Protective Effects of Terpenes on the Cardiovascular System: Current Advances and Future Perspectives

Article *in* Current Medicinal Chemistry · September 2016

DOI: 10.2174/0929867323666160907123559

CITATIONS
50

READS
2,638

5 authors, including:

Jorge Miguel Alves-Silva
University of Coimbra
36 PUBLICATIONS **764** CITATIONS
SEE PROFILE

Mónica Zuzarte
University of Coimbra
80 PUBLICATIONS **2,147** CITATIONS
SEE PROFILE

Carla Marques
University of Coimbra
55 PUBLICATIONS **1,293** CITATIONS
SEE PROFILE

Henrique Girao
Faculty of Medicine, University of Coimbra
179 PUBLICATIONS **5,508** CITATIONS
SEE PROFILE

Send Orders for Reprints to reprints@benthamscience.ae

Current Medicinal Chemistry, 2016, *23*, 1-42

REVIEW ARTICLE

Protective Effects of Terpenes on the Cardiovascular System: Current Advances and Future Perspectives

Jorge M. Alves-Silva[a,#], Monica Zuzarte[b,#,*], Carla Marques[b], Lígia Salgueiro[a] and Henrique Girão[b]

[a]*CNC.IBILI, Faculty of Pharmacy, University of Coimbra, Azinhaga de S. Comba 3000-354 Coimbra, Portugal;* [b]*CNC.IBILI, Faculty of Medicine, University of Coimbra, Azinhaga de Sta Comba, 3000-354 Coimbra, Portugal*

ARTICLE HISTORY

Received: May 05, 2016
Revised: July 11, 2016
Accepted: September 02, 2016

DOI: 10.2174/0929867323666160907123559

Abstract: ***Background:*** Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality worldwide that seriously affect patient's life quality and are responsible for huge economic and social burdens. It is widely accepted that a plant-based diet may reduce the risk of CVDs by attenuating several risk factors and/or modulating disease's onset and progression. Plants are rich in secondary metabolites, being terpenes the most abundant and structurally diverse group. These compounds have shown broad therapeutic potential as antimicrobial, antiviral, anti-inflammatory and antitumor agents. Despite their popularity, scientific evidence on terpenes cardiovascular effects remains sparse, limiting their potential use as cardioprotective and/or cardiotherapeutic agents.

Objective: Bearing in mind the lack of comprehensive and systematic studies, the present review aims to gather the knowledge and some of the most scientific evidence accumulated over the past years on the effect of terpenes in the cardiovascular field with focus on CVDs namely ischemic heart disease, heart failure, arrhythmias and hypertension.

Method: Several popular search engines including *PubMed*, *Science Direct*, *Scopus* and *Google Scholar* were consulted. The bibliographic research focused primarily on English written papers published over the last 15 years.

Results: A systematic and comprehensive update on the cardiovascular effects of terpenes is provided. Moreover, whenever known, the possible mechanisms of action underlying the cardiovascular effects are pointed out as well as an attempt to identify the most relevant structure-activity relationships of the different classes of terpenes.

Conclusion: Overall, this review enables a better understanding of the cardiovascular effects of terpenes thus paving the way towards future research in medicinal chemistry and rational drug design.

Keywords: Terpenes, cardioprotective, heart disease, hypotensive, vasorelaxant, structure-activity relationship.

1. INTRODUCTION

It is widely accepted by the scientific community that herbal medicine has contributed to the development of several commercial drugs with immeasurable benefits to humankind. For example, the discovery of avermactin and artemisinin revolutionized the treatment of parasitic diseases, being the global impact of these discoveries recognized worldwide through 2015's Medicine Nobel Laureates. Importantly, natural products and their derivatives represent one third of Food and Drug Administration (FDA) approved new molecular entities (NMEs) being 25% of these from plant origin [1]. The first approved plant NME was morphine, extensively used as a potent analgesic. Despite

*Address correspondence to this author at CNC.IBILI, Faculty of Medicine, University of Coimbra, Azinhaga de Sta Comba, 3000-354 Coimbra, Portugal; Tel: +351 239480029;
Fax: +351239480217; E-mail: mzuzarte@uc.pt
[#] *Authors contributed equally to this work*

0929-8673/16 $58.00+.00

the huge therapeutic potential, plant-based drug discovery is a challenging task, shifting pharmaceutical industry investment towards synthetic compounds that are easier to produce and resupply. Nevertheless, with this new synthetic trend, the number of new drugs reaching the market has tendentiously declined, thus renewing the interest in plant-derived drugs [2]. In fact, structural differences between natural and synthetic compounds, namely significant lower number of chiral centers, lower size, and higher flexibility of synthetic compounds, are often responsible for their weaker and less specific activity [3].

The large pool of potentially interesting natural sources, including unexplored plants, constitutes an inestimable reservoir of putative lead compounds for the development of effective and cheaper drugs. Terpenes are the largest group of natural compounds and have been widely applied in several products such as flavors, fragrances, perfumery and cosmetics [4]. Moreover, many of these compounds have biological properties justifying their use for preventive/therapeutic purposes. Several terpenes such as D-limonene, 1,8-cineole, boswellic acid, betulinic acid, β-sitosterol and ursolic acid have undergone clinical trials, thus evidencing the relevance of these compounds [4]. Also, many terpenes are included in the Generally Recognized As Safe (GRAS) list fully approved by the FDA and Environmental Protection Agency (EPA) in the USA for addition to food and beverages, which emphasizes human tolerance to these compounds.

It is well established that cardiovascular diseases (CVDs) constitute a heavy economic burden for healthcare systems of developed countries. It is estimated that by 2020 heart disease and stroke will become the leading cause of death and disability worldwide, being the number of deaths around 24 million by 2030 [5]. Given the socio-economic impact of CVDs, the need for cardiovascular preventives and/or therapies constitutes a global health imperative, despite diagnostic improvements and novel therapeutic strategies available in the last years. Herbal medicines have been used since ancient times to treat cardiovascular disorders, including congestive heart failure (CHF), systolic hypertension, angina pectoris, atherosclerosis, cerebral and venous insufficiencies and arrhythmia [6]. Moreover, many of these herbal medicines have contributed to the development of drug preparations used in our days in the clinic. For example, the drugs digitoxin derived from *Digitalis purpurea* and *D. lanata* and digoxin derived from the later, are extensively used in the treatment of CHF [6]. There is also growing evidence of the role of herbal medicine in the attenuation of major risk factors of CVDs such as high levels of low-density lipoprotein, cholesterol, hypertension, and diabetes [7], thus reinforcing the clinical potential of these compounds for the prevention and/or treatment of these maladies. Despite the long history in the use of herbal medicines and the scientific evidence of their promising cardiovascular effects, many remedies remain insufficiently standardized, compromising their clinical validation and consequent therapeutic recommendation. Moreover, clinical trials with plant extracts or plant-derived compounds have focused primarily on cancer and neurodegenerative diseases, with very few studies on the cardioprotective potential of these compounds.

Taking into account the importance of plant products as lead compounds and the huge burden of cardiovascular disorders, the purpose of this review is to provide updated and systematized information on the potential of plant metabolites, namely terpenes in CVDs. This review highlights the cardiovascular effects of terpenes and points out possible mechanisms of action underlying such effects. A structure-activity relationship is proposed in order to explore in more depth the therapeutic potential of these compounds and path the way towards future research opportunities in medicinal chemistry and rational drug design. To achieve this aim, a literature rummage was carried out using several search engines including *PubMed*, *Science Direct*, *Scopus* and *Google Scholar*, over the last 15 years.

1.1. Terpenes

1.1.1. Classification

Terpenes, also called terpenoids or isoprenoids, are natural products formed by rearrangements of five-carbon isoprene molecules. These compounds are generally colorless, soluble in organic solvents and optically active [8]. They represent the largest group of secondary metabolites primarily produced by plants, being involved in several biological processes including plant growth, development, reproduction and defense [9].

Over 36,000 terpenes have been identified [10], being classified according to the number of skeletal isoprene units as hemiterpenes (C_5H_8), monoterpenes ($C_{10}H_{16}$), sesquiterpenes ($C_{15}H_{24}$), diterpenes ($C_{20}H_{32}$), sesterterpenes ($C_{25}H_{40}$), triterpenes ($C_{30}H_{48}$), tetraterpenes ($C_{40}H_{64}$) and polyterpenes ($[C_5H_8]n$). Besides the number of isoprene units, additional subclasses can be identified according to the number of rings in the structure of the compound and classified as acyclic (open

structure), monocyclic (one ring), bicyclic (two rings), tricyclic (three rings), tetracyclic (four rings) and so on [8]. Moreover, different functional groups may be present such as alcohols, aldehydes, ketones, ethers, esters and lactones [11], forming a very diverse and complex group of secondary metabolites. In fact, this high structural diversity correlates with the functional variability of these compounds [12] and broad biological activities, thus boosting their interest as potential lead molecules for preventive and/or therapeutic purposes.

Terpenes are very popular as flavor and fragrant agents, being included in many food and beverages as well as perfumes and cosmetics [4]. Some terpenes have also been used as industrial raw materials to manufacture coatings, adhesives, emulsifiers and chemicals [12]. Since terpenes are the main compounds present in many essential oils, they are also highly valorized in aromatherapy. Strikingly, many of these compounds have a wide range of biological activities being used for medical purposes, namely against cancer, malaria, inflammation and infectious diseases [13]. Examples of common terpenes, representative of different chemical groups, are shown in Table **1**, together with their chemical structure and main natural source.

1.1.2. Biosynthesis

Although terpenes are very popular compounds, their biosynthetic pathways have only recently been depicted in detail. In summary, the biosynthesis of all terpenes involves two five-carbon isomers: isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP). These precursors can be synthetized *via* two distinct pathways: the mevalonate or mevalonic acid (MVA) pathway that occurs in the cytosol, or the non-mevalonate (mevalonate independent), methylerythritol phosphate (MEP) or deoxyxylulose phosphate (DOXP) pathway, characteristic of chloroplasts (Fig. **1**).

Overall, the biosynthetic pathways of terpenes can be divided into four main stages. The first stage involves the formation of IPP and its allylic isomer DMAPP. In the MVA pathway, IPP results from the condensation of 3 molecules of acetyl coenzyme A, thus forming mevalonic acid that is then pyrophosphorylated, decarboxylated and dehydrated; in the MEP pathway, the formation of IPP involves 2 C-metil-D-erythritol-4-phosphate and 1-deoxy-D-xylulose-5-phosphate, the latter resulting from the condensation of glyceraldehyde 3-phosphate and pyruvate [14]. In the second stage, the precursors IPP and DMAPP condense and lead to the formation of linear prenyl diphosphates: geranyl diphosphate (GPP), farnesyl diphosphate (FPP) and geranyl geranyl diphosphate (GGPP). These molecules, in the third stage, undergo several cyclizations and rearrangements, forming the parent carbon skeleton of each class of terpenes. In this way, GPP is the precursor of monoterpenes, FPP forms sesquiterpenes and finally GGPP originates diterpenes. Moreover, both FPP and GGPP can dimerize to form triterpenes and tetraterpenes, respectively. Finally, the fourth stage consists of several transformations including oxidations, reductions, isomerizations and conjugations, responsible for the conversion of the parent skeletons into a diversity of terpene metabolites [12, 13, 15]. It is generally accepted that sesquiterpenes and triterpenes are synthetized though the cytosolic mevalonic acid pathway and monoterpenes, diterpenes and tetraterpenes are formed *via* the chloroplastic MEP pathway. Nevertheless, crosstalk between these two pathways has also been described [16].

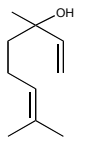
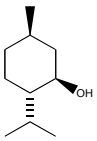
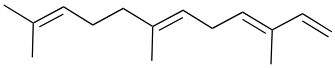
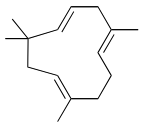
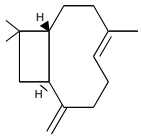
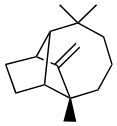
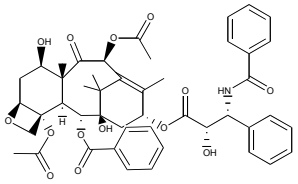
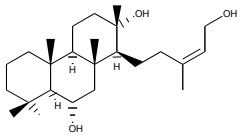
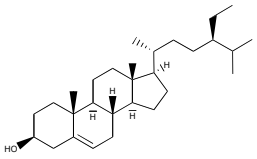
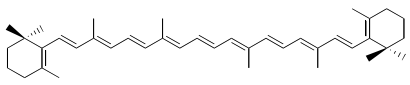
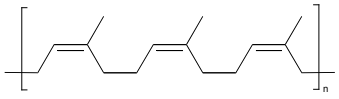
Since plants produce terpenes in relatively low amounts, the procedure to extract them directly from plants can be expensive. On the other hand, chemical synthesis is a challenging task due to their complex and diverse structure. For this reason, the identification of key enzymes and specific synthetic pathways is a crucial step aiming the production of terpenes in biological "factories" such as plants and yeasts.

1.2. Pathophysiology of Cardiovascular Diseases

Cardiovascular diseases a general term used to describe disorders that affect the heart and blood vessels, constitute a major health burden for health care systems of developed countries, being responsible for over 17 million annual deaths and the leading cause of mortality in Europe. It is well known that women are more affected then men (51% *vs.* 42%) and mortality rate tends to increase with age [17].

Atherosclerosis is the major cause of CVDs and refers to a condition where a plaque builds up in the arteries, disturbing blood flow. The atherosclerotic plaque is made up of fat, cholesterol, calcium, and other substances found in the blood. According to the arteries where plaque accumulates, it originates distinct types of disease, namely coronary heart disease (CHD), ischemic heart disease (IHD), peripheral arterial disease (PAD), and cerebrovascular disease. In summary, CHD is characterized by the deposit of plaque in the lumen of coronary arteries, thus compromising the supply of oxygen-rich blood to the cardiac muscle. This blood flow restriction (ischemia) either chronic or acute, causes the muscle to weaken and leads to arrhythmias, that can ultimately lead to heart failure

Table 1. Common terpenes found in nature.

Compounds		Example	Chemical Structure	Main Source	Interesting features
Monoterpenes	Acyclic	Linalool		Lavender (*Lavandula* spp.)	Floral scent, with a touch of spiciness
	Monocyclic	Menthol		Mint (*Mentha* spp.)	Cooling characteristic minty smell
	Bicyclic	Pinene		Pine resin (*Pinus* spp.)	Classic pine tree scent
Sesquiterpenes	Acyclic	(*E,E*)-α-Farnesene		Apple coating (*Malus domestica*)	Green apple odor
	Monocyclic	α-Humulene		Hops (*Humulus lupulus*)	Gives beers their "hoppy" aroma
	Bicyclic	(-)-β-Caryophyllene		Clove (*Syzygium aromaticum*)	Contributes to the spiciness of black pepper
	Tricyclic	(+)-Longifolene		Pine resin (*Pinus* spp.)	Woody-type aroma
Diterpenes		Paclitaxel (Taxol®)		Pacific yew bark (*Taxus brevifolia*)	Anti-cancer drug
Sesterterpenes		Cheilanthatriol		Fern (*Cheilanthes farinosa)*	Present in several aquatic organisms
Triterpenes		β-Sitosterol		Avocado (*Persea americana*)	Plant sterol similar to cholesterol
Tetraterpenes		β-Carotene		Algae *(Dunaliella salina)*	Red-orange pigment
Polyterpenes		*cis*-Polyisoprene		Rubber tree latex *(Hevea brasiliensis)*	Used in rubber products

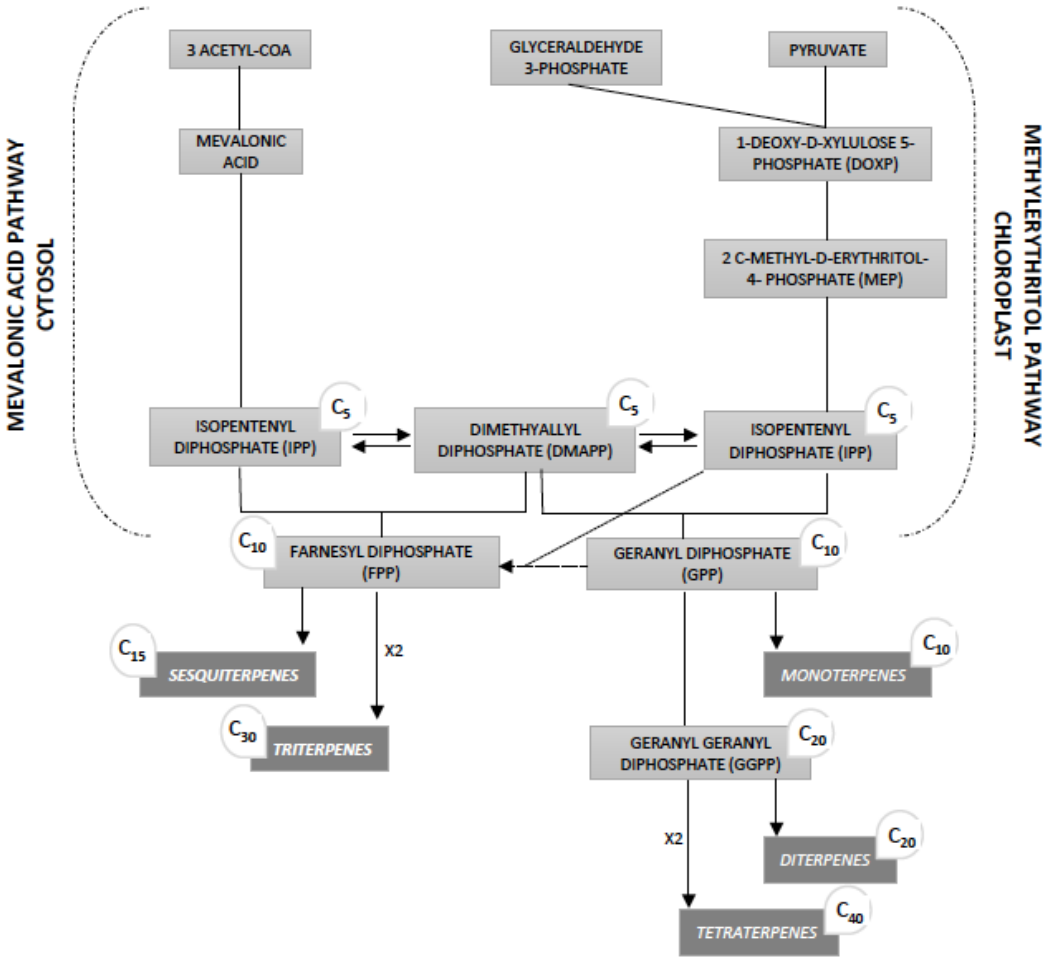


Fig. (1). Schematic representation of terpene biosynthesis (Adapted from [16]).

(HF), a clinical condition when the heart cannot pump efficiently enough blood to meet the body's needs. Similarly, PAD usually occurs due to a build-up of plaque in the arteries that restrict blood supply to leg muscles. Cerebrovascular disease, commonly called stroke, occurs when the blood supply to part of the brain is partially or totally blocked, causing brain damage and possible death. In addition, other diseases not directly related to atherosclerosis are also included in CVDs, such as raised blood pressure (hypertension), rheumatic heart disease, congenital heart disease and HF. Hypertension is the most common disease in industrialized nations and is associated with persistent high blood pressure in the arteries.

Neurohumoral and biomechanical processes that normally occur in hypertension encompasses cardiac hypertrophy, which predisposes the individual to HF through apoptotic mechanisms [18]. Rheumatic heart disease is a disorder where damage to the heart muscle and heart valves is associated with rheumatic fever, caused by bacteria, whereas congenital heart disease results from malformations of heart structure since birth [19]. Both genetic predisposition and infectious diseases have been also associated with heart failure. Early indicators of heart attack include the inflammatory marker CD40 and the cardiac myofilament protein troponin. The inflammatory indicator C - reactive protein (CRP) is considered a marker of disease progression. Moreover, an impaired endothelial function followed by inflammation of the vessel walls is responsible for the formation of atherosclerotic lesions that can underlie myocardial infarction and stroke [20]. If these situations are not treated promptly, the affected part of the muscle dies and is replaced by scar fibrotic tissue. Over time, the scar tissue decreases the heart ability to pump blood efficiently and may lead to ischemic cardiomyopathy. In addition, the heart muscle that lacks blood supply is not able to properly and efficiently conduct electrical impulses, leading to ventricular tachycardia, fibrillation and consequently sudden death. In cardiomyopathy and in HF, a disordered calcium signaling to the myofilaments occurs.

The major risk factors of CVDs include aging, high blood pressure, cholesterol, obesity, elevated blood glucose (diabetes), tobacco use, physical inactivity, unhealthy diet and excessive alcohol [18, 21]. Due to the rising age of population, the incidence of CVDs tends to further increase, thus intensifying the need for the development of innovative and efficient treatments. Moreover, diagnostic improvements are also crucial, since detecting diseases at early stages allows the focus of therapy to be shifted towards prevention. Conventional drugs such as angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, as well as angiotensin II receptor antagonists, have shown cardioprotective effects in both preclinical and clinical studies [22]. Notwithstanding the importance of these pharmacological agents, there is a growing awareness of the importance of diet and herbal medicines for the prevention and/or treatment of cardiovascular diseases [7], including long-term prevention of heart attack in high risk patients [22]. In fact, the Mediterranean diet is broadly recognized for its positive impact in health and life quality and is mostly associated with the consumption of plants and bioactive compounds from herbs. This type of diet has gained popularity and emerged as a great promise to improve health and prevent chronic diseases, including CVDs [23]. Medicinal plants have long been used in patients with several cardiovascular disorders such as congestive heart failure, systolic hypertension, angina pectoris, atherosclerosis, cerebral insufficiency, venous insufficiency, and arrhythmia [6]. Moreover, they have been also used as preventive strategies by attenuating some major risk factors of CVDs such as high levels of low-density lipoprotein, cholesterol, hypertension, and diabetes [7].

1.3. Cardiovascular Effects of Terpenes

1.3.1. Naturally Occurring Terpenes

Despite the increasing number of research studies, a comprehensive review on the cardioprotective effects of terpenes, one of the largest groups of secondary metabolites present in plants, is lacking. The term 'cardioprotective' is, herein, applied in a broad sense and includes compounds that prevent or ameliorate cardiovascular pathologies and associated comorbidities. Indeed, it has been shown that terpenes can have an impact on some of the major risk factors of cardiovascular diseases, such as high cholesterol and diabetes. Therefore, it is conceivable to speculate that terpenes present a beneficial effect acting directly upon the cardiac muscle, or indirectly through the vascular system.

In an attempt to gather information on the cardiovascular effects of terpenes, Table **2** summarizes the main studies, pointing out possible mechanisms of actions. The compounds are listed according to the predominant chemical group and, in each group, compounds are organized in alphabetical order. Complex molecules namely terpene glycosides were also considered since key modifications such as glycosylation are often relevant for reducing therapeutic doses, increasing solubility, and expanding biological activity spectrum [24].

Amongst the panoply of terpenes assessed for their cardiovascular effects, diterpenes and triterpenes are by far the most studied. Overall, the main cardiovascular effects include direct effects on the vascular system (*e.g.* vasorelaxation and hypotension) and on the heart, affecting for example heart rate (HR), opening/closing of ionic channels, and infarcted area.

Briefly, vasorelaxation studies are carried out using animal-based approaches namely isolated artery or aortic rings. Contractions in these models are generally induced with potassium chloride (KCl), phenylephrine (PHE) or calcium chloride ($CaCl_2$) and the ability of the tested compound to revert this effect is evaluated (relaxation). Reported relaxation effects occur through mechanisms that involve inhibition of Ca^{2+} influx in vascular smooth muscle or *via* quenching of reactive oxygen species (ROS) and stimulation of nitric oxide (NO) synthesis (Table **2**). To assess hypotensive effects non-anesthetized normotensive rats are generally preferred. These effects seem to result from bradycardia and peripheral vasodilatation (Table **2**).

Terpenes can also have a direct impact upon the heart homeoatasis and fuction. Indeed, it has been reported that terpenes affect heart rate, electrophysiology, infarcted area, and inhibit myocardial enzymes such as the creatine kinase (CK), the MB isoenzyme of creatine kinase (CK-MB), lactate dehydrogenase (LDH) and cardiac troponin T (cTnT). In addition, approaches based on ischemic/reperfusion injury using both *in vitro* and *in vivo* models are frequent. The attenuation of post-ischemic injury may occur *via* an AKT-dependent activation of hypoxia-inducible factor 1-alpha (HIF-1α); survival pathways such as phosphoinositide 3-kinase/Protein kinase B (PI3K/AKT), extracellular signal-regulated kinase (ERK1/2), and AMP-activated protein kinase (AMPK); downregulation of nuclear factor kappa B (NF-κB) signaling pathway and inhibition of apoptosis. Moreover, the cardioprotective potential can be associated with other biological activities of terpenes namely their antioxidant, anti-apoptotic and

Table 2. Cardiovascular effects of terpenes.

