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Anti-Inflammatory and Antipyretic Effects of an Ethanolic Extract of *Capparis erythrocarpos* Isert Roots

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ABSTRACT

Capparis erythrocarpos Isert (Caparaceae) is a plant used traditionally in Ghana for the treatment of inflammation, fever and pain. The aim of the study was to assess the activity of an ethanolic extract of *Capparis erythrocarpos* Isert roots in the carrageenan-induced foot oedema model in chicks, an acute inflammatory model and baker's yeast-induced pyrexia in rats. Pre-treatment with the extract (10-300 mg kg^{-1}; p.o.) significantly inhibited foot oedema in the chicks with maximal inhibition of 48.86±20.41%; however, the effect was U-shaped. The reference NSAID used, diclofenac (10-100 mg kg^{-1}, i.p.), dose-dependently reduced the oedema with a maximal effect of 58.77±17.15%. Similarly, the steroidal anti-inflammatory drug, dexamethasone (0.3-3 mg kg^{-1}, i.p.), completely inhibited the oedema produced dose-dependently. The effect of the extract on pyrexia was also appreciable. *C. erythrocarpos* (30-300 mg kg^{-1}; p.o.), significantly and dose-dependently decreased baker's yeast induced fever. Paracetamol (10-100 mg kg^{-1}; p.o.), used as the reference drug also dose-dependently decreased baker's yeast induced pyrexia. In summary, *C. erythrocarpos* has anti-inflammatory and antipyretic activity and these findings support the use of the extract in traditional medicine for treating inflammatory conditions.

Key words: Carrageenan, inflammation, chicks, yeast, pyrexia, rats

INTRODUCTION

In Ghana, several medicinal plants are used alone or in combination with orthodox medicines in the treatment of inflammation, fever and pain. *Capparis erythrocarpos* Isert (Family Caparaceae) is one of such plants. Locally, in Ashanti it is known as *woresenakyiame* (salute me when passing); Ewe aŋŋo (Thorns); Fante *okyerabran* (giant catcher); Ga aŋmaŋma and Twi *apana* (Mshana *et al*., 2000).

The plant *C. erythrocarpos* is an indigenous plant common in thickets of the coastal scrub and also in fringing forests (Irvine, 1961). It is used for swellings of the joints, rheumatism, conjunctivitis, otitis, mastitis, inflammatory pain and intermittent fevers (Abbiw, 1990). The roots are dried, powdered and one teaspoonful of the powder is added to beverage or soup and taken twice daily for rheumatoid arthritis (Mshana *et al*., 2000).

Although, the medicinal uses and general safety of this plant are well known to the native people, its place is yet to be rationalized in therapeutics, using current methodology. Scientific

studies are therefore required to judge its efficacy and some of the medicinal properties popularly claimed, as well as other limitations to widen the scope of this drug. The fact that traditional health care and the use of medicinal plants is familiar, affordable and available at the local level is enough evidence to suggest that it will continue to play an important role in national healthcare delivery of most countries well into the twenty-first century.

Apart from the antinociceptive effect of *Capparis erythrocarpos* Isert roots reported by Woode *et al.* (2009a) not much work has been done on this plant. However, other medicinal plants that are being used traditionally have been validated scientifically to have anti-inflammatory and antipyretic effects (Akindele and Adeyemi, 2007; Gupta *et al.*, 2007; Boakye-Gyasi *et al.*, 2008; Woode *et al.*, 2009b).

This study therefore was to investigate the anti-inflammatory properties of the extract in carrageenan-induced foot oedema in chicks. Intraplantar injection of carrageenan into the footpad of the 7-day-old chick has been found to elicit a measurable, reliable and relatively short lasting state of oedema that is differentially attenuated by systemic administration of typical anti-inflammatory compounds (Roach and Sufka, 2003). The yeast-induced hyperthermia in rats described by Tomazetti *et al.* (2005) was also employed to investigate the antipyretic activity of the extract.

