August 30, 2019

PharmacologyOnLine

Archives • 2019 • vol.2 • 152-160

EVALUATION OF THE PHYTOCHEMICAL SCREENING, ANTI-PYRETIC AND ANALGESIC ACTIVITIES OF EXTRACT OF *FAGARA ZANTHOXYLOIES* ROOT-BARK

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Abstract

Pain and fever are symptoms for diagnosing various diseases and its associated conditions. They are associated with poor quality of life and socioeconomic burden to the victim. Conventional analgesic and anti-pyretic drugs that are used to manage pain and fever are not readily available and are associated with adverse effects. Thus, the use of herbal medicine from medicinal plants which are known to contain secondary metabolites capable of relieving pain and fever and consequently healing diseases. It is an age old practice used by many rural and urban dwellers to cure diseases. Fagarazanthoxyloides (family Rutaceae) is a West African tree used in traditional medicine for the treatment of toothaches and abdominal pain. The present study thus, evaluated on analgesic and anti-pyretic potentials of Fagarazanthoxyloidesmethanolic root-bark extract of in animal models, as wella s the phytochemical constituents. Phytochemical screening of the extract revealed the presence of tannins (13.312 ± 0.004 mg/100g), terpenoids (1021.315 ± 0.3995 mg/100g), steroids (5.575 ± 0.009 mg/g), phenols (2386.321 ± 0.007 mg/100g), alkanoids (810.311 ± 1.731 mg/100g), flavonoids (1931.753 ± 0.009 mg/100g) and saponins (1.321 ± 0.004 mg/g). The extract at 100, 200 and 400mg/kg b. w. significantly ($p < 0.05$) inhibited yeast-induced pyrexia in rats when compared to the control. Methanol extract of Fagarazanthoxyloides root-bark (100, 200 and 400 mg/kg b. w.) significantly ($p < 0.05$) reduced the number of writhings induced by 0.6% acetic acid solution in a dose dependent manner. These results can supports the folkoric use of the plant root-bark in treatment of pain (tooth-ache) and fever related ailments.

Keywords: *Analgesic, Anti-pyretic, pyrexia, Fagarazanthoxyloides.*

Introduction

Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage [1]. 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]. Harmful stimuli lead to activation of nociceptors through the release of variety of chemical mediators, such as excitatory amino acids, vasoactive amines (histamine, serotonin), proteins, peptides, nitric oxide (NO), arachidonic acids (prostaglandins E2, leukotrienes), and cytokines [TNF-α and interleukin-1], which act on specific receptors and ion channels, contributing to the induction of pain [3]. Pyrexia or Fever is defined as an elevation of body temperature. It is a response due to tissue damage, inflammation, malignancy or graft rejection. Again pyrexia or fever is caused by a secondary impact of inflammation [4]. Fever occurs due to infection produced by a generation of pyrogens including, ILs, TNF-α, interfere in which induces PGE2 production in the hypothalamus and its temperature set point. Therefore, it may be said that inflammation, pain and fever are all associated with enhanced production of prostaglandins [4]. Analgesics relieve pain as a symptom, without affecting its cause [5]. Currently available analgesic and antipyretic drugs such as opiates and NSAIDs are not useful in all cases due to their side effect profile. As a result, there is a high demand for the search of new drugs with lesser or no side effects [6]. Many researchers have focused in recent years on medicinal plants derived natural products such as flavonoids, steroids, polyphenols, coumarins, terpenes and alkaloids due to their full range of pharmacological significance including analgesic, antipyretic, anti-inflammatory and antioxidant activities with lesser side effects [7]. Drugs of natural origin are an essential source for the treatment of many diseases worldwide [8]. Medicinal plants used in the folkloric treatment of pain related ailments have a long and popular usage especially in developing countries [9]. In the context, the current trend of research has shifted towards medicinal plants because of their affordability and accessibility with lesser side effects [6].

