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COMBINED ADMINISTRATION OF SPONDIAS MOMBIN AND FICUS EXASPERATA LEAF EXTRACTS STALL INDOMETHACIN-MEDIATED GASTRIC MUCOSAL ONSLAUGHT IN RATS.

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Abstract

Background: Despite the rapidly changing concept of gastric ulcer management from conventional vagotomy, H_2 receptor antagonists and antacids to proton pump inhibitors, gastrointestinal toxicity remains an impediment to their application in clinical practice. Combined administration of two or more plant extracts with therapeutic efficacy may proffer solution to this menace. This study investigated the combined gastroprotective effects of Spondias mombin and Ficus exasperata leaf extracts against indomethacin-induced gastric ulcer in rats.
Materials and Methods: Thirty rats were randomized into six groups of five animals each and ulceration was induced by a single oral administration of indomethacin (30 mg/kg body weight). Ulcerated rats were orally administered with Spondias mombin, Ficus exasperata at 200 mg/kg body weight and esomeprazole (a reference drug) at a dose of 20 mg/kg body weight once daily for 21 days after ulcer induction. At the end of the experiment, gastric secretions and antioxidant parameters were evaluated.
Results: We observed that the significantly increased ($P < 0.05$) ulcer index, gastric acidity, malondialdehyde level and pepsin activity were markedly reduced following co-administration of S. mombin and F. exasperata. The extracts also effectively attenuated the reduced activities of superoxide dismutase and catalase as well as pH, mucin content and reduced glutathione level in the ulcerated rats.
Discussion and Conclusion: These findings are indicative of gastroprotective and antioxidative attributes of the two extracts which is also evident in the % protective index value obtained. The available evidences in this study suggest that the complementary effects of S. mombin and F. exasperata proved to be capable of ameliorating indomethacin-mediated gastric ulceration and the probable mechanisms are via antioxidative and proton pump inhibition.

Key words: Esomeprazole; Gastroprotective; NSAIDS; Proton pump inhibitor; Ulceration.

Introduction

Gastrointestinal toxicity has been identified as a major factor militating against applications of non-steroidal anti-inflammatory drugs (NSAIDS) in clinical practice (Hawkey, 1990). An estimated 25% of gastric ulcer cases which ranked fourth in causing morbidity and mortality in the world have been linked to the use of NSAIDs like indomethacin (Lancaster-Smith et al., 1991; Halter et al., 2001). Inspite of the dominance of orthodox therapies in the management of diseases including gastric ulcer, a considerable proportion of the world now rely on traditional systems of medicine (WHO, 2000). This has been prompted, in part, by obvious side effects, microbial resistance and high cost of synthetic drugs (Hawkins and Hanks, 2000). Hence, there is a specific need to develop non-toxic, efficacious, readily available and more affordable antiulcer herbal formulations. These are common attributes of many medicinal plants.

The medicinal part of a plant may be administered either solely or in combination with part (s) of other plants to exercise their full medicinal effects. Synergistic effects of plant extracts have long been studied and advocated for use in medicinal practice. Sivaraj et al. (2009) reported the anti-hyperglycemic and anti-hyperlipidemic effects of combined administration of *Cassia auriculata* and *Aegle marmelos* leaf extracts in streptozotocin induced diabetic rats. Combined administration of Telfaira occidentalis and Vernonia amygdalina has also been reported to ameliorate garlic-induced hepatotoxicity in rats (Sabiu et al., 2014). Inspite of the inherent medicinal potentials of many plants, the potency of their combined administration is yet to be scientifically investigated.

Spondias mombin commonly known as 'Iyeye' in the south-western part of Nigeria is a fructiferous tree in the Family Anacardiaceae. The plant grows in rain forests and coastal areas, attaining a height of 15-22 meters (Ayoka et al., 2008). It is commonly used in folk medicine to cure many diseases due to its potent bioactive principles including tannins, saponins, flavonoids, phenolics and anthraquinone glycosides (Abo et al., 1999; Maduka et al., 2014). Antioxidant vitamins; alpha-tocopherol and ascorbic acid have been detected in its leaf extracts (Mada et al., 2014). Tea from its flowers and leaves is taken as an analgesic and anti-inflammatory cure against stomach ache and discomfort (Villegas et al., 1997). Ayoka et al. (2008) have also reported decoction from its leaves to be therapeutic against urethritis, cystitis as well as eye and throat inflammations. The gum from *S. mombin* has also been exploited as an expectorant and vermifuge. The leaf extract of the plant has been outstandingly advocated for use in speedy wound healing processes, hemorrhoids and inflamed mucous membrane due to its tannin content (Njoku and Akumefula, 2007). Its pharmacological potencies such as antioxidative, antimicrobial, antimalarial and antibacterial have also been documented (Corthout et al., 1994; Villegas et al., 1997; Abo et al., 1999; Caraballo et al., 2004).