MATERIALS AND METHODS

Plant material: Roots of the plant *C. erythrocarpos* were obtained and authenticated at the Centre for Scientific Research into Plant Medicine (CSRPM), Mampong-Akwapim, Ghana and a voucher specimen (No. FP/08/024) was kept in the Faculty of Pharmacy Herbarium. This study was conducted from September 2007 to May 2008.

Preparation of extract: The roots were chopped into pieces, sun-dried for four days and powdered using a hammer-mill. Cold maceration of the root powder using 70% (v/v) ethanol over a period of 6 days produced the ethanolic extract which was filtered and concentrated under reduced pressure at a temperature of 60°C in a rotary evaporator to yield a brown syrupy mass. This was dried on a water bath to obtain a brown semi solid which was air-dried at room temperature (29°C) for 24 h. The yield (9.0% w/w) was kept in a desiccator and is subsequently referred to as the extract or CEE.

Animals: Cockerels (*Gallus gallus*, strain Shaver 579, Akropong Farms, Kumasi, Ghana); (50-85 g) were obtained 1-day post-hatch and were housed in stainless steel cages (34×57×18 cm^3) at a population density of twelve chicks per cage. Food (Chick Mash, GAFCO, Tema, Ghana) and water were made readily available. Room temperature was maintained at 29°C and overhead incandescent illumination was maintained on a 12 h light-dark cycle. Daily maintenance of the cages was conducted during the first quarter of the light cycle. Chicks were tested at 7 days of age. Group sample sizes of five were utilized throughout the study.

Sprague-Dawley rats (120-200 g) of both sexes were purchased from Noguchi Memorial Institute for Medical Research, University of Ghana, Legon, Ghana and housed in the animal facility of the Department of Pharmacology, Kwame Nkrumah University of Science and Technology (KNUST). The animals were housed in groups of 6 in stainless steel cages

(34×57×18 cm^3) with soft wood shavings as bedding, fed with normal commercial pellet diet (GAFCO, Tema, Ghana), water available *ad libitum* and maintained under laboratory conditions (temperature 26-29°C, relative humidity 60-70% and 12 h light-dark cycle). The animals were transferred to the experimental room 2 h before the experiment for acclimatization to the environment. All procedures and techniques used in these studies were in accordance with the National Institute of Health Guidelines for the Care and Use of Laboratory Animals (NIH, Department of Health and Human Services publication No. 85-23, revised 1985) and were approved by the Departmental Ethics Committee (reference no. P/col/C12[E]).

Drugs and chemicals: Diclofenac sodium was purchased from Troge, Hamburg, Germany; dexamethasone from Pharm-Inter, Brussels, Belgium; paracetamol from Phyto-Riker Pharmaceuticals, Accra, Ghana, carrageenan sodium salt from Sigma-Aldrich Inc., St. Louis, MO, USA and baker's yeast from Saf do Brasil Produtos Alimenticias Ltd. Brazil.

Phytochemical analysis: The presence of saponins, tannins, alkaloids, triterpenes, flavonoids, glycosides and reducing sugars were tested by simple qualitative methods of Trease and Evans (1989) and Sofowora (1993).

Carrageenan-induced oedema: The carrageenan foot oedema model of inflammation in chicks previously described by Roach and Sufka (2003) with some modifications by Boakye-Gyasi *et al.* (2008) was used to evaluate the anti-inflammatory properties of the extract and compared to dexamethasone and diclofenac as reference drugs. Carrageenan (10 µL of 2% suspension in saline) was injected intraplantar into the right footpads of the chicks. Foot volume was measured before injection and at hourly intervals for 5 h after injection by water displacement plethysmography as described by Fereidoni *et al.* (2000). The oedema component of inflammation was quantified by measuring the difference in foot volume before carrageenan injection and at the various time points.

