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].

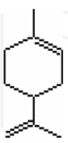
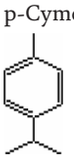
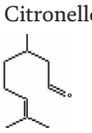
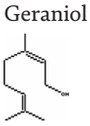
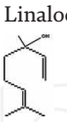
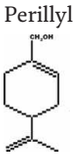
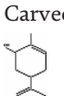
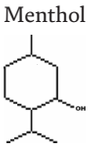
Studies in the literature demonstrate that the natural (present in essential oils—EO) monoterpenes and monoterpenoids have one or several biological/pharmacological activities, among which the most frequently reported are antioxidant, anticarcinogenic, anti-inflammatory, repellent, gastroprotective,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

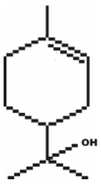
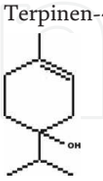
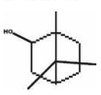
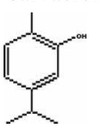
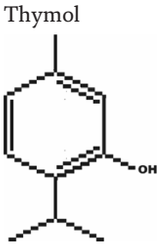
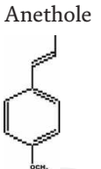
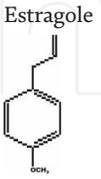
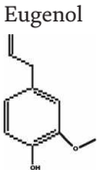
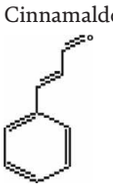
Among the most prominent and therapeutically potentially promising activities of natural monoterpenes and monoterpenoids are those on the cardiovascular system [6]. Reports on literature, here reviewed and discussed, reveal their effect on heart (rate and inotropism), systemic blood pressure (SBP), and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

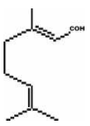
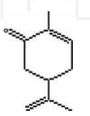
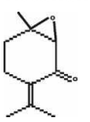
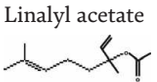
These effects are frequently attributed to activity on ion channels, such as voltage-dependent Ca^{2+} channels (VDCC) [11]. These substances can affect the contractions mediated by electromechanical excitation-contraction coupling (EMC; ex.: the KCl-induced contraction) or pharmacomechanical excitation-contraction 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 Emax = 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]	*Citrus limon*, *Lippia alba*
	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]	*Eucalyptus tereticornis*, *Citrus lemon*
β-Pinene 	Hypotensive	1–20 mg/kg[A]	[14]	>2.0 g/kg (v.o.—mice) [15]	*Eucalyptus tereticornis*, *Citrus lemon*
p-Cymene 	Vasorelaxant	$5.8 \pm 1.6 \times 10^{-5}$ M[C]	[16]	4.7 g/kg (v.o—rat); >5 g/kg (v.o —rabbit) [17]	*Eucalyptus camaldulensis*, *Origanum acutidens*
Citronellol 	Hypotensive	1–20 mg/kg	[14, 18, 19]	3.45 g/kg (v.o —rats) [20]	*Cymbopogon winterianus*, *Lippia alba*
	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]	*Cymbopogon martinii*, *C. nardus*, *C. winterianus*.
Linalool 	Hypotensive (normotensive animals)	1–20 mg/kg	[14, 23]	2.7 g/kg (v.o —rats) [24]	*Lavandula angustifólia*, *Ocimum basilicum*, *Citrus bergamia*
	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]	*Dracocephalum kotschyi*
	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]	*Citrus reticulata*, *Anethum graveolens*
Menthol 	Antihypertensive	Diet plus 0.5% menthol	[29, 30]	2.9–6 g/kg (v. o—mice and rats) [31, 32]	*Mentha* genus
	Vasorelaxant	100–500 mM[A]	[33]		

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

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]	*Lippia alba e Pectis brevipedunculata*
Citronellal 	Antihypertensive	200 mg/kg, v.o.	[55]	2.42 g/kg (v.o.—rats) [56]	*Cymbopogon winterianus*; *Cymbopogon citrates*
	Hypotensive	10–40 mg/kg, i.v.	[55]		
	Vasorelaxant	10^{-6} - 10^{-1} M	[55]		
Carvone 	Vasorelaxant	$6.2 \pm 2.6 \times 10^{-4}$ M[C]	[57]	1.6 g/kg (v.o.—rats) [17]	*Mentha spicata*, *Carum carvi*
Rotundifolone 	Hypotensive	1–30 mg/kg, i.v.	[58]	Not available (for mammals)	*Mentha rotundifolia*, *M. spicata L.*, *and M. x villosa*
	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]	*Croton nepetaefolius*; *Alpinia zerumbet*
	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]	*Lavandula angustifolia* and *Salvia sclarea*
	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.
[A]Range of doses or concentration employed.
[B]IC_{50} for KCl-induced contraction (electromechanical coupling) in presence of endothelium.
[C]IC_{50} for phenilephrine-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 (LD_{50} 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 monoterpenoid [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 ($IC_{50} \sim 130$ μM) and KCl, the effectiveness reached 100%. This monoterpenoid 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 monoterpenoid 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 Nω-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 ± 5.46 μM) and PHE-induced (IC_{50} 443.3 ± 66.83 μM) 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 ± 225.20 μM) and KCl (IC_{50} 662.1 ± 32.85 μM), 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 μM) and KCl (IC_{50} 344.25 μM) [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]quinoxal in-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 μg/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 ± 23.48 μM) and PMC (IC_{50} 802.50 ± 13.8 μM). It has been suggested that this effect involves the NO and COX pathway. 4TERP relaxed, with similar potency, the contractions

induced by BayK, $BaCl_2$, and K^+, presenting IC_{50} values of 454.2 ± 28.7, 450.5 ± 71.1, and 421.43 ± 23.48 μM, respectively. This suggest the possible inhibitory effect of 4TERP on VDCCs. It has been suggested that 4TERP also acts on other components of myocytes, such as the IP_3 pathway and the sensitivity of contractile proteins to Ca^{2+} [9].

In ventricular myocytes isolated from rats, 4TERP (30 μM) promoted a small increase (10.6 ± 2.6%) of L type Ca^{2+} currents. Above 300 μM the effect was reversed; 4TERP reduced the amplitude of these currents (IC_{50} of 1203 ± 0.224 μM). 4TERP increased the Ca^{2+} spark frequency at low concentrations and decreased the amplitude of Ca^{2+} 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 $CaCl_2$, BayK8644, and caffeine and the authors suggested probable activities of this monoterpenoid on VDCCs or intracellular Ca^{2+} 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 Ca^{2+}-free medium. These data together suggested the hypothesis that the vasorelaxant mechanism of this monoterpenoid involves multiple mechanisms: the IP_3 pathway, the sensitivity of contractile proteins to Ca^{2+}, 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 Ca^{2+}-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 IP_3 pathway, the sensitivity of contractile proteins to Ca^{2+}, 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 stablishes (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 (predominantly 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 (IC_{50} 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 (IC_{50} of 234.2 ± 11.3 μM) or pre-contracted with K^+ (IC_{50} 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 μg/mL) and KCl (IC_{50} 110.80 μg/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 × 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 (Emax = 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 μg/ml (1.1 mM)) and PHE (IC_{50} 185 μg/ml), with maximum efficacy. As a mechanism of this effect, a possible blocking of VDCCs and of the release of Ca^{2+} from sarcoplasmatic reticulum by RT was suggested [58, 59]. Others also observed the vasorelaxing effect of RT in the mesenteric artery of rats contracted with PHE (pD2 = 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 μg/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_{max} = 88.8%) and IC_{50} 3.6×10^{-4} 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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