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Evaluation of the Healing Properties of *Pentaclethra macrophylla* BENTH (Fabaceae) Seed Pod on Diabetic Wounds

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ABSTRACT

Background: *Pentaclethra macrophylla* has gained attention in recent years for its potential as a wound-healing agent. *Pentaclethra macrophylla*, also known as Oil Bean tree, is a plant that is native to tropical Africa and has a long history of use in traditional medicine for various ailments. However, one part of the plant has been overlooked as a waste product- the seed pod. While studies have shown that the seed has some wound healing property, little study has been carried out on the seed pod of *Pentaclethra macrophylla*.

Methods: The pulverized seed pods were extracted by maceration in a mixture of Dichloromethane and Methanol in a 1:1 ratio and dried on a rotary evaporator. Subsequently, the Phytochemical and GCMS analysis were carried out and the extracts were formulated into creams in the following concentrations: 250 mg, 500 mg, 750 mg and 1000 mg respectively. Diabetes was induced in the rats by using Alloxan Monohydrate. The extract formulations of P. macrophylla seed pods were administered topically to evaluate the wound healing potential in the excision wound model for fourteen days. Thermazene was used as a positive control for wound healing in the excision wound model.

Results: The phytochemical content was found to contain tannins and triterpenoids. The GC-MS analysis showed the presence of twelve (12) chemical compounds, with five of them having pharmacological potential. These compounds include E-7-Octadecene, Hexadecanoic acid, methyl ester, 9,12-Octadecadienoic acid (Z,Z)-, methyl ester, 10-Octadecenoic acid, methyl ester and 12-Methyl-E,E-2,13-octadecadien-1-ol. The Results of the wound healing study demonstrated that the activity of the Thermazene treated group was comparable with the 250 mg extract and 500 mg extract-treated groups. While, the 750 mg and 1000 mg extracts were significantly more potent at $P<0.05$ than Thermazene at day 14.

Conclusion: These results confirm that the seed pod of *Pentaclethra macrophylla* has a beneficial influence on the various phases of wound healing wound resulting in faster healing. This activity may be attributed to the phytoconstituents such as tannins and triterpenoids in higher concentrations, which enhance wound healing due to their individual or cumulative effect. These findings therefore justify the inclusion of this plant in the management of wound healing.

Keywords: *Pentaclethra macrophylla*, Wound healing, GC-MS

1 INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Diabetic patients are at a higher risk of developing wounds, and the healing process of these wounds is often impaired due to various factors such as neuropathy, vascular disease, and immune dysfunction. Diabetic wounds are a significant health concern, as they can lead to serious complications such as amputation, infections, and even death. The impaired wound healing in diabetic patients is multifactorial. Neuropathy

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leads to reduced sensation and poor blood supply to the wound site, which impairs the initial inflammatory response. Vascular disease impairs blood flow, leading to reduced delivery of oxygen and nutrients to the wound site. Immune dysfunction leads to impaired immune cell recruitment and reduced cytokine production, which impairs the inflammatory response. These wounds, often located on the lower extremities, pose a substantial challenge due to delayed healing, increased susceptibility to infections, and the potential for severe complications such as amputation. Current medical interventions have limitations in achieving optimal healing outcomes. *Pentaclethra macrophylla*, Benth, also known as Oil bean or Ugba amongst the Igbos, is a large deciduous tree belonging to the family Fabaceae. It is native to tropical Africa and is found in several countries in West and Central Africa, including Nigeria, Sudan, Angola, [1] Cameroon, Congo, Gabon, and Ghana. It grows in a variety of habitats, including lowland and montane forests, and is often found near rivers or in swampy areas [2]. It is commonly called Ugba among the Igbos, Apara in Yoruba, while among the Urhobos' it is called Okpaga. *Pentaclethra macrophylla* is a tall tree that can grow up to 45 metres high, with a trunk diameter of up to 2 metres. The leaves are alternate, pinnately compound, and can grow up to 40 cm long, with 6-10 leaflets. The flowers are yellow and borne in clusters, and the fruit is a large pod that can grow up to 25 cm long, containing up to 15 seeds. The seeds are used for various purposes, including food, medicine, and industrial products. A decoction of the bark is applied as a topical treatment for sores and wounds [3]. In parts of Nigeria, leaf extracts are used in traditional medicine for the treatment of diarrhoea-related ailments. Studies have reported that the extract of stem bark, leaf, root bark and seed pulp of *P. macrophylla* oil has anti-inflammatory and antihelminthic activities, hence it is used to treat gonorrhea, convulsions, dysentery, taken as an analgesic, laxative, emollient against itch and is used to induce abortion [4]. Recent pharmacological studies on stem bark and leaves of the plant revealed its antinociceptive, [5] Antidiarrheal, antimicrobial and hepato-protective activities. A decoction of fermented extract of seeds of this plant has been known to be effective in the management of malnutrition, gastrointestinal disorders and dental caries. [6] The extracted oil from the seeds is used as a remedy against pruritus, worms and dysentery. While traditional medicine has utilized *Pentaclethra macrophylla*, commonly known as the oil bean, for its purported therapeutic properties, there exists a gap in scientific understanding regarding its efficacy in diabetic ulcer healing. The need for alternative and effective approaches to enhance the healing process in diabetic ulcers, coupled with the potential pharmacological properties of *Pentaclethra macrophylla*, underscores the importance of investigating its application in diabetic wound care.

