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Therapeutic Effect of N-Hexane Extract of Zingiber Officinale (Ginger Oil) on Loperamide Induced Constipation in Wistar Rats

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ABSTRACT

Constipation is a common gastrointestinal disorder that affects people of different ages, but is more common in elderly females. The disease has negative impact on the quality of life and can cause many complications including faecal incontinence, anal fissures, bowel perforation and bloating if not treated. This research was carried out to investigate the effect of n-hexane extract of *Zingiber officinale* (ginger oil [GO]) on loperamide-induced constipation in Wistar rats. Twenty four (24) Wistar rats of both sexes were randomly separated into 6 groups (n=4). Group 1 (control) received normal saline (NS) only, while groups 2 to 6 were treated with 4 mg/Kg/day loperamide. After 1 hour of loperamide treatment, Groups 2, 3, 4, 5 and 6 received 1 mL/kg/day NS, 100 mg/Kg/day GO (LDGO), 200 mg/Kg/day GO (MDGO), 400 mg/Kg/day GO (HDGO), and the standard drug bisacodyl (5 mg/Kg/day). All drugs were administered orally. Daily faecal pellet counts, weight and water content were measured. Intestinal transit of charcoal meal was determined while colon samples were harvested at sacrifice, homogenized and centrifuged. The supernatant was used to assay for SOD and MDA. Colonic tissue was also analyzed for histological changes. The result showed that, compared to control, loperamide significantly decreased the number, weight and water content of faeces while GO significantly increased all these parameters in a dose dependent manner. Ginger oil also significantly increased intestinal transit ratio and the activity of SOD but reduced MDA relative to loperamide + NS. Furthermore, histomorphology revealed that GO treatment increased the number of mucus secreting goblet cells and the thickness of the colon mucosa relative to Loperamide + NS treated rats. In conclusion, ginger oil ameliorated loperamide-induced constipation by increasing the faecal count, faecal water content and intestinal motility. Furthermore, GO showed protective effect on the colon through antioxidant activity while reducing lipid peroxidation and by also increasing the number of goblet cells and the mucosa thickness of the colon.

INTRODUCTION

The symptom or condition known as constipation is characterized by difficult and sporadic bowel motions, usually occurring three or less times each week. It is one of the most prevalent gastrointestinal issues in the western nations and frequently results in a patient being referred to gastroenterologists and colorectal surgeons. Constipation is a common ailment that is sometimes overlooked until the patient experiences after effects, such as anorectal problems (Peery *et al.*, 2019; Bharucha *et al.*, 2020). Various laxatives stool softeners as well as secretagogue and prokinetic drugs are used in the treatment of constipation (Sharma & Rao, 2017).

Unfortunately, these drugs/therapies may produce adverse reactions such as diarrhoea, abdominal pain, nausea, abdominal discomfort, flatulence and headache etc. Treatment with traditional elements like extra-virgin olive oil, coconut oil, sweet almond oil and ginger aqueous extract have been shown to alleviate symptoms of constipation (Faghihi *et al.*, 2021; Abidi *et al.*, 2022; Faghihi *et al.*, 2022). This necessitated this study on the therapeutic effect of n-hexane extract of zingiber officinale (ginger oil) on loperamide induced constipation in Wistar rats.

LITERATURE REVIEW

Constipation has a negative impact on the quality of life and can cause many complications including faecal incontinence, anal fissures, bowel perforation and bloating if not treated (Tvistholm *et al.*, 2017). Low fibre intake, inactivity, decreased thirst sensation, low fluid intake, electrolyte disturbances, endocrine and metabolic disorders, neurological disorders, psychological disorders and medications (such as calcium channel blockers, opiate analgesic etc.) are implicated in constipation. Other causes of constipation include the use of organic compounds such as morphine, stress, nutritional disorders, secretory dysfunction, gastrointestinal motility dysfunction and alterations in gastrointestinal innervation (Park *et al.*, 2016; Adeniyi *et al.*, 2020; Diaz *et al.*, 2023).

