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Original Article

Evaluation of Analgesic Activity of Ficus Palmata

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Abstract

Ficus palmata (FI) is an important and widely used medicinal plant. It is principally used as an item of diet in the treatment of constipation and diseases of the lungs and bladder. The sap is used in the treatment of warts. Ficus palmata plant is used in various disease e.g. gastrointestinal, hypoglycemic, antitumor, anti-ulcer, anti-diabetic, lipid lowering and antifungal activities. This study evaluates both the central and peripheral analgesic effect of the different extracts of Ficus palmata in the experimental animals. Methods: Acute toxicity test was done following the Organization of Economic Co-operation and Development guidelines. Ficus palmata extracts (250 mg/kg, 500 mg/kg) body weight was evaluated for central analgesic activity by the hot plate method, tail immersion method and formalin test models using tramodol (20 mg/kg b.w.) as the standard drug. Results: In all the models, chloroform extract showed significant inhibition as well as the elongation of time at a dose of 500 mg/kg body weight. A linear dose response relationship was also observed which was comparable with that of the standard drug tramodol ($p<0.01$, $p<0.05$). Conclusion: The study showed significant central and peripheral analgesic activity of Ficus palmata which may be attributed to the inhibition of prostaglandin synthesis, phospholipase A2, and tumor necrosis factor alpha. Ficus plamata as a commercial source of analgesic drug should be subjected to further research.

Keywords: Ficus palmata, Analgesic activity, Hot plate method, Tail immersion method, Formalin test.

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1. Introduction

Pain is a disabling accompaniment of many medical conditions and pain control is one of the most important therapeutic priorities [1]. Pain has been officially defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. It is

always a warning signal and primarily protective in nature but often causes a lot of discomfort and lead to many adverse effects [2]. Analgesics are drugs used to treat or reduce pain and the classical analgesic drugs notably opiates and non-steroidal anti-inflammatory drugs have their origin in natural products but many synthetic compounds that act by the same mechanism have been developed and are associated with serious adverse effects such as ulceration, gastrointestinal bleeding, additive potential, respiratory distress, drowsiness, nausea, *etc* [3,4].

Based on these therefore, there is the need for the search for bioactive compounds from natural products especially from medicinal plants for use as alternative analgesics with little or no side effects.

Ficus palmata is an Herb belonging to the family Moraceae. It is a highly variable and common wild fig occurring in North West hills on hot, dry slopes in clay-loam soils in Uttarakhand, Punjab and Kashmir in India, Nepal, Pakistan, Afghanistan, Iran, Arabian Peninsula, Somalia, Sudan, Ethiopia and South Egypt. It is common in wastelands, forests, fields and villages [5].The phytochemical screening of the *Ficus palmata* plant extracts showed the presence of alkaloids, tannins, flavonoids, terpenoids and cardiac glycosides.

Phytochemical investigation of the aerial parts of *Ficus palmata* utilizing liquid-liquid fractionation and different chromatographic techniques resulted in the isolation of a new isomer of psoralenoside namely, trans-psoralenoside in addition to, one triterpene: germanicol acetate, two furanocoumarins: psoralene, bergapten, one aromatic acid vanillic acid and the flavone glycoside rutin [6].

The fruit is demulcent, emollient, laxative and poultice. They are principally used as an item of diet in the treatment of constipation and diseases of the lungs and bladder. The sap is used in the treatment of warts. *Ficus palmata* plant is used in various diseases e.g. gastrointestinal, hypoglycemic, antitumor, antiulcer, antidiabetic, lipid lowering and antifungal activities 7]. Traditionally stem latex is applied to extract spines deeply lodged in the flesh. The whole fruit, along with the seeds, is edible. Fruit is raw and very tasty. It is sweet and juicy, having some astringency, which is due to the presence of white latex just beneath the epicarp. The astringency can be removed by keeping the fruits immersed in water for about 10 to 15 minutes before eating [8]. The overall fruit quality is excellent. The unripe fruits and young growth are cooked and eaten as a vegetable. They are boiled, the water is removed by squeezing and they are then fried [9]. The pliable wood is of little value but has been used for making hoops, garlands, ornaments etc. Excess use of this plant may cause allergic reactions.

