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Original Article

Effects of Beta-Carboline Alkaloids of Peganum Harmala on Induced Rat Ileum Contractions

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ABSTRACT

Peganum harmala L., Zygophyllaceae popularly known as Wild Syrian rue, a well-known plant in folk medicine for many pharmacological uses including antispasmodic activity. Chemical composition of the plant showed that the most important constituents of this plant are beta-carboline alkaloids such as harmalol, harmaline, and harmine. In this work, we aimed to evaluate the effects of these three major harmala alkaloids on induced rat ileum contractions, induced by acetylcholine, $BaCl_2$ and KCl. Of these three harmala alkaloids, harmalol and harmaline produced a concentration-dependent spasmolytic activity, which was found to be reversible (i.e. disappeared after tissue wash-up. Both alkaloids inhibited acetylcholine and KCl-induced ileum contractions but $BaCl_2$ -induced contractions were only inhibited by harmalol but not harmaline. Harmine did not show any inhibitory activity.

Key words: Peganum *Hermala* L; β-Carbolines alkaloids; Harmine; Harmaline; Harmalol; Rat; Ileum; Spasmolytic.

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INTRODUCTION

Peganum harmala L. also known as Syrian rue, that belongs to the Family of Zygophyllaceae, is a perennial herbaceous, glabrous plant, which grows in a dry grassland with high temperature in the summer and low temperature in the winter (or grows in a desert climate) and sandy soils. It may grow up to 100 cm^1 with white flowers between June and August. The flowers are single, small with five petals. Each flower tends to develop into a fruit[2], the fruits are green and change to orange-brown when mature, the fruits are also preserved in a capsule with three chambers, each capsule contains more than 50 small black-brown triangular seeds.[2,3]

Peganum harmala L. is widely used as a medicinal plant that can be found in North Africa, Mediterranean, the Middle East, Pakistan, India and southern parts of Iran, and recently has also been found to grow in Australia and southwest of America.[3]

Through history, the usage of *P. harmala* was traced, for example, in west Asia this plant used as a talisman against voodoo and evil eye[4], in the middle east it is used as psychoactive substance for spiritual experiences and it is also found to be used as a hallucinogenic aid by ancient Persian and Indian.[5] In traditional medicine, *P. harmala* has been used for the treatment of different conditions, like asthma, lumbago, colic, jaundice and to stimulate menstrual flow.[6] However, in recent pharmaceutical studies, *P. harmala* found to have an antispasmodic[7], antimicrobial, emmenaguage and abortive effects[8], blocking different types of intestinal calcium channels[9], mono amine oxidase inhibition and anti-depressant effect[10,11], analgesic[12], vasorelaxant activity against phenylephrine-induced contraction of isolated rat aorta[13], anti-platelet aggregation effects[14], hallucinergic, and anti-neoplasm effect.[15-18]

The active pharmacological compounds of *P. harmala* are alkaloids, β-carbolines (like harmine, harmaline, harman and harmalol) which can be found in high levels in seeds, roots and least found in leaves and stems.[16] Quinazoline alkaloids (such as vasicine and vasicinone) have also been identified.[2] The major alkaloids of *P. harmala* can be found in seeds and roots, harmaline (also known as harmidine) and harmine (banisterine) have the same pharmacological action but harmine (banisterine) is considered as less toxic. The active alkaloids of harmal seeds are the monoamine oxidase inhibitor A (MAOI-A) compounds, for this reason the popularity of this plant among western psychonauts as a psychoactive drug.[17]

Previous study suggested that *P. harmala* alkaloids, β-carbolines (harmine, harmaline, and harmalol) have a relaxant effect on smooth muscle of the trachea contracted by KCl[19], in another study, β-carbolines (harmaline) found to inhibit acetylcholine induced ileal contraction.[20]

Therefore, the present study was carried out to examine the spasmolytic activity of the three major harmala alkaloids i.e., harmine, harmaline, and harmalol on the isolated rat ileum preparations induced by different stimulants like, acetylcholine (Ach), $BaCl_2$ and KCl.

