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HOW *FICUS EXAPERATA* LEAVES EXTRACT FACILITATE CHILDBIRTH IN PARTURIENT WOMEN?

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ABSTRACT

The aim of present work was to identify and examine the effects *Ficus exasperata* leaf extract on some physiological parameters that contribute significantly to the success of childbirth. According to previous studies, this plant extract has utérotonic, hypotensive, antihypertensive, anxiolytic, anticonvulsant, anti-inflammatory, analgesic and antipyretic activities which could facilitate labor. In conclusion, *Ficus exasperata* (Moraceae) has some pharmacological properties thus supporting its folkloric use to facilitate childbirth in parturient women.

Key words: *Ficus exasperata*, Childbirth, Parturient women.

INTRODUCTION

Despite the availability of modern medicine, many people in the developing countries still rely on traditional healers and medicinal plants to meet their primary healthcare needs and that of their domestic animals [1-3]. Plant-extract-based medicine is quite appreciated and culturally well accepted by rural and even urban population. The practice of ethnomedicine is a complex multi-disciplinary system, comprising the use of plants, spirituality and the natural environment and has been the source of healing for people for millennia [3,4]. Herbal remedies are becoming indispensable and constitute an integral part of primary health care systems in so many nations [5-7]. Several documentations on the medicinal importance of traditional plants and their active ingredient(s) have been reported [3,8]. Herbal plant contains number of medicinal properties and one of such plants is *Ficus exasperata* Valh. [9,10].

Commonly named "Papier de verre" in French and "Sandpaper fig tree, white fig tree" in English, *F. exasperata* Vahl. [Syn. *Ficus asperrima* Roxb., *Ficus punctifera* Warb., *Ficus scabra* Willd., *Ficus silicea* Sim.] [11], belonging to the family Moraceae, is a terrestrial afro-tropical shrub or small tree with scabrous, with ovate leaves that grows up to about 20 m tall and prefers evergreen and secondary forest habitats [12]. In African traditional medicine, different parts of this plant (fruit, leaf, sap, bark, and root) are considered medicinally important. The leaves of *F. exasperata* are much valued in the treatment of a variety of diseases/disorders. The leaves are commonly used by African traditional birth attendants (TBAs) to facilitate deliveries in parturient women. Irene and Iheanacho [13] reported the traditional use of the plant in hastening the expulsion of placenta in cows after calf delivery and its use by traditional birth attendants in hastening childbirth. According to some another authors, the leaves of *Ficus exasperata* Vahl. (Moraceae) are used by traditional healers in Southern Nigeria to arrest pre-term contractions and are also used as an abortifacient in some parts of Africa [14]. The present study is conducted in order to provide a scientific basis for the use of *F. exasperata* to facilitate deliveries in the parturient woman. How *Ficus exaperata* Leaves Extract Facilitate Childbirth in Parturient Women? So, it is necessary to examine previous studies, identify and examine the effects of this herbal on some physiological parameters that contribute significantly to the success of childbirth.

Pharmacological Properties

Uterotonic activity

Several studies on the uterotonic activity were summarized by Ahmed *et al.* [15]. There have been contradictory usages of *F. exasperata* leaves with respect

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its effect on uterus. Some herbal practitioners use them for relaxing the uterus [16], while others use them for enhancing uterine contractions [17]. Considering this observation, Bafor and co-workers extensively studied the effects of various concentrations of aqueous leaf extract of *Ficus exasperata* on uterine contractions *in vitro* [14,18,19]. Aqueous leaf extract of *F. exasperata* at the dose of 1.0×10^{-2} mg/mL inhibited oxytocin-induced uterine contractions without significantly affecting acetylcholine or ergometrine-induced uterine contractions in isolated rat uterus. The results also indicated that the extract had no significant effect on the amplitude and frequency of spontaneous contractions [19]. In another study, the extract at doses of 2.5×10^{-2} - 1 mg/mL directly stimulated uterine contractions and significantly increased the frequency but not the amplitude of spontaneous contractions similar to that of acetylcholine. The authors opinioned that, as the extract stimulate uterine contractility at higher doses, it might be helpful in easing childbirth [18]. In order to determine the mechanism of action, the contractile effect of extract (5×10^{-2} - 100×10^{-2} mg/mL) and oxytocin were examined in the presence of atropine, indomethacin, verapamil, phentolamine and diphenhydramine. The results indicated no significant difference in the EC_{50} and E_{max} of the extract in the presence of atropine, verapamil and indomethacin. However, diphenhydramine and phentolamine significantly inhibited the extract suggesting stimulation of uterine contractility by the extract might be due to the activation of histamine H1- and/or α-adrenergic receptors, interference with calcium channels and/or stimulation of prostaglandin synthesis *in utero* [14].

