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ORIGINAL RESEARCH

Phytochemical Profiling and Wound Healing Activity of *Gigantochloa apus* Liquid Smoke in *Mus Musculus*

Desi Natalia Tarigan[1], Yenni Gustiani Tarigan[2], Vinsa Cantya Prakasita[1], Aniek Prasetyaningsih[1], Baxter HK Kachingwe[3]

[1]Faculty of Biotechnology, Duta Wacana Christian University, Yogyakarta, Indonesia; [2]Faculty of Pharmacy and Health Sciences, Sari Mutiara Indonesia University, Medan, Indonesia; [3]Pharmacy Department, Kamuzu University of Health Sciences, Blantyre, Malawi

Correspondence: Baxter HK Kachingwe, Pharmacy Department, Kamuzu University of Health Sciences, Mahatma Ghandi Road, Private Bag 360, Chichiri, Blantyre, Malawi, Tel +2650994400776, Email bkachingwe@kuhes.ac.mw

Purpose: Rope bamboo (*Gigantochloa apus*) is traditionally used for medicinal purposes, and extracts from stem leaves and shoots have been shown to possess antioxidant and anti-inflammatory activity. Thus, this study looked at the potential compounds present in and the usefulness of Rope bamboo liquid smoke preparations in the wound healing process in mice.

Methods: The fingerprinting of the liquid smoke was done by liquid chromatography-mass spectrometry. In-vivo experiments were conducted to observe the diameter and percentage of wound healing in mice for 14 days using topical formulations containing liquid smoke concentrations of 100%, 50%, 25%, positive control and negative control. Statistical analyses were conducted using the Kruskal–Wallis test and Spearman correlation.

Results: The phytochemical fingerprint showed the presence of alkaloids, flavonoids, vitamins, phenols, and lipids. The 100% undiluted liquid smoke accelerated wound healing faster compared to 50% and 25% dilutions. The differences in wound diameters were statistically significant across treatments having a *p-value* of 0.020 and dose-dependent ($p = 0.029$).

Conclusion: Liquid smoke acceleration of the wound healing process was dose-dependent compared to controls. This dose-dependency indicates that the wound healing effects were probably due to the anti-inflammatory, antioxidant, and antimicrobial activities of the elucidated constituents of Rope bamboo liquid smoke.

Keywords: dose-dependent, wounds healing, *Gigantochloa apus*, Rope bamboo, liquid smoke, mice

Introduction

Wounds are any disruption of the integrity of skin, mucous membrane, or organ tissue that may cause damage or loss of part of body tissue.[1] Wounds are caused by animal bites, sharp objects, burns, gunshots, and fractures among others.[2] Wound care aims to promote healing while preventing microbial contamination, as well as preventing any further damage to the tissues on the wound.[1,3,4] A wound that does not heal within thirty days is no longer classed as acute but chronic.[5] The use of antiseptics in wound care is well known and the antiseptics commonly used include povidone-iodine, chlorhexidine, polyhexanide, and octenidine preparations.[1,3,6] Povidone-iodine-containing antiseptics are the most commonly used and are not recommended for patients with thyroid, kidney failure, burns with an area of more than 20%, and infants younger than 6 months.[7]

Wound healing has three stages, the first is the inflammatory phase, which is characterized by the presence of rubor (redness) on the wound and tissue as well as tissue oedema (tumour), dolour (pain), and warmth (colour). The purpose of the inflammatory phase is to prevent bleeding through vasoconstriction, which can result in blood clots or scabs. This phase occurs in 0–3 days. The second phase is proliferative; this phase reduces the lesion area by contracting fibroplasia to form an epithelial barrier to activate keratinocytes. The last stage is remodelling, this stage restores normal tissue