MATERIALS AND METHODS

Drugs and chemicals

All chemicals used in this study were of analytical grade and were obtained from St. Louis, MO, USA.

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Harmaline, harmine, harmalol, acetylcholine chloride (≥ 98.0% purity) were also purchased from Sigma Aldrich and a stock solutions was prepared on daily basis. Kreb's solution was prepared fresh, just before the experiment and consisted of (in mm): NaCl (118.1), KCl (4.7), $CaCl_2$ (2.5), $MgSO_4$ (1.2), $NaHCO_3$ (25) and glucose (5.6).

Experimental animals

Three-month-old male Wister rats (250–300 g) were obtained from the animal facilities of the Faculty of Medicine, The University of Jordan. The animals were housed under standard husbandry conditions, which included an ambient temperature 20–22 °C and a 12/12 h light/dark cycle, with free access to food and water. All animal experiments were conducted in concordance with the University of Jordan's "Regulations and Ethical Guidelines for the Care and Use of Laboratory Animals".

Ileum-tissue isolation and sample mounting

Four segments of each rat ileum were used on each day of the experiment. The animals were anesthetized by ether and sacrificed. The abdominal cavity was opened by a midline incision aseptically. One cm from the flexure of the intestine was cut and the segment of the ileum was dissected out and placed in oxygenated Krebs solution at (pH 7.4) at room temperature. The ileum tissue was carefully flushed out with freshly prepared Krebs solution maintained at 37°C bubbled with gas mixture of 95% O_2 and 5% CO_2. From a resting tension of 2 g, isotonic contractions, elicited by KCl, $BaCl_2$ and Ach, were recorded using Radnoti, 159901A, the isometric force transducers with computerized data acquisition system. Before the start of the experiment, all preparations were allowed to equilibrate for at least 30-45 min, during which Krebs solution was replaced twice. To study the spasmolytic effect of harmaline, harmine or harmalol, contractile agents such as ACh-chloride, potassium chloride (KCl) or $BaCl_2$ were added according to Shatarat *et al.* (2014), directly to the organ bath in volumes usually not exceeding 5% of the bath volume (20 ml organ bath). The ACh-chloride at (3×10^{-5} M), potassium chloride KCl (60 mM) or $BaCl_2$ (5 mM) were added to the organ bath in the absence (control) or in the presence of various concentrations of harmaline, harmine, or harmalol.

Statistical analysis

Mean and standard error of the mean (S.E.M.) values were calculated for each group of results and the significance of difference between the means was calculated using one-way analysis of variance (ANOVA) followed by Dunnett's test. Differences were considered statistically significant when $P < 0.05$. Harmaline, harmine or harmalol -evoked spasmolytic effect were expressed as a percentage of relaxation from spasmogen induced plateau contraction from the concentration – response curve by data fitting using GraphPad Prism version 5.02 for Windows (GraphPad Software, San Diego, CA, USA).

RESULTS

Effects of harmaline, harmine or harmalol on ACh induced ileum contraction

A single application of Ach (3×10^{-5} M) evoked 100% contraction (Figure 1). Harmine had no significant effect on baseline tension but harmaline and harmalol inhibited the Ach induced contractile responses, harmaline at 5 µM and 10 µM (*P < 0.05) and harmalol at 5 and 10 µM (***P < 0.0001) respectively. These inhibitory effects could be seen within 10 min of contact with the tissue and were maintained as long as these alkaloids present in the bath.

