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RESEARCH ARTICLE

Antinociceptive, anti-inflammatory and antipyretic properties of an aqueous extract of *Corchorus capsularis* leaves in experimental animal models

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Abstract

The present study was carried out to establish the antinociceptive, anti-inflammatory and antipyretic properties of an aqueous extract of jute plant leaves, *Corchorus capsularis* L. (Tiliaceae), in experimental animals. The antinociceptive activity was measured using the abdominal constriction, hot plate and formalin tests, while the anti-inflammatory and antipyretic activities were measured using the carrageenan-induced paw edema and brewer's yeast-induced pyrexia tests, respectively. The extract, obtained after 72 h soaking of the air-dried leaves in distilled water, freeze-drying for 72 h and then prepared in dosages of 11.57, 57.85, and 115.7 mg/kg, was administered subcutaneously (10 ml/kg) 30 min prior to subjection to the above mentioned assays. The extract was found to exhibit significant (antinociceptive, anti-inflammatory and anti-pyretic, activities in a dosage-independent manner. In conclusion, the aqueous extract of *C. capsularis* possesses antinociceptive and antipyretic activities and supports the previous claim of its traditional use to treat various ailments.

Keywords: *Corchorus capsularis; aqueous extract; antinociceptive; anti-inflammatory; antipyretic; dosage-independent*

Introduction

Corchorus capsularis L. (Tiliaceae) is a jute plant also known to the Malays as *kancing baju* (PFAF, 2004). *C. capsularis* leaves have been eaten as vegetables in Africa, the Middle East, and Southeast Asia, including Malaysia, for a long time; in Bangladesh, particularly, *C. capsularis* is used as a vegetable more than *C. olitorius* L. due to the bitter taste of the latter (EBPS, 2006). The leaves, which are the most edible part of *C. capsularis*, are directly added to salad if they are younger leaves or cooked as a pot-herb if they are older leaves. The dried leaves are also used as a thickener in soups but usually prepared as tea (PFAF, 2004). In addition, the Japanese have been using the leaves of *C. capsularis* as health-food, in which the dry leaves were substituted for coffee or tea. Traditionally, the leaves of *C. capsularis* are used as demulcent, appetizer, laxative, carminative, stomachic and stimulant, while its infusion is used in the treatment of fevers, dysentery, constipation, dyspepsia and liver disorders (PFAF, 2004). In addition, a decoction of the roots and unripe fruits can also be used to treat dysentery while the seeds, which contain a substance that produced a less intense action on the heart when compared to digitalin, are used in the treatment of heart problems (PFAF, 2004).

Due to lack of scientific studies to support its traditional use as demulcent and pyrexia relieving agent, as well as to establish its other potential pharmacological properties, this study was undertaken to evaluate the antinociceptive, anti-inflammatory and antipyretic properties of an aqueous extract of *C. capsularis* (AECC) leaves.

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Materials and methods

Plant material

The leaves of *C. capsularis* were collected in July–September, 2005 from its natural habitat in Kg. Kuala Kangkong, Simpang Ampat, Alor Setar, Kedah, Malaysia by Mohd. Suhaimi Ismail. It was identified by Shamsul Khamis, a botanist at the Institute of Bioscience (IBS), Universiti Putra Malaysia, (UPM), Serdang, Selangor, Malaysia, and a voucher specimen (SK 856/05) was deposited at the Herbarium of the Laboratory of Natural Products, IBS, UPM, Malaysia.

Preparation of an aqueous extract of C. capsularis

The leaves of *C. capsularis* were washed and rinsed with water to remove all the dirt and unwanted particles and then air-dried for 1-2 weeks at room temperature (27 ± 2°C). The dried leaves were then ground into powder form, weighed and added with distilled water (dH_2O) in a ratio of 1:20 (w/v). This mixture was then left for 72 h and the supernatant was collected and filtered using Whatman No. 1 filter paper while the remaining plant residue was kept in an oven for future use (i.e., extraction using an organic solvent such as chloroform for antimicrobial study). The supernatant obtained, labeled as AECC and considered as stock solution with 100% concentration/strength, was prepared in the concentrations/strengths of 10% and 50% by diluting the stock solution with dH_2O for the pharmacological studies described earlier. A 30 ml portion of the obtained supernatant was also subjected to freeze-drying process and yielded 0.347 g of crude dried AECC (23.13% of yield). Based on the amount of crude dried AECC obtained, it was estimated that the 10, 50, and 100% concentrations AECC were approximately equivalent to the dosages of 11.57, 57.85, and 115.7 mg/kg, respectively.