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Ficus exasperata Valh, called 'Epin', 'Anwerenwa' and 'Kawusa' respectively among the Yorubas, Igbos and Hausas in Nigeria, is commonly known as 'sand paper tree' belonging to Moraceae Family. Phytochemical analysis of the leaf extract of *F. exasperata* has revealed the presence of flavonoids, tannins, saponnins, alkaloids and cyanogenic glycosides (Ijeh and Ukweni, 2007). Its medicinal efficacy in treating many diseases has been researched. For instance, the South-Western people of Nigeria uses the decoction and infusion of F. exasperata leaves for the management, control and treatment of hypertension, diabetes mellitus and certain cardiovascular dysfunction (Odiba et al., 2012). Leaves of *F. exasperata* cooked with bananas are eaten for the treatment of gonorrhea (Anowi et al., 2012). Its leaf extract is also taken to suppress stomach ache, treat peptic ulcer and as antidote to poison (Akah et al., 2008).

Based on the remarkable attributes of *S. mombin* and *F. exasperata* particularly in alleviating stomach ache related disorders, the present study investigated their combined therapeutic efficacy on indomethacin-mediated gastric ulceration in rats.

Materials and Methods

Chemicals and Drugs

Indomethacin and thiobarbituric acid (TBA) were products of Sigma Chemical Co. (St. Louis, MO, USA). Esomeprazole was procured from Ranbaxy Laboratories, India. Distilled water was obtained from Biochemistry Laboratory, Kwara State University, Malete, Nigeria. Assay kits used were products of Randox Laboratories limited, United Kingdom. Other chemicals used were of analytical grade from reputable companies in the world.

Plant collection and authentication

Fresh leaves of *S. mombin* and *F. exasperata* (voucher numbers UIH001/1148 and UIH002/883 respectively) were collected from the botanical garden of University of Ilorin, Ilorin, Nigeria. The leaves were authenticated by Dr. A.A. Abdulrahaman of the Department of Biological Sciences (Botany Unit) of the University. Voucher specimens were prepared and deposited at the University Herbarium.

Experimental animals

Wistar strain albino rats with a mean weight of 180.00 ± 1.85 g were obtained from the Animal House of Kwara State University, Malete, Nigeria. The animals were kept in clean stainless cages placed in a well-ventilated room with optimum condition (temperature: 23 ± 1^{O}C, photoperiod: 12 h natural light and 12 h dark, relative humidity: 45-50%). They were acclimatized to animal house conditions for one week and were allowed free access to standard pellet feed (Top feeds Limited, Ibadan, Nigeria) and water ad libitum. The research was carried out following approval from the Ethical committee on the use of Laboratory Animals of the University.

Preparation of extracts

Leaves of *S. mombin* and *F. exasperata* were chopped into small pieces, air-dried at room temperature for 8 days to a constant weight and subsequently pulverized into fine powder used for the study. The powdered samples (400 g) of each plant were separately suspended in 4 litres of distilled water for 48 hrs. The solutions obtained for each plant were filtered and the resulting filtrates lyophilized. These were then stored in a desiccators for further use.

Ulcer induction

Gastric ulceration was induced in the animals according to the procedure described by Sayanti et al. (2007). Briefly, rats were administered with a single oral dose of indomethacin (30 mg/kg body weight (b.w.)). They were deprived of food but had free access to water 24 hours prior to ulcer induction. Various degrees of ulceration have manifested 4 hours after indomethacin administration.

