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Original Article

Indomethacin-induced gastric ulceration in rats: Ameliorative roles of *Spondias mombin* and *Ficus exasperata*

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Abstract

Context: *Spondias mombin* Linn (Anacardiaceae) and *Ficus exasperata* Valh (Moraceae) are botanicals with known phytotherapeutic potentials in the traditional system of medicine in the world.

Objective: The objective of this study is to investigate the quantitative polyphenolic constituents and gastroprotective effects of aqueous leaf extracts of *Spondias mombin* and *Ficus exasperata* against indomethacin-induced gastric ulcer in rats.

Materials and methods: Ulceration was induced by a single oral administration of indomethacin (30 mg/kg body weight (b.w.)). Ulcerated rats were orally administered

mombin and *Ficus exasperata* at a dose of 100 and 200 mg/kg b.w. once daily for 21 d after ulcer induction. Gastric secretions and antioxidant parameters were thereafter evaluated.

Results: The significantly increased ($p < 0.05$) ulcer index, gastric volume, malondialdehyde level, and pepsin activity by indomethacin were effectively reduced by 65.40, 36.47, 45.71, and 53.79%, respectively, following treatment with *F. exasperata* at 200 mg/kg b.w. *S. mombin* at this regimen also attenuated these parameters by 71.70, 46.62, 50.16, and 55.73%. Moreover, the extracts significantly increase the reduced activity of superoxide dismutase as well as pH and mucin content in the ulcerated rats.

Discussion and conclusion: These findings are indicative of gastroprotective and antioxidative potentials of the extracts which is also evident in the degree of % inhibition against ulceration. The available data in this study suggest that the extracts proved to be capable of ameliorating indomethacin-induced gastric ulceration and the probable mechanisms are via antioxidative and proton pump inhibition.

Antacid antioxidative gastroprotective NSAIDS proton pump inhibitor vagotomy

Introduction

Gastric ulceration is a benign lesion on the mucosal epithelium on exposure of the stomach to excess acid and aggressive pepsin activity (Khazaei & Salehi, [2006](#)). It is the most prevalent gastrointestinal disorder ever known, accounting for an estimated 15 000 mortality yearly (Shristi et al., [2012](#)). In spite of the rapidly changing concept of gastric ulcer management from conventional vagotomy, prostaglandin analogues, H₂ receptor antagonists, and antacids to proton pump inhibitors, gastrointestinal toxicity remains an impediment to their application in clinical practice. Specifically, gastrointestinal toxicity of non-steroidal anti-inflammatory drugs (NSAIDs) origin may be as high as 4–8% per year and the complications are even higher for those with additional risk factors such as prior history of ulcer disease (Griffin & Scheiman, [2001](#)). Various synthetic antiulcer drugs are presently available and some of these like

manage and cure NSAID-induced gastric ulcer. However, each of these drugs confers simpler to severe side effects, prompting a search for non-toxic, easily accessible, and affordable antiulcer medication (Akah et al., [1998](#); Hawkins & Hanks, [2000](#)). Investigation on the phytotherapy of medicinal plants that are highly valued and widely used in the traditional systems of medicine might provide efficient formulation for better management. *Spondias mombin* (SM) and *Ficus exasperata* (FE) belongs to this class of therapeutic plants.

Spondias mombin Linn (Anacardiaceae), commonly known as “Iyeye” in south-western Nigeria, is a fructiferous tree. The plant grows in rain forests and coastal areas, attaining a height of 15–22 m (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](#)). Antioxidant vitamins; α -tocopherol, and ascorbic acid have been detected in its leaves extract (Maduka 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](#)) also reported that decoction from its leaves is therapeutic against urethritis, cystitis, as well as eye and throat inflammations. The gum from SM has also been exploited as an expectorant and vermifuge. The leaf extract of the plant has been strongly advocated for use in speedy wound-healing processes, hemorrhoids, and inflamed mucous membrane due to its tannin content (Njoku & Akumefula, [2007](#)). Its pharmacological potencies such as antioxidative, antimicrobial, antimalarial, and antibacterial have also been documented (Abo et al., [1999](#); Caraballo et al., [2004](#); Corthout et al., [1994](#); Villegas et al., [1997](#)).

