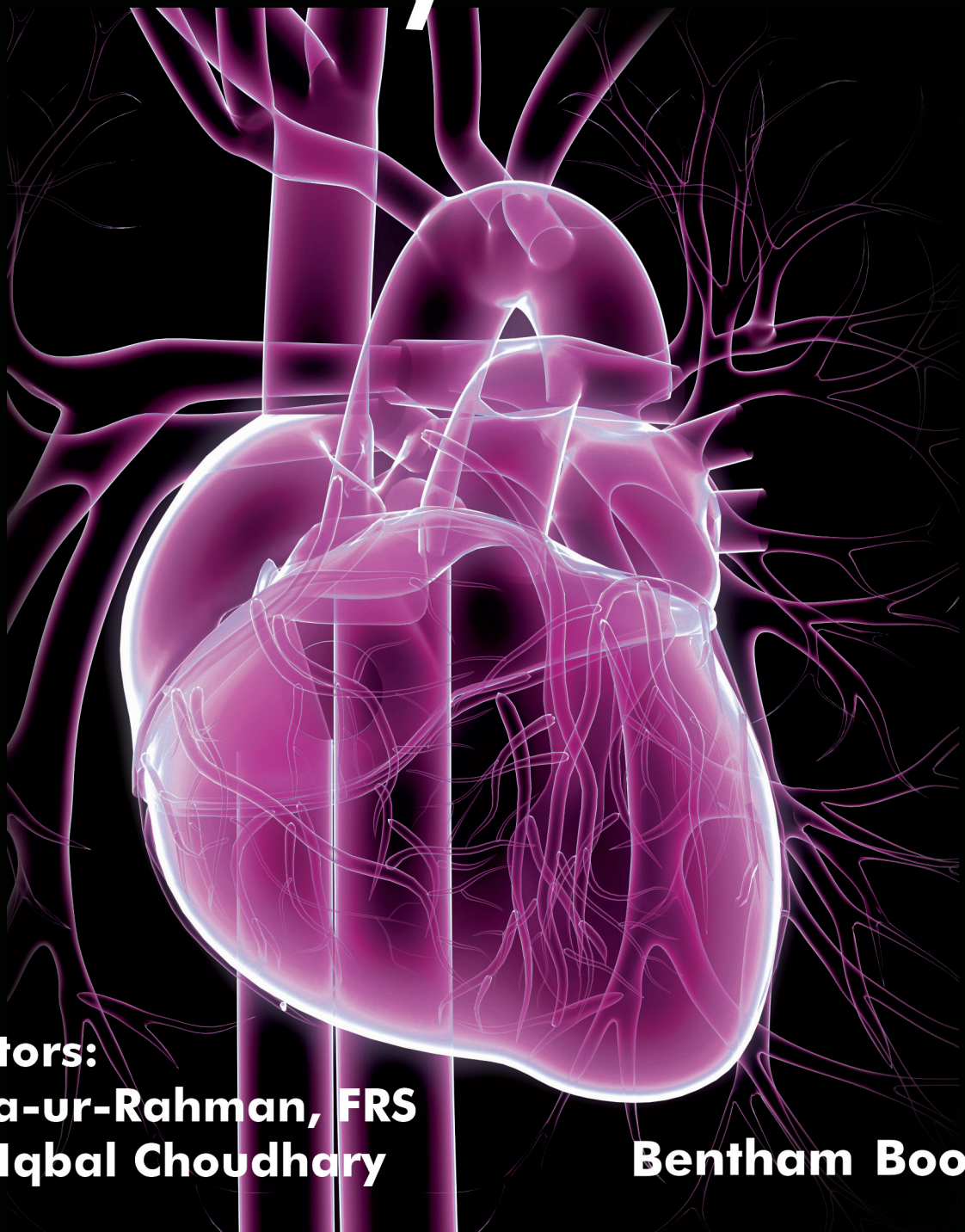
Frontiers in Cardiovascular Drug Discovery



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Frontiers in Cardiovascular Drug Discovery

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Frontiers in Cardiovascular Drug Discovery

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PREFACE

According to the World Health Organization, cardiovascular diseases (CVDs) are globally the number one cause of death. Over 18 million lives are lost globally due to heart attack alone. CVDs range from benign arrhythmias to massive heart failures and from chronic hypertension to ischemic strokes. They occupy a central place in non-communicable diseases, and they are often the result of complex chronic metabolic disorders. Extensive researches are been conducted on the causes and treatments of CVDs. Changing lifestyle with high calories diets, sedentary life style, and smoking are among the key causes. Volume 5 of the book series ***"Frontiers in Cardiovascular Drug Discovery"*** covers 7 comprehensive reviews contributed by leading researchers. These reviews broadly cover various drug targets and new classes of therapies for the prevention or treatment of cardiovascular diseases.

The review by Ramachandran *et al* focusses on a fiercely debated topic in CVD, *i.e*. lipid hypothesis. Cholesterol and LDLs have since long been considered as risk factors of cardiovascular diseases. However, there is mounting evidence that challenge this dogma. The authors have carefully reviewed the scientific literature and conclude that the theory stands valid. Huynh *et al* present exciting new advancements of SGLT2i (Sodium-glucose cotransporters 2) inhibitors as an important new class of drugs. These inhibitors increase renal glucose excretion, and lead to natriuresis and glycosuria with subsequent reduction in blood glucose and associated CVDs in diabetic patients Platelet aggregation and thrombosis are the major causes of morbidity and mortality worldwide. Piato and Graebin have the reviewed recent literature on the development of antithrombotic agents of natural and semi-synthetic origins, with a higher level of safety. Santos *et al* have contributed a chapter on the significance of transient receptor potential (TRP) channels as potential drug targets against cardiometabolic diseases. Mutations in some of the TRP channels are implicated in various metabolic and cardiovascular disorders, and thus activations of TRP channels through natural products may lead to the development of a new class of drugs.

Raynaud's phenomenon (RP), vasospasm due to cold exposure and emotional stress, is a common disorder. Lambova discuss various molecular approaches towards the treatment of RP. Traditional medicines have played an important role in the treatment of human diseases, including cardiovascular disorders. Ravindran *et al* have reviewed pharmacological, toxicological, and informatics studies, carried on various polyherbal formulations, in order to scientifically validate their efficacy against CVDs. The chapter by Roy and Mishra is focused on the applications of system biology approach in developing a better understanding of the molecular basis of the CVDs and its comorbidities. Special emphasis is paid to the identification of biomarkers for early diagnosis of CVD for a better management of the disease states.

We would like to express our gratitude to all the authors of above cited review articles for their excellent contributions in this dynamic and exciting field of biomedical and pharmaceutical research. The efforts of the team of Bentham Science Publishers, particularly Ms. Mariam Mehdi (Assistant Manager Publications), and Mr. Mahmood Alam (Director Publications) are deeply appreciated.

