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Anti-Ulcer and Antioxidant Activities of *Chrysophyllum albidum* G. Don. Seeds Cotyledons

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Abstract

Background*: Gastric ulcers are prevalent gastrointestinal disorders with significant global implications owing to their prevalence and potential complications. Side effects associated with synthetic drugs have led to the search for alternative treatments. Chrysophyllum albidum, a plant traditionally used to manage various diseases, has been investigated for its potential to alleviate ulcerative conditions.* ***Methods:*** *This study assessed the efficacy of extracts from C. albidum seed cotyledons in mitigating ethanol- and diclofenac-induced ulcers in rats. Phytochemical screening was performed using standard methods and antioxidant activities were evaluated using DPPH scavenging and $ABTS^+$-reducing assays.* ***Results:*** *For ethanol-induced gastric ulcers, extracts at doses of 100, 200, and 400 mg/kg produced lesion indices of 7.04 ± 0.44, 5.18 ± 0.38, and 2.53 ± 0.46 mm, respectively, compared to omeprazole's 0.9 ± 1.09 mm. The highest dose showed 87.93% inhibition, which was comparable to that of omeprazole (93.63% inhibition). A similar trend was observed for diclofenac-induced ulcers. Phytochemical analysis revealed the presence of active compounds, such as steroids, flavonoids, polysaccharides, alkaloids, and cardiac glycosides. Antioxidant activity results indicated significant free radical scavenging properties, with an IC_{50} value of 49.24 µg/mL for DPPH and 15.1 µg/mL for $ABTS^+$ at a dose of 400 mg/kg. These findings demonstrate the notable dose-dependent anti-gastritis and anti-ulcer effects of the extract.* ***Conclusion:*** *This study highlights the potential of C. albidum seed cotyledons as a valuable candidate for gastroprotective drug development and supports their traditional use in treating and preventing gastritis and gastric ulcers.*

Keywords*: antioxidant, alternative treatment, DPPH, phytochemicals, ulcer*

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INTRODUCTION

Plants play a significant role in contemporary drug discovery and development, with medicinal plants being historically used to manage and treat various diseases, including ulcers (Shahzad et al., 2023). Gastritis and gastric ulcers are among the most common gastrointestinal disorders, and their prevalence and complications have increased in recent decades, leading to substantial global morbidity and mortality (Sun et al., 2023). Ulcers result from an imbalance between harmful factors, such as acid and pepsin, and the protective mechanisms that maintain mucosal integrity (Périco et al., 2022). Managing gastritis and ulcers involves a combination of medications including proton pump inhibitors, anticholinergics, histamine receptor antagonists, and antibiotics (Arunachalam et al., 2023). Although these drugs are effective, their potential side effects, limited efficacy, and interactions pose significant challenges (Périco et al. 2022). Consequently, there is a growing interest in natural remedies, which are perceived to have fewer side effects and lower costs.

Antioxidants help manage ulcers by counteracting oxidative stress, which is a key factor in the development of gastric and duodenal ulcers. Oxidative damage exacerbates inflammation and mucosal injury, contributing to ulcer formation and hindering healing (Beiranvand et al. 2021). Research suggests that antioxidants, such as vitamin C, vitamin E, flavonoids, polyphenols, and plant-based compounds, can reduce oxidative damage, protect the gastric mucosa by neutralizing free radicals, suppressing inflammatory pathways, and promoting mucosal repair (Beiranvand et al., 2018; Beiranvand et al., 2021). Additionally, they may help lower gastric acid secretion, potentially improve ulcer healing, and reduce the risk of recurrence (Khan et al., 2024). Antioxidants also help combat bacteria such as H. pylori and inhibit pepsinogen production, thereby preventing ulcer formation. Some antioxidants have been shown to boost the levels of prostaglandins and mucus in the gastric mucosa, thereby demonstrating cytoprotective effects. Additionally, several of these compounds can prevent gastric mucosal ulcers triggered by various experimental models and safeguard the gastric lining from various harmful agents (Alharbi et al., 2022).