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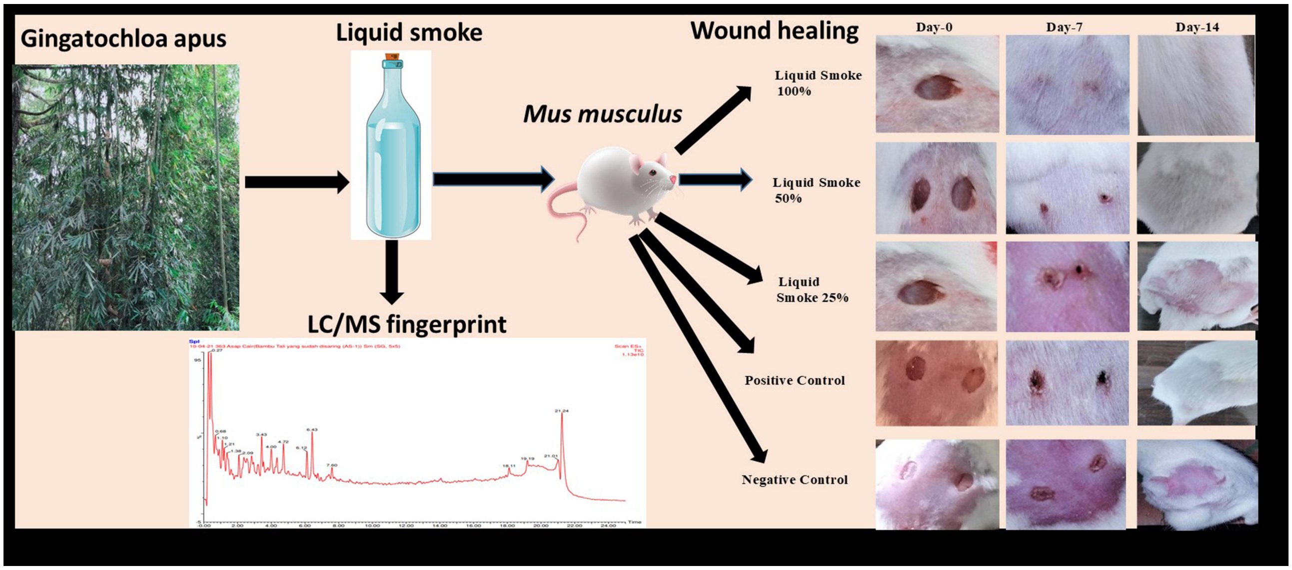
Graphical Abstract



structure and granulation tissue is gradually repaired, forming cellular and vascular scar tissue and showing a progressive increase in the concentration of collagen fibres.[8]

Globally there are over 1600 species of bamboo and the two largest bamboo forests are in China and India. Indonesia has approximately 21,000 km^2 of bamboo forest containing about 160 bamboo species, 88 of which are exclusively found in Indonesia.[9,10] In Indonesia, the most common bamboo species include *Gigantochloa apus* (Tali or Rope Bamboo), *Dendrocalamus asper, Gigantochloa atter, Gigantochloa pseudoarundinacea, Gigantochloa aya, Gigantochloa galuh*, and *Gigantochloa nigrocillata*.[9–13]

Rope bamboo (*Gigantochloa apus*) belongs to the Bambusoideae (J.A & J.H Schultes) Kurz subfamily within the Poaceae family. It is in the monocotyledonae class with the order Poales and belongs to the angiosperms subdivision plants within the spermatophyta division. Rope bamboo has a dark green stem that can be straight or bent. Rope bamboo can reach a height of up to 10 m with a stem diameter of 2–4 cm, the length of the bamboo rope leaves ranges from 20 to 30 cm with a width of 3–4 cm.[12,14–17] Rope bamboo has long been used for structural, nutrition, and medicinal purposes with active nutrients and minerals that can be extracted from the roots, stems and bamboo shoots, all of which have antioxidant, anti-bacterial, anti-viral, and anti-aging properties.[9,10,18–21] A population survey in Indonesia showed that the population uses Rope bamboo roots for cough, hypertension, breast cancer diabetes, and liver problems. Culms are used for heartburn and skin rejuvenation.[14] Antioxidant activity of Rope bamboo shoots and leaf extracts has been demonstrated in-vitro using 2,2-diphenyl-1-picrylhydrazyl (DPPH).[22,23] Rope bamboo extracts have also been shown anti-inflammatory activity by decreasing the levels of pro-inflammatory interleukin 7(IL-7) and increasing the levels of anti-inflammatory interleukin 10 (IL-10) in rabbits.[24] Ethanolic and methanolic extracts of Rope bamboo leaves inhibited the growth and replication of *E. coli*, with methanolic extract showing the highest antibacterial activity.[25]

