

Harnessing the power of phytochemicals: Natural strategies for the prevention of heart disease

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Abstract. About 30% of all fatalities globally are caused by cardiovascular diseases (CVDs), which continue to be a significant global health concern. Genetic susceptibility, lifestyle decisions, and underlying medical disorders like hypertension, dyslipidemia, and arrhythmias are all part of the complicated etiology of CVDs. The use of phytochemicals, natural substances derived from plants, as potential treatments for preventing and managing heart disease has become a focus due to the growing prevalence of heart disease. Resveratrol, curcumin, and berberine are examples of phytochemicals that have various advantageous qualities, such as lipid-modulating, anti-inflammatory, and antioxidant actions. To preserve cardiovascular health, these substances have shown promise in lowering oxidative stress, enhancing endothelial function, and modifying lipid profiles. Furthermore, phytochemicals offer additional health benefits, including immune system support, wound healing, and protection against chemotherapy-induced toxicity. Recent advancements in phytochemical research have also highlighted novel therapeutic approaches, such as targeting ferroptosis, a form of cell death associated with cardiovascular dysfunction. This review paper explores the therapeutic potential of phytochemicals in CVD management, their mechanisms of action, and their emerging role in integrated treatment strategies. By examining the latest research and clinical findings, the paper aims to underscore the importance of incorporating phytochemicals into conventional cardiovascular disease management to improve patient outcomes and reduce global CVD-related morbidity and mortality.

1. Introduction

According to the World Health Organization (WHO), cardiovascular diseases are now one of the major causes of death and morbidity worldwide, contributing to around 30% of all fatalities. The complicated character of CVDs is caused by a confluence of lifestyle, environmental, and genetic variables, such as stress, smoking, excessive alcohol use, poor eating habits, and sedentary behaviour. Furthermore, the risk of cardiovascular problems is greatly increased by diseases including arrhythmias, dyslipidemia, and hypertension [1]. Effective prevention and treatment options are desperately needed as the frequency of CVDs rises worldwide. Recent advancements in medical research have highlighted the promising potential of phytochemicals derived from plants in managing and preventing CVDs.

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Phytochemicals, such as resveratrol, curcumin, and berberine, possess antioxidant, anti-inflammatory, and lipid-modulating properties, making them ideal candidates for cardiovascular health management [2]. These bioactive compounds can influence various molecular pathways, including reducing oxidative stress, improving endothelial function, and promoting a balanced lipid profile [3]. Furthermore, phytochemicals play a significant role in enhancing the body's immune response, reducing chronic inflammation, and supporting the healing process of tissues, thus contributing to overall cardiovascular health. This review paper aims to explore the various aspects of phytochemicals in the treatment and prevention of cardiovascular diseases, focusing on their mechanisms of action, health benefits, and potential therapeutic applications. It will also examine emerging research in this field, such as targeting ferroptosis, a form of programmed cell death, to enhance the efficacy of CVD treatments. By understanding the therapeutic potential of phytochemicals, this review seeks to provide insights into the integration of natural remedies into conventional medical practices, offering a holistic approach to cardiovascular disease prevention and management [3].

2. Causes of CVDs

CVD is a leading cause of death and morbidity globally. There are various aspects by which we can classify the reasons behind the cause of CVD. According to the World Health Organization, CVD causes 17.9 million deaths globally annually, or almost one-third of all deaths. Cardiovascular disease is influenced by genetic predispositions, health conditions, and lifestyle decisions. Sometimes accumulation of highly lipidic substances will result in the cause of many diseases. Also, the arrhythmia-like condition will be observed. irregular movements of flaps that are present in the heart. due to consumption of alcohol, drugs, and smoking, and high blood pressure, these are some reasons by which the occurrence of CVD in humans increases. An unhealthy diet and family history are also known reasons for the cause of it. Several non-modifiable risk factors are the relevance of genetic variability in the development of diseases like hypertension and dyslipidemia, which are known precursors to cardiovascular disease (CVD), and the heritability of cardiovascular traits 2020 [4].

2.1 Several modified risk factors

One of the worst lifestyle choices for cardiovascular health is still smoking. It greatly contributes to the development and aggravation of cardiovascular disorders by causing endothelial dysfunction, promoting inflammation, and causing clot formation. Although ambient air pollution can increase the risk of cardiovascular disease, it is still unclear how much of a risk there is at lower fine particulate matter (PM2.5) levels. Stress and Psychosocial Factors: Over time, stress can harm the cardiovascular system by causing a variety of physiological reactions, such as elevated blood pressure and heart rate. Furthermore, a higher incidence of cardiovascular events is associated with negative emotional states, including anxiety and depression, highlighting the need for comprehensive strategies that integrate mental health assistance into cardiovascular treatment.