Chrysophyllum albidum G. Don, a tree from the *Sapotaceae* family, is commonly found in lowland rainforests of East and West Africa (Erukainure et al., 2022). Known as the African Star Apple or Agbalumo and Udara in Nigeria, this fruit is enjoyed as a nutritious snack and is believed to offer health benefits (Imaga et al., 2023; Erukainure et al., 2022). The fruit contains approximately 50 mg/100 g ascorbic acid in its exocarp and pulp (Tsado et al., 2023). Phytochemical analyses have revealed both saturated (palmitic and myristic acids) and unsaturated (linoleic and oleic acids) fatty acids in fruits (Izuakor et al., 2024). Additionally, fruit juice contains significant phenolic compounds such as catechin, chlorogenic acid, caffeic acid, epicatechin, cyanidine-3–O-glycoside, rutin, quercitrin, quercetin, and kaempferol (Ajayi et al., 2024). Ethnomedicinally, C. albidum was used to treat diarrhea, hypertension, malaria, and wounds (Ogunleye et al., 2020). The fruit pulp and peel extracts have demonstrated various pharmacological activities, including anti-nociceptive, anti-inflammatory, hypolipidemic, and antidiabetic effects (Akomolafe et al., 2019; Asagba et al., 2019; Ajayi et al.,2020a; 2020b), and anti-ulcer effects on the bark (Salami et al., 2022). However, the anti-ulcer activity of the seed cotyledons of this plant is yet to be evaluated scientifically; therefore, this study focused on evaluating the anti-ulcer potential of extracts derived from the seed cotyledons of *C. albidum*.

MATERIALS AND METHODS

Materials

C. albidum seeds were sourced from ripe fruits (Figure 1) purchased from local markets in Ewu, Esan, Edo State, Nigeria. The seeds were identified and authenticated at the Pax Herbal Clinic and Research Laboratories, where they were assigned voucher numbers Pax/12/668 and a specimen was deposited. Wistar rats were obtained from the Pax Herbal Clinic and Research Laboratories Animal House and handled according to animal ethics standards. The other materials used were acacia gum, 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) ($ABTS^{+}$), 2,2-diphenyl-1-picrylhydrazyl (DPPH), ascorbic acid (Aldrich), potassium persulfate, monosodium phosphate monohydrate, disodium phosphate heptahydrate, methanol, ethanol, and chloroform. All other reagents were of analytical grade and the solvents were redistilled before use.

Tools

The study utilized various apparatus and equipment, including a heating mantle, hot air oven (DHG-9053A), water bath, Soxhlet extractor, grinding machine (DE-DAMAK; GX160, Japan), centrifuge, UV Spectrophotometer (Surgifield; SM-23D, England), and a water circulator.

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Method

Extraction

Two hundred grams of the Powdered cotyledons (200 g) were subjected to Soxhlet extraction using methanol as the solvent. Following extraction, the extract was concentrated under reduced pressure using a rotary evaporator, yielding a semi-solid pale-yellow paste, which was then weighed, and the percentage yield of the extract was calculated using the formula.

$$\% \text{ yield} = \frac{\text{Weight of extract}}{\text{Weight of original plant material}} \times 100$$

Phytochemical screening

Phytochemical analysis was performed to detect the presence of various bioactive compounds in the extracts. The tests included alkaloids, flavonoids, saponins, cardiac glycosides, terpenoids, steroids, reducing sugars, and polysaccharides (Owolabi and Salome, 2022). Briefly, 5 g of the extract was dissolved in 5 mL of methanol and diluted with 100 mL of double-distilled water. The resulting solution was used for the following phytochemical tests.

Alkaloid test

To 3 mL of the extract, 3 mL of 1% HCl was added, heated in steam for 30 min, cooled, and centrifuge at 2000-3000 rpm for 10 min. The supernatant was tested with

a) Drangedroff reagent (orange precipitate indicates alkaloids)

b) Mayer's reagent (creamy precipitate indicates alkaloids)

c) Wagner's reagent (reddish-brown precipitate indicates alkaloids)

Flavonoid test

Then, 2 mL of the extract was added to 2 mL of dilute ammonia solution, and then 1 mL of concentrated H2SO4 was added. The yellow coloration, which fades upon standing, confirms the presence of flavonoids.

Saponin test

The extract (0.5 mL) and distilled water (5 mL) were added, and the mixture was shaken vigorously. Persistent frothing indicated the presence of saponins.

Cardiac glycoside test

Two milliliters of the extract, 2 mL of glacial acetic acid, 1 mL of 0.1% FeCl3, and 1 mL of concentrated H2SO4. The green-blue coloration confirms the presence of cardiac glycosides.

Terpenoid test

Add 2 mL of the extract to six drops of Brady's reagent. The yellowish-orange color indicates the presence of terpenoids.

Steroid test

mL of the extract with acetic acid anhydride (0.5 mL) was mixed and cooled on ice, and chloroform (0.5 mL of chloroform and 1 mL) were H2SO4 carefully. A reddish-brown ring at the interface confirms the presence of steroids.

