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EVALUATION OF ANALGESIC AND ANTI-INFLAMMATORY ACTIVITY OF STANDARDIZED METHANOLIC EXTRACT OF *COPTIS TEETA* (WALL.) RHIZOMES

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Abstract:

Objective: *To evaluate the analgesic and anti-inflammatory potential of standardized methanolic extract of Coptis teeta Wall. (C. teeta) using validated rodent models.*

Methods: *Methanolic extract of C. teeta rhizomes were standardized by the TLC and HPTLC for berberine content. The effect of single oral dose (30, 100 and 300 mg/kg/day) of standardized methanolic extract of C. teeta were assessed on acetic acid induced writhing and hot plate in mice model as well as carrageenan-induced paw edema in rat model.*

Results: *Methanolic extract of C. teeta rhizome was found to contain 0.8% w/w berberine. Standardized methanolic extracts of C. teeta (MECT) rhizome possess significant ($P<0.05$) effect in dose dependent manner on all four validated pharmacological tests.*

Conclusions: *Outcome of the designed study reveals the analgesic and anti-inflammatory activity of the standardized MECT; and validates the pharmacological background to the traditional use of C. teeta.*

Keywords: *Coptis teeta, Analgesic activity, Anti-inflammatory activity.*

Introduction

The immune response, which occurs when immunologically competent cells are activated in response to foreign organisms or antigenic substances, liberated during the acute or chronic inflammatory response. The outcome of the immune response for the host may be beneficial, as when it causes invading organisms to be phagocytosed or neutralised. On the other hand, the outcome may be deleterious if it leads to chronic inflammation without resolution of the underlying injurious process (Furst *et al* 2011). Pain that accompanies inflammation and tissue injury probably results from local stimulation of pain fibres and enhanced pain sensitivity (hyperalgesia), in part a consequence of increased excitability of central neurones in the spinal cord. Steroidal and non-steroidal anti-inflammatory drugs are the most accepted chemical therapies for the treatment of inflammation and related diseases. The biggest disadvantage of the

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presently available synthetic drugs is various side-effects like ulcer, habit forming potentialities and reoccurrence of symptoms after discontinuation (Shakya *et al* 2015).

C. teeta (Ranunculaceae) is a perennial herb found in the Himalayan region and especially endemic to Mishmi hills of Arunachal Pradesh in India (Pandit and Babu 1998). The plant has become endangered in its natural habitat because of unwanted digging as well as poor germinative and abortive properties of the seed (Tandon *et al* 2007). Traditionally the local people of Arunachal Pradesh use it for a wide range of ailments beginning with fever, diarrhea, cuts and wounds to complicated indications such as malaria while other species of *Coptis* are used in Traditional Chinese Medicine (TCM) to suppress fever, dispelling dampness, removing toxicosis and detoxification (Tang *et al* 2009). According to Chinese Pharmacopoeia, the rhizomes of three species of genus *Coptis* makes up Huanglian, these are namely *C. chinensis* Franch., *C. deltoidea* CY Chenget Hsiao, *C. teeta*. The metabolites differentiating them into three distinct species are not identified till now (Fan *et al* 2012).

A number of protoberberine alkaloids have been isolated from the rhizomes of plants belonging to *Coptis species*, among which three alkaloids, berberine, coptisine and palmatine were found in greater amount with berberine the most abundant (Tang and Eisenbrand 1992; Sun and Tseng 2005). In absence of proper standardisation of *C. teeta*, the rhizomes are frequently adulterated with those of *Thalictrum foliolosum* DC., *Picrorhiza* species and the roots of *Swertia* species and are sold as substitute (Zhang *et al* 2008; Tsai *et al* 2004). So, the present work has been designed to standardized and evaluate the analgesic and anti-inflammatory potential of *C. teeta* on basis of the ethnomedicinal use of the rhizomes by ethnic tribes of Arunachal Pradesh.

Materials and methods

Plant material

The rhizomes of *C. teeta* were collected from Roying, Arunachal Pradesh, India during the month of August 2013. The plant was identified and authenticated at Botanical Survey of India, Eastern Regional Centre, Shillong. A voucher specimen (Specimen no. DU/PSC/HRB/A-01-2014, Reference No. BSI/ERC/Tech/Plant identification/2014) was kept in Department of Pharmaceutical Sciences, Dibrugarh University, Assam for future references.

