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PRELIMINARY TOXICITY STUDY, ANTI-NOCICEPTIVE AND ANTI-INFLAMMATORY PROPERTIES OF EXTRACTS FROM *SIDA RHOMBIFOLIA* L. (MALVACEAE)

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ABSTRACT

Background: *Sida rhombifolia* L. (Malvaceae) is in flora of Asian medicinal herbs and used traditionally in West of Burkina Faso for the treatment of inflammatory diseases, fever, pain and possesses analgesic properties. The aim of the study was to access the biological activities of extract (acetone/water extract) and alkaloid extracts from *Sida rhombifolia* L. (Malvaceae) in the carrageenan-induced paw edema and croton oil-induced ear edema on the one hand, evaluate their analgesic capacity in Swiss mice and on the other, with an aim to provide a scientific basis for the traditional use of this plants to the treatment of inflammatory diseases.

Method: In acute toxicity test, mice received doses of extract (acetone/water extract) from *Sida rhombifolia* L., extract by intraperitoneal route and LD_{50} was determined in Swiss mice. However, in anti-inflammatory activity, the carrageenan-induced paw edema and oil croton-induced ear edema in Swiss mice. As for analgesic effects, acetic acid writhing and hot plate methods were used in mice.

Results: About preliminary study in acute toxicity test, we obtained LD_{50} value more than 5000 mg/kg b.w. extracts at the doses of 100; 200 and 400 mg/kg body weight produced significant and a dose-dependent anti-inflammatory activity. The dose-dependent inhibition of oedema was observed at 1; 2 and 3 h. However, extracts showed a dose-dependent inhibition of croton oil induced ear edema, at doses of 200; 300 and 500 µg/ear. As for analgesic activity, extracts produced significant analgesic effects in acetic acid writhing and hot plate method ($p \leq 0.05$) and in a dose-dependent inhibition was observed.

Conclusion: In summary, *Sida rhombifolia* L. has the anti-inflammatory and analgesic properties. These findings support the use of the extract in traditional medicine for treating inflammatory and analgesic conditions.

INTRODUCTION: Inflammation is the response to injury of cells and body tissues through different factors such as infections, chemicals, thermal and mechanical injuries [1]**.** Various endogenous mediators like histamine, serotonin, bradykinin, prostaglandins etc are most abundant in inflammatory cell and among then prostaglandins are ubiquitous substances that indicate and modulate cell and tissue responses involved in inflammation. These mediators even in small quantities can elicit pain response. Pain results in dropped muscular activities.

Most of the anti-inflammatory drugs now available are potential inhibitors of cyclooxygenase (Cox) pathway of arachidonic acid metabolism which produces prostaglandins. Prostaglandins are hyperalgesic, potent vasodialators and also contribute to erythema, edema and pain. Hence, for treating inflammatory diseases analgesic and anti-inflammatory agents are required [2]**.**

Non steroidal anti-inflammatory drugs ($NSAID_S$) are the most clinically important medicine used for the treatment of inflammation related diseases like arthritis, asthma and cardiovascular disease [3]**.** Having various and severe adverse effects like gastric lesions for $NSAID_S$, adverse cardiovascular thrombotic effects for selective cyclooxygenase-2 (COX-2) inhibitors [4] and tolerance and dependence induced by opiates, use of these drugs as anti-inflammatory and analgesic drugs lacking those effects are being searched all over the world as alternatives to $NSAID_S$ and opiates.

Research on biological properties, natural products from medicinal plant is nowadays growing and many species have been screened for these biologic activities. Among such plants, there is *Sida rhombifolia* L. (Malvaceae) a medicinal herb from south Burkina Faso and Asian's flora [5, 6]. *Sida rhombifolia* L. has been used as a therapeutic agent in China medicine and other Asian medicines [6, 7]**.**

Some studies *on Sida rhombifolia* L.**,** showed *in vitro* antioxidant and anti-inflammatory activities of its fractions [8, 9]**.** But, there is yet no recently scientific report validating the ethnomedicinal uses of extracts of this herb in the treatment of inflammation, pain and analgesic properties.

The present study was therefore planned to the possible anti-inflammatory and analgesic properties of extract and alkaloid extracts from *Sida rhombifolia* L.

MATERIALS AND METHODS:

Identification of plants material: *Sida rhombifolia* L. (Malvaceae) was collected fresh in August 2008 in Gampela, 25 Km east of Ouagadougou, capital of Burkina Faso. The plant was botanically identified by Prof. Millogo-Rasolodimby from the plants Biology Department of the University of Ouagadougou. Voucher specimen was deposited in the Herbarium of the La.B.E.V. (Laboratory of Plant Ecology and Biology, UFR/SVT of University of Ouagadougou) from the University of Ouagadougou.

