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Original Research Article

Piper guineense (Schum and Thonn) Seed Extract Exhibits Efficient Bowel Cleansing Efficacy for Radiographic Imaging in Female Wistar rats

Samuel A. Efanga[1], Emmanuel O. Esien-Umo[2], Affiong I. Ngaji[1], Samson O. Paulinus[2], Daniel U. Owu[3]*, Itoro Efanga[2], Akintunde O. Akintomide[1]

[1]*Radiology Department, University of Calabar, Calabar, Cross River State, Nigeria*
[2]*Radiography and Radiological Sciences Department, University of Calabar, Calabar, Cross River State, Nigeria*
[3]*Department of Physiology, Faculty of Basic Medical Sciences, University of Calabar, Calabar, Nigeria.*

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ABSTRACT

Radiographic imaging of the gastrointestinal tract for diagnostic screening procedures is dependent on efficient bowel cleansing. Dulcolax has been the choice agent for bowel cleansing though with some undesirable results. The aim was to study the propensity of *Piper guineense* seed extract to vigorously clean bowel loops in comparison with dulcolax for radiological procedures. Twenty female Wistar rats weighing 140 to 150 g were used for this study. Five rats each were allocated into four groups. Group 1 was the control group and had food and water, Group 2 was treated with 0.75 mg/kg dulcolax, Group 3 and 4 were treated with low dose (4 mg/kg) and high dose (6 mg/kg) of *Piper guineense* aqueous seed extract respectively. An oral acute toxicity test was conducted using the up-and-down method. Radiographic images were obtained and used to assess the bowel-cleansing suitability using the 4-point scale grading system. Mean bowel cleansing efficacy of *Piper guineense* in Group 4 was significantly higher than the mean bowel cleansing efficacy in Group 2 and Group 3 ($p< 0.01$). Three-quarters of Group 2 rats were observed to have dehydration and postural dizziness more than the other groups and the mean body weight loss recorded in Group 2 was significantly ($p < 0.01$) greater than the mean body weight loss in Group 3. The results of this study suggest that *Piper guineense* at 6 mg/kg has a high bowel cleansing efficacy with minimal side effects than dulcolax in female Wistar rats.

Keywords: Body weight, Bowel cleansing, Bowel preparation, Dulcolax, *Piper guineense*, Radiographic images

Introduction

The effectiveness of bowel preparation prior special radiological procedures (such as barium meal and enema, small bowel enema, intravenous urography, CT colonography and CT urography), colonoscopy, and abdominopelvic surgeries have a substantial impact on procedure outcome, quality and efficiency.[1,2,3] Poorly prepared bowels frequently lead to delays in the commencement of these procedures which usually have repercussions of varying magnitude on the patient, society, health practitioners, resources, level of services rendered, and risk of complications.[1,4,5,6] An ideal bowel preparation agent should be harmless, effective, tolerable, and inexpensive.[2,7,8] The efficacy of a bowel cleansing agent depends both on its intrinsic laxative capacity and also on its tolerability.[6,9] Many patients (5-15%) do not complete the bowel preparation procedure as a result of poor acceptable taste of some agents used for bowel cleansing in addition to the high amount of cleansing agent required to be taken[2], and the development of undesirable effects such as abdominal distension, gastrointestinal discomfort, nausea, and vomiting.[2,3]

*Corresponding author Email: d_owu@yahoo.com
Tel: +2348061650527

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Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

Poor bowel preparation can be predictable to a certain extent in a patient based on two broad factors such as co-morbidities and the person's health literacy. In radiological practice, the accomplishment of a thoroughly cleansed bowel requires the enforcement of certain instructions that are clear, concise and culturally appropriate before the day earmarked for any special procedure. Several methods have been formulated to assess the bowel cleansing efficacy of diverse bowel cleansing agents or regimens, such as Boston bowel preparation scale scores (BBPS), Harefield cleansing scale, and Ottawa bowel preparation scores.[1,2,10]

