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Evaluation of Antiemetic Activity of Aqueous Leaf Extract of *Chrysophyllum Albidum* George Don (Sapotaceae) in Rodents

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ABSTRACT

Emesis or vomiting is a means by which gastrointestinal tract gets rid of its content when the upper portion of the tract is excessively irritated, over-distended or even over-excited. A large amount of stomach contents is pushed upwards to flow back into the oesophagus, which then exits through the mouth or nose. Medicinal plants have been much widely employed, and they have proved reliable in the treatment of various diseases, as well as in the discovery of newer agents.

The plant, *Chrysophyllum albidum* (Linn), also known as African star apple, belongs to the family Sapotaceae. It is primarily a forest tree species with its natural occurrences in diverse ecozones in Uganda, Nigeria and Niger Republic (Bada, 1997). Across Nigeria, it is known by several local names and is generally regarded as a plant with diverse ethno-medicinal uses (Amusa *et al.*, 2003). The plant is known as 'Agbalumo' in Yoruba.

The present aim was to evaluate antiemetic activities of *Chrysophyllum albidum* (in copper sulphate-induced emesis, cisplatin-induced emesis in chicks, as well as in ipecac-induced emesis in rats.

Both copper sulphate (50 mg/kg, orally) and cisplatin (10 mg/kg i.p) were administered to seven groups (n = 5) of chicks, while ipecac (0.03 ml orally) was used to induce emesis in rats (n = 4). Group 1 received distilled water (control), groups 2, 3, and 4 were given doses of *C. albidum* (100, 200 and 400 mg/kg, p.o), while groups 5, 6 and 7 were treated with standard antiemetic drugs (promethazine 25 mg/70kg, p.o; metoclopramide 50 mg/kg, i.p; and ondansetron 24 mg/70 kg, p.o). Emesis was induced thirty minutes later, and number of retching was counted for ten minutes. *Chrysophyllum albidum* at the doses employed showed significant ($p<0.001$) antiemetic when compared to the control and standard antiemetic drugs in all the models employed.

The findings in this study validate the folkloric use of the plant in treating emesis.

Keywords: Rats, chicks, emesis, plant, and *Chrysophyllum albidum*.

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INTRODUCTION

Emesis is a protective reflex which expels substances from the stomach and intestine, and prevents their further ingestion. It could be induced and employed generally as a protective mechanism to remove harmful substances ingested, but physiologically, it can also occur from many unrelated infectious and inflammatory conditions in the body. It is a complex process, which comprises of three phases including (a) pre-ejection phase (gastric relaxation and retroperistalsis), (b) retching (rhythmic action of respiratory muscles preceding vomiting and consisting of contraction of abdominal, intercostals and diaphragmatic muscles against a closed glottis) also called 'dry heaving' can also occur without vomiting, or can precede or follow vomiting and (c) ejection (intense contraction of the abdominal muscles and relaxation of the upper esophageal sphincter).[1] Emesis is mediated through the coordinated actions of central and peripheral receptors like dopamine type-2 (D_2), serotonin ($5HT_{1A}$, $5\text{-}HT_3$ and $5\text{-}HT_4$), muscarinic cholinergic (ACh-M), histamine (H_1), opioids (μ_2), cannabinoids (CB1), Gamma-aminobutyric acid ($GABA_{B1}$) and neurokinin (NK1).[2] Commercially available antiemetic brands may cause excessive sedation, dry mouth, dysphoria, extra-pyramidal signs, hypotension and hallucination.[3]

Plants and their derivatives play a key role in world health, and have long been known to possess biological activity useful for therapeutic purposes, or which serve as precursors for the synthesis of useful drugs,[4] as it has been reported that thirty percent of all modern drugs are derived from medicinal plants.[5] Over 5,000 plants are known to be used for medicinal purposes in Africa, but only a few have been described or studied,[6] therefore, there is a growing interest in exploiting plants for medicinal purposes, especially in Africa.[7]

Chrysophyllum albidum, commonly called white star apple, belonging to the family of *Sapotaceae* (which has up to 800 species) is a lowland rain forest tree species that grows up to 25 to 37 m in

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height at maturity with a girth varying from 1.5 to 2 m. The Scottish Botanist George Don, described it as a forest fruit tree,[8] and it is common throughout the tropical Central, East and West Africa regions including Nigeria, Uganda, Niger, Cameroun and Cote d' Ivoire, as well as in other parts of the world.[9]

Leaves are simple, dark green above, pale tawny below when young and silver-white below when mature, oblong-elliptic to elongate obovate elliptic, 12-30 cm long, 3.8-10 cm broad; apex shortly acuminate, base cuneate; primary lateral nerves widely spaced, 9-14 on each side of the midrib; secondary lateral nerves indistinct or invisible; petiole 1.7-4.2 cm long. Flowers shortly pedicellate, in dense clusters in the leaf axils or from above the scars of fallen leaves; calyx 5-lobed, 3 mm long, rusty pubescent outside, creamy white, the lobes equaling the tube in length. Fruits almost spherical, slightly pointed at the tip, about 3.2 cm in diameter, greenish-grey when immature, turning orange-red, yellow-brown or yellow, sometimes with speckles, 5 celled, with 5 brown seeds in yellowish, pleasantly acid pulp. Seeds 1-1.5 x 2 cm, beanlike, shiny when ripe, compressed, with one sharp edge and a star-shaped arrangement in the fruit.