2.3 Potential risk factors for CVD

High levels of low-density lipoprotein cholesterol, smoking, high blood pressure, diabetes, abdominal obesity, psychological problems, and insufficient physical exercise have been identified as the primary risk factors for these illnesses throughout time (Fig. 1).

Myocardial infarction, heart failure, and stroke are the main causes of atherosclerosis, which is primarily found in the intima of medium and wide arteries [5]. Diabetes mellitus is a known epidemiological risk associated with the increasing prevalence of CVD.

The main causes of atherosclerosis are cholesterol accumulation and dyslipidemia in the arterial endothelium. Low-density lipoprotein cholesterol functions as a stand-alone CVD risk factor and is pro-inflammatory and immunogenic when oxidized [6]. The development of atherosclerosis is directly impacted by the rise in oxidized LDL cholesterol, which also contributes to endothelial dysfunction. The Interheart study found that traditional risk variables explained more than 90% of the population's risk of myocardial infarction, despite ongoing research to better identify an individual's cardiovascular risk in terms of genetic factors, additional lipid features, and inflammatory markers.

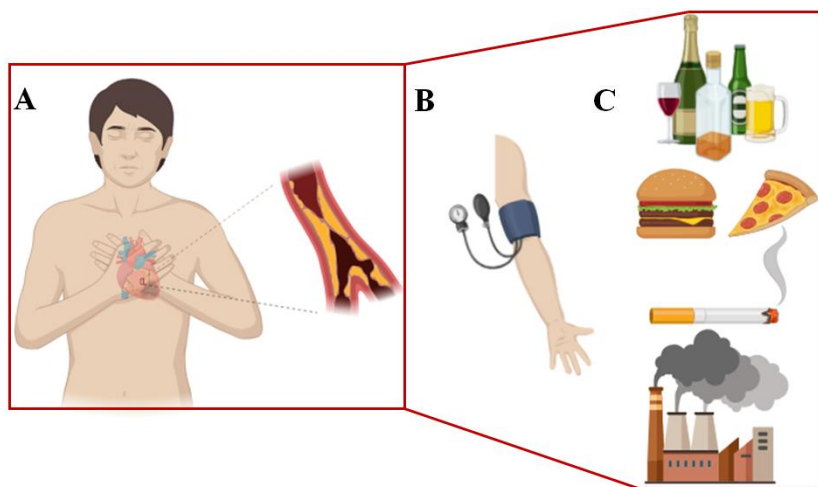


Fig 1. Major modifiable and non-modifiable risk factors contributing to cardiovascular disease. A) cardiovascular disease; B) hypertension; C) risk factors.

3. Symptoms of CVD

Angina, which is sometimes referred to as chest pain or discomfort, might feel like burning, tightness, squeezing, or pressure in the chest. The back, neck, jaw, shoulders, and arms may also experience it [7]. Breathlessness: Having trouble breathing or feeling out of breath can happen when exercising or at rest, and it may be a sign of underlying cardiac problems. Persistent wheezing or coughing, particularly in heart failure, may be a sign of lung fluid accumulation. A racing or fluttering heart is an example of an abnormal heartbeat that may be a sign of arrhythmias or other cardiac disorders. Especially in women, unusual weariness or fatigue might be a warning sign of cardiovascular issues. By educating the public about the signs of cardiovascular disease, people can take control of their heart health and make sure they get the help they need from a doctor as soon as possible.

4. What is the need to use the phytochemicals?

Phytochemicals make it less likely for germs and viruses to proliferate within the body. Preliminary findings indicate that phytochemicals can guarantee your immune system responds appropriately when an infection does occur. Moreover, they can lessen persistent inflammation brought on by inflammatory illnesses. Fruits, vegetables, whole grains,

legumes, beans, herbs, spices, nuts, and seeds all contain phytochemicals, also known as phytonutrients. These substances are categorized based on their chemical structures and functional characteristics. Also helps in chemotherapy by providing protection from the negative effects of cytotoxic medicines; phytochemicals are essential for chemotherapy. They can enhance the overall effectiveness of chemotherapy by interfering with different cellular processes, such as autophagy and apoptosis, that are important in cancer survival and growth. Phytochemicals may increase the efficacy of conventional chemotherapeutic drugs by focusing on these pathways while protecting healthy cells from related toxicities [8].

