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Safety Assessment and Potential Anti-Inflammatory Effect of Ethanolic Extract of *Syzygium aromaticum* in Albino Rats

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Abstract

The present study was undertaken to investigate the effect of the ethanolic extract of *Syzygium aromaticum* to albino rats. Forty eight Albino rats were employed to test the safety and the anti-inflammatory effect of the extract. Safety of the extract was examined on experimental animal's model at three dose levels of the extract orally in daily doses for three weeks. Effects of *S. aromaticum* on rats revealed no significant effect on biochemical or haematological parameters. The anti-inflammatory effect of the extract was tested in four equal groups; groups 1 and 2 were treated with 250 and 500 mg/kg of the extract, respectively, group 3 was treated with indomethacine and group 4 was the untreated control. Carrageenan was used as an acute form inducer of inflammation. Indomethacine, the non-steroidal anti-inflammatory drugs (NSAIDs), was used as a reference compound. Oedema size was monitored at the 1st, 2nd, 4th, 6th and after 24 hours. The ethanolic extract of *S. aromaticum* showed significant ($P < 0.001$) decreased in the oedema size at efficacy rates of 79.41%, 82.39% and 63.92% for the dose, 500 mg/kg body weight at the 2nd, 4th and 6th hour respectively higher than that produced by indomethacine.

Keywords

Syzygium aromaticum, Ethanolic Extract, Safety, Anti-Inflammatory, Rats

1. Introduction

Syzygium aromaticum is an opened bud growing on a tree belongs to the family Myrtaceae. It is indigenous to Moluccas and Southern Philippines, India, Zanzi-

bar, Mauritius and Srilanka. It also cultivated in Africa including Madagascar and United Republic of Tanzania. It is known as Clove [1]. Several researches reported the properties of *S. aromaticum* such as anticarcinogenic, aphrodisiac, antimutagenic, mosquito repellent, cytotoxicity, antimicrobial, chemopreventive for lung cancer, antioxidant, anti inflammatory effect and enhancement of gemcitabine cytotoxic effect on human cervical cancer cells. [2]-[9] The traditional uses of clove oil in veterinary medicine include treating foreign matter in dog and cat ears and as a painkiller to treat tooth pain [10] This study was designed to investigate the effect of the ethanolic extract of *S. aromaticum* to rats.

2. Materials and Methods

2.1. Materials

2.1.1. Extraction of the Plant Materials

S. aromaticum fruits 200 gram were obtained from a local market Khartoum North, cleaned, dried and finely ground by an electric mill. The powder obtained was successively extracted with ethanol for 14 hrs using Soxhlet apparatus. The ethanolic extract was occasionally shaken during the first four hours and was then filtrated. The filtrate was evaporated under vacuum, and the residue is brownish in colour and weighed 23 gram (11, 50% yield).

2.2.2. Animal Housing

Healthy Wister (Albino) rats weighing 100 - 130 gram were obtained from the Medicinal and Aromatic Plants Research Institute, National Center for Research Khartoum, Sudan, where they were housed in cages (each of dimensions 12 × 12 × 12 cm. accommodating one dose-group) and maintained in a room under standard environmental condition, controlled temperature (22˚C ± 2˚C), relative humidity (60%) with free access to water and formula rat feed (2.5 Mcal and 20% crude protein). Rats were apparently healthy and they were identified by tail colour marks. The rats were acclimatized for one week to laboratory condition before the start of the experiment the end of the adaptation period. The experiment protocol and animal care ethics was taken as the guidelines approved by Medicinal and Aromatic Plants Research Institute, National Center for Research Khartoum, Sudan.

3. Methods

3.1. Safety Assessment of the Extract

Twenty four albino rats were divided into four groups each of 6 rats. Rats in group 1 were the un-dosed control *S. aromaticum* ethanolic extract dried material was re-dissolved in distilled water and given orally in daily doses at 250, 500 and 1000 mg/kg body wt./rat to groups 2, 3 and 4 respectively. Dosing continued for three weeks. Clinical signs and mortality rates were recorded. Blood samples were obtained from the ocular vein before the start of dosing and thereafter at the end of the experiment for haematological investigations and serum analysis. Haemog-

lobin concentration (Hb), Packed Cell Volume (PCV), Red Blood Cell (RBC) and White Blood Cell (WBC) counts were estimated [11]. Sera were analyzed for the activities of ALP and AST, using commercial kits (Randox Laboratories Ltd., UK) and also for the concentrations of total protein, albumin, bilirubin, urea and creatinine. Rats were slaughtered, under anaesthesia, at weeks 3 and post-mortem changes were recorded. Specimens of liver, kidneys, heart, intestines and spleen were fixed in 10% neutral buffered formalin, embedded in paraffin wax, sectioned at 5 μm and stained with haematoxylin and eosin (H&E) using Mayer's haemalum.