Ficus exasperata Valh (Moraceae), called “Epin”, “Anwerenwa”, and “Kawusa”, respectively, among the Yorubas, Igbos, and Hausas in Nigeria, is commonly known as “sand paper tree”. Phytochemical analysis of the leaf extract of FE has revealed the presence of flavonoids, tannins, saponins, alkaloids, and cyanogenic glycosides (Ijeh & Ukwemi, [2007](#)). Its medicinal efficacy in treating many diseases has been researched. For instance, the south-western people of Nigeria use the decoction and the infusion of FE leaves for the management, control, and treatment of hypertension, diabetes mellitus, and certain cardiovascular dysfunction (Odiba et al., [2012](#)). Leaves of FE cooked with bananas are eaten for the treatment of gonorrhoea (Anowi et al., [2012](#)). Its leaf extract is also taken to suppress stomach ache, treat peptic ulcer, and as an antidote to poison (Akah et al., [1998](#)).

With the remarkable attributes of SM and FE particularly in alleviating stomach ache-related disorders and wound-healing enhancement, the present study compared their therapeutic efficacy on indomethacin-induced gastric ulceration in rats.

Materials and methods

Chemicals and drugs

Indomethacin and esomeprazole were, respectively, procured from Kapit Pharmaceutical Limited, Abuja, Nigeria and Ranbaxy Laboratories, Mumbai, India. Trichloroacetic acid (TCA), dimethylaminobenzaldehyde, epinephrine, acetyl acetone, bovine serum albumin (BSA), gallic acid, aluminium chloride, quercetin, and thiobarbituric acid (TBA) were products of Sigma Chemical Co. (St. Louis, MO). Distilled water was obtained from Biochemistry Laboratory, Kwara State University, Malete, Nigeria. Assay kits used were from 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 SM and FE were collected in April 2014 following identification of the two plants by Dr. A. A. Abdulrahman of the Department of Biological Sciences (Botany Unit) of the University of Ilorin, Ilorin, Nigeria. The leaves were authenticated at the University's Herbarium, where voucher specimens (nos. 14/20567 and 14/20568) were prepared and deposited.

Experimental animals

Albino rats of the Wistar strain at a mean weight of 180.00 ± 1.85 g were used for the study. The animals were obtained and reared as described by Sabiu et al. (2014), following approval from the Independent Ethical Committee on the Use and Care of Laboratory Animals of the Kwara State University, Malete, Nigeria. A certified number KSU/IECCULA/001/05/014 was assigned and issued for the research.

Preparation of extracts

Leaves of SM and FE were air dried at room temperature for 10 d to constant weight. The dried samples were then pulverized with an electric blender (model MS 222;

Powdered samples (500 g each) of both plants were separately extracted in 5 L of distilled water for 48 h with continuous shaking by orbital shaker maintained at 300 rpm. The solutions obtained were then filtered (with Whatman No. 1 filter paper) and the resulting filtrates were lyophilized to give 15.5 g (SM) and 12.4 g (FE) residues, corresponding to yields of 3.1 and 2.48%, respectively. The lyophilized samples were separately reconstituted in distilled water to give doses of 100 and 200 mg/kg body weight (b.w.) of each extract used in the study.

Determination of total phenolics

Following the reported method of Wolfe et al. ([2003](#)), the total phenol contents in the plant extracts were determined. Briefly, an aliquot of each extract (1 mL) was mixed with 5 mL Folin-Ciocalteu reagent (previously diluted with water 1:10 v/v) and 4 mL (75 g/L) of sodium carbonate. The tubes were vortexed for 15 s and allowed to stand for 30 min at 40 °C for color development. An absorbance was read at 765 nm using a spectrophotometer (Beckman, DU 7400, Beckman Coulter Inc, Brea, CA). Extracts were evaluated at a final concentration of 1 mg/mL. The total phenolic content was expressed as mg/g gallic acid equivalent using the equation obtained from a calibration curve of gallic acid.