Preparation of Extract: Fifty grams of powdered (dried in laboratory condition) plant material was extracted with 500 ml of acetone 80% for 24 h under mechanic agitation (SM 25 shaker, Edmund BÜHLER, Germany) at room temperature. After filtration, acetone was removed under reduced pressure in a rotary evaporator (BÜCHI, Rotavopor R-200, Switzeland) at approximately 40°C and freeze-dried (Telstar Cryodos 50 freeze-dryer). The extract were weighed before packing in waterproof plastic flasks and stored at 4°C until use.

Preparation of Alkaloid Extracts: The harvested plant materials fresh (broken into leaf stems) were dried in the laboratory at room temperature (20-25°C), afterwards samples were ground and made alkaline and 50 g were used with 28% ammonia and extracted with chloroform at room temperature for a total period of 24 h and then the extract was partitioned between 5% HCL and Chloroform. The aqueous phase was made alkaline again with ammonia and partitioned between water and chloroform. Finally chloroform was totally evaporated from the organic phase to form the alkaloids powder.

Animals handling: Swiss NMRI mice (25-30 g) of both sexes were selected for this study. All animals were housed in cage under controlled conditions of 12-h light/12-h dark cycle and 25°C. They all receive pellets food enriched with protein 20% and water *ad libitum*. All animals deprived of food for 15h with excess of drinking water and weighed before the experiments. Experiments on the animals were performed according

to the protocols already approved by the Institute of Health Sciences Research/University of Line Ouagadougou (Burkina Faso) and met the international standards for animal study.

Toxicity studies:

Acute Toxicity study in mice: Healthy male and female Swiss mice (25-30g) were randomly divided into 7 groups (1 control group and 6 treated assay groups) of 6 animals (3 male and 3 female). The control group received water containing 10% dimethylsulfoxide (DMSO) administered intra-peritoneally. The water/ acetone extract of *Sida rhombifolia* L. suspended in 10% DMSO was administered intra-peritoneally at doses of 1; 2; 2.5; 3; 4; 5 and 6g/kg. The general behaviour of the mice was observed for 120 min after the treatment (certain animals were sad, the different one agitated). The animals were observed for morbidity and mortality once a day for 14 days. The number of survivors after the 14 days period was noted. The toxicological effect was assessed on the basis of mortality for 14 days, which was expressed as the median lethal dose (LD_{50}) (Lethal Dose 50) was estimated from the regression of log-probit mortality rate[10].

Anti-inflammatory property

Carrageen-induced paw edema test: The anti-inflammatory activity was evaluated according to [11]. The acute inflammation was induced by injection of 50 µl of 1% w/v carrageenan in normal saline into the subplantar region of right hind paw. Swiss mice were divided into five groups, each containing six mice. Extract or Alkaloid extracts (100; 200 and 400 mg/kg body weight), phenylbutazon and distilled water were orally administered (2.5 to 3 ml) 1 h prior to injection of carrageenan. The edema volume was recorded at 0, 1, 3 and 5 h after carrageenan injection using plethysmometer (Ugo Basile, No 7141, Italy). The average volumes of the right hind paw of each mouse was calculated from three readings. The inhibitory activity was calculated according to following formula:

% Inhibition= (A-B) control – (A – B) treated/(A – B) control x100

A is the paw circumference at time t, B is the paw circumference before carrageen injection, A – B is edema, (A – B) control is edema or paw size after carrageenan injection to control mice at time.

Croton oil-induced ear edema: Topical inflammation was carried out according to [12]. Swiss mice were divided into four groups, each containing six mice. Animals were anaesthetized with 150 mg/kg ketamine hydrochloride; inflammation was induced in the morning between 10.00 a.m. and 12.00 noons to avoid inflammatory response variation due to circadian fluctuation of endogenous corticosteroids.

Cutaneous inflammation was induced by applying 5 µl of solution of croton oil dissolved in extract or alkaloid extracts (100; 200 and 400 mg/kg body weight) and hydrocortisone on the inner surface of the right ear. Control mice received only the irritant solution. Six hours later, the mice were sacrificed and the plug (diameter = 7 mm) was removed from both the treated (right) and the untreated (left) ears. Edematous response was measured as the weight difference between the two plugs. The anti-inflammatory activity was expressed as percentage reduction of edema in treated mice compared with the control mice.

Analgesic capacity:

Acetic acid-induced writhing test: The analgesic activity of the samples was studied using acetic acid-induced writhing model in mice model [13]. Nociception was induced by an intraperitoneal injection of 0.6% acetic acid solution in a value of 10 ml/kg body weight. The animals were divided into five groups with six mice in each group. Group I, animals received vehicle (10% DMSO in water, 10ml/kg body weight), animals of group II received paracetamol 100 mg/kg body weight while animals of group III; group IV and group V were treated with 200; 300 and 500 mg/kg body weight of extract or alkaloid extracts dissolved in 10% DMSO 1h orally before acetic acid injection.

The number of writhes occurring between 5 and 20 min after acetic acid injection was recorded. The analgesic effect was expressed as the percentage reduction of writes in treated mice compared to those in the control group. The percentage inhibition was calculated using the following equation 1:

(%) inhibition = (A – B/A) × 100, where A is mean for the control group and B is mean for the treated group.

