Revista Brasileira de Farmacognosia
Brazilian Journal of Pharmacognosy
21(4): 764-771, Jul./Aug. 2011

Cardiovascular effects of monoterpenes: a review

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Review

Received 8 Oct 2010
Accepted 26 Jan 2011
Available online 8 Jul 2011

Keywords:
cardiovascular system
essential oils
monoterpenes
review

ISSN 0102-695X
doi: 10.1590/S0102-695X2011005000119

Abstract: The monoterpenes are secondary metabolites of plants. They have various pharmacological properties including antifungal, antibacterial, antioxidant, anticancer, anti-spasmodic, hypotensive, and vasorelaxant. The purpose of this research was to review the cardiovascular effects of monoterpenes. The data in this resarch were collected using the Internet portals Pubmed, Scopus, and ISI Web of Knowledge between the years 1987 and 2010. In the study 33 monoterpenes were included, which were related to each of the thirteen individual words: artery, cardiovascular, heart, myocyte, vasorelaxant, vessel, hypotension, hypotensive, cardiomyocyte, ventricular, vasodilatory, aorta, and aortic. The research utilized 22 articles published mainly in the journals Phytomedicine, Fundamental Clinical Pharmacology, Planta Medica, Life Science, European Journal of Pharmacology, and Brazilian Journal of Medical and Biological Research. Of the 33 monoterpenes studied surveyed, sixteen of them had already been studied for their effects on the cardiovascular system: carvacrol, citronellol, *p*-cymene, eucalyptol (1,8-cineole), linalool, menthol, myrtenal, myrtenol, α-pinene, rotundifolone (piperitenone oxide), sobrerol, thymol, α-limonene, α-terpinen-4-ol, α-terpineol, and perillyl alcohol. The main effects observed were vasorelaxation, decreased heart rate and blood pressure. This review showed that the monoterpenes may be considered promising agents for prevention or treatment of diseases of the cardiovascular system.

Introduction

It is estimated that about 80% of the world's population uses traditional medicine for its primary health care (Balick et al., 1994). Most of these therapies involve the use of plant extracts or their active compounds, such as terpenoids (Wagner & Elmadfa, 2003).

The terpenoids, also known as isoprenoids, are formed by repetition branched units of five carbons, similar to units of isoprene (Sharkey & Yeh, 2001). They are derived from mevalonic acid and sometimes called active isoprenes (Simões et al., 2004). The generalization that terpenes could be seen as composed of isoprene units became known as the isoprene rule, which investigators used to work out structures of isoprenoids (Sharkey & Yeh, 2001). However, isoprenoids are not made from isoprene. The biological precursors to the isoprenoids are isopentenyl pyrophosphate (IPP) and its isomer dimethylallyl pyrophosphate (DMAPP), sometimes called active isoprenes (Sharkey & Yeh, 2001).

The nomenclature of terpenoids depends on the number of isoprene structures and can be classified as monoterpene, sesquiterpene, diterpene, triterpene, tetraterpene, and polyterpene (Table 1). The terpenoids present cyclic or acyclic structures, which result from changes of isoprenoid chain reactions as reductions, oxidations, cyclizations (involving the formation of carbocations), ring breaks, or rearrangements (Chappell, 1995). Because of this, they are the most numerous and structurally diverse natural plant products (Zwenger & Basu, 2008).

Monoterpenes can be divided into three subgroups: acyclic (myrcene, linalool, geraniol), monocyclic (α-terpineol and terpinolene), and bicyclic (α-pinene, thujone, camphor, fenchone). In each of these subgroups, there are other classifications: unsaturated hydrocarbons (limonene), alcohols (menthol), aldehydes and ketones (myrtenal, carvone), lactones (monoterpene lactones are called iridoids, ex. nepetalactone), and tropolonas (γ-thujaplicin) (Simões et al., 2004).

Monoterpenes, as well as the sesquiterpenes

Table 1. Cardiovascular effects of monoterpenes.