Within the pulp are three to five seeds which are not usually eaten. The seed-coats are hard, bony, shiny, and dark brown, and when broken reveals white-coloured cotyledons. The fruit is seasonal (usually from the months of December to March). The plant is a crop of commercial value in Nigeria, the seeds are also used for local games or discarded, and the fleshy fruit pulp is suitable for jams and is eaten especially as snack by many locals.[9]

Tannins, flavonoids, terpenoids, proteins, carbohydates and resins are the phytochemicals that have been reported in *C. albidum*.[10]

The fruit was found to have the highest content of ascorbic acid per 100 g of edible fruit, which is about 100 times that of oranges and 10 times that of guava and cashew. The fruits also contain 90% anacadic acid, which is used industrially in protecting wood and as source of resin.[11]

The physicochemical and mineral analyses of *Chrysophyllum albidum* revealed the following; moisture (48.38 and 47.02%), crude protein (2.75 and 2.68%), carbohydrate (24.26 and 25.17%), ash (4.175 and 4.68%), crude fat (10.94 and 10.79%) and energy value (206.50 and 208.53 Kcal) for ethanol and aqueous extract. Also, 100 g mineral composition (mg) of the fruit contains sodium (123.05), iron (42.45), zinc (34.45), magnesium (34.05), calcium (24.55), manganese (4.1) and potassium (2.05). The vitamins analyzed in mg/100 g indicated vitamin K (35.36), vitamin B1 (18.68), folate (2.02), vitamin C (3.084) and vitamin B6 (3.26).[12]

Among the reported pharmacological activities of *Chrysophyllum albidum* are antioxidant properties[8] hypoglycemic and hypolipidemic, antimicrobial, hepatoprotective, and lastly, anti-plasmodial, as well as anti-fertility properties.

This study was designed to investigate the antiemetic effect of aqueous leaf extract of *Chrysophyllum albidum*.

MATERIALS AND METHODS

Drugs and Chemicals

Promethazine (Avomine, Manx Pharma, Cyprus), ondansetron (Vomistat, Lincolin Pharmaceuticals Limited India), metoclopramide (Reglan, Baxter Pharmaceuticals United Kingdom, England), cisplatin (cisplatin, Pharmacia India Pvt. Limited), dopamine (Martindale Pharmaceuticals United Kingdom, England), histamine (Bioniche Pharmaceuticals United Kingdom England), copper sulphate (Tianjin Kermel, Tianjin Kermel Chemical Reagent Co. Ltd China),

Experimental Animals

The animals used in this study were Swiss albino mice of six to eight weeks weighing (15-20 g), chicks of two to four days old weighing (39-40 g) and albino rats of either sex of six to eight weeks old weighing (100-120 g). They were obtained from the Laboratory Animal Centre of the College of Medicine, University of Lagos, Nigeria. The Animals were housed in plastic cages with wooden shavings as beddings at room temperature under standard environmental conditions (12 hours light/dark cycle), fed on standard rodent diet, and given free access to drinking water *ad libitum*. Rats were acclimatized for 14 days before the commencement of the experiment, while chicks were acclimatized for two days. The protocol used in this study was in accordance with the United States National Institutes of Health Guidelines for Care and Use of Laboratory Animals in Biochemical Research.[13]

Collection and identification of plant

Fresh leaves of *Chrysophyllum albidum* were obtained from Ogbe-ogume in Ndokwa West Local Government Area, Delta State, and authenticated at the Department of Botany, Faculty of Science, University of Lagos Nigeria, by Professor J.D. Olowokudejo, with a voucher specimen LUH: 7593, which was kept in the laboratory for future reference.

Preparation of the plant extract

The leaves of *Chrysophyllum albidum* were rinsed under a running tap, and thereafter dried in an

electric oven at 45 °C for about two weeks. The leaves were ground into powder form using electrical grinding machine (Machine type: 8 LAB MILL, Christy and Morris Limited Process with serial number 50158) at the Department of Pharmacognosy, Faculty of Pharmacy, University of Lagos, Nigeria. The resultant fine powder was kept in an airtight container at room temperature until the time of use. A known weight 583.3 g of the plant material was soaked in 6000 ml of hot water for 72 hours to obtain crude extract. The resulting mixture was rapidly filtered using a white handkerchief, and the filtrate dried in an oven at 40°C; was stored airtight in a sample bottle, refrigerated until time of experimentation.

