NATURAL PRODUCTS IN CARDIOVASCULAR DISEASE TREATMENT- A COMPREHENSIVE REVIEW

By

Sadia Nowshin Urmi
Student ID-20146017

A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

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Declaration

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Student's Full Name & Signature:

Sadia Nowshin Urmi
20146017

Approval

The thesis titled "Natural Products in Cardiovascular Disease Treatment: A Comprehensive Review" submitted by Sadia Nowshin Urmi (20146017), of Spring, 2020 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on September, 2024.

Supervised By:

Dr. Raushanara Akter
Professor
School of Pharmacy
Brac University

Approved By:

Dean:

A.F.M. Yusuf Haider, PhD
Acting Dean, School of Pharmacy
Professor, Department of Mathematics and Natural Sciences
Brac University

Ethics Statement

This project does not involve any kind of animal and human trial.

Abstract

Cardiovascular diseases (CVDs), including coronary artery disease, heart failure, hypertension, and stroke, are major global health concerns, contributing to significant disease burden and economic strain. Conventional treatments, while effective, often come with high costs and side effects, highlighting the need for alternative therapies. Natural products derived from plants, animals, and microorganisms have been found to have therapeutic potential in treating CVDs due to their bioactive compounds and reduced toxicity. This review focuses on the role of natural products in CVD treatment. Compounds such as polyphenols, flavonoids, alkaloids, and terpenoids have demonstrated positive effects on oxidative stress, inflammation and lipid profiles, crucial in CVD progression. Notable examples include omega-3 fatty acids, curcumin, and resveratrol, which have shown cardioprotective properties in research. The review is intended to present an up-to-date overview of natural products in CVD prevention and treatment as well as discuss potential directions for further research.

Keywords: Cardiovascular diseases (CVD), coronary artery disease (CAD), hypertension, congestive heart failure, natural products, oxidative stress.

Dedication

Dedicated to my dearest parents who always supported me strongly and encouraged me in every step I have made and prayed for me. I would like to express my deep gratitude to my friends and beloved ones for their support and encouragement during this process.

Acknowledgement

First, I would like to thank the Almighty Allah for providing me with the power, the knowledge and the determination to finish this degree. It is through His blessings that I have been able to overcome the challenges along the way.

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For my loving parents, I'm grateful for their sacrifices and unmeasurable support and belief which have been my key motivating factors and inspiration to work hard in achieving my goals and aspirations.

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List of Acronyms

CVD	Cardiovascular Diseases
CAD	Coronary Artery Disease
CHF	Congestive Heart Failure
HTN	Hypertension
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
MI	Myocardial Infarction
EPA	Eicosapentaenoic Acid
DHA	Docosahexaenoic Acid
TG	Triglycerides
PUFA	Polyunsaturated fatty acids
FA	Fatty Acids
RCT	Randomized Controlled Trial
NO	Nitric Oxide
CRP	C-Reactive Protein
LDL	Low-Density Lipoprotein
HDL	High-Density Lipoprotein
ACE	Angiotensin-Converting Enzyme
NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
TNF-α	Tumor Necrosis Factor-alpha
ROS	Reactive Oxygen Species
GSH	Glutathione
IL-6	Interleukin-6
SOD	Superoxide Dismutase
HMG-CoA	3-Hydroxy-3-Methyl-Glutaryl-Coenzyme A
CNS	Central Nervous System

Chapter 1

Introduction

CVDs are a category of diseases that involve the heart or blood vessels, especially due to atherosclerosis or plaque accumulation in the arteries that often causes CAD, heart failure, stroke, and high blood pressure (WHO, 2021). CVDs can be severe and can lead to myocardial infarction commonly referred to as a heart attack, angina or chest pain, arrhythmias, and sudden cardiac death (AHA, 2022). They are also a cause of morbidity and severe disability, having a detrimental effect on life expectancy and quality, including worsening of mental health status and reduced physical activity.

The relevance of CVDs is based on the fact that they are a significant threat to the population's health, as they are still the primary reason for death. Cardiovascular diseases, in fact, cause the highest number of deaths globally and according to the World Health Organization, more people die from cardiovascular diseases annually than from any other disease (WHO, 2021). Additionally, the cases of CVDs continue to rise significantly, making it necessary to seek for better methods of prevention and management of these diseases to minimize the pressure on the healthcare facilities across the globe.

Some of the precursors that lead to the development of CVDs are risky diets, physical inactivity, tobacco intake, and a high alcohol intake (Roth et al., 2020). Other factors include high blood pressure, high cholesterol, diabetes, and family history of heart diseases. Considering the increasing prevalence of CVDs, especially in low- and middle-income countries, further attention should be paid to these risk factors to mitigate the global effects of CVDs.

1.1 Statistics on the prevalence and impact of CVD globally

Globally, cardiovascular diseases are estimated to cause 17% of all deaths, an indication that they are a significant cause of mortality. 9 million globally every year, which accounts approximately for 32 percent of global deaths (WHO, 2021). Among such fatalities, 85 percent are as a result of heart attacks and other related ailments such as stroke which can be eradicated through lifestyle changes and proper control of risk factors. Hence, the Global Burden of Disease Study reveals that

CVDs cause loss of more than 400 million years of life every year and contribute significantly to disability-adjusted life years (DALYs) (Roth et al., 2020).

The cost implication of CVDs is high, more so in the low- and middle-income countries where CVD related deaths are estimated to be 75 percent (WHO, 2021). Such areas have poor health care access, thereby posing challenges in early detection, diagnosis, and treatment of cardiovascular diseases. With increasing healthcare costs, the total economic burden of CVDs is likely to increase to about $1 trillion by 2030, largely due to direct medical costs, lost wages and productivity, as well as the eventual cost of long-term care (Bloom, et al., 2011).

The observed trends of CVDs are strongly associated with demographic shifts, including aging of populations and a decline in physical activity levels, unhealthy diets, and increasing rates of urbanization. For instance, such lifestyle changes such as consumption of nutrient-poor foods with high levels of saturated fats, processed foods and refined sugars have magnified the prevalence of obesity, hypertension and hyperlipidemia, precursors to cardiovascular diseases (AHA, 2022). Like smoking, tobacco consumption which is still widespread in numerous countries accounts for a high proportion of global CVD incidence.

Due to expansion of CVDs prevalence across the global population, efforts for primary prevention by public health and health care systems are being directed on healthy diet, exercise and non-tobacco use. However, the increasing global burden of CVDs should encourage further research on other therapeutic interventions which may be safer and cheaper than conventional treatments for cardiovascular diseases.

1.2 Limitations of current conventional treatments for CVD

Poor dieting, excessive consumption of fatty foods, smoking, and excessive alcohol intake, among other social and behavioral characteristics, amongst other physiological characteristics like diabetes, obesity, and hypertension, contribute to CVD. Nevertheless, with the progress of medical science, CVD continues to increase globally, therefore, the drawbacks of the current conventional therapies are evident. Though these treatments have been known as effective means for controlling the symptoms and mortality rates, the side effects are usually severe. Pharmaceutical interventions

also involve some risk in formation of medication resistance in addition to possible severe side effects. Also, treatments through surgeries are often inevitable but it is associated with many risks due to incisions done while operating. Some of the limitations include:

Severe Side Effects

Beta-blockers and statins, which are commonly prescribed for CVD, may have some undesirable side effects, including fatigue, dizziness, and muscle pain (Wong et al., 2015). This may also cause liver or kidney problems, affect the patients' compliance and thus lowers the treatment efficacy (Thompson et al., 2016).

Medication Resistance

In the long run, patients are likely to develop resistance to the medications like diuretics and antihypertensive thus, minimizing effectiveness of the medication (Egan & Zhao, 2020). This resistance often requires a higher concentration to achieve the desired therapeutic effect, which leads to drug toxicity and other complications (Burnier et al., 2019).

