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Original article

ANALGESIC AND ANTI-INFLAMMATORY ACTIVITY OF MONOTERPENOID MYRTENAL IN RODENTS

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ABSTRACT

Inflammation and pain are common phenomena associated with a number of diseases. The search for new pharmacological agents is an important factor in delivering better therapy. Many plants and their active ingredients monoterpenes exhibit analgesic and anti-inflammatory activity but have not been fully studied.

Purpose The bicyclic monoterpenoid Myrtenal (M) is a component of many plants essential oils. Researches on total plant extracts as well as on essential oils reveal a wide range of biological effects with various mechanisms. However, there is no data in the literature about Myrtenal effects in pain and inflammation. Aim of this study is to investigate the M effects in models of pain and inflammation in laboratory rodents.

Materials and methods Anti-nociceptive activity of M (30 mg/kg, b. wt., i. p.) was tested in male ICR mice after single and repeated administration on two established experimental pain models - Acetic acid writhing test (antipyretic type analgesia) and Hot plate test (narcotic type analgesia). Anti-inflammatory activity of M (40 mg/kg, b. wt., i. p.) was evaluated on the 24th h from the last treatment after 5-d administration via carrageenan-induced inflammation model on rat paw and was compared with this of the non-steroid anti-inflammatory drug (NSAID) Ketoprofen (2.5 mg/kg, b. wt., i. p.) as a referent.

Results In our experiments on Wistar rats and ICR mice M demonstrated significant anti-inflammatory and anti-nociceptive properties (toward both peripheral and thermal pain). In acute administration, significantly decreased the abdominal writhing number at 15th ($p < 0.01$) and 20th min ($p < 0.05$) by 47.25 % and by 50.55 % respectively. Myrtenal decreased ($p < 0.001$) the number of jumps versus control group after repeated treatment – by 40.4 % on 7th and by 43.1 % on the 14th d in comparison to the controls.

Conclusions Possible mechanisms are complex, and they probably include sedative and antioxidant properties of Myrtenal.

Keywords: Myrtenal, anti-nociceptive, anti-inflammatory effects, rodents

INTRODUCTION

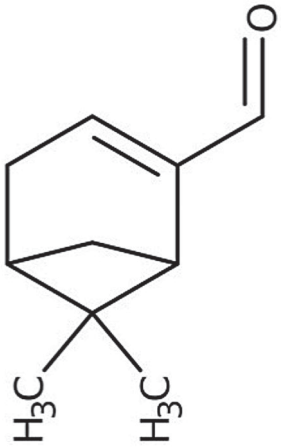
Terpenes form the basic skeleton of many plant-derived biologically active substances as glycosides, saponins, alkaloids, vitamins and others. The substances from this large group exhibit a wide range of biological activities in cancers, malaria, inflammatory processes, and infectious (viral and bacterial) diseases [1].

Low-molecular monoterpenes, which are a basic component of essential oils, are of great interest to scientific circles. Monoterpenes as secondary plant metabolites have been shown to exert antimicrobial, antiviral, anti-atherosclerosis, cardioprotective, antiulcerogenic, cytotoxic, antineoplastic, mutagenic, antidiabetic, anti-inflammatory, antioxidant, anti-aging, antihepatotoxic, antihypertensive, hypolipidaemic and antiplatelet activities.

The role of inflammation in the pathogenesis of many diseases is known. These conditions are accompanied by different pain manifestations. Monoterpenes successfully affect inflammation [2] and chronic pain [3]. Many plant essential oils rich in monoterpenes exhibit experimental pain-relieving effects [4]. The anti-inflammatory activity of pinene has been established [5] as well as its anti-nociceptive activity [6]. Myrtenol is a mono-oxidized isomer of pinene, which also exhibits anti-inflammatory properties combined with analgesic activity [7].

A representative of monoterpenes Myrtenal is a bicyclic derivative of α-pinene ((“)-Myrtenal, (1R)-2-Pinen-10-al, (1R)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-carboxaldehyde) (Fig. 1).

