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Short Communication

The Effect of Systemic Administration of Monoterpenes on Visceral Pain in an Animal Model

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ABSTRACT

Introduction: Pain is one of the primary and fundamental issues associated with various diseases that every individual will encounter throughout their lifetime. Non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are commonly used for pain control, but they have significant side effects. The current study aimed to evaluate the effect of systemic administration of monoterpenes on visceral pain in an animal model.
Materials and methods: In this experimental study, 30 male albino rats weighing approximately 21 to 25 grams were used. The rats were randomly divided into three groups of 10. The control group did not receive any drug, while the first treatment group received d-limonene orally at a dose of 10 milligrams per kilogram, known as a monoterpene compound. The second treatment group received tramadol orally at a dose of 20 milligrams per kilogram. To assess the effects of monoterpenes on colonic pain, intraperitoneal injection of 6% acetic acid (4 mg/kg) was used, and the number of reflex contractions, which could be easily distinguishable and lasted for several seconds, was observed and counted for 90 minutes. Data were collected and averaged every 5 minutes and then subjected to initial statistical analysis.
Results: A significant difference in terms of visceral pain was observed between these two groups. The rats in the first treatment group that received limonene perceived significantly less visceral pain than those in the control group. The findings indicated a significant difference between treatment groups 1 and 2, meaning that tramadol creates a greater analgesic effect.
Conclusion: This finding suggests that monoterpenes cannot produce the same level of analgesic effects on visceral pain as opioids.

1. Introduction

Pain is one of the primary and fundamental issues associated with various diseases that every individual will encounter throughout their lifetime[1]. For instance, according to a report published by the American Pain Society, over fifty million individuals in the United States suffer from pain annually, with an expenditure of more than a hundred million dollars for pain management [2]. Currently, Non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are commonly used for pain control, but they have significant side effects[3]. Non-steroidal anti-inflammatory drugs can cause gastrointestinal (GI) disturbances, kidney damage, and allergic reactions[4]. Opioids can lead to nausea, constipation, drowsiness, respiratory depression, and dependence with chronic use[5]. Acute pain, which is a natural sensation, is triggered when the nervous system alerts an individual of potential injury to ensure self-care[6]. However, chronic pain has a different nature[7]. Identifying the causes of pain can help provide assistance to many individuals, and various approaches can be employed to alleviate the effects of chronic pain[8]. Scientists believe that advancements in neuroscience will lead to better and more extensive pain treatments in the coming years[9]. Researchers are investigating the impact of stress on the experience of chronic pain[10]. Chemists are developing new analgesic drugs and discovering pain-relieving properties in medications that are not typically used for pain relief. These issues have led scientists to search for drugs that are not only free from the mentioned drug side effects but are also

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affordable and accessible[11]. In this regard, attention has turned towards medicinal plants[12]. Medicinal plants, with their immense potential, can play a significant role in therapeutic and pharmaceutical applications, as well as in the food, cosmetics, and personal care industries, particularly in economies less reliant on oil[13-15]. Currently, medicinal plants and their derivatives account for 20% of pharmaceutical prescriptions in developed countries and 80% in developing countries[16,17]. The United States is the largest market for herbal medicines globally, while Japan is the largest importer of medicinal plants in Asia[18]. Therefore, the current study aimed to evaluate the effect of systemic administration of monoterpenes on visceral pain in animal model.

2. Materials and Methods

2.1. Ethical approval

This study was conducted according to the ethical guidelines of the faculty of Veterinary Medicine, Islamic Azad University of Karaj, Karaj, Iran. The certification code was 10/2018/17.

2.2. Study design

In this experimental study, 30 male albino rats weighing approximately 21 to 25 grams were purchased from the Pasteur Institute of Iran. The rats were kept under a 12-hour light-dark cycle at 22 to 24°C and had free access to food and water. The rats were randomly divided into three groups of 10. The control group did not receive any drug, while the first treatment group received d-limonene orally at a dose of 10 milligrams per kilogram, known as monoterpene compound. The second treatment group received tramadol orally at a dose of 20 milligrams per kilogram. The second group received tramadol at an oral dose of 20 ml/kg. It is worth mentioning that environmental conditions, such as temperature, lighting, and nutrition, were controlled among the groups.

2.3. Colonic pain

To evaluate the impact of monoterpenes on colonic pain, a 6% acetic acid intraperitoneal injection at a dosage of 4 mg/kg was administered. Reflex contractions, easily discernible and lasting several seconds, were monitored and counted for 90 minutes. Data were collected and averaged every 5 minutes, followed by an initial statistical analysis.

2.4. Statistical analysis

The obtained data from the histopathological study was analyzed using SPSS software (version 19). The results were analyzed in one-way variance analysis (ANOVA) and reported as mean ± standard deviation. The statistical differences between the treatments and the control groups were checked via the Tukey test at the significance level of $p < 0.05$.