Bowel preparation agents or regimens are classified into three groups namely, isosmotic, hypo-osmotic, and hyper-osmotic bowel cleansing agents. Isosmotic bowel cleansing agents include high volume polyethylene glycol (PEG) preparations which typically passes through the intestines without absorption. Low-volume PEG is ideally prepared as 2 L PEG-ELS (electrolyte solution) coupled with ascorbic acid and the highly palatable Sulphate-free PEG-ELS, which is formulated to improve the gustation and smell of PEG-ELS.[1,10] The hypo-osmotic bowel cleansing agents is PEG-3350 (PEG-SD) which is usually taken with an electrolyte solution. Hyper-osmotic bowel cleansing agents such as magnesium citrate, stimulates the secretion of cholecystokinin that leads to the accumulation of intraluminal fluid in the small and large intestines. Others are sodium sulfate, and dulcolax, a diphenylmethane derivative that is not well absorbed in the gut and a commonly used bowel cleanser.[1,10,11]

Plants have been sources of traditional remedy in many diseases that affect mankind. One of such plants is *Piper guineense*, a tropical plant in West and Central Africa that belongs to the Piperaceae family. This plant is potentially of profound benefit in the management of cardiac diseases, bowel mucosal inflammatory diseases, renal disorders, and hepatic disorders.[12] The plant produces peppery berry fruits and the leaves and seeds are not only common recipes for cuisine but have medicinal uses such as treatment of infections.[13,14] The administration

of *Piper guineense* can cause vigorous and persistent contraction of the gastrointestinal tract smooth muscles[14] which can result in the cleaning of the small and large intestines. However, studies involving the possible use of *Piper guineense* seed extract as a regimen for bowel preparation are scarce. Therefore, this study seeks to compare the cleansing efficacy of bowels by dulcolax and *Piper guineense* for radiological procedures and to determine the dosage that can be efficient with minimal adverse effects on the body.

Materials and Methods

Preparation of the seed
The seeds of *Piper guineense* were purchased at a popular market in Calabar and was identified by a Taxonomist in the Department of Botany and Ecological Studies, University of Calabar, Calabar. The seeds were washed with distilled water, and dried in the air for seven days. The seeds (240 g) were crushed into fine powder using a grinder. Aqueous extract of *Piper guineense* was prepared following the method reported previously[15] with modification. Briefly, the powder (80 g) was soaked in 1 L of distilled water and left for 48h with occasional agitation. The mixture was filtered using a muslin cloth. The filtrate was evaporated to dryness at 40°C and stored at 4°C till further use.

Acute toxicity test (Lethal Dose$_{50}$)
An oral acute toxicity test was carried out using the OECD (Organization for Economic Cooperation and Development) test guideline No. 425.[21] Using this technique, single animals were given several doses of the local *Piper guineense* extracts spaced 48 hours apart. Following the first dose of 4 mg/kg, the results of the prior dose were used to determine the next dose. The dose was changed downward when mortality was noted at the higher dose, then upward when the rats survived the subsequent dose. A constant factor was used to alter the dose either upward or downward. When the maximum limit (2500–3000 mg/kg) was reached without causing death or the test's LD50 (lethal dose) was determined, the testing was stopped.[16] The lethal dose was calculated using the formula.

LD_{50} = Weight of test animal (g) x dose /1000

Experimental animals
Female weighing between 140-150 g were purchased from the animal house of the Department of Physiology, University of Calabar, Calabar, Nigeria for the study. The rats were divided into four groups and were kept for one week to acclimatize before the administration of extract and drug. The animals were housed in four cages at room temperature of 27±2°C with 12 h light: 12 h dark cycle and proper hygiene was maintained. They had free access to food and drinking water *ad libitum*. The approval for the study was obtained from the Animal Research Ethical Committee of the Faculty of Allied Health Science of the University with approval number UC/ECRA/23/06.

