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Chapter

Effects of Terpenes and Terpenoids of Natural Occurrence in Essential Oils on Vascular Smooth Muscle and on Systemic Blood Pressure: Pharmacological Studies and Perspective of Therapeutic Use

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Abstract

Terpenes are a class of chemical compounds with carbon and hydrogen atoms in their structure. They can be classified into several classes according to the quantity of isoprene units present in its structure. Terpenes can have their structure modified by the addition of various chemical radicals. When these molecules are modified by the addition of atoms other than carbon and hydrogen, they become terpenoids. Terpenes and terpenoids come from the secondary metabolism of several plants. They can be found in the leaves, fruits, stem, flowers, and roots. The concentration of terpenes and terpenoids in these organs can vary according to several factors such as the season, collection method, and time of the day. Several biological activities and physiological actions are attributed to terpenes and terpenoids. Studies in the literature demonstrate that these molecules have antioxidant, anticarcinogenic, anti-inflammatory, antinociceptive, antispasmodic, and antidiabetogenic activities. Additionally, repellent and gastroprotective activity is reported. Among the most prominent activities of monoterpenes and monoterpenoids are those on the cardiovascular system. Reports on literature reveal the potential effect of monoterpenes and monoterpenoids on systemic blood pressure. Studies show that these substances have a hypotensive and bradycardic effect. In addition, the inotropic activity, both positive and negative, of these compounds has been reported. Studies also have shown that some monoterpenes and monoterpenoids also have a vasorelaxing activity on several vascular beds. These effects are attributed, in many cases to the blocking of ion channels, such as voltage-gated calcium channels. It can also be observed that monoterpenes and

monoterpenoids can have their effects modulated by the action of the vascular endothelium. In addition, it has been shown that the molecular structure and the presence of chemical groups influence the potency and efficacy of these compounds on vascular beds. Here, the effect of several monoterpenes and monoterpenoids on systemic blood pressure and vascular smooth muscle will be reported.

Keywords: terpenes, terpenoids, arterial pressure, pharmacological effect, toxicity, perspective of therapeutic use, anti-hypertensive

1. Introduction

1.1 Terpenes and terpenoids

Terpenes and terpenoids are names frequently interchangeably used. Most frequently terpene is defined as a hydrocarbon with one or several isoprene units. When terpene molecules are modified by the addition of atoms other than carbon and hydrogen, they are more appropriately named terpenoids [1].

Terpenes and terpenoids come from the secondary metabolism of several plants. They can be found in the leaves, fruits, stem, flowers, and roots [2]. They can be classified into several classes according to several criteria: 1—the quantity of isoprene units present in its structure, among which we can mention the monoterpenes, diterpenes, sesquiterpenes, and others; 2—the number of cyclic components in their molecular structure, according to which we have the acyclic, monocyclic, and bicyclic monoterpenes [1, 3, 4].

Studies in the literature demonstrate that the natural (present in essential oils—EO) monoterpenes and monoterpenoids have one or several biological/pharmacological activities, among which the most frequently reported are antioxidant, anticarcinogenic, anti-inflammatory, repellent, gastroprotective, antinociceptive, antispasmodic, and antidiabetogenic activities [4, 5].

Among the most prominent and therapeutically potentially promising activities of natural monoterpenes and monoterpenoids are those on the cardiovascular system [6]. Reports on literature, here reviewed and discussed, reveal their effect on heart (rate and inotropism), systemic blood pressure (SBP), and blood vessels (direct (myogenic) and indirect (endothelium mediated)) [7–10].

These effects are frequently attributed to activity on ion channels, such as voltage-dependent Ca^{2+} channels (VDCC) [11]. These substances can affect the contractions mediated by electromechanical excitation-contraction coupling (EMC; ex.: the KCl-induced contraction) or pharmacomechanical excitation-contraction coupling (PMC; ex.: the Phenylephrine-induced contraction). In addition, it has been shown that the molecular structure and the presence of chemical groups influence the potency (pharmacodynamic potency) and efficacy (pharmacodynamic efficacy) of these compounds on vascular beds [10]. Here we will call simply maximum efficacy when, at appropriate concentration, total blockade of a response is induced (it is: complete blockade of contraction or $E_{\text{max}} = 100\%$).

Here, we described the effects of monoterpenes and monoterpenoids on SBP and vascular smooth muscle (VSM). This research was carried out predominantly using articles present in the Pubmed and Pubchem databases. The search included articles published between 2000 and 2020. The search included 42 monoterpenes and monoterpenoids. The words used in the research include “monoterpenes”, “monoterpenoids” and the name of the compounds associated with “cardiovascular”, “vasorelaxant”, “hypotension”, “hypotensive”, “antihypertensive”, “vascular

smooth muscle”, or “toxicity”. For easiness of posterior consultation, we presented the information related to a substance under a heading, which was the common name of the substance and organized the most important information on a table

Substance	Pharmacological cardiovascular activities	Dose (mg/kg)/ concentration (μM)	Ref.	LD ₅₀	Plant source
Limonene	Hypotensive	20–40 mg/kg ^A	[12]	4.4–5.1 g/kg (v.o.—rats); 5.6–6.6 g/kg (v.o.—mice) [13]	<i>Citrus limon</i> , <i>Lippia alba</i>
	Vasorelaxant	941.6 ± 28.02 μM ^B 2159.1 ± 203.62 μM ^C	[10]		
α-Pinene	Hypotensive	1–20 mg/kg ^A	[14]	>2.0 g/kg (v.o.—mice) [15]	<i>Eucalyptus tereticornis</i> , <i>Citrus lemon</i>
β-Pinene	Hypotensive	1–20 mg/kg ^A	[14]	>2.0 g/kg (v.o.—mice) [15]	<i>Eucalyptus tereticornis</i> , <i>Citrus lemon</i>
p-Cymene	Vasorelaxant	5.8 ± 1.6 × 10 ^{−5} M ^C	[16]	4.7 g/kg (v.o.—rat); >5 g/kg (v.o.—rabbit) [17]	<i>Eucalyptus camaldulensis</i> , <i>Origanum acutidens</i>
Citronellol	Hypotensive	1–20 mg/kg	[14, 18, 19]	3.45 g/kg (v.o.—rats) [20]	<i>Cymbopogon winterianus</i> , <i>Lippia alba</i>
	Vasorelaxant [18]	6.4 × 10 ^{−4} to 1.9 M	[18]		
Geraniol	Vasorelaxant [21]	10–300 μM ^A	[21]	3.6 g/kg (v.o.—rats) [22]	<i>Cymbopogon martinii</i> , <i>C. nardus</i> , <i>C. winterianus</i> .
Linalool	Hypotensive (normotensive animals)	1–20 mg/kg	[14, 23]	2.7 g/kg (v.o.—rats) [24]	<i>Lavandula angustifolia</i> , <i>Ocimum basilicum</i> , <i>Citrus bergamia</i>
	Hypotensive (hypertensive animals)	100–200 mg/kg	[23, 25]		
	Vasorelaxant [23]	6.4 × 10 ^{−6} –6.4 × 10 ^{−3} M	[23]		
Perillyl alcohol	Vasorelaxant [10]	277.7 ± 5.46 μM ^B , 443.3 ± 66.83 μM ^C	[10]	2.1 g/kg (v.o.—rats) [26]	<i>Dracocephalum kotschyi</i>
	Vasorelaxant	1–2 mM ^A	[27]		
Carveol	Vasorelaxant	662.1 ± 32.85 μM ^B ; 1333.3 ± 225.20 μM ^C	[10]	3.0 g/kg (v.o.—rats) [28]	<i>Citrus reticulata</i> , <i>Anethum graveolens</i>
Menthol	Antihypertensive	Diet plus 0.5% menthol	[29, 30]	2.9–6 g/kg (v.o.—mice and rats) [31, 32]	<i>Mentha</i> genus
	Vasorelaxant	100–500 mM ^A	[33]		