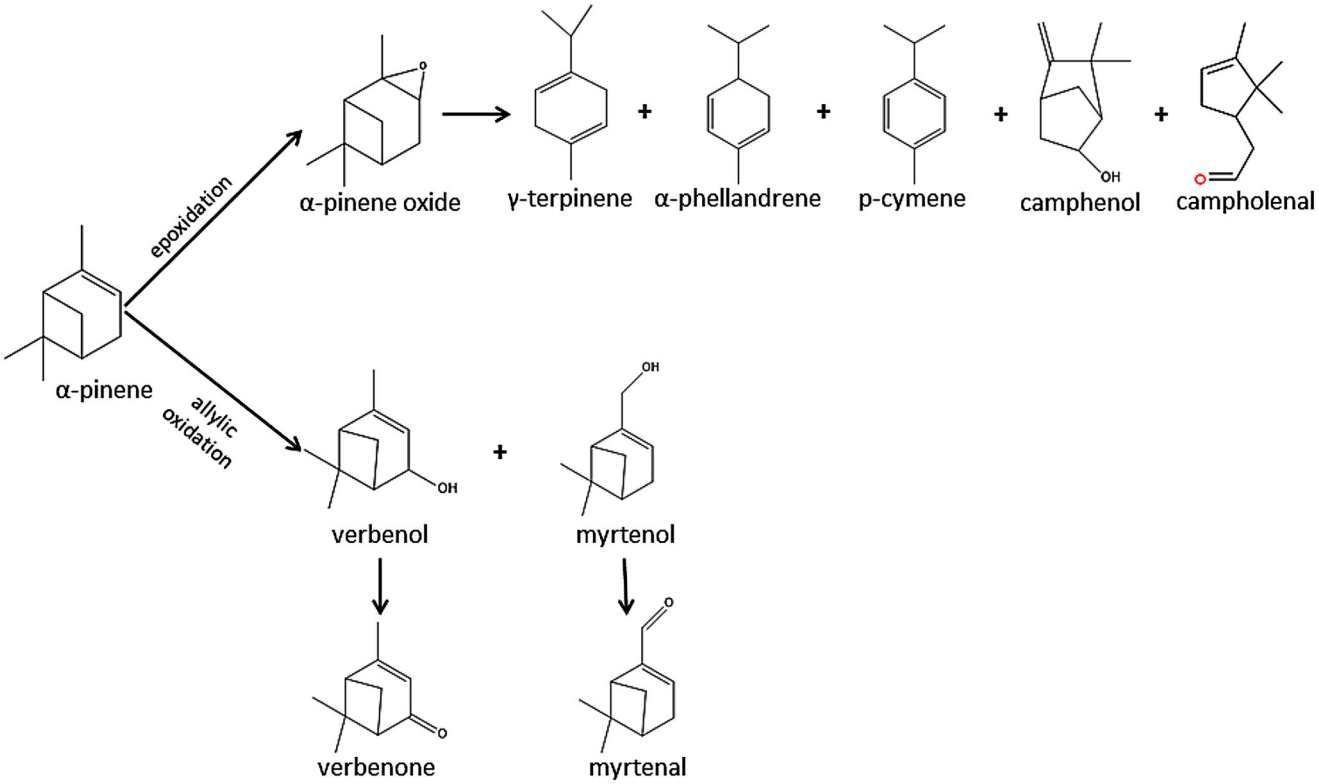
Fig. 1. Structure of Myrtenal



Myrtenal (M) is a pinene metabolite in plants [8]. Bio-catalytically, α-pinene is transformed into Myrtenol with subsequent conversion to Myrtenal [9] (Fig. 2).