Liquid smoke is the result of the pyrolysis of plants or wood at a temperature of about 400°C. Liquid smoke is obtained from the condensation of vapours after incomplete combustion of materials containing lignin, cellulose, hemicellulose, and other carbon compounds involving decomposition reactions that are influenced by heat, polymerization, and condensation.[26–28] Liquid smoke has many advantages that include ease of application, relatively quick and easy production process, less polluting to the environment, the product characteristics aroma, colour, and taste and contains minimal amounts of carcinogens such as polycyclic aromatic hydrocarbons.[28–32]

Rope bamboo liquid smoke should help in wound healing as it is traditionally used as a skin rejuvenator and a treatment for several ailments in humans and animals. The wound healing effects should be possible due to the different chemical classes discovered in various parts of these plants that suggest a richness in potentially medicinal use due to the antioxidant, anti-bacterial, and anti-inflammatory activities essential in the wound healing process. In addition, the less carcinogenic and environmentally friendly nature of liquid smoke preparations led to this study aimed at determining whether Rope bamboo liquid smoke can help to accelerate wound healing in mice and looking for the phyto-compounds present that may be responsible for the activity.

Materials and Methods

Plant Material

Rope bamboo culms together with branches and leaves were collected from a Rope bamboo plantation at Balai Penerapan Standar Instrumen Lingkungan Hidup dan Kehutanan (BPSILHK), Aek Nauli, North Sumatra under the guidance of Dr Wanda Kuswanda, S.Hut, M.Sc. and Erwin Patriot Manik. Identification of species was done at the National Research and Innovation Agency (BRIN) of Indonesia by botanist Dr. Ratih Damayanti, S.Hut., M.Si. and voucher no. B-2955/II.6.2/IR.01.02/8/2024 was archived i9n BRIN.

Animals

Male mice (*Mus musculus)* of approximately 2 months old weighing between 25 and 30 g were sourced from Tikus Lover Jogja, Yogyakarta City, Special Region of Yogyakarta, Indonesia 55198. Males were used to control for the effects of oestrogen on wound healing that may be present in female mice.[33–35] The mice were housed individually at a controlled temperature of between 20°C and 24°C and relative humidity of approximately 60% and fed with standard rodent chow, water was provided ad libitum. The mice had to adapt to a new environment for 5 days to reduce stress before experiments and were euthanized at the end of experiments. The experimental conditions were reviewed and approved by the Health Research Ethics Commission, Faculty of Medicine Duta Wacana Christian University (No. 1328/C.16/FK/2021). The National Guidelines on Health Research Ethics. 2011. Health Research Ethics Committee, the Ministry of Health, Republic of Indonesia were used in the care of animals.

Chemicals and Reagents

The following chemicals were used: Povidone-iodine 10% (Betadine; Kimia Farma Tbk, Jakarta, Indonesia), Chloroform (Bratachem, Yogyakarta City, Indonesia). Food and drink for mice were obtained from Surya Sains Indonesia. Aquadest was obtained from the Duta Wacana Christian University Laboratory. High-performance liquid chromatography (HPLC) grade ethanol, acetonitrile, and formic acid were purchased from Merck Germany.

Equipment

Liquid smoke furnace, bucket, funnel, measuring cup, test tubes, pipette, pro pipette, scalpel, tweezers, biopsy punch, mouse cage, cage cover, callipers, feeding and drinking containers for mice.