Determination of total flavonoids

Total flavonoids were estimated using the method of Ordon-ez et al. ([2006](#)). In brief, 0.5 mL of 2% AlCl₃ ethanolic solution was added to 0.5 mL of the extracts. After 1 h at room temperature, the absorbance was read at 420 nm. The development of yellow color was taken as an-indication of the presence of flavonoids. Samples of the extract were evaluated at a final concentration of 1 mg/mL. The total flavonoid content was calculated as quercetin equivalent (mg/g) using the equation obtained from the calibration curve.

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 b.w.). They were deprived of food but had free access to water 24 h prior to ulcer induction. Various degrees of ulceration have manifested 4 h after indomethacin administration.

Forty-nine albino rats were randomized into seven groups of seven rats each. Group 1 (normal control) animals received only distilled water. Group 2 (ulcerated control) rats were given only indomethacin and were sacrificed 4 h after indomethacin administration. Animals in group 3 were given indomethacin and esomeprazole (20 mg/kg b.w.). Groups 4, 5, 6, and 7 comprised ulcerated rats treated with FE (100 mg/kg b.w.), FE (200 mg/kg b.w.), SM (100 mg/kg b.w.), and SM (200 mg/kg b.w.). Treatments with the reference drug and extracts commenced 4 h after indomethacin administration and lasted for 21 d. These were orally administered once daily using oral intubator with ad libitum provision of food and water throughout the experimental period.

Isolation of stomach and collection of gastric juice

On the 22nd day, the animals were humanely sacrificed by cervical dislocation. The abdomen was opened and the stomach was excised. The stomach was thereafter opened along greater curvature and the gastric content was drained into a centrifuge tube. Distilled water (5 mL) was added and the resultant solution was centrifuged at 3000 rpm for 10 min. The supernatant obtained was thereafter used for biochemical analyses.

Determination of gastric ulceration parameters

Gastric acid output (volume) was determined in the supernatant (2 mL) by titration with 0.0025 N NaOH using Toepfer's reagent as an indicator. 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 vascular congestions and lesions/hemorrhagic erosions) as presented in [Table 1](#). 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 inhibition against ulceration was determined using the expressions:

Table 1. Ulcer scores and descriptive remark.

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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 was centrifuged at 2500 rpm for 10 min. The resulting supernatant was thereafter used for assay of antioxidants status.

The activity of superoxide dismutase (SOD) and the level of lipid peroxidation measured in terms of malondialdehyde (MDA) were, respectively, assayed in the stomach homogenate by the methods of Marklund and Marklund ([1974](#)) and Devasagayam and Tarachand ([1987](#)).

Statistical analysis

Inhibition against ulceration was expressed in percentage. Other results were expressed as a mean of seven determinations \pm standard error of mean. One-way analysis of variance (ANOVA) complemented with Student's t-test using SPSS software package for windows (Version 16, SPSS Inc., Chicago, IL) for differences between means was used to detect any significant difference ($p < 0.05$) between the treatment groups in this study.

Results

Quantitative phytochemical analysis of aqueous leaf extracts of SM and FE revealed the presence of total phenols and flavonoids ([Table 2](#)).

Table 2. Total phenolic and flavonoid contents of aqueous leaf extracts of *S. mombin* and *F. exasperata*. Values expressed per g of plant extract.

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The effect of aqueous leaf extracts of SM and FE on the ulcer index and % inhibition

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 inhibition against ulceration was, however, observed following treatment with the extracts. The extracts at 200 mg/kg b.w. offered better protection against ulceration than the 100 mg/kg b.w. regimens and compared well with the standard drug (Esomeprazole) used.

Table 3. Effect of aqueous leaf extracts of *S. mombin* and *F. exasperata* on ulcer indices of indomethacin ulcerated rats ($n = 7$, $X \pm SEM$).

