International Journal of Medicine, 5 (1) (2017) 90-93

International Journal of Medicine

Website: www.sciencepubco.com/index.php/IJM
doi: 10.14419/ijm.v5i1.7282
Research paper

Anti-nociceptive and antipyretic activities of *Solanum violaceum* ortega

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Abstract

Solanum violaceum Ortega has been used by the traditional medicine practitioners in pain and fever. This study aimed at investigating anti-nociceptive and antipyretic activities of methanol extract of leaf (MELSV), fruit (MEFSV) and root (MERSV) of *S. violaceum* in *Swiss* albino mice. Anti-nociceptive activity was evaluated using hot plate method while antipyretic by brewer's yeast induced hyperpyrexia. In both tests, test animals were divided into eight groups of six in each. The groups were treated as negative control (distilled water), standard and tests (250 and 500 mg/kg of MELSV/ MERSV/ MERSV). Diclofenac sodium (150 mg/kg) and paracetamol (150 mg/kg) were taken as standards for anti-nociceptive and antipyretic tests, respectively. All the treatments were administrated *via* oral gavages (p.o.). Results suggest that, the plant extracts dose-dependently increased retention time compared to the control groups. MELSV at 500 mg/kg significantly increased retention time on the hot-pate of the test animals than the MEFSV and MERSV treated groups. In the antipyretic test, both 250 and 500 mg/kg of MELSV and 500 mg/kg of MEFSV significantly ($p < 0.05$) decreased temperature to the experimental animals 30, 60, 120 minutes. In conclusion, the crude extracts of *S. violaceum* exhibited anti-nociceptive and antipyretic activities. *S. violaceum* may be one of the good sources of anti-nociceptive and antipyretic compounds.

Keywords: *Anti-inflammation; Pain; Fever; Mus musculus.*

1. Introduction

It is doubtless that, more than 80% of the world populations depend on natural medicines (Kaur and Jaggi 2010). According to Islam et al (2016a), about 25% pharmaceutically consumed drugs are derived from natural origins. Plants are the potential sources in this context. Notably, researches on natural products are growing day by day due to their economy, availability and evidences over generations. Millions of vines, herb, shrubs and trees have rendered a wide variety of cures (Rates 2001). *Solanum violaceum* Ortega, locally known as Titbegun is mainly a vegetable. It belongs to the family Solanaceae, which consists more than 2,700 species under 98 genera (Olmstead and Bohs 2006). Being indigenous to the tropical and temperate regions, this plant has reportedly been used in the traditional practice over the years (Jain and Borthakur 1986).

Paste prepared from the root of *S. violaceum* is reported to use in vomiting and indigestion, while the decoction of leaves and fruits in headache by the Bangladeshi tribes (Malek et al. 2012; Seraj et al. 2013). Otherwise, the folkloric use of *S. violaceum* is also evident in some countries of Southeast Asia. Moreover, some tribes in India use the fruits of this plant in diabetes (Raghavendra et al. 2015) and other parts in asthma, dry cough and chronic febrile infection (Singh et al. 2014). It is also evident to use in diarrhea, intestinal worms, sore between the fingers (BEOD 2015), colic, flatulence, dysuria, toothache, nasal ulcers, pruritus and leucoderma (MPB 2015).

To be mentioned that a number of bioactive steroidal compounds have been synthesized from *S. violaceum* (Chang et al. 2013; Bu et al. 2014). The wound healing activity of the plant extract was reported previously (Manjunatha 2006). Furthermore, antihelmentic and antimicrobial activities were also demonstrated along with the presence of alkaloid, carbohydrate, flavonoids, phenols, glycoside, saponin, gums, diterpenes, proteins and tannins as phytoconstituents (Raju et al. 2013). It is also evident to have antioxidant (Tzekuei and Tsuiching 2009), cytotoxic and anti-inflammatory activities (Yen et al. 2012).

Inflammation involves the biosynthesis of prostaglandin (PG), plays a key role to produce pain and pyrexia. Thus, the present study was aimed to evaluate anti-nociceptive and antipyretic effects of methanol extract of root, fruit and leaf of *S. violaceum* in *Swiss* mice.

