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Gastroprotective potentials of aqueous extract of *Persea americana* seed against Aspirin-induced ulcer in Wistar rats

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ABSTRACT: The study was designed to evaluate the gastro-protective potential of aqueous seed extract of *Persea americana* on aspirin-induced gastric ulcer in rats. Thirty adult rats were randomly divided into six groups of five. Group 1 was not induced with aspirin while groups 2-6 received a single-dose of aspirin of 400 mg/kg bw to induce gastric ulcer. Groups 2 and 3 received water and omeprazole respectively; while groups 4, 5 and 6 received the aqueous extract (110, 220 and 440 mg.kg bw respectively) for 14 days. Ulcer index, gastric volume, gastric pH, total acidity, total carbohydrate, total protein, pepsin of gastric juice and antioxidant activity of the plant extracts were determined. The extract showed a significant ($p<0.05$) decrease in ulcer index and total acidity in the extract-treated and the omeprazole-treated groups when compared to the control group. There was no significant difference in the gastric juice volume and total protein of the gastric juice of all the extract-treated groups when compared to the control. There was a significant ($P<0.05$) decrease in malondialdehyde level in the gastric tissues of the extract-treated and an increase in the reduced Glutathione, catalase, superoxide dismutase, activities compared to the control. The histology of the stomach tissues in the extract-treated groups showed slight and moderate ulceration when compared to the normal control group. The extract therefore has protective activity on aspirin-induced gastric ulceration in rats.

Keywords: *Persea americana*, avocado, aspirin, gastric ulcer, ulcer index, antioxidant.

Introduction

Gastric ulcers are frequent and severe diseases, which have been a significant cause of morbidity and mortality for more than a century (Hoogerwer and Pasricha, 2006). The pathophysiology of gastric ulcer disease is based on an imbalance between aggressive and protective factors in the stomach (Vell, 2005). Gastric ulcers are caused by psychological and physiological stress, excessive acid, free radicals, alcohol use, the side effect of non-steroidal anti-inflammatory drugs (NSAIDs), Helicobacter infection or free radicals or a combination of two or more of these causes (Harbison and Dempsey, 2005).
Currently, the non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and indomethacin are preferred drugs for various diseases like arthritis, inflammation, and cardiovascular protection. However, they cause gastrointestinal complications such as ulcers and erosions.

Non-steroidal anti-inflammatory drugs NSAIDs also generates oxygen free radicals that are known to play a role in the pathogenesis of mucosal injury (Biswas *et al*., 2003). Aspirin exerts its effect through

inhibition of cyclooxygenase the enzyme responsible for the synthesis of prostaglandin. The most adverse effect of aspirin is irritation of the gastric mucosa. Various synthetic anti-ulcer drugs are presently available, and some of these like misoprostol esomeprazole, omeprazole, lansoprazole, pantoprazole is specifically used to cure the NSAID induced gastric ulcer. However, each of these drugs confers simpler to severe side effects, warranting a search for non-toxic and inexpensive antiulcer medication (Miederer, 1986, Yesilada and Gurbuz, 2003).

Plants are essential in our everyday existence. They provide our foods, produce the oxygen we breathe, and serve as raw materials for many industrial products such as clothes; foot wears and so many others. Plants also provide raw materials for our buildings and in the manufacture of biofuels, dyes, perfumes, pesticides, adsorbents and drugs. The plant kingdom has proven to be the most useful in the treatment of diseases, and they provide an essential source of all the world's pharmaceuticals. The most important of these bioactive constituents of plants are steroids, terpenoids, carotenoids, flavonoids, alkaloids, tannins and glycosides. Plants in all facet of life have served a valuable starting material for drug development (Ajibesin, 2011). Antibiotics or antimicrobial substances like saponins, glycosides, flavonoids and alkaloids etc. are found to be distributed in plants. Yet, these compounds were not well established due to the lack of knowledge and techniques. The phytoconstituents which are phenols, anthraquinones, alkaloids, glycosides, flavonoids and saponins are antibiotic principles of plants.