Experimental design
This was a randomized, placebo-controlled, observational study that involved twenty female Wistar rats. The Wistar rats were randomly distributed into four groups of five rats each labelled Group 1 to 4.
Administration of Piper guineense seed extract and Dulcolax
Group 1 was designated the control and was administered with 0.1 ml normal saline. Dulcolax was purchased from Krishart Pharmaceutical Industries Limited, Ibadan, Nigeria. It was dissolved in 1 ml normal saline and administered orally at a dose of 0.75 mg/kg body weight to animals in Group 2.[17] The seed extract of *Piper guineense* was dissolved in 10 ml of distilled water and administered orally to rats in Groups 3 (PELD) and 4 (PEHD) at a dose of 4 and 6 mg/kg body weight respectively. All administrations were done by gavage once on the day of experimentation. The rats were released and returned to their cages for observation. The dose was selected based on the toxicity studies.

Evaluation of side effects of Piper guineense on the test animals
The Wistar rats in each group were carefully examined for the features of untoward effects of the test materials in each group. The observation of any side effects in a test animal of a group such as weight loss, postural dizziness, and dehydration, were determined and recorded for the group. The body weight of each rat was evaluated after the whole procedure. In addition, the moisture content of the fecal matter defecated by the test animals was assessed following a previous method.[18]

Radiographic image acquisition and bowel cleansing efficacy of the test materials
A GE Definium 8000 digital X-ray machine (BRIVO XR575, GE, China) with a maximum kV of 125 and a maximum mA of 400 was utilized to acquire images of each Wistar rat. The views were taken using 8 x 10 (16 x 24 cm) films within appropriate cassettes with exposure factors of 50 kVp (kilo-voltage peak) on 5.0 mAs (milliampere second) respectively and a focus-to-film distance (FFD) of 100cm. Preliminary and post-bowel preparation radiographic images of the abdomen were taken at the Radiology Department of the University of Calabar Teaching Hospital attached to the tertiary institution, with the rats immobilized and
kept supine.
The preliminary films which were taken before the introduction of the test material and post-administration radiographs were taken after the administration of the plant extract and Dulcolax. The rats were sedated with pentobarbital sodium (35 mg/kg) before taking the preliminary (Antero-posterior view) films to help determine the proper collimation measures, the normal renal outline of the kidney calyces, and the normal status of the abdominal organs and bowel loops. The post-bowel preparation radiographic images were taken at least 8 hours after the test extracts and dulcolax were administered.
The radiographic images obtained from the *Piper guineense* treated groups (Group 3 and Group 4) were compared with those collected from the dulcolax group (Group 2) by three professional radiologists to assess the efficacy of the test material for bowel preparation in the rats. The body weight of each rat after the whole procedure and the moisture content of the feces of the animals were assessed. The image scoring system was the 4-point scale grading system based on the degree of fecal residue in the abdomen of plain radiographic images. The presence of fecal residue in more than two-thirds of a specific film area was assigned a score of 0, the presence of fecal residue in more than one-third of an area of the film, but less than two-thirds, was assigned a score of 1, the presence of fecal residue in less than one-third of an identified film area was assigned a score of 2 and if no residual fecal material was seen, the assigned score was 3. To assess the degree of fecal residue, the specific film areas of the abdomen in the plain radiographic image of each rat were the xiphoid, symphysis pubis, and iliac crests.[3]

Statistical analysis
The values obtained were reported as means ± SEM. The GraphPad Prisms version 8.0 software (GraphPad Software Inc., San Diego, CA, USA) was employed for data analyze the data obtained. Analysis was done ANOVA followed by Tukey test where F-value was significant. A p value < 0.05 was considered statistically significant.

Results and Discussion

Acute toxicity test
The acute toxicity test of the seed extract of *Piper guineense* showed a mortality of one rat at a dose above 7 mg/kg body weight while a mortality was also reported at a dose of dulcolax above 0.8 mg/kg body weight.

