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Full Length Research Paper

Role of gastrointestinal motility/gastric emptying in cisplatin-induced vomiting in pigeon

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In this study we screened various crude fractions of *Cannabis sativa* indigenous to Pakistan against cisplatin-induced vomiting in pigeon and to find the involvement of gastrointestinal (GIT) motility and gastric emptying in said complication. *Cannabis sativa* hexane (CS-HexFr 5, 10 and 15 mg/kg), n-butanol (CS-ButFr 5 and 10 mg/kg) and methanol fractions (CS-MetFr 10 and 15 mg/kg) were examined against cisplatin-induced vomiting and their possible effects on GIT motility/gastric emptying in pigeon by charcoal propulsion method. Standard prokinetic drugs metoclopramide (MCP, 30 mg/kg) and carbachol (0.1 mg/kg) were screened in combination with CS-HexFr to estimate the involvement of gastric emptying and GIT motility in cisplatin-induced vomiting. CS-HexFr at the dose of 10 mg/kg once and twice daily attenuated cisplatin-induced vomiting up to 55.45 and 68.86% ($P < 0.01$), respectively. CS-MetFr and CS-ButFr failed to reduce cisplatin-induced vomiting ($P > 0.05$). CS-HexFr 10 mg/kg caused up to 26.62% suppression in GIT motility as compared to vehicle treatment group. MCP (30 mg/kg) and carbachol (0.1 mg/kg) completely antagonized the suppression caused by CS-HexFr 10 mg and in combination enhanced the antiemetic profile at 12 to 24 h, while no enhanced activity was observed at 0 to 12 h. The findings suggest that the decrease in GIT motility/gastric emptying is playing a role at least in part in the vomiting induced by cisplatin commencing just after the peak vomiting response of acute phase in pigeon.

Key words: Cisplatin, vomiting, gastrointestinal motility, *Cannabis sativa*, carbachol.

INTRODUCTION

Cisplatin is one of the broad spectrum anti-cancer agents indicated for various carcinomas including ovarian, testicular, lungs, head and neck, bladder and breast carcinomas (Jarve and Aggarwaı, 1997). Aside from its useful broad spectrum anti-cancer activity, it has a lot of adverse reactions as well including oxidative stress (Sodhi and Gupta, 1986), lipid peroxidation (Sugihara et al., 1987), hypocalcemia, hypomagnesia (Hodgkinson et al., 2006; Lajer *and* Daugaard, 1999; Martin et al., 1992), nausea and vomiting (Qiu-hai et al., 2010), ototoxicity (Rybak et al., 2007), stomach distention and nephrotoxicity (Aggarwal et al., 1994). Nausea and vomiting (Glaus et al., 2004; Topal et al., 2005) are the major dose limiting adverse reactions which leads to discontinuation of curative therapy (Naylor and Rudd, 1996). Cisplatin induces biphasic vomiting named acute and delayed. The acute phase last up to 24 h in humans (Tavorath and Hesketh, 1996) and it is mediated by 5-HT_3 receptors as 5-HT_3 receptor antagonists are proving themselves to be effective, while delayed phase last up to several days (Kris et al., 1998) and is poorly controlled even by using combination regimen of currently available antiemetics.

The poor control of delayed phase in 60 to 80% of patients (Kris et al., 1985) is 48 to 72 h post treatment of cisplatin by 5-HT_3 receptor antagonists indicating the involvement of other triggering mechanisms.

In India, *Cannabis sativa* preparations have been used against vomiting (Mechoulam and Feigenbaum, 1987). Furthermore, Sallan et al. (1975) found that the active component of *C. sativa* have antiemetic property, which reside in its ability to stimulate cannabinoid receptor type

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1 (CB_1) (Darmani, 2001a). Presynaptically, located CB_1 receptors stimulation have inhibitory effect on neuro-transmitter (serotonin, norepinephrine, dopamine, and acetylcholine) release (Darmani et al., 2003) and this inhibition of ongoing contractile transmitter release in the enteric nervous system leads to depression of gastrointestinal (GIT) motility (Pertwee, 2001a). Moreover, cisplatin also dose dependently inhibits gastric emptying in rats and mice (Sharma and Gupta, 1998). As distention of the stomach has been shown parallel to nausea and vomiting (Roos et al., 1981), the present study was designed (1) to test and screen *C. sativa*'s various crude fractions for their antiemetic profile against cisplatin-induced vomiting in pigeon and (2) to find out the role of GIT motility/gastric emptying in cisplatin-induced vomiting.

