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## Preliminary screening of anti-ulcerative colitis activity of aqueous leaf extract of *Spondias mombin* Linn. (Anacardiaceae) and the possible mechanisms of action in rats

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### ABSTRACT

*Spondias mombin* L. (Anacardiaceae) commonly known as 'yellow mombin' is a multipurpose herb cultivated in parts of the Brazilian Northeast for its edible fruits, oil and leaves. The bark is used to carve figures and leaves and roots used as medicine. Efforts in this study were devoted to evaluating the effect of aqueous leaf extract of *Spondias mombin* Linn. on SMB sub-acute dosing in a rat model of acetic acid-induced ulcerative colitis and acetic-acid induced ulcerative colitis (curative) models. Three graded doses of the extract were administered orally (50, 100 and 200mg/kg) for the prophylactic model and 200mg/kg for the curative model. The involvement of endogenous nitric oxide, prostaglandins and potassium ion in the cytoprotective action of *S. mombin* L. was also investigated. The extract showed a significant ( $p < 0.05$ ) colonic cytoprotective effect in acetic-acid induced ulcerative colitis (prophylactic) and acetic-acid induced ulcerative colitis (curative) models when compared to control. Antioxidant analysis showed the ability of *S. mombin* L. to attenuate oxidative stress by decreasing the lipid peroxide level and to inhibit accumulation of free radicals' generation during LPO (lipid peroxidation) process. *S. mombin* L. showed presence of flavonoids, tannins, reducing sugar, cardiac glycosides and steroids/terpenes. *S. mombin* L. exhibited cytoprotective effects in all acetic-acid induced ulcer models via the mechanism of reducing the aggressive activity of the immune system on the colonic mucosa thereby protecting the colonic mucosa.

**Keywords:** *Spondias mombin*, ulcerative colitis, extract, plant, inflammation.

### INTRODUCTION

Inflammatory Bowel disease includes ulcerative colitis and Crohn's disease. Ulcerative colitis is an inflammatory bowel disease of the large intestine, resulting in the formation of ulcers and inflammation of the inner lining of the colon. The disease is characterized by abdominal pain, diarrhea and rectal bleeding. It usually affects the lower section (sigmoid colon) and the rectum, but it can affect the entire colon. Annually, 2 to 14 people are diagnosed with ulcerative colitis per 100,000 persons [1]. In the United States, ulcerative colitis is more common in the Northeast and Midwest compared with the South and West. In Nigeria, it has been reported that the occurrence of this disease is on the increase, about 37 to 246 cases in about 100,000 people [2], are reported annually.

Anti-inflammatory drugs, Immune system suppressors, antibiotics, anti-diarrheal medications, iron supplements and pain relievers are the major used for standard treatment of the disease. However, adverse effects, inconvenient dosing schedules, and exorbitant pricing restricts their long-term use. There is thus the need for the development and discovery of new targets or leads that would combine efficacy with convenient dosing and such alternatives will have fewer side effects. *Spondias mombin* (SMB) of the Anacardiaceae family is native to Brazil [3]. Mainly found in the north and northeast regions of Brazil and also in some parts of West Africa such as Nigeria [4]. Its leaves are used in ethnomedicine for the treatment of several topical and systemic inflammatory diseases such as ulcerative colitis and for gastrointestinal disorders. Its roots are used as purgative, its bark as emetic, a remedy for diarrhea, hemorrhoids and gonorrhoea. Previous pharmacological investigations on the activities of the leaf extracts of SMB include antidiarrheal [5], arbotifacient [6], anti-inflammatory [7], antiepileptic, antipsychotic [5], anti-anemic [8], anti-fertility [9], anxiolytic [10], and anti-aging activities [11]. However, it appears that the information on beneficial effect of *S. mombin* in the treatment of colitis is limited. Thus, this study aims at evaluating the beneficial effects of the aqueous leaf extract of *S. mombin* and its possible mechanism of action in a rat model of colitis.

## MATERIALS AND METHODS

### Chemicals and reagents

The normal saline used was purchased from Changzhou Longkang Pharmaceuticals; Changzhou-City, Jiangsu, China, prednisolone was purchased from Alps Pharmaceutical Industry Co., Ltd., JAPAN, Vitamin E from Glenmark Pharmaceuticals Ltd., Mumbai, India, Acetic Acid from Airedale Chemical Holdings Group; West Yorkshire, UK, L-NAME, L-Arginine from Rochem International Inc. Hauppauge, NY, Glibenclamide from Prudence Pharmaceuticals; Gujarat, India, and Indomethacin from Chemimpex International; Illinois, USA.

