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SCREENING MODELS OF LAXATIVE ACTIVITY

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ABSTRACT: Substances that loose stools and boost bowel movements are laxatives, purgatives, or aperitives. They are used to treat constipation and to stop it. Constipation relates to infrequent or difficult to transfer bowel movements. Often the stool is hard and dry. Other symptoms may include abdominal pain, bloating, and feeling as if the bowel movement has not been fully passed. Hemorrhoid's anal fissure or fecal impaction may be complications from constipation. It is a common gastrointestinal functional disorder. IBS is considered to be a complex condition with physiological and psychosocial elements in which stimuli from the central nervous system modulates altered bowel motility or sensation. Medical treatments for constipation include the provision of bulk laxatives, osmotic agents, stimulants, lubricants, and neuromuscular agents. Animal models are important tools in experimental medical science to understand the pathological process of human diseases. Animal models include drug-induced constipation in rat model, canine slow transit constipation model, low-fiber diet-induced constipation in rats, gastrointestinal motility test, castor oil-induced enter pooling. Gastrointestinal motility depicts the muscle contraction in the gastrointestinal tract that mixes and propels contents. Medicines associated with constipation include opioids, diuretics, antidepressants, antihistamines, antispasmodics, anticonvulsants, and aluminum antacids. While a number of therapies are available, the best way to treat constipation is to make fundamental changes to bring more fiber into the diet, remain hydrated, and add exercise to the patient's daily routine. Recently, as novel therapeutic solutions for chronic constipation therapy and its related disorders, many herbal plants and medicinal products have gained study attention since they can effectively improve a range of circumstances without severe adverse side effects.

INTRODUCTION: Constipation is a hetero-geneous disease with various causes including insufficient diet, medication use, concurrent illnesses, and bowel structure or function disorders [1]. This is described as feces evacuation that is rare or hard [2].

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It is a functional gastrointestinal disorder globally [3]. Constipation seems to be more prevalent in older people, females, non-whites, and people in reduced cultural-economic and educational groups in particular [4, 5]. Constipation massively affects constipated people's health-related quality of life [4, 5, 6].

The main mechanism for slow transit constipation is a gastric motility failure to transfer luminous contents *via.* the colon resulting in more time for stool solid bacterial deterioration and more time for salt and water absorption, thus, dramatically decreasing stool frequency and stool weight [7, 8, 9].

Constipation medical therapy includes traditional laxatives and agents. The former may cause defecation or alter the consistency of the stool to facilitate defecation, whereas the latter targets assumed flaws in colonic neuromuscular function [10]. Constipation is a prevalent community issue the symptoms differ from a comparatively mild bowel habit disruption to rare severe sequelae, including intestinal obstruction and fecal impaction [11].

Constipation is a prevalent motility gastrointestinal disorder characterized by symptoms such as strain, difficult stool, and irregular defecation [12]. Severe constipation and irritable constipation bowel syndrome are two main types of functional constipation [13, 14, 15, 16]. It is presumed that IBS is a complicated disease with physiological and psychosocial elements in which input from the central nervous system modulates changed motility or sensation in the intestine [17]. Constipation intensifies during aging and maybe a longterm chronic condition that requires the use of laxatives [18].

Although there are a variety of treatments available, the best way to treat constipation is to make basic alterations to introduce more fiber into the diet, stay hydrated and add exercise to the everyday routine of the patient. However, it is also possible to prescribe chemical drugs (laxatives) such as senna, correctol, exlax, senokot, and gaviscon to aid patients to pass faeces [19, 20]. In a multitude of preparations, there are many classes of agents available. Chronic constipation medical treatments include the supply of bulk laxatives, osmotic agents, stimulants, lubricants and neuro-muscular agents [21, 22]. Bisacodyl, castor oil, cascara, senna, and phenolphthalein are stimulating laxatives. While short-term and occasional use is relatively safe, elderly people are particularly susceptible to dehydration, malabsorption, and the need to increase doses [23-26]. It has been shown that saline laxatives such as magnesium-containing compounds are effective in relieving constipation in the aged. However, its use in patients with renal insufficiency and in patients with cardiovascular disease who may not tolerate a salt load should be considered [27, 28]. Constipation-related medicines include opioids, diuretics, anti-depressants, antihistamines, antispasmodics, anticonvulsants and antacids of aluminum [29].

Types of Screening Models of Laxative:

1. Drug-induced constipation in rat model [30].
2. Canine slow transit constipation model.
3. Low-fiber diet-induced constipation in rats.
4. Gastrointestinal motility test [31].

