THE INFLUENCE OF ROSEMARY ESSENTIAL OIL APPLIED *PER OS* ON THE PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES OF PARACETAMOL

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Introduction: Rosemary essential oil can be used for treating dyspepsia, mild spasmodic disorders of the gastrointestinal tract, externally as analgetic in muscular and articular pain and minor peripheral circulatory disorders. It is important to explore its analgesic potential and its influence on the pharmacodynamic and pharmacokinetic properties of paracetamol. Methodology: Rosemary essential oil was applied to mice orally (doses: 10 and 20 mg/kg b.w.) for pharmacodynamic tests for seven days. Rats treated with rosemary essential oil for seven days orally (5 and 10 mg/kg b.w.) were used for the examination of the influence of essential oil on the pharmacokinetic properties of paracetamol (applied on the 7th day p.o. or i.v.). Pharmacokinetic parameters were analyzed in blood samples obtained from rats' tail veins, with the HPLC method. Results: The essential oil of rosemary shows analgetic properties. The rosemary essential oil increases pharmacological effects of paracetamol and does not change paracetamol bioavailability. Conclusion: The herbal drugs could change the pharmacodynamic and the pharmacokinetic properties of classical drugs and they could also change the safety of classical drugs use in human population.

***Key words**: Rosemary, Herb-Drugs Interactions, Paracetamol*

INTRODUCTION

The use of herbal medicinal products to relieve pain has been increasing in recent years because they are often perceived as being natural and therefore harmless [1,2]. Herbal medicines are often taken in combination with conventional drug therapies and some of their pharmacologically active ingredients might interact with synthetic drugs [3]. Drugs that are substrates for metabolism mediated by cytochrome P450 (CYP) enzymes are particularly subject to herb-drug interactions, which can be attributed to the ability of many herbal compounds to induce or inhibit these enzymes [4].

Rosemary (*Rosmarinus officinalis* L., Lamiaceae) is widely cultivated all over the world as an ornamental and aromatic plant, and has been commonly used for flavoring food, but also for different medicinal purposes. In traditional medicine, rosemary was used as mild analgesic, for relieving renal colic pain, dysmenorrhea, respiratory disorders, due to its antispasmodic properties [5,6]. Recently, essential oil isolated from rosemary and monoterpenes as its main active compounds have been of great interest due to their various health benefits and therapeutic effects. According to the recommendation of European Medicines Agency (EMA) from 2010, rosemary essential oil (REO) can be used for treating dyspepsia and mild spasmodic disorders of the gastrointestinal tract, as well as an adjuvant in the relief of minor muscular and articular pain and in minor peripheral circulatory disorders [7]. Besides, the experiments conducted with REO have demonstrated some of its notable pharmacological effects, such as antioxidant and antimicrobial [8], anti-inflammatory and antinociceptive [9], among others.

On the other hand, there are several well-established interactions of rosemary preparations with different drugs, such as antibiotics, anxiolytics and anticoagulant medicines, in terms of potentiating of their activity [3,10]. Given that REO was found to exert analgesic effects in different experimental models of nociception, its potential interactions with analgesics may be assumed. Besides, it was demonstrated that REO and its main components induce catalytic activities of microsomal enzymes, and therefore may interact with drugs metabolized by cytochromes or UGT [11,12].

Paracetamol (acetaminophen) is one of the most widely used drugs for the treatment of pain in both acute and chronic settings. It has a unique position among analgesic drugs, having a spectrum of action similar to that of NSAIDs, but with negligible anti-inflammatory and antirheumatic activities. The mode of action of paracetamol has still not been fully elucidated, but there is some evidence supporting a central analgesic effect. It is now generally accepted that it inhibits COX-1 and particularly COX-2 through metabolism by the peroxidase function of these isoenzymes [13,14]. Recently, it was discovered that paracetamol may act as a prodrug by triggering the CB_1 receptor - mediated effects of the cannabinoid system. At therapeutic doses, the greater part of paracetamol is conjugated with glucuronic acid and, to a lesser extent, with sulphate or cysteine. A fraction usually ranging from 5 to 15% is oxidized by CYP2E1, CYP1A2,

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CYP3A4, and CYP2A6 subfamilies of cytochromes P450, resulting in the formation of the highly reactive and hepatotoxic *N*-acetyl-*p*-benzoquinoneimine (NAPQI), which is quickly conjugated with glutathione to form non-toxic cysteine and mercapturic acid conjugates [15]. Hepatic enzymes induction may increase paracetamol hepatotoxicity, and therefore the potential for interactions of paracetamol with herbal medicinal products should be carefully considered.