Plants are now occupying a prominent position in allopathic medicine, herbal medicine, homoeopathy and aromatherapy. Medicinal plants are the sources of many essential drugs of the modern world. Many of these indigenous medicinal plants are used as spices and food plants; they are also sometimes added to foods meant for pregnant mothers for medicinal purposes (Akinpela and Onakoya, 2006). Many plants are cheaper and more accessible to most people, especially in the developing countries than orthodox medicine, and there is a lower incidence of adverse effects after use. These reasons might account for their worldwide attention and use. The medicinal properties of some plants have been documented by some researchers (Akinpelu and Onukoya, 2006). Medicinal plants are of great importance to the health of individuals and communities. It was the advent of antibiotics in the 1950s that led to the decline of the use of plant derivatives as antimicrobials. Medicinal plants contain physiologically active components which, over the years, have been exploited in the traditional medical practices for the treatment of various ailments (Ajibesin, 2011). A relatively small percentage of less than 10% of all the plants on earth is believed to serve as sources of medicine.

Plants have been used for medicine from time immemorial because they have fitted the immediate personal need, are easily accessible and inexpensive. In the recent past, there has been a tremendous increase in the use of plant-based health products in developing as well as developed countries resulting in exponential growth of herbal products globally. Herbal medicines have a strong traditional, or conceptual base and the potential to be useful as drugs in terms of safety and effectiveness leads to treating different diseases. No studies have been reported for its antiulcer activity. Therefore, an attempt has been made to evaluate the antiulcer potential of aqueous extract of *Persea americana* seed (Avocado) due to its potential in antiulcer traditionally in some part of Ilorin

Persea americana (avocados) is one of the 150 varieties of avocado pear. The tree is widely cultivated in tropical and subtropical areas (Lu *et al.*, 2005). The seed of *Persea americana* (avocado seed) has diverse application in ethnomedicine, ranging from treatment for diarrhoea, dysentery, toothache, intestinal parasites, skin treatment and beautification. The avocado seed oil has much health benefits, e.g. for controlling human weight (mainly used for obese for weight loss) (Lopez *et al.*, 1996; Roger, 1999). *Persea americana* leaves have been reported to have or possess anti-inflammatory and analgesic activities (Adeyemi *et al.*, 2002). Antioxidant activity and phenolic content of seeds of avocado pear were found to be higher than 70% (Song and Barlow, 2004). The edible part (fruit) is trendy in vegetarian cuisine, making a substitute for meat in sandwiches and salads, because of its high-fat content and high in valuable, health-promoting fats (Lu *et al.*, 2005). The fruit is not sweet but fatty, almost distinctly, yet subtly flavoured, and of smooth, almost creamy texture. Avocado fruits in many countries such as Mexico, Brazil, South Africa and India are frequently used for milkshakes and occasionally added to ice-cream (Zeldes, 2010).

Materials and Methods

Equipment:

The major equipment used for the study were 1ml insulin springe, oral cannula, oven, water bath, dissecting set, electrical weighing balance, pH meter, centrifuge, spectrophotometer and chemical are of analytical grade.

Plant sample collection and identification:

The plant fruit was collected from Ilorin, Kwara State and authenticated at the Herbarium unit in the Department of Plant Biology, University of Ilorin, Ilorin. Where voucher number UILH/002/748 was obtained.

Methodology

Preparation of plant sample

The fruit of *Persea americana* was obtained from Ipata market in Ilorin, and the seed was removed, the seed of *Persea americana* samples were rinsed in clean water, cut into small piece and oven-dried 45^{o}C temperature. The dried seed samples were pulverized into powder using mortar and pestle, and the powder obtained was used to prepare the extracts.

Aqueous extract preparation:

Five hundred grams of powdered seed, 2.5L portion of distilled water was added and stored at room temperature for 48 hours and shaken at intervals. At the end of the extraction, the crude extract was filtered using a muslin cloth and Whatman filter paper No.1. The aqueous extract obtained was concentrated to dryness at 45^{o}C using a water bath. The dried extract was stored in an airtight sample bottle until required for analysis.

Proximate Analysis:

This refers to the determination of the major constituents of the food sample, and it is used to assess if a sample is within its normal compositional parameters or has somehow been contaminated. This method partitioned nutrients in food samples into six components: water, ash, crude protein, fat, crude fibre and moisture

Qualitative phytochemical screening

Phytochemical analysis extract was carried out using the method described by Sofowora (1993) for the detection of saponins, tannins, phenolics, alkaloids, steroids, triterpenes, phlobatannins, glycosides and flavonoids.

