ADVANCEMENTS IN CARDIOVASCULAR RESEARCH AND THERAPEUTICS:

MOLECULAR AND NUTRACEUTICAL PERSPECTIVES

Editors:
V. V. Sathibabu Uddandrao
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Advancements in Cardiovascular Research and Therapeutics: Molecular and Nutraceutical Perspectives

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Advancements in Cardiovascular Research and Therapeutics: Molecular and Nutraceutical Perspectives

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FOREWORD

I was delighted when I received a request from Dr. P. Brahmanaidu and Dr. V. V. Sathibabu Uddandrao to write a brief foreword to the reprint of this book because, for many years, I have admired their incredible contribution to research especially in the field of metabolic disorders and nutraceuticals. I was excited when they started writing a book on "Advancements in Cardiovascular Research and Therapeutics: Molecular and Nutraceutical Perspectives" and I would be first in line to buy it. In fact, editors sent me a copy of the book draft and I was humbled. Not only was this a great book, but it was also a great way to write and construct chapters.

Looking through this magnificent volume, I am absolutely amazed by the way they presented this book about the pathophysiology of cardiovascular disorders and their novel treatment approaches by nutraceuticals. It is more than a book of lovely illustrations and a mine of information, demonstrating therapeutic approaches and it is a source of inspiration and information in the field of cardiovascular pharmacology. This book is unique and surely a work of treasure for anyone who is interested in cardiovascular research. So, I strongly recommend you to read it, enjoy it and learn from it.

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PREFACE

Cardiovascular diseases (CVD) belong to the most severe health problems and are considered the main cause of morbidity and mortality in modern society. CVDs consist of a broad spectrum of diseases, including atherosclerosis, hypertension, myocardial ischemia, cardiomyopathy, and heart failure. Risk factors for CVDs include hypertension, hyperlipidemia, obesity, diabetes mellitus, metabolic syndrome, and a sedentary lifestyle. Therapeutic effects against CVD have been demonstrated by several medicinal plants and nutraceuticals thus presenting new possibilities for the treatment of CVD risk. Evidence suggests that this approach is very promising. So, the aim of this book is to present an update on the most recent evidence related to the use of nutraceuticals in the context of the prevention and treatment of CVD.

Chapter 1 discusses CVD and nutraceuticals and the underlying mechanism and therapeutic biomarkers. The chapter presents the beneficial effects of nutraceuticals on the heart and also gives an insight into the bioinformatics approach to identify novel therapeutic biomarkers in order to update the practitioner's awareness of the use of nutraceuticals for CVD management. Chapter 2 provides detail about congestive heart failure and insight into pharmacotherapy. This chapter explains possible pharmaceutical approaches to treat congestive heart failure. Chapter 3 provides a review of diet, inflammation, and CVDs. The chapter reveals the role of diet in the prevention of vascular inflammation and the usefulness of antioxidants in preventing CVD. Chapter 4 represents the applications, advantages and disadvantages of various rodent and non-rodent animal models in the research on CVD especially while evaluating nutraceuticals' effects against CVD. On the other hand, chapter 5 discusses the CRISPR-cas9 technologies in the 21st century and their applications in cardiovascular diseases.

Chapter 6 discloses the role of Indian Ayurvedic approaches to the cardiovascular system, etiopathogenesis, and therapeutic strategies. The chapter highlights the precipitants that attenuate Vyana Vayu and addresses curative measures to restore Vyana Vayu. Chapter 7 depicts nutraceuticals as potential agents to rescue the human race from CVD. The chapter point outs the current scenario of CVD, pathophysiology, therapeutic drugs available, the role of nutraceuticals in treating CVD, and their mode of action with a special emphasis on commonly used kitchen spices. Chapter 8 explains the therapeutic potential and mode of action of Biochanin-A, a natural compound predominantly found in soy, chickpea, peanuts, alfalfa sprouts, and red clover against hypertension in experimental rats. Chapter 9 concentrates on the ameliorative potential of Zingiberene, a monocyclic sesquiterpene that is the principal constituent of ginger (Zingiber officinale) against obesity and cardiomyopathy. Finally, chapter 10 presents the amelioration of myocardial infarction through the attenuation of pro-inflammatory cytokines and matrix metalloproteinase production by Betaine, a well-known nutraceutical widely occurring in plants, animals and rich dietary sources.

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CHAPTER 1

Cardiovascular Diseases and Nutraceuticals: Underlying Mechanism and Therapeutic Biomarkers

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Abstract: Food and nutrients are essential for the body's regular functioning. They aid in the preservation of an individual's health and the reduction of the danger of certain diseases. As a result of the widespread recognition of this fact, a link was established between "nutrition and health," and the term "nutraceuticals" was coined. Nutraceuticals are therapeutic foods that aid in maintaining well-being, enhancing health, regulating immunity, and preventing as well as curing certain diseases. Nutraceuticals might thus be thought of as one of the missing pieces in a person's overall health. More than any other illness, cardiovascular disease has numerous risk variables that are susceptible to nutraceutical treatment. It is critical to see nutraceuticals' ability to improve cardiovascular risk factors as a huge opportunity in the treatment of a disease that affects so many people. Nutraceuticals show promise in clinical treatment since they have the potential to minimize the risk of chemotherapy-related side effects while also lowering the overall cost of health care. In this study, an attempt was made to summarize some of the most recent research findings on garlic, omega-3 fatty acids, soy products, dietary fibers, vitamins, antioxidants, plant sterols,

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flavonoids, prebiotics, and probiotics that have beneficial effects on the heart, as well as to provide insight into a bioinformatics approach to identify novel therapeutic biomarkers in order to keep practitioners up to date.

Keywords: CVD, Diet, Heart disease, Metabolic syndrome, Nutraceuticals, Nutrition.

1. INTRODUCTION

1.1. Cardiovascular Disorders

The term “cardiovascular disorders” (CVD) or “heart disease” refers to a variety of illnesses that affect the heart and blood arteries [1]. Coronary artery disease, cerebrovascular disease, angina, heart attack, heart failure, dilated and hypertrophic cardiomyopathy, peripheral arterial disease, rheumatic heart disease, heart rhythm problems (arrhythmias), congenital heart defects, deep vein thrombosis, and pulmonary embolism are all diseases that fall under the heart disease umbrella. Electrocardiogram (ECG), Holter monitoring, Echocardiogram, Stress test, cardiac catheterization, cardiac computed tomography (CT) scan, and cardiac magnetic resonance imaging are commonly used to diagnose it (MRI) [2]. CVD has surpassed cancer as the top cause of mortality worldwide, and it is a major public health issue. Obesity, metabolic syndrome, atherosclerosis, hyperlipidemia, type 2 diabetes, hypertension, and lifestyle risk factors such as smoking, physical inactivity, and dietary factors are all common and growing in popularity across the world [3]. Reducing risk variables in the population, particularly blood pressure control and cholesterol reduction can have an influence on CVD mortality [4]. Hypertension is to blame for 45% of heart attacks and 51% of strokes, as well as 9.4 million CVD-related deaths throughout the world [5]. Despite significant advancements in medical care, the prognosis for CVD remains dismal, and identifying causes and new therapeutic methods remains a high priority [6].

1.2. Cardiovascular Diseases Burden: Global and National

Cardiovascular diseases (CVDs) are the leading cause of death worldwide and a significant contributor to poor quality of life [7]. CVD claimed the lives of 17.8 million people globally in 2017, resulting in 330 million years of life lost and another 35.6 million years of disability [8]. Heart attacks and strokes account for four out of every five CVD fatalities, with one-third of these deaths occurring before the age of 70 [9]. Furthermore, case fatality due to CVD appears to be

significantly greater in low-income nations than in middle- and high-income countries [10].

The burden of cardiovascular disease (CVD) in India is one of the highest in the world. Noncommunicable diseases (NCDs), including cardiovascular disease (CVD), are projected to account for 60% of all adult fatalities in India, with CVD accounting for approximately 26% of these deaths [11]. The yearly number of CVD fatalities in India is expected to increase from 2.26 million in 1990 to 4.77 million in 2050 (2020). The age-standardized CVD mortality rate in India is 272 per 100,000, which is higher than the global average of 235 per 100,000 [8]. Over the last 25 years, the incidence of CVD risk factors has been significantly increasing in India, particularly in metropolitan areas [12].