Formalin-induced nociception: The analgesic effect of *Sida rhombifolia* L. was also evaluated using formalin-induced paw licking method[14]**.** The animals were divided into five groups with six mice in each group. Group I, animals received vehicle (10% DMSO in water, 10ml/kg body weight), animals of group II received paracetamol 200 mg/kg body weight while animals of group III; group IV and group V were treated with 100; 200 and 300 mg/kg body weight of extract or alkaloid extracts dissolved in 10% DMSO were orally administered. One hour after drug administration, 20µl of formalin (2.5% in normal saline) was injected into the plantar surface of the left hind paw of mice. The time spent in licking the injected paw was recorded and expressed as the total licking time in early phase (0 to 5 min) and late phase (15 to 30 min) after formalin injection. The percentage inhibition was calculated following equation 1.

(%) inhibition = (A – B/A) × 100, where A is mean for the control group and B is mean for the treated group.

Statistical analysis: The data were expressed as Mean±Standard deviation (SD) of six determinations (n=6). Results were analyzed by one-way ANOVA followed by Dunnett's *t*-test using Prism 4 software. The level of significance was accepted at p≤0.05.

RESULTS:

Acute toxicity study in mice: all doses (100; 200 and 400 mg/kg) of the *Sida rhombifolia* aqueous acetone extract (SRE) employed for acute toxicity studies were found to be non-toxic.

The value of LD_{50} is greater than 5000 mg/kg. No significant difference in body weight gain of the treated assay groups over the period of observation. *Sida rhombifolia* aqueous acetone extract (SRE) didn't produce any mortality even at the highest dose (400 mg/kg) employed. Three submaximal doses (100; 200 and 400) which were found to be safe in mice were employed for further biochemical investigations.

Anti-inflammatory properties:

Carrageenan-induced paw edema test: Subplanar injection of carrageenan in rats showed to a time-dependent increase in paw thickness (**Figure 1 and Figure 2**); this increase was observed at 1h and was maximal at 3h after administration of Carrageenan injection in the vehicle treated groups. However, carrageenan induced inflammation was decrease and increase significantly (100 mg/kg body weight; $p<0.05$, $p<0.01$; 200 mg/kg body weight; $p<0.05$, $P<0.05$ and $p<0.01$; 400 mg/kg body weight; $P<0.01$) reduced in all phases of the experiment by treatment with SRE and increase significantly (100 mg/kg body weight; $p<0.01$; 200 mg/kg body weight; $p<0.01$ and 400 mg/kg body weight; $p<0.01$) with *Sida rhombifolia* alkaloid extracts (SRAE) comparatively to the control (reference drug).

Croton oil-induced ear edema: SRE and SRAE showed dose-dependent inhibition of croton oil induced ear edema, at doses of 200; 300 and 500 mg/kg body weight. Moreover, inhibition of croton oil induced ear edema was decrease significantly (100 mg/kg and 300 mg/kg body weight; $p>0.01$) and increased significantly (500 mg/kg body weight; $p>0.05$ or $p>0.01$). Results were summary in (**Figure 3**).

So, in this section of our work, it appears clear that, SRAE have the best anti-inflammatory activities comparatively to the SRE (Figure 1, Figure 2 and Figure 3).

Analgesic capacity:

Acetic acid-induced writhing test: Figure 4 shows the pain behaviour of writhing response which was presented as cumulative abdominal stretching response. The treatment of mice with SRE and SRAE (200; 300 and 500 mg/kg) was decrease significantly with SRE (200 mg/kg body weight; $p<0.01$) and increase significantly with SRAE with the same dose. However, one observed an increase significantly with SRE and SRAE (300 mg/kg body weight; $p<0.05$ and $p<0.01$; 500 mg/kg body weight; $p<0.01$). A dose-depend inhibition in abdominal writhes produced by acetic acid was noticed. It was noticed moreover that comparatively to the SRE, SRAE presented the best inhibition in abdominal writhes produced by acetic acid.

Formalin-induced nociception: In **figure 5 and Figure 6,** it is showed that pretreatment with paracetamol (200 mg/kg) or SRE and SRAE (100; 200 and 300 mg/kg) produce a dose-dependent and significant ($p<0,01$) reduction in licking time when one compared control group (paracetamol) and treated groups (SRE and

SRAE). The extracts inhibited the early (0 to 5 min) and the second (15 to 30) phases of inflammation induced by formalin. The reference drug, paracetamol produced higher inhibition than the highest dose (300 mg/kg body weight) of SRE or SRAE. But as for concerned extracts activity, it appears clear that SRAE presented the best activity.

