JJBS
Jordan Journal of Biological Sciences

Volume 5, Number 1, March 2012
ISSN 1995-6673
Pages 31 - 36

Analgesic and Anti-inflammatory Activities of Ethanolic Root Extract of *Swertia chirata* (Gentianaceae)

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Received on September 7, 2011, Accepted October 29, 2011

Abstract

Swertia chirata, a Gentian species, can be traced through the medicinal history as a nontoxic and safe ethnomedicinal herb and has been mentioned in medical papyri to expel fever, relieve headache, to draw out inflammation and to stimulate CNS. The ethanolic root extract of *Swertia chirata* was chosen for pharmacological screening and analgesic and anti-inflammatory activities in animal models. The anti-inflammatory activity was assessed using the carrageenan-induced rat paw edema model. The analgesic effect was measured in mice using the acetic acid-induced writhing test and the radiant heat tail-flick method. In rat paw edema model induced by carrageenan, the extract was found to reduce significantly (p<0.001) the formation of edema at the 400 mg/kg dose level and showed 57.81% (p<0.001) inhibition of edema volume at the end of 3 h. In the acetic acid-induced writhing test in mice, the extract at 200 and 400 mg/kg doses level showed 41.76% (p<0.001) and 58.29% (p<0.001) inhibition of writhing, respectively. In radiant heat tail-flick method, the root extract produced 43.88% (p<0.001) and 64.81% (p<0.001) increase in reaction time 30 min after oral administration at the 200 and 400 mg/kg doses level, respectively. *Swertia chirata* possesses evident analgesic and anti-inflammatory activities. The results signify the traditional uses of *Swertia chirata*, for inflammation and pain.

Keywords: *Swertia chirata,* analgesic, anti-inflammatory, carrageenan, Gentianaceae.

1. Introduction

Swertia chirata belongs to the family Gentianaceae and it has an erect, about 2–3 ft long stem, the middle portion is round, while the upper is four-angled, with a prominent decurrent line at each angle. The stems are orange brown or purplish in color, and contain large continuous yellowish pith (Chaudhuri *et al*., 2007; Balaraju *et al*., 2011). The root is simple, tapering and stout, short, almost 7 cm long and usually half an inch thick (Clarke, 1985). Some authors have described *Swertia chirata* as an annual and others as biennial or pluri-annual (Keil *et al*., 2000; Edwards, 1993). It is widely used in India to treat fever, malaria and liver diseases (Banerjee *et al*., 2000). Concoction of *Swertia chirata* with cardamom, turmeric and kutki is given for gastrointestinal infections, and along with ginger it is considered good for fever (Keil *et al*., 2000). When given along with neem, manjishta and gotu kola, it serves as a cure for various skin problems. It is used in combination with other drugs in case of scorpion bite (Joshi and Dhawan, 2005).

Swertia chirata, a Gentian species, can be traced through the medicinal history as a nontoxic and safe ethnomedicinal herb utilized for its bitter bioactive compounds (Jensen and Schripsema, 2002). The chemical constituents of *Swertia chirata* include secoiridoid bitters, alkaloids, xanthones and triterpenoids (Wang *et al.*, 2003; Balasundari *et al.*, 2005; Brahmachari *et al.*, 2004). Amarogentin, amaroswerin, gentiopicroside and swertiamarin are the reported bitter secoiridoid glycosides of the plant (Friedhelm and Hans, 1956; Takino *et al.*, 1980; Friedhelm, 1955; Bhattacharya *et al.*, 1976). A xanthone rich extract of this plant has shown significant anti-inflammatory activity in acute, subacute, chronic and immunological models and swerchirin, a xanthone from *Swertia chirata* is a potent hypoglycaemic agent (Mandal *et al.,* 1992; Bajpai *et al.*, 1991; Saxena *et al.*, 1991). Methanol extracts of this plant having antidiabetic activity contain mangiferin, amarogentin, amaroswerin, sweroside and swertiamarin as active constituents (Suryawanshi *et al*., 2009). Xanthone derivatives like mangostin, isomangostin and mangostin triacetate are known to possess significant anti-inflammatory activities. Reports also suggest that several varieties of xanthones show potent anti-platelet, anti-cancer, CNS stimulant, anti-fungal and antimalarial effects (Banerjee *et al*., 2000).