Monoterpenes	Study type	Tissue and/or Species	Effects	References
Carvacrol (**3**)	*In vitro*	Isolated canine and human ventricular cardiomyocytes	Cardiac arrhythmias	Magyar et al. (2004)
	In vivo	Anesthetized rat	Decreased heart rate	Aydin et al. (2007)
	In vitro	Rat isolated aorta	Vasorelaxation	Aydin et al. (2007)
	In vitro	Cerebral and cerebellar arteries of rat	Vasorelaxation	Earley et al. (2010)
	In vitro	Rat isolated aorta	Vasorelaxation	Peixoto-Neves et al. (2010)
Citronellol (**8**)	*In vivo*	Normotensive rat	Hypotension	Bastos et al. (2010)
	In vitro	Rat mesenteric artery	Vasorelaxation	Bastos et al. (2010)
	In vivo	Non-anaesthetized normotensive rat	Hypotension and tachycardia	Menezes et al. (2010)
Eucalyptol (**10**)	*In vitro*	Left ventricular papillary muscle of rat	Negative inotropic effect	Soares et al. (2005)
1,8-Cineole (**10**)	*In vivo*	Normotensive anesthetized and conscious rats	Hypotension	Lahlou et al. (2002)
	In vitro	Rat isolated aorta	Vasorelaxation	Lahlou et al. (2002)
	In vitro	Rat isolated aorta	Vasorelaxation	Pinto et al. (2009)
Limonene (**13**)	*In vivo*	Rat	Reduction and prevention of cardiovascular injuries caused by pulmonary hypertension	Touvay et al. (1995)
(+)-Linalool (**14**)	*In vivo*	Human (Inhalation)	Cardiovascular system stimulant	Höferl et al. (2006)
(-)-Linalool (**15**)	*In vivo*	Human (Inhalation)	Cardiovascular system depressant	Höferl et al. (2006)
(±)-Linalool (**14** and **15**)	*In vivo*	Non-anaesthetized normotensive rat	Hypotension and tachycardia	Menezes et al. (2010)
Menthol (**17**)	*In vitro*	Human forearm cutaneous vessels and rat arteries	Vasorelaxation	Johnson et al. (2009)
	In vitro	Myocytes isolated from rabbits	Negative inotropic effect	Baylie et al. (2010)
Myrtenal (**19**)	*In vivo*	Rat	Hypotension	Saito et al. (1996)
Myrtenol (**20**)	*In vivo*	Rat	Hypotension	Saito et al. (1996)
p-Cymene (**9**)	*In vivo*	Urethane anaesthetized rat	Hypotension and bradycardia	El Tahir et al. (2003)
Perillyl alcohol (**25**)	*In vivo*	Rat	Hypotension	Saito et al. (1996)
Rotundifolone (**27**)	*In vivo*	Normotensive rats	Hypotension and bradycardia	Lahlou et al. (2001) Guedes et al. (2002)
	In vitro	Rat isolated aorta	Vasorelaxation	Guedes et al. (2002)
	In vitro	Rat isolated aorta	Vasorelaxation	Guedes et al. (2004)
Sobrerol (**28**)	*In vivo*	Rat	Regulate the development of pulmonary hypertension	Touvay et al. (1995)
Thymol (**33**)	*In vitro*	Isolated canine and human ventricular cardiomyocytes	Cardiac arrhythmias	Magyar et al. (2002)
	In vitro	Canine and guinea pig cardiac preparations	Negative inotropic effect	Szentandrássy et al. (2004)
	In vitro	Isolated canine and human ventricular cardiomyocytes	Cardiac arrhythmias	Magyar et al. (2004)
	In vitro	Rat isolated aorta	Vasorelaxation	Peixoto-Neves et al. (2010)
	In vitro	Rat isolated aorta	Vasorelaxation	Peixoto-Neves et al. (2010)
(+)- α-Pinene (**23**)	*In vivo*	Urethane anaesthetized rat	Hypotension and bradycardia	El Tahir et al. (2003)
(+)- α-Pinene (**23**)	*In vivo*	Non-anaesthetized normotensive rat	Hypotension and tachycardia	Menezes et al. (2010)
(-)- β-Pinene (**24**)	*In vivo*	Non-anaesthetized normotensive rat	Hypotension and tachycardia	Menezes et al. (2010)
Terpinen-4-ol (**30**)	*In vivo*	Conscious rat	Hypotension	Lahlou et al. (2002)
	In vivo	Normotensive rat	Hypotension	Lahlou et al. (2003)
	In vivo	DOCA-salt hypertensive rat	Antihypertensive effect	Lahlou et al. (2003)
Terpineol (**29**)	*In vivo*	Rat	Hypotension	Saito et al. (1996)
	In vitro	Rat isolated mesenteric vascular bed	Vasorelaxation	Magalhães et al. (2008)
	In vivo	Conscious rats	Hypotension	Ribeiro et al. (2010)
	In vitro	Rat isolated mesenteric	Vasorelaxation	Ribeiro et al. (2010)