Based on the above-mentioned facts, the aim of our study was to examine the analgesic effects of REO and its pharmacodynamic interactions with paracetamol in mice, as well as pharmacokinetic interactions in rats.

MATERIAL AND METHODS OF WORK

Plant material and chemicals

Aerial parts of cultivated plants of rosemary were obtained from the Institute for Medicinal Plants Studies, Dr Josif Pančić, Belgrade. A voucher specimen of the plant (*Rosmarinus officinalis* L. 1753 subsp. *officinalis* No 2-1746, det.: Goran Anačkov) was confirmed and deposited in the Herbarium of the Biology and Ecology Department, Faculty of Natural Sciences, University of Novi Sad. The essential oil, used in our experiments, was isolated from the obtained plant material.

Paracetamol was purchased from Sigma-Aldrich (St Louis, MO, USA).

Isolation and analysis of essential oil

The essential oil was isolated from air-dried aerial parts of rosemary by hydrodistillation, according to the procedure of the European Pharmacopoeia 4 [16]. N-hexane was used as a collecting solvent, which was afterwards removed under vacuum from the obtained essential oil.

The identification and quantification of chemical constituents of the essential oil were carried out by gas chromatography coupled with flame ionization detection (GC/FID) and mass spectrometric detection (GC/MS). GC/FID analysis was performed using a Hewlett-Packard HP 5890 series II chromatograph equipped with an auto sampler and a split/splitless injection system. The capillary column used in this study was HP-5 (25 m × 0.32 mm; film thickness of 0.52 μm), coupled to the flame ionization detector (FID). The injector and detector temperatures were set at 250°C and 300°C, respectively, and the column temperature was programmed from 40 to 260°C at a rate of 4°C/min. The flow rate of hydrogen as a carrier gas was 1 ml/min. A sample of 1% solution of the oil in ethanol (1 μl) was injected in split mode (split ratio, 1:30). GC/MS analysis was carried out using a Hewlett-Packard HP G1800C series II GCD system under the same analytical conditions as in GC/FID. The column HP-5MS (30 m × 0.25 mm; film thickness 0.25 μm) and helium as a carrier gas were used in this analysis. The system was operated in electron ionization (EI) mode at 70 eV, in the mass (m/z) range 40-450 Da.

The identification of essential oil constituents was performed by comparison of the obtained mass spectra and retention indexes with those of reference compounds or those from mass spectra libraries and literature data. The quantitative analysis provided the percentage composition of the essential oil components, calculated by FID peak area normalization method.

Animals and treatment

Experiments were carried out on adult, sexually mature NMRI mice of both sexes, weighing 25-35 g, which were obtained from the Veterinary Institute Novi Sad, Serbia, and on adult, sexually mature Wistar rats of both sexes, weighing 250-300 g, which were obtained from Vojnotehnički institut VMA, Belgrade. Animals were housed in standard laboratory cages at a controlled temperature (23 ± 1 ºC) and humidity (55 ± 1.5 %) under standard circadial rhythm (day/night), with free access to pelleted food and water. Animal care and experimental procedures were conducted in accordance with the Guide for the Care and Use of Laboratory Animals edited by Commission of Life Sciences, National Research Council (USA). The experimental procedures were approved by Ethical Committee for Animal Use in Experiments of the University of Novi Sad (No. 01-153/6-2).

