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Folkloric uses of *Jatropha gossypifolia* in emesis and gut motility disorders: Pharmacological validation

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Abstract

Jatropha gossypifolia is used in folkloric system to manage emesis and gastrointestinal motility disorders such as constipation and diarrhea. The present study was undertaken to provide pharmacological evidences for these folkloric uses by *in vivo* and *in vitro* experimental setting. Ethanolic extract of *J. gossypifolia* showed the significant antiemetic potential ($p<0.05$) against different emetogenic stimuli, when compared with chlorpromazine. The extract (0.01-1.0 mg/mL) on application to isolated rabbit jejunum preparation exerted spasmogenic effect, followed by the spasmolytic effect (3-10 mg/mL). In the presence of atropine, spasmogenic effect was blocked while spasmolytic effect was emerged, suggesting the involvement of muscarinic receptor activation. *J. gossypifolia* caused relaxation of high K^+ (80 mM)-induced contraction and shifted the Ca^{2+} concentration-response curve to the right in a manner similar to verapamil, thus conforming its Ca^{2+}-channel blocking activity. These findings provide pharmacological validation for the presence of antiemetic and gut modulator (spasmogenic and spasmolytic) activates, validating its folkloric uses.

Introduction

Constipation is a heterogeneous condition associated with infrequent bowel movements and/or difficulty in defecation or both (Talley et al., 2003). Untreated constipation may cause urinary and gastrointestinal disorders (Imanzadeh et al., 2012).

Emesis is protective reflex which expels out the toxic substances from the stomach and intestine, and is associated with indigestion of toxicants, cancer chemotherapy, post-operative procedures and drug adverse effects (Gilman and Goodman, 2001). Commercially available antiemetic may cause excessive sedation, dysphoria, extra-pyramidal signs, and hallucination (Griffin et al., 1996).

Jatropha gossypifolia Linn. (Euphorbiaceae) is a bushy gregarious shrub; known as tua-tua (English) and laal bagharenda (Local) and is native to Brazil but cultivated as an ornamental plant in all over world (Khare, 2007).

Phytochemical investigation revealed the presence of histamine, triterpenes, alkaloids, flavonoids, jatropholone A, jatrophatrione, tannins, macrocyclic diterpene, jatrophine, jatrodien, gossypiline (Das et al., 1998; Matsuse et al., 1999), latex contains cyclogossine A and B (Morton, 1980) whereas seeds contain hydroxyl jatrophone and jatropholones A and B (Horsten et al., 1996).

J. gossypifolia has been reported to have hepatoprotective, anti-inflammatory, anticancer, antiseptic, anti-fertility and antipyretic activities (Panda et al., 2009; Falodun et al., 2012). Decoction of the plant has been used as purgative, anti-diarrheal, antiemetic, antidote for snakebite and blood purifier (Kirtikar and Basu, 1996; Khare, 2007). The present study was aimed to pharmacologically evaluate the possible mechanism

of action *J. gossypifolia* in emesis and gastrointestinal motility disorders such as constipation and diarrhea.

Materials and Methods

Collection and extraction of J. gossypifolia

Fully grown aerial parts of *J. gossypifolia* were collected in the month of November (2013) from the botanical garden of The University of Faisalabad and were identified by the Curator, Botany Department of same University. Adulterants free and electrically grinded coarse powdered material (#40) was subjected to triple maceration (Hussain et al., 2013), with 80% ethanol-aqueous mixtures to produce the ethanolic extract of *J. gossypifolia*.

Animals used and their housing conditions

Animals (♂/♀) including, Swiss albino mice (32-48 g, 4-5 weeks old), chicks (75-85 g, 10-15 days old) and rabbits (1.2-1.7 kg, 8-10 months old) were used and were provided with standard diet and *ad libitum* with tap water under controlled environmental condition (25 -28°C). Chicks were housed in plastic cages with sawdust as bedding with 12 hours/12 hours dark-light cycle.

