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Deepana and *Pachana* activities of *Pippali* and *Pippalimula* (fruits and roots of *Piper longum* L.) and its effects on digestive enzymes of albino rats

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Pippali and *Pippalimula* are different parts of the plant *Piper longum* L. that belongs to the Piperaceae family. They have diversity in their *Rasapanchaka* (five attributes of drug) and hence may possess dissimilar pharmacological actions. This research study has been carried out to explore and compare the effects of these drugs on *Deepana-Pachana* activity, metabolic enzymes and hormones secreted in the gastrointestinal tract of albino rats. The effects of test drugs were assessed on food and water intake, food conversion ratio, gastric and intestinal enzymes and digestive hormones. *Pippalimula* showed significant results in body weight gain, water intake, as well as quantitative increase in amylase, lipase and trypsin levels in intestinal mucosa. While, *Pippali* demonstrated significant results in body weight gain and quantitative increase in Pepsin secretion in gastric mucosa of albino rats. Both the test drugs significantly increased food conversion ratio indicating improvement in digestion, metabolism, absorption and assimilation of food in albino rats. The findings underline that, *Pippalimula* has pronounced effects on intestinal digestive enzymes, while *Pippali* enhances the absorption and assimilation of food, indicating its *Rasayana* effect alongside *Pippali's Deepana* action. These differences reflect the unique modes of action of the two parts of *Piper longum* L. based on inherent qualities, thus supporting the Ayurvedic perspective of drug-specific therapeutic applications.

Keywords: *Deepana*, Digestive enzymes, *Pachana*, *Pippali*, *Pippalimula*, *Rasapanchaka*

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Classical texts of Ayurveda say that *Agnimandya* (diminution of *Agni*) is the main cause of every disease condition[1] and hence *Agnideepana* (increase in power of *Agni*) becomes a vital factor in maintaining as well as improving health. *Deepana* and *Pachana* are fundamental therapeutic approaches in Ayurvedic clinical practice, often serving as the first line of treatment for a wide range of diseases. According to Ayurvedic classical texts, there are 13 types of *Agni*[2] (digestive and metabolic fire), and *Agnimandya* (vitiation of *Agni*) that can occur in one or more of these types. Accurate diagnosis of the specific type of *Agnimandya* and selecting a drug with an appropriate mode of action facilitates faster and more effective disease management. This study has been undertaken to evaluate the mode of action of *Agnideepana* category drugs, focusing on differences in their inherent qualities.

Pippali (*Piper longum* Linn., Family: Piperaceae) has been extensively used as a medicine since the Vedic period. Various Ayurvedic texts also describe *Pippali* fruit and its root (*Pippalimula*) for various disease conditions as *Arsha* (haemorrhoids), *Grahaniroga* (derangement of *Agni* situated in *Grahaṇī* part of the gastro-intestinal tract), *Shwasa* (respiratory diseases), *Kasa* (cough)[3] etc. *Pippali* fruit termed as *Pippali*[4] and *Pippali* root called *Pippalimula*[5] both possess *Agnideepana* property and are used separately in many diseases. They are also grouped under the category of *Deepaniya Mahakashaya*[6] in Charaka Samhita, one of the major classical texts of Ayurveda. Although being different parts of the same plant, literature review of Ayurvedic classics shows that these drugs are indicated for distinct conditions during management of diseases and rarely mentioned for substitution with one another. Various lexicons also underline the difference in their pharmacological properties, which signifies the varied modes of action.

Modern science explains the process of digestion primarily through the coordinated actions of various digestive enzymes and regulatory hormones that facilitate breakdown, absorption, and assimilation of nutrients. This study is based on the Ayurvedic

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principle that *Pippali* and *Pippalimula* exhibit distinct actions in digestion due to differences in their pharmacological properties. Bridging traditional knowledge with modern scientific understanding, we evaluate gastric and intestinal enzyme activities, along with key digestive hormones, to investigate their differential roles in the digestive process. This study investigates the effects of *Pippali* and *Pippalimula* on selective digestive enzymes, such as amylase, trypsin and lipase, as well as key hormones involved in digestion, including ghrelin and cholecystokinin, in Wistar albino rats. The research employs a pre-clinical model to evaluate and compare the *Deepana* and *Pachana* activities of these two *Pippali* plant parts.

