Analgesic, anti-inflammatory and antipyretic activity of *Salvia moorcroftiana*

Liaqat Hussain[1], Noor-ul-Ain[1], Muhammad Sajid Hamid Akash[1], Rehana Iqbal[2], Muhammad Irfan[1] and Muhammad Imran Qadir[3]*

[1]Faculty of Pharmaceutical Sciences, Government College University, Faisalabad, Pakistan
[2]Institute of Pure and Applied Biology, Bahauddin Zakariya University, Multan, Pakistan
[3]Institute of Molecular Biology & Biotechnology, Bahauddin Zakariya University, Multan, Pakistan

Abstract: *Salvia moorcroftiana* is an herbaceous plant commonly known as "Kallijari" in Pakistan and belongs to the family Lamiaceae. This study was carried out to evaluate its scientific base for its traditional use in pain, fever and inflammation. The powdered plant was extracted by the method of cold maceration using aqueous methanol (70:30) as solvents. Hot plate, flick tail and acetic acid induced writhing test were utilized for analgesic assessment. Anti-inflammatory activity was evaluated by carageenan-induced mice paw edema. Brewer's induced pyrexia was used for the evaluation of antipyretic activity. Non-significant ($p<0.01$) results as compared to the standard were obtained in all experiments. It was evident from acute toxicity study that plant was non-toxic in nature. It is concluded from the study that plant had the potential to be safely used for pain, fever and inflammation.

Keywords: Analgesic, Anti-inflammatory, Antipyretic, Mice, Toxicity, *Salvia moorcroftiana* (Wall.)

INTRODUCTION

Salvia moorcroftiana is herbaceous and perennial, which belongs to the family Lamiaceae. It grows at high altitude, approximately 5000-9000 feet height. The plant is about 2.5 feet tall. Leaves are attached to the stem and are attached in the form of cluster. Margins of leaves are toothed and cover with wool. Plant bore pale blue flowers. Flowering season is May to June (Zahid *et al.*, 2002). *Salvia moorcroftiana* is known by the name "Kallijari" in Pakistan. It is used widely as a remedy for a variety of ailments. Its roots and seeds are used for the treatment and management of cancer. For the treatment of piles, its seeds and roots were used in past (Zahid *et al.*, 2003). Plant leaves were used in the form of poultice for the healing of wounds. Itch is miraculously relieved by its leaf poultice (Ahmad *et al.*, 2000; Zahid *et al.*, 2002). Seeds and leaves treat the cough (Bakshi *et al.*, 1984). Plant bears pale blue flowers, which are given as traditional remedy for throat complaints (Brunton *et al.*, 2006). The plant is distributed in India, Afghanistan, Bhutan, Nepal, and Central Asia. Phytochemical analysis of the plant showed the presence of flavonoid and glycoside (Zahid *et al.*, 2002). An ester was from the aerial parts of the plant (Ishurd *et al.*, 2001). The aim of present wok was to ascertain the folkloric claim in the treatment of pain, fever and inflammation.

MATERIALS AND METHODS

Plant material

Salvia moorcroftiana whole plant without roots was collected from the new botanical garden of Agriculture University of Faisalabad in the month of April and was verified by the Dr. Manzoor, Department of Botany, Agriculture University of Faisalabad. A voucher specimen 234-1-13 was deposited in the herbarium. Dust, sand and damage parts were removed after collection then dried and ground to coarse powder. Cold maceration procedure with aqueous methanolic solvent was used for extract preparation.

Animals

Young and healthy *Swiss* albino mice were selected for the study which were1-2 months of age. The animals were procured from animal house of University of Agriculture, Faisalabad, Pakistan and were kept in the animal house of Government College, University, Faisalabad. Mice were kept under hygienic condition in polypropylene cages. The room temperature was maintained at 20±0.5°C. The animals were kept under 12 hour light and dark cycle. All the animals were fed with rodent pellet diet and water *ad-libitum.* The experiments on animals were performed in accordance to the guidelines and approval by Ethical Review Committee (Pharm-ERC 07) of Department of Pharmacy, Government College University, Faisalabad, Pakistan.