Fig. 2. Mechanism of α-Pinene in catalytical oxidation showing two competitive rows as the allylic oxidation being considered as the main route of the process

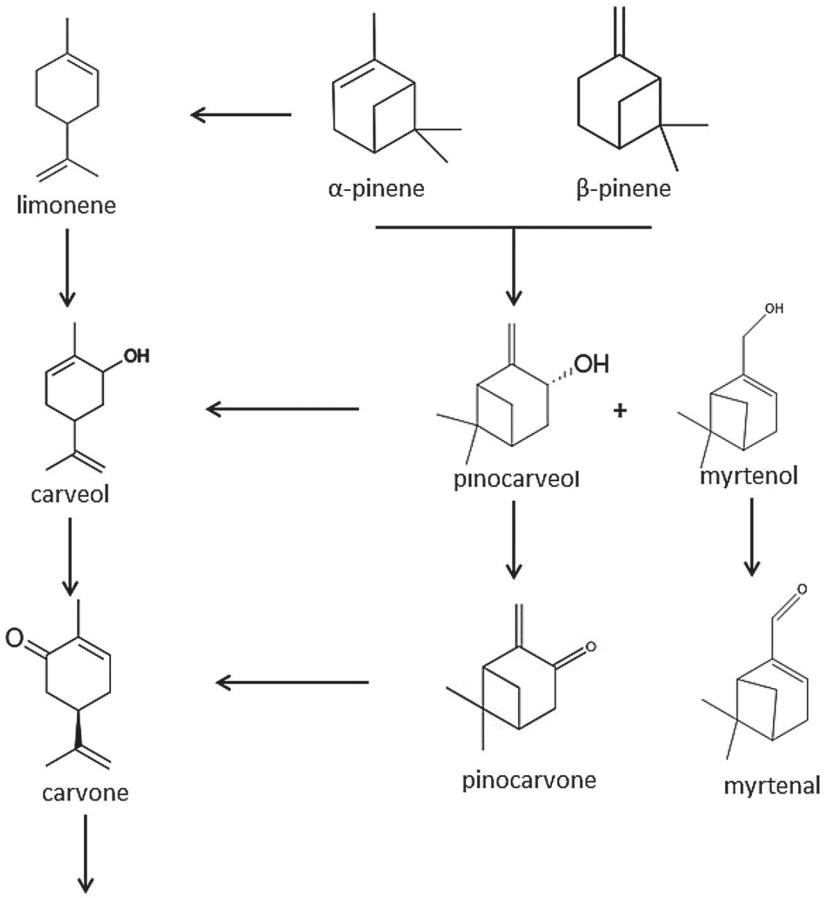
Source: Modification by Negoi A, Parvulescu VI, Tudorache M. Peroxidase-based biocatalysis in a two-phase system for allylic oxidation of α-pinene. *Catalysis Today.* 2018 May; 306:199-206. [9]



Metabolic conversions between individual agents in the monoterpene group of substances have also been observed *in vitro* studies [10] (Fig. 3).

Fig. 3. Metabolism of α- and β-Pinene in Bacillus pallidus isolated from an alpha-pinene enriched culture

Source: Modification by Savithiry N, Gage D, Fu W, Oriel PJ. Degradation of Pinene by Bacillus pallidus BR425. *Biodegradation*. 1998 Sep;9(5):337-341. [10]



The bicyclic monoterpenoid Myrtenal is found in many plants essential oils - *Myrtus communis* – 5 % [11], *Artemisia spp*. – Myrtenal in combination with Myrtenol was found to be at the highest concentrations in *A. pontica, L, A. vulgaris, L and A. alba, L* [12], *Rosmarinus officinalis* – 5% [13], *Cuminum cyminum* – 28-43.5 % in some varieties [14], *Piper nigrum* [15], *Origanum vulgare* [16], *Thymus spp*. [17] and many more. It was also found in essential oils of orange, lemon, peppermint, juniper, ginger, parsley and others [18], as well as in propolis [19].

Myrtenal has a complex mechanism of action in most of its established *in vivo* and *in vitro* effects – acetylcholinesterase inhibition (*in vitro*) [20], bronchodilation, anti-inflammatory, anti-aggregative and antihemolytic (*in vitro*), antibacterial (vs. G(+) pathogens) [21], anti-diabetic [22], antioxidant and antitumor [23, 24], etc.