2. METHODS AND MATERIALS

2.1 Materials

2.1.2 Chemicals, Reagents and Equipment

Grinding machine, weighing balance, measuring cylinders, wide mouth bottles, spatula, foils, rotary evaporator, water bath, desiccator, airtight container, separating funnel etc. Dichloromethane (Sigma-Aldrich brand), methanol (Sigma-Aldrich brand), water, n-hexane, Diphenyl picryl hydralazine, Dimethyl sulfoxide (Sigma-Aldrich brand), hydrochloric acid, magnesium metal, sodium hydroxide, ferric chloride, dragendorff's reagent, wagner's reagent, olive oil, hydrochloride acid, chloroform, acetic anhydride, sulphuric acid, Fehling's solution A + B, molisch reagent, million's reagent, glacial acetic acid, picric acid solution, distilled water.

2.2 Methods

2.2.1 Collection of Plant Materials

The seed pod of the *Pentaclethra macrophylla* plant was collected from a bioreserve in the Delta State area of Nigeria. The sample was identified and authenticated procedures conducted by a Taxonomist, Dr. Suleiman Mikailu, of the Department of Pharmacognosy and Phytotherapy, Faculty of Pharmaceutical Sciences, University of Port-Harcourt. The Voucher Specimen Number is UPHF0598. Soon after collection, the seed pods were cleaned and shade-dried. After drying, they were crushed to a powder and stored in an airtight plastic container for further use.

2.2.2 Extraction of the Plant Materials

Using the American National Cancer Institute (NCI) method of extraction,[7] the pulverized powder (600 g) was extracted with a 1:1 mixture of dichloromethane-methanol by continuous extraction in a Soxhlet extractor. The filtrate was concentrated using a rotary evaporator to obtain the dichloromethane-methanol extract of *Pentaclethra macrophylla*. The obtained crude extract was weighed and stored at 4°C for further analysis.

2.2.3 Phytochemical Tests

Preliminary phytochemical screening was carried out on all the crude leaf extracts (dichloromethane and methanol) using standard procedures as described by [8, 9, 10]

2.2.4 Formulation of Cream

Ingredients: Starch, finely sifted (5 g), White soft paraffin (10 g)
Type of preparation: cream
The white soft paraffin was melted and then both the extract and starch was incorporated into the mixture. It was then stirred until cold and packaged in a suitable container.

2.2.5 Pharmacological Study

2.2.5.1 Animals and Management

Wistar albino rats (30) weighing between 150 g - 200 g were obtained from Department of Experimental Pharmacology & Toxicology animal house, University of Port Harcourt. They were sorted, housed in standard cages with housing conditions of 12:12 light: dark cycles. They were fed with standard rat pellets and water ad libitum. The rats were maintained at room temperature.

2.2.5.2 Drug

Commercially available Thermazene was used as the control drug. It was applied topically over the wound area.

2.2.5.3 Induction of Diabetes

Diabetes was induced in the rats by using Alloxan Monohydrate (Sigma-Aldrich), a compound that has preferential toxicity towards pancreatic beta cells. Diabetic conditions were induced by a single intraperitoneal injection of Alloxan at a concentration of 150 mg/kg body weight in overnight fasted rats. After three days of induction, blood samples were collected from the tail and measured using an Accu-Check glucometer. Animals with fasting blood glucose levels from 10 mMol/L were considered diabetic.