According to Ayurvedic literature, *Pippali* is characterised by *Madhura Vipaka* and *Snigdha Guna*, which contribute to its mild laxative effect and support bowel evacuation. In contrast, *Pippalimula* possesses *Katu Vipaka* and *Ruksha Guna*, which do not facilitate bowel clearance but exert a comparatively stronger digestive stimulation. These differences form the basis for their differentiated roles in digestive health management. This study bridges classical Ayurvedic concepts that *Gunasamyoga* differentiates the pharmacological action, with modern pharmacological techniques paving the way for evidence-based integration of traditional Ayurvedic principles in digestive health management.

Materials and Methods

Animal selection

Wistar strain albino rats of either sex weighing between 200±20 g were used for the experiments. The animals were obtained from the Animal house attached to ITRA, Jamnagar. Animals were housed in each cage made up of poly-propylene with a stainless steel top grill. The corn cob was used as bedding material and was changed every morning. The selected animals were kept under acclimatization for one week before experiments. The animals were exposed to 12-h light and 12-h dark cycles with the relative humidity of 50 to 70% and the ambient temperature during the period of experimentation was 22±03ºC. Animals were fed with VRK brand rat pellet feed supplied by Keval Sales Corporation, Vadodara. The drinking water was given *ad libitum*. The experimental protocols were approved by the Institutional Animal Ethics Committee (IAEC/32/2023/02) in accordance with the guideline formulated by CCSEA, India.

Drug

Pippali (*Pippali* fruit) and *Pippalimula* (*Pippali* root) procured from Pharmacy of ITRA, Jamnagar in the month of June 2023 and authenticated by subject experts of ITRA, Jamnagar. The voucher specimen no. 6709 is kept in Pharmacognosy, ITRA, Jamnagar for future reference. The test drugs were pulverized to prepare powder, sieved through #120 mesh, and preserved in an air-tight glass bottle.

Dose fixation

The dose for experimental study was calculated based on body surface area ratio as per table of Paget and Barnes[7]. The clinical therapeutic dose of *Pippali* (*Pippali* fruit) and *Pippalimula Churna* (*Pippali* root) is 1 g per day according to Ayurvedic Pharmacopoeia of India. Therefore, the rat dose was calculated as 90 mg/kg body weight (multiplying factor- 0.018 for 200 g rat). The fine powder was made into suspension in distilled water and administered in uniform volume (10 mL/kg) according to the body weight of the albino rats by oral route with the help of oral gastric cannula.

Experimental protocol

The wistar albino rats of either sex weighing between 200±20 g were divided into three groups each consisting of six rats as mentioned below.

Group I: Control group, received distilled water (10 mL/kg, po)

Group II: Pippali *Churna* (90 mg/kg, po)

Group III: *Pippalimula Churna* (90 mg/kg, po)

The study was carried out in two phases as below.

Phase I preliminary study

The preliminary study was conducted for 4 consecutive days. Initial body weights (Table 1) of the rats were recorded and each rat was placed in a separate metabolic cage. In this preliminary phase, test drugs were not administered to the rats. In this phase, below mentioned parameters (Table 2) were measured and recorded on a daily basis for 4 consecutive days. Preliminary study was carried out prior to the experimental study to understand the normal base line values of albino rats.

Phase II experimental study

The experimental study was conducted for 14 consecutive days. Initial body weights of the rats were recorded at the starting and end of experimental study. Each rat was placed in a separate metabolic cage. *Pippali* (fine powders of fruits of *Piper longum* L.) and *Pippalimula Churna* (fine powders of roots of

Table 1 — Changes in body weight of albino rats

Groups	Control	*Pippali Churna*	*Pippalimula Churna*
Preliminary phase	224.33±18.05	218.42±15.47	216.17±18.32
Experimental phase (7th day)	227.08±17	222.42±17.15	224.00±18.76##
Experimental phase (14th day)	228.17±16.48	251.62±12.37##	241.0±26.44#
% change	1.71 ↑	15.20 ↑	11.49 ↑

Data: Mean±SEM, ↑- Increase
#p<0.05, ##p<0.01, when compared to initial value (Paired 't' test)