A. Assessment of intestinal transit.

B. Assessment of gastric motility.

C. Measurement of gastrointestinal transit.

D. Measurement of colon motility.

E. Long term recording of intestinal mechanical and electrical activity.

F. Assessment of GIT motility in dogs.

5. Castor oil-induced enter pooling [32, 33].

1. **Drug-Induced Constipation in Rat Model:** Thirty rats of either gender (180 to 220 g) were assigned randomly to five groups of six each and were fasted for 12 h before the experiment, but with *ad libitum* water supplied. The first group (G-I) administered with saline (5 mL/kg, p.o.) was used as a control. Constipated control was caused by the second group (G-II) as loperamide (3 mg/kg). The third (G-III) and fourth (G-IV) groups received 300 and 600 mg/kg (p.o.) of the drug extract in normal saline BWT for 3 days in 0.9% NaCl). The fifth group (GV) got gaviscon (10 mg/kg, p.o), which served as the reference laxative drug by releasing active anthraquinones into the colon. The animals were placed immediately after weight administration (at the moment of dosing) [19]. The output of feces (total amount of normal and wet feces) was quantified in all four groups by evaluating feces weight, was monitored up to 16 h [34-43].

2. **Canine Slow Transit Constipation Model:** Baseline data were measured in 8 beagle dogs, randomly dividing these animals into the control group and model group. A diet of canned meat and a mixture of compound diphenoxylate and alosetron hydrochloride for 5 weeks were provided to the dogs in the model group. With no special intervention, dogs in the control group were provided an ordinary diet. The tool frequency and

consistency were noted and recorded daily, and every week, the gastrointestinal transit time (GITT) was evaluated. All animals underwent midline laparotomy, and the colonic tissues were taken from the rectosigmoid colon, then investigated by light microscopy, electron microscopy, and immune-histochemistry to assess changes in the protein gene product 9.5, synaptophysin, and c-kit among two groups [44].

3. **Low-Fiber Diet-Induced Constipation in Rats:** Male SD rats (6 weeks old) were bought. The animals were kept at room temperature controlled (24.5 to 25.0 °C) with a light / dark cycle of 12/12 h *ad libitum* was supplied with food pellets and tap water [45, 46].

Stool Parameters: The stool's frequency and weight were evaluated over 16 h. as the frequency and total wet weight per rat. **Fig. 1C** ethanolic drug extract (150, 300, and 600 mg/kg) and senna (150 and 300 mg/kg) was given orally once a day for 14 days. **Fig. 1A** gum Arabic (5% w/w) was orally administrated as a vehicle. Carmine (10 mg/ body) was given immediately following sample administration *via* the same path. The frequency, weight, and water content of each rat stools were evaluated for 16 h at 2 h intervals (*e.g.* 0-2 h, 2-4 h, 4-6 h, *etc.*). Every rat evaluated carmine egestion at 2 h intervals for 24 h. Rats were then put separately in a stainless steel cage (24 × 38 × 20 cm) and fasted for 8 h but supplied with water *ad libitum*.