Drugs

Aspirin (Bayer, Germany), Tramadol (Searle, pakistan), Paracetamol (Glaxo Smith Kline, U.K), Diclofenac sodium (Pfizer, U.S).

Chemicals

Methanol 95% (Merck, Germany), Normal saline (Immunasol NS, A.Z. Pharmaceuticals Co.pak), Acetic acid (International petrochemicals Pvt Ltd), Brewer's yeast (Lewis Labs, U.S), Carageenan.

*Corresponding author: e-mail: mrimranqadir@hotmail.com

Evaluation of analgesic activity

Chemical (acetic acid induced writhing) and Thermal (Hot plate and flick tail tests) tests were used for evaluation of analgesic potential.

i) Acetic acid induced writhing test

Mice were divided into five groups. Groups 2nd, 3rd and 4th were treated with aqueous methanolic extract of plant at the doses of 100mg/kg, 200mg/kg and 300mg/kg respectively. The 5th group was treated with standard drug, Diclofenac sodium at the dose of 150mg/kg. Control group (group 1) was given normal saline. One hour after the treatment 0.6% v/v (10ml/kg) of acetic acid solution was administered by intraperitoneal injection. Abdominal wriths were counted for 15 minute and inhibition of wriths was determined afterwards.

ii) Hot plate method

Mice were divided into 5 groups with six mice in each group. Treatment (drug or extract) was given. After 30 minutes of treatment, animals in each group were placed one by one on Analgesiometer and noted the reaction time at different time intervals

iii) Flick tail test

Animals were divided into different groups: control, E1, E2, E3 and standard. Animals were kept on fast 12 hours before the start of experiment but free access to water *ad libitum.* Animals in the control group were given normal saline 10ml/kg while E1, E2, E3 were treated with aqueous methanolic extract of *Salvia moorcroftiana* at the dose of 100mg/kg, 200mg/kg, 300mg/kg respectively. Animals in the standard group were treated with Tramadol 30mg/kg. After 30 minutes, time for the each mouse to take tail out from water (maintained at 55±0.2˚C) was noted down.

Anti-inflammatory activity by carageenan induced inflammation

Inflammation is the body response to injury or infection. Mice were acclaimed to laboratory condition before the start of experiment. Animals in the control group were given normal saline 10ml/kg p.o. while E1, E2, E3 were treated with graded doses of aqueous methanolic extract of *Salvia moorcroftiana*. Animals in the standard group were treated with standard anti-inflammatory drug Aspirin 150mg/kg p.o. 30 minutes after the treatment, Carrageen an was administered in the right hind paw. Left for some time (almost for 30 minutes) after Carrageen an injection and then measured the paw size at 1hour interval.

Antipyretic activity by brewer's yeast induced pyrexiaa

Five groups of *Swiss* albino mice were taken. Mice in all groups were deprived of food six hour before the experiment but free access to water *ad libitum.* All mice were treated with suspension of yeast 15% subcutaneously. After 20 hour of the yeast treatment, rectal temperature of all mice were noted. Next step was drug treatment; Control group was given normal saline 10ml/kg p.o. while other groups were treated with aqueous methanolic extract of *Salvia moorcroftiana* at different doses. 5th group was treated with Paracetamol 150mg/kg p.o. Afterwards rectal temperature was noted at various time intervals.

Phytochemical analysis

Phytochemical analysis is a method to determine the type of chemical compounds is present in plant extract. So in the present study Phytochemical analysis of aqueous methanolic extract of *Salvia moorcroftiana* was carried out according to the accepted procedures (Tadesse and Dekebo, 2012).

Toxicity study

The purpose of toxicity study is to check that a substance is harmful or not to living tissue. Toxicity was performed according to the method explained by Oduola and his companions Mice were divided into five groups. Mice were on fast before the start of experiment. Graded doses of extract were given to different groups of mice. All groups were observed for 24 hour for toxic signs (Oduola *et al.*, 2010).