Table 2 — Effects of test drugs on various parameters in albino rats

Groups	Control	*Pippali Churna*	*Pippalimula Churna*
Food consumption (g%)			
Preliminary phase	4.891±0.32	5.013±0.318	5.033±0.406
Experimental phase	4.92±0.3	6.36±0.181##@@	7.43±0.359###@@
% change	0.593 ↑	26.81 ↑	47.55 ↑
Water intake (ml%)			
Preliminary	8.507±0.559	9.831±0.54	8.638±0.606
Experimental phase	7.477±0.13	9.838±0.4@@	10.754±0.977##@
% change	12.11 ↓	0.07 ↑	24.49 ↑
Faecal output (g%)			
Preliminary	0.919±0.103	0.882±0.0926	0.765±0.107
Experimental phase	0.81±0.076	0.739±0.046	0.775±0.074
% change	11.861 ↓	16.213 ↓	1.307 ↑
Urine output (mL%)			
Preliminary	0.166±0.019	0.209±0.043	0.18±0.014
Experimental phase	0.205±0.056	0.198±0.053	0.207±0.051
% change	23.49 ↑	5.26 ↓	15.00 ↑
Food Conversion Ratio			
Preliminary	5.556±0.529	5.867±0.476	6.971±0.713
Experimental phase	6.288±0.468	9.183±0.551##@@	10.975±0.563##@@
% change	13.17 ↑	56.52 ↑	57.44 ↑

Data: Mean±SEM, ↓- Decrease, ↑- Increase
##p<0.01, ###p<0.001, when compared to initial value (Paired 't' test)
@@p<0.01, when compared to control group (Anova followed by Dunnett's multiple 't' test)

Piper longum L.) were administered daily as per calculated doses for 14 consecutive days. In this phase, below mentioned parameters (Table 2) were measured and recorded on a daily basis. Experimental study was carried out to understand the effect of test formulation on the below mentioned parameters in albino rats.

Body weights were recorded at the start of both phases, on the 7th day, and at the end of the experimental phase. For food intake, each rat was provided 30 g of dry pellets/day. Residual food was reweighed the next day. Food consumption was calculated as grams per day and as a percentage of body weight. For water intake, 50 mL of water was provided to each rat daily. Residual water was re-measured to calculate intake in ml/day and as a percentage of body weight. Total faecal matter was weighed on each day, dried in an oven at 80°C for 6 h, and re-weighed. Faecal matter output was calculated as grams per day and as a percentage of body weight. FCR was calculated per rat per day by dividing food consumed (g/day) by faecal matter passed (g/day).

On the 15th day, one hour after drug administration, blood was collected from overnight-fasted animals via the retro-orbital plexus under ether anaesthesia. Serum was separated for digestive hormone analysis. The ELISA method was employed to measure levels of serum ghrelin and cholecystokinin (Rat Ghrelin ELISA Kit Cat: ELK1944, Rat Cholecystokinin ELISA Kit Cat: ELK2632) Final body weights were recorded, and rats were sacrificed. The stomach and intestine were dissected for enzyme assessment.

Stomach and intestinal samples were prepared[8] by carefully excising the organs, scraping the mucosal layer, and homogenizing the mucosal content in ice-cold saline. Gastric mucosa was homogenized (2.5%) and intestinal mucosa (5%) concentration in normal saline. Both were centrifuged, and the supernatant was used for enzyme estimation. The gastric

parameters include Pepsin activity[9] and Total protein[10]. The intestinal enzymes include Amylase[11], Lipase[12] and Trypsin[13].

Statistical analysis

The obtained data have been presented as mean±standard error of mean. The difference between the groups, statistically determined by ANOVA followed by Dunnett's multiple t-test to assess the statistical significance between the groups. The value $p<0.05$ is considered as statistically significant.

Results

Progressive weight gain of albino rats was observed in all three groups. *Pippali* (*Pippali* fruit) treated group showed significant weight gain of albino rats on day 14, while *Pippalimula* (*Pippali* root) treated group showed significant weight gain on 7th as well as 14th day in comparison to initial body weight of albino rats (Table 1).

A significant increase in food consumption of albino rats was observed in *the Pippali-treated* group, while, *Pippalimula-treated* group showed a highly significant increase in food consumption when compared to initial as well as when compared to control group of rats. Both experimental groups showed an increase in water intake of albino rats when compared to the control group. *Pippalimula-treated* group showed more consumption of water in albino rats. Both *Pippali* and *Pippalimula*-treated groups showed a decrease in faecal output of albino rats, however, the results were not statistically significant. *Pippali* (*Pippali* fruit) treated group showed a decrease in urine output of albino rats. *Pippalimula*- treated group showed an increase in urine output of albino rats. However, the results were statistically non-significant. The food conversion ratio was improved in all the groups when compared to initial values. *Pippalimula* (*Pippali* root) treated group showed a highly significant increase in food conversion ratio (Table 2).