### Plant collection and extraction

The leaves of *S. mombin* were obtained from a leaf vendor in Mushin market, Lagos. Five hundred grams of the leaves were air dried, pulverized and macerated in distilled water at room temperature for 48 hours. The aqueous extract was filtered, the filtrate was then oven dried after which the dried extract was scraped into sample bottles.

**Experimental animals:** Ninety (90) seven-week-old Wistar rats weighing between 80 and 120 g and twenty-five (25) seven-week-old mice (weighing between 18 and 22 g) were purchased from the Laboratory Animal Centre, College of Medicine, University of Lagos. The animals were housed in conventional wire mesh cages under standard laboratory conditions. They were allowed free access to water and rodent pelleted food throughout the period of experiment; having given them two weeks to acclimatize.

### Ethical consideration

Experimental procedures and protocols used in this study conform to the "Guide to the care and use of animals in research and teaching accordance with the National Institute of Health guidelines for the care and use of laboratory animals [12].

### Acute toxicity of the aqueous extract of *S.mombin*

Twenty-four (24) mice were distributed into two sets of four (4) groups. One set were administered 10, 100, 1000 or 2500 mg/kg of SMB orally and the other set were administered 10, 100, 500 or 1000 mg/kg intraperitoneally. The animals were observation for two weeks to monitor behavior and mortality [13].

### Identification of the phytoconstituents in *S. mombin*

#### Qualitative test

The aqueous extract of SMB was assayed for the presence of phytoconstituents such as alkaloids, tannin, phenols, steroids, flavonoids, glycosides and terpenes [14].

### Investigation of the effect of SMB sub-acute dosing in acetic acid-induced ulcerative colitis in rats

Experimental animals were randomly distributed into seven (7) groups of four (4) animals each. Three of the seven group of animals were pretreated orally for seven days with 50, 100 or 200 mg/kg of the aqueous extract of the leaves of SMB. The fourth and the fifth groups (control healthy group and control colitis group) were pretreated with 1 mL/kg saline. The sixth group (positive control) was pretreated with 4 mg/kg prednisolone, while the seventh group (positive control) was pretreated with - 30 µg/kg/day of vitamin E.

### Induction of ulcerative colitis

On the sixth day, experimental animals were anesthetized with 40 mg/kg intraperitoneal sodium pentobarbitone. Colitis was induced by a single intracolonic administration of 1 mL 4% acetic acid into the descending colon by means of a soft pediatric catheter introduced 8cm

into the anus of the animal. The rats were kept in a head-down position during and briefly after the acetic acid administration. They were returned to their respective cages after recovery from anaesthesia and given free access to water and food [15].

### Assessment of colonic damage and response to treatment

All the experimental animals were euthanized 48 hours after post-colitic induction with an over dose of sodium pentobarbitone. The distal colon of each animal was excised and the luminal contents flushed out with cold normal saline. The colon was weighed and its length measured. The effects of test agents and increase in colitis parameters such as stool consistency, colonic mucus, colon weight/length ratio, ulcer score and ulcer index were assessed [16].

### Investigation of the curative potential of SMB in ulcerative colitis

Experimental animals were randomly distributed into four (4) groups of four (4) animals each. Ulcerative colitis was induced with 4% acetic acid before treatment commenced. One group received 200 mg/kg of the aqueous extract of the leaves of SMB. The second group received 4mg /kg prednisolone. The third group received 1 mg/kg saline, while the fourth group served as the healthy control group, which received 1 ml/kg saline.

### Assessment of colonic damage and response to treatment

All the experimental animals were euthanized 84 hours after post-colitic induction with an over dose of sodium pentobarbitone. The distal colon of each animal was excised and the luminal contents flushed out with cold normal saline. The colon was weighed and its length measured. The effects of test agents and increase in colitis parameters such as stool consistency, colonic mucus, colon weight/length ratio, ulcer score and ulcer index were assessed [16].

### Investigation of the possible involvement of endogenous nitric oxide (NO) in the cytoprotective action of SMB

L-Arginine, a precursor of NO was administered to a group of four animals subcutaneously fifteen minutes before the administration of 200 mg/kg of the extract orally. Colitis was induced using 4 mL of acetic acid thirty minutes later and animals were sacrificed 48 hours post-induction and the index was scored. To another group containing four animals, L-Arginine a precursor of NO was administered subcutaneously. Colitis was induced using 2 mL of acetic acid thirty minutes later and animals are sacrificed 48 hours post- induction and the index was scored.

