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Original Article

INFLUENCE OF METOCLOPRAMIDE AND 6-GINGEROL ON GASTRIC EMPTYING AND METABOLIC PARAMETERS IN A RAT MODEL OF DIABETIC GASTROPARESIS

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ABSTRACT

Diabetic gastroparesis is a neuromuscular condition decelerating gastric motility and gastric emptying in diabetic patients, and it is a condition that is linked to diabetic peripheral neuropathy. Metoclopramide is the only food and drug administration-approved prokinetic agent that treats delayed gastric emptying in diabetic gastroparesis, but it has negative side effects which have made clinicians mention pausing, taking it after four weeks. Zingiber officinale, or Ginger, is a spice that has been traditionally used like a prokinetic agent. 6-gingerol as the main bioactive compound of ginger could have this prokinetic potential of gingerol. Studies investigated the ability of 6 gingerol to improve gastric emptying in diabetic gastroparesis rats, in comparison with metoclopramide. Streptozotocin (40 mg/kg, intraperitoneal injection) injected in male rats to induce diabetes, then fed high-fat high-sugar chow for four weeks to persuade gastroparesis in them. After three weeks of streptozotocin injection, the sample rats were divided into four groups: diabetic gastroparesis, diabetic gastroparesis rats injected with metoclopramide, diabetic gastroparesis rats gavaged with 6-gingerol, and finally a normal control group. Fasting blood glucose, gastric emptying, body weight and relative organ weight, food and water intake, some biochemical parameters, and glutathione peroxidase level by ELISA kit were assessed in this experiment. Diabetic gastroparesis disrupted all of parameters. Metoclopramide and 6-gingerol had improved fasting blood glucose, gastric emptying, food intake, low-density lipoprotein, total cholesterol, and glutathione peroxidase level. The 6-gingerol specifically improved kidney function parameters. Our study concluded that the 6-gingerol might be taken as an alternative to metoclopramide, but further studies should be conducted to determine its mechanism and confirm its clinical usage and applicability.

Keywords: Diabetic Gastroparesis, Metoclopramide, 6-Gingerol, Gastric Emptying, Streptozotocin.

1. INTRODUCTION

The prevalence of diabetes mellitus (DM) is on the rise alongside the population. By 2045, it is anticipated that almost 783.2 million people globally will have diabetes, representing an almost 46% rise from the current total of 536.6 million (Khan *et al*., 2024). Diabetes mellitus is associated with neuronal tissue injury in various regions of the central nervous system (CNS) and peripheral nervous system (PNS), directing to a prevalent, uncomfortable complication known as diabetic peripheral neuropathy (DPN) (Niknia *et al*., 2019). Diabetic Gastroparesis (DGp), initially defined by Kassander in 1958 (Camilleri *et al*., 2022), is a persistent neuromuscular condition affecting the upper gastrointestinal system (Camilleri *et al*., 2018). Diabetic gastroparesis is linked to peripheral neuropathy (PN), autonomic dysfunction, and vagal dysfunction (Gaddipati *et al*., 2006). It is defined as a prevalent and preventable complication of uncontrolled DM that results in impaired gastric motility and delayed gastric emptying (GE) without mechanical obstruction, significantly impacting patients' quality of life (Camilleri *et al*., 2018; Uppaluri *et al*., 2024), and leading to nutritional depletion, whether related to micronutrients or macronutrients (Abell *et al*., 2003).

Diabetic gastroparesis impacts metabolic and biochemical parameters, including blood glucose, body weight, and glutathione peroxidase (GPx). Diabetic gastroparetics had prolonged postprandial hyperglycemic profile as compared to non-gastroparetic diabetics (Krishnasamy & Abell, 2018). On the other hand, DGp patients showed reduction in their body weight due to improper digestion and nutrient deficiency (Amjad *et al*., 2021). Hyperglycemia is believed to lead to oxidative stress, which is an important mechanism for many complications of diabetes, including DGp and results in cell dysfunction and tissue diseases. Therefore, anti-oxidation modulators may be a sensible choice for DGp (Hosseini & Abdollahi, 2013). The optimum control of DGp can be difficult to achieve due to the paucity of treatment options (Pasricha *et al*., 2015). The management of DGp involves lifestyle modifications, such as the consumption of small, frequent meals, the regulation of glycemic levels, and the avoidance of high-fat high-sugar (HFHS) diets (Horowitz *et al*., 2002).

Prokinetic agents are medications that enhance and regulate the contractions of the gastrointestinal muscles (Acosta & Camilleri, 2015). Metoclopramide (MCP) ($C_{14}H_{22}ClN_3O_2$) belongs to the prokinetic agents (Giacosa *et al*., 2015) and is the sole medicine licensed by the FDA for the treatment of DGp. Metoclopramide has been

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approved by the FDA for the treatment of acute and recurrent DGp for a duration of 4 to 12 weeks. Metoclopramide enhances gastric motility by targeting dopamine D_2 and 5-HT4 receptors in the gastrointestinal wall (Malone *et al*., 1991; Pawlikowski *et al*., 1992). M medication is recognized for inducing both acute and chronic CNS side effects. Prolonged treatment may induce depression or anxiety. Infrequent instances of tardive dyskinesia have been documented with prolonged treatment (Parkman *et al*., 2012). The dose of 5 mg/kg lies within the range of doses pharmacologically administered to rodent models to cause significant prokinetic effects, without causing acute toxicity. Experiments of gastric emptying in rats have shown that MCP doses of 1-10 mg/kg give dose-dependent increase of gastric transit with the highest effectiveness of MCP being seen at 5-7.5 mg/kg (Goineau *et al*., 2015; Zuccato *et al*., 1992).

Ginger (Zingiber officinale) is a spice, and its chemical components are recognized to provide beneficial health effects, namely as antioxidants and anti-inflammatory agents with the potential to operate as immunomodulators (Ayustaningwarno *et al*., 2024). Ginger has been traditionally used as a prokinetic substance employed to alleviate nausea, vomiting, and indigestion (Giacosa *et al*., 2015). Ginger's antioxidant mechanism is linked to nuclear factor erythroid 2–related factor 2 (Nrf_2) signaling pathway activation. Its anti-inflammatory mechanism is linked to serine/threonine kinase (Akt) inhibition and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-KB) activation, triggering the release of anti-inflammatory cytokines while reducing proinflammatory cytokines (Ayustaningwarno *et al*., 2024). 6-gingerol ($C_{17}H_{26}O_4$) is the active component of ginger, which is partially responsible for the strong pungent taste of ginger (Özdemir *et al*., 2023). This compound has been correlated with many bioactivities of ginger, and it is present in much higher amounts in fresh ginger roots compared to the dried roots because drying converts it into 6-shogaol through a water elimination (Mahomoodally *et al*., 2021). It is also essential for the preservation of blood glucose homeostasis by modulating insulin secretion and promoting glucose clearance in insulin-responsive peripheral tissues (Rani *et al*., 2011). The 2 mg/kg dose is consistent with the preclinical dose-dependent evidence of pharmacologic dose effects on gastric function with the low-to-moderate concentrations (Adetuyi & Farombi, 2021). 6-gingerol has been demonstrated to reduce nausea and intestinal inflammation induced by cisplatin in the range of sub-5 mg/kg dosage via the 5-HT3R/Ca2+/CaMKII/ERK1/2 and inhibition of NF-kB activation (Mo *et al*., 2023). Furthermore, the used dosage 2mg/kg has been shown to reduce neuroinflammation and redox balance without toxicity (Zhang *et al*., 2017).

The prokinetic effects of 6-gingerol and MCP have been investigated separately, but little is known about how 6-gingerol, the active ingredient in ginger, may affect GE in DGp. Investigating the therapeutic effects of 6-gingerol and MCP on GE, as well as metabolic and biochemical parameters, in DGp rats is the main goal of this study. Additionally, since no previous study has used this particular model duration, the four-week induction of DGp in this study presents a novel approach. This study intends to close the existing knowledge gap and evaluate 6-gingerol's potential as a therapeutic agent for reducing metabolic and gastrointestinal dysfunctions in DGp.

2. MATERIALS AND METHODS

Animals:

Forty healthy male Sprague Dawley (SD) albino rats were obtained from the Experimental Animal House of Soran University. Weighing between 250 and 300 g, these rats were aged between 6 to 8 weeks and underwent a one-week adaptation period. The Academy and Ethics Committee of Soran University approved the experiments in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals and Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines. The rats were given ad libitum tap water and a normal rodent chow of 20% maize, 20% rice, 12% bone meal, 7.5% soy oil, 20% gluten, 0.35% salt, 3.5% mineral mixture, 1.65% vitamin mixture and 1.5% starch for one week before the experiment commenced (Matias *et al*., 2018). The experiments were conducted in animal quarters that were environmentally controlled and maintained at a temperature of 23 $\pm$ 2 °C, with a 12-hour light/dark cycle and a humidity of 35–60% (Mahmud *et al*., 2025).

Experimental Design:

Initial construct validity was ensured by the induction method which was able to recreate the enduring hyperglycemia observed in DGp human patients. Face validity was determined by recording a major difference in the delay of GE between diseased and healthy controls. This is necessary to state that the model reflects the major clinical manifestation of the disease. Lastly, the model showed predictive validity by responding to conventional prokinetic treatment, which proves the model to be a reliable platform of assessing human therapeutic outcomes. In one-week post-adaptive feeding, ten rats were randomly designated as normal control (NC) and treated routinely. Additional rats were utilized to create a model of DGp. The model rats had a 12-hour fasting period. They received an intraperitoneal injection (I.P.) of 40 mg/kg STZ Santa Cruz Biotechnology, Heidelberg, Germany), freshly dissolved in a 10 mM citrate buffer solution (pH 4.5) to induce diabetes. The rats in the NC group received an identical volume of citrate buffer. Seven days after injection, blood was obtained from the tail veins of all rats, and their fasting blood glucose (FBG) levels were assessed using a GlucoNavii blood glucose meter and test strips (SD Biosensor, Suwon-si, Gyeonggi-do, Republic of Korea). If the 7-day FBG level exceeded 300 mg/dL, the diabetes model was considered effective (Furman, 2021). To induce DGp, all rats, excluding the NC group, were administered an HFHS chow comprising 70% standard food, 10% sucrose, and 20% lard for a duration of four weeks (Lu *et al*., 2018). Fasting blood glucose of rats was assessed again on the last day of the experiment, and the daily food and water consumption of all rats was documented throughout the trial. At the end of 3rd week of diabetes induction, animals were divided into three groups (n=10), i.e. DGp rats (DGp), Metoclopramide injected DGp rats (DGp + MCP) and 6-gingerol orally administrated DGp rats (DGp + 6G). Metoclopramide was injected by dissolving it in normal saline (5 mg/kg BW/day, I.P.) for 7 days (Ahmad Khan *et al*., 2004; Silva *et al*., 2011). 6-gingerol was administered orally in corn oil (2 mg/kg BW /day) for 7 days, and it was purchased from ChemFaces, Wuhan, China (Chatturong *et al*., 2018).

Gastric Emptying:

Five animals per group were utilized for the GE examination. At the completion of the fourth week, the rats were anesthetized using Ketamine hydrochloride (50 mg/Kg, I.P.) and Xylazine (10 mg/Kg, I.P.). The rats were subjected to an 18-hour fast and permitted access to water. The GE of liquids was evaluated by administering a 1.5 ml solution of 0.05% phenol red (Sigma Chemicals, St. Louis, MO, USA) in a 5% glucose solution via gavage, 20 minutes before euthanasia. The animals were euthanized, the abdomen was incised, the pylorus and lower esophagus were ligated, and the stomach was excised in its whole form. The gastric contents were mixed with 8 mL of 1N sodium hydroxide (NaOH). Following centrifugation at 2,500g for 20 minutes, 1 ml of the supernatant was combined with 9 ml of 1N NaOH, and the absorbance of the sample was measured at a wavelength of 560 nm using a spectrophotometer. Phenol red obtained from animals euthanized immediately following the delivery of the test meal served as a baseline control (Sebai *et al*., 2019). The percentage of GE was determined using the following formula:

$$GErate(\%) = \frac{phenolredamountoftestsample}{phenolredamountofbaselinecontrol} \times 100 \quad (1)$$

Body Weight and Relative Organ Weight:

On the first day of the experiment, the rats were weighed to determine their initial body weight (IBW), followed by weekly assessments of body weight (BW) to monitor changes. Ultimately, at the end of the study, the rats were weighed again to ascertain their final body weight (FBW) with an accuracy of 0.1 g using an analytical balance (ADB 100-4, KERN, Germany) (Mahmud *et al*., 2021). Following

an 18-hour fast, the rats were euthanized, the abdomen was incised, and the spleen, both lungs, stomach, heart, pancreas, liver, and both kidneys were removed, devoid of adipose tissue, and their wet organ weights were recorded (Sharma *et al*., 2021). The relative organ weight (ROW), expressed as a percentage of fasting BW at the day of sacrificing, was calculated using this formula:

$$ROW(\%) = \frac{Wetorganweight(g)}{FastingBW(g)} \times 100 \qquad (2)$$

Collection of Blood Samples and Biochemical Assessment:

At the end of the experiment and after anesthetizing of rats, blood samples were collected via cardiac puncture into chilled, ethylenediaminetetraacetic acid (EDTA)-free gel tubes. The samples were centrifuged at 3000 rpm for 15 minutes, and the obtained serum was stored at -85°C in chest freezer (VF 20085, LAUDA, Dr. R. Wobser GmbH & Co. KG, Germany) for biochemical assessment (Khdhr & Mahmud, 2023). The serum levels of kidney function tests (uric acid (UA), creatinine (Cr), blood urea, and blood urea nitrogen), liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP)), and lipid profile (T.Chol, high-density lipoprotein (HDL), LPL) were assessed by a BS-230 chemistry analyzer (Mindray, Shenzhen, China), using BS-series reagent kits (Mindray, Shenzhen, China) (Qader *et al*., 2021).

