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Possible role of serotonin in the gastrokinetic activity of *Amorphophallus paeoniifolius* tuber

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ABSTRACT

Background: : *Amorphophallus paeoniifolius* (Dennst.) Nicolson (Araceae) tuber is consumed by various tribes for the treatment of constipation, hemorrhoids, functional dyspepsia and abdominal pain as ethnomedicinal practices. In our previous study, the tuber extract showed alteration of gastric emptying in healthy rats and ameliorated the gastrointestinal motor disorders, constipation and piles.

Aim of the study: : Hence, the present study evaluated the effect of *Amorphophallus paeoniifolius* tuber on experimentally-induced delayed gastric emptying in rats as well as investigated the plausible mechanism involved therein.

Methods: : Methanolic extract of *Amorphophallus paeoniifolius* (APME) was orally administered at the doses of 125, 250 and 500 mg/kg for 7 days. Delayed gastric emptying was induced in rats by cisplatin (10 mg/kg, i.p.) on the last day of extract treatment and gastric emptying was studied. To study the involvement of serotonergic system, the effect of APME (500 mg/kg) was investigated on gastric emptying in p-chlorophenylalanine (PCPA, a serotonergic neurotoxin) treated rats. Ex-vivo studies in isolated tissue preparation were also conducted to test the effect of APME on fundus contractility.

Results: : APME significantly reversed the delayed gastric emptying caused by cisplatin comparable to standard prokinetic drug, metoclopramide. Interestingly, the co-administration of sub-maximal doses of APME and metoclopramide showed synergistic effect on delayed gastric emptying. Further, in PCPA treated rats, APME (500 mg/kg) did not show any significant influence on delayed gastric emptying similar to metoclopramide. In Ex-vivo studies, the contractile response of APME remained unaltered in presence of atropine while it was potentiated significantly ($P < 0.001$) in presence of 5-HT as compared to the individual responses of 5-HT or APME. Phytochemical studies revealed the presence of betulinic acid in APME which is partial serotonergic agonist.

Conclusion: : The tuber of *Amorphophallus paeoniifolius* exhibited gastrokinetic activity and may be beneficial on functional dyspepsia. The effect may be ascribed to modulation of serotonergic neurotransmission in GIT.

Abbreviations

ANOVA	Analysis of variance
APME	Methanolic extract of *Amorphophallus paeoniifoius*
CPCSEA	Committee for the purpose of control and supervision of experiments on animal
FD	Functional dyspepsia
GIT	Gastrointestinal tract
HPLC	High performance liquid chromatography
IAEC	Institutional animal ethics committee
MET	Metoclopramide
PCPA	p-chlorophenylalanine

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Introduction

Dyspepsia may be termed as feeling of pain or discomfort in the upper and middle position of abdomen near the ribs and can be categorized as acute or chronic. If the dyspepsia complaint is not caused by organic abnormality, systemic or metabolic disease, then it is considered as functional dyspepsia (FD). Currently there are two categories of FD - postprandial distress syndrome (PDS) induced by meal and epigastric pain syndrome (Loyd and McClellan, 2011; Tack et al., 2006). Previous epidemiological studies suggest that approximately 15% of population suffers from FD in western countries (Shaib and El-Serag, 2004). Though etiology and pathophysiology of FD is unclear; however, delayed gastric emptying has been found to be underlying cause in many clinical situations (Talley et al., 2006). Although the clinical course of FD is benign, the impact can be substantial for the affected patients with regard to the decrease in quality of life, and for society with regard to the economic implications (Tack and Janseen, 2011). Current available agents for the treatment of dyspeptic disturbances include the use of prokinetic drugs (Giurcan and Voiosu, 2010) such metoclopramide, domperidone, cisapride, mosapride, ranzapride and macrolides (Motilin agonists) (Sharma and Sharma, 2008). However, their use is limited due to side effects associated with them (Desta et al., 2002). As the available pharmacological therapy for patients with FD is overall unsatisfactory (Holtmann and Gapasin, 2008; Brun and Kuo, 2010), alternative remedies like herbal products for symptomatic relief are widely used by dyspeptic patients (Suzuki et al., 2009).