Animal grouping and treatments

Thirty albino rats were randomized into six groups of five rats each. Group 1 (normal control) animals received only distilled water. Group 2 (ulcerated control) rats received only indomethacin and were sacrificed 4 hours after indomethacin administration. Animals in group 3 were given indomethacin and esomeprazole (20 mg/kg b.w.). Groups 4, 5 and 6 comprised ulcerated rats treated with F. exasperate (200 mg/kg b.w.), S. mombin (200 mg/kg b.w.) and both extracts co-administered respectively. Treatments with the reference drug and extracts commenced four hours after indomethacin administration and lasted for 3 weeks. These were orally administered once daily using oral intubator with ad libitum provision of food and water throughout the experimental period. The protocol conforms to the guidelines of the National Institute of Health (NIH, 1985) for laboratory animal care and use, and in accordance with the principles of good laboratory procedure (WHO, 1998).

Stomach excision and collection of gastric juice

On the twenty second day, the animals were humanely sacrificed under diethyl ether anaesthetization. The abdomen was opened and the stomach excised. The stomach was thereafter opened along greater curvature and gastric content was drained into a centrifuge tube. Five ml of distilled water was added and the resultant solution was centrifuged at 3,000 rpm for 10 minutes. The supernatant obtained was thereafter used for biochemical analyses.

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Determination of gastric ulceration parameters

Gastric acid output (volume) was determined in the supernatant by titration with 0.0025N NaOH. Free and total acidity were subsequently determined adopting the method of Grossman (1963). The pH of gastric juice was determined using a pH meter, while the procedures of Sanyal et al. (1971) and Corne et al. (1974) were used to determine specific pepsin activity and mucin concentration respectively.

Quantification of ulceration

Degrees of ulceration in the animals were quantified using the procedure outlined by Szabo et al. (1985). Briefly, cleaned stomachs were pinned on a corkboard and ulcers were scored using dissecting microscope with square-grid eyepiece based on grading on a 0–5 scale (depicting severity of hyperemia and lesions) as follows:
0—almost normal mucosa; 1—hyperemia; 2—one or two lesions; 3—severe lesions; 4—very severe lesions; 5—mucosa full of lesions
*Hyperemia: vascular congestions, Lesions: hemorrhagic erosions.

Areas of mucosal damage were expressed as a percentage of the total surface area of the glandular stomach estimated in square millimeters. Mean ulcer score for each animal was expressed as ulcer index (U.I) and the percentage of ulcer protective index was determined using the expressions: U.I = [Ulcerated Area/Total stomach area] X 100. %Protective index = [U.I in control- U.I in test] x 100/ U.I in control.

Preparation of stomach homogenate and assay of antioxidant indices

The stomach was homogenized in ice cold 0.1 M phosphate saline buffer (1:4 w/v, pH 7.4) and the homogenate centrifuged at 2500 rpm for 10 min. The resulting supernatant was thereafter used for assay of antioxidants status. Activities of superoxide dismutase (SOD) and catalase (CAT) were assayed using the methods of Marklund and Marklund (1974) and Sinha (1972) respectively. Reduced glutathione (GSH) level was estimated based on the method of Habig et al. (1974). Following the procedure described by Devasagayam and Tarachand (1987), level of lipid peroxidation measured in terms of malondialdehyde (MDA) was determined in the stomach homogenate.

Statistical analysis

Ulcer Protective index was expressed in percentage. Other results were expressed as mean of five determinations ± standard error of mean. One way analysis of variance (ANOVA) complemented with Student's t-test using SPSS software package for windows (Version 16) for differences between means was used to detect any significant differences ($p < 0.05$) between the treatment groups in this study.

Table 1: Effect of *S. mombin* and *F. exasperata* leaf extracts on ulcer indices of indomethacin ulcerated rats (n = 5, X ± SEM)

Group	Treatments	Ulcer index	% Protective index
1	Distilled water (Normal control)	00.00	-
2	IND (Ulcerated control)	19.14 ± 0.30^{a}	-
3	IND + ESP (20 mg/kg b.w)	3.53 ± 0.12^{b}	83.65
4	IND + F.E	6.63 ± 0.20^{c}	65.88
5	IND + S.M	5.42 ± 0.17^{b}	71.68
6	IND + F.E + S.M	4.00 ± 0.14^{b}	79.10

Values with different superscripts along the same column for the parameters are significantly different ($P < 0.05$).
IND: indomethacin (30 mg/kg b.w.), ESP: esomeprazole (20 mg/kg b.w.), F.E: *F. exasperata* (200 mg/kg b.w.), S.M: *S. mombin* (200 mg/kg b.w.).