Substance	Pharmacological cardiovascular activities	Dose (mg/kg)/ concentration (μM)	Ref.	LD ₅₀	Plant source
α -Terpineol	Hypotensive Vasorelaxant Vasorelaxant	1–30 mg/kg ^A $10^{-12} - 10^{-5} \text{ M}$ 300 $\mu\text{g/ml}$ (1.94 mM)	[34] [34] [36]	3.0 g/kg (v.o.—mice) [35]	<i>Eucalyptus camaldulensis</i> , <i>Croton nepetaefolius</i> .
Terpinen-4-ol	Hypotensive Vasorelaxant	1–10 mg/kg ^A , i.v. $421.43 \pm 23.48 \mu\text{M}^{\text{B}}$; $802.50 \pm 13.8 \mu\text{M}^{\text{C}}$	[7, 37] [9]	4.3 g/kg (v.o.—rats) [32]	<i>Alpinia zerumbet</i> , <i>Croton sonderianus</i>
Borneol	Vasorelaxant	$3 \times 10^{-9} - 3 \times 10^{-4} \text{ M}^{\text{B}}$	[38, 39]	6.5 g/kg (v.o.—rats) [40]	<i>Salvia officinalis</i> , <i>Cinnamomum camphora</i>
Carvacrol	Hypotensive Hypotensive Vasorelaxant Vasorelaxant	100 $\mu\text{g/kg}$, i.p. 1–20 mg/kg i.v. $78.80 \pm 11.91 \mu\text{M}^{\text{B}}$; $145.40 \pm 6.07 \mu\text{M}^{\text{C}}$ $10^{-8} - 3 \times 10^{-4} \text{ M}$	[41] [43] [44] [43]	0.8 g/kg (v.o.—rats) [42]	<i>Thymus vulgaris</i> , <i>Origanum compactum</i> , <i>Lippia sidoides</i>
Thymol	Vasorelaxant	$64.40 \pm 4.41 \mu\text{M}^{\text{B}}$; $106.40 \pm 11.37 \mu\text{M}^{\text{C}}$	[44]	0.9 g/kg (v.o.—rats) [44]	<i>Acalypha phleoides</i> , <i>Lippia sidoides</i> , <i>L. organoides</i>
Anethole	Antihypertensive Hypotensive Vasorelaxant	125–250 mg/kg ^A 5–10 mg/kg, i.v. ^A $9.01 \pm 2.44 \times 10^{-4} \text{ M}^{\text{C}}$	[45] [47] [48]	<3.0 g/kg (v.o.—rats) [46, 17]	<i>Pimpinella anisum</i> , <i>Croton zehntneri</i> , <i>Foeniculum vulgare</i>
Estragole	Hypotensive Vasorelaxant	5–10 mg/kg, i.v. ^A $4.34 \pm 0.3 \times 10^{-4} \text{ M}^{\text{C}}$	[47] [48]	1.8 g/kg (v.o.—rats) [32]	<i>Croton Zehntneri</i> , <i>Ocimum basilicum</i> , <i>Artemisia dracunculus</i>
Eugenol	Hypotensive Vasorelaxant Vasorelaxant	1–10 mg/kg, i.v. ^A $0.31 \pm 0.05 \text{ mM}$ $323.3 \pm 14.0 \mu\text{MB}$	[49–51] [49] [11]	2.6 g/kg (v.o.—rats) [17]	<i>Croton zehntneri</i> , <i>Ocimum gratissimum</i>
Cinnamaldehyde	Vasorelaxant	$334 \pm 30 \mu\text{M}$	[52]	2.22 g/kg (v.o.—rats) [17]	<i>Cinnamomum osmophloeum</i> , <i>C. zeylanicum</i>

Substance	Pharmacological cardiovascular activities	Dose (mg/kg)/ concentration (μM)	Ref.	LD ₅₀	Plant source
Citral	Vasorelaxant	110.80 μg/ml (727.8 μM) ^B , 99.34 μg/ml (652.56 μM) ^C	[53, 54]	4.9 g/kg (v.o.—rats) [17]	<i>Lippia alba e Pectis brevipedunculata</i>
Citronellal	Antihypertensive	200 mg/kg, v.o.	[55]	2.42 g/kg (v.o.—rats) [56]	<i>Cymbopogon winterianus</i> ; <i>Cymbopogon citrates</i>
	Hypotensive	10–40 mg/kg, i.v.	[55]		
	Vasorelaxant	10 ⁻⁶ - 10 ⁻¹ M	[55]
Carvone	Vasorelaxant	6.2 ± 2.6 × 10 ⁻⁴ M ^C	[57]	1.6 g/kg (v.o.—rats) [17]	<i>Mentha spicata</i> , <i>Carum carvi</i>
Rotundifolone	Hypotensive	1–30 mg/kg, i.v.	[58]	Not available (for mammals)	<i>Mentha rotundifolia</i> , <i>M. spicata</i> L., and <i>M. x villosa</i>
	Vasorelaxant	184 (1.1 mM) ^B and 185 (1.11 mM) ^C μg/ml	[58, 59]		
	Vasorelaxant	pD2 = 4.0	[60]
1,8-cineole	Antihypertensive	0.1 mg/kg, i.p.	[61]	2.48 g/kg (rat, v.o); >5 g/kg (v.o, rabbit) [17]	<i>Croton nepetaefolius</i> ; <i>Alpinia zerumbet</i>
	Hypotensive	0.3–10 mg/kg, i.v.	[62]		
	Vasorelaxant	1.09 mM ^B , 663.2 μg/ml (4.22 mM) ^C	[62, 63]
Linalyl acetate	Antihypertensive	10–100 mg/kg, i.p.	[64]	10.0 g/kg (v.o—rats); 13.3 g/kg (v.o—mice) [24]	<i>Lavandula angustifolia</i> and <i>Salvia sclarea</i>
	Hypotensive	10–100 mg/kg	[64–66]		
	Vasorelaxant	3.6 × 10 ⁻⁴ M ^C	[67]		

Ref., Reference. ip, Intraperitoneally. v.o, Orally. i.v., Intravenous.

^ARange of doses or concentration employed.

^BIC₅₀ for KCl-induced contraction (electromechanical coupling) in presence of endothelium.

^CIC₅₀ for phenylephrine-induced contraction (pharmacomechanical coupling) in presence of endothelium.

Table 1.
Monoterpenes and monoterpenoids with hypotensive and vasorelaxant effects.

(Table 1). In order to allow some basis for evaluation of the therapeutic potential of these compounds, we include information on toxicity (LD₅₀ values in mammals; Table 1).

2. Monoterpenes

Monoterpenes are compounds with two isoprene units in their structure. They can be subdivided according to the number of cycle components in its structure into acyclic, monocyclic, and bicyclic [68, 69]. Of the natural monoterpenes studied, we have not found, in any publications, report of cardiovascular effects for myrcene, ocimene (acyclic), terpinenes, phellandrenes, terpinolene, thujene (monocyclic) and, –3-carene, camphene, sabinene (bicyclic), and tricyclene on SBP and VSM. However, several studies in the literature demonstrate that EO containing these compounds have interesting cardiovascular effects.

2.1 Limonene

Limonene (LM) is one of the most common monoterpenes on nature. Studies have demonstrated that it has low toxicity and have suggested its promising effect [13]. The LM had a dose-dependent hypotensive effect, associated with bradycardia in rats (**Table 1**). LM is also reported to cause delayed ventricular relaxation and negative inotropism. It has been suggested that these effects are due to an action of LM on VDCC [12]. In spontaneously hypertensive rats (SHR) with cerebral ischemia, LM attenuated the elevation of the blood pressure of the animals [70].

In rat aorta, the LM promoted a marked vasorelaxing effect when administered in presence of the contractions induced by a solution with a high concentration of K^+ or phenylephrine (PHE). The IC_{50} values were dependent on the endothelium and maximum efficacy was documented for both types of contraction. The potency in endothelium-intact arteries was greater in EMC than in PMC. LM was also able to relax the contraction induced by BayK8644, a VDCC activator [71], effect in which the LM presented the greatest potency, suggesting a possible effect of this monoterpene on VDCCs [10].

2.2 Pinene

α - and β -pinene are two isomeric bicyclic monoterpenes [72] which, in awake rats, induced arterial hypotension and tachycardia. $(-)$ - β -pinene was significantly more effective than $(+)$ - α -pinene. The authors suggested that the exocyclic double bond of $(-)$ - β -pinene contributes more to the pharmacological effect than the endocyclic double bond of $(+)$ - α -pinene. They explained tachycardia as a reflex response to the hypotension [14].

2.3 p-cimene

P-cymene is a monocyclic monoterpene that in rat's aorta showed a reversible vasorelaxant effect, with maximum efficacy and in a concentration-dependent manner. This effect, independent of the endothelium, indicated a myogenic effect. Additionally, the participation of K^+ channels in the vasorelaxant effect of p-cymene has been suggested [16].

3. Monoterpenoids

Monoterpenoids are compounds found in several plant species (**Table 1**). Concerning their chemical functions, they can be: alcohols, phenolics, phenylpropanoids, aldehydes, ketones, ethers, or esters. For the following natural monoterpenoids, no studies were found that described effect on SBP and VSM: lavandulol, fenchol, chrysanthenol and nerol (alcohols); apiol, myristicin and safrole (phenylpropanoids).

3.1 Alcohols

3.1.1 Citronellol

Citronellol is a low toxicity acyclic monoterpene [20]. Regarding hemodynamic parameters, citronellol (1–20 mg/kg, i.v.) is reported to induce hypotension associated with tachycardia in non-anesthetized rats [18]. This hypotensive effect was interpreted to occur probably due to a direct vasorelaxant action of citronellol

in VSM without the participation of the NO and cyclooxygenase (COX) pathway [18]. In another study, in anesthetized and awake rats, citronellol (1–20 mg/kg, i.v.) also had a hypotensive effect, but associated with bradycardia. As a probable cause of this discrepancy, the chirality of the compound was suggested [19].

In rat mesenteric arteries, citronellol had an endothelium-independent vasorelaxing effect. On the contraction induced by PHE ($IC_{50} \sim 130 \mu M$) and KCl, the effectiveness reached 100%. This monoterpene was able to block the influx of Ca^{2+} and contraction induced by caffeine and this finding led the authors to also suggest that it acts on influx and the mobilization of Ca^{2+} stores [18, 19].