Body weight of animals
Following the commencement of the experiment, the mean body weight of rats in the control group was 142.7±2.3 g, while it was 144.0±3.9 g in dulcolax Group. The mean body weight in the *Piper guineense*-treated low-dose and high dose groups were 143±2.5 g and 144.0±1.5 g respectively. At the end of the experiment, the mean body weight of rats in the control group was 147±2.1 g and, 133.0±2.2 g in dulcolax-treated Group. The mean body weight of animals in the *Piper guineense*-treated low-dose and high dose groups after the experiment were 137.2±1.3 g and 134.4±2.3 g respectively (figure 1A). The weight gain in the control group was 3.5±0.5% while a significant weight loss ($P = 0.01$) was

recorded in dulcolax, *Piper guineense*-treated low-dose and high dose groups as 8.0±1%, 5.8±0.3%, 6.7±0.3% respectively (figure 1B). The mean weight loss observed in the Wistar rats in dulcolax-treated Group was significantly (P = 0.01) greater than the mean weight loss in the *Piper guineense*-treated groups.

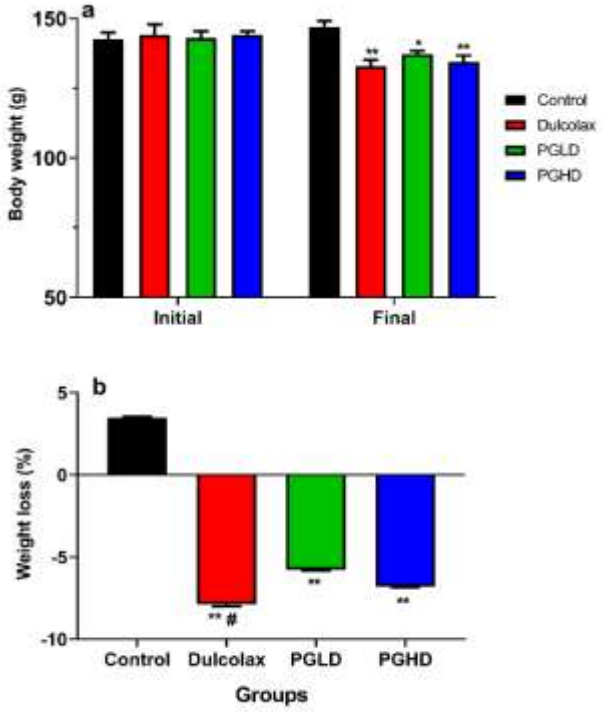

Figure 1: Body weight changes and weight gain in control and experimental rats treated with Dulcolax and *Piper guineense* seed extract
** = p< 0.01 compared with control; * = p<0.05 compared with control; # = p<0.05 compared with PGLD and PGHD groups respectively

Clinical evaluation of side effects on test animals
Dehydration and postural dizziness were not observed in the Control and *Piper guineense* low dose (PGLD) groups. However, these conditions were observed in the dulcolax-treated group with three rats that had features of dehydration and three rats had postural dizziness. Only dehydration was observed in dulcolax-treated group (Table 1).

Bowel fecal residue and cleansing efficacy
There was a single finding of fecal residue in more than two third specific film areas in the dulcolax-treated and PGLD-treated groups in the radiographs evaluated (Table 2). There was none observed in *Piper guineense* high dose (PGHD)-treated group. Four observations were made of fecal residue in more than one third but less than two third specific film areas in dulcolax-treated and PGLD-treated groups but a single observation was made in PGHD-treated group. While three observations were noted in PGLD and PGHD-treated groups Wistar rats with fecal residue less than one third specific film area, four observations were made in those in dulcolax-treated group. There were five observations of no fecal residue in the radiographs of the Wistar rats in the PGHD group while none was observed in PGLD group. The mean bowel cleansing efficacy in Groups dulcolax, PGLD and PGHD groups were 1.3±0.2, 1.6±0.2 and 2.4±0.2 respectively (Figure 2).
The mean bowel cleansing efficacy of dulcolax (Group 2) Wistar rats was significantly ($p < 0.01$) lesser than that of PGHD-treated groups. The mean bowel cleansing efficacy of high-dose *Piper guineense* (Group 4) rats was significantly ($p < 0.01$) greater than that of low-dose *Piper guineense* (Group 3) Wistar rats. However, the difference in the mean bowel cleansing efficacy of dulcolax (Group 2) and that of low-dose *Piper guineense* (Group 3) rats was comparable (figure 2).

