorectal cancer pathogenesis.[242] Alkaloids are bioactive compounds that are also known as anticancer agents. Alkaloids are found to enhance cytotoxicity, modulate the survival pathways, induce DNA damage, promote apoptotic cell death, enhance caspase activity, cause the arrest of the cell cycle, and suppress the NF-kB pathways as mentioned in Figure 6.

By targeting various molecular pathways, alkaloids have protective effects on breast cancer. Alkaloids increase the levels of ROS (reactive oxygen species) in breast cancer and cause DNA damage.[243] Several naturally occurring phytonutrients can act as a therapeutic agent for breast cancer; phytonutrients affecting the proliferation of estrogen independent and dependent cells of breast cancer potentially affect the population through breast cancer stem cells, while various compounds are limited due to their bioavailability. So, it is important to formulate or refine these phytonutrients to treat the hormone-refractory breast tumors effectively.[244] Curcumin is a naturally present polyphenol phytonutrient obtained from turmeric rhizome. It gives a yellow color to turmeric. Different studies demonstrate that curcumin has ideal and excellent cancer therapy properties. Curcumin acts as an anticarcinogenic, antioxidant, antiproliferative, antimetastatic, anti-inflammatory, antiangiogenic, radio protective, apoptotic and chemosensitizing agent.[243] There is an increase in public interest in different strategies to prevent cancers. Cancer is steadily increasing globally with escalating problems with drug resistance.[233] For the many types of cancers, cisplatin based therapeutic regimes are commonly used. Most of the time, resistance to cisplatin develops in patients and leads to treatment failure. Phytonutrients or phytochemicals are plant-based nutrients that enhance cisplatin's anticancer ability or activity with minor side effects. Some well-known phytonutrients like curcumin increase the efficacy of cisplatin but, on the other hand, also reduce the toxicity induced through cisplatin. Besides this, the exact underlying mechanism of action is still unclear.[245]

The mixture of different phytonutrients with several bioactivities found in whole foods may have synergistic and additive effects on the carcinogenesis. Practically and clinically, it is necessary to compare the effect of the mixture of phytochemicals with the isolated phytochemicals present in the plant derived food items.[246] Phytoestrogens and their derivatives are also effective for cancer prevention through the inhibition of estrogen synthesis and metabolism, which may lead to antimetastatic, antiangiogenic and epigenetic effects.[247] Phytoestrogens play a key role in cancer prevention and treatment. Chemoprevention is a process in which we control, repress, overturn, and prevent the premalignancy before the occurrence of cancer invasion by using specified synthetic chemical agents and natural products. Numerous naturally present food items have protective effects on different types of cancer. Examples are cereal, grains, nuts, spices, herbs, vegetable, fruits, beverages and medicinal plants and several phytonutrients, including flavonoids, carotenoids, phenolics, and nitrogen-containing and organ sulfur compounds.[248]

GLSs (glucosinolates) are the secondary metabolites occurring in plant foods and have useful anticarcinogenic effects. Glucosinolates could be converted into different breakdown products based on plant tissue damage and through the gut microbiotas. Glucosinolates' bioactivities are associated with the breakdown products rather than the glycosylates themselves.[249] Phytosterol is also a useful phytochemical, which decreases the risk of cancer by 20%. Phytosterol affects the hosts and produces the antitumor response by enhancing the immune response of cancer recognition, also affecting hormone-dependent endocrine tumors or cancer and via the modulation of sterol biosynthesis. Phytosterol has characteristics which will stop the growth of tumor cells by decreasing the progression of cell cycling, induction of apoptosis and inhibition of tumor cell metastasis.[250]

Neurodegenerative Diseases and Phytonutrients. In neurodegenerative disorders, progressive loss of neurons occurs, which is linked with the deposition of proteins, indicating the change in physiochemical characteristics in the brain and peripheral organs. Neurodegenerative diseases are classified (molecular) based on proteins. Protein is commonly involved in the neurodegenerative diseases pathogenesis, namely TAR DNA binding protein 43 kDa, prion protein, tau protein, alpha synuclein, amyloid beta and fused in sarcoma protein.[251] Commonly known neurodegenerative disorders are Alzheimer's disease, Parkinson's disease, Lewy bodies' dementia, front temporal dementia and its variants, corticobasal degeneration, progressive supranuclear palsy, Huntington's disease and multiple system atrophy.[252] Some neurodegenerative disorders such as multiple sclerosis, motoneuron, Parkinson's disorder, Alzheimer's disease, Huntington's disorder and human prion are not curable and the emotional control and deterioration in social communication and social behavior characterize all these.[253] Parkinson's disease is the most known neurogenerative problem in males compared to females and increases in people aged 60 or above. Commonly seen symptoms are shaking at rest, bradykinesia, stiffness and postural instability.[254] Alzheimer's is a subtype of dementia; in this illness, gradual loss of memory occurs, which leads to reduction of behavioral functions like thinking, language skills and memory.[255] Huntington's disorder is an inherited disorder that occurs due to the autosomal dominant trait. In this disease obsessive compulsive disorder, psychosis, cognitive impairment, depression and abnormal movements occur.[256]