Effect of extract and drugs on carrageenan-induced oedema: The experiment was carried out to study the effect of the drugs when given preemptively (30 min for i.p. route and 1 h for oral route) before the carrageenan challenge. Chicks were randomly divided into groups of 5 for the following treatments:

Diclofenac (10, 30 and 100 mg kg^{-1} i.p.), dexamethasone (0.3, 1.0 and 3.0 mg kg^{-1}, i.p.), *C. erythrocarpos* (10, 30, 100 and 300 mg kg^{-1}, p.o.) and control.

Baker's yeast-induced pyrexia: This was done according to the method described by Tomazetti *et al.* (2005). Rectal temperature (T_R) was measured by inserting a lubricated digital thermometer 2.8 cm (external diameter: 3 mm) into the rectum of the rat. The rats had their basal T_R measured and were injected with a pyrogenic dose of Baker's yeast (0.135 mg kg^{-1} i.p). T_R changes were recorded every hour up to 4th h, when the antipyretic paracetamol (10, 30, 100 mg kg^{-1} p.o.), *C. erythrocarpos* extract (30, 100, 300 mg kg^{-1} p.o.) and vehicle only were administered orally. The T_R was monitored over the following 4 h. Basal rectal temperature and changes in rectal temperature were expressed as Means±SEM.

Analysis of data: In the carrageenan-induced foot oedema model, raw scores for right foot volumes were individually normalized as percentage of change from their values at time 0 and then averaged for each treatment group. The time-course curves for foot volume was subjected to two-way (treatment×time) repeated measures analysis of variance with Bonferroni's post hoc t-test. Total foot volume for each treatment was calculated in arbitrary unit as the area under the curve (AUC) and to determine the percentage inhibition for each treatment using Eq. 1 below:

$$\text{Inhibition of oedema (\%)} = \left(\frac{AUC_{control} - AUC_{treatment}}{AUC_{control}}\right) \times 100 \quad (1)$$

Similarly, in the bakers yeast-induced pyrexia model raw scores for basal temperature and changes in rectal temperature were individually normalized as percentage of change from their values at time 0 and then averaged for each treatment group. The time-course curves for changes in rectal temperature were subjected to two-way (treatment×time) repeated measures analysis of variance with Bonferroni's post hoc t test. Total change in rectal temperature for each treatment was calculated in arbitrary unit as the Area under the Curve (AUC).

Differences in AUCs were analyzed by ANOVA followed by Student-Newman-Keuls' post hoc test. ED_{50} (dose responsible for 50% of the maximal effect) for each drug was determined by using an iterative computer least squares method, with the following nonlinear regression (three-parameter logistic) Eq. 2:

$$Y = \frac{a + (b - a)}{\left(1 + 10^{(LogED_{50} - X)}\right)} \quad (2)$$

where, X is the logarithm of dose and Y is the response. Y starts at a (the bottom) and goes to b (the top) with a sigmoid shape. The fitted midpoints (ED_{50}) of the curves were compared statistically using F-test (Miller, 2003; Motulsky and Christopoulos, 2003). GraphPad Prism for Windows version 4.03 (GraphPad Software, San Diego, CA, USA) was used for all statistical analyses and ED_{50} determinations. $p<0.05$ was considered statistically significant.

RESULTS

Phytochemical analysis: Phytochemical screening revealed the presence of alkaloids and flavonoids as predominant chemical constituents in the crude extract of *C. erythrocarpos*.

Carrageenan-induced oedema: Administration of 10 μL of 2% carrageenan induced moderate inflammation resulting in foot oedema in the 7 day old chicks peaking at 2-3 h as described by Roach and Sufka (2003). Figure 1a-f shows the time course and the total oedema response for the effects of *C. erythrocarpos* (CEE), dexamethasone and diclofenac in carrageenan-induced oedema. Two-way ANOVA (treatment×time) revealed a significant effect of drug treatment for CEE ($F_{4,100} = 3.69$, $p = 0.02$), diclofenac ($F_{3,80} = 5.46$, $p = 0.01$) and dexamethasone ($F_{3,80} = 1.62$, $p = 0.22$). Total oedema produced by each treatment is expressed in arbitrary as area under the time-course curve (AUC).