Liquid Smoke Production

The production of liquid smoke was done at the Balai Penerapan Standar Instrumen Lingkungan Hidup dan Kehutanan (BPSILHK), Aek Nauli, North Sumatra. Fresh Rope bamboo was cut, and 50 kg of Rope bamboo cuttings were neatly packed into the liquid smoke-making furnace and burnt at 400°C for 6–8 hours using fuel made of Rope bamboo as well. After burning, the resulting liquid smoke was filtered using zeolite, activated charcoal, filter paper, quartz sand, and palm fiber composite filter to reduce PAH, larger particulates and adjust flavour and colour.[36,37]

Liquid Chromatography Mass Spectrometry

The liquid chromatography mass spectrometry (LCMS) profiling was conducted at Gajah Mada University, Yogyakarta. The LCMS scan was carried out in ESI positive mode and a mass range of 100–1300, the mobile phases used were

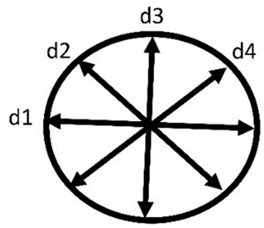


Figure 1 The method used in wound diameter measurement.

0.01% formic acid in water and 0.01% formic acid in acetonitrile. The samples were dissolved in ethanol and then filtered with a 0.22µm Millex-GP syringe filter, and then 5µL was injected at a source temperature of 500°C and a voltage of 30V. Separation was achieved using a normal-phase column.

In-Vivo Test of Liquid Smoke's Wound Healing Potential

The study was a post-test-only control group design. Twenty-five male mice were allowed to adapt to a new environment for 5 days to reduce stress.[38] The superior dorsal caudal surfaces of mice were shaved before wound excision using the biopsy method with a tool size of 4mm and splinted. Mice were divided into five groups containing five mice. Each group received wound treatment by topical application of formulations of liquid smoke 100%, 50%, 25%, povidone-iodine 10% as positive control and distilled water as negative control for 14 days. The 50% and 25% preparations were diluted with distilled water. The concentrations of 100%, 50% and 25% were chosen to delineate any dose dependency due to chemical constituents as the two doses are at half-dose strength of the subsequent.

Wound Healing Activity Measurement

The treatment was given twice a day at 09.00 and 15.00 West Indonesian time. Observations were carried out once a day at 15.00 for 14 days. The wound size was determined using a calliper by measuring the four diameters of the wound as shown in Figure 1.[39]

The average diameter value was calculated using the formula as below;

$$dx = \frac{d1 + d2 + d3 + d4}{4}$$

where *dx* is the wound diameter in a single day and d (1,2,3,4) are wound diameters measured in four directions in millimeters (mm).

The estimation of the percentage of wound healing (*p%*) was done using the following formula;

$$P\% = \frac{\mathrm{d0} - \mathrm{dp}}{\mathrm{d0}} \times 100\%$$

where *d0* is the initial diameter and *dp* is the daily diameter after initiation of treatment.

Clinical Wound Healing Stage Assessment

Visual observation of clinical symptoms was done for 14 days, with a value of 0 given when a wound is completely healed and a value of 1 when a wound was in the proliferative stage and where a wound had started to dry and there was granulation tissue and ultimately epithelialisation; score 2 for the inflammation stage where a wound is still fresh but clotted and has erythema, warmth, and edema.[8] During the treatment period, the number of mice with wounds in various stages of healing was plotted on a histogram.

Data Analysis

In this study data analysis was done using Statistical Package for the Social Sciences (SPSS) version 21. The Shapiro-Wilk statistical test showed that the data was not normally distributed ($p < 0.05$). Kruskal Wallis was used to determine within-group and between-group differences in wound healing. The correlation of doses and wound clinical stages was assessed using the Spearman test. Analysis of LCMS fingerprinting results was done using MassBank Databases version 2.1.8.

Results

LCMS Fingerprinting

The compounds were identified from spectra (Supplementary Figure 1) extracted from total-ion chromatogram (Supplementary Figure 2) of rope bamboo liquid smoke including alkaloids such as cotarnine, harmine, pseudojervine, and hydrocotarnine; flavonoids including methylcatechin and cianidanol; and oleic acid, benzoic acid and niacinamide (Table 1).

