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RESEARCH ARTICLE

ANTIINFLAMMATORY AND ANTINOCICEPTIVE ACTIVITY OF *MORINGA OLEIFERA*

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ABSTRACT

The *Moringa plant*, found in tropical and subtropical countries, provides a rich and rare combination of zeatin, quercetin, kaempferom and many other phytochemicals. It is very important for its medicinal value. Various parts of the plant such as the leaves, roots, seed, bark, fruit, flowers and immature pods act as cardiac and circulatory stimulants, possess antitumour (Makonnen et al, 1997), antipyretic, antiepileptic, anti-inflammatory and antiulcer (Pal et al, 1995).

In this study, the antiinflammatory and antinociceptive activity of the 50% ethanolic extract of the *Moringa oleifera* leaf in animals is described.

Key words: *Moringa plant,* antitumour, *Moringa oleifera*

INTRODUCTION:

There are about thirteen species of Moringa trees in the family Moringaceae. Moringa oleifera Lam. (synonym: Moringa pterygosperma Gaertn.) is the most widely known species but other species deserve further research as to their uses (M. L., 2000).

Moringa oleifera is commonly known as drumstick .It is found widely in the sub Himalayan range and commonly cultivated in all places of India .It is a very popular backyard tree that grows to over 9 m height .It has soft, white corky trunk and branches bearing a gummy bark. Each tripinnately compound leaf bears several small leaflets. The flowers are white and the three winged seeds are scattered by the wind. The flowers, tender leaves and pods are eaten as vegetable. The leaves are rich in iron and therefore highly recommended for expectant mothers. Since all essential amino acids are present Moringa may be rightly called a complete food for total nutrition. The whole *Moringa oleifera* plant is used in the treatment of psychosis, eye diseases, fever and as an aphrodisiac, (Nadakami et al, 1973).

The aqueous extracts of roots and barks of it were found to be effective in preventing implantation, (Shukla et al, 1988) whereas the aqueous extracts of its fruits have shown significant anti-inflammatory activity. Methanolic extracts of its leaves have shown anti-ulcer activity while ethanolic extracts of seeds exhibited anti-tumour activity (Guevara et al, 1999). Different parts of this plant contain a profile of important minerals, and are a good source of protein, vitamins, β – carotene, amino and various phenolics acids (Farooq et al, 2007).

The *Moringa plant*, found in tropical and subtropical countries, provides a rich and rare combination of zeatin, quercetin, kaempferom and many other phytochemicals. It is very important for its medicinal value. Various parts of the plant such as the leaves, roots, seed, bark, fruit, flowers and immature pods act as cardiac and circulatory stimulants, possess antitumour (Makonnen et al, 1997), antipyretic, antiepileptic, anti-inflammatory and antiulcer (Pal et al, 1995).

In this study, the antiinflammatory and antinociceptive activity of the 50% ethanolic extract of the *Moringa oleifera* leaf in animals is described.

2. METHODOLOGY:

2.1. Plant collection and identification:

The plant leaves of *Moringa oleifera* Lam. (Family - Moringaceae) were collected from herbal garden of MGIP. Lucknow. The plant material was identified and authenticated taxonomically at Mahatma Gandhi Institute of Pharmacy, Lucknow. A voucher specimen of the collected sample was deposited in the departmental herbarium for future reference.

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2.2. Preparation of the extracts:

The freshly collected leaves (4 kg) of *Moringa oleifera* were first washed with distilled water dried in tray dryer under controlled conditions and powdered. The powdered plant materials (1000g) was macerated with petroleum ether to remove fatty substances and the marc was further exhaustively extracted with 50% ethanol for 3 days (3 X 5L). The extract was separated by filtration and concentrated on rotavapour (Buchi, USA) and then dried in lyophilizer (Labconco, USA) under reduced pressure. The yield of dried extract obtained was 95.0 g (9.5 % w/w MOE : 50% Ethanolic extracts of *moringa olifera* leaf).

