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A comparative study of analgesic property of whole plant and fruit extracts of *Fragaria vesca* in experimental animal models

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Abstract

The aim of the study was to compare the analgesic activities of ethanolic extract of fruits and whole plant of *Fragaria vesca* in experimental animal models. The extracts were prepared by percolation method and oral toxicity testing was performed as per OECD guidelines. Analgesic activity was assessed by tail flick method (for central action) and acetic acid-induced writhing test (for peripheral action). Fruit extract, whole plant extract and aspirin showed significant analgesic activity, both central and peripheral, as compared to control ($p<0.01$). Although fruit extract at dose of 500 mg/kg showed better activity than 250 mg/kg ($p<0.05$). Analgesic activities of fruit extract 250 mg/kg and whole plant extract 500 mg/kg were almost equivalent while aspirin was most potent among all with significantly greater activities as compared to all the extracts ($p<0.05$).

Introduction

Pain is an unpleasant sensation no doubt, but on the whole it is usually beneficial to man (or animal). Pain is mainly a protective mechanism for the body. It occurs whenever any tissues are being damaged, and it causes the individual to react to remove the pain stimulus (Guyton and Hall, 2006).

Fragaria vesca is a cousin of the wild strawberry. It is found in woods and grasslands in Europe, Western Asia, North America, and temperate areas in Chile. The berries, leaves, and roots of *F. vesca* have all been used medicinally in the past. The root was once a popular household remedy for diarrhea and the stalks for wounds. Anti-oxidant properties have recently been discovered in the fruit, making them a valuable preventive for cancer. The leaves are gently astringent. One can make a tea with the leaves for diarrhea, digestive upsets, and to stimulate the appetite (Alpine strawberry, 2008).

F. vesca (wild strawberry), belongs to the family rosaceae. Plants contain flavonoids, tannins, volatile oils, methyl salisylate and borneol (Agarwal and Paridhavi, 2007). The fruits contain salicylic acid and are beneficial in the treatment of liver and kidney complaints, as well as in the treatment of rheumatism and gout (Phillips and Foy, 1990). Taking this into account the following study is carried out to find out analgesic property of *F. vesca*, as there are no previous studies for the same.

Materials and Methods

Fresh plants of *F. vesca* were collected from Assam Medical College campus, Dibrugarh, Assam in the month of February-April 2008. Plant samples were identified and confirmed from the Department of Botany, Dibrugarh University.

Fruits were separated from the plants and both fruits and rest of the plant were air dried. These were then powdered and ethanolic extracts were prepared using 95% ethanol by percolation method (The Chemist and Druggist, 1950) followed by steam evaporation. A net yield of 32.4 g was obtained by percolating 470 g of dry

powder of plant while from 120 g of fruits, net yield was 17.2 g.

Both ethanolic extracts of whole plant and fruits of *F. Vesca* were tested for acute oral toxicity (OECD 2001 guidelines).

Central analgesic activity

The central analgesic activity was tested by tail flick method in Albino rats (D'Armour and Smith, 1941). Healthy rats of either sex weighing 100-200 g were fasted overnight and divided into eight groups with six animals in each group. The tail flick latencies (reaction time) of the animals were assessed by analgesiometer (Elite). Basal reaction time to radiant heat was taken by placing the tip (last 2 cm) of the tail on the radiant heat source. Tail withdrawal from the heat (flicking response) was taken as the end point. A cut of period of 10 sec was observed to prevent damage to the tail. The tail flick latencies were recorded at pre-drug, 15, 30, 60, 90, 120, 150 and 180 min after administration of vehicle or drugs. Pethidine was taken as standard drug (Goyal, 2006) while naloxone 1 mg/kg (Ghosh, 2005a) was used to determine mechanism of action.

Peripheral analgesic activity

The peripheral analgesic activity was tested by glacial acetic acid-induced Writhing test in Albino mice (Witkin et al., 1961). Healthy mice of either sex weighing 20-30 g were fasted overnight and divided into five groups with six animals in each group. One hour after administration of the drugs, induction of writhing was done in mice by giving intraperitoneal injection of acetic acid at a dose of 10 mL/kg body weight. The number of writhing responses were counted and recorded for 20 min. Aspirin was taken as standard drug at a dose of 100 mg/kg p.o. (Ghosh, 2005b).