Fagarazanthoxyloides (family Rutaceae) is a West African tree used in traditional medicine. It is well known for its various uses in traditional medicinal practices.Itis used as chewing stick in Nigera. The root-bark extract is used in treating a host of many ailments; elephantiasis, toothache, sexual impotence, gonorrhea, malaria, dtamenorrhea and abdominal pain [10]. Water extract from the plant was effective against bacteria significant to periodontal diseases [11, 12]. It has also been found that the alcoholic extracts of the root-bark possesses considerable antibacterial activity [13]. Anti-sickling [14] and anti-inflammatory [15] agents have been isolated from the plant. Workers in West Africa have reported the anti-sickling and antimicrobial activity of the extracts of the plant [16]. The root extracts of the plant was shown to have some cytotoxic effects on the human erythroleukaemia cell line. Also the radical scavenging activity of the stem extract [17], as well as the antidiabetic and hypolipidaemic effects of the leaf extract [18] have been reported.There are little or no documented reports on the use of this plant as an analgesic and antipyretics; hence this study was designed to evaluate the anti-inflammatory potential of Fagarazanthoxyloides and to validate the used of the plant in folkoric medicine in the treating of toothache.

Materials and Methods

Chemicals

Chemicals and reagents: all chemicals and reagents were obtained from Sigma- Aldrich Chemical Co. (St Louis, MO, USA). All the chemicals used including the solvents, were of analytical grade

Collection and Identification of Plant Material

Fresh root-barks of F. zanthoxyloides were collected, from Opanda-Nimbo, Uzo-uwani Local Government Area of Enugu State, Nigeria. The root-bark was authenticated by Mr. Alfred Ozioko of the Bioresources Development and Conservation Programme (BDCP) Research Centre, Nsukka, Enugu State, Nigeria.

Preparation and Extraction of Plant Crude Extract

Fresh F. zanthoxylodes root-bark was collected and washed. The plant was cut into pieces and air

dried with regular turning to avoid decaying, until crispy. The dried root-bark was pulverized into powdered form using a mechanical grinder. A known weight of the pulverized sample (1000 g) was macerated in 3.5liters of absolute methanol, vigorously shaken and allowed to stand for 72 hours. The mixture was filtered using Whatman No.1 filter paper and the filtrate concentrated under reduced pressure using a rotary evaporator at 45 oC to obtain the crude methanol extract. The concentrated extract was stored in an air-tight container in a refrigerator at 4 oC until required.

Phytochemical screening

The preliminary phytochemical screening was performed for identifying the phyto-constituents present in methanol extracts of root-bark of F. zanthoxylodes by standard test for the presence of secondary metabolites including alkaloi-ds, flavonoids, phenols, tannins, steroids, glycosides and saponins.

Antipyretic Activity Test

The antipyretic activity of methanol extract of Fagarazanthoxyloides root-bark in rats was investigated by a combination of the methods described by [19, 20]. These were carried out in an air- conditioned room (250C and 50% humidity). The animals (20 rats, 4 in each group) were kept in the room for 18 hours to acclamatize them before starting the experiment. Feed and water were withheld overnight and until the test was completed. Three rectal measurements, the average of which form the basal temperatures were taken in each rat at 30 minutes intervals before the injection of the pyrogen. Pyrexia was induced in albino rats each by subcutaneous injection of 50% dried brewer's yeast suspension in 0.9% NaCl (1ml/100g body weight). Initial rectal temperature was recorded. After 18 hours, animals that showed an increase of 0.3-0.50C in rectal temperature were selected. The extract (100, 200 and 400mg/kg) was administered to three groups. The control received the saline vehicle. Paracetamol (100mg/kg) was used as the reference drug. Rectal temperature was measured 1 and 2 hours after extract/ reference drug administration.

Analgesic Activity Test

To determine the analgesic activity of methanol extract, the writhing test was carried out according to the method described by [21]. Vehicle (5mg/kg), aspirin (200mg/kg), three scalar amounts (100, 200 and 400mg/kg) of the extract were respectively administered (p. o.) to 5 groups of 4 animals each. Thirty minutes afterwards, 0.6% acetic acid (10mg/kg) intraperitoneally injected into each animal. The number of writhings and stretching was counted over a 20 minutes period.