However, Myrtenal is relatively little studied, and there is no data on its effects on pain and inflammation.

Aim of this study is to investigate the anti-inflammatory and analgesic effects of M in acute and repeated treatment of laboratory rodents.

MATERIALS AND METHODS

• **Experimental animals** (adult rodents) – ICR male mice (20-25g) and male Wistar rats (180-200 g), provided by the Vivarium of Medical University of Varna, and Bulgarian Academy of Sciences. Animals were kept in standard plastic cages under controlled environmental conditions (temperature 25 ± 2° C), a 12 h light / dark cycle with free access to food and water. All experimental protocols were approved by The National Ethics Committee.

• **Reagents used**:

- (-)-Myrtenal 98 %, purchased from ACRÔS Organics, Lot: A0363097, injected intraperitoneally as an emulsion, prepared with Tween 80 (0.05%)

- Carrageenan, iota type, purchased from Alfa Aesar, Lot: P18C041

- Ketoprofen – purchased as Profenid 100 mg powder and solvent for solution for injection, SANOFI AVENTIS

• **Experimental design and methods**

Analgesic activity of Myrtenal

On male ICR Albino mice, we studied the effect of M (30 mg/kg b. wt., i. p.) both in single and repeated treatment (at 7th and 14th d) for analgesic activity. Anti-nociceptive activity of M has been tested on two established experimental pain models - Acetic acid writhing test (antipyretic type analgesia) and Hot plate test (narcotic type analgesia).

- ***Acetic acid induced writhing test***

Acute visceral pain was evaluated by Acetic acid writhing test [25]. Peripheral pain was induced by intraperitoneal injection of a 0.1 % solution of glacial acetic acid. Animals were injected with M emulsion (prepared ex tempore) (in dose 30 mg/kg b. wt., i.p., 30 min before acetic acid injection). We tracked the results in a single, 7- and 14-d application of M at the 5th, 10th, 15th and 20th min. Writhing and stretching number were recorded, and percent protection was determined.

- ***Hot plate test***

Peripheral pain (thermal pain sensitivity, indicator of nociceptive threshold) was evaluated according Hot plate test [26] by tracking the number of paw licks and jumps over a period of 3 min at a surface temperature of about 56-58 ° C. We reported the results for a single, 7- and 14-d administration of M at a dose of 30 mg/kg body weight.

Anti-inflammatory activity of Myrtenal

Anti-inflammatory activity of M (40 mg/kg, b. wt., i. p.) was evaluated on the 24th h from the last treatment after 5 d administration via carrageenan-induced inflammation model on rat paw [27]. A 1% carrageenan (CG) solution prepared with a physiological saline solvent (1% dimethyl cellulose) injected subcutaneously with a volume of 0.1 ml in the right hind paw of the rats inducing a model inflammatory reaction. Effect of Myrtenal was compared with this of Ketoprofen (2.5 mg/kg, b. wt., i. p. for 5 d) as a NSAID referent. The displaced fluid volume from rat paws was determined at 6th, 22nd and 24th h.

• **Statistical processing**

Experimental data were presented as mean values with their corresponding standard errors (m ± S.E.M). The differences between the groups were considered to be reliable at the level of significance p <0.05. Each experimental group contained minimum 6 animals.

The statistical processing of the results was performed with a one-factor dispersion analysis (ANOVA), MS Excel 2007 and GraphPad Prism 7.