Statistical analysis

Statistical analysis was done using one-way ANOVA followed by Dunett's and Bonferoni's test. Significance level of <0.05 was considered as significant (Rao, 1999).

Results

The above study showed that the ethanolic extracts of fruits and whole plant of *F. vesca* and standard drug aspirin showed significant central and peripheral analgesic activities when compared to control ($p<0.01$). The central analgesic activity of fruit extract at 500 mg/kg was significantly more than fruit extract at 250 mg/kg and whole plant extract at 500 mg/kg ($p<0.05$); although when compared to standard, aspirin showed significantly more analgesic activity ($p<0.05$) than fruit extract 500 mg/kg (except at 15 and 30 min), fruit extract 250 mg/kg and whole plant extract (Table I). For peripheral analgesic activity, again the fruit extract at 500 mg/kg showed significantly better analgesic action than fruit extract at 250 mg/kg and whole plant extract at 500 mg/kg; although analgesic effect of standard drug aspirin was significantly more than all the extracts ($p<0.05$) (Table II).

LD_{50} of both fruit and whole plant extracts was found to be more than 2,000 mg/kg.

Discussion

The above study showed that ethanolic extracts of fruits and whole plant of *F. vesca* produced significant analgesia, both centrally and peripherally. The central action is probably mediated via opioid receptors as seen with the tail flick responses. Pre-treatment with naloxone significantly decreased the reaction time creating hyperalgesia, while when naloxone was given along with the test drug, there was significant increase in reaction time as compared to naloxone alone without causing hyperalgesia, showing some partial agonistic activity for the opioid receptors as probable mechanism of central analgesic action. This indicates the involvement of endogenous opioid peptides in mediation of antinociceptive response of *F. vesca*. As the analgesic effect is reduced partially after naloxone, some other nonopioid mechanisms may also be involved.

Aspirin offers relief from inflammatory pain by suppressing the formation of pain substances in the peripheral tissues, where prostaglandins and bradykinin were suggested to play an important role in the pain process (Hirose et al., 1984). Prostaglandins elicit pain by direct stimulation of sensory nerve endings and also sensitize sensory nerve endings to other pain provoking stimuli (Campbell, 1991). Moreover, prostaglandins especially PGE_1 was reported to act on cell membrane during inflammatory conditions leading to changes in lipoprotein structure of cell membrane. This causes destabilization of cell membrane furthering to degenerative cellular changes (Rao et al., 1987). Therefore, it is likely that *F. vesca* fruit and whole plant extracts might suppress the formation of these substances or antagonize the action of these substances and thus exerts its peripheral analgesic activity in acetic acid-induced writhing test.

On comparing the analgesic property of ethanolic extract of fruits of *F. vesca*, it showed a dose-dependent central and peripheral analgesic activity, with fruit extract 500 mg/kg showing significantly more activity than fruit extract 250 mg/kg. Also the analgesic action of fruit extract 500 mg/kg was significantly more than the whole plant extract 500 mg/kg. Aspirin was most potent among these. The analgesic activity, both central

Table I

Central analgesic activity of *Fragaria vesca* extract on the tail flick response in Albino rats