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CHAPTER 1

The Lipid Hypothesis: From Resins to Proprotein Convertase Subtilisin/Kexin Type-9 Inhibitors

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Abstract: The validity of the lipid hypothesis has been debated recently in both, the media and the medical press. In this chapter we review the relevant evidence to evaluate whether it is still applicable in cardiovascular prevention. After a brief description of developments leading to the lipid hypothesis we consider prospective epidemiological studies, paying particular attention to the Framingham Heart Study as it was conceived at a time when lipid lowering therapy was unavailable. We also present the predictive factors of the other commonly used cardiovascular risk scoring models. All the algorithms show cholesterol (total or low density lipoprotein – cholesterol) and high density lipoproteins to predict cardiovascular disease. Our own data from the Whickham Study where subjects were recruited in the pre-statin era also show total cholesterol to be significantly associated with coronary heart disease. We then discuss intervention randomised controlled studies using agents that lower low density lipoprotein – cholesterol (resins, statins, ezetimibe and Proprotein convertase subtilisin/kexin type 9 inhibitors) paying particular attention to studies not demonstrating reduction in cardiovascular outcomes. Apart from patients with heart failure and possibly on dialysis the lipid hypothesis appears to be true. This is reinforced by a meta-analysis carried out by the Cholesterol Treatment Trialists' Collaboration. We do not feel that outcomes from cohort studies consisting of patients subject to multiple guideline driven treatments can be used as good quality evidence against the lipid hypothesis. We do acknowledge that more research is required rega-

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rding heterogeneity and describe a non-invasive way in which atherogenesis of the individual may be measured. We would like future randomised controlled trials to incorporate study of disease mechanism(s) within the study design.

Keywords: Cardiovascular disease, Cardiovascular disease prediction, Coronary heart disease, Ezetimibe, Framingham Heart Study, Lipid hypothesis, LDL-cholesterol, Peak systolic velocity, Proprotein convertase subtilisin/kexin type 9 inhibitors, Randomised Controlled Trials, Statins, Total cholesterol, Whickham study.

INTRODUCTION

Atherosclerotic obstruction of arteries by plaque formation leading to cardiovascular disease (CVD) is one of the most common causes of mortality globally. Although the incidence has been decreasing [1], CVD still remains a leading cause of death in the United Kingdom [2]. Interestingly the prevalence of CVD has remained constant at about 3% [3] even though incidence has decreased, perhaps due to a fall in mortality. Thus, incidence and mortality rates and not prevalence may be the best indicators to evaluate CVD prevention measures. The Cholesterol Treatment Trialists' (CTT) Collaboration carried out meta-analyses of randomised controlled trials (RCTs) with a minimum of 1000 participants and concluded that a 1 mmol/l reduction in low density lipoprotein (LDL) -cholesterol was associated with a reduction in myocardial infarction, revascularisation and ischaemic stroke by just over 20% [4]. The lipid hypothesis describes this widely observed association between CVD risk and raised serum total cholesterol and LDL- cholesterol. Thus, a recent editorial in the New England Journal of Medicine describing the results of the IMPROVE-IT study, convincingly supported the hypothesis on the basis of prospective longitudinal studies showing significant decreases in CVD following use of LDL-cholesterol reducing agents, such as statins and ezetimibe [5].

However, there are publications arguing against the causative effect of cholesterol and LDL-cholesterol in the pathogenesis of atheroma and these have raised doubts regarding the benefit of lipid lowering therapy and indeed, the validity of the lipid hypothesis [6, 7]. This view contrasts with data showing statistically significant reductions in CVD using drugs that reduce LDL-cholesterol by different mechanisms. We speculate that the prevalent guideline culture in clinical medicine requires complex diseases to be simplified to aid the use of treatment pathways. Heterogeneity of populations, based on the degree of risk and mechanisms leading to risk, is often not considered [8]. After describing the history of the development of the lipid hypothesis we will consider epidemiology and interventional trials and how they fit in with the lipid hypothesis. In this

chapter it is not our intention to list details of the various trials, but to discuss and place the lipid hypothesis in the context of CVD prevention.

CHOLESTEROL

Cholesterol is found in body tissues and plasma of animals and is a ubiquitous constituent of cell membranes. It is a precursor of bile acids, vitamin D and steroid hormones such as cortisol, aldosterone, testosterone, oestrogens and progesterone. Further, it is important in the development / functioning of the nervous system, and is involved in signal transduction and sperm development. The structure of cholesterol is shown in Fig. (**1**) and the molecule can exist in either free or esterified (a fatty acid covalently attached to the hydroxyl group at position 3 of the ring) forms.

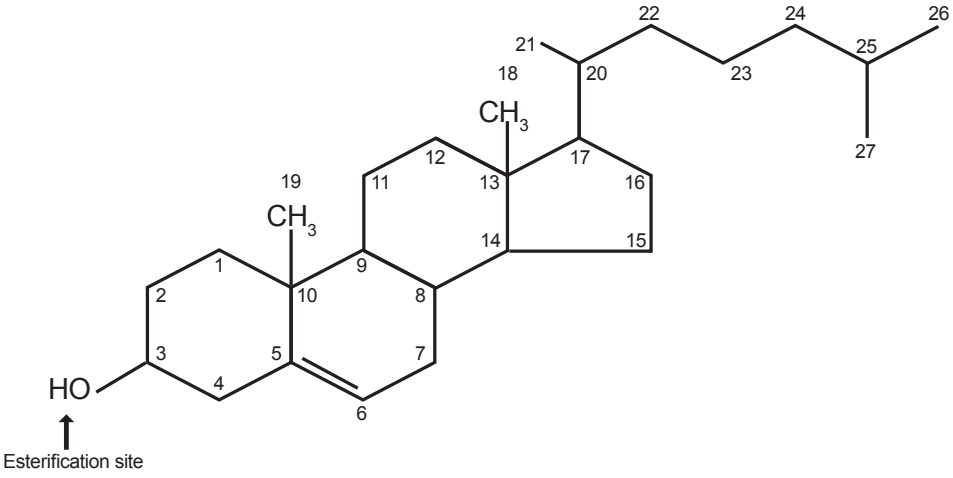

Fig. (1). Structure of cholesterol with the point of esterification highlighted.