The Pippali-treated group showed an increase in ghrelin levels, while the *Pippalimula*-treated group showed a decrease in ghrelin levels when compared to the control group. The results are statistically not significant. Both *Pippali* and *Pippalimula*-treated groups showed a non-significant increase in serum CCK levels in albino rats when compared to the control group. Both *Pippali* and *Pippalimula* treated groups showed a significant increase in pepsin activity in the stomach mucosa of albino rats, while *Pippali* showed a decrease in protein content and *Pippalimula* (*Pippali* root) treated group shows significant decrease in total protein levels when compared to control group. *Pippalimula* treated group showed significant increase in lipase activity in intestinal mucosa of albino rats. Both *Pippali* and *Pippalimula* treated groups showed significant increase in Amylase and trypsin activities when compared to control groups (Table 3).

Discussion

Both *Pippali* (*Pippali* fruit) and *Pippalimula* (*Pippali* root) groups showed a significant increase in body weight over the study period, indicating an enhancement in nutritional status and digestion. Piperine is one of the active constituents present in both drugs. Piperine has been shown to enhance the bioavailability therapeutically[14] leading to nutrient absorption seen as weight gain without alteration in activity levels in experimental animals. *Pippalimula* showed significant effects on body weight, noticeable from the 7th day, which indicates prompt activation of the digestive system. *Pippali* demonstrated body

Table 3 — Effects of test drugs on digestive enzymes and hormones in albino rats selected for *Deepana- Pachana* activity

Groups	Control	*Pippali Churna*	*Pippalimula Churna*
Serum Hormones			
Ghrelin (pg/mL)	948.54±149.49	990.08±170.27	844.59±136.78
Cholecystokinin (pg/mL)	203.552±29.114	258.32±44.464	234.037±16.697
Stomach mucosal tissue parameters			
Pepsin (µmoles of tyrine released/g)	512.49±22.36	736.91±48.14$^{@@}$	688.03±33.22$^{@@}$
Total Protein (µg/g)	223.36±21.963	209.203±20.936	116.992±9.271$^{@@}$
Intestinal mucosal enzymes			
Lipase (units/mg protein)	0.277±0.029	0.333±0.003	1.033±0.109$^{@@}$
Amylase (Unit/mg protein)	0.367±0.053	0.827±0.077$^{@@}$	1.262±0.14$^{@@}$
Trypsin (Unit/mg protein)	0.248±0.0363	0.476±0.0394$^{@}$	0.813±0.088$^{@@}$

Data: Mean±SEM
$^{@}p<0.05$, $^{@@}p<0.01$, compared to control group (Anova followed by Dunnett's multiple 't' test)

weight gain, especially noticeable on the 14th day, suggesting stronger assimilative effects, potentially due to its influence on enhancing digestive capacity, gastrointestinal blood flow and modulating intestinal enzyme activity. *Pippali* has *Rasayana* property, which justifies these results. Both *Pippali* and *Pippalimula* significantly increased food consumption during the experimental phase. It indicates the *Deepana* effect of both drugs. *Pippalimula* has a greater impact on appetite stimulation, as indicated by the highly significant increase in food consumption. It suggests that *Pippalimula* is especially potent in stimulating the *Agni* (digestive fire), which enhances the appetite.

Pippalimula significantly increases appetite, seen as increased food intake, but the weight gain of albino rats is not as pronounced as compared to *Pippali*. As *Pippali* possesses both *Rasayana* and *Deepana* actions, it accounts for the greater weight gain observed compared to *Pippalimula*, which primarily exhibits *Deepana* action. Both *Pippali* and *Pippalimula* groups showed an increase in water intake during the experimental phase, with *Pippalimula* displaying a more substantial effect. The stimulation of thirst occurred as part of the digestive process. Additionally, *Pippalimula* has *Ruksha Guna*[15], which accounts for *Kleda Shoshana* effect, enhancing thirst, leading to increased water intake.