MATERIALS AND METHODS

Animals

Pigeons of either sex (mixed breed, Department of Pharmacy, University of Peshawar, Pakistan) in weight range of 250 to 350 g were used. Animals were housed in group of eight and 24 h acclimatization time was given to each group before starting the experiment. Free access to food (locally available food; Millet + Wheat) and water was there before and during experimentation, temperature was maintained at 22 to 26°C with 12 h light dark cycle (light on at 07:00). All the experimental procedures were approved by the Ethics committee, Department of Pharmacy, University of Peshawar and are in accordance with the Animal Scientific Procedure ACT (1986) (United Kingdom).

Materials and drugs

Cisplatin (generously donated by Korea United Pharm. Inc Korea) was dissolved in normal saline at 65 to 70°C with continuous shaking until it appears clear and followed by cooling up to 45 to 50°C administered immediately. Metoclopramide (MCP) was purchased in solution from GlaxoSmithKline Pakistan Limited. Carbachol was from Sigma Gmbh Germany. Methanol, n-hexane and n-butanol were from Haq Chemicals Peshawar (Pakistan).

Extraction of *Cannabis sativa*

The plant was collected at a farm with permission, from Malakand Division (Khyberpukhtoon Khwa, Pakistan) at its bloom season. The plant was authenticated by Prof. Dr. Muhammad Ibrar, Department of Botany, University of Peshawar). Leaves and flowering tops were separated, shade dried, coarsely grinded and then extracted with n-hexane (yield 6.7%), n-butanol (yield 1.5%) and methanol (yield 1.8%) with their increasing order of polarity using maceration method. For administration, each fraction was dissolved in absolute ethanol, mixed with emulsifier and make the volume with distilled water in such a way that the final mixture consists of ethanol : emulsifier : distilled water in a ratio of 5:5:90 (Feigenbaum et al., 1989).

Drug administration

Neoject 2 ml non-pyrogenic syringes with sharp painless needles of 27G × 1/2" and 23G × 1" were used for intravenous and intramuscular routes, respectively. Cotton wool and methylated spirit were used for sterilization prior to drug administration.

Intravenous and intramuscular administration was done through brachial wing vein and chest muscle, respectively while oral route was used for charcoal administration.

Cisplatin-induced vomiting

On the day of experiment, the pigeons were transferred to individual cages specially designed for video observation and cisplatin (7 mg/kg) was administered intravenously via the brachial wing vein (Tanihata et al., 2000). The dose of cisplatin was selected on the basis of our previous studies in which it induced vomiting in all the animals tested (Unpublished data). The behavior of the pigeon was recorded with a video recording setup up to 24 h. Food and water were available during the observation period and each animal was used once. The response with or without oral expulsion was considered as one vomiting episode (Preziosi et al., 1992), one vomiting episode comprised of 2 to 80 jerks (emetic behaviors). Latency to first emesis, emetic episodes and jerks were recorded. The parameter to split two emetic episodes was the complete relaxation of the animal. The antiemetic effects of various fractions of *C. sativa* and drug combinations were studied. *C. sativa* hexane fraction (CS-HexFr) 5, 10 and 15 mg/kg, *C. sativa* n-butanol fraction (CS-ButFr) 5 and 10 mg/kg and *C. sativa* methanolic fraction (CS-MetFr) 10 and 15 mg/kg were administered 1.3 h before cisplatin administration; CS-HexFr 10 mg/kg was administered twice 1.3 h before and 12 h after cisplatin administration. MCP 30 mg/kg and carbachol 0.1 mg/kg were administered alone and in combination with CS-HexFr 10 mg/kg. All the drugs were administered intramuscularly except cisplatin and charcoal meal which were administered intravenously and orally, respectively.