Drug	Pre-drug reaction time (sec)	Time (min)						
		15	30	60	90	120	150	180
Gum acacia (3%; 10 mL/kg)	3.6 ± 0.2	3.6 ± 0.02	3.6 ± 0.1	3.7 ± 0.02	3.5 ± 0.04	3.7 ± 0.1	3.7 ± 0.06	3.8 ± 0.1
Naloxone (1 mg/kg)	3.2 ± 0.1	3.1 ± 0.1[a]	3.0 ± 0.1[a]	2.9 ± 0.1[a]	2.6 ± 0.1[a]	2.6 ± 0.1[a]	2.7 ± 0.1[a]	3.0 ± 0.1[a]
Fruit extract (250 mg/kg)	3.8 ± 0.03	4.5 ± 0.05[a,c]	5.7± 0.1[a,c]	5.8 ± .04[a,c]	6.1 ± 0.2[a,c]	5.9 ± 0.06[a,d]	5.6 ± .1[a,c]	5.1 ± 0.1[a,c]
Fruit extract (500 mg/kg)	3.1 ± 0.2	4.2 ± 0.1[a,d]	4.7± 0.1[a,d]	5.7 ± 0.1[a,c]	6.1± 0.2[a,c]	6.1± 0.2[a,c]	5.6 ± 0.06[a,c]	5.4 ± 0.1[a,c]
Fruit extract (500 mg/kg) + Naloxone (1 mg/kg)	2.9 ± 0.1	3.5 ± 0.03[b,c]	4.1 ± 0.04[a,c]	4.6 ± 0.04[a,c]	4.7 ± 0.06[a,c]	4.6 ± 0.1[a,c]	4.4 ± 0.1[a,c]	4.1 ± 0.1[b,d]
Plant extract (500 mg/kg)	4.0 ± 0.1	4.4 ± 0.1[a,d]	5.2 ± 0.1 [a,d]	5.6 ± 0.1 [a.c]	6.0 ± 0.1[a,c]	5.5 ± 0.2 [a,d]	4.9 ± 0.1 [a,c]	4.5 ± 0.1[a,d]
Plant extract (500 mg/kg) + Naloxone (1 mg/kg)	3.6 ± 0.2	3.9 ± 0.1 [a,d]	4.2 ± 0.1 [a,c]	4.5 ± 0.1 [a,c]	4.9 ± 0.1[a,c]	4.6 ± 0.1 [a,c]	4.1 ± 0.1[a,c]	3.8 ± 0.1[b,d]
Pethidine (5 mg/kg)	3.7 ± 0.1	4.1 ± 0.1[a]	5.0 ± 0.04[a]	5.1 ± 0.05[a]	6.9 ± 0.1[a]	5.6 ± 0.06[a]	4.8 ± 0.1[a]	4.2 ± 0.1[a]
F	2.0	46.8	75.4	253.3	172.1	161.9	108.6	57.37
df	40,7	40,7	40,7	40,7	40,7	40,7	40,7	40,7
p	> 0.05	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01

n= 6; [a]p<0.05, [b]p>0.05 when compared to the control; [c]p<0.05, [d]p>0.05 when compared to the standard, ANOVA followed by Dunnet's and Bonferroni's Test ; Data are (mean ± SEM)

Table I

Analgesic activity of the ethanolic extract of *Fragaria vesca* on glacial acetic acid-induced writhing test in Albino mice

Group	Drug	Number of writhing movements (Mean ± SEM) 20 min	%Protection
	10 mL/kg	69.5 ± 2.2	–
Fruit extract	250 mg/kg	43 ± 1.9[a,b]	38.1
Fruit extract	500 mg/kg	19.5 ± 2.5[a,b]	71.9
Whole plant extract	500 mg/kg	47 ± 2.2[a,b]	32.4
Aspirin	100 mg/kg	7 ± 1.5[a]	89.9
One-way ANOVA	F	179.7	
	df	19,3	
	p	< 0.01	

n= 6; [a]p<0.01 when compared to control; [b]p<0.05 when compared to standard; ANOVA followed by Dunnet's & Bonferroni's test

and peripheral, of all drugs in decreasing order was found to be as: Aspirin >fruit extract 500 mg/kg >fruit extract 250 mg/kg ≈ plant extract 500 mg/kg.

Conclusion

Both ethanolic extracts of fruits and whole plant, possess significant central and peripheral analgesic activity with fruit extract showing better action than plant extract and also fruit extract producing analgesia in a dose-dependent manner.

Ethical Issue

All the animals used in the study were taken care of under ethical consideration, with approval from Institutional Ethical Committee, Assam Medical College, Dibrugarh (Registration No. 634/02/a/CPCSE).

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