50% ethanolic extracts obtained was further subjected to toxicological and pharmacological investigations. Preliminary qualitative phytochemical screening of extract for alkaloids, glycosides, flavonoids, saponins carbohydrates, protein, amino acids, lipids, steroids, phenolic acid and tannins were performed (Trease and Evans 1983). For the pharmacological tests the 50% ethanolic extract of leaves of *Moringa oleifera* (MOE) was suspended in double distilled water containing carboxymethyl cellulose (1%, w/v, CMC). for further studies 100, 200 and 400 mg/kg (p.o.) of maximum dose were employed.

2.3. Animals:

Male Swiss albino mice weighing 20–25 g and Sprague–Dawley rats weighing 140–160 g were procured from the animal house of the Central Drug Research Institute, Lucknow. They were kept in departmental animal house in well cross ventilated room at 27±2 ^{o}C, and relative humidity 44–56%, light and dark cycles of 10 and 14 h, respectively, for 1 week before and during the experiments. Animals were provided with standard rodent pellet diet (Amrut, India) and the food was with drawn 18–24 h before the experiment thought, water was allowed *ad libitum*. All the experiments were performed in the morning according to current guidelines for the care of the laboratory animals and the ethical guidelines for the investigation of experimental pain in conscious animals (Amresh et al., 2007a). The standard orogastric cannula was used for oral drug administration.

2.4. Antiinflammatory activity:

2.4.1. Carrageenan-induced rat paw edema:

The Sprague–Dawley rats were divided into five groups, each group had six rats. Edema was induced by Carrageenan (0.1 ml of 1% suspension) was injected into the subplantar region of the right hind paw of each rat. The different dose of 100, 200 and 400 mg/kg of MOE (50% ethanolic extracts of *moringa olifera* leaf) was administrated orally to rats 1 h before carrageenan. Control rats received (1%, w/v, CMC) and indomethacin (5 mg/kg) was used as a reference drug. Increase in linear paw circumference was taken as a measure of edema volume (Winter et al; 1962; Hess and Milonig, 1972; Olajide et al., 1997, Olajide et al., 2000).

2.4.2. Cotton pellet granuloma in rats:

The Sprague–Dawley rats were divided into five groups, each group had six rats. A sterilized cotton pellet weighing 30mg was introduced subcutaneously into rats. They were then treated orally with the dose of 100, 200 and 400mg/kg of MOE for 4 consecutive days. Control rats received (1%, w/v, CMC) where as indomethacin (5mg/kg) was administered in the reference group. On the fifth day, the rats were killed and the pellets removed, dried overnight at 60 ^{0}C, and weighed (Olajide et al. 1999; Ismail et al. 1997).

2.4.3. Acetic acid–induced vascular permeability in mice:

The Male Swiss albino were divided into five groups, each group had six mice. One hour after oral administration of the MOE 100,200 and 400 mg/kg, mice were injected with 0.25 ml (i.p.) of 0.6% solution acetic acid. Control mice received (1%, w/v, CMC) where as indomethacin (5mg/kg) served as the reference drug. Immediately after administration, 10 ml/kg of 10% Evan's blue was injected *i.v*. into all the mice. Thirty minutes after Evan's blue injection, the mice were sacrificed, and the amount of dye that leaked into the peritoneal cavity was measured spectrophotometrically at 610 nm (Whittle, 1964).

2.5. Analgesic activity:

2.5.1. Acetic acid–induced writhing's in mice:

Male Swiss albino were divided into five groups, each group had six mice. The MOE 100, 200 and 400mg/kg was administered orally 1 h before writhing induction with 10 ml/kg (0.6%) acetic acid in mice. Control groups received (1%, w/v, CMC) whereas indomethacin (5mg/kg) was administered in the reference group. Writhings occurring between 5 and 15 min after acetic acid were counted (Koster et al., 1959).

2.5.2. Formalin-induced paw lickings in mice:

Male Swiss albinos were divided into five groups, each group had six mice Formalin (20 ml, 1%) was injected into the left hind paw of mice 1 h after MOE 100, 200 and 400mg/kg administration. Control groups received (1%, w/v, CMC) where as indomethacin (5mg/kg) was administered in the reference group. Mice were observed for time spent licking the injected paw (licking time), and this was recorded. Mice were observed for the first 5 min post formalin (early phase) or for 10 min starting at the 20th min post formalin (late phase)(Huskaar and Hole 1987).

