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Full Length Research Paper

Investigation of Anti-nociceptive Activity of Sage (*Salvia officinalis*) on Acetic Acid induced Writhing in Rats

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The objective of this study was to investigate the antinociceptive activity of *Salvia officinalis* leaf extract in rats. Five doses of *Salvia officinalis* ethanolic extract (50,100,200,400,600 mg/kg) were administered intraperitoneally (i.p.) to investigate their potential anti-nociceptive activity using acetic acid induced writhing in rats compared to morphine and diclofenac sodium as standard drugs. The extract exhibited dose-dependent anti-nociceptive effect. High protection (98.74 %) was produced by 600 mg/kg, followed by 400mg/kg and 200mg/kg, respectively, while less activity was elicited by the dose 50 mg/kg compared to the positive controls (morphine and diclofenac sodium) which showed 100% protection. Based on the results obtained, it can be concluded that *Salvia officinalis* leaf extract could be a potential source of anti-nociceptive principles.

Keywords: *Salvia officinalis*, Acetic acid induced writhing, Anti-nociceptive activity.

INTRODUCTION

Substances derived from natural products have been utilized for centuries for various purposes, including the treatment of pain. Opium, for example, has been used since the earliest records of time, some 7000 years ago. Not until the 19th century where individual components of different natural product remedies identified and purified. Today, drug discovery has become a complex field far beyond the use of only natural products. However, natural products have dominated the drug industry for many years and several marketed drugs are based on isolates from such natural products (Christopher and Stephen, 2005). Nociception is the process by which intense mechanical, thermal or chemical stimuli are detected by nociceptors through the activation of many types of ionotropic channels and metabotropic receptors (Julius and Basbaum, 2001; Scholz and Woolf, 2002; Tominaga, 2007). Due to having adverse side effects, like gastric lesions, caused by non-steroidal antiinflammatory drugs (NSAIDs), tolerance and dependence induced by opiates, the use of these drugs as analgesic agents were not successful in all the cases. Therefore, analgesic drugs lacking those effects are being searched all over the world as alternatives to NSAIDs and opiates. During this process, the investigation of the efficacy of plant-based drugs used in the traditional medicine have been paying great attention because they are cheap, have little side

effects and according to world health organization (WHO) still about 80% of the world population rely mainly on plant-based drugs (Zulfiker et al., 2010).

The genus *Salvia* is one of the largest genera of the Lamiaceae family and is represented by more than 900 species spread throughout the world. Numerous species of the *Salvia* genus are economically important since they are used as spices and flavoring agents in the field of perfumery (Zhiming et al., 2013). Leaves of *Salvia officinalis* (sage) are used as a culinary herb and in folk medicine to treat sore throats, dyspepsia, and diverse inflammatory diseases in the Western world (Johnson, 2011). Some biological activities have been described for different extracts of *Salvia officinalis*, like antibacterial (Mounyr et al., 2014), gastroprotective (Mayer et al., 2009), anti-inflammatory (Qnais et al., 2010; Melissa et al., 2012), antioxidant (Khakpour et al., 2014), anticancer (Fateme et al., 2013) and antihyperglycaemic (Alarcon-Aguilar et al., 2002).

Materials and Methods

Plant material

Salvia officinalis leaves were obtained from United Arab of Emirates in June 2014. The plant was identified by the Department of Pharmacognosy, Faculty of Pharmacy, and University of Gezira, Sudan.

Drugs

Diclofenac sodium 75mg/5ml (Dar Eldwa, Jordan) and morphine 10mg/ml (Neuenhof, Switzerland) were used as standard drugs. Acetic acid (Central Drug House, India) was used to induce writhing in rats.

Preparation of the ethanolic extract

Two hundred and seventy five grams of coarsely powdered leaves of *Salvia officinalis* were extracted by maceration using ethanol 98% in a conical flask for 72 hours. Thereafter, the liquid extract was filtered and dried at room temperature. The extract yield 28 grams, then kept in refrigerator until use.

Antinociceptive activity

Preparation of working solutions

Freshly prepared solutions of *Salvia officinalis* extract dissolved in distilled water were used. The required concentrations of acetic acid (0.6%), diclofenac sodium (75mg/kg) and morphine (5mg/kg) were also prepared with distilled water.

Experiment design

In the present study, rats (90-140 gm) of both sexes were used. Five groups of rats (n=5) received an ethanolic extract of *Salvia officinalis* (50,100,200,400,600 mg/kg i.p.). In the control, three groups of rats (n=5) were used, whereas, group one was untreated (negative control), group two received morphine (5mg/kg i.p.), and the third group received diclofenac sodium (75mg/kg i.p.). One hour later each rat received acetic acid (0.6% ip) in a dose of 10mg/kg, which is known to induce writhing in rats. Abdominal writhes observed 10 minutes after acetic acid administration for a period of 20 minutes. Percentage of protection from writhes induced by acetic acid was calculated as follows:

$$\text{Protection \%} = \frac{MW_{ut} - MW_t}{MW_{ut}} \times 100$$

Where:

MW_{ut} = Mean number of writhes of an untreated group (negative control).