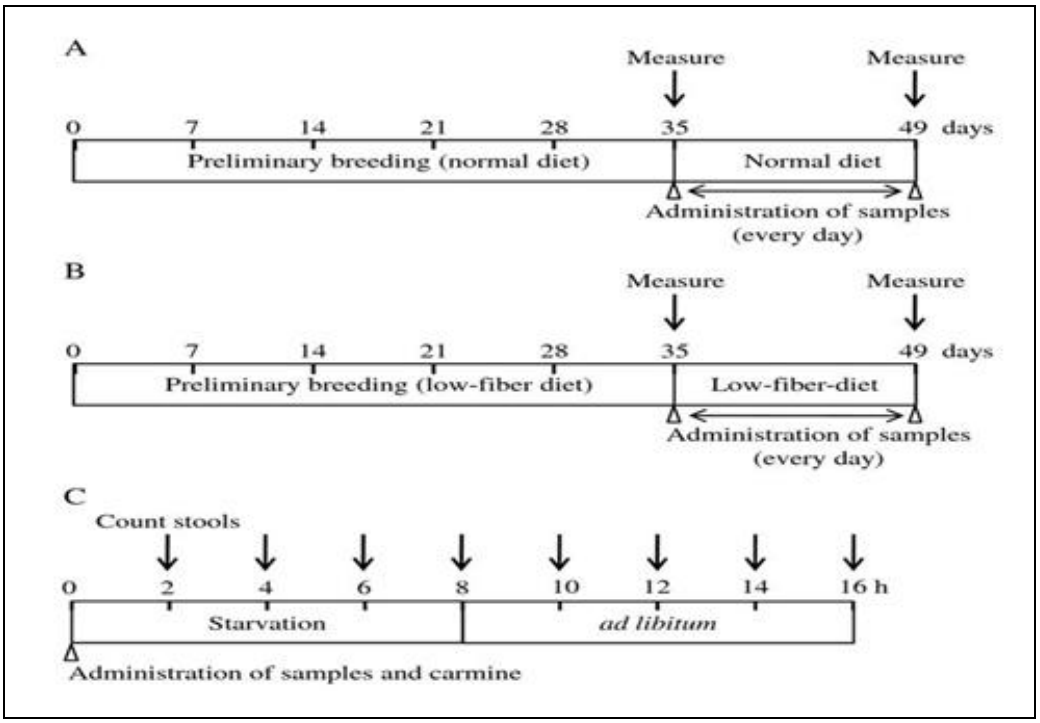

FIG. 1: THE SCHEDULE OF EXAMINATION PERFORMED IN THIS STUDY

TABLE 1: COMPOSITION OF THE NORMAL DIET AND LOW-FIBER DIET

Ingredients	Contents (%)	
	Normal diet	Low-fiber diet
Moisture	9.3	9.0
Crude protein	25.1	21.9
Crude fat	4.8	6.1
Crude fiber	4.2	0.1
Crude ash	6.7	5.9
NFE	50.0	57.0

NFE: Nitrogen free extract from laxative effects of agarwood on low-fiber diet-induced constipation in rats

Induction and Evaluation of Constipation: Rats have been kept for 5 weeks on a low fiber diet to cause constipation before the experiments **Fig. 1**. The low fiber diet included 41.5 percent maize starch, 24.5 percent casein milk, 10.0 percent sucrose, 10.0 percent dextrin, 7.0 percent mineral mixture, 6.0 percent maize oil, and 1.0 percent vitamin combination **Table 1**.

4. Gastrointestinal Motility Test:

1. Assessment of Intestinal Transit: Intestinal transit measurement is a commonly used method to evaluate the behavior and mechanisms by which compounds affect intestinal motility. Intestinal transit is generally quantified to move along the

length of the small intestine by evaluating the movement of charcoal, dyes, radio-opaque pellets or radioactive markers that have been instilled into the conscious animal's stomach or intestinal lumen after overnight food deprivation.

1.1 Measurement of Small Intestinal Transit:

1.1.1. Marker Methods: Inert, non-digestible, distinct color with appropriate viscosity (*e.g.* phenol red, charcoal meal, chromic acid) or radioactive markers are given intragastrically (*i.e.* 0.3 ml for mice or 0.5 ml for rats) to overnight food-deprived animals. If the route of administration is i.p, or *i.e.* the drug being investigated may be provided 10 to 30 min before testing meal. If the drug should be administered orally, it should be administered at least 8 h before dinner. Other groups should be treated with vehicle. Any other oral consumption within this period should not be permitted. After the prescribed time span, animals are sacrificed and distance traveled by the marker front in the intestine is observed and expressed as a % small intestinal transit (SIT) with reference to the entire length of the intestine [47].

1.1.1.1. Charcoal Meal Method: For an overnight period, appropriate numbers of animals are deprived of food. Each mouse (0.3 ml) or rat (0.5 ml) in a group is given of suspension of charcoal meal (10% w/v wood charcoal in 5% w/v gum acacia aqueous suspension) *i.e.* Using oral feeding needle animals are slaughtered by cervical dislocation after 20 min, the abdomen is opened, the marker's leading-edgee is found. The intestine at the leading edge is attached to a cotton thread or instantly immersed in 5 percent formalin solution to stop the peristalsis after excising the entire intestine (from the pyloric end of the abdomen to the ileocaecal intersection). The distance traveled by the charcoal leading edge and the complete intestine length are evaluated.

1.1.1.2. Phenol Red Test Meal: In 100 ml of distilled water, fifty milligrams of phenol red is dissolved and filtered. The filtrate is heated to 70 ºC, with constant stirring, about 750 mg of methylcellulose is added. The solution is quickly refrigerated to 37 ºC. Following overnight food deprivation, mice or rats are used. After *i.g.*, administration of marker (0.3 ml for a mouse or 0.5 ml for rat), as it reaches the small intestine due to motility, the color of the marker changes to red due to the alkaline nature of contents. Then % SIT is determined [48-50].

1.1.1.3. Radioactive Markers: Adult Wistar rats are implanted in the proximal duodenum with an indwelling silastic cannula. Approximately 0.2 ml of radio chromium 51 (0.5 mic ci Na CrO in saline) is instilled into the small 4 intestines *via* the silastic cannula after 30 min of drug administration. Twenty-five min later, an appropriate method is used to sacrifice the animals. Carefully removes the small intestine and divides it into 10 equal sections. These organs are then put on a controlled template and subsequently put in individual culture tubes and the radioactivity in each tube is determined by using a tracer analytic automatic gamma counter to count for 1 min for each mouse, in which values range from a minimum of 1.0 to a maximum of 10, transit along the intestine is calculated. Although the outcomes are expressed as GI transit, only 7 marker transit along the small intestine is measured [51, 52].