2. Materials and methods

2.1. Collection of plant materials

S. violaceum was collected in the summer from the Chittagong hill-tracts of Bangladesh and subsequently identified by the taxonomist by Bangladesh Forest Research Institute (BFRI-H), Chittagong. A voucher specimen was deposited as BFRI-H-SA-264 was provided and the plant specimen was deposited in BFRI for future reference.

2.2. Reagents and chemicals

All the chemicals and reagents used in this study were purchased from Merck, India.

2.3. Preparation of crude extracts

The plant materials (roots, fruits and leaves) were washed with running tap-water, and then followed by shed drying (temperature not exceeding 50 ^{O}C) and milling to obtain the course powders. The coarse powder was separately extracted with methanol using a Soxhlet apparatus (Quickfit, England) for 48-72 h to obtain the crude methanolic extract.

2.4. Experimental animals

Swiss albino mice (20-25 g; two months) of both sexes were purchased from the Animal Resources Branch (ARB), International Centre for Diarrheal Disease Research, Bangladesh (ICDDR,B) and maintained in a well-ventilated room with 12/12 h light/dark cycle in polypropylene cages for 1 week to acclimatize to laboratory conditions before starting the experiment. The animals were fed with standard pellet feed and water *ad libitum*. The research work was done in the Medicinal Chemistry Lab, Department of Pharmacy, Southern University Bangladesh after receiving an approval by the Research Supervision Committee of Southern University Bangladesh (approval #SUB-999-10-40) as per Guidelines of the Animal experimentation from the International Centre for Diarrheal Disease Research, Bangladesh (ICDDR,B).

2.5. Evaluation of anti-nociceptive activity

This study was conducted by slightly modified hot plate method as described by (Sultana et al. 2015). Briefly, the animals were grouped in eight different groups, six in each. The groups divided as: NC (distilled water 10 ml/kg), PC (diclofenac sodium; 150 mg/kg), MERSV-I (250 mg/kg), MERSV-II (500 mg/kg), MEFSV-I (250 mg/kg), MEFSV-II (500 mg/kg), MELSV-I (250 mg/kg) and MELSV-II (500 mg/kg). The treatments were given orally (p.o.) to the overnight fasted mice and the animals were then placed individually in a thermostatically controlled heated beaker at 55 ± 1 ℃ and the pain reaction (paw licking, shaking and jumping) time of each animal was recorded in seconds for 5 minutes at 0, 30, 60 and 120 minutes after treatments received. The cutoff time was fixed to 15 seconds to avoid the damage to the paw of the animals. The latency was recorded for every action period.

2.6. Evaluation of antipyretic activity

Antipyretic activity was evaluated by the slightly modified brewer's yeast induced hyperpyrexia method as described by Nur et al (2015). The number of animals and groups were similarly grouped as said in anti-nociceptive test. In this case, paracetamol at 150 mg/kg (p.o.) was administered to the standard treated group. Pyrexia was induced by subcutaneous injection of 20% (w/v) brewer's yeast suspension in distilled water at a dose of 10 ml/kg to the overnight fasted animals. Before that, the rectal temperature of each mouse was recorded to compare after an 18 h of yeast treatment effect. The animals showing a rise in rectal temperature of at least 2 °F were selected and subsequently treated as groups marked. After treatments, the rectal temperature was recorded at 0, 1, 2 and 3 h.

2.7. Preliminary phytochemical analysis

Preliminary phytochemical analysis has been done by the methods reported by Sultana et al (2015).

2.8. Statistical analysis

The results were expressed as mean ± standard error of mean (SEM). Statistical analysis was performed using one-way ANOVA for multiple comparisons and followed by *t*-Student-Newman-Keuls as *post hoc* test by GraphPad Prism (version 6.0; GraphPad San Diego, California, USA. copyright © 1994-1999) by considering statistically significant when $p < 0.05$.

3. Results

3.1. Evaluation of anti-nociceptive activity

The results of anti-nociceptive activity test of methanol extracts of *S. violaceum* parts and controls are presented in Table 1. At 0 min, mice of all groups showed a latent response of no longer than 5 seconds, which eventually increased at 30, 60 and 120 min in the PC and extracts groups. All the extracts at doses of 250 and 500 mg/kg showed a statistically significant ($p < 0.05$) dose dependent increase in latency when compared to the NC group. There was a dose-dependent anti-nociceptive capacity of the crude extracts, in which MELSV-II, MEFSV-II and MERSV-II exhibited better retention time on the hot plate of the experimental animals.