Terpene	Study Model	Cardiovascular Effect/Mechanism of Action	References
HEMITERPENES AND MONOTERPENES			
(+)-Campholenol-10-O-β-D-Glu and (+)-Campholenol-10-O-β-D-Api-(1→6)-β-D-Glu	H_2O_2-induced damage in H9c2 rat cardiomyocytes	↑ Cell viability	[28]
Carvacrol	Isolated rat aortic rings	Induced relaxation in PHE- and KCl-pre-contracted rings; Inhibited the response to PHE and KCl; ↓ $CaCl_2$-induced contractions	[29]
		↓ Contraction in PHE-contracted rings and in PHE- and Pb(II)-induced contraction	[30]
	Isolated rat mesenteric artery rings	↓ PHE-induced contractions with or without endothelium; ↓ $CaCl_2$-induced contractions; Induced relaxation in S(-)-Bay K8644-pre-contracted rings	[31]
	Isolated rat left atria	Demonstrated a negative inotropic and chronotropic effect	
	Isolated canine and human ventricular cardiomyocytes	Supressed cardiac Ca^{2+} channels	[32]
	Isolated rat cerebral and cerebellar arteries	Induced vasorelaxation	[33]
	Anesthetized, normotensive rats	↓ HR, MAP, SBP and DBP; Inhibited L-NAME-induced hypertension	[34]
	Non-anesthetized, normotensive rats	Induced hypotension associated with bradycardia	[31]
	Rat aortic smooth muscle cells	Inhibited PDGF-BB-stimulated migration; ↓ NOX-1 expression, MAPK phosphorylation and ERK1/2 response; ↓H_2O_2 generation; ↓ NOX activity; Inhibited sprout outgrowth and balloon injury-evoked vascular neointimal formation	[35]
	HFD-induced C57BL/6J diabetic mice	↓ TC, TG, FFA, PL in plasma, heart, liver and kidney; ↑ HDL-c; ↓ LDL-c, VLDL-c; ↓ Fat accumulation in adipocytes; ↓ TNF-α and IL-6 expression	[36]
Carvone	PHE-pre-contracted isolated aortic segments	Induced relaxation in aortic rings unexposed (66% control) and exposed to As(III) (61% control) and Hs(II) (60% control)	[37]
Catalpol	HCC diet-fed New Zealand rabbits	↓ Atherosclerotic lesion (58% of HCC control); ↓ Aortic cholesterol content; Inhibits intima hyperplasia and macrophage infiltration; ↓ TC, TG and LDL levels and ↑ HDL levels in serum; ↓ MDA, oxLDL and LOX-1 plasma levels; ↑ SOD and GPx activity	[38]
1,8-Cineole/Eucalyptol	Isolated rat left ventricle papillary muscles	↓ Isometric contractions, time to peak and relaxation time; ↑ Relative potentiation; ↓ Tetanic force	[39]
	Isolated aortic rings	Induced endothelium-dependent relaxation	
	Pentobarbital-anesthetized and normotensive rats	↓ MAP and HR	[40]
	Conscious and normotensive rats		
	Rat isolated thoracic aorta preparations	↓ KCl-induced contractions	

(Table 2) contd…

Terpene	Study Model	Cardiovascular Effect/Mechanism of Action	References
Citral	Pre-contracted isolated aortic rings	↓ PHE-induced contraction in endothelium-intact (IC_{50} = 1.42 mM) and endothelium-denuded (IC_{50} = 1.33 mM) aortic rings; ↓ KCl-induced contractions in endothelium-denuded aortic rings; ↓ Ca^{2+}-induced contractions in endothelium-denuded aortic rings	[41]
(±)-Citronellol	Non-anesthetized normotensive rats	Induced transitory hypotension associated with tachycardia	[42, 43]
	Endothelium-intact rat mesenteric artery rings	Induced vasorelaxation in PHE- and KCl-pre-contracted rings	[43]
	Endothelium-denuded rat mesenteric artery rings	Induced vasorelaxation in PHE- and KCl-pre-contracted rings; Inhibited $CaCl_2$-induced contractions; Reduced PHE- and Caf-induced contractions in Ca^{2+}-free medium	
Geniposide	HCD-fed $ApoE^{-/-}$ mice	↓ TC, TG and LDL; ↑ HDL; ↓ Atherosclerotic lesion area; ↑ TGF-1β and IL-10 serum levels; ↑ FoxP3 protein and mRNA expression	[44]
Geniposidic acid	Atherosclerosis rabbit model	↓ Atherosclerotic plaque area; ↓ Intima/media thickness ratio and number of foam cells	[45]
	Primary cultured endotelial cells	↑ Cell proliferation	
Geraniol	NIH *nu/nu* female mice	↓ Serum cholesterol and TG; ↓ Fatty acid synthesis at 50 and 75 mmol G/Kg chow; ↓ Nonsaponifiable-lipid synthesis; ↑ HMGCR mRNA expression; ↓ HMGCR protein levels and specific activity; ↓ ACACA mRNA levels; ↑ VLDL-receptor mRNA levels	[46]
	Hyperlipidaemic hamsters	↓ Plasma, liver, heart and aorta lipids (TC, TG, FFA, PL) levels; ↓ Atherogenic index; ↑ HDL-C and ↓ LDL-C and VLDL-C levels; ↓ CRP activity; ↓ HMG-CoA reductase activity; ↑ LPL and LCAT activities; Alleviates cardiac hypertrophy	[47]
	Isolated guinea pig left atria	Induced a negative inotropic effect; ↓ Ca^{2+} influx; Impaired BAY K8644-induced increase in atrial force	[48]
	Isolated mice ventricular cardiomyocytes	↑ APD and ↓ Maximal dp/dt	
	Isolated guinea pig heart	↓ LVP and PVE; ↑ PRi	
	Ouabain-induced arrhythmias	↓ Tonotropic effect; Delays arrhythmia onset	
(±)-Linalool	Non-anesthetized normotensive rats	Induced transitory hypotension associated with tachycardia	[42]
	Normotensive conscious rats	Induced hypotension and tachycardia	[49]
	Goldblatt hypertensive conscious rats	↓ MAP without affecting HR	
	Isolated mesenteric artery rings	Induced relaxation in PHE-pre-contracted endothelium-intact and endothelium-denuded rings; Induced relaxation in KCl-pre-contracted endothelium-denuded rings; ↓ Contractions induced by $CaCl_2$ in endothelium-denuded rings; Inhibited transient contractions induced by PHE and Caf in endothelium-intact rings in Ca^{2+}-free medium	
(-)-Linalool	Human (inhalation)	↓ SBP, DBP and HR	[50]
(+)-Linalool		↑ SBP, DBP and HR	
	PHE-pre-contracted isolated aortic segments	Induced relaxation in aortic rings unexposed (71% control) and exposed to As(III) (64% control) and Hs(II) (63% control)	[37]

(Table 2) contd…

Terpene	Study Model	Cardiovascular Effect/Mechanism of Action	References
Menthol	Rat proximal tail artery, thoracic aorta and mesenteric artery	↓ PHE- and KCl-induced contraction	[51]
	Isolated rat aortic, mesenteric and coronary artery rings	↓ KCl-induced contractions (E_{max} = 93.72%, 96.52% and 98.48%, respectively) and PHE-induced contractions (E_{max} = 86.39% and 97.59% in aortic and mesenteric rings); ↓ Ca^{2+}-induced contraction in Ca^{2+}-free medium with high K^+ and Ca^{2+} influx	[52]
Picroside II	H/R-induced H9c2 cardiomyocyte apoptosis	↑ Cell viability; ↓ CK and LDH levels; ↓ % Apoptotic cells; ↓ ROS levels; ↓ Caspase-3 mRNA levels and activity; ↓ mPTP opening; ↓ MMP depolarization; ↓ cytC release	[53]
(+)-α-Pinene and (-)-β-Pinene	Non-anesthetized normotensive rats	Induced transitory hypotension associated with tachycardia	[42]
Piperitone oxide	Anesthetized normotensive rats	↓ MAP and HR	[54]
	Non-anesthetized normotensive rats	Induced hypotension and bradycardia	[55]
	Isolated rat atria preparations	Negative inotropic and chronotropic effect on left and right atria, respectively	
	Isolated aortic rings	↓ PHE-induced contractions in a endothelium-dependent manner	
		Inhibited PHE and KCl contractile effects; ↓ $CaCl_2$-induced contractions	[56]
Safranal	ISO-induced myocardial infarction	↓ CK-MB and LDH activity; ↓ MDA levels in heart; Attenuated myocardial injury	[57]
Taxilluside C/D	KCl-induced Ca^{2+} intracellular increase	↓ F_{max}/F_0 of KCl (1.7/1.8 *vs.* 4.6 fold increase)	[58]
Terpinen-4-ol	DOCA-salt hypertensive rats	↓ MAP	[59]
	Isolated rat aortic rings	Induced relaxation in high K^+ and PHE-pre-contracted endothelium-intact rings; ↓ Ba^{2+}-, PHE- and phorbol 12,13-dibutyrate-induced contractions in Ca^{2+}-free medium; ↓ BAYK-8644-induced contractions	[60]
α-Terpineol	Conscious, normotensive rats	Induced hypotension followed by tachycardia	[61]
	PHE-contracted mesenteric artery rings	Induced a endothelium-dependent relaxation	
	Rabbit aortic endothelial cell line	↑ NO levels	
	Rat mesenteric vascular bed preparations	Induced relaxation of KCl-induced contractions	[62]
Thujone	Alloxan-induced diabetes	↓ TC; ↑ TG	[25]
Thymol	Isolated rat aortic rings	Induced relaxation in PHE- and KCl-pre-contracted rings; Inhibited the response to PHE and KCl; ↓ $CaCl_2$-induced contractions	[29]
	Isolated canine and human ventricular cardiomyocytes	Supressed cardiac Ca^{2+} and K^+ channels	[63]
	Guinea pig and canine heart preparations	Negative inotropic effect; Induced SR Ca^{2+} release and inhibited Ca^{2+} pump activity	[64]
	HFD-induced T2DM in C57BL/6J mice	↓ HbA1c, BG, insulin, TG, TC, FFA, LDL-c, leptin; ↑ HDL-c, adiponectin	[65]

(Table 2) contd…

Terpene	Study Model	Cardiovascular Effect/Mechanism of Action	References
	Isolated canine and human ventricular cardiomyocytes	Supressed cardiac Ca^{2+} channels	[32]
SESQUITERPENES			
Artemisinin	Myocardial infarction model	↑ FS, EF; ↓ LVEDP, LVESD and LVEDD; Attenuated MI-induced myocyte hypertrophy; ↓ Perivascular and interstitial fibrosis in the non-infarcted area	[66]
		↓ TNF-α plasma levels; ↓ MI-induced ventricular arrhythmia; ↑ resistance to ventricular fibrillation; ↑ Cx43 mRNA and protein expression; ↓ MI-induced Cx43 disarray	[67]
	AngII-induced cardiac hypertrophy in isolated cardiomyocytes	↓ Leucine incorporation, cardiomyocyte area and ANP and BNP protein expression	[68]
	TAC-induced cardiac hypertrophy	↓ ANP and BNP mRNA and protein expression; ↓ LVEDD (6.8 *vs.* 7.9 mm), LVESD (3.6 *vs.* 4.6 mm), IVSd (1.90 *vs.* 2.25 mm), LVPWd (1.92 *vs.* 2.26 mm) and FS (50.1 *vs.* 40.8%); ↓ NF-κB activity and IL-6, TNF-α and MCP-1 levels	
Artesunate	WD-fed New Zealand rabbits	↓ TC, TG and LDL plasma levels; Prevented neointimal hyperplasia in aorta root; ↑ KLF-2 and ↓ VCAM-1 protein levels	[69]
(-)-α-Bisabolol	Non-anesthetized normotensive rats	Transitory hypotension associated with bradycardia	[42]
	Isolated rat aortic and mesenteric rings	↓ High K^+- and PHE-induced contractions on endothelium-intact and endothelium-denuded aortic rings and endothelium-intact mesenteric rings	[70]
	Isolated rat aortic rings	↓ KCl- and PHE-induced contractions; ↓ $CaCl_2$-induced contractions in KCl-stimulated rings under Ca^{2+}-free medium	[71]
	Fluo-4 AM-loaded isolated rat mesenteric rings	↓ Tension and Ca^{2+} cytosolic levels in response to K^+	
β-Caryophyllene	STZ-induced T2DM model	↓ BG; ↑ Insulin, GSH, SOD, CAT; GR, GPx, GST, Vit. E, Vit. C, Ceruplasmin	[26]
Costunolide	STZ-induced T2DM model	↓ BG, TC, HbA1c, TG; LDL-c; ↑ Plasma insulin, glycogen, HDL-c, protein, AST, ALT, LDH, ALP, ACP	[72]
Farnesol	Oral administration in rats	↓ Infarct size at 1 mg after I/R	[73]
	Isolated cardiomyocytes	↓ Cell death induced by simulated I/R	
Huperzine A	Acute myocardial infarction	↓ Infarct area; ↓ Cardiac markers levels; ↑ MDA, SOD, GPx and GSH activities; ↓ Caspase-3 activity; ↓ NF-kB, TNF-α and IL-1β levels; ↓ Bax and caspase- 3 levels and ↑ Bcl-2 levels	[74]
Kanshone E	Isolated neonatal rat cardiomyocytes	↓ Cell death induced by H_2O_2	[75]
Narchinol A/B	Isolated neonatal rat cardiomyocytes	↓ Cell death induced by H_2O_2	[75]
Nardosinanone F/I and Nardosinonediol	Isolated neonatal rat cardiomyocytes	↓ Cell death induced by H_2O_2	[75]
Nardosinone	AngII-induced H9c2 cardiomyocyte hypertrophy	↓ Cell area; ↓ ANP, BNP and β-MHC mRNA expression both dose- and time-dependant manner; ↓ PI3K, Akt, mTOR. p70S6K and MEK/ERK phosphorylation	[76]

(Table 2) contd…

Terpene	Study Model	Cardiovascular Effect/Mechanism of Action	References
Nerolidol-3-O-α-L-rham(1-4)-α-L-rham(1-2)-[α-L-rham(1-6)]-β-D-glc	Alloxan-induced T1DM model	↓ BG	[77]
(+)-Nootkatone	*In vitro* platelet aggregation *Ex vivo* platelet aggregation *In vivo* bleeding time	↓ Thrombin- and collagen-induced platelet aggregation both *in vitro* and *ex vivo* ↑ Bleeding times	[78]
iso-S-Petasin	Isolated ventricular myocytes	↓ PS in a time-dependent (38.6% after 5 min) and dose-dependent manner (51% at 100 μM); ↓ + dL/dt and - dL/dt; ↓ CICR in a dose-dependent manner (31.0% at 100 μM)	[79]
Zerumbone	Isolated rat aortic rings	↓ Both high K^+- and low K^+-induced contraction; ↓ Ca^{2+}-induced contraction; ↓ (S)-(-)-Bay K 8644-induced tone stimulation; ↓ PHE-induced contractions in endothelium-intact and endothelium-denuded rings; Antagonised the PHE-induced extracellular Ca^{2+} influx	[80]
DITERPENES			
7-*oxo*-Abieta-9,12,14-triene	Anesthetized rats	↓ Blood pressure to values similar to that of regitine and propranolol	[81]
ent-3-Acetoxy-labda-8(17),13-dien-15-oic acid	Isolated aortic rings	↓ KCl-induced contractions in both endothelium-intact and endothelium-denuded rings; ↓PHE- and serotonin-induced contractions in both endothelium-intact and endothelium-denuded rings; ↓ $CaCl_2$-induced contractions in endothelium-denuded rings in Ca^{2+}-free medium containing either PHE or KCl; Vasorelaxant effect on PHE- and KCl-precontracted rings; ↑ Nitrite production and cGMP levels in endothelium-intact rings; ↑ NO levels in endothelial cells	[82]
	Non-anesthetized normotensive rats	↓ MAP	
Aconine	Isolated bullfrog heart	↑ Heart amplitude (21% increase)	[83]
Aethiopinone	Anesthetized rats	↓ Blood pressure to values similar to that of regitine and propranolol	[84]
Andrographolide	*Porphyromonas gingivalis*-induced atherosclerosis in rabbits	↓ TC, TG, LDL and ↑ HDL levels in serum; ↓ CRP levels in serum; ↓ IL-1β and IL-6 activity; ↓ Thickening of intima layer and % of foam cells; ↑ α-Smooth muscle actin protein expression; ↓ CD36 expression	[85]
		↓ TC, LDL, TAG and ↑ HDL levels in serum; ↓ MDA and ↑ GSH levels; ↑SOD, CAT and GPx activity; ↓ MCP1 and nitrotyrosine levels in aorta homogenate; ↓ Atherosclerotic injury	[86]
	Alloxan-induced T1DM model	↓ BG; ↑ Insulin	[87]
	Langendorff-perfused isolated rat heart model	↓ Coronary perfusion pressure	[88]
ent-15β-Angeloyloxy-9α-OH-kaur-16-en-19-oic acid	PHE-induced contractility in isolated rat aortic rings	↓ PHE-induced contractions in a concentration- and time-dependent manner (36.8%, inhibition at 10^{-4} M after 30 min)	[89]
Beiwutinine	Isolated bullfrog heart	↑ Heart amplitude (71.5% increase)	[90]
Bilobalide	*In vitro* administration in isolated rat heart	↑ Heart amplitude (71.5% increase)	[83]

(Table 2) contd…

Terpene	Study Model	Cardiovascular Effect/Mechanism of Action	References
Cryptotanshinone	Hypoxia-induced H9c2 cardiomyocyte injury	↓ HIF-1α expression (1.1 *vs.* 1.7 fold increase); ↓ Cell death and caspase-3 activity; ↓ Mitochondrial membrane hyperpolarization; Inhibited cytC translocation; ↑ Bcl-2 and Bcl-xl expression; ↓ Bak and Bax expressions	[91]
N-Deethylaconine and N-Deethylneoline	Isolated bullfrog heart	↑ Heart amplitude (28.0% increase and 21% increase, respectively)	[83, 90]
Dehydroabietic acid	KK-Ay mice	↓ Adipose tissue, BG and insulin, TG, MCP-1, TNF-α protein and mRNA levels; ↑ Adiponectin protein and mRNA levels	[92]
trans-Dehydrocrotonin	Anesthetized normotensive rats	Induced hypotension associated with bradycardia	[93]
	Isolated rat atria	Negative chronotropic effect (IC_{50} = 69.3 μg/mL)	
	Isolated rat aortic rings	↓ PHE-induced contractions in endothelium-intact and endothelium-denuded rings	
	STZ-induced T2DM model and EtOH-induced hypertriglyceridemia	↓ BG and TG	[94]
Dehydroisohispanolone	Isolated rat heart	↓ LDH release after I/R; ↓ Apoptotic cells; ↑ pAKT, pAMPK, pPDK1 and antiapototic proteins levels; ↓ Caspase-3 activity; ↑ HIF-1α levels and activity; ↓ κB binding activity	[95]
	In vivo myocardial infarction model	↓ Caspase-3 levels and activity; ↓ Apoptosis in heart; ↑ pAKT, pAMPK, pPDK1 and antiapoptotic proteins levels; ↓ Ventricular dilatation; Preserved EF and FS; ↑ Contraction of the left ventricular anterior wall; ↓ Infarct area; Prevent myocardial remodelling	
Dehydroisohispanolone and 8,9-Dehydrohispanolone 15,16-lactol	Isolated rat cardiomyocytes	↑ pAKT and pAMPK levels after A/R; ↓ Cell death after A/R	[95,96]
	H9c2 cells	↓ LDH release; ↓ Caspase-3 levels and activity; ↑ pAKT and pAMPK levels; ↑ Bcl-2 protein family expression	
6,7-Dehydroroyleanone	Anesthetized rats	↓ Blood pressure to values similar to that of regitine and propranolol	[84]
14-Deoxyandrographolide	Langendorff-perfused isolated rat heart model	↓ Coronary perfusion pressure	[88]
	Isolated rat aortic rings	↓ PHE-induced contractions in endothelium-intact (EC_{50} = 32.9 μM) and endothelium-denuded (EC_{50} = 44.6 μM) aortic rings; ↓ KCl-induced contractions in endothelium-intact (EC_{50} = 12.3 μM) and endothelium-denuded (EC_{50} = 18.5 μM); ↓ Ca^{2+}-, Caf- and NA-induced contractions in Ca^{2+}-free medium	[97]
14-Deoxy-11,12-didehydroandrographolide	Langendorff-perfused isolated rat heart model	↓ Coronary perfusion pressure	[88]
	Anesthetised rat	↓ MAP (37.6% decrease) and HR (18.1% decrease)	[98]
	Isolated rat atria	Induced negative chronotropic effect; Attenuated ISO-induced positive chronotropic effect	
N-Dethylaconine	Isolated bullfrog heart	↑ Heart amplitude (28% increase)	[83]
Ferruginol	Anesthetized rats	↓ Blood pressure to values similar to that of regitine and propranolol	[81, 84, 99]
Ginkgolide A	*In vitro* administration in isolated rat heart	Ameliorated hemodynamic parameters	[100, 101]
	In vivo administration	Alleviated I/R-induced changes in hemodynamic parameters	[101]
Ginkgolide B	*In vitro* administration in isolated rat heart	Decreased I/R-induced changes in hemodynamic parameters	[100, 101]

(Table 2) contd…

Terpene	Study Model	Cardiovascular Effect/Mechanism of Action	References
	STZ-induced diabetic rats	↓ TG, TC, LDL, MDA content, eNOS activity and NOX2/NOX4 protein expression; ↑ HDL, body weight, NO production, SOD activity and GPX-1 expression; ↑ Ach-induced relaxation; ↓ PHE-induced contraction; ↑ H_2S in plasma and production; ↓ CBS and CBE expression	[102]
Ginkgolide C	*In vitro* administration in isolated rat heart	Decreased I/R-induced changes in hemodynamic parameters	[103]
Grandiflorenic acid	PHE-contracted isolated rat thoracic aorta rings	Induced relaxation in endothelium-intact (79.27%, $IC_{50} = 1.71*10^{-5}$ M) and endothelium-denuded (84.84%, $IC_{50} = 2.84*10^{-5}$ M) rings	[104]
Guan-Fu base A/G/Q/S	Whole-cell patch voltage-clamp technique	Blocked sodium currents (IC_{50} = 3.48 - 82.65 μM)	[105]
15α-Hydroxyneoline	Isolated bullfrog heart	↑ Heart amplitude (38.5% increase)	[90]
		↑ Heart amplitude (38.5% increase)	[83]
Hypaconine	Isolated bullfrog heart	↑ Heart amplitude (118% increase); Modulate dP/dt_{max} in a time-dependent manner (1025 mmHg/s at 40 min); ↓ LVEDP in a time-dependent manner (-20.1 mmHg)	[90]
		↑ Heart amplitude (118% increase)	[83]
Hetisine	Whole-cell patch voltage-clamp technique	Blocked sodium currents (IC_{50} = 75.72 μM)	[105]
Jhanidiol	PHE-contracted isolated rat thoracic aorta rings	Induced relaxation (28.15%) in endothelium-intact rings	[104]
Jhanidiol acetate		Induced relaxation in endothelium-intact (51.61%, $IC_{50} = 1.09*10^{-4}$ M) and endothelium-denuded (62.14%, $IC_{50} = 7.29*10^{-5}$ M) rings	
ent-Kaur-16-en-19-al	PHE-induced contractility in isolated rat aortic rings	↓ PHE-induced contractions in a concentration- and time-dependent manner (34.1% inhibition at 10^{-4} M after 30 min)	[89]
	PHE-contracted isolated rat thoracic aorta rings	Induced relaxation (26.36%) in endothelium-intact rings	[104]
ent-methyl-Kaur-16-en-19-oate	Isolated rat aortic rings	↓ KCl-induced contractions in endothelium intact (E_{max} = 0.95 g at 100 μM) and endothelium denuded (E_{max} = 1.12 g at 100 μM) rings; ↓ $CaCl_2$-induced contractions in endothelium denuded rings in Ca^{2+}-free medium (E_{max} = 0.77 g at 100 μM); ↓ PHE- (E_{max} = 53.68%) and KCl-pre-contracted aortic rings (70.55%)	[106]
ent-Kaur-16-en-19-oic acid (Kaurenoic acid)	Endothelium-intact rat aortic rings	↓ PHE- and KCl-induced contraction; Induced relaxation in PHE-pre-contracted aortic rings	[107]
	Isolated rat aortic rings	↓ KCl-induced contractions in endothelium intact (E_{max} = 0.44 g at 100 μM) and endothelium denuded (E_{max} = 0.47 g at 100 μM) rings; ↓ $CaCl_2$-induced contractions in endothelium denuded rings in Ca^{2+}-free medium (E_{max} = 0.38 g at 100 μM); ↓ PHE- (E_{max} = 73.09%) and KCl-(82.57%)-pre-contracted aortic rings	[106]
	Endothelium-denuded rat aortic rings	↓ PHE-, KCl- and $CaCl_2$-induced contraction; Induced relaxation in PHE-pre-contracted aortic rings	[107]
ent-Kaur-16β-ol	PHE-induced contractility in isolated rat aortic rings	↓ PHE-induced contractions in a concentration- and time-dependent manner (39.3% inhibition at 10^{-4} M after 30 min)	[89]
Labd-8(17)-en-15-oic acid	Anesthetized normotensive rats	Induced hypotension and tachycardia	[108]

(Table 2) contd…

Terpene	Study Model	Cardiovascular Effect/Mechanism of Action	References
	Non-anesthetized normotensive rats	Induced hypotension and tachycardia; ↓ Blood pressure and ↑ HR	[108]
	Spontaneously hypertensive rats	↓ MAP and ↑ HR	[109]
	Isolated rat aortic rings	↓ KCl-induced contractions in endothelium-intact (IC_{50} = 313.6 μg/mL) and endothelium-denuded (IC_{50} = 440.8 μg/mL) rings	[108]
8(17),12E,14-Labdatrien-18-oic acid	Non-anesthetized normotensive rats	Induced hypotension associated with tachycardia	[110]
	Isolated mesenteric artery rings	Induced relaxation on PHE-induced contractions and on KCl-pre-contracted rings; ↓ $CaCl_2$-induced contractions on Ca^{2+}-free medium	[110]
(+)-2-Oxomanoyl oxide	PHE-contracted isolated rat thoracic aorta rings	Induced relaxation (26.88%) in endothelium-intact rings	[104]
Marrubenol	Isolated rat aortic rings	↓ KCl-induced contraction in endothelium-intact rings (IC_{50} = 536.5 μg/mL)	[109]
Marrubiin	*In vitro, ex vivo* and *in vivo* anticoagulant and antiplatelet aggregation	Prolonged activated partial thromboplastin time; ↓Fibrin and D-dimer formation; Supressed calcium mobilization and TXB_2 synthesis	[111]
	Obese model	↓ TG, TC, LDL-c, AI; ↑ HDL-c	[112]
	Rat thoracic aortic rings without endothelium	Vasorelaxant on high potassium- and PHE-induced contractions	[113]
	Isolated rat aortic rings	↓KCl-induced contractions	[114]
Mesaconine	Isolated bullfrog heart	↑ Heart amplitude (82.0% increase); Modulated dP/dt_{max} in a time-dependent manner (1258 mmHg/s at 40 min); ↓ LVEDP in a time-dependent manner (-22.8 mmHg)	[90]
		↑ Heart amplitude (82% increase)	[83]
Phlomeoic acid	Rat thoracic aortic rings without endothelium	Vasorelaxant on high potassium- and PHE-induced contractions	[113]
ent-Pimara-8(14),15-dien-19-oic acid	Isolated rat aortic rings	↓ PHE-induced contraction in endothelium-intact (E_{max} = 0.44 *vs.* 1.68 g) and endothelium-denuded (E_{max} = 0.96 *vs.* 2.34 g) rings; ↓ $CaCl_2$-induced contraction in Ca^{2+}-free medium with PHE (E_{max} = 0.20 *vs.* 1.15 g) and KCl (E_{max} = 0.24 *vs.* 1.35 g); Relaxed PHE-pre-contracted endothelium-intact (92.64%) and endothelium-denuded (98.82%) rings; Relaxed KCl-pre-contracted endothelium-intact (97.44%) and endothelium-denuded (95.95%) rings	[115]
	Isolated carotid rings	↓ PHE-induced contraction (72.20% at 20 μg/mL) in a dose-dependent manner; ↓ KCl-induced contraction in a time-dependent manner	[116]
4,14- and 4,12-diOHsaprorthoquinone	Anesthetized rats	↓ Blood pressure to values similar to that of regitine and propranolol	[84]
Scoparic acid D	STZ-induced T2DM model	↓ BG; ↑ Insulin	[117]
Serofendic acid	Rat model of I/R	↓ Infarct area; Prevented $\Delta\Psi_m$ loss during ischemic period; Delayed $\Delta\Psi_m$ loss in reperfusion period	[118]
	H_2O_2-induced neonatal rat cardiac ventricular myocytes injury	↓ TUNEL-positive cells; ↑ Cell viability; Prevented $\Delta\Psi_m$ loss in a concentration-dependent manner; ↓ Intracellular ROS production; Attenuated mitochondrial Ca^{2+} overload	[119]