and diterpenes, are secondary metabolites because they are classified as nonessential for viability; however, they mediate important interactions between plants and their environment (Chappell, 1995). Several monoterpenes are widely used in the agriculture, cosmetic, and food industries, and as a general antiseptic in medical practice (Aeschbach et al., 1994; Lee et al., 1997; Manou et al., 1998). Most of the aroma from citrus fruit oil, cherries, and mint is due to the high content of monoterpenes, but they have no nutritional value because they are exclusively vegetable (Serrano et al.,2006).

Studies have shown that monoterpenes have various pharmacological properties including antifungal, antibacterial, antioxidant, anticancer, and anti-spasmodic (Garcia et al., 2008; Kato et al., 1990; Singh et al., 2010; Karkabounas et al., 2006; Magalhães et al., 1998).

Besides the activities described above, monoterpenes also produce significant effects on the cardiovascular system, promoting, among other actions, vasorelaxation, decreased heart rate, and hypotension (Peixoto-Neves et al., 2010; Bastos et al., 2010; Aydin et al., 2007; Magalhães et al., 2008). Thus, these monoterpenes can be useful as agents for prevention and/or treatment of cardiovascular diseases (CVD).

The CVD are the lead death cause in developed and developing countries (American Heart Association, 2008; Brazilian Society of Cardiology, 2007), causing great impact not only on human health, but also in social and economic areas (Lefkowits & Willerson, 2001). In an attempt to reduce this impact, several research groups in recent decades have worked extensively to seek advances in the treatment of CVD, among them the discovery of new therapies (Lefkowits & Willerson, 2001).

Based on this and knowing that the monoterpenes are the major constituents of various essential oils of medicinal aromatic plants, most recently, pharmacological studies have focused on efforts to investigate the effects of this group of substances on the cardiovascular system. Thus, the aim of this work was to review the effects of the monoterpenes on this system.

Methods

The data in this research were collected using Pubmed, Scopus, ISI Web of Knowledge, and Scifinder portal databases. The search included articles published between 1987 and 2010 in refereed journals, which are written in English and internationally recognized. The search included 33 monoterpenes which were related to each of thirteen individual words: artery, cardiovascular, heart, myocyte, vasorelaxant, vessel, hypotension, hypotensive, cardiomyocyte, ventricular, vasodilatory, aorta, and aortic. The articles that presented results of monoterpenes added to mixtures as well as those that appeared in congress abstracts, monographs, theses, or dissertations were not considered in this review.