Amorphophallus paeoniifolius (Dennst.) Nicolson (Araceae) tuber has got remarkable effects on the gastrointestinal tract (GIT) and corrects various gastrointestinal motility disorders (Dey et al., 2012). It is consumed by various tribes of India for mitigation of constipation, hemorrhoids, dyspepsia, and abdominal pain as ethnomedicinal practices (Rahman et al., 2013; Devi Prasad et al., 2013; Yesodharan and Sujana, 2007). Previously, we reported the beneficial effect of the tuber extracts on constipation (Dey et al., 2020), hemorrhoids (Dey et al., 2016a), and ulcerative colitis (Dey et al., 2017a). Our previous studies on normal gastrointestinal functions revealed that the methanolic extract of the tuber of *A. paeoniifolius* induced alteration in gastrointestinal motility (Dey et al., 2016b). These pieces of evidence contemplate that it may exert a beneficial effect on a functional motor disorder like functional dyspepsia. Hence, the present study investigated the effect of methanolic extract of *A. paeoniifolius* (APME) on cisplatin-induced delayed gastric emptying, an animal model of functional dyspepsia representing its one characteristic feature i.e. delayed gastric emptying.

Serotonin is in an important neurotransmitter in the GIT and central nervous system. About 95% of body serotonin is found in the GI tract mainly in enterochromaffin cells and the serotonergic neurons of myenteric plexus. The remainder of 5% serotonin is found in the brain (Gershon et al., 1965). The serotonergic receptors mainly 5-HT3 and 5-HT4 are involved in the prokinetic activities of the gastrointestinal tract (Sikander et al., 2009). Besides serotonin, cholinergic neurotransmission as a part of the enteric nervous system has an equally important role to play in GI motor and other functions through muscarinic receptors (McConalogue and Furness, 1994). Hence, attempts were also made to elucidate the plausible mechanism involved in the gastrokinetic activity of APME.

Materials and methods

Drug and chemicals

Cisplatin (KEMOPLAT, Fresenius Kabi Oncology Ltd., Baddi, India) was purchased as injectable, while metoclopramide HCl (PERINORM, IPCA Laboratories Ltd., Mumbai, India) was procured as syrup from Chemist shop from the local market. Parachlorophenylalanine was purchased from Sigma-Aldrich, USA.

Collection, authentication, and processing of the tuber

The tubers of *Amorphophallus paeonnifolius* were collected from the local market of Gwalior in December 2011 and identified by Dr. N.K. Pandey, Taxonomist of the Institute. A voucher specimen No. 5–4/10–11/NRIASHRD/Tech/Survey/1611 was deposited in the herbarium of the Institute. The tubers were chopped into thin pieces, shade dried and coarsely powdered. The powdered tuber was extracted with methanol in a Soxhlet extractor, dried in a rotary evaporator, and stored in a desiccator for further use. The standardized extract of APME (Dey et al., 2016b, 2020) by HPLC and HPTLC was used in the present experiments.

Animals

Healthy adult male Wistar rats of 8–10 weeks of age and 220–250 g weight were used for the study. The animals were housed at standard experimental conditions of temperature (25 ± 2 °C) with a relative humidity of 50 ± 5% under a 12 h light: dark cycle. They were fed standard rodent chow (Ashirwad brand, Chandigarh, India) and water ad libitum. Experiments were performed in accordance with the guidelines of CPCSEA, Ministry of Environment, Forest and Climate Change, Govt. of India, after approval IAEC (IAEC Proposal No. NRIASHRD-GWL/IAEC/2013/01).

Cisplatin-induced delay in gastric emptying

Rats were divided into 8 groups each containing 6 animals as follows.