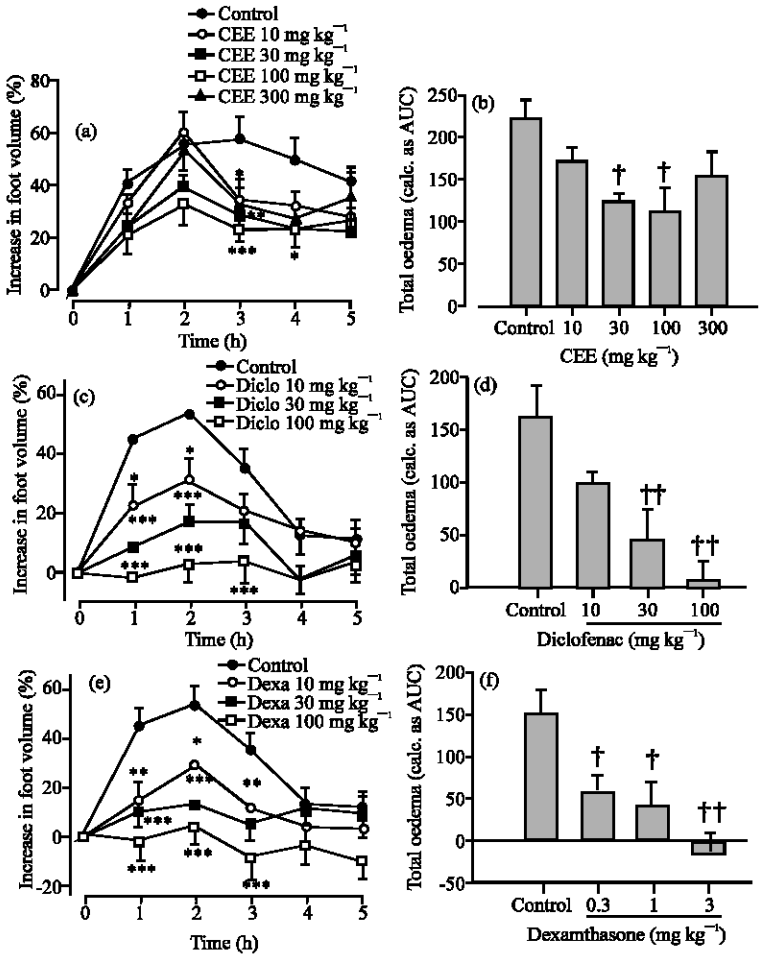

Fig. 1: Effect of CEE (10-300 mg kg^{-1}; 1 h p.o.), diclofenac (10-100 mg kg^{-1}; 30 m, i.p.) and dexamethasone (0.3-3 mg kg^{-1}; 30 m, i.p.) on time course curves (A) and the total oedema response for 5 h, defined as the area under the time course curves (AUC) (B) in carrageenan-induced foot oedema in chicks. Each point and column represents the Mean±SEM (n = 5). ***p<0.001; **p<0.01; *p<0.05 compared to vehicle-treated group (Two-way ANOVA followed by Bonferroni's post hoc test). †p<0.05, ††p<0.01 compared to vehicle-treated group (One-way ANOVA followed by Neuman-Keul's post hoc test)

CEE (10-300 mg kg^{-1}) significantly reduced the total foot oedema with maximal effect of 48.86±20.41%; however, the effect was not dose-dependent but U-shaped (Fig. 1). Dexamethasone (0.3-3 mg kg^{-1}), a steroidal anti-inflammatory agent, completely and dose dependently inhibited the carrageenan-induced oedema (Fig. 1). The NSAID, diclofenac (10-100 mg kg^{-1}) dose dependently reduced the oedema with a maximal effect of 58.77±17.15% (Fig. 1).