In Alzheimer's disease, mitochondrial involvement is helpful for improving clinical properties such as low oxygen and glucose in the brain metabolism, which is also supported by the various molecular and microscopic findings, which include the altered mitochondrial morphology, impaired mitochondrial DNA, and abnormal respiratory chain functions. Mitochondrial dysfunction and amyloid pathology are both directionally

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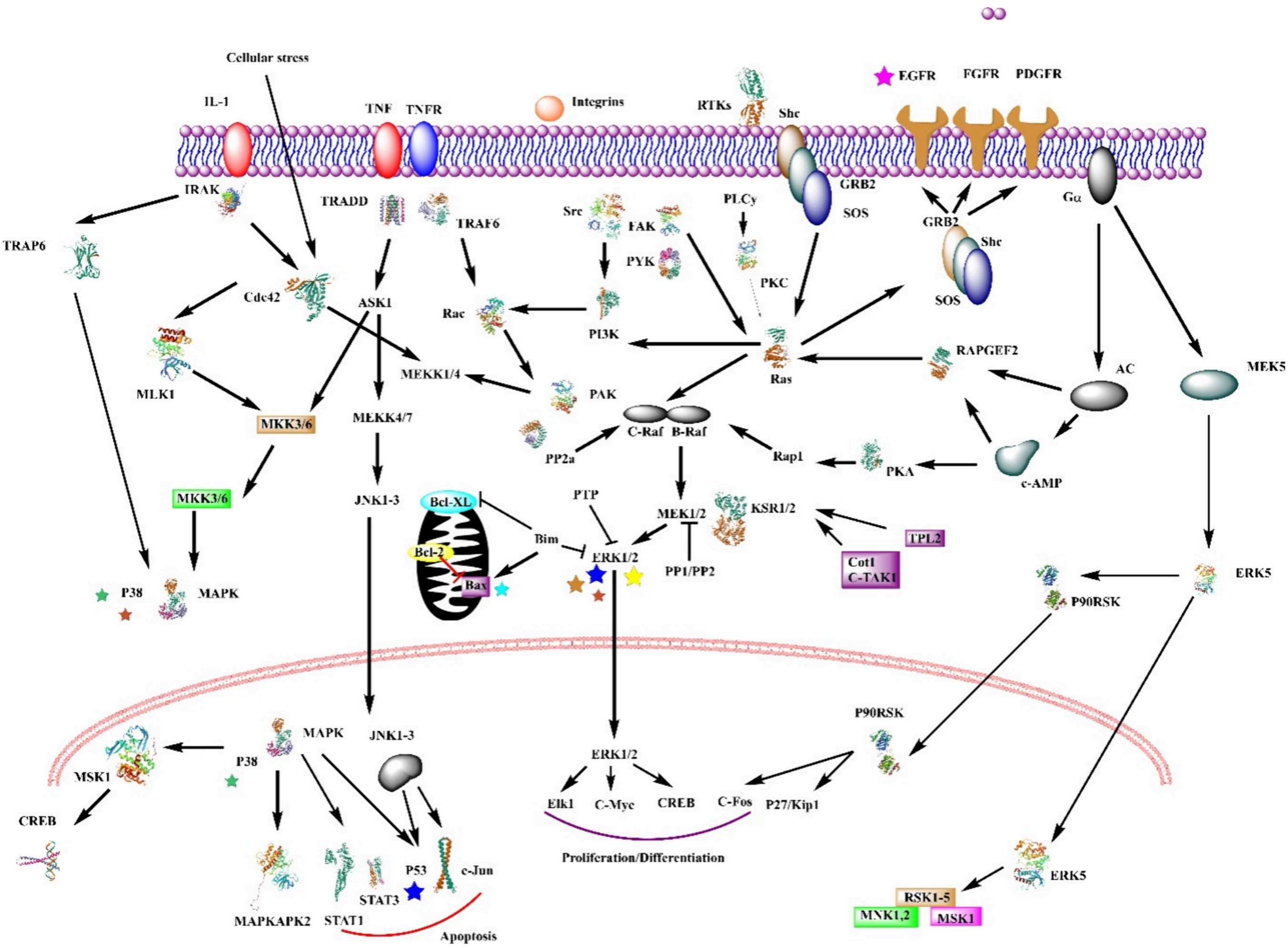