3. Results

The mean scores obtained from the pain-related behaviors in the control and treatment groups, as well as the standard deviation of these groups, are presented in Table 1.

The obtained results indicated a significant difference between the first treatment and the control groups in terms of visceral pain ($p < 0.05$). The first treatment group perceived significantly less visceral pain, compared to the rat in the control group ($p < 0.05$). Then, to examine the similar effects of monoterpenes with opioid analgesics, two treatment groups were compared. A significant difference was observed between the perceived pain in treatment groups 1 and 2 rats, indicating a greater analgesic effect of tramadol ($p < 0.05$). This finding suggested that monoterpenes could not produce the same level of analgesic effects on visceral pain as opioids.

Table 1. The descriptive data obtained from the control and experimental groups of rats

	Control	Monotrepene	Opioid
1	134	130	125
2	130	131	128
3	135	129	130
4	132	131	125
5	130	129	122
6	137	128	129
7	135	130	128
8	139	131	127
9	132	128	126
10	133	130	127
Mean (SD)	2.908	1.160	2.312

SD: Standard deviation

4. Discussion

Limonene can have a positive impact on reducing visceral pain perception. Monoterpenes, such as opioid drugs, can reduce visceral pain[19]. The findings of the current study, indicating a significant effect of limonene on reducing visceral pain induced by acetic acid injection in the intraperitoneal cavity of rats, are in complete agreement with the results of other research in this area. For instance, plant oils contain a range of biological properties, including antipyretic, anticonvulsant, anxiolytic, and anti-inflammatory effects, most of which are attributed to the properties of monoterpenes[20]. D-limonene (R (+) isomer) is one of the common monoterpenes found in plant oils[21]. Some studies in which limonene was present have reported its anti-inflammatory properties[22,23]. When consumed orally, limonene can suppress inflammation, including the migration of inflammatory cells and the inhibition of nitric oxide and gamma interferon production[24]. Inhalation of R (+) limonene can significantly alleviate bronchial obstruction and pre-bronchial and perivascular inflammation in rats. These results were obtained from functional and pathological lung experiments. Recently, plant oils have been found to have analgesic effects, some of which are attributed to the presence of R (+) limonene[25]. The formalin test is a valid test for assessing chronic pain, whether mechanical or thermal[26]. Pain induced

by formalin causes the release of various substances and intracellular secretions that stimulate pain-related nerve terminals. The pain response from formalin can directly stimulate pain-related nerve fibers, thereby inducing the secretion of inflammatory mediators[27].

Based on the pain manifestation inhibition rates obtained after administering various doses of R (+) limonene, its analgesic capability can be compared to indomethacin. Indomethacin and other non-steroidal anti-inflammatory drugs inhibit cyclooxygenase in peripheral tissues, reducing the production and secretion of inflammatory mediators, and thus suppressing the stimulation of pain-related nerve fibers. The analgesic mechanism of R (+) limonene is likely to involve inhibiting synthesis and/or secretion of inflammatory mediators and preventing pain induction in nerve terminals, similar to indomethacin and other NSAIDs. Experimental results have revealed that certain stimulatory mediators, such as histamine, serotonin, bradykinin, amino acids, and prostaglandins, can be involved in the development of inflammatory pain and are sensitive to a wide range of NSAIDs, such as acetylsalicylic acid, indomethacin, and naproxen[28,29]. In this model, R (+) limonene significantly inhibits licking and gasping reactions at the injection site in the second phase. Furthermore, previous research indicates the sedative and anxiolytic effects of terpenoid compounds and monoterpenes[30]. This effect, along with a general decrease in central nervous system excitability due to terpenoid compound-induced depression, can inhibit behavioral responses to pain and, as a result, increase pain threshold, similar to the findings obtained in the present study.

5. Conclusion

Pain is one of the primary and fundamental issues associated with various diseases that every individual will encounter throughout their lifetime. Non-steroidal anti-inflammatory drugs and opioids are commonly used for pain control, but they have significant side effects. Monoterpenes indicate a significant effect of limonene on reducing visceral pain induced by acetic acid injection in the intraperitoneal cavity of rats. This finding suggests that monoterpenes cannot produce the same level of analgesic effects on visceral pain as opioids.

Declarations

Competing interests

The authors declare no conflict of interest.

Author's contributions

Ahmad Asadi Ardebili wrote the manuscript, analyzed the data, and revised the manuscript. The author read and approved the final version of the study.

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The author received no funding to conduct the study.

Ethical considerations

Ethical considerations (including plagiarism, consent to publish, misconduct, fabrication and falsification of data, dual publication and submission, and redundancy) were checked by all authors.

Availability of data and materials

Data from the manuscript are available upon reasonable request.

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