Different studies about this plant include: Antibacterial, antioxidant & antiproliferative activities, antimicrobial, antiulcer, antidiabetic [9, 10, 11, 12, 13, 14].

2. Materials and Methods

2.1. Identification and Collection of Plant Material

The whole plant of *Ficus palmata* was collected from surrounding area of Machilipatnam and Gudivada. These plants were identified and authenticated by the Department of Botany Hindu Collage, Machilipatnam. The plants were sorted, cleaned and air dried at room temperature for one week. Then it was ground to powder. Powdered sample was collected and stored in air and water proof containers protected from direct sunlight and heat until used for extraction.

2.2. Preparation of Extract by Using Soxhlet Apparatus

The powdered material of *Ficus palmata* was extracted for 18 hr with petroleum ether, chloroform, ethanol and distilled water in soxhlet apparatus (INCO company). The extracts were concentrated to dryness till free from the solvents [15].

2.3. Phytochemical Analysis

Phytochemical analysis of extract was carried out for the presence of saponins, tannins, flavanoids, alkaloids, glycosides, steroids, carbohydrates, proteins, and phenols by different methods [16].

2.4. Experimental Animals

Male Mice weighing 60-80 gm are kept in polypropylene cages, 3 in each cage, at an ambient temperature of 25 ± 2^{o}C and relative humidity of 55-65%. A 12 hour light and dark schedule was carefully maintained in the air conditioned animal house. All the mice are fed with common diet for 1 week after arrival and then divided into groups with free access to food and water. All experimental animals were handled according to Institutional Animal Ethic Committee (IAEC) guidelines guiding the use of experimental animals.

2.5. Acute Toxicity Studies

According to OECD (Organization for Economic Co-operation and Development) guidelines 423 we have conducted the acute toxicity studies [17]. Animals are divided in groups (n=5). For about 4-5 hours prior to experiments, all the animals are fasted with free access to only distilled water. The suitable extract of *Ficus palmata* are administered to different groups of mice in doses of 5, 50, 300, 1000 mg/kg by gavage and observed for mortality and considerable physical and behavioral changes for over 14 days.

2.6. Assessment of Analgesic Activity of Different Extract of Ficus Palmata

2.6.1. Study Design

The mice were randomly assigned into 10 groups of five mice for different experimental animal models.

Group I : Received only normal saline (Control)

Group II : Tramadol (20 mg/kg)

Group III: Petroleum ether extract of *Ficus palmata* (PEFP, 250 mg/kg)

Group IV: Petroleum ether extract of *Ficus palmata* (PEFP, 500 mg/kg)

Group V : Chloroform extracts of *Ficus palmata* (CEFP, 250 mg/kg)

Group VI: Chloroform extracts of *Ficus palmata* (CEFP, 500 mg/kg)

Group VII : Ethanolic extract of *Ficus palmata* (EEFP, 250 mg/kg)

Group VIII : Ethanolic extract of *Ficus palmata* (EEFP, 500 mg/kg)

Group IX: Aqueous extract of *Ficus palmata* (AEFP, 250 mg/kg)

Group X : Aqueous extract of *Ficus palmata* (AEFP, 500 mg/kg)

2.6.2. Hot Plate Method

The analgesic activity of the aqueous extract of *Ficus palmata* was measured by using Eddys hot plate (INCO company) in Hot plate method [18].To the respective group of mice, above mentioned drug and extract was given orally. The mice are placed on a hot plate maintained at temperature of 55 ± 0.5^0C. The reaction time was taken as the time interval from which the instant animal reached the hot plate maintained at temperature of 55±0.5^0C until the moment animal licked or lifted its feet or jumped out of the plate. To avoid any thermal injury to the paws, a cut off time of 10 sec was followed. After 30, 60, 90, 120 and 180 min following administration of test and standard drug, the reaction time was recorded. For each treated group, the mean reaction time was determined with that obtained for each group before treatment.