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Table 4 shows the effect of aqueous leaf extracts of SM and FE on gastric secretions of indomethacin ulcerated rats. Indomethacin administration caused significant ($p < 0.05$) decrease in the pH value with a corresponding significant ($p < 0.05$) increase in gastric volume of gastric content. Treatment with the extracts produced significant increase in the pH value coupled with significant decrease in gastric volume when compared with ulcerated control rats.

Table 4. Effects of aqueous leaf extracts of *S. mombin* and *F. exasperata* on gastric volume and pH of indomethacin ulcerated rats ($n = 7$, $X \pm SEM$).

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Indomethacin administration brought about a significant ($p < 0.05$) increase in specific pepsin activity as well as significant reduction ($p < 0.05$) in the mucin content of gastric juice of ulcerated rats when compared with the normal control (Table 5). The observed changes in these parameters were significantly attenuated ($p < 0.05$) after treatment with the leaf extracts of SM and FE. Treatment with SM revealed more potent efficacy in the modulation of both pepsin activity and mucin contents of gastric juice of ulcerated rats.

Table 5. Effect of aqueous leaf extracts of *S. mombin* and *F. exasperata* on gastric pepsin activity and mucin content of indomethacin ulcerated rats ($n = 7$, $X \pm SEM$).

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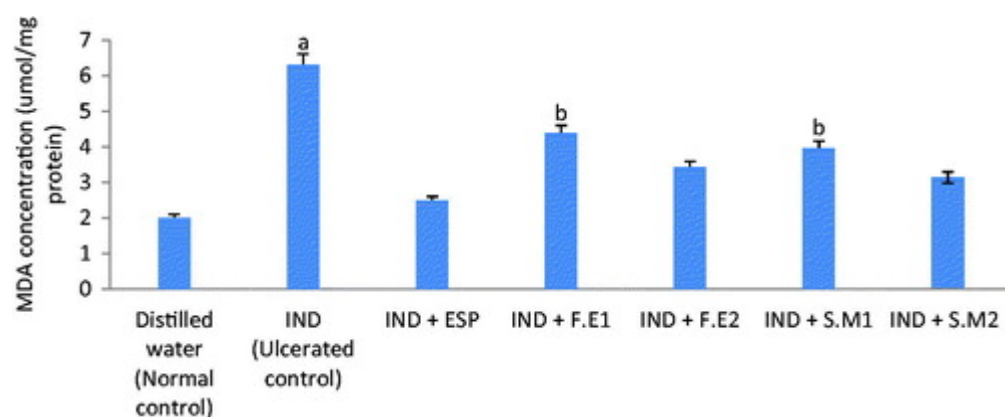
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Observable from [Figures 1](#) and [2](#) are the effects of aqueous leaf extracts of SM and FE on the lipid peroxidation and SOD activity of gastric mucosal of indomethacin-ulcerated rats. The MDA level was significantly increased ($p < 0.05$) in the ulcerated animals ([Figure 1](#)). A significant reduction ($p < 0.05$) was also observed in the activity of SOD ([Figure 2](#)) in the indomethacin-induced animals. Commendably, both extracts particularly at 200 mg/kg b.w. regimen attenuated these parameters and the observable effects compared favorably well with both normal control and standard drug employed in the study.

Figure 1. Effect of aqueous leaf extracts of *S. mombin* and *F. exasperata* on gastric Malondialdehyde (MDA) level of indomethacin ulcerated rats ($n = 7$, $X \pm SEM$).

