

## Advanced Nutraceuticals for the Treatment of Various Diseases

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### ABSTRACT

The growing popularity of nutraceuticals is driven by consumer demand for natural and effective alternatives that offer physiological benefits and disease prevention. Plant-based extracts, rich in bioactive compounds such as lipids, phytochemicals, and pigments, are increasingly used in the food, pharmaceutical, and cosmetic industries. Traditional extraction methods like Soxhlet extraction are time-consuming and solvent-intensive. As a result, there is a rising demand for more efficient extraction techniques that reduce time, solvent usage, and environmental impact. Modern methods such as ultrasound-assisted extraction, microwave-assisted extraction, supercritical fluid extraction, and accelerated solvent extraction have been developed to address these challenges, offering faster and more sustainable ways to obtain valuable plant-derived compounds. These innovations support the growth of nutraceuticals, nutritional therapy, and phytotherapy, contributing to improved health and reduced healthcare costs.

### I. INTRODUCTION

Lijun Wang\* and Curtis L. Weller reviewed regarding Recent advances in extraction of nutraceuticals from plant

Nutraceuticals are becoming increasingly popular as consumers seek alternative and helpful goods. Natural dietary supplements and nutraceuticals are gaining popularity for their physiological advantages and disease prevention.

Plants include a variety of bioactive components, including lipids, phytochemicals, pharmaceuticals, tastes, perfumes, and pigments. Plant extracts are commonly used the food, pharmaceutical, and cosmetic sectors. Extraction strategies have been extensively studied to obtain such Plants provide useful natural chemicals commercialization.<sup>1</sup>

Nutraceuticals, nutritional treatment, phytonutrients, and phytotherapy are some of the new concepts emerging from this trend . Functional

or therapeutic foods, phytonutrients, and phytomedicines can improve health and immunological function, preventing particular diseases and perhaps lowering healthcare costs.

Soxhlet extraction, a traditional process used for decades, is time-consuming and requires significant amounts of solvents (Luque de Castro & Garcia-Ayuso, 1998).

New extraction techniques are in high demand due to shorter extraction times, lower organic solvent use, and improved pollution avoidance. Ultrasound-assisted extraction (Vinatoru, 2001), microwave-assisted extraction (Kaufmann & Christen, 2002), supercritical fluid extraction (Marr & Gamse, 2000; Lang & Wai, 2001; Meireles & Angela, 2003), and accelerated solvent extraction (Kaufmann & Christen, 2002; Smith, 2002) are efficient methods for extracting chemicals from solid plant matrixes. These approaches can function at higher temperatures and pressures, reducing extraction time significantly.<sup>2</sup>

### Classification of Nutraceuticals

The food sources used as nutraceuticals are all natural and can be categorized as

1. Dietary Fiber
2. Probiotics
3. Prebiotics
4. Polyunsaturated fatty acids
5. Antioxidant vitamin
6. Polyphenols
7. Spices (kalia AN, 2005)

**Nutraceuticals** are biological medicines that are non-specific and are used to control symptoms, prevent malignant processes, and promote wellness.

The following categories can be used to group these:

**Nutrient:** A component of feed that is added in a way and in a concentration that will support an animal's life. The main categories of nutrients used

in feed are minerals, vitamins, proteins, fats, and carbs.

#### **A dietary supplement:**

A product that incorporates the diet as concentrations, components, extracts, or metabolites of these substances, as well as one or more of the following dietary ingredients: vitamin, mineral, herb, or other botanical, amino acid (protein).

#### **Herbals:**

Plant materials in the form of extracts and concentrates. Herbs are as old as human civilization and offer a vast array of cures for both acute and chronic illnesses. India possesses the oldest documented history of using "Ayurveda," a system of natural treatments that offers numerous efficient ways to guarantee health care. Key component medicinal herbs contain a multitude of nutraceuticals.

#### **Probiotics:**

- Bacteria are commonly associated in disease transmission. The human body contains both beneficial and harmful germs.
- Probiotics, also known as "good" or "helpful" bacteria, promote gut health.
- Probiotics are naturally present in your body. They can also be found in some foods and supplements.
- Since the mid-1990s, there has been increased interest in probiotics and their potential health advantages. Doctors often recommend them to treat stomach issues. They've gained popularity and can now be found in a variety of products, including yogurt and chocolate.

#### **Prebiotics :**

These are fiber compounds that pass undigested through the upper gastrointestinal system. They stimulate the growth of beneficial bacteria that colonize the large bowel by functioning as a substrate (Gibson GR et al., 1991). Prebiotics, like probiotics, are considered a functional dietary component that falls somewhere between foods and pharmaceuticals. Regulatory scrutiny of health claims varies by country and is often moderate.