2. Assessment of Gastric Motility: Stomach function includes the initiation of digestion by exocrine secretions such as acid and pepsin, which are controlled by hormone endocrine secretion, which also coordinates intestinal motility [53].

2.1. Evaluation of Gastric Emptying by Phenol Red: Animals (rats or mice) are overnight deprived of food. Phenol red test meal (0.5 ml for a mouse or 1.5 ml for a rat) is given *i.e.*, Two animals are sacrificed by cervical dislocation from the group immediately after administration of the test meal (0 min). In order to locate the stomach, laparotomy is conducted and clamped/linked at cardiac and pyloric ends. The clamped stomach is separated from the duodenum and washed its surface with normal saline. The stomach is transmitted into 0.1 N NaOH (50 ml for mice or 100 ml for rats,) solution and homogenized. 0.5 ml of trichloroacetic acid is added to 5 ml of homogenate and centrifuged for 20 min, at 300 rpm. By aspiration with a syringe needle, the transparent supernatant fluid is removed from the centrifuge tube and then added 4 ml of 0.5 NaOH. The absorbance of the resulting pink colored liquid is evaluated at 560 nm spectrophotometrically. The outcome correlates

with the phenol red meal concentration in the stomach, which in turn depends on the GE. After 20 min, the treated animals are slaughtered and GE is 9 determined [54].

2.2. Evaluation of Gastric Emptying by Weighing Method: Three milliliters of a semi-solid test meal, based on methylcellulose are given, *i.g.,* to rats fasted overnight before the experiment. The mice are sacrificed, laparotomies and the stomachs are removed at a designated moment after the test meal. After weighing the complete stomach they are opened and rinsed. Excess moisture is blotted and the empty stomachs are weighed again. The differentiation is subtracted from the test meal's weight of 3 ml, showing the quantity emptied from the stomach during the test period. GE increases by Gastric motor stimulants (metoclopramide) and reduces by anti-cholinergic compounds [55-57].

3. Gastrointestinal Transit Measurement with Fluorescent Beads in Mice: The mice are stood deprived overnight. In order to avoid coprophagy during fasting, each animal is housed separately in a wire mesh cage. The microbeads, used as markers. They are 6 mm in diameter, marked with a yellow-green fluorescent dye and emit yellow-green fluorescence when excited with an argon laser of 488 nm.

A flow cytometer was used to measure the amount of fluorescent microbeads in each sample. Saline 0.2 ml, containing the 6 mm fluorescent microbeads together with the 2.14 mm non-fluorescent microbeads (2 ml), is inserted into the stomach *via* a metal cannula. Thirty minutes later, with an appropriate means, the animals are sacrificed. The esophagus, which is proximal to the gastric fundus and the duodenum, which is only distal to the pylorus, is cross clamped, and the stomach is removed.

The small intestinal tract is also removed at several places by clamping the tract to minimize content motions. The intestinal tract is placed on a controlled template and split into 10 equal sections. The stomach is put in individual tubes comprising 5 ml of phosphate-buffered saline and each section of the intestinal tract. Each tube is vortexed, and a cell strainer filters the supernatant liquid and undergoes cytometry flow. The 6 mm microbeads are chosen using flow cytometry by their distinct forward light dispersion and by their sidelight dispersion profiles. For the presence of intense fluorescence, the gated particles are further analyzed [23]. A GC technique is used to evaluate gastrointestinal transit.

4.1. Assessment of Colon Motility in Anesthetized Rats: In anesthetized mice, the impact of spasmolytic drugs on the rise in colonic motility induced by carbachol can be evaluated. This technique was also used to study the 13 enkephalin analog pentapeptide stimulation of colonic motility [58]. Procedure: Rats are anesthetized with pentobarbital, *i.e.,* a pressure-sensitive tip catheter is inserted into the ascending colon, and the signals of modifications in intraluminal pressure are recorded *i.e.* injection of 3 mg/kg carbachol, stimulates the colonic contractions. The height of the contractions and their duration are recorded. Then the test compound is injected *i.e.,* The decline in contractions is assessed, and the period of spasmolytic activity is determined by repeated carbachol administration at 15 min intervals until the contractions are not substantially distinct from the carbachol response alone [59].

4.2. Measurement of Colon Transit Time in Rats: Rats are anesthetized with 50 mg/kg pentobarbitone sodium. A PVC catheter is implanted into the caecum with the distal end fixed on the neck of an animal. The animals are permitted to recover and are put in a wire meshed cages separately to allow the faeces to fall through on blotting paper.