Glutathione Peroxidase Quantification and Enzyme Linked Immuno-Assay (ELISA):

Serum was utilized for ELISA detection of GPx enzyme, following the manufacturer's instructions for the GPx ELISA Kit (Sunlong Biotech, Hangzhou, Zhejiang, China). Serum samples were aliquoted into the wells of a 96-well plate coated with an antibody specific to GPx enzyme. The wells were washed, and a biotinylated anti-GPx antibody was placed in it. Following the removal of unbound biotinylated antibody, horseradish peroxidase (HRP)-conjugated antibody specific for GPx was added to the wells. The wells were rewashed, and a 3,3′,5,5′-Tetramethylbenzidine (TMB) substrate solution was introduced, resulting in color development proportional to the quantity of bound marker. The Stop Solution altered the color from blue to yellow, with the color intensity quantified at 450 nm via an ELISA microplate reader (Model BK-EL10C; BIOBASE, Jinan, Shandong, China) (Smail *et al*., 2025).

Statistical Analysis:

Using the GraphPad Prism 10 program (Version 10) (GraphPad Software, USA), statistical analyses were conducted. Before proceeding any further, the data distribution was tested and confirmed as being normal by the Shapiro-Wilk test. Unpaired Student's t-test for comparisons between two experimental groups, or one-way ANOVA followed by Tukey post-test for comparisons, involving more than two groups, was used in the analysis. Values were deemed significantly different when $p<0.05$. In all figures, the symbols (*, **, ***, and ****) represent that mean differences are significant at the 0.05, 0.01, 0.001, and 0.0001 levels, respectively. Results are presented as mean values accompanied with standard deviation (SD) (Smail *et al*., 2025).

3. RESULTS

Fasting Blood Glucose:

Streptozotocin significantly increased fasting blood glucose FBG (386.2 ± 46.47 mg/dL, $p < 0.0001$) after 7 days in DGp group as compared to NC group (84.55 ± 30.58) (Figure 1A). At the end of experiment, the FBG of NC group was (91.8 ± 17.04 mg/dL) which was significantly ($p<0.0001$) increased in DGp group to (677 ± 79.06 mg/dL). Following administration of MCP and 6G, MCP significantly ($p<0.001$) decreased (548.3± 69.69 mg/dL) FBG of DGp+MCP rats but 6G non significantly decreased (604.3 ± 73.54 mg/dL) FBG in comparison with DGp group (Figure 1B).

Gastric Emptying:

At the end, the data obtained showed that after 18-hour fast, the GE in DGp group significantly reduced (24.40 ± 7.67%, $p<0.0001$) as compared to NC group (73.55 ± 2.86%). In DGp rats, the administration of MCP and 6G effectively ($p<0.0001$ and $p < 0.001$) improved GE rates to (60.95 ± 1.21%) and (45.26 ± 3.72%), respectively (Figure 2).

Food and Water Intake:

At first, second, and third-weeks the food intake in DGp rats was markedly ($p<0.0001$) increased to (2240.26 ± 125.6 gr/week), (2264.8 ± 84.16 gr/week) and (2359 ± 112.11 gr/week) respectively as compared to NC rats' group (1845.38 ± 51.48 gr/week) (2030.8 ± 38.51 gr/week) and (2100.5 ± 87.09 gr/week) respectively (Figure 3A). From the fourth week of the study the food intake in DGp group was strongly increased (2651 ± 152.2 gr/week, $p<0.0001$) in comparison to NC group (2109 ± 95.66 gr/week), but the administration of MCP and 6G significantly ($p<0.0001$) increased the rate of food intake (2223 ± 82.23 gr/week) and (2326 ± 127.6 gr/week) respectively toward the NC group value in contrast to food intake in DGp group (Figure 3 B).

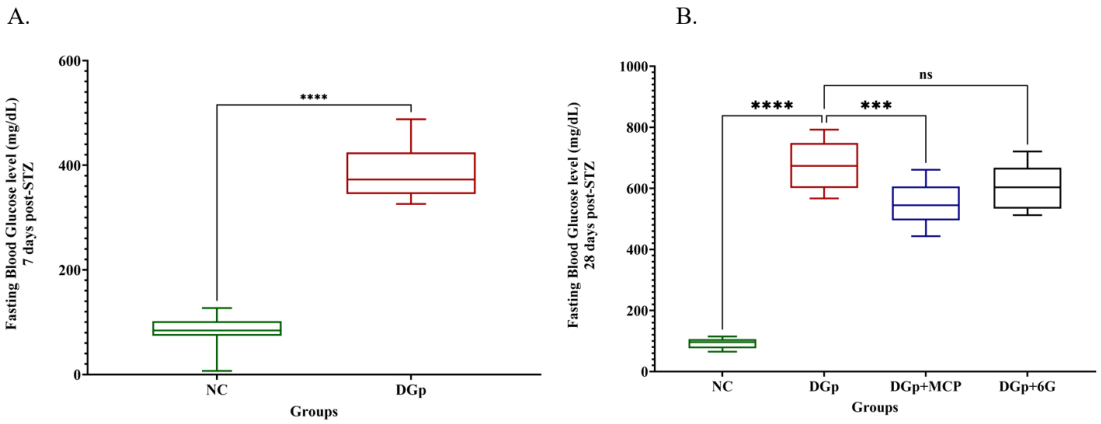

Figure 1: Changes in fasting blood glucose (FBG) levels in normal control rats (NC), diabetic gastroparesis rats (DGp), diabetic gastroparesis rats treated with metoclopramide (DGp+MCP), and diabetic gastroparesis rats treated with 6-gingerol (DGp+6G), measured on the seventh (A), and 28th day (B) of the experiment. Data are presented as mean ± SD.

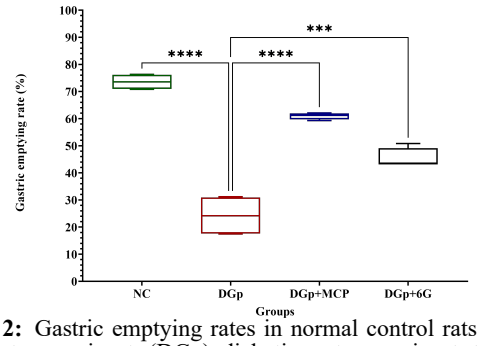

Figure 2: Gastric emptying rates in normal control rats (NC), diabetic gastroparesis rats (DGp), diabetic gastroparesis rats treated with metoclopramide (DGp+MCP), and diabetic gastroparesis rats treated with 6-gingerol (DGp+6G). Gastric emptying was assessed using the phenol red meal method. Data are presented as mean ± SD.

Food and Water Intake:

At first, second, and third-weeks the food intake in DGp rats was markedly ($p<0.0001$) increased to (2240.26 ± 125.6 gr/week), (2264.8 ± 84.16 gr/week) and (2359 ± 112.11 gr/week) respectively as compared to NC rats' group (1845.38 ± 51.48 gr/week) (2030.8 ± 38.51 gr/week) and (2100.5 ± 87.09 gr/week) respectively (Figure 3A). From the fourth week of the study the food intake in DGp group was strongly increased (2651 ± 152.2 gr/week, $p<0.0001$) in comparison to NC group (2109 ± 95.66 gr/week), but the administration of MCP and 6G significantly ($p<0.0001$) increased the rate of food intake (2223 ± 82.23 gr/week) and (2326 ± 127.6 gr/week) respectively toward the NC group value in contrast to food intake in DGp group (Figure 3 B).

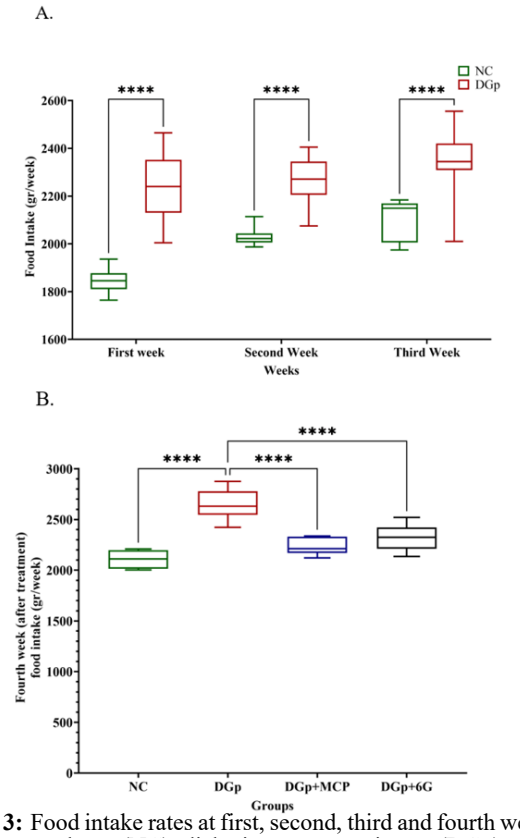

Figure 3: Food intake rates at first, second, third and fourth weeks, in normal control rats (NC), diabetic gastroparesis rats (DGp), diabetic gastroparesis rats treated with metoclopramide (DGp+MCP), and diabetic gastroparesis rats treated with 6-gingerol (DGp+6G). Data are presented as mean ± SD.

Similarly to food intake, the water intake in first, second, and third weeks was significantly ($p<0.0001$) elevated (10381.06 ± 1218.88 mL/week), (11059.11 ± 855.14 mL/week) and (10551.41 ± 1234.68 mL/week) respectively, following STZ injection in DGp compared to NC group (3128.22 ± 614.93 mL/week) (3018.75 ± 538.89 mL/week) and (2905 ± 172.25 mL/week) respectively. At the end of the experiment, the water intake in DGp rats was significantly raised (11526.25 ± 768.70 mL/week, $p<0.0001$), as compared to NC rats' group (3173 ± 264 mL/week). Neither MCP (11110 ± 823.02 mL/week) nor 6G (10608 ± 991.50 mL/week) significantly affected water intake in DGp rats, in contrast to DGp (Figure 4 A, B).

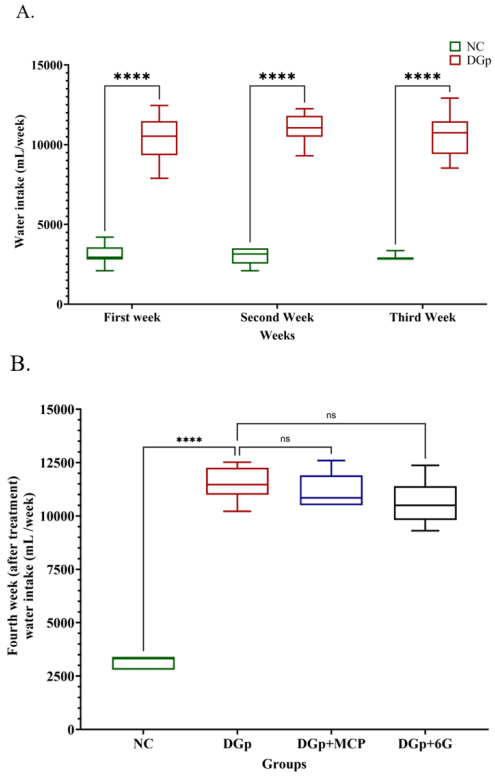

Figure 4: (A&B). Water intake rates at first, second, third and fourth weeks, in normal control rats (NC), diabetic gastroparesis rats (DGp), diabetic gastroparesis rats treated with metoclopramide (DGp+MCP), and diabetic gastroparesis rats treated with 6-gingerol (DGp+6G). Data are presented as mean ± SD.