#### **POLY UNSATURATED FATTY ACIDS:**

There are two types of polyunsaturated fatty acids (PUFAs): omega-3 (n-3) and omega-6 (n-6), which differ in the position of the first double

C-bound. Two PUFAs, known as essential fatty acids, cannot be produced in the human body but are crucial for physiological function. Therefore, they must be received from diet. Linoleic acid (LA) belongs to the n-6 family. The other one is  $\alpha$ -linolenic acid (LNA), which belongs to the n-3 family. The human body can convert necessary parent chemicals to longchain (LC) fatty acids, but not n-3 and n-6 fatty acids.<sup>3</sup>

#### **ANTIOXIDANTS:**

Free radicals are thought to damage cells, contributing to aging and disease progression. Antioxidants play a crucial role in preventing free radical damage and promoting overall health. Oxygen, a highly reactive element, can form potentially harmful compounds known as "free radicals." Free radicals can damage healthy cells, leading to loss of structure and function. Antioxidants stabilize and deactivate free radicals, preventing them from attacking cells. Antioxidants are essential for sustaining healthy cells and systems.

- Nutrient-derived antioxidants include vitamin C (ascorbic acid), vitamin E (tocopherols and tocotrienols), carotenoids, glutathione, and lipoic acid.
- Antioxidant enzymes, including superoxide dismutase, glutathione peroxidase, and glutathione reductase, help quench free radicals.
- Metal binding proteins, including ferritin, lactoferrin, albumin, and ceruloplasmin, store free iron and copper ions and catalyze oxidative processes.
- Antioxidant phytonutrients can be found in many plant diets.

#### **POLYPHENOLS:**

Polyphenols are naturally occurring phytochemical compounds found in plant-based foods such as fruits, vegetables, whole grains, cereals, legumes, tea, coffee, wine, and cocoa. Over 8000 polyphenolic compounds, including phenolic acids, flavonoids, stilbenes, lignans, and polymeric lignans, have been identified in whole plant foods. Plant secondary metabolites provide defense against UV radiation, oxidants, and infections.

Polyphenols are characterized by their number of phenol rings and the structural components that connect them.

Phenolic acids make up roughly one-third of polyphenolic compounds in the diet. They are classified into two types: hydroxybenzoic acid

derivatives (protocatechuic acid, gallic acid, p-hydroxybenzoic acid) and hydroxycinnamic acid derivatives (caffeic acid, chlorogenic acid, coumaric acid, Ferulic acid, sinapic acid). Foods high in phenolic acids include berry fruits, kiwi, cherry, apple, pear, chicory, and coffee.<sup>4</sup>

Flavonoids are classified into six subclasses: anthocyanins, flavonols, flavanols, flavanones, flavones, and isoflavones. Anthocyanins (cyanidin, pelargonidin, delphinidin, malvidin) can be found in berries such as red wine, red cabbage, cherry, black grape, and strawberry.<sup>4</sup>

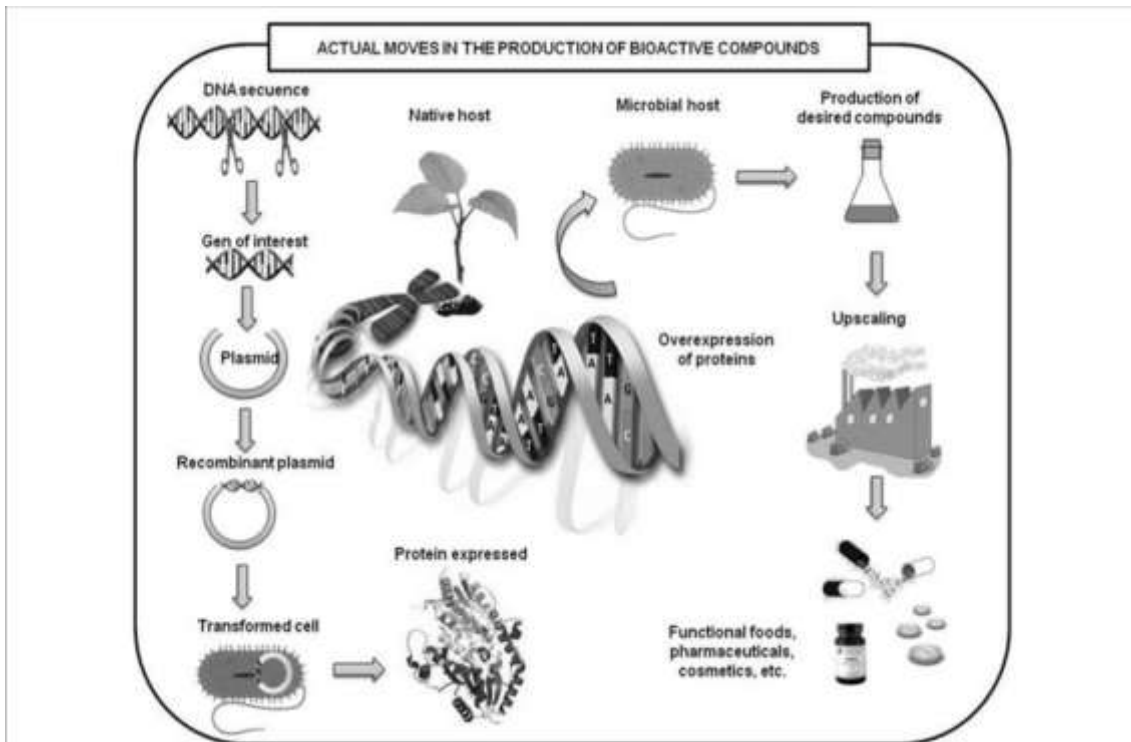


Figure 1–Systematic strategies to achieve high-yield production of natural bioactive compounds utilizing metabolic engineering.