Preparation of extracts

Young and tender rhizomes were cut into pieces, washed thoroughly with water and then dried partially under sunlight and partially under the shade for a week. The dried rhizomes were then pulverised in the mechanical grinder and stored in airtight

containers free from moisture. The plant material was extracted with Petroleum ether (40- 60^0C), Chloroform, Ethyl Acetate, Methanol, Water successively by continuous hot percolation method using soxhlet extractor. The resulting extract was then filtered, concentrated and dried under reduced pressure at 40^0C and stored in the refrigerator. The methanolic extract [MECT; yield 2.56% (w/w) with respect to the dry material] of *C. teeta* was used for experiments.

Drugs and chemicals

Solvents for extraction were purchased from Himedia Laboratory, Mumbai, India and Rankem Chemicals, Faridabad, India and all chemicals were of analytical grade. The standard drugs were purchased from Sigma-Aldrich, Banglore, India. Standard berberine for HPTLC was obtained from Sigma Chemicals, Germany.

Thin layer chromatographic (TLC)

TLC of MECT was analysed on pre–coated aluminium silica gel plates 60 F_{254} as stationary phase. Mobile phases used for developing the chromatogram were composed *n*-Propanol: Formic acid: Water in a ratio of 90:1:9 (v/v/v). The process of development of plates and determination of retention factor for berberine in the crude extracts of namely *Berberidis radix* and *Hydrastis rhizome* as described by Wagner and Bladt was taken as a basis (Wagner and Bladt 1996).

High-performance thin layer chromatography (HPTLC) standardization.

Stock standard solutions containing 1 mg/10ml of berberine in methanol were freshly prepared before use. This same solution was used for making the calibration curve by applying a different volume of the standard to get a different amount of standard per spot. The sample solution was prepared by dissolving 50 mg of MECT in methanol and making up the volume to 5 ml to get the concentration of 10 mg/ml. The spots were applied as bands with a band length of 5 mm and the distance between the tracks as 10 mm with the help of CAMAG HPTLC applicator Linomat V. Stationary phase used was precoated silica gel $60F_{254}$ plates (20cm x 10cm) from E-Merck and the mobile phase composition was optimized to *n*-Propanol: Formic acid: Water in a ratio of 7:2.4: 0.5 (v/v/v). The plate was developed in a CAMAG twin trough chamber after a chamber saturation time (10 minutes) for mobile phase. After developing, the TLC plates were dried by air blowing. Densitometric analysis was performed on a CAMAG TLC Scanner in the absorbance mode at 254 nm. Calibration curves for the standard berberine were prepared by applying a series of spots of standard with different volume so as to get a different amount of berberine per spot. They were prepared with respect to height and area *vs* amount per spot.

Animals

Wistar rats (80-140 g) of either sex were used to carry out the anti-inflammatory studies whereas Albino mice (20-30g) of either sex were used for the analgesic studies of MECT. Animals were acclimatised in the animal house for at least one week prior to experimentation. Animals were kept at 22 ± 3^0 C and 55 ± 5% relative humidity during the whole experiment. Standard food pellets and water were supplied *ad libitum*. All tested compounds were dispensed in 0.3 % CMC suspension in distilled water. The experiments were performed after the approval of the protocol by the Institutional Animal Ethical Committee (vide approval number IAEC/DU/65, dated 24.09.2013). All experiments were carried out in accordance with the current guidelines for the care of laboratory animals and the ethical guidelines for investigations of experimental pain in conscious animals (OECD guideline 1998; Zimmermann 1983).

Acute toxicity studies

Toxicological studies of the test compounds as a suspension in 0.3 % CMC were carried out by administering a high dose of 2000 mg/kg body weight in Female Wistar rats (80-140 g). Animals were kept in fasting condition prior to dosing. Following the period of fasting, the animals were weighed, properly marked and the test substance administered. After administration of test compounds, the food was withheld for a further 1-2 hours. OECD Guideline No. 425 method was adopted for toxicity studies.