To another group of four animals, N<sup>G</sup>- nitro L- arginine methyl ester, an inhibitor of NO synthase activity, was administered subcutaneously fifteen minutes before the administration of the extract orally. Colitis was induced using 2 mL of acetic acid thirty minutes later and the animals were sacrificed 48 hours post-induction and the index was scored.

### Investigation of the possible involvement of prostaglandin (PG) in the cytoprotective action of SMB

To a group of four animals, Indomethacin was administered subcutaneously followed by an oral administration of the extract. Colitis was then induced by the administration of 2mL acetic acid thirty minutes after drug administration. The animals are sacrificed 48 hours later and the ulcer index scored.

### Investigation of the possible involvement of potassium ion in the cytoprotective action of SMB

To a group of four animals, Glibenclamide (2 mg/kg) was administered orally thirty minutes before an oral administration of the extract. Colitis was then induced by the administration of 2mL acetic acid thirty minutes after drug after the administration and the ulcer index is scored

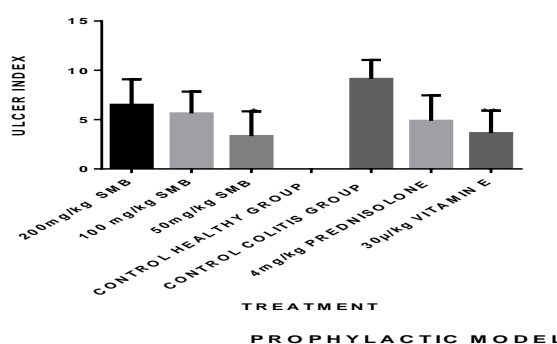
**Investigation of single doses of extract on acetic acid- induced ulcerative colitis**

Animals are randomly distributed into four (4) groups containing four (4) animals each. Three of the seven group of animals were pretreated orally for seven days with 50, 100 or 200 mg/kg of the aqueous extract of the leaves of SMB. The fourth (control colitis group) was pretreated with 1 mL/kg saline. One hour later, colitis was induced with two milliliters (2 mL) acetic acid. Animals were sacrificed 48 hours after the administration of acetic acid and the ulcer index is scored.

**RESULTS**

In the oral acute toxicity test carried out in mice, the extract produced no toxic symptoms or mortality at 10, 100, 1000 and 2500 mg/kg respectively, however at doses lower than 1000 mg/kg via the intraperitoneal route, the mice showed abdominal contraction and frequent bowel movements at a mean onset of action of fifteen minutes and sedation at a mean onset of action of 45 minutes. At 1000 and 2500 mg/kg, abdominal contraction at mean onset of action of fifteen minutes, frequent bowel movements, and sedation at a mean onset of action of 45 minutes were observed. No death was recorded thereby showing that the extract is probably lethal at a dose greater than 2500 mg/kg for the oral administration and 1000mg/kg for the intraperitoneal administration. Phytochemical screening of the aqueous extract of SMB revealed the presence of secondary metabolites like flavonoids, alkaloids, phytosterols, terpenoids, tannin, antioxidants and phenolic compounds etc. A significant (p<0.05) reduction in ulcer index (63.5% protection) when compared with the control was produced by dose of 50 mg/kg oral administration of aqueous leaf extract of SMB for seven (7) days the activity, which compared with Vitamin E, the standard which produced significant (p<0.01) reduction in ulcer index (60.3% protection) when compared to the control colitis group. At 100 mg/kg and 200mg/kg of the extract evaluated, a reduction in ulcer index of 38.4% and 28.8% protection was produced respectively, while prednisolone produced an ulcer index of 46.6% protection (Fig 1). Stool consistency was scored in the animals from each group; induction of UC recorded an increase. The groups that received the extract and the standard drugs featured a steady decrease; 50 mg/kg SMB produced the highest efficacy and followed by Vitamin E.