The mice for pharmacodinamic tests were divided into 5 experimental groups, each containing 6 individuals, and treated as follows:

- ConS: control group, saline solution p.o. for 7 days, where the last dose on the 7th day was applied 30 minutes before i.p. administration of saline solution
- REO: REO (20 mg/kg) p.o. for 7 days, where the last dose on the 7th day was applied 30 minutes before i.p. administration of REO
- Par: saline solution p.o. for 7 days, where the last dose on the 7th day was applied 30 minutes before i.p. administration of paracetamol
- ParR10: REO (10 mg/kg) p.o. for 7 days, where the last dose on the 7th day was applied 30 minutes before i.p. administration of paracetamol

- ParR20: REO (20 mg/kg) p.o. for 7 days, where the last dose on the 7th day was applied 30 minutes before i.p. administration of paracetamol

Applied daily doses of REO for mice were 10 mg/kg and 20 mg/kg, and those for rats were 5 mg/kg and 10 mg/kg. Recommended human daily dose of REO of 40 mg/day for a male of approximately 70 kg weight [7,17] was adapted for the experimentation on mice. Each mouse received appropriate dose of REO in the volume of 10 ml of solution *per* kg of body weight, by *per os* gavage and each rat received dose of REO in the volume of 1 ml of solution per kg of body weight, by *per os* gavage. The tested drug, paracetamol (60 mg/kg for mice and 20 mg/kg for rats), was administered intraperitoneally (i.p.) for mice and p.o. and i.v. for rats, 30 min after the last REO intake. The control group of animals received an equivalent volume of saline solution.

The rats for pharmacokinetic examination were divided into 6 experimental groups, each containing 6 animals, and treated as follows:

- $Con_7+PAR_{p.o.,}$ control group, saline solution p.o. for 7 days, where the last dose on the 7th day was applied 30 minutes before p.o. administration of paracetamol;
- $Con_7+PAR_{i.v.}$, control group, saline solution p.o. for 7 days, where the last dose on the 7th day was applied 30 minutes before i.v. administration of paracetamol;
- $Reo5_7+PAR_{p.o.}$; REO (5 mg/kg) p.o. for 7 days, where the last dose on the 7th day was applied 30 minutes before p.o. administration of paracetamol;
- $Reo5_7+PAR_{i.v,}$ REO (5 mg/kg) p.o. for 7 days, where the last dose on the 7th day was applied 30 minutes before i.v. administration of paracetamol;
- $Reo10_7+PAR_{p.o.}$; REO (10 mg/kg) p.o. for 7 days, where the last dose on the 7th day was applied 30 minutes before p.o. administration of paracetamol;
- $Reo10_7+PAR_{i.v.}$, REO (10 mg/kg) p.o. for 7 days, where the last dose on the 7th day was applied 30 minutes before i.v. administration of paracetamol.

Hot plate test

Hot plate test was performed by placing mice individually on a hot plate and assessing their response to the thermal stimulus. The temperature of the metal plate enclosed by plexiglas walls was maintained at 52.5 ^{0}C. The response time was measured in seconds at which the animal licked or flinched one of the hind paws, or jumped off the plate. To prevent tissue damage, a cut-off time was used as a double value of latencies measured before drug application. Response latencies were first determined two times before the application of the tested compound, in order to determine a pre-treatment response for each mouse, and then 5, 10, 15, 20, 30, 40, 50, 60 minutes following the drug administration. After responding or reaching the cut-off time, mice were removed from the plate. Analgesic effect determined in seconds was expressed as percentage of prolongation of measured reaction time compared to control reaction time [18].

(A−B)/B*100 = % of analgesic effect

A – measured reaction time (sec)

B – control average reaction time

Pharmacokinetic tests

From all experimental groups a blood sample was taken from tail veins, before paracetamol was given. The paracetamol was applied 30 min after last dose of REO. The samples were taken at 0, at 15th, 30th, 45th, 60th, 90th, 120th, 180th, 240 and 300th minute after paracetamol was applied per os or I.V.. The animals were imobilised and their tails were washed with hot water. Then they were given massage to produce hyperemia. The perforation of skin was done 1 cm from the top of the tail and 200 microliters of blood was taken. Those samples were centrifugated for 10 minutes on 6000 o/min.