Analgesic activity

Acetic acid induced writhing

Acetic acid induced writhing study was carried out as per the method described by Muhammad and co-workers (Muhammad *et al* 2012). In this method, Albino mice of either sex (n = 6) weighing 20-30 g were used. All animals were withdrawn from food 2 h before the start of the experiment and were divided into five groups. The vehicle control group received 0.3 % CMC (10 ml/kg, *p.o.*). The standard control mice were treated with diclofenac potassium (10 mg/kg, *p.o.*) while remaining three test groups was treated orally by MECT using three different dose levels (i.e. 30, 100 and 300 mg/kg, *p.o.*). MECT was always administered as a suspension in 0.3% (w/v) carboxymethyl cellulose (CMC) solution in this study. After 30 min of 0.3 % CMC, diclofenac potassium and plant extract administration, the animals were treated intraperitoneal (*i.p.*) with 1% acetic acid. The numbers of abdominal constrictions (writhes) were counted after 5 min of acetic acid injection for the period of 10 min. The percent inhibition (analgesic activity) of the number of writhings was determined using the formula:

$$\text{Percent inhibition} = \{(A-B)/A\} \times 100,$$

Where, A represents the number of writhings in vehicle-treated control mice and B as a number of writhings of the sample treated group.

Hot plate method

Albino mice of either sex (n = 6) weighing 20–30g were used. Animals were then subjected to pre-testing on a hot plate maintained at 55 ± 0.1°C. Animals having latency time greater than 15 s on hotplate during pre-testing were rejected (latency time). All the animals were divided into five groups each of six mice. The vehicle control group received 0.3 % CMC (10 ml/kg*, p.o.*). The standard control group was administered with tramadol (15 mg/kg, *p.o.*) while the test groups were administered orally with 30, 100 and 300 mg/kg of MECT respectively. After 30 min of treatment, the animals were placed on a hot plate and the latency time (time for which mouse remains on the hot plate (55 ± 0.1°C) without licking or flicking of hind limb or jumping) was measured in seconds. In order to prevent the tissue damage a cut-off time of 30 s were imposed for all animals. The latency time of each individual mice of all the groups was recorded before (0 min) and 30, 60 and 120 min after the treatment (Shakya *et al* 2014). Percent analgesia was calculated using the following formula (Muhammad *et al* 2012).

$$\% \text{ Analgesia} = \{(\text{Test latency} - \text{control latency})/ (\text{Cut-off time} - \text{control latency})\} \times 100$$

Anti-inflammatory activity

Carrageenan-induced rat paw oedema method

Wistar rats weighing 80-140 g were used. The left hind paw was marked just beyond the lateral malleolus, so as to fix a constant level up to which the rat's paw must be dipped in water. Acute inflammation was produced by injecting 0.1 ml of carrageenan (1% in 0.9 % w/v normal saline) under the plantar aponeurosis of the left hind paw. For the experiment, 5 groups of rats were used and they were divided into groups of 6 animals each. The control group received vehicle (0.3 % CMC). For the standard group, Indomethacin (25 mg/kg, *p.o.*) was used as the standard drug, while the test groups were administered orally with 30, 100 and 300 mg/kg of MECT respectively. One hour after the designed treatment, carrageenan was injected subcutaneously (*s.c.*) into the plantar surface of the left hind paw. Hind paw volume was recorded by plethysmometer (IITC Life Science Inc., Woodland, USA) after 0 hours and then after an interval of 3 hours after administration of carrageenan injection. The paw oedema was measured by calculating the difference between final (3 h) and initial (0 h) paw volume (Shakya *et al* 2015). The average foot swelling in a drug-treated animal, as well as standard, was compared with that of control and the percentage inhibition (anti-inflammatory activity) of oedema was determined using the formula (Muhammad *et al* 2012).

$$\text{Percent inhibition} = \{(A-B)/A\} \times 100$$

Where, A represents oedema volume of vehicle-treated control rats and
B as paw oedema of sample treated group.