Body Weight and Relative Organ Weight:

Streptozotocin injection significantly ($p<0.0001$) decreased body weight (244.7 ± 13.29 gr), (236.16 ± 20.37 gr), and (224.76 ± 18.23 gr) in accordance to NC group (301.1 ± 21.08 gr), (313.9 ± 20.05 gr), and (330.9 ± 20.78 gr) in first, second, and third weeks, respectively. Moreover, after 28 days in DGp group body weight was significantly decreased (219.1 ± 22.81 gr, $p<0.0001$) relatively to NC group (347.3 ± 20.83 gr). Metoclopramide treatment did not make any change in DGp rats and 6G non-significantly induced farther reduction body weight as compared to DGp group (Figure 5 A, B).

Weight gain/loss between IBW and FBW of groups were NC (61.4 ± 14.38 gr), DGp (-94.5 ± 25.74 gr), DGp+MCP (-79.5 ± 17.14 gr), and DGp+6G (-99.2 ± 34.97 gr). Clearly DGp has significant ($p<0.0001$) reduction in weight according to NC group, also a non-significant effect is seen in DGp+MCP and DGp+6G groups weight difference in comparison with DGp group (Figure 6).

There was not a significant difference in ROW of kidneys, heart, lungs, and pancreas among the experimental groups. The ROW of liver, and stomach increased significantly ($p<0.0001$) and ($p< 0.001$) respectively in DGp group as compared to NC group. The spleen ROW showed a significant ($p< 0.05$) decline in DGp rats as compared to NC group rats. the MCP and 6G couldn't make any significant changes in any ROW as compared to DGp rats (Table 1).

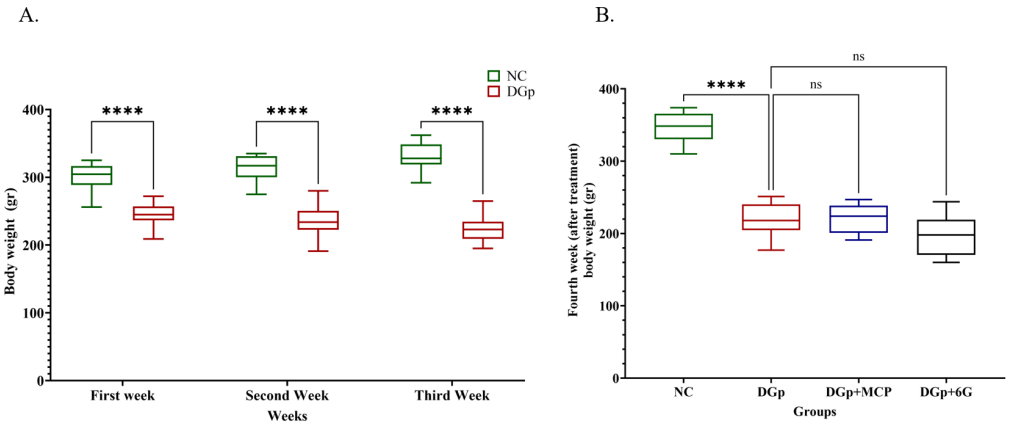

Figure 5: (A&B). Water intake rates at first, second, third and fourth weeks, in normal control rats (NC), diabetic gastroparesis rats (DGp), diabetic gastroparesis rats treated with metoclopramide (DGp+MCP), and diabetic gastroparesis rats treated with 6-gingerol (DGp+6G). Data are presented as mean ± SD.

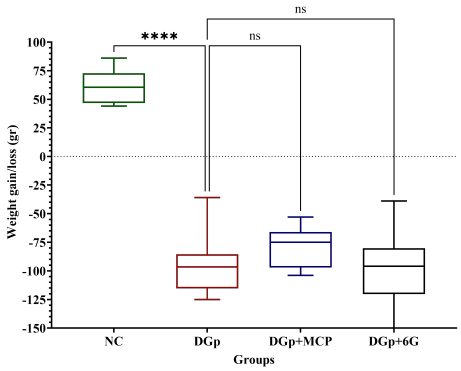

Figure 6: Body weight gain/ loss in normal control rats (NC), diabetic gastroparesis rats (DGp), diabetic gastroparesis rats treated with metoclopramide (DGp+MCP), and diabetic gastroparesis rats treated with 6-gingerol (DGp+6G). Data are presented as mean ± SD.

Kidney Function Parameters:

In diabetic gastroparesis group rats kidney function parameters Cr, UA, BUN and BU were significantly (P<0.0001) increased (0.65 ± 0.05 mg/dL), (6.98 ± 1.13 mg/dL), (65.70 ± 12.27 mg/dL), and (120.8 ± 12.66 mg/dL) respectively, relatively to their values in NC group (0.46 ± 0.02 mg/dL), (2.65 ± 0.57 mg/dL), (21.34 ± 2.46 mg/dL), and (45.64 ± 5.19 mg/dL) respectively. Metoclopramide didn't make any significantly effect on Cr, UA, BUN and BU in STZ induced DGp rats in accordance to DGp rats, but 6G had a significant (p<0.0001) therapeutic effect on Cr (0.45 ± 0.06 mg/dL), UA (4.28 ± 1.22 mg/dL), BUN (37.72 ± 10.49 mg/dL), and BU (85.86 ± 9.73 mg/dL), respectively which declined their values toward the NC group value (Figure 7).

Liver Function Parameters:

Statistical analysis showed a significant (p<0.0001) elevation in serum liver enzymes, AST (313.5 ± 54.4 U/L), ALT (175.76 ± 30.82 U/L), and ALP (1247.79 ± 282.94 U/L) DGp group rats, as compared to rats in NC group (175.37 ± 10.22 U/L, 52.75 ± 7.32 U/L, and 423.16 ± 61 U/L), respectively. In DGp rats MCP non-significantly decreased AST (258.22 ± 26.06 U/L) and ALP (1083.07 ± 299.27 U/L), but significantly ((p<0.05) decreased ALT (140.08 ± 25.68 U/L), also 6G non-significantly diminished AST (270.22 ± 66.74 U/L), ALT (157.1 ± 23.69 U/L), and ALP (1227.29 ± 221.17 U/L) relatively to DGp rats group (Figure 8).

Lipid profile parameters:

In DGp rats, the T. Chol and LDL values significantly (p<0.0001) increased (107.79 ± 9.72 mmol/L) and (37.45 ± 6.03 mmol/L) respectively as compared to their values in control rats (85.86 ± 5.93 mmol/L) and (16.37 ± 3.16 mmol/L) respectively. In contrast, the HDL concentration significantly decreased (12.68 ± 6.93 mmol/L, p<0.0001) when compared to control rats group (33.56 ± 4.34 mmol/L). Administration of MCP to STZ rats induced DGp showed a significant therapeutic effect by decreasing T. Chol (88.22 ± 5.86 mmol/L, p<0.0001) and LDL (25.63 ± 6.63 mmol/L, p<0.001), and elevation of HDL (21.81 ± 5 mmol/L, p<0.01) in direction of control rats value. Furthermore, 6G given similarly to MCP significantly decreased T.Chol (26.21 ± 3.2 mmol/L, p<0.05) and LDL (26.21 ± 3.22 mmol/L, p<0.001) in DGp rats as compared to DGp rats and had non-significant positive effects on HDL concentration (Figure 9).

Lipid profile parameters:

Glutathione peroxidase level in DGp group was (88.72 ± 7.918 IU/mL), which was significantly (p<0.001) lower than NC group (104.1 ± 2.378 IU/mL). Metoclopramide and 6G both significantly increased GPx level into (97.79 ± 4.191 IU/mL, p<0.05) and (105.3 ± 7.913 IU/mL, p<0.001) (Figure 10).

Table 1: Relative organ weights (%) of kidneys, heart, liver, spleen, lungs, stomach, and pancreas in normal control rats (NC), diabetic gastroparesis rats (DGp), diabetic gastroparesis rats treated with metoclopramide (DGp+MCP), and diabetic gastroparesis rats treated with 6-gingerol (DGp+6G). Data are presented as mean ± SD.

Organs	***Groups (Relative organ weight %)***			
	NC	DGp	DGp+MCP	DGP+6G
Kidneys	0.39 ± 0.02^{ns}	0.57 ± 0.09	0.57 ± 0.04^{ns}	0.64 ± 0.07^{ns}
Heart	0.34 ± 0.06^{ns}	0.37 ± 0.06	0.36 ± 0.03^{ns}	0.39 ± 0.04^{ns}
Liver	$2.81 \pm 0.11^{****}$	4.46 ± 0.25	4.23 ± 0.18^{ns}	4.47 ± 0.75^{ns}
Spleen	$0.47 \pm 0.08^{*}$	0.22 ± 0.07	0.34 ± 0.10^{ns}	0.33 ± 0.07^{ns}
Lungs	0.48 ± 0.05^{ns}	0.60 ± 0.06	0.62 ± 0.09^{ns}	0.65 ± 0.08^{ns}
Stomach	$0.57 \pm 0.03^{***}$	0.96 ± 0.10	0.99 ± 0.12^{ns}	0.93 ± 0.09^{ns}
Pancreas	0.54 ± 0.08^{ns}	0.52 ± 0.05	0.56 ± 0.05^{ns}	0.56 ± 0.06^{ns}

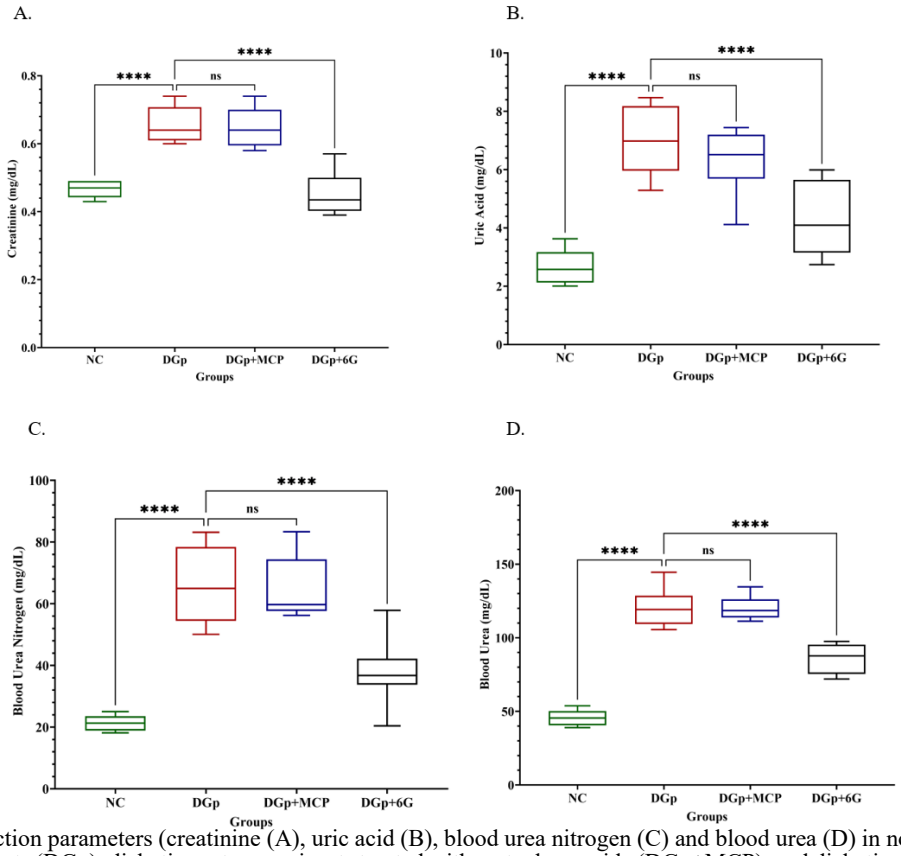

Figure 7: Kidney function parameters (creatinine (A), uric acid (B), blood urea nitrogen (C) and blood urea (D) in normal control rats (NC), diabetic gastroparesis rats (DGp), diabetic gastroparesis rats treated with metoclopramide (DGp+MCP), and diabetic gastroparesis rats treated with 6-gingerol (DGp+6G). Data are presented as mean ± SD.