(Table 2) contd…

Terpene	Study Model	Cardiovascular Effect/Mechanism of Action	References
	H_2O_2-induced rat myocyte injury	Protected against $\Delta\Psi_m$ loss in a concentration-dependent manner	[120]
Sodium tanshinone IIA silate	OGD/R-induced cardiomyocyte injury	↑ Cell viability and MMP levels; ↓ Caspase-3 and -8 activity; ↓ Caspase-3 cleavage; ↑ Bcl-2 family expression; ↓ Bax family expression; ↓ NF-kB expression and translocation; ↓ NF-kB DNA-binding; ↓ IKKβ phosphorylation and Ikβ phosphorylation and ubiquitination; ↓ TNF-α activation	[121]
	HG-induced VSMC proliferation	↑AMPK phosphorylation; ↓ HG-induced proliferation by cell cycle arrest at G_0/G_1; ↓ HG-induced cyclin D1; ↑ p53 and p21 expression; ↓ Cell migration, MMP-2 expression and activity and NF-kB translocation	[122]
	Type 2 diabetes rat model	↑ AMPK phosphorylation	
Stevioside	Anesthetized dogs	↓ SBP, DBP and MAP at 30 - 120 min at 200 mg/kg after nasogastric administration; ↓ SBP (130.2 *vs.* 165.8 mmHg), DBP (65.1 *vs.* 108.0 mmHg) and MAP (86.6 *vs.* 127.3 mmHg) at 50 mg/kg after intravenously administration	[123]
	Spontaneously hypertensive rats	↓ MAP (167 *vs.* 186.2 mmHg)	[124]
	Isolated aortic rings	↓ Vasopressin-induced contraction in Ca^{2+}-containing medium in the absence (54.9%) or presence (60.3%) of methylene blue	
	Cytosolic Ca^{2+} in A7r5 cells	↓ Vasopressin-induced Ca^{2+} intake (112.4 *vs.* 346.8 nmol/L); ↓ PHE-induced Ca^{2+} intake (220.6 *vs.* 464.8 nmol/L) in Ca^{2+}-containing medium	[123]
Tanshinone IIA	Hypoxic ischemia-induced H9c2 cardiomyocytes injury	↑ Cell viability at 24h and 48h; ↑JAK2 and STAT3 phosphorylation	[125]
	I/R-induced myocardial injury in STZ-induced T2DM	↓ IS, LVESV, LVEDV, % Apoptotic cells, caspase-3 activity, pNF-kB, cytokines and leucocyte infiltration; ↑ +LV and -LV dP/dt, LVEF, pAkt	[126]
	Cardiomyopathy in STZ-induced T2DM model	↑ +LV and -LV dP/dt, LVEF; ↓ LVESV, LVEDV, % apoptotic cells, Caspase-3 levels, inflammatory cytokines; Protected cardiomyocytes from diabetes-induced damage	[127]
	MI in rats	↓ Arrhythmias and mortality; ↓ I_{K1} Current and Kir2.1 protein; ↓ SRF expression	[128]
	ISO-induced neonatal rat cardiomyocytes hypertrophy	↓ Cell surface area; ↓ ANP, BNP and β-MHC mRNA and protein levels; ↓ Intracellular Ca^{2+} intake; ↓ Cn and NFATc3 protein expression	[129]
	AngII-induced neonatal rat cardiomyocyte apoptosis	↓ Caspase-3 activation; ↓ % Apoptotic cells; ↓ Cleaved caspase-3 and cytosolic cytC levels; ↓ Intracellular ROS generation; ↑ Akt phosphorylation	[130]
	STZ-induced diabetic rat model	↓ BP; ↑ eNOS mRNA and protein expression; ↑ cGMP and NO concentrations; Attenuated Ach-induced vasorelaxation impairment	[131]
	Hypertension-induced left ventricular hypertrophy	↓ LV mass, LV mass/BW ratio, IVSd and LVPWd; ↑ Cardiomyocyte viability; ↓ Caspase-3 and Bax expression and Bax/Bcl-2 ratio; ↑ Bcl-2 expression; ↓ MDA levels and ↑ SOD activity; ↓ Interstitial collagen content; MMP-2 protein expression; ↑ TIMP2 expression; ↓ MMP-2/TIMP2 ratio; ↑ bFGF and c-Myc protein expression; ↓ TGF-1β, Foxh1 and p-Smad3 protein expression; ↑ Plasma apelin levels; ↓ APJ protein expression	[132]

(Table 2) contd…

Terpene	Study Model	Cardiovascular Effect/Mechanism of Action	References
	HG-treated human umbilical vein endothelial cells	↑ eNOS mRNA and protein expression; ↑ cGMP and NO concentrations; ↑ eNOS mRNA and protein half-life; ↑ eNOS dimer/monomer ratio; ↓Diabetes-induced O_2^- increase; ↑ Ser1177 phosphorylation; ↓ PP2A-A membrane translocation; ↓ PP2A-A/eNOS complex formation	[131]
	Hypoxia-induced H9c2 cardiomyocyte injury	↓ HIF-1α expression (1.1 *vs.* 1.7-fold increase); ↓ Cell death and caspase-3 activity; ↓ Mitochondrial membrane hyperpolarization; Inhibited cytC translocation; ↑ Bcl-2 and Bcl-xl expression; ↓ Bak and Bax expression	[91]
	H_2O_2-induced HUVEC injury	↑ Cell viability; ↓ LDH release; ↓ % Apoptotic cells; ↓ p53 Expression; ↓ Caspase-3 activity; ↑ ATF-3 mRNA expression	[133]
	I/R rat model	↓ % Apoptotic cells	[125]
ent-18-OH-Trachyloban-3-one	Isolated rat aortic rings	↓ KCl- and NA-induced contraction; Attenuated ACh- and SNAP-induced relaxation	[134]
ênt-Trachyloban-14,15-dione		↓ KCl- and NA-induced contraction, Inhibited cytosolic calcium increase in a dose-dependent manner; Attenuated ACh- and SNAP-induced relaxation	
Triptolide	STZ-induced diabetic rats	Ameliorated echocardiographic parameters; ↑pHi, ATP and pCr levels; ↑ p38 MAPK expression and protein levels; Attenuated myocardial filament degeneration	[135]
	STZ-induced T2DM model	↓ LVEDD, LVESD, total collagen, Col I, Col III, macrophages and T lymphocytes accumulation, cardiac inflammation; ↑ LVEF, FS	[136]
	ISO-induced cardiac remodelling model	Prevented cardiomegaly and improved cardiac function; ↓ Inflammatory cells, collagen fibres and collagen I expression; ↓ Collagen volume fraction and perivascular collagen area as well as HYP concentration; ↓ TGF-1β, Smad3 and p38 MAPK protein and mRNA levels	[137]
TRITERPENES			
Acanthopanax senticosides B	H_2O_2-induced isolated rat cardiomyocyte unjury	↓ Pseudopodia induced by H_2O_2 in a concentration-dependent manner; ↑ Cell viability; ↓ MDA levels; ↑ LDH, SOD, GPx and CAT activity	[138]
β-Amyrin palmitate	STZ-induced T2DM model	Ameliorated serum biochemical parameters	[139]
	Alloxan-induced T1DM model	Ameliorated serum biochemical parameters	[139]
Asiatic acid	TGF-1β-induced hypertrophic response in isolated neonatal rat ventricular cardiomyocytes	↓ ANP mRNA expression; ↓ Cardiomyocytes size; ↓p38 and ERK1/2 phosphorylation; ↓ NF-kB activity	[140]
	TAC-induced cardiac hypertrophy mice model	↓ HW/BW ratio; ↓ IVSD and LVPWD; ↑ LVEDD and %FS; ↓ Cross-sectional area; ↓ ANP mRNA expression in myocardium; ↓ TGF-1β mRNA and protein expression; ↓ p38 and ERK1/2 phosphorylation; ↓ NF-kB activity	
	Goto-Kakizaki T2DM model	↓ FBG, Fasting insulin, fibronectin mRNA; Prevented islet fibrosis	[141]
	STZ-induced diabetic rats	↑ Insulin and ↓ BG; ↓ TG, TC, VLDL, LDL, FFA, PL and atherogenic index; ↑ HDL	[142]

(Table 2) contd…

Terpene	Study Model	Cardiovascular Effect/Mechanism of Action	References
		Prevented body weight loss (18.6 g/mouse *vs.* 12.8 g/mouse); ↓ Feed (3.4 *vs.* 5.8 g/mouse/day) and water (4.0 *vs.* 6.1 ml/mouse/day) intake; ↓ Plasma glucose (17.1 *vs.* 28.2 mM), HbA1c (6.5 *vs.* 12.1%), ↑ Insulin levels (7.4 *vs.* 5.3 nM), ↓ CPK (113.5 *vs.* 202.2 IU/L) and LDH (90.3 *vs.* 166.4 IU/L) activities; ↓ vWF (267 *vs.* 411%), fibrinogen (3.91 *vs.* 5.08 g/L) levels and FVII (225 *vs.* 313 %) and PAI-1 (19.0 *vs.* 20.2 kU/L) activity; Retained AT-III (105 *vs.* 68%) and protein C (79 *vs.* 54%) activity; ↑ GSH levels (15.2 *vs.* 8.8 nmol/mg protein), ↓ ROS levels (0.63 *vs.* 1.25 RFU/mg protein); ↓ Glycative factors; ↓ MCP-1 (41.6 *vs.* 79.5 pg/mL), IL-6 (47.8 *vs.* 92.1 pg/mL) and TNF-α (52.6 *vs.* 108.6 pg/mL), NF-kB p65, p-p38 and p50 and pERK1/2 cardiac expression	[143]
	HG-induced H9c2 cardiomyoblast injury	↑ Cell viability and ↓ LDH release; ↓ ROS and GSSH and ↑ GSH, GPx, GR and CAT levels/activity; ↓ IL-6, TNF-α and MCP-1 levels; ↑ N^+/K^+-ATPase activity; ↓ Caspase-3 activity; ↓ NF-kB and MAPK expression/activity; ↑ Bcl2 protein expression and ↓ Bax protein expression	[144]
Asperosaponin VI	Hypoxia-induced cardiomyocyte apoptosis	↑ Cell viability (72.1% *vs.* 54.2%); ↓ LDH and CK levels; ↓ % Apoptotic cells (17.5% *vs.* 31.2%); ↑ Akt and CREB phosphorylation; ↑ Bcl2/Bax ratio (1.17 *vs.* 0.22); ↓ Caspase-3 activity	[145]
	MI-induced cardiac injury	↑ Survivability; ↓ CK-MB (708.31 *vs.* 1107.54 U/L), GOT (260.37 *vs.* 413.64 U/L), LDH (1912.24 *vs.* 3311.59 U/mL) and cTnT (2.87 *vs.* 4.61 ng/mL); ↑ CAT (9.80 *vs.* 6.53 U/mg protein), GPx (89.94 *vs.* 53.49 U/mg protein) and SOD (3.09 *vs.* 1.93 U/mg protein); ↓ MDA (10.46 *vs.* 12.98 nmol/mg protein); ↑ SDH (383.13 *vs.* 299.64 nmol/min/mg protein), ICDH (539.94 *vs.* 359.27 nmol/h/mg protein), MDH (222.31 *vs.* 130.55 nmol/min/mg protein), α-KCDH (99.25 *vs.* 64.82 nmol/h/mg protein), ATP (2.49 *vs.* 1.67 nmol/mg protein); ↓ Ca^{2+} (9.12 *vs.* 12.12 nmol/mg protein)	[146]
	H_2O_2-induced isolated rat cardiomyocytes injury	↑ Cell viability in a dose-dependent manner; ↓ ROS (38.13 *vs.* 71.16 FD), LDH (225.15 *vs.* 417.47 U/L) and MDA (1.98 *vs.* 2.66 nmol/mg protein); ↑ SOD (62.49 *vs.* 32.64 U/mg protein)	
Astragaloside IV	Isolated vascular smooth muscle cells	↓ CN activity and PHE-induced CN activation; ↓ LPS-induced MAPK8 phosphorylation	[147]
	Hypoxia-induced isolated rat cardiomyocyte damage	↑ Cell viability and ↓ MDA levels; ↑ SOD-1 activity, mRNA and protein expression; ↓ ROS levels	[148]
	HG-induced proliferation of VSMCs	↓ Cell proliferation; ↑ Apoptosis; ↓ MMP; ↑ α-SMA	[149]
	Human umbilical veins	↓ ACE activity	[147]
	ADR-stimulated injury in isolated neonatal mice cardiomyocytes	↓ LDH release; ↑ Bcl2/Bax ratio	[147]
	ISO-induced cardiac hypertrophy	↓ LVEDP; ↑ LVSP, $+d_p/d_tmax$ and $-d_p/d_tmax$; ↓ HW/BD and LVW/BW ratios; ↓ Heart thickness; ↓ ANP and BNP mRNA levels; ↑ ATP/AMP ratio; ↓ FFA concentration; ↑ ATP5D expression; ↓ Nuclear p65 expression; ↑ Cytosolic p65 expression and PGC-1α	[150]
		↓ HMI and LVMI; ↓ ANP mRNA expression; Inhibited ISO-induced morphological changes; ↓ TLR4 mRNA expression; ↑ IkBα and ↓ p65 protein expression; ↓ TNF-α and IL-6 expression	[151]
	Isoprenaline-induced ischemic injury	↑ LVSP, +dp/dt and -dp/dt in both left and right ventricule; ↓ LVEDP, RVSP and RVEDP; Ameliorated cardiac function; ↓ Ionic calcium and total calcium in heart tissue; ↑ Ca and Na pump activity; Improved myocardial ultrastructure	[152]

(Table 2) contd…

Terpene	Study Model	Cardiovascular Effect/Mechanism of Action	References
	ISO-treated isolated neonatal mice ventricular myocytes	↓ Cell surface area, ANP and BNP mRNA levels and protein content; ↑ ATP/AMP ratio; ↓ FFA concentration; ↑ ATP5D expression; ↓ Nuclear p65 expression; ↑ Cytosolic p65 expression and PGC-1α	[150]
	Primary neonatal rat cardiomyocytes	↑ Cell viability (50.4% at 50 μM); ↓ LDH release and apoptotic index; ↑ HIF-1α and iNOS protein levels; ↑ Bcl2 protein levels; ↓ Caspase-3 protein levels	[153]
	Langendorff-perfused rat heart	↑ HR, LVDP, CF and +dP/dt; ↓ Infarct area and apoptotic cardiomyocytes; ↓ LDH release ↑ iNOS mRNA levels; ↑ HIF-1α, iNOS and Bcl2 protein levels; ↓ Caspase-3 protein levels	
	STZ-induced diabetic rats	↓ FPG and HbAlc; ↑ NO and eNOS content; Attenuated morphological changes in abdominal aorta endothelium; ↓ Ox-LDL presence in serum; ↓ TNF-α and MCP-1 mRNA levels; ↓ TNF-α, MCP-1 and NF-kB p65 protein levels;	[154]
	I/R-induced myocardial damage	↓ Infarct area; Attenuated MBF loss; ↓ LVDP, LVEDP and -dp/dtmax and ↑ +dp/dtmax; ↑ cTnI in myocardial tissue and ↓ cTnI in serum; ↑ both ATP/AMP and ATP/ADP; ↓ % Apoptotic cells and Bax/Bcl2 ratio	[155]
		↓ Infarct area and apoptosis; ↓ Caspase-3 and Bax and ↑ Bcl2 protein expression; ↓ TLR4 mRNA and protein expression; ↓ p65 Nuclear expression; ↓ TNF-α and IL-1β serum levels	[156]
Betulinic acid	NA pre-contracted isolated rat aortic rings	Induced vasorelaxation (E_{max} = 79.01%) in a concentration-dependent manner (EC_{50} = 58.46 μM)	[157]
6β-OH-Betulinic acid	Spontaneously hypertensive rats	↓ MAP (17.2% reduction) and ↑ HR (41.2% increase)	[158]
	Platelet aggregation assay	↓ ADP- (61.6% aggregation), AA- (89.1% aggregation) and collagen- (32.5% aggregation) induced platelet aggregation	
6β,30-DiOH-Betulinic acid	Spontaneously hypertensive rats	↓ MAP (60.1% reduction) and ↑ HR (11% increase)	
	Platelet aggregation assay	↓ ADP- (22.9% aggregation), AA- (87.5% aggregation) and collagen- (18.5% aggregation) induced platelet aggregation	
6β,30-DiOH-Betulinic acid Glu ester	Platelet aggregation assay	↓ ADP- (90.6% aggregation), AA- (49.5% aggregation) and collagen- (13.6% aggregation) induced platelet aggregation	
Boswellic acid	HG-induced H9c2 cadiomyoblast injury	↑ Cell viability and ↓ LDH release; ↓ ROS and GSSH and ↑ GSH, GPx, GR and CAT levels/activity; ↓ IL-6, TNF-α and MCP-1 levels; ↑ N^+/K^+-ATPase activity; ↓ Caspase-3 activity; ↓ NF-kB and MAPK expression/activity; ↑ Bcl2 protein expression and ↓ Bax protein expression	[144]
11-*keto*-β-Boswellic acid	Myocardial I/R rat model	↓ Infarct area and LDH activity; ↑ GPx and MPO activity; ↓ TNF-α content; ↓ ICAM-1, 5-LOX, COX-2 and NF-kB mRNA expression; ↑Nrf2 and HO-1 mRNA expression; ↓ % Apoptotic cells and DNA fragmentation	[159]
Celastrol	Hypoxia-induced H9c2 cardiomyoblast ischemic injury	Activate PI3K/Akt and ERK1/2 pathways dependent on ROS signalling; Induces HSF1 protein activation; ↑ Cell viability	[160]
	MI animal model	↑ HO-1 expression; ↑ LVEF and LVES; ↓ Infarct area; ↓ αSMA protein expression; ↓ Fibrosis; ↓TGF-3β, collagen I and III expressions; Attenuated global heart damage; ↓ Macrophage infiltration	
	oxLDL-induced oxidative stress in RAW 264.7	↓ Foam cell formation; ↓ LOX-1 mRNA and protein expression; ↓ ROS generation; ↓ p47 Phosphorylation and MPO activity; ↑ GSH/GSSG ratio; ↓ NF-kB p65 expression, IkBα phosphorylation and degradation; ↓ iNOS expression; ↓ NO production	[161]

(Table 2) contd…

Terpene	Study Model	Cardiovascular Effect/Mechanism of Action	References
	HFD-induced atherosclerosis in ApoE$^{-/-}$ mice	↓ Atherosclerotic lesion; ↓ Superoxide levels; ↓ LOX-1 expression, plasma oxLDL, TNF-α and IL-6 levels and NF-kB activity	
Chikusetsu saponin IVa	STZ-NA-induced T2DM model	↓ BG, TG, FFA, LDL-c	[162]
		↓ FBG; ↑ Fasting insulin	[163]
Corosolic acid	KK-Ay mice	↓ BG and plasma insulin	[164]
	ApoE$^{-/-}$ mice	↓ Atherosclerotic lesion in aortic valve (11.36% *vs.* 17.52%), aortic arch (21.19% *vs.* 40.11%) and abdominal aorta (6.16% *vs.* 46.56%); ↑ BW gain (13.37g *vs.* 12.23g); ↓ TG (2.47 mM *vs.* 3.14 mM), glucose (4.86 mM *vs.* 6.79 mM) and MDA (20.39 mM *vs.* 27.28 mM); ↑ SOD levels (277.51 U/mL *vs.* 147.06 U/mL); ↓ MCP-1 protein levels in serum (1.21-fold) and aortic supernatant (1.30-fold); ↓ MCP-1 mRNA levels (4.61-fold) and CCR-2 mRNA levels (2.08-fold)	[165]
	LPS-induced THP-1 cells	↓ MCP-1 mRNA levels; ↓ p65 (1.61-fold), p50 (2.75-fold) and RelB (1.76-fold) activation; ↑ c-Rel (1.23-fold) and p52 (1.39-fold); ↓ Monocyte adhesiveness and migration	
Cycloart-23-*ene*-3β, 25-diol	STZ-NA-induced T2DM model	↓ Acute and chronic serum glucose; Normalized hematologic parameters	[166]
Cynarasaponin E methyl ester	H_2O_2-induced H9c2 cardiomyocyte injury	↑ Cell viability in a dose-dependent manner (89.34% at 200 μM)	[167]
20S,24R-epoxy-Dammarane-3β, 6α,12β,25-tetraol	ISO-induced myocardial injury	↓ CK and LDH activity and MDA levels; ↑ SOD and GPx activity, T-AOC levels; ↓ Myofibrillar degeneration	[168]
Dehydroeburicoic acid	STZ-induced T2DM model	↓ BG, TG, TC, leptin; ↑ Insulin, adiponectin	[169]
16β,22:16α,30-Diepoxydammar-24-ene-3β,20-diol and 16β,23:16α,30-Diepoxydammar-24-ene-3β,20-diol heterosides	H_2O_2-induced neonatal rat cardiomyocyte injury	↑ Cell viability in a dose-dependent manner	[170]
19α,23-Dihydroxyurs-12-en-28-oic acid esters	H_2O_2-induced H9c2 cardiomyocyte injury	↑ Cell viability in a dose-dependent manner (74.42 - 91.29% at 200 μM)	[167, 171]
3β,19α-diOHurs-12,20(21)-diene-28-oic acid	STZ-induced T2DM model	↓ BG, TG, TC, LDL-c, VLDL-c	[172]
Elatoside C	H/R-induced H9c2 cardiomyocyte injury	↑ Cell viability; ↓ Mitochondrial ROS; ↑ Mitochondrial membrane potential; ↓ GRP78, p-JNK, cleaved caspase-12 and CHOP expression levels; ↑ Bcl2/Bax ratio; ↑ pSTAT3/STAT3 ratio	[173]
Ginsenoside Rb1	MI/R-induced myocardial injury in STZ-induced diabetic rats	↑ HR, MAP and RPP; ↓ Infarct area (42.3% *vs.* 51.3%); ↓ LDH, CK-MB and caspase-3 activity;↓ % Apoptotic cells; ↑ pAKT	[174]
	HFD-induced obesity	↓ Body fat, diabetic symptoms; ↑ PI3K/Akt	[175]
	I/R-induced myocardial injury in STZ-induced T2DM model	↓ IS, LDH and CK levels, MDA levels, myocardial injury; ↑ SOD levels, NO production, eNOS expression	[176]
Ginsenoside Rb3	*In vitro* myocardial I/R-induced H9c2 cardiomyocyte injury	↓ % Apoptotic and dead cells; ↓ NF-kB activation and Ik-Bα phosphorylation; ↓ p65 Nuclear translocation; ↓ NF-kB binding activity; ↓ IL-6, MCP-1, MMP-2, MMP-9 and TNF-α mRNA levels; ↓ JNK phosphorylation	[177]

(Table 2) contd…

Terpene	Study Model	Cardiovascular Effect/Mechanism of Action	References
	Alloxan-induced diabetes model	↓ BG; ↑ Islets area	[178]
	ISO-induced MI	↓ LDH and CK activity; ↓ Granulocyte infiltration and myocardial disorganization; ↑ LVSP (105.3 *vs.* 83.5 mmHg); ↓ LVEDP (6.1 *vs.* 9.7 mmHg); ↑ + dp/dt (2734 *vs.* 2002 mmHg/s) and - dp/dt (2829 *vs.* 1919 mmHg/s); ↑ CAT and SOD activity; ↓ MDA levels	[179]
	I/R-induced myocardial injury	↓ Infarct size; ↓ CK-MB and LDH activity; ↓ Granulocyte infiltration and myocardial disorganization; ↓ MDA levels; ↑ SOD activity; ↓ Endothelin and AngII levels	[180]
Ginsenoside Rg1	Ischemic hind limb in STZ-induced T2DM model	↑ Foot perfusion, vascular density, VEGF expression, p-eNOS; ↓ % Apoptotic cells	[181]
	STZ-induced T2DM model	↓ FBG, TC, TG, cTn1, CK-MB, MDA, % Apoptotic cells, caspase-3 levels; ↑ CAT, GSH, SOD, Bcl-xL levels	[182]
Ginsenoside Rd	Myocardial I/R rat model	↓ LVSP and LVEDP; ↑ +dp/dtmax and -dp/dtmax; ↓ Infarct size and CK, LDH levels and caspase-3 activity and apoptotic index	[183]
	Simulated I/R in neonatal rat cardiomyocytes	↑ Cell viability; ↓ LDH leakage and apoptotic index; ↓ ROS production; ↑ MMP; ↓ CytC cytosolic translocation and caspase-3 and 9 activation; ↑ Bcl-2 protein expression; ↑ Akt and GSK-3β phosphorylation	
Glycyrrhetinic acid	Isolated and Langendorff perfused rat hearts	Induced negative ionotropic and lusitropic effects; ↑ HR; Caused vasodilatation (10^{-12} M to 10^{-7} M) and vasoconstriction (10^{-6} M and 10^{-5} M)	[184]
	STZ-induced T2DM model	↓ BG, TC, TG, LDL-c, VLDL-c, FFA, PL in serum; ↓ TC, TG, FFA, PL in heart; ↑ HLD-c	[185]
	STZ-induced T2DM model	↓ BG, HbA1c; ↑ Insulin, Hb	[186]
	Isolated rat heart mitochondria	At 5 μM: ↓ cytC and AIF release induced by Ca^{2+}; ↓ Ca^{2+} transport; ↑ GSH/GSSG ratio; ↑ %GSH; ↑ % Reduced thiol groups; ↓ MPT induced by Ca^{2+}	[187]
Glycyrrhizin	I/R-induced myocardial injury	↓ Myocardial fibre disruption and infarct area size; ↓ TpT, AST and LDH plasma levels: ↓ HGMB1, IL-6 and TNF-α serum concentrations; ↓ % Apoptotic cells, caspase-3 activity, Bax mitochondrial and cytC cytosol concentration; ↓ p-JNK/t-JNK ratio	[188]
	Isolated and Langendorff perfused rat hearts	Induced positive ionotropic and lusitropic effects; ↑ HR and CP	[184]
	I/R-induced myocardial injury	↓ Infarct area (13% *vs.* 27.5% of left ventricle area); ↓ MPO activity (36.3%)	[189]
Jujuboside A	H_2O_2-induced injury in neonatal rat cardiomyocytes	↑ Cell viability in a dose-dependent manner	[170]
methyl-3β-OH-Lanosta-9,24-dien-21-oate	HFD-induced hyperlipidaemia in rats	↓ TC and LDL while ↑ HDL levels in serum; ↓ Atherogenic index and coronary risk index	[190]
	STZ-induced T2DM model	↓ BG, MDA; ↑ SOD, CAT, antioxidant status	[191]
Limonin	p38 MAPK activation in HASMCs	↓ p38 MAPK activation (19%)	[192]
Maslinic acid	Vascular smooth muscle cells	↑ HO-1 protein and mRNA levels and activity; ↑ pAkt levels; ↑ Nrf2 expression; ↑ Cell viability in H_2O_2-induced injury	[193]

(Table 2) contd…

Terpene	Study Model	Cardiovascular Effect/Mechanism of Action	References
	NA-contracted rat aortic rings	In mixture with Salvin A induced relaxation (63.57%, EC_{50} = 1.999 mg/L)	[194]
	STZ-induced diabetic rats	Prevented body weight loss (19.2 g/mouse *vs.* 12.8 g/mouse); ↓ Feed (3.2 *vs.* 5.8 g/mouse/day) and water (3.7 *vs.* 6.1 ml/mouse/day) intake; ↓ plasma glucose (16.0 *vs.* 28.2 mM), HbA1c (7 *vs.* 12.1%), ↑ insulin levels (7.7 *vs.* 5.3 nM), ↓ CPK (109.6 *vs.* 202.2 IU/L) and LDH (96.8 *vs.* 166.4 IU/L) activities; ↓ vWF (198 *vs.* 411%), fibrinogen (4.04 *vs.* 5.08 g/L) levels and FVII (208 *vs.* 313 %) and PAI-1 (19.1 *vs.* 20.2 kU/L) activity; Retained AT-III (107 *vs.* 68%) and protein C (77 *vs.* 54%) activity; ↑ GSH levels (14.7 *vs.* 8.8 nmol/mg protein), ↓ ROS levels (0.59 *vs.* 1.25 RFU/mg protein); ↓ glycative factors; ↓ MCP-1 (38.3 *vs.* 79.5 pg/mL), IL-6 (45.2 *vs.* 92.1 pg/mL) and TNF-α (48.6 *vs.* 108.6 pg/mL), NF-kB p65, p-p38 and p50 and pERK1/2 cardiac expression	[143]
Morolic and Moronic acids	NA pre-contracted isolated rat aortic rings	Induced vasorelaxation (E_{max} = 73.75 and 92.01%%) in a concentration-dependent manner (EC_{50} = 94.19 and 16.11 μM)	[157]
	STZ-NA-induced diabetes model	↓ BG (39.18% and 29.20% decrease)	[195]
Nicotinic acid derivative of lupeol	Dyslipidemic hamsters	↓ TG, TC, glycerol; ↑ HDL-c	[196]
	STZ-induced T2DM model	↓ BG	[196]
Nomilin	p38 MAPK activation in HASMCs	↓ p38 MAPK activation (38%); ↓ TNF-α-induced p38 MAPK activation (31% at 6h)	[192]
Deacetyl nomilin and Defuran nomilin	p38 MAPK activation in HASMCs	↓ p38 MAPK activation (19% and 17%, respectively)	[192]
Notoginsenoside R1	LPS-stimulated H9c2 cardiomyocytes	↑ Cell viability; ↑ ER_{α} expression; ↓ Apoptotic cells and caspase-3 activity; ↓ NF-kB p65 phosphorylation and I-kBα degradation and nuclear translocation of NF-kB; ↓ IL-1β and IL-6 expression; ↓ TNF-α expression TNF-α-induced cell apoptosis and caspase-3 activation	[197]
	HFD diet-induced atherosclerosis in $ApoE^{-/-}$ mice	↓ Atherogenic lesion in aorta root; ↓ Lipid accumulation in lesion; ↓ Fibrosis in aorta root intima layer; ↑ SOD, GSH levels in serum; ↓ MDH; ↓ TC, TG, LDL and ox-LDL serum levels; ↑ HDL serum levels; ↓ IL-2, IL-6, TNF-α and IFN-γ levels; ↑ miRNA-21, miRNA-26a expression and ↓ miRNA-20 expression	[198]
Oleanolic acid	HG-induced H9c2 cadiomyoblast injury	↑ Cell viability and ↓ LDH release; ↓ ROS and GSSH and ↑ GSH, GPx, GR and CAT levels/activity; ↓ IL-6, TNF-α and MCP-1 levels; ↑ N^{+}/K^{+}-ATPase activity; ↓ Caspase-3 activity; ↓ NF-kB and MAPK expression/activity; ↑ Bcl2 protein expression and ↓ Bax protein expression	[144]
	HFD-induced obesity	↓ TG, TC, visceral fat, BG, ALT, AST, ALP; ↑Insulin	[199]
	STZ-NA-induced diabetes model	↓ BG (21.92% decrease)	[195]
	H9c2 cardiomyocyte under hyperglycemia	↓ Oxidative stress, % Apoptotic cells	[200]
	Isolated rat heart under hyperglycemia	↑ Cardiac function, SOD levels; ↓ IS, O22- levels, caspase-3 level and activity	[200]
	STZ-induced T2DM model	↑ IS, BG, cardiac function; ↓ HB, SBP, DBP	[200]
	Dexa-induced hypertension in rats	↓ SBP (126 *vs.* 149 mmHg); ↓ Lipid peroxidation; ↑ NOx plasma concentration	[201]