Cotton pellet induced granuloma test

Wistar rats were divided into five groups, each group consisting of six rats. After shaving off the fur, the animals were anaesthetized. Sterile pre-weighed cotton pellets (50±1 mg) were implanted in the lumbar region of each rat through an incision. The control group received vehicle (0.3 % CMC, 10 ml/kg, *p.o.*) (Trnavsky 1965). Indomethacin (10 mg/kg, *p.o.*) was used as the standard drug and administered in positive control rats. Remaining three test groups of the rats were administered orally with 30 mg/kg, 100 mg/kg and 300 mg/kg of MECT. All the animals were treated repeatedly daily once for 14 consecutive days. 24 hours after the treatment animals were sacrificed and the cotton pellets were excised, which were then dried until the weight remained constant. The increase of the pellet weight was considered as granuloma tissue deposit. The percent inhibition (anti-inflammatory activity) of granuloma was determined using the formula.

$$\text{Percent inhibition} = \{(A-B)/A\} \times 100,$$

Where, A represents weight of the cotton pellet before incision in the rats and B is the weight of the incised cotton pellet.

Statistical analysis

The results obtained were expressed as mean ± SEM (Standard error of the mean) of six animals. The significance between groups was tested by one-way ANOVA followed by Newman-Keuls multiple comparison tests and wherever needed two-way ANOVA followed by Bonferroni post-tests. Effects were considered to be significant at the $P<0.05$ level.

Results

TLC

TLC analysis of MECT gives a lemon yellow coloured band at a R_f of 0.25 which is consistent with berberine for the extracts of *Berberidis radix* and *Hydrastis rhizome* as described by *Wagner and Bladt*.

HPTLC standardization of MECT

The mobile phase resolved berberine efficiently from other components of *C. teeta*. The R_f of berberine was found to be 0.13 [Figure 1(a) and 1(b)]. The calibration plot was

linear in the range of 250 - 200 mg of berberine and the correlation coefficient of 0.9997 were indicative of good linear dependence of peak area on concentration. The concentration of berberine in the extract was found to be 0.8% w/w.

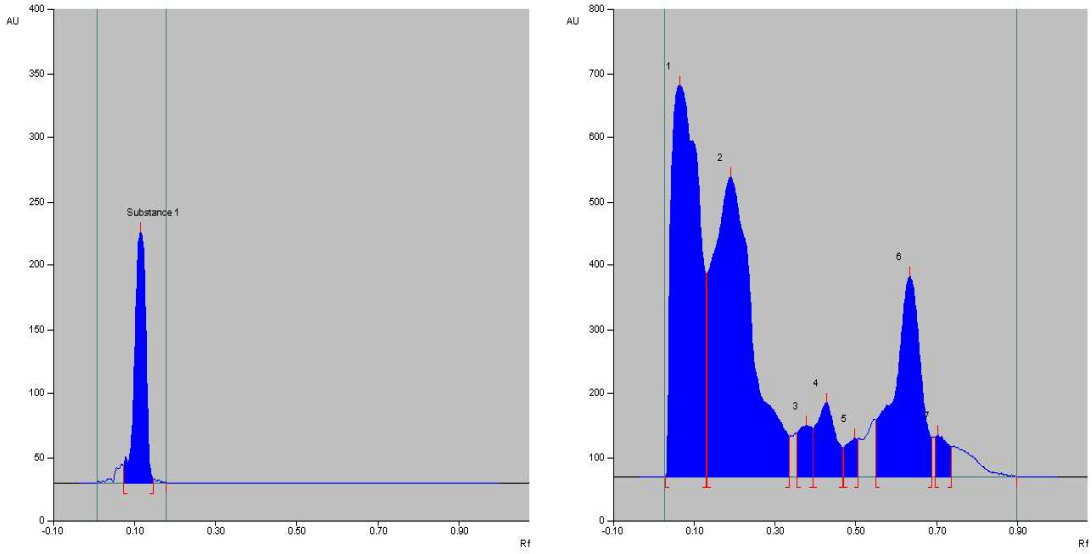

Figure 1: HPTLC chromatogram of (a) standard berberine and (b) of methanolic extract of Coptis teeta.

Acute toxicity test

MECT was found to be safe at a test dose 2000 mg/kg (*p.o.*). During 24 h assessment time, test animals were found normal. The Acute toxicity study was validated using AOT425statpgm (Version: 1.0).

