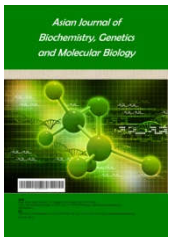

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Antiulcer and Antioxidant Potential of *Eucalyptus camaldulensis* Leaves Methanol Extract in Albino Rats

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Authors' contributions

This work was carried out in collaboration among all authors. Author AJA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author JN managed the analyses of the study. Author AA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aim: This research is aimed at assessing the antiulcer and antioxidant potential of *Eucalyptus camaldulensis* leaves methanol extract in albino rats.
Methodology: Fresh leaves of *Eucalyptus camaldulensis* were harvested from the Department of Plant Science and Biotechnology, Kebbi State University of Science and Technology, Aliero. The dried pulverized leaves were extracted using Soxhlet apparatus with methanol as the solvent. Thirty male albino rats weighing between 200 g and 250 g were used in this study. The rats were randomly divided into six (6) groups of five (5) rats each. Antiulcer and antioxidant activity was evaluated using ethanol-induced ulcer model. Ulcer was induced in all groups except Group 1 which served as the control and received distilled water only. Group 2 was not treated while Group 3 was treated with omeprazole (50mg/kg). Groups 4, 5 and 6 were treated with 200mg/kg, 400mg/kg and 800mg/kg of the extract respectively. After seven days of treatment, the albino rats were humanely sacrificed, ulcer index determined and the serum assessed for antioxidants levels.

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Results: The gastric mucosal lesions produced in the untreated group were very visible and had an ulcer index of 12.83. Pre-treatment with omeprazole and graded doses of the extract showed significant reductions (P<.05) in ulcer index in a dose dependent manner. The SOD, CAT, GPx, GSH and MDA levels were significantly reduced (P<.05) in the untreated group with progressive reduction in the treated groups as the extract concentration reduced. The antioxidant vitamins (Vitamin A, C and E) reduced in concentration significantly (P<.05) without any significant difference between the untreated group and the groups that received 200mg/kg and 400mg/kg of the extract. Meanwhile, the group treated with 800mg/kg of the extract significantly increased (P<.05) the concentrations of these vitamins when compared to the group that received ethanol only.
Conclusion: *Eucalyptus camaldulensis* leaves methanol extract possesses both antiulcer and antioxidant activity. This justifies the use of *Eucalyptus camaldulensis* leaves in traditional medicine in the management of ulcer and validates its antiulcer potential.

Keywords: Antiulcer; antioxidant; Eucalyptus camaldulensis; ulcer index.

1. INTRODUCTION

Ulcer disease is a problem of the gastrointestinal tract characterized by a break in the normal gastric mucosa integrity secondary to gastric acid and pepsin secretion [1]. It represents a serious and growing health problem in the whole world [2]. It has a worldwide prevalence of about 40% in the developed countries and 80% in the developing countries [1]. It is the most prevalent gastrointestinal disorder ever known, accounting for an estimated 15 mortalities out of every 15,000 complications yearly in the world [2].

Research on oxidants and antioxidants over the past few years has shown a link between most disease like cardiovascular disease, cancer, osteoporosis, degenerative diseases etc. and production of reactive oxygen species (ROS) along with oxidative stress [3]. Free radicals mainly act by attacking the unsaturated fatty acid in the bio-membranes which causes lipid peroxidation, decrease in membrane fluidity and reduction of enzymes and receptors activity and damage to membrane protein which finally triggers the cell inactivation and death [4]. Therefore, antioxidants can be used to reverse the harmful and pathological action of free radicals. Oxidative stress reflects an imbalance between the systemic manifestation of reactive oxygen species and a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage [5]. During the last two decades, the use of plants for the prevention, treatment and/or management of Ulcer disease has been advocated. This is due to several reasons, namely, orthodox drugs provoke many adverse effects, perceived effectiveness, affordability, ease of accessibility and safety of medicinal plants. Moreover, a large percentage of the world's population does not have access to conventional pharmacological treatment [6].