Various laxatives stool softeners as well as secretagogue and prokinetic drugs are used in the treatment of constipation (Sharma & Rao, 2017). There are issues of strong drug dependence, high recurrence rate, and high cost with the orthodox treatments which limit their application in individuals suffering from constipation. In addition, these drugs/therapies may produce adverse reactions such as diarrhoea, abdominal pain, nausea, abdominal discomfort, flatulence and headache etc.

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studies have shown that treatment with traditional elements like extra-virgin olive oil, coconut oil, sweet almond oil and ginger aqueous extract have been shown to alleviate symptoms of constipation (Faghihi *et al*., 2021; Abidi *et al*., 2022; Faghihi *et al*., 2022).

Zingiber officinale belongs to the Zinberaceae family is a medicinal plant that has been widely used all over the world for various purposes. The plant is indigenous to warm tropical climates, particularly south eastern Asia. As a result of its pungency, aroma, nutrients and pharmacological activities and neglible side effects, it is now widely cultivated in many countries like India, Nigeria, Jamaica, Mexico, Greece, and Hawaii (Kiyama, 2020; Mohammed *et al*., 2022). The plant is widely used for variety of purposes. A review of the medicinal uses of ginger in health include blood pressure reduction (Hasani *et al*., 2019), as a potent antioxidant (Zhang *et al*., 2022), hepatoprotective effect (Chuljerm *et al*., 2018), prevention and treatment of nausea and vomiting in pregnancy and after chemotherapy (Palatty *et al*., 2013; Chrichton *et al*., 2019), prevention of neurodegenerative diseases (Arcusa *et al*., 2022), management of inflammatory diseases such as Crohn's disease, ulcerative colitis, rheumatoid arthritis and Lupus erythematosus (Ballester *et al*., 2022), reduction in blood sugar levels (Hajimoosayi *et al*., 2020), as well as pain reducing effect (Rondanelli *et al*., 2020).

One of the forms of ginger preparation is ginger oil. The health benefits of ginger essential oil are identical to the medicinal health benefits of fresh ginger; in fact, the essential oil is stated as the most potent form of ginger (Ugbabe *et al*., 2019). Ginger oil was found to improve appetite and symptoms of anxiety, fatigue, nausea in cancer patients (Williams *et al*., 2022). Ginger oil is also used to relieve stomach ache (Liju *et al*., 2015) and also found to be effective against rheumatic disease (Barão Paixão & Freire de Carvalho, 2021). Ginger oil is an excellent dietary source of fibre, vitamin E (alpha tocopherol), vitamin B6, iron, manganese, potassium and selenium (IMARC, 2023). Ginger rhizomes are a good source of fatty oils (3-6%), proteins (9%), carbohydrates (60-70%), crude fiber (3-8%), ash (8%), water (9-12%), and volatile oil (2-3%) (Mbaveng & Kuete, 2017).

In this study, a rat model of constipation was established by oral administration of loperamide. The therapeutic effects of n- hexane extract of ginger on constipation were investigated.

MATERIALS AND METHODS

Animal Procurement and Care

Twenty four (24) Wistar rats of 190g mean weight were purchased from the Animal House College of Health Sciences, Benue State University, Makurdi. They were housed in the same facility, under an environmental temperature of 23 ± 2oC; humidity, 55 ± 15% and 12 h light/dark cycle. The rats were kept in wire-meshed cages for two weeks to allow for acclimatization before onset of the research, during which period they were fed with a standard rat chow (Vital feeds, Grand Cereals LTD, Jos, Plateau State, Nigeria) and water ad libitum and handled according to international guidelines for animal care (Simmonds, 2018).

Fresh *Zingiber officinale* rhizome (ginger root) was obtained from Wurukum Market, Makurdi, Benue State and certified by the botanist at Botany Department of Benue State University Makurdi.