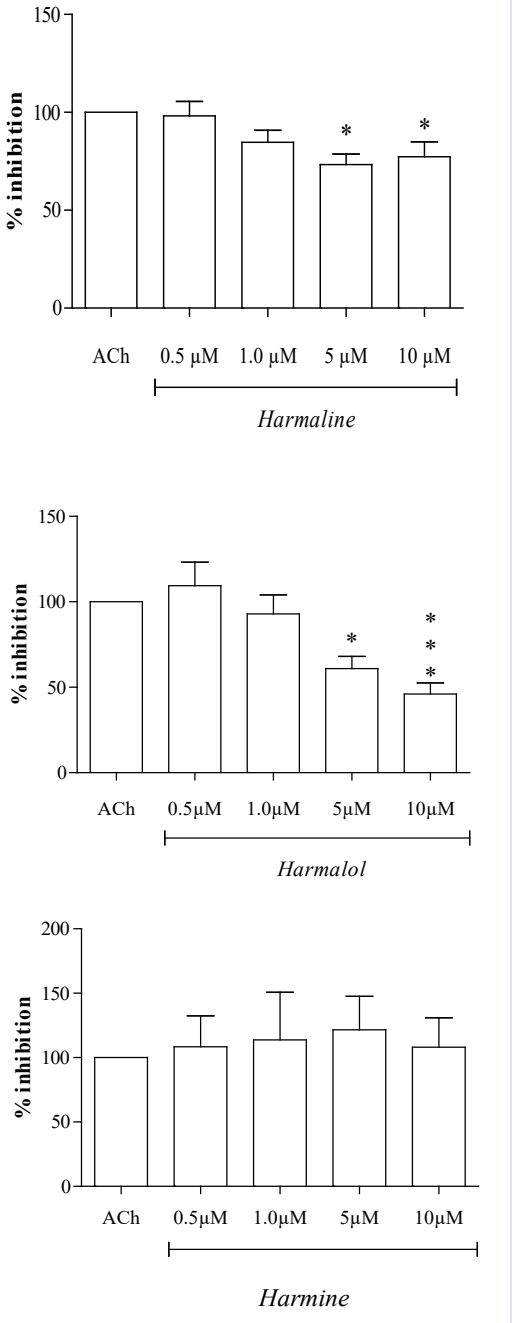

Figure 1: Effect of Harmaline, Harmalol and Harmine (0.5-10 µM) on Ach induced contractions of rat isolated ileum preparations. Data are mean ± S.E.M (n = 8, 8, 12 respectively in each group) and expressed as % of control tension.

*P < 0.05, ***P < 0.0001, ANOVA followed by Dunnett's test.

Effects of harmaline, harmine or harmalol on KCl induced ileum contraction

The effect of harmalol, harmaline, and harmine on KCl induced contractions was investigated using the ileum tissue that was exposed to KCl (60 mM) solution for 30 minutes before the experiments were commenced. The percentage inhibition of contraction induced by KCl in the presence of each concentration of the alkaloid was calculated. As in the case of Ach-induced contraction, the ileum preparation was

exposed to increasing concentration of harmine without showing any effect. However, harmaline at (1 and 5 μM) concentrations induced inhibition in contraction that was significant. Data are mean ± S.E.M and expressed as % of control tension. *P < 0.05 ANOVA followed by Dunnett's test (Figure 2).

Effects of harmaline, harmine or harmalol on $BaCl_2$ induced ileum contraction

As shown in (Figure 3), harmalol was the only alkaloid that produced significant inhibitory effect on $BaCl_2$ reducing the maximum induced contraction at 10 μM, **P < 0.01 (ANOVA followed by Dunnett's test). No significant decrease was observed when the preparation was pretreated with harmaline or harmine.