Right after administration of the test drug, carmine red (10 mg in 0.4 ml of normal saline per animal) is injected through the catheter. The time until the appearance of the first colored feces is noted [60].

4.3. Colon Transit Assessment of Bead Expulsion in Mice: Colonic bead expulsion (CBE) is an easy technique of measuring colonic propulsion of boluses 16 through the intestinal and external anal sphincters. A glass bead (3 mm diameter) is placed into the rectum of the mouse immediately after the injection of the test compound. Bead's expulsion time was observed as the time limit with 100 min. Mice that do not expel

the bead in that period are excluded from the research. Data expressed as % inhibition of CBE, calculated in the following manner [61].

Percentage inhibition = 100 (Test time – mean control time) / (100 - control time)

5. Long Term Recording of Intestinal Mechanical and Electrical Activity in Un-Restrained Rats: This model was created to study GIT's concurrent mechanical and electrical activity in the conscious rats [62]. Cyclic motor activity happens in almost all sections of the GIT due to the GIT's electrical activity of migrating myoelectric complex 18 (MMC) [63].

6.1. Assessment if Gitmotility in Dogs: A duodenal Mann and Bollman (1931) fistula according to Tasaka and Farrar (1976) or in the loop of a Thiry-Vella fistula can be used to measure intraluminal stress and motility of the small intestine in unanesthetized animals with balloon catheter systems [64, 65].

Procedure: Small intestine fistula is developed in 20 g male beagle dogs. The animals are anesthetized with 40 mg/kg pentobarbital *i.v.* and fixed on a table of operations. A midline incision is produced after shaving and thorough skin disinfection. An ileum length of 10-15 cm is excised, roughly 15 cm from the caecum. The rest of the ileum is end-to-end anastomosed. The excised ileum is anastomosed, end to side, to the proximal or middle jejunum. To guide the direction for subsequent intubation, radio-opaque tantalum markers are sutured to serosa distal to this anastomosis.

The other end is sutured to the skin. Small amounts of muscle, fascia and subcutaneous tissue are excised from the abdominal wall to produce a skin ileostomy that does not shrink quickly. An air-filled device is used to measure the pressure inside the intestine. An air-filled 190 polyethylene catheter (I.D. 1.19 mm) attached with a length of 120 cm are air-filled latex balloons, 5 cm in diameter. Three assemblies of the balloon-catheter pressure are tied 5 cm apart with the balloons. The catheters are linked to the transducers of pressure and a polygraph. Repeated application of latex to all links makes the transducers airtight. Before the experiment, the animals are deprived of food, but not water 18 h. The assemblies of the balloon catheters are introduced through the fistula and secured in a suitable position. At a pressure of 10 mm Hg, the system is filled with air. Similarly, it is possible to introduce balloon-catheter assemblies into a thiry-vella fistula. Continuously measure intraluminal pressure and record the amplitude of pressure waves. The test drug is administered orally or s.c. after a period of 1 h and the above-described parameters are registered at intervals of 10 min [66].

6.2. Thiry-Vella Loop Preparation in Dogs: Male beagle dogs of weight 20 kg are used. Dogs have fasted 12 h before the test. Satisfactory anesthesia is provided by pentobarbital sodium (30 mg/kg; *i.e.*) with an electric clipper, the abdominal part is shaved, then with a razor. The skin has been disinfected. A midline linea Alba incision is made. A jejunum loop, about 70 cm long, is divided, leaving the blood supply intact through the mesenterium. Both distal and proximal ends are externalized and supplied with stomata through the abdominal wall. End to endjejuno-jejunal anastomoses is performed. The proximal ostium introduces alatex balloon linked to a pressure transducer via a polyethylene catheter. Changes in intragastric pressure are evaluated on a frequency measurement bridge and recorded continually. As for indicators of intestinal motor activity, the number and height of the pressure waves are used [67].

4. Castor Oil Induced Enter Pooling: Castor oil-induced enter pooling test enables to determine the capacity of extract to prevent fluid accumulation. Both sex rats (95-100 g) fasted for eighteen h. The rats chosen were divided into four groups (n = 5) for this experiment. Group, I (controlled group) received normal saline (2 mL/kg) orally while group II (standard group) was given loperamide (5 mg/kg). A methanol extract of medication (200 and 400 mg/kg b. wt. i.p. resp.) was obtained by the remainder of the groups (groups III-IV). All groups got castor oil after 1 h, orally 1 mL per animal. All rats were sacrificed 2 h later, and the small intestine was isolated from the pylorus to the caecum. In a graduated tube, the intestinal contents were gathered and their quantity was evaluated [68-69].