STATISTICAL ANALYSIS

All the results were expressed as mean ± SEM. Difference among different groups under study was assessed by ANNOVA (analysis of variance). $p<0.01$ was considered significant.

RESULTS

To check peripheral analgesic effect writhing test was performed. In the first step drug treatment was given. After treatment 100mg dose produced 61 wriths in 15 minutes causing 25% inhibition. 200mg/kg and 300mg/kg doses produced 45 and 40 wriths causing 44% and 50% inhibition, while the group which was treated with standard Diclofenac produced 39 wriths and produced 51% inhibition, showing that *Salvia moorcroftiana* extract at 300mg dose produced peripheral analgesic effect comparable with standard Diclofenac (table 1).

An effective way to assess central analgesic effect is hot plate method. Different groups of *Swiss* albino mice were pretreated with aqueous methanolic extract of *Salvia moorcroftiana* at the doses of 100mg/kg, 200mg/kg and 300mg/kg orally and also with standard Tramadol at dose of 30mg/kg. Then these mice were placed on the hot plate and reaction time was noted at 30, 60 and 90 minutes interval. The reaction time is given in table 2.

Different groups of Swiss albino mice were pretreated with aqueous methanolic extract of *Salvia moorcroftiana*

Table 1: Effect of aqueous methanolic extract of *Salvia moorcroftiana* (E) in acetic acid induced writhing test

Drug	Dose	Number of writhing in 15minutes(mean ± SEM)	Percent inhibition of writhing
N/S	10ml/kg	80.4±0.245	-------
E1	100mg/kg	60.6±0.245	25%
E2	200mg/kg	45.2±0.2	44%
E3	300mg/kg	40.2±0.374*	50%
Diclofenac sodium	150mg/kg	39.2±0.2	51%

Table 2: Effect of aqueous methanolic extract of *Salvia moorcroftiana* (E) in hot plate test in mice Model

Drug	Dose	Reaction Time before any treatment (mean ±SEM)	30 min (mean ±SEM)	60 min (mean ±SEM)	90 min (mean ±SEM)
N/S	10ml/kg	5±0.224	5.2±0.122	4.88±0.049	3.98±0.0735
E1	100mg/kg	4.7±0.122	5±0.224	5.9±0.447	6.76±0.0245
E2	200mg/kg	4.8±0.122	5.6±0.187	6.8±0.0316	6.94±0.0678
E3	300mg/kg	4.8±0.2	6.5±0.224	7.44±0.06	8.74±0.04*
Tramadol	30mg/kg	4.8±0.2	8.8±0.122	8.1±0.0374	8.6±0.0316

Table 3: Effect of aqueous methanolic extract of *Salvia moorcroftiana* (E) in flick tail test

Drug	Dose	Reaction Time before any treatment was given (mean ±SEM)	30 min (mean ±SEM)	60 min (mean ±SEM)	90 min (mean ±SEM)
N/S	10ml/kg	1.06±0.049	0.96±0.04	1.06±0.04	0.94±0.04
	100mg/kg	1.1±0.0447	0.92±0.049	2.78±0.049	2.98±0.02
E2	200mg/kg	1.14±0.0245	2.42±0.049	3.06±0.04	3.24±0.0245
E3	300mg/kg	1.2±0.0510	5.04±0.04	5.36±0.04	5.52±0.0583*
Tramadol	30mg/kg	1.2±0.0374	5.2±0.126	5.98±0.049	6.08±0.0583

Table 4: Anti-inflammatory activity of aqueous methanolic extract of *Salvia moorcroftiana* (E) in carrageen an induced inflammation in mice model