Extract of *Swertia chirata* is used as anthelmintic and hepatoprotective agents whereas antimalarial and hypoglycemic activities of this medicinal plant are also

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known (Brahmachari *et al.,* 2004). It is also reputed for its antidiarrhoeal properties (Dahanukar *et al.,* 2000).

The present study is undertaken to investigate the analgesic and anti-inflammatory potentials of ethanolic root extract of *Swertia chirata* scientifically.

2. Materials and Methods

2.1. Plant collection

The root part of fresh unadulterated *Swertia chirata* was collected from Chawk bazaar, Dhaka and taxonomically identified by the National Herbarium of Bangladesh, Mirpur, Dhaka, Bangladesh. A fresh sample was dried at room temperature (25–30°C) for 10 days. The dried root sample was then ground in coarse powder using high capacity grinding machine in the Phytochemical Research Laboratory, Faculty of Pharmacy, University of Dhaka and preserved in air tight container.

2.2. Extraction of the plant materials and sample preparation

The dried and ground root (1.5 kg) part of the plant was macerated with ethanol (95%) for 15 days. Then the extract was filtered and concentrated with a rotary evaporator and was subsequently defatted to get the dried extract yielding 13% root (195 g) (Ahmed *et al*., 1991). For the pharmacological tests, the extract was dissolved in 0.1% Tween-80 in normal saline solution to prepare 200 mg/kg and 400 mg/kg concentrations.

2.3. Drugs and Chemicals

Aminopyrine, carrageenan and diclofenac were purchased from Sigma-Aldrich, Germany. Morphine was obtained from Square Hospital, Dhaka, Bangladesh following required formalities. Acetic acid was purchased from Merck, Germany.

2.4. Experimental animals

Swiss albino mice weighing 20-30 g and Long-Evans rats weighing 160-200 g were used in this study. They were obtained from the Animal Research Branch of the International Centre for Diarrhoeal Diseases and Research, Bangladesh (ICDDR, B). The animals were housed in polyvinyl cages with not more than six animals per cage and maintained under standard laboratory conditions (temperature 25 ± 2^0C) and a 12/12 h dark/light cycle and received feed, formulated by ICDDR, B and water *ad libitum*. To keep the hydration rate constant, food and water were stopped 12 h before the experiments. Experiments on animals were performed strictly in accordance with the guidelines provided by the Institutional Animal Ethics Committee.

2.5. Anti-inflammatory activity

2.5.1. Carrageenan-induced rat hind paw edema

The anti-inflammatory potential of the ethanolic root extract of *Swertia chirata* was assessed by the carrageenan-induced right hind paw edema method (Winter *et al*., 1962; Saha *et al*., 2007). Briefly, acute inflammation was produced by subplantar injection of 0.1 ml of 1% suspension of carrageenan in normal saline, in the right hind paw of the rats 1 h after the oral administration of test materials. The paw volume was measured by plethysmometer (Ugo Basile, Italy) at 0 h, and 3 h after the carrageenan injection (Winter *et al*., 1962). The extract was administered at 200 and 400 mg/kg body weight by gavage. Diclofenac at a dose of 25 mg/kg body weight was used as standard anti-inflammatory agent. The negative control group received 0.1% Tween-80 in saline solution.

The anti-inflammatory effect of the extract was calculated by the following equation (Asif and Kumar, 2009):

Anti-inflammatory activity (%) = (1-D/C) X100

Where, C= Mean paw volume of control,

D= Mean paw volume of test.

2.6. Analgesic activity

2.6.1. Acetic acid induced writhing method

The peripheral analgesic activity of root extract of *Swertia chirata* was measured by the acetic acid induced writhing test in mice (Saha and Ahmed, 2009; Koster *et al*., 1959). The abdominal writhing was induced by intraperitoneal injection of acetic acid solution (0.7%) at a dose of 0.1 ml/10 g of body weight to each mouse, a model of visceral pain. Aminopyrine at oral dose of 50 mg/kg was used as standard analgesic agent. The extract was administered at 200 and 400 mg/kg body weight. The extract, standard drug and control (normal saline solution, 1 ml/kg) were orally administered 1 h prior to the injection of acetic acid. The number of writhing was calculated for 10 min after the application of acetic acid.