Surgical Risks

Coronary artery bypass or an angioplasty is a big risk as it involves a surgical operation which in the process has consequential risks as they include; Infection, bleeding and damages to tissues around the specific area to be operated on (Hart et al., 2019). Besides this, recovery from these procedures may cause complications, including stroke or heart attacks, which in turn increase the length of time it takes for an individual to be fully rehabilitated (Taggart, 2018).

High Costs of Treatment

The cost of managing CVD especially through medications and surgeries is high especially where healthcare facilities are rare in low income countries. These high costs usually lead to poor compliance with the adherence of treatment plans hence leading to delayed care and worse health status (Heidenreich et al., 2011).

Lack of Personalization

Traditional CVD therapies provide few customized treatments in contrast to standard treatments that do not even incorporate an individual patient's genetics or health habits (Roth et al., 2020). This in turn hampers the efficacy of treatments in certain categories of patients, which leads to less than desired therapeutic outcomes (Benetos et al., 2019).

Long-Term Dependency

Many individuals with CVD take medications for their remaining lifetime, which is costly and incurs side effects (Tinetti et al., 2019). These treatments can help control the symptoms of CVD but are ineffective in tackling the root causes, including lifestyle practices and heredity (Ference, et al., 2017).

1.3 Rationale of the study and Scope of the review

Even with the modern approaches in CVD, conventional treatments pose major challenges in treatment such as severe side effects, high costs, and potential development of drug resistance. Polyphenols, flavonoids and terpenoids from natural products have displayed the possibility of solving these problems because of their impact on inflammation, oxidative stress and lipid profile.

This review seeks to assess effectiveness and mode of natural products in CVD management, safety and possibility of utilizing them in combination with current therapeutic processes. Thus, through a methodological review of contemporary research, the paper aims at discovering how these natural compounds can support or optimize regular treatments and indicate further research avenues.

1.4 Aim and Objectives

The present review seeks to comprise a comprehensive synthesis of the available scientific literature on natural products for the treatment of CVD.

The objectives are as follows:

- To screen and study plenty of natural substances for therapeutic uses in CVD.

- The mechanisms of action by which these natural products produce their effects were also determined.
- To consider natural products safety and effectiveness based on the preclinical and clinical investigations.
- To identify gaps in knowledge which the existing research has left and then to suggest where future research may usefully be directed.
- In an effort to provide policymakers, researchers, and medical professionals with information regarding the possibility of natural products as supplementary or alternative interventions for CVD.

This review is therefore intended to contribute to the understanding of the therapeutic value of natural products in CVD and their useful applications by integrating data from different sources and to help formulate better treatment strategies.

Chapter 2

Methodology

The literature search was carried out in order to find all the published works on the part played by natural products in CVD therapy. The following databases were systematically searched: and attempted to publish in relevant peer-reviewed journals inclusive of PubMed, Scopus, and Web of Science. These databases were selected due to their broad indexing of biomedical literature, regional and international, open access, peer-reviewed literature and systematic reviews.

Search terms used were natural Products, Phytochemicals, Plants and Plant Extracts, Herbal Medicine, Cardiovascular disease, heart disease, hypertension, coronary artery disease, stroke and clinical trial and so on.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria:

- Investigated the effects of natural products (derived from plants, animals, or microorganisms) on cardiovascular health outcomes.
- Included clinical trials, observational studies, systematic reviews, and meta-analyses.
- Published in English language.

Studies were excluded if they were:

- Not relevant to the effects of natural products on cardiovascular diseases.
- Animal studies without relevance to human cardiovascular health.
- Studies not published in English or lacking full-text availability.

Chapter 3

Overview of Cardiovascular Diseases

Cardiovascular diseases (CVD) encompass a range of conditions affecting the heart and blood vessels, each with distinct pathophysiological mechanisms. This section provides an overview of the major CVDs along with their risk factors.

3.1 Pathophysiology of Major Cardiovascular Diseases

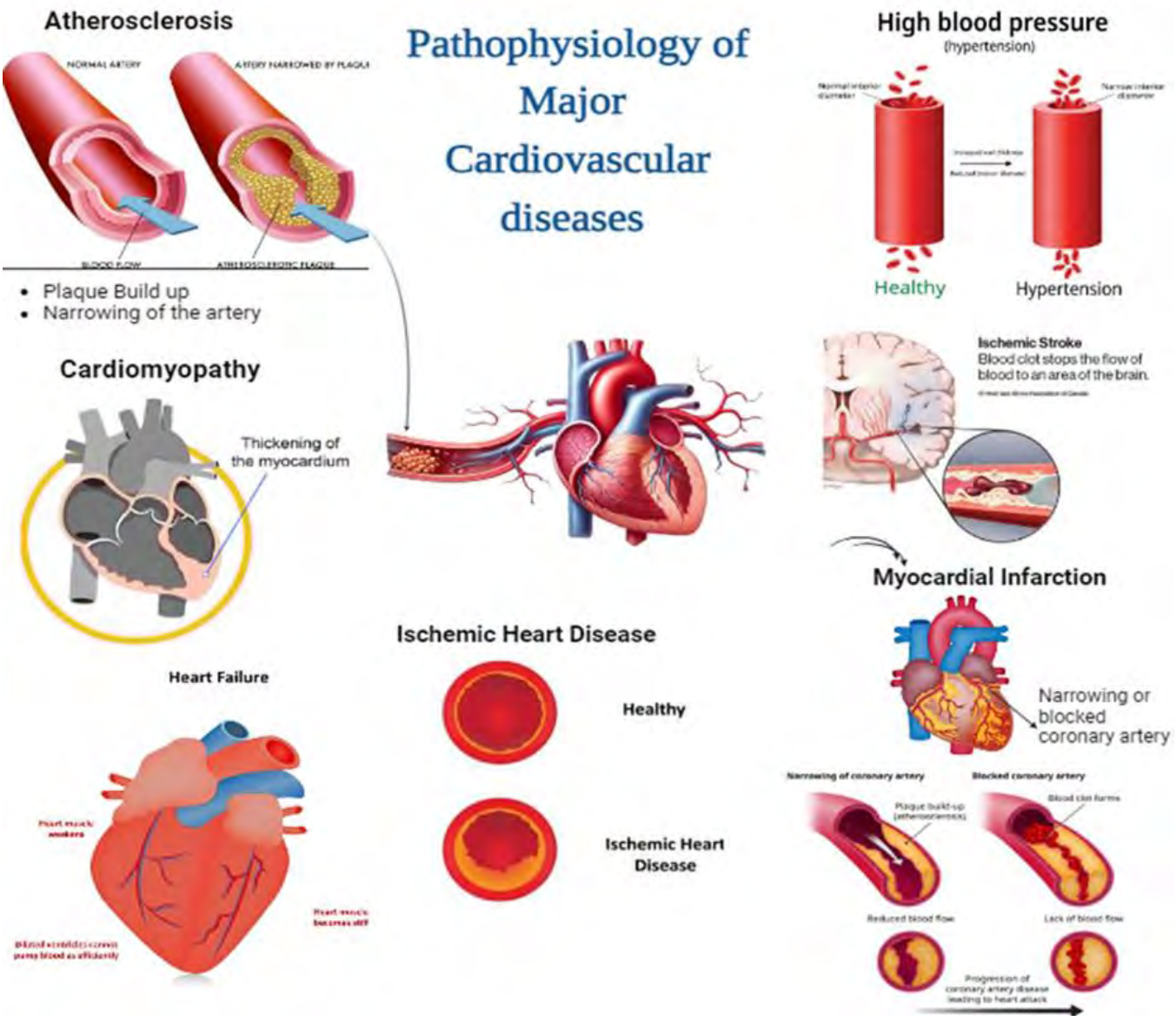

Figure 1: Pathophysiology of major cardiovascular diseases

Coronary Artery Disease (CAD)

Ischemic heart disease commonly referred to as CAD occurs when blood supply to the heart muscles is restricted due to blocked arteries as a result of atherosclerosis. The plaques that accumulate on the inner arterial walls consist of lipids and can cause the rupture of the plaque to form blood clots that may possibly lead to a myocardial infarction or a heart attack. Their onset occurs at the endothelial stage due to various causes such as high cholesterol, hypertension and others. LDL cholesterol gets modified through oxidation, penetrating the arterial wall and eliciting an inflammatory response where it forms foam cells along with fatty streaks. These later develop into fibrous plaques, which narrows the arteries and cause ischemia and angina (Libby & Theroux, 2005).