Oral administration of Prednisolone produced significant (p<0.01) and (p< 0.05) reduction in colon weight and length respectively when compared to control. 200mg/kg extract produced significant (p<0.01) and (p<0.05) reduction in colon weight and length respectively with a colon weight/ length ratio of 0.1576 when compared to control. 100mg/kg extract produced significant (p<0.01) reduction in colon weight and colon length when compared to control. 50mg/kg extract produced significant (p<0.001) and (p<0.01) reduction in colon weight and length respectively. Vitamin E produced significant (p< 0.01) and (p<0.05) reduction in colon weight and length respectively while significant (p<0.001) reduction in colon weight and colon length was observed when compared to control (Table 1). The aqueous leaf extract (50mg/kg) produced the lowest colon weight/length ratio followed by the standard drug Vitamin E, 200mg/kg extract, 100mg/kg extract and prednisolone (Table 6). High mucus content was observed in the colon of the groups that received 50mg/kg and Vitamin E. Moderate mucus content was observed in the group that received 100mg/kg aqueous leaf extract while Low mucus content was observed in the groups that received 200mg/kg aqueous leaf extract and prednisolone. There was no mucus content in the control colitis group (Table 2).



**Figure 1:** Bar chart showing the effect of SMB sub-acute dosing in acetic acid-induced ulcerative colitis in rats

Values are mean± S.E.M (n=4) \*p<0.05, \*\*p<0.01 when compared to control. (One-way ANOVA followed by Dunnett’s multiple comparisons test).

**Table 1:** The effect of aqueous extract of SMB sub-acute dosing on colon weight (g), colon length (cm) and colon weight/length (g/cm) ratio colitic rats.

Parameters	Prednisolone	200 mg/kg SMB	100 mg/kg SMB	50 mg/kg SMB	Control healthy group	Control colitis group	Vitamin E
weight (g)	0.84± 0.12	1.04± 0.06	0.99± 0.05	0.73± 0.05	0.65± 0.02	1.76 ± 0.04	0.81± 0.08
length (cm)	5.98± 0.41	6.35± 0.266	6.18± 0.25	5.90± 0.25	5.80± 0.12	7.88± 0.32	6.40± 0.50
weight/length ratio (g/cm)	0.17	0.16	0.16	0.13	0.12	0.22	0.13

Values are represented as mean ± S.E.M

**Table 2:** Mucus content for the effect of SMB sub-acute dosing in acetic acid induced ulcerative colitis in rats

Prednisolone	200 mg/kg SMB	100 mg/kg SMB	50 mg/kg SMB	control healthy group	control colitis group	Vitamin E
Low	Low	Moderate	High	High	None	High

The oral administration of 200mg/kg SMB leaf extract and prednisolone, a standard drug produced significant (p<0.05) reduction in ulcer index when compared to control. At 200mg/kg, the extract produced a protection of 80.4%, while the standard drug prednisolone produced a 72.0% protection (Fig 2). There was an increase in stool consistency on induction of UC, but a steady decrease was observed on administration of plant extract and standard drug. A dose of 200 mg/kg of the plant extract produced a higher decrease in stool consistency compared to prednisolone, a standard drug.

No mucus content was found in the colon of the animals treated with 200 mg/kg plant extract and prednisolone (Table 2). Oral administration of 200 mg/kg SMB leaf extract produced significant (p<0.0001) reduction in colon weight and colon length when compared to control. The standard drug, prednisolone produced significant (p<0.0001) reduction in colon weight and significant (p<0.01) reduction in colon length when compared to control, while the control healthy group produced significant (p<0.0001) reduction in colon weight and colon length when compared to control. (Table 3).

Prednisolone produced the lowest colon weight/ length ratio. (Table 3). High mucus content was observed in the colon of the groups that

received 200 mg/kg and Prednisolone, there was no mucus content in the control colitis group (Table 3).

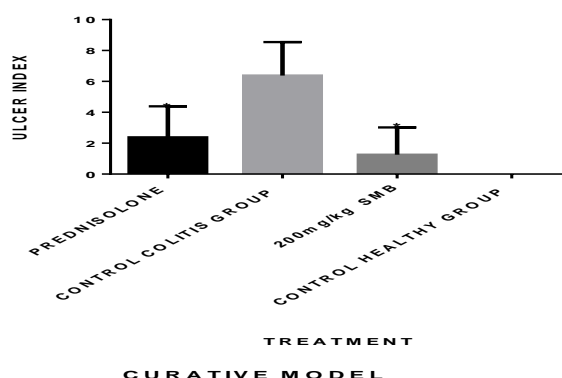


Figure 2: Bar chart showing investigation of curative potential of SMB in ulcerative colitis induced by acetic acid in rats

Values are mean ± S.E.M (n=4) \*p<0.05 when compared to control.

(One-way ANOVA followed by Dunnett’s multiple comparisons test).