Chemicals and drugs used

Research grade and highest purity chemicals, solvents, and drugs were used in the experimental study and were purchased from the Sigma Chemicals (USA), Merck (Germany), Sharlab Labs (Spain) and Highnoon Pharmaceutical (Pakistan).

Acute toxicity test

Acute toxicity testing was performed by orally administering the 2, 4 and 6 g/kg of ethanolic extract to the mice, as described previously (Hussain et al., 2015a).

In vivo estimation of antiemetic potential

Chick emetic model was adopted to estimate the antiemetic potential of the extract (Eda et al., 2005; Hussain et al., 2015b). Acclimatize and healthy chicks were separated in 8 groups of 4 chicks in each group. Chicks of Group 1 (control) and Group 2 (standard) were given an oral dose of normal saline (0.9%) and chlorpromazine (150 mg/kg body weight) respectively, while the chicks of Group 3 and 4 (experimental) were given an oral dose of 50 and 100 mg/kg body weight of ethanolic extract respectively, dissolved in 10 mL/kg of 0.9% saline containing 5% DMSO and 1% tween 80. After 15 min, 50 mg/kg body weight of copper sulfate was administered orally to chicks of all groups. Same process was repeated by using fresh juice of *Brasica compestris* (10 mg/kg; oral), instead of copper sulfate while other protocols remain same as before, then number of retches was counted for the next 15 min. The percentage retching inhibition was calculated as:

Retching inhibition (%) = [(A-B)/A] x 100

Where, A and B represents the frequency of retching in control and experimental groups respectively

In vitro assessment of spasmogenic and spasmolytic activities

Possible presence of spasmogenic and spasmolytic activity was assessed by applying ethanolic extract on isolated rabbit jejunum segments (2-3 cm) hanged in tissue baths containing 10 mL of Tyrode's solution with following composition (mM); KCl (2.68), NaCl (136.9), $MgCl_2$ (1.05), $NaHCO_3$ (11.90), NaH_2PO_4 (0.42), $CaCl_2$ (1.8) and glucose (5.55), aerated with carbogen (37°C) (Gilani et al., 1994; Janbaz et al., 2014). A preload of 1 g was applied and jejunum responses were recorded through isotonic transducers by Power Lab Data Acquisition System (AD Instrument, Sydney, Australia) attached to a computer installed with Lab Chart Reader Software (version 7). The jejunum tissues were allowed to stabilized (spontaneous rhythmic contraction) for at least 30 min. After 30 min, ethanolic extract was added to stabilized jejunum segment in a cumulative fashion, without prior addition of any agonist for the testing of spasmogenic and/or spasmolytic effect (Hussain et al., 2014). Contractile effect of the extract was calculated as the percent of the maximum effect produced by 1.0 µM of acetylcholine.

Assessment and conformation of Ca^{2+} channel blocking activity

For the assessment of calcium channel blockade, jejunum preparations were depolarized by exposing to high K^+ (80 mM), resulting in sustained contraction (Arshad et al., 2012; Hussain et al., 2015c). Ethanolic extract was applied in a cumulative manner to the sustained contractions to achieve concentration-dependent inhibitory response (Farre et al., 1991). The observed relaxant effect of the extract on K^+ (80 mM)-induced contraction was expressed as percent of the control response mediated by K^+.

Calcium channel blocking effect of the ethanolic extract was confirmed by the previously reported method (Gilani et al., 2005). The isolated rabbit jejunum preparations were allowed to stabilize in normal Tyrode's solution, which were subsequently replaced with Ca^{2+}-free Tyrode's solution to which EDTA (0.1 mM) was added for 30 min, in order to remove calcium from the tissues. This bath solution was further replaced with K^+-rich and Ca^{2+}-free Tyrode's solution, having the following composition (mM): $MgCl_2$ (1.05), KCl (50), $NaHCO_3$ (11.90), NaCl (91.04), glucose (5.55), NaH_2PO_4 (0.42), and EDTA (0.1). Subsequent to an incubation period of 30 min, cumulative Ca^{2+} concentrations were applied to the tissue bath to obtain control calcium dose-response curves. On achievement of the

superimposable control calcium dose-response curves (usually after two cycles), the tissues were then washed and incubated with the plant extract for 60 min. Then concentration response curves of Ca^{2+} were constructed and compared to the control curves. The concentration response curves for Ca^{2+} were developed in the presence of different concentrations of the plant to assess a possible Ca^{2+} channel blocking effect (Bolton, 1979).