Table 2: Effects of leaf extracts of *S. mombin* and *F. exasperata* on some gastric secretion indices of indomethacin ulcerated rats (n = 5, X ± SEM)

Treatments	Gastric volume (ml)	Free acidity (mEq/L)	Total acidity (mEq/L)	pH
Distilled H_20 (Normal control)	1.96 ± 0.11^{a}	13.28 ± 0.17^{a}	22.32 ± 0.89^{a}	6.40 ± 0.18^{a}
IND (Ulcerated control)	8.28 ± 0.13^{b}	51.90 ± 0.40^{b}	82.84 ± 1.58^{b}	2.30 ± 0.08^{b}
IND + ESP	2.12 ± 0.15^{a}	17.17 ± 0.75^{a}	26.32 ± 0.53^{a}	5.50 ± 0.31^{a}
IND + F.E	5.26 ± 0.09^{c}	37.08 ± 0.31^{c}	56.92 ± 0.77^{c}	4.18 ± 0.21^{a}
IND + S.M	4.42 ± 0.23^{a}	29.34 ± 0.26^{a}	49.86 ± 0.20^{a}	4.86 ± 0.15^{a}
IND + F.E + S.M	3.30 ± 0.56^{a}	22.24 ± 0.84^{a}	41.70 ± 0.92^{a}	5.42 ± 0.04^{a}

Values with different superscripts along the same column for the parameters are significantly different ($P < 0.05$).
IND: indomethacin (30 mg/kg b.w.), ESP: esomeprazole (20 mg/kg b.w.), F.E: *F. exasperata* (200 mg/kg b.w.), S.M: *S. mombin* (200 mg/kg b.w.).

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Table 3: Effect of leaf extracts of *S. mombin* and *F. exasperata* on gastric pepsin activity and mucin content of indomethacin ulcerated rats (n = 5, X ± SEM)

Group	Treatments	Pepsin activity (µg/ml)	Mucin content (µg/m)
1	Distilled water (Normal control)	100.21 ± 0.03[a]	396.23 ± 0.20[a]
2	IND (Ulcerated control)	295.03 ± 0.05[b]	195.35 ± 0.30[b]
3	IND + ESP	110.65 ± 0.01[a]	382.43 ± 0.10[a]
4	IND + F.E	136.32 ± 0.20[a]	263.12 ± 0.30[c]
5	IND + S.M	130.63 ± 0.04[a]	345.39 ± 0.40[a]
6	IND + F.E + S.M	115.26 ± 0.09[a]	369.28 ± 0.50[a]

Values with different superscripts along the same column for the parameters are significantly different (P < 0.05).
IND: indomethacin (30 mg/kg b.w.), ESP: esomeprazole (20 mg/kg b.w.), F.E: *F. exasperata* (200 mg/kg b.w.), S.M: *S. mombin* (200 mg/kg b.w.).

Results

Table 1 showed the effects of leaf extracts of *S. mombin* and *F. exasperata* on the ulcer index and % ulcer protective index in the experimental animals. Oral administration of 30 mg/kg b.w. of indomethacin caused a significant ($p < 0.05$) increase in the degree of ulceration (Ulcer index) in the rats. A significant improvement in the level of protection against ulceration was however observed following treatment with the extracts. Co-administration with both extracts offered highest protection relative to F. exasperata alone and compared well with the standard drug (Esomeprazole) used.

Effects of leaf extracts of *S. mombin* and *F. exasperata* on gastric secretions of indomethacin ulcerated rats was presented in Table 2. Indomethacin administration caused significant ($p < 0.05$) decrease in pH value with a corresponding significant ($p < 0.05$) increase in gastric volume and thus, free and total acidity of gastric content. Treatments with the extracts produced significant increase in pH value coupled with significant decrease in gastric volume free and total acidity when compared to untreated-ulcerated rats. The efficacious effects were however more pronounced in the rats wholly treated with S. mombin and those co-administered with both extracts.