Group I: Normal control (NC) received normal saline

Group II: Cisplatin control group received vehicle (1% Tween 80, 5 ml/kg, orally)

Group III-IV: Standard drug, metoclopramide (MET) (1.5 and 3 mg/kg, orally)

Groups V–VII: received APME (125, 250, and 500 mg/kg, orally)

Group VIII: received MET (1.5 mg/kg, orally) and APME (250 mg/kg, orally)

The above treatments were given for 7 days. On day 7 rats fasted for 16 h with free access to water. The doses of APME were determined as per the previous oral toxicity studies (Dey et al., 2017b). On day 8, cisplatin (10 mg/kg) was administered intraperitoneally (i.p) to Group II-VIII, 30 min before the test meal administration for induction of delayed gastric emptying, a characteristic of functional dyspepsia (Sharma and Gupta, 1997). Briefly, a 1.5 ml test meal (0.05% phenol red in 1.5% aqueous methylcellulose solution) was administered to rats by the intragastric route. After 30 min, the abdomen was cut open in anesthetized rats, and the stomach was dissected out after careful ligation at the cardiac and pyloric ends and washed with normal saline. The stomach was cut into pieces and homogenized with 25 ml of 0.1 N NaOH. To this 5 ml homogenate, 0.5 ml of trichloroacetic acid (20% w/v) was added and centrifuged at 3000 rpm for 20 min. To 1 ml of supernatant, 4 ml of 0.5 N NaOH was added. The absorbance of the pink-colored liquid was measured spectrophotometrically at 560 nm. Phenol red recovered from the stomach of rat sacrificed immediately after a meal was considered the average amount of phenol red from a standard stomach. The percent gastric emptying was calculated as below

% Gastric emptying = [1 - (Amount of phenol red recovered from test stomach/ Average amount of phenol red recovered from standard stomach] × 100

Estimation of gastric emptying in p-chlorophenylalanine (PCPA) treated rats

PCPA depletes 5-HT by inhibiting tryptophan hydroxylase, rate-limiting enzyme in the biosynthesis of 5-HT (Koe and Weissman, 1966). Hence, to study the involvement of the serotonergic system, the effect of APME was investigated on gastric emptying in p-chlorophenylalanine (PCPA), a serotonergic neurotoxin-treated rats.

Grouping and treatments

The rats were divided into 4 groups each containing 6 animals as follows.

Group I: Normal control received normal saline

Group II: PCPA control group received vehicle (1% Tween 80, 5 ml/kg, orally)

Group III: Standard drug, MET (3 mg/kg. orally) treated

Groups IV: received APME (500 mg/kg, orally)

Animals of Group II to IV were administered with PCPA (100 mg/kg/day) for 2 consecutive days (Hirata et al., 2012) prior to vehicle or drug treatments. Group III and IV were treated with effective doses of APME and MET, respectively for 7 days. On day 8, gastric emptying was studied in 16 h fasted rats.

Fundus contractility

A separate group of adult Wistar albino rats were fasted overnight with free access to water, and then they were sacrificed. The stomach was dissected out and placed in Krebs solution at 37 °C. The gray fundal part was separated, cut longitudinally to strips, and mounted in the organ bath as per the standard procedure. The effect of the cholinergic antagonist, atropine on the contractile response of ACh and APME in fundus was evaluated by incubation with their submaximal doses which were determined in our previous ex-vivo study where the submaximal doses of acetylcholine and APME on fundus were 4.17 and 779.8 µg, respectively (Dey et al., 2016b). Further, the various concentrations of (5-HT) (1, 2, 4, 6, 8, 16, 32, 64 µg) from the stock solution (10 µg/ml) were injected into the tissue bath till the maximum ceiling effect was observed. The concentration-response curve was plotted and EC_{50} was found to be 6.29 µg. Further, the contractile response was evaluated by incubation with a sub-maximal dose of APME and a sub-maximal dose of 5-HT. The experiments were done in triplicate.

Statistical analysis

The data were analyzed using Prism Pad statistics software version 4.0. All data were analyzed by one-way ANOVA followed by Tukey's multiple comparison post-hoc test. A statistical difference of $P < 0.05$ was considered significant in all cases.

Results

Effect on cisplatin-induced gastric emptying

Results indicated that cisplatin administration significantly ($P < 0.001$) decreased gastric emptying when compared to normal control rats. Pretreatment with APME (250 and 500 mg/kg) ($P < 0.01$, $P < 0.001$, wherever applicable) and MET (3 mg/kg) significantly attenuated ($P < 0.001$) delay in gastric emptying when compared to cisplatin-treated control group (Fig. 1). However, lower doses of APME (125 mg/kg) and MET (1.5 mg/kg) did not show any significant effect. The combined administration of APME (250 mg/kg) and MET (1.5 mg/kg) significantly ($P < 0.001$) attenuated delay in gastric emptying due to cisplatin.