Eucalyptus camaldulensis belong to family of *Myrtaceae,* is one of the species of *Eucalyptus* introduced into Nigeria [7]. In Hausa, it is called "IccheTurare" and "River red gum Tree" in English. It is heavily-branched and it can grow up to 20 metres tall. The plant has been used in Nigerian traditional medicine to treat sore throat, bacterial infection of the respiratory and urinary tracts, catarrh, nasal congestion and ulcer diseases [7].

Continuous usage of herbal medicine by a large proportion of the population in the developing countries is largely due to high cost of synthetic drugs, expensive health care and adverse side effects. Furthermore, most of these synthetic drugs produce many serious adverse effects including gynaecomastia, arrhythmias, impotence, arthralgia, hypergastrinemia and haemopoeitic changes, stomach distention, belching, constipation and ulcer perforation are characteristics adverse effects of antacids. Other issues include the long-term duration of the treatment period and also associated incomplete eradication of ulcers. Ulcer disease has been associated with oxidative stress. Therefore, other alternative approach is necessary that may lead to discovery of new antiulcer agents or drug compounds that are more effective, show better patient tolerance, less expensive and without side effects. In this context, plant extracts may be promising substances in the search for new therapies of Ulcer disease. It is against this back drop, that this work is designed to evaluate the antioxidant and antiulcer potential of *Eucalyptus camaldulensis* extract in wistar albino rats.

2. MATERIALS AND METHODS

2.1 Collection of Plant Material, Identification and Preparation of Extract

The *Eucalyptus camaldulensis* leaves were collected from the Kebbi State University of Science and Technology garden and was identified by a taxonomist from Plant Science and Biotechnology Department, Faculty of Life Sciences, Kebbi State University of Science and Technology, Aliero and given a voucher number C-128. The extraction of 500g of *Eucalyptus camaldulensis* leaf in 2500mls of methanol yielded 19.3%. The extract was soluble in water, black in colour and with a sticky texture.

2.2 Induction of Ulcer in Rats

Thirty (30) male albino rats weighing between 200-250g were used for the study. The induction of ulcer in rats was achieved by oral administration of ethanol, absolute at a dose of 5ml/kg body weight by intragastric gavage according to the method of Almasaudi et al. [8]. Thirty (30) male albino rats were randomly divided into six (6) groups of five (5) rats each and were treated for seven days once daily. Group 1 received distilled water at 5ml/kg body weight. Ulcer was induced in Groups 2 to 6 with ethanol at a dose of 5ml/kg. Group 2 was left untreated while group 3 was administered orally with omeprazole at a dose of 50mg/kg. Groups 4, 5 and 6 were administered orally with 200mg/kg, 400mg/kg and 800mg/kg of the extract respectively.

At the end of the experiment, all the animals were fasted for one day and sacrificed after being anesthetized with chloroform. The stomach were removed, cut along the greater curvature and the mucosa was washed with 0.9% saline solution to clean away the blood and other contents. This was followed by macroscopic examination of the stomach for the detection of any hemorrhagic lesions on the glandular mucosa. The length in mm of each lesion was measured to determine the mean ulcer index (UI).

2.3 Measurement of Ulcer Score

The ulcer score was measured by scoring of severity of mucosal lesions as reported by Mahmood et al. [9].This was done as follows:

0 = Normal coloured stomach, 0.5 = Red coloration, 1 = Spot ulcers, 1.5 = Haemorrhagic streak, 2 = Ulcers and 3 = Perforation.

2.4 Measurement of Ulcer Index

The length in mm of each lesion was measured by determining the mean ulcer index according to Mahmood et al. [9].

Mean ulcer score for each animal is expressed as ulcer index.

$$Ulcer\ Index\ (UI) = \frac{Total\ ulcer\ score\ for\ each\ group}{n}$$

Where; n = Number of animals per group

2.5 Measurement of Percentage Inhibition

The percentage inhibition was calculated using the method of Mahmood et al. [11.

$$Percentage\ Inhibition = \frac{Ulcer\ Index\ of\ Control - Ulcer\ index\ of\ test}{Ulcer\ index\ of\ Control} x100$$

2.6 Determination of Oxidative Stress Biomarkers

The method described by Rutkowski et al. [10] was followed for the estimation of Vitamins A, Vitamins C and Vitamins E. Catalase activity (CAT) and Superoxide Dismutase (SOD) were measured according to the method of Aebi [11] Malondialdehyde **(**MDA) was induced and assayed according to the method of Shah and Walker's [12] Reduced glutathione (GSH) was assayed accordingly the method of Habig et al. [13].