Acute toxicity studies

Toxicity test on the leaves of *Chrysophyllum albidum* was determined.[14] Mice were fasted for 12 hours and divided into five groups of 5 mice each. In order to determine the lethal dose (LD_{50}) of the crude extract, different doses 10, 100, and 1000, mg/kg were administered intraperitonally to different groups of mice, while the control group received 10 ml/kg distilled water (pH = 6.9). Also, 500, 1000, 1500, and 2000 mg/kg dose of the crude extract were administered orally to another set of mice divided into five groups with four groups administered doses of *Chrysophyllum albidum,* while the fifth group received 10ml/kg distilled water orally. Animals were observed for 2 hours post-administration for behavioural changes, signs of toxicity and mortality. Mortality within 24 h was also observed and recorded, and the surviving mice were kept under further observation for the next 14 days for possible signs of delayed toxicity. The lethal dose (LD_{50}) was estimated by the use of log dose-probit analysis method.

Phytochemical Analysis and Antioxidant property of *C. albidum*

Qualitative Screening C. albidum

The qualitative and quantitative chemical analysis of *Chrysophyllum albidum* was carried out to test for the presence of anthraquinones, tannins, saponnins, steroids, cardiac glycosides, flavonoids, terpenoids and alkaloids using the method adopted in similar surveys.[15]

Quantitative Screening C. albidum

Standardized methods were employed.

Determination of antioxidant activity

Biochemical assays were carried out to determine antioxidant activity of the crude extract of *Chrysophyllum albidum*. These assays included DPPH, nitric oxide, THC, reducing power, phenol, lipid peroxidation, flavanoid, FRAP and tannin.

Ethical considerations

All the experimental procedures for this study were consistent with Animal Welfare Guidelines. The number of animals used in this study was minimized to the number necessary to obtain scientifically valid data.[16] The animals were handled with care to minimize distress and pain. This was essential not only for the sake of the animals but also to ensure that the results obtained from the study was not compromised by stress on the animals. The animals were given food and water *ad libitum*.

EXPERIMENTAL DESIGN

Ipecac-induced Emesis in Rat

Male and Female Wistar rats were used in this study. In these animals which lack emetic reflex, retching was observed and recorded.

Twenty eight rats randomly divided into seven groups (n = 4) were used for ipecac-induced emesis, and treated as follows:

Group 1: Control, Group 2: *C. albidum* 100 mg/kg, Group 3: *C. albidum* 200 mg/kg, Group 4: *C. albidum* 400 mg/kg, Group 5: Promethazine 25mg/70kg given orally, Group 6: Metoclopramide 50mg/kg given orally, Group 7: Ondansetron 24mg/70kg given orally.

Test samples were administered orally for nine days and on the ninth day thirty minutes after administration of test sample, ipecac (0.03 ml) was administered to induce emesis, and number of retchings were observed and recorded for ten minutes.[17]

The percent inhibition was calculated by the following formula:

$$\text{Inhibition (\%)} = [(A-B)/A] \times 100$$

Where A = Frequency of retching in control groups. B = Frequency of retching in test groups.

Cisplatin-induced emesis in chicks

Cisplatin-induced emesis was done using two to four days old chicks of either sex.[18] Cisplatin 10 mg/kg was given intraperitoneally.

Each chick was set aside for 10 minutes to stabilize in a large beaker. Test samples were administered orally following the same schedule above, and cisplatin, one hour later. Number of retchings were observed and recorded for ten minutes.[17] Percent inhibition was thereafter calculated.

Copper sulphate-induced emesis

Test samples were administered, followed by copper sulphate one hour later, and number of retchings was observed and recorded.[17]

Possible Mechanism of Action of *Chrysophyllum albidum* through dopaminergic pathway

Three groups of chicks were treated with 10 ml/kg distilled water, 400 mg/kg extract and 50 mg/kg metoclopramide and thirty minutes later emesis was induced with dopamine (500 mg/kg orally) and number of retching was observed for ten minutes.

Possible Mechanism of Action of *Chrysophyllum albidum* through histaminergic pathway

Three groups of chicks were separately treated as before, followed by 10 mg/kg histamine.

Data analysis and interpretation

Data was presented as mean ± standard error of mean (SEM). Test of statistical significance was carried out using a one-way and two-way ANOVA. P value less than 0.05 ($p<0.05$) was considered statistically significant.

RESULTS

Phytochemical Screening

Phytochemical screening of *C. albidum* confirmed the presence of tannins, cardiac glycosides, saponins, flavonoids and phenols.