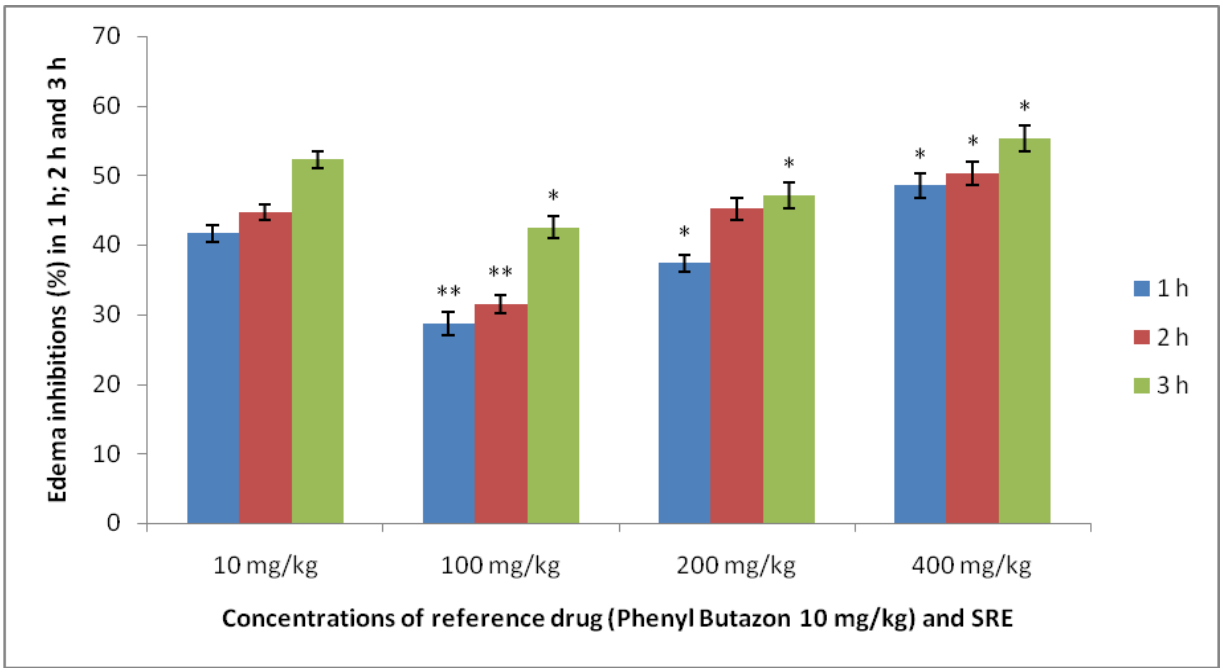

FIGURE 1: EFFECTS OF EXTRACT OF *SIDA RHOMBIFOLIA* L. (SRE) AND REFERENCE CHEMICAL ON MICE PAW EDEMA INDUCED BY CARRAGEENAN (CARR). Values are Mean ± SEM (n=6 in each group) one-way ANOVA followed by Dunnett's t-test: Compare all vs. Control group (reference drug): $^{ns}P<0.05$; *P<0.05; **P<0.01 compared with control (the reference drug group).