Early Evolution of the Relationship between Cholesterol and Atherogenesis

We now consider major historical landmarks in the evolution of the lipid hypothesis, including the advent of evidence-based medicine *via* clinical trials. Controversy regarding the lipid hypothesis has ranged ever since Nikolai Anitschkow in 1913 demonstrated that rabbits when fed with purified cholesterol dissolved in sunflower oil developed vascular lesions similar to atheroma, this not being the case when the animals were fed just sunflower oil [9]. Anitschkow's findings were not confirmed in rats or dogs, hence the observation was considered to be specific to the rabbit model and cast aside. The fact that dietary cholesterol in rats and dogs did not translate into elevated serum cholesterol, perhaps due to high conversion of cholesterol to bile acids as suggested by Anitschkow, was not

CHAPTER 2

The Role of SGLT2i in the Prevention and Treatment of Heart Failure

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Abstract: Diabetes mellitus (DM) is an important independent risk factor for incident heart failure (HF). DM is also a prominent prognostic factor for major cardiovascular (CV) adverse events in patients with established HF with reduced (HFrEF) or preserved ejection fraction (HFpEF). Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are recently approved drugs for DM treatment. SGLT2i lead to natriuresis and glycosuria with subsequent reductions in blood glucose, intravascular volume, and blood pressure. SGLT2i demonstrated a remarkable relative risk reduction in hospitalization for heart failure in large CV outcome trials of patients with DM. In addition, there was a more modest but also a relevant reduction in CV mortality with empagliflozin. SGLT2i reduce recurrent myocardial infarctions in patients with prior myocardial infarction. SGLT2i were subsequently evaluated in patients with HFrEF, including those without DM. Dapagliflozin was associated with reductions in the primary composite endpoint of worsening heart failure or CV death and each component separately. Considering their remarkable CV benefits and nephroprotection, SGLT2i represent invaluable therapy for the primary and secondary prevention of heart diseases in patients with DM or HFrEF. Ongoing trials may confirm the potential impact of SGTL2i in patients with HFpEF and acutely decompensating HF.

Keywords: Diabetes Mellitus, Heart Failure, SGLT2 Inhibitors.

INTRODUCTION

Diabetes Mellitus (DM) is a common disease associated with debilitating microvascular and macrovascular consequences [1, 2]. Macrovascular diseases can lead to acute coronary syndromes, heart failure (HF), and cardiovascular (CV) death, which is the most common cause of death in this population [3 - 5].

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The mainstay of DM management is optimal glycemic control [1, 2].

In 2008, the American Food and Drug Administration (FDA) mandated a compulsory assessment of long-term CV outcomes in all trials evaluating novel anti-diabetic agents [6]. Similar requirements were also set forth by the European Medicines Agency [7]. Both recommendations were in response to a meta-analysis by Nissen and colleagues, which showed 43% and 64% increased odds of myocardial infarction and CV death, respectively, associated with rosiglitazone [8]. Subsequently, rosiglitazone was banned or severely restricted globally. In the later ten years following the above recommendation, 22 randomized controlled trials (RCTS) were completed or ongoing to assess CV outcomes in anti-diabetic agents [9]. Almost all novel anti-diabetic agents were non-inferior to placebo for CV safety [10 - 14] except for one notable exception with increased risk of heart failure (HF) hospitalizations (HHF) associated with saxagliptin [15]. Glucagon-like peptide 1 agonists show excellent glycemic control and weight loss [12]. In 2016, the LEADER trial showed a reduction in the major adverse cardiovascular outcome (MACE), including CV death with liraglutide [16]. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) emerged with promising CV benefits in several safety trials [17 - 19]. In this chapter, we will review the impact of SGLT2i in the primary and secondary prevention of CV diseases with an emphasis on HF.

HEART FAILURE

HF is a complex clinical condition characterized by the heart's inability to provide adequate forward flow or filling without pulmonary congestion [20 - 22]. HF has been declared a global pandemic affecting over 26 million people worldwide [23]. HF is classified into two main categories. HF with preserved left ventricle's ejection fraction and HF with reduced left ventricle's ejection fraction [21]. The importance of HF resides in two essential facts. First, HF is common with an annual incidence of 1% and a lifetime risk of 20% [24, 25]. Second, HF is generally associated with poor outcomes [26]. The Initiation Management Predischarge Process for Assessment of Carvedilol Therapy for Heart Failure (IMPACT-HF) study reported six-month mortality and repeated HHF approximating 5% and 23%, respectively [27].

The Canadian Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study demonstrated 30-day and 1-year heart failure readmissions of 4.9% and 16.1%, as well as mortality of 7.1% and 25.5%, respectively, in 1,570 patients with HFrEF [28]. During the last two decades, angiotensin pathway inhibitors, beta-blockers, and mineralocorticoid receptor antagonists (so-called triple therapies) have markedly improved heart failure outcomes [29]. However, despite

the triple therapies, the residual risks of HF-related hospitalization and mortality remain high and innovative approaches are needed.

Patients with DM have more than twice the risk of developing HF than individuals without DM [30]. DM-induced cardiomyopathy has been postulated as HF in the absence of coronary artery disease and hypertension in patients with DM [31]. The potential causal factors of DM cardiomyopathy include oxidative stress, inflammation, apoptosis, and microvascular coronary artery disease. In the Framingham Heart Study, DM independently increased the risk of HF up to two-fold in men and five-fold in women compared with age-matched controls (adjusted for age, hypertension, dyslipidemia, and coronary artery disease) [32, 33]. The prevalence of DM in HF patients is three to four-fold higher than the general population [34]. Moreover, DM is independently associated with increased risks of death and HHF in individuals with HF [35, 36]. HF was responsible for a substantial mortality burden of patients with DM in the TECOS trial [37].

Since elevated HbA1c level is associated with an increased incidence of HF [38], one may postulate that intensive glycemic control would reduce CV, and specifically HF-related outcomes. Unexpectedly, trials designed to evaluate the above hypothesis showed the contrary. The ADVANCE trial (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) demonstrated that intensive glucose control, aiming for HbA1c 6.5% or better, failed to reduce macrovascular events or total mortality [39]. The ACCORD trial (Action to Control CV Risk in Diabetes), showed that intensive glycemic control (HbA1c of 6% and less) increased mortality by 22% compared to patients in the standard treatment arm [40]. Castagno *et al* completed a meta-analysis of eight RCTs evaluating the reduction in HF by an intensive glucose-lowering regimen compared to standard treatment in 37,229 patients [41]. The mean difference in the HbA1C level between the standard treatment and an intensive regimen was 0.9% (follow-up ranging from two to ten years) [41]. Overall, the risk of HF-related events was similar between the intensive and standard treatment arms (odds ratio (OR)1.20; 95% confidence interval (CI): 0.96-1.48) [41].

MECHANISMS OF ACTION OF SGLT2 AND SGTL2I

In this section, we will examine the potential mechanisms by which SGLT2i may be beneficial in the prevention and treatment of HF. We summarize the mechanisms by which SGLT2i exert its cardioprotective effects in Fig. (**1**).