By using the following formula, percentage increase in reaction time (I%) was derived:

$$I\% = \{(I_t - I_o)/I_o\} \times 100$$

Where,

I_t= reaction time at time t

I_o = reaction time at time zero

2.6.3 Tail Immersion Method

The method of Luiz *et al*., 1988 was used for the evaluation of the analgesic activity. Mice were randomly allocated into 10 groups of five mice [19]. In a suitable restrainer, they are gripped in position with the tail extending out of the chamber. 2-3 cm area of the tail of the animal was marked and immersed in water bath thermostatically maintained at 55^0C. The withdrawal time of the tail from hot water was noted as reaction time, with a cut off time of immersion set as 10 sec, to avoid injury to the tissues of tail. The reaction time was recorded after 30, 60, 90, 120, and 180 min following administration of test and standard drug. As reported by Janssen et al., 1964the criterion for analgesia was post-drug treatment which was greater than pre-drug treatment [20]. After drug administration, mean increase in latency produced by test and standard drugs was used as an identification for the analgesic activity.

2.6.4. Formalin Test

The technique adopted is as described by Shibata et al., 1989 [21]. The mice were randomly allocated into 10 groups of 5 mice, were pre-treated by administration of formalin. After 30 min, 0.05 ml of 1% formalin was injected into the right hind paw of each mice subcutaneously. The licking or biting of the formalin injected right hind paw was calculated in 2 phases. The 1st phase was the first 5 min immediately after the injection of the formalin and the 2nd phase was 15-30 min after injection of the formalin. A reduction in the number of paw licking or biting is an indication of analgesic activity.

2.7. Statistical Analysis

Results are presented as mean ± SEM. Data

Table 1. Phytochemical screening of different extracts of *Ficus palmate*.

Phytoconstituents	Method	PEFP	CEFP	EEFP	AEFP
Flavonoids	Shinoda Test	-	+	+	+
	Zn. Hydrocholride Test	-	+	+	+
	Lead acetate Test	-	+	+	+
Volatile Oil	Stain Test	+	-	-	-
Alkaloids	Wagner Test	-	+	-	-
	Hager's Test	-	+	-	-
Tannins & Phenols	$Fecl_3$ Test	-	-	-	-
	Pot.Dichromate Test	-	-	-	-
Saponins	Foaming Test	-	+	-	-
Steroids	Salkowski Test	-	-	-	-
Carbohydrates	Molish Test	-	+	+	-
Acid Compounds	Litmus Test	-	-	-	-
Glycoside	Keller-Killani Test	-	+	+	-
Amino Acids	Ninhydrin Test	-	-	-	+
Proteins	Biuret	-	+	-	+

Table 2. Assessment of analgesic activity of different extracts of *Ficus palmata* by Hot plate method in mice.