Figure 7. Schematic of selected phytochemical affections on MAPK signaling pathways: yellow star, Sulphoraphane and erucin; blue star, Resveratrol; purple star, Silibinin; light blue star, Luteolin; green star, Genistein; red star, Glabridin.

correlated. Mitochondria have more remarkable function in Parkinson's disorder.[257] Through oxidative damage of the neurons, amyloid beta participates in developing AD's. Phytonutrients such as saponins, isoflavones, and proanthocyanin's genistein inhibit amyloid beta induced neurotoxicity.[258] Bananas have important pharmaceutical and nutraceutical values due to the presence of polyphenols, flavonoids and phenol in their flesh and peels.[259] In the pulses/legumes, phenolic phytonutrients are present such as proanthocyanins, flavanols, flavanols, isoflavones, and hydroxycinnamic acids, and a major non-phenol phytonutrient is saponins. Legumes are beneficial for the neurodegenerative disorder due to the presence of biologically active phytonutrients.[260] Numerous studies indicate that resveratrol acts as an anti-inflammatory, antioxidative, and neuroprotective. In Alzheimer's disease patients, resveratrol reduces the aggregation and toxicity of Aβ peptides in the hippocampus, promotes neurogenesis, and prevents hippocampal damage. The antioxidant activity of resveratrol plays a significant role in the differentiation of neurons by activating SIRT1 (silent information regulator-1). Silent information redulator-1 plays a key role in the differentiation and growth of the neurons and is also involved in the prevention of the apoptotic death of the mentioned neurons by deacetylating and repressing the p53 activity, but the exact mechanisms is still unclear.[261]

The many changes in lifestyle along with the increased consumption of junk drinks, fast foods and ready to eat foods are giving an overloaded oxidative stress, which causes weakening of the defense mechanism for the removal of free oxygen radicals by destroying the antioxidants. Neurodegenerative disorders and oxidative stress pathogenesis occur due to the imbalance between the preoxidant and antioxidants levels. If the pro-oxidant levels are higher, then NDD pathogenesis will occur.[39,40,262] Epicatechin and catechin flavonols are most abundantly present in grape juice and seeds. Grape juice is helpful in the inhibition of the glutamate excitotoxicity, which is implicated majorly in the pathology of neurological disorders like Alzheimer's disease and Huntington's disease.[263] Orange fruits, juice, and drink have carotenoids, which are helpful in the prevention of neurodegenerative diseases. Carotenoids stop the onset of neurodegenerative diseases by mechanisms such as an increase in the regulation of the antioxidant enzyme system and regulate the amyloid oligomer induced signaling and antioxidant capacity through reactive oxygen species quenching.[264] Organic sulfur and isocyanate derivatives significantly affect various diseases, specifically neurodegenerative diseases. Garlic has the sulfur derivative S-allyl cysteine as a major component of garlic extract with neuroprotective and anti-inflammatory potential. Olive oil is also a main part of the Mediterranean diet. Neurodegenerative diseases are preventable mainly using antioxidants such as vitamin C and Vitamin

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E, polyphenols, and flavonoids. Antioxidants are effective for human health because they can also decrease aging by fighting free radicals.[265,266]

Polysaccharides are important phytonutrients, and various studies give details about their benefits. They are also effective in treating several pathological conditions like neurological disorders. Sixteen out of 21 types of plant-based polysaccharides show the neuroprotective effect. Various in vitro and in vivo studies explain that the polysaccharide-rich extracts give the neuroprotective effects by promoting the neurite outgrowth, PI3K/Akt, Nrf2/HO-1, NF-Kb and MAPK signaling pathways, as mentioned in Figure 7.[267]

Oxidative stress is involved in the pathogenesis of neurodegenerative disorders like Parkinson's disease. Quercetin is a bioflavonoid present in vegetables and fruits, also having antioxidative properties. But the underlying mechanism has not been well-known until now. Quercetin is a therapeutic agent for neurodegenerative diseases, which are induced by oxidative stress.[268] Several classes of polyphenols such as phenolic acids, phenolic alcohols, flavonoids, stilbenes, and lignans will focus on the toll like receptor (TLR) signaling pathway. Moreover, some of the polyphenols suppress the overexpression of the inflammatory regulator by the intervention in the TLR/NF-Kb/STAT signaling pathways; others will decrease the neuronal apoptosis through modulating TLR4/NF-Kb/MyD88 pathways in macrophages or microglia. Activation of the TLR signaling modulation through natural sources will give positive and effective therapeutic effects on the neurodegenerative diseases.[269] Studies indicate the powerful link between the polyphenol's intake and lower development of neurological diseases.[270] Polyphenols are very useful and healthy phytonutrients for the prevention and treatment of different pathological disorders like neurodegenerative disorders. Polyphenols food sources include tea, coffee, vegetables, and fruits. Almost all the polyphenols are neuroprotective because they reduce oxidative stress, inflammation, and protein fibrillation and enhance cognitive functions.[271] They also reduce the risk of brain disorders. The brain controls the hypothalamus pituitary gonad axis secretion of estrogen. Estrogen therapy is also effective for neurodegenerative disorders. The neuroprotective effects of the phytoestrogens are associated with their antioxidant characteristics and interaction with estrogen.[247]