2.7 Statistical Analysis

All data were presented as Mean ± SD. Statistical software SPSS 20.0 was utilized. The results were statistically analyzed using a one-way analysis of variance (ANOVA) test. Statistical differences of $P<.05$ were considered to be significant.

3. RESULTS AND DISCUSSION

3.1 Percentage Yield of Methanol Extract of Dried Leaf of *Eucalyptus camaldulensis*

The gastric mucosal lesions produced in the ulcer control group were very visible and had an ulcer index of 12.83. Treatment with omeprazole (50mg/kg) and graded doses of the extract (200 mg/kg, 400mg/kg and 800 mg/kg), showed significant reductions ($P<.05$) in ulcer index in a dose dependent manner when compared to the negative control group. Even though the ulcer index of the treated groups was significantly ($P<.05$) lower than that of the group treated with ethanol only, the highest dose of 800mg/kg showed a lower percentage protection (56.51%) than that of the standard drug (68.82%). The group that received 800mg/kg only did not show less ulceration Table 1.

The induced-control group showed significant ($P<.05$) decrease in serum of vitamin C and E when compared to the normal control group. There was significant reduction in vitamin A concentration between the group that received the highest dose and the standard drug. However, treatment with *Eucalyptus camaldulensis* methanol leaf extract (200 - 800mg/Kg body weight) showed a dose-dependent increase in serum of both vitamin A, C and E which was significantly ($P<0.05$) different from the standard drug (omeprazole) Table 2.

The results showed a significant reduction ($P<.05$) in the level of the enzymatic antioxidants, superoxide dismutase (SOD), Catalase (CAT) and glutathione peroxidase (Gpx) activities in the induced-control group when compared with the normal control group Table 3. However, treatment with *Eucalyptus camaldulensis* methanol leaf extract (200 - 800mg/Kg body weight) and omeprazole (50mg/Kg) significantly elevated ($P<.05$) the enzymatic antioxidants. Lipid peroxidation was increased significantly ($P<.05$) in the induced-control group as revealed by elevated MDA levels, when compared with normal control group in both the serum and stomach mucosa homogenate. There was also a decline in reduced glutathione (GSH) in induced-control group compared to normal control. The effect of the extract (800mg/kg) in reducing MDA is comparable to that of omeprazole (50mg/Kg) in serum, meanwhile it was significantly reduced in gastric mucosa homogenate.

4. DISCUSSION

Eucalyptus camaldulensis like other plants play a great role in drug development [14]. Antioxidants have being reported to not only play a significant role in the protection of gastric mucosal injury but also in inhibiting the progression of gastric ulcer. The formation of gastric mucosal lesions following induction of ethanol involves different mechanisms like the production of reactive oxygen species which leads to the reduction of mucosal non-protein sulfylhydryl level, reduction in gastric blood flow, solubilization of mucus constituents and increase in xanthine oxidase activity [15]. It also produces necrotic lesions in the gastric mucosa of animals by a direct toxic effect thereby reducing the secretion of bicarbonates and depleting gastric mucus production in animals [16]. Earlier studies revealed that ethanol induces gastric mucosal injury by causing extensive damage to mucosal capillaries resulting in increased vascular permeability, oedema formation and epithelial lifting [17-18]. Ethanol is also known to reduce effectively endogenous derived NO level in the gastric mucosa [19]. Nitric oxide (NO) is considered to be one of the most important defensive endogenous agents in the gastric mucosa [20].