Statistical Analysis

The data obtained were expressed as Mean ± SD. Significant differences of the result were established by one-way and two-way ANOVA and the acceptance level of significance was $p< 0.05$ for all the results. This was done using the Statistical Package for Social Sciences (SPSS) version 22.0.

Table 1 shows the results of the quantitative photochemistry of methanol extract of Fagarazanthoxyloides root-bark. These secondary metabolites have been reported to exhibit varied biochemical and pharmacological effects in animals and microorganisms when ingested. The results obtained correlated with the qualitative results obtained above. The root-bark methanol extracts constitutes respectively; tannins (13.312 ± 0.004 mg/100g), terpenoids (1021.315 ± 0.3995 mg/100g), steroids (5.575 ± 0.009 mg/g), phenols (2386.321 ± 0.007 mg/100g), alkanoids (810.311 ± 1.731 mg/100g), flavonoids (1931.753 ± 0.009 mg/100g) and saponins (1.321 ± 0.004 mg/g).

Table 2 shows the effect of the extract on brewer's yeast-induced pyrexia. The yeast caused the rats to become hyperpyretic. The anal temperature of all groups were higher 18hours after yeast induction when compared to their basal temperatures. The anal temperatures (1hour after treatment) of all doses of the extract (100mg/kg, 200mg/kg, and 400mg/kg) and paracetamol (100mg/kg) were significantly ($p < 0.05$) lower than the analtemperature before treatment. There was no significant ($p > 0.05$) difference between the anal temperatures of 1hour post treatment and 2hours post treatment in all doses of the extract (100mg/kg, 200mg/kg, 400mg/kg) and the standard drug. At 1hour post treatment, all doses of the

extract (100mg/kg, 200mg/kg, and 400mg/kg) and paracetamol were significantly ($p < 0.05$) lower when compared with control. Also, at 2hour post treatment, all doses of the extract (100mg/kg, 200mg/kg, and 400mg/kg) and paracetamol were significantly ($p < 0.05$) lower when compared with control. The extract at 400mg/kg showed the lowest anal temperature at 1hour post treatment (36.0±0.4) with extracts 100mg/kg, 200mg/kg, paracetamol 100mg/kg and control having (36.7±0.6),(36.5±0.7), (36.4±0.8) and (38.6±0.3) respectively. The extract at 400mg/kg showed the lowest anal temperature at 2hour post treatment (35.2±0.2) with extracts 100mg/kg, 200mg/kg, paracetamol 100mg/kg and control having (36.4±0.5),(35.9±0.1), (36.0±0.2) and (37.8±0.4) respectively.

In Table 3, the plant extract (400mg/kg) caused significant ($p < 0.05$) suppression of nociceptive response (41.99%) in the rats when compared to the control. This showed that the extract possessed analgesic property. The number of writhings in all doses of the extract (100mg/kg, 200mg/kg, 400mg/kg) and Aspirin (200mg/kg) were significantly ($p < 0.05$) lower than the number of writhings in the control group. The analgesic effect of the extract was dose dependent. The number of writhings in the highest dose of the extract (400mg/kg) was non-significantly lower when compared with standard drug (Aspirin 200mg/kg). The % analgesic activity of extracts 100mg/kg, 200mg/kg, 400mg/kg and Apirin 200mg/kg were 13.26%, 27.62%, 41.99%, and 44.44% respectively. This indicates that the highest dose of the extract had similar analgesic properties when compared with the standard drug and can serve the same function.