Hypertension

High blood pressure is a chronic illness that results in blood vessels exerting elevated pressure on the artery linings, creating a higher risk of CAD, heart failure, and stroke. It can be attributed to endothelial dysfunction, overactivity of the sympathetic nervous system, and increased stimulation of the RAAS. The RAAS is involved in the control of blood pressure and fluid volume; the overstimulation leads to vasoconstriction and sodium retention, raising blood pressure. Chronic hypertension results in arteriosclerosis, which decreases blood vessel compliance (Saxena et al., 2018).

Heart Failure

Heart failure is a condition whereby the heart is unable to deliver the blood supply that the body requires. It can result from CAD, hypertension, or cardiomyopathies, with two primary mechanisms: systolic dysfunction (the heart fails to contract properly) and diastolic dysfunction (the heart does not relax effectively). Systolic heart failure is characterized by a diminished capacity for the heart to pump blood due to myocardial infarction or chronic hypertension drastically lowering the cardiac output. Diastolic heart failure is due to stiffening of the ventricles and subsequently, high filling pressures. Both lead to pathologic changes in heart structure, such as hypertrophy, which in turn activate neurohormonal equipment, including the renin angiotensin aldosterone system (RAAS), thus contributing to the deterioration of heart function (Kemp &

Conte, 2012).

Stroke

Stroke is a condition that arises from a disruption in blood flow towards the brain leading to death of the affected tissue. There are two main types: can be ischemic – which accounts for 87 percent of cases, due to a thrombus or an embolus in a cerebral artery – and hemorrhagic – which results from the rupture of a blood vessel. Ischemic stroke is caused by atherothrombosis or cardioembolism, which leads to permanent cell death due to lack of oxygen and glucose. Hemorrhagic stroke may occur due to hypertension, aneurysms or vascular malformations leading to increased intracranial pressure and parenchymal injury (Kuriakose & Xiao, 2020).

Ischemic Heart Disease (IHD)

IHD, also referred to as coronary heart disease which is a medical condition whereby the blood supply to the heart muscles is reduced because of blocked arteries. This is mainly due to the arterial disease known as atherosclerosis and it results in ailments such as angina, heart attacks, and heart failure. IHD remains as one of the leading causes of morbidity and mortality with a higher prevalence among the aging population (Lim et al., 2022).

Cardiomyopathy and Myocarditis

Cardiomyopathy can be defined as diseases of the heart muscle that affects the size, shape and the structure of the heart leading to heart failure. Myocarditis, on the other hand, is the inflammation of the heart muscle, often caused by viral infections. These both affect the heart's optimal performance in pumping blood and can cause abnormal heart rhythms or rate, heart failure as well as sudden cardiac death (Cihakova & Rose, 2008).

Atherosclerosis

Atherosclerosis is defined as the formation of plaque on the arterial walls due to accumulation of fat products, cholesterol and other substances. It also leads to the arteries becoming constricted and undergoing the process of the formation of fatty deposits on the inner walls of the arteries hence minimizing blood circulation, and a high tendency for clotting. Atherosclerosis is known to be one of the primary causes of CAD, IHD, stroke, and peripheral artery diseases. It has been

found to be associated with other risk factors like smoking, high cholesterol, hypertension, and diabetes (Scott, 2004)

3.2 Risk Factors for Cardiovascular Disease

Genetic Factors

It is evident that genetic factors have a profound influence on the development of CVD. Various genotypes can affect lipid profiles, blood pressure, and inflammation, all of which are associated with CVD risk. For instance, familial hypercholesterolemia is a genetic disease of increased LDL cholesterol levels causing premature atherosclerosis and CAD (Goldstein & Brown, 2015). Further, variability in genes that have been reported to influence blood pressure regulation and/ or hypertension risk includes single nucleotide polymorphisms on the renin angiotensin aldosterone system involving the ACE genes (Mozaffarian et al., 2008).

Lifestyle Factors

Primary determinants of CVD risk are lifestyle factors. Dietary nutrients such as saturated fat, trans fat and salt have been found to cause dyslipidemia and hypertension. Sedentary lifestyle enhances the possibility of obesity, insulin resistance and undesirable lipid profile. Other specific modifiable risk factors include smoking and abnormal alcohol intake which increases the CVD risk. Tobacco use is linked to enhancing the risk of atherosclerosis and thrombosis while consuming more alcohol leads to hypertension and cardiomyopathy (Mozaffarian et al., 2008).

Environmental Factors

Socioeconomic factors, stress and pollution are amongst the determinants of CVD, both modifiable and non-modifiable. Low SES is associated with poor health literacy, poor access to healthcare services, and poor dietary practices, which are determinants of poor cardiovascular health (SC, 2017). It is also known that high-stress levels increase blood pressure and impair metabolism, which also influences cardiovascular risk (Steptoe & Kivimäki, 2012). Also, increased exposure to fine particulate matter has been linked with cardiovascular events as well as the progression of atherosclerosis (Mozaffarian et al., 2008).

Chapter 4

Natural Products and Their Mechanisms of Action in CVD

4.1 Introduction to Natural Products and Phytochemicals

Medicinal compounds, sourced from plants, animals, and microorganisms, have been essential in traditional medicine because of their therapeutic values. These substances include phytochemicals, which are important in the health of horticultural societies (Cowan, 1999). Definition of phytochemicals can be described as chemical substances that are also referred to as plant derived pharmacological agents. They are categorized depending on their functional groups and chemical compositions that include polyphenols, alkaloids, terpenoids, and fatty acids (Bhattacharya et al., 2023).

4.2 Natural Products with CVD Treatment Potential

4.2.1 Polyphenols

Resveratrol: Resveratrol which is found in grapes, berries and red wine is known for its antioxidant activity and health benefits especially in the cardiovascular system. One of the ways it operates is by activating sirtuins – enzymes that are linked to longevity and to cellular-stress resistance; it also suppresses oxidative stress and inflammation, the duo being highly linked to CVD (Quiñones et al., 2012).

Quercetin: This flavonoid which is present in fruits, vegetables and grains has proven antioxidant and anti-inflammatory properties. It scavenges free radicals, reduces inflammation and may improve endothelial function thus having a positive impact on cardiovascular health (Quiñones et al., 2012).

4.2.2 Alkaloids

Berberine: Berberine which is extracted mostly from plants such as Berberis species has also proved to enhance lipid profile and insulin level which have direct impact on the heart. It stimulates

AMP-activated protein kinase which is involved in cell energy balance and has a positive impact on lipid metabolism (Zhang et al., 2016).

4.2.3 Terpenoids

Ginkgo biloba: They are extracted from the dried leaves of the Ginkgo biloba tree and they include terpenoids which include; ginkgolides and bilobalide. These compounds possess antioxidant and anti-inflammatory activity and may enhance blood flow through the mechanism of vasodilation and hence be beneficial in management of hypertension and peripheral vascular disease (Mahadevan & Park, 2007).