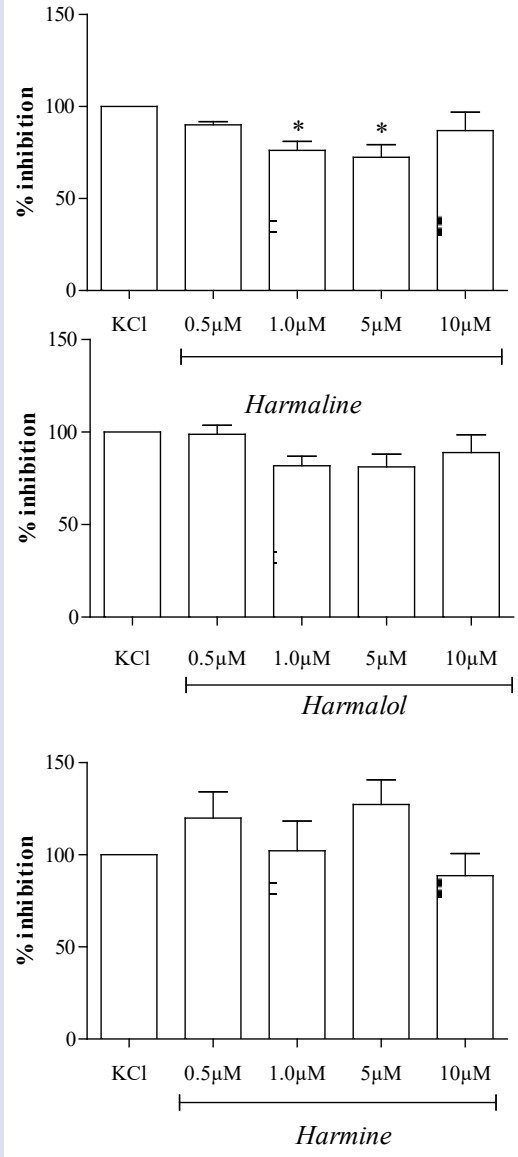

Figure 2: Effect of harmaline, Harmalol and Harmine (0.5-10 μM) on KCl induced contractions of rat isolated ileum preparations. Data are mean ± S.E.M (n= 4,8,7 respectively in each group) and expressed as % of control tension.

*P < 0.01, ANOVA followed by Dunnett's test.

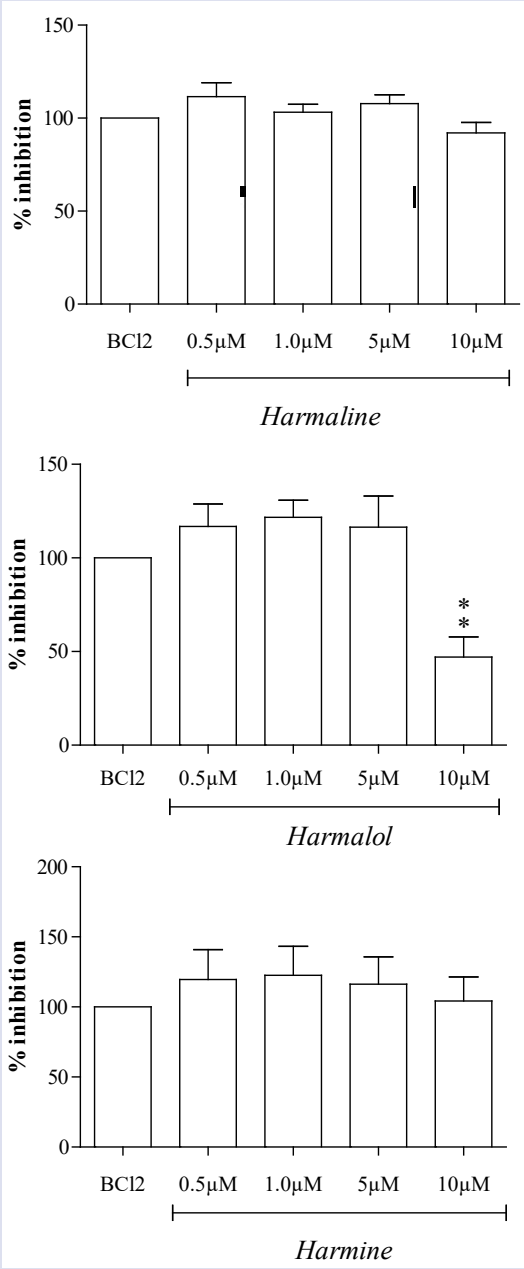

Figure 3: Effect of Harmaline, Harmalol and Harmine (0.5-10 μM) on BaCl2 induced contractions of rat isolated ileum preparations. Data are mean ± S.E.M (n= 4, 8 ,8 respectively in each group) and expressed as % of control tension.