Experimental animals:

A total of 30 healthy Wistar rats weighing between 150-200g (6-8 weeks) old were obtained and kept in well-aerated laboratory cages in the animal house, Department of Biochemistry, University of Ilorin, Ilorin, Nigeria. They were allowed to adjust to the laboratory environment for two weeks before the commencement of the experiment. The animals were fed with growers mash and water was provided *ad libitum* during the stabilization period. The animals were divided into extract treatment groups and the control groups.

Animal Grouping

The rats were randomly divided into six groups, with five animals per group. The extracts were reconstituted in distilled water and administered orally daily for 14 days.

Group 1: Normal control was fed standard growers mash and water *ad libitum.*
Group 2: Animals were administered a single-dose of aspirin orally (400 mg/kg).
Group 3: Animals were administered a single-dose of aspirin 400mg/kg and treated with omeprazole 40mg/kg for 14 days
Group 4: Animals were administered single-dose of aspirin 400mg/kg and treated with aqueous extract of *Persea americana* 110mg/kg for 14days
Group 5: Animals were administered a single-dose of aspirin 400mg/kg and treated with aqueous extract of *Persea americana* 220mg/kg for 14 days
Group 6: animals were administered single of aspirin 400mg/kg and treated with aqueous extract of *Persea americana* 440mg/kg

Histopathological study

The stomachs were washed thoroughly with saline before tissue samples were collected and stored in 10% formalin solution. Biopsies were obtained from these samples. Sections (5 μm) were taken from the biopsies and stained with hematoxylin and eosin (H & E) before visual inspection for damage under a light microscope (100×) (Oloyede *et al.*, 2015).

Statistical analysis

The values are reported as means ± S.E.M. Statistical difference was determined using ANOVA and differences in the ways were tested by GraphPad prism 6.

Results

Qualitative phytochemical screening of aqueous extract of *Persea Americana* seed

Medicinal plants are the backbone of the traditional system of medicine and are enriched in phytochemical constituents which serve as lead compounds in drug discovery and design. In the current study, the aqueous extract of *Persea Americana* was prepared, and phytochemical analysis was performed that confirms the presence of saponin, alkaloids, glycosides, anthocyanin, fixed oil.

Table 1: Qualitative and quantitative phytochemical screening of aqueous extract of *Persea americana* seed

Phytochemical parameters	Qualitative	Quantitative
Saponin	+	0.17 ± 0.00 (mg/100g)
Tannin	-	
Phenolics	-	
Phlobatanin	-	
Steroids	+	17.10 ± 1.75 (μg/100g)
Flavonoids	-	
Anthocyanin	+	11.56 ± 0.05 (μg/100g)
Terpenoids	-	
Glycosides	+	1.86 ± 0.07 (mg/100g)
Triterpenes	-	
Alkaloids	+	17.23 ± 0.05 (mg/100g)
Coumarin	-	
Fixed oil	+	

Key:- (+) indicates the presence of an insufficient phytochemical amount, while (-) indicates the absence of a phytochemical and results are mean ± S.E.M. (n = 3). $P<0.05$ were considered as statistically.

Proximate analysis result

Table 2: Proximate Composition of aqueous extract of Avocado seed (*Persea americana*)

Sample	Concentration %
Crude protein	5.79
Crude lipid	2.55
Total ash	22.50
Moisture content	7.18
Crude fibre	0.25
Carbohydrate	61.82

Determination of Gastric Ulcer Parameters

Biochemical Analysis

Table 3: Effect of *Persea americana* aqueous seed extract on gastric pH, total acidity gastric juice volume and ulcer index in the stomach of rats