Figure 2 shows dose response curves obtained for the doses used in this study. From the ED_{50} values (Table 1) calculated from the dose response curves in Fig. 2, CEE was approximately 165 times less potent than dexamethasone and 1.65 times less potent than Diclofenac. Thus CEE was the least potent of the drugs tested.

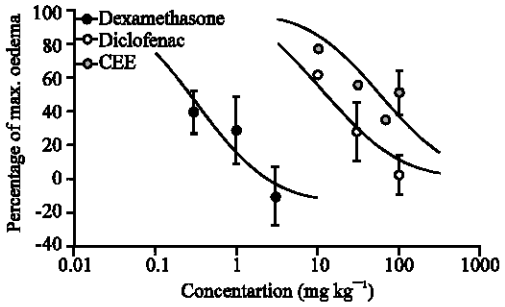

Fig. 2: Dose-response curves of the effects of the drugs under test. CEE, after oral administration, exhibited significant potency ($F_{4, 20} = 3.947$, $p = 0.02$) when it was administered 1 h before carrageenan. Dexamethasone showed the greatest potency ($F_{3, 16} = 6.386$, $p = 0.01$) when it was administered 30 min before carrageenan. Similarly, the NSAID, diclofenac also exhibited a significantly greater potency ($F_{3, 16} = 5.902$, $p = 0.01$) when it was administered 30 min before carrageenan

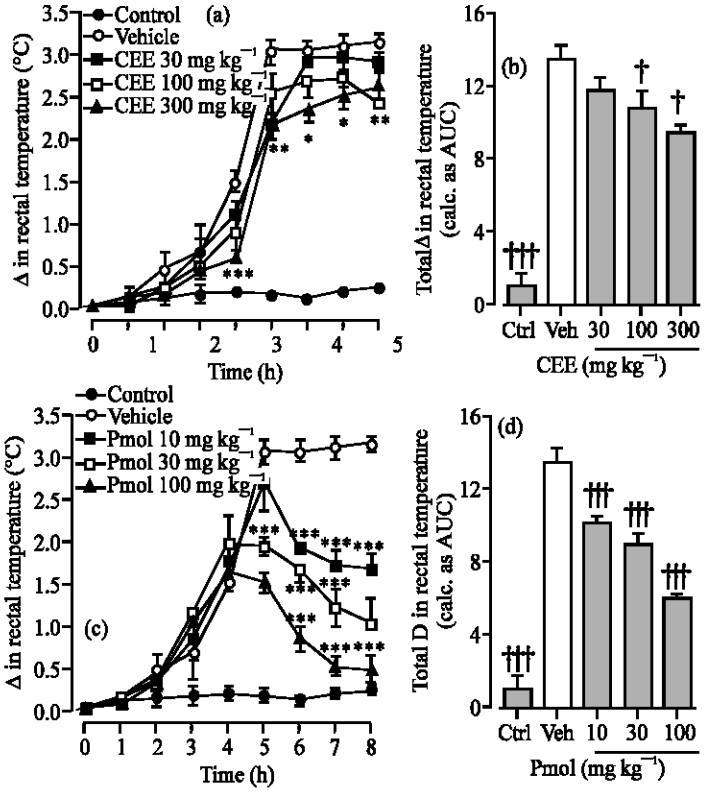

Fig. 3: Effect of CEE (10-300 mg kg^{-1} p.o) and paracetamol (10-100 mg kg^{-1} p.o.) on time course curve of baker's yeast-induced fever (a and c) and the AUC (b and d). Data was presented as Mean±SEM. n = 5 of change from baseline rectal temperature; ***p<0.001; **p<0.01; *p<0.05 compared to vehicle-treated group (Two-way ANOVA followed by Bonferroni's post hoc test). †††p<0.0001 †p<0.05 compared to vehicle-treated group (One-way ANOVA followed by Neuman-Keul's post hoc test)