Group	Treatment	Dose	Reaction time					
			0 min	30 min	60 min	90 min	120 min	180 min
I	Control	2 ml/kg	3.16±0.11	3.11±0.06	3.09±0.26	3.21±0.06	3.25±0.05	3.22±0.12
II	Tramodol	20 mg/kg	3.24±0.24	4.61±0.18 (42.28%)	5.89±0.07 (81.79%)	5.25±0.13 (62.03%)	5.11±0.15 (57.71%)	4.99±0.08 (54.01%)
III	PEFP	250 mg/kg	3.21±0.15	3.54±0.18 (10.28%)	3.76±0.21 (17.13%)	3.97±0.16 (23.67%)	3.63±0.09 (13.08%)	3.41±0.14 (6.23%)
IV	PEFP	500 mg/kg	3.18±0.21	3.94±0.19 (23.89%)	4.01±0.09 (26.10%)	4.11±0.08* (29.24%)	4.01±0.13 (26.10%)	3.54±0.16 (11.32%)
V	CEFP	250 mg/kg	3.33±0.18	3.94±0.23 (18.31%)	4.21±0.03+ (26.42%)	4.43±0.27* (33.03%)	4.09±0.29 (22.82%)	3.85±0.26 (15.61%)
VI	CEFP	500 mg/kg	3.27±0.09	4.11±0.14 (25.68%)	4.65±0.09 (42.20%)	5.31±0.31* (62.38%)	4.61±0.26 (40.97%)	4.23±0.31+ (29.35%)
VII	EEFP	250 mg/kg	3.32±0.03	3.54±0.12 (6.62%)	3.67±0.15 (10.54%)	3.71±0.07 (11.74%)	3.69±0.11 (11.14%)	3.49±0.15 (5.12%)
VIII	EEFP	500 mg/kg	3.23±0.15	3.61±0.21 (11.76%)	3.72±0.18 (15.17%)	3.89±0.09+ (20.43%)	3.58±0.06 (10.83%)	3.51±0.05 (8.66%)
IX	AEFP	250 mg/kg	3.29±0.04	3.43±0.03 (4.25%)	3.56±0.13 (8.20%)	3.71±0.20 (12.76%)	3.66±0.17 (11.24%)	3.52±0.15 (6.99%)
X	AEFP	500 mg/kg	3.26±0.18	3.63±0.14 (11.34%)	3.76±0.16 (15.33%)	3.94±0.07+ (20.85%)	3.59±0.12 (10.12%)	3.49±0.08 (07.05%)

The results are indicated as mean ± SEM for each group. The data was calculated by one-way ANOVA. *P<0.01, +P<0.05 was considered statistically significant

comparisons between treatments groups were done by use of one-way ANOVA followed by Dunnetts multiple comparison test. Values were considered statistically significant at P< 0.05, < 0.01.

3. Results and Discussion

3.1. Preliminary Phytochemical Analysis

Phytochemical analysis of Chloroform extract of *Ficus palmata* whole plant showed the presence of saponins, flavanoids, alkaloids, glycosides, carbohydrates and proteins (Table 1). Secondary metabolites such as the flavonoids have been reported to be present in *Ficus palmata*. Since prostaglandins involved in pain perception are diffident by flavonoids, it can be suggested that reduced availability of prostaglandin by flavonoids are responsible for analgesic activity.

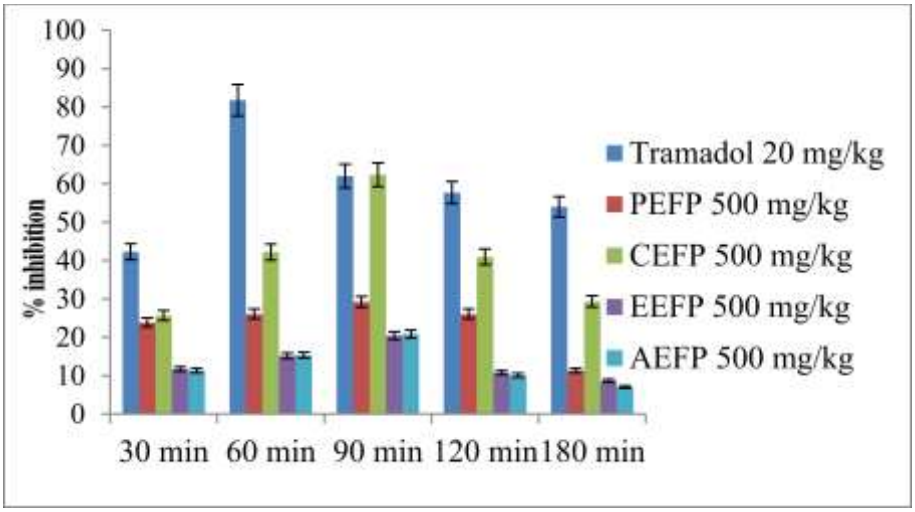

Figure 1. Assessment of analgesic activity of different extracts of *Ficus palmata* by Hot plate method in mice.