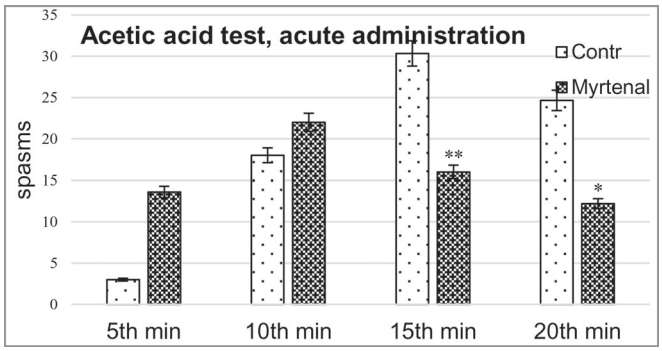
RESULTS:

➢ **Anti-nociceptive effect of M was studied in mice using two tests:**

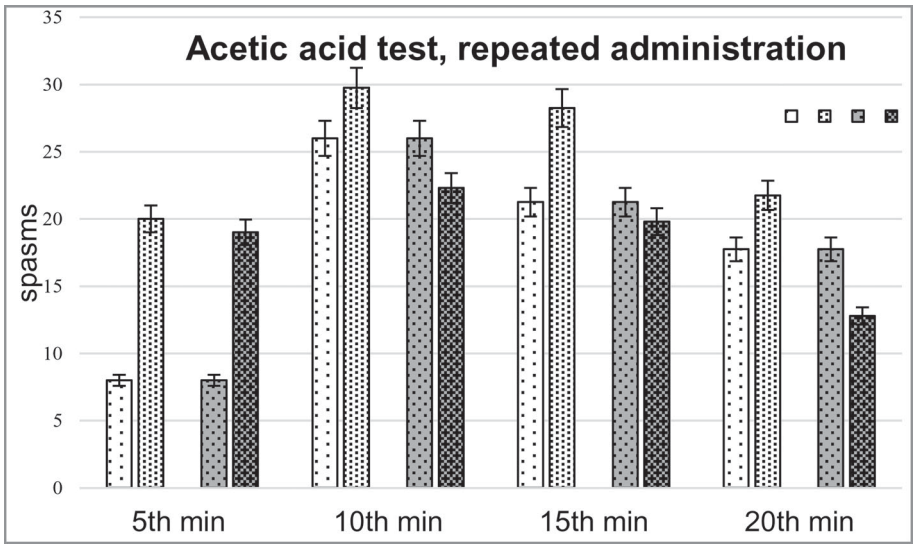
• Effect of M on visceral pain according to Acetic acid test

In acute administration, M (30 mg/kg) significantly decreased the abdominal writhing number at 15th ($p < 0.01$) and 20th min ($p < 0.05$) by 47.25 % and by 50.55 % respectively (Fig. 4) despite the initially observed increase in the number of spasms after M application. This observation was probably due to Myrtenals' locally irritating effect probably because it was in the form of an emulsion.

Fig. 4. Effect of M on pain according to Acetic acid test after acute administration



* $p < 0.05$, ** $p < 0.01$ vs. controls

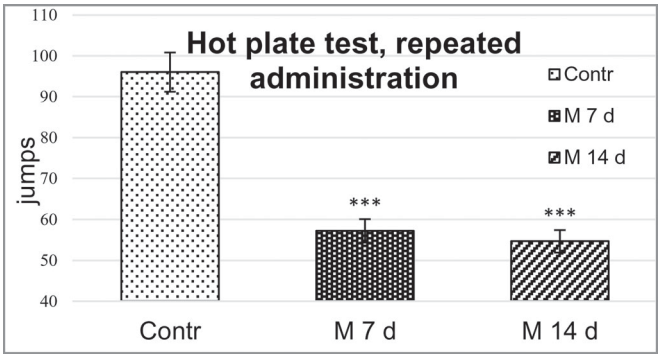


Repeated administration of Myrtenal did not reduce the pain sensitivity. Even an increase of the parameter (spasms) in M-treated group of mice was observed for both 7- and 14-d administration (Fig. 4A).