Anti-aging Phytonutrients. Aging is a biological process characterized by the continuous reduction in cellular function and by decreased tissue renewal ability, and it will lead to less capability to counteract the stressors of the environment. The aging process could be controlled through various heterogeneous mechanisms including environmental, genetic, and epigenetic factors.[272,273] According to clinical and biological perspectives, skin undergoes two processes. Intrinsic aging of the skin is the first process that indicates aging in chronological terms and affects the same process by which all other internal organ aging occurs. Extrinsic aging of the skin is the second process due to external risk factors such as smoking, sleep deprivation, pollution, environmental factors, chronic exposure to the sun and to ultraviolet radiation, and inappropriate nutritional intake. Studies suggest that phytonutrients acting as an antioxidant, for example, tocopherols, carotenoids, flavonoids, different vitamins like vitamin A, Vitamin C, Vitamin E and Vitamin D, some proteins, omega 3 fatty acids and lactobacilli agents, are helpful in the promotion of the skin's health and beauty.[274] Aging causes various and multiple changes in biological processes such as nutrient sensing, metabolism of energy, and decreased cellular proliferation, and it causes cellular senescence. Through the multiple bioactivities of the polyphenol phytonutrient, resveratrol is considered to lower the negative effects of aging.[275]

The human body depends on the different aging defense mechanisms to reduce damage through pronging aggressors. This kind of protective mechanism may be compromised and leads to accelerated aging.[276] We identified that the phytonutrients present in tomatoes regulate the expression of ultraviolet inducible genes (ICAM-I, MMP-1, HO-1 etc.), which act as biomarkers for skin health.[277] Phytonutrients act as antiaging components. Moreover, detailed studies of epicatechin, curcumin, resveratrol and quercetin reported new phytochemicals for aging; for example, amino acid L-theanine is isolated from green tea, and lignans arctigenin and matairesinol are isolated from the *Arctium laoopa* seeds.[278] According to research, 4 capsules per day were consumed for 8 weeks. Each daily dose contains 30 mg of resveratrol, 1000 mg of DHA plus EPA from the ultrapure fish oil, 100 mg of alpha lipoic acid, 75 mg of quercetin, 30 mg of Coenzymes Q10, 5 mg of lycopene, 1 mg of astaxanthin, 4 mg of lutein, 50 mg of d-limonene, 1000 IU of vitamin D3 and 200 mg of citrus bioflavonoids. Intake of these 4 capsules daily for 8 weeks will positively affect the aging defense mechanism. It will protect from skin damage due to ultraviolet radiation and improve skin health.[276] Another study was conducted to analyze the phytonutrient constituents, nutrient composition, and antioxidative properties of dried rose petals. The secondary metabolite phytonutrients present in dried rose petal power solvent extracts are flavonoids, phenols, alkaloids, glycosides, saponins, tannins, carbohydrates, terpenoids, and steroids. Rose power has the good quality of phytochemicals and antioxidative activities.[279]

Different phenolic compounds, carotenoids and ascorbic acid are present in the various plants and have the ability to give protection to the skin from ultraviolet radiation, lower the oxidative stress and inflammation and affect the different signaling pathways or mechanisms.[280] Beta carotene is helpful in the prevention of night blindness and age associated macular degeneration. It also maintains the health of the skin, nails, hair, gums, teeth, bones, and glands. Beta carotene is present in various food items such as yellow, green, and orange vegetables and fruits, for example, broccoli, kale, squash, carrots, spinach, cantaloupe, apricot, sweet potatoes, and peaches. Zeaxanthin and lutein are also protective for cataracts and age related macular. Zeaxanthin and lutein are found in green pea, green turnip, spinach, broccoli, kale, and collard greens.[281] Carotenoids are a group of phytonutrients that are very helpful for skin health. They increase the skin's resistance against UV-rays' B-induced erythema (sunburn).[282] Oral intake of polyphenols and carotenoids is recommended to produce the photoprotective effects. Combination of polyphenols and carotenoids is more beneficial for the skin cells.[283] Intake of fruits and vegetables rich in beta carotene has more light protective positive effects, and intake of beta carotene for 12 weeks daily leads to decreased ultraviolet induced erythema.[284] Astaxanthin from the carotenoid is also protective against cellular alternation caused by ultraviolet radiation. Lycopene is also a carotenoid red pigment and a phytonutrient component present in red vegetables and fruits such as tomatoes, red carrots, watermelons and papaya.[285] Another study demonstrated that the intake of whole fruits or extracts