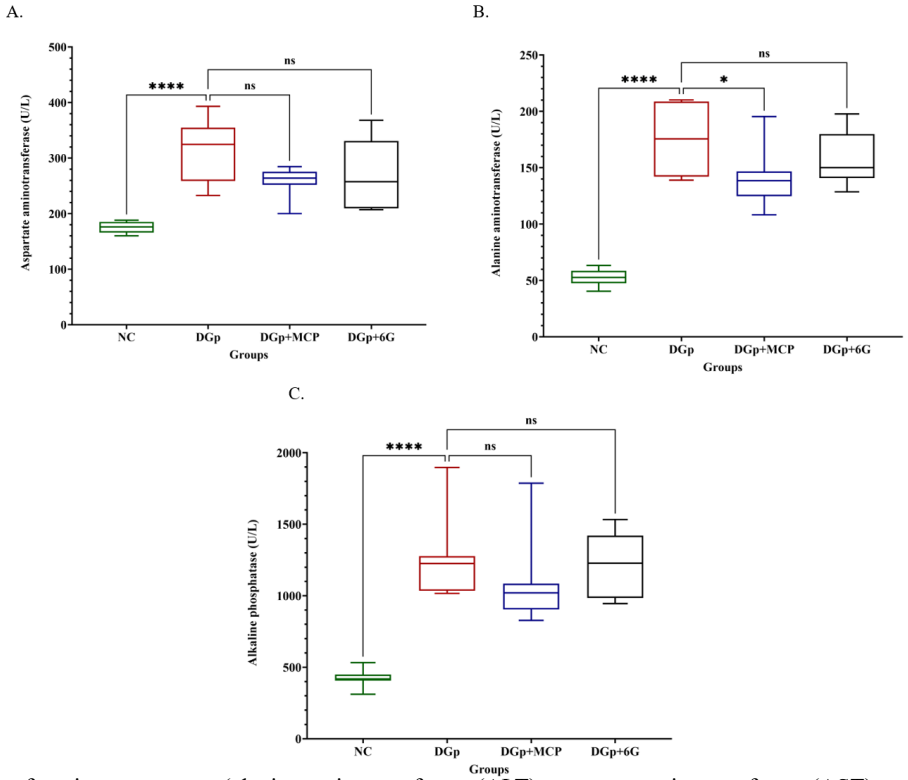

Figure 8: (A&B). Liver function parameters (alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP)) in normal control rats (NC), diabetic gastroparesis rats (DGp), diabetic gastroparesis rats treated with metoclopramide (DGp+MCP), and diabetic gastroparesis rats treated with 6-gingerol (DGp+6G). Data are presented as mean ± SD.

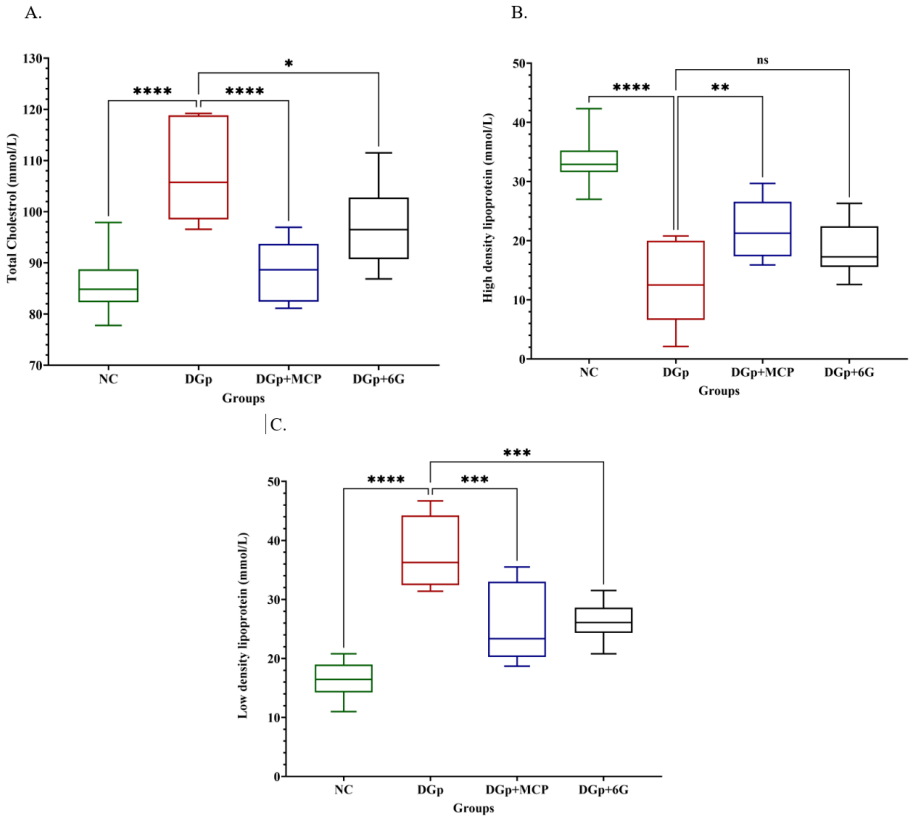

Figure 9: Lipid profile parameters (Total cholesterol (T.Chol) (A), high-density lipoprotein (HDL) (B), low-density lipoprotein (LPL) (C)) in normal control rats (NC), diabetic gastroparesis rats (DGp), diabetic gastroparesis rats treated with metoclopramide (DGp+MCP), and diabetic gastroparesis rats treated with 6-gingerol (DGp+6G). Data are presented as mean ± SD.

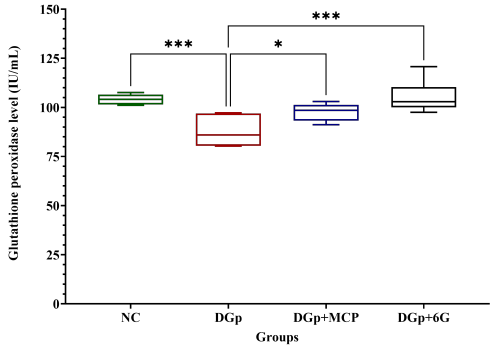

Figure 10: Lipid profile parameters (Total cholesterol (T.Chol) (A), high-density lipoprotein (HDL) (B), low-density lipoprotein (LPL) (C)) in normal control rats (NC), diabetic gastroparesis rats (DGp), diabetic gastroparesis rats treated with metoclopramide (DGp+MCP), and diabetic gastroparesis rats treated with 6-gingerol (DGp+6G). Data are presented as mean ± SD.

4. DISCUSSION

The present study has investigated that the MCP and 6G play an important role in improvement of GE and metabolic parameters in STZ- induced DGp rats. Taking the tradition of using Ginger for indigestion and 6G being its main bioactive compound, this study aimed to evaluate the ability of 6G in improving GE, and if it could alternate to MCP which is the only FDA approved drug for delayed GE and solve the problem of paucity and side effects of MCP. In addition, HFHS diet was used as a thrust to make the DGp model in 4 weeks, because other previous studies made the model in 6 weeks (Zhang *et al*., 2017), 7 weeks (H. Li *et al*., 2021), and 8 weeks (Song *et al*., 2024), but not less than 6 weeks.

This study demonstrated that 7 days post-STZ injection, FBG level in DGp rats significantly increased, and then gradually increased to the end of experiments. Furthermore, MCP and 6G both significantly decreased FBG in DGp rats compared to the DGp control group, but MCP exerted more significant effect on FBG than 6G. The observed dramatic rise in FBG level in DGp rats and then a continued elevation level of the glucose level all through the experiment is in accordance with the known models of chemically induced diabetes (El-Bassossy *et al*., 2016; Farida *et al*., 2020; Mehrabadi *et al*., 2021). Streptozotocin targets the pancreatic β-cells selectively resulting in deficiency of insulin and consequent hyperglycemia. This persistent and acute increase in FBG validates that there is induction of a diabetic state in the DGp rat model making it applicable in testing possible hypoglycemic agents (Deeds *et al*., 2011). The prolonged hyperglycemia indicates the chronicity of uncontrolled diabetes and its severe effect on glucose homeostasis (He *et al*., 2024). The reason of decreased FBG in DGp+MCP group that was observed in the study may be an indirect effect of the known effects of MCP on gastrointestinal functioning (Kuo *et al*., 2010). It is possible that MCP could change the kinetics of nutrient absorption by controlling gastrointestinal motility and thus resulting in a more regulated glucose release and consequently a lesser FBG. However, this remains speculative until some more detailed mechanistic studies are carried out. The role of gastrointestinal motility disorders in hepatic blood perfusion and metabolic function as a whole is becoming more and more appreciated, which points out to a complicated interaction between gut health and the metabolism (Tonghui *et al*., 2025). 6-gingerol has already shown to be antidiabetic such as it reduces hyperglycemia. STZ induced diabetic rats have been found to respond effectively to 6G treatment that inhibits FBG increase and enhances cardiac complications. This may be mediated by its antioxidant and anti-inflammatory effects, which may have the effect of alleviating the STZ-induced pancreatic injury and enhance insulin sensitivity (Gunawan *et al*., 2023). Natural compounds and extracts have also been reported to decrease

FBG in diabetic models induced by STZ including Pithecellobium dules plant extracts, Abrus precatorius leaf extract, Nigella sativa extract, and purple sweet potato flavonoids (Alimohammadi *et al*., 2013; Boye *et al*., 2020; Jiang *et al*., 2011; Upadhayay *et al*., 2018). Thus, MCP, that have a more marked effect on FBG than 6G, is indicative of either an undescribed direct metabolic pathway or an indirect effect which has not been studied in detail.

Gastric emptying in this study was shown to be significantly delayed following 4 weeks of STZ induction and abstaining the HFHS diet. This result describes successful establishment of DGp model. High-Fat high-Sugar diet played a crucial role in DGp model establishment in 4 weeks, which is a prominent achievement for this experiment. Metoclopramide and 6G reversed this reduction significantly in GE after 7 days of administration. However, MCP has better therapeutic potential effects on GE than 6G, which is the first study to show these results. Previous researches confirmed these results. The STZ combined with a HFHS diet used to induce a DGP model is in line with the existing methodological practices (H. Li *et al*., 2021; Niu *et al*., 2020). Grover *et al*. (2019) evidenced that after STZ induction, and resulting from FBG elevation, abnormality in vagal nerves signaling occurs which leads to disruption in GE function and delays it. GE is influenced by some factors including meal composition (liquid or solid), caloric content, and meal volume as well as fiber and fat content (Homko *et al*., 2015). However, a diet rich in sugars and fats such as HFHS used in this experiment also leads to metabolic dysregulation, which shortens gastrointestinal complications and GE development, insulin resistance and hyperglycemia, which are major risk factors of STZ induced diabetes, also are negatively affected by the diet (Zhang *et al*., 2017).

It has been proven that MCP is effective in enhancing the GE and relieving patients with diabetic gastroparesis of their symptoms like nausea, vomiting, fullness and early satiety (McCallum *et al*., 1983; Snape *et al*., 1982). Metoclopramide is also reported to increase the proportional cumulative area under the curve of paracetamol in measuring of liquid gastric emptying significantly in diabetic individuals after 20 minutes (McCallum *et al*., 1983). 6-gingerol is traditionally used as an antiemetic because of its antioxidant and anti-inflammatory properties. 6G acts by enhancing superoxide dismutase (SOD) and catalase (CAT) activity and reducing malondialdehyde (MDA) in gastrointestinal mucosa (Wulandari *et al*., 2024). Studies showed that antioxidants can salvage delayed GE in diabetic mice (Sampath *et al*., 2021). This antioxidant activity of 6G might be the reason for its capability in enhancing GE in the present investigations. As studied by Endo *et al*. (2020), antioxidant activities of cinnamaldehyde and curcumin had a positive effect on GE. Furthermore, 6G could improve GE because it is an agonist of ligand-gated transient receptor potential vanilloid ion channel 1 (TRPV1) (Andersen *et al*., 2023) which is involved in release of neuropeptides such as Substance P (SP) (İlhan *et al*., 2022), SP controls 5-HT4 (Gong *et al*., 2023; Xiao *et al*., 2023) and decreases in rats with DGp (Smiley *et al*., 2020). Metoclopramide had better therapeutic effects on GE than 6G, such effect may be explained by the direct prokinetic effect of MCP on gastrointestinal smooth muscle, as well as by its central antiemetic effect, which may lead to a more immediate and powerful improvement in GE than the potentially indirect or slower-acting action of 6-gingerol, which may involve the regulation of oxidative stress and inflammation (Lee and Kuo, 2010; Poli *et al*., 2022).