Treatment Preparation and Administration

Ginger oil was prepared from mature ginger rhizomes by maceration method using n-hexane as solvent for the extraction according the method described by Srivastava *et al.* (2021). Constipation was induced with loperamide (LP) at a dosage of 4mg/kg/day (Adeniyi *et al*., 2020).

Three groups from the constipated animal models were given n-hexane extract of ginger (ginger oil) at various doses after one 1 hour of pre-treatment with loperamide (Lim *et al*., 2019). The protocol for treatment was as follows:

- Group 1(control): oral administration of 1ml physiological saline
- Group 2: oral intake of 1ml physiological saline with loperamide at 4mg/kgbw daily
- Group 3: oral 100mg/kgBw ginger oil (GO) and 4mg/kgBw loperamide daily

Group 4: oral GO at 200mg/kgBw and 4mg/kgBw loperamide daily

- Group 5: oral GO at 400mg/kgBw and 4mg/kgBw loperamide daily
- Group 6: oral bisacodyl at 5mg/kgBw and 4mg/kgBw loperamide daily

Animals were weighed daily before treatment throughout the study. Faecal pellets were collected from each animal daily, weighed to obtain the wet weight, then air dryed for 7 days and re-weighed to obtain the dry weight. The water content of the faecal pellets was thereafter estimated according to Lim *et al* (2019) as follows;

Faecal Water Content (%)=[(wet weight of feces -dry weight of feces)g]/Wet weight x100

Specimen and Analysis/Examination

The animals were fasted overnight after the treatment and each animal given their treatment accordingly. Thereafter, they were fed with charcoal meal at 1ml orally and sacrificed by cervical dislocation 30minuts later. The intestines were harvested for determination of intestinal transit of the charcoal meal (Choi *et al*., 2014) using the calculation;

Charcoal transit ratio (%) = [total distance traveled by charcoal meal/total small intestine length] × 100.

Colonic samples were collected into various sterile bottles containing physiological saline and 10% formaldehyde. The tissue samples in the phosphate buffer were stored at less than 4°C.

Superoxide Dismutase (SOD)

Level in the colon homogenates was determined by spectrophotometry method based on the inhibition

of the reduction of nitroblue tetrazolium (NBT). Tissue supernatant was mixed with 0.1 mol/L of ethylenediaminetetraacetic acid (EDTA), 0.15 mg/mL of sodium cyanide, 1.5 mmol/L of NBT, 0.12 mmol/L of riboflavin, and 0.067 mol/L of phosphate buffer in a 300 µL volume. The sample absorbance was read at 560 nm, and the percentage of SOD inhibition was compared with that of the blank. The concentration of the sample was calculated using the amount of protein required to achieve 50% inhibition and expressed as U/mg of protein (Tan *et al*., 2015)

Malondiadehyde (MDA)

Is a major secondary product of lipid peroxidation was determined spectrophotometrically by measuring the thiobarbituric acid (TBA) reaction (Tang *et al*., 2019). Each 500 µl of colon homogenate supernatant had 1 ml of 15% trichloroacetic acid added thoroughly mixed and centrifuged at 3000 rpm for 10 minutes. One milliliter of the supernatant was added to 0.5 ml of 0.7% TBA then the mixture was heated for 60 min at 90 °C. The pink color was obtained, which was measured spectrophotometrically at 532 nm. The results were expressed as micromoles per gram of protein.

Histological Analysis

Colonic tissue slides were prepared at the Anatomical Department of Benue State University Teaching Hospital by the pathologist and analysed for changes in mucous secretions and colonic mucosa thickness using Alcian blue and H&E stains. The goblet cells in 0.2 mm2 of the mucosa tunic of all slides were quantified and mucosal wall thickness determined through direct measurement from microscopic visualization. All measurements were carried out using a Motic B5 optical microscope and digital camera (Moticam 2000, 2.0 M Pixel) as previously reported (Wu *et al*., 2019).