Statistics

All data was expressed as mean ± SEM of triplicate. EC_{50} values were given with 95% confidence intervals (95% CI) and the logarithmic dose response curves of different treatments were then plotted using computer software "Graph pad Prism" version 6, (Graph Pad Software, San Diego, CA, USA). Concentration-response curves were analyzed by nonlinear regression sigmoidal response curve (variable slope). Unpaired Student *t*-test was used for assessment of the observations. $p<0.05$ and $p<0.005$ were believed to be statistically significant and most significant values respectively.

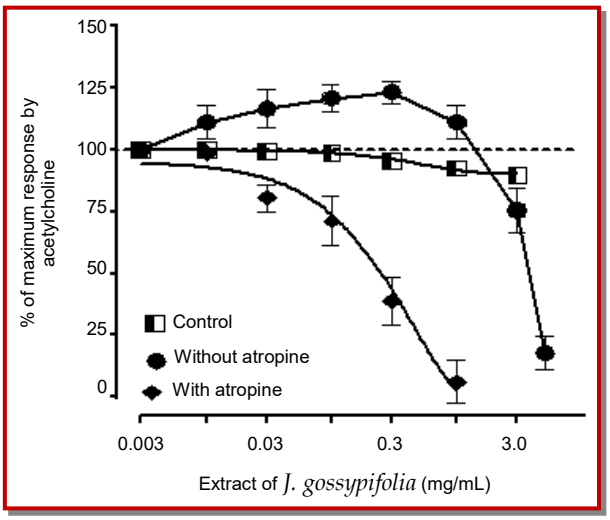

Figure 1: Concentration–response curves, showing the effect of *J. gossypifolia* in the absence and presence of atropine (0.1 µM) on spontaneously contracting rabbit jejunum preparation. The spasmogenic responses are expressed as percent of acetylcholine maximum (values are expressed as mean ± SEM, n=3)

Results

Acute toxicity

Acute toxicity testing of *J. gossypifolia* (2, 4 and 6 g/kg) indicates that the extract is safe up to the maximal tested dose (6 g/kg) because there was no mortality and no toxic effects, such as anorexia, diarrhea and gastrointestinal spasms.

Antiemetic potential

The chicks of control groups, to whom normal saline (10 mL/kg) was administered, followed by copper sulfate and fresh juice of *B. compestris*, showed the numbers of retches 78 ± 1.10 and 77 ± 1.11 respectively. While in the chicks of the experimental groups (75 mg/kg), number of retches were reduced with %inhibition of emesis of 53.9 and 49.4, whereas at the dose of 150 mg/kg, number of retches were significantly reduced with %inhibition of emesis of 74.4 and 76.6 followed by copper sulfate and fresh juice of *B. compestris* respectively, which were comparable to standard drug chlorpromazine, indicating the antiemetic potential of *J. gossypifolia* (Table I).