2.2.5.4 Evaluation of Wound Healing Effect of Pentaclethra macrophylla on Excision Wound

On the fourth day after the induction of the Alloxan, the diabetic rats were randomly classified into 6 groups.
Group 1 (diabetic untreated)
Group 2 (diabetic treated with thermazene)
Group 3 (diabetic treated with 250 mg of the extract)
Group 4 (diabetic treated with 500 mg of the extract)
Group 5 (diabetic treated with 750 mg of the extract)
Group 6 (diabetic treated with 1000 mg of the extract)
Induction of Wound
On wounding day, the rats were anaesthetized with diethyl ether prior to creation of the wounds. The dorsal fur of the animal was shaved with an electric clipper and the area of the wound to be created was outlined on the back of the animals. A full thickness of the excision wound of 1.5 cm in width was created along the markings using toothed forceps, a surgical blade and pointed scissors. The entire wound was left open. All the surgical procedures were carried out under sterile conditions. After 24 hr of wound creation, the cream was applied gently to cover the wounded area once daily for 14 days. Wound area and wound contraction were monitored.

2.2.5.5 Estimation of Parameters

Measurement of Wound Contraction
The progression of wound healing was judged by the periodic assessment of the contraction of excision wounds. Wound contraction was monitored by tracing the outline of the wound on tracing sheet and then using graph sheet to calculate the area of the wound size. All animals in each group were monitored until complete healing of wounds occurred and the day at which each wound healed was recorded. Mean of all healed wounds was determined.

It was calculated using: $\frac{total\ area - healed\ area}{total\ area} \times 100$

2.2.5.6 Gas Chromatography Mass-Spectroscopy (Gc-Ms) Characterization

The compounds' identities were determined using an Agilent GC-MS model QP-2010 equipped with a Restek column measuring 30 m in length, 0.25 mm in internal diameter, and 0.25 m in thickness. Helium gas was used as the carrier gas and the GC was in splitless mode with the flow rate set at 1 ml/min. The injection temperature was kept constant at 250 °C, and the sample injected volume was 8 µl. The programmed column temperatures were: 60 °C (1.50 min), 260 at 14 °C min-1 (1.50 min), and 300 °C at 14 °C min-1 (3.3 min). At an interface temperature of 250 °C and an ion source temperature of 230 °C, samples were automatically injected into the MS. Electron impact ionization (EI) at 70 eV was performed. As identification criteria, the retention time and abundance of the confirmation ions relative to the quantification ions were used. The fragmentation pattern was compared to the National Institute of Standards and Technology data (NIST).

2.3 Statistical Analysis

Each test was carried out in triplicate. The values were expressed as mean ± standard error of mean (SEM). The Dunnett one-way analysis (ANOVA) was used to determine the significant differences among all columns against control and the *P* value < 0.05 was considered as significant. All statistical analysis was performed using Graph Pad Prism version 8.0 software.

3 RESULTS

3.1 Result of Phytochemical Screening

The Phytochemical screening was carried out on dichloromethane-methanol extract of the seed pod of *Pentaclethra macrophylla*. The extract exhibited the presence of several classes of secondary metabolites, that could be linked to the plant's biological activities. The results are presented in Table 1.

Table 1: Phytochemical constituents of the dichloromethane-methanol extract of the seed pod of *Pentaclethra macrophylla*

Constituent	Present/Absent
Alkaloids	absent
Tannins	present
Saponins	absent
Flavonoids	absent
Anthraquinones	absent
Steroids	present
Triterpenoids	present
Cardiac glycosides	present

3.2 Characterization using Gas Chromatography – Mass Spectroscopy (GC-MS)

The GC-MS Analysis revealed a diverse range of compounds including, Fatty acids (dodecanoic acid, tetra decanoic acid, tridecanoic acid, n-hexadecanoic acid), Fatty acid esters (hexadecenoic acid, methyl ester), Unsaturated fatty acid derivatives (9,12-octadecadienoic acid, methyl ester, 9,12,15-octadecatrienoic acid, methyl ester), Long chain

unsaturated hydrocarbon (1-docosene), Chlorinated ester (dichloroacetic acid, 4-hexadecyl ester) and a Carotene derivative (lycopersene). A well detailed GC-MS profile is presented in Table 2.