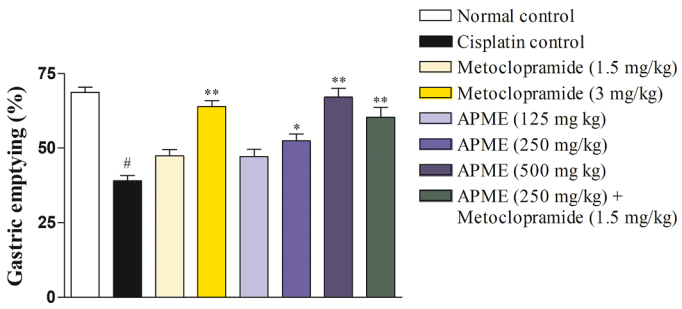

Fig. 1. Effect of APME on cisplatin-induced gastric emptying. Doses are expressed in mg/kg; Results are expressed as mean±SEM ($n = 6$) *$P < 0.001$ when compared to normal control, *$P < 0.01$, **$P < 0.001$ when compared to cisplatin treated control.

Effect on gastric emptying in PCPA treated rats

Results indicated that PCPA administration caused a significant ($P < 0.001$) delay of gastric emptying when compared to normal control rats. Treatment with MET (3 mg/kg) and APME (500 mg/kg) caused a significant ($P < 0.001$) increase in gastric emptying when compared to normal control rats. Treatment with MET (3 mg/kg) and APME (500 mg/kg) did not show any significant ($P > 0.05$) influence on delayed gastric emptying when compared to PCPA treated control group (Fig. 2). There is a significant decrease ($P < 0.001$) in gastric emptying when comparisons were made between MET (3 mg/kg) with and without PCPA treatment as well as APME (500 mg/kg) with and without PCPA pretreatment.

Effect of atropine on contractile response of ACh and APME in fundus

The incubation of isolated rat fundus tissue with the cholinergic antagonist, atropine attenuated the contractile response of ACh in the fundus ($P < 0.01$) when compared with ACh alone whereas the contractile response of APME ($P > 0.05$) remained unaltered (Fig. 3).

Effect on fundus contractility by combination of 5-HT and APME

The incubation of isolated rat fundus tissue with a sub-maximal concentration of 5-HT along with the sub-maximal concentration of APME showed significant ($P < 0.001$) potentiation of the contractile response of 5-HT as compared to the individual responses of 5-HT or APME (Fig. 4).

Discussion

In view of the gastrokinetic effect of *Amorphophallus paeonifolius* tuber extract in the previous studies, attempts were made to demonstrate its influence on FD, a functional motors disorder of GIT. Cisplatin, a chemotherapeutic anti-cancer drug, delays gastric emptying in rats (Sharma and Gupta, 1997), which is one of the characteristic features of functional dyspepsia. Hence, the effect of APME was studied on cisplatin-induced delayed gastric emptying. Cisplatin causes the release of 5-HT from the mucosal enterochromaffin cells in the GIT (Horikoshi et al., 2001). 5-HT activates both intrinsic and extrinsic primary afferent neurons to, respectively initiate peristaltic and secretory reflexes and to transmit information to the central nervous system (Sikander et al., 2009). It acts on peripheral 5-HT_3 receptors on the vagal afferent fibers and stimulates the vomiting center through the chemoreceptor trigger zone and nucleus tractus solitarius (Andrews et al., 1990). GIT also constitute 5-HT_4 receptors which are G-protein linked receptor. Ligand binding activates an increase in cAMP via adenyl cyclase and subsequently activates a protein kinase, which inhibits $K+$ channels, preventing hyperpolarization, thereby enhancing excitability of the cell and causing gastrokinetic effect (Spiller, 2002). In the present study, cisplatin treatment delayed gastric emptying as compared to control animals. The results were consistent with the previous study (Sharma and Gupta, 1997). Treatment with APME showed dose-dependent attenuation of cisplatin-induced delayed gastric emptying. Standard prokinetic drug- MET also exhibited similar action. The increased gastric emptying of nutrient meal by APME may be due to its prokinetic action (Dey et al., 2016). The prokinetic action of the plant may be in part due to increased peristalsis or gastric motility along with the secretary action of the extract or its influence on the neurotransmitters system like 5-HT.