MW_t = Mean number of writhes of a treated group.

Data analysis

The *Salvia officinalis* extract was analyzed using descriptive statistic. The obtained data were expressed as mean number of writhes \pm standard deviation (SD). Statistical difference was analyzed by analysis of variance (ANOVA). Multiple comparisons were made using paired sample t-test. The P-value is considered significant if P-value \leq 0.05.

Results and Discussion

Table (1) and Figure 1 represent the total number of writhes induced in rats by acetic acid 10 minutes after administration during an observational period of 20 minutes.

Results showed that, the ethanolic extract exhibited dose-dependent anti-nociceptive effect. High protection (98.74 %) was produced by 600 mg/kg, followed by 400mg/kg and 200mg/kg, respectively, while less activity was elicited by the dose 50 mg/kg compared to the experimental control agents (morphine and diclofenac sodium) which showed (100%) protection.

Acetic acid induces pain by releasing endogenous substances that excites pain nerve endings centrally and the observed abdominal constriction produced by acetic acid is related to sensitization of nociceptive receptors to prostaglandins. Diclofenac and other non-steroidal anti-inflammatory drugs (NSAIDs) are known to inhibit the number of writhes by inhibiting cyclooxygenase in peripheral tissue, thus interfering with the mechanism of transduction in primary afferent nociceptors by blocking the effect or the synthesis and/or release of inflammatory mediators (prostaglandins). Morphine acts by combining with opioids receptors, which are found in the central nervous system and the peripheral tissue (Woode et al., 2009).

These results were similar to other studies (Qnais et al., 2010; Bauer et al., 2012; Melissa et al., 2012). The antinociceptive effect of *Salvia officinalis* may be attributed to certain phytoconstituents present therein (carnisol and carnosic acid) by their action in prostaglandin E2 (PGE2) (Bauer et al., 2012).

Conclusion

At the five tested doses, *Salvia officinalis* leaf extract exhibited a remarkable anti-nociceptive effect, thus it could be a potential source of anti-nociceptive principles.

Acknowledgements

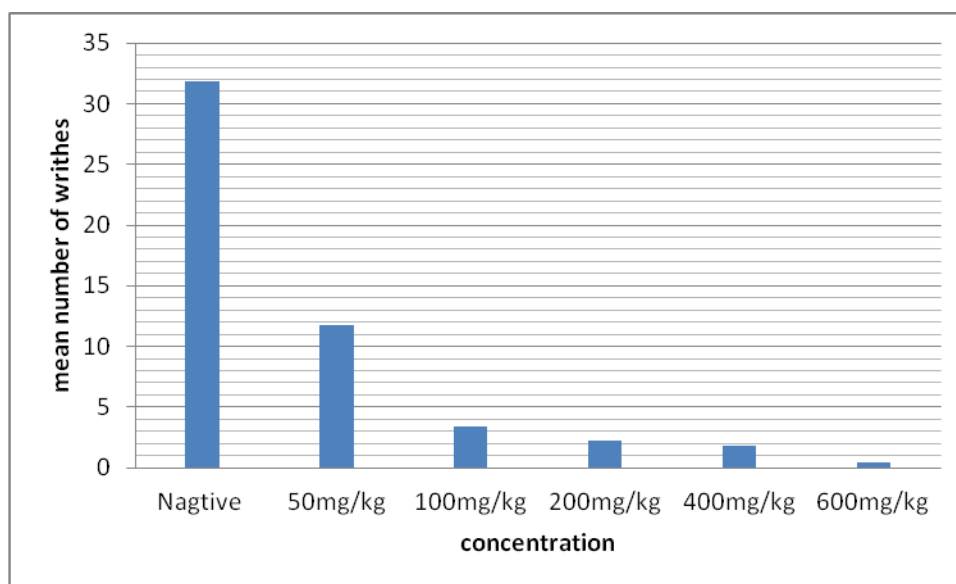
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Table 1: Effect of *Salvia officinalis*, morphine, and diclofenac sodium on acetic acid induced writhing in rats

Treatment	Dose /mg/kg	Mean of writhing \pm SD	Protection%
Acetic acid (Negative control)	—	31.8 \pm 5.89	0.00
Morphine (Standard drug)	5	0.00	100%**
Diclofenac sodium (Standard drug)	75	0.00	100%**
<i>Salvia officinalis</i>	50	11.8 \pm 7.36	62.89%**
	100	3.4 \pm 1.52	89.3%**
	200	2.2 \pm 1.79	93.08%**
	400	1.8 \pm 0.84	94.3%**
	600	0.4 \pm 0.89	98.74%**

* = P-value < 0.05

** = P-value < 0.01

Figure 1:- Anti-nociceptive activity of *Salvia officinalis* extract

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