Table 2. Chemical Profile from Gas chromatography – Mass spectroscopy (GC-MS) characterization of the dichloromethane/methanol extract of *Pentaclethra macrophylla*

Retention Time	Quantity (%)	Compound
15.7901	0.6034	3,3,3-Trifluoro-N-(2-fluorophenyl)-2-(trifluoromethyl)propionamide
15.8758	9.0129	1H-Azepine, hexahydro-1-nitroso-
19.6295	0.1912	1-Tetradecene
24.0667	0.2944	E-7-Octadecene
26.5842	0.3385	Hexadecanoic acid, methyl ester
28.1004	0.2076	1-Docosene
29.0896	0.0218	12-Methyl-E,E-2,13-octadecadien-1-ol
29.2202	0.4031	9,12-Octadecadienoic acid (Z,Z)-, methyl ester
29.3151	0.5135	10-Octadecenoic acid, methyl ester
29.6354	0.3883	Heptadecanoic acid, 16-methyl-, methyl ester
31.9324	40.879	12-Methyl-E,E-2,13-octadecadien-1-ol
33.6753	32.8875	9,12-Octadecadienoic acid (Z,Z)-

The GC-MS chromatogram is shown in Figure 2, below. A closer look revealed the presence of 12 compounds.

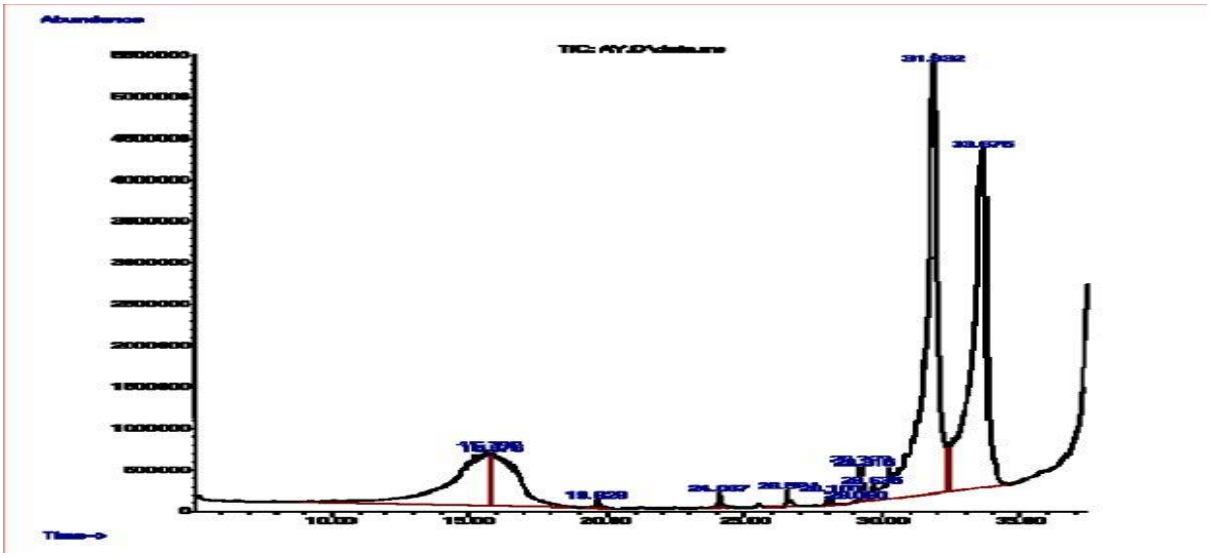
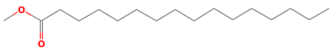
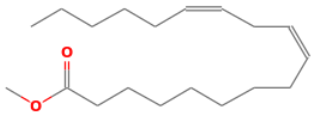
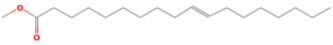
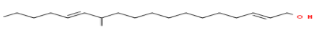


Fig 1: Chromatogram of the dichloromethane-methanol extract of *Pentaclethra macrophylla* seed pod.