(Table 2) contd…

Terpene	Study Model	Cardiovascular Effect/Mechanism of Action	References
	Insulin-resistant hypertension model	↓ BG, TC, LDL and TG levels; ↑ HDL levels and GPx and SOD activity; Prevented hypertension and induced bradycardia	[202]
Platycodin D	oxLDL-treated HUVEC	↓ MDA levels; ↑ NO levels; ↓ VCAM-1 and ICAM-1 mRNA expression; ↓ Monocyte adhesion	[203]
20(S)-Protopanaxatriol	ISO-induced myocardial injury	↓ CK and LDH activity and MDA levels; ↑ SOD and GPx activity, T-AOC levels; ↓ Myofibrillar degeneration	[168]
Rubiarbonol C	HepG2 cell culture	↓ TG levels (45.0% inhibition at 100 μM)	[204]
Rubiarbonone C	HepG2 cell culture	↓ TG levels (48.1% inhibition at 100 μM); ↑ Glucose uptake	[204]
3,4-*seco*-Olean-18-ene-3,2,8-dioic acid	NA pre-contracted isolated rat aortic rings	Induced vasorelaxation (E_{max} = 66.17%) in a concentration-dependent manner (EC_{50} = 141.23 μM)	[157]
β-Sitosterol glycoside	NA-contracted rat aortic rings	Induced relaxation (52.43%, EC_{50} = 1.178 mg/L)	[194]
Triterpenic acid	STZ-induced T2DM model	↓ BG, FMN, MDA, NO, NOS activity; ↑ SOD	[205]
Ursolic acid	Insulin-resistant hypertension model	↓ BG, TC, LDL and TG levels; ↑ HDL levels and GPx and SOD activity; Prevented hypertension and induced bradycardia	[202]
	STZ-NA-induced diabetes model	↓ BG (38.01% decrease)	[195]
	STZ-induced T2DM in LDL-R-/-C57BL/6J mice	↑ Survivability; ↓ BG, TC, TG, % Atherosclerotic lesion, macrophage infiltration	[206]
	NA pre-contracted isolated rat aortic rings	Induced vasorelaxation (E_{max} = 72.59%) in a concentration-dependent manner (EC_{50} = 11.7 μM)	[157]
	WD-fed New Zealand rabbits	↓ TC, TG and LDL plasma levels; Prevented neointimal hyperplasia in aorta root; ↑ KLF-2 and ↓ VCAM-1 protein levels	[69]
	STZ-induced diabetic rats	↓ Glucose, fructosamine and glycated haemoglobin levels; ↓ AGEs levels; ↓ TNF-α and MDA serum levels; ↓ Aortic injury; ↓ RAGE protein expression; ↓ p22phox Expression↓ NF-kB activation and nucleus translocation	[207]
	Heat exposure-induced mouse cardiomyocytes *in vivo* damage	↑ +dp/dt and -dp/dt; Attenuated apoptosis; ↓ Troponin I plasma levels; ↓ cytC, cleaved caspase-3 and -9; ↓ PERK and eIF2α phosphorylation and CHOP activation; ↓ Puma expression and ↑ Mcl1 expression; ↑ GSH levels and GSH/GSSH ratio; ↓ GSSH levels; ↓ MDA and LDH plasma levels	[208]
Ursolic acid and derivatives	STZ-induced T2DM model	↓ FBG, TC, TG, LDL-c; ↑ Insulin, albumin, total protein, HDL-c	[209]
Zizyphus saponin II	H_2O_2-induced neonatal rat cardiomyocyte injury	↑ Cell viability in a dose-dependent manner	[170]

5-LOX - 5-lipoxygenase; A/R - Anoxia/reperfusion; AA - Arachidonic acid; ACACA - acetyl-CoA carboxylase; ACE- Angiotensin converting enzyme; Ach - Acetylcholine; ACP - Acid phosphatase; DP - Adenosine 5'-diphosphate; ADR - Adriamycin; AGE - Advanced glycation endproducts; AI - Atherogenic índex; AIF - Apoptosis inducing factor; AKT - Protein kinase B; ALP - Alkaline phosphatase; ALT - Alanine aminotransferase; AMPK - 5' adenosine monophosphate-activated protein kinase; AngII - Angiotensin II; ANP - Atrial natriuretic peptide; APD - Action potential duration; Api - Apiofuranosyl; APJ - Apelin receptor; Arab - Arabinopyranosyl; As(III) - Arsenic (III); AST - Aspartate aminotransferase; ATF-3 - Activating transcription factor; AT-III - Antithrombin-III; ATP - Adenosine triphosphate; ATP5D - Mitochondrial ATP synthase subunit delta; Bax - bcl-2-like protein 4; Bcl-2 - B-cell lymphoma 2 protein; Bcl-xL - B-cell lymphoma-extra large protein; bFGF - Basic fibroblast growth factor; BG - Blood glucose; BNP - Brain natriuretic peptide; BP - Blood pressure; BW - Body weight; $CaCl_2$ - Calcium chloride; Caf - Caffeine; CAT - Catalase; CBS - cystathionine β synthetase; CCR2 - C-C chemokine receptor type 2; cGMP - Cyclic guanosine monophosphate; CHOP - CCAAT/enhancer binding protein homologous protein; CICR - Ca2+-induced Ca2+ release; CK or CK-MB - Creatine Kinase; Cn - Calcineurin; Col I - Collagen I; Col III - Collagen III; COX-2 - cyclooxygenase 2; CPK - Creatine phosphokinase; CRP - C-reactive

protein; CSE - cystathionine γ lyase; cTnI - cardiac troponin I; Cx43 - Connexin 43; CytC - cytochrome c; DBP - Diastolic blood pressure; DOCA - Deoxycorticosterone-acetate; EF - Ejection fraction; eIF2α - Initiation factor 2-alpha; eNOS - Endothelial nitric oxide synthase; ERK1/2 - Extracellular-signal-regulated kinase 1/2; FBG - Fasting blood glucose; FFA - Free fat acid; FMN - frutoseamine; Foxh1 - Forkhead box H1; FoxP3 - Forkhead/winged helix transcription factor 3; FS - Fraction shortening; FVII - Coagulation factor VII; Glu - Glucopyranosyl; Gluc - Glucuronopyranosyl; GPx - Glutathione peroxidase; GR - Glutathione reductase; GSH - Glutathione oxidase; GSSH - Reduced glutathione; H2S - Hydrogen sulphide; HB - heart beat; Hb - Hemoglobin; HbAlc - Hemoglobin A1c; HCC - High cholesterol chow; HDL - High-density lipoprotein; HDL-c - High-density lipoprotein cholesterol; HFD - High fat diet; HG - High glucose; HGMB-1 - High-mobility group box 1; HIF-1α - Hypoxia-induced factor 1α; HMGCR - 3-hydroxy-3-methylglutarylcoenzyme-A reductase; HMI - Heart mass index; HO-1 - Hemeoxigenase-1; HR - Heart rate; Hs(II) - Mercury (II); HW - Heart weight; HYP - Hydroxyproline; I/R - Ischemia/reperfusion; ICAM-1 - Intercellular Adhesion Molecule 1; ICDH - Isocitrate dehydrogenase; IFN-γ - Interferon gamma; IKKβ - Inhibitor of nuclear factor kappa-B kinase subunit beta; IL-1β/6 - Interleukin 1β/6; iNOS - Inducible nitric oxide synthase; IS - infarct size; ISO - Isoproterenol; IVSd - Interventricular septal thickness at end diastole; JNK - Janus kinase; KCl - Potassium chloride; KLP-2 Krüppel-like Factor 2; LCAT - Plasma lecithin cholesterol acyl transferase; LDH - Lactate dehydrogenase; LDL - Low-density lipoprotein; LDL-c - Low-density lipoprotein cholesterol; L-NAME - L-NG-Nitroarginine methyl ester; L-NAME - Nω-Nitro-L-arginine methyl ester hydrochloride; LOX-1 - Lectin-like oxidized low density lipoprotein receptor-1; LPL - Plasma lipoprotein lipase; LPS - lipopolysaccharide; LV - Left ventricular; LVEDD - Left ventricular end diastolic diameter; LVEDP - Left ventricular end diastolic pressure; LVESD - Left ventricular end systolic pressure; LVMI - Left ventricular mass index; LVP - Left ventricular parameters; LVPWd - Left ventricular posterior wall thickness at end diastole; LVSP - Left ventricular systolic pressure; MAP - Mean arterial blood pressure; MAPK - Mitogen activating protein kinase; MBF - Myocardial blood flow; MCP-1 - Monocyte chemoattractant protein-1; MDA - Malondialdehyde; MDH - Malate dehydrogenase; MEK - Mitogen-activated protein kinase; MI - Myocardial injury; MMP - Mitochondrial membrane potential; MMP-2/9 - Matrix metalloproteinase 2/9; MPO - Myeloperoxidase; MPT - Mitochondrial permeability transition; mPTP - Mitochondrial permeability transition pore; mTOR - Mammalian target of rapamycin; NA - Noradrenaline; NAFTc - Calcineurin/nuclear factor of activated T cells; NF-κB - Nuclear factor kappa B; NO - Nitric oxide; NOS - nitric oxide synthase; NOX2/4 - NADPH oxidase 2/4; Nrf2 - Nuclear factor (erythroid-derived 2)-like 2; OGD/R - Oxygen-glucose deprivation/recovery; OH - hydroxyl; Ox-LDL - oxidized low-density lipoprotein; PAI-1 - Plasminogen activator inhibitor-1; pAKT - phosphorylated AKT; pAMPK - phosphorylated AMPK; Pb(II) - plumb (II); pCr - Phosphocreatine; PDGF - Platelet-derived growth factor; p-eNOS - phosphorylated eNOS; PERK - PKR-like eukaryotic initiation factor 2α kinase; PGC-1α - Peroxisome proliferator-activated receptor-γ coactivator 1α; PHE - Phenylephrine; pHi - Intracellular pH; PI3K - Phosphoinositide 3-kinase; PKD-1 - 3-phosphoinositide dependent protein kinase-1; PL - Phospholipids; pPDK-1 - phosphorylated PKD-1; p-p38 - phospho p38 mitogen-activated protein kinase; PS - Peak shortening; RAGE - Membrane-anchored AGE receptor; Rham - Rhamnopyranosyl; ROS - Reactive oxygen species; RPP - Rate pressure product; RV - Right Ventricule; RVEDP - Right ventricular end diastolic pressure; RVSP - Right ventricular systolic pressure; SBP - Systolic blood pressure; SDH - Succinate dehydrogenase; SHR - spontaneously hypertensive rats; Smad3 - Drosophila mothers against decapentaplegic protein 3; SOD - Superoxide dismutase; SR - Sarcoplasmic reticulum; SRF - Serum response factor; STAT3 - Signal transducer and activator of transcription 3; STZ - Streptozotocin; T1DM - type 1 diabetes mellitus; T2DM - type 2 diabetes mellitus; TAC - Transaortic constriction; TAG - Triacylglycerol; TC - Total cholesterol; TG - Total triglyceride; TGF-1β - Transforming growth factor beta 1; TIMP2 - Tissue inhibitor of matrix metalloproteinases type 2; TLR4 - Toll-like receptor 4; TNF-α - Tumor necrosis factor alpha; TpT - Plasma troponin-T; TXB2 - Thromboxane B2; VCAM-1 - Vascular cell adhesion molecule 1; VEGF - Vascular endothelial growth factor; VLDL - Very low density lipoprotein; VSMC - Vascular smooth muscle cells; vWF - von Willebrand factor; WD - Western Diet; Xyl - Xylospyranosyl; α-KCDH - α-ketoglutarate dehydrogenase; α-SMA - alpha-smooth muscle actin; β-MHC - β-myosin heavy chain

anti-inflammatory properties. Anti-apoptotic effects focus on the levels of caspase-3, pro-apoptotic factor Bax and apoptosis regulator Bcl-2 as well as the inhibition of the opening of the mitochondrial permeability transition pore (mPTP) (Table **2**).

Indirect cardiovascular effects occur *via* modulation of major risk factors, such as cholesterol and diabetes. Elevated cholesterol in the blood, builds up in the walls of arteries, causing atherosclerosis. To study the inhibition of atherosclerosis development, the apolipoprotein E knockout mice is a well-accepted model. Inhibition of atherosclerosis occurs *via* lipids regulation as well as immunoregulation. Regarding lipids regulation several parameters are considered namely hepatic lipid profiles, *e.g.* levels of triglyceride (TG), total cholesterol (TC), phospholipids (PL) and free fatty acid (FFA) and high density lipoprotein cholesterol (HDL-c); lipid metabolizing enzymes such as lecithin cholesterol acyltransferase (LCAT), lipoprotein lipase (LPL) and 3-hydroxy 3-methylglutaryl coenzyme A reductase (HMG-CoA). Diabetes mellitus associated with chronic hyperglycaemia, dyslipidaemia and oxidative stress is another relevant risk factor [25] which leads to several comorbidities such as ischemic heart disease and stroke [26]. Animal studies in which the antidiabetic effects of terpenes are assessed upon drug induced diabetes, are mostly carried out on streptozotocin-induced diabetes for mimicking type 2 diabetes or alloxan-induced diabetes for simulating type 1 diabetes [27]. In addition, some spontaneously diabetic *in vivo* models are available, including KK-Ay mice and Goto-Kakizaki rats. Due to the importance of dyslipidaemia in diabetes-associated comorbidities, some studies induce hyperlipidaemia on diabetic animals using high-fat diet, after which the effect of terpenes on haematological (blood glucose, insulin, lipid profile) and haemodynamic parameters (blood pressure, heart rate) as well as the antioxidant profile (enzymatic and non-enzymatic antioxidant agents) are evaluated (Table **2**).

1.3.2. Synthetic and Semi-synthetic Terpenes

In addition to the use of naturally occurring terpenes, the cardioprotective effect of synthetic or semi-synthetic ones has also been assessed, in order to explore new directions for the development of terpene-based drugs. For example, Hipólito and colleagues [210] synthetized and investigated the vascular and blood pressure effects of a semi-synthetic derivative of kaurenoic acid (*ent*-16α-methoxykauran-19-oic acid). The authors showed that this compound significantly

inhibited the contractions induced by KCl and decreased both the maximal effect (E_{max}) generated by the agonist and pD_2 (−log EC50) in a dose-dependent manner on phenylephrine-induced contractions in both endothelium-intact and endothelium-denuded rings. It was demonstrated that this compound diminished $CaCl_2$-induced contractions in a Ca^{2+}-free medium containing phenylephrine or KCl. When comparing the activity of the synthetic derivative with that of the naturally occurring compound, it was concluded that the derivative had a more pronounced effect.

Another example includes the synthetic derivatives of trachylobane-type diterpenes that have been assessed for their vasorelaxant activity [211]. Chemical modifications of these compounds, including the presence of an extra carbonyl or hydroxyl group at C-3 or the halogenation at C-3 or the presence of a less polar functionality at C-15, decreased the vasorelaxant activity of these compounds. On the other hand, the addition of a bromide at C-18 or a carbonyl group at C-14, showed a slight positive effect on the vasorelaxant activity.

Several derivatives of oleanolic and ursolic acids have been synthetized in order to improve their biological properties. The most effective modifications have been performed at the C-17 position of 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO), imidazolide (CDDO-Im), nitrile (di-CDDO, TP-225), or amides (methyl amide - CDDO-MA, ethyl amide - CDDO-EA or trifluoroethyl amide - CDDO-TFEA) [212]. CDDO-Im, the imidazolide derivative of CDDO has been described as being able to improve the cardiac function of the right ventricle (RV) after cigarette smoke exposure, by avoiding the increase on RV end systolic pressure (RVESP) and isovolumetric relaxation time (IVRT) and the decrease on RV ejection fraction (RVEF) [213]. The synthetic terpenoid, dihydro-CDDO-trifluoroethyl amide (dh404) was able to reduce the oxidative stress induced by angiotensin II in cardiomyocytes by suppressing the formation of superoxide and peroxynitrite. In addition, it was able to induce nuclear factor (erythroid-derived 2)-like 2 (Nrf2) activation in cardiomyocytes and murine hearts [214], inhibit the hypertrophic growth and cell death in a primary culture of rat cardiomyocytes as well as the proliferation of cardiac fibroblasts. In addition, it was able to inhibit the pathological remodeling and dysfunction induced by transverse aortic arch constriction (TAC) as well as the associated mortality. It was also able to increase Nrf2 levels in the myocardium and its nuclear translocation [215]. Bardoxolone methyl, the methyl ester derivative of CDDO, was able to ameliorate the pathological modifications on the heart induced by high fat diet in mice namely, decrease heart weight, increase myocyte count, decrease lipid droplets and decrease the macrophage inflitration [216]. Importantly, this compound is now under a phase II clinical trial as a therapeutic agent for pulmonary arterial hypertension (LARIAT, identification number: NCT02036970).

The presented results using synthetic oleanolic acid derivatives demonstrated that the cardioprotection exerted by these compounds is mediated by the activation of Nrf2, an important mediator in the endogenous antioxidant system. Therefore, future research on the development of new synthetic oleanolic acid derivatives with cardioprotective effects should be conducted envisioning the activation of Nrf2 or the inhibition of Nrf2 antagonists. Similarly, the derivatization of kaurenoic acid at C-16 with a α-methoxy group seems to improve the vasorelaxant activity of this compound by a more preeminent blockade of Ca^{2+} influx and activation of nitric oxide / cyclic guanosine monophosphate pathway (NO-cGMP). Thus, future studies on synthetic or semi-synthetic compounds with a kaurenoic acid skeleton should focus on a stronger Ca^{2+} blocking effect and/or NO-cGMP activating effect.

1.3.3. Terpenes vs. Conventional Drugs

Some terpenes show similar or even enhanced cardioprotective effects than commercial drugs. For example, two lupane-type triterpenoids, 6β,30-dihydroxybetulinic acid and 6β-hydroxybetulinic acid, isolated from *Licania cruegeriana* were able to decrease arterial pressure and increase heart rate being the former more potent than losartan and the latter similar to the reference drug [158]. Two terpenes isolated from *Salvia syriaca*, ferruginol and 3β-hydroxystigmast-5-en-7-one, showed hypotensive effects similar to that of two conventional drugs, propranolol and regitine, without affecting the heart rate [99]. Similarly, five diterpenes isolated from *Salvia eriophora*, 4,14-dihydroxysaprorthoquinone, aethiopinone, ferruginol, 4,12-dihydroxysapriparaquinone and 6,7-dehydroroyleanone demonstrated similar effects to that of propranolol and regitine [84]. Opposing, citronellol and linalool, two monoterpene alcohols found in several aromatic plants, have been described as hypotensive with responses weaker than those of nifedipine, a reference drug for hypertension [43, 49].

Some studies comparing the effect of terpenes to reference drugs have focused on risk factors, such as dyslipidemia, atherosclerosis and diabetes. For exam-

ple, catalpol was more effective than atorvastatin, a cholesterol-lowering drug, in decreasing the atherosclerotic lesion in a rabbit model. The terpene also showed a stronger effect than the reference compound concerning the attenuation of neo-intimal hyperplasia and regulation of lipid disorder induced by high cholesterol diet and its consequent oxidative stress [38]. The triterpene, methyl-3β-hydroxylanosta-9,24-dien-21-oate, isolated from the bark of *Protorhus longifolia*, demonstrated an hypolipidemic effect stronger than that of the antihyperlipidemic drug lovastatin [190] in an high fat diet. Triptolide was able to maintain the cardiac function and decrease cardiac fibrosis in rats similarly to captopril, an antihypertensive drug [137]. Asiatic acid, a triterpenoid isolated from *Centella asiatica*, showed antidiabetic and antihyperlipidemic effects similar to that of glibenclamide, an antidiabetic drug [142]. Wang and colleagues [69] demonstrated that artesunate and ursolic acid decreased plasma triglycerides to values similar to that of atorvastatin but failed to do so on total cholesterol and LDL levels. Astragaloside IV attenuated the vascular endothelial dysfunction induced by type 2 diabetes with a performance close to that of metformin, an antidiabetic drug [154]. Geraniol, a terpene found in the essential oils of several aromatic plants, has been described as hypolipidemic showing an effect at 100 mg/kg of body weight (BW) similar to that of simvastatin at 50 mg/kg BW [46]. The compound, dehydroeburioic acid, was able to decrease blood glucose, triglycerides, total cholesterol while increasing insulin and adiponectin with a more preeminent effect than those of metformin and fenofibrate, two reference antidiabetic drugs [169]. The diterpenoid, marrubiin, significantly reduced the diabetic symptoms on an obese rat model with an activity more potent than that of antidiabetic drugs, sulphonylurea and metformin [112]. The sesquiterpene, β-caryophyllene, attenuated the oxidative and inflammatory stresses induced by hyperglycemia in a diabetic rat model with an activity similar to that of glibenclamide [26]. Similarly, asiatic acid demonstrated an antidiabetic activity similar to that of glibenclamide [141]. The triterpene, methyl-3β-hydroxylanosta-9,24-dien-21-oate, isolated from *Protorhus longifolia* stem bark showed an antihyperglicemic activity similar to that of metformin [191]. Carvacrol, a monoterpene widely distributed in nature, had an antidiabetic effect similar to that of rosiglitazone, an antidiabetic reference drug [36]. The terpenoid, β-amyrin palmitate, significantly demonstrated antidiabetic effects on both type 1 and type 2 diabetes animal models with values close to those of insulin and glibenclamide [139]. The triterpene, oelanolic acid has been described as an anti-obesity agent by de Melo and colleagues [199] with an activity similar to that of sibutramine, the synthetic reference drug. Badole and colleagues [166] have described the antidiabetic activity of cycloart-23-ene-3β,25-diol which was similar to that of glibenclamide. The diterpene, dehydroabietic acid, has been described as being able to improve the diabetes and hyperlipidaemia in an obese diabetic model with activity similar to two reference drugs, bezafibrate and pioglitazone [92]. The aglycone of glycyrrhizin, 18β-glycyrrhetinic acid, demonstrates an antihyperglycaemic and hypolipidaemic effect similar to that of glibenclamide [185, 186]. The terpenoid, costunolide, has demonstrated a normo-glycemic and a hypolipidemic effect close to that of glibenclamide on a diabetic animal model [72]. Astragaloside IV improves the vasculature in hyperglycaemic conditions with results similar to those of rosiglitazone [149]. The sesquiterpenes glycoside, nerolidol-3-O-α-L-rhamnopyranosyl(1-4)-α-L-rhamnopyranosyl(1-2)-[α-L-rhamnopyranosyl(1-6)]-β-D-glucopyranoside, had an hypoglycaemic activity close to that described for gliclazide [77]. A nicotinic acid derivative of lupeol has been described as antihyperglycemic and antidyslipidemic with a slightly weaker activity than that of metformin and fenofibrate [196]. Despite the significant antihyperglycemic and hypolipidemic properties of Chikusetsu saponin IVa, the biological activity is weaker than glibenclamide [162]. Four pentacyclic acid triterpenoids, ursolic, oleanolic, morolic and moronic acids, have been described as having antidiabetic activity, however all compounds present weaker effects than glibenclamide [195]. Zhang and colleagues [87] have described the hypoglycaemic effect of andrographolide in a diabetic animal model however weaker than that of glibenclamide.

Some studies evaluated *in vitro* effects of terpenes and compared the results to those of reference drugs. Terpinen-4-ol demonstrated a relaxant activity on high-KCl induced contraction similar to that of nifedipine [60]. A naturally occurring diterpene, *ent*-18-hydroxy-trachyloban-3-one, and a synthetic diterpene of similar structure, *ent*-trachyloban-14,15-dione, attenuated acetylcholine-induced contraction with a similar behavior to that described for verapamil [134]. Geraniol inhibited the contraction on electro stimulated guinea pig atria however it's effect was weaker than nifedipine [48]. Marrubenol and marrubiin isolated from *Marrubium vulgare* inhibited the aortic contraction induced by high KCl although both are less potent than verapamil, an antihypertensive drug [114]. Three *ent*-kaurane type diterpenes isolated from *Oyedaea ver-*

besinoides, *ent*-kaur-16-en-19-al, *ent*-15β-angeloyloxy-9α-hydroxy-kaur-16-en-19-oic acid and *ent*-kaur-16β-ol, were able to inhibit PHE-induced contractions in aortic rings to a less extent than the response induced by nifedipine [89]. A diterpenoid isolated from *Andrographis paniculata*, 14-deoxyandrographolide, inhibited PHE and KCl pre-contracted aortic rings with a lower extent than that of verapamil [97]. Stevioside, a glucoside derivative of steviol, decreased the contraction induced by vasopressin to lower extent than that attained by nifedipine [124].

Despite the promising results presented, more studies need to be done in order to ensure the safety and efficacy of these compounds to further exploit their pharmacological application.

1.3.4. Side-effects

As presented on Table **3**, some terpenes have been assessed for their side effects on humans. Although some side effects were pointed out, in the majority of the studies it was not conclusive if the reported side effect was due to the consumption of the terpenes. Moreover, the usage of ginsenosides and carotenoids have been around for millennia, thus side effects of these compounds are scarce or absent.

1.3.5. Clinical Trials

In what concerns the cardiovascular effect of terpenes, very few clinical trials have been performed, with primary focus on steviol glycosides, namely stevioside [220-224] and rebaudioside A [218, 219], ginsenosides obtained from *Panax* spp. [225, 226] and several carotenoids [227-237]. Overall randomized, double-blinded and placebo controlled studies are performed.

Briefly, steviol glucosides have been tested for their hypotensive effects. In a multicenter, two-year study, 168 individuals with mild essential hypertension were medicated twice a day with capsules containing 500 mg of stevioside powder during 2 years. A significant decrease in systolic and diastolic blood pressure was observed and patients showed good tolerability to the compound with only eight of them demonstrating adverse effects that vanished after one week of treatment [222]. Similarly, in another study with 106 hypertensive subjects, capsules containing 250 mg stevioside were administrated twice a day. Three months following the first administration the systolic and diastolic blood pressure significantly decreased and stabilized until the end of the trial. Overall good tolerability was registered with only eight patients showing side effects, with this number decreasing to four after a week of treatment [220]. Another long-term study, including individuals with type 1 diabetes, type 2 diabetes and normotensive healthy subjects, demonstrated that the administration of capsules with 250 mg stevioside twice a day had no effect on blood pressure [221]. Geuns and colleagues [223] using 9 healthy volunteers demonstrated that stevioside presented a good tolerability without affecting systolic and diastolic blood pressure. Maki and colleagues evaluated the hypotensive effects of rebaudioside A, a steviol glycoside that differs from stevioside by an extra glucose moiety [218], on two different studies using the same concentration (1000 mg/day) on healthy individuals for 4 weeks [219] and on patients with type 2 diabetes for 16 weeks [218] and concluded that the compound has no hypotensive effect.