Coronary heart disease prevalence rates in India have varied from 1.6% to 7.4% in rural populations and from 1% to 13.2% in urban populations during the last several decades [13]. Ischemic heart disease (IHD) and stroke account for the bulk of CVD mortality in India (83%) [14]. The ratio of IHD to stroke mortality in India is significantly greater than the worldwide norm and equivalent to that in Western developed nations [15]. IHD and stroke account for more than a twentieth (21.1%) of all deaths and one-tenth of all years of life lost in India [16]. The Macroeconomic Commission for Health predicted that the number of IHD patients in India would increase from 36 million in 2005 to 62 million in 2015 (70% increase). In general, India's stroke incidence and stroke-related case fatality rates are greater than those of Western industrialised nations, but the rates among women are especially high. Haemorrhagic strokes are more prevalent in India than in the Western population, according to current neuroimaging research [17].

Hypertensive heart disease, among other cardiovascular diseases, is a serious problem in India, with 1.47 million fatalities in 2019, up 138%from 1990 [18]. Rheumatic heart disease (RHD) is a concern in many regions of India, with an estimated 88,674 fatalities (7 per 100,000 population) in 2010. Though, from 2000 to 2010, the Indian Council of Medical Research (ICMR) began community management and prevention of RHD using hospital-based passive monitoring and secondary prophylaxis as part of the Jai Vigyan Mission Mode Project [19]. At the national level, there is no systematic program for the prevention and control of RHD. However, following adopting an economic liberalization and globalization strategy in 2000, India's socioeconomic situation, improved living circumstances, and increased connectivity and access to health-care institutions are predicted to have resulted in a decrease in the burden of RHD [20]. According to estimates from the Global Burden of Disease research, atrial fibrillation and flutter contribute very little to the total CVD burden in India. Furthermore, other types of

CHAPTER 2

Congestive Heart Failure: Insight on Pharmacotherapy

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Abstract: Congestive Heart Failure (CHF) is the inability of the heart to supply blood to other organs and tissues to meet its need for metabolism. Over 64.3 million people around the world live with heart failure. Some of the common causes of CHF include myocardial infarction, increase in blood pressure, atrial fibrillation and cardiomyopathy. The complete etiology of CHF is complex. Patients with HF often experience fatigue, dyspnea, and pain, lack of energy, cognitive impairment and depression. Left ventricular ejection fraction (LVEF) is a measure of the amount of blood pumped from the heart's left ventricle during each contraction. It is used as a phenotypic marker in the indication of the pathophysiological mechanism and sensitivity to therapy. The pathogenesis of HF with low ejection fraction is that of a progressive state. The various classes of drugs used clinically for the treatment of congestive heart failure are diuretics, beta blockers, ACE inhibitors and vasopressin receptor antagonists. The management of Heart failure includes acute decompensation, chronic management and palliative care. Cardiac glycosides are a varied group of naturally obtained compounds used in the treatment of CHF. They exhibit their action by binding to and inhibiting Na^+/K^+-ATPase. Then, they consequently increase the force of myocardial contraction. The primary structure of these drugs is a steroidal framework, which is the pharmacophoric component that is responsible for their activity. The most familiar cardiac glycosides are digitoxin, digoxin, oleandrin, bufalin, ouabain, marinobufagenin, telocinobufagin and aerobufagenin. Among other cardiac glycosides, digoxin has been proven to improve symptom alleviation, functional capacity, quality of life and exercise tolerance in patients with mild to moderate HF in clinical trials. Early detection and prevention interventions, as well as lifestyle changes, are essential.

Keywords: Cardiac glycosides, Causes, Congestive heart failure, Digoxin, LVEF, Pathogenesis, Treatment.

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1. INTRODUCTION

Heart failure (HF) or Congestive heart failure (CHF) or cardiac failure is classically defined as "Clinical syndrome caused by the inability of the heart to supply blood to the tissues according to the metabolic needs of the tissues". Heart Failure results from ventricular dysfunction with volume or pressure overload, either separately or together. It also involves circulatory, neurohormonal, and molecular abnormalities [1]. Diastolic dysfunction is defined as a raised end-diastolic pressure in a normal-sized chamber, whereas systolic dysfunction is described as a lower ejection fraction and refers to the inability to fill and relax the left ventricle. Ischemic (Coronary artery disease [CAD]) and non-ischemic (hypertension, thyroid illness, valvular disease, myocarditis, adult congenital heart disease) diseases are the cause of HF [2]. Coronary artery disease or coronary heart disease, including a previous myocardial infarction (heart attack), high blood pressure, valvular heart disease, atrial fibrillation, excessive alcohol consumption, infection, and cardiomyopathy of unclear cause, are all common causes of HF [3]. Coronary artery disease is considered to be the cause of congestive heart failure (CHF) in nearly 65% of patients [4].

Heart failure patients often experience symptoms of fatigue and lack of energy, depression, pain, dyspnea and cognitive impairment. The etiology of heart failure symptoms is complex and is not completely understood. Although most patients suffer worsened dyspnea with episodes of volume overload, HF-related dyspnea and exertional fatigue are not directly related to pulmonary capillary wedge pressure or cardiac output, rather to broader, systemic effects of HF, including generalized myopathy. Some of the symptoms may also overlap with comorbid problems, which are particularly common in older individuals with heart failure. Symptoms reported by HF patients are significantly impacted by depression and by the patient's perceived control over their condition [5]. LVEF (left ventricular ejection fraction) is a clinically valuable phenotypic trait that indicates underlying pathophysiological processes and therapeutic sensitivity. Heart failure patients are currently classified as having heart failure with reduced (HFrEF; LVEF 40%–49%), mid-range (HFmrEF; LVEF 40–49%), or preserved ejection fraction (HFpEF; LVEF 50%) ejection fraction. Cut-off values are arbitrary and vary from one guideline to the next. The classification of LVEF has been challenged for oversimplifying a complex condition [2].

Congestive Heart Failure (CHF) with left ventricular systolic dysfunction has been the focus of research (LVSD). Heart failure with normal ejection fraction (HFnEF, also known as "preserved systolic function" and "diastolic dysfunction") has similar pathologic abnormalities in inflammatory and neuroendocrine function [4]. The severity of heart failure can be explained symptomatically. The commo-

nly used system is the New York Heart Association (NYHA) functional classification [6].

CLASS	SYMPTOMS
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity
II	Mild symptoms and slight limitation during ordinary activity
III	Significant limitation in activity due to symptoms. Comfortable only at rest
IV	Severe limitations. Symptoms even while at rest

1.1. Hypertrophic Cardiomyopathy (HCM)

Hypertrophic cardiomyopathy (HCM) is a condition marked by left ventricular (LV) or septal hypertrophy in the presence of normal to hyperdynamic systolic function, no ventricular chamber dilation, and no other cardiac or systemic disease that would explain the hypertrophy.

1.2. Left Ventricular Noncompaction (LVNC)

LVNC (left ventricular noncompaction) is a cardiomyopathy marked by LV hypertrabeculation. Normal LV size and systolic and diastolic function can be related to left ventricular noncompaction. In other situations, however, underlying arrhythmias are present.

1.3. Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is an uncommon cardiomyopathy with an incidence of 1 in 1000 to 1 in 5000 in the general population. ARVC is hypothesised to be caused by mutations in desmosomal genes such as desmoplakin (DSP), plakophilin-2 (PKP2), desmoglein-2 (DSG2), desmocollin-2 (DSC2), and plakoglobin(JUP), which cause problems in cellular adhesion.

1.4. Restrictive Cardiomyopathy (RCM)

According to data from the PCMR, restrictive cardiomyopathy (RCM) is extremely rare in children, affecting only about 5% of paediatric cardiomyopathy patients. The prognosis for these children is frequently poor, and heart transplantation is frequently required [1].