4.2.4 Omega-3 Fatty Acids

Omega-3 fatty acids are EPA and DHA that are present mainly in fatty fishes such as salmon and mackerel and Flax seed. These fatty acids are also involved in cardiovascular disease risk factors such as decreasing triglyceride levels, prevention of platelet aggregation and having antioxidant properties that are cardioprotective (Calder, 2017).

Table 1: Summary of Natural Products with potential Cardiovascular Benefits

Natural Product	**Source**	**Bioactive Compounds**	**Mechanism of Action**	**Cardiovascular Benefits**	**References**
Resveratrol	Grapes, berries	Polyphenols	Antioxidant, anti-inflammatory, antiplatelet	Reduces atherosclerosis, improves endothelial function	(Quiñones et al., 2012)
Omega-3 Fatty Acids	Fish oil, flaxseed	EPA, DHA	Anti-inflammatory, lipid-lowering	Lowers triglycerides, reduces risk of arrhythmias	(Calder, 2017)
Quercetin	Onions, apples	Flavonoids	Antioxidant, antihypertensive	Lowers blood pressure, improves vascular health	(Quiñones et al., 2012)

Berberine	Goldenseal, barberry	Alkaloids	Lipid-lowering, glucose regulation	Reduces LDL cholesterol, improves insulin sensitivity	(Zhang et al., 2016).
Ginkgo Biloba	Ginkgo tree leaves	Terpenoids, flavonoids	Vasodilatory, antioxidant	Improves circulation, reduces blood pressure	(Mahadevan & Park, 2007)

4.3 Mechanisms of Action of Natural Products in CVD Treatment

Natural products have garnered significant attention for their potential role in the prevention and treatment of cardiovascular diseases due to their diverse bioactive compounds. This section provides an overview of the mechanisms through which these natural products exert their beneficial effects in CVD treatment.

Antioxidant Properties

Oxidative stress has been reported to be a significant factor in CVD due to its contribution towards endothelial dysfunction, lipid peroxidation and inflammation in blood vessels. Polyphenols (for instance, resveratrol, quercetin) belonging to the category of antioxidants found in natural products neutralize free radicals and thus limit peroxidation impacts on lipids, proteins, and DNA. These compounds help maintain the redox balance to reduce endothelial dysfunction and further slowdown the development of atherosclerosis (Chang et al., 2020).

Anti-inflammatory Effects

CVD is initiated and progressed by chronic inflammation since it slows down the endothelial function and increases plaque instability. Non synthetic constituents of plants, such as resveratrol, quercetin and curcumin, have anti-inflammatory properties attributed to suppression of pro-inflammatory cytokines like TNF-alpha, interleukins and by engaging in regulation of signaling pathways such as NF-kB. It also inhibits inflammation within vascular tissue and thereby may lower the risk of atherosclerosis plaque development and cardiovascular disease (Chang et al.,

2020).

Lipid-Lowering Effects

Hyperlipidemia or Dyslipidemia involving raised levels of LDL cholesterol and triglycerides is one of the prominent risk factors of atherosclerosis and CVD. Products from nature including berberine and omega-3 acids also assist in lipid metabolism regulation. Berberine stimulates the AMPK that builds up the lipid oxidative activity in hepatocytes and suppresses the synthesis of cholesterol. Thus omega-3, especially EPA and DHA, have the potential to decrease triglyceride concentration, to increase high density lipoprotein cholesterol and, in some cases, to alter the size of LDL cholesterol which all lead to the effective management of lipid profile and cardiovascular disease (Chang et al., 2020).

Vasodilatory Effects

It plays a very crucial role to do with regulation of blood pressure as well as the circulation of blood to crucial organs. Ginkgo biloba, as one of the most used natural products, can affect the vessels' dilation by modulating NO, a crucial agent for vessel's relaxation. NO enhances the endothelial function, increases blood vessel width and decreases vascular resistance which might be beneficial in hypertensive and peripheral arterial disease subjects by improving blood circulation (Chang et al., 2020; Mahadevan & Park, 2008).

Antiplatelet and Anticoagulant Properties

Platelet aggregation and thrombus formation are prerequisites to acute cardiovascular events, such as myocardial infarction and ischemic stroke. Dietary constituents including omega-3 fatty acids reduce the ability of platelets to activate and clump together and thereby lessen the tendency towards clot formation. Also, some phytochemicals such as curcumin possess the property of affecting coagulation factors and fibrinolysis which may lead to the prevention of clot formation and other threats such as thromboembolisms. Hence, natural products represent a rich source of bioactive compounds with diverse mechanisms of action that may benefit cardiovascular health. Polyphenols, alkaloids, terpenoids, and omega-3 fatty acids exert antioxidant, anti-inflammatory, lipid-lowering, vasodilatory, and antiplatelet effects, collectively contributing to their potential in preventing and managing CVD (Chang et al., 2020; Calder, 2020).

Table 2: Mechanisms of Action of Natural Products in CVD Treatment

Natural Product	**Antioxidant Properties**	**Anti-inflammatory Effects**	**Lipid-lowering Effects**	**Vasodilatory Effects**	**Antiplatelet/Anticoagulant Properties**	**References**
Resveratrol	Scavenges free radicals	Inhibits NF-κB pathway	Reduces LDL oxidation	Enhances nitric oxide (NO) production	Inhibits platelet aggregation	Quiñones et al., 2012
Curcumin	Neutralizes reactive oxygen species	Suppresses cytokines like IL-6	Lowers total cholesterol	Improves endothelial function	Inhibits clot formation	Chang et al., 2020
Omega-3 Fatty Acids	Reduces oxidative stress	Lowers C-reactive protein (CRP)	Lowers triglycerides	Enhances vascular reactivity	Reduces blood viscosity	Calder, 2017
Quercetin	Inhibits oxidative enzymes	Reduces inflammatory markers (TNF-α)	Improves HDL function	Induces vasorelaxation via K+ channels	Reduces thromboxane A2 production	Chang et al., 2020
Berberine	Enhances antioxidant enzymes	Modulates macrophage activity	Lowers LDL cholesterol	Improves endothelial function	Inhibits pro-coagulant factors	Chang et al., 2020

Chapter 5

Evidence from Preclinical Studies

Preclinical studies, involving studies like animal and in vitro model systems, are significant for understanding safe and effective therapeutic profiles of natural products for cardiovascular disease (CVD). It also examines data on the efficacy of natural products in lowering CVD markers in humans that include blood pressure, lipid profile, and inflammation and proven evidence from case and experimental studies (Simmons et al., 2020; Vogel et al., 2019).

5.1 Animal Models and *In-vitro* studies

Rodent small animals (mice, rats) and large animals (rabbits, pigs) are some of the models that can be used to mimic most aspects of human cardiovascular physiology and disease. Another reason for conducting the *in-vitro* studies is the ability of the researchers to investigate the cellular and molecular mechanisms of the effects of natural products when used in these animal models (Xu et al., 2021).

Animal Models

Several experimental animal studies have shown the ability of natural products to either decrease or increase cardiovascular risk factors and cardiovascular diseases. For instance, the treatment of hypertensive animal models supplemented with resveratrol results in lowering systolic blood pressure through the increase in the NO bioavailability and the improvement of endothelial function (Dolinsky et al., 2013). Likewise, omega-3 PUFAs have been shown to possess anti-lipidemic properties at various doses in animal studies – these involve decreasing serum triglycerides and LDL cholesterol (Calder, 2020).

In-vitro Studies

In vitro studies investigate the utilization of natural products and determine the relationship between the product and the cellular activities linked to CVD. Flavonoids such as quercetin and curcumin supplements have been indicated to modulate the NF-kB pathway and lower the synthesis of inflammatory cytokines in endothelial cells and macrophages. These studies offer

molecular details on how some of these natural products may reduce inflammation in the blood vessel walls and contribute to a decreased rate of atherosclerosis (Mancuso & Santangelo, 2017; Yang et al., 2019).