The water solutions were prepared with water HPLC degree –JT Baker.

Stock solution was made in concentration 1 mg/ml.

The sample analysis was done on the Dionex HPLC with UV detector. The system for chromatography detecting of paracetamol was made from the following elements: column ZORBAX Extend C-18 Narrow-Bore 2.1 mm x 150 mm 5-Micron; subcolumn ZORBAX Eclipse Plus-C 18, Analytical Guard Column 4.6 m x12.5 mm 5-Micron.

In the examination, isocratic elution was used, with constant flow of mobile phase of 0.4 ml/min. The mobile phases were made of water and acetonitrile w/w: H2O : ACN = 88 : 12.

The samples were injected by using autosampler ASI 100 autosampler plus. The volume of injection was 20 µl. The part with column was at the temperature of 20°C. The paracetamol was detected by detector UV at the wave of λ=254 nm. The time of retention of paracetamol in biological samples was 2.2 minutes, and the duration of analysis was 8 minutes.

The control of the chromatographic system was done by the programme CHROMELEON v.6.70, Chromatography management system, Dionex, 2005.

The concentration of paracetamol was calculated from the area under the curve of different concentration of external standards.

The pharmacokinetic parameters were analyzed in blood samples obtained from rats' tail veins. The HPLC method was used for measurement of paracetamol concentration in blood samples. Those concentrations were used for calculation of the pharmacokinetic parameters.

Statistical analysis

The level of significance between the groups was assessed with the Student's t-test for small independent samples using MedCalc 9.2.0.1 software. All data are expressed as a mean ± standard deviation (SD). A value of $p < 0.05$ was considered to be statistically significant.

RESULTS AND DISCUSSION

The essential oil obtained from rosemary had a pale yellow color and a strong odor, and the obtained yield of the essential oil was 1.03% (v/w in dry matter). The total number of identified chemical constituents was 29, representing 99.87% of the total oil content. As presented in Table 1., the isolated essential oil contains a complex mixture of 95.10%, of monoterpenes and 4.77% of sesquiterpenes. It was found to be composed mainly of oxygenated monoterpenes (63.88%), followed by monoterpene hydrocarbons (31.22%) and sesquiterpene hydrocarbons (4.77%). The major compounds that were identified and quantitated by GC-FID and GC-MS were 1,8-cineole (43.77%), camphor (12.53%), α-pinene (11.51%), β-pinene (8.16%), camphene (4.55%), and β-caryophyllene (3.93%).

In our study, REO (20 mg/kg) significantly increased the latency time of animal response to heat-induced pain between 20th and 50th minute of the test (Table 2), when compared to saline-treated group. We showed that analgesic effect of REO was slightly higher than that of paracetamol.

Table 1. Total amount of identificated compounds in the examined sample of essential oil of rosemary (% m/m)

Compounds	The number of identificated compounds	Total amount, percent %(m/m)
Monoterpenes	14	31.22
Oxygenated monoterpenes	9	63.88
Sesquiterpenes	6	4.77
Total number/amounts of identificated compounds	29	99.87
Amount of non-identificated Compounds		0.13

Table 2. The reaction of mice on hot stimulus during hot-plate test

Interval of measurement [min] / Group of animals	0	5	10	15	20	30	40	50	60
ConS	11.63± 2.57	11.11± 4.52	9.87± 2.17	12.47± 3.27	10.06± 1.84	10.91± 2.87	10.27± 1.91	11.58± 1.64	11.88± 2.70
REO	10.91± 2.80	12.92± 3.30$^{\#}$	13.85± 7.70	15.21± 3.00	14.17± 3.20$^{*\#}$	14.66± 7.50	14.24± 6.50	15.58± 3.10$^{*\#}$	14.44± 3.90
Par	10.91± 2.61	10.34± 1.05	12.38± 3.97	11.73± 2.32	11.08± 3.85	11.56± 2.92	12.42± 1.80*	13.32± 2.28	12.10± 5.08
ParR10	10.91± 2.61	10.91± 2.61	11.97± 2.55	13.08± 4.00	12.63± 2.26*	12.20± 3.15	13.68± 2.04*	11.93± 1.40*	13.41± 3.85
ParR20	10.91± 2.61	13.17± 3.18$^{\#}$	11.53± 7.59	14.45± 8.80	13.25± 4.19*	16.53± 5.35$^{\#*}$	15.48± 5.57*	18.50± 6.40*	12.78± 3.25