Results and Discussion

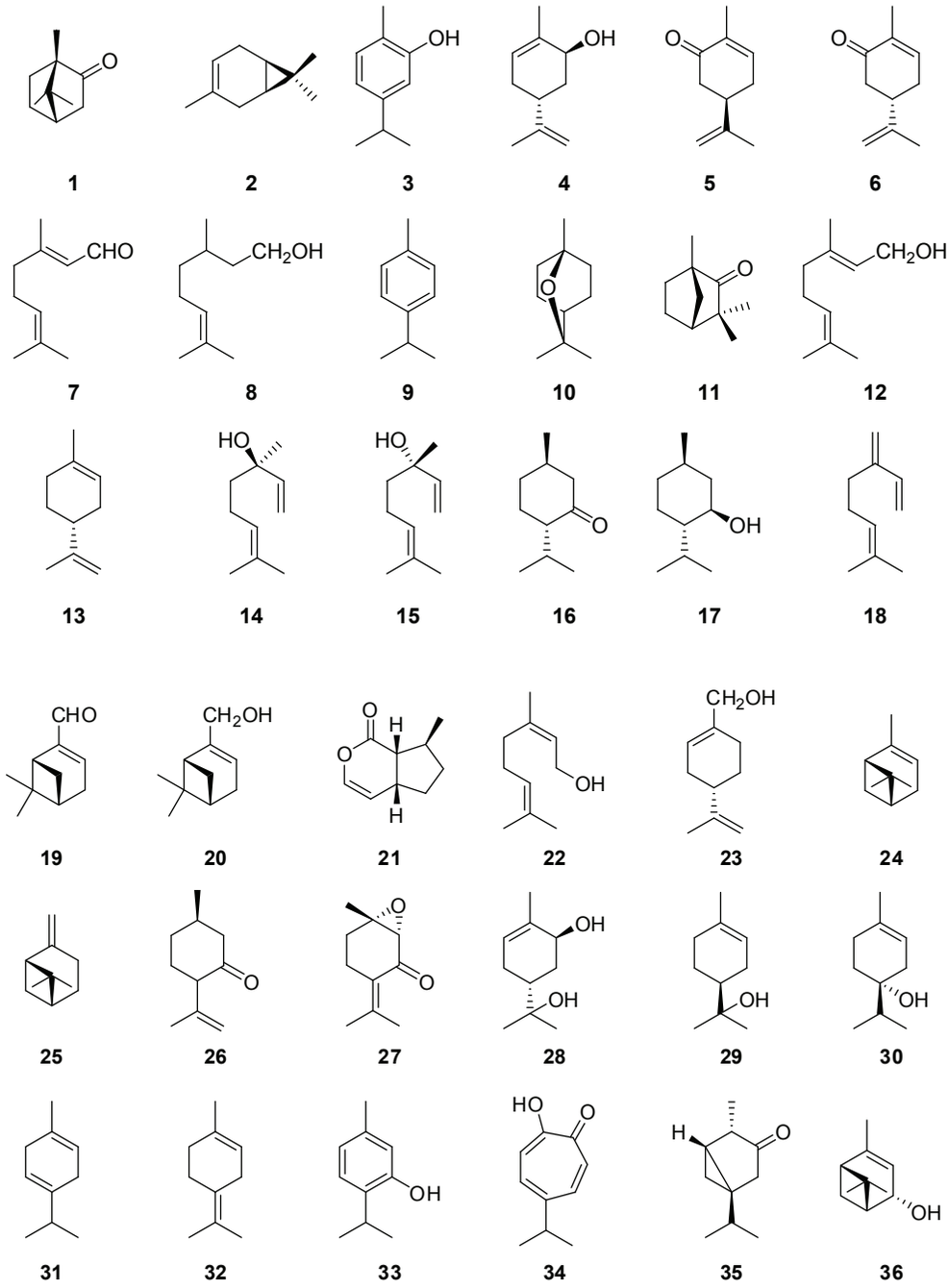
This study utilized seventeen articles published mainly in the journals Phytomedicine, Fundamental Clinical Pharmacology, Planta Medica, Life Science, European Journal of Pharmacology, and Brazilian Journal of Medical and Biological Research.

Among the 33 monoterpenes researched because of their cardiovascular activity, sixteen of them were carvacrol (**3**), citronellol (**8**), eucalyptol (1,8-cineole) (**10**), (-)-linalool (**14**), (+)-linalool (**15**), menthol (**17**), myrtenal (**19**), myrtenol (**20**), rotundifolone (piperitenone oxide) (**27**), sobrerol (**28**), thymol (**33**), α-limonene (**13**), α-terpinen-4-ol (**30**), α-terpineol (**29**), *p*-cymene (**9**), perillyl alcohol (**23**), α-pinene (**24**) and β-pinene (**25**). The seventeen remaining, which have not been found in any publications, were camphor (**1**), carene (**2**), carveol (**4**), (*S*)-carvone (**5**), (4*R*)-carvone (**6**), citral (**7**), fenchone (**11**), γ-thujaplicin (**34**), geraniol (**12**), menthone (**16**), myrcene (**18**), thujone (**35**), nerol (**22**), pulegone (**26**), γ-terpinene (**31**), terpinolene (**32**), nepetalactone (**21**), and verbenol (**36**). The sixteen monoterpenes and their cardiovascular effects are summarized in Table 1.