Both *Pippali* and *Pippalimula* caused a reduction in dry faecal output during the experimental phase. The findings are opposite to the qualities mentioned in the Ayurvedic texts. Bhavaprakasha Nighantu, one of the lexicons, describes *Pippali* as *Rechini*[3], and *Pippalimula* as *Bhedana*[15], which means both have laxative properties. It has been proven in previous research that *Piper longum* plays a role as a bioavailability enhancer might explain why it could lead to increased food intake while also promoting better absorption of nutrients, possibly leading to reduced faecal bulk[16]. The decrease in faecal output observed in the *Pippali* group suggests that this drug improves food assimilation and absorption, where food is efficiently metabolised and incorporated into body tissues.

The results showed a slight increase in urine output in *Pippalimula* treated group, while *Pippali* treated group showed a slight decrease in urine output, which suggests no influence of the test drugs on renal excretion of albino rats. The food conversion ratio (FCR) was observed to be increased in both groups. This highlights the *Deepana* and *Pachana* effect of these drugs, seen as improvement in digestion and assimilation, leading to increased food consumption and less excretion of undigested matter as faecal output.

Ghrelin is a hormone primarily produced by enteroendocrine cells of the gastrointestinal tract, especially the stomach, and is often called a "hunger hormone" because it increases the drive to eat. Ghrelin is a participant in regulating the complex process of energy homeostasis[17]. In recent years, ghrelin has been found to have a plethora of central and peripheral actions in distinct areas including learning and memory, gut motility and gastric acid secretion, sleep/wake rhythm, reward seeking behaviour, taste sensation and glucose metabolism[18].

In the study, the *Pippali*-treated group showed an increase in serum ghrelin levels, while the *Pippalimula*-treated group showed a decrease in ghrelin levels compared to the control. However, these changes were not statistically significant. The slight increase in ghrelin levels in the *Pippali* group suggests its appetite-stimulating effect as well as maintenance of homeostasis in energy utilization. By modulation of metabolic pathways and gut-brain signalling, *Pippali* might influence ghrelin dynamics indirectly by acting on associated neuroreceptor pathways. Piperine, the active alkaloid in *Piper longum*, has been linked to metabolic regulation, potentially influencing hormones like ghrelin indirectly by affecting pathways related to energy balance, appetite, and gastrointestinal function[19]. Piperine has demonstrated effects on reducing gastric emptying, which could alter ghrelin levels since this hormone increases before meals and decreases after eating. Slower gastric emptying may prolong satiety, reducing ghrelin secretion[19].

Cholecystokinin is a peptide hormone of the gastrointestinal system responsible for stimulating digestion in the small intestine[20]. CCK triggers the pancreas to secrete digestive enzymes (e.g., amylase, lipase, and proteases) that aid in breaking down carbohydrates, fats, and proteins in the small intestine[19]. The increased CCK levels in both groups suggest an enhancement in the digestive process, supporting the *Deepana-Pachana* effects of these drugs. *Pippali* showed a higher increase in CCK when compared to *Pippalimula. Pippali* increased both ghrelin (appetite stimulation) and CCK (digestive stimulation), which aligns with its balanced role in

promoting both appetite and digestion. *Pippalimula*, by reducing ghrelin while increasing CCK, indicated its potential to enhance digestive efficiency.

In gastric mucosa of albino rats, both experimental drugs increased pepsin levels. Pepsin is an enzyme found in gastric juice that hydrolyses proteins[21] from the food material. Its digestive power is greatest in the highly acidic environment of gastric juice[22]. Since both the experimental drugs had acidic pH[4,5], it led to a significant increase in peptic activity in both the treated groups when compared to the control group, with *Pippali* showing a slightly stronger effect.

In the *Pippali* and *Pippalimula* groups, there is a decrease in total protein levels in gastric mucosa. The results were following previous studies on *Pippali*, which showed that *Pippali* increased gastric juice volume and acid-pepsin secretions, while decreasing the protein content in the gastric mucosa[23]. *Pippali* and *Pippalimula* may have a mild irritant effect on the gastric mucosa, which could induce a protective response leading to alterations in protein synthesis or turnover[24].