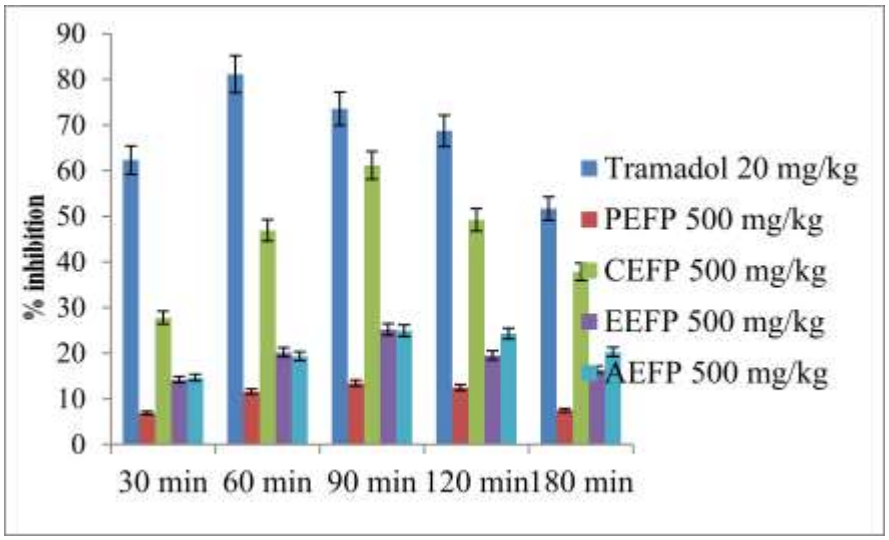

Figure 2. Assessment of analgesic activity of different extracts of Ficus palmata by Tail immersion method in mice.

3.2. Acute Toxicity Studies

According to acute toxicity studies the *Ficus palmata* is found to be safe up to 1000 mg/kg. Half of the safe dose *i.e.*, 500 mg/kg and 250 mg/kg are selected for assessment of analgesic activity.

3.3. Assessment of Analgesic Activity of Different Extract of Ficus Palmata

3.3.1. Hot plate Method

Results of hot plate method for different extracts of *Ficus palmata* are presented in table 2 and figure 1. The extracts were found to

Table 3. Assessment of analgesic activity of different extracts of *Ficus palmata* by Tail immersion method in mice

Group	Treatment	Dose	Reaction time					
			0 min	30 min	60 min	90 min	120 min	180 min
I	Control	2 ml/kg	3.01±0.09	3.11±0.25	3.26±0.21	3.19±0.11	3.23±0.07	3.17±0.05
II	Tramodol	20 mg/kg	3.29±0.11	5.34±0.16 (62.31%)	5.96±0.13 (81.15%)	5.71±0.06 (73.55%)	5.55±0.12 (68.69%)	4.99±0.06 (51.67%)
III	PEFP	250 mg/kg	3.13±0.13	3.26±0.15 (4.15%)	3.39±0.09 (8.30%)	3.33±0.15 (6.38%)	3.21±0.11 (2.55%)	3.19±0.08 (1.91%)
IV	PEFP	500 mg/kg	3.19±0.14	3.41±0.12 (6.89%)	3.56±0.16 (11.59%)	3.62±0.13 (13.47%)	3.59±0.18 (12.53%)	3.43±0.07 (7.52%)
V	CEFP	250 mg/kg	3.21±0.16	3.81±0.05 (18.69%)	4.11±0.19* (28.03%)	4.23±0.06 (31.77%)	4.09±0.18+ (27.41%)	3.91±0.07 (21.80%)
VI	CEFP	500 mg/kg	3.09±0.08	3.95±0.21 (27.83%)	4.54±0.09 (46.92%)	4.98±0.07* (61.16%)	4.61±0.09* (49.19%)	4.26±0.08 (37.86%)
VII	EEFP	250 mg/kg	3.22±0.07	3.42±0.16 (6.21%)	3.51±0.07 (9.00%)	3.63±0.02 (12.73%)	3.55±0.08 (10.24%)	3.46±0.04 (7.45%)
VIII	EEFP	500 mg/kg	3.17±0.09	3.62±0.12+ (14.19%)	3.81±0.11 (20.18%)	3.97±0.15 (25.23%)	3.79±0.14 (19.55%)	3.69±0.12 (16.40%)
IX	AEFP	250 mg/kg	3.15±0.12	3.32±0.14 (5.39%)	3.45±0.09 (9.52%)	3.51±0.13* (11.42%)	3.46±0.16 (9.84%)	3.39±0.09 (7.61%)
X	AEFP	500 mg/kg	3.21±0.15	3.68±0.08 (14.64%)	3.83±0.15 (19.31%)	4.01±0.11 (24.92%)	3.99±0.05 (24.29%)	3.86±011* (20.24%)