2.6.2. Radiant heat tail-flick method

The central analgesic activity of the root extract was studied by measuring drug-induced changes in the sensitivity of the pre-screened (reaction time: 2-4 sec) mice to heat stress applied to their tails by using a Medicraft Analgesiometer Mask-N (D'Amour and Smith, 1941). The current intensity passing through the naked nichrome wire was maintained at 5 ampere. The distance between the heat source and the tail skin was 1.5 cm and cut-off reaction time was fixed at 10 sec to avoid any tissue damage. Morphine was used to compare the analgesic effect of the plant extract. The extract was orally administered at 200 and 400 mg/kg body weight. Morphine was administered sub-cutaneously at a dose of 2 mg/kg body weight.

2.7. Statistical analysis

Data were analyzed by one-way ANOVA followed by Dunnett's test and p value *of* 0.05 was considered statistically significant.

3. Results

3.1. Anti-inflammatory activity

The anti-inflammatory activity of the extract was measured at a dose of 200 and 400 mg/kg b.w. against acute paw edema induced by carrageenan. A strong inhibition of the paw edema was observed with the different doses of the extract and with diclofenac. The two doses tested (200 and 400 mg/kg) produced significant (p<0.001) anti-inflammatory activity and reduced the paw

volume by 37.76% and 57.81% respectively, whereas diclofenac caused 65.89% reduction when used as a reference drug (Table 1).

3.2. Analgesic activity

3.2.1. Acetic acid induced writhing method

The root extract of the plant *Swertia chirata* at the doses of 200 and 400 mg/kg b.w. and aminopyrine 50 mg/kg b.w induced a significant (p<0.001) decrease in the number of writhes when compared to control untreated groups. The two doses tested (200 and 400 mg/kg) produced significant (p<0.001) analgesic activity and reduced the paw volume by 41.76% and 58.29% respectively, whereas aminopyrine caused 63.77% reduction when used as a reference drug (Table 2).

3.2.2. Radiant heat tail-flick method

In the radiant heat tail-flick test, the root extract prolonged the heat stress tolerance capacity of the mice, indicating the possible involvement of a higher center (Whittle, 1964). In radiant heat tail-flick test, the root extract produced 43.88% (p<0.001) and 64.81% (p<0.001) elongation of the reaction time to tail flicking 30 min after oral doses of 200 and 400 mg/kg body weight respectively. After 60 min the extract caused 30.81% (p<0.001) and 46.44% (p<0.001) increase in reaction time to tail flicking of 200 and 400 mg/kg body weight respectively and after 120 min the extract caused 13.34% and 19.69% (p<0.01) increase in reaction time to tail flicking of 200 and 400 mg/kg body weight respectively. Morphine caused 78.88% (p<0.001), 54.00% (p<0.001) and 25.13% (p<0.001) increase in reaction time to tail flicking after 30, 60 and 120 min respectively when used as a reference drug at 2 mg/kg body weight (Table 3).

Table 1. Effects of *Swertia chirata* extract (SCE) on carrageenan induced rat paw edema.

Group	Dose (mg/kg)	Paw volume increase after 3 h (ml)[a]	Percentage (%) of inhibition
Control	-	0.64 ± 0.032	-
SCE	200	0.40 ± 0.025***	37.76
SCE	400	0.27 ± 0.014***	57.81
Diclofenac	25	0.22 ± 0.017***	65.89

[a]Each datum represents the mean paw volume increase after 3 h (ml) ± SEM (n = 6)

***p<0.001 compared with the control group (Dunnett's test)

Table 2. Effects of *Swertia chirata* extract (SCE) on acetic acid induced writhing response in mice.

Group	Dose (mg/kg, p.o.)	Writhing[a]	Percentage (%) of inhibition
Control	-	21.17 ± 0.477	-
SCE	200	12.33 ± 0.333***	41.76
SCE	400	8.83 ± 0.703***	58.29
Aminopyrine	50	7.67 ± 0.494***	63.77

[a]Each datum represents the mean writhing number ± SEM (n = 6)

***p<0.001 compared with the control group (Dunnett's test)

Table 3. Effects of *Swertia chirata* extract (SCE) on radiant heat tail-flick response in mice.