Table 1: ED_{50} values for Chick carrageenan-induced oedema

Drugs	ED_{50} (mg kg^{-1})
Dexamethasone	00.36±00.24
Diclofenac	36.01±13.67
C. erythrocarpos	59.37±18.83

Baker's yeast-induced pyrexia: Subcutaneous injection of the pyrogenic dose of yeast produced elevated changes in rectal temperature of the rats which peaked by 5 h as shown in Fig. 3a-d. Two-way ANOVA (treatment ×time) revealed a significant effect of drug treatment for CEE ($F_{4, 120}$ = 63.76, p<0.0001) and paracetamol ($F_{4, 120}$ = 88.84, p<0.0001). Total change in rectal temperature produced by each treatment is expressed in arbitrary as AUC of the time-course curves. Treatment with extract (30-300 mg kg^{-1}) caused a significant reduction ($F_{4, 15}$ = 51.85, p<0.0001) in the rectal temperature in a dose dependent manner up to the 8th h (Fig. 3). However, paracetamol (10-100 mg kg^{-1}) caused a greater reduction in the rectal temperature of the rats in a dose-dependent manner which was significant ($F_{4, 15}$ = 78.87 p<0.0001). The antipyretic effect started as from the 1st h after drug administration and was sustained for 4 h as shown by the time course curves.

DISCUSSION

Acute inflammatory process involves the synthesis or release of mediators at the injured site. These mediators include prostaglandins, especially of the E series, histamine, bradykinins, leukotrienes and serotonin, all of which also cause pain and fever (Asongalem *et al.*, 2004). Inhibition of these mediators from reaching the injured site or from bringing out their pharmacological effects will normally ameliorate the inflammation and other symptoms associated with it.

Carrageenan-induced oedema is a well-established and widely used model for studying anti-inflammatory drugs, both steroidal and non-steroidal, since it involves several mediators (Winter *et al.*, 1962; Garcia *et al.*, 2004; Hocking *et al.*, 2005). It induces an inflammatory reaction in two different phases; the initial phase which occurs between 0-2 h after injection of the phlogistic agent has been attributed to the action of histamine, serotonin and bradykinin on vascular permeability (Vinegar *et al.*, 1976; Kaur *et al.*, 2004). The oedema volume reaches its maximum approximately 3 h post-treatment and then begins to decline. The late phase (2-6 h) which is also a complement-dependent reaction, has been shown to be a result of over production of prostaglandins in tissues (Di Rosa, 1974).

The results of this experiment show that the ethanolic extract of *C. erythrocarpos* roots exhibited anti-inflammatory effect, since there was a significant inhibition of acute oedema in the carrageenan-induced chick oedema model used. CEE inhibited the oedema from the first hour acting in both the earlier phase and the later phase. This indicates that the extract could inhibit different aspects and chemical mediators of inflammation (histamine, serotonin, bradykinin, prostaglandins) (Garcia *et al.*, 2004) and this is in support of the fact that inhibitors of various mediators of inflammation ameliorate inflammation. The extract has been shown to be effective in reducing the inflammation with the 100 mg kg^{-1} dose being the most potent and the effects comparable to diclofenac and dexamethasone which are well known prostaglandin inhibitors. The highest dose of the extract (300 mg kg^{-1}) did not give significant inhibition and this could be explained by the presence of possible pro-inflammatory compounds in the crude extract which

might have become predominant as the concentration of the extract was increased and thus masked anti-inflammatory activity (Damas *et al.*, 1985; Vieira *et al.*, 2001). This is possible because the crude extract is made up of several chemical constituents which could be acting via opposing mechanisms. The exact mechanism of action and the active principles responsible for such activities remain to be confirmed but there is an indication that the anti-inflammatory activity exhibited could be attributed to the inhibition of the synthesis, release or action of inflammatory mediators that are known to be involved in carrageenan-induced inflammation which include cytoplasmic enzymes and serotonin from mast cells and also bradykinin, prostaglandins and other cyclooxygenase products.