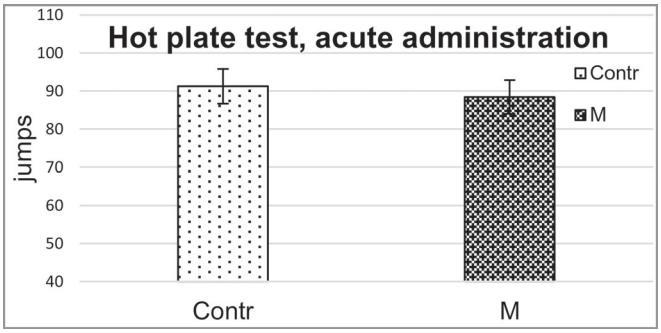
• Effect of M on pain according to Hot plate test

According to this test for anti-nociceptive activity, Myrtenal significantly decreased the number of jumps versus control group after repeated treatment (7 and 14 d). The observed effect of M was significant ($p < 0.001$), the number of jumps was decreased in M-group by 40.4 % on 7th and by 43.1 % on the 14th d respectively in comparison to the controls. (Fig. 5)

Fig. 5. Effect of M on pain according to Hot plate test after repeated administration and in acute treatment (5A)



*** p < 0.001 vs. controls



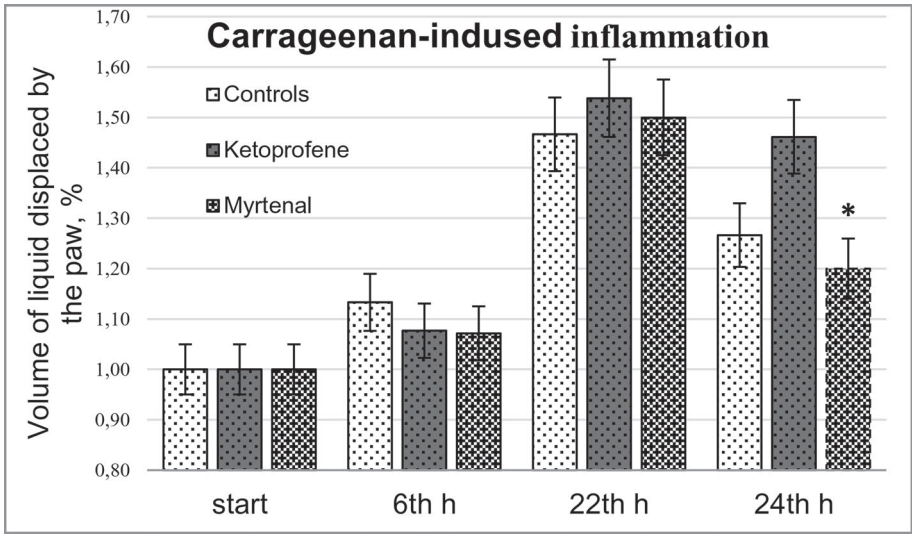
The observed heat pain reflexes - paw lickings and jumps, are due to leg contact with the hot surface. Jumping is a more complex response and covers the emotional component of the escape. After single application, M did not show up anti-nociceptive properties (Fig. 5A).

A single and repeated administration of M showed an increase in the number of paw licks in the animals compared to controls – by 8.57% for a single injection and by 31.34% for 7- and 14-d treatment.

➢ **Anti-inflammatory effect of Myrtenal**

On the 6th h after carrageenan injection in rat paw, Ketoprofen exhibited a moderate anti-inflammatory effect. Similar was the effect of Myrtenal (Fig. 6). However at the 24th h, the effect of M on inflammation was significantly much better than this of the standard used (longer duration). Another of our experiments conducted with Diclofenac as a reference for anti-inflammatory activity (unpublished data) confirmed the presence of the most prominent effects of M on the progression of the inflammatory process at 24 h after carrageenan injection.

Fig. 6. Effect of M in carrageenan-induced inflammation model



* p<0.05 vs. Ketoprofen group

A microscopic examination of a smear from exudate (from rat paws) with standard express coloration was performed. Some changes in the cellular composition of the exudate also were established. In the M-treated rat group, no cells (polymorphonuclear lymphocytes as well as granulocytes) were observed in the exudate, which was clear. The results were similar to those in the NSAID reference group. No pus and bacteria were detected in the test material from all rat groups.