CHAPTER 3

Diet, Inflammation and Cardiovascular Disorders

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Abstract: Diet has been implicated in cardiovascular inflammation and the development of cardiovascular disorders. Several studies have correlated the dietary pattern with cardiovascular disease incidences. Especially high carbohydrate diet consists of refined starches, sugar, and saturated and trans-fatty acids shown to cause vascular inflammation and its related CVDs. To modify or prevent CVD complications, studies have highlighted and recommended a dietary pattern rich in protein and fibers with low carbohydrates. However, the long term effects of these low carbohydrate diets have not been analysed. Further, the diet consumed in Asian countries is rich in spices and they are loaded with antioxidants. Hence, this has to be reviewed thoroughly to conclude on the role of antioxidants in preventing CVDs. Therefore, in this chapter diet-induced inflammation, the role of low carbohydrate and high fat/protein diets in preventing vascular inflammation and their long term effects on health and the usefulness of antioxidants in preventing cardiovascular diseases will be reviewed elaborately.

Keywords: Antioxidants, Atherosclerosis, Dietary interventions, High Carbohydrate diet, Metabolic syndrome, Vascular inflammation.

1. INTRODUCTION

1.1. Diet Induced Inflammation

The Sedentary lifestyle and unhealthy diets of modern society lead to the increased incidence of cardiovascular diseases. Obesity, metabolic syndrome and type-2 diabetes mellitus is on the rise and predisposing for cardiovascular diseases predisposing factors for cardiovascular diseases [1]. Meal ingestion itself causes mild oxidative stress, which leads to the raise in the levels of circulatory

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inflammatory mediators [2]. It is demonstrated that glucose intake promotes reactive oxygen species generation [3] and full fat meal with saturated fats activates endothelium. It is evident that post-prandial state abnormalities are the major contributing factors for cardiovascular diseases [1]. Although several studies have examined the pro-inflammatory effects of individual macronutrients, it is pertinent to note that all the ingredients of a diet should be considered to get an insight to the overall diet related inflammation. A study by O'Neil *et al*. [4] showed the positive correlation between pro-inflammaotry diet and CVDs development in Australian men. Further, saturated fatty acid intake alone did not predict the CVD events. Therefore, dietary inflammatory index scores can be useful for recommending the best-suited diet for CVD predisposed population.

1.2. Dietary Inflammatory Index (DII)

It is a quantitative measurement for assessing diet-associated inflammation, which was first introduced in 2009 and subsequently, several modifications and additions were made. Basically, it scores the inflammatory values of dietary ingredients and classifies them as pro-inflammatory or anti-inflammatory. DII scores are comparable with the Alternative Healthy Eating Index or Mediterranean Diet (MED) score and moderately correlated with the glycemic index score. However, a moderate negative correlation was observed between DII scores and Healthy Eating Index and Mediterranean Dietary Index. Albeit, updated DII is said to be superior to the other indices as it has considered different population and their diets and the experimental evidence [5]. Including a large population and their dietary patterns and experimental evidence of individual macro/micro nutrients showing pro/ anti-inflammatory effects will provide a robust DII.

Diets consisting of a high amount of saturated and trans unsaturated fatty acids like red meats, hydrogenated fats, refined oils and high glycemic index carbohydrates, has been positively associated with dietary inflammation, while diets based on fruits, vegetables, unsaturated fatty acids, fish, yoghurt, whole grains and wine tend to reduce cardiovascular inflammation. Micronutrients such as omega-3 fatty acids, vitamins B1 (thiamine), B2 (riboflavin), B3 (niacin), folic acid, vitamin A, vitamin C, vitamin E, beta-carotene, magnesium, and zinc are proven to be anti-inflammatory [6 - 8].

2. DIFFERENT PATTERNS OF DIET AND THEIR CHARACTERISTICS

Globally several diet patterns are being practiced. Among them, a few diet patterns are practiced especially for weight reduction, weight gain and prevention

of lifestyle diseases. In Ayurveda, dietary plan is one of the principles being followed for treating diseases.

2.1. The Zone Diet

This diet consists of low carbohydrates with protein and fats. This has a fixed percentage of carbohydrates (40%), protein (30%) and fat (30%) in everyday meal. This diet plan is similar to our ancestor's diet where, meat, vegetables and fruits were their dietary sources [9]. The zone diet consists of carbohydrates from unrefined cereals and fats. As the major energy source in this diet is shifted from carbohydrates to fats, a better control of blood sugar and weight loss can be achieved. The zone diet also said to be anti-inflammatory and healthy insulin to glucagon ratio can be maintained. This eventually leads to a decline in chronic disease risk, immuno-competency, better physical and mental health, longevity and lifelong weight control [10].

2.2. Ketogenic Diet

The ketogenic diet is said to cure some medical conditions like Alzheimer's disease, cancer, polycystic ovary syndrome, epilepsy, *etc*., However, it was initially prescribed for controlling diabetes. The ketogenic diet is distinct from the zone diet with its exceptionally high-fat content (70% to 80%), Generally, ketogenic diets consist of 70-80% fat, 5-10% carbohydrate and 10-20% protein [11]. Unsaturated fatty acids or healthy fats-rich foods like avocados, coconuts, brazil nuts, oil seeds, fish and olive oil are added as a part of the diet plan. This diet artificially creates a condition called ketosis. Wherein the absence of glucose for generating energy leads to the breakdown of fats and the formation of ketone bodies [12]. This diet plan can be used for reversing metabolic syndrome such as insulin resistance, high blood pressure, dyslipidemia. Along with this, weight loss can be achieved in a very short period time. Ketogenic diet and other low carbohydrate diets are being focused on controlling type 2 diabetes [13, 14].

2.3. Mediterranean Diet

The Mediterranean diet is being followed among the people of Crete, Greece, and southern Italy, which are the populations bordering the Mediterranean Sea. Further, this pattern of diet is also consumed in Spain, southern France, and Portugal. It is primarily plant-based diet that includes whole grains, olive oil, fruits, vegetables, beans, legumes, nuts, herbs, and spices in their regular meal. In 1993, the Harvard School of Public Health, Old ways Preservation and Exchange

CHAPTER 4

Rodent and Non-Rodent Animal Models for CardioVascular Diseases

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Abstract: Cardiovascular diseases (CVD) come under non-communicable disease (NCD) that are responsible for the leading cause of death, globally. They involve a range of pathologies *viz*. coronary artery disease, cerebro-vascular disease, venous thrombo-embolism, peripheral vascular disease, myocardial infarction, cardiac arrhythmias and stroke. Each pathology is the result of the complex interplay of many factors which determine the prognosis of the condition. Animal experimentation has played an important role in the fundamental understanding of pathologies of cardiac diseases and discovered improved methods of diagnosis and treatment. Researchers have used a number of lab animals that involve rodents (mice, rats, hamsters, and rabbits) and non-rodent animal models (dogs, pigs, sheep, primates) as a biological system to mimic cardiovascular diseases for translational research. An ideal animal-model system should be cheap, readily manipulable, reproducible, ethically sound and reflect the complexity of cardiovascular diseases. Rodent animal models are considered the prime model for human research. Common rodent models include mice, rats and hamsters; rabbits are used for studies on cardiac hypertrophy, heart failure, aortic constriction, pulmonary vein constriction, atherosclerosis and cholesterol regulation studies. With the advancement in genetic engineering, several transgenic/humanized rodent models are available which can mimic better human systems for translational application. Among non-rodent animal models, pigs, dogs, sheep, and non-human primates serve as an excellent model in cardiovascular research; owing to the similarity in heart structure, atrio-ventricular valves, lipid metabolism and vasculature with humans. In the current chapter, we will deal with the importance of the models and their characteristic features, advantages and limitations.

Keywords: Animal Models, Cardio-vascular Diseases, Non-Rodents, Rodents.

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1. RODENT MODELS FOR CVD

Cardiovascular diseases (CVDs) are the leading principal cause of death and morbidity, globally. CVDs are a group of disorders of the heart and blood vessels that include coronary heart disease, cerebro-vascular disease, rheumatic heart disease, and other conditions. About 17.9 million people die annually (approximately 31%) due to CVDs. More than three-quarters of deaths occuring in low- and middle-income countries are due to cardiovascular diseases, depicting a serious burden on the medical field. The etiologies for cardiac and vascular complications are very complex, in which both genetic and environmental factors are implicated along with lifestyle changes [1]. Generally overweight, increased blood pressure and blood sugar level may cause cardiovascular diseases and they are categorized under two major disorders belonging to lipid metabolism and metabolic syndromes [2].