Antioxidant activity of *Chrysophyllum albidum*

Reducing power of Chrysophyllum albidum

Chrysophyllum albidum showed a significant reduction of free radicals ($p<0.001$) compared to the control group. The antioxidant activity could also be seen in various concentrations in all the doses of the crude aqueous of *Chrysophyllum albidum*.

Nitric oxide scavenging activity of Chrysophyllum albidum

Chrysophyllum albidum in all the doses of the crude aqueous showed a significant reduction of free radicals ($p<0.001$) compared to the control group.

DPPH scavenging activity of Chrysophyllum albidum

Chrysophyllum albidum in all the doses of the crude aqueous showed a significant reduction of free radicals ($p<0.001$) compared to the control group.

Lipid peroxidation scavenging activity of Chrysophyllum. albidum

Chrysophyllum albidum showed a significant reduction of free radicals ($p<0.001$) compared to the control group.

Physical properties of Chrysophyllum albidum

The crude extract of *Chrysophyllum albidum* leaf was dark brown, coarse in nature, with pungent smell, soluble in water and unstable in air.

Acute Toxicity Test in Mice

Acute toxicity determining the lethal dose of *Chrysophyllum albidum* using intraperitoneal route.

Antiemetic effect of Chrysophyllum albidum on ipecac induced emesis on rats

Antiemetic drugs (Promethazine, Metoclopramide and Ondansetron) caused a significant reduction ($p<0.001$) compared to the control group; the same trend of activity was recorded with the extract.

Antiemetic effect of Chrysophyllum. albidum on cisplatin-induced emesis on chicks

Antiemetic drugs (Metoclopramide and Ondansetron) produced a significant reduction ($p<0.01$) while $p<0.05$ with promethazine, all compared to the control group. *Chrysophyllum albidum* groups (100, 200, and 400 mg/kg) behaved similarly ($p<0.05$).

Antiemetic effect of Chrysophyllum. albidum on copper sulphate-induced emesis on chicks.

All the test agents caused a significant ($p<0.01$; $p<0.001$) antiemetic activity.

Possible Mechanism of Action of Chrysophyllum. albidum through Dopaminergic Pathway on dopamine induced emesis in chicks

The activity of dopamine was significantly ($p<0.05$) reduced by both metoclopramide and the extract. The herbal drug's effect was superior to the standard drug in both the ipecac and the copper sulphate models.

Possible Mechanism of Action of Chrysophyllum albidum through Histaminergic Pathway on histamine induced emesis in chicks

Chrysophyllum albidum and promethazine similarly and significantly ($p<0.01$) reduced the activity of histamine.

DISCUSSION

The present study explored the antiemetic activity of *C. albidum* using standard laboratory models. It

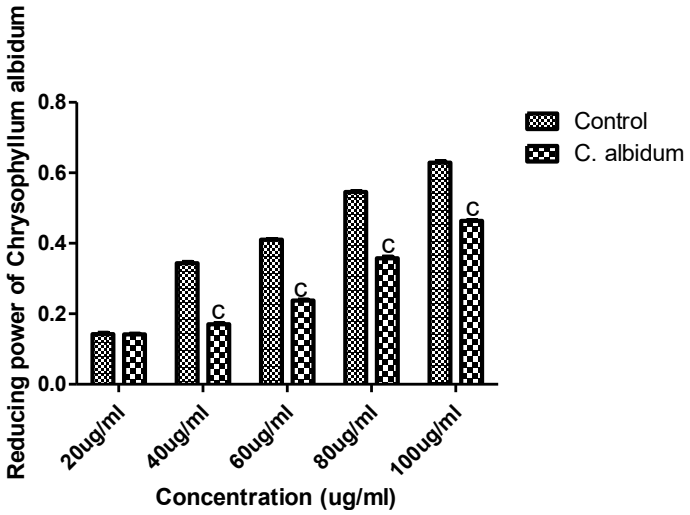


Figure 1 Reducing power activity of the crude extract of *Chrysophyllum. albidum*
Data represent MEAN ± SEM (n=4) $^{C}P<0.001$ statistically significant compared to control using two-way ANOVA follow by Bonferroni posttests

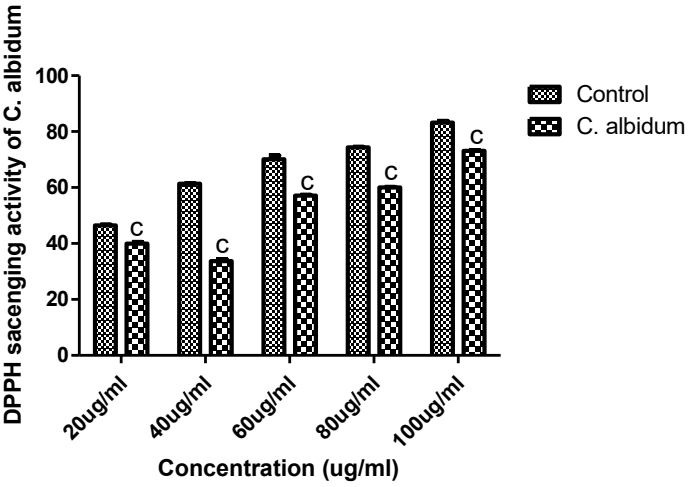


Figure 3 The result of DPPH scavenging activity of the crude extract of *Chrysophyllum. albidum*
Data represent $^{C}P<0.001$ statistically significant compared to control using two-way ANOVA follow by Bonferroni posttests