Table 3: The effects of aqueous extract of SMB on Colon weight (g), colon length (cm) and colon weight/length ratio (g/cm) ratio of acetic acid induced ulcerative colitis in a curative rat model

Parameters	200 mg/kg SMB	Prednisolone	Control healthy group	Control colitis group
Weight(g)	0.7775± 0.1108	0.8360± 0.1147	0.7175± 0.0670	1.748±0.0588
Length(cm)	6.050± 0.1258	6.775± 0.0854	6.150± 0.2327	7.950± 0.2102
weight/length(g/cm)	0.1285	0.1234	0.1167	0.2199

Values are represented as mean ± S.E.M

The pre-treatment with N<sup>G</sup>- nitro L-arginine methyl ester (L-NAME 10 mg/kg) intraperitoneally produced no significant decrease in the ulcer index of extract at 50mg/kg compared to the control group. Pre-treatment with L-NAME produced 18.20% protection, while the oral Pre-treatment with L-Arginine at 750mg/kg produced a significant (p<0.01) reduction in the ulcer index of extract at 50mg/kg compared to the control group. Pre-treatment with L-Arginine produced 50.65% protection. The oral administration of L-Arginine at 750mg/kg produced a significant (p< 0.05) reduction in ulcer index when compared to control with a 42.9% protection. At 50 mg/kg extract, oral pre-treatment with Indomethacin (10 mg/kg) produced a significant (p<0.05) decrease in the ulcer index compared to the control group. Pre-treatment with Indomethacin produced 49.80% protection. At 200 mg/kg extract, oral pre-treatment with glibenclamide (2 mg/kg) produced a significant (p<0.05) decrease in the ulcer index compared to the control group. Pre-treatment with glibenclamide produced 46.75% protection. (Fig 3)

Values are mean ± S.E.M (n=4) \*p<0.05, \*\*p<0.01, \*\*\*p<0.001 when compared to control. (One-way ANOVA followed by Dunnett’s multiple comparisons test).

At 50 mg/kg and 100 mg/kg single dose oral administration of SMB, there was significant (p<0.01) reduction in ulcer index when compared to control, while 200 mg/kg single dose oral administration produced no significant reduction in ulcer index when compared to control. The maximum effect occurred at 100 mg/kg (86.6% protection). The effect produced was a non-dose dependent with 100 mg/kg, 50 mg/kg and 200 mg/kg producing 86.6%, 74.5% and 50.7% percentage protection respectively (Fig 4).

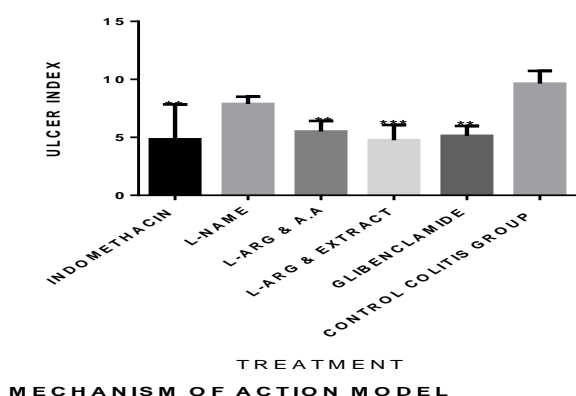


Figure 3: Bar chart showing investigation of mechanism of action of SMB

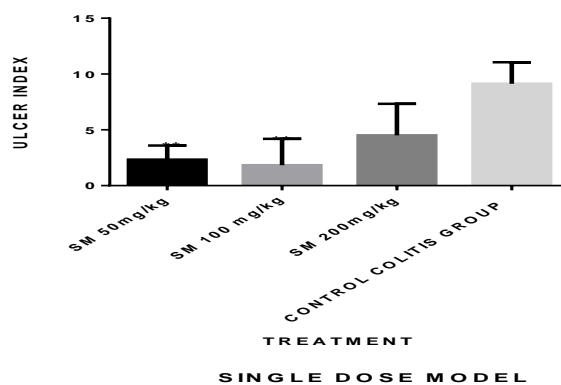


Figure 4: Bar chart showing investigation of single doses of extract on acetic acid-induced ulcerative colitis results

Values are mean ± S.E.M (n=4) \*\*p<0.01 when compared to control. (One-way ANOVA followed by Dunnett’s multiple comparisons test).

