AMLS Archives of Medical Laboratory Sciences

Original Article

The Effect of a Mixed Extract of Peppermint, Mentha, Evening Primrose, and Eucalyptus on Lowering Body Temperature in Rats

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Received: October 26, 2021; Accepted: February 14, 2022

Abstract

Background and Aim: Increased body temperature (fever) is a common clinical indicator of disease and can lead to altered metabolism and subsequently threaten life. studies have shown antimicrobial, analgesic/antipyretic effect for some Eucalyptus and Mentha species. Therefore, in the present study we assessed the effect of the combination of mint (Mentha), eucalyptus, evening primrose, and basil on lowering body temperature.

Methods: This experimental study was performed on 30 rats in five groups. A hydroalcoholic extract was prepared from each plants using ethanol as solvent and concentrated with a rotary apparatus. Then the extracts were combined in equal proportions. To induce fever, the brewer's yeast fever induction method was used by intraperitoneal injection of a 20% aqueous suspension. The febrile rats were then divided into groups receiving different doses of the mixed extract (200, 500, 750 mg/kg); normal saline and paracetamol were used in control groups. Rectal temperature was measured with a digital thermometer before injection and 6, 8, 12, and 16 hours after extract injection. The analysis of variance with repeated measurements was used to evaluate the effect of hydroalcoholic plant extracts on fever changes.

Results: The mean fever in the intervention groups with all effective doses decreased over the hours, and the mean fever with a dose of 750 mg decreased more than in the other groups (P-value < 0.05). We had the lowest fever at a dose of 750 mg and a time of 16 hours (P-value < 0.05).

Conclusion: The results show that the combined extract can reduce body temperature in rats, and by increasing the effective dose, the recovery rate and temperature reduction are faster and more effective.

Keywords: Fever; Herbal; Mentha; Ocimum Basilicum; Eucalyptus.

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Please cite this article as: Gholizadeh Doran Mahalleh R, Abdollahi Gonbaj A, Razavi M. The Effect of a mixed extract of Peppermint, Mentha, Evening Primrose, and Eucalyptus on Lowering Body Temperature in Rats. Arch Med Lab Sci. 2022;8:1-6 (e7). https://doi.org/10.22037/amls.v8.36547

Introduction

Fever is one of the oldest and most common clinical indicators of disease in mammals (1). Most often, fever occurs in response to infection, inflammation, or trauma. There is increasing evidence that fever represents a complex adaptive host response to various infectious and noninfectious immune challenges; however, an increase in body temperature is not always a sign of fever (2). The complexity of the fever response may be due to the effects of multiple systems influenced by endocrine, neuronal, immunologic, and behavioral mechanisms. In addition to regulated hyperthermia, fever is also associated with various diseases, changes in metabolic and physiological properties of body systems, and immune responses (1). Non-pyrogenic hyperthermia increases the transport of bacteria in the intestine and the gastrointestinal tract appears to be more permeable to toxins than the heat norm (3). In recent decades, the therapeutic use of herbal products has increased significantly. In many countries, medicinal and aromatic plants are used in primary health care, especially in rural areas.

In developing countries, 80% of the population uses traditional sources and considers them an essential source of medicine (4, 5). Many types of research have addressed the composition of herbal extracts, their biological activities, and optimization of extraction procedures, which will be recognized as viable therapeutic options in the future since medicinal plants provide reliable, safe, and acceptable medicines for humans (6). Eucalyptus spp. is a large genus of Myrtaceae that includes about 900 species and subspecies. This tall evergreen tree is native to Australia and Tasmania and belongs to the genus Acacia, which is the second-largest tree genus in existence after Acacia (7). In ancient times, eucalyptus was used as an antiseptic and to treat respiratory diseases (8). Colds, flu, sore throat, and chest diseases such as bronchitis and pneumonia can be treated with the leaves of this tree (9). Several studies have shown that the essential oil (EO) of E. globulus has an antimicrobial effect on gram-negative and gram-positive bacteria (10). It has been shown that the extract can stimulate a phagocytic response, reduce the secretion of proinflammatory cytokines, and act as receptor- mediated phagocytosis. The conversion of the innate immune response of mediator cells was also observed after the administration of EO in vivo, which consisted mainly of peripheral blood monocytes/granulocytes (11).

Mint, or Mentha, is an edible vegetable consisting of plants with continuous dicotyledonous petals that constitute the high class of mint. M. longifolia is often used to treat sore throat, oral discomfort, and throat irritation (12). The presence of oxygen monoterpenes in the chemical compositions of Mentha plants has been shown to have potent antibacterial activity. The antimicrobial activity of the essential oil of M. longifolia has been demonstrated (13). An aqueous extract of M. longifolia leaves showed analgesic and antipyretic effects in one study. The nontoxicity of plant extracts in rats was confirmed by relatively high LD 50 values obtained with oral and intraperitoneal administration of plant extracts (14).