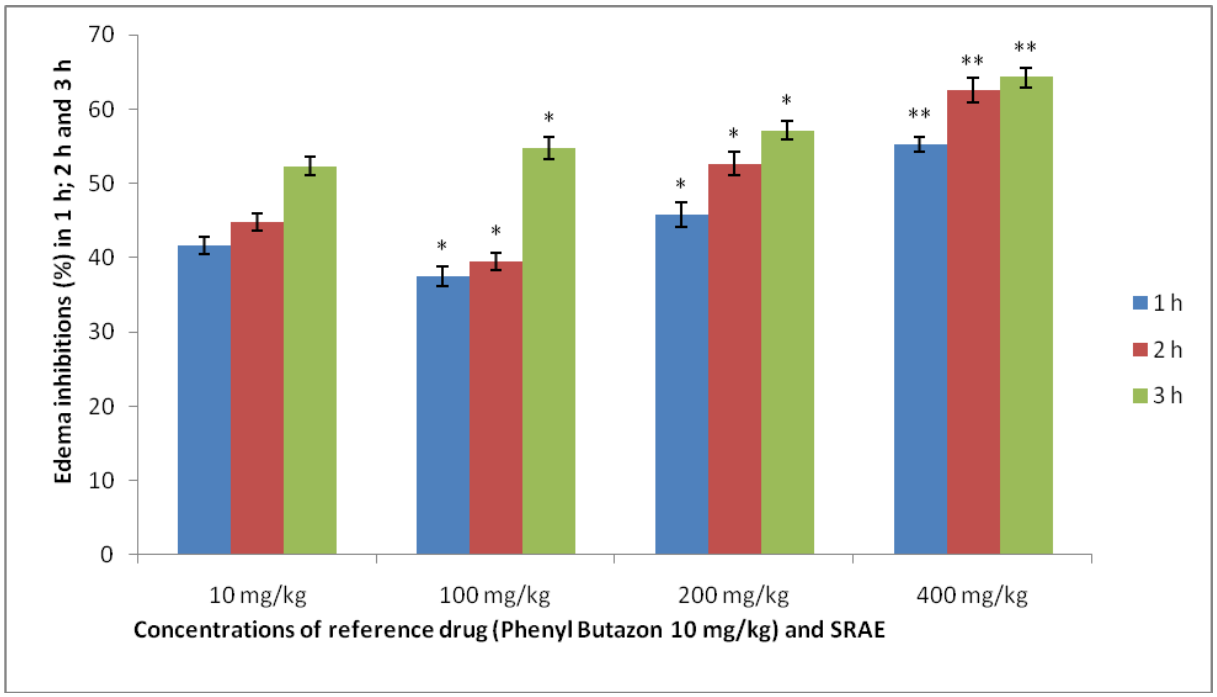

FIGURE 2: THE EFFECTS OF ALKALOID EXTRACTS FROM *SIDA RHOMBIFOLIA* L. (SRAE) AND REFERENCE CHEMICAL ON MICE PAW EDEMA INDUCED BY CARRAGEENAN (CARR). Values are Mean ± SEM (n=6 in each group) one-way ANOVA followed by Dunnett's t-test: Compare all vs. Control group (reference drug): $^{ns}P<0.05$; *P<0.05; **P<0.01 compared with control (the reference drug group).

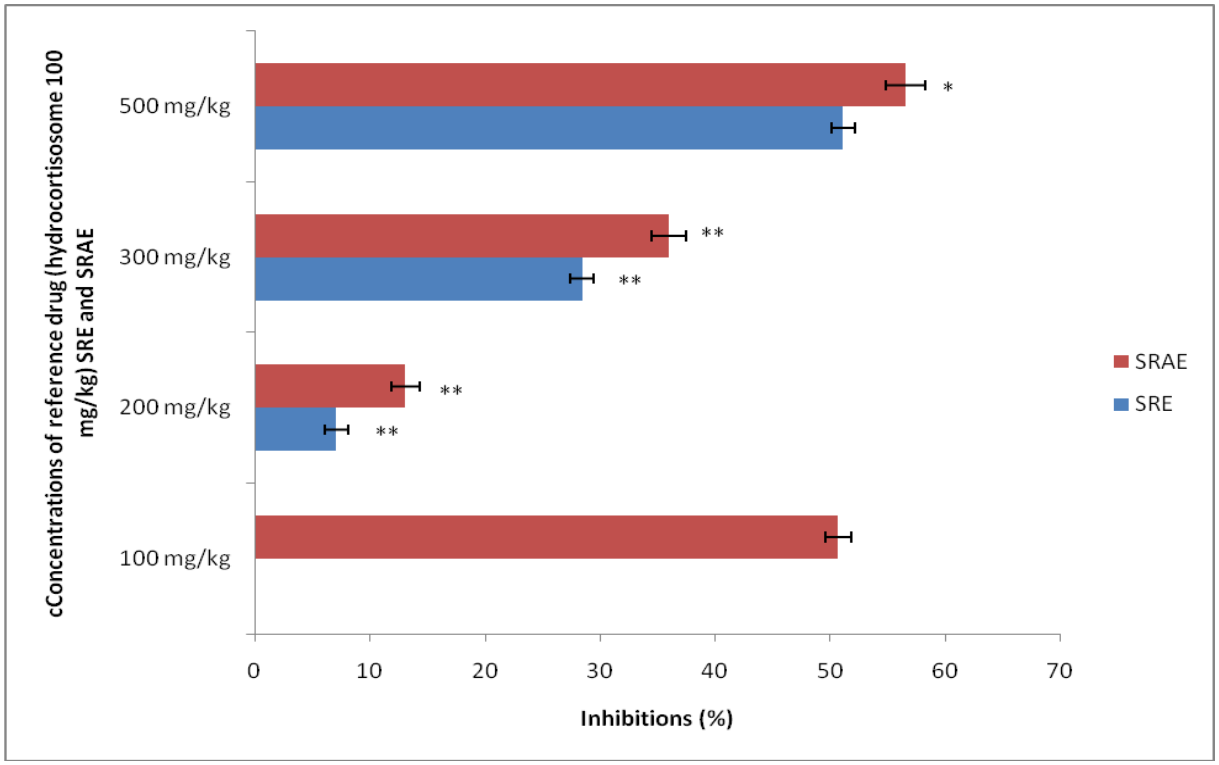

FIGURE 3: THE EFFECTS OF SRE, SRAE AND (REFERENCE CHEMICAL) ON MICE EAR EDEMA INDUCED BY CROTON OIL (CO). Values are Mean ± SEM (n=6 in each group) one-way ANOVA followed by Dunnett's t-test: Compare all vs. Control group (reference drug): ^{ns}P<0.05; *P<0.05; **P<0.01 compared with control (the reference drug group).