Table 3. Structural and pharmacological potentials of major bioactive compounds identified from dichloromethane-methanol extract of *Pentaclethra macrophylla*

Compound Name	Structure	Medicinal Uses
E-7-Octadecene		Lubricant
Hexadecanoic acid, methyl ester		antibacterial
9,12-Octadecadienoic acid (Z,Z)-, methyl ester		anti inflammatory
10-Octadecenoic acid, methyl ester		antibacterial, antidiabetic
12-Methyl-E,E-2,13-octadecadien-1-ol		Anti-cancer and antioxidant

3.3 Pharmacological Studies Results

3.3.1 Evaluation of Wound Healing Effect of Pentaclethra macrophylla Seed Pod in Excision Wound Model

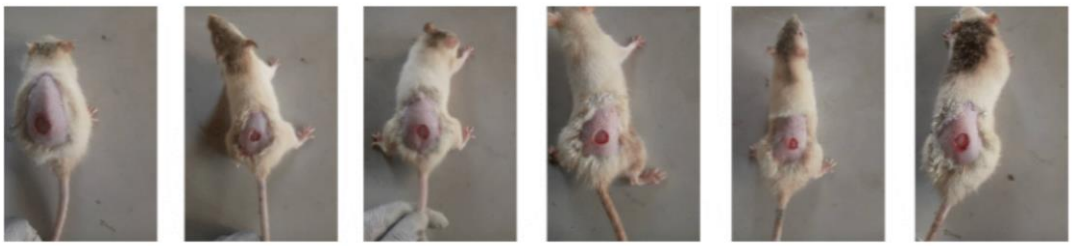


Fig 2: Wound contraction on excision wound model on 1st day

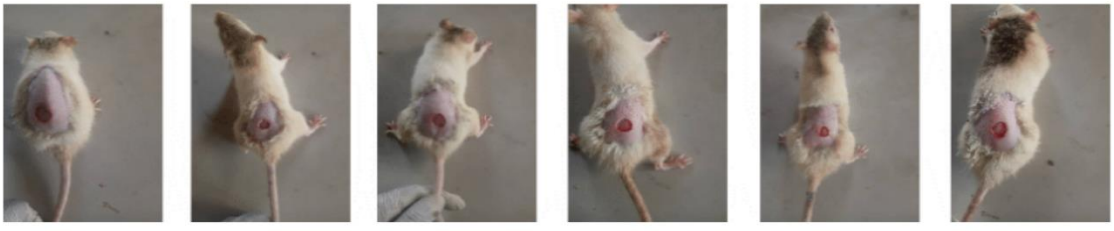


Fig 3: Wound contraction on excision wound model on 14th day

Wound Contraction

The results of the wound healing studies are presented in figure 4 below.

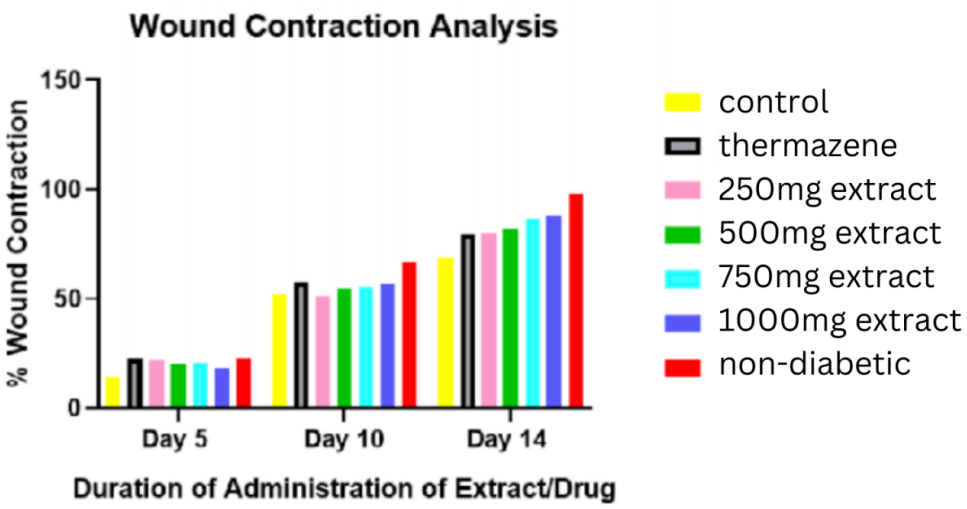


Fig 4: Wound contraction analysis of the control and extract treated groups

Further analysis of the wound contraction was done to determine the potency of the extracts and shown in Table 4.

Table 4: Percentage of wound contraction of control and extract-treated groups

DAY	Control	Non-diabetic	Thermazene	250 mg	500 mg	750 mg	1000 mg
5	14.00	22.67	22.67	22.00	20.00	20.67	18.00
	52.00	66.67	57.33	51.33	54.67	55.33	56.67
	68.87	97.93	79.33	80.00	82.00	86.67	88.00

Wound Healing

The wound-healing activities of the extracts were determined and represented in Figure 5.