Drug	Dose	Mice hind paw size (mm)				
		0 time (before induction of inflammation) (mean ± SEM)	1 hour (mean ± SEM)	2 hour (mean ± SEM)	3 hour (mean ±SEM)	4 hour (mean ±SEM)
N/S	10ml/kg	0.3±0.00707	0.69±0.00816	0.6775±0.021	0.675±0.00645	0.665±0.00289
E1	100mg/kg	0.3±0.00913	0.6925±0.00946	0.64±0.0158	0.615±0.00289	0.5725±0.0025
E2	200mg/kg	0.285±0.00866	0.7±0.00108	0.6425±0.0189	0.535±0.0150	0.4825±0.0025
E3	300mg/kg	0.287±0.0075	0.7±0.00108	0.5375 ±0.0131	0.4175±0.0144	0.355±0.00289*
Aspirin	150mg/kg	0.2925±0.00629	0.6925±0.0170	0.4825±0.0125	0.38±0.0129	0.33±0.00408

Table 5: Antipyretic activity of aqueous methanolic extract of *Salvia moorcroftiana* (E) on Brewer's yeast induced pyrexia

Drug	Dose	Rectal temperature (°F)					
		Before yeast injection (mean ±SEM)	After 20 hr of yeast injection (mean ±SEM)	1 hr (mean ±SEM)	2hr (mean ±SEM)	3hr (mean ±SEM)	4hr (mean ±SEM)
N/S	10ml/kg	98.6±0.155	103.8±0.21	103.9±0.1	103.68±0.08	103.76±0.04	103.56±0.04
E1	100mg/kg	98.36±0.16	104±0.141	102.4±0.114	101.2±0.049	99.92±0.08	99.56±0.04
E2	200mg/kg	98.26±0.144	103.94±0.0748	101.14±0.0872	100.16±0.0245	98.92±0.08	98.82±0.02
E3	300mg/kg	98.36±0.103	103.9±0.0894	98.2±0.11	98.32±0.049	98.68±0.049	98.6±0.0632*
Paracetamol	150mg/kg	98.1±.045	103.9±0.0447	98.28±0.08	98.56±0.04	98.52±0.049	98.64±0.04

* Non-significant ($p<0.01$) as compared to standard

at the doses of 100mg/kg, 200mg/kg and 300mg/kg orally and also with standard Tramadol at the dose of 30mg/kg. Then tails of mice were placed in the water bath maintained at 55±0.2˚C. For *Salvia moorcroftiana* reaction times for 100mg/kg were 0.92, 2.78, 2.98 seconds and at 200mg/kg were 2.42, 3.06, 3.06 seconds respectively. 5.04 sec, 5.36 sec, 5.52 sec were the time for flicking the tail at 300mg/kg dose. Tramadol had mean reaction time (in seconds) as 5.2, 5.98, 6.08 respectively (table 3).

Aqueous methanolic extract of *Salvia moorcroftiana* at 100mg/kg dose had given these readings 0.6925, 0.64, 0.615 and 0.5725. At 200mg/kg paw size measurements were 0.7, 0.6425, 0.535 and 0.4825 and at 300mg/kg dose were 0.7, 0.5375, 0.4175 and 0.355 respectively (table 4).

Saliva moorcroftiana extract dose at 100mg/kg had given the readings as 102.4, 101.2, 99.92 and 99.56. These were the average values of rectal temperature for E1 group at one-hour interval. For E2 (200mg/kg) values were 101.14, 100.16, 98.92 and 98.82. E3 (300mg/kg) group was given highest dose of extract and the temperatures observed were 98.2, 98.32, 98.68 and 98.60 (table 5).

Results of phytochemical screening showed that *Salvia moorcroftiana* possessedsaponins, tannins, terpenoids, flavonoids and alkaloids. The purpose of toxicity study was to evaluate whether plant extract was toxic in nature or not. In the present study plant extract showed no weight changes, no mortality even after 24 hours and at maximum dose of 4000mg/kg.