Treatment (n = 5)	pH	Total acidity	Gastric volume	Ulcer index
Normal control group	6.35±0.23^{a}	10.0±0.57^{a}	2.56±0.18^{a}	-
300 mg/kg Aspirin-induced untreated	1.60±0.21^{c}	2.05±0.28^{c}	3.18±0.13^{a}	11.15±0.12^{c}
40 mg/kg Omeprazole	5.35±0.49^{a}	7.67±0.67^{b}	2.60±0.15^{a}	3.54±0.19^{a}
110 mg/kg *P. americana*	2.05±0.06^{b}	4.50±0.64^{c}	2.90±0.175^{a}	8.91±0.05^{b}
220 mg/kg *P. Americana*	4.28±0.15^{a}	9.0±0.57^{a}	2.75±1.11^{a}	4.92±0.05^{a}
440 mg/kg *P. Americana*	3.45±0.26^{b}	6.75±0.75^{b}	2.66±0.24^{a}	6.67±0.24^{b}

Results are mean ± S.E.M. (n = 3). P<0.05, were considered statistically significant when compared to uninduced untreated (control) group.

Specific activities of *P. Americana* on biochemical parameters

Table 4: Effect of aqueous seed extract *Persea americana* on pepsin activity, total protein and total carbohydrate level in gastric juice of rats stomach

Treatment (n = 5)	Total CHO g/100g	Total protein mg/dl	Pepsin activity
Normal control group	22.50±8.85^{a}	4.189±1.05^{a}	25.50±0.09^{a}
300 mg/kg Aspirin-induced untreated	29.6±3.20^{a}	5.63±0.50^{a}	16.93±0.62^{b}
40 mg/kg Omeprazole	18.0±1.00^{b}	3.82±0.50^{a}	24.49±0.06^{a}
110 mg/kg *P. americana*	24.6±4.80^{a}	3.45±0.24^{a}	20.96±1.48^{b}
220 mg/kg *P. Americana*	26.4±3.60^{a}	3.57±1.28^{a}	22.84±0.28^{a}
440 mg/kg *P. Americana*	26.05±10.05^{a}	4.24±0.99^{a}	25.75±0.59^{a}

Results are mean ± S.E.M. (n = 3). P<0.05, were considered statistically significant when compared to uninduced untreated (control) group.