In the present investigation, food intake in DGp rats was significantly increased following STZ injection, both MCP and 6G refined food intake by significantly reducing it. The initial increase in food intake in STZ induced diabetic models is a long-standing phenomenon, commonly known as polyphagia, caused by hyperglycemia and cellular inefficiency in utilizing glucose, which causes a condition of perceived starvation despite high blood glucose levels (Shi *et al*., 2024). The observation of DGp is defined by slow GE, which normally results in such symptoms as early satiety, nausea, vomiting and bloating (Nawaz *et al*., 2024). Nevertheless, the metabolic disturbances associated with uncontrolled diabetes may counterintuitively result in the enhancement of appetite in spite of dysfunction of the GE that resulted from DGp. Bukowska (2022) described food intake increase in diabetes by the consequences of insulin deficiency produced from STZ-destruction of pancreatic islet β-cells which leads to reduced leptin production, also impairment of satiety control in hypothalamus because of lack of insulin signaling in PI3K and mTOR signaling cascade in adipose tissues and Neuropeptide Y (NPY) neurons. This is a complicated interaction in which the demand on the system level by the metabolism exceeds the local gastric pain in the initial phases of the disease model. The diet which was applied to achieve the DGP model, worsens the resistance to insulin and metabolic disturbances, leading to the overall diabetic appearance and resulting polyphagia (Shi *et al*., 2024). Research done by Alphin *et al*. (1972) found the anorexigenic effect of MCP, as they observed the reduced food intake of rats treated with MCP. Incompatible with the present investigation, a newly published article by Di Girolamo *et al*. (2025) showed that MCP has no effect on food intake. Metoclopramide, which facilitated GE by accelerating transfer of food from the stomach to the small intestine, probably prevents the gastric stasis of DGP, which otherwise would lead to abnormal feeding behaviors, and encourages more consistent satiety cues (McCallum *et al*., 1983), its ability to reduce food intake in this context suggests that improved GE and subsequent nutrient absorption may help regulate appetite and caloric consumption in DGp models. Gunawan *et al*. (2023) showed that food intake was decreased by 6G administration in metabolic syndrome rats and promoted weight loss. The positive effect of 6G on GE by the mitigation of oxidative stress may indirectly functions in improving appetite and food intake, also its antiemetic effect is also involved as it removes nausea that blocks the normal eating behavior (Sampath *et al*., 2021).

The present study investigated that STZ injection induced elevation of water intake, moreover MCP and 6G did not have influence on water intake. The elevation in water intake is likely due to osmotic diuresis caused by glucosuria (DeFronzo *et al*., 2012; Jung *et al*., 2024; Masuda *et al*., 2020). Glucosuria stimulates compensatory water intake (Masuda *et al*., 2020). Recently, it was proved that prokinetics do not have effect on water intake (Di Girolamo *et al*., 2025). Prokinetics do not have interactions with the central processes that regulate water intake, including the hypothalamus, the kidneys, and hormonal signals such as angiotensin II and antidiuretic hormone (ADH), which described by (Di Girolamo *et al*., 2025; Sukalingam *et al*., 2013).

The data of this study showed decrease of body weight in DGp, DGp+MCP, and DGp+6G groups regarding to control group, in addition MCP or 6G did not influence body weight in STZ-induced diabetic rats. Hammersjö *et al*. (2016) showed the same results of body weight reduction, they discussed that aberrant gastric motility leads to abnormal insulin and leptin hormone production that regulate energy expenditure, both insulin and leptin hormone signaling participate in body weight stability. In contrast to the present study, research was conducted in 2018 showed that MCP non significantly increase body weight in female lactating rats (Emmanuel *et al*., 2018). Controversy to the present study, Almatroodi *et al*. (2021) showed that 6G increased body weight in STZ-induced diabetic rats. However, other research in high-fat diet-induced obese mice, 6G decreased body weight (Gunawan *et al*., 2023). The precise mechanism of action of 6G with the endocrine pathways is not clearly known and the role of hormonal feedback mechanism in its metabolic effects in DGp is yet to be fully understood.

It has been shown in the present study that liver and stomach ROW increased after STZ injection in DGp rats, and they had a lower relative spleen weight. Moreover, MCP and 6G did not affect ROW of the spleen, lungs, stomach, heart, pancreas, liver, or kidneys. This accomplishment aligns with previous studies. Mohammed and Islam (2018) proved that postprandial glycemia which is one of the complications of delayed GE, causes hepatic lipogenesis that results in increased liver ROW. An increase in stomach ROW was observed in former research by Nørgaard *et al*. (2020) in male 129/Sv mice. They explained it along with gastric dilation that prompted by delayed GE, because delayed GE is a reason for stomach enlargement and increase in stomach ROW. In another study by Steinsvik *et al*. (2022), they observed the same results of stomach enlargement after GE delay. Previously, Ebaid *et al*. (2015) discussed that spleen ROW increases in STZ-induced DGp, because STZ administration leads to rats' splenic atrophy. The results gathered from the present investigation correlate with prior research. Parkman *et al*. (2012) explained that prokinetic agents enhance gastrointestinal function, but it does not influence systemic metabolic processes or cellular signaling pathways that regulate organ size and weight.

In this study's DGp rats, kidney function parameters (Cr, UA, BU,

and BUN) level increased, after administration of MCP and 6G, MCP does not have effect on kidney function parameters, but 6G normalized Cr, UA, BU, and BUN level in DGp rats' serum. The increase in parameters of kidney function, observed in STZ induced diabetic rats, is directly connected to the development of renal dysfunction. hyperglycemia is one of the key drivers of renal pathology, which is able to start changes in the structure and functioning of the kidneys, resulting in the inability of the kidneys to filter and excrete, and, accordingly, the production of waste products such as Cr, UA, BU, and BUN in the bloodstream (Liu *et al*., 2020). Diabetic gastroparesis in itself may have an indirect effect on the health of the kidney. Gastroparesis, symptoms which include persistent nausea and vomiting, may result in dehydration, electrolyte imbalance, and poor nutrition intake, all of which may cause further stress to the kidneys (Shen *et al*., 2019). Metoclopramide does not have effect on kidney's function and the parameters of kidney performance that are raised (Kasa *et al*., 2025). Almatroodi *et al*. (2021)studied the ability of 6G in attenuating renal damage in STZ-induced diabetes rats. Joshi *et al*. (2017) as well proved that 6G alleviate kidney dysfunction by ease of oxidative stress level. These reports intellectualize the 6G's capability in regulating Cr, UA, BU, and BUN level the present study results.

The present study showed that liver enzymes concentration increased in DGp rats. Furthermore, MCP had effect on ALT by decreasing it, but 6G did not impact on liver enzymes concentration. This result gives critical contributions to the liver complications to DGp and the exact action of these agents. High ALT, AST, and ALP have been well accepted as the biomarkers of hepatocellular injury (Lin *et al*., 2025). This hepatic pathology is the result of hyperglycemia, oxidative stress, and inflammation that are typical characteristics of DGp (Wang *et al*., 2025). The absence effect of MCP on liver enzymes is as expected based on the pharmacological profile of the drug. Metoclopramide's mechanism of action does not directly affect liver enzymes (Parkman *et al*., 2012), but since it has decreasing effect on ALT, it is reasonable to consider that there is direct or indirect hepatoprotective effects of MCP but it is not its major acknowledged effect. The action of immunomodulation has been observed on murine macrophages. This type of immunomodulatory effect, when applicable in hepatic inflammation, may lead to lower levels of ALT (Aydemir, 2025). On the other hand, researches have established that 6G have hepatoprotective activity because it can decrease liver enzyme levels in acetaminophen-induced hepatotoxicity and hepatic I/R injury mice (Sabina *et al*., 2011; Yu *et al*., 2024).

Regarding the lipid profile in the current study, a disruption in T.Chol, LDL, and HDL levels occurred in the DGp group; however, treatment with both MCP and 6G improved the T.Chol and LDL levels. Our findings coincide with those of prior studies. The T.Chol, LDL, and HDL levels disturbance, observed in the DGp group, is consistent with metabolic dysregulation states in occurrence of dyslipidemia in the diabetes, where the condition is very common and is characterized by a high level of T.Chol and LDL, and a low level of HDL (Rajendra *et al*., 2024). The MCP and 6G effect on T.Chol and LDL refinement indicate a possible therapeutic intervention to enhance lipid profiles. Both T.Chol and LDL are essential markers with high levels of the two being closely correlated with atherosclerosis and higher cardiovascular risk (Poznyak *et al*., 2020). Metoclopramide's direct effect on lipid metabolism, namely, T.Chol and LDL are not its major pharmacological effect. Thus, any apparent refinement of T.Chol and LDL in the conditions of the present study would probably be indirectly mediated, and it needs further studies to clarify it. Although the prokinetic effects of metoclopramide, including faster gastric emptying and transit of the small bowel, have the potential to affect nutrient absorption and lipid metabolism, any impact of metoclopramide on overall lipid profiles would probably be indirect and indirect (Nawaz *et al*., 2024). Research has revealed that 6G is able to reduce hyperlipidemia and enhance it by controlling diverse physiological pathways. As an example, 6G has been detected to reduce cellular total cholesterol and free cholesterol in HepG2 cells through up-regulation of LDL receptor expression and cholesterol efflux related gene (X. Li *et al*., 2018).

A decrease of GPx levels in DGp group was observed in the current study. The results showed improvement of GPx by both MCP and 6G, nevertheless, 6G revealed to be more effective than MCP. Reduction in GPx is a complication of DM and DN (Kornhauser *et al*., 2008). The results were compatible with previous experiments in increasing GPx by MCP (Hamza *et al*., 2020) and by 6G (Liu *et al*., 2022). Reduced GE normalizes inflammation and oxidative stress by reduction in nutrient deficiency (Dresen *et al*., 2023; Sampath *et al*., 2021). Metoclopramide and 6G both enhanced GE in the current study, which may elucidate the improvement in GPx levels. 6-Gingerol is well known for being a strong antioxidant. It can directly scavenge free radicals and make endogenous antioxidant enzymes like GPx, superoxide dismutase (SOD), and catalase (Almatroodi *et al*., 2021), which may explain a stronger activity of 6G compared with MCP in the present study.

5. CONCLUSION

The study has effectively shown that the administration of STZ and HFHS diet in the DGp group results in severe metabolic dysregulation, which is manifested by the extreme elevation of FBG, impaired GE, altered food and water intake, lower body mass, weight changes of organs (increased liver and stomach weight and reduced spleen weight relative to total organ weight), kidney function impairment (elevated creatinine, uric acid, BUN, BU), liver damage (elevated AST, ALT and ALP), and an altered lipid profile. Furthermore, metoclopramide made a significant improvement on FBG and GE, normalized T.Chol, and significantly increased HDL and glutathione peroxidase. The two therapies MCP and 6G were shown to have beneficial impact on different DGp complications and thus they could be considered useful as alternative therapy. In general, MCP is still the stronger prokinetic; however, 6G is a promising alternative, especially because it has good metabolic and antioxidant effects and may have fewer side effects. Our results underscore the necessity for additional research into the clinical utility of 6G as a supplementary or alternative treatment for DGp, and confirm the validity of this abbreviated model in preclinical investigations.

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Ethical Statment:

All animal experiments have been conducted following the approval by the Academy and Ethics Committee of Soran University, reference no. 648/1/1, issue date 28-8-2025. All animal experiments were complied with the ARRIVE guidelines and carried out following the National Research Council's Guide for the Care and Use of Laboratory Animals.

Conflict of Interests:

The authors declare no competing interests.

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Author Contributions:

A.O.M., & S.A.M., Design of the Project, Animal Breeding, Experimental Works, Sample Collection, Laboratory Analysis and Writing. S.A.M., & M.S.S., Supervision, Project Administration, Validation, Review & Editing, Data Analysis.