Preparation of drugs

Acetylsalicylic acid (ASA) (100 mg/kg; Bayer, Singapore) and morphine (5 mg/kg; Sigma, Germany), used for the purposed of comparison, were prepared by dissolving them in dH_2O.

Experimental animals

Male Balb-C mice (25-30 g; 5-7 weeks) and Sprague-Dawley rats (180-200 g; 8-10 weeks old), obtained from the Animal Source Unit, Faculty of Veterinary Medicine, Universiti Putra (UPM), Serdang, Selangor, Malaysia, were used in this study. All of the animals were kept at room temperature (27° ± 2°C; 70-80% humidity; 12 h light/darkness cycle) in the Animal Holding Unit, Faculty of Medical and Health Sciences, UPM for at least 48 h before use. Food and water were supplied *ad libitum* up to the beginning of the experiments. At all times the rats were cared for in accordance with current UPM principles and guidelines for the care of laboratory animals and the UPM ethical guidelines for investigations of experimental pain in conscious animals as adopted from Zimmermann (1983).

All mice were equally divided into 10 groups of 7 mice each (n = 7) and received (sc) DH_2O, ASA (100 mg/kg) or AECC (11.57, 57.85 or 115.7 mg/kg) 30 min prior to subjection to the abdominal constriction or hot plate tests, respectively. All rats were equally divided into 16 groups of 5 rats each (n = 5). The first batch, consisting of six groups of rats, were used in the formalin test and received (sc) dH_2O, 100 mg/kg ASA, 5 mg/kg morphine or AECC (11.57, 57.85, and 115.7 mg/kg), respectively, 30 min prior to subjection to the test. The second and third batches, consisting of five groups of rats each, were used in the anti-inflammatory and antipyretic studies, and received (sc) dH_2O, 100 mg/kg ASA or AECC (11.57, 57.85, or 115.7 mg/kg), respectively, 30 min prior to subjection to the said tests. All of the test solutions were administered in the volume of 10 ml/kg body weight.

Antinociceptive assay

Abdominal constriction test

The abdominal constriction test (Dambisya & Lee, 1995) was used with slight modifications as described by Zakaria et al. (2005) to evaluate the chemically induced peripheral antinociceptive activity of AECC.

Hot plate test

The 50°C hot-plate test (Wilson et al., 2003), with slight modification as described by Zakaria et al. (2005), was used to assess the thermally induced central antinociceptive activity of AECC.

Formalin test

The formalin test (Hunskaar & Hole, 1987) was used, with slight modifications as described by Zakaria et al. (2006a), to assess the non-anti-inflammatory, antinociceptive effects of AECC.

Anti-inflammatory assay

The carrageenan-induced paw edema test (Chakraborty et al., 2004) was used, with slight modification as described Zakaria et al. (2006a), to assess the anti-inflammatory properties of the AECC.

Antipyretic assay

The antipyretic activity of AECC was measured using the Brewer's yeast induced pyrexia test (Reanmongkol et al., 2002) with slight modifications (Zakaria et al., 2006b).

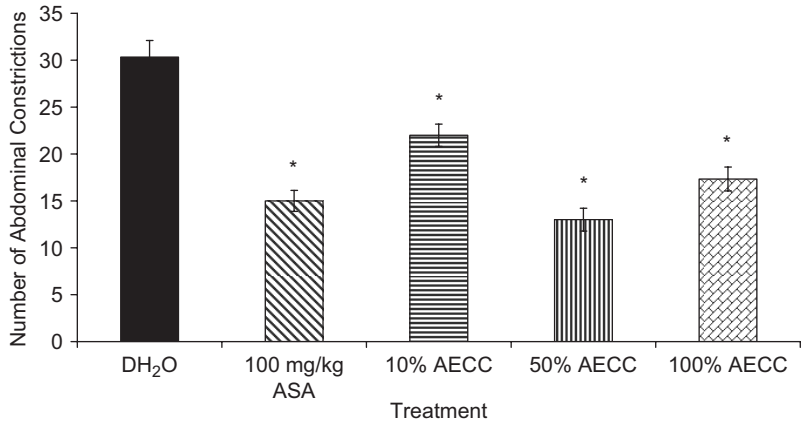

Figure 1. The antinociceptive profile of AECC assessed by the abdominal constriction test in mice.