Antioxidant potential of *P. americana* on gastric tissue of Wistar rat

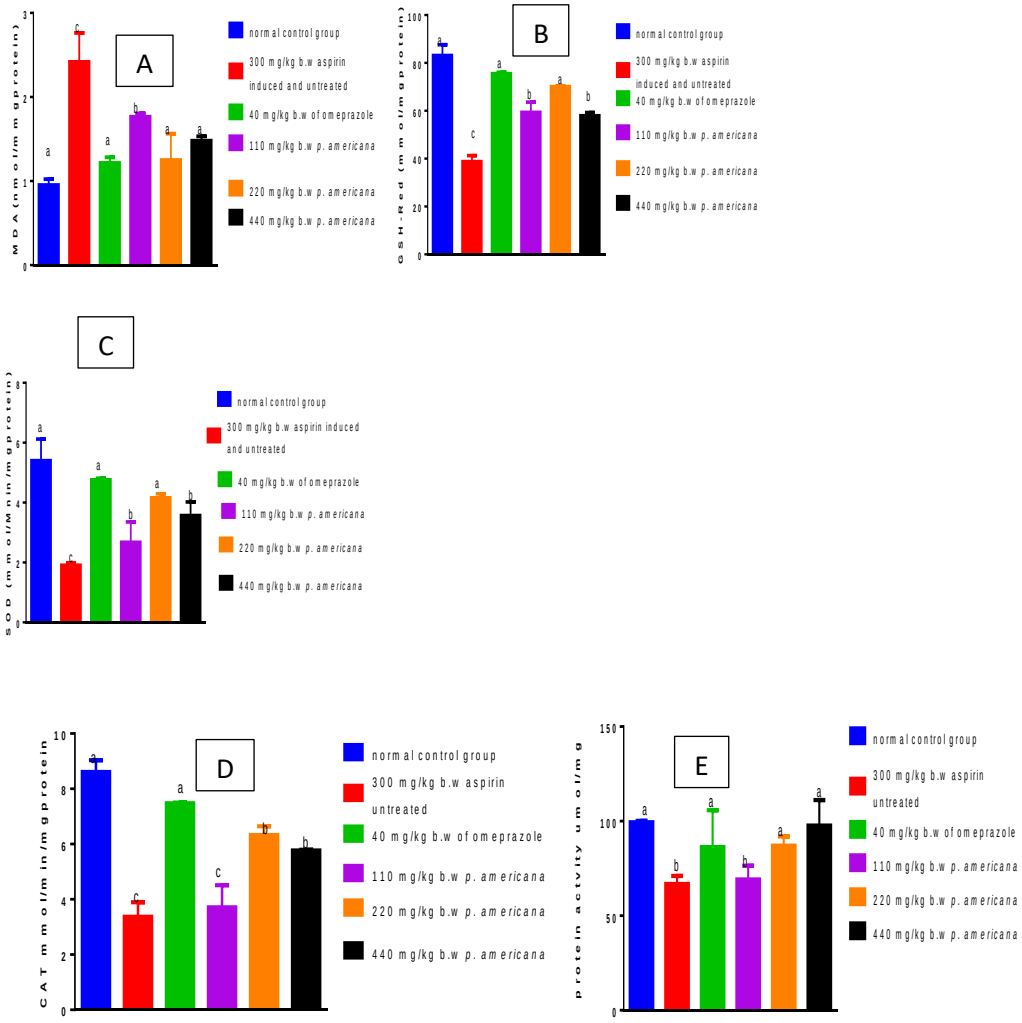

Figure 1: (A)Specific activities Malondialdehyde (MDA) on gastric tissue treated with *Persea americana* and omeprazole (B) Specific activities reduced glutathione (GSH-Red) on gastric tissue treated with *Persea americana* and omeprazole (C) Specific activities Superoxide Dismutase (SOD) on gastric tissue treated with *Persea americana* and omeprazole (D) Specific activities Catalase (CAT) on gastric tissue treated with *Persea americana* and omeprazole (E) Protein level of gastric tissue treated with aqueous extract of *Persea americana* seed omeprazole

Results are mean ± S.E.M. (n = 3). $p<0.05$, were considered statistically significant when compared to uninduced untreated (control) group.