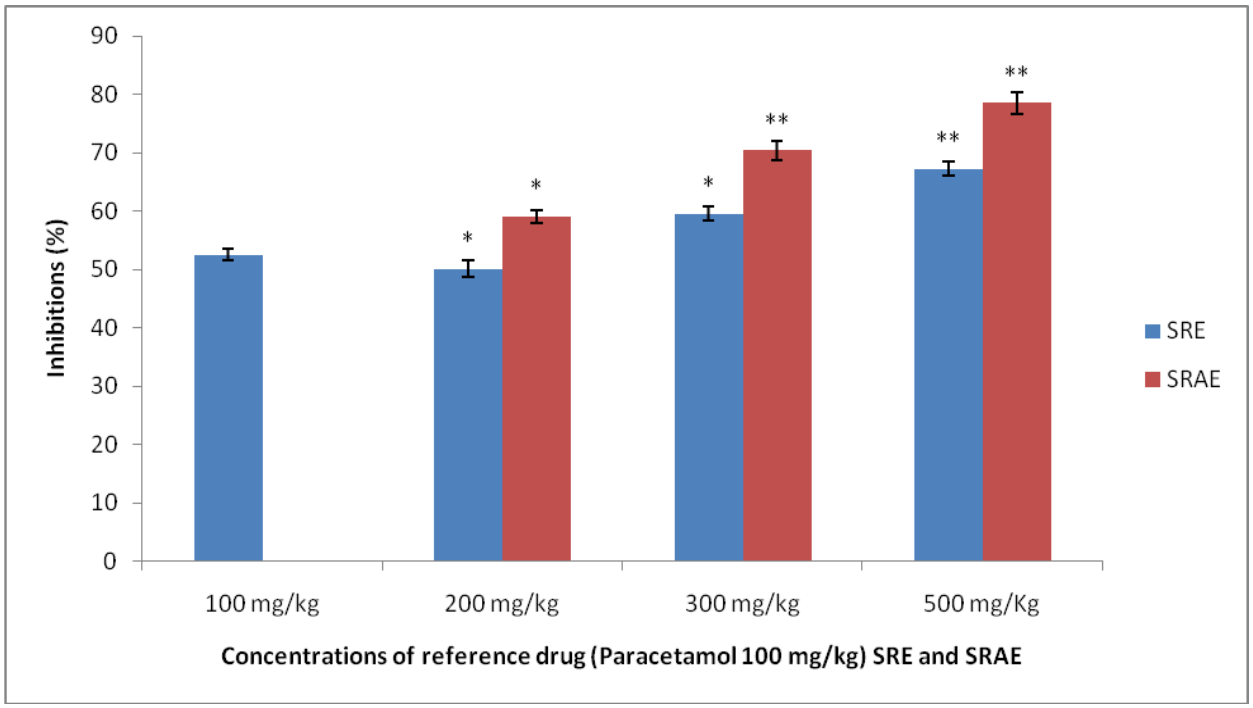

FIGURE 4: EFFECT OF EXTRACT AND ALKALOID EXTRACTS FROM OF *SIDA RHOMBIFOLIA* L. ON WRITHING-INDUCED BY ACETIC ACID. Values are Mean ± SEM (n=6 in each group) one-way ANOVA followed by Dunnett's t-test: Compare all vs. Control group (reference drug): ^{ns}P<0.05; *P<0.05; **P<0.01 compared with control (the reference drug group).