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of stems and seeds containing phytonutrients will enhance skin health. Phytonutrient rich foods help reduce DNA damage by increasing its repair, act as a sunblock/sunscreen, decrease inflammation and oxidative stress and promote the skin barrier functions.[286] Polyphenols in green tea, grape seed proanthocyanins, silimarine, resveratrol, and genistein are great for good skin health. These polyphenols are also beneficial in managing skin cancer.[287] The Mediterranean diet is also full of antioxidants and phytonutrients in vegetables and fruits. It has a very low risk of various age-related diseases. It was also demonstrated that the phytochemicals present in the Mediterranean diet increase the healthful effects.[288]

Various products are present in nutricosmetics and cosmeceuticals. Active compounds present in the various products are extracted from vegetables, fruits, pulses, medicinal herbs and plants with antiaging power.[289] A plant named *Alpinia galangal* is a well reputed medicinal plant which has been used in food and medicine for a long time. Flavonoids are phytonutrients which are very beneficial and commonly used in the development of cosmetic or cosmeceutical products due to their antiaging and antioxidant functions.[290] Lotus plant's other name is Nelumbo Nucifera Gaertn. It is used in the formation of teas, traditional medicine, and foods. Evaluation of the stamen extract as an antiaging skin protector concluded that it has more power to stop tyrosinase and collagenase than the whole flower.[291]

Inflammatory Bowel Disease and Phytonutrients. IBD is a chronic inflammatory disease. It affects the gastroenteric tissues, which are characterized with intestinal inflammation. In this disorder, intestinal mucosa become inflamed and cause episodic abdominal pain, blood in the stool, diarrhea, weight loss, and influx of neutrophils and macrophages which produce cytokines, free radicals and proteolytic enzymes that result in ulceration and inflammation.[292] Chronic inflammatory bowel disorders include ulcerative Colitis and Crohn's disorder. They have almost the same symptoms that cause digestive system inflammation.[293] The rate of prevalence is gradually increasing in western countries, and there is a rapid increase in the rate of incidence in newly industrialized countries.[294] Another study demonstrated a comparison of the population-based data for the West and East. It indicates that the incidence of inflammatory bowel disease is rapidly increasing in the East and plateauing in the West. Patients in the East with this disease have more complications.[295]

Several in vivo and in vitro practicals represent that the secondary metabolite or phytonutrients are plant based and have alkaloids, terpenoids, glucosinolates, phenolic compounds, oligosaccharides, and quinones. All of these phytonutrients will reduce the permeability and ameliorate associated dysfunctions with good results. Most of them suppress the inflammatory transcriptional factors, decrease the pro-inflammatory cytokine secretions, help with oxidative stress, and modulate the enzymatic activity.[296] Various biologically active components present in the functional agent have received attention by indicating powerful therapeutic effects against inflammatory bowel disease.[297] Trillions of microorganisms are colonized in the intestine of the host. So, it is reported that the gut microbiota are involved in the pathophysiology of inflammatory bowel disorder. Flavonoid phytonutrients have been given more attention because of their antioxidant and anti-inflammatory properties.[298]

On the surface of the immune cell, flavonoids interact with the toll-like receptors; then they enter the cytosol and transfer into the nucleus. Then they attach to the aryl hydrocarbon (Ah) receptor in the nucleus. Then aryl hydrocarbon receptors become bound with the aryl hydrocarbon receptor nuclear translocator. Then through the aryl hydrocarbon response element helpful protective enzymes and cytokines will be induced. This mechanism will lead to the up regulation of the anti-inflammatory effect. Hence, phytonutrients like flavonoids bind with the nuclear aryl hydrocarbon receptor, producing protective enzyme activities.[299] Polyphenol is another example that is present in plant foods. It synergistically interacts with the microbiome of the gut to repress inflammation and increase the symptoms of inflammatory bowel disease. Polyphenols increase the availability of healthy bacteria, stop the pathogenic species, and enhance the diversity of the gut microbiota. Polyphenols are not absorbed in the small intestine. They will be catabolized in the colon through the microbiota into the microbial metabolites. Most of them have more bioavailability and anti-inflammatory properties than the precursors.[300] Different classes of polyphenols (anthocyanins, stilbenoids, and flavonols) are also healthful for treating inflammatory bowel syndrome. According to studies, supplementing the diet with red grapes skin (having flavonals, stilbenoids and anthocyanins) will give positive and beneficial protection.[301] Polyphenol antioxidants are effective for treating experimental colitis. Green tea curcumin, wheat grass juice, resveratrol, bilberry anthocyanins, fish oil and superoxide dismutase are effective for treating inflammatory bowel disease.[302] Green tea polyphenols also play a key role in the down regulation of the signaling pathways. Green tea-based polyphenols give beneficial antioxidant properties and regulate the toll like receptor 4 expression by the specific receptors and inhibit the endotoxin mediated TNF-α's production through blockage of the transcription NF-kB upstream of the mediated I kappa B kinase complex path activities and also the intrusion with the flow of cytokines and synthesis of COX-2 (cyclooxygenase-2).[303]