5.2 Efficacy of Natural Products in Reducing CVD Markers

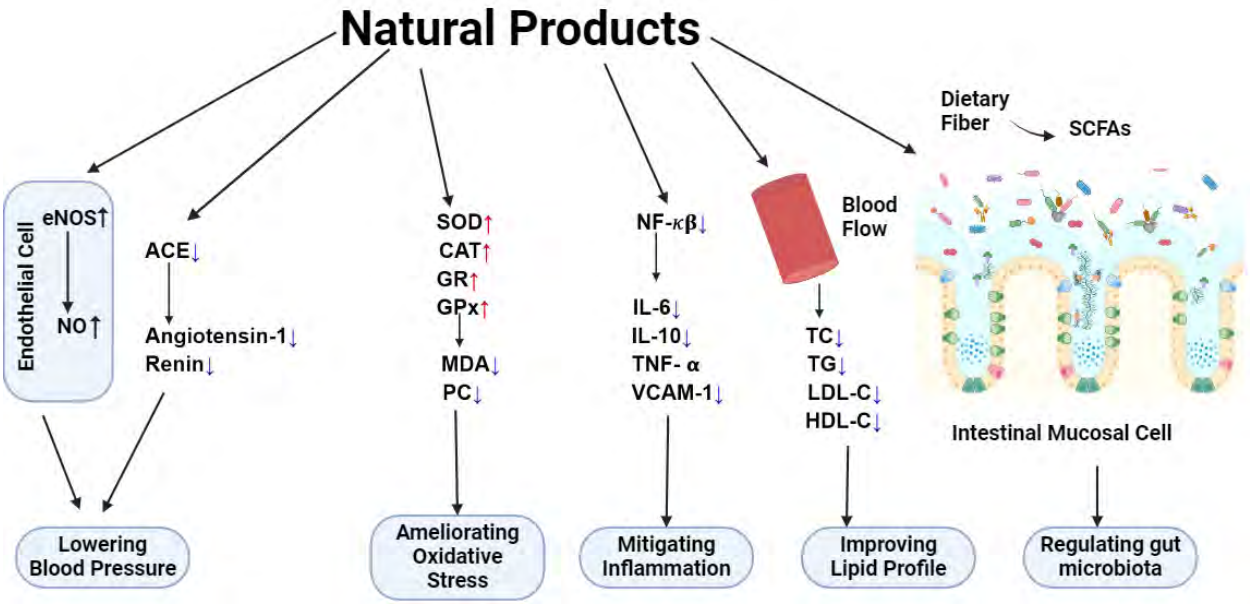

Figure 2: The mechanisms of natural products against CVD (Guodong Zhang,2021)

Effects on Blood Pressure

Hypertension is identified as one of the significant precursors of CVD including myocardial infarction, stroke, and heart failure. Natural products have shown potential as antihypertensive treatments in preclinical research. For example, berberine, which is an alkaloid derived from plants, has been shown to possess hypotensive properties due to its actions to increase the dilation of blood vessels as well as inhibit calcium channels present in the smooth muscle of blood vessels (Zeng et al., 2019). Also, the ginkgo biloba extracts are known to dilate blood vessels by stimulating the release of NO thus reducing blood pressure in hypertensive experimental animals (Goh & Woodman, 2019).

Effects on Lipid Profile

High levels of LDL cholesterol and triglycerides are associated with atherosclerosis and higher cardiovascular risk. Preliminary research supports that natural products can intercede lipid metabolism regulation and lipid parameters. Omega-3 fatty acids, notably EPA and DHA, lower serum triglyceride concentrations through suppression of hepatic TG synthesis as well as increased FA oxidation in animal studies (Calder, 2020). In addition, natural plant derived sterols and stanols which are available in certain plant foods reduce cholesterol intake at the gut level which in turn minimizes LDL cholesterol (Lichtenstein et al., 2018).

Anti-inflammatory Effects

Another important factor that contributes to the development of atherosclerosis and other CVDs is chronic inflammation. Lipophilic polyphenols including dietary green tea catechins and resveratrol are potent antioxidants that also reduce inflammation in preclinical studies. These compounds have immunosuppressive effects and interaction with signaling pathways implicated in inflammation and oxidative stress, thus helping to prevent endothelial cell dysfunction and reduce plaque growth (Li et al., 2020). For instance, curcumin, a polyphenol derived from turmeric, suppresses the production of pro-inflammatory cytokines and adhesion molecules from endothelial cells, thus reducing vascular inflammation (Wang et al., 2019).

5.3 Case Studies and Notable Preclinical Research Findings

Resveratrol

Numerous in vitro and in vivo animal studies have suggested that resveratrol has several beneficial actions on cardiovascular physiology, essentially because of its antioxidant and anti-inflammatory properties as well as its lipid-lowering efficacy. Some animal studies demonstrated that resveratrol has beneficial effects on plaque size and plaque stability, which may translate to a lower risk of MI and stroke (Cheng et al., 2019).

Berberine

Experimental animal data derived from *in vivo* and *in vitro* experiments suggested that

antihypertensive, lipid-lowering and insulin sensitizing properties of berberine exist. These effects are due to its actions as a potent activator of AMP-activated protein kinase (AMPK), which is involved in regulating energy homeostasis in cells (Zhang et al., 2018). A number of researchers have also found that this compound has the potential to decrease LDL cholesterol and triglyceride concentration in models of dyslipidemia (Cicero & Begging, 2016).

Omega-3 Fatty Acids

The positive effects of omega-3 and specifically EPA and DHA on cardiovascular health are backed by many preclinical studies. These compounds lower triglyceride levels, prevent blood clot formation, and exhibit anti-inflammatory activities, all of which are beneficial in protecting the heart (Calder, 2020). A clinical study has shown that omega-3 fatty acids reduce myocardial damage and enhance cardiac performance in animal models of ischemic events (Barceló-Coblijn & Murphy, 2009). The available preclinical data suggest that some natural products investigated as potential treatments for CVDs have demonstrated significant efficacy. In experimental animals, in vitro studies have shown that polyphenols, alkaloids, terpenoids, and omega-3 fatty acids reduce BP, control lipid levels, and reduce inflammation – all of which are potential pathways involved in CVD (Shi et al., 2019). While these findings are encouraging, boosting the effect of these compounds to human subjects with clinical diseases remains challenging based on these findings, as translating preclinical findings to appropriate clinical applications necessitate clinical trials that demonstrate efficacy besides safe dosing regimens in human subjects. However, a growing body of preclinical literature supports the role of natural products as supplemental remedies for the promotion of cardiovascular health and the alleviation of the global burden of cardiovascular diseases (Tsao et al., 2019).

Chapter 6

Clinical Evidence and Trials

Clinical trials are used to determine the safety and efficacy of natural products for treatment and chronicling of cardiovascular diseases (CVD). It gives overviews of clinical trials of natural products, specific trials, results of trials, and trial design and methodology, as well as findings, outcomes, and a look into their effectiveness and safety versus conventional therapies.

6.1 Overview of Clinical Trials Involving Natural Products for CVD

Studies evaluating natural products for CVD consequently examine their impact in relation to cardiovascular risk factors, progression of CVD and clinical outcomes. These trials differ based on their design and may include only RCTs, observational trials or meta-analysis. In order to determine the medicinal effects of natural products and their lack of side effects, they frequently contrast them with placebo or traditional treatments (Calder, 2020).

Some of the polyphenols reported in clinical trials are resveratrol, quercetin, omega-3 fatty acids, plant sterols and herbal medicine like ginkgo biloba, garlic extract. These products are assessed in terms of their effectiveness in lowering blood pressure, modifying lipid profiles, improving endothelial function, and preventing inflammation that is linked to CVD (Shi et al., 2019).