Spasmogenic and spasmolytic effect

In spontaneously contracting isolated rabbit jejunum preparations, the ethanol extract showed the spasmogenic effect in concentration range of 0.01-1.0 mg/mL, which did not sustained and was subsequently followed by spasmolytic effect at the next higher concentration (3-10 mg/mL) with EC_{50} value of 1.9 mg/mL (95% CI: 1.40-2.40, n=3) (Figure 1). The observed contractile responses to *J. gossypifolia* was expressed as percentage of the maximal response to acetylcholine (0.3 µM), i.e. 14.6 ± 1.7, 22.3 ± 0.8, 26.3 ± 1.7, 32.3 ± 1.2, and 10.2 ± 5.2 (mean ± SEM, n=3), at the concentration range of 0.01, 0.03, 0.1, 0.3 and 1.0 mg/mL, respectively (Figure 2). In

Table I

Antiemetic effect of crude extract of *J. gossypifolia* on copper sulfate and *Brasica* juice-induced emetic chicks

Treated groups	Copper sulfate-induced		*Brasica*-induced	
Treated groups	Mean number of retches	%Inhibition	Mean number of retches	%Inhibition
Control (10 mL/kg)	78 ± 1.1	____	77 ± 1.1	____
Chlorpromazine (150 mg/kg)	44 ± 0.3	43.6[a]	42 ± 0.5	45.5[a]
Ethanolic extract of *J. gossypifolia* (75 mg/kg)	36 ± 1.3	53.8[a]	39 ± 1.2	49.4[a]
Ethanolic extract of *J. gossypifolia* (150 mg/kg)	20 ± 0.8	74.4[b]	18 ± 0.8	76.6[b]

([a]$p<0.05$ and [b]$p<0.005$ vs control showing significant and most significant values by using student's *t*-test)

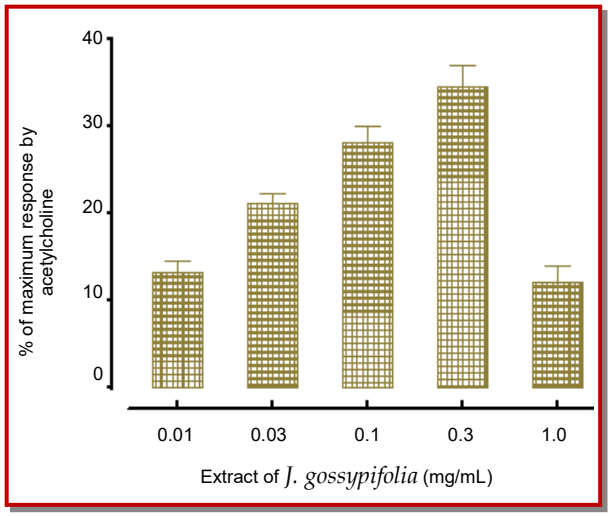

Figure 2: Bar diagram showing the effect of *J. gossypifolia* in comparison to the acetylcholine maximum response in rabbit jejunum preparation

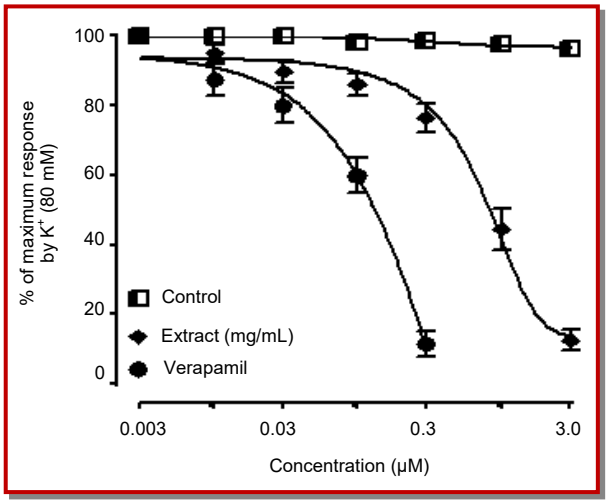

Figure 3: Concentration-dependent inhibitory effect of *J. gossypifolia* and verapamil against K^+(80 mM)-induced contractions in isolated rabbit jejunum preparations (values are expressed as mean ± SEM, n=3)