Gastrointestinal motility

The pigeons of either sex or breed (n = 6) weighing 250 to 350 g were used in GIT motility study. Animals were starved from food for 18 h prior to experiment, but were allowed free access to water. After 80 min of CS-HexFr or normal saline (SAL) administration, 2 ml of a 10% charcoal slurry in 5% powdered gum acacia was administered to each pigeon orally (Singh et al., 1996). For antagonism, MCP (30 mg/kg) or carbachol (0.1 mg/kg) was administered intramuscularly 5 min before drug administration. Pigeons were killed 20 min after being administered with charcoal meal, abdomen was opened, and small intestine was dissected out, and was placed on a clean surface. The distance travelled by the charcoal meal from the pylorus was measured. The entire length of the small intestine was also measured. The percentage distance travelled by the charcoal plug along the small intestine (from the pylorus to the ceacum) was then estimated for CS-HexFr, MCP, carbachol and SAL-treatment groups and their combinations. Percent GIT motility was calculated with the help of following formula:

% GIT motility = (Distance travelled by charcoal through small intestine / total length of small intestine) × 100

Statistical analysis

The values were presented as Mean ± SEM. The differences among means were evaluated using one way analysis of variance(ANOVA) followed by post hoc analysis using either Dunnett or Tukey multiple comparison tests. $P < 0.05$ to 0.001 was considered as significant.

Table 1. Effect of Cannabis sativa hexane fraction (CS-HexFr), n-butanol fraction (CS-ButFr), methanol fraction (CS-MetFr) and standard Metoclopramide (MCP) on cisplatin-induced vomiting and jerking during a 24 h observation period.

Drug treatment	Dose and route	Pigeons tested/ vomited	Vomiting Episodes Mean ± SEM	Latency to first vomit (min) Mean ± SEM	Jerks Mean ± SEM	Wt loss (%) Mean ± SEM
Cisplatin (Control)	7 mg/kg iv	8/8	44±3.1	69±3.7	595 ± 70	15.5±1.1
MCP (Std)	30 mg/kg im	8/8	24 ± 1.3**	204 ± 61.3*	351 ± 21	12.3 ± 1.4
CS-HexFr	5 mg/kg im	8/8	35 ± 6.6	195 ± 67	435 ± 92	9.4 ± 1.5
	10 mg/kg im	5/5	19 ± 3.9**	289 ± 126	328 ± 94	9.5 ± 2.7
	15 mg/kg im	8/8	29 ± 3.1	234 ± 49	444 ± 62	10 ± 1.7
	10 mg/kg im BD	8/8	13.7 ± 3.2**	271 ± 72*	238 ± 77*****	9.2 ± 1.2*****
CS-ButFr	5 mg/kg im	6/6	38 ± 5.4	105 ± 10.7	614 ± 107	10.7 ± 2.7
	10 mg/kg im	6/6	42 ± 6.7	91 ± 12.6	771 ± 168	13.7 ± 1.5
CS-MetFr	10 mg/kg im	7/7	31 ± 4.7	164 ± 76	460 ± 104	11.1 ± 1.9
	15 mg/kg im	7/7	31 ± 4.2	116 ± 27	339 ± 69	7.7 ± 2.7*****
Combination 1	(CS-HexFr 10 mg + MCP 30 mg) BD	8/8	14 ± 2.1**	164 ± 39	212 ± 41	13.6 ± 2.6
Combination 2	(CS-HexFr 10 mg + Carbachol 0.1 mg)BD	6/6	19 ± 2.9**	132 ± 28.3	339 ± 59	8.13 ± 2.2

The latency to first vomit, number of vomiting episodes and jerks and % weight loss is shown for the 24 h observation period. Values significantly different compared to control are indicated as *p< 0.05, **p< 0.01 ***p< 0.001 (ANOVA followed by Tukey post hoc analysis).

RESULTS

Vomiting induction

Cisplatin at the dose of 7 mg/kg induced vomiting in all of the pigeons tested without lethality with a mean latency, vomiting episodes and jerks of 69 ± 3.7, 44 ± 3.1 and 595 ± 70.0, respectively (Table 1). The intense response occurred at 1 to 3 h (Figure 1). The increase in cisplatin dose only resulted in the increase of vomiting intensity through the observation period (Unpublished data)

Antiemetic profile of crude *Cannabis* fractions

Cisplatin at the dose of 7 mg/kg induced reliable vomiting in all the animals tested. In these experiments, cisplatin-induced vomiting following a latency of ~69 min and comprised ~44 episodes. CS-HexFr at 5, 10 and 15 mg attenuated cisplatin-induced vomiting in non-dose dependant manner (Figure 2), showing significant reduction with 10 mg/kg once (OD) and twice (BD) daily up to 55.45 and 68.86%, respectively ($P < 0.01$; Table. 1) during 24 h of observation period, while standard Metoclopramide (MCP) provided protection upto 45.45 % ($P < 0.01$, Table 1) and the suppression was observed upto 8 h (Figure 3A). The n-butanol and methanol fractions failed to provide any protection up to the observation period (Figures 3B & C). The CS-HexFr was found to be superior to other fractions as it suppressed vomiting up to 16 h of observation period (Figure 3A).