Another class of compounds that have been tested in humans is the ginsenosides obtained from ginseng root (*Panax* spp.). In an acute crossover design, 16 healthy participants were administered capsules containing 105 mg of a ginsenoside mixture (Rb1, Rb2, Rc, Rd, Rg3, Rg1, Re, Rf) and assessed for endothelial function. The results showed that the mixture was able to increase the maximal vasodilation as assessed for flow-mediated vasodilatation (FMD) while having no effect on the brachial blood pressure and showing no adverse or side effects [225]. Another study demonstrated that the administration of capsules containing a ginsenoside mixture was able to significantly decrease the augmentation index but had no visible effect on the blood pressure [226].

Carotenoids have also been evaluated for their effect on CVDs risk factors such as dyslipidemia. In a study with moderately hypertriglyceridemic subjects, it was shown that the administration of 6 and 12 mg/day of the carotenoid astaxanthin was able to increase HDL-cholesterol concentration while the doses of 12 and 18 mg/day decreased triglycerides and increased adiponectin in subjects with mild hyperlipidemia [232]. In another trial, the effect of lutein on carotid intima-media thickness was evaluated in Chinese subjects with subclinical atherosclerosis. Results show that increasing the serum levels of lutein, the thickness of carotid intima-media decreases [227]. Lutein supplementation on healthy nonsmoker individuals was able to increase serum lutein, total antioxidant capacity while decreasing malondialdehyde and C-reactive protein [229]. On individuals with early atherosclerosis lutein supplementation significantly decreases IL-6, MCP-1 serum levels as well as the LDL-cholesterol and triglycerides while having no significant effect on ApoE levels [234]. The Beijing Atherosclerosis study demonstrated that high levels of serum lutein decreased the

Table 3. Human side effects reported for terpenes.

Terpene	Patients	Dosage	Adverse Effect [a]	References
Ginsenoside-Rd	Patients with ischemic stroke	10 mg	Urinary tract infection (1/65) Myocardial infarction (1/65) Infusion reaction (1/65)	[217]
		20 mg	Liver dysfunction (1/67) Hypertension (1/67) Pulmonary infection (1/67)	
Rebaudioside A	Patients with type 1 or 2 diabetes	1000 mg	Individuals that experienced side effects (27/60): Gastroenteritis (5%) Upper respiratory tract infection (10%) Influenza-like symptoms, namely gastrointestinal hemorrhage and cyst	[218]
	Patients with normal or normal/low blood pressure	1000 mg	Individuals that experienced side effects (16/50): Vagal response to blood draw (1/16)	[219]
Stevioside	Patients with hypertension	750 mg/day	Individuals that experienced side effects (7/60) of which continuous experience (3/7), disappeared after 1 week (4/7): Abdominal fullness, muscle tenderness, nausea and asthenia	[220]
	Type 1 or 2 diabetes or normal/normal-low blood pressure individuals		Side effects (3/36): Abdominal fullness, headache, dizziness, nausea and asthenia (irrelevant after 1 week)	[221]
	Patients with mild essential hypertension	1500 mg/day	Abdominal fullness (2/85) Nausea (2/85) Asthenia (1/85) Dizziness (1/85) Headache (1/85), myalgia (1/85)	[222]

[a] Numbers in parenthesis represent the number of individuals with the side-effects / total number of individuals analyzed.

carotid intima-media thickness on individuals with early atherosclerosis [235]. The same results were corroborated by the Los Angeles Atherosclerosis study on healthy individuals [236]. In a single-blind, randomized controlled intervention trial with healthy and moderately overweight middle-aged volunteers the consumption of lycopene at doses of 10 mg/day for 12 weeks had no effect on CVDs risk factors [228]. Opposing, another single-blind, randomized controlled study involving moderately overweight healthy individuals, lycopene consumption (225-300 mg/day or 70 mg/day) improved HDL functionality while reducing systemic and HDL-associated inflammation [230]. Lycopene supplementation effect on individuals with statin-treated CVDs or healthy individuals was assessed. The results demonstrated that improves endothelial function on CVDs patients but has no effect on healthy patients [231]. In the Rotterdam study, the consumption of lycopene decreased the risk of progression of atherosclerosis and on individuals with aortic atherosclerosis, this effects is more preeminent on current and former smokers [237].

Some of these trials provide strong evidence on the potential of terpenes in the medical field. Nevertheless further studies to monitor long-term adverse effects and assess additional safety and efficacy data are warranted for the development of new drugs. Moreover, many terpenes are rapidly absorbed and metabolized through cytochrome P450 being excreted as conjugated metabolites by the kidney. Therefore, strategies that improve terpenes stability and bioavailability such as nanoencapsulation should also be considered.

1.4. Structure -Activity Relationship

As previously referred terpenes are a diverse group of compounds suitable for drug discovery [238]. For this reason, structure-activity relationships (SARs) are very important as they allow the identification of chemical entities and/or structural adaptations responsible for the activity or inactivity of the compound. Moreover, SARs allow the identification of terpenes safety profile [238, 239], an important step to consider in the design of efficacious molecules for the prevention and/or treatment of CVDs. In fact, several investigators have analysed the structural hallmarks that explain the activity of different terpenic compounds, including monoterpenes [42, 240], phenolic derivatives [32], ginkgolides [103], hesitine-type C_{20}-diterpenoid alkaloids [105], aconitine-type C_{19}-diterpenoid alkaloids [83], kaurane-type diterpenoids [106, 241], limonoids [192], pentacyclic triterpenoids [157], lupane-type triterpenoids [158], 20(S)-protopanaxatriol and epimers [168] and ursane-type triterpenoid saponins [171].

Briefly, it seems that the key structural requirements for cardioprotective effects of cyclic monoterpenes are associated with the position of the double bond and/or epoxy group. Also, the chirality and the stereochemistry are relevant for the cardiovascular activity of these compounds [42, 240]. For example, comparing the effect on both the mean arterial blood pressure and heart rate of (+)-α-pinene (-35% and 13%, respectively [42]) and (-)-β-pinene (-46% and 16%, respectively [42]), it seems that the exocyclic double bond found on the later compound contributes to the stronger hypotensive activity of this compound (Table **4**). Also, the chiral differences at the carbon 1 and 5 influences the cardiovascular action of these compounds [42]. Regarding acyclic monoterpenes, it has been described that primary alcohols are responsible for more hypotensive effects than tertiary ones [42]. In fact, as shown in Table **4**, (±)-citronellol has a more potent effect on mean arterial blood pressure and heart rate (-48% and 21%, respectively [42]) than (±)-linalool (-40% and 19%, [42, 43, 49]. Similarly to cyclic monoterpenes, the chirality also influences the effect of both linalool enantiomers, with *S*-(+)-linalool increasing the blood pressure as well as the heart rate, while its enantiomer *R*-(-)-linalool decreases heart rate and has no effect on blood pressure [50] (Table **4**). Also, comparing the supressing activity of carvacrol and thymol which differ by the distance between the hydroxyl group and the hydrophobic tail, it was shown that carvacrol (with a greater distance between both0 substituents) exhibits a stronger activity (Table **4**). This suggests that the greater the distance between the hydroxyl moiety and the hydrophobic tail, greater the supressing activity on mean arterial blood pressure and heart rate [32].

Diterpenoids have distinct key features that are responsible for their cardioprotective effect. For example, gingkolides, diterpenic trilactones isolated from *Ginkgo biloba*, have specific characteristics required for their anti-platelet-activating factor (PAF) effect, as schematized in Table **4**. Namely, a *tert*-But substituent at C-8 is essential for PAF antagonism. Conversely, the presence of polar substituents (*e.g.* OH at C-7) decreases the anti-PAF properties as they weaken the linkage between the *tert*-But group and the hydrophobic zone of the PAF membrane receptor (Table **4**). Stereochemistry also influences the PAF antagonism of ginkgolides since the inversion of the configuration at C-7 slightly increases the anti-PAF activity of these compounds. Moreover, structural modifications at secondary C-1 and/or C-10 yield ginkgolides with stronger anti-PAF activity [103]. For example, in an ischemic-reperfused isolated rat heart, 7-O-(4-methylphenyl) ginkgolide C (7.89 IU CK/mg protein and 3.81 IU LDH/mg protein, [103]) had a stronger activity than both 7-α-O-(4-methylphenyl) ginkgolide C (6.82 IU CK/mg protein and 3.14 IU LDH/mg protein, [103]) and ginkgolide C (6.61 IU CK/mg protein and 3.11 IU LDH/mg protein, [103]). Also, in the same model, the malondialdehyde (MDA) content was decreased significantly by both methylated derivatives, although 7-O-(4-methylphenyl) ginkgolide C still showed a stronger activity (30% decrease *vs*. 16% decrease) [103]. For the anti-PAF effect of ginkgolide C and its derivatives, it has been ascribed that 7-α-O-(4-methylphenyl) ginkgolide C has a more potent anti-PAF effect when compared to the ginkgolide C (IC_{50} = 8.2 μM *vs*. 17.1 μM, [103]).

Other cardioprotective diterpenoids belong to the hesitine-type C_{20}-diterpenoid alkaloids. It has been shown that higher number of acetyl moieties at C-2, C-11 and C-13 (Table **4**) are responsible for the increasing Na^+-current blockade of hesitine (IC_{50} = 75.72 μM, [105]), Guan-Fu base A (IC_{50} = 41.17 μM, [105]) and Guan-Fu base G (IC_{50} = 23.81 μM, [105]). On the other side, the presence of a cyclic double bond between C-15 and C-16, found in Guan-Fu base N (IC_{50} > 100 μM, [105]) has no effect on the current supressing activity of hesitine-type C_{20}-diterpenoid alkaloids. Contrarily, a double bond between C-2 and C-3, present in Guan-Fu base S (IC_{50} = 3.48 μM, [105]) strongly increases the blocking potential of these compounds, as represented in Table **4**. C_{19}-Diterpenoid alkaloids can

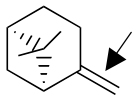
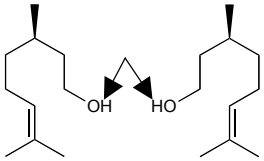
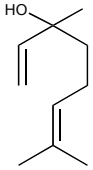
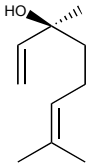
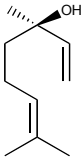
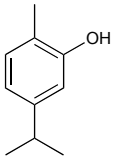
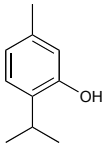
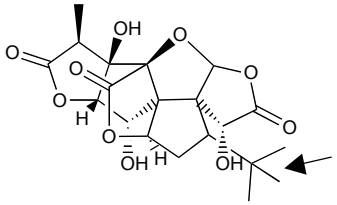
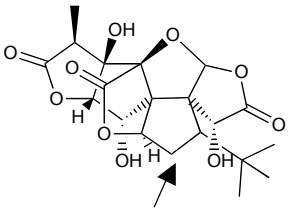
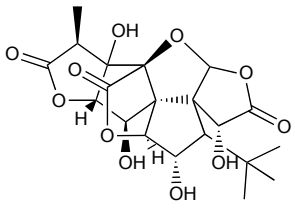
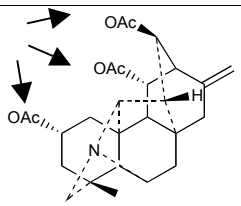
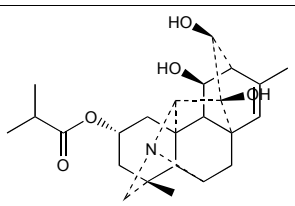
be divided into six types: aconitine-type, lycoctonine-type, pyro-type, lactone-type, 7,17-*seco*-type and rearranged-type [242]. The first two are the most abundant and can be distinguished by the presence (lycoctonine-type) or absence (aconitine-type) of an oxygen-containing functionality at C-7 [242]. In addition, in the first type the oxygen-containing moiety at C-6 has β-orientation, while in the latter it has α-orientation [242]. Lycoctonine-type compounds lack any cardiac activity, while aconitine-type ones show cardiac effects that are mainly controlled by the presence or absence of an ester group [83]. In compounds without an ester group, several structural modifications help to improve the cardiac function. Conversely, the presence of an ester group removes the cardiac activity. Moreover, in aconitine-type compounds, the presence of a hydroxyl group at C-15 and C-8 greatly improves the cardiac function, as shown in Table **4** for aconine (21% amplitude increase [83]). Also, N-methylation in this group of compounds greatly increases their cardiac effect as shown in Table **4** for mesaconine (82% amplitude increase [83]). Also, the presence of an N-ethyl group gives the compound protective cardiac effects however, these are weak or of short duration. Conversely, the presence of either N-deethyl groups or N-ethyl-N-methyl groups confers strong cardiac effect, *e.g.* N-deethylaconine (28% amplitude increase [83]). Comparing the activity of compounds differing by the presence of 1α-OMe and/or 1α-OH the investigators highlighted the importance of these functional groups as their absence diminishes the cardiac effect of the compounds (*e.g.* Compound 28) [83] as outlined in Table **4**. In addition, by comparing 15α-hydroxylneoline (38.5% amplitude increase, [83]) and 15β-hydroxylneoline (0% amplitude increase, [83]), it was suggested that the presence of a 15α-OH moiety is a key factor for the cardiac effect of these compounds [83], as schematized in Table **4**. The different activity of both N-deethylaconine (28% amplitude increase, [83]) and mesaconine (82% amplitude increase, [83]) suggests that the presence of an N-methyl group instead of two N-ethyl groups improves the cardiac effects of this type of diterpenoid alkaloids. Liu and colleagues [90] described mesaconine as having cardioprotective effects including improved ionotropic effect and left ventricular diastolic pressure. Shifting the 3α-OH to a 3β-OH the cardiac effect of mesaconine greatly decreased (82% *vs.* 45% amplitude increase, [83]), thus suggesting that 3α-OH bond improves the protective effects of aconitine-type diterpenoid alkaloids without ester groups as schematized in Table **4**.

Kaurane-type diterpenoids are also described as having protective cardiac effects. In fact, Ambrosio and colleagues [106] compared the activity of kaurenoic acid and its methylated derivative, *ent*-methyl-kaur-16-en-19-oate, on several cardiac parameters, *e.g.* relaxant effect on PHE-pre-contracted aortic rings (73.06% *vs.* 53.68% relaxation, [106]). These results suggested that the methylation of the carboxylic group at C-19 decreased the vasorelaxant activity of *ent*-kaur-16-en-19-oic acid (Table **4**). Despite the importance of the carboxylic group at C-19 [106, 241], other findings have shown that compounds lacking this group also exert relaxative effects [89]. For example, Muller and colleagues [89] described that *ent*-kaur-16β-ol induced maximal relaxation after 60 min of incubation, whereas other kaurane-type diterpenoids lacking the carboxylic group at C-19 (*ent*-kaur-16-en-19-al) were able to achieve maximal relaxation after 45 min. However, when the carboxylic group is present at C-19, the maximal relaxation was achieved on a much lower time lapse, *e.g. ent*-15β-angeloyloxy-9α-hydroxy-kaur-16-en-19-oic acid which achieved that value after 5 min incubation.

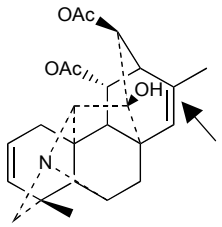
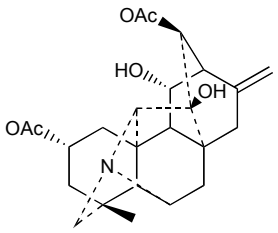
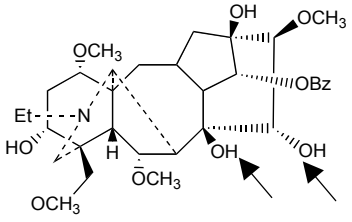
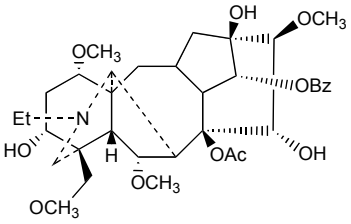
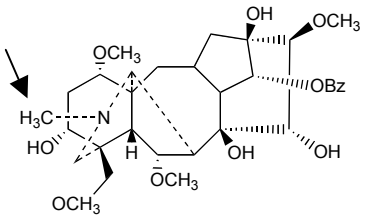
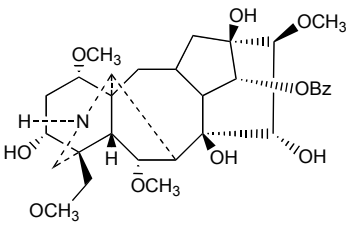
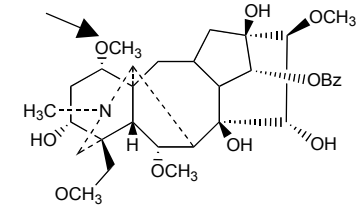
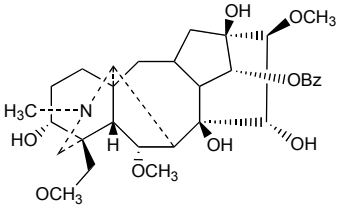
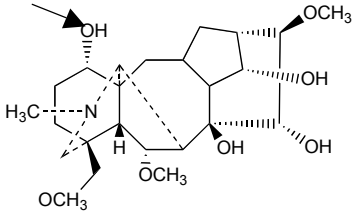
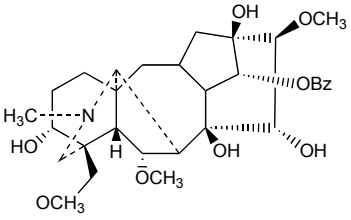
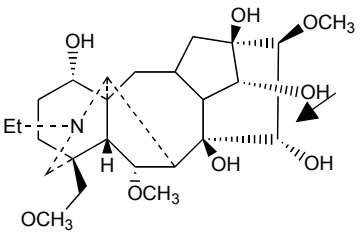
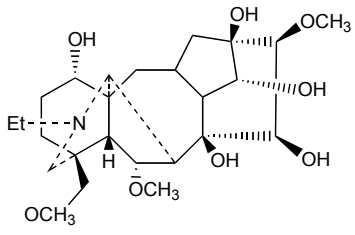
Plants from the genus *Citrus* are a source of several compounds including limonoids and tetranorterpenoids, responsible for the bitterness of these plants [192]. Amongst their health benefits, the inhibition of p38 MAPK activation is reported. Of the tested limonoids, defuran limonin and methyl nomilinate showed no effect on the phosphorylation of p38 subunit while obacunone, which has a double bond in C-1 in the A ring, promoted the phosphorylation. In opposition, nomilin, limonin, deacetyl nomilin and defuran nomilin, inhibited p38 phosphorylation by 38, 19, 19 and 17%, respectively [192]. These results suggested that the inhibition is mainly affected by the seven-membered A ring with an acetoxy group and the furan moiety. In addition, it appears that saturation of the A ring with an acetyl group seems to change the conformation of the structure thus leading to p38 phosphorylation inhibition by nomilin [192], as schematized in Table **4**.

Triterpenoids are also well-known cardioprotective agents. For example, pentacyclic triterpenoid acids isolated from *Phoradendron reichenbachianum* have shown vasorelaxant effects on aortic rings [157]. The tested compounds included ursolic acid (EC_{50} = 11.7 μM, [157]), moronic acid (EC_{50} = 16.11 μM, [157]), morolic acid (EC_{50} = 94.19 μM, [157]), betulinic acid (EC_{50} = 58.46 μM, [157]) and 3,4-*seco*-Olean-18-ene-3,2,8-dioic acid (EC_{50} = 141.23 μM, [157]). Structural

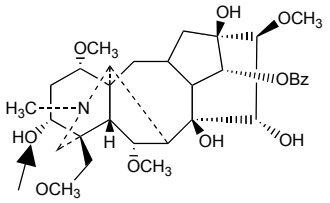
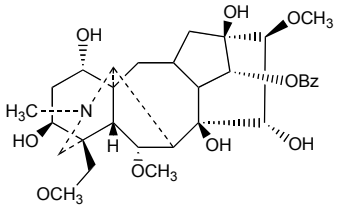
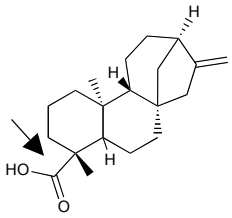
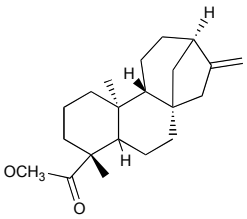
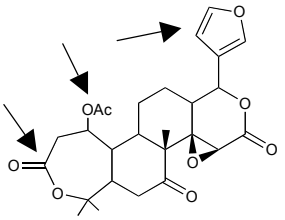
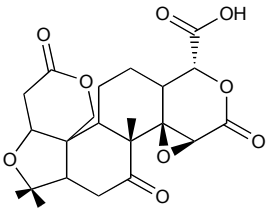
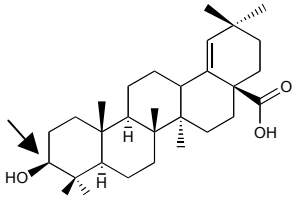
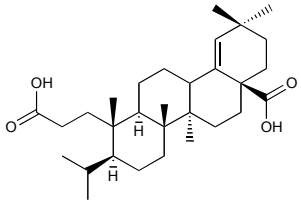
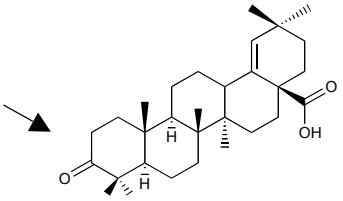
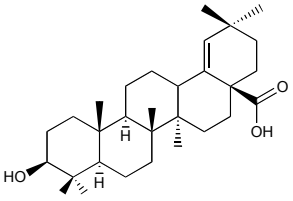
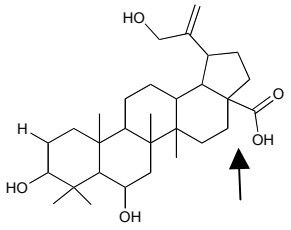
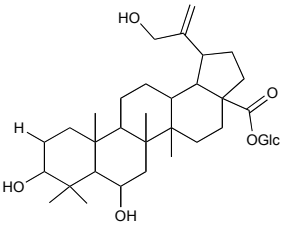
Table 4. Key structural requirements for terpenes cardiovascular effects.

Chemical Differences	Stronger Activity	Weakest Activity
MONOTERPENES		
Exocyclic double bond	 (−)-β-Pinene	 (+)-α-Pinene
Primary alcohols	 (±)-Citronellol	 (±)-Linalool
S-enantiomer	 *S*-(+)-Linalool	 *R*-(-)-Linalool
Greater distance between the hydroxyl moiety and the hydrophobic tail	 Carvacrol	 Thymol
DITERPENOIDS		
tert-But substituent at C-8	 Ginkgolide B	
Absence of polar substituents at C-7	 Ginkgolide B	 Ginkgolide C
Number of acetyl moieties at C-2, C-11 and C-13	 Guan Fu base G	 Guan Gu base N

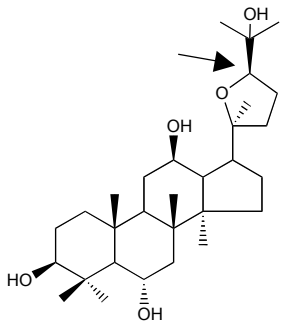
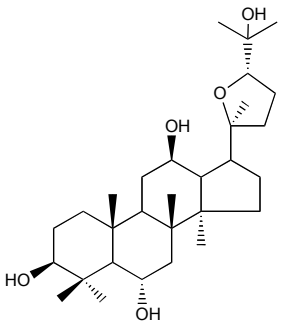
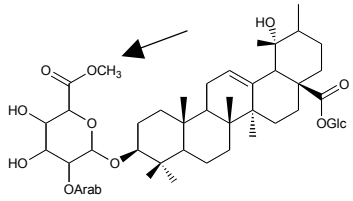
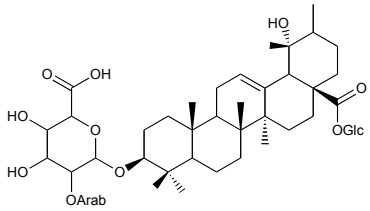
(Table 4) contd….

Chemical Differences	Stronger Activity	Weakest Activity
Cyclic double bond between C_2 and C_3	 Guan Fu base S	 Guan Fu base A
Absence of a ester groups and presence of hydroxyl groups at C_8 and C_{15}	 Aconine	 Aconitine
N-methylation	 Mesaconine	 N-Deethylaconine
Presence of 1α-OCH_3	 Mesaconine	 Compound 28
Presence of 1α-OH	 Compound 7	 Compound 28
Stereochemistry at 15α-OH	 15α-Hydroxyneoline	 15β-Hydroxyneoline

(Table 4) contd….

Chemical Differences	Stronger Activity	Weakest Activity
Stereochemistry at 3α -OH	 Mesaconine (3α-OH)	 Compound 24 (3β-OH)
Absence of methylation at C-19	 *ent*-Kaur-16-en-19-oic acid	 *ent*-methyl-Kaur-16-en-19-oate
Seven-membered A ring with and acetoxy ring and a furan moiety	 Nomilin	 Defuran Limonin
TRITERPENOIDS		
Preservation of pentacyclic skeleton	 Morolic acid	 3,4-*seco*-Olean-18-ene-3,28-dioic acid
Presence of hydrogen bound acceptor at C_3	 Moronic acid	 Morolic acid
Preservation of carboxylic group at C_{19}	 6β,30-Dihydroxybetulinic acid	 6β,30-Dihydroxybetulinic acid glucopyranosyl ester

(Table 4) contd….

Chemical Differences	Stronger Activity	Weakest Activity
Configuration of C_{24} at furan ring	 20S,24R-epoxy-Dammarane-3β,6α,12β,25-tetraol	 20S,24S-epoxy-Dammarane-3β,6α,12β,25-tetraol
Esterification of glucuronic acid	 3β-O-[α-L-arabinopyranosyl-(1→2)-β-D-glucuronopyranoside-6-O-methyl ester]-19α-hydroxyurs-12-en-28-oic acid 28-O-β-D- glucopyranosyl ester	 3β-O-[α-L-arabinopyranosyl-(1→2)-β-D-glucuronopyranosyl]-19α-hydroxyurs-12-en-28- oic acid 28-O-β-D-glucopyranosyl ester

requirements for the vasorelaxant activity of these compounds are shown in Table **4** and can be summarized as follows: (i) preservation of the pentacyclic skeleton (*e.g.* morolic acid *vs.* 3,4-*seco*-olean-18-ene-3,28-dioic acid); (ii) five- or six-membered E ring; (iii) integrity of rings; (iv) presence of a hydrogen bound acceptor at C-3 (*e.g.* ketone in moronic acid) and (v) small lipophilic groups at C-19 and C-20 [157].

Lupane-type triterpenoids isolated from *Licania cruegeriana* have also been tested on hypertensive rats [158]. The triterpenoids 6β,30-dihydroxybetulinic acid glucopyranosyl ester (1), 6β,30-dihydroxybetulinic acid (2) and 6β-hydroxybetulinic acid (3) were assessed for their effect on mean arterial blood pressure (MABP) and HR. Only (2) and (3) were able to decrease mean arterial blood pressure (60.1 and 17.2%, respectively, [158]) and increase heart rate (11.0 and 41.2%, respectively, [158]). The structure-activity relationship analysis carried out suggested than the esterification of the carboxylic acid with a glycoside greatly decreases the cardiovascular effects, whereas the hydroxylation of the betulinic moieties at C-6 and C-30 augments the hypotensive effect [158], as shown in Table **4**. Dammarane-type tetracyclic triterpenoids have also been ascribed as having cardiovascular effects. Namely, 20(*S*)-protopanaxatriol and its epimeric derivatives have been tested for their cardiovascular activity on a model of heart ischemia/reperfusion induced by isoproterenol [168]. Of the three tested compounds only 20(*S*)-protopanaxatriol and 20*S*,24*R*-epoxy-dammarane-3β,6α,12β,25-tetraol had significant activity thus suggesting that the configuration of C-24 at furan ring is involved in the pharmacological effect of these type of compounds (Table **4**). Finally, ursane-type triterpenoid saponins, namely 3β-O-[α-L-arabinopyranosyl-(1→2)-β-D-glucuronopyranosyl]-19α-hydroxyurs-12-en-28-oic acid 28-O-β-D-glucopyranosyl ester (80.95% viability at 200 μM, [171]) and 3β-O-[α-L-arabino-pyranosyl-(1→2)-β-D-glucuronopyranoside-6-O-methylester]-19α-hydroxyurs-12-en-28-oic acid 28-O-β-D-glucopyranosyl ester (89.33% viability at 200 μM, [171]) have been described as protective of H9c2 cardiomyocytes under the effect of H_2O_2. The results suggest that the esterification of glucuronic acid (Table **4**) augments the protective effect of these compounds [171].