Analgesic activity

Acetic acid induced writhing test

The results showed that the pain relief was achieved in a dose-dependent manner as shown by the number of writhings in Figure 2, at all test doses of MECT (30, 100 and 300 mg/kg). Maximum inhibition (43.62%) was observed at 300 mg/kg dose of MECT. The percentage inhibition of writhing is shown in Table 1. The inhibitory effect of diclofenac (52.82%) was greater than that of the highest dose of MECT.

Hot plate test

The results of the hot plate test revealed that the percentage analgesia was significantly ($P<0.05$) increased from 32.41 to 65.04 at the dose of 30 to 300 mg/kg of MECT. The

effect was dose dependent and the maximum effect was observed after 120 minutes as shown in Figure 3. The most significant ($P<0.05$) increase in percentage analgesia was noticed for MECT (300 mg/kg) was 65.83 whereas the most significant ($P<0.05$) increase in percentage analgesia of the standard drug tramadol (15 mg/kg) was found to be 80.12 as shown in Table 2.

Table 1: Effect of single dose of standardized methanolic extract of Coptis teeta (MECT; 30, 100 and 300 mg/kg) on the percentage inhibition in acetic acid induced writhing test on mice.

S. No.	Treatment group	% inhibition
1	Vehicle control	-
2	Diclofenac-10 mg/kg	52.82
3	MECT-30 mg/kg	29.09
4	MECT -100 mg/kg	37.10
5	MECT -300 mg/kg	43.62

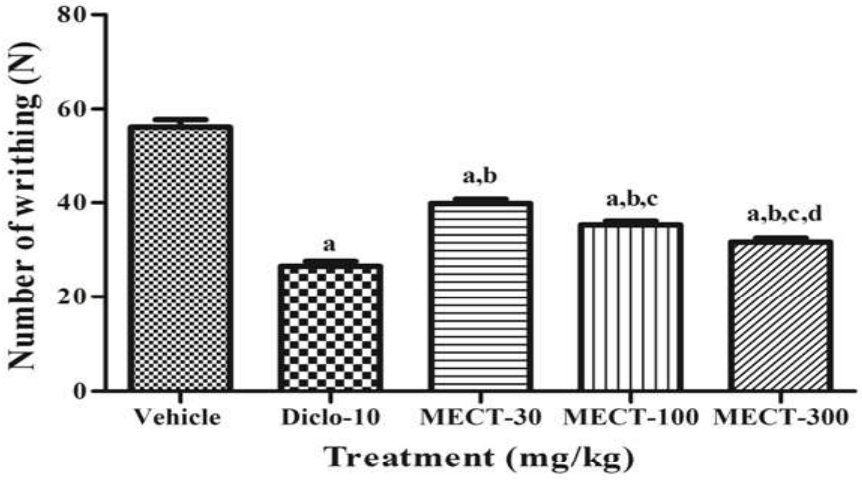

Figure 2: Effect of single dose treatment of standardized methanolic extract of *Coptis teeta* (MECT; 30,100 and 300 mg/kg) and Diclofenac potassium (Diclo; 10 mg/kg) on acetic acid induced writhings in mice. Each column represents Mean ± SEM of a number of writhes for the group (n=6). a, b, c and d indicated statistically significant values from vehicle control ($^{a}P<0.05$), Diclo-10 mg/kg ($^{b}P<0.05$), MECT-30 mg/kg ($^{c}P<0.05$) and MECT-100 mg/kg ($^{d}P<0.05$) respectively.

Table 2: Percentage analgesic effect of single dose of standardized methanolic extract of *Coptis teeta* (MECT; 30, 100 and 300 mg/kg) in hot plate test on mice

S. No.	Treatment group	% Analgesia		
		30 min	60min	120 min
1	Vehicle control	-	-	-
2	Tramadol-15 mg/kg	79.23	80.12	78.27
3	MECT-30 mg/kg	29.69	31.93	32.41
4	MECT-100 mg/kg	59.78	58.57	60.14
5	MECT-300 mg/kg	62.27	65.83	65.04