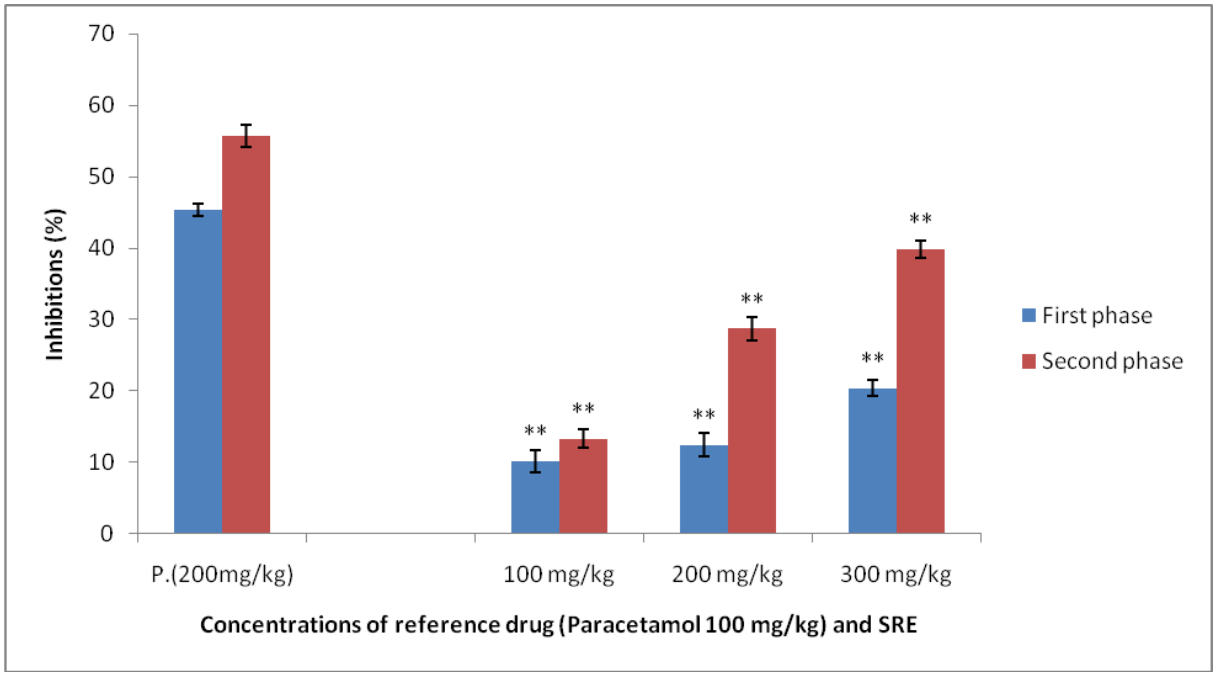

FIGURE 5: EFFECT OF EXTRACT FROM *SIDA RHOMBIFOLIA* L. (SRE) ON LICKING THE HIND PAW-INDUCED BY FORMALIN INJECTION. Values are Mean ± SEM (n=6 in each group) one-way ANOVA followed by Dunnett's t-test: Compare all vs. Control group (reference drug): $^{ns}P<0.05$; *P<0.05; **P<0.01 compared with control (the reference drug group).

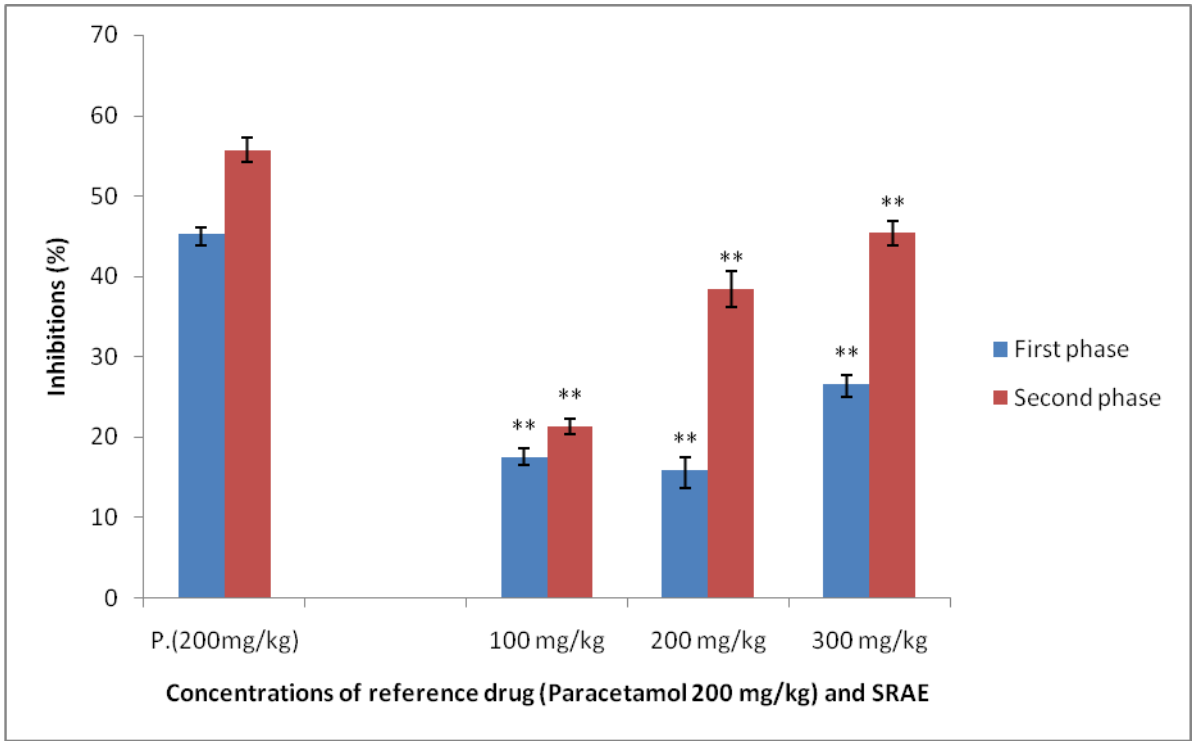

FIGURE 6: EFFECT OF ALKALOID EXTRACTS FROM *SIDA RHOMBIFOLIA* L. (SRAE) ON LICKING THE HIND PAW-INDUCED BY FORMALIN INJECTION. Values are Mean ± SEM (n=6 in each group) one-way ANOVA followed by Dunnett's t-test: Compare all vs. Control group (reference drug): $^{ns}P<0.05$; *P<0.05; **P<0.01 compared with control (the reference drug group).

DISCUSSION: Herbal plants are an important source of new chemical substances with potential therapeutic uses. Approximately 119 pure chemical substances extracted from higher plants are used in medicine throughout the world [15].

The increase interest on plant medicines in today's world is from the belief that green medicine is safe and dependable, compared with costly synthetic drugs that have adverse effects [16].