CONCLUSION: Recently, many herbal plants and medicinal products have gained study attention as novel therapeutic approaches for the therapy of

chronic constipation and its associated conditions, since they can enhance a range of circumstances efficiently without important adverse side effects.

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REFERENCES:

1. Talley NJ, Jones M, Nuyts G and Dubois D: Risk factors for chronic constipation based on a general practice sample. The Ame J of Gastroenter 2003; 98(5): 1107-11.
2. Higgins PDR and Johanson JF: Epidemiology of constipation in North America: a systematic review. Am J Gastroenterol. 2004; 99(4): 750-59.
3. Peppas G, Alexiou VG, Mourtzoukou E and Falagas ME: Epidemiology of constipation in Europe and Oceania: a systematic review. BMC Gastroenterol 2008; 8(1): 5.
4. Wald A, Scarpignato C, Kamm M, Mueller-Lissner S, Helfrich I, Schuijt C, Bubeck J, Limoni C and Petrini O: The burden of constipation on quality of life: results of a multinational survey. Al Pharm Ther 2007; 26(2)): 227-36.
5. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ and Muller-Lissner SA: Fuctional bowel disorders and functional abdominal pain. Gut 1999; 45(2): 43-47.
6. Olden KW and Schuster MM: Irritable bowel syndrome. in sleisenger and fordtran's gastrointestinal and liver disease: Path physiology Diagnosis Management Edition 6th Edited by Feldman M, Scharschmidt BF and Sleisenger MH 2: 1536-48.
7. Stewart WF, Liberman JN, Sandler RS, Woods MS, Stemhagen A, Chee E, Lipton RB and Farup CE: Epidemiology of constipation (EPOC) study in the United States: relation of clinical subtypes to sociodemographic features. Am J Gastroenterol 1999; 94(12): 3530-40.
8. Emmanuel AV, Tack J, Quigley EM and Talley NJ: Pharmacological management of constipation. Neuro-gastroenterol Motil 2009; 2(2): 41-54.
9. Schiller L: The therapy of constipation. Aliment Pharm Therap 2001; 15(6): 749-63.
10. Tack J: Current and future therapies for chronic constipation. Best Pract Res Cl Ga 2011; 25(1): 151-58.
11. Heaton KW, Radvan J and Cripps H: Defecation frequency and timing, and stool form in the general population: a prospective study. Gut 1992; 33: 818-24.
12. Wald A, Scarpignato C, Kamm MA, Mueller-Lissner S, Helfrich I, Schuijt C, Bubeck J, Limoni C and Petrini O: The burden of constipation on quality of life: results of a multinational survey. Alim Pharma Ther 2007; 26: 227-36.
13. Cash BD, Chang E, Talley NJ and Wald A: Fresh perspectives in chronic constipation and other functional bowel disorders. Rev Gastroenterol Disor 2007; 7: 116-33.
14. Kojima R, Doihara H, Nozawa K, Kawabata-Shoda, E, Yokoyama T and Ito H: Characterization of two models of drug-induced constipation in mice and evaluation of mustard oil in these models. Pharm 2009; 84(4): 227-33.
15. Walia R, Mahajan L and Steffen R: Recent advances in chronic constipation. Curr Opin Pediatr 2009; 21: 661-66.
16. McCallum IJ, Ong S and Mercer-Jones M: Chronic constipation in adults. BMJ 2009; 338: 831.
17. Camilleri M and Choi MG: Review article: irritable bowel syndrome. Aliment Pharmacol Ther 1997; 11: 3-15.