Antihypertensive and hypotensive activities

Ayinde *et al*. [20] reported the hypotensive effect of *F. exasperata* leaf aqueous extract in rabbits. The water extract showed a dose related reduction in mean arterial blood pressure. At 10 mg/kg, a reduction of 16.6 ± 1.1 mmHg was observed, whereas at 30 mg/kg, a fall in mean arterial pressure of 38.3 ± 0.6 mmHg was obtained. The hypotensive effect of the extract was significantly reduced with a prior administration of 2.5 mg of either atropine or chlorpheniramine. This suggests the probable stimulation of muscarinic receptors in the heart or release of histamine into the circulatory system thereby causing the initial fall in blood pressure.

Amonkan *et al.* [21] examined the effects of aqueous extract of leaves of *F. exasperata* (FEFIX) on rabbit blood pressure and the contractile activity of isolated rat heart to check the interest of the use of this plant in the African pharmacopoeia for the treatment of edema and hypertension. Increasing doses of the aqueous extract of FEFIX were administered to rabbits to determine the ED50. The effect of FEFIX was evaluated in the presence of atropine, methylene blue and after hypertension induced by adrenaline. Different concentrations of FEFIX were perfused an isolated heart. The results show that FEFIX induced a dose-dependent hypotension with an ED50 equal to 5.46 ± 2.12 mg / kg bw This hypotension is reduced in the presence of atropine and in the presence of methylene blue. FEFIX reduces hypertension induced by adrenaline and does not alter significantly the contractile activity of isolated rat heart way. At the end of this work, it appears that the hypotensive effect of FEFIX result of its cholinomimetic effect and its involvement in the release of nitric oxide (NO), while the antihypertensive effect is due to the interaction of its chemical compounds with adrenergic receptors.

Adewole *et al*. [22] evaluated the hypotensive potential of *F. exasperata* leaf extract in streptozotocin-induced diabetic rats (spontaneously-hypertensive and obese Zucker rats). Oral administration of the extract (100 mg/kg) for 4 weeks significantly reduced blood pressure and restored the microanatomy of the blood vessels to almost normal levels. Histopathological examination of the aortic blood vessels showed extensive collagen fiber formation as well as perivascular fibrosis; these changes were significantly reversed towards normalization by the extract suggesting the usefulness of *F. exasperata* in hypertension. Considering the above results, it is felt that scope exists to evaluate the angiotensin converting enzyme inhibitory activity of the extract to elucidate the possible mechanism of action.

Anxiolytic Activity

Ahmed *et al.* [15] summarized various studies relating to this property. Anxiety affects nearly one-eighth of the world population and benzodiazepines, a major class of compounds used for its treatment presents a narrow margin of safety between the anxiolytic effect and unwanted side effects has prompted research into natural products having less undesirable effects [23]. The anxiolytic activity of hydroethanol extract (30:70 v/v) of *F. exasperata* leaves was assessed at doses of 30, 100 and 300 g/kg (p.o.) in 3 animal models of anxiety; open field test, elevated plus-maze and hole board test in mice. The extract exhibited significant dose dependent anxiolytic activity similar to diazepam in all the anxiety models. In open filed test, number of center entries, percentage number of center entries, center time and percentage center time were increased. Similarly, the frequency and duration of open arm exploration in the elevated plus-maze was increased tract treatment. In hole-board paradigm, the frequency and duration of head-dips were increased without any significant changes in locomotor activity at all doses tested [24].