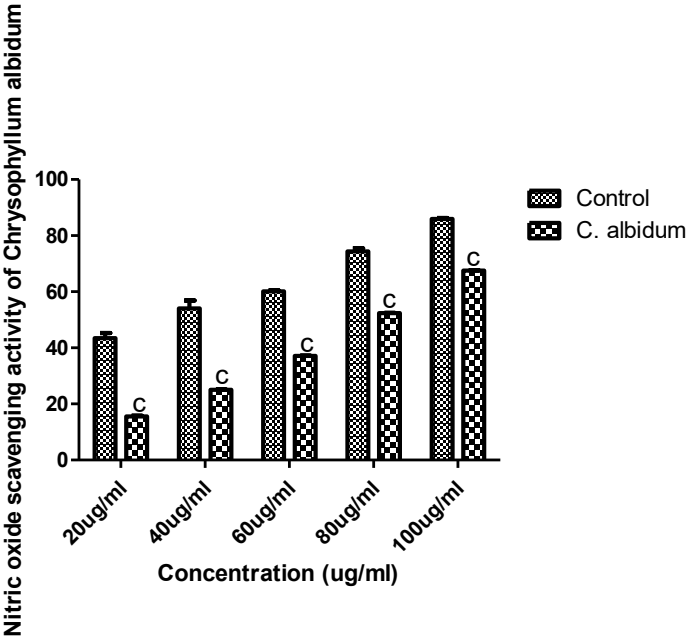


Figure 2 Result showing the nitric oxide scavenging activity of the crude extract of *Chrysophyllum albidum*
Data represent MEAN ± SEM (n=4) $^{C}P<0.001$ statistically significant compared to control using two-way ANOVA follow by Bonferroni post tests

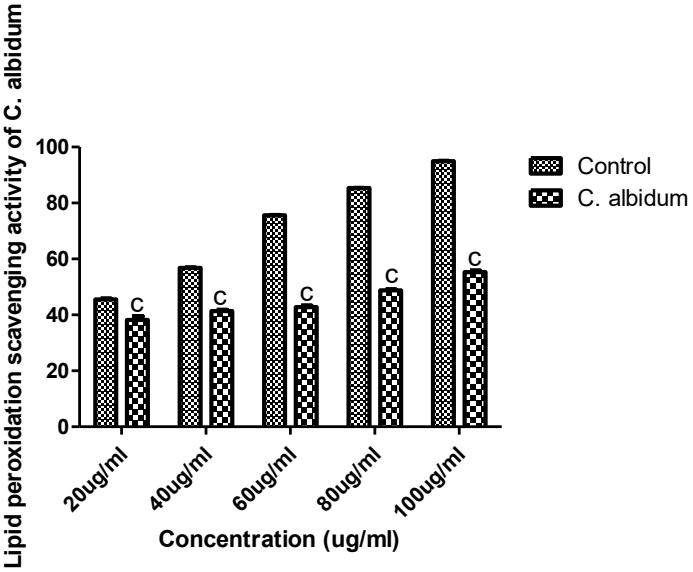


Figure 4 The Lipid peroxidation scavenging activity of the crude extract of *Chrysophyllum albidum*
Data represent $^{C}P<0.001$ statistically significant compared to control using two-way ANOVA follow by Bonferroni posttests.