Reducing sugar test

The extract (2 mL) was added to 2 mL of Fehling's solutions A and B, and then heated for 30 min. The red coloration confirms the presence of reducing sugars.

Starch/polysaccharide test

Add 2 mL of the extract to six drops of iodine solution. The blue-black coloration indicates the presence of starch.

Anti-ulcer activity: ethanol and diclofenac-induced gastric ulcer

All animal experimental procedures were conducted in strict adherence to the approved ethical committee on animal handling guidelines of the Research and Ethical Review Committee, Igbinedion University (approval number: IUO/Ethics/054/24), which aligns with the United States National Institute of Health (NIH) Guidelines for the Care and Use of Laboratory Animals in Biomedical Research (NIH, 1985).

Briefly, adult Wistar rats were fasted for 24 h before the experiment although they had free access to water. The rats were randomized and divided into five groups, each containing five rats. Groups 1–3 were treated with *C. albidum* seed cotyledon extract at doses of 100, 200, and 400 mg/kg orally. These doses were chosen based on the previously reported LD_{50} of the seed to be greater than 1000 mg/kg (Onyegbule et al., 2019; Onyegbule et al., 2020). Group 4 received vehicle, while group 5 was administered omeprazole at a dose of 20 mg/kg. After 60 min, each rat was orally administered 1 mL of 96% ethanol or diclofenac via an orogastric cannula. One hour after ethanol/diclofenac administration, the animals were sacrificed under ether anesthesia. The stomachs were then dissected, opened along the greater curvature, rinsed under running water to remove blood clots, fixed in 10% formalin, and examined for lesions using a hand lens. The total number, shape, and coloration of all the lesions in each stomach were observed using a 10X hand lens and recorded as the ulcer index (UI), which was calculated as follows:

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Ulcer index (UI) = UN + US + (UP/10)

UN is the average number of ulcers per animal, UP is the percentage of animals with ulcers, and US is the average severity score, which is shown in table below:

Table 1. Severity scores of ulcer indices

S/N	Observable indices	Scores
1	Normal colored stomach	0
2	Coloration	0.5
3	Spot ulcer	1
4	Hemorrhagic streak	1.5
5	Deep ulcer	2
6	Perforation	3

The percentage of inhibition of ulceration was calculated using the following formula:

$$\% \text{ Inhibition} = \frac{(UI_{control} - UI_{treated})}{UI_{control}} X\ 100$$

Antioxidant activity

The antioxidant potential of the extracts was evaluated using the DPPH (2,2-diphenyl-1-picrylhydrazyl) and $ABTS^+$ (2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid)) assays (Munteanu & Apetrei, 2021).

DPPH radical scavenging capacity

DPPH radical scavenging capacity was determined using standard methods (Munteanu & Apetrei, 2021). A 2.4 mL solution (0.1 mM) in ethanol was mixed with 1.6 mL of the extracts at varying concentrations (0-200 µg/mL). The reaction mixture was thoroughly vortexed and incubated in the dark at room temperature for 30 min. Absorbance was measured using a spectrophotometer (Surgifield; SM-23D, England) at 517 nm. The percentage of DPPH radical-scavenging activity was calculated using the following equation:

$$\text{Scavenging activity} = \frac{(A_0-A_1)}{A_0} X\ 100$$

where A_0 is the absorbance of the blank, and A_1 is the absorbance of the sample. The percentage inhibition was plotted against the concentration, and the IC_{50} value was determined from the graph.

Calculation of EC_{50} value

To calculate the EC_{50} value, the plant extract solution in methanol was further diluted and tested using the DPPH assay to determine the concentration required for 50% inhibition. The EC_{50} values were calculated using a graphical method. The EC_{50} value of ascorbic acid (AA) was determined.