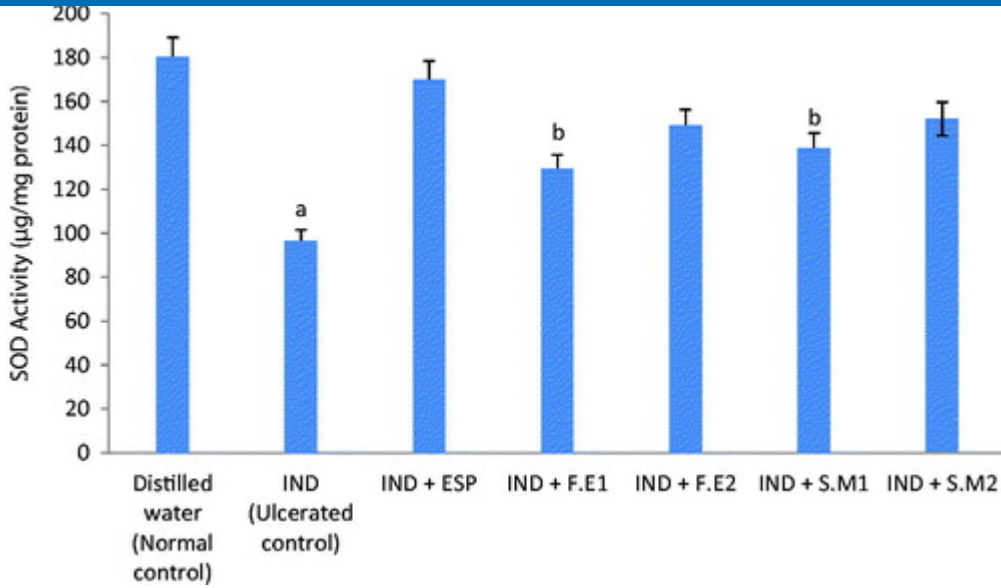
^aSignificantly different from the normal control group ($p < 0.05$). ^bSignificantly different from the indomethacin-ulcerated control group ($p < 0.05$). IND, indomethacin (30 mg/kg b.w.); ESP, esomeprazole (20 mg/kg b.w.); F.E1, *Ficus exasperata* (100 mg/kg b.w.); F.E2, *Ficus exasperata* (200 mg/kg b.w.); S.M1, *Spondias mombin* (100 mg/kg b.w.); S.M2, *Spondias mombin* (200 mg/kg b.w.).



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Figure 2. Effect of aqueous leaf extracts of *S. mombin* and *F. exasperata* on gastric superoxide dismutase (SOD) activity of indomethacin ulcerated rats ($n = 7$, $X \pm SEM$).

^aSignificantly different from the normal control group ($p < 0.05$). ^bSignificantly different from the indomethacin-ulcerated control group ($p < 0.05$). IND, indomethacin (30 mg/kg b.w.); ESP, esomeprazole (20 mg/kg b.w.); F.E1, *Ficus exasperata* (100 mg/kg b.w.); F.E2, *Ficus exasperata* (200 mg/kg b.w.); S.M1, *Spondias mombin* (100 mg/kg b.w.); S.M2, *Spondias mombin* (200 mg/kg b.w.).



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Discussion

Inhibitory action of indomethacin on prostaglandin synthesis coupled with free radicals formation has been opined as critical biochemical events in the pathogenesis of gastric ulceration (Ajani et al., [2014](#); Hong et al., [2014](#); Inas et al., [2011](#); Lichtenberger, [2005](#)). An understanding of these events might be of utmost relevance in designing new antiulcer drugs. With the inherent adverse 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.

Phytotherapy is rapidly gaining grounds in sustaining human health and in the prevention of certain diseases like gastric ulcer resulting from drug toxicity (Ajani et al., [2014](#); Raji et al., [2011](#)). This has been ascribed to possession of phytonutrients with excellent antioxidant properties that play significant roles in managing toxicity-related disorders. Interestingly, studies have revealed the presence of some of these bioactive principles in SM and FE as well as reported them to promote good health (Abo et al., [1999](#); Akah et al., [1998](#); Ayoka et al., [2008](#); Ijeh & Ukwemi, [2007](#)). In this study, we have also specifically quantified the polyphenolic constituents of aqueous leaf extracts of SM and FE as well as compared their gastroprotective effects on indomethacin-induced ulceration in rats.