Discussion

Medicinal values of plants and plant materials lie in some chemical substances that have a definite physiological action on the human body. Findings from the quantitative phytochemical screening of the extract revealed that Fagarazanthoxyloides is rich inflavonoids, terpenoids, phenols, steroids, saponins, alkaloids and tannins in varying proportions. Some of these constituents are believed to be responsible for the anti-inflammatory activities of some plants [22-24]. Secondary metabolites like flavonoids and alkaloids have been linked to possess analgesic, antipyretic, and other properties [25-27]. Flavonoids are the main constituents that have capacity to interfere with eicosanoids biosynthesis pathways [28], and are suggested to decrease the release of arachidonic acid through inhibition of neutrophils degranulation [29]. Both of these actions result in suppression of inflammatory mediators like prostaglandins and lipoxygenase end products responsible for inflammation, pain, and fever.

Yeast induced fever, which represents pathogenic fever, presents an economical and reliable method for assessing new antipyretics [30]. The presence of proteins in yeast is linked to fever via inflammatory reaction in this method [31]. Further, the production of proinflammatory cytokines such as interleukin-1β (IL-1β) and IL-6, interferon-α (IFN-α), and tumor necrosis factor-α (TNF-α) and prostaglandins like PGE2 and PGI2 are responsible for elevating the body temperature by acting on brain [32,33]. Antipyretics such as paracetamol used in management of fever act through several ways by reducing levels of prostaglandins acting on cyclooxygenase enzymes, enhancing antipyretic message within brain and stimulating anti-inflammatory signals at injury site [34]. The methanol extract of Fagarazanthoxyloide root-bark significantly ($p < 0.05$) lowered the anal temperature of animals induced with yeast. The lowering of temperature was almost in a similar manner to that of reference drug, paracetamol, suggesting that the plant have antipyretic property which can be assumed to be mediated through interference of prostaglandin synthesis and inhibition of cytokines release. The studies conducted by various researchers have revealed that the medicinal plants showing analgesic property have also demonstrated antipyretic as well as anti-inflammatory activities [25, 35] as the mechanism for suppression of pain, fever, and inflammation can be correlated via inhibition of inflammatory mediators. This further reinforces the evaluation of root extract of this plant for anti-inflammatory potential.

The methanol extract was evaluated for analgesic effect against acetic acid induced visceral pain. Intraperitoneal administration of acetic acid

produced an abdominal writhing response by activating the chemosensitivenociceptors in animals. The characteristic of pain activity generated by intraperitoneal injection of acetic acid is presented with contraction of abdominal muscle followed by extension of hind limbs and elongation of body part and such constriction is thought to be mediated by local peritoneal receptor [36]. The acetic acid provoked writhing is simple and commonly used method for screening analgesic drugs [37]. Studies have revealed the accumulation of higher levels of prostaglandins especially PGE2, PGF2α, PGI2, lipoxygenase products [38], and peritoneal mast cells [39], in peritoneal fluids treated with algogenic acetic acid. Prostaglandin itself does not cause pain but acts indirectly either by stimulating or by sensitizing the nociceptors to the pain producing substances released from the damaged tissue of the inflamed area. Acetic acid can also potentiates the pain through capillary permeability. The major contribution of prostaglandins to eliciting pain response is mainly due to interaction with endogenous mediators like histamine, serotonin, bradykinin, and substance P which further stimulate the sensitization of pain receptors to these mediators. It is well established that NSAIDs relieve the pain response peripherally by inhibiting production of prostaglandins, thromboxane, and other inflammatory mediators by acting on cyclooxygenase enzymes. Any substance lessening the number of constrictions induced by acetic acid can be considered to have analgesic potential. Methanol extract of Fagarazanthoxyloide root-bark at 100, 200 and 400 mg/kg significantly($p < 0.05$) reduced the number of writhe induced by a 0.6% acetic acid solution in a dose dependent manner similar to that of the standard drug, aspirin. This strongly suggests that the plant under study possesses peripheral analgesic property, possibly mediated through same mechanism of inhibition of prostaglandins generating pathways and local peritoneal inflammation. The inhibition of acetic acid writhing shows that the extracts may have central effects on the nervous system and depressant effect on the nervous system since central nervous system depressants have been shown to reduce the number of writhing in acetic acid pain models. These results concur with other research studies on the evaluation analgesic activity of herbal plants extract using laboratory animals. Reduction in the number of abdominal writhing's in this study is in agreement with a study carried out by [40]. on analgesic properties of acetone leaf extracts of Carissa spinarum in mice. The findings are also in line with studies by [41] onantinociceptive activity of Toddaliaasiatica (L) Lam in models of central and peripheral pain.