From the studies, it is hypothesized that the changes in the diet will be helpful. According to the hypothesis, decreased exposure to pro-inflammatory antigens, for example, emulsifiers, omega 6 fatty acids, and additives, and enhanced intake of anti-inflammatory compounds such as curcumin and omega 3 fatty acids in the foods or diet will tip the balance toward a low inflammatory profile.[304] Anthocyanin in plant food is also very helpful for inflammatory bowel disorder. A new therapeutic option is also available: intake of anthocyanin enriched dietary supplements with the existing medication will be a good treatment option for IBD.[305] An anthocyanin rich diet (fruits and vegetables) protects from inflammation, enhances gut permeability, and is also beneficial for colon health due to its ability to change bacterial metabolism and microbial milieu in the intestine.[306] Probiotics are also very beneficial in inflammatory bowel disease and ulcerative colitis.[307] Probiotics treat ulcerative colitis, specifically when various strains are concomitantly administered. The most used genera are *Bifidobacterium and Lactobacillus.* Some studies even demonstrate a benefit if we replace medical nutrition therapy with the probiotic supplementation.[308]

Stress-Sleep and Phytonutrients. Systemic inflammation and oxidative stress are the main reasons for the deleterious effect of chronic psychological stress. Dietary supplementation of the macular carotenoids lutein, meso-zeaxanthin and

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Table 3. Effect of Food Processing and Procedures on the Phytonutrient Content and Antioxidant Activity

Food Processing and Procedure	Food Matrix	Investigated Phytonutrients	Effects on phytonutrients Content and/or Antioxidant Activity	Reference
Tomato-sauce production cooking for 60 min at 99 °C and crushing	Tomato	Phenolic acids	Phenolic acids decrease 43.18%.	314
		Flavanones	Flavanones increase 245.03%.	
		Flavonols	Flavonols increase 17.21%.	
Drying at 70 °C for 36 h	Tomato	TPC	Compared with raw tomatoes, dried tomatoes had higher TPC and TFC values during digestion.	315
		TFC		
Freeze-drying drying at:	Berries	Anthocyanins	Anthocyanins from berries are best maintained by freeze-drying and breaking down at 130 °C. Berries had the highest polyphenol content after freeze-drying at 65 °C. Berry variety impacts ABTS, radical removal, and ferric reduction. Highest ABTS occurs in raspberry and boysenberry drying at 65 °C, and redcurrant and blackcurrant freeze-drying.	327
50 °C for 48 h		TPC		
65 °C for 20 h				
130 °C for 2 h				
Until a moisture 89 content below 15% was obtained				
Slow Freezing vs quick freezing	Strawberries	Total polyphenol capacity	Strawberries total polyphenolic capacity and total monomeric anthocyanin's content is higher in the quick-frozen samples as compared to slow samples.	317
		Total anthocyanin content		
Boiling, Steaming, Microwaving	Cassava	Total extractable polyphenols	The extractable polyphenols increase 152% after boiling, 236% after steaming, and 164% after microwaving. Cassava antioxidant activity rises 151.56, 208.60, and 173.44% after boiling, steaming, and microwaving.	319
Cooking in water for 10 min, Steaming for 15 min at 97 ± 2 °C, Microwaving for 5 min with 800 W, Baking for 15 min at 200 °C	Sweet potatoes (2 varieties grown in Slovakia and Croatia)	TPC	After treatment, all samples except Beauregard from Croatia gained anthocyanin and polyphenolic capacity. All samples except steaming Beauregard from Slovakia had reduced neochlorogenic and chlorogenic acids after treatment. All treatments except boiling reduced Tran's ferulic acid. The antioxidant capacity of all treated samples increases.	320
		TAC phenolic acids (chlorogenic, neochlorogenic, and trans-ferulic)		
Freezing by immersion at liquid nitrogen, Freeze-drying at −50 °C	Apples	TPC	The total polyphenol capacity is reduced before the digestion in both freezing methods, and the antioxidant activity also reduced before and after digestion.	321
Freeze-drying vs hot-air-drying vs infrared-drying at 35, 40, 50, and 60 °C vs pasteurization	Apples puree	Total polyphenols	The highest urine polyphenol excretion of three individuals in an in vivo crossover testing was pasteurized apple puree, followed by hot air-dried and freeze-dried samples.	322
Canning in industrial vs domestic settings	Apricots	TPC, procyanidins, phenolic acids	Procyanidins drop 44% in industrial environments and 2.4% in home settings, whereas total polyphenol capacity decreases 13−47%. Industrial cooking decreased phenolic acids more than household cooking.	323
Ting fermentation (at different time and temperature regimes)	Sorghum	TPC, total flavonoid and total tannin content	All the analyzed compound's optimal values at 27 °C for 72 h and the antioxidative properties are best which was found in the sample fermented at 27 °C for 24 h.	324
Pickling	Green beans, green pepper, chili pepper, white cabbage, cauliflower, cucumber, sneak melon, tomato, carrot, garlic	TPC	Vegetables exhibited reduced total polyphenol capacity after 15 days, although it rose after 30 and 60 days. Green peppers, green beans, chili pepper, white cabbage, cauliflower, cucumber, and sneak melon lost antioxidants after 15 days but gained them after 30 and 60 days, whereas tomatoes, garlic, and carrots boosted them.	326