Table 1. CS-MetFr at 15 mg/kg also reduced weight loss significantly ($P < 0.05$, Table 1). The weight loss and jerking for all other treatment

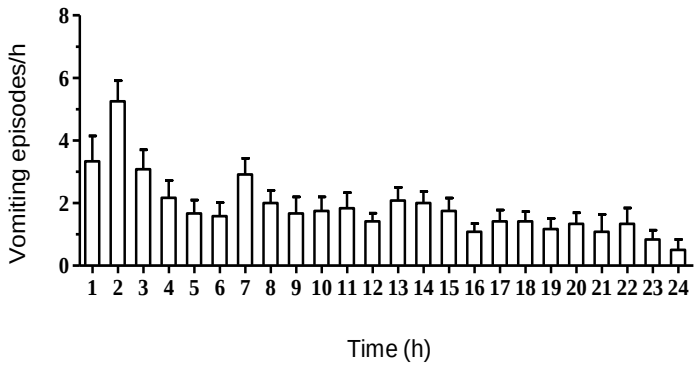

Figure 1. The sketch of cisplatin (7 mg/kg i.v.) induced vomiting in pigeon during 24 h of observation period. Each hourly bar represents mean ± SEM (n = 8) of vomiting episodes.

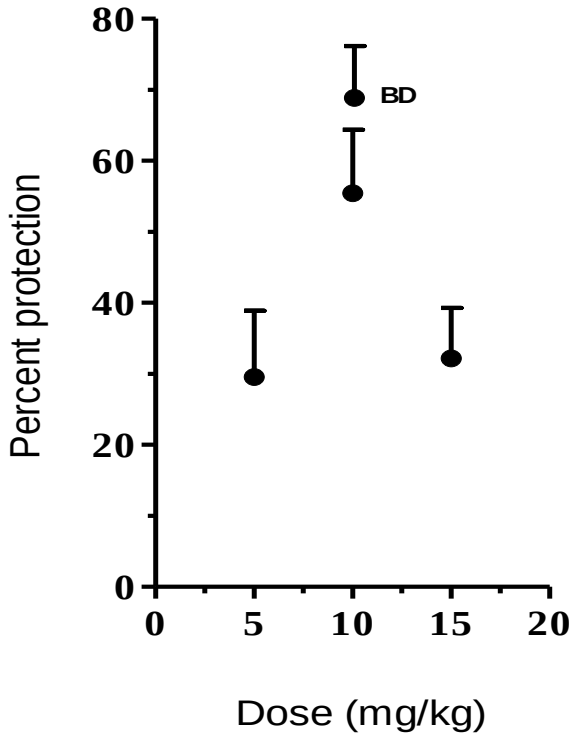

Figure 2. Dose response of Cannabis sativa hexane fraction (CS-HexFr) 5, 10 (once (OD) and twice (BD) and 15 mg/kg against cisplatin-induced vomiting. The values represent Mean ± SEM of 5 to 8 determinations.

were statistically non-significant (P > 0.05).

Effects on cisplatin-induced jerking and weight loss

CS-HexFr 10 mg/kg twice dosing reduced both weight loss and jerking; these differences were found significant as compared to control (P < 0.05, Table 1). CS-MetFr at 15mg/kg also reduced weight loss significantly (P < 0.05, Table 1). The weight loss and jerking for all other treatments were statistically non-significant (P > 0.05).