## DISCUSSION

Ulcerative colitis is characterized by mucosal inflammation and ulcerations with a variable extent and severity, is a major ailment that affects humans and develops as a result of an abnormality in the function of the immune system, in which it overreacts to normal bacteria in the digestive tract. Conventional therapies remain the cornerstone of treatment for the majority of patients with ulcerative colitis and an effective antiulcer drug will act either by reducing the aggressive activity of the immune system on the colonic mucosa or by increasing mucosal resistance against them.

Rectal administration of 4% Acetic-acid to experimental rodents to induce UC is a well-established animal model, which phenotypically resembles human colon inflammation [17]. It also causes colonic epithelial lesions and necrosis associated with neutrophils and macrophages infiltration to the damaged colon, indicating inflammatory conditions.

In present study, the 4% acetic-acid administration resulted in a significant increase in colonic weight and induced severe ulceration and tissue necrosis associated with inflammatory infiltrate and goblet cell hyperplasia as indicated in the results of the histopathological estimations. Similar pathological impairments were reported in earlier studies using the same animal model [18]. Further observation was the reduction in colonic mucus content, which also corroborated the findings of Ahmed *et al.*, (2012) [19]. Colonic mucus plays an important protective role against chemically induced ulceration, which may also facilitate the repair of the damaged epithelium [20]. Although, numerous pharmacotherapies have been suggested for UC treatment, the side effects and toxicities of these medications are a major clinical problem [21]; hence, the need for development of safer therapies.

In this present study, the aqueous extract of SMB showed significant amelioration of the damaging effects of acetic acid in a rat model of ulcerative colitis. This protective activity could be attributed to its antioxidant and anti-inflammatory properties. The aqueous leaf extract (50 mg/kg) of SMB produced significant reduction in ulceration in the effect of SMB sub-acute dosing in acetic acid-induced ulcerative colitis rats. The reduction of colon /length ratio observed at all doses of the extract administered, indicative of its ability to treat or reduce inflammation. The high mucus content observed in the colon of the groups that were treated with 50 mg/kg and 100 mg/kg aqueous leaf extract of SMB further validated the beneficial effect of the decoction in UC.

At a dose of 200 mg/kg SMB, a high rate (80.4 %) of protection, and a steady increase in stool consistency was observed, which was superior to the activity (72.0 %) recorded by prednisolone. Consequent to the high efficacy displayed by SMB in the disease condition, the possible involvement of endogenous nitric oxide (NO), endogenous prostaglandins and endogenous potassium ion were explored in order to elucidate the mechanism of action. Nitric oxide (NO) is considered one of the most important defensive endogenous agents in the gastrointestinal tract [22]. It is synthesized by nitric oxide synthase (NOS) from L-arginine [23]. The assessment of the involvement of endogenous NO in colitis rat models showed a significant reduction in the protective effect attributable to the extract. These finding indicate the possible participation of NOS pathway in the cytoprotection exerted by SMB, supporting the premise of the free radical scavenging effect of this extract.

Prostaglandins represent one of the most important components of mucosal defense in the small intestine and colon. Prostaglandins derived from COX-2 are important in promoting the healing of mucosal injury, in protecting against bacterial invasion, and in down-regulating the mucosal immune system. Suppression of COX-2 in a setting of gastrointestinal inflammation and ulceration has been shown in experimental models to result in impairment of healing and exacerbation of inflammation-mediated injury. The assessment of the involvement of endogenous prostaglandins and potassium ions in an

ulcerative colitis rat model recorded a non-significant increase in ulcer index.

Aqueous extract of SMB contains flavonoids, tannins, cardiac glycosides, reducing sugars, steroids and terpenoids. The presence of flavonoids facilitates the increase in mucosal prostaglandin levels and the inhibition of histamine release, this could possibly contribute to the positive protective effect of the extract [24]. Tannins, another group of constituents of SMB help prevent ulcer formation as a result of their protein precipitating and vasoconstricting effects [25]; their astringent action helps to precipitate microproteins on ulcer site, thereby, forming an impervious layer over the lining, which hinders induced colonic ulcer in rats [25]. The effect of aqueous leaf extract of SMB in this study may be due to one or a combination of these phytoconstituents.

## CONCLUSION

The study showed that the aqueous leaf extract of *Spondias mombin* is beneficial for UC management. However, the efficacy is higher both after a single dose exposure and also for curative purpose than when administered sub-acute and indicated for prophylaxis.

Nitridergic pathway might be possibly involved in its cytoprotective action.

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#### HOW TO CITE THIS ARTICLE

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