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zeaxanthin will decrease the stress cortisol and improve symptoms of physical and emotional health.[309] According to research, affron is a standardized stigma extract from *Crocus Sativus L.* and is used for the treatment of sleep quality, stress, anxiety, and mood swings in healthy adults. They perform this research on 128 participants with self-reporting low mood but not depression diagnosed. They were given affron of 22 mg/day, 28 mg/day or a placebo treatment in a double blind, randomized, and placebo-controlled trail for 4 weeks. Improvements were seen in the group taking the 28 mg/day dose.[310] Another study was also performed to check the efficacy of the crocetin on the architecture of the sleep and subjective sleep parameters in healthy adults with mild sleep complaints. Thirty participants were divided into the 2 groups. One group treated with crocetin 7.5 mg/day and with the placebo. The results of this study recommend that the crocetin supplementation is very beneficial for the maintenance of sleep and also involves improving the quality of sleep.[311] Insomnia is a chronic condition that is most common in the elderly population. According to the findings, Montmorency tart cherry juice is useful for treating insomnia. Cherry juice increases the sleep efficiency and sleep time. Cherry juice is procyanidin B-2, which stops the IDO, reduces inflammation, enhances tryptophan availability, and is also partially effective for insomnia patients.[312]

Bioavailability. Bioavailability is a term used to explain the proportion of phytonutrients absorbed, digested, and utilized in normal metabolism. Moreover, the bioavailability measurement depends on the estimation of the antioxidants absorbed.[313] Most common phytonutrients such as polyphenols, curcumin, and green tea polyphenols are not satisfied with all these chemical specifications and exhibit lower bioavailability. Following are examples of the bioavailability of different food items. The first example is tomatoes (food matrix), whose food processing procedures may change the availability of its nutrients. If tomato sauce is cooked for 60 min at 99 degrees centigrade and crushed, the phenolic acid phytonutrients level will reduced by 43.18% and the levels of flavonols and flavanones will be increased by 12.21% and 245.03%, respectively.[314] Upon drying of the tomatoes at 70 degrees centigrade for 36 h, the in vitro gastrointestinal digestion model gives a higher total polyphenol capacity and total flavonoid capacity than those for raw tomatoes.[315]

In another study, berry availability was checked by the freeze-drying method. The berries were dried at 130 °C for 2 h, 65 °C for 20 h, and 50 °C for 48 h until 89 moisture content was obtained below the 15%. Anthocyanins in the berries are best preserved by the freeze-drying method and degraded at 130 °C. In the berries, the highest value of the total polyphenol capacity is obtained from the drying at 65 °C through the freeze-drying method. Antioxidant activity includes ABTS, radical removing activity, and ferric reducing power, which varied depending on the berries type. Raspberry and boysenberry give the highest ABTS in the case of drying at 65 °C and redcurrant and blackcurrant in the case of freeze-drying.[316] Strawberries total polyphenolic capacity and total monomeric anthocyanin's content are higher in quick-frozen samples than in slow-frozen samples.[317] The total polyphenols are reduced but not significantly, and total anthocyanins were reduced significantly by 42.2%. Chlorogenic acid increased significantly by 23.46%, and total procyanidins, quercetin, caffeic acid and ferulic acids increased but not significant.[318]

In the Cassava, total extractable polyphenols are increased to 152% after boiling, 236% after steaming, and 164% after microwaving. The antioxidant activity of the cassava is also enhanced 151.56% after boiling, 208.60% after steaming and 173.44% after microwaving.[319] To determine the availability of sweet potatoes (2 varieties grown in Slovakia and Croatia), they were cooked in water for 10 min, steamed for 15 min at 97 ± 2 °C, microwaved for 5 min at 800 W, and baked for 15 min at 200 °C. Total anthocyanins' capacity is increased in all the samples, Total polyphenolic capacity is increased after all the treatments of all the varieties, except in Beauregard from Croatia. Neochlorogenic acid was reduced in all the samples after treatment, and chlorogenic acid level also decreased in all the samples of treatment except after steaming of Beauregard from Slovakia. trans-Ferulic acid decreased in all samples of treatment except in boiled. The antioxidant capacity of all the samples of treatment is increased.[320]