Thymol

Thymol (**33**) is a phenolic monoterpene carvacrol (**3**) isomer (Peixoto-Neves et al., 2010). Because it is often used as a general antiseptic and in medical practice, the cardiovascular effects of thymol have been extensively studied (Periago & Moezelaar, 2001). Magyar et al. (2002) showed that thymol induced cardiac arrhythmias in venticular myocytes isolated from dogs. These effects were mediated by inhibition of K^+ and Ca^{2+} currents. Recently, Magyar et al. (2004), studying the effects of thymol in ventricular cardiomyocytes isolated from humans and canines, and using the technique of "patch clamp" in the "whole-cell" configuration, showed that thymol was able to inhibit the currents for L-type Ca^{2+}. Moreover, the effects of thymol were also investigated in perfused guinea pig heart using the Langendorff technique, and in canine ventricular trabecula (Szentandrássy et al., 2004). These studies showed that thymol induced a cardiopressant effect caused by a reduction in the calcium content of sarcoplasmic reticulum, due mainly to the inhibition of the calcium pump (Szentandrássy et al., 2004).

Vasorelaxant effects of thymol (**33**) were also observed. In isolated rat aorta, Peixoto-Neves et al. (2010) demonstrated that thymol induced an endothelium-



1 **2** **3** **4** **5** **6**

7 **8** **9** **10** **11** **12**

13 **14** **15** **16** **17** **18**

19 **20** **21** **22** **23** **24**

25 **26** **27** **28** **29** **30**

31 **32** **33** **34** **35** **36**

independent relaxation, possibly involving inhibition of Ca^{2+} release from the sarcoplasmic reticulum, reducing the sensitivity of contractile elements to Ca^{2+} and blocking the influx of Ca^{2+} across the membrane.

Carvacrol

Carvacrol (**3**) is a phenolic monoterpene cyclic isomer of the monoterpene **33** (Periago & Moezelaar, 2001). It is commonly used by the food and cosmetic industries as a preservative and antioxidant (Manou et al., 1998). It is present in the essential oil of oregano, which contributes approximately 65% of its composition (Earley et al., 2010). Cardiovascular effects of carvacrol were studied both *in vivo* and *in vitro*. In normotensive rats, carvacrol at a dose of 100 mg/kg (*i.p.*) reduced blood pressure and heart rate, and inhibited the hypertension induced by L-NAME (Aydin et al., 2007). However, in isolated rat aorta, although Aydin et al. (2007) did not observe any significant effect of carvacrol, Peixoto-Neves et al. (2010) demonstrated that this monoterpene induced an endothelium-independent relaxation, possibly

involving inhibition of Ca^{2+} influx through the membrane. In the cerebral artery of rats, carvacrol also caused potent vasodilation, but this effect was endothelium-dependent (Earley et al., 2010). According to Earley et al. (2010), this effect was attributed to the action of carvacrol on the TRPV3 channel. This monoterpene caused an influx of Ca^{2+} in endothelial cells by increasing intracellular Ca^{2+} and leading to activation of K^+ channels sensitive to Ca^{2+} medium (IKCa) and low (SKCa) conductance. This activation produces hyperpolarization of the plasma membrane of endothelial cells and vascular smooth muscle, thereby resulting in vasodilatation.

In studies using the technique of patch clamp in the whole-cell configuration, it was shown that, like thymol (**33**), carvacrol (**3**) was also able to inhibit the currents for L-type Ca^{2+} in cardiomyocytes isolated from canine and human ventricles (Magyar et al., 2004).

Eucalyptol (1,8-cineole)

Due to its pleasant aroma and spicy taste, eucalyptol (**10**) has been extensively used in the food industry as a flavoring and flavor enhancer (Santos & Rao, 2001). Its cardiovascular effects were studied by Lahlou et al. (2002), using a combined approach in vivo and in vitro. In this research, the authors demonstrated that intravenous administration of eucalyptol significantly reduced the blood pressure of both conscious and anesthetized rats. In the same paper, an assay with isolated rat aorta showed that eucalyptol has vasorelaxant activity which led the authors to suggest that the hypotensive effect was probably due to a reduction in peripheral vascular resistance caused by direct relaxation of vascular smooth muscle. Recently, Pinto et al. (2009) demonstrated that this vasorelaxation seems to be dependent on the integrity of the vascular endothelium and nitric oxide releasing.