Antioxidants have being reported to not only play a significant role in the protection of gastric mucosal injury but also in inhibiting the progression of gastric ulcer [21]. The decrease in Vitamin A, C and E levels were in accordance with several previous reports [22-23]. Vitamin C protects cells against various water-soluble radicals. It is a marker of oxidative stress and its reduced levels are in accordance with enhanced oxidative stress [22]. Vitamin E is a non-enzymatic antioxidant which effectively reacts with organic lipid radicals produced in the process of lipid peroxidation. Vitamins C and E are chain breaking antioxidants and could individually halt the chain of oxidative reactions

that ultimately lead to pathology [23]. In this study, the depletion of vitamin C and E observed in induced-control suggests enhanced lipid peroxidation during tissue damage and failure of antioxidant defense mechanism to prevent formation of excessive free radicals. It could also be correlated with the excessive utilization of non-enzymatic antioxidants in scavenging enormous free radicals produced by ethanol and this corroborates with the widely studied role of antioxidants like vitamins C and E in xenobiotic-induced oxidative stress and hepatoprotection [23-24]. The significant decrease in the level of Vitamin A, C and E in stomach tissue homogenate may be due to increased production of reactive oxygen radicals resulting in increased utilization of these enzymes and vitamins. Meanwhile, the serum of the groups that received the extract showed minimal or no change in levels of vitamin C and E when compared with the normal control. The extract may have impacted positively on the Nrf2 (Nuclear factor erythroid-derived 2), a transcription factor that regulates the expression of antioxidant proteins which mopped up the oxidants, thereby conserving Vitamin C and E. *Eucalyptus camaldulensis* methanol extract may act as an antioxidant preventing lipid

Table 1. Antiulcer effect of *Eucalyptus camaldulensis* methanol leaves on ethanol-induced ulcerogenic rats

Treatment	Ulcer index	Percentage Inhibition (%)
5mls/kg (Distilled water)	-	-
5ml/kg (Ethanol)	12.83 ± 0.78^{c}	-
50mg/kg (Omeprazole)	4.00 ± 0.42^{a}	68.82
200mg/kg b.wt	11.08 ± 1.01^{c}	13.63
400mg/kg b.wt	7.00 ± 1.05^{b}	45.44
800mg/kg b.wt	5.58 ± 1.01^{ab}	56.51

Values are expressed as mean ± standard error of mean, n = 5, mean values having common superscript letters in a column are not significantly different (P<.05) (one-way ANOVA followed by Duncan's multiple range test)

Table 2. Effect of *Eucalyptus camaldulensis* methanol leaves extract on antioxidant vitamins on ethanol-induced ulcerogenic rats

TREATMENT	Vitamin A (mg/dl)	Vitamin C (mg/dl)	Vitamin E (mg/dl)
5ml/kg (Distilled water)	6.20 ± 0.42^{c}	4.60 ± 0.37^{d}	3.38 ± 0.26^{c}
5ml/kg (Ethanol)	3.40 ± 0.44^{a}	1.95 ± 0.51^{bc}	1.20 ± 0.25^{a}
50mg/kg (Omeprazole)	4.94 ± 0.38^{b}	3.25 ± 0.33^{c}	2.65 ± 0.23^{b}
200mg/kg b. wt	3.32 ± 0.29^{a}	1.45 ± 0.10^{a}	1.60 ± 0.08^{a}
400mg/kg b. wt	3.51 ± 0.27^{a}	2.68 ± 0.40^{bc}	2.57 ± 0.27^{b}
800mg/kg b. wt	5.21 ± 0.28^{bc}	2.73 ± 0.30^{bc}	3.36 ± 0.17^{c}

Values are expressed as mean ± standard error of mean, n = 5. Mean values having common superscript letters in a column are not significantly different (P<.05) (one-way ANOVA followed by Duncan's multiple range test).

Table 3. Effect of administration of *Eucalyptus camaldulensis* methanol leaves extract on oxidative stress biomarkers in ethanol-induced ulcerogenic rats