Indomethacin administration brought about a significant ($p < 0.05$) increase in specific activity of pepsin as well as significant reduction ($p < 0.05$) in mucin content of gastric juice of ulcerated rats when compared with the normal control (Table 3). The observed changes in these parameters were significantly attenuated ($p < 0.05$) after treatment with either extracts of *S. mombin/F. exasperata* or both extracts co-treated rats. Co-administration of both extracts revealed more potent efficacy in the modulation of both pepsin and mucin contents of gastric juice of ulcerated rats.
Figures 1-3 revealed the effects of *S. mombin* and *F. exasperata* on the lipid peroxidation and antioxidant status of gastric mucosal of indomethacin ulcerated rats. MDA level was significantly increased ($p < 0.05$) in the ulcerated animals (Figure 1). Interestingly, both extracts in all formulations significantly reduced ($p < 0.05$) the level of MDA comparable to normal. A significant elevation ($p< 0.05$) was also observed in the activities of SOD, CAT (Figure 2) and GSH level (Figure 3) in the extracts treated rats. Except for CAT activity, leaves extract of *F. exasperata* remarkably proved effective in ameliorating the effect of indomethacin on stomach antioxidant status of the animals, treatment with *S. mombin* alone and combined administration with both extracts offered better therapeutic intervention and compared favourably well with both normal control and standard drug used in the study.

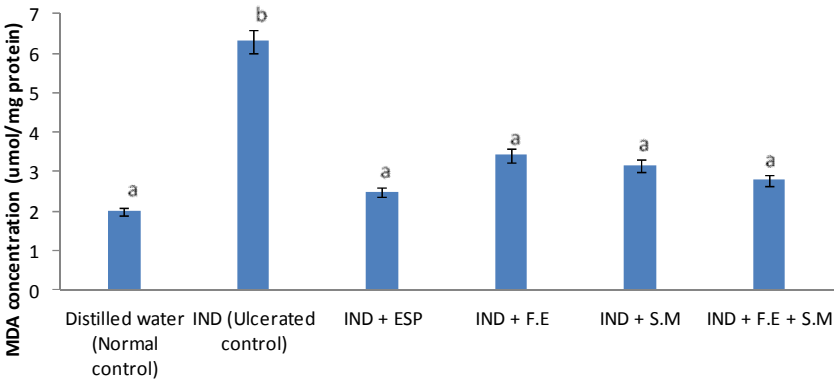

Figure 1: Effect of leaf extracts of *S. mombin* and *F. exasperata* on gastric malondialdehyde (MDA) level of indomethacin ulcerated rats (n = 5, *X* ± SEM)

Bars with different superscripts for the parameter are significantly different (P < 0.05).
IND: indomethacin (30 mg/kg b.w.), ESP: esomeprazole (20 mg/kg b.w.), F.E: *F. exasperata* (200 mg/kg b.w.), S.M: *S. mombin* (200 mg/kg b.w.).

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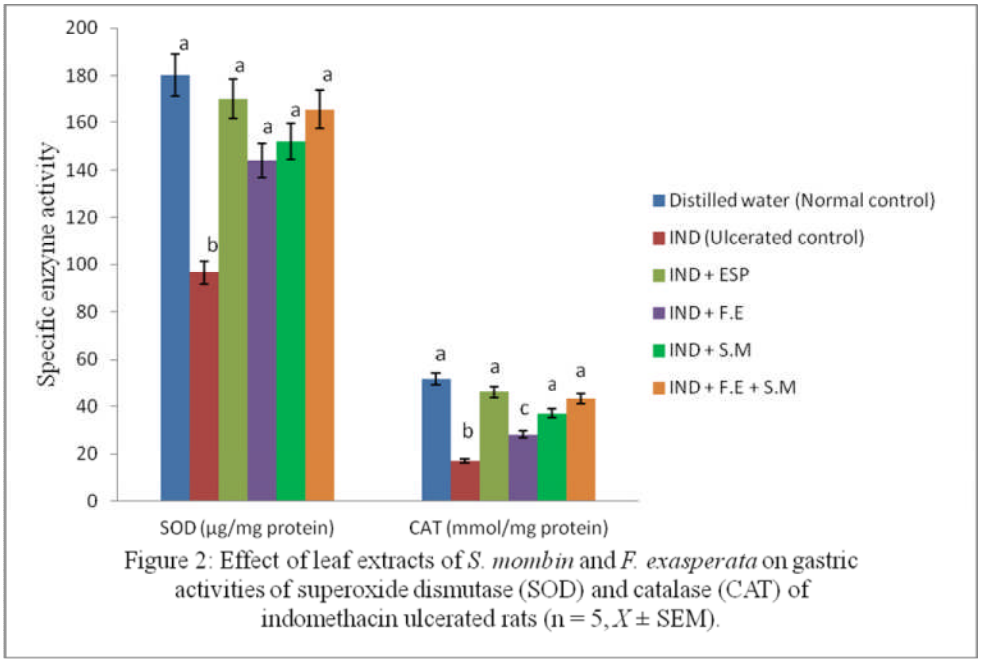

Figure 2: Effect of leaf extracts of *S. mombin* and *F. exasperata* on gastric activities of superoxide dismutase (SOD) and catalase (CAT) of indomethacin ulcerated rats (n = 5, $\bar{X} \pm$ SEM).