Involvement of GIT motility/gastric emptying in cisplatin-induced vomiting

CS-HexFr at 10 mg/kg caused GIT motility suppression up to 26.62 ± 1.02% as compared to saline. MCP (10 and30 mg/kg) and carbachol (0.1 mg/kg) antagonized the suppression caused by CS-HexFr (10 mg/kg) significantly (P < 0.001, Figure 5). MCP 30 mg/kg and carbachol 0.1 mg/kg in combination with CS-HexFr 10 mg/kg showed better suppression against cisplatin-induced vomiting after second dosing at 12 h, while no synergism/potentiation was seen at the first dosing at t = 0 (Figures 4A, B and C). Carbachol (0.1 mg/kg) did not induce vomiting by itself when tested alone. The 4 h sketch of vomiting episodes indicates the more pronounced suppression in vomiting after second dosing (Figure 3D).

DISCUSSION

Cisplatin is one of the chemotherapeutic agents which has been used in the clinical management of various carcinomas like ovarian, testicular, head and neck carcinomas (Muggia, 2009) having one of the severe limiting side effect of nausea and vomiting (Topal et al., 2005). The vomiting caused by chemotherapeutic drugs is multifactorial. Among these factors, the delay in gastric emptying and decrease in gastrointestinal motility are playing its role inpart. Cisplatin dose dependently causes suppression of gastric emptying (Sharma and Gupta, 1998). The antiemetics in clinical use like MCP and serotonin receptor antagonists have been shown to alter the gastric motility produced by cisplatin in rats.

Delta-9-tetrahydrocannabinol (Δ^9 THC) and other synthetic cannabinoids have been screened for their antiemetic activity against cisplatin-induced vomiting in various animal models. The cannabinoids whether from natural sources or synthetic are reported to act through the activation of presynaptically located CB_1 receptors, which leads to the inhibition of monoaminergic transmitter release in the GIT tract (Darmani, 2001b).

In our studies we used pigeon as a vomiting model for assessment of the emetic potential of cisplatin as this species has been used in emesis research for many years (Gupta and Dhawan, 1960; Preziosi et al., 1992). We screened various crude fractions of *C. sativa* for their potential to suppress cisplatin-induced vomiting in this species. CS-HexFr at 10 mg/kg showed up to 56.8% (P < 0.01) protection, while 5 and 15 mg/kg showed protection up to 20.45 and 34%, respectively (P > 0.05, Figure 2).