3.1.2 Geraniol

Geraniol (GER) is an acyclic monoterpene with low toxicity (**Table 1**) [73]. In diabetic animals, the GER attenuated the cardiac changes caused by diabetes mellitus (DM). The authors suggested that the mechanism for this effect was the attenuation of changes caused by DM in contractility and systolic duration by GER [74].

In the aorta of normoglycemic animals, GER (30–300 μM) had a vasorelaxing effect on contractions induced by PHE and KCl. This effect was more effective on EMC, suggesting inhibition of Ca^{2+} channels in the plasma membrane of smooth cell. The authors demonstrated that the NO, COX, and K^+ channels do not participate in this vasorelaxant effect. In the aorta of diabetic rats, GER (30–300 μM) reduced tissue hyperresponsiveness to PHE [21].

3.1.3 Linalool

Linalool (LN) is an acyclic tertiary alcohol. In normotensive animals, LN (1–20 mg/kg, i.v.) led to hypotension and tachycardia. Hypotension was attenuated by N ω -Nitro-L-arginine methyl ester (L-NAME) and atropine but not by indomethacin, thus suggesting that the NO and muscarinic receptor pathways participate in promoting this effect [14, 23]. In Goldblatt hypertensive animals, LN (200 mg/kg) caused hypotension, of magnitude similar to nifedipine (NIF), without altering heart rate (HR) [23]. LN also had a hypotensive effect at a dose of 100 mg/kg in SHR [25].

In the mesenteric bed of normotensive animals, LN showed an endothelium-independent vasorelaxant effect on PMC and EMC, with maximum efficacy. Additionally, LN inhibited contractions induced by $CaCl_2$ and caffeine, which led the authors to suggest that the mechanism of action involves the mobilization of Ca^{2+} from intracellular stores and the influx of Ca^{2+} through the plasma membrane. The direct relaxing effect of LN on VSM has been suggested to be responsible for the hypotensive effect of this compound. In the aorta of normotensive rats with endothelium, LN (100 μM) had a relaxing effect on PHE-induced contraction [23, 75].

3.1.4 Perillyl alcohol

Perillyl alcohol (POH) is a monocyclic alcohol. It had a reversible vasorelaxing effect in rat aorta, dependent on concentration and maximum efficacy on the KCl ($IC_{50} 277.7 \pm 5.46 \mu M$) and PHE-induced ($IC_{50} 443.3 \pm 66.83 \mu M$) contractions (**Table 1**). Among the contractions inhibited by POH, which also inhibited contractions induced by phorbol dibutyrate (PDB) or by BayK8644, the greatest pharmacological potency was over the contractions induced by KCl and BayK8644, which suggested that the mechanism of the relaxing effect of POH was inhibition of VDCCs. However, other mechanisms have not been ruled out [10]. POH (1–2 mM)

when incubated overnight prevented KCl-, 5-HT-, and U46619-induced contractions in coronary arteries [27].

3.1.5 Carveol

Carveol (CV) is a monocyclic alcohol found in the mint EO. In rat aorta, the CV (10–5000 μM) had a vasorelaxing effect, over contractions induced by PHE (IC_{50} $1333.3 \pm 225.20 \mu\text{M}$) and KCl (IC_{50} $662.1 \pm 32.85 \mu\text{M}$), which was reversible and independent of the vascular endothelium. The CV also inhibited contractions induced by PDB and BayK8644. Due to the greater potency of CV on contractions induced by KCl and BayK8644, the mechanism of its relaxing effect was attributed to a probable inhibitory effect on VDCCs [10].

In the human umbilical artery, the CV (1–5000 μM) reduced the basal tone by approximately 72% and relaxed contractions induced by 5-HT (IC_{50} of $175.82 \mu\text{M}$) and KCl (IC_{50} $344.25 \mu\text{M}$) [76].

3.1.6 Menthol

Menthol is a monocyclic alcohol. In hypertensive animals, menthol (0.5% dietary) attenuated the elevation of vasoconstriction (on PHE- and U46619-induced contraction), blood pressure, the production of reactive oxygen species (ROS), and mitochondrial dysfunction. This effect probably occur due to the TRPM8 activation by menthol and involve the calcium signaling-mediated RhoA/Rho kinase pathway [29, 30].

Menthol showed cutaneous vasorelaxing activity in individuals in normotensive or in essential hypertension condition, an activity that has been suggested to involve the endothelium derived hyperpolarizing factor (EDHF) and NO [33, 77].

3.1.7 α -Terpineol

α -Terpineol (1–30 mg/kg, i.v.), a monocyclic alcohol, induced a reduction in SBP and tachycardia. These effects were mitigated by L-NAME and suggested to involve the NO pathway [34].

In mesenteric arteries, α -terpineol induced an endothelium-dependent vasorelaxant effect on contractions induced by PHE. The vasorelaxant effect of α -terpineol was not affected by atropine and indomethacin, but by treatment with L-NAME and 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ), suggesting the involvement of the NO/cGMP pathway [34]. In a cannulated mesenteric bed contracted by perfusion with KCl, α -terpineol (300 $\mu\text{g}/\text{ml}$ (1.94 mM)) increased (by 93%) the mesenteric flow. The vasorelaxant effect of α -terpineol was abolished by L-NAME, suggesting the participation of NO in this effect [36].

3.1.8 Terpinen-4-ol

Terpinen-4-ol (4TERP) is a monocyclic alcohol. In hypertensive DOCA-salt and normotensive animals, uninefrectomized or not, 4TERP (1–10 mg/kg, i.v.) induced a reduction in SBP and bradycardia, with a peak between 20–30 s after administration. This effect lasted 1–10 minutes for all doses [7, 37].

In VSM of rats, 4TERP showed vasorelaxing effect, reversible and with maximum effectiveness, on contractions mediated by EMC (IC_{50} $421.43 \pm 23.48 \mu\text{M}$) and PMC (IC_{50} $802.50 \pm 13.8 \mu\text{M}$). It has been suggested that this effect involves the NO and COX pathway. 4TERP relaxed, with similar potency, the contractions

induced by BayK, BaCl₂, and K⁺, presenting IC₅₀ values of 454.2 ± 28.7, 450.5 ± 71.1, and 421.43 ± 23.48 μM, respectively. This suggests the possible inhibitory effect of 4TERP on VDCCs. It has been suggested that 4TERP also acts on other components of myocytes, such as the IP₃ pathway and the sensitivity of contractile proteins to Ca²⁺ [9].

In ventricular myocytes isolated from rats, 4TERP (30 μM) promoted a small increase (10.6 ± 2.6%) of L type Ca²⁺ currents. Above 300 μM the effect was reversed; 4TERP reduced the amplitude of these currents (IC₅₀ of 1203 ± 0.224 μM). 4TERP increased the Ca²⁺ spark frequency at low concentrations and decreased the amplitude of Ca²⁺ transients at low and high concentrations [78]. Thus, among the effects of 4TERP on the cardiovascular system, the effect on ion channels was highlighted as a possible mechanism of action.

3.1.9 Borneol

Borneol is a bicyclic alcohol. In rat aorta, borneol had a vasorelaxing effect on contraction induced by KCl and PHE. This effect was reduced by L-NAME and indomethacin, showing the involvement of the NO and COX pathway in its mechanism [38]. In another study, in rat aorta, borneol inhibited contraction induced by CaCl₂, BayK8644, and caffeine and the authors suggested probable activities of this monoterpenoid on VDCCs or intracellular Ca²⁺ stocks as components of its mechanism of action [39].

3.2 Phenolics

3.2.1 Carvacrol

In anesthetized rats, carvacrol (100 μg/kg, i.p.) decreased HR, SBP, systolic and diastolic pressure [42]. In normotensive non-anesthetized rats, carvacrol (1–20 mg/kg, i.v.), had a hypotensive and bradycardic effect [43].

On aorta of rats, on contractions induced by KCl and PHE, carvacrol (1–1000 μM) showed a reversible inhibitory effect, with maximum efficacy, concentration-dependent and not dependent on the endothelium. In addition, carvacrol inhibited contractions in a Ca²⁺-free medium. These data together suggested the hypothesis that the vasorelaxant mechanism of this monoterpenoid involves multiple mechanisms: the IP₃ pathway, the sensitivity of contractile proteins to Ca²⁺, and the blocking of VDCCs [44]. In mesenteric arteries, carvacrol (10⁻⁸ – 3 × 10⁻⁴ M) had a concentrations-dependent vasorelaxing effect on PHE-, U46619, and KCl-induced contractions. This effect was endothelium independent and probably involves VOCCs, receptor operator channels (ROC), and store operator channels (SOC) channels [43]. Carvacrol also has a vasorelaxing effect on cerebral parenchymal arteries. In this case, this effect was endothelium-dependent and promoted through the activation of TRPV3 channels that consequently activated the low and medium conductance Ca²⁺-activated K⁺ channels [79].

3.2.2 Thymol

Thymol is a carvacrol isomer. In aorta of rats, thymol (1–1000 μM) has a reversible and concentration-dependent vasorelaxant effect (in contractions induced by KCl and PHE). The experiments to elucidate the mechanism of action showed results very similar to those of carvacrol and led to similar conclusions: the involvement of the IP₃ pathway, the sensitivity of contractile proteins to Ca²⁺, and the blocking of VDCCs [44].