Also, help in wound healing through various pathways, such as anti-inflammatory effects, stimulation of angiogenesis, and promotion of cellular processes necessary for tissue repair; phytochemicals can influence wound healing. Phytochemicals hold great potential for enhancing wound healing through their multifaceted actions on inflammatory pathways, cellular proliferation, and angiogenesis (Fig. 2). Phytochemicals are present in plants and have a number of positive health impacts. The functions of these bioactive substances in nutrition, illness prevention, and health maintenance are becoming more well acknowledged [9].



Fig 2. Pleiotropic health benefits and mechanisms of action of dietary phytochemicals.

5. Commonly used phytochemicals for treatment

5.1 Resveratrol

It is a natural polyphenolic compound that is present in various types of fruits like grapes, berries, etc. Oxidative stress, vascular inflammation, and platelet aggregation are the three main characteristics of resveratrol; in fact, it decreases the production of reactive oxygen species (ROS) and increases the endogenous antioxidant systems, including superoxide dismutase (SOD) enzymes, in endothelial cells (ECs) and cardiac myoblasts [10]. It exists in both *cis*- and *trans*-configurations, of which *trans*-resveratrol is the principal biologically active form.

Target areas: Resveratrol interacts with a variety of targets in age-related illnesses, cancer, heart and brain disorders, and other conditions. The primary molecular process underlying the biological action of resveratrol impacts the silent mating type information regulation-1 (SIRT-1)/adenosine monophosphate-activated protein kinase (AMPK) pathway. The three main characteristics of resveratrol are related to platelet aggregation, vascular inflammation, and oxidative stress. Indeed, in endothelial cells and cardiac cells,

resveratrol increases the endogenous antioxidant systems, including superoxide dismutase enzymes, myoblasts, and it lowers the generation of ROS.

The health advantages of resveratrol in preventing cardiovascular disease: The intimal layer of the arterial wall is most impacted by atherosclerosis. It is distinguished by the migration and proliferation of location, as well as the deposition of extracellular lipids. smooth muscle cells, as well as a persistent inflammatory response. Clinical events, including coronary artery disease, peripheral arterial disease, or stroke, are brought on by luminal constriction and/or thrombus development. Because lipids, particularly low-density lipoproteins (LDLs), are involved in the atherosclerotic process, improving the lipid profile would be of importance (Fig. 3).

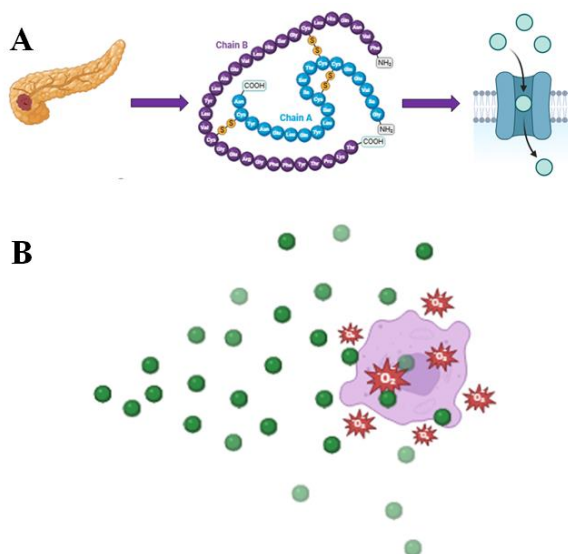


Fig 3. Pleiotropic health effects of resveratrol on key physiological systems. A) improved insulin sensitivity; B) improved antioxidant activity.

Resveratrol's anti-ageing effects are primarily mediated through reducing oxidative stress, which is a major contributing factor to ageing and the development of age-related diseases. Resveratrol improves the antioxidant defence system, which scavenges free radicals and reduces cellular damage, which is important for extending cellular lifespan and enhancing overall health. Mainly through affecting a number of important signalling pathways implicated in the development of cancer, resveratrol has antineoplastic actions [11]. The Nrf2 Signaling pathway is one well-known mechanism that is essential to cellular protection against oxidative stress. By activating Nrf2, resveratrol reduces oxidative damage and encourages cancer cells to undergo apoptosis by increasing the expression of antioxidant genes [12]. Given the frequent association between oxidative stress and carcinogenesis, this activation is crucial. Clinically, it is proven that resveratrol is beneficial in maintaining cholesterol levels (according to certain research, resveratrol may help alter lipid profiles by lowering levels of triglycerides, total cholesterol, and low-density lipoprotein cholesterol (LDL-C)) and in the regulation of blood pressure (supplementing with resveratrol can result in notable drops in blood pressure, both diastolic and systolic).