Biochemical analysis of gastric secretions (for pH, gastric volume, bicarbonate, and pepsin) and mucosal integrity for stomach is usually employed to ascertain its status following exposure to pharmacological agents (Biplab et al., [2011](#)). The pH gives an idea of the level of acidity and volume of gastric secretions. Low pH value is a manifestation of decreased hydrogen ion concentration in gastric juice. This has been linked to pathogenesis of ulcer and gastric damage in experimental animals (Lüllmann et al., [2000](#)). Inas et al. ([2011](#)) have also attributed gastrointestinal injury to eroded mucin content. This erosion is facilitated by onslaughts of both internal (pepsin and oxidants produced in the gastric lumen) and external (drugs and chemicals) aggressive agents on mucosal epithelia.

In the present study, the significant increase in ulcer index and gastric volume 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 attributed to impaired gastroprotection and increased gastric secretion which are important events in the etiology 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 these parameters. In fact, the effects noticed for pH compared favorably well with both normal control and standard drug used in this study and indeed suggestive of their possible gastroprotective attributes.

A combination of events including the release of preformed mucus, wound retraction, and re-epithelialization is involved in ulcer-healing process after toxicological injury (Naito et al., [1995](#); Szabo, [1985](#)). Besides providing significant buffering capacity for the neutralization of luminal acid, the mucus also offers protection against both endogenous aggressors and exogenous gastro-toxic agents such as indomethacin, thereby enhancing the rate of local healing process (Alanko et al., [1999](#)). In this study, the increased pepsin activity coupled with decrease in mucin secretion in the indomethacin-ulcerated rats indicated altered hydrophobicity and reduced protective ability of the mucosal membrane against hemorrhagic erosion, thus, resulting in tissue damage. This implied decreased ability of the gastric mucosa to withstand the offensive onslaught of indomethacin. Besides antioxidant action that protects the mucus layer and arrests ulcer progression, drugs that increase the synthesis and the secretion of gastric mucus would accelerate gastric ulcer healing. Treatment with the extracts

pepsin activity and elevated mucin level in the gastric mucosa. This in turn has encouraged speedy wound healing of the ulcerated areas of the mucosal epithelia and shielded the gastrointestinal membrane, thus abrogating the catastrophic influence of indomethacin in the ulcerated rats (Naito et al., [1995](#)). This is indicative of enhanced mucus modulation by the extracts and suggestive of their significant role in ulcer-healing process. Healing of mucosa epithelia cells was prominently displayed by the extracts at 200 mg/kg b.w. dose, depicting a better ulcer healing capacity and compared favorably well with the reference drug used.

Tissues are in a stable state if the rates of free radical formation and scavenging capacity are essentially constant and in equilibrium. However, an imbalance between them results in oxidative stress which further deregulates cellular functions leading to different pathological conditions (Sabiou et al., [2014](#)). In the present study, the increased concentration of MDA as well as reduced activity of SOD in the stomach of indomethacin-ulcerated rats is a manifestation of facilitated lipid peroxidation and over production of free radicals resulting in mucosal damage. Free radicals deplete antioxidant enzyme 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 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 coupled with marked increase in the activity of SOD following treatment with aqueous leaf extracts of both plants is an obvious indication of antiperoxidative potential and thus antioxidative potential.

The therapeutic effect elicited by aqueous leaf extracts of SM and FE against indomethacin-induced gastric ulceration in this study may be linked to their beneficial medicinal attributes occasioned by phytometabolite 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 Gege-Adebayo et al. ([2013](#)), where gastroprotective potentials of plant extracts against indomethacin-ulcerated rats were associated with their polyphenolic compounds and other various bioactive principles. Since esomeprazole is a proton pump inhibitor, the

by modulating cells in the mucosal lining of the stomach against excess acid secretion (Fornai et al., [2011](#); Tulassay et al., [2008](#)).

Conclusion

Overall, the attenuation of gastric affronts of indomethacin by administration of aqueous leaf extracts of SM and FE at 200 mg/kg b.w. regimen is indicative of their excellent gastroprotective and antioxidative potentials in rats. Efforts are ongoing to investigate the exact antiulcerogenic principle(s) in these extracts and also harness their possible synergistic efficacy against gastric ulcer.

Declaration of interest

The authors report that they have no conflicts of interest.

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