Ocimum basilicum is a member of the Lamiaceae family, which includes over 200 species (15-17). According to sources, the leave of Solanum nigrum L. (SN) is used in traditional medicine to treat seizures and epilepsy, as well as pain, ulcers, inflammation, diarrhea, some eye infections, and jaundice. The leaves are used to cure mouth ulcers in Indian folk medicine. Interestingly, medical studies have been conducted on the aqueous extract of SN leaves (18, 19). (18, 19). Various servings of this vegetable have shown potential health benefits in studies. Peppermint or Mentha Piperita is a common herb grown in Europe and North America. The oil of peppermint has always been used for various purposes, including the treatment of headaches, colds, and neuralgia. Evening primrose (OenotheraL.) is a plant of the Onagraceae family, in which the most numerous species is Oenothera biennis. Some plants belonging to the genus OenotheraL. are characterized by biological activity. This study aimed to assess the effect of the mixed extract of peppermint (Mentha × Piperita L.), mentha (Mentha spicata), evening primrose (Oenothera biennis L), and eucalyptus (Eucalyptus globulus Labill.) extract on lowering body temperature in rats.

Methods

Based on previous studies, 30 adult (2.5 months) Wistar rats weighing 5 ± 250 g were included in the study (20). The rats were maintained in a controlled environment with a temperature of 23±2ºC and a 12-hour light/dark cycle. They were provided with a standard pellet diet and access to water at all times. The care, and handling of the animals followed the protocols established by the Canadian Council on Animal Care. The plants were extracted in the Research Institute of Medicinal Plants of Tehran University of Medical Sciences based on hydroalcoholic extraction by Soxhlet with 70% ethanol after they were identified and approved by botanists of Tehran University of Medical Sciences.

The hydroalcoholic extract of the plants was first prepared: At the beginning, the crushing plant was placed in a suitable vessel (glass) and ethanol was poured over it. To avoid chemical reactions caused by exposure of the plant components to light, the extraction was performed in a place protected from direct sunlight. We prevented the solvent from evaporating by tightly closing the lid of the extraction vessel. We allowed the extraction to run for another 5 days at room temperature, shaking and stirring frequently. After this time, when the equilibrium concentration of the solvent and plant tissue was reached, we terminated the extraction, filtered the resulting extract, and pressed out the plant residue with a press. To settle the sediments and turbidities, the extracts were combined in equal proportions and stored at a temperature lower than 15°C for 5 days. The solid extract was obtained after they were dried in a vacuum using a rotary evaporator. The rats were provided by the Experimental Research Centre of the University of Iran, and the experiment was performed entirely there.

Rats were observed for one week before the start of the animal experiment to check their health status and to maintain homogeneity of environmental and feeding conditions. The rats were divided into five groups and their cages were completely emptied, cleaned, and disinfected every two days to reduce the risk of mortality and microbial infections. All rats were fed the same diet and lived in the same environment.

Initially, a Beaver digital thermometer manufactured in China was used to measure and record the rectal temperature of all rats. We used the method of fever induction with brewer's yeast, which is more successful in inducing fever and raising the temperature. Unlike the microbial induction process, there are no unwanted variables. In this procedure, it is not necessary to prepare or initiate a microbial culture. The normal body temperature of each rat was measured with a digital thermometer and then a 20% V/V aqueous suspension (brewer's yeast- 10 ml/kg) was injected intraperitoneal to induce fever. All groups were not given meals overnight but had unlimited access to water. Fever induction in the rats was determined by an increase in rectal temperature of at least 0.5°C, which was monitored and recorded 6, 8, 12 and 16 hours after injection (21).

The febrile rats were then divided into five groups of six members as follows:

Group 1: Consisted of a control group or a negative control group (normal saline).

Group 2: Positive control group (150 mg/kg paracetamol)

Group 3: A dose of 200 mg/kg of the hydroalcoholic extract was given to the experimental group.

Group 4: A dose of 500 mg/kg of the hydroalcoholic extract was given to the experimental group.

Group 5: A dose of 750 mg/kg of the hydroalcoholic extract was given to the experimental group.

Statistical Analysis:

One- way repeated-measures ANOVA was applied to evaluate the effect of hydroalcoholic plant extracts on fever changes. Statistical significance was based on two- sided design-based tests evaluated at a 0.05 level of significance. All the statistical analyses were performed by SPSS software.

