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Antinociceptive Activity Evaluation of an Indonesian Herbal Preparation Cleng Marem

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ABSTRACT

The antinociceptive activity of an Indonesian Jamu herbal product Cleng Marem was evaluated by acetic acid-induced abdominal pain model in mice. The product, when administered at doses of 50, 100, and 200 mg per kg body weight in mice, decreased the number of pain-induced abdominal constrictions (writhings) in mice, respectively, by 34.5, 41.4, and 48.3%. At a dose of 25 mg per kg body weight, there was no alleviation of pain as measured by the number of writhings. A standard antinociceptive drug, aspirin, when administered at a dose of 200 mg per kg body weight in mice, reduced the number of writhings by 37.9%. Thus the product can be considered an effective herbal preparation for alleviation of pain. Since herbal preparations can be more available at cheaper prices than standard allopathic pain-killing drugs, such products merit further scientific attention to attest to their efficacy and possible side-effects.

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INTRODUCTION

Pain is a feeling triggered in the nervous system and may be sharp or dull. It may be acute, which may arise from causes such as burns or stubbing a finger, or it may be acute, where it can be caused by a multitude of factors like cancer, rheumatism, or migraine. Chronic pain affects an estimated 86 million American adults to some degree. A number of over the counter (OTC) drugs like aspirin or acetaminophen are available for alleviation of pain, but these drugs suffer from adverse side-effects if taken for long time periods or over dosage. For instance, heavy ingestion of aspirin has been linked to perforated peptic ulceration [11]. It has been reported that acetaminophen causes a potentially fatal, hepatic centrilobular necrosis when taken in overdose [18]. Other opioid drugs like codeine or morphine can cause severe addictive problems. As a result, new pain alleviating drugs without the adverse side-effects can prove beneficial to human beings suffering pain for prolonged time periods.

Herbal formulations have been claimed as a safer way to get relief from pain without having any adverse side-effects. Traditional herbalists in many countries have such formulations, which are claimed to be effective pain relievers. A number of ethnomedicinal studies have also documented use of selective plant species against pain. For instance, the plant *Solanum marginatum* has been reported to be used by the Ethiopian people of the Kilte Awulaelo district, Tigray region of Ethiopia for treatment of abdominal pain [51]. The six tribal communities, namely, Malappandaran, Urali, Maya-arayan, Ulladan, Malavedan, and Malakurava of Pathanamthitta district, Kerala, India use several plant species like *Asparagus racemosus*, *Celastrus paniculatus*, *Elaeagnus conferta*, *Flemingia strobilifera*, *Gouania microcarpa*, *Helicteres isora*, *Kunstleria keralensis*, *Myristica malabarica*, and *Sphenodesme involucrata* for treatment of body pain [9]. Stems of *Alangium salviifolium* and rhizomes of *Alpinia calcarata* are used by the Paliyan tribes of Sirumalai Hills of southern India to treat stomach pain [19]. The traditional Jamu medicine of Indonesia also has a number of herbal formulations to deal with pain arising from various conditions like stomach problems or rheumatism.

Ethnomedicinal surveys among the folk and tribal medicinal practitioners of Bangladesh are being conducted for the last several years by our research team members [24-33,35-40]. From the information obtained from the traditional healers, further studies are conducted on selected floral species towards evaluation of their antinociceptive, antihyperglycemic, and cytotoxic potential [6,15,22,34,48,5,8,14,15,23,50,3,7,13,46]. Pain-alleviating plants have formed a major part of our ethnomedicinal surveys and pharmacological studies not

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only to evaluate their potential as alternate medications, but also because allopathic drugs are difficult to get, particularly in the remote villages of Bangladesh.

Towards an extension of our research on pain relieving plants, we have recently started to conduct pharmacological (particularly antinociceptive activity) studies on medicinal plant formulations of other countries. In this connection, antinociceptive activity studies have been conducted with a number of Indonesian traditional Jamu herbal products like Pegal Linu, Sendai, Ulu Hati, Sekalor, Anrat, and Donrat [45,4,1,44,20]. The objective of the present study was to evaluate the antinociceptive potential of another Indonesian Jamu herbal formulation, namely Cleng Marem.