Group	Dose (mg/kg)	Reaction time (sec)[a]		
		30 min (% elongation)	60 min (% elongation)	120 min (% elongation)
Control	-	4.50 ± 0.24	4.62 ± 0.18	4.97 ± 0.23
SCE	200	6.32 ± 0.46*** (43.88)	6.05 ± 0.28**(30.81)	5.63 ± 0.18 (13.34)
SCE	400	7.22 ± 0.39*** (64.81)	6.55 ± 0.25*** (46.44)	5.93 ± 0.21** (19.69)
Morphine	2	8.15 ± 0.86*** (78.88)	7.15 ± 0.31*** (54.00)	6.20 ± 0.12*** (25.13)

[a] Each datum represents the mean reaction time (sec) ± SEM (n = 6)

***p<0.001, **p<0.01 compared with the control group (Dunnett's test)

4. Discussion

Pain and inflammation are associated with the pathophysiology of various clinical conditions such as arthritis, cancer and vascular diseases. Inflammatory reactions are not only the response of living tissues to injury and infection, but also are relevant to disease developments, such as asthma, multiple sclerosis, colitis, inflammatory bowel disease and atherosclerosis. Many natural products are used in traditional medical systems to relieve the symptoms from pain and inflammation (Kaplan *et al*., 2007; Marrassini *et al*., 2010).

Results from the present study shows that the ethanolic root extract of *Swertia chirata* has a potent antinociceptive effect against chemical pains provoked by acetic acid and a good activity against mechanic pain induced by heat. The extract also presents important anti-inflammatory effects on acute edema induced by carrageenan.

The paw edema induced by carrageenan involves several chemical mediators such as histamine, serotonin, bradykinin, and prostaglandins (Vinegar *et al*., 1987; Chang *et al*., 2011). In the carrageenan-induced rat paw edema model, root extract of *Swertia chirata* showed significant inhibitory effect on the edema formation. This effect started from the first hour and was maintained in all the inflammatory phases, suggesting that the main mechanism of action of the tested extract may involve prostaglandin biosynthesis pathway and may influence other mediators of inflammation. The extract is found to be less active than diclofenac even when used in higher doses.

As the carrageenan-induced inflammation model is a significant predictive test for anti-inflammatory agents acting by inhibiting the mediators of acute inflammation, these results are an indication that *Swertia chirata* can be an effective for acute inflammatory disorders (Mossa *et al.*, 1995).

In the acetic acid-induced writhing test, local peritoneal receptors are postulated to be partly involved in the abdominal writhing response and the mechanism of the reaction to this nociceptive stimulus seems to be related to the prostanoid system (Nguemfo *et al*., 2007). The constriction response of abdomen produced by acetic acid is a sensitive procedure for peripheral analgesic agents, and has also been associated with prostanoids in general, for example, increased levels of PGE2 and PGF2α in peritoneal fluids (Ronaldo *et al*., 2000; Deraedt *et al*., 1980) as well as lipoxygenase products (Levini *et al*., 1984; Dhara *et al*., 2000). The extract of *Swertia chirata* and aminopyrine exhibit marked inhibitory effect on the writhing response induced by acetic acid. These results strongly suggest that the extract possesses peripheral analgesic activity and its mechanism of action may be mediated through inhibition of local peritoneal receptors or arachidonic acid pathways, involving cyclo-oxygenases and/or lipoxygenases.

The phytochemical analysis of this extract revealed that it contains xanthones flavonoids, terpenoids, iridoids, secoiridoid glycosides and saponin (Wang *et al.*, 2003; Balasundari *et al.,* 2005; Brahmachari *et al.,* 2004; Ghosal *et al.*, 1973; Phoboo *et al*., 2010; Bhargava *et al*., 2009). Of these, flavonoids and saponins are well known for their ability to inhibit pain perception. Flavonoids also have anti-inflammatory properties due to their inhibitory effects on enzymes involved in the production of the chemical mediator of inflammation (Owoyele *et al*., 2005). Flavone and its methoxy derivatives exhibited significant dose-dependent analgesic activity (Thirugnanasambantham *et al*., 1990). Previous studies showed that ethanolic root extract of *Swertia chirata,* is rich in xanthone and xanthone derivatives has anti-inflammatory activity (Banerjee *et al*., 2000; Wang *et al.*, 2003; Balasundari *et al.*, 2005). It was also reported that mangiferin was a potent anti-inflammatory compound. Therefore, the activity of *Swertia chirata* can be attributed to magniferin (Kumar *et al*., 2003).

In conclusion, this study has shown that the ethanolic root extract of *Swertia chirata* possesses significant analgesic and anti-inflammatory effects that may be mediated through inhibition of cell mediators such as bradykinin, and prostaglandins. These results support the traditional use of this plant in some painful and inflammatory conditions.

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