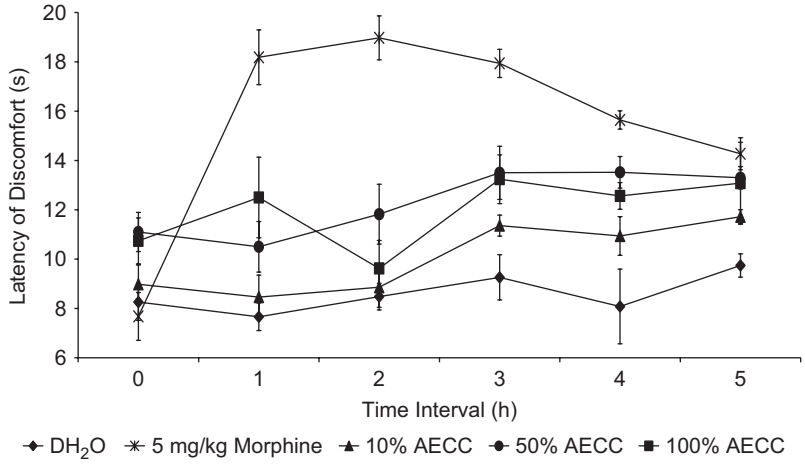

Figure 2. The antinociceptive profile of AECC assessed by the hot plate test in mice.

Statistical analyses

The results are presented as mean ± standard error of mean (SEM). Data for the abdominal constriction and formalin tests were analyzed and compared using the one-way ANOVA with Dunnett post-hoc test while the formalin, paw edema and pyrexia tests were analyzed and compared using the two-way ANOVA, with $P < 0.05$ as the limit of significance.

Results

Figure 1 shows the antinociceptive profile of AECC assessed using the acetic acid-induced abdominal constriction test in mice. The extract exhibited a dosage-dependent antinociception as seen in the first two dosages used followed by a significant ($P < 0.05$) decreased but still retained activity. Interestingly, the 57.85 mg/kg AECC produced an antinociception that was equipotent to that of 10 mg/kg ASA.

Figure 2 shows the antinociceptive profile of AECC assessed using the hot plate test in mice. The AECC was also found to show a dosage-dependent antinociception for the first two dosages used. However, the 115.7 mg/kg AECC showed an inconsistent activity, at least for the first two hours of the time interval. Unexpectedly, the 115.7 mg/kg AECC did not produce significant effect on the latency of discomfort after 30 min of its administration when compared to the other two dosages of AECC. Furthermore, the AECC-produced antinociception lasted until the end of the experiment.

Figure 3 shows the antinociceptive profile of AECC assessed using the formalin test in rats. The extract was found to produce significant ($P < 0.05$) antinociception in the early and late phases of the test in a non-dosage-dependent manner. The AECC, at all of the dosages used, produced an equieffective activity in the early phase. However, in the late phase, the extract's antinocicepetion decreased slightly as the dosages of AECC increased from 11.57 to 57.85 mg/kg before

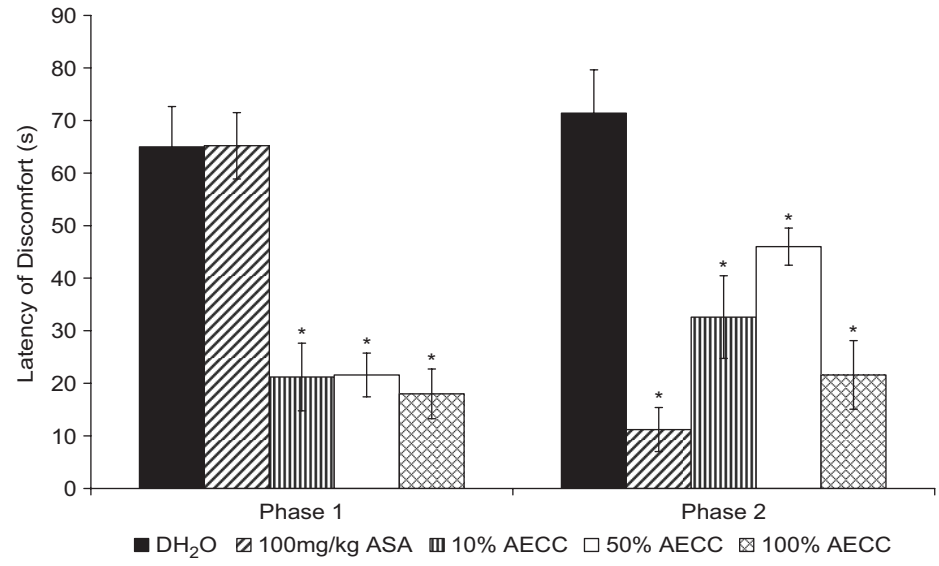

Figure 3. The antinociceptive profile of AECC assessed by the formalin test in rats.