Results

Thirty rats were studied, divided into five groups with positive, negative control, and three groups and three doses of 200, 500 and 750 mg/kg of the mixture of the extract were used for these groups according to traditional doses used in the local city. To evaluate the effect of the treatments with the hydroalcoholic extract on the average fever in the different hours, the analysis of variance with repeated measurements was used. The default assumption for the use of this test is the normality of the response variable (dependent) in the different groups. According to the results, the Shapiro-Wilk test is used, which shows a normal distribution according to the results of the dependent variable in all the different hours (P-value > 0.05), except for normal temperature. Therefore, it can be concluded that the complementary therapy in all three groups may have a positive effect on relieving the symptoms of this disease (Table 1).

Table 1. Investigating and comparing the significance of the data in the experimental groups.

Variable name	P-value	F
Fever at normal temperature	0.01	0.353
Fever in 6 hours	0.059	0.823
Fever in 7 hours	0.06	0.972
Fever in 12 hours	0.08	0.985
Fever in 16 hours	0.09	0.988

Because of the normality of the response variables in each group, to perform analysis of variance with repeated data, the sphericity of the variance must be demonstrated (sphericity), or in other words, the variance of the dependent variable (mean fever) must be constant or equal between groups. The Mauchly statistic used after the results of equality of variance of the dependent variable in the different groups was rejected (P-value > 0.05). The results showed that the mean fever values are significantly different at the different time points and the interaction of time and group on the mean fever is significantly different, that is the mean fever among the different groups and at the different time points is significantly different and the recovery time is faster in the high-dose groups (the latest recovery time in the control group is negative, and the fastest treatment time is observed in the 750 mg/kg treatment group (P-value <0.05) (Table 2).

Table 2. Evaluation and analysis of variance test results with duplicate data (Greenhouse- Geiser report).

Variable name	significance level	Degree of freedom	F
Time	<0.001	4	49.8445
Group time	<0.001	16	20.327
Error	-	80	-

The mean fever in the control group is higher than in the other groups and is lower in 750 mg group than in

the other groups, according to the results of the pairwise comparison test (the difference between the mean of this group and all groups is negative). This indicates that the drug reduced fever at higher doses. In addition, when comparing the mean fever over time, we can see that the mean fever at 16 hours is lower than the mean fever at 6, 8, and 12 hours. All relevant tests were also negative (P-value < 0.05) (Table 3).

Table 3. Investigating and comparing the mean difference and confidence interval in the experimental groups

Group		P-value	Lower CI	Upper CI	Mean difference
Control	Paracetamol	0.001	0.901	1.044	0.972
	Dose 200 mg/kg	<0.001	0.142	0.285	0.213
	Dose 500 mg/kg	<0.001	0.396	0.529	0.468
	Dose 750 mg/kg	<0.001	0.906	0.906	0.978
Group 5 (Dose 750 mg/kg)	Control	<0.001	-1.49	-0.906	-0.978
	Paracetamol	<0.001	-0.077	-0.066	-0.005
	Dose 200 mg/kg	<0.001	-0.836	-0.693	-0.764
	Dose 500 mg/kg	<0.001	-0.851	-0.439	-0.510
Normal temperature	6 hours	<0.001	-1.790	-1.588	-1.686
	8 hours	<0.001	-1.447	-1.280	-1.364
	12 hours	<0.001	-1.180	-0.95	-1.065
	16 hours	<0.001	-0.992	-0.838	-0.915
16 hours	Normal temperature	<0.001	0.838	0.992	0.915
	6 hours	<0.001	-0.827	-0.721	-0.774
	8 hours	<0.001	-0.467	-0.430	-0.448
	12 hours	<0.001	-0.238	-0.062	-0.150

*Confidence interval

Discussion

There is evidence that the extract of M. longifolia leaves has analgesic and antipyretic properties, and the relatively high values of LD 50 obtained when the plant extract was injected orally and intraperitoneally confirmed the nontoxicity of the plant extract to mice (22). Many polyphenolic chemicals are found in the extracts of Solanum nigrum L. (SN). Polyphenols, such as phenolic acids and flavonoids, are abundant in the leaves. Zaidi et al. have demonstrated that the extract from the leaves of SN can reduce oxidative stress in mice and, in particular, the potential of the extract to prevent and alleviate stress-related disorders such as oxidative damage to cellular components, especially in the brain. The presence of the above- mentioned polyphenolic chemicals in the stems and leaves of SN could explain the antioxidant effect. Sun et al. reported that oxidative stress is associated with a variety of clinical diseases, including the central nervous system, and it may help delay systemic diseases and physiological aging of the brain (23, 24). Mehrdad Modarresi et al. studied the anticonvulsant effect of hydroalcoholic basil extract in 48 mice in six groups of eight in an animal model of seizures with pentylenetetrazol. The experimental groups consisted of a control group, and four treatment groups that received intraperitoneal doses of 100, 250, 300, and 350 mg/kg of the extract, respectively. The 100 mg/kg group had the most epileptic seizures, according to the results of this study. Compared with the other groups, the samples at the two doses of 100 and 250 mg/kg showed the most and least myoclonic contractions, respectively. The frequency of seizures and the mortality rate were significantly increased and decreased respectively in the treatment group with a dose of 250 mg/kg, 65 minutes before the injection of three-component pentylenetetrazol. Thus, it can be inferred that the focus of this research is on the beneficial effects of this extract in the treatment of seizures. It is worth noting that fever is one of the most common causes of seizures, and our results are in line with this concept (25).