Table 1: Anti-nociceptive Activity of Methanol Extracts of *S. violaceum*

Treatment Groups (p.o.)	Retention time in seconds in 5 min at-			
	0 min	30 min	60 min	120 min
NC (10 ml/kg)	4.71 ± 0.43	4.43 ± 0.29	4.96 ± 0.15	4.57 ± 0.46
PC (150 mg/kg)	5.40 ± 0.25*	12.03 ± 0.24*	12.88 ± 0.64*	10.37 ± 0.38*
MELSV-I	5.57 ± 0.65*	7.33 ± 0.96*	7.46 ± 0.42*	5.93 ± 1.09*
MELSV-II	4.73 ± 0.64	9.06 ± 1.40*	8.23 ± 0.59*	8.23 ± 1.21*
MEFSV-I	3.96 ± 0.75	6.83 ± 0.78*	6.93 ± 0.11*	6.86 ± 0.67*
MEFSV-II	4.56 ± 0.98	7.24 ± 0.9*	9.03 ± 0.49*	7.90 ± 0.27*
MERSV-I	4.30 ± 0.25	5.36 ± 0.45*	6.33 ± 0.41*	5.92 ± 0.84*
MERSV-II	3.84 ± 0.69	6.29 ± 0.28*	6.26 ± 0.26*	7.12 ± 0.73*

Values are mean ± SEM, *p <0.05 compared to the NC group; NC: negative control (distilled water); PC: positive control (diclofenac sodium); MERSV: methanol extract of root of *S. violaceum*; MEFSV: methanol extract of fruit of *S. violaceum*; MELSV: methanol extract of leaf of *S. violaceum*.

3.2. Evaluation of antipyretic activity

The results of antipyretic activity test of the methanol extracts of S. violaceum parts and controls are presented in Table 2. In this test, all the extracts at two different doses reduced rectal temperature up to 3 hours in experimental animals when compared to NC group. Dose dependent activity was observed with all the treatments. MELSV with 250 and 500 mg/kg and MERSV at 500 mg/kg were found to reduce rectal temperature almost similarly that of the PC group.

Table 2: Antipyretic Activity of Methanol Extracts of *S. violaceum*

Treatment Groups (p.o.)	Rectal temperature (°F) during 3 h of observation period				
	-18 h	0 h	1 h	2 h	3 h
NC (10 ml/kg)	98.71 ± 0.75	102.24 ± 0.12	101.90 ± 0.51	102.44 ± 0.96	102.68 ± 1.15
PC (150 mg/kg)	99.10 ± 0.52	102.11 ± 1.14	98.34 ± 0.37*	98.90 ± 0.72*	98.37 ± 0.07*
MELSV-I	98.21 ± 0.79	101.55 ± 0.26	98.65 ± 0.67*	99.28 ± 0.77*	99.87 ± 1.12*
MELSV-II	98.49 ± 1.45	102.28 ± 0.46	98.97 ± 0.65*	98.62 ± 0.33*	98.70 ± 0.48*
MEFSV-I	99.46 ± 0.82	102.17 ± 0.26	99.88 ± 0.39*	100.25 ± 0.49*	100.48 ± 0.57*
MEFSV-II	99.27 ± 0.41	101.85 ± 0.70	99.52 ± 0.35*	99.93 ± 0.28*	99.14 ± 0.11*
MERSV-I	98.54 ± 0.63	101.77 ± 0.21	100.91 ± 0.78	100.89 ± 0.17*	101.34 ± 0.19
MERSV-II	98.22 ± 1.03	101.56 ± 0.54	100.25 ± 0.58	100.70 ± 0.68*	100.12 ± 1.07*

Values are mean ± SEM, *p <0.05 compared to the NC group; NC: negative control (distilled water); PC: positive control (paracetamol); MERSV: methanol extract of root of *S. violaceum*; MEFSV: methanol extract of fruit of *S. violaceum*; MELSV: methanol extract of leaf of *S. violaceum*.