DISCUSSION

The common complaints, which we encounter in our routine life are fever, pain and inflammation. With the passage of time, there is advancement in the field of medicine for diagnosis (Qadir, 2016); and management of diseases by the use of polymers (Khalid *et al.*, 2009; Hussain *et al.*, 2011; Massud *et al.*, 2015; Irfan *et al.*, 2016) or through nanotechnology (Naz *et al.*, 2012; Ehsan *et al.*, 2012), synthesis of new drugs, either by the use of proteomics (Qadir, 2011; Qadir and Malik, 2011; Farooq *et al.*, 2016), or synthesis from lactic acid bacteria (Masood *et al.*, 2011), or marine microorganisms (Javed *et al.*, 2011) and further use of phage therapy (Qadir, 2015). However, now a days, the trend is being changed from synthetic drugs to the natural drugs either from plants or microbes to control the diseases (Iqbal *et al.*, 2014). The natural products are constantly being screened for their possible pharmacological value particularly for their analgesic (Parveen *et al.*, 2014) anti-inflammatory (Qadir, 2009; Qadir *et al.*, 2016), hypotensive (Qadir, 2010), antihyperlipidaemic (Ahmad *et al.*, 2012) hepatoprotective (Ali *et al.*, 2013; Mallhi *et al.*, 2014; Saleem *et al.*, 2014a; Qadir *et al.*, 2014), hypoglycaemic (Qadir and Malik, 2010; Qadir *et al.*, 2013), amoebicidal (Asif and Qadir, 2011), anti-fertility, cytotoxic (Saleem *et al.*, 2014b), antibacterial (Amin *et al.*, 2012; Azam *et al.*, 2013; Saleem *et al.*, 2014c; Mannan *et al.*, 2016), anti-viral (Ali *et al.*, 2012; Aslam *et al.*, 2012; Janbaz *et al.*, 2013) spasmolytic (Janbaz *et al.*, 2014), bronchodilator (Janbaz *et al.*, 2013a**)**, antioxidant (Janbaz *et al.*, 2012; Afzal *et al.*, 2016), anti-diarrheal (Janbaz *et al.*, 2013b), anti-cancer (Ali *et al.*, 2013a & b; Saleem *et al.*, 2013) and anti-Parkinsonism properties. *Salvia moorcroftiana* is a perennial herbaceous plant. Writhing test is a good procedure for evaluating the peripheral analgesic effect (Woolf, 2004). Acetic acid when injected intraperitoneally stimulated the release of endogenous substances. Abdominal constrictions are produced in response to these endogenous substances. Plant extract significantly reduced abdominal constrictions. To check peripheral analgesic effect tests were flick tail and Analgesiometer test. In these tests tissue damage was minimal and given good results even in partial impairment of motor activity (Plummer *et al.*, 1999).

Positive results were obtained in all these tests. It was proved that plant extracts with flavonoid content showed analgesic effect and without flavonoid content no analgesic effect (Oweyele *et al.*, 2005). So analgesic effect produced may be due to presence of flavonoids. Carrageen an was employed for the study of anti-inflammatory activity because systemic side effects were minimal with it. Carrageenan produced acute inflammation (Mossa *et al.*, 1995). Flavonoids showed anti-inflammatory activity due to inhibition of chemical mediators of inflammation (Singh *et al.*, 2003). The current study revealed that plant extract showed good anti-edematous activity and may be due to of flavonoid content. Fever is an immune response to infection and injury. Hypothalamus is a thermoregulatory centre in the body. Fever is produced when PGE affects the hypothalamus and resets it at a higher temperature then fever is produced through intricate procedure (Qadrie *et al.*, 2009).

All doses of aqueous methanolic extract of *Salvia moorcroftiana* decreased the pyrexia. Antipyretic potential of alkaloids and flavonoids was reported in many research works (Singh *et al.*, 2000). Phytochemical analysis of plant extract showed the presence of flavonoids and alkaloids. Indicating that analgesic, anti-inflammatory and antipyretic activity may be due to presences of these phytoconstituents. Toxicity study profile showed that plant was non-toxic even at 4000mg/kg. All positive results obtained were pointed that plant had the potential to be used for pain, fever and inflammation.

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