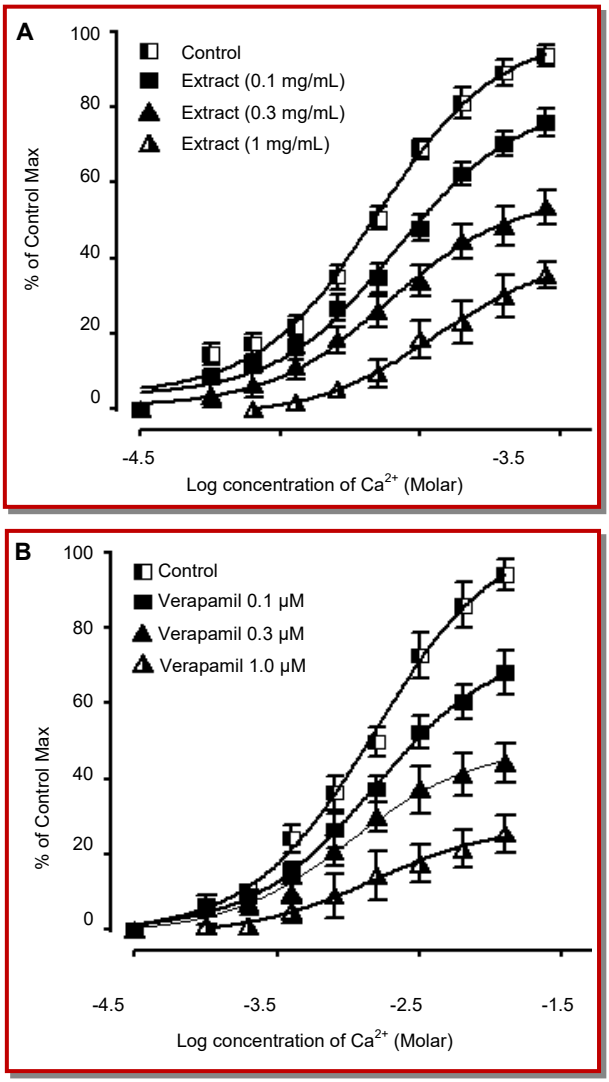

Figure 4: Concentration-response curves of Ca^{2+} in the absence and presence of different concentrations of (A) *J. gossypifolia* and (B) verapamil in isolated rabbit jejunum preparations (values are expressed as mean ± SEM, n=3)

the presence of atropine (0.1 μM), spasmogenic effect was abolished while the spasmolytic effect was observed with EC_{50} value of 1.7 mg/mL (95% CI: 0.32-2.95, n = 3).

J. gossypifolia was unable to relax the K^+ (25 mM)-induced spastic contractions, but exhibited complete relaxation of K^+ (80 mM)-induced contractions in isolated rabbit preparations, with EC_{50} value of 1.4 mg/mL (95% CI: 0.72-1.95, n=3). Verapamil (standard drug) inhibited the K^+ (80 mM)-induced contractions, with EC_{50} value of 0.14 mg/mL (95% CI: 0.07-0.45, n=3) (Figure 3). Moreover, pretreatment of the isolated rabbit jejunum preparations with *J. gossypifolia* caused a rightward shift of the Ca^{+2}-concentration response curves at the dose range of (0.1-1.0 mg/mL, n=3), in a manner similar to that of verapamil (Figure 4)

Discussion

Ethanolic extract of *J. gossypifolia* was tested for acute toxicity on healthy mice at oral dose ranges of 2, 4 and 6 g/kg and it was found that *J. gossypifolia* is safe because it did not produced the lethality, behavioral changes and toxic effect, even at the dose range of 6 g/kg, which is more greater than normal therapeutic dose range. *J. gossypifolia* has folkloric repute for use in the management of emesis in traditional system of medicine; hence, *in vivo* pharmacological study was carried out by adopting chick emetic model to evaluate its possible antiemetic effect. Emesis is either caused by the activation of the vomiting centre located in medulla oblongata or by the activation of motor pathway. Additionally, signals from following four principal regions, i.e., chemoreceptor trigger zone, GIT, cortex,