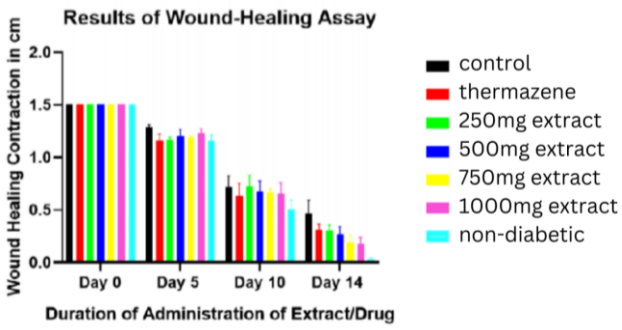


Fig 5: Healing effect of the dichloromethane-methanol extract *Pentaclethra macrophylla* seed pod in excision wound model on control, non-diabetic and extract treated groups.

The wound-healing activities are further displayed in Table 5.

Table 5: Table showing the wound healing contraction in centimetres of the control, non-diabetic and extract treated groups

	Control	Thermazene	250 mg extract	500 mg extract	750 mg extract	1000 mg extract	Non-diabetic

Day 0	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Day 5	1.29 ± 0.03	1.16 ± 0.06	1.17 ± 0.03	1.2 ± 0.06	1.19 ± 0.01	1.23 ± 0.04	1.16 ± 0.05
Day 10	0.72 ± 0.11	0.64 ± 0.11	0.73 ± 0.1	0.68 ± 0.1	0.67 ± 0.03	0.65 ± 0.11	0.5 ± 0.1
Day 14	0.47 ± 0.13	0.31 ± 0.05	0.30 ± 0.06	0.27 ± 0.07	0.2 ± 0.06	0.18 ± 0.07	0.031 ± 0.01

The fasting glucose blood sugar levels of the rats were determined at intervals to ensure that rats remained diabetic throughout the study duration. The blood sugar readings are contained in Table 6.

Table 6: Table showing the blood sugar readings for the various groups throughout the experiment showing the diabetic or non-diabetic group

	before induction	after induction	7th day	14th day
Group 1	4.7 ± 0.4	11.2 ± 0.7	11.5 ± 0.7	12.9 ± 1.1
Group 2	4.4 ± 0.4	11.3 ± 0.6	11.2 ± 1.0	11.8 ± 1.6
Group 3	4.8 ± 0.5	11.9 ± 0.6	11.3 ± 0.7	15.3 ± 1.4
Group 4	4.5 ± 0.2	11.2 ± 0.9	11.4 ± 0.8	14.0 ± 1.6
Group 5	4.1 ± 0.5	11.2 ± 0.3	11.6 ± 0.9	15.1 ± 2.3
Group 6	4.0 ± 0.5	11.4 ± 0.6	12.0 ± 0.8	14.9 ± 1.7

4 DISCUSSIONS

In recent years, scientific studies have been conducted to investigate the wound-healing potential of some species of the *Pentaclethra* genus, with promising results [11]. One of the major active components of *Pentaclethra macrophylla* seeds is tannins, which are known for their astringent and antimicrobial properties, making them useful in the treatment of wounds [12]. In a study by Lin et al., [13] on the anti-inflammatory and skin barrier repair activities of tropical applications of some plant oils, *Pentaclethra macroloba*; an Amazonian species demonstrated optimal activities on wound healing, reducing the healing time and improving the quality of the healed tissue. Another study by Simmons evaluated the wound healing potential of a topical anhydrous silicone base containing fatty acids from *Pentaclethra macroloba* oil in a patient with a diabetic ulcer with promising results [14]. Similarly, the antiulcerogenic potentials of the fermented aqueous extract of *Pentaclethra macrophylla* (Benth) seeds have been documented [15]. Phytochemical screening of the dichloromethane-methanol extract of *Pentaclethra macrophylla* seed pod revealed the presence of alkaloids, tannins, cardiac glycosides, steroids, and triterpenoids, with tannins and triterpenoids being the potential compounds responsible for the wound healing properties [11]. Tannins are a class of naturally occurring polyphenolic compounds widely distributed in plants [12]. They have astringent properties that enable them to bind to proteins, leading to the tightening of tissues and precipitation of proteins [16]. Tannins have been found to have various biological activities, including antioxidant, anti-inflammatory, antimicrobial, and wound-healing properties [17]. Studies have shown that tannins can enhance tissue repair and reduce inflammation, making them effective in promoting diabetic wound healing [18]. Tannins can also increase the expression of growth factors such as vascular endothelial growth factor (VEGF) and transforming growth factor beta (TGF-β), which are vital for tissue repair and regeneration [18]. The use of gas chromatography-mass spectrometry (GC-MS) for a detailed evaluation of non-polar bioactive chemicals in plant-based compounds is a well-accepted approach. The GC-MS analysis of the seed pod of *Pentaclethra macrophylla* showed the presence of twelve (12) chemical compounds, with five of them having pharmacological potential. These compounds include E-7-Octadecene with lubricant properties; and an analogue of this compound- 9-octadecene was recently reported to possess both antimicrobial and antioxidant activities [19]. Hexadecanoic acid, methyl ester, (Antibacterial activities) [20] and 9,12-Octadecadienoic acid (Z,Z)-, methyl ester with anti-inflammatory activity [21]. Other compounds such as 10-octadecenoic acid, methyl ester with both anti-