The results are indicated as mean ± SEM for each group. The data was calculated by one-way ANOVA. *P<0.01, +P<0.05 was considered statistically significant

display a dose dependent increase in latency when compared with control. At 90 min the percent inhibition with two doses (250 mg/kg and 500 mg/kg) of chloroform extract was found to be 33.03% and 62.38% respectively (P<0.01, P<0.05 was considered statistically significant difference). This was compared with the standard tramadol 20 mg/kg which showed percent inhibition of 81.79% at 60 min.

3.3.2. Tail Immersion Method

The extracts produced a significant analgesia after 90 min in the dose of 250 mg/kg and 500 mg/kg. These effects are comparable with the standard drug used in the present study. At 90 min the percent inhibition with two doses (250 mg/kg and 500 mg/kg) of chloroform extract was found to be 31.77% and 61.16% respectively (P<0.01, P<0.05 was considered statistically significant difference). This was

Table 4. Assessment of analgesic activity of different extracts of *Ficus palmata* by Formalin test in mice.

Group	Treatment	Dose	Licking of hind paw (sec)			
			0-5 min	%	15-30 min	%
I	Control	2 ml/kg	120	---	131	---
II	Tramodol	20 mg/kg	46	61.66	32	75.57
III	PEFP	250 mg/kg	93	22.50	85	35.11
IV	PEFP	500 mg/kg	86	28.33	79	39.69
V	CEFP	250 mg/kg	81	32.50	74	43.51
VI	CEFP	500 mg/kg	63	47.50^{+}	55	58.01*
VII	EEFP	250 mg/kg	89	25.83	83	36.64
VIII	EEFP	500 mg/kg	76	36.66	68	48.09^{+}
IX	AEFP	250 mg/kg	85	29.16	77	41.22
X	AEFP	500 mg/kg	74	38.33*	69	47.32*

The results are indicated as mean ± SEM for each group. The data was calculated by one-way ANOVA. $^{*}P<0.01$, $^{+}P<0.05$ was considered statistically significant

compared with the standard tramadol 20 mg/kg which showed percent inhibition of 81.15% at 60 min (Table 3 and Figure 2). The activity manifested by this extract is of substantial and considerable importance and justified its use in pain.

3.3.3. Formalin Test

In the formalin induced pain test, the extract caused a reduction in hind paw licking in the two early and late phases of analgesia. There was a dose dependent significant inhibition in both phases of the formalin induced pain in chloroform extract pretreated mice. Percent inhibition at 250 mg/kg was found to be 32.50% and 43.51% and at 500 mg/kg it was 47.50% and 58.01% in the early and late phase (Table 4 and Figure 3) of formalin test respectively ($P<0.01$, $P<0.05$ was considered statistically significant difference).

Several acute and sub-acute tests which differ with respect to stimulus eminence, intensity and period, were employed in evaluating the analgesic effect of *Ficus palmata* to ascertain the nociceptive properties of a compound considering behavioral nociceptive tests [22].