Statistical Analysis

Results of this work were presented as mean ± SEM (n=4). Differences between the group means were determined using One-Way analysis of variance (ANOVA) with Turkey post hoc test. Data analysis was done using IBM SPSS version 22.0 software (Inc, Armonk, NY, USA). Differences were considered statistically significant when $P < 0.05$.

Ethical Clearance

Institutional Ethical clearance and certification (no CREC/RES/003) was obtained from the Research and Ethics committee of college of health sciences, Benue state university, Makurdi.

RESULTS AND DISCUSSION

Results

Result of the effect of ginger oil treatment on faecal pellet output is presented in table 1 below. It was observed in this study that ginger oil (GO) at various dosages increased faecal pellet output in loperamide induced constipation on a dose dependent basis. This action of GO is comparable to the effect of bisacodyl, the standard drug. This implies that GO improves faecal outlet in constipations.

Effect of GO on faecal water content is presented in table 2. It was observed faecal weights (wet and dry) and water content were increased in groups treated with GO in a dose dependent. In the HDGO group, the faecal water content is not significantly different from that of the Control and LP + Bisacodyl groups implying that HDGO potentially restores faecal water content in constipation.

Table 1: Effect of ginger oil on faecal pellet output

GROUP	DAY 1	DAY2	DAY3	DAY4
CONROL	24.35±2.33	33.67±0.88	40.00±1.15	45.35±1.30
LP +PS	18.00±0.58	11.35±0.67^{a}	10.33±0.33^{a}	8.35±0.67^{a}
LP+ LDGO	19.00±1.53	15.00±0.58^{a}	17.33±0.67^{a}	19.67±0.33^{ab}
LP+MDGO	21.67±0.88	23.67±0.88^{ab}	22.68±1.76^{a}	29.66±3.00^{ab}
LP+HDGO	23.00±1.5	27.32±1.45^{ab}	35.32±6.49^{b}	41.00±1.53^{b}
LP+BISACODYL	20.94±0.70	27.33±1.44^{ab}	33.33±2.84^{b}	37.67±3.71^{b}

Data presented as Mean ± SEM (n=24). Values in same column with alphabets are significantly different (P < 0.05). LP= loperamide, PS = physiological saline LDGO = low dose ginger oil, MDGO = medium dose of ginger oil, HDGO = high dose ginger oil

Table 2: Effect of ginger oil on faecal water content (%)

GROUPS	DAY 1	DAY 2	DAY 3	DAY 4
CONTROL	31.20±1.16	23.63±1.34	32.22±1.11	37.30±1.79
LP + PS	19.76±0.85^{a}	14.63±1.85	13.11±4.11	15.42±1.22^{a}
LP + LDGO	19.20±2.01^{a}	19.88±1.21	22.60±1.81^{b}	23.74±1.26^{b}
LP + MDGO	19.08±0.53^{a}	21.30±0.13	32.33±1.6^{b}	33.13±1.43^{b}
LP + HDGO	21.76±0.76	22.59±9.16	33.99±6.17^{b}	31.31±1.01^{b}

LP + BISACODYL	30.71±1.56[a]	31.54±1.96[ab]	33.59±1.71[b]	35.25±0.59[ab]

Data presented as Mean ± SEM (n=24). Values in same column with alphabets are significantly different (P < 0.05). LP= loperamide, PS = physiological saline LDGO = low dose ginger oil, MDGO = medium dose of ginger oil, HDGO = high dose ginger oil.

Table 3 shows the effect of treatments on intestinal transit ratio. The intestinal charcoal transit ratio (ITR) was increased in a dose dependent manner in the groups treated with GO at 61.79±1.00%, which though not statistically different from those of Control and LP + Bisacodyl groups, was numerically higher than all the groups. This implies that GO potentially improve gut emptying in state of constipation.