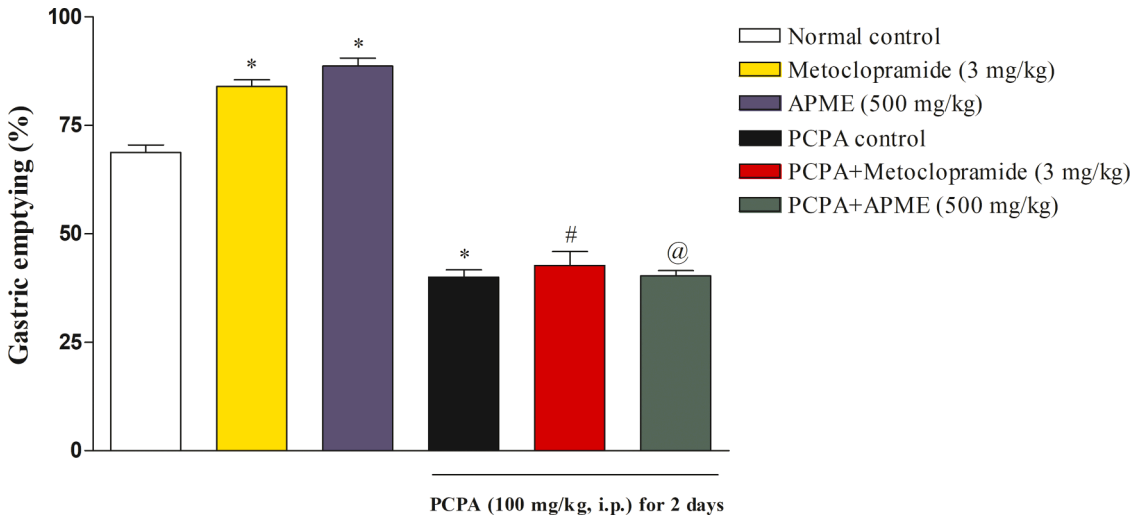

Fig. 2. Effect on gastric emptying in PCPA treated rats doses are expressed in mg/kg; Results are expressed as mean ± SEM ($n = 6$) *$P < 0.001$ when compared to normal control, #$P < 0.001$ when compared between MET (3 mg/kg) with and without PCPA treatment, @$P < 0.001$ when compared between APME (500 mg/kg) with and without PCPA pretreatment.

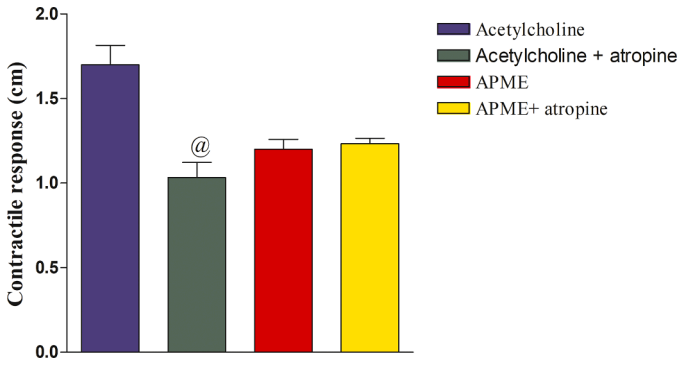

Fig. 3. Effect of atropine on contractile response of ACh and APME in fundus. Results are expressed as mean ± SEM ($N = 3$) @$P < 0.01$ when compared to ACh.

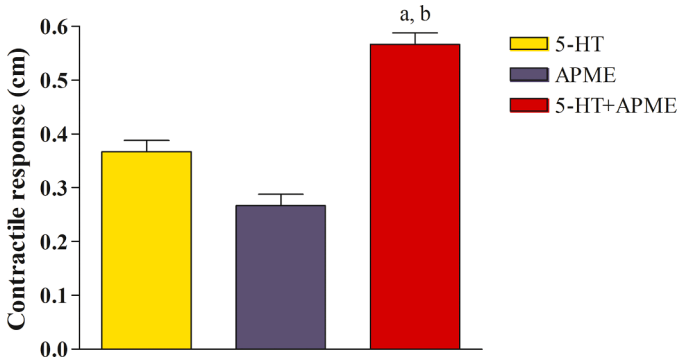

Fig. 4. Effects on fundus contractility by combination of 5-HT and APME. Results are expressed as mean ± SEM ($N = 3$) a $P < 0.001$ when compared to 5-HT, b $P < 0.001$ when compared to APME.