2.7. Statistical test:

Values were represented as mean ± S.E.M. and data were analyzed by paired-*t*-test using SPSS software for the Windows 11.0 package.

3. RESULTS:

3.1. Phytochemical test:

Preliminary qualitative phytochemical test of 50% ethanolic of leaves of *Moringa oleifera* extract give positive tests for alkaloids, glycosides, flavonoids, saponins carbohydrates, protein, amino acids, lipids, steroids, phenolic acid and tannins.

3.2. Carrageenan-induced rat paw edema:

The 50% ethanolic extract of leaves of *Moringa oleifera* (MOE) produced statistically significant inhibition of the edema induced by carrageenan at different doses of the extract. The significantly percentage inhibition were 27.86 (P <0.05), 45.90 (P <0.001) and 68.03 (P <0.001) at dose of 100, 200 and 400 mg/kg of the MOE respectively, while indomethacine (5mg/kg) had 70.49% (P <0.001) at the third hour post carrageenan treatment when compared to control group of animals (Fig. 1).

3.3. Cotton pellet granuloma in rats:

The percentage inhibitions in weight of cotton pellets in treated group were comparable to control group. The percentage inhibitions of weight of cotton pellets statically significant 25.45 (P <0.05), 32.30 (P <0.001), 69.54 (P <0.001) at dose of 100, 200 and 400 mg/kg of MOE while indomethacin showed 87.72 (P <0.001) percent protection (Fig. 2). The maximum inhibition was observed in higher dose of extract.

3.4. Acetic acid–induced vascular permeability in mice:

Intraperitoneal administration of acetic acid into mice pretreated with control group resulted in the leakage of 63.7± 3.5 mg Evan's blue from the capillaries into the peritoneal cavity. However, pretreatment with the MOE 100, 200 and 400 mg/kg resulted in a significant and dose-related reduction in the amount of dye leakage, in comparison with the control animals. The percentage inhibition of dye leakage were inhibited by 27.49 (P <0.01), 40.03 (P <0.001), and 59.81 (P <0.001) with 100, 200 and 400 mg/kg of the MOE respectively. Indomethacin (5 mg/kg) produced the highest inhibition i.e. 68.13% (P <0.001) (Fig. 3).

3.5. Acetic acid–induced writhings in mice:

50% ethanolic extract of *Moringa oleifera* (MOE) caused a statistically significant and dose-dependent reduction in the writhing response following injection with acetic acid. The percentage inhibition of writhings were 37.60 (P <0.05), 48.76 (P <0.01), 53.71 (P <0.01) at the dose of 100, 200 and 400 mg/kg of MOE while indomethacin (5 mg/kg) showed 60.74 (P <0.001) percent protection (Fig. 4).

3.6. Formalin-induced paw lickings in mice:

It is shown that pretreatment with the different dose of MOE could not produce a significant reduction of licking time in the early phase while the licking time was, however, reduced in mice that received indomethacin. In the late phase, a dose-dependent and significant reduction in licking time was observed in treated mice. The percentage licking time were 32.80 (P <0.05), 38.33 (P <0.01), 45.84 (P <0.01) and 55.73 (P <0.001) at dose of 100, 200, 400 mg/kg of MOE and 5 mg/kg of indomethacin (Fig. 5).