Anticonvulsant activity

Woode *et al*. [25] evaluated the anticonvulsant effect of hydroethanol extract (30:70 v/v) of *F. exasperata* leaves against seizures induced by pentylenetetrazole,

picrotoxin or maximal electroshock in mice. The extract (30-300 g/kg, p.o.) significantly delayed the onset and decreased the duration of pentylenetetrazole and picrotoxin-induced convulsions and also reduced the duration of maximal electroshock-induced tonic hind limb extension. In rotarod experiment, the extract significantly decreased the time spent on the rotating rod. The authors concluded that, *F. exasperata* extract possesses significant anticonvulsant activity in mice and thus validating its use as an antiepileptic agent in African traditional medicine.

Anti-inflammatory activity

The synthesis of some works on the anti-inflammatory activity of this herb was made by Ahmed *et al.* [15]. Different parts of *F. exasperata* are used in African traditional medicine for inflammatory conditions, the anti-inflammatory properties of hydroethanol extract (30:70 v/v) of *F. exasperata* leaves against carrageenan-induced foot edema in 7 day old chicks were investigated [26]. The extract (10-300 mg/kg p.o.) showed significant, dose dependent anti-inflammatory as reflected by reduction of foot volume induced carrageenan. The extract also significantly decreased carrageenan-induced edema with an IC_{50} of 46 mg/kg, thus validating the folklore usage of *F. exasperata* as an anti-inflammatory agent. Although, the study clearly demonstrates the anti-inflammatory potential of *F. exasperata* extract, studies involving its effect of cyclooxygenases, lipooxygenases and phospholipases are needed for better management of pain and inflammation.

Analgesic activity

The formalin test is one of the most widely used methods for the rapid and easy screening of pharmacological targets in drug evaluation [27,28]. Intraplantar injections of formalin evoke a characteristic biphasic licking response. In the early phase (0-10 min post formalin injection) formalin directly stimulates nociceptors that corresponds to acute neurogenic pain which is sensitive to central analgesics [29]. The late phase involves inflammatory components with the release of different pain mediating substances sensitive to nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids as well as analgesics with central effects [30,31]. Oral administration of hydroethanol leaf extract at doses of 30, 100 and 300 mg/kg, 30 min before the injection of formalin showed significant and dose dependent inhibition of formalin-induced paw licking and biting by 15-66 % and 52-77 %, respectively in the early and late phases [26].

Antipyretic activity

Woode *et al*. [26] reported that, oral administration of hydroethanol leaf extract at doses of 100 and 300 mg/kg produced slight antipyretic effect between 5^{th} and 7^{th} h after intraperitoneal injection of yeast, after which temperature raised gradually. The authors concluded that the extract possesses week antipyretic activity at doses of 100 and 300 mg/kg. However, Bafor *et al*. [32] evaluated the effects of hexane, ethylacetate, and aqueous extracts of *F. exasperata* leaves on normal body temperature and yeast-induced pyrexia in mice as traditional African healers extensively use the leaves for fevers particularly malarial fever. The results indicated that, all the extracts possess time dependent antipyretic activity with reasonable onset and duration of action against yeast-induced pyrexia in mice, however hexane and aqueous extracts were found to be more potent. It was also noted that, the extracts did not have any significant effect on normal body temperature. The study thus provided experimental evidence justifying its use by traditional healers and the natives for febrile conditions.

Toxicity studies

Several toxicity studies have been conducted on various extracts of *F. exasperata* leaves. Few have shown potential toxic effects, while others have rendered the extracts to be relatively safe. A summary of the toxicity studies is presented here [15].