### Diet-related diseases.

Diet-related disorders are on the rise in Western countries, driven by increased access to high-calorie foods and sedentary lifestyles.

Diet-related diseases, such as obesity, diabetes, atherosclerosis, and neurodegeneration, all include low-grade inflammation.

Functional foods and nutraceuticals may offer a new way to prevent or manage diet-related diseases by reducing inflammation. Activating intestinal T regulatory cells and regulating the gut microbiota can lower low-grade inflammation in diet-related illnesses.<sup>4</sup>

### NUTRACEUTICALS IN THE MANAGEMENT OF ANTIBACTERIAL, ANTIPARASITIC, ANTIVIRAL ACTIVITY

A aqueous extract from the Bulgarian medicinal plant *Geranium sanguineum* L (Geraniaceae) effectively prevented the

multiplication of herpes simplex virus Types 1 and 2, resulting in reduced virus-induced cytopathogenicity and cell protection. In preliminary trials, the extract prevented the development of herpetic vesicles in albino guinea pigs infected with HSV1. The inhibitory effect on virus replication was linked to the presence of polyphenol components such as flavonoids, catechins, polyphenolic acid, and condensed tannins, albeit no mechanism of action was revealed.

*Artocarpusheterophyllum* methanolic extracts include two isoprenylflavones that have strong antibacterial and cariogenic activity against streptococci. In a study of 13 flavanones, tetrahydroxyflavanones from *Sophoraexigua* and *Echinosophorakoreensis* effectively inhibited methicillin-resistant *Staphylococcus aureus* growth.<sup>4</sup>

## NUTRACEUTICALS IN THE MANAGEMENT OF ANTICANCER ACTIVITY

The use of nutraceuticals as chemopreventative agents has been investigated, and promising findings have been produced in terms of cancer prevention and treatment. Nutraceuticals from many origins have been found to have anti-cancer properties. Plants including garlic, ginseng, curcumin, ginger, and green tea extract have multiple methods to combat cancer. Such mechanisms include the suppression of DNA alkylation, tumor initiation, proliferation, and metastasis, as well as the stimulation of autophagy and intrinsic apoptosis. Furthermore, nutraceuticals have been shown to inhibit cancer signaling pathways that are thought to have a role in carcinogenesis. Oral cancer, prostate cancer, breast cancer, lung cancer, and colon cancer

Many studies have been undertaken to examine nutraceuticals' modes of action against various types of cancer. A wide range of nutraceuticals have been discovered to express anti-cancer capabilities against oral cancer, prostate cancer, breast cancer, lung cancer, and colon cancer cells.

Activation of the vitamin D receptor (VDR) causes cell cycle arrest, apoptosis, and anti-angiogenesis. This is an intracellular nuclear receptor found in organs and tissues. The active form of vitamin D interacts to VDR, activating the growth arrest gene and the DNA damage-inducible gene. This leads to the conclusion that vitamin D shortage causes a variety of diseases, whereas adequate vitamin D consumption helps to avoid disease. Furthermore, the anti-cancer mechanisms of vitamins A, C, and D have been investigated. Clinacanthus nutans, a nutraceutical herb, has been studied as a supplementary therapy with gemcitabine.

The impact of prebiotics and probiotics in colorectal cancer has been extensively studied.

Prebiotics and probiotics are thought to be beneficial to human health, particularly in the gastrointestinal tract. A study looking into the anti-cancer effects of prebiotics found that eating a lot of fiber increases the number of short chain fatty acids (SCFAs), which produces bacteria and reduces the incidence of colon tumors. A study found that oral administration of *Lactobacillus rhamnosus* inhibited inflammation associated with tumor development by increasing the expression of inflammatory proteins like NF $\kappa$ B-p65, TNF $\alpha$ , and iNOS, indicating its prophylactic activity against CRC carcinogenesis.

Furthermore, consuming probiotics reduces tumor incidence, multiplicity, and size. *Lactobacillus acidophilus*, *Bifidobacteria* spp., and a mixture of fructooligosaccharide and maltodextrin.

Polyphenols, especially those found in green tea, have been demonstrated to target prostate, breast, skin, lung, and liver cancer as chemo-preventive agents. Green tea contains catechins that have antioxidant, anti-inflammatory, antiproliferative, and antiangiogenic properties against cancer.