4. DISCUSSION:

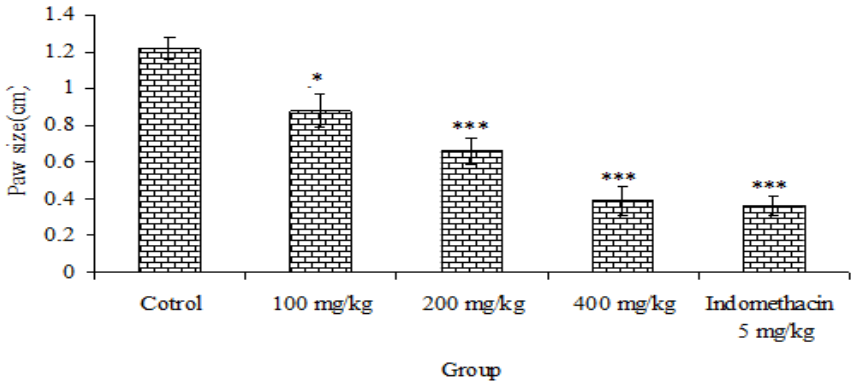
The presence of edema is one of the prime signs of inflammation (Sur et al., 2002). Carrageenan induced paw edema is the most prominent acute experimental model in search for new antiinflammatory drugs due to sensitive to cycloxygenase (COX) inhibitors and has been used to evaluate the effect of non-steroidal antiinflammatory agents (Rao et al., 2005; Morebise et al., 2002; Di-Rosa et al., 1971; Badilla et al., 2003; Asres et al., 2005; Loro et al., 1999). The subplantar injection of carrageenan in rats leads to paw edema. Carragenan induced edema is biphasic response. Its first phase results from the concomitant release of mediators: histamine, serotonin and kinins on the vascular permeability (Amresh et al.,

2007b). The second phase is correlated with the elevated production of prostaglandins, oxygen-derived free radicals, and production of inducible cyclooxigenase (Panthong et al., 2004; Brito and Antonio, 1998).

50% ethanolic extract of the leaf of plants of *Moringa oleifera* was found to exhibit significant antiinflammatory activity by inhibiting the edema induced by the injection of carrageenan into the hind paw of rats. The maximum significant (68.03%) inhibition at higher dose of extract was comparable to indomethacin group 70.49% (Fig.1). Extract could be exerting its antiinflammatory effects in the same manner as the nonsteroidal antiinflammatory drugs (NSAIDs). The NSAIDs have been known to exhibit antiinflammatory actions by the inhibition of prostaglandin biosynthesis (Vane, 1971). In order to assess its efficacy against proliferative phase of inflammation in which tissue degeneration and fibrosis occur, the widely used cotton pellet granuloma test was employed. During the repair process of inflammation, there is proliferation of macrophages, neutrophils, fibroblasts and multiplication of small blood vessels, which are the basic sources of forming a highly vascularised reddish mass, termed granulation tissue (Amresh et al., 2007c; Swingle, 1974; Bhattacharya et al., 1992). The extract significantly inhibited the weight of cotton pellet granuloma at different dose in treated groups of animals. The maximum percentage inhibition was 69.54 (400 mg/kg) which indicates that the extract is more effective in acute than in chronic, established inflammation (Fig.2). The 50 % ethanolic extract of *Moringa oleifera* also produced significant inhibition of the acetic acid–induced increased vascular permeability in mice (Fig.3) as compared to control groups of animals. The acetic acid–induced writhings test is a highly sensitive and useful test for analgesic drug development, and it is a model of visceral pain (Vyklicky, 1979). The results strongly suggest that the mechanism of action of the extract may be linked partly to lipoxygenases and/or cycloxygenases. These writhings are related to the increase in the peritoneal fluid level of PGE_2 and $PGF_{2\alpha}$ (Deraedt et al., 1980). The maximum percentage inhibition of writhings was 53.71 (P <0.01) at the dose of 400 mg/kg of ALE while indomethacin (5 mg/kg) 60.74 (P <0.001) (Fig. 4).This observation substantiates the results of the carrageenan-induced edema in the paw of rats, as both models involve the exudation of fluid from within the blood vessels. The 50% ethanolic extract of *Moringa oleifera* exhibited analgesic activity in mice, by the inhibition of the writhing response to a comparable degree as indomethacin, an established NSAID. In spite of the usefulness of the acetic acid–induced writhing assay in drug development, it is not a selective pain test. It gives false positives with sedatives, muscle relaxants and other pharmacological activities (Elisabetsky et al., 1995). The acetic acid-induced for abdominal constriction while formalin test is sensitive to NSAIDs. The test possesses two distinct phases, reflecting different types of pain. The earlier phase reflects a direct effect of formalin on nociceptors (neurogenic pain), whereas the late phase reflects inflammatory pain (Amresh et al., 2007c; Hunskaar and Hole, 1985). Drugs that act primarily on the central nervous system inhibit both phases equally while peripherally acting drugs inhibit the late phase (Chen et al., 1995). The formalin test is a very useful method for not only assessing antinociceptive drugs but also helping in the elucidation of the action mechanism. The neurogenic phase is probably a direct result of stimulation in the paw and reflects centrally mediated pain with release of substance P while the late phase is due to the release of histamine, serotonin, bradikynin and prostaglandins (Amresh et al., 2007b; Rao et al., 2003). The maximum percentage licking time was 45.84 (P <0.01) at dose of 400 mg/kg of MOE while (5 mg/kg) indomethacin 55.73% (P <0.001) (Fig. 5). The extract of *Moringa oleifera* lacked activity in the early phase but produced significant and dose-dependent inhibition of the late phase. This observation further reflects the effect of the plant extract on inflammatory events. In phytochemical investigation of 50% ethanolic extract of leaf of *Moringa oleifera* contain various chemical constituents.