	SOD (µmol/g)	CAT (µmol/g)	GPx (µmol/g)	GSH (µmol/g)	MDA (nmol/ml)
5ml/kg body (Distilled water)	10.19 ± 0.52^{e}	51.33 ± 0.89^{e}	25.16 ± 0.81^{e}	9.15 ±0.36^{b}	5.05 ± 0.49^{a}
5ml/kg (Ethanol)	4.93 ± 0.20^{b}	23.90 ± 0.92^{a}	12.08 ± 0.75^{a}	6.42 ± 1.19^{a}	8.74 ± 0.4^{b}
50mg/kg (Omeprazole)	3.60 ± 0.36^{a}	36.68 ± 0.94^{c}	22.19 ± 0.91^{e}	9.25 ± 0.64^{b}	5.87 ± 0.46^{a}
200mg/kg b. wt	5.43 ± 0.10^{b}	27.97 ± 1.66^{b}	14.25 ± 0.59^{b}	7.95 ± 0.52^{ab}	5.47 ± 0.29^{a}
400mg/kg b. wt	7.94 ± 0.46^{c}	39.78 ± 1.44^{c}	16.63 ± 0.59^{c}	7.42 ± 0.57^{ab}	4.64 ± 0.50^{a}
800mg/kg b. wt	9.85 ± 0.39^{d}	47.91 ± 0.69^{d}	21.00 ± 0.79^{d}	8.15 ± 0.78^{ab}	5.64 ± 0.23^{a}

Values are expressed as mean ± standard error of mean, n = 5. Mean values having common superscript letters in a column are not significantly different (P<.05) (one-way ANOVA followed by Duncan's multiple range test). (SOD = Superoxide Dismutase, CAT = Catalase, GPx = Glutathione Peroxidase)

peroxidation thereby reducing ROS [14]. In the event of a reduced ROS generation, vitamins C and E are preserved, hence the increase in their values in groups that received the extract and omeprazole.

The enzymatic antioxidants play a significant role in the sustaining of physiological levels of O_2 and H_2O_2 and eradicating the peroxides generated from inadvertent exposure to toxic drugs [23]. In the present study, ethanol induction decreased the levels of gastric SOD, CAT and GPx activities indicating increased oxidative stress. SOD, CAT and GPx constitute mutually a supportive team of defense against reactive oxygen species. GPx is a major low molecular weight scavenger of free radicals in the cytoplasm and an important inhibitor of free radical mediated lipid peroxidation. GPx in tissues has been proposed to be a potential chemopreventive agent due to its antioxidant and detoxification properties. Glutathione peroxidase is a selenoenzyme, which plays a major role in the reduction of H_2O_2 and hydroperoxide to non-toxic products [21]. In the present study, the decline in the activities of the serum SOD, CAT and GPx in induced-control group might be due to enhanced superoxide radical formation leading to oxidative stress in the tissue. The protection offered by the extract can be linked to increase secretion of bicarbonate, production of mucus and decrease in vascular permeability. Previous studies have also shown that administration of antioxidants can inhibit ethanol induced gastric damage [23,22] The significant decrease in ulcer index observed in this model may also be indicative of the ability of the extract and its fraction to scavenge generated free radicals and toxic metabolites.

The observed decrease in GSH level suggests enhanced lipid peroxidation during tissue damage and failure of antioxidant defense mechanism to prevent formation of excessive free radicals [15]. The administration of methanol leaves extract of *Eucalyptus camaldulensis* increased the levels of GSH. This suggests that the extract has antioxidant activities which suffice for reduced glutathione. Oxidative stress plays an important role in the pathogenesis of various diseases including peptic ulcer disease. MDA the end product of lipid peroxidation acts as a marker of oxidative stress [23]. Previous studies have reported the elevation of gastric mucosal MDA in ethanol induced ulcer. The elevation could have resulted from peroxidation of a polyunsaturated fatty acid component of the membrane by generated free and oxygen-derived radicals. Peroxidation of membrane lipids is associated with loss of membrane fluidity, impaired ion transport and membrane integrity and ultimately a loss of cellular function. This observed reduction in MDA could be due to the ability of the extract to prevent the formation of ROS and subsequently inhibit lipid peroxidation of stomach tissue.

5. CONCLUSION

The present findings have revealed that *Eucalyptus camaldulensis* possesses antiulcer activity. This activity might have been mediated by either anti-secretory or cytoprotective mechanisms. As such, to fully exploit the potency of this plant, the mechanism of action needs to be elucidated. This research therefore justifies the basis for the use of the plant by traditional medicine practitioners in the management of ulcer.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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