A study found that drinking green tea on a regular basis lowers the risk of prostate cancer. Furthermore, treatment of the prostate cancer cell line PC-3 with green tea polyphenol E caused cell death via inducing intracellular oxidative stress, which then inhibits the pro-survival pathway Akt. EGCG inhibited lung cancer cell proliferation by generating reactive oxygen species (ROS) and caused oxidative DNA damage. Aside from that, a practical study evaluating the effect of EGCG on mammary tumors found that poly E administration resulted in slower tumor progression, decreased metastasis, inhibited mammary ductal growth, and influenced angiogenesis by lowering vascular endothelial growth factor (VEGF) levels.<sup>5</sup>

Type of Cancer	Mode of Action	Nutraceutical
Prostate cancer	Antiproliferation, cell cycle inhibition, angiogenesis inhibition and promotion of apoptosis	Vitamin D
	Antioxidation, antiproliferation, and promotion of apoptosis	Catechins in green tea
Colon cancer	Tumor marker suppression, promotion of apoptosis, metastasis inhibition, and antiproliferation	Polyphenols
	Antioxidant, antiproliferation, promotion of apoptosis, inflammatory protein inhibition	Terpenoids
Breast cancer	Autophagy induction and promotion of apoptosis	Alkaloids
	Induction of DNA hypomethylation, promotion of apoptosis, and antiproliferation	Micronutrients
	Antiproliferation, angiogenesis inhibition, and promotion of apoptosis	Allicin in garlic
Oral cancer	Antiproliferation and promotion of apoptosis	Curcumin
	Cell cycle inhibition, promotion of apoptosis, and inhibition of metastasis	Vitamin D
	Prevent tumor initiation	Strawberry
Oral cancer	Antioxidation	Rosemary
	Antiproliferation, promotion of apoptosis, and angiogenesis inhibition	Geraniol

### NUTRACEUTICALS IN THE MANAGEMENT OF DIABETES

Diabetes mellitus is a rapidly increasing metabolic disorder in India that affects lipid and glucose metabolism, causing physical and mental health issues. As understanding of the disorder's variety grows, there is a greater need for tailored treatment options.

Traditional herbal medicines are a safe alternative to conventional hypoglycemic agents in Non-insulin-dependent diabetes mellitus (NIDDM) and Insulin-dependent diabetes mellitus (IDDM). Synthetic drugs have a limited role and are prone to drug tolerance, requiring higher dosages or a change of drug. Ayurvedic herbs, high in critical phytonutrients, can act as "potentiators" for diabetic medications and improve quality of life. Ayurvedic medicinal herbs and Indian traditional medicine hold significant potential. CSIR, ICMR, DBT, and

academics have investigated the effect of herbal nutraceuticals, nutritionals, and naturals in metabolic illnesses such as diabetes.<sup>6</sup>

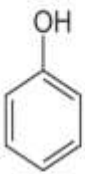
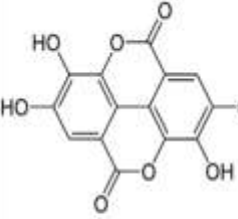
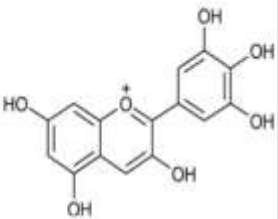
#### The need for diabetes-preventive nutraceuticals

While very-low-fat and lower-glycemic-index diets, regular exercise, and weight control help prevent type 2 diabetes, many at-risk individuals may continue to eat whatever they want, avoid exercise, and remain overweight. Given the enormous cost of diabetes, both in terms of monetary resources and human misery, it would be extremely desirable to have effective nutraceuticals and medicines that such people might utilize to minimize their risk of diabetes.

The number of nutraceutical substances with efficacy in this area is growing. There is potential for developing solutions that combine effective doses of several compounds.<sup>7</sup>



### Phytochemical Compounds: Structure, Food Sources, Bioavailability, and Metabolism<sup>8</sup>

		
<b>Phenol group</b>	<b>Polyphenol</b>	<b>Flavonoid (e.g. anthocyanin)</b>

Phenolic chemicals, abundant in fruits, vegetables, cereals, chocolate, and beverages, control cellular development, play infection defense, and protect against UV radiation. They react with bacterial cells, limit enzyme activity, alter protein regulation, and capture metals and substrates. Phenolic chemicals, which can affect food's bitterness, astringency, color, and oxidative stability, can be consumed in excess of 900 mg daily, depending on dietary habits and lifestyle, with modest coffee and tea consumption increasing significantly.<sup>10</sup>

#### Quercetin

Quercetin, a flavonoid found in vegetables and fruits, has various health benefits, including metabolic, anti-oxidative, anti-apoptotic, and renoprotective properties. Despite being found to be mutagenic in a 1970s study, it was not found to be carcinogenic to humans in 1999. Research on quercetin and diabetes began in 1975 to prevent cataracts. Studies have shown quercetin can reduce blood pressure in overweight-to-obese patients without affecting other risk factors. Further research is needed to determine its optimal dosage and efficacy in diabetic patients.<sup>10</sup>