Macroscopic view of gastric tissue

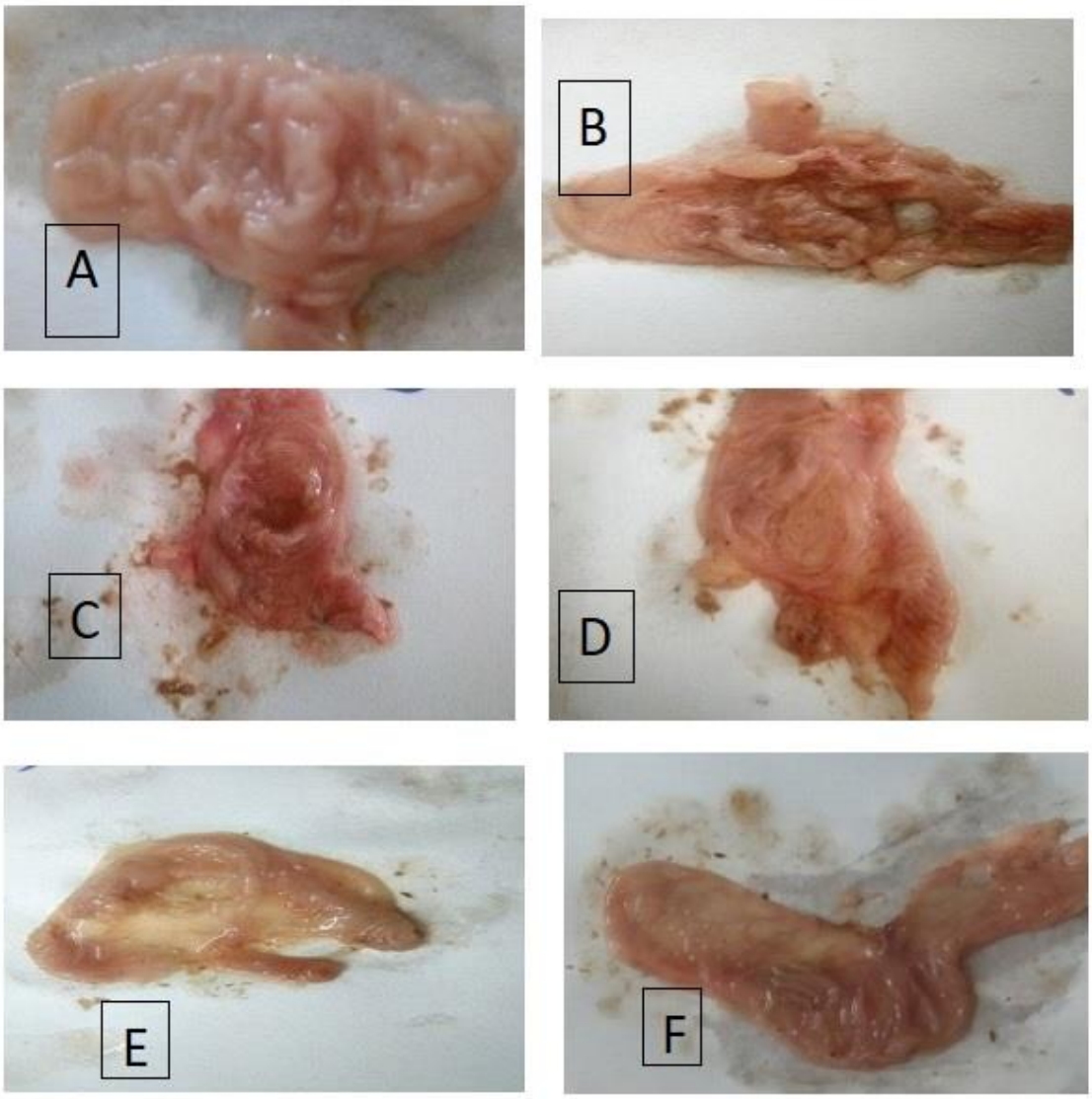

Plate 1 : Photomacrograph showing the potential of *Persea americana* on cross morphology of gastric mucosal of ulceration rat (A) Normal control group distilled water (B) Aspirin untreated 300 mg/kg (C) Omeprazole group 40 mg/kg (D) Aqueous Extract 110 mg/kg (E) Aqueous Extract 220 mg/kg (F) Aqueous Extract 440 mg/kg