5.2 Curcumin

A naturally occurring phenolic molecule called curcumin (diferuloylmethane) was extracted from the spice turmeric (*Curcuma longa*) as a yellow pigment [13]. This substance has drawn interest because of its diverse pharmacological and biological properties [14]. Its medicinal benefits have been widely examined, especially in the management of inflammatory illnesses and cancer. Their therapy and prevention of cardiovascular disease by means of antioxidant and anti-inflammatory properties, improved endothelial function, and beneficial effects on lipid profiles (Fig. 4) [15]. Since curcumin is a lipophilic substance, eating lipids alongside it can greatly increase its absorption in the digestive system. This is important since the chemical is not well absorbed on its own; thus, other delivery methods are being considered to increase its bioavailability [16]. Further large-scale, carefully planned clinical trials are required to show conclusive advantages and ideal dose regimens for curcumin's usage in the treatment of cardiovascular disease, even if it seems promising as a supplemental approach to cardiovascular health management.

According to studies, curcumin may aid in the control of inflammation both during and after chemotherapy and radiation therapy. Curcumin targets numerous inflammatory mediators, including nuclear factor κ B (NF- κ B), cyclooxygenase-2, and inducible nitric oxide synthase, which reduce the production of chronic free radicals and attenuate the release of proinflammatory and profibrotic cytokines, ultimately reducing tissue toxicity [17]. Curcumin also inhibits angiogenesis, tumour development, and metastasis via modulating NF- κ B and its downstream signaling cascade. Curcumin's cytoprotective properties in healthy tissues are associated with its low toxicity [18]. This phytochemical may be used as an adjuvant in cancer treatment because of its defensive properties as well as its ability to make tumour cells more sensitive to radiation and chemotherapy treatment [19].

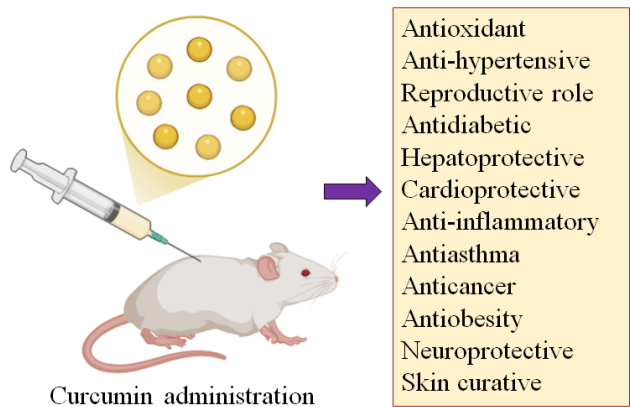


Fig 4. Health benefits of curcumin across major physiological systems.

5.3 Berberine

Additionally, berberine may be useful in the treatment of long-term, complex illnesses such as diabetes, hyperlipidemia, heart disease, cancer, and neurological illnesses, as well as inflammatory diseases (Fig. 5). By boosting insulin secretion, promoting glycolysis, inhibiting adipogenesis, and elevating glucokinase activity as well as glucagon-like peptide (GLP-1) and glucose transporter-4 (GLUT-4), berberine had an impact on glucose metabolism [20]. According to research, berberine can modify pathways, including AMP-activated protein kinase and nuclear factor kappa B (NF- κ B), by suppressing the

production of inflammatory cytokines and mediators. Due to this, we can say that berberine has anti-inflammatory properties.

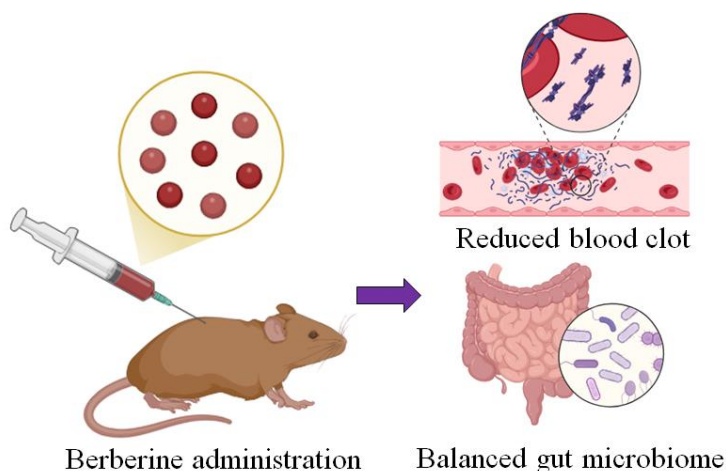


Fig 5. Therapeutic health benefits of berberine.