#### Silymarin

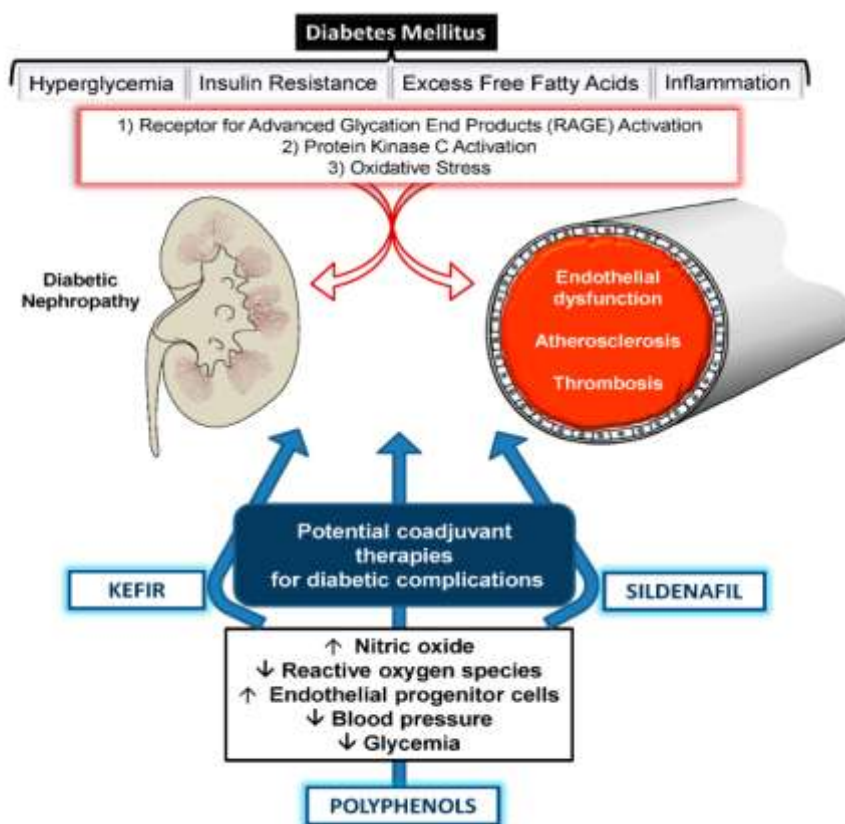
Silymarin, a dry flavonoid from *Silybum maritimum* seeds, contains seven primary components including taxifolin, silychristin, silydianin, silybin A, silybin B, isosilybin A, and isosilybin B. It has been used to treat liver diseases and has antidiabetic properties, making it a promising candidate for preventing and treating diabetes complications in both experimental and human studies.

Further research is needed to explore the cytoprotective effects of silymarin. Recent studies have shown that silymarin can protect cardiomyocytes against apoptosis in diabetic rats and improve neuroprotection by reducing lipoperoxidation and increasing SOD activity. Additionally, silymarin has been found to provide DNA protection and reduce oxidative stress in a brain-specific area in rodents. A study two decades ago found that silymarin supplementation had positive benefits in insulin-treated diabetics with alcoholic cirrhosis, lowering insulin resistance and endogenous insulin hypersecretion. Ten years later, 25 diabetic individuals treated with silymarin showed reduced glycemia, glycated hemoglobin, and improved lipid profiles in liver biomarkers.<sup>10</sup>

#### Treatments with Kefir

Fermented milk kefir, originating in the Northern Caucasus Mountains, is a probiotic with numerous health benefits, including modulating cardiovascular and metabolic dysfunctions like hypertension and diabetes. Kefir grains, formed during milk fermentation by a symbiotic combination of yeasts, lactic and acetic acid bacteria, are the main functional component of the beverage. Common bacterial genera include *Lactobacillus*, *Lactococcus*, and *Streptococcus*.

Kefir, an exopolysaccharide found in kefir grains, has been linked to lower blood pressure and glucose levels in animal models of diabetes mellitus (DM). Kefiran-kefir may improve glucose absorption into insulin-responsive muscle cells. Kefir treatment has been proven to lower total cholesterol, triglycerides, LDL-cholesterol, and enhance HDL-cholesterol levels in DM models. Studies suggest kefir can be used as a supplemental or adjuvant therapy to improve glycemic control.<sup>10</sup>



### Anthocyanins

Anthocyanins are water-soluble pigments found in fruits, flowers, and legumes that produce red, violet, and blue colors. Over 500 anthocyanins have been identified, with cyanidin-3-O-glucoside accounting for half of them. Blackberries and blackcurrants contain up to 2-4 g of anthocyanins per kilogram, while red grapes can contain 2.5 g per kg. Red wines, particularly young ones, can contain up to 1 g per liter, depending on the grape variety and year of production.<sup>9</sup>

### NUTRACEUTICALS IN THE MANAGEMENT OF CVD

Cardiovascular disease (CVD) is prevalent in adults over sixty and causes 17.3 million deaths annually worldwide. It accounts for 200 billion Euros of healthcare expenditure in Europe. Risk factors include obesity, hypertension, hyperlipidemia, diabetes, metabolic syndrome, unhealthy diet, smoking, and physical inactivity. Dietary factors also contribute to CVD risk. Reducing risk factors, particularly blood pressure and lipid-lowering, can significantly impact CVD mortality.<sup>11</sup>

### Sterols/stanols

Plant sterols, also known as stanols, can be found in a variety of plant products such as fruits, vegetables, cereals, seeds, and nuts. Their biological function stems from their chemical structural similarities to cholesterol.<sup>11</sup>