CHAPTER 3

Natural Products and Semi-Synthetic Compounds as Antithrombotics: A Review of the Last Ten Years (2009-2019)

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Abstract: Pathologies associated with hypercoagulable states, including myocardial infarction, deep vein thrombosis, and pulmonary embolism, are one of the most important causes of morbidity and mortality worldwide. Despite the approval of several new synthetic (including orally active) antithrombotic agents in recent years for treating such diseases, mainly direct thrombin, and factor Xa inhibitors, concerns still exist for side-effects, especially bleeding. There is still a therapeutic demand for safe and effective anticoagulant agents that present fewer side effects than the currently available drugs. Natural products and semi-synthetic molecules, as well as molecules inspired by natural scaffolds, have been an important source of drugs in the past decades. This chapter covers reports published in the last ten years concerning natural (or semi-synthetic) products that have been reported as *in vitro* and/or *in vivo* antithrombotic agents.

Keywords: Antithrombotics, Anticoagulants, Antiplatelets, Drug Discovery, Fibrinogen, Factor Xa, Medicinal Chemistry, Natural Products, Platelet Aggregation, Semi-Synthesis, Thrombin.

INTRODUCTION

Cardiovascular diseases (CVDs) (or circulatory diseases) is a collective term for a group of diseases and disorders of the heart and blood vessels, such as coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism [1].

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According to data from the World Health Organization (WHO), CVDs are the major cause of death globally, both in developed and developing countries. In 2016, an estimated number of 17.9 million people (31% of all global deaths) died from CVDs, being 85% of these deaths due to heart attacks and strokes. The annual mortality of CVDs is expected to reach approximately 23.6 million deaths by 2030 [1 - 4]. The WHO also estimates that at least 75% of the CVD-related deaths occur in low and middle-income countries, mostly due to the lack of preventive care and access to effective and equitable health care services [5, 6]. Also, the economic burden of CVDs in low and middle-income countries is significant; some studies affirm that CVDs and the burden they bring to patients can be a cause of poverty itself [7]. In the past few years, the number of CVD deaths in high-income countries has declined but there is evidence pointing that this long-term decline is either staggering or reversing [8].

Natural products, with their chemical diversity and remarkable and complex structures, have been a significant source of therapeutic agents used to treat several diseases throughout the last centuries. Furthermore, semi-synthetic (*i.e.* compounds that were obtained from organic synthetic methods employing a natural product as starting material) and fully synthetic molecules whose pharmacophoric group is directly inspired from a natural source have also been an important source of new drugs [9 - 11]. Although it seemed that, in the past few years, natural products were being pushed aside in favor of fully synthetic drug candidates [12], it can be said that they are expendable experiencing a return of sorts as useful sources of hit and lead compounds [13-15]. In addition to that, the growing interest in natural products from marine sources [16] is revealing new and interesting bioactive molecules that are structurally diverse from ground-based natural products [17, 18].

Nonetheless, this "going out/in favor" trend regarding the use of natural products as drug candidates was not reflected in the scientific literature. Our search in the SCOPUS database [†] , looking for articles reporting the antithrombotic activity of natural products (search key:*TITLE-ABS-KEY ("natural products" OR alkaloid OR flavonoid OR terpene OR saponin OR polysaccharide) AND (antithrombotic OR antiplatelet OR anticoagulant OR thrombin OR "factor Xa" OR platelet)* in the last 20 years has returned a steady growing trend (Fig. **1**) which indicates that, despite the perceived lack of therapeutic applicability for natural products in the pharmaceutical industry in the past, the global community of researchers investigating the antithrombotic activity of natural products kept and continues to investigate these molecules and their biological properties.

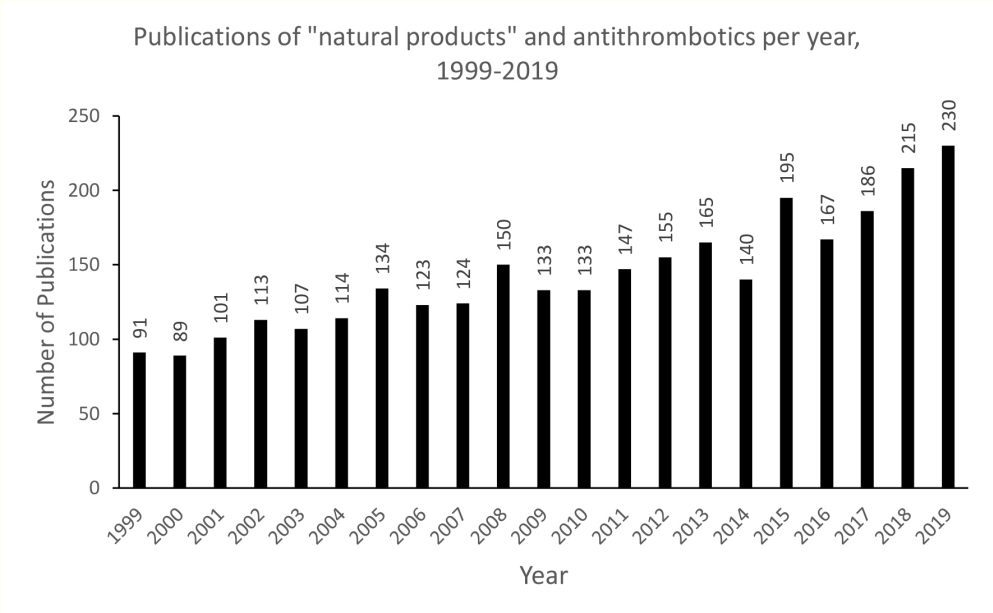

Fig. (1). The plot of the number of published articles regarding the antithrombotic activity of natural products during 1999-2019. Search terms: ("natural products" OR alkaloid OR flavonoid OR terpene OR saponin OR polysaccharide) AND (antithrombotic OR antiplatelet OR anticoagulant OR thrombin OR "factor Xa" OR platelet) Source: SCOPUS.

Despite the recent approval of several new synthetic (including orally active) anticoagulant agents in recent years for treating such diseases, mainly direct thrombin, and factor Xa (fXa) inhibitors (Fig. **2**), concerns still exist for side-effects, in particular the bleeding associated with their use [19 - 22]. Therefore, there is still a therapeutic demand for safe and effective antithrombotic agents that present fewer side effects than the currently available drugs.

In the past few years, several reports discussing the antithrombotic activity of natural (and semi-synthetic) products from several sources (plants, microorganisms, and marine organisms) have been published [23 - 27]. This chapter aims to cover these reports published in the last ten years concerning natural (or semi-synthetic) products that have been reported as *in vitro* and/or *in vivo* anticoagulants. Since one of the aims of this chapter is to highlight the molecular diversity of the natural products reported, we decided to focus our literature survey on isolated products. Reports concerning whole-extract activities without any indication of the active compound (or compounds) were, consequently, excluded. In order to have a more comprehensive discussion of the chemical entities reported, we decided to separate our findings into four categories: a) natural products from marine sources; b) natural products from

CHAPTER 4

Transient Receptor Potential Channels: Therapeutic Targets for Cardiometabolic Diseases?