3.2. The Anti-Inflammatory Assay

Twenty four albino rats divided randomly to 4 groups each of 6 rats. All groups' individuals were injected subcutaneously with 0.1 ml of a 10% w/v carrageenan (Sigma Chemical Co.; St Louis, Mo, USA) suspension (0.1 ml of a 1% suspension in 10% saline in the sub-planter region of the left hind limb as a local acute oedema inducer, 30 minutes subsequent to extract injection. The ethanolic extract of *S. aromaticum* was re-dissolved in distilled water and given orally to rats of group 1 at 250 mg/kg body wt. and 500 mg/kg body wt. to rats of group 2. Rats in group 3 were treated orally with indomethacine (Hikma Pharmaceutical, Amman, Jordan) 10 mg/kg body wt. as a reference drug. Group 4 rats were the un-treated negative control and received orally 1 ml/kg body wt. of normal saline.

3.3. Statistical Methods

The difference between mean values of data was analyzed by the paired students-t-test [12]. The efficacies were obtained by calculating the differences between the edema size in the treated and the control and the values were transformed into percentage using mean index using the formula:

$$(a-b)/a*100 = \text{efficacy}$$

where a is mean of the edema size in the control and b the edema size in the treated rats.

4. Results

4.1. Safety Assessment of the Extract

4.1.1. Clinical Signs

All groups showed no clinical signs or mortalities during the experimental period (3 weeks). No abnormal behaviours were recorded in the un-dosed control rats (group1) and also no mortalities recorded.

4.1.2. Pathological Changes

For all test groups 2, 3 and 4, no gross changes were observed at post-mortem at the end of the experiment (3 weeks). No fatty changes, no congestion and no pathological lesions were observed in all experimental groups.

4.1.3. Changes in Serum Constituents

Table 1 is summarizing the changes in serum constituents of rats treated with *S. aromaticum* ethanolic extract. The activities of AST and ALT showed no significant ($P > 0.05$) changes for all groups. Normal values were recorded in the control group. Also all groups showed no significant ($P > 0.05$) changes in the concentration of total protein, albumin, billirubin urea and creatinine. No abnormal values were recorded in the control group.

4.1.4. Hematological Changes

Table 2 summarized the hematological changes in blood of rats treated with *S. aromaticum* ethanolic extract. In all groups there were no significant ($P > 0.05$) changes in the number of WBCs and RBCs and in the values of Hb and PCV. The control group showed no abnormalities.

4.1.5. Histopathological Changes

S. aromaticum treated rats showed histopathological changes mainly, dilatation of the cortical tubules (Figure 1), congestion in renal blood vessels and dilatation (Figure 2). Liver showed congestion in the portal tract with slight necrosis of hepatocytes in liver (Figure 3).

4.2. Anti-Inflammatory Effect

The anti-inflammatory effects of *S. aromaticum* ethanolic extract on rats are shown in Table 3 and Table 4 as edema volume and inhibition percentage respectively.

Table 1. Average (mean ± s.d.) values of serum constituents of rats treated with *S. aromaticum* ethanolic extract for 3 weeks.

Group/dose	AST (i.u/L)	ALT (i.u/L)	T. Protein (g/dL)	Albumin (g/dL)	Billirubin (mg/dL)	Urea (mg/dL)	Creatinine (mg/dL)
G_1 (un-dosed control)	7.00 ± 0.71	08.00 ± 1.41	06.95 ± 0.35	04.80 ± 0.14	0.65 ± 0.07	24.50 ± 0.71	0.75 ± 0.07
G_2 (250 mg/kg/day)	6.67 ± 1.15 NS	11.67 ± 4.93 NS	7.03 ± 0.21 NS	3.77 ± 0.32 NS	0.53 ± 0.15 NS	25.33 ± 2.52 NS	0.77 ± 0.15 NS
G_3 (500 mg/kg/day)	10.33 ± 1.53 NS	9.67 ± 03.79 NS	7.20 ± 0.26 NS	4.17 ± 0.74 NS	0.10 ± 2.65 NS	24.67 ± 2.52 NS	0.73 ± 0.15 NS
G_4 (1000 mg/kg/day)	09.33 ± 1.15	8.67 ± 5.51 NS	7.13 ± 0.35 NS	3.67 ± 0.21 NS	0.70 ± 4.58 NS	21.67 ± 2.08 NS	0.77 ± 0.15 NS

Student's t-test, ($P < 0.05$), NS; Not significant.

Table 2. Average (mean ± s.d.) hematological values of rats treated with *S. aromaticum* ethanolic extract for 3 weeks.