Furthermore, Soares et al. (2005) investigated eucalyptol effects on the papillary muscle preparations from rat ventricle. In these preparations, the eucalyptol produced a relaxation, possibly caused by inhibition of Ca^{2+} influx through the membrane.

Menthol

Menthol (**17**), which can be extracted from plants of the *Mentha* genus, is widely used in food, beverages and toiletries for its fragrance and its well-known effect of eliciting a refreshing and cooling sensation (Baylie et al., 2010). In study performed by Johnson et al. (2009), was demonstrated that menthol is able to cause a profound dilatation in human forearm cutaneous vessels. This effect appears to involve activation of muscarinic receptors and/or production of nitric oxide. However, in contrast to the human studies, the major part of vasodilatation induced by menthol, in rat arteries appears to be independent of cholinergic/nitric oxide pathways (Johnson et al., 2009) and mediated by activation of transient receptor potential melastatin 8 (TRPM8) (Venkatachalam & Montell, 2007; Johnson et al., 2009).

In studies using the technique of patch clamp in the whole-cell configuration, it was shown that, menthol was also able to inhibit the currents for L-type Ca^{2+} in right ventricular myocytes isolated from rabbits (Baylie et al., 2010).

Rotundifolone (piperitenone oxide)

Rotundifolone (**27**) is the main constituent of the essential oil of *Mentha* x *villosa*, an aromatic herb known as "the mint-leaf-girl" and extensively used for the treatment of worms (Guedes et al., 2002). In this oil, rotundifolone contributes approximately 63% of its content (Lahlou et al., 2001; Guedes et al., 2002). According to Guedes et al. (2002), intravenous administration of rotundifolone in rats significantly reduced blood pressure and heart rate. To investigate the mechanisms involved in these responses, Guedes et al. (2002) performed experiments in vitro using isolated preparations of atrial and aortic rings, both from rats. These experiments have demonstrated that rotundifolone was able to induce negative inotropic and chronotropic effects in atrium (Guedes et al., 2002) and in aorta vasorelaxation (Guedes et al., 2004). The vasorelaxation was due to inhibition of Ca^{2+} influx through the membrane and the release of Ca^{2+} from intracellular stores (Guedes et al. 2004). From these results, the authors concluded that the hypotensive effect was possibly due to a reduction in heart rate associated to a reduction of peripheral vascular resistance, both due to muscarinic activation.

α-Terpineol

The cardiovascular effects of α-terpineol (**29**) were first reported by Saito et al. (1996). The authors demonstrated that α-terpineol had a hypotensive effect in rats at a dose of 5 mg/kg administered intravenously. Magalhães et al. (2008), using perfused rat mesenteric vascular bed, showed that α-terpineol also induces vasorelaxation which was abolished in the presence of L-NAME, suggesting the involvement of NO in this vasorelaxation. Possibly the hypotensive effects reported by Saito et al. (1996) may have been caused by a reduction in peripheral vascular resistance as a result of vasorelaxation (Magalhães et al., 2008).

Recently, studies performed by Ribeiro et al. (2010), by using combined functional and biochemical approaches, demonstrated that hypotension and vasorelaxation induced by α-terpineol (**29**) were mediated, at least in part, by the endothelium, most likely via NO release and activation of the NO-cGMP pathway.

α-Terpinen-4-ol

The monoterpene α-terpinen-4-ol (**30**) is the major constituent of the essential oil of the species *Alpinia zerumbet* or *Alpinia speciosa* (Blume) D. Dietr., Zingiberaceae. This medicinal plant is popularly known as Colony and is widely used by the population as a tea in the treatment of arterial hypertension. Studies have shown that intravenous administration of α-terpinen-4-ol caused immediate blood pressure reduction in a dose-dependent manner in both normotensive (Lahlou et al., 2002) and hypertensive rats (Lahlou et al., 2003). In preparations of isolated rat aorta pre-contracted with depolarizing solution of K^+, α-terpinen-4-ol was able to induce a concentration-dependent vasorelaxation (Lahlou et al., 2003).