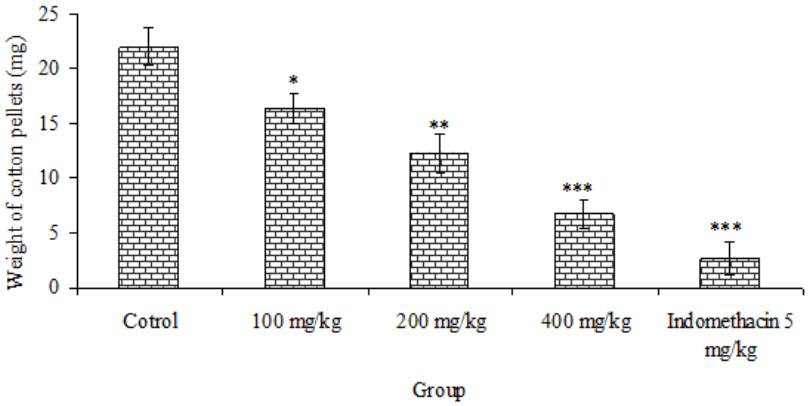
Its confirms that 50% ethanolic extract contain alkaloids, glycosides, flavonoids, saponins, carbohydrates, protein, amino acids, lipids, steroids, phenolic acid and tannins. Some researchers have already reported that flavonoids have antiinflammatroy and antioxidant effects (Patak et al., 1991; Pelzer et al., 1998). Polyphenol and flavonoids are an important class of natural compounds that possess various biological activities which may be responsible for antiinflammatory and analgesic activity of 50% ethanolic extract of leaf of *Moringa oleifera.* Beta-Carboline alkaloids belonging to indole class of compounds was found to have antioxidant and free radical scavenging and antiallergic activity (Herraiz and Galisteo, 2003, 2004; Sun et al., 2004). No death or development of adverse reactions was observed on the animals within the study period. This is an indication that the 50% ethanolic extracts, from *Moringa oleifera* was not toxic at the doses employed in this study. In conclusion, the results obtained in the present study illustrate that correlations exist between the popular ancestral perception and genuine anti-inflammatory and antinociceptive activities of the whole plant of *Moringa oleifera.*

Figure 1: Effect of MOE on carrageenan-induced paw edema in rat.



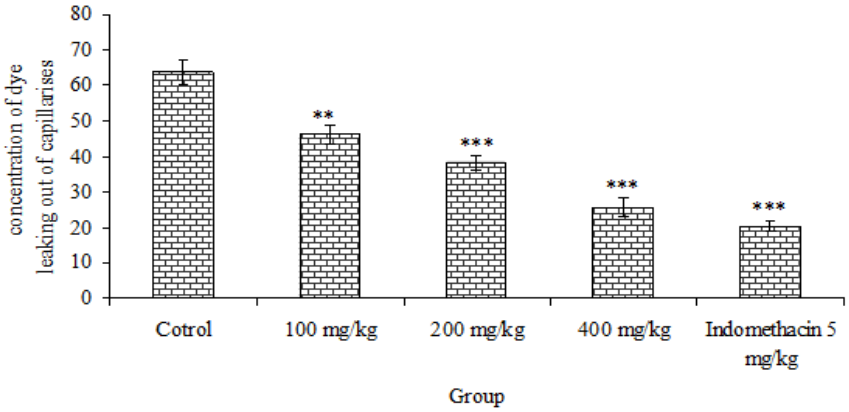
100 mg/kg, 200 mg/kg and 400mg/kg represent the dose of 50% ethanolic extract of *Moringa oleifera* leaf (MOE).
Value expressed as ± S.E.M., n = 6 rats.
* P < 0.05, ** P < 0.01, *** P < 0.001 compare to control group.