MATERIALS AND METHODS

Cleng Marem Anoman Dasamuka was obtained from an herbal shop in Kuala Lumpur, Malaysia in 2012. The product was sold in 6g sealed packets, the contents of which were to be used for a single dosage. The front side of the packet (Fig 1) bore the title Jamu Cleng Marem. The front side also had the words DEPKES RI No. TR 773200651. The address of the manufacturer was given as Usaha, Abdulkadir, JI. KH. Dahlan Prapatan, Sucen Kajeksan no. 1, Kudus - Indonesia. Indications as mentioned on the reverse of the packet (translated into English by the authors) described the contents as "Useful for treating rheumatic diseases, lethargy, heavy work out, coughs and colds". Directions as mentioned on the reverse of each packet mentioned "Mix a sachet of Clem Mareng (± 6g) into a half glass of boiled water (100 cc). Take twice a week. Pregnant woman should not take; may cause abnormalities in fetus" (Fig 2). The composition as described on the reverse side of the packet mentioned Pipiris Pructus – 10%; Zingeberis Rhisoma – 4%; Cinamoni Cortex – 3%; Curcuma Rhisoma – 4%; Dan bahan lain – 79%; and Jumlah – 100%.

Fig. 1: Cleng Marem packet viewed from the front side.

Experimental dosages for mice experiments were determined on the basis of the packet information of 6g per human being, the average weight of a human being taken as 70 kg, i.e. nearly 1g per 10 kg body weight, or 100 mg per kg body weight. The various doses for experimental purposes were fixed based on this afore-mentioned calculation as 25, 50, 100 and 200 mg per kg body weight of mice. Stock solution of Cleng Marem was made by suspending 1g of packet contents (powder) in 10 ml distilled water.

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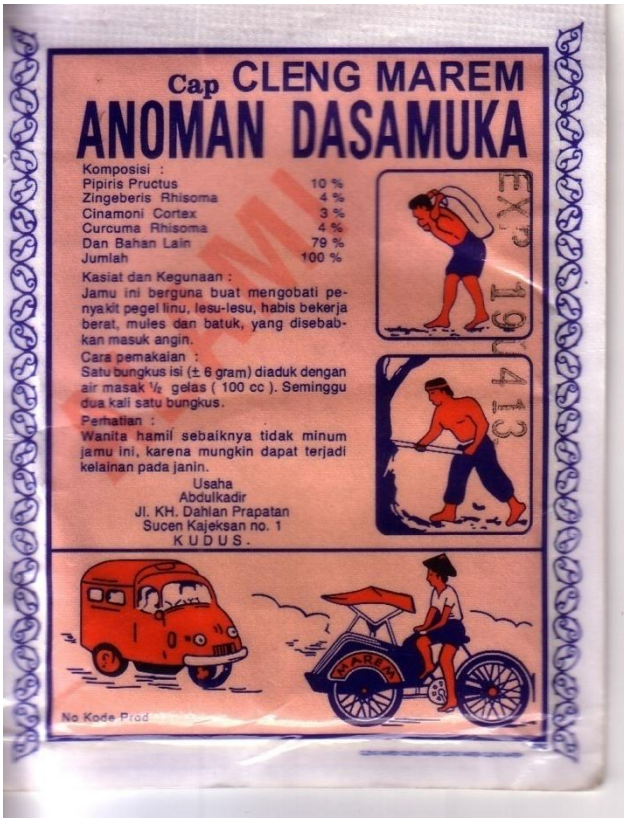

Fig. 2: Cleng Marem packet viewed from the reverse side.

Chemicals:

Glacial acetic acid was obtained from Sigma Chemicals, USA; aspirin was obtained from Square Pharmaceuticals Ltd., Bangladesh.

Animals:

In the present study, Swiss albino mice (male), which weighed between 15-18g were used. The animals were obtained from International Centre for Diarrheal Disease Research, Bangladesh (ICDDR,B). All animals were kept under ambient temperature with 12h light followed by a 12h dark cycle. The animals were acclimatized for three days prior to actual experiments. The study was conducted following approval by the Institutional Animal Ethical Committee of University of Development Alternative, Dhaka, Bangladesh.