6.2 Specific Case Studies and Trial Results

Resveratrol

Study Design and Methodology: The study undertaken to determine the impact of resveratrol supplementation (1g/day) on CVD risk factors in type 2 diabetic patients was a double blinded placebo controlled trial. Volunteers were followed for 45 days and their blood pressure levels, serum lipid and glucose profiles as well as levels of key inflammatory markers were tested (Zordoky et al., 2015).

Key Findings and Outcomes: Resveratrol has shown promising cardiovascular benefits in preclinical studies including improving endothelial function, lowering blood pressure and reducing inflammation. However, clinical data remain limited. Most human trials have focused on

metabolic diseases, with cardiovascular disease (CVD) being a secondary outcome. The largest trial to date enrolled only 66 patients, and the short-term nature of these studies makes it difficult to evaluate long-term cardiovascular effects. Moreover, some trials have used polyphenolic mixtures rather than pure resveratrol, complicating the interpretation of results.

Comparison with Conventional Treatments: Compared to conventional treatments like statins and ACE inhibitors, resveratrol's cardiovascular benefits are less conclusive. The lack of large-scale, double-blinded, placebo-controlled clinical trials limits its clinical application. While it shows potential, especially in diabetic patients where CVD is a common comorbidity, resveratrol's effectiveness and safety in treating CVD remain unproven. Long-term studies are needed to assess its therapeutic value in comparison to established CVD treatments (Zordoky et al., 2015).

Omega-3 Fatty Acids

Study Design and Methodology: Many RCTs have been done looking at the cardiovascular outcomes of omega-3 PUFAs particularly EPA and DHA in many different groups of patients including those with hypertriglyceridemia, coronary artery disease, and heart failure. These trials usually involve supplementation with fish oil capsules of particular concentrations of EPA and DHA for several months to years (Calder, 2020).

Key Findings and Outcomes: Omega-3 fatty acids have yielded significant reductions in triglyceride levels and favorable changes in lipid profile. They also display antiarrhythmic properties and may have potential cardioprotective effects as well as prevent complications such as myocardial infarction and sudden cardiac death. However, their effects on major CVD outcomes such as stroke and all-cause mortality have shown variations in the different trials (Barceló-Coblijn & Murphy, 2009).

Comparison with Conventional Treatments: Omega-3 fatty acids are recommended to patients with hypertriglyceridemia as a supportive treatment and to patients with cardiovascular disease, especially those with high risk profile. It is advisable to monitor for gastrointestinal side effects with patients on these drugs and for interaction with other drugs. (Calder, 2020).

Garlic Extract

Study Design and Methodology: This meta-analysis systematically reviewed and synthesized clinical trials assessing the efficacy and safety of garlic extract on patients' hypertension. The review involved placebo-controlled RCTs of garlic intake versus garlic with antihypertensive agents or placebo over different periods (Ried et al., 2016).

Key Findings and Outcomes: Garlic-extract intervention was observed to cause a small reduction in both SBP and DBP compared with placebo. The decrease in blood glucose levels was more profound in hypertensive patients, hinting at possible antihypertensive effects similar to conventional drugs. But the degree of the reduction in blood pressure has not been the same in all the trials and therefore the trial period of the garlic extract has not yet been conclusively determined (Ried et al., 2016).

Comparison with Conventional Treatments: Antihypertensive properties of garlic extract are relatively weaker compared to standard drugs such as ACE inhibitors or calcium channel blockers. Proper usage of drugs may be employed in the management of mild to moderate hypertension or in individuals who may prefer herbs or complementary medicine or patients who may have developed medication intolerance (Ried et al., 2016).

Quercetin

Study Design and Methodology: The study undertaken was a randomized, double blind, placebo-controlled crossover trial with 41 hypertensive patients over a period of 4 weeks to evaluate the role of quercetin supplementation. The patients were administered with quercetin every day and their blood pressure as well as the endothelial function and inflammatory biomarkers were recorded throughout the trial (Edwards et al., 2007).

Key Findings and Outcomes: The outcomes of the trial also showed that quercetin supplementation resulted in reduction of systolic blood pressure and improvement in endothelium function. It has been found to have antioxidant and anti-inflammatory properties, which can protect

blood vessels, reduce blood pressure and inhibit the formation of blood clots (Edwards et al., 2007).

Comparison with Conventional Treatments: This indicated that quercetin was moderately effective as an antihypertensive agent as compared to conventional medications like ACE inhibitors and calcium channel blockers. Although this action is relatively weaker compared to standard drugs, quercetin's antioxidant activity further promotes cardiovascular health that may not always be available in pharmaceutical drugs (Edwards et al., 2007). However, to determine its applicability to various clinical settings, more studies that are long-term are required.

Curcumin

Study Design and Methodology: This randomized, double-blind, placebo-controlled trial involved 72 patients with acute myocardial infarction. Participants were divided into two groups: the intervention group (n = 38), which received 500 mg/day of curcumin with piperine for 8 weeks, and the control group (n = 34), which received a placebo. The study measured ejection fraction, cardiac troponin I (cTnI), lipid profile, HbA1C, liver enzymes, and renal function parameters at the beginning and end of the trial (Tabaee et al., 2021).

Key Findings and Outcomes: Curcumin supplementation significantly improved lipid profiles (lowered LDL, increased HDL) and reduced HbA1C and liver enzymes levels. However, it did not affect ejection fraction, cardiac troponin I (cTnI), or renal function parameters in myocardial infarction patients (Tabaee et al., 2021).

Comparison with Conventional Treatments: While curcumin improved lipid profiles and glycemic control, it did not match conventional treatments like **statins** or **ACE inhibitors**, which more effectively reduce cardiovascular risk and improve key heart function indicators. Curcumin may serve as a complementary therapy but cannot replace standard treatments for myocardial infarction (Tabaee et al., 2021).

Table 3: Clinical Trials of Natural Products in Cardiovascular Disease Treatment

Natural Product	Study Design	Sample Population	Dosage regimen	Key Findings	References
Resveratrol	Randomized, placebo-controlled double-blinded parallel	Patients with type 2 diabetes (n = 66)	1 g/day for 45 days	↓SBP ↓LDL, ↑HDL, No change in total triglycerides and total Cholesterol.	Zordoky et al., 2015; Movahed et al., 2013
Omega-3 Fatty Acids	Multiple RCTs and meta-analyses	Patients with hypertriglyceridemia, coronary artery disease	6 months to several years	↓triglyceride levels, antiarrhythmic effects, cardioprotective properties	Calder, 2020; Barceló-Coblijn & Murphy, 2009
Garlic Extract	Meta-analysis of RCTs	Hypertensive patients	Varies across studies	Small reductions in systolic and diastolic blood pressure compared to placebo	Ried et al., 2013
Quercetin	Randomized, double-blind, placebo-controlled, crossover trial	41 hypertensive patients	730 mg/day orally for 28 days	↓systolic blood pressure, No change in oxidative stress→	Edwards et al., 2007; Zhang et al., 2023
Curcumin	Randomized, double-blind, placebo-controlled trial	72 patients with acute myocardial infarction, aged 18–75 years	500 mg with piperine supplement for 8 weeks	Modified lipid profile, liver enzymes, and glycemic status	Tabaee et al., 2021

6.3 Discussion on the Safety and Efficacy of Natural Products

Safety

Studies conducted on natural products employed in clinical trials of CV disease show that most of them possess low or minimal toxicity levels. Antioxidants, polyphenols, omega-3 fatty acids, and garlic and ginkgo biloba have been reported to elicit mild side effects in most consumers (Kris-

Etherton et al., 2002; Macan et al., 2022). However, the issues that have to be taken into consideration are their interaction with other drugs (e. g. anticoagulants, antiplatelet agents) and variations in quality of product and its purity (Gross et al., 2016).