In the study by Fatemeh Hedayatifar et al, the effect of Eucalyptus extract on the body temperature of white mice was investigated. Mice weighing about 20 to 25 grams were divided into 3 groups: Group 1 (aqueous Eucalyptus extract at a dose of 100 mg/kg), Group 2 (aqueous Eucalyptus extract at a dose of 400 mg/kg), and control group (saline 10 ml/kg). Before injection,

the basal temperature of each mouse was measured with a sensitive rectal probe. Fifteen minutes after injection, they measured the body temperature of the mice for up to 90 minutes. The results of their experiment showed that low and high doses of Eucalyptus extract could not lower the normal body temperature of mice compared to saline, which was due to the use of a single plant and a low dose of the extract or an error in testing. However, the authors conducted another study in which the mice were divided into three groups: Group 1 (200 mg/kg of extract), Group 2 (400 mg/kg of extract), and Group 3 (10 mg/kg of atropine). Fifteen minutes after the last injection, the body temperature of the mice was measured with a sensitive rectal probe, every 10 minutes to 90 minutes. This time, the results showed that the Eucalyptus extract decreased body temperature of the mice (26).

In another study, Mehdi Noureddini et al. experimentally investigated the analgesic effect of Mentha sweat in male rats. Mentha sweat was prepared using traditional methods and the analgesic effect was studied on six groups of 10 male rats using the hot plate method. The experimental groups received Mentha sweat at a dose of 450, 60, 27, 0.9 mg/kg, the positive control group received paracetamol at a dose of 100 mg/kg and the negative control group received normal saline at a dose of 0.1 ml/100 g animal weight as IP. The results of this study showed that Mentha sweat has an analgesic effect and the strength of the effect increases with increasing dose ($p < 0.05$). The analgesic effect starts at a dose of 27 mg/kg and reaches its maximum at a dose of 60 mg/kg. When comparing the analgesic effect of the effective dose of Mentha sweat with aspirin (100 mg/kg), we found that Mentha sweat has a stronger analgesic effect than aspirin ($p < 0.05$). The results of this study are in agreement with our study (27).

In a study, Arash Abdolmaleki et al. investigated the analgesic and anti-inflammatory effects of an aqueous extract of peppermint. The extract was injected intraperitoneal into mice at doses of 20, 40, 60, 90, and 120 mg/kg. Subsequently, its analgesic and anti-inflammatory effects were determined using formalin and xylene assays. The results showed that all doses of the extract exhibited a significant anti-inflammatory effect in inhibiting xylene-induced ear inflammation compared to the control group ($p < 0.05$). Doses of 40, 60, 90 and 120 mg/kg significantly reduced pain ($p < 0.05$). It can be speculated that this plant has many anti-inflammatory or analgesic effects. The results of this study are consistent with our study. Fever alone is not an absolute symptom. Various symptoms such as microbes and inflammation are observed in its etiology, which can also indirectly reduce fever and temperature by eliminating these causes (28).

Conclusion

The results of this study suggest that as time increases, the average fever decreases and that the average fever decreased more at a dose of 750 mg than in the other groups. Therefore, we had the minimum fever (maximum decrease) along with increasing effective times and doses. Thus, it can be concluded that the combined extract is quite effective in reducing fever in rats; however, further studies are needed to confirm this.

Acknowledgments

Not declared.

Conflict of Interest

The authors declare no conflict of interest.

Funding/Support

This study was financially supported by Zahedan University of Medical Sciences.

Ethics

This study was approved by Ethics committee of Zahedan University of Medical Sciences; Ethical code: IR.ZAUMS.REC.1398.273.

Authors Contributions

Conceptualization, RGD. and MR.; methodology, RGD.; laboratory studies, AAG and MR.; writing-original draft preparation, RGD.; writing- review and editing, RGD.; visualization, RGD; supervision, RGD.; funding acquisition, RGD and MR".

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