The use of animal models has contributed immensely to increasing the knowledge about pathophysiology and focused approaches to improve the diagnostic and the early treatment of diseases [3]. The CVDs' preventative and ameliorative treatments depend on animal models that mimic human disease processes. Generally, rodents are widely accepted as the model organism for studying the diseases of humans, especially for mice, with whom they share 99% of their genes. Rodents have been regarded as a reliable research species mainly due to their small size, abbreviated (short) lifespan, reproductive affluence, known genetic background, as well as ease in handling and housing practices. With the development of biotechnologies and medico-veterinary field, various manipulations allow the establishment of rodent models which accurately mimic the human disease model of interests and accurately reflect the morphological and biochemical aspects of disease pathogenesis [4 - 6]. Experimental rodent models are widely used for cardiovascular diseases research due to the effective simulation of human cardiovascular diseases, stronger reproductive ability, and detection of physiological indicators in contrast to large animal models [7]. Henceforth, in this article, we will summarize the most common models of cardiovascular diseases, and modeling methods to provide a reference for research on cardiovascular diseases. In particular, we will briefly describe atherosclerosis and diabetic models, with models of heart failure.

2. ATHEROSCLEROSIS AND DIABETIC MODELS

Atherosclerosis is a chronic inflammatory condition and one of the underlying factors of cardiovascular diseases. Atherosclerosis is a disease in which plaque builds up inside human arteries. Both the blood vessel walls and the immune

system are implicated in atherogenesis. Plasma lipoproteins, genetics and the hemodynamics of the blood flow in the artery all play important roles in the development of atherosclerosis. Animal models are valuable tools for providing insights into the etiology and pathophysiology of this disease. They can be used for testing the efficacy and safety of different pharmacological therapies. As per the extensive literature survey, mouse models particularly knockout and transgenic mouse models for atherosclerosis have proved to be useful to study the development and progression of the atherosclerotic lesion, understand the molecular and cellular mechanisms involved in atherogenesis, and evaluate the effectiveness of new and existing atherosclerotic drugs [8].

Generally, wild-type mice are resistant to atherosclerotic lesion development. The current mouse models used for atherosclerosis are based on genetic modifications of lipoprotein metabolism with additional dietary changes. Among them, low-density lipoprotein receptor-deficient mice (LDLR−/− mice) and apolipoprotein E-deficient mice (apoE−/− mice) are the most widely used mouse models for atherosclerosis research. Both LDLR and APOE are important for the removal of cholesterol and triglyceride-rich lipoprotein particles from the blood. APOE is a plasma glycoprotein constituent on the surface of most lipoproteins including very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL) and chylomicron lipoprotein particles. LDLR is a cell-surface receptor that recognizes the ApoE, apoprotein B 100, and apolipoprotein B (APOB) to clear the lipoprotein particles from the blood. Human mutations in LDLR and APOE are associated with several hereditary dyslipidemic disorders and increase the susceptibility to atherosclerosis for the mutation carrier.

2.1. LDLR−/− Mice

The LDLR−/− mice (low-density lipoprotein, LDL, receptor) are the models for studying familial hypocholesterolemia [3]. These models have a mutation that affects the LDLR level and resembles humans' plasma lipoprotein profile. The genetic modification in the model leads to delayed clearance of very-low-density lipoprotein (VLDL) and LDL from the plasma and therefore results in an increased plasma level of cholesterol on the normal chow diet [9]. Besides, the inclusion of high-fat and high-cholesterol content in the diet increases the severity of atherosclerotic lesions and hypercholesterolemia in LDLR−/− mice [10]. The plasma levels of LDLR−/− mice fed on a high-fat western diet were 10 times higher than those of wild type, and plaques formed on the aortic roots, showing symptoms of atherosclerosis. Pan *et al*. fed 7-week-old male LDLR−/− mice (C57BL6/J background) with a western diet containing 20% fat, 20% sugar, and 1.25% cholesterol till 16 weeks of age. The evaluation of aortic atherosclerotic

CHAPTER 5

Application of 21st Century Genetic Engineering Tools and CRISPR-Cas9 Technologies to Treat Most Advanced Cardiovascular Diseases of Humans

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Abstract: 21st Century Genome-editing technologies have been rapidly emerging as the most powerful tool capable of creating genetically altered cells or organisms for explicit gene functions and mechanisms for causing several human ailments. While clinical gene therapy celebrates its first taste of success, with several products approved for clinical usage and several thousands of them awaiting stages in pipelines, unfortunately, there are no gene therapy treatment methods available for many cardiovascular diseases (CVD). Despite sustained medical advances over the last 50 years in CVD, the main cause of death is still uncertain in the developed world. The management of genetic expression by using small molecule RNA therapeutics and the development of accurate gene corrections may lead to several applications, such as cardiac revitalization after myocardial infarctions and gene corrections for the inherited cardiomyopathies but certainly with some limitations. CRISPR/Cas9 technology can be utilized to realign DNA modifications ranging from a single base pair to multiplepairs of mutations in both *in vitro* and *in vivo* models. This book chapter emphasizes various types of applications by CRISPR technologies in cardio-vascular research, and genome-editing novel therapies for future medicines.

Keywords: CRISPR/Cas9, Myocardial infarction, Gene Therapy, Myocardial infarction, Induced pluripotent stem cells (iPSCs).

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1. INTRODUCTION

Gene editing technologies are promising methods to investigate disease mechanisms at the gene level. By employing these technologies, scientists could introduce, modify or remove mutations at specific locations or points of the target gene and can make a successful model disease organism to prevent the incidence of many diseases. In 1996, the First and Second generations of Gene Technologies *i.e.*, transcription activator-like effector nucleases (TALEN's) and zinc-finger nucleases (ZFN's) evolved independently. However, the high costs and also low efficiencies involved in their procedure have restricted their accessibility and usage in various applications [1]. In 2013, CRISPR technology emerged as the 3rd generation of gene-correcting methods and has been quickly put to use by various scientists for its merits of high efficacy, speed, and cost reduction [2]. In recent times, this modern CRISPR technology has been applied to many fields such as agriculture, drug design, and discovery and medical research [3].

Exploring the genetic basis of several diseases will enable significant inputs into medical research. The successful finishing of the Human Genome Project (HGP) and the DNA sequencing knowledge extracted from several patients have allowed us to understand the relationships between genetic components and human diseases [4]. Alternations and genetic mutations in over 3000 genes that are linked to many diseases and disorders in humans have already been studied [5].

In contrast to cancer and diabetes, which are multifactorial illnesses brought on by a variety of genetic alterations and environmental factors, Huntington's disease, Thalassemia, Sickle Cell Anemia, and Cystic Fibrosis are monogenetic genetic disorders caused by the mutation of a single gene [6]. Unfortunately, there are many disorders without appropriate treatments. However, Genomic therapies can offer potential and effective therapeutic tools to fight many genetic diseases [4] and it is now the first and foremost choice of many medical practitioners and incorporates refinement of target genetic corrections by using precise gene editors. Genetic therapies sketchily include the deletion of a faulty gene or group of genetic alterations by incorporation of external DNA and correcting the changed gene at the inherent site [7]. Despite the benefits of this technology, there are several flaws and challenges associated with the applications that make the insertion of exogenous DNA risky. Some of the negative outcomes with unwanted implications include the insertion and activation of off-target gene modifications and erroneous findings generated by the induced genes. Additionally, only a few hereditary diseases are still the exclusive beneficiaries of direct applications nowadays [7].