The extract was compared to the standard drugs diclofenac and dexamethasone which both showed a dose dependent inhibition of carrageenan-induced oedema. The extent of inhibition of foot oedema by CEE was less than the standard anti-inflammatory drugs; this is however, expected since the crude extract contains principles other than the anti-inflammatory principle(s). The anti-inflammatory effect of diclofenac, a Non Steroidal Anti-Inflammatory Drug (NSAID), is mediated chiefly through inhibition of the cyclooxygenase pathway and thus inhibit the release of arachidonic acid metabolites like prostaglandins which are well known mediators of inflammation (Seibert *et al.*, 1994; Al-Majed *et al.*, 2003; Wise *et al.*, 2008). The anti-inflammatory effect of dexamethasone, a steroidal anti-inflammatory drug, is mediated through their suppressive effects on the inflammatory cytokines and on other lipid and glucolipid mediators of inflammation (Masferrer *et al.*, 1994; Kaur *et al.*, 2004; Enomoto *et al.*, 2007; Li *et al.*, 2007).

Antipyretic activity is a characteristic of drugs or compounds which have an inhibitory effect on prostaglandin-biosynthesis and an indispensible role of prostaglandins in the febrile response has been demonstrated (Panthong *et al.*, 2003; Romanovsky *et al.*, 2005). From the anti-inflammatory test, there is an indication that the extract has possible inhibitory effects on cyclo-oxygenase - an enzyme which produces prostaglandins responsible for the genesis of fever (Brune and Alpermann, 1983; Hinz and Brune, 2000). Therefore antipyretic activity of the extract could be expected. Fever may be a result of infection or one of the sequelae of tissue damage, inflammation, graft rejection, or other disease states (Ryan and Levy, 2003). Baker's yeast (a lipopolysaccharide which is a cell wall component of gram negative bacteria) is an exogenous pyrogen which binds to an immunological protein called Lipopolysaccharide-Binding Protein (LBP). The binding results in the synthesis and release of various endogenous cytokine factors such as interleukin 1 (IL-1), interleukin 6 (IL-6) and the tumor necrosis factor-alpha which in turn activate the arachidonic acid pathway and ultimately results in the synthesis and release of prostaglandin E_2 (PGE_2). PGE_2 is the ultimate mediator of the febrile response; it slows the rate of firing of warm sensitive neurons and results in increased body temperature. The set-point temperature of the body will remain elevated until PGE_2 is no longer present (Santos and Rao, 1998; Ryan and Levy, 2003).

The yeast-induced fever in rats employed to investigate the antipyretic activity of the extract showed that *C. erythrocarpos* caused a reduction in rectal temperature however, the effect was not as pronounced and sustained as compared to paracetamol. Systemic inflammation is accompanied by changes in body temperature (Romanovsky *et al.*, 2005; Yesilada and Kupeli, 2007) hence these results seems to support the view that *C. erythrocarpos* has some influence on prostaglandin-biosynthesis, because prostaglandin is believed to be a regulator of body temperature (Romanovsky *et al.*, 2005).

The presence of many biologically active phytochemicals such as triterpenes, flavonoids, alkaloids, steroids, tannins and glycosides in various plant extracts may be responsible for their

respective pharmacological properties (Liu *et al*., 1996; Singh *et al*., 2002; Agarwal and Rangari, 2003; Mbagwu *et al*., 2007; Narendhirakannan *et al*., 2007). *Capparis erythrocarpos* was found to contain flavonoids which are known to interfere prostaglandins involved in the late phase of acute inflammation and pain perception (Damas *et al*., 1985; Rajnarayanan *et al*., 2001). Hence, the presence of flavonoids may contribute to the anti-inflammatory activity of the ethanolic extract of *C. erythrocarpos* roots.

CONCLUSION

Capparis erythrocarpos roots have anti-inflammatory and antipyretic effect and this provides a rationale for the use of the plant in fever and inflammatory disorders.

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