Radiological images and findings
The radiographic images obtained from rats treated with dulcolax and *Piper guineense* are presented in figures 3 to 5. The images in the dulcolax-treated group showed a large amount of fecal loading in the ascending colon, transverse colon and the upper end of the descending colon and fluid was also noted in the small intestine (Figure 3b). The images obtained from the rats treated with *Piper guineense* showed fecal loading within the ascending colon which extended to the middle of the transverse colon, and fluid was also noted in the small intestine in PGLD (Figure 4b), whereas in PGHD (Figure 5b) fecal loading was only noted in the ascending colon and fluid was present in the small intestines as well.

Table 1: Clinical evaluation of side effects of Dulcolax and *Piper guineense* rats

GROUP	Dehydration	n	Postural Dizziness	n
Control	Not Observed	0	Not Observed	0
Dulcolax	Observed	3	Observed	3
PGLD	Not Observed	0	Not Observed	0
PGHD	Observed	2	Not Observed	0

The fundamental criteria for a good bowel preparation is a significant reduction or total absence of fecal residue in the small and large intestines, and a lucid visualization of the bowel mucosal outline.[1] The capacity for a bowel cleansing regimen to engender good bowel preparation is partly influenced by its appearance, taste, and, its efficacy.[19] In this study, the bowel cleansing efficacy was significantly more substantial in the group that was administered both low and high-doses of *Piper guineense* than the group treated with dulcolax.

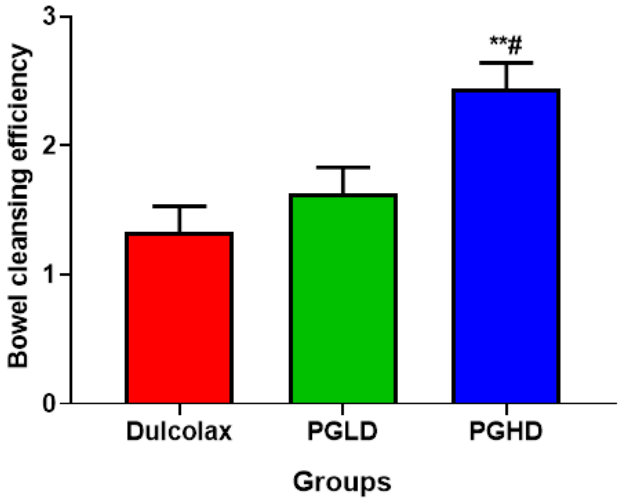

Figure 2: Bowel cleansing efficiency of Dulcolax and *Piper guineense* extracts in Wistar rats.
** = p<0.01 compared with Dulcolax group; # = p<0.05 compared with PGLD group.

Table 2: Frequency and score of the bowel cleansing efficacy of the test materials.

Parameter	**GROUP 2**		**GROUP 3**		**GROUP 4**	
	n	Score	n	Score	n	Score
Fecal residue more than 2/3 specific film area	1	0	1	0	0	0
Fecal residue more than 1/3 but less than 2/3 specific film area	4	4	4	4	1	1
Fecal residue less than 1/3 specific film area	4	8	3	6	3	6
No fecal residue	0	0	1	3	5	15
Total		12		13		22
Mean ± SEM	1.33±0.24		1.63±0.26		2.44±0.24	