Group/dose	Hb (g/dl)	PCV (%)	RBCs (10^6 mm/mm^3)	WBCs (10^4 mm/mm^3)
G_1 (un-dosed control)	0.50 ± 0.57	32.50 ± 3.54	1.31 ± 0.08	0.58 ± 0.02
G_2 (250 mg/kg/day)	12.70 ± 2.20 NS	31.30 ± 1.53 NS	2.18 ± 0.18 NS	0.56 ± 0.06 NS
G_3 (500 mg/kg/day)	5.46 ± 2.17 NS	29.00 ± 15.59 NS	2.49 ± 0.45 NS	0.50 ± 0.02 NS
G_4 (1000 mg/kg/day)	12.26 ± 1.40 NS	36.66 ± 6.35 NS	2.00 ± 0.12 NS	0.54 ± 0.11 NS

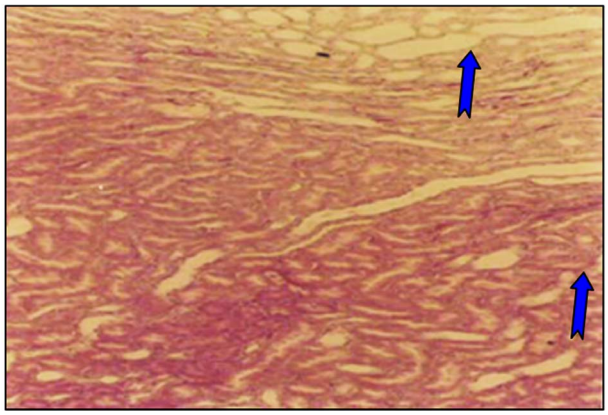

Figure 1. Necrosis in the cortical tubules (blue arrows) in kidneys of a rat treated with *S. aromaticum* ethanolic extract at 1000 mg/kg at the end of week 3. *H&E* ×100.

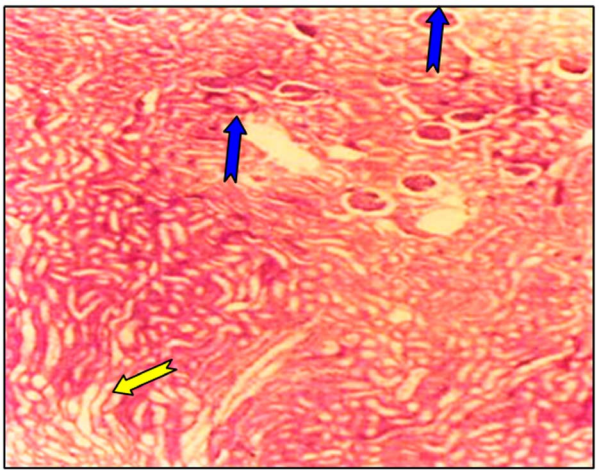

Figure 2. Congestion in renal blood vessels (blue arrows) and dilatation in kidney tubules (yellow arrows) of a rat treated with *S. aromaticum* ethanolic extract at 1000 mg/kg at the end of week 3. *H&E* ×100.

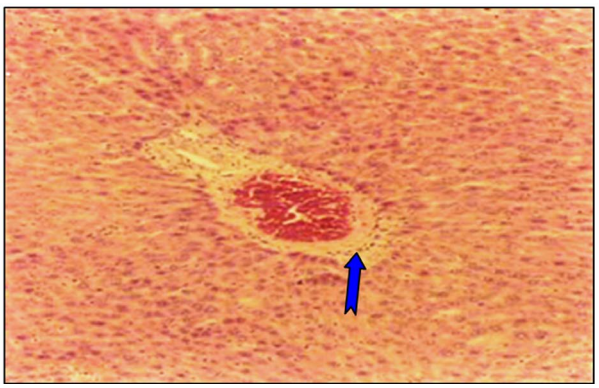

Figure 3. Congestion in the portal tract (blue arrows) with slight necrosis of hepatocytes in liver of a rat treated with *S. aromaticum* ethanolic extract at 1000 mg/kg at the end of week 3. *H&E* ×100.

Table 3. Volume of paw oedema (mm) in rats treated with *Syzygium aromaticum* ethanolic extract on carrageenan-induced oedema.

Time (Hours)	G_1 (250 mg/kg)	G_2 (500 mg/kg)	G_3 (10 mg/kg indomethacine)	G_4 (un-treated control
1	0.53 ± 0.12 NS	0.48 ± 00.5 NS	0.73 ± 00.19 NS	01.00 ± 00.28
2	0.78 ± 0.22**	0.35 ± 00.08**	1.10 ± 00.48 NS	01.70 ± 0.19
4	0.65 ± 0.16**	0.25 ± 014***	0.67 ± 0.12***	01.42 ± 0.0
6	0.63 ± 0.21 NS	0.35 ± 00.22*	0.63 ± 0.08**	0.97 ± 00.1
24	0.18 ± 0.12 NS	0.20 ± 0.90*	0.2 ± 0.23 NS	0.65 ± 00.1

*Denotes $P < 0.05$. **denotes $P < 0.001$. NS = Not significant.