3.3 Phenylpropanoids

3.3.1 Anethole

Anethole (AN) is a phenylpropanoid with very low toxicity, it has been suggested to have great therapeutic potential [46].

AN (5–10 mg/kg, i.v.) induced, in a concentration-dependent manner, in conscious normotensive rats, hypotension and bradycardia (phase 1), followed by pressoric and bradycardic response (phase 2) [47]. In animals with nicotine-induced hypertension associated with immobilization stress, AN (125–250 mg/kg, i. p.) had an anti-hypertensive effect with efficacy similar to physical exercise and NIF [45].

Soares et al. [48] reported, in relation to concentration, a biphasic effect of AN on the aortic artery. Between 10^{-6} to 10^{-4} M, AN induced an increase in basal tone and PHE-induced contraction in preparations with endothelium. Between 10^{-4} and 10^{-3} the Figure 2b [48] shows this contraction vanishes and full relaxation stabilizes (maximum efficacy). It was suggested that the activity on VDCC (activation (10^{-6} to 10^{-4} M) and inhibition (10^{-3} to 10^{-2} M)) is the probable mechanism of this effect [48]. Another study with AN in aortic rings reported only vasorelaxing effects, with higher potencies (for EMC and PMC, IC₅₀: 50–75 µg/ml (0.34–0.51 mM)) [80]. This discrepancy was not explained.

3.3.2 Estragol

Estragole (ES) is an isomer of AN which, at 5–10 mg/kg, i.v., induced effects on blood pressure very similar to those of AN (see above) [47, 81]. In the aorta artery of rats with intact endothelium, the ES also had a similar effect to the AN (pre-dominantly vasorelaxant), except that the amplification effect of the contraction was smaller and without statistical significance [48].

3.3.3 Eugenol

Eugenol (EUG) is a phenylpropanoid with a long effect half-life and low toxicity [82]. EUG is probably the most investigated monoterpenoid with effects on the cardiovascular system. EUG (1–10 mg/kg, i.v.) caused reduction of SBP and HR, in dose-dependent manner, in normotensive animals (conscious or anesthetized) and in hypertensive animals (DOCA-salt model). It was suggested that the hypotensive effect is due to the direct vasorelaxing activity of the EUG [49, 50].

In blood vessels, EUG has a relaxing, reversible effect, partially dependent on the endothelium [51, 83]. In rat aorta, with endothelium, this phenylpropanoid inhibited PHE-induced contraction in normotensive (EUG at 1–100 µM) and hypertensive animals (EUG at 0.006–6 mM, DOCA-salt model) [48, 75, 84].

The vasorelaxant effect of the EUG was confirmed with flow measurements. In normotensive animals, EUG induced an increase in flow through the vascular mesenteric bed pre-contracted with KCl (IC₅₀ 0.31 ± 0.05 mM) or noradrenaline (0.2, 2 or 20 µM) [50, 85].

EUG also has a vasodilatory effect on pressurized cerebral artery of rats (IC₅₀ of 234.2 ± 11.3 µM) or pre-contracted with K⁺ (IC₅₀ of 323.3 ± 14.0 µM) [11].

The hypotensive and vasorelaxing effect of the EUG is due to multiple mechanisms, the effect of which on ion channels stands out. In VSM cells, the EUG blocks VDCCs by the channel pore blocking mechanism and by changing the steady state of channel inactivation [11, 51]. Consistent with this effect, in rat heart muscle, it was suggested that the negative inotropic effect of EUG (0.1–0.5 mM) is due to the

blocking of Ca^{2+} channels without, however, altering the activity of the contractile intracellular machinery [85]. Similar results were also observed in canine myocytes, where EUG reduced the amplitude and changed the kinetics of the Ca^{2+} current of VDCC L-type channel [86].

Studies have also shown that endothelial TRP channels can participate in the vasorelaxant effect of EUG (5 mg/kg, i.v). EUG at low concentrations (100 μM) is able to activate TRPV4 currents in these cells, triggering actions that lead to vasorelaxation [51].

It is known that among the predominant pathological changes in DM are blood vessel alterations. Nangle et al. [87] demonstrated that the EUG (200 mg/kg/day, p.o.) was able to reverse the increase in sensitivity to PHE and the reduction of ACh-induced relaxation in the renal artery of diabetic rats. This mechanism probably occurred through NO and EDHF.

As EUG has low toxicity, affects several vascular beds and has an inhibitory effect on Ca^{2+} channels, it has therapeutic potential in treatment of DM and Hypertension.

3.4 Aldehydes

3.4.1 Cinnamaldehyde

In rat aorta, cinnamaldehyde has an endothelium-dependent relaxing effect on contraction induced by KCl, prostaglandin F₂ (PGF₂), and NE [88]. Endothelium dependence, however, has been refuted by Xue et al., since the vasorelaxant effect induced by cinnamaldehyde was not mitigated by pretreatment with L-NAME or ODQ [89]. In addition, these authors reported that COX, K^+ channels, and β -adrenergic receptors are not involved in the vasorelaxant effect of Cinnamaldehyde [52, 88, 89].

In the coronary artery, cinnamaldehyde has a concentration-dependent and endothelium-independent relaxing effect of maximum efficacy on contractions induced by U46619 and KCl [90].

The cinnamaldehyde relaxation mechanism is suggested to occur due to alterations of the sensitivity of contractile proteins to Ca^{2+} and, mainly, by inhibiting VDCCs, as this monoterpenoid inhibited the contraction induced by BayK 8644 in the coronary artery [52, 90]. Additionally, cinnamaldehyde has been shown to reduce L-type Ca^{2+} currents in VSM cells (IC_{50} of 0.81 ± 0.02 mM; maximum efficacy) [52].

In the aorta and mesenteric artery of diabetic mice, cinnamaldehyde added to the diet (% 0.02) improved the endothelial response to ACh without changing SBP. Additionally, cinnamaldehyde prevented the production of ROS and depletion of NO, with beneficial effect in DM [91, 92]. In DM, cinnamaldehyde (20 mg/kg/day) also protected against the elevation of diastolic pressure, the increase in responsiveness to contracting agents and the hyporesponsiveness to ACh [93].

3.4.2 Citral

Citral is a monoterpenoid considered to be non-toxic and of therapeutic relevance [54, 96]. Citral reversibly inhibited contractions induced by PHE (IC_{50} 99.34 $\mu\text{g/mL}$) and KCl (IC_{50} 110.80 $\mu\text{g/mL}$) in aorta of healthy rats with maximum efficacy. The authors suggested that this effect occurs due to the blockade of VDCCs, since citral inhibited contractions induced by BaCl_2 and BayK 8644 [53, 54].

Relaxing effect of citral was observed in the aortic artery of SHR. This monoterpenoid in concentrations of 0.00624 mM–6.24 mM, induced a relaxing effect partially dependent on the NO pathway. Additionally, citral blocked the contraction induced by reposition of Ca^{2+} to nutrient solution, and this suggested the hypothesis that this compound inhibits Ca^{2+} influx through VDCC channel [95].

3.4.3 Citronellal

Citronellal is a monoterpenoid composed of a racemic mixture of two enantiomers present in plants [96]. In normotensive animals, citronellal (10–40 mg/kg) induced hypotension, bradycardia, and sinoatrial node block. The bradycardic effect probably involves muscarinic receptors as it has been inhibited by atropine. In hypertensive animals, citronellal (200 mg/kg) induced a hypotensive effect of greater duration than that of NIF (1 h of NIF $\times$ 3 h in citronellal) [55]. On contractions induced by PHE and KCl in the superior mesenteric artery of normotensive rats, citronellal had a endothelium-independent and concentration-dependent vasorelaxing effect, with maximum efficacy [55].

3.5 Ketone

3.5.1 Carvone

Carvone is a monocyclic monoterpenoid. Heuberger and collaborators [97] investigated the effects of (–)-carvone and (+)-carvone inhalation on the autonomic nervous system. Inhalation of (–)-carvone caused an increase in HR and systolic blood pressure; (+)-carvone inhalation increased systolic and diastolic blood pressure [97]. In rat aorta, carvone had a vasorelaxant effect ($E_{\text{max}} = 58.9\%$) for both enantiomers. The IC_{50} values for (+)-carvone in contractions induced by PHE was 0.62 mM [57].

3.5.2 Rotundifolone

Rotundifolone (RT) is a monocyclic monoterpenoid. RT (1–30 mg/kg, i.v.) had a hypotensive (partial efficacy = 51%) and bradycardic (partial efficacy = 87%) effect in non-anesthetized rats. The hypotensive effect of RT was attenuated by atropine and L-NAME, suggesting the participation of muscarinic receptors in this effect [58].

On isolated aorta from rats, RT inhibited contractions induced by KCl (IC_{50} 184 $\mu\text{g}/\text{ml}$ (1.1 mM)) and PHE (IC_{50} 185 $\mu\text{g}/\text{ml}$), with maximum efficacy. As a mechanism of this effect, a possible blocking of VDCCs and of the release of Ca^{2+} from sarcoplasmic reticulum by RT was suggested [58, 59]. Others also observed the vasorelaxing effect of RT in the mesenteric artery of rats contracted with PHE ($\text{pD}_2 = 4.0$, maximum efficacy). As a mechanism for this effect, activity on TRPM8 channels, activation of large conductance Ca^{2+} -activated K^+ (BK_{Ca}) channels, and inactivation of VDCCs were suggested [60, 98, 99].