Oral administration of the ethanol leaf extract (50, 100 and 150 mg/kg) for 8weeks significantly increased the levels of aspartate aminotransferase (AST), alkaline phosphatase (ALP), alanine transaminase (ALT), total bilirubin and conjugated bilirubin in Wistar rats. The histological architecture of the liver and kidney cortex revealed several damages, especially in the kidney cortex. Authors indicated that the explicit use of *F. exasperata* leaf extract in herbal medicine might be dangerous to health [33]. Similarly, oral administration of the ethanol extract (50, 200 and 500 mg/kg) significantly increased body weights, mean relative kidney weights, serum urea and sodium concentrations in a dose dependent manner in albino rats suggesting that higher doses of the extract could affect kidney function [34].

In an acute toxicity study, oral administration of single dose of the aqueous leaf extract (2.5, 5, 10 and 20 g/kg) did not produce any mortality and changes in behaviour and any other physiological activity in mice over 24 hrs. The extract did not affect the body temperature, body weights, blood cell counts and haemoglobin. The LD_{50} value could not be determined in oral administration route; however it was determined by intraperitoneal administration of the extract (0.1, 0.2, 0.4, 0.8 and 1 mg/kg). An LD_{50} value of 0.54 g/kg was deduced for the extract through intraperitoneal administration. The extract was further evaluated for 14 day toxicity study, wherein mice were dosed with the extract (2.5, 5, 10 and 20 g/kg) daily for 14 days. The results indicated significant increase in body temperature and a significant decrease in the red blood cell count, haemoglobin and haematocrit values. It was concluded to be relatively safe for short-term oral administration [35].

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In another study, hydroethanol extract (20:80 v/v) of leaves from *F. exasperata* showed no toxic effects in brine shrimp lethality test, inhibition of telomerase activity, and induction of chromosomal aberrations *in vivo* in rat lymphocytes rendering it relatively safe for possible human consumption [34].

Recent toxicity studies in rats involving crude aqueous and ethanol extract of the leaves have indicated potential hepatic and renal toxicity as reflected by significantly increased serum transaminases and bilirubin. The biochemical findings were substantiated by the histopathological studies which indicated that high doses of the ethanol leaf extract could lead to toxic injury in the kidneys which might interfere with renal tubular function and induce renal failure [36,37].

In another acute toxicity study involving a Nigerian polyherbal tea containing *Anthocleistavogelii*, *Ficus exasperata* leaves and *Viscum album*, a 100 % mortality was produced at the dose of 20.0 g kg^{-1} in mice over 72 hrs. However, no mortality occurred in animals that received < 5.0 g/kg of the extract. Based on these finding an LD_{50} value of 9.0 g kg^{-1} was assigned to the extract. In a sub-chronic toxicity model, dosing of the rats with the extract (100, 250 and 500 g kg^{-1}) significantly reduced plasma glucose and low density lipoprotein (LDL) and increased high density lipoprotein (HDL)-cholesterol compared to control rats. The study also evidenced no significant changes in body weights, (AST) and creatinine levels but ALT levels were significantly decreased suggesting the safety of the formulation [38].

Anowi *et al.* [39] also studied the toxicity of *F. exasperata*. The LD_{50} was carried out using the method employed by Lorke [40]. It involves a total of 12 mice. This test was carried out in two phases. Phase 1 employed a total of 9 mice. They were grouped into 3 groups of 3 mice per group. Group i received 10 mg/kg of the extract. Group ii received 100 mg/kg, while Group iii received 1000 mg/kg. All the administration was by intraperitoneal (i.p.) route. The animals were constantly monitored for the next 4 hrs, Then intermittently for the next 6 hrs. Then over a period of 24 hrs. The number of dead animals was noted. From the result got in the first phase, the second phase was carried out. In this phase, A total of 4 mice were used. They were grouped into 4 groups of 1 moucee per group. Group 1 received 2000 mg/kg of the extract, group II received 3000 mg/kg, group III received 4000 mg/kg, while group IV received 5000 mg/kg. The animals were monitored for another 24 hrs for any death. From the result of the LD_{50}, the extract was well tolerated even at dose up to 5000 mg/kg. So it was safe for acute administration.