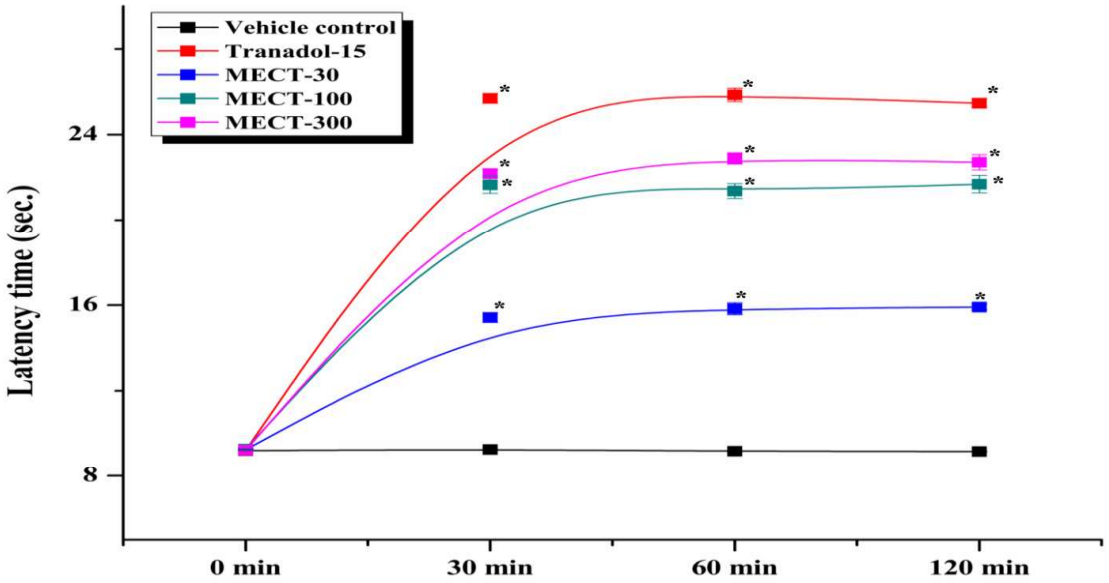

Figure 3: Effect of single dose treatment of standardized methanolic extract of *Coptis teeta* (MECT; 30, 100 and 300 mg/kg) and Tramadol (15 mg/kg) on latency time of mice in hot plate test. Each value represents Mean ± SEM of the latency time (sec) of mice (n=6) on the hot plate.* represent the P<0.05 values significant from vehicle control.

Anti-inflammatory activity

Carrageenan-induced rat paw oedema method

The injection of the carrageenan in paw created an inflammatory oedema which increased gradually. MECT at the dose of 300 mg/kg (Figure 4) exhibited an anti-inflammatory activity that became significant (P<0.05) 3 h after the injection of

carrageenan and was maintained all along the experiment with a maximum effect of 57.14%. MECT (30, 100 and 300 mg/kg) induced significant ($P<0.05$) anti-inflammatory effect and the anti-inflammatory effect of indomethacin (25 mg/kg) was greater than that of MECT (30, 100 and 300 mg/kg) as presented in Table 3.

Table 3. Effect of single dose of standardized methanolic extract of *Coptis teeta* (MECT; 30, 100 and 300 mg/kg) on percentage inhibition in paw oedema (ml) on carrageenan induced paw oedema test in rats

S. No.	Treatment group	% inhibition
1	Vehicle control	-
2	Indomethacin-25 mg/kg	71.43
3	MECT-30 mg/kg	35.06
4	MECT-100 mg/kg	48.05
5	MECT-300 mg/kg	57.14