Histopathatology of gastric tissue

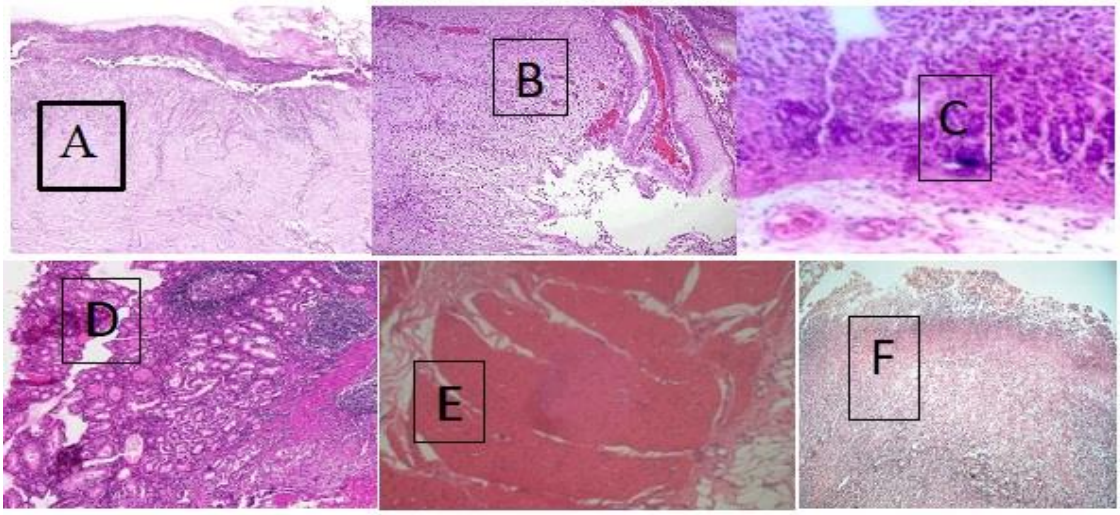

Plate 2: Photomicrograph showing the potential of *Persea americana* on cross morphology of gastric mucosal of ulceration rat (A) Normal control group distilled water showing normal mucosa with intact architecture of the lining. (B) Aspirin untreated 300 mg/kg showing necrosis and severe disruption of the entire mucosal lining. (C) Omeprazole group 40mg/kg showing highly reduced ulcer area on the mucosal lining (D) Aqueous Extract 110 mg/kg showing protection but a deep ulceration on some areas of the mucosal lining without necrosis (E) Aqueous Extract 220 mg/kg showing partial protection but with slight necrosis of the mucosa lining (F) Aqueous Extract 440 mg/kg showing protection but a deep ulceration on some areas of the mucosal lining without necrosis (x100) H & E Stain

Discussion

Persea americana fruits are rich sources of bioactive phytochemicals (Ding *et al.*, 2007) The medicinal values of a plant depends on the phytochemicals such as alkaloids, steroid, saponin, glycoside, anthocyanins and other nutrients like as amino acid, proteins, which produce definite physiological actions on the human body (Abhishek and Avinash, 2013).

The observed protective effect of aqueous seed extract and ability to reduce ulcer index groups treated with the *Persea americana* is an indication of its vasoconstricting impact due to some phytochemicals (saponin) present in the plants. These results compared favourably with the gastric ulcer lowering effects of *Exoecaria aggallocha* (Thirunavukkarasu and Ramanathan, 2009) and the astringent action of saponin (Enechi and Nwodo, 2014). The free radical scavenging ability of anthocyanin has been reported to protect the gastrointestinal tract from ulcerative and erosion lesion. Also, the reduction in the ulcer index in the

extracts pretreated group could be due to the antioxidant activity of the plant; this is in agreement with the report of (Havsteen, 2002; Repetto and Llesuy, 2002).

These results show that moisture content is low, as revealed. The moisture content of any food is an index of its water activity (Frazier and Westoff, 1978). It is used as a measure of stability and the susceptibility to microbial contamination, implying that aqueous seed extract of *Persea americana* will be very likely to have a long shelf life because of its low moisture content.

The protein content of aqueous seed extract *Persea americana* is not appreciably high to meet the required daily protein of 23-55 g (Chaney, 2006). The use of aqueous seed extract of *Persea americana* as a protein source is therefore not encouraged, however, in extreme conditions of protein deficiency; aqueous seed extract of *Persea Americana* may be used as a protein source.

Ash content of 22.5% for aqueous seed extract of *Persea americana* suggests the right level. Ash content of aqueous seed extract of *Persea americana* indicates it contains the right level of mineral materials because low ash content suggests high mineral composition (Egharevba and Kunle, 2010).

Carbohydrate level of 61.8% for aqueous seed extract of *Persea americana* indicates that aqueous seed extract of *Persea americana* is a rich carbohydrate source and has potentials to provide fuel and energy for daily activities (Yisa *et al*., 2010).

The volume of acid present in the gastric secretion, which encompasses HCl, pepsinogen, mucus, bicarbonates, intrinsic factor and protein reflects acid volume. Exposure of unprotected lumen of the stomach to accumulating acid could facilitate ulceration (Olsen, 1988). Another major aggressive factor responsible for ulcers is the content of acid present in the gastric juice. Over secretion of histamine contributes to an increased flow of gastric juice (Grossman, 1978). When the concentration of hydrogen ions in gastric juice decreases, it is reflective of high pH. The genesis of ulcer and gastric damage is facilitated by hydrogen ions which serve as another driving factor (Lullmann *et al.*, 2000). Decreased prostaglandin level impairs almost all aspects of gastroprotection and increases acid secretions which, in turn, aggravate the ulcer (Miller, 1983). Histamine (H2) receptor activity stimulates adenylate cyclase system and in turn causes increases in calcium ion concentrations (Enechi and Nwodo., 2014), which ultimately leads to activation of proton pump and consequently leads to hyperacidity and ulcer (Al-Mofleh *et al.*, 2006).