CONCLUSION

This review highlights the high potential of terpenes as cardioprotective compounds, bringing new insights for the development of effective and innovative pre-

ventive and/or therapeutic cardiovascular agents that could attenuate the burden of CVDs. In fact, robust evidence from the literature, in the last years, including *in vitro* and *in vivo* studies have pointed out the cardioprotective effects of these compounds. Indeed, effects on both the vascular system and heart as well as indirect effects through modulation of major risk factors have demonstrated the wide array of terpene's effects on CVDs.

Overall, some of the most effective terpenes include citronellol, linalool, 6β-hydroxybetulinic acid, 6β,30-dihydroxybetulinic acid, ferruginol, 3β-hydroxy-stigmast-5-en-7-one, 4,14-dihydroxysaprorthoquinone, aethiopinone, 4,12-dihydroxysapriparaquinone, 6,7-dihydroroyleanone as potential agents for the treatment of hypertension; (+)-nootkatone and caryophyllene oxide for the prevention of thrombosis and triptolide to prevent or ameliorate myocardial infarction. In addition, catalpol showed potential to treat atherosclerosis, methyl-3β-hydroxylanosta-9,24-dien-21-oate, artesunate, ursolic acid and geraniol to ameliorate dyslipidemia, and asiatic acid and astragaloside IV to prevent the CVDs associated with diabetes. Some clinical trials have also provided strong evidence on the potential of terpenes in the medical field with primary focus on steviol glycosides, ginsenosides and carotenoids. Moreover, the cardioprotective effect of synthetic or semi-synthetic terpenes have pointed out potential cardiovascular drugs and the herein depicted structure-activity relationships brings new insights towards the design of more effective cardiovascular agents.

Markedly, the research carried out in the field gave rise to international patents. Indeed, the joined search for "terpenoid and cardiovascular" held six patents on Espacenet (European Patent Office) and 9 on WIPO (World Intellectual Property Organization) for terpenoids and cardiotherapeutic formulations, which underpins the interest of the scientific and medical community in these compounds.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Patridge, E.; Gareiss, P.; Kinch, M.S.; Hoyer, D. An analysis of FDA-approved drugs: natural products and their derivatives. *Drug Discov. Today,* **2015**, *21*(*2*), 204-207.

[2] Atanasov, A.G.; Waltenberger, B.; Pferschy-wenzig, E. Europe PMC funders group discovery and resupply of pharmacologically active plant- derived natural products: A review. *Biotechnol. Adv.,* **2015**, *33*(*8*), 1582-1614.

[3] Feher, M.; Schmidt, J.M. Property distributions: Differences between drugs, natural products, and molecules from combinatorial chemistry. *J. Chem. Inf. Comput. Sci.*, **2003**, *43*(*1*), 218-227.

[4] Singh, B.; Sharma, R. A. Plant terpenes: defense responses, phylogenetic analysis, regulation and clinical applications. *Biotech*. **2015**, *5* 129-151.

[5] Fuster, V. Global burden of cardiovascular disease: Time to implement feasible strategies and to monitor results. *J. Am. Coll. Cardiol.*, **2014**, *64*(*5*), 520-522.

[6] Rastogi, S.; Pandey, M.M.; Rawat, A.K.S. Traditional herbs: A remedy for cardiovascular disorders. *Phytomedicine,* **2016**, *23*(11), 1082-1089.

[7] Walden, R.; Tomlinson, B. Cardiovascular Disease, in: I. Benzie, S. Wachtel-Galor (Eds.), *Herbal Medicine Biomolecular and Clinical Aspects,* 2nd ed. Taylor & Francis, FL, **2011**.

[8] Yadav, N.; Yadav, R.; Goyal, A. Chemistry of Terpenoids. *Int. J. Pharmacol. Sci. Rev.*, **2014**, *27*(*45*), 272-278.

[9] Wink, M.; Van Wyk, B.-E. Mind-Altering and Poisonous Plants of the World, Timber, Portland, OR, **2008**.

[10] Buckingam, J. Dictionary of Natural Products, Chapman and Hall/CRC, London, **2007**.

[11] Santos, M.R. V; Moreira, F. V.; Fraga, B.P.; de Sousa, D.P.; Bonjardim, L.R.; Quintans, L.J. Cardiovascular effects of monoterpenes: A review. *Brazilian J. Pharmacogn.*, **2011**, *21*(*4*), 764-771.

[12] Ashour, M.; Wink, M.; Gershenzon, J. Biochemistry of Terpenoids: Monoterpenes, Sesquiterpenes and Diterpenes, in: M. Wink (Ed.), *Annu. Plant Rev.* Vol. 40 *Biochem. Plant Second. Metab.,* 2nd ed. Wiley-Blackwell, Oxford, UK, **2010**: pp. 258-303.

[13] Wang, G.; Tang, W.; Bidigare, R.R. Terpenoids As Therapeutic Drugs and Pharmaceutical Agents, In: L. Zhang, A.L. Demain (Eds.), *Natural Products: Drug Discovery & Therapeutic Medicine:* Humana Press, Totowa, NJ, **2005**: pp. 197-227.

[14] Baser, K.H.C.; Demirci, F. Chemistry of Essential Oils. In: R.G. Berger (Ed.), Flavours Fragrances - Chem. Bioprocess. Sustain. Springer, Berlin, **2007**: pp. 43 - 86.

[15] Aharoni, A.; Jongsma, M.A.; Kim, T.-Y.; Ri, M.-B.; Giri, A.P.; Verstappen, F.W.A.; Schwab, W.; Bouwmeester, H.J. Metabolic engineering of terpenoid biosynthesis in plants. *Phytochem. Rev.*, **2006**, *5*(*1*), 49-58.

[16] Taiz, L.; Zeiger, E.; Møller, I.M.; Murphy, A. Appendix 4 - Secondary Metabolites, In: Plant Physiology and Development, 6th ed. Sinauer Associates, **2015**: pp. 605-606.

[17] Nichols, M.; Townsend, N.; Scarborough, P.; Rayner, M. Cardiovascular disease in Europe 2014: epidemiological update. *Eur. Heart J.*, **2014**, *35*(*42*), 2950-2959.

[18] Scott, J. Pathophysiology and biochemistry of cardiovascular disease. *Curr. Opin. Genet. Dev.*, **2004**, *14*(*3*), 271-279.

[19] WHO, Cardiovascular Diseases - Factsheet. Available at: http://www.who.int/mediacentre/factsheets/fs317/en/.

[20] Dimmeler, S. Cardiovascular disease review series. *EMBO Mol. Med.*, **2011**, *3*(*12*), 697.

[21] Organization, W.H.O. Cardiovascular diseases. Available at: http://www.who.int/cardiovascular_ diseases/en/.

[22] Sun, J.; Huang, S.H.; Tan, B.K.H.; Whiteman, M.; Zhu, Y.C.; Wu, Y.J.; Ng, Y.; Duan, W.; Zhu, Y.Z. Effects of purified herbal extract of *Salvia miltiorrhiza* on ischemic rat

myocardium after acute myocardial infarction. *Life Sci.*, **2005**, *76*(*24*), 2849-2860.

[23] Ferrari, C.K.B. Functional foods, herbs and nutraceuticals: Towards biochemical mechanisms of healthy aging. *Biogerontology*. **2004**, *5*(*5*), 275-289.

[24] Tolstikova, T.G.; Tolstikov, A.G.; Tolstikov, G.A. On the way to low-dose medicines. *Her. Russ. Acad. Sci.*, **2007**, *77*(*5*), 447-453.

[25] Baddar, N.W.A.-H.; Aburjai, T. a; Taha, M.O.; Disi, A.M. Thujone corrects cholesterol and triglyceride profiles in diabetic rat model. *Nat. Prod. Res.*, **2011**, *25*(*12*), 1180-4.

[26] Basha, R.H.; Sankaranarayanan, C. β-Caryophyllene, a natural sesquiterpene lactone attenuates hyperglycemia mediated oxidative and inflammatory stress in experimental diabetic rats. *Chem. Biol. Interact.*, **2016**, *245* 50-58.

[27] Rohilla, A.; Ali, S. Alloxan induced diabetes : mechanisms and effects. *Int. J. Res. Pharm. Biomed. Sci.*, **1943**, *3*(*2*), 819-823.

[28] Fei, Y.; Zhao, J.; Liu, Y.; Li, X.; Xu, Q.; Wang, T.; Khan, I.A.; Yang, S. New monoterpene glycosides from sunflower seeds and their protective effects against H_2O_2-induced myocardial cell injury. *Food Chem.*, **2015**, *187* 385-390.

[29] Peixoto-Neves, D.; Silva-Alves, K.S.; Gomes, M.D.M.; Lima, F.C.; Lahlou, S.; Magalhães, P.J.C.; Ceccatto, V.M.; Coelho-de-Souza, A.N.; Leal-Cardoso, J.H. Vasorelaxant effects of the monoterpenic phenol isomers, carvacrol and thymol, on rat isolated aorta. *Fundam. Clin. Pharmacol.*, **2010**, *24*(*3*), 341-50.

[30] Shabir, H.; Kundu, S.; Basir, S.F.; Khan, L.A. Modulation of Pb(II) caused aortal constriction by eugenol and carvacrol. *Biol. Trace Elem. Res.*, **2014**, *161*(*1*), 116-122.

[31] Dantas, B.P.V.; Alves, Q.L.; de Assis, K.S.; Ribeiro, T.P.; de Almeida, M.M.; de Vasconcelos, A.P.; de Araújo, D.A.M.; de Andrade Braga, V.; de Medeiros, I.A.; Alencar, J.L.; Silva, D.F. Participation of the TRP channel in the cardiovascular effects induced by carvacrol in normotensive rat. *Vascul. Pharmacol.*, **2015**, *67-69* 48-58.

[32] Magyar, J.; Szentandrássy, N.; Bányász, T.; Fülöp, L.; Varró, A.; Nánási, P.P. Effects of terpenoid phenol derivatives on calcium current in canine and human ventricular cardiomyocytes. *Eur. J. Pharmacol.*, **2004**, *487*(*1-3*), 29-36.

[33] Earley, S.; Gonzales, A.L.; Garcia, Z.I. A dietary agonist of transient receptor potential cation channel V3 elicits endothelium-dependent vasodilation. *Mol. Pharmacol.*, **2010**, *77*(*4*), 612-620.

[34] Aydin, Y.; Kutlay, Ö.; Ari, S.; Duman, S.; Uzuner, K.; Aydin, S. Hypotensive effects of carvacrol on the blood pressure of normotensive rats. *Planta Med.*, **2007**, *73*(*13*), 1365-1371.

[35] Lee, K.P.; Sudjarwo, G.W.; Jung, S.H.; Lee, D.; Lee, D.Y.; Lee, G.B.; Baek, S.; Kim, D.Y.; Lee, H.M.; Kim, B.; Kwon, S.C.; Won, K.J. Carvacrol inhibits atherosclerotic neointima formation by downregulating reactive oxygen species production in vascular smooth muscle cells. *Atherosclerosis*. **2015**, *240*(*2*), 367-373.

[36] Ezhumalai, M.; Ashokkumar, N.; Pugalendi, K.V. Combination of carvacrol and rosiglitazone ameliorates high fat diet induced changes in lipids and inflammatory markers in C57BL/6J mice. *Biochimie*. **2015**, *110* 129-136.

[37] Kundu, S.; Shabir, H.; Basir, S.F.; Khan, L.A. Inhibition of As(III) and Hg(II) caused aortic hypercontraction by eugenol, linalool and carvone. *J. Smooth Muscle Res.*, **2014**, *50*(*0*), 93-102.

[38] Liu, J.Y.; Zhang, D.J. Amelioration by catalpol of atherosclerotic lesions in hypercholesterolemic rabbits. *Planta Med.*, **2015**, *81*(*3*), 175-184.

[39] Soares, M.C.M.S.; Damiani, C.E.N.; Moreira, C.M.; Stefanon, I.; Vassallo, D. V, Eucalyptol, an essential oil, reduces contractile activity in rat cardiac muscle. *Braz. J. Med. Biol. Res.*, **2005**, *38*(*3*), 453-61.

[40] Lahlou, S.; Figueiredo, A.F.; Magalhães, P.J.C.; Leal-Cardoso, J.H. Cardiovascular effects of 1,8-cineole, a terpenoid oxide present in many plant essential oils, in normotensive rats. *Can. J. Physiol. Pharmacol.*, **2002**, *80*(*12*), 1125-1131.

[41] Pereira, S.L.; Marques, A.M.; Sudo, R.T.; Kaplan, M.A.C.; Zapata-Sudo, G. Vasodilator activity of the essential oil from aerial parts of *Pectis brevipedunculata* and its main constituent citral in rat aorta. *Molecules*. **2013**, *18*(*3*), 3072-3085.

[42] Menezes, I.A.C.; Barreto, C.M.N.; Antoniolli, Â.R.; Santos, M.R. V; de Sousa, D.P. Hypotensive activity of terpenes found in essential oils. *Zeitschrift Fur Naturforsch. - Sect. C J. Biosci.*, **2010**, *65 C*(*9-10*), 562-566.

[43] Bastos, J.F.A.; Moreira, Í.J.A.; Ribeiro, T.P.; Medeiros, I.A.; Antoniolli, A.R.; De Sousa, D.P.; Santos, M.R. V, Hypotensive and vasorelaxant effects of citronellol, a monoterpene alcohol, in rats. *Basic Clin. Pharmacol. Toxicol.*, **2010**, *106*(*4*), 331-337.

[44] Liao, P.; Liu, L.; Wang, B.; Li, W.; Fang, X.; Guan, S. Baicalin and geniposide attenuate atherosclerosis involving lipids regulation and immunoregulation in ApoE-/- mice. *Eur. J. Pharmacol.*, **2014**, *740* 488-495.

[45] Gao, Y.; Chen, Z.; Liang, X.; Xie, C.; Chen, Y. Anti-atherosclerotic effect of geniposidic acid in a rabbit model and related cellular mechanisms. *Pharm. Biol.*, **2015**, *53*(*2*), 280-285.

[46] Galle, M.; Kladniew, B.R.; Castro, M.A.; Villegas, S.M.; Lacunza, E.; Polo, M.; De Bravo, M.G.; Crespo, R. Modulation by geraniol of gene expression involved in lipid metabolism leading to a reduction of serum-cholesterol and triglyceride levels. *Phytomedicine*. **2015**, *22*(*7-8*), 696-704.

[47] Jayachandran, M.; Chandrasekaran, B.; Namasivayam, N. Effect of geraniol, a plant derived monoterpene on lipids and lipid metabolizing enzymes in experimental hyperlipidemic hamsters. *Mol. Cell. Biochem.*, **2015**, *398*(*1-2*), 39-53.

[48] de Menezes-Filho, J.E.R.; Gondim, A.N.S.; Cruz, J.S.; de Souza, A.A.; dos Santos, J.N.A.; Conde-Garcia, E.A.; de Sousa, D.P.; Santos, M.S.; de Oliveira, E.D.; de Vasconcelos, C.M.L. Geraniol blocks calcium and potassium channels in the mammalian myocardium: useful effects to treat arrhythmias. *Basic Clin. Pharmacol. Toxicol.*, **2014**, *115*(*6*), 534-544.

[49] Anjos, P.J.C.; Lima, A.O.; Cunha, P.S.; De Sousa, D.P.; Onofre, A.S.C.; Ribeiro, T.P.; Medeiros, I. a; Antoniolli, A.R.; Quintans-Júnior, L.J.; Santosa, M.R. V, Cardiovascular effects induced by linalool in normotensive and hypertensive rats. *Zeitschrift Für Naturforschung. C - A J. Biosci.*, **2013**, *68*(*5-6*), 181-90. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23923614.

[50] Höferl, M.; Krist, S.; Buchbauer, G. Chirality influences the effects of linalool on physiological parameters of stress. *Planta Med.*, **2006**, *72*(*13*), 1188-1192.

[51] Johnson, C.D.; Melanaphy, D.; Purse, A.; Stokesberry, S.A.; Dickson, P.; Zholos, A. V, Transient receptor potential melastatin 8 channel involvement in the regulation of vascular tone. *Am. J. Physiol. - Hear. Circ. Physiol.*, **2009**, *296*(*6*), H1868-H1877.

[52] Cheang, W.S.; Lam, M.Y.; Wong, W.T.; Tian, X.Y.; Lau, C.W.; Zhu, Z.; Yao, X.; Huang, Y. Menthol relaxes rat aortae, mesenteric and coronary arteries by inhibiting calcium influx. *Eur. J. Pharmacol.*, **2013**, *702*(*1-3*), 79-84.

[53] Li, J.Z.; Yu, S.Y.; Mo, D.; Tang, X.N.; Shao, Q.R. Picroside II inhibits hypoxia/reoxygenation-induced cardiomyocyte apoptosis by ameliorating mitochondrial function through a mechanism involving a decrease in reactive oxygen species production. *Int. J. Mol. Med.*, **2015**, *35* 446-452.

[54] Lahlou, S.; Carneiro-Leão, R.F.L.; Leal-Cardoso, J.H.; Toscano, C.F. Cardiovascular effects of the essential oil *Mentha x villosa* and its main constituent, piperitenone oxide, in normotensive anaesthetised rats: role of the autonomic nervous system. *Planta Med.*, **2001**, *67* 638-643.

[55] Guedes, D.N.; Silva, D.F.; Barbosa-Filho, J.M.; Medeiros, I.A. Muscarinic agonist properties involved in the hypotensive and vasorelaxant responses of rotundifolone in rats. *Planta Med.*, **2002**, *68*(*8*), 700-704.

[56] Guedes, D.N.; Silva, D.F.; Barbosa-Filho, J.M.; Medeiros, I.A. Calcium antagonism and the vasorelaxation of the rat aorta induced by rotundifolone. *Brazilian J. Med. Biol. Res.*, **2004**, *37*(*12*), 1881-1887.

[57] Mehdizadeh, R.; Parizadeh, M.R.; Khooei, A.R.; Mehri, S.; Hosseinzadeh, H. Cardioprotective effect of saffron extract and safranal in isoproterenol-induced myocardial infarction in wistar rats. *Iran. J. Basic Med. Sci.*, **2013**, *16*(*1*), 56-63.

[58] Ding, B.; Dai, Y.; Hou, Y.L.; Wu, X.M.; Chen, X.; Yao, X.S. Four new hemiterpenoid derivatives from *Taxillus chinensis*. *Fitoterapia*. **2013**, *86*(*1*), 1-5.

[59] Lahlou, S.; Interaminense, L.F.L.; Leal-Cardoso, J.H.; Duarte, G.P. Antihypertensive effects of the essential oil of *Alpinia zerumbet* and its main constituent, terpinen-4-ol, in DOCA-salt hypertensive conscious rats. *Fundam. Clin. Pharmacol.*, **2003**, *17*(*3*), 323-330.

[60] Maia-Joca, R.P.M.; Joca, H.C.; Ribeiro, F.J.P.; Nascimento, R.V. Do; Silva-Alves, K.S.; Cruz, J.S.; Coelho-De-Souza, A.N.; Leal-Cardoso, J.H. Investigation of terpinen-4-ol effects on vascular smooth muscle relaxation. *Life Sci.*, **2014**, *115*(*1*), 52-58.

[61] Ribeiro, T.P.; Porto, D.L.; Menezes, C.P.; Antunes, A.A.; Silva, D.F.; De Sousa, D.P.; Nakao, L.S.; Braga, V.A.; Medeiros, I.A. Unravelling the cardiovascular effects induced by α-terpineol: A role for the nitric oxide-cGMP pathway. *Clin. Exp. Pharmacol. Physiol.*, **2010**, *37*(*8*), 811-816.

[62] Magalhães, P.J.C.; Lahlou, S.; Jucá, D.M.; Coelho-De-Souza, L.N.; Da Frota, P.T.T.; Da Costa, A.M.G.; Leal-Cardoso, J.H. Vasorelaxation induced by the essential oil of *Croton nepetaefolius* and its constituents in rat aorta are partially mediated by the endothelium. *Fundam. Clin. Pharmacol.*, **2008**, *22*(*2*), 169-177.

[63] Magyar, J.; Szentandrássy, N.; Bányász, T.; Fülöp, L.; Varró, A.; Nánási, P.P. Effects of thymol on calcium and potassium currents in canine and human ventricular cardiomyocytes. *Br. J. Pharmacol.*, **2002**, *136*(*2*), 330-8.

[64] Szentandrássy, N.; Szigeti, G.; Szegedi, C.; Sárközi, S.; Magyar, J.; Bányász, T.; Csernoch, L.; Kovács, L.; Nánási, P.P.; Jóna, I. Effect of thymol on calcium handling in mammalian ventricular myocardium. *Life Sci.*, **2004**, *74*(*7*), 909-921.

[65] Saravanan, S.; Pari, L. Role of thymol on hyperglycemia and hyperlipidemia in high fat diet-induced type 2 diabetic C57BL/6J mice. *Eur. J. Pharmacol.*, **2015**, *761* 279-87.

[66] Gu, Y.; Wang, X.; Wang, X.; Yuan, M.; Wu, G.; Hu, J.; Tang, Y.; Huang, C. Artemisinin attenuates post-infarct myocardial remodeling by down-regulating the NF-kappaB pathway. *Tohoku J. Exp. Med.*, **2012**, *227*(*3*), 161-170.

[67] Gu, Y.; Wu, G.; Wang, X.; Wang, X.; Wang, Y.; Huang, C. Artemisinin prevents electric remodeling following myocardial infarction possibly by upregulating the expression of connexin 43. *Mol. Med. Rep.*, **2014**, 1851-1856.

[68] Xiong, Z.; Sun, G.; Zhu, C.; Cheng, B.; Zhang, C.; Ma, Y.; Dong, Y. Artemisinin, an anti-malarial agent, inhibits rat cardiac hypertrophy *via* inhibition of NF-κB signaling. *Eur. J. Pharmacol.*, **2010**, *649*(*1-3*), 277-284.

[69] Wang, Y.L.; Wang, Z.J.; Shen, H.L.; Yin, M.; Tang, K.X. Effects of artesunate and ursolic acid on hyperlipidemia and its complications in rabbit. *Eur. J. Pharm. Sci.*, **2013**, *50*(*3-4*), 366-371.

[70] de Siqueira, R.J.B.; Freire, W.B.S.; Vasconcelos-Silva, A. a.; Fonseca-Magalhães, P.A.; Lima, F.J.B.; Brito, T.S.; Mourão, L.T.C.; Ribeiro, R. a.; Lahlou, S.; Magalhães, P.J.C. *In vitro* characterization of the pharmacological effects induced by(-)-α-bisabolol in rat smooth muscle preparations. *Can. J. Physiol. Pharmacol.*, **2012**, *90*(*1*), 23-35.

[71] de Siqueira, R.J.B.; Ribeiro-Filho, H. V.; Freire, R.S.; Cosker, F.; Freire, W.B.S.; Vasconcelos-Silva, A.A.; Soares, M.A.; Lahlou, S.; Magalhães, P.J.C.(-)-α-Bisabolol inhibits preferentially electromechanical coupling on rat isolated arteries. *Vascul. Pharmacol.*, **2014**, *63*(*1*), 37-45.

[72] Eliza, J.; Daisy, P.; Ignacimuthu, S.; Duraipandiyan, V. Normo-glycemic and hypolipidemic effect of costunolide isolated from *Costus speciosus* (Koen ex. Retz.)Sm. in streptozotocin-induced diabetic rats. *Chem. Biol. Interact.*, **2009**, *179*(*2-3*), 329-334.

[73] Szűcs, G.; Murlasits, Z.; Török, S.; Kocsis, G.F.; Pálóczi, J.; Görbe, A.; Csont, T.; Csonka, C.; Ferdinandy, P. Cardioprotection by farnesol: role of the mevalonate pathway. *Cardiovasc. Drugs Ther.*, **2013**, *27*(*4*), 269-77.

[74] Sui, X.; Gao, C. Huperzine A ameliorates damage induced by acute myocardial infarction in rats through antioxidant, anti-apoptotic and anti-inflammatory mechanisms. *Int. J. Mol. Med.*, **2014**, *33*(*1*), 227-233.

[75] Zhang, J.B.; Liu, M.L.; Li, C.; Zhang, Y.; Dai, Y.; Yao, X.S. Nardosinane-type sesquiterpenoids of *Nardostachys chinensis* Batal. *Fitoterapia*. **2015**, *100* 195-200.

[76] Du, M.; Huang, K.; Gao, L.; Yang, L.; Wang, W.S.; Wang, B.; Huang, K.; Huang, D. Nardosinone protects H9c2 cardiac cells from angiotensin II-induced hypertrophy. *J. Huazhong Univ. Sci. Technol. - Med. Sci.*, **2013**, *33*(*6*), 822-826.

[77] Chen, J.; Li, W.L.; Wu, J.L.; Ren, B.R.; Zhang, H.Q. Hypoglycemic effects of a sesquiterpene glycoside isolated from leaves of loquat (*Eriobotrya japonica*(Thunb.) Lindl.). *Phytomedicine*. **2008**, *15*(*1-2*), 98-102.

[78] Seo, E.J.; Lee, D.U.; Kwak, J.H.; Lee, S.M.; Kim, Y.S.; Jung, Y.S. Antiplatelet effects of *Cyperus rotundus* and its component(+)-nootkatone. *J. Ethnopharmacol.*, **2011**, *135*(*1*), 48-54.

[79] Esberg, L.; Wang, G.; Lin, Y.; Ren, J. Iso-S-petasin, a hypotensive sesquiterpene from *Petasites formosanus*, depresses cardiac contraction and intracellular Ca^{2+} transients in adult rat ventricular myocytes. *Am. J. Physiol. Cell Physiol*. **2003**, *284*(*2*), C378-388.

[80] Fusi, F.; Durante, M.; Sgaragli, G.; Khanh, P.N.; Son, N.T.; Huong, T.T.; Huong, V.N.; Cuong, N.M. *In vitro* vasoactivity of zerumbone from *Zingiber zerumbet*. *Planta Med.*, **2015**, *81*(*4*), 298-304.

[81] Kolak, U.; Ari, S.; Birman, H.; Ulubelen, A. Cardioactive diterpenoids from the roots of *Salvia amplexicaulis*. *Planta Med.*, **2001**, *67* 761-763.

[82] Simplicio, J.A.; Pernomian, L.; Simão, M.R.; Carnio, E.C.; Batalhão, M.E.; Ambrosio, S.R.; Tirapelli, C.R. Mechanisms underlying the vascular and hypotensive actions of the labdane ent-3-acetoxy-labda-8(17),13-dien-15-oic acid. *Eur. J. Pharmacol.*, **2014**, *726*(*1*), 66-76.

[83] Jian, X.-X.; Tang, P.; Liu, X.-X.; Chao, R.-B.; Chen, Q.-H.; She, X.-K. Structure-cardiac activity relationship of c19-diterpenoid alkaloids. *Nat. Prod. Commun.*, **2012**, *7*(*6*), 713-720.

[84] Ulubelen, A.; Birman, H.; Öksüz, S.; Topçu, G.; Kolak, U.; Barla, A.; Voelter, W. Cardioactive diterpenes from the roots of *Salvia eriophora*. *Planta Med.*, **2002**, *68*(*9*), 818-821.