In another study, the content of the phytonutrients in apples was determined by two types of freezing methods: freezing by immersion at liquid nitrogen and freeze drying at the 50 °C. The total polyphenol capacity is reduced before digestion by both freezing methods, and the antioxidant activity is also reduced before and after digestion (CUPRAC, FRAP and ABTS assays).[321] Another experiment was also performed on apple puree; the methods used were freeze-drying, hot-air-drying, infrared-drying at 35, 40, 50, and 60 °C and pasteurization. In the human in vivo crossover study, three subjects' % of urine excretion of total polyphenols was highest in pasteurized apple puree followed by the hot air-dried and then freeze-dried samples.[322] When apricot canning was studied in industrial vs domestic thermal processing, it was found that the total polyphenol capacity was reduced 13 to 47% in the industrial and 2 to 33% in the domestic settings; procyanidins decrease by 44% in the industrial environment and by 2.4% in domestic locations. Phenolic acids are being utilized in industrial settings as compared to domestic cooking.[323]

The Ting fermentation method is performed at different time and temperature regimes to analyze the content of the antioxidants and phytonutrients in sorghum. TPC, total flavonoid, and total tannin content are investigated. So, all the analyzed compound's optimal values at 27 °C for 72 h and the antioxidative properties are best found in the sample fermented at 27 °C for 24 h.[324] Fermentation of the 8 pulses such as mottled cowpea, black cow gram, speckled kidney beans, small rice beans, lentil, 2 soybeans, and small runners' beans was performed with naturally occurring bacteria and lactic acid bacteria. Total polyphenol capacity is enhanced in all the legume samples, and antioxidant activities are also higher in the speckled kidney beans, mottled cowpeas and small rice beans and no significant changes are seen in the other treatment samples.[325] Pickling of the green peppers, green beans, chili peppers, white cabbage, cauliflower, sneak melon, cucumbers, tomatoes, carrots, and garlic was done to find the availability. It was observed that the total polyphenol capacity of all these vegetables was reduced after 15 days but enhanced after 30 and 60 days in all the vegetables. The antioxidant capacity also was reduced after 15 days and then was enhanced after 30 and 60 days in the green peppers, green beans, chili peppers, white cabbage, cauliflower, cucumber and sneak melon; for the tomatoes, garlic and carrots, it was enhanced during all the time points (as shown in Table 3).[326] A large body of evidence highly supports that the use of

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polyphenol rich food and food products is excellent for the prevention and treatment of several chronic disorders. It is also estimated that their bioavailability is of great interest to draw a straightforward conclusion about their original efficacy.[266]

CONCLUSION AND FUTURE PERSPECTIVES

Chronic diseases are the leading causes of death. Various pathological conditions are occurring due to increased amounts of harmful oxidants such as reactive oxygen and nitrogen species. It is required to lower oxidative stress to reduce all of these disease-causing oxidants. These plant-derived compounds, including polyphenols, flavonoids, and carotenoids, play pivotal roles in countering oxidative stress and inflammation, thereby contributing to the management of diverse ailments. Phytonutrients are plant-based bioactive compounds present in dietary sources and are also used in the nutraceutical industry. All the observed studies show a positive effect of phytonutrients on disease prevention and management. The major phytonutrients discussed are polyphenols, anthocyanin, resveratrol, phytosterol (stigmasterol), flavonoids, isoflavonoids, limonoids, terpenoids, carotenoids, lycopene, quercetin, phytoestrogens, glucosinolates, and probiotics. All of these phytonutrients are present in several fruits, vegetables, legumes, beans, nuts, seeds, and other medicinal plants. It is concluded that the intake of phytonutrients through the diet has beneficial effects on disease prevention and treatment such as diabetes mellitus, obesity, hypertension, cardiovascular disorders, different types of cancers, neurological disorders, age-related diseases, inflammatory disorders, and other biological activities. Despite the acknowledged limitations, the integration of phytonutrient-rich foods into one's diet holds significant promise for improving overall health. Ongoing research and a nuanced understanding of individual variability are critical to fully harness the potential of phytonutrients in disease prevention and treatment. Future perspectives should explore personalized approaches to harness the potential of phytonutrients, leveraging advancements in omics technologies and precision nutrition while also investigating novel sources and synergistic combinations to enhance their therapeutic applications.

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Notes

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