Figure 2: Effect of MOE on cotton pellets granuloma formation in rats.



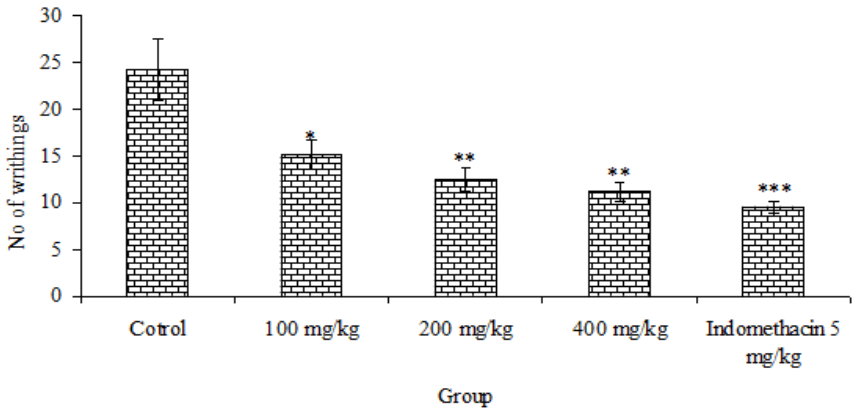
100 mg/kg, 200 mg/kg and 400mg/kg represent the dose of 50% ethanolic extract of *Moringa oleifera* leaf (MOE).
Value expressed as ± S.E.M., n = 6 rats.
* P < 0.05, ** P < 0.01, *** P < 0.001 compare to control group.

Figure 3: Effect of MOE on acetic induced vascular permeability in mice.



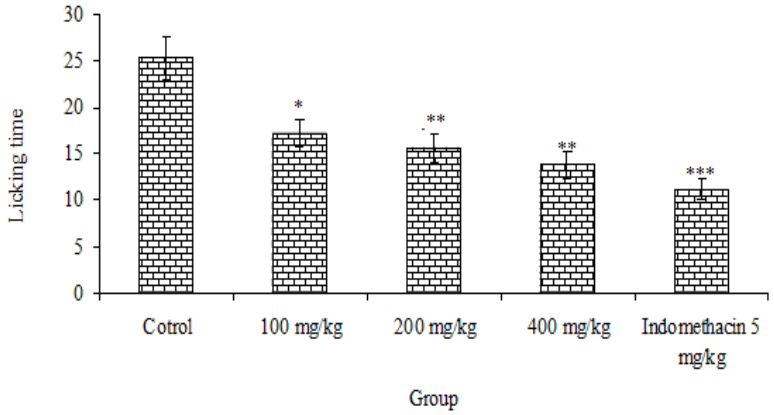
100 mg/kg, 200 mg/kg and 400mg/kg represent the dose of 50% ethanolic extract of *Moringa oleifera* leaf (MOE).
Value expressed as ± S.E.M., n = 6 mice
* P < 0.05, ** P < 0.01, *** P < 0.001 compare to control group.

Figure 4: Effect of MOE on acetic acid induced writhings in mice.



100 mg/kg, 200 mg/kg and 400mg/kg represent the dose of 50% ethanolic extract of *Moringa oleifera* leaf (MOE). Value expressed as ± S.E.M., n = 6 rats.
* P < 0.05, ** P < 0.01, *** P < 0.001 compare to control group.

Figure 5: Effect of MOE on formalin-induced paw lickings in mice.



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