Lipase is the enzyme responsible for a class of enzymes that catalyzes the hydrolysis of fats, breaking down fats into fatty acids and glycerol[25]. Both the drugs increased lipase activity in intestinal mucosa, wherein *Pippalimula* showed a statistically significant increase, indicating a strong effect on stimulating fat digestion. These results were similar to a previous study done on *Trikatu Churna*, (*Pippali* being one of the contents of *Trikatu*) wherein the *Trikatu* treated group showed an increase in lipase secretion[26]. This difference in the breakdown of fats with *Pippalimula* and *Pippali*, accounts for *Ruksha guna* of *Pippalimula* which facilitates digestion of *Meda Dhatu*[27] (~fats).

Amylase is the enzyme responsible for breaking down carbohydrates (specifically starches)[28] into simpler sugars, which are then absorbed in the intestines. The significant increase in amylase activity seen in both groups suggests that *Pippali* and *Pippalimula* enhance intestinal carbohydrate digestion. Also, this increase was within normal limits[29]. According to previous research, piperine showed a reduction in symptoms of human metabolic syndrome in high carbohydrate and high fat-fed rats by reducing inflammation and oxidative stress[30]. This indicated that piperine-containing drugs like *Pippali* and *Pippalimula* improve carbohydrate metabolism, which is seen in the results. The more increase in amylase levels in the *Pippalimula* group suggests that it has a stronger effect on carbohydrate metabolism compared to *Pippali*. The study published previously examined effects of various dietary spices, including Piperine, on pancreatic digestive enzymes in albino rats; found that, dietary piperine significantly enhanced the activities of pancreatic lipase, amylase, trypsin and chymotrypsin[31].

Trypsin enzyme is involved in protein digestion in the intestines, breaking down proteins into peptides and amino acids[32]. When the pancreas is stimulated by cholecystokinin, trypsinogen is then secreted into the first part of the small intestine (the duodenum) via the pancreatic duct. Once in the small intestine, the enzyme enterokinase (also called enteropeptidase) activates trypsinogen into trypsin by proteolytic cleavage. The trypsin then activates additional trypsin, chymotrypsin and carboxypeptidase[33]. An increase in cholecystokinin levels was seen in this experiment; it substantiates the notable increase in trypsin activity with both *Pippali* and *Pippalimula.* This suggests that these drugs are effective in enhancing protein digestion. Pepsin is also involved in protein digestion. The site of action of pepsin is in the stomach while that of trypsin is in the intestine. *Pippali* showed higher pepsin levels and *Pippalimula* showed higher trypsin levels indicating the difference in their site of action. *Pippali* has stronger protein digestive action in the stomach while *Pippalimula* shows stronger protein digestion in the intestines.

This experiment strongly justified the *Deepana karma* attributed to *Pippali* while *Pachana* to *Pippalimula* as given in the classical text Bhavaprakasha Nighantu. *Pachana Dravyas* kindle the digestive fire along with metabolising the undigested matter. They produce stronger effects than *Deepana Dravyas* which is evident in the experiment. This suggests that *Pippalimula* acts on intestinal mucosa rather than gastric mucosal tissues; while *Pippali* has a balanced effect on the overall GI tract. This research study certainly rationalised the broader spectrum of action of *Pippali*, than *Pippalimula*, accounting for its versatility in foundational qualities.

Conclusion

The findings highlight Ayurvedic principles of drug action, showing distinct roles of *Pippali* and *Pippalimula* in modulating digestion and metabolism. Both drugs enhance digestion, absorption, and metabolism in albino rats. *Pippalimula* significantly

increases digestive enzyme secretion in the intestinal mucosa, while *Pippali* promotes digestion in the gastric mucosa, further improving assimilation and absorption of food. These results also validate *Pippali's Rasayana* effect alongside its *Deepana* action as described in classical texts. The observed differences emphasise the unique modes of action of the two drugs, as per their inherent pharmacological properties, thus supporting the Ayurvedic perspective of drug-specific therapeutic applications.

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Conflict of Interest

There are no conflicts of interest.

Author Contributions

GP: Conceptualizing the study, drafting the manuscript, carried out the experiments, collected data, and performed statistical analysis. MN and BP: reviewed the manuscript and provided critical revisions.

Ethics Approval

The experimental animals were approved by the Institutional Animal Ethics Committee (IAEC) of ITRA Jamnagar, approval number IAEC/32/2023/02 and the study was conducted according to Committee for Control and Supervision of Experiments on Animals (CCSEA) guidelines.

Data Availability

The authors confirm that all the data supporting the findings of this study are available within the article.

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