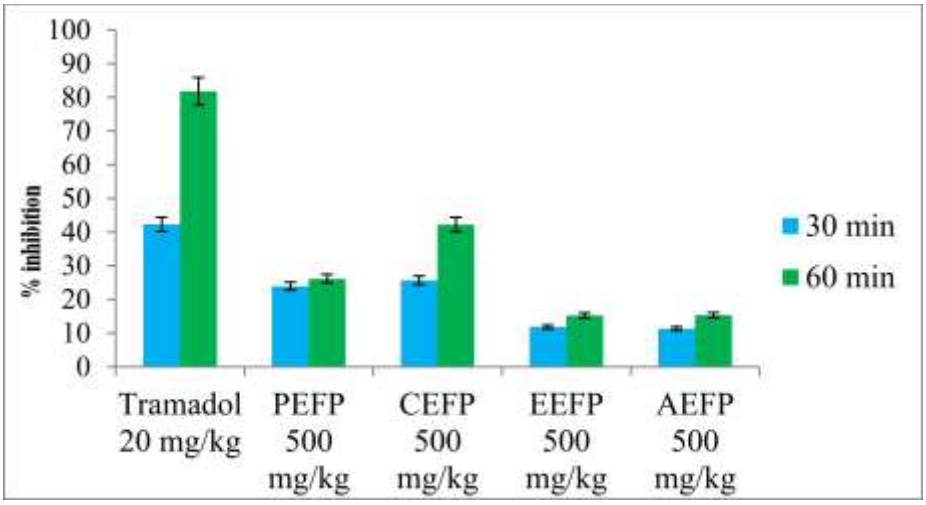

Figure 3. Assessment of analgesic activity of different extracts of *Ficus palmata* by Formalin test in mice

The chloroform extract under investigation showed a dose dependent inhibition in pain. In hot plate method and tail immersion method, extract at 500 mg/kg elevated pain threshold of animals towards heat and pressure. In formalin test, chloroform extract at 500 mg/kg hindered both the early and late phases of formalin instigated pain, arguing that the analgesic effect of extract may act via centrally and peripherally mediated pain control [23].

In the hot plate technique and tail immersion method, oral pre-treatment with the chloroform extract caused a fervent and dose associated analgesia in the processed mice although the analgesic effect of the extract was less effective than standard [24]. The above two procedures consists of behavioral procedures that have been evolved to report nociception in animals. The animal response in these tests is usually integrated at the subsidiary degree in the central nervous system, therefore, giving information about the pain threshold [25].They are, therefore, used to identify narcotic and non-narcotic nociceptives.

The formalin induced pain as an experimental model of analgesia is useful for illuminating technique of pain and analgesia since it evaluates the acknowledgement to a long-lasting nociceptive incentive and, consequently, favours clinical pain [26]. Subcutaneous administration of dilute formalin into mice hind paw fabricate biphasic nociceptive retaliation namely: the 1st transient phase is provoked by the direct reaction of formalin on sensory C-fibers and the 2nd prolonged phase is affiliated with the evolution of the injury persuaded spinal sensitization, accountable for facilitated pain procedure, a

central sensitization of the dorsal horn neuron happen in inflammatory pain [27]. Results of the formalin test showed that chloroform extract inhibits both the early and late phases of formalin instigated pain, hence, concluding its central and peripheral anti-nociceptive effect. Prior studies have manifested that substance P engage in the early phase, while serotonin, histamine, prostaglandins and excitatory amino acids are intricated in the late phase of formalin trial with bradykinin affecting both phases [28, 29, 30]. Significant protection was observed in the chloroform extract treated groups of animals and it compared favorably with the standard drug. Secondary metabolites such as the flavonoids have been reported to be present in the chloroform extract [31]. Since prostaglandins involved in pain perception are diffident by flavonoids, it can be suggested that reduced availability of prostaglandin by flavonoids are responsible for analgesic activity. The chloroform extract demonstrated promising anti-nociceptive activity in the diversified animal models used in this evaluation, asserting its efficacy in the treatment of pain in its users [32].

4. Conclusion

We thus conclude the current research findings based on the observations and results obtained, it is evident that CEFP whole plant possess promising analgesic activity. The analgesic activity may be attributed to prostaglandins involved in pain perception are diffident by flavonoids, which may be due to the presence of flavonoids in the extracts. But further studies are required to support the present assumption and to elucidate detailed analgesic activity mechanism.

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