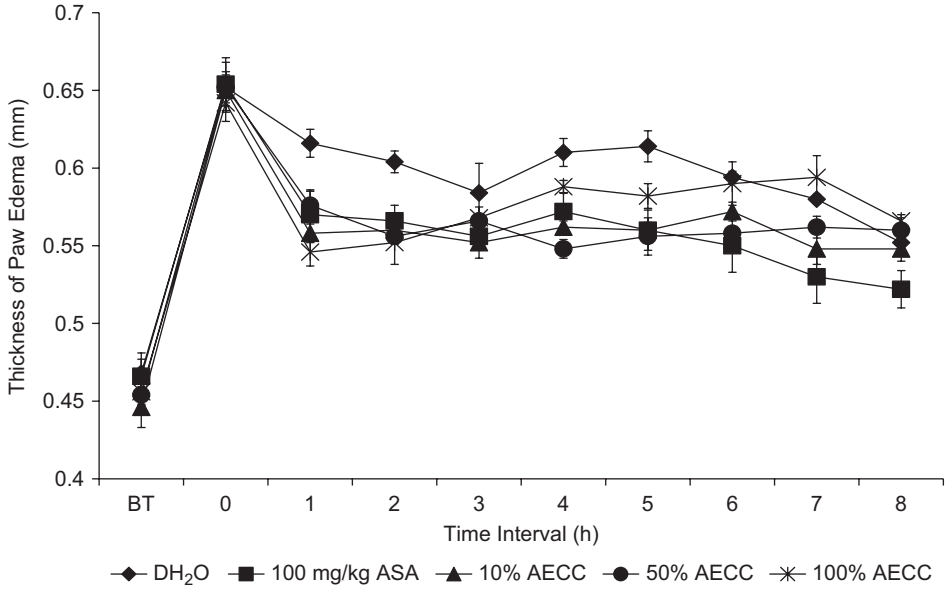

Figure 4. The anti-inflammatory profile of AECC assessed by the carrageenan-induced paw edema test in rats.

significantly (P <0.05) increasing as the dosage of AECC reached 115.7 mg/kg.

Figure 4 shows the anti-inflammatory profile of AECC assessed using the carrageenan-induced paw edema test in rats. The extract produced a significant (P <0.05) anti-inflammatory activity in a dosage-independent manner with the 115.7 mg/kg AECC exhibiting a less remarkable activity as indicated by its low reduction between the interval time of 4-5 h when compared to the other dosages of AECC. Interestingly, all dosages of the AECC lost their anti-inflammatory activity at the end of the experiment.

Figure 5 shows the antipyretic profile of AECC assessed using the Brewer's yeast (BY)-induced pyrexia in rats. The extract produced an antipyretic activity only for the first four hours regardless of the dosages of AECC used. The dosage-dependent antipyretic activity was observed between the 57.85 and 115.7 mg/kg of the AECC. The 11.57 mg/kg AECC was found to produce an activity that was as effective as that of the 57.85 mg/kg AECC. Interestingly, the AECC antipyretic activity started to diminish after 4 h of its administration regardless of the dosage used.