### Spirulina

Spirulina is a blue-green microalga (Cyanobacterium). Spirulina is a nutrient-dense food that contains protein, vitamins, minerals, carotenoids, and phycocyanins. It has a long history of human consumption with no safety issues.<sup>11</sup>

### Dyslipidemia

Dyslipidemia refers to lipid abnormalities that increase the risk of CVD. Reducing total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) is effective in both primary and secondary prevention of CVD events. Low LDL-C levels are linked to lower rates of major coronary events. Nutraceuticals that modify the plasma lipid profile may reduce the burden of CVD.<sup>11</sup>

### Cocoa

Daily flavonoids intake reduces the risk of coronary heart disease, stroke, and overall cardiovascular diseases (CVDs). Food flavonoids, like cocoa, have antioxidant and anti-inflammatory properties, improving NO metabolism and endothelial function. Cocoa flavonoids increase NO bioavailability, protect vascular endothelium, and decrease risk factors for CVDs like insulin resistance and systemic inflammation. Clinical trials show cocoa increases peripheral vasodilatation, improves antioxidant status, and decreases blood pressure.

Cocoa administration has been shown to improve coronary function in humans, enhancing coronary vasodilatation and endothelial function. In healthy subjects, 821 mg/d flavanol-rich cocoa for 5 days improved peripheral vasodilatation and vasodilatation response to ischemia. High-flavonoid chocolate administration for 2 weeks improved flow-mediated vasodilatation of the brachial artery and increased plasma epicatechin concentration.

Healthy subjects with cardiovascular risk factors showed improved flow-mediated vasodilatation and increased nitrosated and nitrosylated species levels after 15-day cross-over administration of dark chocolate with catechin and epicatechin vs. flavanol-free white chocolate. Similar improvements were observed in smoker and diabetic subjects. Despite heterogeneity in trials and need for better characterization of vascular effects, cocoa's potential as a cardiovascular health promoter is suggested.<sup>11</sup>

### Curcumin

Curcumin, a yellow/orange pigment, has been linked to beneficial cardiovascular effects, including anti-oxidative, anti-inflammatory, and anti-proliferative properties. It reduces blood pressure and prevents vascular smooth cell proliferation. In rat models, curcumin prevented hypertension by lowering AT1R expression and acetylating GATA 4. It also protected against nephrectomy-induced hypertension by enhancing Nrf2 expression. Supplementation with 2000 mg/day for 12 weeks showed cardioprotective effects.<sup>12</sup>

### Whole grains

Whole grain products are rich in fiber and trace elements, and contain phytoprotective chemicals that may lower cardiovascular risk. They improve insulin sensitivity, blood pressure, lipid levels, and inflammation. The anti-inflammatory

mechanism is unclear, but it may be linked to antioxidant elements in whole grain germ. Whole grains have a lower glycemic index than processed grains, and postprandial glucose spike reductions are linked to lower reactive oxygen production, lower inflammation, and CVD risk.<sup>13</sup>

### Soy proteins

Miso soup and tofu are the main sources of soy protein in Japan, which contains polyunsaturated fatty acids, fiber, vitamins, and minerals. Consuming more than 6g of soy protein per day can reduce total cholesterol, LDL-C, ischaemic and cerebrovascular events. Soy products contain isoflavonoids, which act as natural phytoestrogens to block LDL oxidation and reduce the risk of atherosclerosis. Consuming soy protein has been shown to reduce the oxidation susceptibility of LDL particles in healthy individuals. However, the impact of soy meals and isoflavone supplementation on blood lipids in clinical trials is unclear. More research is needed to determine differences between whole meals, soy protein, and isoflavone extract.<sup>13</sup>

### Flavonoids

Plant-derived flavonoids, found in vegetables, fruits, and beverages like chocolate, tea, and wine, are the most common polyphenols in the human diet. Phytoestrogens, or nonsteroidal plant elements mimicking estrogen, are found in oilseeds, cereal grains, vegetables, fruits, and legumes. Flavonoid-rich foods like chocolate, red wine, and green tea may reduce blood pressure and improve endothelial function.<sup>13</sup>

### Vitamin C

Vitamin C's antioxidant properties help prevent cardiovascular disease (CVD) by reducing tissue reactive oxygen species, inhibiting smooth muscle proliferation, and lowering oxidized LDL cholesterol. However, research on its role in CVD risk has been inconsistent, and no significant correlation has been found between vitamin C, vitamin E, and  $\beta$ -carotene.<sup>13</sup>

### Carotenoids

Carotenoids, including lycopene and beta-carotene, can improve immune function and reduce the risk of degenerative diseases like cancer, CVD, and cataracts. They lower oxidative stress and inflammatory indicators, potentially playing a role in CVD. However, research on the relationship between dietary carotenoids and CVD risk is