3.5.3 1,8-cineol

1,8 cineole (CIN), also known as eucalyptol, in anesthetized and conscious normotensive animals, CIN (0.3–10 mg/kg, i.v.) induced hypotension, with maximum effect in 20–30 s after administration and duration of 1–5 min. This effect was independent of the autonomic nervous system, and a probable dependence on vascular relaxation was suggested [62]. CIN (0.1 mg/kg, i.p.) has been shown to

attenuate the elevation of systolic blood pressure in hypertensive rats induced by chronic nicotine exposure [61].

In another study, in the aorta of normotensive rats, CIN inhibited PHE-induced contraction (IC_{50} of 663.2 $\mu\text{g/ml}$ (4.29 mM)). This effect was altered by the presence of L-NAME but was not affected by indomethacin or tetrathylamonium [63].

3.5.4 Linalyl acetate

In hypertensive rats, the linalyl acetate (LA, 10–100 mg/kg, i.p.) attenuated the increase in systolic and diastolic blood pressure. LA also modulates the expression of Endothelial NO Synthase (eNOS), preventing its suppression by ROS. This suggested a possible antihypertensive effect of LA [64, 65]. In rats with hypertension induced by chronic exposure to nicotine and stress, LA (10–100 mg/kg), had a hypotensive effect [66].

It was reported that diabetic animals exposed to chronic stress showed a reduction in endothelial function, changes in SBP and HR. LA (100 mg/kg) was able to revert these parameters to close to control values [100].

In a rabbit carotid artery, LA induced a relaxing effect on PHE-induced contraction, with partial efficacy ($E_{\text{max}} = 88.8\%$) and $IC_{50} 3.6 \times 10^{-4} \text{ M}$. According to the authors, the cGMP-NO pathway and phosphorylation of myosin light chain, are involved in the relaxing effect of this monoterpenoid, since it was attenuated by L-NAME and ODQ [67]. It was also observed that the LA (300 μM) showed a relaxing effect of PHE-induced contraction in the aorta of mice exposed to nicotine [101].

4. Final considerations

Based on these studies, it can be concluded that the vast majority of those monoterpenes and monoterpenoids investigated and here presented have a hypotensive and vasorelaxant effect. Concerning the hypotensive effect, the studies did not include medium or long-term treatments; they were all about acute effects. In terms of results obtained, there was great variation in the repercussion on heart rate: concomitant tachycardia, in most cases, which was generally interpreted as a reflex reaction to a hypotensive effect of primary vascular origin; bradycardia or no change in heart rate in other cases. Concerning the investigation of the hypotensive effect, in terms of the methodology of administration of monoterpene or monoterpenoid, there was great variation in the route of administration employed, intraperitoneal in some cases, intravenous and oral in others, which makes comparisons more difficult. Additionally, concerning the perspective of therapeutic use, this is a relevant issue, since for long lasting treatment, as is the case with essential hypertension, the oral route of administration is largely preferable, if not mandatory.

Regarding the vasorelaxant effect, most studies describe a relaxing effect in rat aortic rings on contractions mediated by EMC and PMC and suggested, as participant in mechanism of action, based on indirect evidence, the inhibitory effect of these pharmacological agents on the activation of L type VDCC. Participation of K^+ and TRP ionic channels, as well as intracellular mechanisms on monoterpene and monoterpenoid-induced relaxation of contraction have been little investigated.

From the point of view of the possible therapeutic use of monoterpenes and monoterpenoids for the treatment of arterial hypertension, it can be concluded that several studies on the pressure and vascular effects have been carried out. These studies point to a potential therapeutic use for several of these agents. However, in general, they were restricted to the initial stages of a preclinical study.

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References

- [1] Cox-Georgian, D.; Ramadoss, N.; Dona, C.; Basu, C. Therapeutic and medicinal uses of terpenes. In *Medicinal Plants: From Farm to Pharmacy*; 2019; pp. 333–359 ISBN 9783030312695.
- [2] Lahlou, M. Methods to Study the Phytochemistry and Bioactivity of Essential Oils. *Phyther. Res.* **2004**, *18*, 435–448.
- [3] Tetali, S.D. Terpenes and isoprenoids: a wealth of compounds for global use. *Planta* **2019**, *249*, doi: 10.1007/s00425-018-3056-x.
- [4] Paduch, R.; Kandefer-Szerszeń, M.; Trytek, M.; Fiedurek, J. Terpenes: substances useful in human healthcare. *Arch. Immunol. Ther. Exp. (Warsz)*. **2007**, *55*, 315–327, doi:10.1007/s00005-007-0039-1.
- [5] Edris, A. Pharmaceutical and therapeutic potentials of essential oils and their individual volatile constituents: a review. *Phyther. Res.* **2007**, *21*, 308–323, doi:10.1002/ptr.
- [6] De Andrade, T.U.; Brasil, G.A.; Endringer, D.C.; Da Nóbrega, F.R.; De Sousa, D.P. Cardiovascular activity of the chemical constituents of essential oils. *Molecules* **2017**, *22*, doi:10.3390/molecules22091539.
- [7] Lahlou, S.; Galindo, C.A.B.; Leal-Cardoso, J.H.; Fonteles, M.C.; Duarte, G.P. Cardiovascular effects of the Essential Oil of *Alpinia zerumbet* leaves and its Main Constituent, Terpinen-4-ol, in rats: Role of the Autonomic Nervous System. *Planta Med.* **2002**, *68*, 1097–1102.
- [8] Vasconcelos, C.M.L.; Oliveira, I.S.N.; Santos, J.N.A.; Souza, A.A.; Menezes-Filho, J.E.R.; Silva Neto, J.A.; Lima, T.C.; de Sousa, D.P. Negative inotropism of terpenes on Guinea pig left atrium: Structure-activity relationships. *Nat. Prod. Res.* **2018**, *32*, 1428–1431, doi: 10.1080/14786419.2017.1344658.
- [9] 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*, 52–58, doi:10.1016/j.lfs.2014.08.022.
- [10] Cardoso-Teixeira, A.C.; Ferreira-da-Silva, F.W.; Peixoto-Neves, D.; Oliveira-Abreu, K.; Pereira-Gonçalves, Á.; Coelho-de-Souza, A.; Leal-Cardoso, J. Hydroxyl Group and Vasorelaxant Effects of Perillyl Alcohol, Carveol, Limonene on Aorta Smooth Muscle of Rats. *Molecules* **2018**, *23*, 1430, doi: 10.3390/molecules23061430.
- [11] Peixoto-Neves, D.; Leal-Cardoso, J. H.; Jaggar, J.H. Eugenol dilates rat cerebral arteries by inhibiting smooth muscle cell voltage-dependent calcium channels. *J. Cardiovasc. Pharmacol.* **2014**, *64*, 401–406, doi:10.1038/jid.2014.371.
- [12] Nascimento, G.A. do; Souza, D.S. de; Lima, B.S.; Vasconcelos, C.M.L. de; Araújo, A.A. de S.; Durço, A.O.; Quintans-Junior, L.J.; Almeida, J.R.G. da S.; Oliveira, A.P.; Santana-Filho, V.J. de; et al. Bradycardic and antiarrhythmic effects of the D-limonene in rats. *Arq. Bras. Cardiol.* **2019**, *113*, 925–932, doi: 10.5935/abc.20190173.
- [13] Sun, J. D-Limonene: safety and clinical applications. *Altern. Med. Rev.* **2007**, *12*, 259–264.
- [14] Menezes, I.A.C.; Barreto, C.M.N.; Antonioli, 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*, 562–566, doi:10.1515/znc-2010-9-1005.