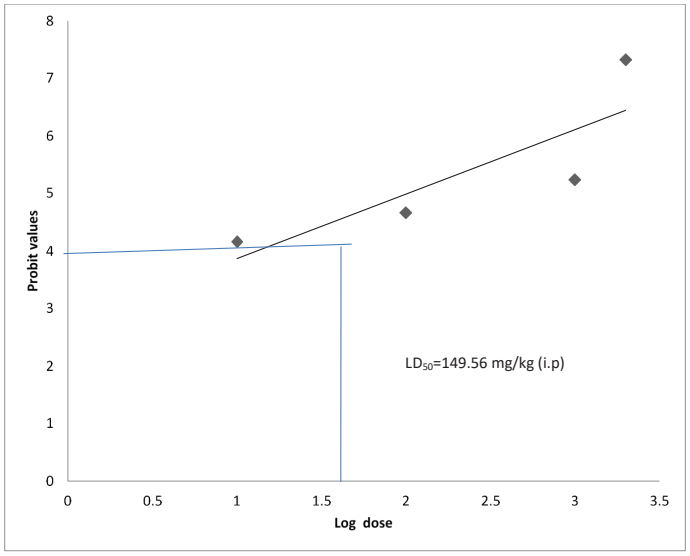


Figure 5 Graph of probit values against log dose

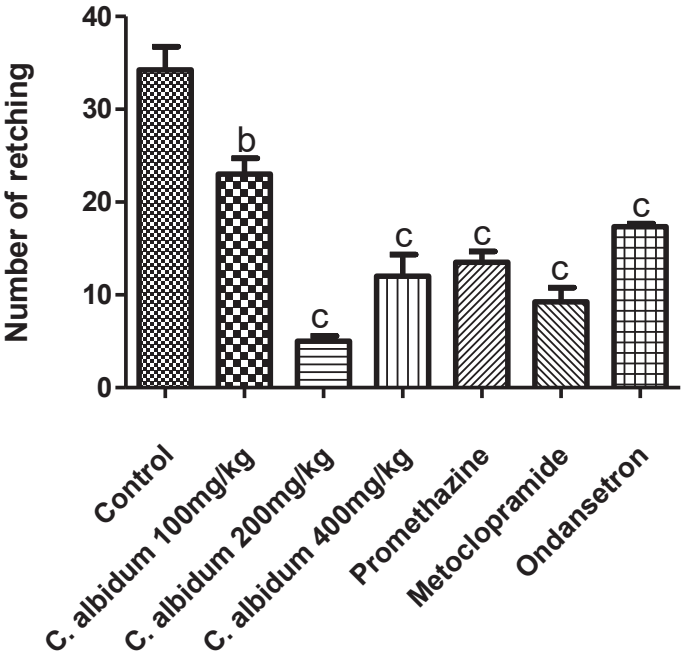
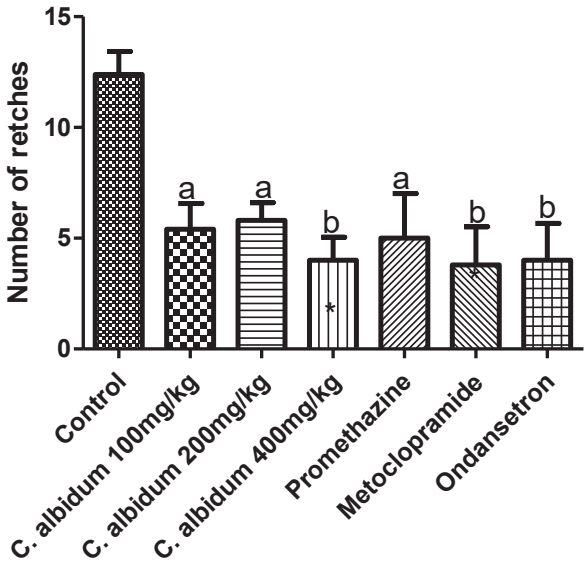
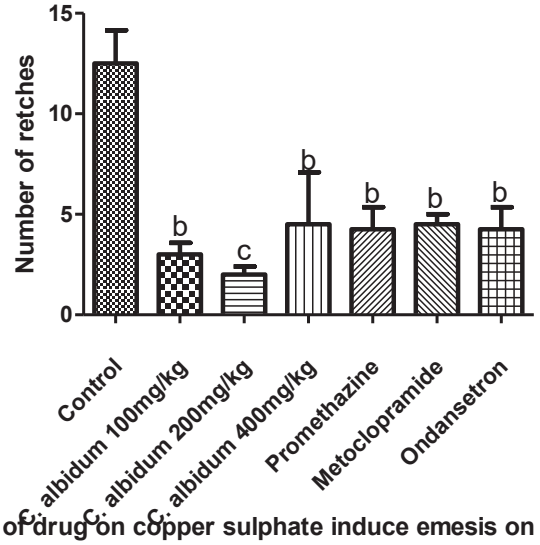


Figure 6 The effect of drugs on ipecac-induced emesis on rats. Data represent MEAN ± SEM (n=4). [c]P<0.001; [b]P<0.01 statistically significant compared to control using one-way ANOVA follow by Tukey's multiple comparison test



Effect of drugs on Cisplatin induce emesis on chicks

Figure 7 The effect of drugs on cisplatin induced emesis on chicks
Data represent MEAN ± SEM (n=5). [a]P<0.05, [b]P<0.01; statistically significant compared to control using one-way ANOVA follow by Tukey's multiple comparison test



Effect of drug on copper sulphate induce emesis on chicks

Figure 8 Effect of drugs on Copper sulphate induced emesis on chicks. Antiemetic effect
Data represent MEAN ± SEM (n=4). [b]P<0.01, [c]P<0.001; statistically significant compared to control using one-way ANOVA follow by Tukey's multiple comparison test