Over the years, dulcolax has been the choice bowel cleansing agent for every radiological procedure in the health facility where this study was conducted. Many radiologists and radiographers have adopted its use since the quality of bowel preparation from it is usually considered suitable for special procedures except in a few cases where compliance with other instructions is regarded as the bane of poor bowel preparation. A study that employed the same bowel cleaning efficacy methodology (4-point scale grading system) in 57 subjects with one group being administered 60 ml of Senna-graph group while the other group received 60 ml of castor oil, reported that the bowel cleansing efficacy of Senna-graph was significantly higher than that of castor oil.[3] The bowel cleansing efficacy of high dose *Piper guineense* in this study was marginally lower than that assessed using Senna-graph and castor oil, and this disparity is due to the variation in the subjects utilized and dosage of agents employed in both studies.

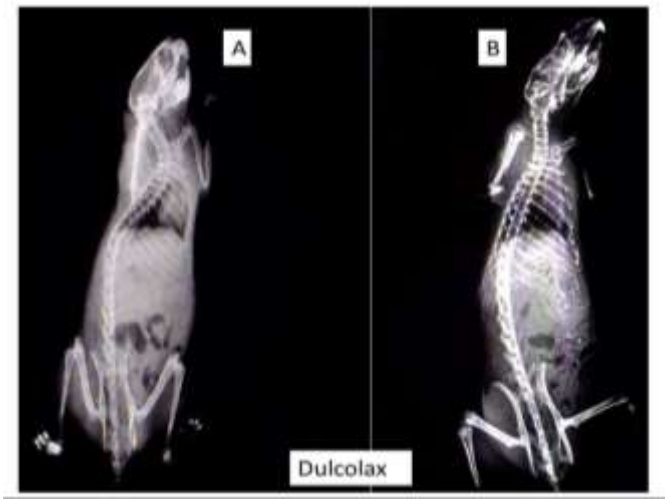

Figure 3: Radiographic image of a Wistar rat in Dulcolax-treated group (a) before administration and (b) after the administration of the Dulcolax drug.

A study involving 187 participants reported that the bowel cleansing quality of dulcolax was significantly reduced than value of polyethylene glycol.[20] In another randomized, controlled, endoscopist-blinded, clinical phase III study involving 315 subjects, it was reported that the bowel cleansing efficacy of Bowklean was better than that of Klean-prep/Dulcolax when evaluated using Ottawa Bowel Preparation Score.[6] Some studies have used single or a combination of bowel cleansing regimens other than dulcolax reported equally effective results for bowel cleansing.[21,22] Our results of bowel cleansing efficiency of *Piper guineense* that was better than dulcolax is in agreement with these studies.

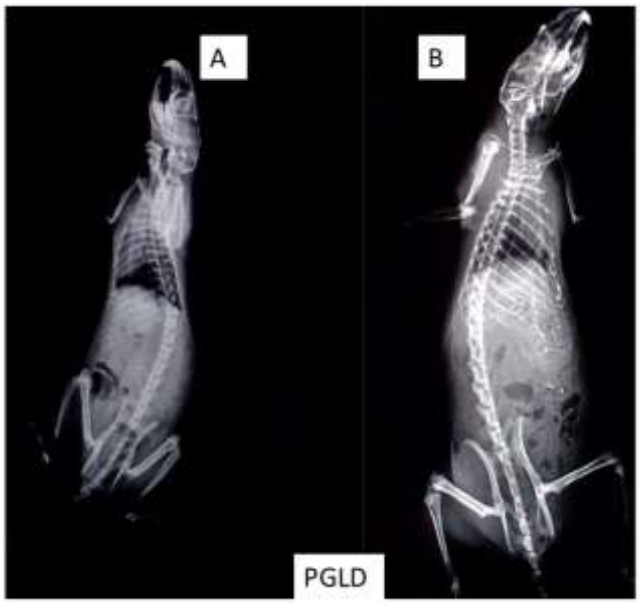

Figure 4: Radiographic image of a Wistar rat in PGLD group (a) before administration and (b) after the administration of the *Piper guineense* extract.