- [15] Felipe, C.F.B.; Albuquerque, A.M.S.; de Pontes, J.L.X.; de Melo, J.Í.V.; Rodrigues, T.C.M.L.; de Sousa, A.M.P.; Monteiro, Á.B.; Ribeiro, A.E. da S.; Lopes, J.P.; de Menezes, I.R.A.; et al. Comparative study of alpha- and beta-pinene effect on PTZ-induced convulsions in mice. *Fundam. Clin. Pharmacol.* **2019**, *33*, 181–190, doi: 10.1111/fcp.12416.
- [16] Silva, M.T.M.; Ribeiro, F.P.R.A.; Medeiros, M.A.M.B.; Sampaio, P.A.; Silva, Y.M.S.; Silva, M.T.A.; Quintans, J. S.S.; Quintans-Júnior, L.J.; Ribeiro, L.A. A. The vasorelaxant effect of p -cymene in rat aorta involves potassium channels. *Sci. World J.* **2015**, *2015*, 6–11, doi: 10.1155/2015/458080.
- [17] Jenner, P.M.; Hagan, E.C.; Taylor, J. M.; Cook, E.L.; Fitzhugh, O.G. Food flavourings and compounds of related structure I. Acute oral toxicity. *Food Cosmet. Toxicol.* **1964**, *2*, 327–343, doi: 10.1016/S0015-6264(64)80192-9.
- [18] Bastos, J.F.A.; Moreira, Í.J.A.; Ribeiro, T.P.; Medeiros, I.A.; Antonioli, 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*, 331–337, doi:10.1111/j.1742-7843.2009.00492.x.
- [19] Ribeiro-Filho, H.V.; De Souza Silva, C.M.; De Siqueira, R.J.; Lahlou, S.; Dos Santos, A.A.; Magalhães, P.J.C. Biphasic cardiovascular and respiratory effects induced by β-citronellol. *Eur. J. Pharmacol.* **2016**, *775*, 96–105, doi: 10.1016/j.ejphar.2016.02.025.
- [20] Lapczynski, A.; Bhatia, S.P.; Letizia, C.S.; Api, A.M. Fragrance material review on dl-citronellol. *Food Chem. Toxicol.* **2008**, *46*, 4–10, doi:10.1016/j.fct.2008.06.043.
- [21] El-Bassossy, H.M.; Elberry, A.A.; Ghareib, S.A. Geraniol improves the impaired vascular reactivity in diabetes and metabolic syndrome through calcium channel blocking effect. *J. Diabetes Complications* **2016**, *30*, 1008–1016, doi:10.1016/j.jdiacomp.2016.04.006.
- [22] Babukumar, S.; Vinothkumar, V.; Sankaranarayanan, C.; Srinivasan, S. Geraniol, a natural monoterpene, ameliorates hyperglycemia by attenuating the key enzymes of carbohydrate metabolism in streptozotocin-induced diabetic rats. *Pharm. Biol.* **2017**, *55*, 1442–1449, doi: 10.1080/13880209.2017.1301494.
- [23] Anjos, P.J.C.; Lima, A.O.; Cunha, P. S.; De Sousa, D.P.; Onofre, A.S.C.; Ribeiro, T.P.; Medeiros, I.A.; Antonioli, Á.R.; Quintans-Júnior, L.J.; Santos, M.R. V. Cardiovascular effects induced by linalool in normotensive and hypertensive rats. *Zeitschrift für Naturforsch. - Sect. C J. Biosci.* **2013**, *68 C*, 181–190, doi:10.1515/znc-2013-5-603.
- [24] Bickers, D.; Calow, P.; Greim, H.; Hanifin, J.M.; Rogers, A.E.; Saurat, J.H.; Sipes, I.G.; Smith, R.L.; Tagami, H.; Api, A.M. A toxicologic and dermatologic assessment of linalool and related esters when used as fragrance ingredients. *Food Chem. Toxicol.* **2003**, *41*, 919–942, doi:10.1016/S0278-6915(03)00016-4.
- [25] Camargo, S.B.; Simões, L.O.; Medeiros, C.F. de A.; de Melo Jesus, A.; Fregoneze, J.B.; Evangelista, A.; Villarreal, C.F.; Araújo, A.A. de S.; Quintans-Júnior, L.J.; Silva, D.F. Antihypertensive potential of linalool and linalool complexed with β-cyclodextrin: Effects of subchronic treatment on blood pressure and vascular reactivity. *Biochem. Pharmacol.* **2018**, *151*, 38–46, doi:10.1016/j.bcp.2018.02.014.
- [26] Bhatia, S.P.; McGinty, D.; Letizia, C. S.; Api, a M. Fragrance material review on p-methya-1,8-dien-7-ol. *Food Chem. Toxicol.* **2008**, *46*, S197–S200, doi: 10.1016/j.fct.2008.06.071.

- [27] Kennedy, S.; Wadsworth, R.M.; Wainwright, C.L. Effect of antiproliferative agents on vascular function in normal and in vitro balloon-injured porcine coronary arteries. *Eur. J. Pharmacol.* **2003**, *481*, 101–107, doi:10.1016/j.ejphar.2003.09.010.
- [28] Bhatia, S.P.; McGinty, D.; Letizia, C. S.; Api, A.M. Fragrance material review on laevo-carveol. *Food Chem. Toxicol.* **2008**, *46*, 88–90, doi:10.1016/j.fct.2008.06.055.
- [29] Sun, J.; Yang, T.; Wang, P.; Ma, S.; Zhu, Z.; Pu, Y.; Li, L.; Zhao, Y.; Xiong, S.; Liu, D.; et al. Activation of cold-sensing transient receptor potential melastatin subtype 8 antagonizes vasoconstriction and hypertension through attenuating RhoA/Rho kinase pathway. *Hypertension* **2014**, *63*, 1354–1363, doi:10.1161/HYPERTENSIONAHA.113.02573.
- [30] Xiong, S.; Wang, B.; Lin, S.; Zhang, H.; Li, Y.; Wei, X.; Cui, Y.; Wei, X.; Lu, Z.; Gao, P.; et al. Activation of transient receptor potential melastatin subtype 8 attenuates cold-induced hypertension through ameliorating vascular mitochondrial dysfunction. *J. Am. Heart Assoc.* **2017**, *6*, 1–17, doi:10.1161/JAHA.117.005495.
- [31] Oz, M.; El Nebrisi, E.G.; Yang, K.H. S.; Howarth, F.C.; Al Kury, L.T. Cellular and molecular targets of menthol actions. *Front. Pharmacol.* **2017**, *8*, 1–17, doi:10.3389/fphar.2017.00472.
- [32] Robu, V.; Covaci, G.; Popescu, I.M. The use of essential oils in organic farming. *Res. J. Agric. Sci.* **2015**, *47*, 134–137.
- [33] Craighead, D.H.; Alexander, L.M. Menthol-induced cutaneous vasodilation is preserved in essential hypertensive men and women. *Am. J. Hypertens.* **2017**, *30*, 1156–1162, doi:10.1093/ajh/hpx127.
- [34] 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*, 811–816, doi:10.1111/j.1440-1681.2010.05383.x.
- [35] Bhatia, S.P.; Letizia, C.S.; Api, A.M. Fragrance material review on alpha-terpineol. *Food Chem. Toxicol.* **2008**, *46*, 280–285, doi:10.1016/j.fct.2008.06.027.
- [36] 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*, 169–177, doi:10.1111/j.1472-8206.2008.00571.x.
- [37] 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*, 323–330.
- [38] Santos, S.E.; Ribeiro, F.P.R.A.; Menezes, P.M.N.; Duarte-Filho, L.A.M.; Quintans, J.S.S.; Quintans-Junior, L.J.; Silva, F.S.; Ribeiro, L.A.A. New insights on relaxant effects of (–)-borneol monoterpene in rat aortic rings. *Fundam. Clin. Pharmacol.* **2019**, *33*, 148–158, doi:10.1111/fcp.12417.
- [39] Silva-Filho, J.C.; Oliveira, N.N.P.M.; Arcanjo, D.D.R.; Quintans-Júnior, L.J.; Cavalcanti, S.C.H.; Santos, M.R. V.; Oliveira, R. de C.M.; Oliveira, A.P. Investigation of mechanisms involved in (–)-borneol-induced vasorelaxant response on rat thoracic aorta. *Basic Clin. Pharmacol. Toxicol.* **2012**, *110*, 171–177, doi:10.1111/j.1742-7843.2011.00784.x.

- [40] Bhatia, S.P.; McGinty, D.; Letizia, C.S.; Api, A.M. Fragrance material review on l-borneol. *Food Chem. Toxicol.* **2008**, *46*, 81–84, doi:10.1016/j.fct.2008.06.054.
- [41] 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*, 1365–1371, doi:10.1055/s-2007-990236.
- [42] Suntres, Z.E.; Coccimiglio, J.; Alipour, M. The Bioactivity and Toxicological Actions of Carvacrol. *Crit. Rev. Food Sci. Nutr.* **2015**, *55*, 304–318, doi:10.1080/10408398.2011.653458.
- [43] Dantas, B.P.V.; Alves, Q.L.; de Assis, K.S.; Ribeiro, T.P.; de Almeida, Mô.M.; de Vasconcelos, A.P.; de Araújo, D.A.M.; de Andrade Braga, V.; de Medeiros, I.A.; Alencar, J.L.; et al. Participation of the TRP channel in the cardiovascular effects induced by carvacrol in normotensive rat. *Vascul. Pharmacol.* **2015**, *67*, 48–58, doi:10.1016/j.vph.2015.02.016.
- [44] 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*, 341–50, doi:10.1111/j.1472-8206.2009.00768.x.
- [45] Seo, E.; Kang, P.; Seol, G.H. Trans - anethole prevents hypertension induced by chronic exposure to both restraint stress and nicotine in rats. *Biomed. Pharmacother.* **2018**, *102*, 249–253, doi:10.1016/j.biopha.2018.03.081.
- [46] Coelho-de-Souza, A.N.; Rocha, M. V.A.P.; Oliveira, K.A.; Vasconcelos, Y.A. G.; Santos, E.C.; Silva-Alves, K.S.; Diniz, L.R.L.; Ferreira-da-Silva, F.W.; Oliveira, A.C.; Ponte, E.L.; et al. Volatile oil of *Croton zehntneri* per oral sub-acute treatment offers small toxicity: perspective of therapeutic use. *Rev. Bras. Farmacogn.* **2019**, *29*, 228–233, doi:10.1016/j.bjp.2018.11.005.
- [47] Siqueira, R.J.B. de; Magalhães, P.J. C.; Leal-Cardoso, J.H.; Duarte, G.P.; Lahlou, S. Cardiovascular effects of the essential oil of *Croton zehntneri* leaves and its main constituents , anethole and estragole , in normotensive conscious rats. *Life Sci.* **2006**, *78*, 2365–2372, doi:10.1016/j.lfs.2005.09.042.
- [48] Soares, P.M.G.; Lima, R.F.; de Freitas Pires, A.; Souza, E.P.; Assreuy, A.M.S.; Criddle, D.N. Effects of anethole and structural analogues on the contractility of rat isolated aorta: Involvement of voltage-dependent Ca²⁺ –channels. *Life Sci.* **2007**, *81*, 1085–93, doi:10.1016/j.lfs.2007.08.027.
- [49] Lahlou, S.; Interaminense, L.F.L.; Magalhães, P.J.C.; Leal-Cardoso, J.H.; Duarte, G.P. Cardiovascular Effects of Eugenol , a Phenolic Compound Present in Many Plant Essential Oils , in Normotensive Rats. *J. Cardiovasc. Pharmacol.* **2004**, *43*, 250–257.
- [50] Leal Interaminense, L.F.; Leal-Cardoso, J.H.; Caldas Magalhães, P.J.; Pinto Duarte, G.; Lahlou, S. Enhanced hypotensive effects of the essential oil of *Ocimum gratissimum* leaves and its main constituent, eugenol, in DOCA-salt hypertensive conscious rats. *Planta Med.* **2005**, *71*, 376–378, doi:10.1055/s-2005-864109.
- [51] Peixoto-Neves, D.; Wang, Q.; Leal-Cardoso, J.H.; Rossoni, L. V.; Jaggar, J.H. Eugenol dilates mesenteric arteries and reduces systemic BP by activating endothelial cell TRPV4 channels. *Br. J. Pharmacol.* **2015**, *172*, 3484–3494, doi:10.1111/bph.13156.
- [52] Alvarez-collazo, J.; Alonso-carbajo, L.; López-medina, A.I.; Alpizar, Y.A.; Tajada, S.; Nilius, B.; Voets, T.; López-