Efficacy

The level of effectiveness of natural products in the prevention and management of CVD depends on the kind of compound used, the appropriate dose, and population type (Bhatt et al., 2020). Within trials several favorable effects on cardiovascular risk factors including heart rate, lipids and inflammation markers are seen, as for clinical end points like cardiovascular death, stroke etc less favorable or positive results are reported (Li et al., 2019). Study design type, study duration, and participants' characteristics define efficacy outcomes (Zhou et al., 2020).

Chapter 7

Integration of Natural Products into Conventional Therapies

Natural products are used as an adjunct, or as a supplement to conventional treatments for CVD. These medications may have additive effects in achieving enhancement of cardiovascular risk factors and life quality (Shao et al., 2017). But as primary treatments or substitutes for conventional medicine, more clinical trials and controlled research, as well as safety profiles, are needed to endorse them.

Clinical trials offer compelling proof of the applicability of natural products for the treatment of cardiovascular disorders. Some of the natural compounds including Resveratrol, omega-3 fatty acid, garlic extract and so on have revealed the efficacy to lower the blood pressure, to support the lipid profiles and to decrease the inflammation which in turn supports the cardiovascular health (Kris-Etherton et al., 2003; Shao et al., 2017). However, further studies are still needed for these natural products to establish their definite effectiveness for the prevention of major cardiovascular incidents and determine their potential benefits, possible adverse effects and the best ways for their utilization in clinical practice. The utilization of natural products in the overall approaches to managing CV disease also has potential for optimizing treatment processes and managing the complex aspects of CVD (Bhatt et al., 2019).

Integration of Natural Products into Conventional Therapies

Natural products have potential therapeutic prospects for integrating with conventional therapies in the treatment and management of cardiovascular diseases (CVD).

This section covers such topics as the possibility of the interaction between natural products and chemical drugs, synergistic and antagonistic effect, difficulties, and precautions in their interaction, legal and quality aspects connected with the use of natural products in combination with chemical drugs, as well as examples of successful use of IP with conventional drugs (Gurib-Fakim, 2006).

Potential for Combining Natural Products with Conventional Drugs

Integrating natural products with the traditional drugs show possibilities of improving the treatment effects and treating the complex factors related to CVD (Schafer & Wink, 2018). Polyphenols, omega-3 fatty acids, and plant extracts have various pharmacological actions that enhance the effects of prescription drugs. For instance, polyphenols possess antioxidant and anti-inflammatory capabilities that may enhance the endothelial function in combination with statins or ACE inhibitors (Li et al., 2019).

Synergistic Effects and Interactions

Potential interactions between natural products and pharmaceutical drugs can increase potency and decrease the impact of side effects (Soleimani et al., 2018). Statin combined with omega-3 fatty acids have been seen to have an added effect of reducing the LDL cholesterol and bettering the lipid profile further as compared to statin therapy alone (Kris-Etherton et al., 2003). Likewise, the mild antihypertensive properties of garlic extract could work synergistically with the actions of ACE inhibitors or calcium channel blockers in managing hypertension (Ried et al., 2013).

Thus, it is crucial to examine certain conflicts between natural products and different medications. For example, omega-3 fatty acids and anticoagulants can combine to raise the risk of bleeding, making it more likely that a patient will experience this complication (Gross et al., 2016). Garlic extract also has this interaction with anticoagulant medications, so the clotting parameters should be supervised (Macan et al., 2006). The safety of patients should always be put into consideration while prescribing drugs and this can be achieved by a proper evaluation of potential drug interactions and adjustment of the treatment regimen.

7.2 Challenges and Considerations

Dosage and Standardization

A major issue with use of natural products in combination with conventional medicine is that products and doses differ considerably (Posadzki et al., 2013). Since natural products may contain variable amounts of bioactive compounds, standardization provides optimal ratios and dosage for therapeutic efficacy (Sarris et al., 2011). However, the variability in sourcing, extraction

techniques, and the quality of life can also influence the bioavailability and potency, therefore, the need to adhere to specific manufacturing practices alongside the quality control protocols (Bent, 2008).

Regulatory and Quality Control Issues

Supervision from the relevant authorities, and standardization and assurance of quality are key issues that practitioners should bear in mind when incorporating natural products into their practices .While NHPs may be categorized as drugs, foods, or other products, there remain differences in how regulatory agencies in different countries regulate, dispense or allow for the marketing of NHPs as well as their safety, efficacy, and labeling standards (Dwyer et al., 2018). The customers of healthcare and the health care givers have to look for products produced by reputable manufacturers who have been third party certified to ensure that the health care supplements being sold in the market are pure, potent and safe.

Table 4: Challenges in Integrating Natural Products into Conventional CVD Therapies

Challenges	**Explanation**	**References**
Lack of Standardization	Variability in the source, composition, and quality of natural products results in variations in clinical effectiveness, which hampers their compatibility with conventional treatments for CVD. The variability inherent in this challenge also limits the ability to replicate studies and make definitive conclusions about their safety and effectiveness.	(Li & Zhang, 2018; Ahmad et al., 2020)
Potential for Drug Interactions	Natural products may have interactions with conventional cardiovascular medications, resulting in either synergistic or antagonistic effects. For instance, garlic and omega-3 fatty acids should not be taken together with anticoagulants since they can cause severe consequences such as bleeding.	(Simons et al., 2019; Martin et al., 2021)

Lack of Robust Clinical Evidence	Most of the natural products that exhibit a positive effect in the first set of experiments have not been subjected to large scale, double blind clinical trials that will determine their effectiveness and safety where they are administered alongside conventional therapy for CVD.	(Zhang et al., 2019)
Bioavailability Issues	Most natural compounds, for instance, curcumin has low bioavailability, hence are hardly absorbed into the system. Thereby they are less effective when administered alongside conventional therapies. For this reason, approaches to enhance their solubility are required.	(Esfandiari et al., 2020)
Quality Control and Regulation	The regulatory requirements for natural products are not near as stringent as those for drugs; hence, differences in product quality and potency exist. Such measures as standardization and quality control should be practiced in natural products to guarantee the safety of products used in complementation with conventional treatment plans.	(Barrett & Chopra, 2020; WHO, 2020)
Patient Compliance	Natural products can be incorporated into treatment regimens and may make treatment regimens more complex, affecting patient compliance. Perceived complexities of the natural products and interactions with the conventional medicines makes it challenging for patients to follow through on the treatment regimens.	(Green et al., 2020; Joannidis & Shenoy, 2021)

7.3 Examples of Successful Integrative Approaches

Coenzyme Q10 (CoQ10) and Statins

Coenzyme Q10 is an antioxidant and a cofactor of mitochondrial respiration and it is known that statin therapy reduces levels of coenzyme Q10, thus causing muscle side effects. Global surveys further suggest that combining CoQ10 with statins eradicates these side effects while probably improving the function of mitochondria as well as overall heart health (Banach et al., 2018; Thompson et al., 2016).

Omega-3 Fatty Acids and Antiplatelet Therapy

In patients with coronary artery disease, EPA and DHA, the two omega-3 fatty acids, enhance the effects of antiplatelet agents such as aspirin in the prevention of thrombotic events. They work against inflammation and blood clotting (Mozaffarian & Wu, 2018; Bistrian et al., 2020). The synergy between the natural products and conventional treatments is that it decreases platelet formation and cardiovascular risk.

The possible application of natural products in conventional therapies suggests a betterment of cardiovascular treatments and patient outcomes. As with any personalized model of treatment, the integration of natural products into the healthcare regimen along with conventional drugs offers a much stronger course of treatment than when used individually. However, there are some limitations like the amount of these compounds, the method of administration, and the interactions, which needs further evaluation and control. Integrative care therefore requires evidence-based approach in the coordination between healthcare providers and clients and should uphold sound quality assurance measures so as to use natural products in the management of cardiovascular diseases safely and effectively (Baum et al., 2020).