[85] Al Batran, R.; Al-Bayaty, F.; Al-Obaidi, M.M.J.; Hussain, S.F.; Mulok, T.Z. Evaluation of the effect of andrographolide on atherosclerotic rabbits induced by *Porphyromonas gingivalis*. *Biomed Res. Int.*, **2014**, *2014*.

[86] Al Batran, R.; Al-Bayaty, F.; Al-Obaidi, M.M.J.; Ashrafi, A. Insights into the antiatherogenic molecular mechanisms of andrographolide against *Porphyromonas gingivalis*-induced atherosclerosis in rabbits. *Naunyn. Schmiedebergs. Arch. Pharmacol.*, **2014**, *387*(*12*), 1141-1152.

[87] Zhang, Z.; Jiang, J.; Yu, P.; Zeng, X.; Larrick, J.W.; Wang, Y. Hypoglycemic and beta cell protective effects of andrographolide analogue for diabetes treatment. *J. Transl. Med.*, **2009**, *7*(*Cdc*), 62.

[88] Awang, K.; Abdullah, N.H.; Hadi, A.H.A.; Fong, Y.S. Cardiovascular activity of labdane diterpenes from *Andrographis paniculata* in isolated rat hearts. *J. Biomed. Biotechnol.*, **2012**, *2012* 876458.

[89] Muller, S.; Tirapelli, C.R.; de Oliveira, A.M.; Murillo, R.; Castro, V.; Merfort, I. Studies of ent-kaurane diterpenes from Oyedaea verbesinoides for their inhibitory activity on vascular smooth muscle contraction. *Phytochemistry*. **2003**, *63*(*4*), 391-396.

[90] Liu, X.; Jian, X.; Cai, X.; Chao, R.; Chen, Q.; Chen, D.; Wang, X.; Wang, F. Cardioactive C19-diterpenoid alkaloids from the lateral roots of *Aconitum carmichaeli* "Fu Zi." *Chem. Pharm. Bull.*(*Tokyo).*, **2012**, *60*(*1*), 144-149.

[91] Jin, H.J.; Xie, X.L.; Ye, J.M.; Li, C.G. Tanshinone IIA and cryptotanshinone protect against hypoxia-induced mitochondrial apoptosis in H9c2 cells. *PLoS One.* **2013**, *8*(*1*), 1-10.

[92] Kang, M.-S.; Hirai, S.; Goto, T.; Kuroyanagi, K.; Kim, Y.-I.; Ohyama, K.; Uemura, T.; Lee, J.-Y.; Sakamoto, T.; Ezaki, Y.; Yu, R.; Takahashi, N.; Kawada, T. Dehydroabietic acid, a diterpene, improves diabetes and hyperlipidemia in obese diabetic KK-Ay mice. *BioFactors*. **2009**, *35*(*5*), 442-448.

[93] Silva, R.M.; Oliveira, F.A.; Cunha, K.M.A.; Maia, J.L.; Maciel, M.A.M.; Pinto, A.C.; Nascimento, N.R.F.; Santos, F.A.; Rao, V.S.N. Cardiovascular effects of trans-dehydrocrotonin, a diterpene from *Croton cajucara* in rats. *Vascul. Pharmacol.*, **2005**, *43*(*1*), 11-18.

[94] Silva, R.M.; Santos, F.A.; Rao, V.S.N.; Maciel, M.A.; Pinto, A.C. Blood glucose- and triglyceride-lowering effect of trans-dehydrocrotonin, a diterpene from *Croton cajucara* benth. in rats. *Diabetes, Obes. Metab.*, **2001**, *3*(*6*), 452-456.

[95] Cuadrado-Berrocal, I.; Gómez-Gaviro, M. V.; Benito, Y.; Barrio, A.; Bermejo, J.; Fernández-Santos, M.E.; Sánchez, P.L.; Desco, M.; Fernández-Avilés, F.; Fernández-Velasco, M.; Boscá, L.; de las Heras, B. A labdane diterpene exerts ex vivo and *in vivo* cardioprotection against post-ischemic injury: Involvement of AKT-dependent mechanisms. *Biochem. Pharmacol.*, **2015**, *93*(*4*), 428-439.

[96] Cuadrado, I.; Fernández-Velasco, M.; Boscá, L.; de las Heras, B. Labdane diterpenes protect against anoxia/reperfusion injury in cardiomyocytes: involvement of AKT activation. *Cell Death Dis.*, **2011**, *2*(*11*), e229.

[97] Zhang, C.Y.; Tan, B.K.H. Vasorelaxation of rat thoracic aorta caused by 14-deoxyandrographolide. *Clin. Exp. Pharmacol. Physiol.*, **1998**, *25*(*6*), 424-429.

[98] Zhang, C.; Kuroyangi, M.; Tan, B.K. Cardiovascular activity of 14-deoxy-11,12-didehydroandrographolide in the anaesthetised rat and isolated right atria. *Pharmacol. Res.*, **1998**, *38*(*6*), 413-417.

[99] Ulubelen, A.; Oksuz, S.; Kolak, U.; Birman, H.; Voelter, W. Cardioactive terpenoids and a new rearranged diterpene from *Salvia syriaca*. *Planta Med.*, **2000**, *66*(*7*), 627-629.

[100] Liebgott, T.; Miollan, M.; Berchadsky, Y.; Drieu, K.; Culcasi, M.; Pietri, S. Complementary cardioprotective effects of flavonoid metabolites and terpenoid constituents of Ginkgo biloba extract (EGb 761) during ischemia and reperfusion. *Basic Res. Cardiol.*, **2000**, *95*(*5*), 368-377.

[101] Pietri, S.; Maurelli, E.; Drieu, K.; Culcasi, M. Cardioprotective and anti-oxidant effects of the terpenoid constituents of Ginkgo biloba extract (EGb 761). *J. Mol. Cell. Cardiol.*, **1997**, *29* 733-742.

[102] Wang, G.-G.; Chen, Q.-Y.; Li, W.; Lu, X.-H.; Zhao, X. Ginkgolide B increases hydrogen sulfide and protects against endothelial dysfunction in diabetic rats. *Croat. Med. J.*, **2015**, *56*(*1*), 4-13.

[103] Billottet, L.; Martel, S.; Culcasi, M.; Drieu, K.; Carrupt, P.; Pietri, S. Influence of lipophilicity and stereochemistry at the c7 position on the cardioprotective and antioxidant effect of ginkgolides during rat heart ischemia and reperfusion. *Drug Dev. Res.*, **2005**, *64* 157-171.

[104] Mondolis, E.; Morán-Pinzón, J.A.; Rojas-Marquéz, F.A.; López-Pérez, J.L.; Abad, A.; Amaro-Luis, J.M.; De León, *E.G.*, Vasorelaxant effects in aortic rings of eight diterpenoids isolated from three Venezuelan plants. *Rev. Bras. Farmacogn.*, **2013**, *23*(*5*), 769-775.

[105] Xing, B.N.; Jin, S.S.; Wang, H.; Tang, Q.F.; Liu, J.H.; Li, R.Y.; Liang, J.Y.; Tang, Y.Q.; Yang, C.H. New diterpenoid alkaloids from *Aconitum coreanum* and their anti-arrhythmic effects on cardiac sodium current. *Fitoterapia*. **2014**, *94* 120-126.

[106] Ambrosio, S.R.; Tirapelli, C.R.; Coutinho, S.T.; de Oliveira, D.C.R.; de Oliveira, A.M.; Da Costa, F.B. Role of the carboxylic group in the antispasmodic and vasorelaxant action displayed by kaurenoic acid. *J. Pharm. Pharmacol.*, **2004**, *56*(*11*), 1407-1413.

[107] Tirapelli, C.R.; Ambrosio, S.R.; Da Costa, F.B.; Coutinho, S.T.; De Oliveira, D.C.R.; De Oliveira, A.M. Analysis of the mechanisms underlying the vasorelaxant action of kaurenoic acid in the isolated rat aorta. *Eur. J. Pharmacol.*, **2004**, *492*(*2-3*), 233-241.

[108] Lahlou, S.; Correia, C.A. de B.; Vasconcelos dos Santos, M.; David, J.M.; David, J.P.; Duarte, G.P.; Magalhães, P.J.C. Mechanisms underlying the cardiovascular effects of a labdenic diterpene isolated from *Moldenhawera nutans* in normotensive rats. *Vascul. Pharmacol.*, **2007**, *46*(*1*), 60-66.

[109] de Barros Correia Junior, C.A.; Bezerra de Siqueira, R.J.; Leal Interaminense, L.F.; Alves-Santos, T.R.; Duarte, G.P.; David, J.M.; David, J.P.; Magalhães, P.J.C.; Lahlou, S. Cardiovascular effects of a labdenic diterpene isolated from *Moldenhawera nutans* in conscious, spontaneously hypertensive rats. *Pharm. Biol.*, **2015**, *53*(*4*), 582-587.

[110] de Oliveira, A.P.; Furtado, F.F.; da Silva, M.S.; Tavares, J.F.; Mafra, R.A.; Araújo, D.A.M.; Cruz, J.S.; de Medeiros, I.A. Calcium channel blockade as a target for the cardiovascular effects induced by the 8(17), 12E,14-labdatrien-18-oic acid(labdane-302). *Vascul. Pharmacol.*, **2006**, *44*(*5*), 338-344.

[111] Mnonopi, N.; Levendal, R.A.; Davies-Coleman, M.T.; Frost, C.L. The cardioprotective effects of marrubiin, a diterpenoid found in *Leonotis leonurus* extracts. *J. Ethnopharmacol.*, **2011**, *138*(*1*), 67-75.

[112] Mnonopi, N.; Levendal, R.A.; Mzilikazi, N.; Frost, C.L. Marrubiin, a constituent of *Leonotis leonurus*, alleviates diabetic symptoms. *Phytomedicine*. **2012**, *19*(*6*), 488-493.

[113] Khan, A.U.; Ullah, R.; Khan, A.; Mustafa, M.R.; Hussain, J.; Murugan, D.D.; Hadi, A.H. Vasodilator effect of *Phlomis bracteosa* constituents is mediated through dual endothelium-dependent and endothelium-independent pathways. *Clin. Exp. Hypertens.*, **2012**, *34*(*2*), 132-139.

[114] El Bardai, S.; Morel, N.; Wibo, M.; Fabre, N.; Llabres, G.; Lyoussi, B.; Quetin-Leclercq, J. The vasorelaxant activity of marrubenol and marrubiin from *Marrubium vulgare*. *Planta Med.*, **2003**, *69*(*1*), 75-77.

[115] Tirapelli, C.R.; Ambrosio, S.R.; Da Costa, F.B.; De Oliveira, A.M. Evidence for the mechanisms underlying the effects of pimaradienoic acid isolated from the roots of *Viguiera arenaria* on rat aorta. *Pharmacology*. **2004**, *70*(*1*), 31-38.

[116] Ambrosio, S.R.; Tirapelli, C.R.; Bonaventura, D.; Oliveira, A.M. De; da Costa, F.B. Pimarane diterpene from *Viguiera arenaria* (Asteraceae) inhibit rat carotid contraction. *Fitoterapia*. **2002**, *73* 484-489.

[117] Latha, M.; Pari, L.; Ramkumar, K.M.; Rajaguru, P.; Suresh, T.; Dhanabal, T.; Sitasawad, S.; Bhonde, R. Antidiabetic effects of scoparic acid D isolated from *Scoparia dulcis* in rats with streptozotocin-induced diabetes. *Nat. Prod. Res.*, **2009**, *23*(*16*), 1528-1540.

[118] Ioroi, T.; Akao, M.; Iguchi, M.; Kato, M.; Kimura, T.; Izumi, Y.; Akaike, A.; Kume, T. Serofendic acid protects against myocardial ischemia-reperfusion injury in rats. *J. Pharmacol. Sci.*, **2014**, *280* 274-280.

[119] Takeda, T.; Akao, M.; Matsumoto-Ida, M.; Kato, M.; Takenaka, H.; Kihara, Y.; Kume, T.; Akaike, A.; Kita, T. Serofendic acid, a novel substance extracted from fetal calf serum, protects against oxidative stress in neonatal rat cardiac myocytes. *J. Am. Coll. Cardiol.*, **2006**, *47*(*9*), 1882-1890.

[120] Akao, M.; Takeda, T.; Kita, T.; Kume, T.; Akaike, A. Serofendic acid, a substance extracted from fetal calf serum, as a novel drug for cardioprotection. *Cardiovasc. Drug Rev.*, **2007**, *25*(*4*), 333-341.

[121] Wu, W.-Y.; Wang, W.-Y.; Ma, Y.-L.; Yan, H.; Wang, X.-B.; Qin, Y.; Su, M.; Chen, T.; Wang, Y.-P. Sodium tanshinone IIA silate inhibits oxygen-glucose deprivation/recovery-induced cardiomyocyte apoptosis *via* suppression of the NF-κB/TNF-α pathway. *Br. J. Pharmacol.*, **2013**, *169*(*5*), 1058-71.

[122] Wu, W.; Yan, H.; Wang, X.; Gui, Y.; Gao, F.; Tang, X.; Qin, Y.; Su, M.; Chen, T.; Wang, Y. Sodium tanshinone IIA silate inhibits high glucose-induced vascular smooth muscle cell proliferation and migration through activation of AMP-activated protein kinase. *PLoS One*. **2014**, *9*(*4*), e94957.

[123] Liu, J.C.; Kao, P.K.; Chan, P.; Hsu, Y.H.; Hou, C.C.; Lien, G.S.; Hsieh, M.H.; Chen, Y.J.; Cheng, J.T. Mechanism of the antihypertensive effect of stevioside in anesthetized dogs. *Pharmacology*. **2003**, *67*(*1*), 14-20.

[124] Lee, C.N.; Wong, K.L.; Liu, J.C.; Chen, Y.J.; Cheng, J.T.; Chan, P. Inhibitory effect of stevioside on calcium influx to produce antihypertension. *Planta Med.*, **2001**, *67*(*9*), 796-799.

[125] Zhang, M.Q.; Tu, J.F.; Chen, H.; Shen, Y.; Pang, L.X.; Yang, X.H.; Sun, R.H.; Zheng, Y.L. Janus kinase/signal transducer and activator of transcription inhibitors enhance the protective effect mediated by tanshinone IIA from hypoxic/ischemic injury in cardiac myocytes. *Mol. Med. Rep.*, **2014**, *11* 3115-3121.

[126] Zhang, Y.; Wei, L.; Sun, D.; Cao, F.; Gao, H.; Zhao, L.; Du, J.; Li, Y.; Wang, H. Tanshinone IIA pretreatment protects myocardium against ischaemia/reperfusion injury through the phosphatidylinositol 3-kinase/Akt-dependent pathway in diabetic rats. *Diabetes, Obes. Metab.*, **2010**, *12*(*4*), 316-322.

[127] Sun, D.; Shen, M.; Li, J.; Li, W.; Zhang, Y.; Zhao, L.; Zhang, Z.; Yuan, Y.; Wang, H.; Cao, F. Cardioprotective effects of tanshinone IIA pretreatment *via* kinin B2 receptor-Akt-GSK-3β dependent pathway in experimental diabetic cardiomyopathy. *Cardiovasc. Diabetol.*, **2011**, *10*(*1*), 4.

[128] Shan, H.; Li, X.; Pan, Z.; Zhang, L.; Cai, B.; Zhang, Y.; Xu, C.; Chu, W.; Qiao, G.; Li, B.; Lu, Y.; Yang, B. Tanshinone MA protects against sudden cardiac death induced by lethal arrhythmias *via* repression of microRNA-1. *Br. J. Pharmacol.*, **2009**, *158*(*5*), 1227-1235.

[129] Tan, X.; Li, J.; Wang, X.; Chen, N.; Cai, B.; Wang, G.; Shan, H.; Dong, D.; Liu, Y.; Li, X.; Yang, F.; Li, X.; Zhang, P.; Li, X.; Yang, B.; Lu, Y. Tanshinone IIA protects against cardiac hypertrophy *via* inhibiting cal- cineurin / Nfatc3 pathway. *Int. J. Biol. Sci.*, **2011**, *7*(*3*), 383-389.

[130] Hong, H.; Liu, J.; Cheng, T.; Chan, P. Tanshinone IIA attenuates angiotensin II-induced apoptosis *via* Akt pathway in neonatal rat cardiomyocytes. *Acta Pharmacol. Sin.*, **2010**, *31*(*12*), 1569-75.

[131] Li, Y.H.; Xu, Q.; Xu, W.H.; Guo, X.H.; Zhang, S.; Chen, Y.D. Mechanisms of protection against diabetes-induced impairment of endothelium-dependent vasorelaxation by Tanshinone IIA. *Biochim. Biophys. Acta - Gen. Subj.*, **2015**, *1850*(*4*), 813-823.

[132] Pang, H.; Han, B.; Yu, T.; Peng, Z. The complex regulation of tanshinone IIA in rats with hypertension-induced left ventricular hypertrophy. *PLoS One*, **2014**, *9*(*3*), 1-9.

[133] Chan, P.; Chen, Y.-C.; Lin, L.-J.; Cheng, T.-H.; Anzai, K.; Chen, Y.-H.; Liu, Z.-M.; Lin, J.-G.; Hong, H.-J. Tanshinone IIA attenuates H_2O_2-induced injury in human umbilical vein endothelial cells. *Am. J. Chin. Med.*, **2012**, *40*(*06*), 1307-1319.

[134] Martinsen, A.; Baccelli, C.; Navarro, I.; Abad, A.; Quetin-Leclercq, J.; Morel, N. Vascular activity of a natural diterpene isolated from *Croton zambesicus* and of a structurally similar synthetic trachylobane. *Vascul. Pharmacol.*, **2010**, *52*(*1-2*), 63-69.

[135] Liang, Z.; Leo, S.; Wen, H.; Ouyang, M.; Jiang, W.; Yang, K. Triptolide improves systolic function and myocardial energy metabolism of diabetic cardiomyopathy in streptozotocin-induced diabetic rats. *BMC Cardiovasc. Disord.*, **2015**, *15*(*1*), 42.

[136] Wen, H.-L.; Liang, Z.-S.; Zhang, R.; Yang, K. Anti-inflammatory effects of triptolide improve left ventricular function in a rat model of diabetic cardiomyopathy. *Cardiovasc. Diabetol.*, **2013**, *12*(*1*), 50.

[137] Liu, M.; Chen, J.; Huang, Y.; Ke, J.; Li, L.; Huang, D.; Wu, W. Triptolide alleviates isoprenaline-induced cardiac remodeling in rats *via* TGF-beta1/Smad3 and p38 MAPK signaling pathway. *Pharmazie*. **2015**, *70* 244-250.

[138] Liang, Q.; Yu, X.; Qu, S.; Xu, H.; Sui, D. Acanthopanax senticosides B ameliorates oxidative damage induced by hydrogen peroxide in cultured neonatal rat cardiomyocytes. *Eur. J. Pharmacol.*, **2010**, *627*(*1-3*), 209-215.

[139] Nair, S.A.; Sabulal, B.; Radhika, J.; Arunkumar, R.; Subramoniam, A. Promising anti-diabetes mellitus activity in rats of β-amyrin palmitate isolated from *Hemidesmus indicus* roots. *Eur. J. Pharmacol.*, **2014**, *734*(*1*), 77-82.

[140] Si, L.; Xu, J.; Yi, C.; Xu, X.; Wang, F.; Gu, W.; Zhang, Y.; Wang, X. Asiatic acid attenuates cardiac hypertrophy by blocking transforming growth factor-β1-mediated hypertrophic signaling *in vitro* and *in vivo*. *Int. J. Mol. Med.*, **2014**, *34*(*2*), 499-506.

[141] Wang, X.; Lu, Q.; Yu, D.S.; Chen, Y.P.; Shang, J.; Zhang, L.Y.; Sun, H. Bin; Liu, J. Asiatic acid mitigates hyperglycemia and reduces islet fibrosis in Goto-Kakizaki rat, a spontaneous type 2 diabetic animal model. *Chin. J. Nat. Med.*, **2015**, *13*(*7*), 0529-0534.

[142] Ramachandran, V.; Saravanan, R.; Senthilraja, P. Antidiabetic and antihyperlipidemic activity of asiatic acid in diabetic rats, role of HMG CoA: *In vivo* and in silico approaches. *Phytomedicine*. **2014**, *21*(*3*), 225-232.

[143] Hung, Y.-C.; Yang, H.-T.; Yin, M.-C. Asiatic acid and maslinic acid protected heart *via* anti-glycative and anti-coagulatory activities in diabetic mice. *Food Funct.*, **2015**, *6*(*9*), 2967-74.

[144] Chan, C.Y.; Mong, M.C.; Liu, W.H.; Huang, C.Y.; Yin, M.C. Three pentacyclic triterpenes protect H9c2 cardiomyoblast cells against high-glucose-induced injury. *Free Radic. Res.*, **2014**, *48*(*4*), 402-411.

[145] Li, C.; Tian, J.; Li, G.; Jiang, W.; Xing, Y.; Hou, J.; Zhu, H.; Xu, H.; Zhang, G.; Liu, Z.; Ye, Z. Asperosaponin VI protects cardiac myocytes from hypoxia-induced apoptosis *via* activation of the PI3K/Akt and CREB pathways. *Eur. J. Pharmacol.*, **2010**, *649*(*1-3*), 100-107.

[146] Li, C.; Liu, Z.; Tian, J.; Li, G.; Jiang, W.; Zhang, G.; Chen, F.; Lin, P.; Ye, Z. Protective roles of Asperosaponin VI, a triterpene saponin isolated from *Dipsacus asper* Wall on acute myocardial infarction in rats. *Eur. J. Pharmacol.*, **2010**, *627*(*1-3*), 235-241.

[147] Zhao, J.; Yang, P.; Li, F.; Tao, L.; Ding, H.; Rui, Y.; Cao, Z.; Zhang, W. Therapeutic effects of astragaloside iv on myocardial injuries: multi-target identification and network analysis. *PLoS One*, **2012**, *7*(*9*), 1-11.

[148] Hu, J.Y.; Han, J.; Chu, Z.G.; Song, H.P.; Zhang, D.X.; Zhang, Q.; Huang, Y.S. Astragaloside IV attenuates hypoxia-induced cardiomyocyte damage in rats by upregulating superoxide dismutase-1 levels. *Clin. Exp. Pharmacol. Physiol.*, **2009**, *36*(*4*), 351-357.

[149] Yuan, W.; Zhang, Y.; Ge, Y.; Yan, M.; Kuang, R.; Zheng, X. Astragaloside IV inhibits proliferation and promotes apoptosis in rat vascular smooth muscle cells under high glucose concentration *in vitro*. *Planta Med.*, **2008**, *74*(*10*), 1259-1264.

[150] Zhang, S.; Tang, F.; Yang, Y.; Lu, M.; Luan, A.; Zhang, J.; Yang, J.; Wang, H. Astragaloside IV protects against isoproterenol-induced cardiac hypertrophy by regulating NF-κB/PGC-1α signaling mediated energy biosynthesis. *PLoS One*, **2015**, *10*(*3*), e0118759.

[151] Yang, J.; Wang, H.X.; Zhang, Y.J.; Yang, Y.H.; Lu, M.L.; Zhang, J.; Li, S.T.; Zhang, S.P.; Li, G. Astragaloside IV attenuates inflammatory cytokines by inhibiting TLR4/NF-kB signaling pathway in isoproterenol-induced myocardial hypertrophy. *J. Ethnopharmacol.*, **2013**, *150*(*3*), 1062-1070.

[152] Li, Z.-P.; Cao, Q. Effects of astragaloside IV on myocardial calcium transport and cardiac function in ischemic rats. *Acta Pharmacol. Sin.*, **2002**, *23*(*10*), 898-904.

[153] Si, J.; Wang, N.; Wang, H.; Xie, J.; Yang, J.; Yi, H.; Shi, Z.; Ma, J.; Wang, W.; Yang, L.; Yu, S.; Li, J. HIF-1α signaling activation by post-ischemia treatment with astragaloside IV attenuates myocardial ischemia-reperfusion injury. *PLoS One*, **2014**, *9*(*9*), e107832.

[154] Yin, Y.; Qi, F.; Song, Z.; Zhang, B.; Teng, J. Ferulic acid combined with astragaloside IV protects against vascular endothelial dysfunction in diabetic rats. *Biosci. Trends*. **2014**, *8*(*4*), 217-226.

[155] Tu, L.; Pan, C.S.; Wei, X.H.; Yan, L.; Liu, Y.Y.; Fan, J.Y.; Mu, H.N.; Li, Q.; Li, L.; Zhang, Y.; He, K.; Mao, X.W.; Sun, K.; Wang, C.S.; Yin, C.C.; Han, J.Y. Astragaloside IV protects heart from ischemia and reperfusion injury *via* energy regulation mechanisms. *Microcirculation*. **2013**, *20*(*8*), 736-747.

[156] Lu, M.; Tang, F.; Zhang, J.; Luan, A.; Mei, M.; Xu, C.; Zhang, S.; Wang, H.; Maslov, L.N. Astragaloside IV attenuates injury caused by myocardial ischemia/reperfusion in rats *via* regulation of toll-like receptor 4/nuclear factor-κb signaling pathway. *Phyther. Res.*, **2015**, *29*(*4*), 599-606.

[157] Rios, M.Y.; López-Martínez, S.; López-Vallejo, F.; Medina-Franco, J.L.; Villalobos-Molina, R.; Ibarra-Barajas, M.; Navarrete-Vazquez, G.; Hidalgo-Figueroa, S.; Hernández-Abreu, O.; Estrada-Soto, S. Vasorelaxant activity of some structurally related triterpenic acids from *Phoradendron reichenbachianum* (Viscaceae) mainly by NO production: *Ex vivo* and *in silico* studies. *Fitoterapia*. **2012**, *83*(*6*), 1023-1029.

[158] Estrada, O.; Contreras, W.; Acha, G.; Lucena, E.; Venturini, W.; Cardozo, A.; Alvarado-Castillo, C. Chemical constituents from *Licania cruegeriana* and their cardiovascular and antiplatelet effects. *Molecules*. **2014**, *19*(*12*), 21215-25.

[159] Elshazly, S.M.; Abd El Motteleb, D.M.; Nassar, N.N. The selective 5-LOX inhibitor 11-keto-beta-boswellic acid protects against myocardial ischemia reperfusion injury in rats: Involvement of redox and inflammatory cascades. *Naunyn. Schmiedebergs. Arch. Pharmacol.*, **2013**, *386*(*9*), 823-833.

[160] Der Sarkissian, S.; Cailhier, J.F.; Borie, M.; Stevens, L.M.; Gaboury, L.; Mansour, S.; Hamet, P.; Noiseux, N. Celastrol protects ischaemic myocardium through a heat shock response with up-regulation of haeme oxygenase-1. *Br. J. Pharmacol.*, **2014**, *171*(*23*), 5265-5279.

[161] Gu, L.; Bai, W.; Li, S.; Zhang, Y.; Han, Y.; Gu, Y.; Meng, G.; Xie, L.; Wang, J.; Xiao, Y.; Shan, L.; Zhou, S.; Wei, L.; Ferro, A.; Ji, Y. Celastrol Prevents Atherosclerosis *via* inhibiting LOX-1 and oxidative stress. *PLoS One*. **2013**, *8*(*6*), 1-11.

[162] Li, Y.; Zhang, T.; Cui, J.; Jia, N.; Wu, Y.; Xi, M.; Wen, A. Chikusetsu saponin IVa regulates glucose uptake and fatty acid oxidation: Implications in antihyperglycemic and hypolipidemic effects. *J. Pharm. Pharmacol.*, **2015**, *1* 997-1007.

[163] Cui, J.; Xi, M.M.; Li, Y.W.; Duan, J.L.; Wang, L.; Weng, Y.; Jia, N.; Cao, S.S.; Li, R.L.; Wang, C.; Zhao, C.; Wu, Y.; Wen, A.D. Insulinotropic effect of Chikusetsu saponin IVa in diabetic rats and pancreatic β-cells. *J. Ethnopharmacol.*, **2015**, *164* 334-339.

[164] Miura, T.; Ueda, N.; Yamada, K.; Fukushima, M.; Ishida, T.; Kaneko, T.; Matsuyama, F.; Seino, Y. Antidiabetic effects of corosolic acid in KK-Ay diabetic mice. *Biol. Pharm. Bull.*, **2006**, *29*(*March*), 585-587.