6. REFERENCES

Abell, T., Lou, J., Tabbaa, M., Batista, O., Malinowski, S., & Al-Juburi, A. (2003). Gastric electrical stimulation for gastroparesis improves nutritional parameters

at short, intermediate, and long-term follow-up. *Journal of Parenteral and Enteral Nutrition*, 27(4), 277–281. DOI:https://doi.org/10.1177/0148607103027004277

Acosta, A., & Camilleri, M. (2015). Prokinetics in gastroparesis. *Gastroenterology Clinics of North America*, 44(1), 97–111. DOI:https://doi.org/10.1016/j.gtc.2014.11.008

Adetuyi, B. O., & Farombi, E. O. (2021). 6-Gingerol, an active constituent of ginger, attenuates lipopolysaccharide-induced oxidation, inflammation, cognitive deficits, neuroplasticity, and amyloidogenesis in rat. *Journal of Food Biochemistry*, 45(4), e13660. DOI:https://doi.org/10.1111/jfbc.13660

Ahmad Khan, H., Al Deeb, S., Al Moutaery, K., & Tariq, M. (2004). Metoclopramide attenuates iminodipropionitrile-induced oxidative stress and neurobehavioral toxicity in rats. *Pharmacology, Biochemistry, and Behavior*, 79(3), 555–561. DOI:https://doi.org/10.1016/j.pbb.2004.09.006

Albibi, R., & McCallum, R. W. (1983). Metoclopramide: pharmacology and clinical application. *Annals of Internal Medicine*, 98(1), 86–95. DOI:https://doi.org/10.7326/0003-4819-98-1-86

Alimohammadi, S., Hobbenaghi, R., Javanbakht, J., Kheradmand, D., Mortezaee, R., Tavakoli, M., Khadivar, F., & Akbari, H. (2013). Protective and antidiabetic effects of extract from Nigella sativa on blood glucose concentrations against streptozotocin (STZ)-induced diabetic in rats: an experimental study with histopathological evaluation. *Diagnostic Pathology*, 8(1), 137. DOI:https://doi.org/10.1186/1746-1596-8-137

Almatroodi, S. A., Alnuqaydan, A. M., Babiker, A. Y., Almogbel, M. A., Khan, A. A., & Husain Rahmani, A. (2021). 6-gingerol, a bioactive compound of ginger attenuates renal damage in streptozotocin-induced diabetic rats by regulating the oxidative stress and inflammation. *Pharmaceutics*, 13(3), 317. DOI:https://doi.org/10.3390/pharmaceutics13030317

Alphin, R. S., Buchholz, S., & Ward, J. W. (1972). Anorexigenic effects of metoclopramide in rats. *European Journal of Pharmacology*, 20(2), 241–242. DOI:https://doi.org/10.1016/0014-2999(72)90155-0

Amjad, W., Qureshi, W., Singh, R. R., & Richter, S. (2021). Nutritional deficiencies and predictors of mortality in diabetic and non-diabetic gastroparesis. *Annals of Gastroenterology*, 34(6), 788–795. DOI:https://doi.org/10.20524/aog.2021.0660

Andersen, G., Kahlenberg, K., Krautwurst, D., & Somoza, V. (2023). [6]-gingerol facilitates CXCL8 secretion and ROS production in primary human neutrophils by targeting the TRPV1 channel. *Molecular Nutrition & Food Research*, 67(4), e2200434. DOI:https://doi.org/10.1002/mnfr.202200434

Aydemir, E. (2025). Immunomodulatory activity of metoclopramide HCl on murine macrophages. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 398(6), 6781–6786. DOI:https://doi.org/10.1007/s00210-024-03715-2

Ayustaningwarno, F., Anjani, G., Ayu, A. M., & Fogliano, V. (2024). A critical review of Ginger's (Zingiber officinale) antioxidant, anti-inflammatory, and immunomodulatory activities. *Frontiers in Nutrition*, 11, 1364836. DOI:https://doi.org/10.3389/fnut.2024.1364836

Boye, A., Acheampong, D. O., Gyamerah, E. O., Asiamah, E. A., Addo, J. K., Mensah, D. A., Brah, A. S., & Ayiku, P. J. (2020). Glucose lowering and pancreato-protective effects of Abrus Precatorius (L.) leaf extract in normoglycemic and STZ/Nicotinamide - Induced diabetic rats. *Journal of Ethnopharmacology*, 258(112918), 112918. DOI:https://doi.org/10.1016/j.jep.2020.112918

Bukowska, M. (2022). Impaired brain insulin signalling, a potential cause of obesity: A review of literature. *Clinical Diabetology*, 11(5), 346–351. DOI:https://doi.org/10.5603/dk.a2022.0040

Camilleri, M., Chedid, V., Ford, A. C., Haruma, K., Horowitz, M., Jones, K. L., Low, P. A., Park, S.-Y., Parkman, H. P., & Stanghellini, V. (2018). Gastroparesis. *Nature Reviews Disease Primers*, 4(1), 41. DOI:https://doi.org/10.1038/s41572-018-0038-z

Camilleri, M., Kuo, B., Nguyen, L., Vaughn, V. M., Petrey, J., Greer, K., Yadlapati, R., & Abell, T. L. (2022). ACG Clinical Guideline: Gastroparesis. *Official Journal of the American College of Gastroenterology | ACG*, 117(8). DOI:https://journals.lww.com/ajg/fulltext/2022/08000/acg_clinical_guideline__gastroparesis.15.aspx

Chatturong, U., Kajsongkram, T., Tunsophon, S., Chanasong, R., & Chootip, K. (2018). Ginger extract and [6]-gingerol inhibit contraction of rat entire small intestine. *Journal of Evidence-Based Integrative Medicine*, 23, 2515690X18774273. DOI:https://doi.org/10.1177/2515690X18774273

Deeds, M. C., Anderson, J. M., Armstrong, A. S., Gastineau, D. A., Hiddinga, H. J., Jahangir, A., Eberhardt, N. L., & Kudva, Y. C. (2011). Single dose streptozotocin-induced diabetes: considerations for study design in islet transplantation models. *Laboratory Animals*, 45(3), 131–140. DOI:https://doi.org/10.1258/la.2010.010090

DeFronzo, R. A., Davidson, J. A., & Del Prato, S. (2012). The role of the kidneys in glucose homeostasis: a new path towards normalizing glycaemia. *Diabetes, Obesity & Metabolism*, 14(1), 5–14. DOI:https://doi.org/10.1111/j.1463-1326.2011.01511.x

Di Girolamo, N., Maranville, R. E., Pathak, D., Womble, W., Hanzlicek, A., Sypniewski, L., & Brandão, J. (2025). The 4 prokinetic drugs metoclopramide, cisapride, pyridostigmine, and capromorelin do not increase fecal output or food intake in healthy New Zealand rabbits (Oryctolagus cuniculus). *Journal of the American Veterinary Medical Association*, 263(6), 755–761. DOI:https://doi.org/10.2460/javma.25.01.0040

Dresen, E., Pimiento, J. M., Patel, J. J., Heyland, D. K., Rice, T. W., & Stoppe, C. (2023). Overview of oxidative stress and the role of micronutrients in critical illness. *JPEN. Journal of Parenteral and Enteral Nutrition*, 47 Suppl 1, S38–S49. DOI:https://doi.org/10.1002/jpen.2421

Ebaid, H., Al-Tamimi, J., Metwalli, A., Allam, A., Zoheir, K., Ajarem, J., Rady, A., Alhazza, I., & Ibrahim, K. (2015). Effect of STZ-Induced Diabetes on Spleen of Rats: Improvement by Camel Whey Proteins. *Pakistan Journal of Zoology*, 47(4), 1109–1116.

El-Bassossy, H. M., Elberry, A. A., Ghareib, S. A., Azhar, A., Banjar, Z. M., & Watson, M. L. (2016). Cardioprotection by 6-gingerol in diabetic rats. *Biochemical and Biophysical Research Communications*, 477(4), 908–914. DOI:https://doi.org/10.1016/j.bbrc.2016.06.157

Emmanuel, N. S., Bako, I. G., Chima, C. N., Ogweje, A. E., Abdulrauf, R. A., Alexander, A. U., Dange, S. A., David, A. B., Muhammad, H. D., Yahuza, M., & Samaila, S. (2018). Body weight changes and serum growth hormone comparative assessment in female lactating wistar rats (Rattus norvegicus) treated with metoclopramide and some atypical antipsychotics. *Journal of Advances in Medical and Pharmaceutical Sciences*, 18(2), 1–6. DOI:https://doi.org/10.9734/jamps/2018/43977

Endo, Y., Muraki, K., Fuse, Y., & Kobayashi, M. (2020). Evaluation of antioxidant activity of spice-derived phytochemicals using zebrafish. *International Journal of Molecular Sciences*, 21(3), 1109. DOI:https://doi.org/10.3390/ijms21031109

Eskandari Mehrabadi, M., Salemi, Z., & Eskandari Mehrabadi, F. (2021). Effect of biochanin A on serum nesfatin-1 level in STZ induced type 1 diabetic rat. *Traditional and Integrative Medicine*. DOI:https://doi.org/10.18502/tim.v6i2.6777

Farida, E., Nuraida, L., Giriwono, P. E., & Jenie, B. S. L. (2020). Lactobacillus rhamnosus reduces blood glucose level through down-regulation of gluconeogenesis gene expression in streptozotocin-induced diabetic rats. *International Journal of Food Science*, 2020, 6108575. DOI:https://doi.org/10.1155/2020/6108575

Furman, B. L. (2021). Streptozotocin-induced diabetic models in mice and rats. *Current Protocols*, 1(4), e78. DOI:https://doi.org/10.1002/cpz1.78

Gaddipati, K. V, Simonian, H. P., Kresge, K. M., Boden, G. H., & Parkman, H. P. (2006). Abnormal Ghrelin and Pancreatic Polypeptide Responses in Gastroparesis. *Digestive Diseases and Sciences*, 51(8), 1339–1346. DOI:https://doi.org/10.1007/s10620-005-9022-z

Giacosa, A., Morazzoni, P., Bombardelli, E., Riva, A., Bianchi Porro, G., & Rondanelli, M. (2015). Can nausea and vomiting be treated with ginger extract? *European Review for Medical and Pharmacological Sciences*, 19(7), 1291–1296. DOI:https://www.ncbi.nlm.nih.gov/pubmed/25912592

Goineau, S., Guillaume, P., & Castagné, V. (2015). Comparison of the effects of clonidine, loperamide and metoclopramide in two models of gastric emptying in the rat. *Fundamental & Clinical Pharmacology*, 29(1), 86–94. DOI:https://doi.org/10.1111/fcp.12086

Gong, Y., Liang, X., Dai, Y., Huang, X., Su, Q., Ma, Y., Chen, F., & Wang, S. (2023). Prokinetic effects of Citrus reticulata and Citrus aurantium extract with/without Bupleurum chinense using multistress-induced delayed gastric emptying models. *Pharmaceutical Biology*, 61(1), 345–355. DOI:https://doi.org/10.1080/13880209.2023.2173249

Grover, M., Farrugia, G., & Stanghellini, V. (2019). Gastroparesis: a turning point in understanding and treatment. *Gut*, 68(12), 2238–2250. DOI:https://doi.org/10.1136/gutjnl-2019-318712

Gunawan, S., Munika, E., Wulandari, E. T., Ferdinal, F., Purwaningsih, E. H., Wuyung, P. E., Louisa, M., & Soetikno, V. (2023). 6-gingerol ameliorates weight gain and insulin resistance in metabolic syndrome rats by regulating adipocytokines. *Saudi Pharmaceutical Journal: SPJ: The Official Publication of the Saudi Pharmaceutical Society*, 31(3), 351–358. DOI:https://doi.org/10.1016/j.jsps.2023.01.003

Hammersjö, R., Roth, B., Höglund, P., & Ohlsson, B. (2016). Esophageal and gastric dysmotilities are associated with altered glucose homeostasis and plasma levels of incretins and Leptin. *The Review of Diabetic Studies: RDS*, 13(1), 79–90. DOI:https://doi.org/10.1900/RDS.2016.13.79

Hamza, R. Z., Al-Salmi, F. A., Laban, H., & El-Shenawy, N. S. (2020). Ameliorative role of green tea and zinc oxide nanoparticles complex against monosodium glutamate-induced testicular toxicity in male rats. *Current Pharmaceutical Biotechnology*, 21(6), 488–501. DOI:https://doi.org/10.2174/1389201020666191203095036

He, J., Liu, B., Du, X., Wei, Y., Kong, D., Feng, B., Guo, R., Asiamah, E. A., Griffin, M. D., Hynes, S. O., Shen, S., Liu, Y., Cui, H., Ma, J., & O'Brien, T. (2024). Amelioration of diabetic nephropathy in mice by a single intravenous injection of human mesenchymal stromal cells at early and later disease stages is associated with restoration of autophagy. *Stem Cell Research & Therapy*, 15(1), 66. DOI:https://doi.org/10.1186/s13287-024-03647-x