**P < 0.01, ANOVA followed by Dunnett's test.

Solvent effect on rat ileum contraction

The alkaloids were dissolved in 5% dimethylsulfoxide (DMSO) in all conducted experiments therefore to determine whether the solvent alone was able to inhibit contractions. Five percent DMSO has been added to some preparations without harmalol, harmaline and harmine. The solvent had no effects on KCl induced contraction of the ileum (Figure 4).

DISCUSSION

Certain similarities as well as distinct difference in the antispasmodic response to the three harmala alkaloids observed on rat ileum

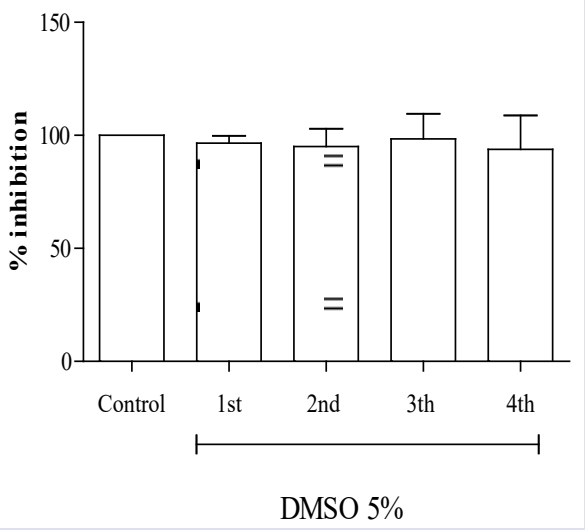

Figure 4: Effect of DMSO (5%) on KCl induced contractions of rat isolated ileum preparations. Data are mean ± S.E.M (n = 8) and expressed as % of control tension.

contractions. Harmalol, harmaline exhibited similar effect, whereas harmine was not active. Increasing concentrations of harmalol and harmaline were found to reduce the intensity of rat ileum contractions (Figures 1-3).

This finding agrees that a methoxy group on the indole nucleus, and the C3-C4 double bond (Harmine) is important for antispasmodic activity. Harmalol in which a 7-hydoxy group replaces the methoxy group of harmaine and no double bond at C3-C4 produces good antispasmodic effect evoked by Ach, $BaCl_2$ and KCl. Harmaline in which 7-methoxy group, similar like harmine but lack C3-C4 double bond also appears to be active. While harmine with both methoxy group on the indole nucleus, and the C3-C4 double bond had no effect. The order of inhibitory of the contraction induced was harmalol > harmaline > harmine.

The Ach, KCl and $BaCl_2$ are commonly used spasmogens to detect the spasmolytic activity of intestinal smooth muscles of different compounds, drugs and plant extracts. The KCl-evoked contractile responses are caused by depolarization of the muscle fibers through an increase of K^+ leading to the opening of L-type Ca^{2+} voltage-dependent channels. Thus, the intracellular Ca^{2+} concentration increases leading to the activation of the myosin light chain and contraction of the smooth muscle.[21-23]

Acetylcholine is considered a neurotransmitter which can cause smooth muscle contraction by activation of muscarinic receptors. Muscarinic receptors are a member of G-protein-coupled receptors found in smooth muscles. The gastrointestinal smooth muscles exhibit two main muscarinic receptors subtypes; M_2 and M_3.[24] The activation of muscarinic receptor enhances the release of Ca^{2+} leading to an increase in the intracellular Ca^{2+} which opens the Ca^{2+}- K^+ channels causing membrane depolarization, increases action potential and muscle contraction.[25,26] Earlier studies have suggested that in the intestinal smooth muscle, $BaCl_2$ caused contraction through excitation of nerve cells (neuronal action)[27] or directly acted on the smooth muscle via an increase of Ca^{2+} influx,[28,29]

In terms of structure activity relationship, the present results indicate that the C3-C4 double bond blocks antispasmodic activity. Functional group in the C7 position plays important role activity enhanced when replaced with (OH) group as in harmalol.