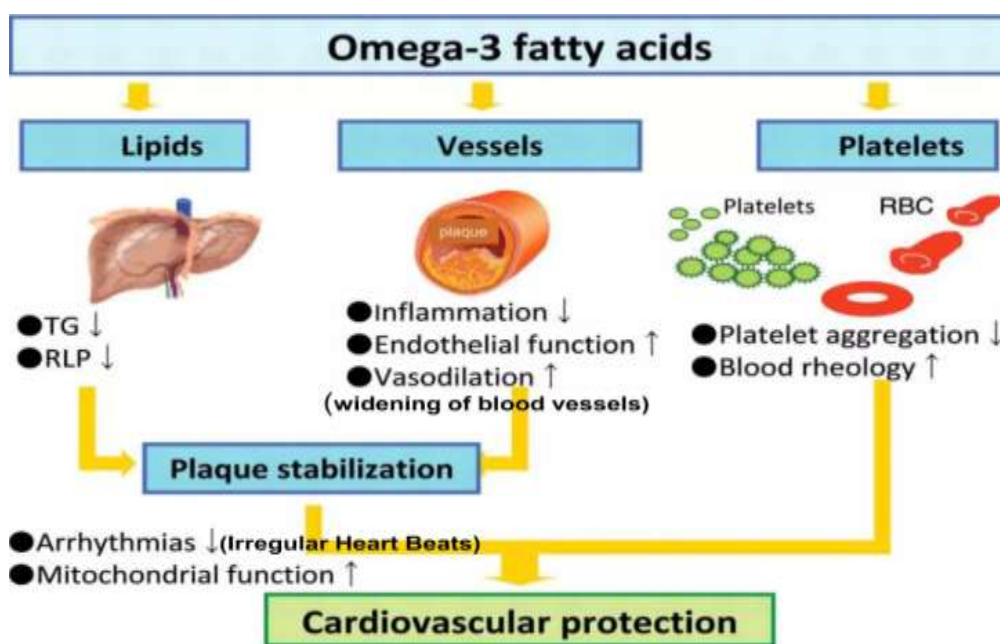


inconsistent. High lycopene consumption from tomato and derivatives may reduce CVD risk.<sup>13</sup>

### Vitamin E

Vitamin E, a free radical scavenger and anti-inflammatory drug, has been linked to cardiovascular disease (CVD) and heart disease risk. However, clinical research does not support

vitamin E supplementation's effectiveness in preventing cardiovascular disease. High-dose vitamin E (400 IU/day) may increase total mortality risk. The negative effects may be due to appropriate dosage and form.  $\alpha$ -tocopherol is most beneficial and safe when received through foods, rather than observational or interventional trials.<sup>13</sup>



### Nutraceuticals in the management of headache sleep disorders

Primary headache disorders, including tension headaches, are common and disabling illnesses affecting children and adolescents, disrupting school, social activities, and quality of life. Over 50% of children and adolescents experience headaches, with recurrent headaches potentially causing academic and behavioral issues. Studies show emotional issues in those with tension headaches and a lower health-related quality of life.

### Melatonin and TTH

Melatonin is a hormone secreted by the pineal gland during darkness and suppressed by light. It interacts with MT1 and MT2 receptors, controlling alertness states and regulating the sleep-wake cycle. Melatonin is particularly effective for sleep onset insomnia, reducing latency and potentially increasing total sleep time. It also has antioxidant and anti-inflammatory effects, participates in free radical scavenging, and can help ameliorate weight gain by reducing body fat accumulation. Melatonin interacts with various

receptors at various central nervous system levels, affecting various biological processes. Melatonin is involved in sleep disorders and headache pathophysiology through various mechanisms. It has antinociceptive effects on inflammatory and neuropathic pain, modulates cytokines, interleukins, and TNF-alpha, and restores circadian rhythms, enhancing adaptive capabilities for chronic pain management. Melatonin also shows anxiolytic effects, potentially aiding in treating chronic pain conditions. Melatonin, a medication with a chronobiological effect, has been shown to reduce headache in patients with circadian rhythm sleep disorders. In a study, 78.6% of 328 patients with circadian rhythm sleep disorders experienced a reduction in headache, while 13.8% experienced a slight headache. Melatonin is generally safe, with common side effects being sleepiness, headache, dizziness, and hypothermia. However, studies on melatonin use in primary headache have limitations, including lack of adequate control and a small sample size.<sup>15</sup>

Magnesium is essential for enzyme reactions and energy metabolism, and low levels

can lead to neuronal dysfunction, often seen in individuals with headaches. It acts as an antagonist of calcium channels, preventing excessive activation of excitatory synapses and downregulating inflammation. Recent evidence suggests a relationship between magnesium deficiency and mild-to-moderate TTH, making magnesium potentially relevant for treating neurological conditions like headaches and potentially reducing attack frequency up to 1500 mg.

A study found that migraine patients had lower magnesium levels during and between attacks compared to healthy individuals. Inadequate magnesium intake is linked to headache in the US, but magnesium appears safe from a tolerability standpoint, with most studies reporting no adverse events.