(*) statistically different value from group ConS, *p<0,05;*

(#) statistically different value from group Par, *p<0,05.*

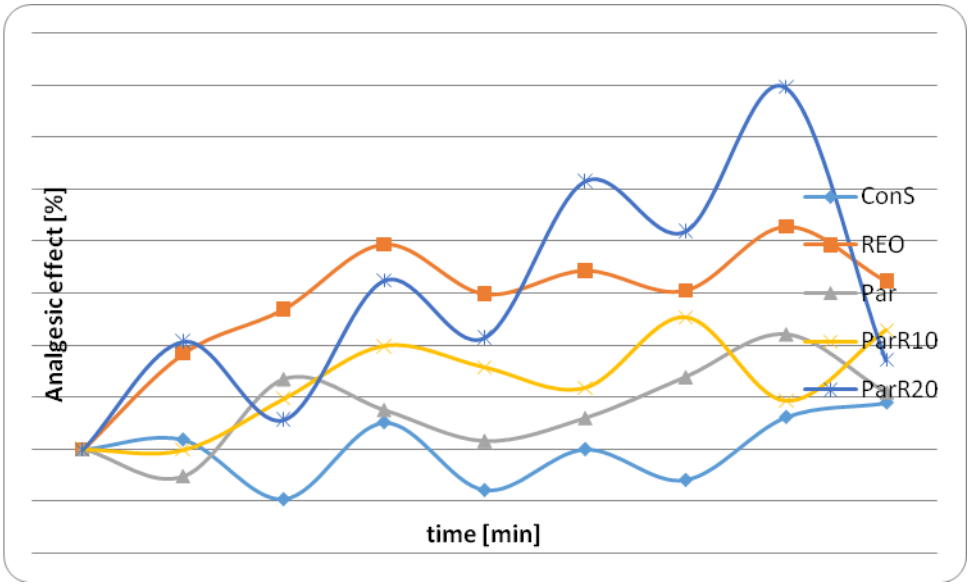

Figure 1. Analgesic effect of essential oil of rosemary compared with those of paracetamol

We demonstrated that percent of analgesic effect of REO was comparable to those of paracetamol, alone and in combinations with REO (Table 2 and Figure 1). The administration of REO in the dose of 20 mg/kg with paracetamol significantly prolonged the reaction time of animals provoked by heat stimuli, when compared to both saline- and paracetamol-treated group, with a maximal response observed between the 30th and 50th minute of the test.

Two main chemotypes of essential oils isolated from rosemary have been reported considering the chemical composition. The main component of the Tunisian, Turkish, Moroccan and Italian oils is 1,8-cineole with usually over 40%, whereas most Spanish, French and Greek oils have 1,8-cineole, α-pinene and camphor with approximately equal ratios (20-30%) [8]. The main constituents in the rosemary essential oil investigated in our study were 1,8-cineole (43.77%), camphor (12.53%), and α-pinene (11.51%), and therefore it can be categorized in the Morocco/Tunisian type. It should be noted that there are several factors that contribute to significant variations in the chemical composition of rosemary essential oils, including the geographic origin, part of the plant, season of harvesting, hence the stage of the plant growth, and also the essential oil isolation method [19]. All effects of REO should be therefore carefully examined, considering the chemical composition of the examined oil.