Homko, C. J., Duffy, F., Friedenberg, F. K., Boden, G., & Parkman, H. P. (2015). Effect of dietary fat and food consistency on gastroparesis symptoms in patients with gastroparesis. *Neurogastroenterology and Motility: The Official Journal of the European Gastrointestinal Motility Society*, 27(4), 501–508. DOI:https://doi.org/10.1111/nmo.12519

Horowitz, M., O'Donovan, D., Jones, K. L., Feinle, C., Rayner, C. K., & Samsom, M. (2002). Gastric emptying in diabetes: clinical significance and treatment. *Diabetic Medicine: A Journal of the British Diabetic Association*, 19(3), 177–194. DOI:https://doi.org/10.1046/j.1464-5491.2002.00658.x

Hosseini, A., & Abdollahi, M. (2013). Diabetic neuropathy and oxidative stress: therapeutic perspectives. *Oxidative Medicine and Cellular Longevity*, 2013, 168039. DOI:https://doi.org/10.1155/2013/168039

İlhan, H. D., Ünal, B., Ayaz, Y., & Erin, N. (2022). Changes in TRPV1 expression as well as Substance P and Vasoactive Intestinal Peptide levels are associated with recurrence of pterygium. *International Journal of Molecular Sciences*, 23(24), 15692. DOI:https://doi.org/10.3390/ijms232415692

Jiang, H.-F., Li, X.-R., & Tang, C. (2011). Effect of purple sweet potato flavonoids on metabolism of glucose and lipids in diabetic rats. *Zhejiang Da Xue Xue Bao. Yi Xue Ban [Journal of Zhejiang University. Medical Sciences]*, 40(4), 374–379. DOI:https://doi.org/10.3785/j.issn.1008-9292.2011.04.005

Joshi, D., Srivastav, S. K., Belemkar, S., & Dixit, V. A. (2017). Zingiber officinale and 6-gingerol alleviate liver and kidney dysfunctions and oxidative stress induced by mercuric chloride in male rats: A protective approach. *Biomedecine & Pharmacotherapie [Biomedicine & Pharmacotherapy]*, 91, 645–655. DOI:https://doi.org/10.1016/j.biopha.2017.04.108

Jung, S.-R., Lee, J.-H., Ryu, H., Gao, Y., & Lee, J. (2024). Lithium and exercise ameliorate insulin-deficient hyperglycemia by independently attenuating pancreatic α-cell mass and hepatic gluconeogenesis. *The Korean Journal of Physiology & Pharmacology: Official Journal of the Korean Physiological Society and the Korean Society of Pharmacology*, 28(1), 31–38. DOI:https://doi.org/10.4196/kjpp.2024.28.1.31

Justin-Besancon, L., & Laville, C. (1964). Antiemetic action of metoclopramide with respect to apomorphine and hydergine. *Comptes Rendus Des Seances de La Societe de Biologie et de Ses Filiales*, 158, 723–727. DOI:https://www.ncbi.nlm.nih.gov/pubmed/14186927

Kasa, M., Rroji, M., Spahia, N., Gjana, G., & Elezi, B. (2025). Clonidine to the rescue: A novel approach to refractory diabetic gastroparesis in the postoperative setting. *Cureus*, 17(2), e79769. DOI:https://doi.org/10.7759/cureus.79769

Khan, I., Kaur, S., Rishi, A. K., Boire, B., Aare, M., & Singh, M. (2024). Cannabidiol and Beta-Caryophyllene combination attenuates diabetic neuropathy by inhibiting NLRP3 inflammasome/NFκB through the AMPK/sirT3/Nrf2 axis. *Biomedicines*, 12(7), 1442. DOI:https://doi.org/10.3390/BIOMEDICINES12071442

Khdhr, A. R., & Mahmud, S. A. (2023). Therapeutic effects of Cratargus azarolus var. Aronia in urolithiatic male albino rats. *Science Journal of University of Zakho*, 11(2), 261–272. DOI:https://doi.org/10.25271/sjuoz.2023.11.2.1106

Kornhauser, C., Garcia-Ramirez, J. R., Wrobel, K., Pérez-Luque, E.-L., Garay-Sevilla, M.-E., & Wrobel, K. (2008). Serum selenium and glutathione peroxidase concentrations in type 2 diabetes mellitus patients. *Primary Care Diabetes*, 2(2), 81–85. DOI:https://doi.org/10.1016/j.pcd.2008.02.003

Krishnasamy, S., & Abell, T. L. (2018). Diabetic gastroparesis: Prin-

ciples and current trends in management. *Diabetes Therapy: Research, Treatment and Education of Diabetes and Related Disorders*, 9(Suppl 1), 1–42. DOI:https://doi.org/10.1007/s13300-018-0454-9

Kuo, P., Bellon, M., Wishart, J., Smout, A. J., Holloway, R. H., Fraser, R. J. L., Horowitz, M., Jones, K. L., & Rayner, C. K. (2010). Effects of metoclopramide on duodenal motility and flow events, glucose absorption, and incretin hormone release in response to intraduodenal glucose infusion. *American Journal of Physiology. Gastrointestinal and Liver Physiology*, 299(6), G1326–33. DOI:https://doi.org/10.1152/ajpgi.00476.2009

Lee, A., & Kuo, B. (2010). Metoclopramide in the treatment of diabetic gastroparesis. *Expert Review of Endocrinology & Metabolism*, 5(5), 653–662. DOI:https://doi.org/10.1586/eem.10.41

Li, H., Cao, W., Zhang, X.-B., Zhang, X.-X., Gu, C., Gu, L.-M., Pan, C.-Y., Tian, Y.-Z., & Lu, M. (2021). Atractylenolide-1 alleviates gastroparesis in diabetic rats by activating the stem cell factor/c-kit signaling pathway. *Molecular Medicine Reports*, 24(4). DOI:https://doi.org/10.3892/mmr.2021.12331

Li, X., Guo, J., Liang, N., Jiang, X., Song, Y., Ou, S., Hu, Y., Jiao, R., & Bai, W. (2018). 6-gingerol regulates hepatic cholesterol metabolism by up-regulation of LDLR and cholesterol efflux-related genes in HepG2 cells. *Frontiers in Pharmacology*, 9. DOI:https://doi.org/10.3389/fphar.2018.00159

Lin, J., Braxton, D., & Fong, T.-L. (2025). Febuxostat-induced hepatocellular injury. *British medical journal Case Reports*, 18(8), e266332. DOI:https://doi.org/10.1136/bcr-2025-266332

Liu, C.-M., An, L., Wu, Z., Ouyang, A.-J., Su, M., Shao, Z., Lin, Y., Liu, X., & Jiang, Y. (2022). 6-Gingerol suppresses cell viability, migration and invasion via inhibiting EMT, and inducing autophagy and ferroptosis in LPS-stimulated and LPS-unstimulated prostate cancer cells. *Oncology Letters*, 23(6), 187. DOI:https://doi.org/10.3892/ol.2022.13307

Liu, Y., Huang, H., Gao, R., & Liu, Y. (2020). Dynamic phenotypes and molecular mechanisms to understand the pathogenesis of diabetic nephropathy in two widely used animal models of type 2 diabetes mellitus. *Frontiers in Cell and Developmental Biology*, 8, 172. DOI:https://doi.org/10.3389/fcell.2020.00172

Lu, X.-Y., Zhou, F.-H., Dong, Y.-Q., Gong, L.-N., Li, Q.-Y., Tang, L., Cai, Z., He, J.-Y., & Liu, M.-H. (2018). Codonopsis tangshen Oliv. amelioration effect on diabetic kidney disease rats induced by high fat diet feeding combined with streptozotocin. *Natural Products and Bioprospecting*, 8(6), 441–451. DOI:https://doi.org/10.1007/s13659-018-0187-5

Mahmud, S. A., Abdulla, I. T., Khdhr, A. R., & Gardi, K. Q. (2025). Protective roles of Lactuca serriola and Glycyrrhiza glabra on ethylene glycol induced urolithiasis in male albino rats (Rattus norvegicus). *Science Journal of University of Zakho*, 13(3), 357–366. DOI:https://doi.org/10.25271/sjuoz.2025.13.3.1494

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Mahomoodally, M. F., Aumeeruddy, M. Z., Rengasamy, K. R. R., Roshan, S., Hammad, S., Pandohee, J., Hu, X., & Zengin, G. (2021). Ginger and its active compounds in cancer therapy: From folk uses to nano-therapeutic applications. *Seminars in Cancer Biology*, 69, 140–149. DOI:https://doi.org/10.1016/j.semcancer.2019.08.009

Malone, H. M., Peters, J. A., & Lambert, J. J. (1991). Physiological and pharmacological properties of 5-HT3 receptors — A patch clamp-study. *Neuropeptides*, 19, 25–30. DOI:https://doi.org/10.1016/0143-4179(91)90080-3

Masuda, T., Muto, S., Fukuda, K., Watanabe, M., Ohara, K., Koepsell, H., Vallon, V., & Nagata, D. (2020). Osmotic diuresis by SGLT2 inhibition stimulates vasopressin-induced water reabsorption to maintain body fluid volume. *Physiological Reports*, 8(2), e14360. DOI:https://doi.org/10.14814/phy2.14360

Matias, A. M., Estevam, W. M., Coelho, P. M., Haese, D., Kobi, J. B. B. S., Lima-Leopoldo, A. P., & Leopoldo, A. S. (2018). Differential effects of high sugar, high lard or a combination of both on nutritional, hormonal and cardiovascular metabolic profiles of rodents. *Nutrients*, 10(8), 1071. DOI:https://doi.org/10.3390/nu10081071

McCallum, R. W., Ricci, D. A., Rakatansky, H., Behar, J., Rhodes, J. B., Salen, G., Deren, J., Ippoliti, A., Olsen, H. W., & Falchuk, K. (1983). A multicenter placebo-controlled clinical trial of oral metoclopramide in diabetic gastroparesis. *Diabetes Care*, 6(5), 463–467. DOI:https://doi.org/10.2337/diacare.6.5.463

Mo, Z., Xian, Y., Zhang, R., Dai, Y., Chen, W., & Nie, K. (2023). 6-Gingerol, a major ingredient of ginger, attenuated cisplatin-induced pica in rats via regulating 5-HT3R/Ca^{2+}/CaMKII/ERK1/2 signaling pathway. *Journal of Functional Foods*, 100(105389), 105389. DOI:https://doi.org/10.1016/j.jff.2022.105389

Mohammed, A., & Islam, M. S. (2018). Spice-derived bioactive ingredients: Potential agents or food adjuvant in the management of diabetes mellitus. *Frontiers in Pharmacology*, 9, 893. DOI:https://doi.org/10.3390/fphar.2018.00893

Nawaz, A., Shah, S., Ahmed, A., & Ullah, M. (2024). Domperidone vs metoclopramide: Comparative evaluation of efficacy in treating diabetic gastroparesis. *Biological and Clinical Sciences Research Journal*, 2024(1), 836. DOI:https://doi.org/10.54112/bcsrj.v2024i1.836

Niknia, S., Kaeidi, A., Hajizadeh, M. R., Mirzaei, M. R., Khoshdel, A., Hajializadeh, Z., Fahmidehkar, M. A., & Mahmoodi, M. (2019). Neuroprotective and antihyperalgesic effects of orexin-A in rats with painful diabetic neuropathy. *Neuropeptides*, 73, 34–40. DOI:https://doi.org/10.1016/J.NPEP.2018.11.001

Niu, Z., Yan, M., Zhao, X., Jin, H., & Gong, Y. (2020). Effect of hawthorn seed extract on the gastrointestinal function of rats with diabetic gastroparesis. *Suid-Afrikaanse Tydskrif Vir Plantkunde [South African Journal of Botany]*, 130, 448–455. DOI:https://doi.org/10.1016/j.sajb.2020.01.032

Nørgaard, S. A., Søndergaard, H., Sørensen, D. B., Galsgaard, E. D., Hess, C., & Sand, F. W. (2020). Optimising streptozotocin dosing to minimise renal toxicity and impairment of stomach emptying in male 129/Sv mice. *Laboratory Animals*, 54(4), 341–352. DOI:https://doi.org/10.1177/0023677219872224

Özdemir, F., Akçay, G., Özkinali, S., & Çelik, Ç. (2023). [6]-Shogaol and [6]-Gingerol active ingredients may improve neuropathic pain by suppressing cytokine levels in an experimental model. *Turkish Journal of Medical Sciences*, 53(6), 1593–1604. DOI:https://doi.org/10.55730/1300-0144.5728

Parkman, H. P., Mishra, A., Jacobs, M., Pathikonda, M., Sachdeva, P., Gaughan, J., & Krynetskiy, E. (2012). Clinical response and side effects of metoclopramide.