Bars with different superscripts for each parameter are significantly different (P < 0.05).
IND: indomethacin (30 mg/kg b.w.), ESP: esomeprazole (20 mg/kg b.w.), F.E: *F. exasperata* (200 mg/kg b.w.), S.M: *S. mombin* (200 mg/kg b.w.).

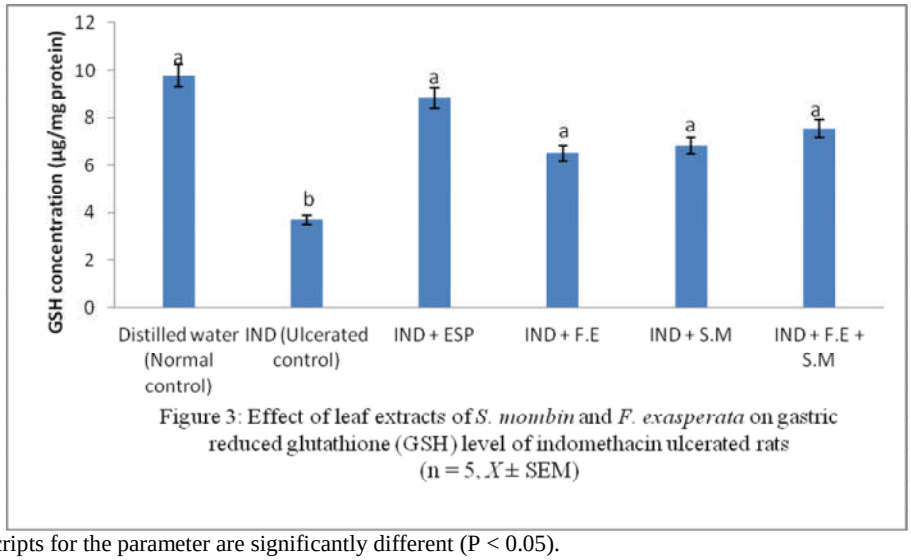

Figure 3: Effect of leaf extracts of *S. mombin* and *F. exasperata* on gastric reduced glutathione (GSH) level of indomethacin ulcerated rats (n = 5, $\bar{X} \pm$ SEM)

Bars with different superscripts for the parameter are significantly different (P < 0.05).
IND: indomethacin (30 mg/kg b.w.), ESP: esomeprazole (20 mg/kg b.w.), F.E: *F. exasperata* (200 mg/kg b.w.), S.M: *S. mombin* (200 mg/kg b.w.).

Discussion

Indomethacin-mediated gastric ulceration has been linked to uncontrolled acid secretion and damage to the mucosal defense system in experimental animals (Lichtenberger, 2005). This is due in part, to inhibition of cyclooxygenase that prevents prostaglandin synthesis and epithelial cell proliferation as well as involvement of free radicals which results in altered permeability and depletion of gastric mucus (Wada et al., 1997; Dae et al., 2014; Hong et al., 2014). An understanding of the role of these factors might be of utmost relevance in designing new antiulcer drugs. With the latent biotoxic side effects and considerably high cost of synthetic drugs, exploiting natural products of plant source which are believed to be non-toxic, efficacious and affordable will be most appropriate in the treatment of gastric ulcer and other toxicity related disorders.

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Medicinal plants play vital role in sustaining human health and in the prevention of certain diseases, including gastric ulcer resulting from drug toxicity (Raji et al., 2011). Their therapeutic potency could either be unitarily or synergistically exploited (Shen-nong, 2002; Sivaraj et al., 2009; Sabiu et al., 2014). In this study, the complementary gastroprotective effect of *S. mombin* and *F. exasperata* leaf extracts on indomethacin-induced ulceration in rats was investigated.