$ABTS^+$ assay

The $ABTS^+$ assay was performed using a modified method from Munteanu and Apetrei (2021). A 7 mM $ABTS^+$ stock solution was prepared in water. The $ABTS^+$ radical cation was generated by reacting the stock solution with 2.45 mM potassium persulfate solution. The solution was kept in the dark at room temperature for 12 h prior to use. It was then diluted 50-fold with phosphate buffer (pH 8.04) to achieve an absorbance of 0.7 at 415 nm. Three milliliters of the $ABTS^+$ solution was added to a 1 cm cuvette, followed by the addition of 150, 300, and 600 µL of methanolic plant extract solutions to achieve final concentrations of 50, 100, and 200 ppm, respectively. Trolox was used as a positive control, whereas the $ABTS^+$ solution was used as a negative control. The absorbance was measured at 415 nm. The percentage inhibition was measured using the following formula:

% inhibition = (Ac-As/Ac) x 100

Where;

Ac = Absorbance of control

As = Absorbance of sample

Statistical Analysis

All experiments were conducted in triplicate and repeated at least twice, and the results are expressed as mean ± standard deviation. Statistical analysis was performed using analysis of variance (ANOVA) (SigmaPlot version 15.0). Differences were considered statistically significant at $P < 0.01$ and $P < 0.05$.

RESULTS AND DISCUSSION

Yields of the plant extract

Following exhaustive extraction using continuous hot extraction, 200 g of powdered *C. albidum* seed cotyledons yielded a crude extract of 21.9583 g, which corresponded to 10.98% of the initial plant powder. Extraction and extraction of solvents are the key determinants of the yield of bioactive constituents obtained after each successful extraction procedure. The extraction method used in this study contributed to the high yield obtained through this procedure.

Phytochemical analysis results

Phytochemical screening identified flavonoids, polysaccharides, alkaloids, terpenoids, cardiac glycosides, and steroids in the methanol extract of *C. albidum* seed cotyledons. However, saponins were not detected. Detailed results are presented in Table 2. Some researchers have reported that *C. albidum* contains alkaloids, tannins, phenols, and flavonoids in the stem

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slash and seed cotyledons (Adeboyejo et al., 2019; Imaga et al., 2023; Izuakor et al., 2024), which agrees with the current study, except for the presence of steroids, which has not been previously reported. These variances can be attributed to differences in geographical sources. The presence of these bioactive compounds likely contributes to the observed anti-ulcer and antioxidant activities, as many researchers have linked the therapeutic effects of plants to their phytochemicals (Owolabi & Ayinde, 2022).

Effects of *C. albidum* seed cotyledon extract on ethanol and diclofenac-induced gastric ulcer

Ulcers are a prevalent gastrointestinal disorder characterized by inflamed lesions or erosion of the mucosa and underlying tissues, resulting from a disparity between harmful factors, such as acid, pepsin, and *H. pylori*, and protective factors, such as gastric mucus, bicarbonate ions, and prostaglandins, along with the inherent resistance of mucosal cells (Périco et al., 2022). The incidence of gastric ulcers and gastritis is notably higher in individuals who smoke, use nonsteroidal anti-inflammatory drugs (NSAIDs), or consume alcohol (Aladainan et al., 2021; Xie et al., 2022). Although conventional treatments are effective, both clinical and experimental studies have shown that traditional herbal medicines offer therapeutic benefits in gastric ulcers (Roy et al., 2023).

In the present study, the methanol extract of *C. albidum* seed cotyledons significantly decreased the ulcer indices in both ethanol- and diclofenac-induced ulcer models in a dose-dependent manner. In the ethanol-induced ulcer model, the vehicle control group had an ulcer index of 8.33 ± 0.73, whereas the groups treated at 100, 200, and 400 mg/kg had ulcer indices of 7.04 ± 0.44, 5.18 ± 0.38, and 2.53 ± 0.46, respectively. These results were comparable to those of the standard omeprazole group, which had an ulcer index of 0.9 ± 1.09, with percentage inhibitions of 12.99, 60.72, and 87.93%, respectively, compared to the omeprazole group (93.63%). A similar trend was observed in the diclofenac-induced ulcer model, where the vehicle group produced an ulcer index of 14.98 ± 0.34. The treated groups at 100, 200, and 400 mg/kg showed ulcer indices of 9.92 ± 0.44, 5.93 ± 0.66, and 3.50 ± 0.73, respectively, while the omeprazole group had an ulcer index of 2.49 ± 0.45, as detailed in Table 3. The methanol extract demonstrated significant efficacy in both in vivo ulcer models, suggesting its potential as a therapeutic agent in ulcer management.

Some researchers have reported *C. albidum* as a traditional treatment for ulcers (Imaga et al., 2023). Although Salami et al. (2022) proved this claim, this study is the first to provide an experimental basis for the anti-ulcer activities of seed cotyledons only on the stem bark of the plant.