18. Mostafa SM, Bhandari S, Ritchie G, Gratton N and Wenstone R: Constipation and its implications in the critically ill patient. Br J Anaesth 2003; 91(6): 815-9.
19. Kim EJ, Go J, Koh EK and Hwang S: Gallotannin-enriched extract isolated from galla rhois may be a functional candidate with laxative effects for treatment of loperamide-induced constipation of sd rats, published: September 2016; 12.
20. Kim1 JE, Go1 J, Sungl JE, Lee1 HA, Yun1 BW, Hong JT and Kim YDH: Uridine stimulates laxative effect in the loperamide-induced constipation of SD rats through regulation of the mAChRs signaling pathway and mucin secretion. BMC Gastroenterology 2017; 17: 21.
21. Siegel JD and Palma DJA: Medical treatment constipation. Clin Colon Rectal Surg 2005; 18: 76-80.
22. Portalatin M and Winstead N: Medical management of constipation. Clin Colon Rectal Surg 2012; 25: 12-19.
23. Schiller LR: Review article: the therapy of constipation. Aliment Pharmacol Ther 2001; 15: 749-63.
24. Ewe K: Effect of bisacodyl on intestinal electrolyte and water net transport and transit. perfusion studies in men. Digestion 37: 247-53.
25. Kienzle-horn S, Vix JM, Schuijt C, Peil H, Jordan CC and Kamm MA: Efficacy and safety of bisacodyl in the acute treatment of constipation: a double-blind, randomized, placebo-controlled study. Ali Pha Ther 2006; 23: 1479-88.
26. Kakino M, Izuta H, Ito T, Tsuruma K, Araki Y, Shimazawa M, Oyama M, Iinuma M and Hara H: Agarwood induced laxative effects *via* acetylcholine receptors on loperamide-induced constipation in mice. Biosci Biotechnol Biochem 2010; 74: 1550-55.
27. Lillo AR and Rose S: Functional bowel disorders in the geriatric patient: constipation, fecal impaction, and fecal incontinence. The American Journal of Gastroenterology 2000; 95(4): 901-05.
28. Lisi, DM: Drug-induced constipation. Archives of Internal Medicine 1994; 154(4).
29. Walia R, Mahajan L and Steffen R: Recent advances in chronic constipation. Curr Opin Pediatr 2009; 21: 661-66.
30. Saito T, Mizutani F, Iwanaga Y, Morikawa K and Kato H: Laxative and anti-diarrheal activity of polycarbophil in mice and Rats. Research and Development Headquarters Hokuriku Seiyaku Co Ltd 1-1 Inokuchi 37, Katsuyama, Accepted March Fukui 2002; 7: 911-55.
31. Peddireddy MKR: *In-vivo* Methods for evaluation of drugs for the treatment of gastrointestinal motility disorders. Indian J Pharm Edu Res 2010; 44(1):
32. Sini JM, Umar IA, Anigo KM, Stantcheva I, Bage EN and Mohammed R: Anti-diarrhoeal activity of aqueous extract of *Combretum sericeum* roots in rats. African Journal of Biotechnology 2008; 7(17): 3134-37.
33. Rahman MK, Chowdhury MA, Islam MT, Chowdhury MA, Uddin ME and Sumi CD: Evaluation of antidiarrheal activity of methanolic extract of *Maranta arundinacea* linn. leaves Adv Pharmacol Sci 2015; 6: 257057.
34. Abdullahi M, Muhammad G and Abdulkadir NU Combretaceae: Medicinal and economic plants of nupeland. Bida Nigeria Jube Evans Books and Publications 2003.
35. Zhou M, Jia P and Zhang J: Laxative effects of salecan on normal and two models of experimental constipated mice. BMC Gastroenterology 2013; 13: 52.