Previous studies have speculated and ruled out the involvement of serotonergic system in delayed gastric emptying and its modulation by herbal extracts (Sharma and Gupta, 1997). In order to study the involvement of the 5-HT neurotransmitter system in the action of APME, the combination of sub-maximal doses of APME with MET was tested. The combined administration of APME and MET exhibited a synergistic effect on gastric emptying. MET exhibits prokinetic action due to its weak 5-HT3 antagonistic and 5-HT4 agonistic action (Mahesh et al., 2005), and its synergistic action with APME further advocates the role of 5-HT neurotransmitter in the action of APME. To confirm the role of 5-HT in the gastrokinetic action of APME, gastric emptying was studied in rats treated with 5-HT neurotoxin, PCPA (Hirata et al., 2012), which is an inhibitor of tryptophan hydroxylase, a rate-limitingPCPA-treated enzyme in 5-HT biosynthesis. APME failed to attenuate the delayed gastric emptying in PCPA treated rats. Thus, the findings of the synergistic effect of APME with MET and non-significant effect of APME on gastric emptying of PCPA treated rats suggest that APME might have exhibited prokinetic action via modulation of serotonergic transmission through weak 5-HT3 antagonistic and 5-HT4 agonistic action as like MET. The significant decrease ($P < 0.001$) in gastric emptying between MET (3 mg/kg) with and without PCPA treatment as well as APME (500 mg/kg) with and without PCPA pretreatment indicates the involvement of 5HT in the prokinetic action of APME. Further, ex vivo studies on rat fundus preparation revealed that the cholinergic antagonist, atropine blocked the contractile response of acetylcholine ($P < 0.05$) whereas the effect of APME ($P > 0.05$) remained unaffected. This indicates that the contractile effect of APME is not mediated through the cholinergic system. Further, the combined incubation of fundus with 5-HT and APME showed ($P < 0.001$) increased contractile response as compared to their individual responses (Fig. 3). This suggests that serotonergic neurotransmission might be mediating the contractile action of APME and strengthens the present findings.

Previously phytochemical studies in our laboratory revealed that APME mainly contains a fair amount of phenolic and flavonoids. We also quantified betulinic acid, a chief constituent by HPLC (Dey et al., 2016b, 2017a), and isolated two important phytoconstituents i.e. betulinic acid and β-sitosterol (Dey et al., 2017a) through column chromatography. Betulinic acid showed a spasmogenic effect by partial agonistic action on the serotonergic (5-HT) receptors in rat fundus preparation (Bejar et al., 1995). Thus, betulinic acid probably might have exerted a modulatory influence on 5HT neurotransmission in GIT to show increased gastrointestinal motility. Hence, it is postulated that the motility-enhancing effect of APME and subsequent amelioration of FD may be attributed to the presence of betulinic acid and other bioactives possibly through a spasmogenic effect via a serotonergic mechanism.

Conclusion

In conclusion, the tuber of *Amorphophallus paeoniifolius* exhibited

beneficial effect on functional dyspepsia through its gastrokinetic effect which may be ascribed to modulation of serotonergic neurotransmission in GIT.

Author agreement statement

We declare that this manuscript is original has not been published before and is not currently being considered for publication elsewhere. We confirm that the manuscript has been read and approved by all authors.. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We understand that the corresponding author is the sole contact for the editorial process. He is responsible for communicating with the other authors about progress submissions of revision and final approval of proofs

Author's contribution

YD, MMW, and DK generated the concept and designed the study. YD executed the study, analyzed the data, and prepared the manuscript. SM and DS assisted in the experimental work. MMW, DK, and JS corrected the manuscript. All authors checked the final MS. All authors have read and approved the manuscript. All data were generated in-house, and no paper mill was used. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Competing Interest

The authors have no competing interests.

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