Table 4. Inhibition percentage (%) in rats treated with *Syzygium aromaticum* ethanolic extract on carrageenan-induced oedema.

Time (Hours)	G_1 (250 mg/kg)	G_2 (500 mg/kg)	G_3 (10 mg/kg indomethacine)	G_4 (un-treated control
1	47.00	52.00	27.00	00.00
2	54.12	79.41	35.29	00.00
4	54.23	82.93	52.82	00.00
6	35.05	63.92	35.05	00.00
24	72.31	69.23	61.23	00.00

The edema size in group1 showed no significant ($P > 0.05$) difference when compared to the control group in the first, six and 24th hours while the edema size was increased at the 2nd and fourth hrs and group 2 rats that treated with 500 mg/kg of the plant extract showed significant reduction in oedema size at hrs 2, 4, 6 and 24. On the other hand the reference drug (group 3) showed significant reduction of oedema size at hrs 4 and 6 only. Table 4 represented the inhibition percentage and revealed that, higher percentage was recorded by group 2 among all groups including the reference drug group and the higher value was recorded at hr 4 of treatment (82.93%). The inhibition percentages of the higher dose of the extract (500 mg/kg) throughout the period of experiment were better than the lower dose of the extract and even better than indomethacine.

5. Discussion

No research has been done to investigate the effect of the ethanolic extract of *S. aromaticum* to Albino rats at the doses used. In this study ethanol was used for extracting *S. aromaticum* fruits. Methanol and ethanol were described to be efficient solvents in extracting phytochemicals from plant material [13] and [14]. The daily oral doses of the ethanolic extract of *S. aromaticum* to rats caused neither mortalities nor clinical signs during the experimental period (3 weeks) at the doses used. Many authors reported that the activities of enzymes AST and ALT in the serum and the concentration of urea and total protein used routinely for evaluat-

ing the liver function and of the renal toxicity in experimental animals [15] and [16]. Similarly the assessment of hematological parameters can be used to determine the effect of plant extracts on the blood constituents of an animal [17].

In the present study rats treated with *S. aromaticum* ethanolic extract showed negligible effect on the hematology parameters tested, same result was found when rabbits treated with *Cymbopogon proximus* oil extract at oral doses of 0.1, 0.25 and 0.5 ml/kg body weight/day for 21 days [18] and in cattle poisoned by *Cassia occidentalis* there was no marked change in hematological parameters [19]. On the other hand no significant changes were recorded in the biochemical constituents although there are mild histopathological changes appeared on liver and kidney. *S. aromaticum* was reported to be safe and possess several medicinal properties but in one study it was shown that, the long-term use could be hazardous to body organ [20]. Safety of medicinal plants was reported in *Chrozophora plicata* [21], in *Crotalaria saltina* [22] and in *Jatropha curcas* [23]. The present study suggests that *S. aromaticum* ethanolic extract had no effect on the kidney as it indicated by normal concentration of creatinine or urea except the mild effect of gross and microscopic renal changes.

It was reported that, carrageenan-induced rat paw edema is associated with three distinct phases. The early first phase (1st hour) is mediated by mast cell degranulation, histamine and seratonin release. The second phase (2nd hour) is characterized by bradykinin release and pain, and in the last phase (3rd - 4th hour) eicosanoid production [24] [25]. In this study carrageenan was used as an acute form inducer of inflammation. The extract administered 30 minutes before the inflammation inducer and this because the inflammation phases were very short.

The mechanism of action by which carrageenan induces the inflammatory processes is a synergism among several mediators (bradykinin, serotonin, prostaglandins, leukotriene B4) [26]. Many studies reported indomethacine, the non-steroidal anti-inflammatory drugs (NSAIDs), as a reference compound and it was used also in our study [27] [28].

The ethanolic extract of *S. aromaticum* showed high inhibition effect at the dose 500 mg/kg. This dose showed neither death nor any untoward effects. This indicates that the extract has a wide range of safety and its administration may not cause immediate toxic effect at least at the doses used in this study. These results agree with the earlier studies of the anti-inflammatory activities of some medicinal plants tested against rat paw edema and no toxicity effect as indicated in *Trigonella foenum-graecum* that possesses an anti inflammatory activity and it was safe at high doses [29]. The same results were found by many researchers [30]-[35]. These findings obtained in the rats paw oedema indicate the anti inflammatory potential of the plant is stronger even than the reference drug indomethacine.

6. Conclusion

It is concluded that in this study *S. aromaticum* ethanolic extract showed no mortality or signs of toxicity to rats at the doses used. The present study demonstrates

the potential anti-inflammatory effect of the extract against rat paw edema**.** However, further studies are important to elucidate the mechanism behind this effect.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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