#### **B vitamin Supplementation and TTH**

B vitamins, particularly vitamin B6, play a crucial role in cellular physiological processes like energy generation and anabolic metabolism. They also aid in the synthesis of neurotransmitters like melatonin and serotonin. A systematic literature review on migraine patients found potential benefits and a safe dosage range of up to 300 mg for vitamin B6 and 400 mcg for vitamin B12.<sup>15</sup>

#### **The Effect of Melatonin, Magnesium, and Vitamin B Complex Supplementation in the Treatment of Insomnia**

A study found that a magnesium-melatonin-vitamin B complex supplementation for three months was highly effective in treating insomnia, reducing night awakenings and improving quality of life. The supplementation, which included magnesium oxide, vitamin B6, and melatonin, was not influenced by the cause of insomnia.<sup>15</sup>

#### **The Impact of Melatonin, Tryptophan, and Vitamin B6 Supplementation on Chronic Headache**

A study involving 34 children with chronic headaches found that 90% reported a reduction in headaches after two months of nutraceutical supplementation, with benefits starting in the first month. Additionally, 78.8% of children showed improvement in nocturnal awakenings, with a significant effect in the group receiving tryptophan and vitamin B6 supplements.

#### **Red yeast rice**

*Monascus Purpureus* fungi ferment rice to produce Red Yeast Rice (RYR), which produces red pigments and prevents hepatic cholesterol synthesis. Monacolin K, found in both lactone and open-ring acid forms, inhibits HMG-CoA reductase, a key cholesterol-producing enzyme. Other monacolins in RYR contribute to this inhibitory mechanism, but to a lower level.

Monacolins in RYR extract have higher bioavailability than pure lovastatin, resulting in increased cholesterol levels per mg. Monacolin K can lower LDL cholesterol by 20-25% at doses ranging from 3 to 10 mg/day. It is chemically identical to lovastatin and is metabolized by cytochrome P450, specifically isoenzyme 3A4. Monacolin K may interact with certain medications. Between 2002 and 2015, Italian researchers observed 55 adverse responses to RYR, with almost all supplements containing 3 mg of Monacolins.<sup>16</sup>

#### **Beta-glucan and dietary fiber.**

Fiber, complex carbohydrates not digested in the stomach, can lower plasma LDL cholesterol levels through dietary and supplementation. It may decrease cholesterol by increasing fecal excretion of cholesterol, bile acids, and other dietary lipids. Viscous soluble fiber, like beta-glucan, absorbs water and forms a gel-like substance in the colon. Beta-glucan is found in grains, cereals, mushrooms, barley, and oats.<sup>16</sup>

#### **Grape polyphenols:**

Red wine, rich in polyphenols, has health benefits, including anti-LDL oxidation and antiatherogenic properties. High saturated fat consumption is linked to coronary heart disease risk in many countries, but not in France or certain wine-consuming regions. Moderate red wine consumption reduces the risk of coronary heart disease due to positive lipoprotein modification.<sup>16</sup>

#### **Tea catechins:**

Tea catechins, found in *Camellia sinensis* leaves, have been linked to reducing cholesterol levels. Tea is the world's most popular beverage, with three varieties: green, oolong, and black, with green being popular in Asia and fermented black in North America and Europe.

Oolong tea, a partially fermented tea primarily produced in Mainland China and Taiwan, contains green tea catechins (GTCs) that undergo oxidation and polymerization in black tea, forming theaflavins and thearubigins. Four GTC derivatives

have been extensively researched for their biological and pharmacological properties, while the biological actions of other TFs in oolong and black tea remain unexplored.<sup>17</sup>

### Berberine

Berberine, a natural alkaloid found in medicinal plants, has poor oral bioavailability and is primarily eliminated through bile after glucuronidation. It inhibits PCSK9 transcription, allowing it to capture more LDL cholesterol from the bloodstream and dispose of it through bile. Berberine's effects are dose-independent, with 500 mg/day reducing LDL cholesterol and triglycerides in hypercholesterolemics, mixed dyslipidemics, type 2 diabetics, and hepatopathics. Its effect on insulin resistance is comparable to metformin, with similar gastrointestinal side effects.<sup>18</sup>

### Policosanol:

Policosanol, a group of 8 long-chain aliphatic alcohols, was first identified in a Cuban study in 1991. It has similar lipid-lowering efficacy to statins but is more effective in boosting HDL-C and has less side effects. Its mechanism of action is unclear, but it is thought to reduce HMG-CoA reductase expression. Policosanol has multiple benefits, including decreasing lipids, delaying LDL oxidation, inhibiting platelet aggregation, and stimulating smooth muscle cell proliferation. However, recent studies outside Latin America have found it ineffective in lowering cholesterol.<sup>19</sup>

## II. CONCLUSION :

Nutraceuticals, including functional foods, dietary supplements, and bioactive compounds, are increasingly important in modern healthcare for disease prevention and treatment. They have antioxidant properties, anti-inflammatory actions, and improved gut health, offering innovative disease management strategies. Integrating nutraceuticals into conventional treatment protocols can enhance therapeutic outcomes, reduce side effects, and improve patients' quality of life. However, further research is needed to establish standardized dosages, efficacy, and safety profiles. Clinical trials and regulatory frameworks are also essential to ensure the products are reliable and effective. As the understanding of nutrition and health continues to evolve, nutraceuticals are expected to become an integral part of holistic healthcare approaches.<sup>20</sup>

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