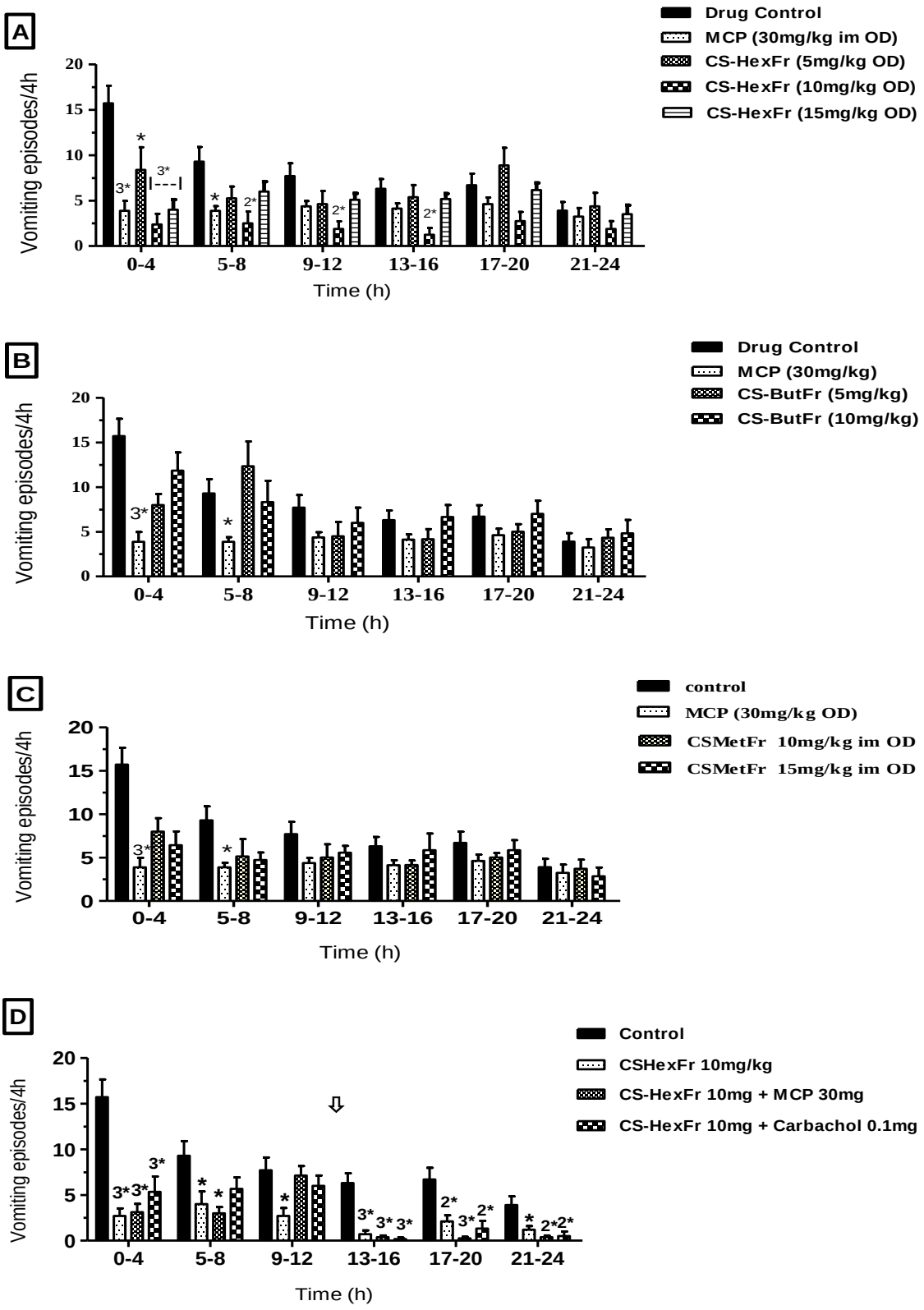

Figure 3. The effect of; **(A),** CS-HexFr (5, 10 and 15 mg/kg); **(B),** CS-ButFr (5 and 10 mg/kg); **(C),** CS-MetFr (10 and15 mg/kg); **(D),** CS-HexFr 10 mg and its combinations, on cisplatin-induced vomiting during a 24 h observation period; MCP at 30 mg/kg is also shown. Each bar represents the mean ± SEM of vomiting episodes occurring during 4 h periods (n = 5 to 8). Values significantly different compared to control are indicated as *p< 0.05, ^{2}* p< 0.01 ^{3}*p< 0.001 (ANOVA followed by Tukey post hoc test). Arrow indicates dosing time. Combination 1 (CS-HexFr 10mg + MCP 30mg), Combination 2 (HexFr 10mg + Carbachol 0.1mg).