[165] Chen, H.; Yang, J.; Zhang, Q.; Chen, L.-H.; Wang, Q. Corosolic acid ameliorates atherosclerosis in apolipoprotein E-deficient mice by regulating the nuclear factor-κb signaling pathway and inhibiting monocyte chemoattractant protein-1 expression. *Circ. J.*, **2012**, *76*(*4*), 995-1003.

[166] Badole, S.L.; Bodhankar, S.L. Antidiabetic activity of cycloart-23-ene-3β, 25-diol(B2) isolated from *Pongamia pinnata*(*L. Pierre*) in streptozotocin-nicotinamide induced diabetic mice. *Eur. J. Pharmacol.*, **2010**, *632*(*1-3*), 103-109.

[167] Li, S.; Zhao, J.; Liu, Y.; Chen, Z.; Xu, Q.; Khan, I.A.; Yang, S. New Triterpenoid Saponins from *Ilex cornuta* and Their Protective Effects against H_2O_2-Induced Myocardial Cell Injury. *J. Agric. Food Chem.*, **2014**, *62*(*2*), 488-496.

[168] Han, B.; Meng, Q.; Li, Q.; Zhang, J.; Bi, Y.; Jiang, N. Effect of 20(S)-protopanaxatriol and its epimeric derivatives on myocardial injury induced by isoproterenol. *Arzneimittelforschung*. **2011**, *61*(*3*), 148-152.

[169] Kuo, Y.H.; Lin, C.H.; Shih, C.C. Antidiabetic and antihyperlipidemic properties of a triterpenoid compound, dehydroeburicoic acid, from *Antrodia camphorata in vitro* and in streptozotocin-induced mice. *J. Agric. Food Chem.*, **2015**, *63*(*46*), 10140-10151.

[170] Wang, Y.; Ding, B.; Luo, D.; Chen, L.Y.; Hou, Y.L.; Dai, Y.; Yao, X.S. New triterpene glycosides from *Ziziphi Spinosae* Semen. *Fitoterapia*. **2013**, *90* 185-191.

[171] Wang, W.; Zhao, J.; Li, S.; Lu, Y.; Liu, Y.; Xu, Q.; Li, X.; Khan, I.A.; Yang, S. Five new triterpenoidal saponins from the roots of *Ilex cornuta* and their protective effects against H_2O_2-induced cardiomyocytes injury. *Fitoterapia*. **2014**, *99* 40-47.

[172] Pérez Gutiérrez, R.M.; Vargas Solis, R.; Garcia Baez, E.; Navarro, Y.G. Hypoglycemic activity of constituents from *Astianthus viminalis* in normal and streptozotocin-induced diabetic mice. *J. Nat. Med.*, **2009**, *63*(*4*), 393-401.

[173] Wang, M.; Meng, X.; Yu, Y.; Sun, G.; Xu, X.; Zhang, X.; Dong, X.; Ye, J.; Xu, H.; Sun, Y.; Sun, X. Elatoside C protects against hypoxia/reoxygenation-induced apoptosis in H9c2 cardiomyocytes through the reduction of endoplasmic reticulum stress partially depending on STAT3 activation. *Apoptosis*. **2014**, *19*(*12*), 1727-1735.

[174] Wu, Y.; Xia, Z.Y.; Dou, J.; Zhang, L.; Xu, J.J.; Zhao, B.; Lei, S.Q.; Liu, H.M. Protective effect of ginsenoside Rb1 against myocardial ischemia/reperfusion injury in streptozotocin-induced diabetic rats. *Mol. Biol. Rep.*, **2011**, *38*(*7*), 4327-4335.

[175] Xiong, Y.; Shen, L.; Liu, K.J.; Tso, P.; Xiong, Y.; Wang, G.; Woods, S.C.; Liu, M. Antiobesity and antihyperglycemic effects of ginsenoside Rb1 in rats. *Diabetes*, **2010**, *59*(*10*), 2505-2512.

[176] Xia, R.; Zhao, B.; Wu, Y.; Hou, J.B.; Zhang, L.; Xu, J.J.; Xia, Z.Y. Ginsenoside Rb1 preconditioning enhances eNOS expression and attenuates myocardial ischemia/reperfusion injury in diabetic rats. *J. Biomed. Biotechnol.*, **2011**, *2011*.

[177] Ma, L.; Liu, H.; Xie, Z.; Yang, S.; Xu, W.; Hou, J.; Yu, B. Ginsenoside Rb3 protects cardiomyocytes against ischemia-reperfusion injury *via* the inhibition of JNK-mediated NF-κB pathway: A mouse cardiomyocyte model. *PLoS One*, **2014**, *9*(*8*), 1-12.

[178] Bu, Q.T.; Zhang, W.Y.; Chen, Q.C.; Zhang, C.Z.; Gong, X.J.; Liu, W.C.; Li, W.; Zheng, Y.N. Anti-diabetic effect of ginsenoside Rb(3) in alloxan-induced diabetic mice. *Med. Chem*. **2012**, *8*(*5*), 934-941.

[179] Wang, T.; Yu, X.; Qu, S.; Xu, H.; Han, B.; Sui, D. Effect of ginsenoside Rb3 on myocardial injury and heart function impairment induced by isoproterenol in rats. *Eur. J. Pharmacol.*, **2010**, *636*(*1-3*), 121-125.

[180] Shi, Y.; Han, B.; Yu, X.; Qu, S.; Sui, D. Ginsenoside Rb3 ameliorates myocardial ischemia-reperfusion injury in rats. *Pharm. Biol.*, **2011**, *49*(*9*), 900-906.

[181] Yang, N.; Chen, P.; Tao, Z.; Zhou, N.; Gong, X.; Xu, Z.; Zhang, M.; Zhang, D.; Chen, B.; Tao, Z.; Yang, Z. Beneficial effects of ginsenoside-Rg1 on ischemia-induced angiogenesis in diabetic mice. *Acta Biochim. Biophys. Sin.*(*Shanghai).*, **2012**, *44*(*12*), 999-1005.

[182] Yu, H.; Zhen, J.; Pang, B.; Gu, J.; Wu, S. Ginsenoside Rg1 ameliorates oxidative stress and myocardial apoptosis in streptozotocin-induced diabetic rats. *J. Zhejiang Univ. Sci. B*. **2015**, *16*(*5*), 344-354.

[183] Wang, Y.; Li, X.; Wang, X.; Lau, W.; Wang, Y.; Xing, Y.; Zhang, X.; Ma, X.; Gao, F. Ginsenoside Rd attenuates myocardial ischemia/reperfusion injury *via* Akt/GSK-3β signaling and inhibition of the mitochondria-dependent apoptotic pathway. *PLoS One*, **2013**, *8*(*8*), e70956.

[184] Parisella, M.L.; Angelone, T.; Gattuso, A.; Cerra, M.C.; Pellegrino, D. Glycyrrhizin and glycyrrhetinic acid directly modulate rat cardiac performance. *J. Nutr. Biochem.*, **2012**, *23*(*1*), 69-75.

[185] Kalaiarasi, P.; Kaviarasan, K.; Pugalendi, K.V. Hypolipidemic activity of 18β-glycyrrhetinic acid on streptozotocin-induced diabetic rats. *Eur. J. Pharmacol.*, **2009**, *612*(*1-3*), 93-97.

[186] Kalaiarasi, P.; Pugalendi, K.V. Antihyperglycemic effect of 18β-glycyrrhetinic acid, aglycone of glycyrrhizin, on streptozotocin-diabetic rats. *Eur. J. Pharmacol.*, **2009**, *606*(*1-3*), 269-273.

[187] Battaglia, V.; Brunati, A.M.; Fiore, C.; Rossi, C.A.; Salvi, M.; Tibaldi, E.; Palermo, M.; Armanini, D.; Toninello, A. Glycyrrhetinic acid as inhibitor or amplifier of permeability transition in rat heart mitochondria. *Biochim. Biophys. Acta - Biomembr.*, **2008**, *1778*(*1*), 313-323.

[188] Zhai, C.; Zhang, M.; Zhang, Y.; Xu, H.; Wang, J.; An, G.; Wang, Y.; Li, L. Glycyrrhizin protects rat heart against ischemia-reperfusion injury through blockade of HMGB1-dependent phospho-JNK/Bax pathway. *Acta Pharmacol. Sin.*, **2012**, *33*(*12*), 1477-87.

[189] Kilgore, K.S.; Tanhehco, E.J.; Park, J.L.; Naylor, K.B.; Anderson, M.B.; Lucchesi, B.R. Reduction of myocardial infarct size *in vivo* by carbohydrate- based glycomimetics 1. *J. Pharmcol. Exp. Ther.,***1998**, *284*(*1*), 427-435.

[190] Machaba, K.E.; Cobongela, S.Z.; Mosa, R. a; Oladipupo, L. a; Djarova, T.G.; Opoku, A.R. *In vivo* anti-hyperlipidemic activity of the triterpene from the stem bark of *Protorhus longifolia*(Benrh) Engl. *Lipids Health Dis.*, **2014**, *13*(*1*), 131.

[191] Mosa, R.; Cele, N.; Mabhida, S.; Shabalala, S.; Penduka, D.; Opoku, A. *In vivo* antihyperglycemic activity of a lanosteryl triterpene from *Protorhus longifolia*. *Molecules*, **2015**, *20*(*7*), 13374-13383.

[192] Kim, J.; Jayaprakasha, G.K.; Muthuchamy, M.; Patil, B.S. Structure-function relationships of citrus limonoids on p38 MAP kinase activity in human aortic smooth muscle cells. *Eur. J. Pharmacol.*, **2011**, *670*(*1*), 44-49.

[193] Qin, X.; Qiu, C.; Zhao, L. Maslinic acid protects vascular smooth muscle cells from oxidative stress through Akt/Nrf2/HO-1 pathway. *Mol. Cell. Biochem.*, **2014**, *390*(*1-2*), 61-67.

[194] Dongmo, A.B.; Azebaze, A.G.B.; Donfack, F.M.; Dimo, T.; Nkeng-Efouet, P.A.; Devkota, K.P.; Sontia, B.; Wagner, H.; Sewald, N.; Vierling, W. Pentacyclic triterpenoids and ceramide mediate the vasorelaxant activity of *Vitex cienkowskii via* involvement of NO/cGMP pathway in isolated rat aortic rings. *J. Ethnopharmacol.*, **2011**, *133*(*1*), 204-212.

[195] Ramírez-Espinosa, J.J.; Rios, M.Y.; López-Martínez, S.; López-Vallejo, F.; Medina-Franco, J.L.; Paoli, P.; Camici, G.; Navarrete-Vázquez, G.; Ortiz-Andrade, R.; Estrada-Soto, S. Antidiabetic activity of some pentacyclic acid triterpenoids, role of PTP-1B: *In vitro*, *in silico,* and *in vivo* approaches. *Eur. J. Med. Chem.*, **2011**, *46*(*6*), 2243-2251.

[196] Papi Reddy, K.; Singh, A.B.; Puri, A.; Srivastava, A.K.; Narender, T. Synthesis of novel triterpenoid(lupeol) derivatives and their *in vivo* antihyperglycemic and antidyslipidemic activity. *Bioorganic Med. Chem. Lett.*, **2009**, *19*(*15*), 4463-4466.

[197] Zhong, L.; Zhou, X.L.; Liu, Y.S.; Wang, Y.M.; Ma, F.; Guo, B.; Yan, Z.Q.; Zhang, Q.Y. Estrogen receptor α mediates the effects of notoginsenoside R1 on endotoxin-induced inflammatory and apoptotic responses in H9c2 cardiomyocytes. *Mol. Med. Rep.*, **2015**, *12*(*1*), 119-26.

[198] Jia, C.; Xiong, M.; Wang, P.; Cui, J.; Du, X.; Yang, Q.; Wang, W.; Chen, Y.; Zhang, T. Notoginsenoside R1 attenuates atherosclerotic lesions in ApoE deficient mouse model. *PLoS One*, **2014**, *9*(*6*), 1-9.

[199] de Melo, C.L.; Queiroz, M.G.R.; Fonseca, S.G.C.; Bizerra, A.M.C.; Lemos, T.L.G.; Melo, T.S.; Santos, F.A.; Rao, V.S. Oleanolic acid, a natural triterpenoid improves blood glucose tolerance in normal mice and ameliorates visceral obesity in mice fed a high-fat diet. *Chem. Biol. Interact.*, **2010**, *185*(*1*), 59-65.

[200] Mapanga, R.F.; Rajamani, U.; Dlamini, N.; Zungu-Edmondson, M.; Kelly-Laubscher, R.; Shafiullah, M.; Wahab, A.; Hasan, M.Y.; Fahim, M.A.; Rondeau, P.; Bourdon, E.; Essop, M.F. Oleanolic acid: a novel cardioprotective agent that blunts hyperglycemia-induced contractile dysfunction. *PLoS One,* **2012**, *7*(*10*), e47322.

[201] Bachhav, S.S.; Patil, S.D.; Bhutada, M.S.; Surana, S.J. Oleanolic acid prevents glucocorticoid-induced hypertension in rats. *Phytother. Res.*, **2011**, *25*(*10*), 1435-9.

[202] Somova, L.O.; Nadar, A.; Rammanan, P.; Shode, F.O. Cardiovascular, antihyperlipidemic and antioxidant effects of oleanolic and ursolic acids in experimental hypertension. *Phytomedicine*, **2003**, *10*(*2-3*), 115-21.

[203] Wu, J.; Yang, G.; Zhu, W.; Wen, W.; Zhang, F.; Yuan, J.; An, L. Anti-atherosclerotic activity of platycodin D derived from roots of *Platycodon grandiflorum* in human endothelial cells. *Biol. Pharm. Bull.*, **2012**, *35*(*8*), 1216-1221.

[204] Gao, Y.; Su, Y.; Huo, Y.; Mi, J.; Wang, X.; Wang, Z.; Liu, Y.; Zhang, H. Identification of antihyperlipidemic constituents from the roots of *Rubia yunnanensis* Diels. *J. Ethnopharmacol.*, **2014**, *155*(*2*), 1315-1321.

[205] Zhou, Q.X.; Liu, F.; Zhang, J.S.; Lu, J.G.; Gu, Z.L.; Gu, G.X. Effects of triterpenic acid from *Prunella vulgaris* L. On glycemia and pancreas in rat model of streptozotozin diabetes. *Chin. Med. J.*(*Engl).*, **2013**, *126*(*9*), 1647-1653.

[206] Ullevig, S.L.; Zhao, Q.; Zamora, D.; Asmis, R. Ursolic acid protects diabetic mice against monocyte dysfunction and accelerated atherosclerosis. *Atherosclerosis*. **2011**, *219*(*2*), 409-416.

[207] Xiang, M.; Wang, J.; Zhang, Y.; Ling, J.; Xu, X. Attenuation of aortic injury by ursolic acid through RAGE-Nox-NFκB pathway in streptozocin-induced diabetic rats. *Arch. Pharm. Res.*, **2012**, *35*(*5*), 877-886.

[208] Yang, Y.; Li, C.; Xiang, X.; Dai, Z.; Chang, J.; Zhang, M.; Cai, H.; Zhang, H.; Zhang, M.; Guo, Y.; Wu, Z. Ursolic acid prevents endoplasmic reticulum stress-mediated apoptosis induced by heat stress in mouse cardiac myocytes. *J. Mol. Cell. Cardiol.*, **2014**, *67* 103-111.

[209] Wu, P.; He, P.; Zhao, S.; Huang, T.; Lu, Y.; Zhang, K. Effects of ursolic acid derivatives on Caco-2 cells and their alleviating role in streptozocin-induced type 2 diabetic rats. *Molecules*. **2014**, *19*(*8*), 12559-12576.

[210] Hipólito, U. V.; Rocha, J.T.; Palazzin, N.B.; Rodrigues, G.J.; Crestani, C.C.; Corrêa, F.M.; Bonaventura, D.; Ambrosio, S.R.; Bendhack, L.M.; Resstel, L.B.; Tirapelli, C.R. The semi-synthetic kaurane ent-16α-methoxykauran-19-oic acid induces vascular relaxation and hypotension in rats. *Eur. J. Pharmacol.*, **2011**, *660*(*2*), 402-410.

[211] Baccelli, C.; Navarro, I.; Block, S.; Abad, A.; Morel, N.; Quetin-Leclercq, J. Vasorelaxant activity of diterpenes from *Croton zambesicus* and synthetic trachylobanes and their structure - Activity relationships. *J. Nat. Prod.*, **2007**, *70*(*6*), 910-917.

[212] Liby, K.T.; Sporn, M.B. Synthetic oleanane triterpenoids: multifunctional drugs with a broad range of applications for prevention and treatment of chronic disease. *Pharmacol. Rev.*, **2012**, *64*(*4*), 972-1003.

[213] Sussan, T.E.; Rangasamy, T.; Blake, D.J.; Malhotra, D.; El-Haddad, H.; Bedja, D.; Yates, M.S.; Kombairaju, P.; Yamamoto, M.; Liby, K.T.; Sporn, M.B.; Gabrielson, K.L.; Champion, H.C.; Tuder, R.M.; Kensler, T.W.; Biswal, S. Targeting Nrf2 with the triterpenoid CDDO-imidazolide attenuates cigarette smoke-induced emphysema and cardiac dysfunction in mice. *Proc. Natl. Acad. Sci. USA*, **2009**, *106*(*1*), 250-5.

[214] Ichikawa, T.; Li, J.; Meyer, C.J.; Janicki, J.S.; Hannink, M.; Cui, T. Dihydro-CDDO-trifluoroethyl amide(dh404), A novel Nrf2 activator, suppresses oxidative stress in cardiomyocytes. *PLoS One*, **2009**, *4*(*12*), 1-10.

[215] Xing, Y.; Niu, T.; Wang, W.; Li, J.; Li, S.; Janicki, J.S.; Ruiz, S.; Meyer, C.J.; Wang, X.L.; Tang, D.; Zhao, Y.; Cui, T. Triterpenoid dihydro-CDDO-trifluoroethyl amide protects against maladaptive cardiac remodeling and dysfunction in mice: a critical role of Nrf2. *PLoS One,* **2012**, *7*(*9*), 1-8.

[216] Camer, D.; Yu, Y.; Szabo, A.; Wang, H.; Dinh, C.H.L.; Huang, X.-F. Bardoxolone methyl prevents the development and progression of cardiac and renal pathophysiologies in mice fed a high-fat diet. *Chem. Biol. Interact.*, **2016**, *243* 10-18.

[217] Liu, X.; Xia, J.; Wang, L.; Song, Y.; Yang, J.; Yan, Y.; Ren, H.; Zhao, G. Efficacy and safety of ginsenoside-Rd for acute ischaemic stroke: A randomized, double-blind, placebo-controlled, phase II multicenter trial. *Eur. J. Neurol.*, **2009**, *16*(*5*), 569-575.

[218] Maki, K.C.; Curry, L.L.; Reeves, M.S.; Toth, P.D.; McKenney, J.M.; Farmer, M. V.; Schwartz, S.L.; Lubin, B.C.; Boileau, A.C.; Dicklin, M.R.; Carakostas, M.C.; Tarka, S.M. Chronic consumption of rebaudioside A, a steviol glycoside, in men and women with type 2 diabetes mellitus. *Food Chem. Toxicol.*, **2008**, *46*(*7 Suppl.*), S47-S53.

[219] Maki, K.C.; Curry, L.L.; Carakostas, M.C.; Tarka, S.M.; Reeves, M.S.; Farmer, M. V.; McKenney, J.M.; Toth, P.D.; Schwartz, S.L.; Lubin, B.C.; Dicklin, M.R.; Boileau, A.C.; Bisognano, J.D. The hemodynamic effects of rebaudioside A in healthy adults with normal and low-normal blood pressure. *Food Chem. Toxicol.*, **2008**, *46* (*7 Suppl.*), 40-46.

[220] Chan, P.; Tomlinson, B.; Chen, Y.J.; Liu, J.C.; Hsieh, M.H.; Cheng, J.T. A double-blind placebo-controlled study of the effectiveness and tolerability of oral stevioside in human hypertension. *Br. J. Clin. Pharmacol.*, **2000**, *50*(*3*), 215-220.

[221] Barriocanal, L.A.; Palacios, M.; Benitez, G.; Benitez, S.; Jimenez, J.T.; Jimenez, N.; Rojas, V. Apparent lack of pharmacological effect of steviol glycosides used as sweeteners in humans. A pilot study of repeated exposures in some normotensive and hypotensive individuals and in Type 1 and Type 2 diabetics. *Regul. Toxicol. Pharmacol.*, **2008**, *51*(*1*), 37-41.

[222] Hsieh, M.H.; Chan, P.; Sue, Y.M.; Liu, J.C.; Liang, T.H.; Huang, T.Y.; Tomlinson, B.; Chow, M.S.S.; Kao, P.F.; Chen, Y.J. Efficacy and tolerability of oral stevioside in patients with mild essential hypertension: a two-year, randomized, placebo-controlled study. *Clin. Ther.*, **2003**, *25*(*11*), 2797-2808.

[223] Geuns, J.M.C.; Buyse, J.; Vankeirsbilck, A.; Temme, E.H.M. Metabolism of stevioside by healthy subjects. *Exp. Biol. Med.*(*Maywood).*, **2007**, *232*(1), 164-173.

[224] Ferri, L.A.F.; Alves-Do-Prado, W.; Yamada, S.S.; Gazola, S.; Batista, M.R.; Bazotte, R.B. Investigation of the antihypertensive effect of oral crude stevioside in patients with mild essential hypertension. *Phyther. Res.*, **2006**, *20*(*9*), 732-736.

[225] Jovanovski, E.; Peeva, V.; Sievenpiper, J.L.; Jenkins, A.L.; Desouza, L.; Rahelic, D.; Sung, M.K.; Vuksan, V. Modulation of endothelial function by korean red ginseng(*Panax ginseng* C.A. meyer) and its components in

healthy individuals: A randomized controlled trial. *Cardiovasc. Ther.*, **2014**, *32*(*4*), 163-169.

[226] Jovanovski, E.; Jenkins, A.; Dias, A.G.; Peeva, V.; Sievenpiper, J.; Arnason, J.T.; Rahelic, D.; Josse, R.G.; Vuksan, V. Effects of korean red ginseng (*Panax ginseng* C.A. Mayer) and its isolated ginsenosides and polysaccharides on arterial stiffness in healthy individuals. *Am. J. Hypertens.*, **2010**, *23*(*5*), 469-472.

[227] Zou, Z.-Y.; Xu, X.-R.; Lin, X.-M.; Zhang, H.-B.; Xiao, X.; Ouyang, L.; Huang, Y.-M.; Wang, X.; Liu, Y.-Q. Effects of lutein and lycopene on carotid intima-media thickness in Chinese subjects with subclinical atherosclerosis: a randomised, double-blind, placebo-controlled trial. *Br. J. Nutr.*, **2014**, *111*(*3*), 474-80.

[228] Thies, F.; Masson, L.F.; Rudd, A.; Vaughan, N.; Tsang, C.; Brittenden, J.; Simpson, W.G.; Duthie, S.; Horgan, G.W.; Duthie, G. Effect of a tomato-rich diet on markers of cardiovascular disease risk in moderately overweight, disease-free, middle-aged adults: A randomized controlled trial. *Am. J. Clin. Nutr.*, **2012**, *95*(*5*), 1013-1022.

[229] Wang, M.-X.; Jiao, J.-H.; Li, Z.-Y.; Liu, R.-R.; Shi, Q.; Ma, L. Lutein supplementation reduces plasma lipid peroxidation and C-reactive protein in healthy nonsmokers. *Atherosclerosis*, **2013**, *227*(*2*), 380-5.

[230] McEneny, J.; Wade, L.; Young, I.S.; Masson, L.; Duthie, G.; McGinty, A.; McMaster, C.; Thies, F. Lycopene intervention reduces inflammation and improves HDL functionality in moderately overweight middle-aged individuals. *J. Nutr. Biochem.*, **2013**, *24*(*1*), 163-168.

[231] Gajendragadkar, P.R.; Hubsch, A.; Mäki-Petäjä, K.M. K.M.; Serg, M.; Wilkinson, I.B.; Cheriyan, J. Effects of oral lycopene supplementation on vascular function in patients with cardiovascular disease and healthy volunteers: A randomised controlled trial. *PLoS One*, **2014**, *9*(*6*),.

[232] Yoshida, H.; Yanai, H.; Ito, K.; Tomono, Y.; Koikeda, T.; Tsukahara, H.; Tada, N. Administration of natural astaxanthin increases serum HDL-cholesterol and adiponectin in subjects with mild hyperlipidemia. *Atherosclerosis*, **2010**, *209*(*2*), 520-523.

[233] Ruscica, M.; Gomaraschi, M.; Mombelli, G.; Macchi, C.; Bosisio, R.; Pazzucconi, F.; Pavanello, C.; Calabresi, L.; Arnoldi, A.; Sirtori, C.R.; Magni, P. Nutraceutical approach to moderate cardiometabolic risk: Results of a randomized, double-blind and crossover study with Armolipid Plus. *J. Clin. Lipidol.*, **2014**, *8*(*1*), 61-68.

[234] Xu, X.-R.; Zou, Z.-Y.; Xiao, X.; Huang, Y.-M.; Wang, X.; Lin, X.-M. Effects of lutein supplement on serum inflammatory cytokines, apoe and lipid profiles in early atherosclerosis population. *J. Atheroscler. Thromb.*, **2013**, *20*(*2*), 170-7.

[235] Zou, Z.; Xu, X.; Huang, Y.; Xiao, X.; Ma, L.; Sun, T.; Dong, P.; Wang, X.; Lin, X. High serum level of lutein may be protective against early atherosclerosis: The Beijing atherosclerosis study. *Atherosclerosis*, **2011**, *219*(*2*), 789-793.

[236] Dwyer, J.H.; Navab, M.; Dwyer, K.M.; Hassan, K.; Sun, P.; Shircore, a; Hama-Levy, S.; Hough, G.; Wang, X.; Drake, T.; Merz, C.N.; Fogelman, A.M. Oxygenated carotenoid lutein and progression of early atherosclerosis: the Los Angeles atherosclerosis study. *Circulation*, **2001**, *103*(*24*), 2922-2927.

[237] Klipstein-Grobusch, K.; Launer, L.J.; Geleijnse, J.M.; Boeing, H.; Hofman, A.; Witteman, J.C.M. Serum carotenoids and atherosclerosis: The Rotterdam Study. *Atherosclerosis*, **2000**, *148*(*1*), 49-56.

[238] de Santana Souza, M.T.; Almeida, J.R.G. da S.; de Souza Araujo, A.A.; Duarte, M.C.; Gelain, D.P.; Moreira, J.C.F.; dos Santos, M.R.V.; Quintans-Júnior, L.J. Structure-Activity relationship of terpenes with anti-inflammatory profile - a systematic review. *Basic Clin. Pharmacol. Toxicol.*, **2014**, *115*(*3*), 244-256.

[239] McKinney, J.D.; Richard, a; Waller, C.; Newman, M.C.; Gerberick, F. The practice of structure activity relationships(SAR) in toxicology. *Toxicol. Sci.*, **2000**, *56*(*1*), 8-17.

[240] De Sousa, D.P.; Júnior, G.A.S.; Andrade, L.N.; Calasans, F.R.; Nunes, X.P.; Barbosa-Filho, J.M.; Batista, J.S. Structure and spasmolytic activity relationships of monoterpene analogues found in many aromatic plants. *Zeitschrift Fur Naturforsch. - Sect. C J. Biosci.*, **2008**, *63*(*11-12*), 808-812.

[241] Ambrosio, S.R.; Tirapelli, C.R.; da Costa, F.B.; de Oliveira, A.M. Kaurane and pimarane-type diterpenes from the *Viguiera* species inhibit vascular smooth muscle contractility. *Life Sci.*, **2006**, *79*(*10*), 925-933.

[242] Wang, F.-P.; Chen, Q.-H. The C19-diterpenoid alkaloids. *Alkaloids. Chem. Biol.*, **2010**, *69*(*10*), 1-577.