Amonkan *et al.* [21] also evaluated the parameters of the acute toxicity of aqueous extract of leaves of *F. exasperata* (FEFIX). Intraperitoneally and the graphical method of Miller and Tainter, FEFIX causes the death of 50 % (LD_{50}) in mice at a dose of 728.79 ± 14.38 mg/kg b.w. In addition, the doses less than or equal to 300 , 61 ± 65.17 mg/kg b.w. (DMT), FEFIX does not induce death in mice. From 1370.25 ± 241.79 mg/kg b.w. (DL_{100}) FEFIX causes the death of all animals. These parameter values of acute toxicity (DMT, LD_{50} and LD_{100}) obtained show that the pharmacological doses used are non-toxic.

DISCUSSION

Childbirth is a biological process that is complex. It is the result of several physiological mechanisms [41-43]. However there are factors that can be described as key or essential factors. These key factors are subject to monitoring during labor for the well-being of the mother and newborn. These key factors are firstly the uterine contractility and arterial blood pressure. To them, it must associate the control of pain, fever and mental status (moral, anxiety and emotion) of the parturient women [44-47].

Previous studies have shown that *F. exasperata* possess uterotonic, hypotensive, antihypertenve, anxiolytic, anticonvulsant, anti-inflammatory, analgesic and antipyretic activities which could contribute strongly to successful of childbirth.

F. exasperata has uterotonic action. This action stimulates uterine smooth muscle and increases the contractile force of the muscle structure. The uterine contraction is the main force that ensures the progress of mobile fetal and expulsion of placenta. [48,49]. Indeed, uterine contraction plays a fundamental role in labor. According to some authors, labor failure is partly due to dysfunction of uterine contraction argued that Ca2+ mobilization is essential during uterine contraction even if the mechanisms underlying this activity of uterus are not completely understood [50]. The hypotensive and antihypertensive effects of *F. exasperata* such as oxytocin and prostaglandins may reduce blood loss due to bleeding of childbirth. Indeed, in practice, the use of oxytocic-like substances is the first treatment to fight against these hemorrhages. These hemorrhages are one of the leading causes of infant and maternal mortality [51-53]. This beneficial action of *F. exasperata* is well known in traditional medicine. *F. exasperata* leaves are used to arrest bleeding [54]. The anxiolytic, analgesic and antipyretic activities of *F. exasperata* would also be beneficial for the parturient woman. It is known that anxiety, pain and fever are negatively correlated with complications in pregnancy and labor. They have a negative impact on the delivery by increasing its duration [55]. Thus, the anxiolytic, analgesic and antipyretic activities of this medicinal plant could reduce the duration of labor [44-47]. The anticonvulsant effect of *F. exasperata* extract could promote serenity in the parturient. She would move less. Finally, on the pharmacological level, it should be noted that the anti-inflammatory properties also helps to fight against possible infections in the mother.

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The results on the toxicity of *F. exasperata* are contradictory. For some authors, this plant is non-toxic, while for others it is slightly toxic. This toxicity as those of many drugs could not be a barrier to its use for therapeutic purposes because all pharmacodynamic substances are toxic when the administered doses are supraliminal [56]. The doses used in the short term by traditional birth attends would be low because the literature does not reveal any toxicity due to its use in the parturient woman and the newborn. The doses used in traditional medicine to facilitate childbirth would be low and therefore safe.

CONCLUSION

In conclusion, the present review study has shown that *F. exasperata* leaves possess uterotonic, hypotensive, antihypertensive, anxiolytic, anti-inflammatory, analgesic, antipyretic and anticonvulsant activities which could contribute strongly to the success of the deliveries. *Ficus exasperata* Vahl. (Moraceae) can be used to facilitate childbirth in parturient women. However, considering the confliction results on the toxicity of *F. exasperata* extracts reported by various researchers, systematic toxicological screening of standardized extracts is the urgent need.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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