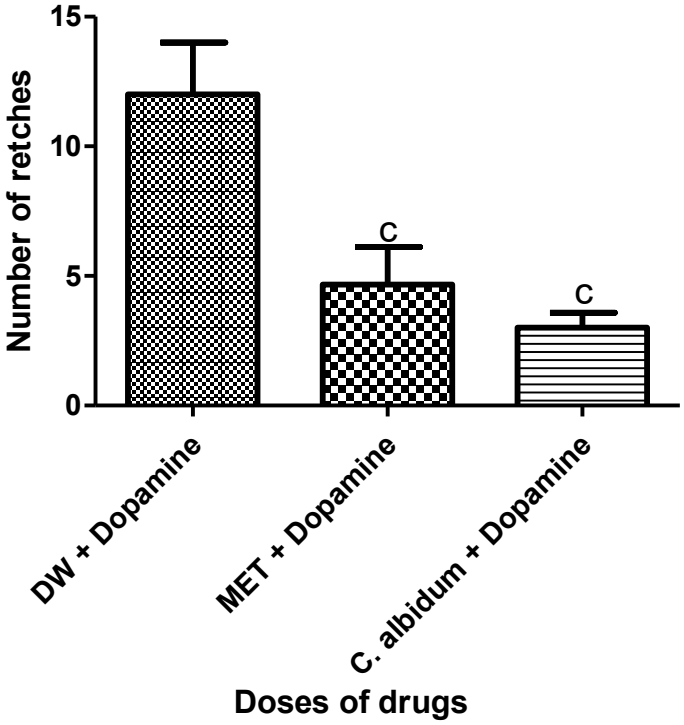


Figure 9 Possible Mechanism of Action of *Chrysophyllum. albidum* as Antiemetic agent on Dopaminergic pathway on chicks
Data represent MEAN ± SEM (n=3). [c]p<0.05; statistically significant compared to control using one-way ANOVA follow by Tukey's multiple comparison test

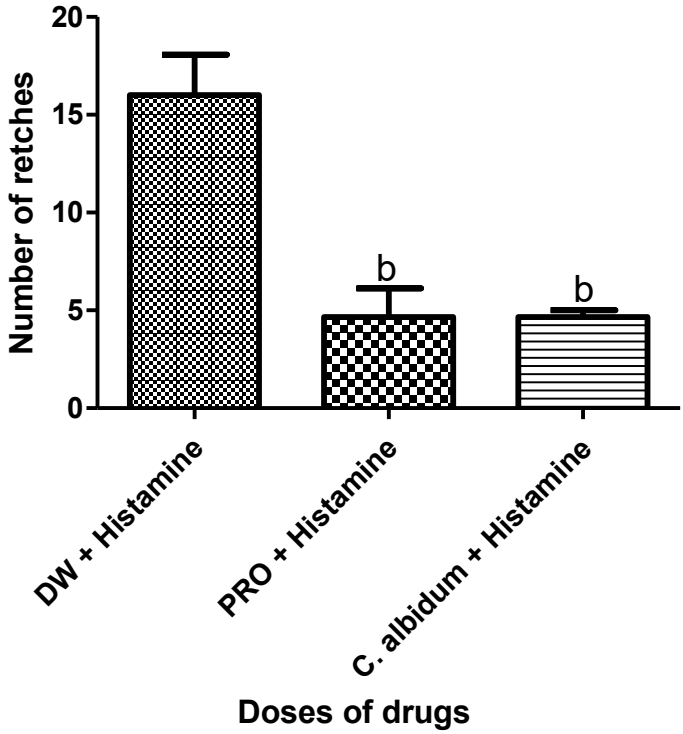


Figure 10 Possible Mechanism of Action of *Chrysophyllum albidum* as Antiemetic agent on histaminergic pathway on chicks
Data represent MEAN ± SEM (n=3). [b]P<0.01; statistically significant compared to control using one-way ANOVA follow by Tukey's multiple comparison test

Table 1 **Acute toxicity on mice using intraperitoneal route**

Groups	Dose (mg/kg)	Log Dose	Number of Animals	Mortality (%)	Probit
Group I	10	1	5	20	4.16
Group II	100	2	5	40	4.75
Group III	1000	3	5	60	5.25
Group IV	2000	3.3	5	100	7.33

Table 2 **Percentage Inhibitions Produced by Test Agents**

	Emetic/Percent Inhibition		
Test Agents/(Doses in mg/kg)	Ipec	Cisp	$CuSO_4$
DW	-	-	-
C. albidum 100	32.85	56.45	76.00
C. albidum 200	85.40	53.23	84.00
C. albidum 400	64.96	67.74	64.23
Promethazine	60.58	59.68	66.46
Metoclopramide	72.99	69.35	64.00
Ondansetron	49.40	67.74	66.65