Table 5: Comparison of Conventional Therapies and Natural Products in CVD

Therapy Type	**Mechanism**	**Advantages**	**Disadvantages**	**Evidence Level**	**References**
Statins	Inhibits HMG-CoA reductase, reduces LDL	Effective in lowering LDL and reducing risk of cardiovascular events	Muscle pain, potential liver damage, drug interactions	High - Supported by numerous large RCTs and meta-analyses	(Thompson et al., 2016)

ACE Inhibitors	Blocks conversion of angiotensin I to II	Lowers blood pressure, reduces heart failure risk	Cough, hyperkalemia, angioedema	High- Proven effective in managing hypertension and heart failure in clinical trials	(Benetos et al., 2019)
Polyphenols (e.g., Resveratrol)	Antioxidant, anti-inflammatory	Natural, may reduce blood pressure and inflammation, offers cardioprotection	Variable efficacy, bioavailability issues	Moderate- Promising preclinical and limited clinical evidence	(Szkudelska & Szkudelski, 2010)
Omega-3 Fatty Acids	Anti-inflammatory, lipid-lowering	Reduces triglycerides, inhibits platelet aggregation, heart health benefits	Fishy aftertaste, potential contamination, may increase bleeding risk, variability in effects across studies.	Moderate to High-Several RCTs supporting efficacy, though with mixed results	(Calder, 2004)
Herbal Remedies (e.g., Ginkgo Biloba)	Vasodilatory, improves blood circulation	Natural, used for centuries	Inconsistent effects, May interact with anticoagulant, risk of bleeding,	Low to Moderate- Limited evidence, mostly preclinical and small trials	(Mahadevan & Park, 2007)

Chapter 8

Challenges and future directions in natural products research for cardiovascular diseases

Plant sources are among the products that have elicited much interest due to their possible use in tackling CVDs; however, several issues still surround their use in research and in practice. This section includes assessment of gaps and limitations of current research, suggestions on future research avenues and the possibility of natural products as prospective solutions for reduction in the global burden of CVD.

8.1 Limitations in Current Research

Lack of Large-Scale, and Long-Term Clinical Trials

Perhaps one of the biggest drawbacks in natural products used for CVD, which is also apparent in this review, is the absence of large-scale and long-term clinical trials. A majority of the research is either conducted on smaller samples or over short durations, which makes it difficult to evaluate the effectiveness, side effects, or other cardiovascular benefits in the long run. The development of proper clinical trials is critical for the determination of the efficacy of natural products as supplementary or replacement treatments to a traditional medicine (Zordoky et al., 2015).

Variability in natural product composition

Natural products contain variation in their chemical makeup because of factors such as genetic variations, geographic location, timing of harvesting, and ways of extracting the bioactive compounds. This variability has implications on the pharmacokinetic profile of the bioactive compounds, their effectiveness and therapeutic value. Herbal formulation and especially of natural products must have standard recipes which must be closely regulated in order to achieve uniform quality and efficacy as observed in clinical studies (Lee et al., 2012).

Bioavailability and Pharmacokinetics

The uptake rate of bioactive compounds from natural products make it difficult to attain

therapeutic levels in the target organs (Nguyen et al., 2020). Some of the attributes of natural products include low bioavailability due to poor absorption, a short biological half-life due to rapid metabolism and tissue distribution thus limiting the effectiveness of natural products in clinical applications. The evaluation of bioavailability with the help of advanced delivery system approaches, formulations, and pharmacokinetic investigation is the key research area for better therapeutic effects (Huang et al., 2024).

8.2 Future Research Priorities:

Identification of Novel Bioactive Compounds

Further research on more extensive natural products libraries for bioactive compounds may likely lead to prospective drugs for CVD. New approaches in analytical methods, metabolites, and bioinformatics enable the discovery of bioactive compounds with significant cardiovascular effects, thus improving drug discovery and targeted therapeutic interventions (Tsakni et al., 2023).

Advanced Delivery Systems for Natural Products

Advanced delivery systems including nanoencapsulation, liposomal formulation, and controlled-release technologies increase the solubility and shelf-life of natural products. Such technologies enhance the/drug bioavailability, or circulation half-life, and enable selective deposition of the drug at the affected tissue/organ in cardiovascular disease. The technology increases the therapeutic efficacy of natural products while reducing side effects through complex delivery systems hence expanding the use of natural products in treatment (Huang et al., 2024).

Personalized Medicine Approaches

It is the clinical approach that applies medical therapy according to variations in genes, behaviors, and surges of diseases. The integration of biomarkers, genotyping, and clinical information empowers natural product treatment to be tailored according to the patient's characteristics and disease manifestations (Lee et al., 2012). Individualized therapy assimilate greater efficacy, lesser toxicities, and better patient compliance to natural products in CVD. (Zhou et al., 2024).

Potential Impact of Natural Products on Global CVD Burden:

Natural products play the role of being complementary with other treatments hence have the potential of having a profound influence on the cardiovascular diseases burden in the world. Its various pharmacological actions, which include antioxidant, anti-inflammatory, lipid profile improvement, and vasodilation, target different aspects of cardiovascular disease. The growth and effective tackling of the problems as well as the progress of further research on natural products for cardiac diseases requires participation and cooperation of researchers, clinical practitioners, governing bodies and other interested parties from the industry. The main issues that need to be addressed include the issues of research design, standardization and bioavailability of the natural products to determine their safety and efficacy and utility in the control of CVD. The focus on new bioactive compounds, further advancements in the delivery systems, and shift towards individualized medicine approach in the future research will open up new horizons and make an enhancement of cardiovascular cure and care a reality internationally. Thus, the chance of employing the opportunities of natural products can lead healthcare systems to a more successful and optimal way in the fight against the increasing epidemiology of cardiovascular diseases worldwide.

Chapter 9

Conclusion and future recommendations

Natural products are promising in the treatment and management of cardiovascular diseases (CVD) due to therapeutic components' available bioactivities. There are many significant polyphenols such as resveratrol and quercetin present in grapes, which at the minimum have antioxidant and anti-inflammatory properties that enable the protection of endothelium lining and decreasing risk of atherosclerosis. Omega-3 fatty acids have positive effects on lipid profile and reduction of cardiovascular risks due to its role in antiplatelet and antiarrhythmic effects. Moreover, plant derivatives like ginkgo biloba and garlic possess vasodilator and antihypertensive properties that may aid conventional medications. Experimental and clinical evidence points to the fact that it is safe to combine natural products with conventional treatment regimens in order to improve cardiovascular health.

However, there are issues like variation in composition, bioavailability and regulations that need to be overcome for better incorporation of natural products in clinical practice. Natural products should always be formulated in a standardized manner so that they can be effective in health management because the standardization of the same natural products varies in different regions Natural products cannot be used in clinical management without regulation and this is because there is always a chance that it may be contaminated or it may not work as required when tested in an individual.

Future Recommendations

Further studies should be directed towards exploring novel bioactive constituents and exploring novel delivery systems, to achieve the maximum beneficial effects in CVD from natural products. Pharmacogenomics, which is the targeted approach in delivering remedies based on patient characteristics, could enhance use of these compounds in controlling cardiovascular diseases (CVDs). Moreover, further experimental studies on animals and humans are needed to confirm the

efficacy, the safety, and the potential health benefits of natural products in different populations.

Collaboration among researchers, healthcare providers, and regulatory authorities is essential to fully integrate natural products into comprehensive CVD management strategies. By incorporating these therapies, healthcare systems can potentially enhance patient outcomes and reduce the global burden of cardiovascular disease.

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