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Abstract: Transient receptor potential (TRP) channels are ubiquitously expressed cellular sensors that respond to changes in the cellular environment. They act in nociception, taste perception, thermosensation, mechanosensing, osmolarity sensing, and signal transduction. Mammalian TRP channels comprise 28 members divided into six subfamilies: TRPA (ankyrin), TRPC (canonical), TRPM (melastatin), TRPML (mucolipin), TRPP (polycystin) and TRPV (vanilloid). TRP mutations that result in either gain or loss of function have been linked to several human diseases, among them hypertension, cardiac hypertrophy, obesity, and diabetes. In the myocardium, TRP channels modulate Ca^{+2} handling and are differentially expressed in models of cardiac remodeling and dysfunction. TRP channels are also involved in insulin release from pancreatic beta-cells and glucose tolerance in rodent models of type 2 diabetes. Some of these channels promote thermogenesis and thus prevent diet-induced obesity. How TRP channels are modulated *in vivo* is still unknown since few endogenous ligands were identified so far. However, a wide range of natural products with therapeutic potential activates TRP channels and might serve as models for new drug discovery and development to prevent cardiometabolic morbidity and mortality. Studies with TRP channels show promising results, but the translation to preventive or therapeutic strategies against cardiometabolic diseases is challenging since they are found in multiple tissues and enrolled in several physiological actions, which increases the risk of adverse effects.

Keywords: Adipose tissue, Cardiovascular diseases, Cardiometabolic syndrome, Heart, Obesity, Pancreas, Type 2 diabetes, Transient receptor potential channels, TRPA1, TRPC, TRPM, TRPV.

INTRODUCTION

Cardiometabolic syndrome (CMS), also known as insulin resistance syndrome,

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syndrome X, Reaven's syndrome, and Beer belly syndrome, is recognized as a disease [1] and has been defined in several different ways [2]. However, the consensus is that it is a combination of metabolic disorders, such as insulin resistance, impaired glucose tolerance, systemic arterial hypertension, central obesity, and atherogenic dyslipidemia [1, 3]. Around 25% of the adult population worldwide is reportedly suffering from CMS [4].

CMS is commonly associated with the development of cardiovascular diseases, and as obesity increases worldwide, it has become a global pandemic [3]. The western way of life, characterized by a sedentary lifestyle and the increased consumption of high caloric unhealthy foods, has created a positive energy balance environment, increasing the risk for CMS and cardiometabolic diseases [3]. CMS is a significant public health concern owing to the financial impact of higher hospitalization rates due to comorbidities; it also impacts physical well-being and the quality of life and reduces the workforce. Therefore, it is crucial to develop therapeutic strategies focusing on both CMS risk factors and treatment of comorbidities [3].

Transient Receptor Potential (TRP) channels have been identified as potential candidates for the treatment of many diseases, including the cardiometabolic ones, as over the last 15 years supporting evidence has emerged on their role in cardiovascular and metabolic functions. TRP channels are a group of non-selective ion channel sensors that responds to a broad spectrum of physical and chemical stimuli, playing a role in the physiological process of signal transmission [5]. They are primary targets for both endogenous and exogenous substances with therapeutic potential [6]. However, translation to preventive or therapeutic strategies remains challenging as they are present in multiple tissues and thus, are enrolled in several physiological pathways, increasing the risk of adverse effects [6].

Here, we discuss whether TRP channels present an opportunity to combat cardiometabolic diseases, which are a high cost to governments and affect patient's well-being. Evidence shows that TRP channels are relevant as a therapeutic strategy, with additional research necessary to prove their safety and efficacy.

TRP CHANNELS

Cosens and Manning described the first TRP channel in a *Drosophila melanogaster* mutant [7]. From then, until 2017, 28 mammalian TRP channel proteins have been identified. The TRP superfamily of channels is categorized into six families based on amino acid homologies: ankyrin (TRPA), canonical (TRPC), melastatin (TRPM), mucolipin (TRPML), polycystin (TRPP), and

vanilloid (TRPV) [5, 8]. The main structure of the TRP channel subunit has six transmembrane domains (TM1 to TM6) that are assembled as homo- or heterotetramers to form selective cation channels with diverse modes of activation and varied permeation properties [9]. They have distinct pharmacological properties, presenting a challenge in drug development [6, 10].

The TRPA family has only one protein identified (TRPA1). The TRPC family contains seven protein members (TRPC1-7), whereas the TRPM family includes eight members (TRPM1-8). The TRPML family contains three members (TRPML1-3), the TRPV family is comprised of six members (TRPV1-6), and the TRPP family has three proteins (TRPP1, TRPP2, and TRPP3) [5]. There is also a family called TRPN (NO-mechano-potential) found in worms, frogs, zebrafish, and *Drosophila,* with no homologous proteins in mammals [5]. TRP channels can be constitutively open or are activated by intracellular cations [5, 10]. While all TRP channels are permeable to cations, two TRP channels are impermeable to Ca^{2+} (TRPM4, TRPM5), and two others are highly Ca^{2+} permeable (TRPV5, TRPV6) [11].

TRP channels are found in the plasma membrane of distinct cell types, and cellular organelles such as lysosomes, endosomes and endoplasmic reticulum (ER), serving as intracellular ion channels [5]. They are activated in response to a variety of stimuli, including temperature, stretch, pressure, chemicals, oxidation/reduction, osmolarity, and pH, and interact with a range of proteins affecting their activity, location, and trafficking [5, 6]. They play a role in the physiological process of signal transmission [5], and are central elements of nociception, converting noxious stimuli into electrical pain signals [8]. Conversely, dysfunction of TRP channels is involved in various pathological conditions such as bladder disorders, cancer, obesity, type 2 diabetes (T2D), heart diseases, respiratory diseases and chronic pain [5]. The main TRP channels expressed in the cardiovascular system, pancreas, and adipose tissue (AT), which are the main focus of this chapter, are shown in Fig. (**1**).

TRPA (ankyrin) Family

The TRPA1 channel is the only member of this family. This chemo-nociceptor is expressed in neurons, C-fibers, and myelinated Aβ-fibers, making it an ideal target for analgesics. It is also found in non-neuronal cells including epithelial cells, melanocytes, mast cells, fibroblasts, and enterochromaffin cells [12].