In hot plate assay, 7-day treatment with REO (20 mg/kg) induced significant analgesic effects in mice, which is in accordance with the results of previous studies. Analgesic activity of REO was confirmed in different nociceptive experimental models. Analgesic effect of REO was confirmed for different monoterpenes that constitute more than 90% of the essential oils [20], but also for the ethanol extract of rosemary [21] and its major constituent carnosol [22], and triterpenes fractionated from the rosemary extract [23].

The observed analgesic effect of REO in hot plate test in our study indicates its central mechanism of analgesia, since both paw licking and jumping are supraspinally integrated responses [24]. Serotonergic and opioid endogenous systems were suggested to be involved in the mechanism of action as an antinociceptive of the essential oil isolated from rosemary[25]. Furthermore, the GABAergic system may be another possible route involved in the pharmacological activity of rosemary [21].

Several studies using different nociceptive in vivo models demonstrated analgesic activity of many monoterpenes [26]. The mechanisms of antinociceptive effects of monoterpenes are still to be elucidated, but are suggested to involve different members of the TRP channel family, as confirmed for camphor [27]. It is generally assumed that acyclic monoterpenes modulate the opioid system, while monocyclic and bicyclic monoterpenes produce analgesic effects mostly by peripheral pathways [20]. The potent analgesic and anti-inflammatory activity of 1,8-cineole, as a dominant component of REO, was shown to be mediated through the inhibition of COX enzymes and suppression of cytokines (TNF-α and IL-1β) production as well [28].

Although it possesses analgesic activity, REO can also influence catalytic activities of cytochromes and thus efficacy of other analgesic drugs. REO rich in 1,8-cineole was found to induce catalytic activities of microsomal enzymes, particularly CYP2B, but also slightly the activity of UDP-glucuronosyltransferase (UGT), and therefore may interact with codeine and paracetamol [12]. The main REO component 1,8-cineole also increased the levels of cytochromes CYP2B1 and 3A2 [11]. It was demonstrated that water extracts of rosemary significantly increased activity of CYP2E1, 1A2 and 3A, which are involved in the formation of hepatotoxic metabolite of paracetamol [29,30]. As shown in Figure 1, the administration of REO in combination with paracetamol exerted distinct effects when applied in different doses. REO in the dose of 20 mg/kg was shown to be more efficient than in the dose of 10 mg/kg, in combinations with paracetamol, which suggests that dose determines whether REO will predominantly induce cytochromes or act as analgesic and

have additive effect with administered antinociceptive drugs. This is in agreement with previous findings that many monoterpenes do not exhibit dose-dependent effects and that it is necessary to find the most appropriate dose range that shows effectiveness [31].

Table 3. The influence of essential oil of rosemary applied per os, during seven days, 5 i 10 μg/kg, on the pharmacokinetic parameters of paracetamol used intravenously, 20 mg/kg, on white laboratory rats (m±Sd)

Pharmacokinetic parameter	Con_7+$PAR_{i.v.}$	$Reo5_7$+$PAR_{i.v.}$	$Reo10_7$+$PAR_{i.v.}$
K (1/min)	$15.92x10^{-3}$ ±$3.28x10^{-3}$	$19.80x10^{-3}$±$11.52x10^{-3}$	$16.88x10^{-3}$± $2.82x10^{-3}$
t ½ min	45.42±11.53	43.55±19.69	42.16±8.48
C_0 μg /ml	47.65±18.39	24.25±11.34*	27.63±12.81
AUC 0-t min*ug/ml	1256.69±441.40	1001.36±428.62	982.58±502.44

Table 4. The influence of essential oil of rosemary applied per os, during seven days, 5 i 10 μg/kg, on the pharmacokinetic parameters of paracetamol used also per os, 20 mg/kg, on white laboratory rats (m±Sd)

Pharmacokinetic parameter	Con_7+$PAR_{p.o.}$	$Reo5_7$+$PAR_{p.o.}$	$Reo10_7$+$PAR_{p.o.}$
K (1/min)	$9.10x10^{-3}$± $4.19x10^{-3}$	$7.32x10^{-3}$ $1.87x10^{-3}$	$10.13x10^{-3}$± $4.43x10^{-3}$
t 1/2 min	89.77±39.58	101.65±34.49	78.13±28.28
t max min	41.25±18.87	36.00±8.22	35.00±12.25
Cmax ug/ml	3.20±0.44	2.38±0.86	2.80±0.74
AUC 0-t min*ug/ml	354.12±102.00	262.11±68.72	272.06±72.10

The influence of REO applied orally was seen through the changes of pharmacokinetic parameters within experimental groups on one side and control group which received paracetamol by intravenous route (Table 3.).