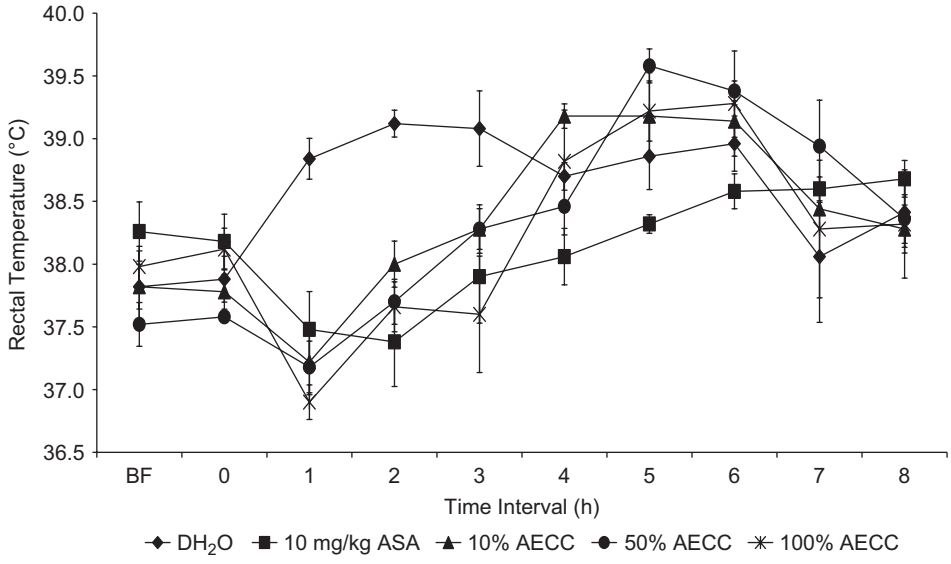

Figure 5. The antipyretic profile of AECC assessed by the brewer's yeast-induced pyrexia test in rats.

Table 1. Phytochemical constituents of *C. capsularis*.

Constituents	*C. capsularis*
Flavonoids	++
Triterpenes	+
Tannins	-
Alkaloids	-
Saponins	+
Steroids	++

For saponins = + – 1-2 cm froth; ++ – 2-3 cm froth; +++ – >3 cm froth
For flavonoids, tannins, triterpenes and steroids = + – weak colour; ++ – mild colour; +++ – strong colour
For alkaloids = + – negligible amount of precipitate; ++ – weak precipitate; +++ – strong precipitate

Discussion

The present study has proven the potential of AECC as antinociceptive, anti-inflammatory, and antipyretic agents, and confirmed the traditional use of *C. capsularis* leaves infusion in the treatment of fever. The AECC was found to exhibit a dosage-independent antinociceptive activity when assessed using the abdominal constriction, hot plate and formalin tests indicating its effectiveness in blocking the nociception induced by chemical and thermal stimuli. The ability to directly stimulate the nociceptor and inhibit the inflammatory mediators releases are suggested since the AECC was also found to exhibit an antinociceptive activity in both phases of the formalin test.

The abdominal constriction test is a very sensitive test since it was able to detect antinociception of compounds/dose levels that may be inactive in other tests like the hot plate or tail-flick tests (Bentley et al., 1981). The assay involved the local peritoneal receptor system stimulation (Bentley et al., 1983) and is due to the prolonged acetic acid-induced irritation of the peritoneal cavity (Deraedt et al., 1980). This will lead to an increase in the prostaglandins levels of peritoneal fluid, which will, in turn, enhance inflammatory pain by increasing the capillary permeability (Vogel & Vogel, 1997). According to Chan et al. (1995), this assay is not specific since it did not specify the involvement of peripheral or central activity. The hot plate and formalin assays are usually performed together with the abdominal constriction test before a final conclusion could be made on the type of mechanism involved in any antinociceptive agents under investigation.

The hot plate test, which measures the complex response to a non-inflammatory, acute nociceptive input, is usually used to indicate the involvement of central antinociceptive mechanism (Pini et al., 1997). Drugs acting centrally inhibit the abdominal constriction and hot plate tests (Hosseinzadeh & Younesi, 2002) while those acting peripherally inhibit only the abdominal constriction test (Amanlou et al., 2005). The activity seen with the hot plate test suggested the ability of AECC to affect the central nociceptive mechanism.

According to Heapy et al. (1987), the injection of formalin into the paw of rat causes an immediate and intense increase in the spontaneous activity of C fiber afferent and evokes a distinct quantifiable behavior indicative of pain (i.e., licking of the injected paw). The formalin test produced a distinct biphasic nociceptive response labeled as the early and late phases (Malmberg & Yaksh, 1992). The early phase is an acute response observed immediately after the administration of formalin and persists for 5 min while the late phase appears between 15 and 60 min after the formalin administration. According to Tjølsen et al. (1992), the acute early phase appeared as a result of direct stimulation of nociceptors by formalin, while the late

tonic phase involved the inflammatory processes and activation of the neurons located in the dorsal horns of the spinal cord. Due to their different properties, the early and late phases have been regarded as very useful tools for assessing the effectiveness of pain relieving compounds and expounding the actual mechanism(s) involved. In terms of this activity, drugs that act centrally (i.e., opioids) have been demonstrated to affect both phases while drugs that act peripherally (i.e., NSAIDs) only influence the late phase (Chan et al., 1995). Cowan (1990) has also suggested the use of formalin test in the assessment of pain relieving agents potential in combating chronic pain due to inflammation. The AECC was demonstrated to affect both phases of the said test which is concomitant with the activity shown by centrally acting analgesic drugs (Chan et al., 1995).