Journal of Clinical Gastroenterology, 46(6), 494–503. DOI:https://doi.org/10.1097/mcg.0b013e3182522624

Pasricha, P. J., Yates, K. P., Nguyen, L., Clarke, J., Abell, T. L., Farrugia, G., Hasler, W. L., Koch, K. L., Snape, W. J., McCallum, R. W., Sarosiek, I., Tonascia, J., Miriel, L. A., Lee, L., Hamilton, F., & Parkman, H. P. (2015). Outcomes and factors associated with reduced symptoms in patients with gastroparesis. *Gastroenterology*, 149(7), 1762–1774.e4. DOI:https://doi.org/10.1053/j.gastro.2015.08.008

Pawlikowski, M., Żerek-Mełeń, G., & Winczyk, K. (1992). Thyroliberin (TRH) increases thymus cell proliferation in rats. *Neuropeptides*, 23(3), 199–202. DOI:https://doi.org/10.1016/0143-4179(92)90123-e

Poli, V., Aparna, Y., & Reddy Motireddy, S. (2022). 6-gingerol, new insights into its anti-diabetic potential with special reference to AMPK pathway: A review. *Journal of Food and Nutrition Research*, 10(10), 681–695. DOI:https://doi.org/10.12691/jfnr-10-10-6

Poznyak, A., Grechko, A. V, Poggio, P., Myasoedova, V. A., Alfieri, V., & Orekhov, A. N. (2020). The diabetes mellitus-atherosclerosis connection: The role of lipid and glucose metabolism and chronic inflammation. *International Journal of Molecular Sciences*, 21(5), 1835. DOI:https://doi.org/10.3390/ijms21051835

Qader, G., Aali, M., Smail, S. W., Mahmood, K., Hasan, B., M-Amen, K., Rahman, D. B., Qadir, F. A., Mohammad, D. K., Najmuldeen, H. H., Rahman, F. M., Ahmad, S. I., Salih, N. S., Khdhr, Z. M., Mohammed, B. A., Majeed, A. M., Hasan, X. M., Khidhir, B. H., Muhammad, E. S., …Salihi, A. (2021). Cardiac, hepatic and renal dysfunction and IL-18 polymorphism in breast, colorectal, and prostate cancer patients. *Asian Pacific Journal of Cancer Prevention: APJCP*, 22(1), 131–137. DOI:https://doi.org/10.31557/APJCP.2021.22.1.131

Rajendra, S., Vaishnavi, S., Hamsavakini, N., Nalini, R., Aravinthan, M., & Shathana, P. (2024). Lipid profile, insulin resistance & non-alcoholic fatty liver disease (NAFLD) among type 2 diabetes patients getting treatment in Jaffna. *Endocrine and Metabolic Science*, 15(100166), 100166. DOI:https://doi.org/10.1016/j.endmts.2024.100166

Rani, M. P., Padmakumari, K. P., Sankarikutty, B., Cherian, O. L., Nisha, V. M., & Raghu, K. G. (2011). Inhibitory potential of ginger extracts against enzymes linked to type 2 diabetes, inflammation and induced oxidative stress. *International Journal of Food Sciences and Nutrition*, 62(2), 106–110. DOI:https://doi.org/10.3109/09637486.2010.515565

Sabina, E. P., Pragasam, S. J., Kumar, S., & Rasool, M. (2011). 6-gingerol, an active ingredient of ginger, protects acetaminophen-induced hepatotoxicity in mice. *Zhong Xi Yi Jie He Xue Bao [Journal of Chinese Integrative Medicine]*, 9(11), 1264–1269. DOI:https://doi.org/10.3736/jcim20111116

Sampath, C., Wilus, D., Tabatabai, M., Freeman, M. L., & Gangula, P. R. (2021). Mechanistic role of antioxidants in rescuing delayed gastric emptying in high fat diet induced diabetic female mice. *Biomedecine & Pharmacotherapie [Biomedicine & Pharmacotherapy]*, 137(111370), 111370. DOI:https://doi.org/10.1016/j.biopha.2021.111370

Sebai, H., Rtibi, K., Selmi, S., Jridi, M., Balti, R., & Marzouki, L. (2019). Modulating and opposite actions of two aqueous extracts prepared from Cinnamomum cassia L. bark and Quercus ilex L. on the gastrointestinal tract in rats. *RSC Advances*, 9(38), 21695–21706. DOI:https://doi.org/10.1039/c9ra02429h

Sharma, P., Mandal, M. B., Katiyar, R., Singh, S. P., & Birla, H. (2021). A comparative study of effects of 28-day exposure of bisphenol A and bisphenol S on body weight changes, organ histology, and relative organ weight. *International Journal of Applied & Basic Medical Research*, 11(4), 214–220. DOI:https://doi.org/10.4103/ijabmr.IJABMR_663_20

Shen, S., Xu, J., Lamm, V., Vachaparambil, C. T., Chen, H., & Cai, Q. (2019). Diabetic gastroparesis and nondiabetic gastroparesis. *Gastrointestinal Endoscopy Clinics of North America*, 29(1), 15–25. DOI:https://doi.org/10.1016/j.giec.2018.08.002

Shi, J., Wang, J., Shan, S., Zhao, M., Bi, C., Li, H., & Li, Z. (2024). Foxtail millet bran-derived phenolic acids ameliorate insulin resistance by non-competitively inhibiting α-glucosidase activity and blocking miR-1-3p /PTP1B signaling axis in diabetic mice. *Journal of Functional Foods*, 115(106105), 106105. DOI:https://doi.org/10.1016/j.jff.2024.106105

Silva, N. G. da, Brandão, A. M., Oliveira, M. V. M. de, Morais, P. H. A. de, Silva, S. M. e, Carneiro, F. P., & Sousa, J. B. de. (2011). Influence of metoclopramide on abdominal wall healing in rats subjected to colonic anastomosis in the presence of peritoneal sepsis induced. *Acta Cirurgica Brasileira*, 26(suppl 2), 92–99. DOI:https://doi.org/10.1590/s0102-86502011000800017

Smail, S. W., Kheder, A. H., Mustafa, H. K., Abdulqadir, S. Z., Jalal, K. F., Yashooa, R. K., Ghayour, M. B., Abdolmaleki, A., & Shekha, M. S. (2025). Kenpaullone attenuates amyloid-beta deposition and neuroinflammation, improving memory in a 5XFAD mouse model of Alzheimer's disease. *Neurological Research*, 1–14. DOI:https://doi.org/10.1080/01616412.2025.2520983

Smiley, R., McCallum, R., & Showkat Ali, M. (2020). Decreased level of neuropeptide Y is associated with gastroparesis in male diabetic rats. *Gastroenterology Research*, 13(6), 246–252. DOI:https://doi.org/10.14740/gr1322

Snape Jr, W. J., Battle, W. M., Schwartz, S. S., Braunstein, S. N., Goldstein, H. A., & Alavi, A. (1982). Metoclopramide to treat gastroparesis due to diabetes mellitus. *Annals of Internal Medicine*, 96(4), 444–446. DOI:https://doi.org/10.7326/0003-4819-96-4-444

Song, B., Zhang, G., Bao, Y., & Zhang, M. (2024). Involvement of oxidative stress-AMPK-Cx43-NLRP3 pathway in extracellular matrix remodeling of gastric smooth muscle cells in rats with diabetic gastroparesis. *Cell Stress & Chaperones*, 29(3), 440–455. DOI:https://doi.org/10.1016/j.cstres.2024.04.005

Steinsvik, E. K., Sangnes, D. A., Søfteland, E., Biermann, M., Assmus, J., Dimcevski, G., Gilja, O. H., & Hausken, T. (2022). Gastric function in diabetic gastroparesis assessed by ultrasound and scintigraphy. *Neurogastroenterology and Motility: The Official Journal of the European Gastrointestinal Motility Society*, 34(4), e14235. DOI:https://doi.org/10.1111/nmo.14235

Tonghui, J., Tiejun, L., Chaoyue, L., & Han, W. (2025). Experimental study and clinical significance of the impact of gastrointestinal motility disorders on hepatic blood perfusion. *Frontiers in Medicine*, 12(1643351), 1643351. DOI:https://doi.org/10.3389/fmed.2025.1643351

Upadhayay, A., Kumari, S., Shalini, S., & Govindaswami, J. (2018). Antihyperglycemic activity of Pithecellobium Dules plant extracts on blood glucose levels of streptozocin-induced diabetic rats. *Journal of Drug Delivery and Therapeutics*, 8(2). DOI:https://doi.org/10.22270/jddt.v8i2.1677

Uppaluri, S., Jain, M. A., Ali, H., Shingala, J., Amin, D., Ajwani, T., Fatima, I., Patel, N., Kaka, N., Sethi, Y., & Kapoor, N. (2024). Pathogenesis and management of diabetic gastroparesis: An updated clinically oriented review. *Diabetes & Metabolic Syndrome*, 18(3), 102994. DOI:https://doi.org/10.1016/j.dsx.2024.102994

Wang, Z., Zan, W., Fan, Z., & Wang, S. (2025). Re-

lationship between hepatic lipid accumulation and type 2 diabetes mellitus. *Biomedecine & Pharmacotherapie [Biomedicine & Pharmacotherapy]*, 193(118723), 118723. DOI:https://doi.org/10.1016/j.biopha.2025.118723

Wulandari, E., Putri Andri, S. A., Soetikno, V., Kusmardi, K., Louisa, M., Gunawan, S., & Arumugam, S. (2024). 6-gingerol as an antioxidant to ameliorate kidney injury in high-fat high-fructose diet-induced metabolic syndrome in rats. *Journal of Applied Pharmaceutical Science*. DOI:https://doi.org/10.7324/japs.2024.184247

Xiao, Y., Zhou, J.-Y., Yin, H.-Z., Liu, Q., Luo, R., Liu, W.-A., Du, G.-S., Zhong, H., & Liu, M. (2023). Effect of electroacupuncture at "Neiguan" (PC 6) and "Zusanli" (ST 36) on gastrointestinal hormone in the antral tissue of rats with functional dyspepsia. *Zhongguo Zhen Jiu [Chinese Acupuncture & Moxibustion]*, 43(12), 1435–1440. DOI:https://doi.org/10.13703/j.0255-2930.20230809-0007

Yu, Q., Li, J., Cui, M., Mei, C., He, Q., & Du, X. (2024). 6-Gingerol attenuates hepatic ischemia/reperfusion injury through regulating MKP5-mediated P38/JNK pathway. *Scientific Reports*, 14(1), 7747. DOI:https://doi.org/10.1038/s41598-024-58392-1

Zhang, C.-C., Lin, Y.-P., Peng, Y., Yue, Z.-H., Chen, H.-J., Yang, J.-W., Liu, W.-W., & Liu, L. (2017). Effects of electroacupuncture on ultrastructure of interstitial cells of Cajal and stem cell factor-kit signal pathway of gastric antrum in diabetic gastroparesis rats. *Zhen Ci Yan Jiu [Acupuncture Research]*, 42(6), 482–488. DOI:https://doi.org/10.13702/j.1000-0607.2017.06.003

Zhang, F., Ma, N., Gao, Y.-F., Sun, L.-L., & Zhang, J.-G. (2017). Therapeutic effects of 6-gingerol, 8-gingerol, and 10-gingerol on dextran sulfate sodium-induced acute ulcerative colitis in rats. *Phytotherapy Research: PTR*, 31(9), 1427–1432. DOI:https://doi.org/10.1002/ptr.5871

Zhang, M.-H., Jiang, J.-Z., Cai, Y.-L., Piao, L.-H., & Jin, Z. (2017). Significance of dynamic changes in gastric smooth muscle cell apoptosis, PI3K-AKT-mTOR and AMPK-mTOR signaling in a rat model of diabetic gastroparesis. *Molecular Medicine Reports*, 16(2), 1530–1536. DOI:https://doi.org/10.3892/mmr.2017.6764

Zuccato, E., Bertolo, C., Salomoni, M., Forgione, A., & Mussini, E. (1992). The effects of S(−) and R(+) sulpiride, metoclopramide, cisapride and domperidone on the small intestine suggest DA2-receptors are involved in the control of small intestinal transit time in rats. *Pharmacological Research: The Official Journal of the Italian Pharmacological Society*, 26(2), 179–185. DOI:https://doi.org/10.1016/s1043-6618(05)80131-8