Gastric analysis of biochemical indices (gastric volume, pH, pepsin, bicarbonate and mucus level) for stomach is often employed to ascertain its integrity following exposure to pharmacological agents (Biplab et al., 2011). High pH value is a manifestation of decreased hydrogen ion concentration in gastric juice. This has been linked to ulcer genesis and gastric damage in experimental animals (Lüllmann et al., 2000). Also, mucin protects the gastric mucosa aided by its viscous and elastic nature. This is due mainly to its water and glycoproteins components that extend over gastrointestinal mucosa thereby conferring high level of protection against heamorrhagic erosions (Inas et al., 2011).

In the present study, the significant increase in ulcer index, gastric juice free and total acidity and pepsin activity as well as reduced mucin content following oral administration of indomethacin in the ulcerated rats may be attributed to either free radicals formation or inhibition of prostaglandin synthesis. Decreased prostaglandin level has been linked to impaired gastroprotection and also implicated in increased gastric secretion which is an important event in the pathogenesis of mucosal ulceration. This agrees with the reports of Bech et al. (2000), Biplab et al. (2011) and Muhammed et al. (2012) where indomethacin was reported to have caused alterations in gastric secretions of rats. Conversely, treatments with the two extracts significantly reduced ulcer index, gastric juice free and total acidity and pepsin activity. A significant increase was also observed in the mucin content of the extracts treated rats. In fact the effects noticed for pH, mucin content and pepsin activity compared favourably well with both normal control and standard drug employed in this study and indeed suggestive of their probable gastroprotective potentials.

An imbalance between free radicals and antioxidant status in animals result in oxidative stress which further deregulates cellular functions leading to different pathological conditions (Sabiu et al., 2014). In the present study, the reduced activity of antioxidant enzymes (SOD and CAT) and GSH level as well as the increased concentration of MDA in the stomach of indomethacin ulcerated rats is a manifestation of excessive free radicals formation and enhanced lipid peroxidation resulting in mucosal damage. Free radicals underscore antioxidant enzymes activities and initiate lipid peroxidation which is an important event in the toxicity mechanism of indomethacin (Halici et al., 2005). Indomethacin has previously been reported to reduce GSH level and decrease antioxidant enzymes (SOD, CAT and GST) activity in rat stomach thereby inducing gastric ulceration (Odabasoglu et al., 2006). This is associated with overpowering of the cellular antioxidant defense systems by free radicals ravaging influence that subsequently results in stomach oxidative injury. However, the significantly reduced concentrations of MDA and GSH coupled with marked increase in the activities of the enzymes following treatment with leaf extracts of *S. mombin* and *F. exasperata* is an obvious indication of antiperoxidative attribute and thus antioxidative potential.

The enhanced therapeutic effect elicited by *S. mombin* than *F. exasperata* in this study may be attributed to its excellent mucus secretory potential which might have facilitated increased mucin content. This in turn has encouraged speedy wound healing of the ulcerated areas of the mucosal epithelia and shielded the gastrointestinal membrane, thus abrogating the deleterious influence of indomethacin in the ulcerated rats. An increase in mucus production has been opined to protect ulcer crater against irritating stomach secretions (HCl and pepsin) thereby enhancing the rate of the local healing process (Naito et al., 1995). Generally, the protection offered by the leaf extracts of *S. mombin* and *F. exasperata* against indomethacin-induced gastric ulceration may be linked to their beneficial medicinal attributes occasioned by phytochemical constituents. These include ability to scavenge free radicals and regulate mucosal membrane permeability thereby countering the effect of indomethacin on gastric acid secretion. This is in agreement with the submissions of Inas et al. (2011), Muhammed et al. (2012) and Gede-Adebayo et al. (2013), where gastroprotective potentials of plant extracts against indomethacin ulcerated rats were associated with their various phytonutrients. Since esomeprazole is a proton pump inhibitor, then the effect produced by the two extracts might have perhaps mimic its mechanism of action by modulating cells in the mucosal lining of the stomach against excess acid secretion (Tulassay et al., 2008; Fornai et al., 2011).

Overall, the attenuation of onslaughts of indomethacin by administration of *S. mombin* and *F. exasperata* extracts is suggestive of their potent gastroprotective and antioxidant attributes in rats. Though, the effects were prominently exhibited by *S. mombin*, their synergistic efficacy is formidable and thus recommended against gastric ulcer.

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