However, gene correction creates a completely new field for modifying human genetics and gene therapy. It is a novel approach that modifies certain target sequences with alterations that are target-oriented and exact. Future research on genetically based medications may provide new therapeutic approaches for treating a variety of human ailments [7]. The primary method of gene correction involves DNA double-strand breaks (DSB) induction and endogenous cellular repair processes [8]. These cut breaks are classically repaired by either of two major pathways: Non-Homologous End Joining (NHEJ) or Homology-based repair (HDR). To target gene-editing technologies, the most critical component is the identification of precise DSB. Currently, four major methods are employed to initiate target-specific DSB's which include Zinc finger nucleases (ZFNs), engineered mega nucleases, Transcription Activator-Like Effector Nuclease (TALENs), and most recently CRISPR/Cas9 systems [7, 8]. The precise targeting of genetic changes in cultured cells, plants, and animals has been made possible by these new methods. CRISPR technologies are superior to other genome-editing techniques because they are less complicated and do not require expensive designed enzymes for each each DNA target locus [8]. In CRISPR technology, the exact results could be achieved by target-oriented RNA and a restriction enzyme mixture represented briefly as Cas9, which is one of the best and most remarkable gene-editing platforms [1]. For the past few decades, the CRISPR system is being applied to many biomedical problems, aimed at developing new curing technologies for monogenic and as well as for multi-factorial diseases [7].

Thus, CRISPR/Cas9 technology can be used in the development of various animal disease models for research purposes to represent diseases or to understand disease progress pathways, by mutating or silencing the relevant genes [2]. However, recently, the horizons of the CRISPR tool were expanded for correcting genes of human embryos as well. The path-breaking discovery of the ability to repair a mutation in the (OCT4 gene)4 octamer-binding transcription factors, a gene involved in the development of the human placenta in ahuman embryo using CRISPR/Cas9 technology, implies immense clinical potential in the future for treating human genetic diseases [3].

Although CRISPR technologies have been identified as the most successful gene therapy tools currently, some problems have surfaced like its reproducible capabilities and human ethical issues, chiefly concerning editing human germ lines [3]. Several impacts of off-side target cleavages are the primary setbacks of the target system and may restrict its usage for some of the therapeutic applications. In light of this, this review emphasizes the current state and future prospects of CRISPR uses in individualized medicine. The review also focuses on the use of CRISPR technologies as the primary therapeutic tool for a number of human diseases and disorders and summarizes its applications in gene therapies,

CHAPTER 6

Role of Vyana Vayu in CardioVascular System, Etiopathogenesis and Therapeutic Strategies: An Ayurveda Perspective

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Abstract: A systems approach to health is the hallmark of Ayurveda. It believes in preventing disease and maintaining and restoring health. The entire concept stands on three fundamental functional units-*Vata, Pitta and Kapha,* where *Vata*, mobilizes the other two units. Depending on their locations, *Vata (Vayu) is* classified into five subtypes, where each has its distinct role to perform. *Vyana Vayu* (VV), an important subtype of Vata, is synthesized in myocytes and responsible for the genesis of the action potential. A key regulator in contractile functions, VV propels out nutrients from the heart. It not only mediates intracrine and paracrine activities but modulates the vascular tone too. Wherever there is scope to flow, VV has its unique role to contribute. Ancient scholars of *Ayurveda* have identified its ubiquitous role in the endogenous system, where all the activities depend on VV. Hence, preventing VV from any stimulus is of paramount importance since they consequently lead to various cardio vascular diseases (CVD). Classical texts have addressed the prognosis in six discrete phases where each phase can be avoided strategically. Highlighting the precipitants that attenuate VV, we focus on addressing those phases along with curative measures so that the functions of *Vyana Vayu* can be restored.

Keywords: Contractile functions, Phases of prognosis, Preventive cardiology, Vascular tone, *Vyana Vayu*.

1. INTRODUCTION

A systems approach to health is the hallmark of *Ayurveda*. It carries the rich tradition of knowledge with epistemological values based on life principles more

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than 3500 years from date [1]. Theories and concepts postulated by *Ayurveda* scholars are valid even today despite the absence of diagnostic tools and gadgets during their times. It has a comprehensive outlook towards every individual that embraces physical, physiological, and spiritual components. Expressed in Sanskrit, there is a need to comprehend the knowledge and translate it scientifically in the present state-of-art as its affluent intellectual property cannot be possessed only by Sanskrit scholars. Its proficiency lies in the appropriate use for mankind.

The entire concept of *Ayurveda* stands on three fundamental pathophysiological units-*Vata, Pitta and Kapha,* where *Vata*, mobilizes the other two. *Vata* is expounded to hold the living system [2], comprising gaseous components, moving through a specific cavity [3]. The gamut of its action is always associated with locomotion (*Gati*). Based on the extent of operations, *Vata* is classified into five subtypes, where each constitutes an independent system with a distinct role to perform [4]. Even though each subtype is confined to perform in a given territory, the *Vyana Vayu* (VV), a unique subtype of *Vata* has a wider role to perform throughout the body. VV is an indigenous component of the heart (*Hrdaya*), responsible for contractile functions. It is due to VV that the heart relentlessly (*Ajasram*) pumps out required nutrients to fulfill the metabolic demands. Diffuse (*Krutsna dehachari*) in nature, VV plays a central role in maintaining homeostasis in the circulatory system (*Rasasamvahana*). It protects the cardiovascular system (CVS) and metabolic system (MS) through anti-inflammatory and anti-oxidant properties [5 - 8]. The slightest imbalance in the bioavailability of VV can give rise to serious pathological conditions. Several intrinsic and extrinsic factors (IEF) can exasperate the balanced state, invoking the pre-determinants of cardiovascular and metabolic disorders (CMD) [9]. Deleterious effects on CMD can be negated if VV's intrinsic properties are preserved. Hence, knowledge of the realm of VV on CVS and MS could provide an alternative approach to detect the prognosis of CMD with complications. Since every cardiac patient has the potential to develop heart failure, there is a need to explore new areas on predisposing factors that leads to CMD prognosis.

If the etiological elements are not curtailed in time, CVD will remain to be the leading cause of death for the next ten years of more than 100 million populations [10, 11]. There is a general agreement that these factors are modifiably associated with environment and lifestyle. WHO has initiated several awareness programs to abridge CVD and its risks, but despite this awareness, there has not been any decline in the number of CVD cases. Technological advancements have considerably improved survival rates from acute cardiovascular events, but surviving inhabitants with compromised functions of the heart have simultaneously increased.

Hence, intending to prevent CMD prognosis and improving the quality of life of survived victims, we explore the knowledge of Ayurveda to extend the horizon of etiology and provide a broader scope for prevention. This can be understood in six discrete phases of pathogenesis where each phase can be strategically avoided. This chapter highlights the analysis of *Vyana Vayu* from physiological and etiopathological aspects, followed by concomitant contemporary concepts and therapeutic strategies.

2. A PREAMBLE TO VATA

The very existence of *Vata* in the endogenous system denotes life. Whether voluntary or involuntary, all actions are governed by *Vata*, right from attending to gross functions such as breathing, swallowing food, belching, sneezing, coughing or excretion of wastes, and many more [12]. It contributes to the manifestation of shape, cell division, cell signaling, and cognition [13]. Processes involving conduction of impulse, metabolite transport, scavenging of free radicals, apoptosis, and necrosis are all governed by it [14]. Due to its gaseous property, it acquires a natural tendency to arid (*Ruksha*). This prevents the cellular components from over-lubrication, at the same time facilitates apoptosis appropriately. Highly unstable (*Chala*), subtle (*Sukhma*), and dynamic nature of Vata varies with time and places of action [15, 16]. Even though it maintains the body's thermal equilibrium by cooling *(Sheeta),* it is highly sensitive to extreme temperatures [17]. Its proficiency is best demonstrated with optimum bioavailability (*Sama*) but becomes pathologic and devastating otherwise *(Vruddhi. Kshaya)* [18]. Whether intracellular or extracellular, the quantum of its kinetic nature is demonstrated through diverse actions.