The carbohydrate content and the total protein content in the gastric secretion were reduced, and the pepsin activity was increased in the animals treated with *Persea americana* extract, showing the active mucous formation of the tissue. The antioxidant enzyme system plays a vital role in defence of cells against oxidative damage. It has been reported that antioxidant properties of anthocyanins from several plant extracts possess stimulatory action and exert a stimulatory effect on transcription and gene expression of certain antioxidant enzymes (Sreelatha *et al.*, 2009)

Lipid peroxidation can be used as an index for measuring the damage that occurs in membranes of tissue as a result of free radical generation, leading to aggravated tissue damage during stomach ulceration (El-Missiry *et al.*, 2001). These present studies are in line with these previous data. Enhanced lipid peroxidation (LPO) is a measure of membrane damage as well as the alteration in the structure and function of cellular membranes (Halliwell, 1995). In this present study, treatment with aqueous seed extract of *Persea americana* significantly reversed the aspirin-induced changes in Malondialdehyde (MDA), these significant reductions in MDA level suggest decreased lipid peroxidation which might be due to the antioxidant properties of the plant against free radical generation and thus its anti-ulcerogenic activity. A similar observation was reported by (Sathish *et al.*, 2011)

This study shows that all treatments with omeprazole and aqueous seed extract of *Persea americana* increased the GSH content significantly ($p<0.05$). This affected the antioxidant defence system positively and reduced the gastric damage considerably. GSH protects gastrointestinal tissue lipids from oxidative damage. As reported in a previous study, in gastric tissue damaged by aspirin, glutathione level is lowered after induction (Albayrak *et al.*, 2015). glutathione detoxifies hydrogen peroxide and organic acids chemically; hydrogen peroxide accumulates in the absence of GSH (Dalle-Donne *et al.*, 2003).

In the present study, SOD activity decreased significantly in the untreated aspirin group of animals, which may be due to the excessive formation of superoxide anions. These excessive superoxide anions

might inactivate SOD and decrease its activity. The activities of the H_2O_2 scavenging enzymes CAT also reduced significantly in the stress-induced group of animals. SOD is a crucial defence enzyme that catalyzes the dismutation of superoxide anions into O2 and H_2O_2 (Manneersk, 1987).

Catalase traps the harmful hydrogen peroxide and converts into water and oxygen. Catalase is a haemoprotein containing four heme groups, that catalyses the decomposition of H_2O_2 to water and O_2 and thus, protects the cell from oxidative damage by H_2O_2 and OH (Gupta *et al.,* 2004). The activity of CAT was found to be decreased in aspirin untreated rats. The inhibition of CAT activity during aspirin-induced ulcer may be due to the increased generation of reactive free radicals, which can create oxidative stress in the cells. There was a significant difference between the aqueous seed extract of *Persea americana* pretreated group and the untreated aspirin group. The administration of aqueous seed extract of *Persea americana* increased CAT activity showing excellent antioxidant properties when compared with the standard drug omeprazole.

Histopathological studies on the gastric mucosa revealed that aspirin administration induced mucosal ulceration associated with a significant increase in lipid peroxidation. This was manifested as mucosa epithelial necrosis, and leukocytic infiltration. This effect on mucosal oxidative stress and histological derangement was following the reports of (Valcheva-Kuzmanova *et al*. 2007 and El-Moselhy *et al*. 2009). the aqueous seed extract of *Persea americana* had some protective effect against aspirin-induced inflammatory infiltration and congestion at the ulcer sites this may be due to its anthocyanin content. anthocyanin could scavenge free radicals, inhibit lipid peroxidation, and increase prostaglandins and mucosal content of the gastric mucosa; showing cytoprotective effects (Alanko *et al.,* 1999),

The decrease in the protein content of the gastric mucosa and increase the in gastric juice of the ulcerogenic group may be due to damage in the gastric mucosa which results, in the leakage of protein into the gastric juice. Treatment with aqueous seed extracts of *Persea americana* increased the mucosal protein which indicates its ability to enhance cell proliferation and stimulates the growth of the gastric mucosa (Sathish *et al.,* 2011)

Conclusion

The aqueous seed extract of *Persea americana* offered some protection against aspirin-induced gastric mucosal damage. The antioxidant compounds present in *Persea americana* seed extract play a protective role against the production of reactive oxygen species and lipid peroxidation. The present study revealed that *Persea americana* extract has promising phytochemicals for the development of alternative treatment against gastric ulcer.

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