In this study, the group that received dulcolax even had a higher weight loss than the group that were administered with high dose *Piper guineense.* Furthermore, while postural dizziness and dehydration were observed in the group that was administered dulcolax, only dehydration was noted in the group that had high-dose *Piper guineense*. A previous study reported that administration of SPMC plus dulcolax led to dizziness in subjects than PEG.[8] A similar study also documented severe adverse effects even though few in incidence, were seen in the subjects administered Klean-prep/Dulcolax, as a bowel cleansing agent than in those who had Bowklean.[6] Our result of loss of body weight and dizziness is in agreement with these reports. The body weight loss could be attributed to the loss of fluid, and the phytochemical such as gamma-butyrolactone (GBL) present in the seed extract of *Piper guineense*.

GBL is a known central nervous system depressant.[23,24] This could probably contribute to the depression noticed in the *Piper guineense*-treated groups.

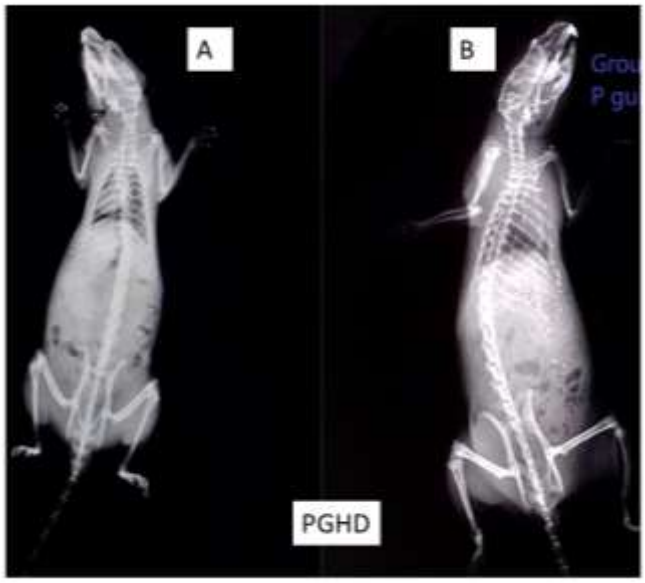

Figure 5: Radiographic image of a Wistar rat in PGHD group (a) before administration and (b) after the administration of the *Piper guineense* extract.

The bowel cleansing efficiency was highest in the high dose group when compared to the standard drug dulcolax. This may be attributed to the phytochemicals present in the seed extract of *Piper guineense*. Herbal medications have been used to treat and achieve regular bowel movement due to some phytochemicals. For instance, anthraquinone glycosides, free anthraquinones, and other polyphenols have been used as natural stimulant laxatives, and to increase intestinal motility.[25] The seeds of *Piper guineense* is rich in organic acids and terpenes,[26] anthraquinones and glycosides,[27,28] that have laxative and bowel cleansing property. Thus, these phytochemicals could contribute to the bowel cleansing efficacy of this plant extract.

There are some limitations in this study. For instance, a bolus administration of the test drugs and extract was given. This could affect the bowel cleansing effect and loss of weight. It is suggested that a comparison between split-dose and bolus dose administration could be carried out in future studies. A report documented that split-dose administration for the three bowel cleansing agents namely, PEG, picosulphate and, sulfate salts yielded a significantly higher frequency of good-and-excellently prepared bowels than continuous intake.[19] A future investigation that will include both sexes is suggested to corroborate the findings of this research and further explore the main active ingredient present in *Piper guineense* that may be attributed to the observed bowel cleansing effect.

Conclusion

High-dose *Piper guineense* produces a significantly higher bowel cleansing efficacy with minimal side effects than dulcolax in female Wistar albino rats. Further research on the bowel cleansing efficacy of *Piper guineense* on higher mammals to explore its potential use as an alternative agent, is advocated.

Conflict of interests

The authors declare no conflict of interest.

Authors' declaration

The authors hereby declare that the work presented in this article is original and that any responsibility for claims relating to the content of this article shall be borne by them.

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