The constants of elimination were increased in both experimental groups and half-life was decreased in both experimental groups. The first measured concetration was statistically lower than in control group.

In the control group where paracetamol was applied orally (Table 4.), the changes of parameteres are different in association with dose which was applied.

In the group treated with 10 mg of REO the elimination was faster, and in the group treated with 5 mg the elimination of drug is lower than in the control group. The same was seen in the parameteres of half-life of drug.

There is no statisticaly significant difference beetween bioavailability of paracetamol, but it is still lower in the group treated with 5 mg of REO (only 2% lower then in control group. This result can't be taken as significant but it should be taken as a reason for precaution when classical drugs and herbal drugs are used together).

CONCLUSIONS

These results could be caused with presistemic metabolism of paracetamol and of influence of REO at the resorption of paracetamol. The paracetamol is the P-glycoprotein substrate, and the extract of rosemary shows influence to this tansport proteine [32].

The decrease of bioavailability of paracetamol after REO use could be explaned with the influence of monoterpene,8-cineole, which is most present in our sample of REO. This monoterpene could interact with microsomal enzymes, sulfur transferase, UDP-glucuronyl transferase and cytochromes CYP3A4, CYP1A2, CYP2D6, CYP2E1, which are used in biotransformation of paracetamol [7,22,33,34].

In summary, it can be concluded that REO possesses centrally acting analgesic properties, as determined in hot plate assay, although a more in-depth evaluation of the mechanisms involved should be performed. Our findings support the folkloric use of rosemary in the management of pain, but also indicate a therapeutic potential of REO in combination with analgesic drugs. Considering nonlinear dose-response relationship of most monoterpenes, the appropriate dose of REO has to be determined in order to obtain an improved therapeutic effect without adverse reactions due to interactions.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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UTICAJ ETARSKOG ULJA RUZMARINA PRIMENJENOG *per os* NA FARMAKODINAMSKA I FARMAKINETSKA SVOJSTVA PARACETAMOLA

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Uvod: Etarsko ulje ruzmarina se koristi za tretman dispepsije, blagih spazama gastrointestinalnog trakta; spolja kao analgetik za lečenje blažih mijalgija i bolova u zglobovima, i za poboljšanje periferne cirkulacije. Stoga je važno ispitati analgetski potencijal etarskog ulja ruzmarina i njegov uticaj na farmakokinetske i farmakodinamske osobine drugih analgetika, odnosno u našem slučaju paracetamola. Metodologija: Etarsko ulje ruzmarina je primenjivano oralno (10 i 20 mg/kg TM) tokom sedam dana za potrebe farmakodinamskih testova. Pacovi su tretirani etarskim uljem ruzmarina per os sedam dana (5 i 10 mg/kg TM). Na njima je ispitivan uticaj etarskog ulja ruzmarina na farmakokinetske osobine paracetamola (primenjenog sedmog dana per os ili intravenski). Farmakokinetski parametri su ispitivani u uzorcima krvi pacova dobijenim iz repne vene HPLC metodom. Rezultati: Etarsko ulje ruzmarina je pokazalo analgetski efekat. Etarsko ulje ruzmarina je pojačalo analgetski efekat paracetamola i ne utiče na biološku raspoloživost paracetamola. Zaključak: Biljni lekovi mogu uticati na farmakodinamiku i farmakokinetiku klasičnih lekova, a time i na bezbednost primene tih lekova u humanoj populaciji.

Ključne reči: *Ruzmarin, interakcije lekovi-lekovite biiljke, paracetamol*

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