- López, J.R.; Talavera, K.; Pérez-García, M.T.; et al. Cinnamaldehyde inhibits L-type calcium channels in mouse ventricular cardiomyocytes and vascular smooth muscle cells. *Pflugers Arch - Eur J Physiol* **2014**, 466, 2089–2099, doi: 10.1007/s00424-014-1472-8.
- [53] da Silva, R.E.R.; de Moraes, L.P.; Silva, A.A.; Bastos, C.M.S.; Pereira-gonçalves, Á.; Kerntopf, M.R.; Menezes, I.R.A.; Leal-Cardoso, J.H.; Barbosa, R. Vasorelaxant effect of the *Lippia alba* essential oil and its major constituent, citral, on the contractility of isolated rat aorta. *Biomed. Pharmacother.* **2018**, 108, 792–798, doi:10.1016/j.biopha.2018.09.073.
- [54] Pereira, S.L.; Marques, A.M.; Sudo, R.T.; Kaplan, M.C.A.; 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, 3072–3085, doi: 10.3390/molecules18033072.
- [55] Andrade, F.C.; Mota, M.M.; Barreto, A.S.; Sousa, D.P.; Quintans-Junior, L.J.; Santos, M.R.V. Antihypertensive therapeutic potential of citronellal. *Lat. Am. J. Pharm.* **2012**, 31, 767–771.
- [56] Citronellal | C10H18O - PubChem Available online: <https://pubchem.ncbi.nlm.nih.gov/compound/7794#section=Toxicity> (accessed on Sep 15, 2020).
- [57] De Sousa, D.P.; Mesquita, R.F.; De Araújo Ribeiro, L.A.; De Lima, J.T. Spasmolytic activity of carvone and limonene enantiomers. *Nat. Prod. Commun.* **2015**, 10, 1893–1896, doi: 10.1177/1934578x1501001120.
- [58] 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, 700–704, doi:10.1055/s-2002-33795.
- [59] 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, 1881–1887, doi:10.1590/S0100-879X2004001200014.
- [60] Silva, D.F.; Araújo, I.G.A.; Albuquerque, J.G.F.; Porto, D.L.; Dias, K.L.G.; Cavalcante, K.V.M.; Veras, R.C.; Nunes, X.P.; Barbosa-Filho, J.M.; Araújo, D.A.M.; et al. Rotundifolone-induced relaxation is mediated by BK Ca channel activation and Ca v channel inactivation. *Basic Clin. Pharmacol. Toxicol.* **2011**, 109, 465–475, doi:10.1111/j.1742-7843.2011.00749.x.
- [61] Moon, H.K.; Kang, P.; Lee, H.S.; Min, S.S.; Seol, G.H. Effects of 1,8-cineole on hypertension induced by chronic exposure to nicotine in rats. *J. Pharm. Pharmacol.* **2014**, 66, 688–693, doi:10.1111/jphp.12195.
- [62] 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, 1125–1131, doi:10.1139/y02-142.
- [63] Pinto, N.; Assreuy, A.; Coelho-de-Souza, A.; Ceccatto, V.; Magalhães, P.; Lahlou, S.; Leal-Cardoso, J. Endothelium-dependent vasorelaxant effects of the essential oil from aerial parts of *Alpinia zerumbet* and its main constituent 1, 8-cineole in rats. *Phytomedicine* **2009**, 16, 1151–1155, doi: 10.1016/j.phymed.2009.04.007.
- [64] Hsieh, Y.S.; Shin, Y.K.; Han, A.Y.; Kwon, S.; Seol, G.H. Linalyl acetate prevents three related factors of vascular damage in COPD-like and hypertensive rats. *Life Sci.* **2019**, 232, 116608, doi:10.1016/j.lfs.2019.116608.
- [65] Hsieh, Y.S.; Kwon, S.; Lee, H.S.; Seol, G.H. Linalyl acetate prevents

hypertension-related ischemic injury. *PLoS One* **2018**, *13*, 1–14, doi:10.1371/journal.pone.0198082.

[66] Kwon, S.; Hsieh, Y.S.; Shin, Y.K.; Kang, P.; Seol, G.H. Linalyl acetate prevents olmesartan-induced intestinal hypermotility mediated by interference of the sympathetic inhibitory pathway in hypertensive rat. *Biomed. Pharmacother.* **2018**, *102*, 362–368, doi: 10.1016/j.biopha.2018.03.095.

[67] Koto, R.; Imamura, M.; Watanabe, C.; Obayashi, S.; Shiraishi, M.; Sasaki, Y.; Azuma, H. Linalyl acetate as a major ingredient of lavender essential oil relaxes the rabbit vascular smooth muscle through dephosphorylation of myosin light chain. *J. Cardiovasc. Pharmacol.* **2006**, *48*, 850–856, doi: 10.1097/01.fjc.0000238589.00365.42.

[68] Santos, M.R. V.; Moreira, F. V.; Fraga, B.P.; Souza, D.P. De; Bonjardim, L.R.; Quintans-Junior, L.J. Cardiovascular effects of monoterpenes: a review. *Rev. Bras. Farmacogn.* **2011**, *21*, 764–771, doi:10.1590/S0102-695X2011005000119.

[69] Oz, M.; Lozon, Y.; Sultan, A.; Yang, K.H.S.; Galadari, S. Effects of monoterpenes on ion channels of excitable cells. *Pharmacol. Ther.* **2015**, *152*, 83–97, doi:10.1016/j.pharmthera.2015.05.006.

[70] Wang, X.; Li, G.; Shen, W. Protective effects of D-limonene against transient cerebral ischemia in stroke-prone spontaneously hypertensive rats. *Exp. Ther. Med.* **2018**, *15*, 699–706, doi: 10.3892/etm.2017.5509.

[71] Marom, M.; Hagalili, Y.; Sebag, A.; Tzvier, L.; Atlas, D. Conformational changes induced in voltage-gated calcium channel Cav1.2 by BayK 8644 or FPL64176 modify the kinetics of secretion independently of Ca²⁺ influx. *J. Biol. Chem.* **2010**, *285*, 6996–7005, doi: 10.1074/jbc.M109.059865.

[72] Salehi, B.; Upadhyay, S.; Orhan, I.E.; Jugran, A.K.; Jayaweera, S.L.D.; Dias, D. A.; Sharopov, F.; Taheri, Y.; Martins, N.; Baghalpour, N.; et al. Therapeutic potential of α - and β -pinene: A miracle gift of nature. *Biomolecules* **2019**, *9*, 1–34, doi:10.3390/biom9110738.

[73] Crespo, R.; Wei, K.; Rodenak-Kladniew, B.; Mercola, M.; Ruiz-Lozano, P.; Hurtado, C. Effect of geraniol on rat cardiomyocytes and its potential use as a cardioprotective natural compound. *Life Sci.* **2017**, *172*, 8–12, doi:10.1016/j.lfs.2017.01.008.

[74] El-Bassossy, H.M.; Ghaleb, H.; Elberry, A.A.; Balamash, K.S.; Ghareib, S.A.; Azhar, A.; Banjar, Z. Geraniol alleviates diabetic cardiac complications: Effect on cardiac ischemia and oxidative stress. *Biomed. Pharmacother.* **2017**, *88*, 1025–1030, doi:10.1016/j.biopha.2017.01.131.