The carrageenan-induced rat paw edema test has been widely used to study the potential anti-inflammatory properties of newly developed drugs or newly discovered natural products (Winter et al., 1962; Chan et al., 1995). The release of kinins, polymorphonuclear leucocytes as well as their proinflammatory factors (i.e., prostaglandins) have been suggested as contributing to the development of edema (Damas et al., 1986). The inflammation caused by carrageenan administration has been categorized into the early and late phases (Vineger et al., 1969; Süleyman et al., 2004). The former was thought to be caused by serotonin and histamine release and observed around 60 min after the irritant administration (Crunkhon & Meacock, 1971) while the latter was thought to be caused by the release of inflammatory mediators (i.e., prostaglandin-like compounds) (Vineger et al., 1969). In line with the claim made by Vineger et al. (1969), the steroidal and non-steroidal anti-inflammatory agents were very effective in inhibiting the late phase (Di Rosa et al., 1971). The significant reduction of paw edema seen with all dosages of the AECC does indicate the presence of anti-inflammatory activity in the said extract. This finding has scientifically confirmed the folklore use of *C. capsularis* leaves as a demulcent. Furthermore, this finding was in line with the claim that compounds with anti-inflammatory activity also possess antinociceptive activity (Attaway & Zaborsky, 1993).

The AECC was also found to possess antipyretic activity when assessed using the BY-induced pyrexia test. This finding has scientifically confirmed the Malay traditional practice of using *C. capsularis* leaves in the treatment of pyrexia or to lower the body temperature. The ability to reduce pyrexia indicates the ability of the extract to cross the blood-brain barrier (BBB) (Begley et al., 2000) since the pyrexia mechanism involved the stimulation of a region that controls the body temperature within the hypothalamus by the centrally synthesized prostaglandin (Uzcátegui et al., 2004). The ability to cross the BBB could also be the key factor that leads to the observed antinociceptive activity that was assessed using the hot plate test.

The term 'therapeutic window' described by Tripathi (2001) could be used to explain the concentration-independent effect of AECC seen in most of the assays. It is a phenomenon in which a certain desired therapeutic effect of a drug is exerted only within a narrow drug dosages or plasma drug concentrations range. According to Tripathi (2001), drugs with therapeutic window phenomenon will produce suboptimal beneficial effects or even decline in effects if the concentrations are below or above this narrow therapeutic range.

Although extensive study on the pharmacological potential of *C. capsularis* active constituents has never been carried out, previous studies have revealed the presence of dammarane triterpene (Hasan et al., 1984), glycoside (Quader et al., 1990), phenolic acids (Mosihuzzaman et al., 1986), xylans (Vignon & Gey, 1998), proteins and amino acids (Ghosh & Raksit, 1994) and carbohydrates (Mosihuzzaman et al., 1989) in various parts of the plant. Of these compounds, dammarane triterpene glycoside (3-glucoside of 20,24-epoxy-3β,12β,25,30-tetrahydroxy-dammarane) and glycoside (25,30-*O*-β-digluco-pyranoside) have been reported to be present in the leaves of *C. capsularis*. A study carried out by Yoshikawa et al. (1997) has demonstrated the presence of dammarane-type triterpene oligoglycosides in the seeds of *Zizyphus jujube*, which were also found to inhibit the release of histamine from rat peritoneal exudate cells induced by antigen-antibody-reaction. Although it has never been proven with the dammarane-type triterpene glycoside of *C. capsularis*, it is plausible to suggest that the ability of the AECC to produce the anti-inflammatory and antinociceptive activities could be due, partly, to the ability of this compound to inhibit the histamine release as mentioned earlier. Finally, we conclude that the AECC possessed antinociceptive, anti-inflammatory, and antipyretic activities and, thus, confirmed its traditional uses in the treatment of various ailments.

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***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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