bacterial and antidiabetic activity [22] and 12-Methyl-E,E-2,13-octadecadien-1-ol with anticancer and antioxidant properties [23]. Anti-inflammatory activity is important, especially in diabetic wounds. Diabetic wounds are a serious complication of diabetes and can be difficult to manage due to the impaired wound healing associated with the condition. One of the major factors that can contribute to delayed healing in diabetic wounds is inflammation. Anti-inflammatory compounds are, therefore, of great importance in the management of diabetic wounds. Anti-inflammatory compounds can help reduce inflammation in diabetic wounds, promoting healing and preventing the development of chronic wounds [24]. Angiogenesis is the formation of new blood vessels, which is an important part of the wound healing process as it helps to deliver oxygen and nutrients to the wound site. Anti-inflammatory compounds have been shown to promote angiogenesis, which can help to speed up the healing process [25]. Cell migration is another essential part of the wound-healing process. Cells need to move into the wound site to promote healing. Anti-inflammatory compounds can enhance cell migration, which can help to speed up the healing process [26]. Collagen is the main structural protein in the skin and is essential for wound healing. Anti-inflammatory compounds can stimulate collagen production, which can help to strengthen the skin around the wound and promote healing [27]. Infection is also a significant risk factor for delayed healing and the development of chronic wounds. Anti-inflammatory compounds can help to prevent infection by reducing inflammation, which can create a less hospitable environment for bacteria to grow [24]. In the context of diabetic wound healing, emollients can play an important role in helping to moisturize the skin around the wound site, which can improve the overall health of the skin and promote healing. In diabetic wounds, the skin around the wound site can become dry and cracked, which can impair the healing process. Emollients can help to moisturize the skin, which can improve its overall health and promote healing. Moisturized skin is also less likely to crack, which can help to prevent the development of new wounds. Emollients also help to improve skin barrier function, which can help to prevent infection and promote healing. From the results obtained it can be seen that the extracts are more potent than the control at day 5, 10 and 14. The 750 mg and 1g extract were also significantly more potent at $P<0.05$ than Thermazene at day 14. These results further confirm that the seed pod of *Pentaclethra macrophylla* has a beneficial influence on the various phases of wound healing like fibroplasias, collagen synthesis, and wound contraction, resulting in faster healing. The extract treated excision wounds showed an increased rate of wound contraction, leading to faster healing as confirmed by the increased healed area when compared to the control untreated group. The non-diabetic rats healed the fastest with the 1000 mg extract treated group having a similar wound contraction activity. The control group treated with Thermazene can also be seen to have a very similar wound contraction activity with the 250 mg extract and 500 mg extract. Tannins in the extract are known to have astringent properties, which helps to tighten and contract the skin around the wound, leading to faster wound closure and contraction.

5. CONCLUSION

This study highlights the wound healing potential of the dichloromethane-methanol extract derived from the seed pod of *Pentaclethra macrophylla*. The extract proved significantly effective in promoting wound contraction and accelerating the healing process compared to control groups. These observed effects are likely attributable to the presence of phytoconstituents like triterpenoids and tannins within the extract.

Conflict of Interest

The authors declare that there is no conflict of interest.

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Authors Contributions

Johnson-Ajinwo conceptualized/designed the study and wrote the manuscript. Ikechukwu carried out the research under the supervision of Johnson-Ajinwo.

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