On colonic oxidative stress, the effect of treatments is presented in table 4. It was observed that SOD activity significantly increased on dose dependent basis with GO treatment (29.65±0.45µ/mg protein) compared to Control and LP + Bisacodyl groups at 25.5±0.46 and 24.84±0.84 µ/mg protein respectively. Lipid peroxidation on the other hand decreased under the same treatment conditions. This implies that GO reduces gut oxidative stress and lipid peroxidation in constipated gut.

Effect of GO treatments on colon histology are shown in table 5 and plate 1. The result showed that GO treatment statistically, but marginally, increase the thickness of the colonic wall as well and its mucosa in constipated rats. Thus, GO could potentially heal constipation associated colonic tissue injuries.

Table 3: Effect of ginger oil on intestinal transit ratio (%)

Groups	Total length of intestine	Distance travelled by charcoal	Intestinal charcoal Transit Ratio (%)
CONTROL	105.17±25.58	47.17±1.93	57.25±3.15
LOPERAMIDE + PS	96.23±7.75	60.93±4.95[a]	27.10±1.19[a]
LP + LDGO	105.33±2.62	53.00±1.59	49.61±1.81[b]
LP + MDGO	100.32±10.08	41.50±6.05[b]	59.05±2.04[b]
LP + HDGO	104.07±8.56	39.93±4.23[b]	61.79±1.00[b]
LP + BISACODYL	100.47±2.82	47.10±3.14[b]	53.05±3.06[b]

Data presented as Mean ± SEM (n=24). Values in same column with alphabets are significantly different (P < 0.05). LP= loperamide, PS = physiological saline LDGO = low dose ginger oil, MDGO = medium dose of ginger oil, HDGO = high dose ginger oil

Table 4: Effect of ginger oil on colonic oxidative stress

GROUP	SOD (u/mg protein)	MDA (nmol/g protein)
CONTROL	25.5±0.46	2.33±0.63
LPOPERAMIDE+PS	19.85±0.38[a]	4.05±0.22[a]
LP+LDGO	26.03±1.43[b]	2.1 ±0.15[b]
LP+MDGO	29.00±0.52[ab]	1.92±10.75[b]
LP+HDGO	29.65±0.45[ab]	1.63 ±0.22[b]
LP+BISACODYL	24.84±0.84[a]	1.93±0.14[a]

Data presented as Mean ± SEM (n=24). Values in same column with alphabets are significantly different (P < 0.05). LP= loperamide, PS = physiological saline, LDGO = low dose ginger oil, MDGO = medium dose of ginger oil, HDGO = high dose ginger oil.

Table 5: Effect of ginger oil on colon histology

Group	Number of goblet cells (H&E)	Number of goblet cells (AB)	Total wall thickness(µm)	Mucosa tunic (µm)
CONTROL	3.05 ±2.89	3.93± 2.03	9.73 ±2.03	1.55 ±2.91
LP+PS	2.36 ±3.48[a]	3.06 ±1.76[a]	9.11 ±2.33[a]	1.25 ±2.91[a]
LP+LDGO	2.95 ±2.91[b]	3.23 ±1.76[b]	10.12 ±1.67[ab]	1.27 ±1.76[a]
LP+MDGO	3.09 ±2.81[b]	3.52 ±2.33[b]	9.85 ±2.91[ab]	1.98 ±3.76[ab]
LP+HDGO	3.24 ±2.31[ab]	3.34 ±2.60[b]	10.21 ±2.08[ab]	1.39 ±1.76[b]
LP+BISACODYL	3.52 ±1.15[ab]	4 36 ±2.96[b]	10.44 ±2.96[ab]	2.01 ±2.31[ab]

Data presented as Mean ± SEM (n=24). Values in same column with alphabets are significantly different (P < 0.05). Values in same column with alphabets are significantly different (P < 0.05). LP= loperamide, PS = physiological saline, LDGO = low dose ginger oil, MDGO = medium dose of ginger oil, HDGO = high dose ginger oil.