Linalool

Linalool (**14** and **15**) is usually found in nature in the form of a racemic blend of various herbs. Its use is common in the cosmetic and food industries as perfumes and food flavorings (Peana et al, 2006). Studies by Höferl et al. (2006), which sought to investigate the effects of linalool on stress, showed that this monoterpene has significant effects on the cardiovascular system of humans. In this study, the effects of the optical isomers (+) and (-)-linalool (**14**) and **15**) on blood pressure and heart rate, administered by inhalation, were independently evaluated in 24 subjects. Interestingly, the results showed that the optical isomers had opposite effects. While (+)-linalool (**14**) showed stimulating effect on the cardiovascular system, (-)-linalool (**15**) had a depressing effect.

Menezes et al. (2010) evaluated the hypotensive activity of (±)–linalool in non-anaesthetized normotensive rats and showed that this monoterpene was able to induce hypotension associated with tachycardia, which could be suggestive of an effect on the peripheral vascular resistance with consequent baroreflex response.

Citronellol

Citronellol (**8**) is a monoterpene found in some plants used in popular medicine with antihypertensive agents, including *Cymbopogon citratus* (Abegaz et al., 1983), *Cymbopogon winterianus* (Quintans-Júnior et al., 2008), and *Lippia alba* (Tavares et al., 2005). Bastos et al. (2010) and Menezes, et al. (2010) showed that citronellol, administered intravenously, produced hypotension and tachycardia in conscious rats. Seeking to investigate the mechanisms involved in these responses, Bastos et al. (2010) performed experiments *in vitro* using preparations of isolated rings of superior mesenteric artery of rats, and showed that citronellol was able to induce vasorelaxation. The vessel relaxation was due to inhibition of Ca^{2+} influx through the membrane and the release of Ca^{2+} from intracellular stores (Bastos et al., 2010). From these results, the authors concluded that the hypotensive effect is probably because of a reduction of peripheral vascular resistance due to a direct effect on vascular smooth muscle.

Limonene and sobrerol

^{D}-limonene (**13**) is one of the most common terpenes in nature. It is the major constituent in several citrus oils (orange, lemon, mandarin, lime, and grapefruit) (Sun, 2007).

Touvay et al. (1995) studied the effects of limonene (**13**) and sobrerol (**28**) on pulmonary hypertension and right ventricular hypertrophy induced by monocrotaline (MCT) in rats. After daily oral administrations at a dose of 400 mg/rat, both limonene and sobrerol were able to significantly decrease the changes induced by MCT. Moreover, both monoterpenes also reduced the increase in medial thickness of the pulmonary artery (Touvay et al., 1995).

Pinene and cymene

α-Pinene (**23**) and *p*-cymene (**9**) monoterpenes are present in the oil essential of *Nigella sativa.* Studies about the pharmacological actions of the volatile oil of the Black seed *Nigella sativa* in both, rats and guinea-pigs revealed its ability in doses of (4-32 μL/kg) (*i.v.*) to decrease the arterial blood pressure and induce bradycardia in a dose-dependent manner (El Tahir et al., 1993; El Tahir & Ageel, 1994).

El Tahir et al. (2003) observed that after intravenous administration of α-pinene and *p*-cymene in urethane anaesthetized rats, both showed hypotension and bradycardia. This effect was probably due to inhibition of vasomotor centre with the consequent decrease in the sympathetic outflow reaching the peripheral blood vessels and the heart resulting in decreases in both the arterial blood pressure and the heart rate (El Tahir et al., 1993). On the other hand, Menezes et al. (2010) demonstrated that the (+)-α-pinene (**23**) and (-)-β-pinene (**24**) showed a hypotensive effect associated with tachycardia in non-anaesthetized normotensive rats (i.v.).

Myrtenal, myrtenol, and perillyl alcohol

It was observed by Saito et al. (1996) that myrtenal (**19**), myrtenol (**20**), and perillyl alcohol (**25**) possess hypotensive effects at doses of 1 and 5 mg/kg, when administered intravenously in rats.

Conclusion

This review showed the therapeutic potential

of monoterpenes in the prevention or treatment of cardiovascular diseases. The main objective of this review was to make researchers aware of the importance of monoterpenes and to stimulate the search for new drugs, as well as to provide a scientific basis for their use. Thus, in the future monoterpenes may be considered as the object of clinical studies, pharmaceutical applications, and as adjuvants in medicine.

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