The TRPA1 channel is activated by various exogenous and endogenous compounds. The exogenous activator ligands are cysteine and lysine reactive electrophilic molecules like the active compound of mustard oil and wasabi (allyl isothiocyanate), cinnamaldehyde extracted from cinnamon, allicin from garlic

CHAPTER 5

Treatment of Raynaud's Phenomenon

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Abstract: Raynaud's phenomenon (RP) represents a clinical expression of recurrent vasospasm of the small arteries and arterioles of the acral parts (most commonly fingers and toes) provoked by cold exposure and emotional stress. Here, the therapeutic strategies in primary and secondary RP in systemic sclerosis (SSc) are discussed that are based on the evolving knowledge about different pathogenic pathways of the peripheral vascular syndrome. The vasospasm in primary RP is reversible while the secondary SSc-related RP is associated with endothelial injury and subsequent structural abnormalities that lead to tissue damage. The disbalance between vasodilators (nitric oxide - NO, prostacycline) and vasoconstrictors (endothelin-1, angiotensin) is the major consequence of the endothelial injury in secondary SSc-related RP. Therapeutic options in primary RP patients include administration of oral, well-tolerated drugs such as herbal extracts from Ginkgo biloba, pentoxifyllin, or calcium channel blockers. European League Against Rheumatism recommends standardised therapeutic approach for management of SSc-related RP that includes administration of dihydropyridine-type calcium channel blockers, fluoxetine, phosphodiesterase type 5 inhibitors and intravenous iloprost. Other approaches have been also studied such as inhibition of renin-angiotensin system, statins, botulinum toxin but currently there is not enough evidence for their use. Scientific knowledge about mechanisms of action of different drugs corresponding to the underlying pathogenesis are discussed as well as available experience in RP regarding efficacy and safety profile. Individualization of therapy with using complex approach and drug combinations in resistant cases of severe RP and digital ulcers are presented.

Keywords: Angiotensin, Antiplatelet drugs, Aspirin, Bosentan, Endothelin, Digital ulcers, Fluoxetine, Iloprost, Nitric oxide, Nifedipine, Pathogenesis, Pentoxifyllin, Phosphodiesterase inhibitors, Prostacyclin, Raynaud's phenomenon, Serotonin, Sildenafil, Systemic sclerosis, Treatment.

Raynaud's phenomenon (RP) represents a clinical expression of recurrent vasospasm of the small arteries, arterioles and arteriovenous shunts of the acral

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parts (most commonly fingers and toes) provoked by cold exposure and emotional stress [1]. It manifests usually in three phases with phasic skin colour changes *i.e.,* white discoloration in the phase of ischaemia, blue – in the subsequent phase of asphyxia and finally red discoloration - in the phase of reactive hyperemia. Skin colour changes are reversible and differ with distinct demarcation between the affected and unaffected area.

RP is classified into two subtypes - primary and secondary RP [1 - 4] that differ in pathogenic, clinical and prognostic aspects and require different therapeutic approaches. Primary RP is not associated with an underlying disease, differs with female predominance, family history, younger age at onset (below 30 years, mainly at puberty), but this phenomenon should be interpreted with caution as primary RP with late onset (above the age of 40) is also possible [5]. Prevalence of primary RP varying from 1.6 to 7.2% (calculated pooled prevalence 4.85%) was reported in a recent systematic literature review [6]. Clinically, primary RP is characterized with benign course, absence of digital ulcers, lack of symptoms and signs of underlying systemic autoimmune disease. Its diagnosis is generally based on the following criteria *i.e.,***1)** vasospastic attacks precipitated by cold or emotional stress; **2)** symmetry of attacks; **3)** absence of digital ulcerations or gangrenes; **4)** normal erythrocyte sedimentation rate; **5)** negative test for antinuclear autoantibodies; **6)** normal capillaroscopic findings [7].

Contrary, secondary RP is a syndrome in the context of underlying disease. Secondary RP is a common clinical symptom in systemic autoimmune rheumatic disease and differs with highest prevalence of approximately 95% in systemic sclerosis (SSc)/scleroderma [2, 4, 8]. Secondary RP in rheumatic diseases is characterized by later age of onset above 30 years, presence of signs of connective tissue disease, more severe course with development of digital ulcers in a part of the cases, thumb involvement [2, 4, 9] (Fig. **1**). Differential diagnosis of RP in rheumatic disease is broad and includes a spectrum of diseases that are characterized with varying prevalence of RP *i.e.*, SSc, mixed connective tissue disease, undifferentiated connective tissue disease, systemic lupus erythematosus, Sjögren syndrome, dermatomyositis, polymyositis, rheumatoid arthritis, systemic vasculitides (Buerger disease, Takayasu arteritis, polyarteritis nodosa, granulomatosis with polyangiitis, *etc.*), fibromyalgia, cryoglobulinaemia. RP could also be a sign of a spectrum of non-rheumatic pathology that also should be recognized and properly differentiated by the rheumatologists in routine clinical practice and includes cases of drug-induced RP by beta blockers, cytotoxic drugs – vinblastine, bleomycin, interferon, *etc.*; paraneoplastic RP – associated with solid tumours and haematological malignancies; vibration-induced white finger; hypothyroidism; carpal tunnel syndrome, *etc.* [2, 4, 8 - 15].

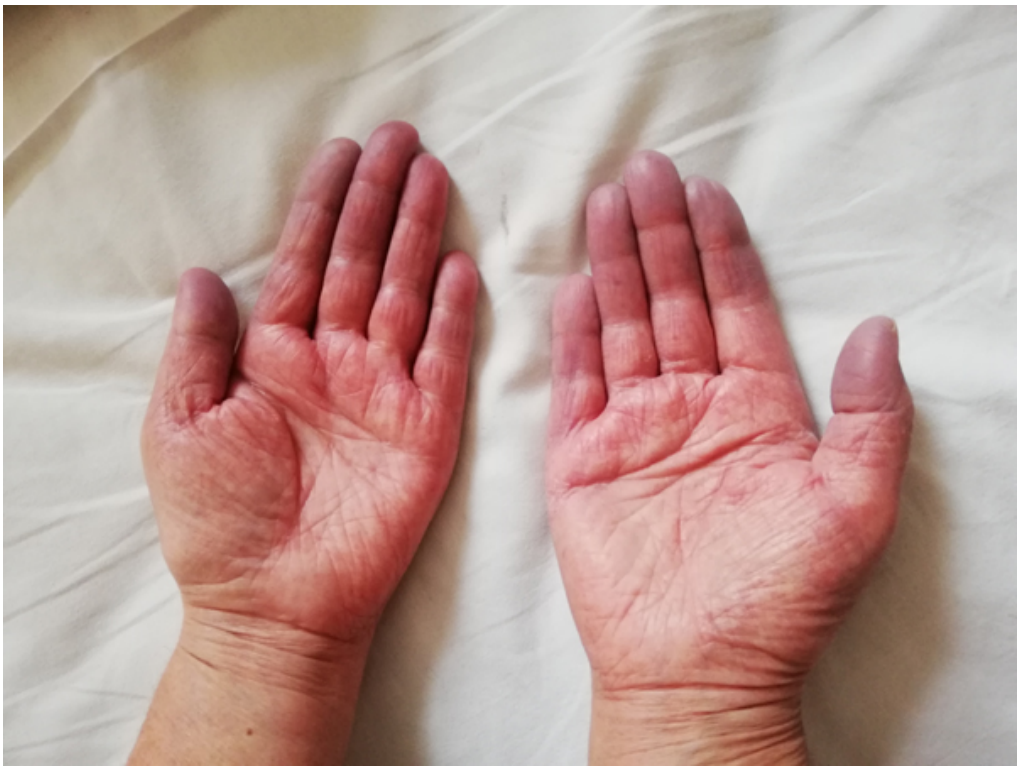

Fig. (1). Vasospastic attack in secondary SSc-related RP, phase of asphyxia with blue discoloration of the fingers; involvement of the thumbs is evident.