Table 3 **Possible Mechanism of Action of *Chrysophyllum albidum*, and their Percentage Inhibition against Histamine-Induced Emesis in Chicks**

Treated group	Percentage inhibition of Emesis (%)
DW plus dopamine	-
Metoclopramide + dopamine	61.17
C. albidum + dopamine	75.00
DW Plus Histamine	-
Promethazine Plus Histamine	70.81
C. albidum Plus Histamine	70.81

belongs to the Sapotaceae family and used in the folklore in the treatment of dermatological infections, malaria, yellow fever, diarrhea and emesis among other uses.[8] Preliminary phytochemical screening detected presence of tannins, flavonoid, phenols, saponins, and cardiac glycoside, as constituents of the crude aqueous extract of *Chrysophyllum albidum,* while it tested negative for the presence of alkaloid, anthraquinones, steroid phlobatannin, and terpenoid. Saponins have been found to have antiprotozoan activities as well as possible defaunating agents in the rumen.[19] This property has been exploited in the treatment of protozoal infections in other animals. The mechanism of action by which saponins work might be through their toxicity to protozoans which may be widespread and non-specific. It might also be as a result of their detergent effect on the cell membranes.[20]

Chrysophyllum albidum has antioxidant properties by scavenging free radicals, decreasing lipid peroxidation and increasing the endogenous blood antioxidant enzymes levels, which is in congruence with the report of Adebayo *et al.*, (2011).[8]

Cancer chemotherapy is associated with generation of reactive oxygen species[21] and oxidative stress has been implicated in the emesis caused not only by cisplatin but other chemotherapeutic drugs as well. Numerous studies have shown that the active metabolite of cisplatin that is, cis-diaqodiammineplatinum generates free radicals that release serotonin from enterochromafin cells which then stimulate 5-HT_3 receptors on vagal afferents and initiate the emetic reflex within the brain stem.[22] The discovery of various neurotransmitters and their receptor sites within the medulla has improved the understanding and development of therapeutic agents. The CTZ area is rich in dopamine D_2 receptors, which are antagonized by drugs such as prochlorperazine, metoclopramide, and droperidol. The serotonin receptor has been found widely in the area postrema and the GI tract. The serotonin receptor antagonists ondansetron and granisetron have been shown to be effective in preventing chemotherapy-induced nausea and vomiting.

Concentrations of cholinergic and histamine receptors are found in the lateral vestibular nucleus and are important in motion sickness. Meclizine, diphenhydramine, and scopolamine act by antagonizing these receptors. Activation of cannabinoid receptors has been found to inhibit the emetic reflex.

The actions of ipecac are mainly those of its major alkaloids, emetine (methylcephalin) and cephalin. They both act peripherally by irritating the gastric mucosa and centrally by stimulating the medullary chemoreceptor trigger zone (CTZ) to induce vomiting. On the basis of results, it can be inferred that antiemetic response of the crude extract of *C. albidum* (200 mg/kg) was more efficacious in ipecac and copper sulphate-induced emesis than even the standard antiemetic drugs such employed.

The established emetic mechanism of copper sulphate is by (a) peripheral stimulation of visceral efferent nerve fibers in the gastrointestinal tract[23] and (b) irritation of gastric mucosa[46] so, both of these mechanisms may cause the release of histamine and serotonin, as vomiting center is rich in histamine receptors (H_1).[24] The ability of *C. albidum* to effectively reduce its ematogenic effect suggests its possible peripheral antiemetic action, which could be due to presence of flavonoids.[25]

It has also been established that the peripheral 5-HT_3, 5-HT_4 and NK_1 receptors are involved in emesis, which potentiates ematogenic stimuli in the brain by stimulating vagus afferent input to the vomiting center. Therefore, it may be hypothesized that the *Chrysophyllum. albidum* produced antiemetic action by the receptor antagonism (5-HT_3, 5-HT_4 and NK_1) and has peripheral antiemetic action.

Diversified multiple receptors blocked mechanism was most likely to be the cause of such effective suppression of ematogenic stimuli. *c albidum* blocked 5-HT_3 receptors of small intestine and entereochromaffin cells fails to release serotonin which is responsible for vagal stimulation which in turn initiate vomiting reflex. Cisplatin has shown to activate GI vagal afferent fibers via 5-HT_3 receptors to emesis.[26] Some studies also suggest that cisplatin-induced emesis can be attributed to cytotoxicity to the enterochromaffin cells in the small intestine. Oxidant injury to these cells could result in 5-HT release, stimulation of 5-HT_3 receptors located on the vagal afferents, and initiation of the emetic reflex in the brain stem.

CONCLUSION

The experimental finding in this study suggests that the leaf extract of *Chrysophyllum albidum* possesses

antiemetic effect, possibly mediated through the various pathways associated with emesis. The results therefore justify the traditional use of the plant extract in the treatment of emesis.

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