[75] 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*, 93–102, doi: 10.1540/jsmr.50.93.

[76] Silva, R.E.R. da; Silva, A. de A.; Pereira-de-Morais, L.; Almeida, N. de S.; Iriti, M.; Kerntopf, M.R.; Menezes, I.R. A. de; Coutinho, H.D.M.; Barbosa, R. Relaxant Effect of Monoterpene (–)-Carveol on Isolated Human Umbilical Cord Arteries and the Involvement of Ion Channels. *Molecules* **2020**, *25*, 1–11.

[77] Craighead, D.H.; Alexander, L.M. Topical menthol increases cutaneous blood flow. *Microvasc. Res.* **2016**, *107*, 39–45, doi:10.1016/j.physbeh.2017.03.040.

[78] Gondim, A.N.S.; Lara, A.; Santos-Miranda, A.; Roman-Campos, D.; Lauton-Santos, S.; Menezes-Filho, J.E. R.; de Vasconcelos, C.M.L.; Conde-Garcia, E.A.; Guatimosim, S.; Cruz, J.S. (–)-Terpinen-4-ol changes intracellular

Ca²⁺ handling and induces pacing disturbance in rat hearts. *Eur. J. Pharmacol.* **2017**, 807, 56–63, doi: 10.1016/j.ejphar.2017.04.022.

[79] Pires, P.W.; Sullivan, M.N.; Pritchard, H.A.T.; Robinson, J.J.; Earley, S. Unitary TRPV3 channel ca²⁺ influx events elicit endothelium-dependent dilation of cerebral parenchymal arterioles. *Am. J. Physiol. - Hear. Circ. Physiol.* **2015**, 309, H2031–H2041, doi: 10.1152/ajpheart.00140.2015.

[80] Tognolini, M.; Ballabeni, V.; Bertoni, S.; Bruni, R.; Impicciatore, M.; Barocelli, E. Protective effect of *Foeniculum vulgare* essential oil and anethole in an experimental model of thrombosis. *Pharmacol. Res.* **2007**, 56, 254–260, doi:10.1016/j.phrs.2007.07.002.

[81] Siqueira, R.J.B. De; Leal-Cardoso, J. H.; COUTURE, R.; Lahlou, S. ROLE OF CAPSAICIN-SENSITIVE SENSORY NERVES IN MEDIATION OF THE CARDIOVASCULAR EFFECTS OF THE ESSENTIAL OIL OF CROTON ZEHNTNERI LEAVES IN ANAESTHETIZED RATS. *Clin. Exp. Pharmacol. Physiol.* **2006**, 33, 238–247.

[82] Guénette, S.; Ross, A.; Marier, J. Pharmacokinetics of eugenol and its effects on thermal hypersensitivity in rats. *Eur. J. ...* **2007**, 562, 60–67, doi: 10.1016/j.ejphar.2007.01.044.

[83] Criddle, D.N.; Madeira, S.V.F.; de Moura, R.S. Endothelium-dependent and -independent vasodilator effects of eugenol in the rat mesenteric vascular bed. *J. Pharm. Pharmacol.* **2003**, 55, 359–365, doi:10.1211/002235702694.

[84] Interaminense, L.F.L.; Jucá, D.M.; Magalhães, P.J.C.; Leal-Cardoso, J.H.; Duarte, G.P.; Lahlou, S. Pharmacological evidence of calcium-channel blockade by essential oil of *Ocimum gratissimum* and its main constituent, eugenol, in isolated aortic

rings from DOCA-salt hypertensive rats. *Fundam. Clin. Pharmacol.* **2007**, 21, 497–506, doi:10.1111/j.1472-8206.2007.00514.x.

[85] Damiani, C.E.N.; Moreira, C.M.; Heng, T.Z.; Creazzo, T.L.; Vassallo, D. V. Effects of eugenol, an essential oil, on the mechanical and electrical activities of cardiac muscle. *J. Cardiovasc. Pharmacol.* **2004**, 44, 688–695, doi: 10.1097/00005344-200412000-00011.

[86] Magyar, J.; Szentandrassy, N.; Bánfáy, 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, 29–36, doi: 10.1016/j.ejphar.2004.01.011.

[87] Nangle, M.R.; Gibson, T.M.; Cotter, M.A.; Cameron, N.E. Effects of eugenol on nerve and vascular dysfunction in streptozotocin-diabetic rats. *Planta Med.* **2006**, 72, 494–500, doi:10.1055/s-2005-916262.

[88] Yanaga, A.; Goto, H.; Nakagawa, T.; Hikiami, H.; Shibahara, N.; Shimada, Y. Cinnamaldehyde Induces Endothelium-Dependent and -Independent Vasorelaxant Action on Isolated Rat Aorta. *Biol. Pharm. Bull.* **2006**, 29, 2415–2418.

[89] Xue, Y.-L.; Shi, H.-X.; Murad, F.; Bian, K. Vasodilatory effects of cinnamaldehyde and its mechanism of action in the rat aorta. *Vasc. Health Risk Manag.* **2011**, 7, 273–280, doi:10.2147/VHRM.S15429.

[90] Raffai, G.; Kim, B.; Park, S.; Khang, G.; Lee, D.; Vanhoutte, P.M. Cinnamaldehyde and cinnamaldehyde-containing micelles induce relaxation of isolated porcine coronary arteries : role of nitric oxide and calcium. *Int. J. Nanomedicine* **2014**, 9, 2557–2566.

[91] Wang, P.; Yang, Y.; Wang, D.; Yang, Q.; Wan, J.; Liu, S.; Zhou, P.;

- Yang, Y. Cinnamaldehyde Ameliorates Vascular Dysfunction in Diabetic Mice by Activating Nrf2. *Am. J. Hypertens.* **2020**, *33*, 610–619, doi:10.1093/ajh/hpaa024.
- [92] Wang, F.; Pu, C.; Zhou, P.; Wang, P.; Liang, D.; Wang, Q.; Hu, Y.; Li, B.; Hao, X. Cinnamaldehyde Prevents Endothelial Dysfunction Induced by High Glucose by Activating Nrf2. *Cell Physiol Biochem* **2015**, *36*, 315–324, doi:10.1159/000374074.
- [93] El-bassossy, H.M.; Fahmy, A.; Badawy, D. Cinnamaldehyde protects from the hypertension associated with diabetes. *Food Chem. Toxicol.* **2011**, *49*, 3007–3012, doi:10.1016/j.fct.2011.07.060.
- [94] Gonçalves, E.C.D.; Baldasso, G.M.; Bicca, M.A.; Paes, R.S.; Capasso, R.; Dutra, R.C. Terpenoids, cannabimimetic ligands, beyond the cannabis plant. *Molecules* **2020**, *25*, 1–47, doi:10.3390/molecules25071567.
- [95] Devi, R.C.; Sim, S.M.; Ismail, R. Effect of *Cymbopogon citratus* and Citral on Vascular Smooth Muscle of the Isolated Thoracic Rat Aorta. *Evidence-Based Complement. Altern.* **2012**, doi:10.1155/2012/539475.
- [96] Lu, J.X.; Guo, C.; Ou, W.-S.; Niu, H. F.; Song, P.; Li, Q.Z.; Liu, Z.; Xu, J.; Li, P.; Zhu, M.-L.; et al. Citronellal prevents endothelial dysfunction and atherosclerosis in rats. *J. Cell Biochem.* **2019**, *120*, 3790–3800, doi:10.1002/jcb.27660.
- [97] Heuberger, E.; Hongratanaworakit, T.; Böhm, C.; Weber, R.; Buchbauer, G. Effects of chiral fragrances on human autonomic nervous system parameters and self-evaluation. *Chem. Senses* **2001**, *26*, 281–292, doi:10.1093/chemse/26.3.281.
- [98] Silva, D.F.; De Almeida, M.M.; Chaves, C.G.; Braz, A.L.; Gomes, M.A.; Pinho-Da-Silva, L.; Pesquero, J.L.; Andrade, V.A.; De Fátima Leite, M.; De Albuquerque, J.G.F.; et al. TRPM8 channel activation induced by monoterpenoid rotundifolone underlies mesenteric artery relaxation. *PLoS One* **2015**, *10*, 1–17, doi:10.1371/journal.pone.0143171.
- [99] Cardoso Lima, T.; Mota, M.M.; Barbosa-Filho, J.M.; Viana Dos Santos, M.R.; De Sousa, D.P. Structural relationships and vasorelaxant activity of monoterpenes. *Daru* **2012**, *20*, 23, doi:10.1186/2008-2231-20-23.
- [100] Shin, Y.K.; Hsieh, Y.S.; Kwon, S.; Lee, H.S.; Seol, G.H. Linalyl acetate restores endothelial dysfunction and hemodynamic alterations in diabetic rats exposed to chronic immobilization stress. *J. Appl. Physiol.* **2018**, *124*, 1274–1283, doi:10.1152/jappphysiol.01018.2017.
- [101] Kim, J.R.; Kang, P.; Lee, H.S.; Kim, K.Y.; Seol, G.H. Cardiovascular effects of linalyl acetate in acute nicotine exposure. *Environ. Health Prev. Med.* **2017**, *22*, 1–7, doi:10.1186/s12199-017-0651-6.