In the present investigation, we have studied the anti-inflammmatory, anti-noceiptive and antimicrobial properties of extracts from *Sida rhombifolia* L. The results of the present study indicated that the extract of *Sida rhombifolia* is not poisonous. During the 14 day period of acute toxicity evaluation, some signs of toxicity were observed, but they were all quickly reversible. Pharmacological substances whole LD_{50} is less than 5 mg/kg body weight are classified in the range of highly toxic substances, those with a LD_{50} between 5 mg/kg body weight and 5000 mg/kg body weight are classified in the range of moderately toxic substances and those with the lethal dose is more than 5000 mg/kg body weight not toxic [8]**.** In this fact, if we refer to this classification we could say that the extract of *Sida rhombifolia* is not toxic and would be regarded as being safe [17]**.**

The results of the present study have been established in both acute and chronic inflammation models. Carrageenan-induced mice paw edema is a suitable test for evaluating anti-inflammatory drugs which are currently used to assess the anti-edematous effect of traditional medicine materials [18]**.** So, extract and alkaloid extracts from *Sida rhombifolia* possess significant anti-inflammatory effect in the acute and chronic anti-inflammatory model of inflammation in mice (Figure 1 and Figure 2). Inflammation is a complex process and ROS play an important role in the pathogenesis of inflammatory diseases [19]**.**

Carrageenan is a strong chemical for the release of inflammation mediators (histamine, kinnin, prostaglandin leukotriene etc.) and proinflammatory cytokinins (tissue necrosis factor, interleukin etc.) [20]**.** The development of edema in the paw of the mice after the injection of carrageenan is due to release of histamine, serotonin and prostaglandin like substances [21]**.** Carrageenan-induced edema involves three phases of chemical mediator release in an orderly sequence [22]**.**

The early phase (1 h) involves the release of histamine and serotonin is characterized by increase in vascular permeability. The second phase (2h) is mediated by release of bradykinin, an important chemical mediator of both pain and inflammation. Release of prostaglandins and cyclooxygenases products takes place in the third and final phase (3 h) [21]**.**

The significant ameliorative activity of the extract and standard drug observed in the present study may due to inhibition of the mediators of inflammation such as histamine, serotonin and prostaglandin. The antihistamine property of extract could be due to the neutralization of histamine and serotonin. The anti-edema effect of extract was highest in the third and final phase which suggests that the extract acts more on the cyclooxygenase enzymes that are involved in the prostaglandin synthesis [23]**.**

The ear edema induced by the application of croton oil is used to evaluate the topical anti-inflammatory activity (property) of chemical substances and drugs. Croton oil application provokes the release of pro-inflammatory mediators such as histamine, serotonin that promote vasodilatation, leukocytes infiltration, plasma leakage [24] and the production of cytokines such as interleukin 1β, tumor necrosis factor alpha (TNF α) [25]**.**

Our results shown that extract and alkaloid extracts were able to inhibit the inflammation response induced by croton oil (Figure 3). It suggests that our extract could inhibit the vasodilatation, leukocytes infiltration and cytokines (IL 1β, TNFα).

Anti-nociceptive activity of extracts (acetone/water extract and alkaloid extracts) from *Sida rhombifolia* was evaluated using both chemical methods of nociception in mice. These methods are used to detect central and peripheral analgesics. Acetic acid-induced writhing test was used for detecting both central and peripheral analgesia, whereas hot plate test is most sensitive to centrally acting analgesic. Intraperitoneal administration of acetic acid releases prostaglandins and sympathomimetic system mediators like PGE_2 and $PGF_{2\alpha}$ and their levels were increased in the peritoneal fluid of the acetic acid-induced mice [26]**.**

Moreover, extracts (acetone/water extract and alkaloid extracts) from *Sida rhombifolia* exhibited a significant and dose-dependent analgesic activity in the acetic-acid induced writhing activity in mice (Figure 4). The possible effect of the alkaloid extract was evaluated by its effect on paw licking induced by formalin. The test possesses two distinct phases, reflecting different types of pain [27]**.** The early phase reflects tissue injury or inflammatory pain [28]**.**

The extracts (extract and alkaloid extracts) produced significant anti-nociceptive effect in both phases (Figure 5 and Figure 6). This probably suggests or indicates that the extract exerts its analgesic effect through both peripheral inhibitory actions on released prostaglandins (inflammatory pain) and central activity relates to antagonistic action of the nociceptors (neurogenic pain) [29].

Certain previous studies have shown that the plant contains phenolic compounds and has antioxidant activity [8]. So, the possible reduction of inflammation and analgesic activity could be explained by made that there is a synergy of action between the alkaloids and phenolic compounds like flavonoids and phenolic acids in the extracts [8, 30].

CONCLUSION: The present finding indicates the efficacy of the alkaloid extract as some efficient therapeutics agent in anti-inflammatory and analgesic conditions comparatively to the extract (acetone/ water extract). Thus, which many explain the traditional basis of using this plant in the treatment of various ailments like fever, inflammatory and analgesic disorders.

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