3.3. Preliminary phytochemical analysis

Phytochemical analysis revealed that, the MELSV and MERSV possess alkaloids, glycosides, tannins, flavonoids, saponins and

gums, while MEFSV contains alkaloids, glycosides, flavonoids saponins and gums.

4. Discussion

Pain is a distressing feeling, often caused by intense or damaging stimuli which may be chemical, mechanical or thermal (Cao et al. 1998). Pain is associated with pathology of various clinical conditions like arthritis, cancer, and vascular diseases. A biochemical called PG acts as the mediator of pain. The synthesis of which is stimulated by cyclooxygenase (COX)-1 and COX-2 enzymes. The non-steroidal anti-inflammatory drugs (NSAIDs) inhibit pain or induce analgesia by blocking the activity of COXs (Conaghan 2012).

In the present study, to what extent the plant extracts could inhibit thermally evoked pain, comparing to NC and PC groups, was determined. The hot plate method is one of the most effective methods to evaluate the analgesic activity of test substances (Mi et al. 2011) in which, as discussed earlier, mice are placed on heated beaker for a period of time and their responses are observed as a pain reaction time. In this context, an increase in the pain reaction time indicates the level of analgesia (Omeh and Ezeja 2013) and can be considered as an important parameter of anti-nociceptive activity rendered by the drug and extracts (Sharma et al. 2013). The hot plate test used to investigate the anti-nociceptive activity of methanol extract of leaf, fruit and root of *S. violaceum* increased latency time than the NC group in a dose-dependent manner.

As, in general, centrally acting agents have been found to show activity in thermally induced pain methods, therefore, the MELSV, MEFSV and MERSV, administered at 250 and 500 mg/kg may have a central analgesic activity. The phytochemical analysis and literature reports revealed that, the parts of *S. violaceum* contain flavonoids and diterpenes. These groups of phytochemicals are evident to have prominent beneficial action in nervous system; especially a number of diterpenes are reported to have an anti-nociceptive effect in animal models (Islam et al. 2016b).

On the other hand, the brewer's yeast induced hyperpyrexia method is a useful method to evaluate the antipyretic potential of test substances involving a subcutaneous injection of brewer's yeast in the test animals to produce fever (Chattopadhyay et al. 2005). The infected or damaged tissue initiates the enhanced formation of pro-inflammatory mediators (e.g. - cytokines, such as interleukin (IL)-1β, IL-α, IL-β, and tumor necrosis factor (TNF)-α) which increase the synthesis of PGE2 near the hypothalamic area and thereby trigger the hypothalamus to elevate the body temperature (Qadrie et al. 2009).

Yeast induced pyrexia is also known as pathogenic fever (Alzubier and Okechukwu 2011) in which yeast produces fever with cytokines in test animals by enhancing the production of PGs mainly PGE2, by elevating the set point of the thermoregulatory center in hypothalamus. Substances having antipyretic activity usually show an inhibitory effect on COX-2, thus ultimately suppress the biosynthesis of PGE2 and consequently reduce the body temperature (Ridtitid et al. 2007).

In the present study, both the PC (paracetamol) and plant extracts reduced the rectal temperature of test animals throughout the 3 h observation period. The possible mechanism for lowering the thermoregulatory set point could be suppression of the peripheral formation of pyrogenic cytokines achieved by COX pathways blocking. As mentioned above, along with other phytochemicals the plant contains flavonoids, and it has been proved in several studies that the presence of this secondary metabolite is the reason behind antipyretic activity of any natural compound (Mutalik et al. 2003).

5. Conclusion

Traditionally, this plant is being used in pain management and to treat febrile condition. This study demonstrating that the methanol extracts of leaf, fruit and root of *S. violaceum*, has analgesic and antipyretic activities. Hence, the study supports its folkloric claims. However, further investigations are required to isolate and characterize of active principles in this plant and to explain the cellular mechanisms of them.

Acknowledgments

All the authors are thankful to the Department of Pharmacy, Southern University Bangladesh for hosting and providing facilities to carry out this study.

Conflicts of interest

None declared.

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