Conclusion

The methanol root-bark extract of F. zanthoxyloides demonstrated anti-pyretic activity on yeast-induced pyrexia and analgesic activities on acetic acid-induced pain in albino rats and mice respectively. The extract inhibited yeast-induced pyrexia in rats when compared to the control and the reference drug. The extract also reduced the number of abdominal writhing's significantly when compared to the reference drug. This study therefore concludes that the medicinal plant possesses analgesic and antipyretics properties. Suppression of pain and fever in this study could be attributed to phytochemical constituents present in the extract. Therefore, it is possible to obtain analgesic and anti-pyretic agents from the plant and serve as an alternative bio-resource in managing pain and fever. However, further research on the mechanism action of the extract should be carried out. The study thus, scientifically confirms the traditional use of the medicinal plant in management of pain and fever related ailments.

Acknowledgements

The authors thank the technical staff of the Department of Biochemistry University of Nigeria, Nsukka and Natural Science Unit, School of General Studies, Unversity of Nigeria, Nsukka for their technical assistance during the study.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Table 1: Quantitative Phytochemistry of Methanol Extract of *Fagarazanyhoxyloide* Root-Bark

Phytochemical Constituents	concentration (mg/100 g) (Mean ± SD)
Tanin	14.312 ± 0.004
Steroid	5.575 ± 0.009
Phenol	2386.321 ± 0.007
Alkanoid	810.311 ± 1.731
Flavonoid	1931.753 ± 0.009
Saponin	1.321 ± 0.004
terpenoids	1021.315 ± 0.3995

Results are expressed in Means ± SD (n = 3)

Table 2: Effect of Methanol Extract of *Fagara zanthoxyloides* Root-Bark on Brewer's Yeast-Induced Pyrexia in Rats.

Treatment Groups	Rectal Temperature (°C)			
	Before Treatment		After Treatment	
	0h	18h	1h	2h
Control (saline vehicle)	36.6±0.3^{Aa}	37.5±0.6^{Ba}	38.6±0.3^{Cb}	37.8±0.4^{Bd}
Paracetamol (100mg/kg)	36.3±0.5^{Aa}	38.2±0.6^{Ba}	36.4±0.8^{Aa}	36.0±0.2^{Abc}
Extract (100mg/kg)	36.8±1.0^{Aa}	38.1±1.0^{Ba}	36.7±0.6^{Aa}	36.4±0.5^{Ac}
Extract (200mg/kg)	37.0±0.6^{Ba}	38.2±0.4^{Ca}	36.5±0.7^{ABa}	35.9±0.1^{Ab}
Extract (400mg/kg)	37.2±1.0^{Ba}	37.6±0.9^{Ba}	36.0±0.4^{Aa}	35.2±0.2^{Aa}

n = 4

Results expressed as Mean ± SD

Mean values having different lowercase letters as superscripts are considered significant ($p < 0.05$) down the column.

Mean values having different uppercase letters as superscripts are considered significant ($p < 0.05$) across the row.

Table 3: Effect of Methanol Extractof *Fagara Zanthoxyloides* Root-Bark and Aspirin on Acetic Acid-Induced Nociceptive Response in Mice.

Treatment groups	No of Writhings (Count/20mins)	%Analgesic activity
Control (saline vehicle)	45.25±4.65[d]	
Extract (100mg/kg B.W)	39.25±1.71[c]	13.26%
Extract (200mg/kg B. W)	32.75±2.99[b]	27.62%
Extract (400mg/kg B. W)	26.25±2.50[a]	41.99%
Aspirin (200mg/kg B. W)	26.50±3.42[a]	41.44%

n = 4
Results expressed as Mean ± SD
Mean values having different lowercase letters as superscripts are considered significant ($p < 0.05$) down the column.