Research has shown that berberine is effective against harmful bacteria such as *Staphylococcus aureus* and *Escherichia coli*, which supports its use in treating respiratory and gastrointestinal disorders. This shows that berberine phytochemicals also contain antimicrobial properties [21]. Endogenous antioxidant enzymes like catalase and superoxide dismutase can be activated by berberine. Additionally, it helps lower reactive oxygen species levels *in vivo*, preventing oxidative damage to cellular integrity

6. Role of phytochemicals in health and nutrition

6.1 Carotenoids

Plants, algae, and certain microorganisms are the main sources of the class of organic colour known as carotenoids [22]. They give many fruits and vegetables, as well as some flowers and animal products, with their vivid yellow, orange, and red hues. Because of their numerous health advantages and significant contributions to plant biology and human nutrition, carotenoids have attracted attention [23].

Furthermore, carotenoids have the capacity to shield cells from excessive oxidation, which could harm them, and so shield the body from a variety of chronic illnesses and cellular components. As a result, carotenoids can stop cell mutation, which in turn stops cancer from growing, and atherosclerosis, a leading cause of cardiovascular disease.

Curcumin: It is mainly found in turmeric. Curcumin gives turmeric its anti-inflammatory, antioxidant, anticarcinogenic, antimutagenic, anticoagulant, and anti-infective qualities, as well as its ability to heal wounds. Due to the presence of all these properties, turmeric is considered majorly for use [24]. Curcumin's well-established anticancer effects result from its ability to inhibit the enzymes that cause cancer to grow [25]. Curcumin can help to prevent and treat type 2 diabetes by enhancing pancreatic β -cell activity and lowering insulin resistance. By preventing the brain's β -amyloid ($A\beta$ peptide) from aggregating, curcumin can prevent Alzheimer's disease by reducing neural inflammation. Due to the presence of these many properties, it is widely used [26].

Flavonoids: Flavonoids are considered one of the largest families, as they have more than 5000 polyphenolic compounds. They are present in plants and released in response to microbial infection [27]. They are also referred to as growth regulators; they are the colouring component of flowering plants and are in charge of preventing oxidative stress. Flavonoids have analgesic and anti-inflammatory properties [28]. Flavonoids have the ability to inhibit inflammatory cells and influence immune system functioning. Flavonoids have also been linked to cancer [29]. Agents that prevent chemotherapy. For instance, eating apples and onions, which are the primary foods that contain the flavonol quercetin, can lower the risk of lung, stomach, prostate, and breast cancer [30].

Advancements in Phytochemical Treatments for Cardiovascular Diseases: Targeting Ferroptosis -The use of phytochemicals to target ferroptosis, a type of programmed cell death linked to several cardiovascular disorders, is an intriguing field of study. According to studies, certain phytochemicals may be able to prevent damage to heart cells by blocking ferroptotic pathways. This method is presently being investigated as a novel therapeutic approach to enhance the outcomes for heart disease patients [31].

7. Conclusion

In conclusion, CVDs are a major health concern since, according to WHO estimates, they account for around 30% of all fatalities globally. Because CVDs are so common in older populations, effective preventive and treatment strategies are required. Phytochemicals derived from medicinal plants are demonstrating potential as natural alternatives with a variety of therapeutic applications. Some bioactive compounds, like resveratrol, curcumin, and berberine, have the potential to be used in the treatment of cardiovascular diseases (CVDs) due to their lipid-modulating, anti-inflammatory, and antioxidant qualities. The ability of CVD therapies to support metabolic health and halt the progression of chronic diseases is a significant advancement. Furthermore, ongoing research into novel mechanisms such as ferroptosis emphasizes the innovative approaches being explored in phytochemical therapy. It is crucial that researchers and medical practitioners look into and include phytochemical therapies in standard medical procedures as knowledge of the advantages of a plant-based diet and the therapeutic potential of these substances grows. In the end, using these natural treatments could greatly improve cardiovascular health outcomes and help lower morbidity and death associated with CVD.

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