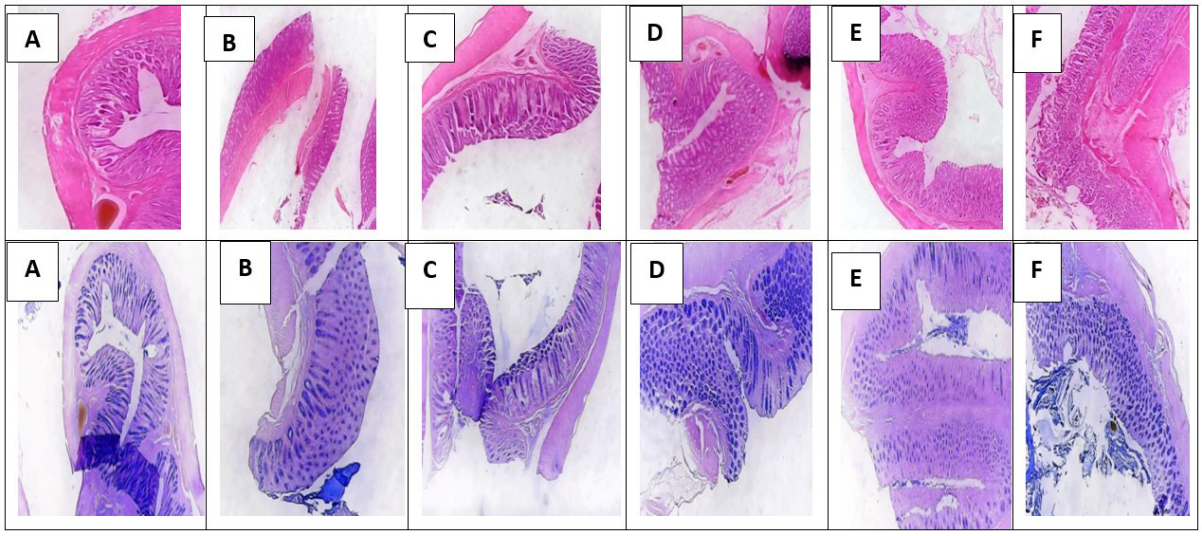

Figure 1: Plate 1. Histological view of colon section (4x) stained by Haematoxylin and Eosin (H&E) and Aacian blue showing mucous producing (goblet) cells and colonic mucosa thickness. A=Group 1, B=Group 2, C=Group 3, D=Group 4, E=Group 5, F=Group 6

DISCUSSION

Constipation is common gastrointestinal condition that has a global interest due to its long-term complications as well as its impact on the quality of life (Turan & Atabek, 2016). The aetiology of constipation is multifactorial ranging from dietary factors, medications to organic diseases, necessitating the use of laxatives, which often have unpleasant side effects. Therapeutic focus has naturally shifted to traditional medicine in bid for safer, cheaper but effective alternatives and thus the need for this research.

In order to evaluate the potential laxative effects of n-hexane extract of *Zingiber officinale* (ginger oil), the changes in faecal parameters (i.e. pellet count, wet/dry weight and water content), gastrointestinal transit ratio (motility), and colonic mucosa histology (i.e., mean colonic mucosa thickness and number of colonic mucous-producing cells) were examined in loperamide- induced rats, a suitable animal model of spastic constipation (Choi *et al.*, 2014a, b). The laxative effects of ginger oil were compared with a standard drug bisacodyl. The protective effects of ginger oil were also determined by analysis of its effect on colonic oxidative stress.

The faecal pellet output was significantly lower in the loperamide group compared to vehicle control indicating that rats were constipated. Faecal pellet output in the different dosages of ginger oil (100mg/kg, 200mg/kg and 400mg/kg) treated rats was significantly increased compared to loperamide control, with the faecal pellet output being significantly higher at 400mg/kg similar to bisacodyl treated group showing that ginger oil was able to relieve the effect of constipation caused by loperamide. This result is similar to that of previous studies and is thought to be as a result of the GI prokinetic and relaxing actions of ginger which are mediated by calcium antagonism and cholinergic agonist, respectively. (Abidi *et al.*, 2022; Foshati *et al.*, 2023).