36. Us MR and Zin T: *In-vivo* study on diuretic and laxative therapeutic properties of hydro-alcoholic extract of lu hui (Lilliaceae) on experimental rodents (*Rattus norvegicus*). Asian Journal of Pharmaceutical and Clinical Research 2014; 7: 4.
37. Capasso F, Mascolo N, Autore G and Romano V: Laxatives and the production of autacoids by rat colon. J Pharm Pharmacol 1986; 38(8): 627-9.
38. Ganapaty S, Dash GK, Subburaju T and Suresh P: Diuretic, laxative and toxicity studies of *Cocculus hirsutus* aerial parts. Fitoterapia 2002; 73(1): 28-31.
39. Schiller LR, Ana SCA, Morawski SG and Fordtran JS: Mechanism of the anti-diarrheal effect of loperamide. Gastroenterology 1984; 86(6): 1475-80.
40. Shimotoyodome A, Meguro S, Hase T, Tokimitsu I and Sakata T: Decreased colonic mucus in rats with loperamide-induced constipation. Comp Biochem Physiol A Mol Integr Physiol 2000; 126(2): 203-12.
41. Wintola OA, Sunmonu TO and Afolayan AJ: The effect of aloe ferox mill. in the treatment of loperamide-induced constipation in wistar rats. BMC Gastroenter 2010; 10: 95.
42. Wintola OA, Sunmonu TO and Afolayan AJ: The effect of aloe ferox mill. in the treatment of loperamide-induced constipation in Wistar rats. BMC Gastroenterol 10: 952010.
43. Kakino M, Izuta H, Ito T, Tsuruma K, Araki Y, Shimazawa M, Oyama M, Iinuma M and Hara H: Agarwood induced laxative effects *via*. acetylcholine receptors on loperamide-induced constipation in mice. Biosci Biotechnol Biochem 2010; 74: 1550-55.
44. Zhu D, Chen S, Yao SK, Li YM and Chen SX: Establishment of a canine slow transit constipation model and evalution of defecation. Gastrointestinal Transit and Pathological Sections 2018; 6-12.
45. Kakino M, Tazawa S, Maruyama H, Tsuruma K, Shimazawa YAM and Hara H: Laxative effects of agarwood on low-fiber diet-induced constipation in rats, published 2010; 10: 68.
46. Ramkumar D and Rao SSC: Efficacy and safety of traditional medical therapies for chronic constipation: systematic review. Am J Gastroente 2005; 100(4): 936-71.
47. Janssen AJ and Jageneau AH: A new series of potent analgesics. J Pharm Pharmacol 1957; 9: 381-400.
48. Purdon RA and Bass P: Gastric and intestinal transit in rats measured by a radioactive test meal. Gastroenterology 1973; 64: 968-76.
49. Jung KY, Choo YK, Kim HM and Choi BK: Raddish extract stimulates motility of the intestine *via*. the muscarinic receptors. J Pharm Pharmac 2000; 52: 1031-36.
50. Summers RW, Kent TW and Osborne JW: Effect of drugs, ileal obstruction and irradiation on rat gastrointestinal propulsion. Gastroenterology 1970; 59: 731-39.
51. Miller MS, Galligan JJ and Burks TF: Accurate measurement of intestinal transit in the rat. J Pharmacol Methods 1981; 6: 211-7.
52. Porreca F and Burks TF: The spinal cord as a site of opioid effects on gastrointestinal transit in the mouse. Journal of Pharmacology and Experimental Therapeutics 1983; 227: 22-7.
53. Pohle T and Domschke W: Gastric function measurements in drug development. Br J Clin Pharmac 2003; 56: 156-64.
54. Matsuda H, Li Y, Yamahara J and Yoshikawa M: Inhibition of gastric emptying by triterpene saponin, momordin, in mice: roles of blood glucose, capsaicin-sensitive sensory nerves and central nervous system. J Pharmacol Exp Ther 1999; 289: 729-34.
55. Droppleman DA, Gregory RL and Alphin RS: A simplified method for assessing drug effects on gastric emptying in rats. J Pharmacol Metho 1980; 11(4): 227-30.
56. Vogel HG and Vogel WH: Activity on the gastrointestinal tract in: vogel HG, vogel WH, editors. Drug discovery and evaluation. Berlin Springer-Verlag 1997; 461-533.
57. Hamano N, Inada T, Iwata R, Asai T and Shingu K: The alpha 2 - adrenergic receptor antagonist yohimbine improves endotoxin-induced inhibition of gastrointestinal motility in mice. Br J Anaesth 2007; 98: 484-90.
58. Bickel M: Stimulation of colonic motility in dogs and rats by an enkephalin analogue pentapeptide. Life Sci 1983; 33(1): 469-72.
59. Maggi CA and Meli A: Eserine-induced hypertone of guinea pig distal colon *in-vivo*: a new pharmacological procedure for testing smooth muscle relaxants. J Pharmacol Methods 1984; 12: 91-96.
60. Leng-peschlow E: Acceleration of large intestine transit time in rats by sennosides and related compounds. J Pharm Pharmacol 1986; 38: 369-73.
61. Koslo RJ, Burks TF and Porreca F: Centrally administered bombesin affects gastrointestinal transit and colonic bead expulsion through supraspinal mechanisms. J Pharmacol Exp Ther 1986; 238: 62-67.
62. Wright JW, Healy TE, Balfour TW and Hardcastle JD: A method for long-term recording of intestinal echanical and electrical activity in the unrestrained rat. J Pharmacol Methods 1981; 6: 233-42.
63. Szurszewski JH: A migrating electric complex of canine small intestine. Am J Physiol 1969; 217: 1757-63.
64. Mann PC and Bollman R: A method for making a satisfactory fistula at any level of the gastrointestinal tract. Ana Surg 1931; 93: 795-97.
65. Tasaka K and Farrar JT: Intraluminal pressure of the small intestine of the unanaesthetized dog. Pflugers Arch 1976; 364: 35-44.
66. Goldenberg MM and Burns RH: Effectiveness of a unique antispasmodic 3, 4 - dihydro - 5 - phenoxybenzo (b) (1, 7) naphthyridin-1 (2H) -one eu-1086, *in-vivo* and *in-vitro*. Arch Int Pharmacodyn Ther 1973; 203: 55-66.
67. Thompson WG and Heaton KW: Functional bowel disorders in apparently healthy people. G 1980; 79: 283-8.
68. Méité S, Bahi C, Yéo D, Datté JY, Djaman JA and N'guessan DJ: Laxative activities of *Mareya micrantha* (Benth.) müll arg. (Euphorbiaceae) leaf aqueous extract in rats. BMC Complement Altern Med 10: 72010.
69. Kim J, Go J, Lee H, Hong J and Hwang D: Spicatoside an in red *Liriope platyphylla* displays a laxative effect in a constipation rat model via regulating mAChRs and ER stress signalling. International Journal of Molecular Medicine 2018; 3960.

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