2.1. Vyana Vayu

The human system is uniquely designed, where all actions are performed through well-defined, well-coordinated, intact, and enclosed channels (*Srotas*) [19]. VV is believed to be activated and spread indefinitely across these intact channels, where ever there is scope to flow. VV facilitates cell trafficking, membrane trafficking, and the exchange of blood to and from the heart (*Gamanaagaman kriya*) and establishes communication between the substrate and circulating metabolite. Whether an organ designed for a specific task or a circulating channel carrying metabolites to the target tissue, VV has its extensive role to perform in it. This is possible only if VV is expressed on the surface of any flowing channel. Classical authors have unanimously expounded on the diffuse nature of VV that originates and regulates several functions from the heart (*Hrdaya*). Whether the intracrine or paracrine, Vata must be functional in space. Furthermore, whether

CHAPTER 7

Nutraceuticals: The Potential Agents to Rescue Human Race from Cardiovascular Diseases (CVDs)

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Abstract: Cardiovascular disease(CVD) is the foremost global health problem that accounts for the highest rate of morbidity, mortality and huge healthcare costs. Food habits and lifestyles predominantly affect the functioning of the cardiovascular system either directly or indirectly through risk factors like hypertension, obesity, dyslipidemia, diabetes, *etc*. Decreased physical activity, increased sedentariness, and growing fast food culture are some of the apparent reasons that make the disease impact more on the younger generation. Several plant species have been reported in ethnomedicine for their therapeutic efficacies against CVDs and other diseases. Even though some preclinical and clinical studies have demonstrated the beneficial effects of dietary plant components in the prevention and treatment of CVDs, they are limited to selected study groups. Therefore, their scope and utility need to be broadened and applied to larger populations to reduce the public health burden of CVDs. Since nutraceutical approach is more preferable than other therapeutic methods, there is a growing interest in functional foods and diet based remedies. In the present chapter, we have presented the current scenario of CVDs, their pathophysiology, the therapeutic drugs available, the role of nutraceuticals in treating CVDs and their mode of action with a special emphasis on commonly used kitchen spices.

Keywords: CVDs, Dyslipidemia, Hypertension, Nutraceuticals, Phytoconstituents, Spices.

1. INTRODUCTION

In recent decades, with advancements in science and technology, human lifestyle has changed dramatically in both developed and developing countries. The consumption of fast foods/energy dense foods, snacking frequency and late night

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meals and snacks have increased. Simultaneously, physical excercise has considerably reduced due to increased conveyance facilities, availability of high end machinery, tools and electronic devices used in every sphere of human activity [1]. As a result, the environment sensed by the brain has become arrhythmic. Taken together, the incidence of CVDs and other metabolic syndrome disorders has been alarmingly rising across the globe [2].

Cardiovascular diseases (CVDs) are a cluster of disorders of blood vessels and heart, including peripheral heart disease, coronary heart disease, cerebrovascular disease (stroke), heart failure, heart attack, cardiomyopathies, congenital heart disease and dyslipidemias. CVDs majorly occur due to impairment in blood supply to organs like the heart or/and the brain because of atherosclerosis, thrombosis and high blood pressure. Fig. (**1**) shows some principle reasons for the occurrence of cardiovascular diseases. As per the WHO report in 2017, CVDs caused 31% annual deaths worldwide. According to the European cardiovascular disease statistics, more than 45% of deaths occur due to CVDs in Europe [3]. In the USA, about 50% of population suffers from one or other form of CVDs as per the American Heart Association report [4]. In India, with more than one billion population and with a high incidence of abdominal obesity, diabetes and hypertension, the CVD morbidity is on the brink of turning into an epidemic [5]. The annual number of deaths from CVDs in India is projected to rise from 2.26 million (1990) to 4.77 million or more by 2020 [4]. Worldwide distribution of various cardiovascular diseases is represented in Fig. (**2**).

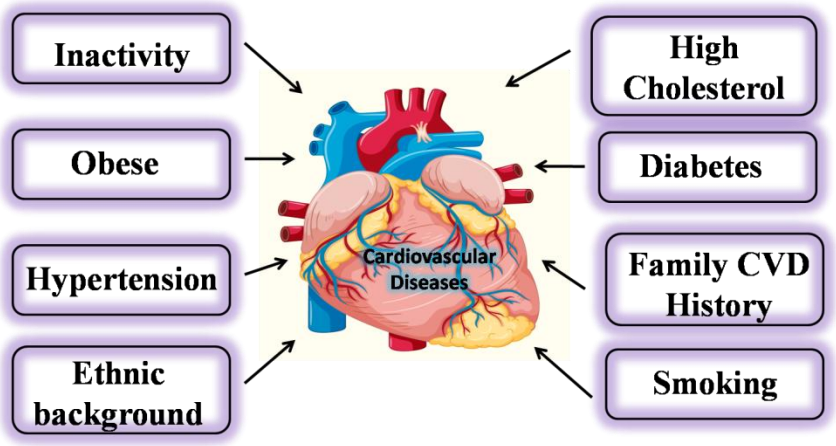

Fig. (1). Principle reasons of CVD.

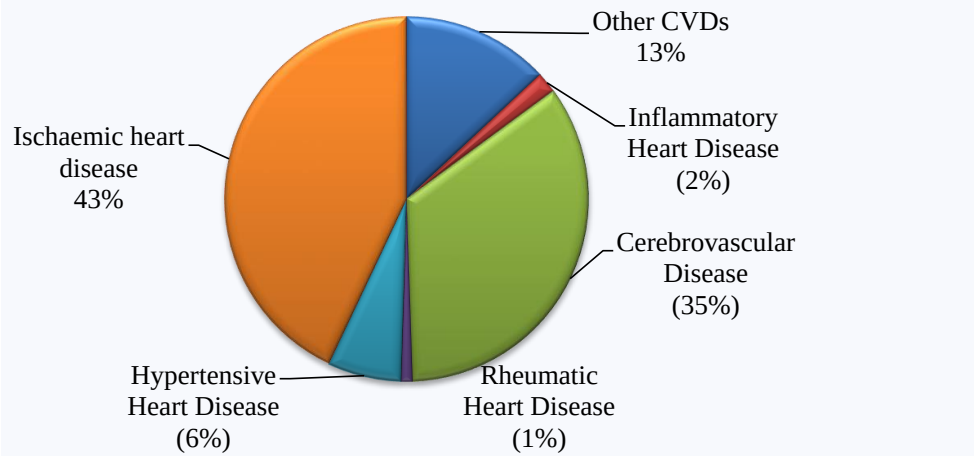

Fig. (2). Worldwide distribution of various CVD.

The common risk factors for CVDs include physical inactivity, obesity, hypertension, ethnic background, family CVD history, smoking, hyperlipidemia, elevated levels of low-density lipoprotein (LDL) cholesterol, reduced levels of high-density lipoprotein cholesterol (HDL) and diabetes [6]. Recent studies confirmed inflammation as a prominent risk factor which is indicated by high levels of highly sensitive C-reactive protein (hs-CRP) and interleukin-6 (IL-6) [7]. Basic symptoms include pain or discomfort in the centre of the chest, arms, left shoulder, jaw and elbows, difficulty in breathing, vomiting or feeling sick, faintness, dizziness and unconsciousness.

2. CVDS: PATHOPHYSIOLOGY

The main pathogenic process identified in CVD patients is atherosclerosis caused by the decreased or lessened blood flow in the blood vessels in the aorta and the arteries. Fig. (**3**) represents the narrowing of arteries due to plaque deposition. Atherosclerosis involves inflammation, endothelial dysfunction, immunologic phenomena and dyslipidemia [8]. A dysfunctional endothelial system causes the deposition of LDL particles and their conversion into oxidized LDL in the intima of blood vessel walls. They trigger the development of fatty plaques due to the accumulation of extracellular matrix and lipid-laden macrophages. It leads to further macrophage recruitment that becomes calcified and transition to

CHAPTER 8

Ameliorative Potential of Biochanin-A against Dexamethasone Induced Hypertension through Modulation of Relative mRNA and Protein Expressions in Experimental Rats

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Abstract: In this study, we made an attempt to attenuate the dexamethasone induced hypertension through Biochanin-A (BCA) in experimental rats. Hypertension was induced in male albino Wistar rats by subcutaneous administration of dexamethasone (10µg/kg body weight). The rats were orally treated with BCA (10mg/kg body weight) once daily for 45 days and Nicorandil-treated group (6mg/kg body weight) included for comparison. We evaluated the changes in mean arterial pressure, heart rate, blood pressure, vascular function, oxidative stress markers, and gene expression of histone deacetylases (HDAC)-1, HDAC-2, and HDAC-8. Administration of BCA or Nicorandil showed noteworthy improvement in vascular function in experimental rats. Moreover, aortic eNOS expression was down regulated, and NADPH oxidase subunit $p47^{phox}$ was up regulated in hypertensive rats. The antihypertensive effects of BCA were connected with concomitant downregulation of $p47^{phox}$ expression and upregulation of eNOS expression. Dexamethasone exposure led to increased mRNA expression of HDACs expression in the kidneys and these were restored after BCA administration. In conclusion, our results are, therefore, BCA reduces hypertension in experimental rats and suggests that BCA might be used against the hypertension.