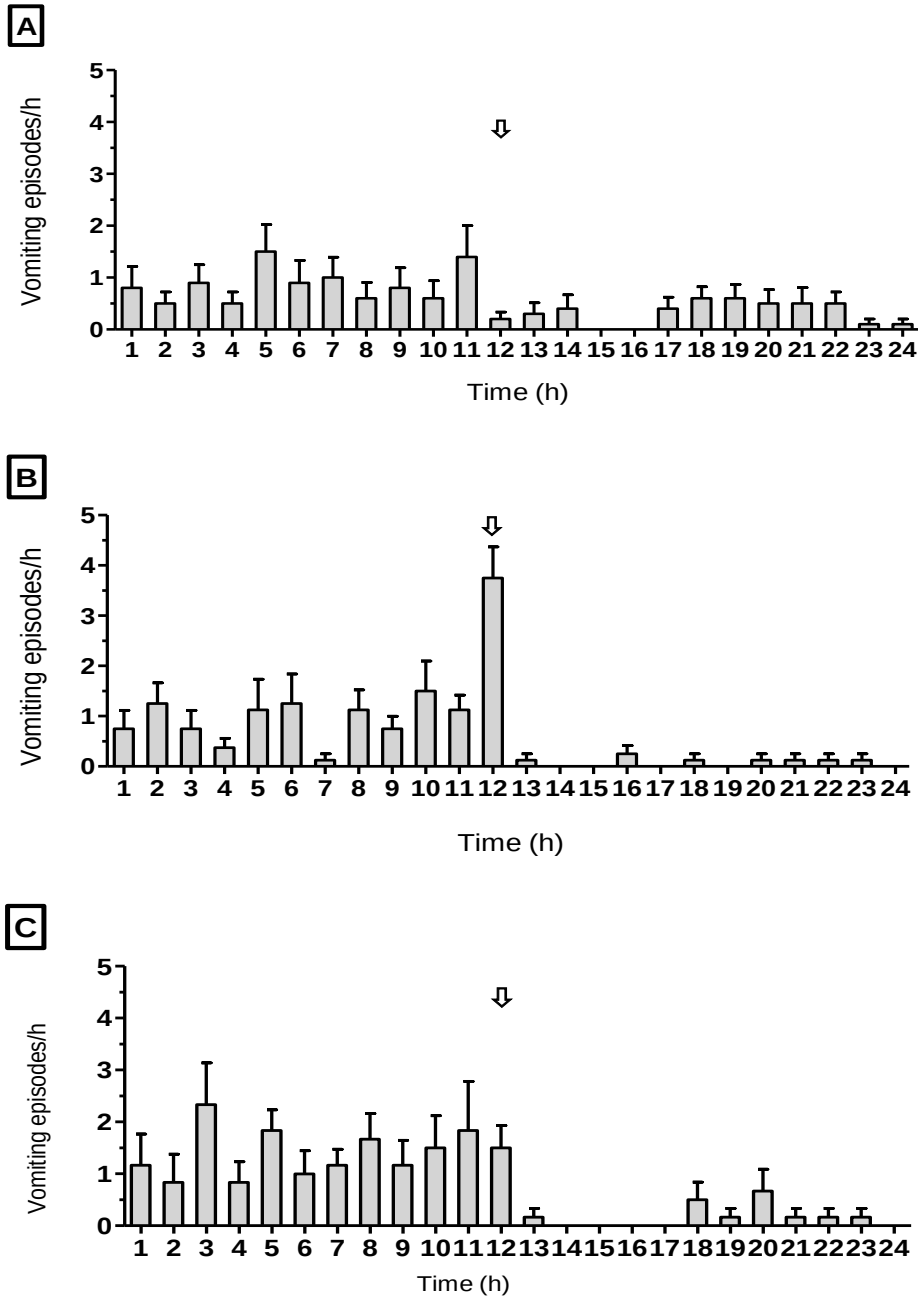

Figure 4. The effect of: **(A),** CS-HexFr 10 mg; **(B),** CS-HexFr 10 mg + MCP 30 mg/kg; **(C),** CS-HexFr 10 mg + carbachol 0.1 mg/kg, administered twice daily on cisplatin-induced vomiting during a 24 h observation period. Each bar represents the mean ± SEM of vomiting episodes occurring during 1 h period (n = 6 to 8). The arrow indicates dosing time.

CS-MetFr and CS-ButFr did not show any significant protection against cisplatin-induced vomiting. Cannabinoids have been reported to cause the suppression of GIT motility (Abalo et al., 2011), as it causes the inhibition of ongoing contractile transmitter release (Pertwee, 2001b). It is hypothesized that this suppression may antagonize the antiemetic activity as cisplatin is causing delay in gastric emptying per se. In the present study, CS-HexFr 10 mg/kg suppressed the GIT motility up to 26.62% as compared to saline. Similarly, we observed the reversal of inhibition by MCP and carbachol. MCP 10 and 30 mg/kg and carbachol at 0.1 mg/kg produced significant reversal ($P < 0.001$; Figure 5). The similar efficacy of these agents incombination with CS-HexFr 10 mg/kg was also observed in our studies against cisplatin-induced

Figure 5. Percent suppression in gastrointestinal (GIT) motility caused by Cannabis sativa hexane fraction (CS-HexFr, 10mg) and its antagonism by Metoclopramide (MCP, 10 & 30mg) and carbachol (0.1mg). Values significantly different compared to control are indicated as ^{3}*p< 0.001 (ANOVA followed by Tukey post hoc test, n = 6).

vomiting in pigeon, but the enhanced suppression was observed after the peak of acute phase.

In conclusion, CS-HexFr at the dose of 10 mg/kg provided maximum protection against cisplatin-induced vomiting in pigeon but cause the suppression of GIT motility/gastric emptying. MCP (30 mg/kg) and carbachol (0.1 mg/kg) antagonize the GIT suppression caused by CS-HexFr (10 mg/kg) and thus, enhances the antiemetic profile, which may indicates the involvement of suppression of cholinergic mechanism responsible fordelay in gastric emptying and suppression in GIT motility.

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