Comparing the chemical structures and the inhibitory effects on ileum contractions of the harmala alkaloids, it is concluded that the presence of 7-OH group increases the inhibitory effect on intestinal smooth muscle while the presence of 6- or 7-methoxy group decrease this inhibitory activity. C3-C4 double bond blocks antispasmodic activity.

From the results, we can conclude that alkaloids β-carbolines mainly harmaline and harmalol have a spasmolytic effect on rat ileum contracted by different stimulants, Ach, KCl and $BaCl_2$. These results could open doors again for traditional medicinal plants in treatment of different gastrointestinal spasms.

This study also demonstrates the potency and selectivity of harmalol in the spasmolytic effect and its potential as a novel compound for the development of new drug for treatment of intestinal spasm.

CONCLUSION

The herein presented results show that harmalol and harmaline have produced a decrease in isolated rat ileum contractions, with 10 μM concentration. Studies conducted in order to determine the potential mechanism of action revealed that this alkaloid inhibits both Ach- and Ca^{2+} - induced contractions. Based on these preliminary studies, it is postulated that harmalol and harmaline significantly affect the motor function of the gastrointestinal tract via mechanisms that most probably involve Ca^{2+} ions. However, this effect can be shown at higher concentrations.

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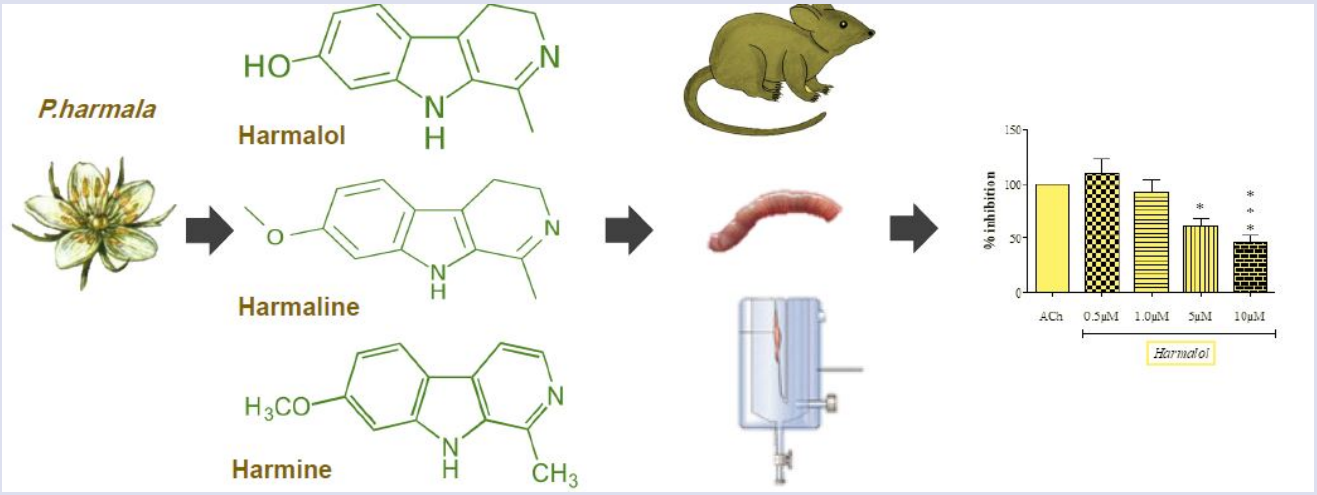
GRAPHICAL ABSTRACT



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