Antinociceptive activity:

Antinociceptive activity of Cleng Marem was examined using previously described procedures [47], in which method, pain was induced in mice through intraperitoneal administration of acetic acid. Briefly, mice were divided into six groups of five mice each. Group 1 served as control and was administered vehicle only. Group 2 was orally administered the standard antinociceptive drug aspirin at a dose of 200 mg per kg body weight. Groups 3-6 were administered Cleng Marem at doses of 25, 50, 100 and 200 mg per kg body weight, respectively. All mice were individually weighed and dose determined on the basis of individual weight. Following a period of 60 minutes after oral administration of standard drug or extract, all mice were intraperitoneally injected with 1% acetic acid at a dose of 10 ml per kg body weight. A period of 15 minutes was given to each animal to ensure bio-availability of acetic acid, following which period, the number of abdominal constrictions was counted for 10 min.

Statistical analysis:

Experimental values are expressed as mean ± SEM. Independent Sample t-test was carried out for statistical comparison. Statistical significance was considered to be indicated by a p value < 0.05 in all cases.

RESULTS AND DISCUSSION

Intraperitoneal administration of acetic acid results in pain in mice, which is manifested by abdominal constrictions or writhings. The number of writhings indicates the measure of pain and any decrease in the

number of writhings through administration of any substance indicates the efficacy of the substance in alleviating pain. Cleng Marem, at doses of 50, 100, and 200 mg per kg body weight, was observed to dose-dependently and significantly reduce the number of writhings in mice. At these three doses, the number of writhings decreased, respectively, by 34.5, 41.4, and 48.3%. Cleng Marem had no effect at all on pain alleviation when administered at a dose of 25 mg per kg body weight. A standard antinociceptive drug, aspirin, when administered at a dose of 200 mg per kg body weight, decreased the number of writhings by 37.9%. The results are shown in Table 1 and suggest that Cleng Marem can act as a pain relieving agent.

Table 1: Antinociceptive effect of Cleng Marem in acetic acid-induced gastric pain model mice.

Treatment	Dose (mg/kg body weight)	Mean number of writhings	% inhibition
Control (Group 1)	10 ml	5.80 ± 0.86	-
Aspirin (Group 2)	200 mg	3.60 ± 0.73	37.9*
Cleng Marem (Group 3)	25 mg	5.80 ± 0.97	-
Cleng Marem (Group 4)	50 mg	3.80 ± 0.37	34.5*
Cleng Marem (Group 5)	100 mg	3.40 ± 0.60	41.4*
Cleng Marem (Group 6)	200 mg	3.00 ± 0.71	48.3*

All administrations (aspirin and Cleng Marem) were made orally. Values represented as mean ± SEM, (n=5); $*P < 0.05$; significant compared to control.

Any sensation of pain has been attributed to increase in the expression of prostaglandins [mainly prostacyclines (PGI2) and prostaglandin- (PG-E)] [43,42. Intraperitoneal administration of acetic acid releases and so increases levels of prostaglandins like PGE2 and PGF2alpha [10]. As such, the antinociceptive activity exhibited by Cleng Marem may be due to the formulation's ability to block any further expression of prostaglandins, which may be mediated through inhibition of cyclooxygenase and/or lipooxygenase activities. It is noteworthy that a similar mechanism has been proposed for antinociceptive activity of *Ficus deltoidea* Jack (Moraceae) aqueous extract in acetic acid-induced gastric pain model [49].

The herbal product, as per the information provided contains a number of plant components. Of the various plant components described, piperine is present in *Piper* species fruits. The analgesic activities of piperine have been reviewed [2]. The analgesic and anti-pyretic activities of *Curcuma longa* (synonym: *Curcuma domestica*) rhizome extracts (which contain curcumin) has been shown in rats [21]. The anti-inflammatory and analgesic properties of *Zingiber officinale* rhizome extract has also been shown [41]. The anti-inflammatory and analgesic properyies of *Cinnamomum zeylanicum* leaf oil has been shown [12]. Thus it can be said that Cleng Marem contains herbal ingredients which may produce a synergistic effect in alleviating pain and so deserves further scientific analysis.

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Authors of this study have no financial interest in any of the product(s) or manufacturer(s) mentioned in this article.

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