Different pathogenesis of primary and secondary RP results in different clinical course, severity, prognosis and respectively requires different therapeutic regimens. Here, the therapeutic strategies in primary and secondary RP in SSc are discussed. The vasospasm in primary RP is reversible while the secondary SSc-related RP is associated with endothelial injury and subsequent structural abnormalities that lead to tissue damage.

PRIMARY RAYNAUD'S PHENOMENON

Non-pharmacological measures represent an integral part of the complex care for RP patients. Patients should be instructed to avoid cold exposure, to wear warm clothes and gloves, and to stop smoking. Moreover, in milder forms of primary RP, these measures may be enough to control the symptoms. In cases of specific exposures that are known to induce peripheral vasospasm, the contact should be restricted such as reduction of caffeine consumption, avoidance of known causative agents *i.e.,* beta blockers, interferons, use of protective devices by patients working with vibration [10].

CHAPTER 6

Traditional Medicine Based Cardiovascular Therapeutics

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Abstract: Cardiovascular diseases continue being the major cause of death worldwide, despite the constant and consistent efforts made towards the management and control of coronary artery diseases. These diseases are resulted by the metabolic imbalance involving elevated energy requirements and deficient oxygen supply to the cardiac myocytes, ultimately leading to myocardial necrosis. These diseases are closely associated with several changes in metabolic and signaling pathways that involve increased oxidative stress, excessive cytoplasmic and mitochondrial calcification, elevated lipid peroxidation, disturbed antioxidant homeostasis, dynamic cellular metabolism, irreversible DNA damage, and other pathophysiological alterations. The mechanism of pharmacological action demonstrated by modern western medicines usually adopt the lock-and-key model that involves the action of a principle therapeutic agent onto a specific and selective target to regulate a prime metabolic and signaling pathway, therefore becoming unsuitable to treat the disorders mediated by multiple molecular pathways. The side-effects associated with the use of such synthetic drugs are also an alarming health concern. The traditional system of medicine applies multiple natural ingredients that contain several active metabolites, therefore imparting a holistic pharmacological effect on multiple targets that orchestrate multiple pathways, without eliciting significant side-effects. This book chapter reviews various Indian and Chinese polyherbal formulations designed and developed according to the traditional system of medicine, which have been appropriately formulated and adequately characterized *in-vitro*, *in-vivo*, and *in-silico* following the stipulated scientific standards and medical regulations. Significant emphasis is also laid to review the informatic branches and cellular models available to evaluate and assess the pharmacology and toxicology of such polyherbal formulations.

Keywords: Ayurveda, Cardiovascular Diseases, Chinese Therapeutics, Cell Lines, Herboinformatics, Indian Therapeutics, *in-vitro*, Polyherbal Formulations, Pharmacoinformatics, Traditional Medicine, Toxicoinformaics.

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INTRODUCTION

Cardiovascular Diseases

Cardiovascular disease is a general term for all types of diseases that affect the heart or blood vessels including numerous problems, many of which are related to a process called atherosclerosis. It is the major threat and cause of heart disease [1]. It is a condition that develops when a substance such as plaque builds up in the walls of the arteries. The build-up generally narrows the arteries making it harder for the blood to flow through. If a clot forms, it can also block the blood flow. Sometimes, this may even lead to a heart attack or stroke. CVD is generally associated with the build-up of fatty deposits inside the arteries and also associated with damage to arteries in an organ such as the brain, heart, kidneys, and eyes. Cardiovascular disease (CVD) is one of the leading causes of disability and death in the world. It is also regarded as the leading cause of mortality and morbidity in both men and women [2].

CVD is a class of diseases that involves heart and blood vessels. It also includes coronary artery diseases (CAD) such as myocardial infarction, commonly known as stroke and angina. Apart from this, other diseases that are associated with CVD are congenital heart disease, venous thrombosis, heart arrhythmia, rheumatic heart, heart failure, cardiomyopathy, stroke, hypertensive heart disease, valvular heart disease, and so on. Atherosclerosis is one of the main causes of CVD that includes the risk factor such as hypertension, hypercholesterolaemia and cigarette smoking, obesity, poor diet, and excessive alcohol consumption [3]. In the United States, 43% of the death rate is due to Cardiovascular disease [4]. In 1990, the death rate due to CVD was estimated to be 12.3 million (25.8%), while the death rate reached as high as 17.9 million (32.1%) in 2015 [5]. The death rate has been more in developing countries while the rate declined in most of the developed countries. Generally, older people are more affected by CVD.

Pathophysiology of CVD

Studies show that atherosclerosis and diabetes are the major precursors for cardiovascular disease (CVD). Apart from this obesity, diabetes mellitus, hypercholesterolaemia, and chronic kidney disease are also often linked with cardiovascular disease [6]. Diabetes is the primary risk factor for CVD. It also affects the heart muscles leading to diastolic and systolic heart failure. Atherosclerosis is a major threat to people with macrovasculature even with or without diabetes [7].

Different Types of CVD

There are many cardiovascular diseases involved in the heart and blood vessels. The type of CVD involved with the blood vessels (arteries, veins or capillaries) is known as vascular disease. They include diseases such as Aneurysm, Buerger`s disease, Raynaud`s disease or phenomenon, Atherosclerosis, Peripheral artery disease, Renal artery disease, Cerebrovascular disease (stroke), Peripheral venous disease, and other blood clotting disorders. The cardiovascular diseases associated with heart or cardiac are Arrhythmia (irregular heartbeat or rhythm), Angina (for both cardiac and vascular disease), Dilated cardiomyopathy, Heart attack, Congenital heart disease, Mitral valve prolapse, Mitral regurgitation, Pulmonary stenosis, Hypertrophic cardiomyopathy, and Rheumatic heart disease (a complication of strep throat) [6, 7].