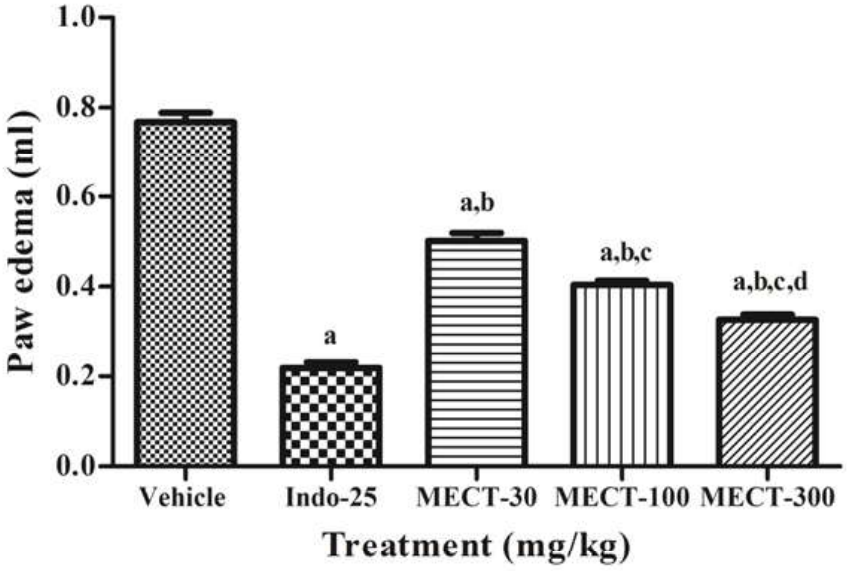

Figure 4. Effect of single dose treatment of standardized methanolic extract of *Coptis teeta* (MECT; 30,100 and 300 mg/kg) and Indomethacin (Indo; 25 mg/kg) in carrageenan induced paw edema test on rats. Each column represents Mean ± SEM the paw edema (ml) of rats (n = 6). a, b, c and d symbolize statistically significant values from vehicle control ($^{a}P<0.05$), Indomethacin-25 mg/kg ($^{b}P<0.05$), MECT-30 mg/kg ($^{c}P<0.05$) and MECT-100 mg/kg ($^{d}P<0.05$) respectively.

3.5.2 Cotton - pellet granuloma test

The anti-inflammatory activity at test doses (30, 100 and 300 mg/kg) of MECT is presented in Table 4 with percentage inhibition of granuloma. A dose-dependent decrease for MECT (30 mg/kg to 300 mg/kg) in granuloma was observed as shown in Figure 5. The percentage inhibition in granuloma was found to be highest in the case of MECT (300 mg/kg) which was 50.14%. Whereas the percentage inhibition in granuloma for standard drug indomethacin (10 mg/kg) was found to be 64.11%.

Table 4. Effect of repeated daily doses (for 14 days) of standardized methanolic extract of *Coptis teeta* (MECT; 30, 100 and 300 mg/kg) on percentage inhibition in granuloma on cotton pellet granuloma test using rats

S. No.	Treatment group	% inhibition in granuloma
1	Vehicle control	-
2	Indomethacin-10 mg/kg	64.11
3	MECT -30 mg/kg	21.88
4	MECT -100 mg/kg	45.31
5	MECT -300 mg/kg	50.14

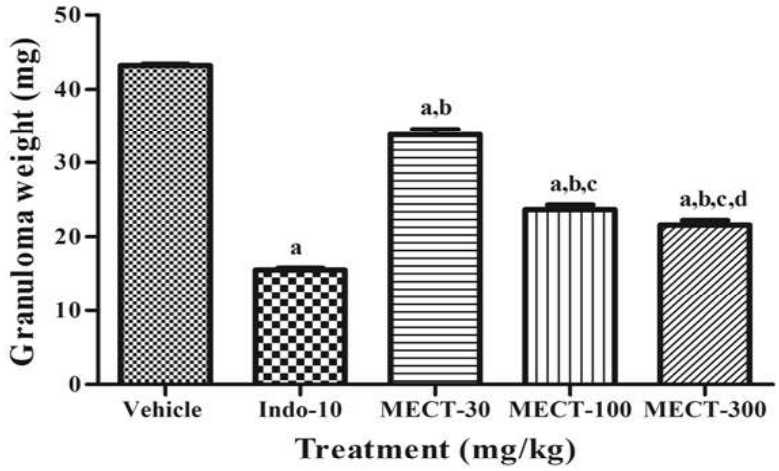

Figure 5. Effect of repeated daily doses (for 14 days) of standardized methanolic extract of *Coptis teeta* (MECT; 30,100 and 300 mg/kg) and Indomethacin (Indo; 10 mg/kg) on granuloma by induction of cotton pellet in rats. Each column represents Mean ± SEM of granuloma weight (mg) of group of rats (n =6). a, b, c and d indicated statistically significant values from vehicle control ($^{a}P<0.05$), Indomethacin-10 mg/kg ($^{b}P<0.05$), MECT-30 mg/kg ($^{c}P<0.05$) and MECT-100 mg/kg ($^{d}P<0.05$) respectively.