Antioxidant effect of *C. albidum* seed cotyledon extract

The extract exhibited some level of antioxidant activity, despite the highest concentration (200 µg/mL) yielding the most effective IC_{50} values of: 49.24 ± 0.978 µg/mL DPPH and 15.1 ± 0.07 µg/mL), which are not comparable to the activities of ascorbic acid (17.24 ± 0.425 µg/mL for DPPH, and 7.01 ± 0.2 µg/mL for $ABTS^{+}$). These results indicate robust free radical-scavenging properties. The detailed results are presented in Table 4.

Oxidative stress is believed to initiate and exacerbate digestive system diseases, including stomach ulcers and gastric carcinomas. Ethanol-induced gastric damage is thought to be mediated by free radicals (Périco et al. 2022). Ethanol metabolism generates superoxide anions and hydroperoxyl free radicals. Recent research suggests that antioxidants may offer protection and promote healing in the stomach by boosting the production of gastric mucus glycoproteins and inhibiting prostaglandin production (da Luz et al., 2019). Free radicals play a significant role in ethanol-induced and NSAID-related mucosal damage (Takeuchi 2012). Antioxidants can neutralize ROS, and are expected to aid in the healing and prevention of gastric ulcers. Akanji (2020) and Adetoun et al. (2023) reported that *C. albidum* pulp and stem bark exhibit antioxidant activities, which was also demonstrated for the first time in the seed cotyledons in the current study. In our experiment, we found a significant scavenging potential that suggests that the extracts would have significant antioxidant action and, therefore, significant anti-gastritis and anti-ulcer activity.

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Figure 1. *Chrysophyllum albidum* A: tree, B: fruits, C: seeds, D: cotyledons

Table 2. Results of the qualitative phytochemical screening of *C. albidum* seeds cotyledons

Phytoconstituents	**Results**
Cardiac Glycoside	++
Terpenoids	++
Saponin	-
Flavonoid	+
Steroid	+++
Alkaloid	+
Polysaccharide/Starch	++

Key:
+ = Mildly Present ++ = Moderately Present
+++ = Abundantly Present - = Absent
Note: +, ++, +++ represent the extent of either coloration or precipitate produced

Table 3. Effect of the *C. albidum* seed cotyledon extract on ethanol-induced and diclofenac-induced gastric ulceration

	Ethanol-induced		**Diclofenac-induced**	
Sample	Ulcer Index	% Inhibition	Ulcer Index	% Inhibition
Acacia gum (0.2%)	8.33 ± 0.73	-	14.98 ± 0.34	-
C. albidum (100mg/kg)	7.04 ± 0.44	12.99	9.92 ± 0.44**	28.43
C. albidum (200mg/kg)	5.18 ± 0.38*	60.72	5.93 ± 0.66**	53.75
C. albidum (400mg/kg)	2.53 ± 0.46*	87.93	3.50 ± 0.73**	84.19
Omeprazole (20 mg/kg)	0.9 ± 1.09**	93.63	2.49 ± 0.45**	96.45

Values represent the mean ± SD (n=5); *P<0.05, **P<0.01, significant when compared to the control

Table 4. Antioxidant activities *C. albidum* seeds cotyledons extracts

Sample	DPPH IC_{50} (μg/mL)	$ABTS^{+}$ EC_{50} (μg/mL)
AA (25 µg/mL)	17.24 ± 0.425	7.01 ± 0.2
100 µg/mL	62.9 ± 1.02	30.32 ± 0.4
200 µg/mL	51.7 ± 1.57	27.72 ± 0.05
400 µg/mL	49.24 ± 0.978	15.1 ± 0.07

AA is Ascorbic acid
Each value is expressed as Mean ± SD (n = 3), at 100 μg/ml. IC_{50} (μg/ml): the concentration at which 50% is inhibited; EC_{50} (μg/ml): effective concentration at which the absorbance is 0.5.

CONCLUSION

C. albidum seed cotyledons exhibit significant anti-ulcer that can be linked to their antioxidant activities, supporting their traditional use in treating gastrointestinal disorders. Further research is needed to isolate and characterize the active compounds responsible for these effects and to investigate their mechanisms of action.

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AUTHOR CONTRIBUTIONS

Conceptualization, O.T.A.; Methodology, O.T.A.; Software, O.P.C.; Validation, O.T.A.; Formal Analysis, O.P.C.; Investigation, O.T.A., O.P.C.; Resources, O.T.A., O.P.C.; Data Curration; O.P.C.; Writing - Original Draft, O.T.A.; Writing - Review & Editing, O.P.C.; Visualization, O.T.A.; Supervision, O.T.A., O.P.C.; Project Administration, O.T.A.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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