INDIAN CARDIOVASCULAR THERAPEUTICS

Following are some of the important Indian cardiovascular therapeutics that have attracted significant research interests:

Ambrex

Ambrex is a licensed polyherbal formulation consisting of five Indian herbs: Withania somnifera, Cycas circirnalis, Orchis mascula, Shorea, robusta, and amber (a resin from Pinus succinifera) that are “Generally safe” are blended together in accordance to the Siddha system of medicine. In a study, FTIR characterization of Ambrex demonstrated C=O stretching in carbonyl compounds contributed by the presence of high content of terpenoids and flavanoids [8], while the GC-MS analysis revealed Methyl-Commate-A as the key metabolite in its volatile-fraction [9]. An *in-vivo* study revealed that pre-treatment with Ambrex increases the ISPH-stimulated down-regulation of TCA-cycle enzymes (ICDH, SDH and α-KGDH) and decreases the ISPH-induced up-regulation of apoptotic genes (p53, bax and caspase-3) and anti-apoptotic gene (bcl-2) to their normal levels [8]. Another study characterized the morphology of Ambrex formulation by SEM and assessed its cardioprotective activity against ISPH-induced myocardial necrosis in rats, by quantifying its effects on different oxidative stress markers and cardiac biomarkers through biochemical and histopathological evaluations. Ambrex serves as a unique metal-deficient to the best of our knowledge in siddha medicine based polyherbal nano-formulation characterized and evaluated in India. Pretreatment with Ambrex significantly maintained the tissue levels of oxidative stress markers and serum levels of cardiac biomarkers at their respective normals. It also attenuated the magnitude of ISPH-induced oxidative stress, ROS generation and LPO as reflected by biochemical evaluations, and ameliorated the degree of ISPH-induced myocardial necrosis and membrane damage as reflected

CHAPTER 7

Cardiovascular Disease: A Systems Biology Approach

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Abstract: In the post-genomic era, the main challenge is to extract meaningful and valuable information from a large pool of data generated by high throughput techniques like microarray and deep sequencing techniques. Systems biology is an emerging discipline that aids in interpreting a large amount of biological data in a meaningful way. It helps to draw significant inference from a large amount of data about the interactions of genes or proteins, by developing quantitative mathematical models. Due to its complex nature, cardiovascular diseases can be better understood using the systems biology concept. Different components of the disease like heart failure and coronary artery disease can be comprehended in a modular fashion, wherein each module consists of multiple genes and their nonlinear interactions. Another approach is population genetics or Genome-Wide Association Studies (GWAS), which has identified over two hundred chromosomal loci that modulate the risk of cardiovascular diseases. These GWAS variation data can be integrated with multi-omics data and gene network data to identify the susceptible pathways, modules and genotyping cause behind it. Identification of a hub gene in a network is one of the main approaches of research in systems biology of cardiovascular diseases. This hub gene can serve as a biomarker for early detection or therapeutic targets. Comorbidities are another cause of increased risk leading to further complications in patients with cardiovascular diseases. Analysis of association of the comorbidities, using a system biology approach, focuses on the prevention of severe vascular events. The most common comorbidities include diabetes, kidney disease, peripheral arterial disease, *etc*. Systems biology can aid in identifying special biomarkers for early diagnosis of cardiovascular comorbidities and the following careful management might lead to prolonged survival of the patient.

Keywords: Bioinformatics, Cardiovascular Diseases, Data analysis, Disease comorbidities, Genome-wide association studies, Integrated omics, Network Biology, Network Medicine, Systems Biology.

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INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of death worldwide, mostly in low and middle-income countries. Despite the increasing economic and social burden of the disease, there is no proper understanding of its underlying mechanism. The Oslerian model is one of the old models in medical practice. According to this model, the presence of a given disease was identified by the anatomical abnormalities in organs and tissues. This practice has been evolved and improved over the last 100 years by methods of adopting a reductionist approach. This approach focuses on the individual analysis of the functional components of an organism. The cardiovascular disease is diversified in origin with a variety of biologically functional components. It can be defined by the presence of a cluster of cardiovascular risk factors, inflammatory changes to the vascular tissue, and development of the atherothrombotic process. The atherothrombotic process includes both atherosclerosis and its thrombotic complications. Atherosclerosis alone is a complex disease, caused by the combination of different facts like an aggregation of inflammatory cells and fibrous tissue in the wall of arteries.

Cell-based Cardiac Disease Models and Animal Models

The aim of the reductionist approach was to define the individual basic units like the genes and pathways of the entire system by eliminating the complexity of it. But at the same time, simply focusing on the individual gene or pathway is not enough in comprehending the whole biological system in disease and health condition. The integration of multigene and multi pathways is the key process in understanding the system. In this context, cell culture-based systems and animal disease models play a major role to model the pathology observed in a patient. High-throughput technologies like microarray and next-gen sequencing technologies generate multifaceted data of these model systems. There is a need for analysis of integrated genomics, transcriptomics and proteomics for those model systems.

Different types of cells that contribute to the normal functioning of the heart are cardiac fibroblasts, endothelial cells, cardiomyocytes or vascular smooth muscle cells, among which the cardiac myocytes play a major role. Isolated primary neonatal cardiomyocytes from mice and rats are considered as excellent sources for differential gene expression studies. Reprogrammed embryonic stem cells (ESC) such as induced pluripotent stem cells (iPSCs) and engineered heart tissues (EHTs)/human cardiac organoids (hCOs) are used to generate cardiomyocytes [1 - 3]. Similarly, the use of zebrafish (*Danio rerio*) and large mammalian animal models has significantly contributed to the understanding of the disease

pathogenesis of cardiovascular disease in human beings. The high throughput data generated as outcomes from the high throughput experiments carried out in these model systems are the key resource of the data. Those data are analyzed using a series of bioinformatics tools or protocols which is called systems biology approach. This systems biology protocol leads to the development of diagnostic strategy and targeted therapies for human cardiovascular diseases.

Table 1. Clinical understanding of chronic cardiac diseases with reductionism (Louridas *et al*.).

Medical Applications	Reductionism's Objectives	Systems Biology Holistic Strategy
Clinical focus	Isolated clinical parameters	Interactions between components, like molecules, networks
Prevention	Isolated culprit molecular and environmental parameters	As an entity the whole range of culpable variables
Diagnosis	Isolated molecules, biomarkers, signs, symptoms	The patient as a "diseased person"
Therapy	Treating causes and symptoms	Treating the patient from a holistic perspective

Post-genomic Era and Systems Biology Concept

Before the genomic era, a biological system was comprehended using a reductionist approach, an approach that believes in understanding complex things by dissecting them into simpler constituents. The molecular biology technique facilitates the studying of the composition, structure, and interactions of essential cellular molecules such as nucleic acids and proteins. Systems biology is not only just a combination of these molecular parts it may have something greater than that. A typical system-based study comprises the following five steps.

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