DISCUSSION:

Plant substances are widely used in modern pharmacotherapy. In most cases, ethnopharmacological data are leading in the search for new pharmacological agents. The active components of plant extracts have complex mechanisms of action that continue to be studied and discovered even with long-established medicinal products.

The anti-inflammatory [28] and anti-nociceptive [29] activity of Myrtus communis, L. as well as anti-inflammatory and anti-nociceptive effects of Myrtenol [7] have been studied in the literature.

Our results demonstrated a significant anti-nociceptive effect of Myrtenal in mice in two established experimental pain models - Acetic acid writhing test (for antipyretic type analgesia) and Hot plate test (narcotic type analgesia).

The observed effects in M application showed that the test substance exhibited peripheral analgesic effects in acute injection as well as central – in prolonged (7 and 14 d) treatment.

Our previous data about Myrtenal applied in acute doses established that Myrtenal potentiated the hypnotic action of benzodiazepines and barbiturates without showing hypnotic or sedative action alone (unpublished). We can suggest that Myrtenal influence the pain sensitivity of animals probably is partly a result of its sedative effect. Also, M exhibited significant ($p < 0.01$) anxiolytic properties better than diazepam in acute application according to Marble burying test (unpublished). Based on above-mentioned results from our previous study, it can be concluded that one of the reasons for the obtained anti-nociceptive activity of Myrtenal can be due to its sedative activity.

In our experiments, Myrtenal have shown also significant anti-inflammatory effects that were longer than the referent used. Probably it can be related to the lipophilic character of the molecule of Myrtenal.

It is known that many natural substances affect inflammatory processes. It is often associated with their antioxidant activity.

In our previous studies, Myrtenal showed significant antioxidant properties confirming the available evidence of the antioxidant potential of M in the literature [23, 30]. Our data about oxidative status in rodents' brain demonstrated decreased lipid peroxidation levels, accompanied with increased tGSH in M treated group compared to controls [31]. In previous data, M had also a positive effect on scopolamine-induced oxidative stress in experimental dementia rat model – decreased hippocampal lipid peroxidation together with increased tGSH levels in cortex and hippocampus [32].

We assume that Myrtenal's antioxidant properties are connected to the established positive influence of M on inflammation process and maybe partly to its observed analgesic activity.

The effects of Myrtle [28] and Myrthenol [33] on pain also have been identified. We suggest that Myrthenal, as a metabolite of Myrthenol, probably is a main carrier of the observed anti-nociceptive properties.

As a confirmation of this hypothesis, there are available data on the analgesic potential of newly synthesized Myrtenal analogues manifested in Acetic acid-induced writhing test and Hot plate test [34].

The established anti-inflammatory and anti-nociceptive effects of plants whose essential oils contain larger amounts of Myrtenal are a basis of our assumption also.

Similar analgesic and anti-inflammatory effects are characteristic of plants whose essential oil is rich in Myrtenal. Essential oil of *Myrtus communis, L.* [28] from Morocco is rich in pinene (48%) and myrtenal (5%) with established anti-inflammatory effects in a model of chronic inflammation and anti-nociceptive effect (in hot plate and writhing tests). Analgesic and anti-inflammatory effects were also manifested in *Piper aleyreanum C.DC* administration in rodents [35] with 4.2 % content of M in the essential oil.

The results we have obtained suggest that as a metabolite of Myrtenol (as well as of Pinene), Myrtenal probably is a carrier of their experimentally established analgesic and anti-inflammatory properties. Further detailed studies will confirm or reject this hypothesis.

CONCLUSION

Observed anti-nociceptive and anti-inflammatory effects of Myrtenal according used experimental models of pain and inflammation give a good basis for a further study of the compound as a potential analgesic and anti-inflammatory agent.

The exact mechanisms underlying these effects are subject to future research. The mechanisms probably are complex, and they include sedative and antioxidant properties of Myrtenal.

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