Result showed that treatment with loperamide significantly decreased the weight of wet and dry fecal pellets relative to the control. However, the wet and dry weights were increased in rats co-administered 400mg/kg ginger oil compared to loperamide group, similar to the effect observed in bisacodyl. The faecal water content was significantly decreased in loperamide group compared to vehicle control. However, there was a dose- dependent significant increase in the faecal water content with a progressive effect noted as the duration of treatment increased. The ginger oil was more effective at the highest dose (400mg/kg). Bisacodyl also showed significant ($P < 0.05$) increase in faecal water content relative to loperamide group. The increase in faecal water content caused by ginger oil may be as a result of its high fibre content which promotes faecal water retention and increase in water secretion thereby promoting peristalsis suggesting that ginger oil has promising laxative properties as observed in previous studies (McRorie & Mckeown, 2017; Zhang *et al.*, 2020).

The intestinal transit ratio (ITR), a marker of intestinal motility, of the loperamide constipated model was significantly decreased compared to the control group, consistent with signs of spastic constipation (Choi *et al.*, 2014a, b). Ginger oil at varying doses showed significantly increased ITR compared to loperamide model in a dose dependent manner with 400mg/kg having greater effect provide indirect evidence that ginger oil has promising laxative effects against loperamide-induced spastic constipation. This is consistent with previous studies (Abidi *et al.*, 2022). Bisacodyl showed similar effects on ITR as ginger oil with no significant difference between the treatment groups.

The effect of ginger oil on colonic oxidative stress was assessed and the results showed that Superoxide dismutase (SOD) activity in loperamide group was significantly decreased compared to control. SOD activity

was significantly increased in the ginger oil treated groups in a dose dependent manner. However, bisacodyl was not significantly different compared to loperamide.

Furthermore, Lipid peroxidation was increased in loperamide group compared to control but decreased significantly in the ginger oil co-treated groups compared to loperamide in a dose dependent manner. As previously stated by Zhanl *et al.* (2021), the inhibition of GI-motility and intestinal secretion induced by loperamide is accompanied by the increase in plasma and colonic lipid peroxidation and decrease of enzymatic antioxidant activity. Also, the antioxidant effect of ginger oil seen in SOD and lipid peroxidation is comparable to previous studies (Zhang *et al*., 2017; Joshi *et al*., 2017) and its lipid peroxidation reduction is considered due to polyphenolic components such as flavonoids (quercetin, kaempferol, apigenin, and luteolin) which are capable of reducing free radical chains through electron and proton transfer and chelating transition metal ions capable of catalysing lipid peroxidation. The antioxidant properties may also be traced to the polysaccharides in ginger which cause a reduction in DPPH radical, hydroxyl and superoxide radicals (Hefnawy, 2016).

Colonic mucosa analysis showed significant decrease in mucous producing cells and mean mucosa thickness in the loperamide constipated group compared with vehicle control. However, significant increases in the number mucous producing cells and mean colonic mucosa thickness was observed with ginger oil treated groups compared with loperamide treated animals. In comparison to the vehicle control, ginger oil showed the maintenance of mucosa thickness integrity and also increased mucous secretions thus been protective against the effects of constipation. This is similar to previous studies and may be as a result of a reduction in inflammatory factors and antioxidant activity of the phenolic compounds in ginger (Zhang *et al*., 2018; Abidi *et al* (2022).

CONCLUSION

This research has shown that n-hexane extract of *Zingiber officinale* (ginger oil) has a potential laxative effect in a dose dependent manner with 400mg/kg being most effective which is comparable to that obtained in bisacodyl. The laxative properties were demonstrated by increasing faecal pellet output and intestinal transit time as well as increasing the faecal water content in loperamide constipated rat models. Ginger oil has also shown to have antioxidant by increasing SOD activity and reducing lipid peroxidation.

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