thalamus, cerebral and vestibular) region may also cause emesis (Hussain et al., 2015a). The chemoreceptor trigger zone is in the proximity to medulla and it is not protected by the blood brain barrier (Becker, 2010). Results clearly indicate that *J. gossypifolia* (150 mg/kg) showed more significant antiemetic response against copper sulfate and *B. compestris* induced emesis which was comparable to chlorpromazine. So, it can be hypothesized that the antiemetic effect of *J. gossypifolia* can be likely mediated through inhibition of chemoreceptor trigger zone while other mechanism cannot be ruled out.

For the inspection of conventional uses of *J. gossypifolia* in gastrointestinal motility disorders, pharmacological study of *J. gossypifolia* was carried out on spontaneously contracting isolated rabbit jejunum preparations, to evaluate its possible effect and mechanism of action. Initially it produced the spasmogenic effect (jejunum contractile effect), which is generally mediated through the action of acetylcholine on cholinergic system (Janbaz et al., 2012; Hussain et al., 2014). For the conformation of this mechanism, spontaneously contracting rabbit jejunum preparations were pre-exposed to 0.1 µM of atropine (Muscarinic receptor blocker) (Ghayur and Gilani , 2005), which resulted in blocking the stimulatory effect of extract, indicating that the *J. gossypifolia* exerted the gut stimulation via cholinergic pathway (Hussain et al., 2015b). Acetylcholine (neurotransmitter) acts on the M_3 muscarinic receptor and regulate the peristaltic movement of GIT while atropine antagonize the muscarinic receptors (Brown and Taylor, 1996). The observed spasmogenic effect of *J. gossypifolia* validates its traditional use as anti-constipative agent in the hypo-motility disorder of the gut. The spasmogenic effect was followed by the spasmolytic effect at next higher doses of the extract, indicating the co-existence of spasmogenic, and spasmolytic constituent (s), which is probably meant by the nature not to allow the spasmogenic effect going beyond the constipation, particularly at higher doses (Janbaz et al., 2012).

Addition of *J. gossypifolia* to the tissue bath completely relaxed the K^+(80 mM)-induced contractions, suggesting that relaxant activity might be due to blockade of Ca^{2+} channels (Gilani et al., 2005). The contractile elements in rabbit jejunum are activated through increase in cytoplasmic free Ca^{2+} concentration via opening of the voltage dependent Ca^{2+} L-type channels (Karaki et al., 1997) or release of Ca^{2+} from sarcoplasmic stores (Godfraind et al., 1986). The extract exhibited relaxant effect through Ca^{2+} channels blockade and further inhibition of sequences of events including decrease of cytosolic Ca^{2+} concentration, decrease in Ca^{2+} binding to calmodulin, decrease in Ca^{2+} calmodulin complex formation, decrease in activation of myosin light chain kinase, decrease in phosphorylation of myosin light chains, decrease in interaction between actin and myosin and inhibition of contractile process. These speculations were confirmed as pretreatment of rabbit jejunum preparation with extract caused rightward shift of Ca^{2+}-concentration response curves, like that caused by verapamil (Fleckenstein, 1977).

J. gossypifolia exhibited the anticholinergic and Ca^{2+} channels blocking activities, which can be attributed due to presence of alkaloids and flavonoids, as these phyto-constituents have been reported to possess the anticholinergic (Broadley, 1996) and Ca^{2+} channel blocking (Revuelta et al., 1997) activities, respectively, while other mechanisms and phytoconstituents cannot be neglected.

Conclusion

This study provides the sound pharmacological back ground for the traditional use of *J. gossypifolia* as aperients (mild laxative) and anti-diarrheal drug, mediated possibly through the activation of M_3-muscarinic receptors and blockade of voltage-dependent Ca^{2+} channels respectively. The observed results also validate its folkloric use in emesis.

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Conflict of Interest

Authors declare no conflict of interest

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