Discussion

Acetic acid-induced writhing is a well-recommended protocol in evaluating medicinal agents for their analgesic property. The pain induction caused by liberating endogenous substances as well as some other pain mediators such as arachidonic acid via cyclooxygenase, and prostaglandin biosynthesis (Shakya *et al* 2012). This pain paradigm is widely used for the assessment of peripheral analgesic activity due to its sensitivity and response to the compounds at a dose which is not effective in other methods. The local peritoneal receptor could be the cause of abdominal writhings (Mbiantcha *et al* 2011). Pain sensation in acetic acid induced writhing paradigm is elicited by producing localised inflammatory response due to the release of free arachidonic acid from tissue phospholipids via cyclo-oxygenase (COX), and producing prostaglandin specifically PGE 2 and PGF 2α, the level of lipoxygenase products may also increase in peritoneal fluids. These prostaglandin and lipoxygenase products cause inflammation and pain by increasing capillary permeability. The substance inhibiting the writhings will have analgesic effect preferably by inhibition of prostaglandin synthesis, a peripheral mechanism of pain inhibition (Duarte *et al* 1988). Regarding the results of MECT in acetic acid-induced abdominal constriction assay, a prominent inhibition of writhing reflex was observed. These findings strongly recommend that MECT has peripheral analgesic activity and their mechanisms of action may be mediated through inhibition of local peritoneal receptors which may be the involvement of COX inhibition potential. The profound analgesic activity of MECT may be due to the interference of their active principle(s) with the release of pain mediators. Thermal nociception model, the hot plate test was used to evaluate central analgesic activity. MECT showed significant ($P<0.05$) analgesic effect in the hot plate test, implicating both spinal and supraspinal analgesic pathways. In the pain paradigms, tramadol, which is similar to the action of opioid agonists (e.g. morphine) and MECT raised the pain threshold level within 30 min of administration. This similarity in the maximum analgesic point could be explained by the similarity in the metabolic rate of each drug. But the potency of tramadol was found to be higher than MECT (300 mg/kg). Carrageenan-induced paw oedema, as well as cotton pellet granuloma test, are well-established animal models to assess the anti-inflammatory effect of natural products as well as synthetic chemical compounds. Oedema formation due to carrageenan in the paw is a biphasic event, during 1–2 hour; the initial phase (1h) is predominately a non-phagocytic oedema followed by a second phase (2–3) hour with increased oedema formation that remained up to 3h. The initial phase has been induced due to the action of mediators such as histamine, serotonin and bradykinin on vascular permeability (Maity *et al* 1998). The late phase or second phase oedema has been shown to be the result of overproduction of prostaglandins (Perez-Guerrero *et al* 2001). The result of pre-treatment of MECT demonstrated that the extract (30, 100 and 300 mg/kg, *p.o.*) is effective in the early phase of inflammation which is due to release of histamine and

serotonin primarily. The anti-inflammatory effect of the extract remains significant up to a 3rd hour of the experiment. In cotton pellet-induced granuloma model, a significant ($P < 0.05$) reduction in dry granuloma weight was observed in the MECT treated groups as compared to control. Cotton pellet-induced granuloma formation is considered to be a reliable experimental model for evaluation of effects on macrophage dysfunction and granuloma formation, central players in the formation, maintenance and progression of granulomas in various disease states. Efficacy of MECT in this model is therefore depictive of inhibitory activity against macrophage activation, infiltration, and aggregation.

Conclusion

As indicated by the available literature (Tang and Eisenbrand 1992; Sun and Tseng 2005) and the results of the preparative TLC and the subsequent standardization by HPTLC during the course of the present study suggested that Berberine is present in the MECT. Results of the present study showed that standardized MECT has marked analgesic and anti-inflammatory effects with a reasonable safety profile. Therefore, the current findings can be attributed to protoberberine group of chemical compounds. Further study is needed on MECT to find the exact mechanism of action for its analgesic and anti-inflammatory effects. However, there is still room for improvement as MECT was not isolated for its individual components, which can further increase its efficacy as a drug of choice for a huge number of ailments owing to its better safety profile and tremendous ethnomedicinal potential.

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