Keywords: Biochanin-A, Hypertension, Natural products, Vascular dysfunction.

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1. INTRODUCTION

Hypertension is a disorder provoked by several factors, which belong to the foremost threat factors dependable for renal dysfunction, cardiovascular and metabolic diseases [1]. There are numerous substantial researches presenting the significance of vascular tone rise through the sympathetic nervous system and the renin angiotensin pathway in vital hypertension. Vascular tone is mostly reliant on the intracellular Ca^{2+} levels in vascular smooth muscle cells, which are synchronized by the endothelium, an essential module of the blood pressure and vascular wall [2]. The endothelium liberates vasodilators, together with prostaglandin I2, endothelium-derived hyperpolarizing factor, and nitric oxide (NO), as well as vasoconstrictors, such as endothelin, angiotensin-2 and thromboxane-A2, an extremely strong vasoconstrictor [3]. In normal states, the vascular quality is maintained by constrictor signals and vasodilator [4]. Nevertheless, in disease conditions, an increase in the endothelium-derived and a reduction in the endothelium-attained vasodilators or inflamed tissue-derived vasoconstrictors subsequently raise blood pressure and vascular tone, and leads to hypertension. In fundamental hypertension, systolic and diastolic blood pressures elevation is reassured by the combination therapy of angiotensin converting - adrenergic receptor blockers, diuretics, and β-enzyme inhibitors, angiotensin receptor blockers [5, 6]. On the other hand, the effectiveness of conventional antihypertensive agents cannot be expected in salt sensitive hypertension, reasonable to brutal hypertension, and metabolic disease induced hypertension to go together with endothelial damage [6]. For that reason, novel anti hypertension medications are necessary to combat against relentless and convoluted hypertension.

Biochanin-A (BCA) is a natural compound that is predominantly found in soy, chickpea, peanuts, alfalfa sprouts, and red clover. It is chemically known as Omethylated isoflavonoid and has several benefits against myocardial infarction [7], antiobesity [8] and obesity cardiomyopathy [9]. However, there was no scientific literature available to point out the antihypertensive efficacy of BCA. Hence, the present study is to evaluate the antihypertensive potential of BCA in dexamethasone (DMS)-induced hypertension in experimental rats.

2. MATERIALS AND METHODS

2.1. Chemicals

BCA was purchased from Sigma-Aldrich (St. Louis, Missouri, USA). All the reagents used in the experiments were analytic grade and had the highest purity.

2.2. Animals

Male Wistar rats were obtained from the Department of Biochemistry, Muthyammal College of Arts and Science, Rasipuram, Namakkal District, Tamilnadu, India. Experimental animals were kept under standard laboratory conditions (temperature; 22±2ºC: moistness; 40-60%), and permitted food and water *ad libitum*. Rats, at first weighing 180-200g, were separated into four groups of six each (n=6). All procedures involving laboratory animals were in accordance with the institutional animal ethical committee of Muthyammal College of Arts and Science (Approval number: IAEC/MCAS/07/2019).

2.3. Induction of Hypertension

In the experimental rats, hypertension was induced by subcutaneous injection of DMS (10µg/kg/d) in the evening [10].

2.4. Experimental Design

Group I: Normal control

Group II: Hypertensive control

Group III: Hypertensive + AA (20mg/kg body weight)

Group IV: Hypertensive + Nicorandil (6mg/kg body weight)

2.5. Measurement of Body Weight

The body weight of each rat was measured. At the end of the experiment, blood was collected from overnight fasted animals under inhalation of anaesthesia by retro-orbital puncture method. Blood was collected in anticoagulant coated vials and permitted for 15 minutes at room temperature. Plasma was separated by centrifugation at 2500 rpm for 15 minutes.

2.6. Indirect Measurement of Blood Pressure in Conscious Rats

Systolic blood pressure (SBP) of rats was determined every week end by non-invasive tail-cuff plethysmography (IITC/Life Science Instrument, USA). In short, awakened rats were positioned in a restrainer when quiet just before measurement. The rat tail was positioned within the tail cuff, and the cuff was

CHAPTER 9

Zingiberene, an Active Constituent from *Zingiber officinale* Ameliorated High-Fat Diet-Induced Obesity Cardiomyopathy in Rats

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Abstract: In the current study, we evaluated the effect of Zingiberene (ZB) is, a monocyclic sesquiterpene that is the principal constituent of ginger (*Zingiber officinale*), against high-fat-diet (HFD)-induced obesity cardiomyopathy (OC) in rats. ZB (50mg/kg/BW) was supplemented on obese rats for the period of 45 days and assessed its effect of body weight, anthropometrical and morphological parameters along with hyperglycemic markers. We also evaluated the effect of ZB on cardiac lipotoxicity and oxidative stress in cardiac tissue. The current study demonstrated that HFD supplementation significantly increased body weight, anthropometrical and morphological parameters, together developed hyperglycemia in rats. On the other hand, ZB supplementation in obese rats attenuated these altered parameters and ameliorated cardiac lipotoxicity as well as oxidative stress by decreasing lipid profiles of heart and enhancing the activities of endogenous antioxidant enzymes in the heart. Therefore, this study suggest that ZB might ameliorate the diet induced OC through the restoration of antioxidant system of the heart and attenuation of dyslipidemia in the cardiac.

Keywords: Nutraceuticals, Obesity cardiomyopathy, Oxidative stress, Zingiberene.

1. INTRODUCTION

Obesity cardiomyopathy (OC) is a multifaceted relationship of indirect and direct pathophysiologic factors connected to obesity. Obesity is an autonomous risk factor for coronary artery disease (CAD) and is robustly linked with diabetes mellitus (DM) and hypertension, which circuitously lead to the development of

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hypertensive, ischemic and cardiomyopathy correspondingly [1]. There are definite structural changes related to OC and body weight and heart weight display a linear bond. Particularly, left ventricular remodelling with augmented wall width and mass, as well as ventricular dilatation are well-established consequences of obesity, even after controlling for age and hypertension [2]. Extreme fatty acids may direct prejudiced myocardial presentation due to the gathering of toxic long-chain non-esterified fatty acids and their by-products such as ceramides and diacylglycerols. This state is referred to as lipotoxic heart disease [3]. Insulin resistance (IR), one of many obesity-associated metabolic derangements, may also arbitrate the progress of cardiomyopathy through mutilation of myocardial oxygen utilization, myocardial fatty acid uptake and oxidation. Prominent myocardial triglyceride levels may also alter myocardial function and structure [4].

On the other hand, elevated oxidative stress in the cardiomyocytes arises through numerous mechanisms, including mitochondrial uncoupling and dysfunction, increased fatty acid oxidation, superior NADPH oxidase activity, and abridged antioxidant capacity [5]. It has been documented that obesity may persuade systemic oxidative stress. Biomarkers of oxidative stress are elevated in patients with obesity and correlate in a straight line with body mass index and the proportion of body fat; on the contrary, an opposite association between central adiposity, body fat and antioxidant capacity has been recommended. A number of processes are concerned with obesity-related oxidative stress, caused by a high intake of fat and carbohydrate meals [6, 7]. These observations point out that the modulation of oxidative stress by antioxidants appears to have an optimistic outcome in the avoidance of OC.

Several attempts have been made to spot the metabolic inconsistency of obesity state, producing a number of drugs like sibutramine, fibrates and orlistat, but they experience from substantial side effects [8]. Therapeutical approaches to obesity devoid of any side effects are still a dispute in the medical system of human beings. There is a mounting demand by individuals to use natural products with antiobesity nature because oral antiobesity drugs have numerous side effects [9]. In the same way, Zingiberene (ZB) is a monocyclic sesquiterpene that is the principal constituent of *Zingiber officinale* and in addition, previous reports indicated that ZB has various therapeutic effects [10]. On the other hand, there was no scientific evidence available on the antiobesity activity of ZB in animal models or any other clinical models. Therefore, the current study intended to find out the therapeutic efficacy of ZB against high-fat diet (HFD)-induced obesity and OC in rats.

2. MATERIALS AND METHODS

2.1. Chemicals

ZB was purchased from Sigma-Aldrich, India.

2.2. Animals

We procured male Wistar rats (weighing 120-140g) from the Nandha College of Pharmacy, Erode, Tamilnadu, India and rats were initially acclimatized for the period of one week with a 12 h day/night cycle, in a temperature of 22 ± 2ºC, and humidity of 45-64%. The protocol of this study was approved by the Institutional Animal Ethical Committee (IAEC), Nandha College of Pharmacy (Approval No: 688/PO/Re/S/02/CPCSEA).

2.3. HFD Composition

HFD was commercially obtained (National Institute of Nutrition, Hyderabad, India) and composed of corn starch (15%), sugar (27.5%), lard oil (17.6%), vitamin mixture (1%), mineral mixture (3.5%), casein (20%), cellulose powder (5%), corn oil (9.9%) and choline bitartrate (0.2%).

2.4. Experimental Design

Obesity was induced by the supplementation of HFD for the period of 15 weeks and treatment with respective drugs was initiated. At the same time, normal control rats were fed with a normal pellet diet. The rats were divided into four groups and each group contained six animals. All the respective drugs were administered orally by using intragastric tube for the period of 45 days once a day.

Group 1: Normal control

Group 2: HFD-induced obese control

Group 3: Obese + ZB (50mg/kg body weight)

Group 4: Obese + Lorcaserin (10mg/kg body weight)

At the end of the 45 days treatment period with respective drugs, all the rats were overnight fasted and blood was collected by retro orbital sinus puncture method with mild anaesthesia. Then, the rats were sacrificed by the cervical decapitation and vital organs were collected immediately and stored at -80ºC until further use.

CHAPTER 10

Betaine, a Nutraceutical Ameliorated Myocardial Infarction by Attenuation of Pro-Inflammatory Cytokines and Matrix Metalloproteinase Production in Rats

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Abstract: Cardiovascular disease is a key community health challenge and presently the condition with the utmost deaths around the globe, even though enormous development has been made in its management but there are still many difficulties. In the current study, we made an attempt to evaluate the therapeutic action of betaine, an active nutraceutical against isoproterenol-induced myocardial infarction (MI) in rats. The rats were pre-treated with betaine (250mg/Kg BW) for the period of 30 days and on the 31st and 32nd days, they were administered with isoproterenol (20mg/Kg BW) to produce MI in rats. Then we evaluated the effects of betaine on the ratio of heart weight to the body weight. Cardiac diagnostic markers and the production of pro-inflammatory cytokines and matrix metallopreoteinases along with their mRNA expressions were also studied in the heart by RT-PCR. We found that there was a significant elevation in the heart size, levels of LDH, CK-MB, CRP, homocysteine and serum pro-inflammatory cytokines (TNF-α, IL-1α, IL-1β, IL-6, MCP-1 and RANTES) and matrix metallopreoteinases (MMP-2 and MMP-9) in MI rats. On the other hand, pre-treatment of MI rats with betaine revealed a noteworthy reduction in the pro-inflammatory cytokines and matrix metallopreoteinases in the serum. RT-PCR study revealed that betaine successfully down-regulated the mRNA expressions of NF-κB, TNF-α, IL-6, MMP-2 and MMP-9 in MI rats. In conclusion, this study revealed that betaine is able to ameliorate MI by restraining the production of pro-inflammatory cytokines and matrix metallopreoteinases. Hence, betaine might be used as a dietary supplement as an alternative for cardio-protection.

Keywords: Betaine, Cardiovascular disease, Myocardial infarction, Natural products, Nutraceuticals.

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1. INTRODUCTION

Cardiovascular disease (CVD) is the main reason for morbidity and mortality both in developing and urbanized countries. A foremost form of CVD is myocardial infarction (MI), which usually comes across as a quiet infarction due to its late diagnosis in the disease development. When the equilibrium between the blood supply to the heart vessels and the necessity of the cardiac tissue is affected, the cardiomyocytes are subjected to a long-lasting ischemic damage ensuing in necrosis, frequently well-known as acute MI [1]. In recent decades, with changes in the way of life and predilection to co-morbidities, the frequency of MI has been found in the adolescent to be mounting with age in the middle and elder age groups, affecting both women and men [2]. The condensed blood supply to the heart results in the deficiency of oxygen to cardiac muscles, which if left untreated, results in permanent necrotic harm to the myocardium. In most cases, the cardiac arrest is sudden with no noticeable symptoms of ache and a severe impulsivity [3].

MI is an extremely multifaceted disorder with multistep progression in which numerous physiological systems contribute. Wide-ranging investigational data exposed that MI is intricately connected with the commencement of an inflammatory reaction [4]. Inflammatory mediators are openly implicated in the pathogenesis of the susceptible plaque, foremost to occlusion of the coronary vessel and consequent necrosis of the myocardial region served by the vessel [5]. Scientific studies have identified critical molecular signals mediating the inflammatory response following MI. Therapeutic interventions in experimental animal models recommended that the balanced reserve of particular inflammatory signals may protect the infarcted heart from acute damage and delay unwanted remodelling following MI [6]. On the other hand, matrix metalloproteases (MMPs) play a vital role in post-MI cardiac remodelling and in the increase of unpleasant outcomes. MMPs synchronize key life activities, along with inflammation and developmen. The changes in MMPs may direct to unwanted circumstances, resulting in the progress of a variety of possible complications, including sudden cardiac arrest, left ventricular rupture, or the increase of congestive heart failure. The potential roles of MMPs as a therapeutic target for MI setting, thus, are warranted. Simultaneously, lots of currently used medications to treat MI encourage MMPs activity. Identifying specific MMPs inhibition approaches for the post-MI patient; predominantly treatments that limit the development of heart failure, remains a greatly needed target [7].

For acute conditions, such as MI, modern drugs have been alleged as the only available therapeutic approach. On the other hand, an understanding pertaining to conventional medicine for MI has been rising. Therapeutic plants have been

mostly used for healthcare around the globe even before the arrival of modern medicine [8], and the consumption of diets rich in plant foods is connected with an abridged CVD risk [9, 10]. Betaine is circulated widely in plants, animals and rich dietary sources which include seafood, spinach and wheat bran [11]. Betaine has several therapeutic effects which include antioxidants [12], antiobesity, antidiabetic [13] and hepatoprotective [14]. However, the protective effect of betaine on myocardial inflammation and the MMP system in experimentally induced MI conditions has not yet been previously explored. Hence, the current study was designed to evaluate the effect of betaine on pro-inflammatory cytokines and MMPs production in isoproterenol (ISO)-induced MI in rats.

2. MATERIALS AND METHODS

Betaine ($(CH_3)_3N^+CH_2COO^-$) and ISO were purchased from the Sigma-Aldrich, India.

2.1. Animals

The Wistar rats (weighing 120-140g) were utilized for this study and obtained from the Nandha College of Pharmacy, Erode, Tamilnadu, India. The animals were maintained at a 12 h day/night cycle, at a temperature of 22 ± 2ºC, and humidity of 45-64%. The protocol of this study was approved by the Institutional Animal Ethical Committee, Nandha College of Pharmacy (Approval No: 688/PO/Re/S/02/CPCSEA).

2.2. Experimental Design

Group 1: Normal control

Group 2: ISO-induced MI untreated control

Group 3: Rats were pre-treated with betaine (250mg/kg BW) orally for 30 days and ISO (20mg/kg BW) administered once a day subcutaneously on the 31st and 32nd days.

Group 4: Rats were pre-treated with α-tocopherol (60mg/kg BW) orally for 30 days and ISO (20mg/kg BW) administered once a day subcutaneously on the 31st and 32nd days.

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