Wound Healing Effects

The wound healing activity of Rope bamboo liquid smoke is shown in Figure 2 by percentage of wound diameter. The preparation with a concentration of 100% achieved wound healing earlier than the other lower concentrations of the liquid smoke preparations and controls. On the 9th day of treatment, 100% liquid smoke treatment group showed complete wound healing, while for treatment groups of 50%, 25% liquid smoke, negative and positive controls experienced complete recovery on day 11. This shows that wound treatment with a 100% concentration of liquid smoke from Rope bamboo can accelerate the wound-healing process in mice. Kruskal–Wallis *H*-test showed that there was a statistically significant difference in wound healing achieved in all treatment groups ($X^2(4) = 11.615$). The largest mean rank value was for a dose of 100% at 224.16, followed by 187.75 and 172.76 mean rank values for 50% and 25%, respectively, and a *p-value* of 0.020. This showed that the higher the concentration of liquid smoke used, the faster the wound-healing process.

The visual clinical wound healing stage assessments in mice (Figure 3) show the effect of liquid smoke on the three stages of the wound healing process inflammation, proliferation, and healing. In groups with 100% and 50% liquid smoke treatment, mice experienced inflammation for a shorter duration than other treatments, which only lasted 2 days. Further, in the 100% liquid smoke treatment group, the wounds proliferate from the 3rd day to the 8th day and heal by the 9th day. However, healing occurs in two of the five mice by day 7 while the rest heal by day 11. At day 10, four out of the five mice heal completely in the 50% liquid smoke treatment group. No single mice achieved healing by day 10 in the 25% liquid smoke treatment group. Spearman correlation test shows a correlation between multilevel doses with a clinical wound healing staging observed (correlation coefficient = 0.113), with a *p-value* of 0.029. The higher the concentration of liquid smoke, the shorter the time for wound healing processes observed in mice. Clinical visualization of wound healing (Figure 4) clearly shows the differences in

Table 1 Chemical Constituents of Rope Bamboo Liquid Smoke Identified from Fingerprinting

Compounds	Relative Abundance (%)	Retention Time (h)	M+H (m/z)
Alkaloid			
Hydrocotarnine	65	2.077	222.3237
Cotarnine	6	2.077	237.2666
Pseudojervine	15	3.430	588.6815
Harmine	7	4.332	213.2930
Flavonoid			
Cianidanol	5	0.911	291.2584
3’-O-methylcatechin	5	3.430	305.3579
Other			
Oleic acid	5	0.672	283.3316
Niacinamide	29	1.370	123.1876
Benzoic acid	48	2.817	123.1226
Ferulic Acid	5	3.251	195.3620
Phytosphingosine	14	7.609	318.5479
Gentiopicroside	5	7.609	357.3392

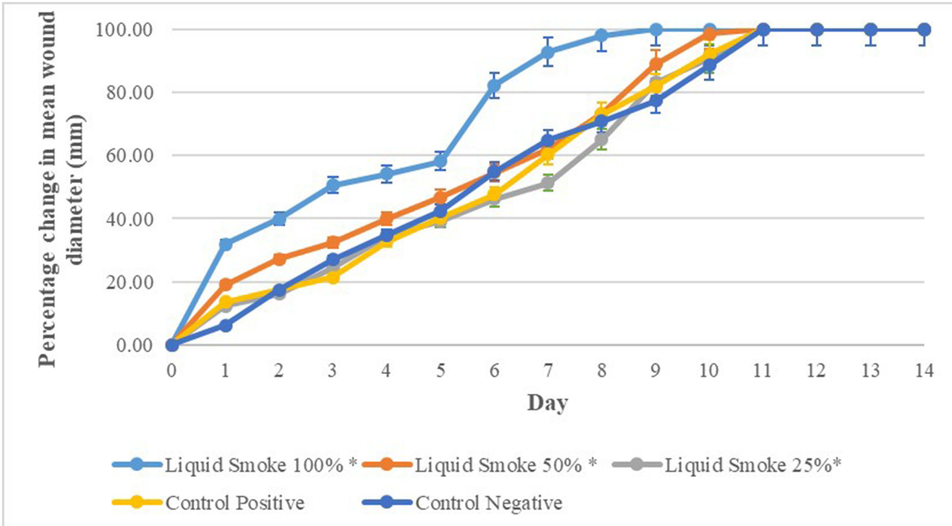


Figure 2 The percentage of wound healing over time in treatment and control groups (*p = 0.29).

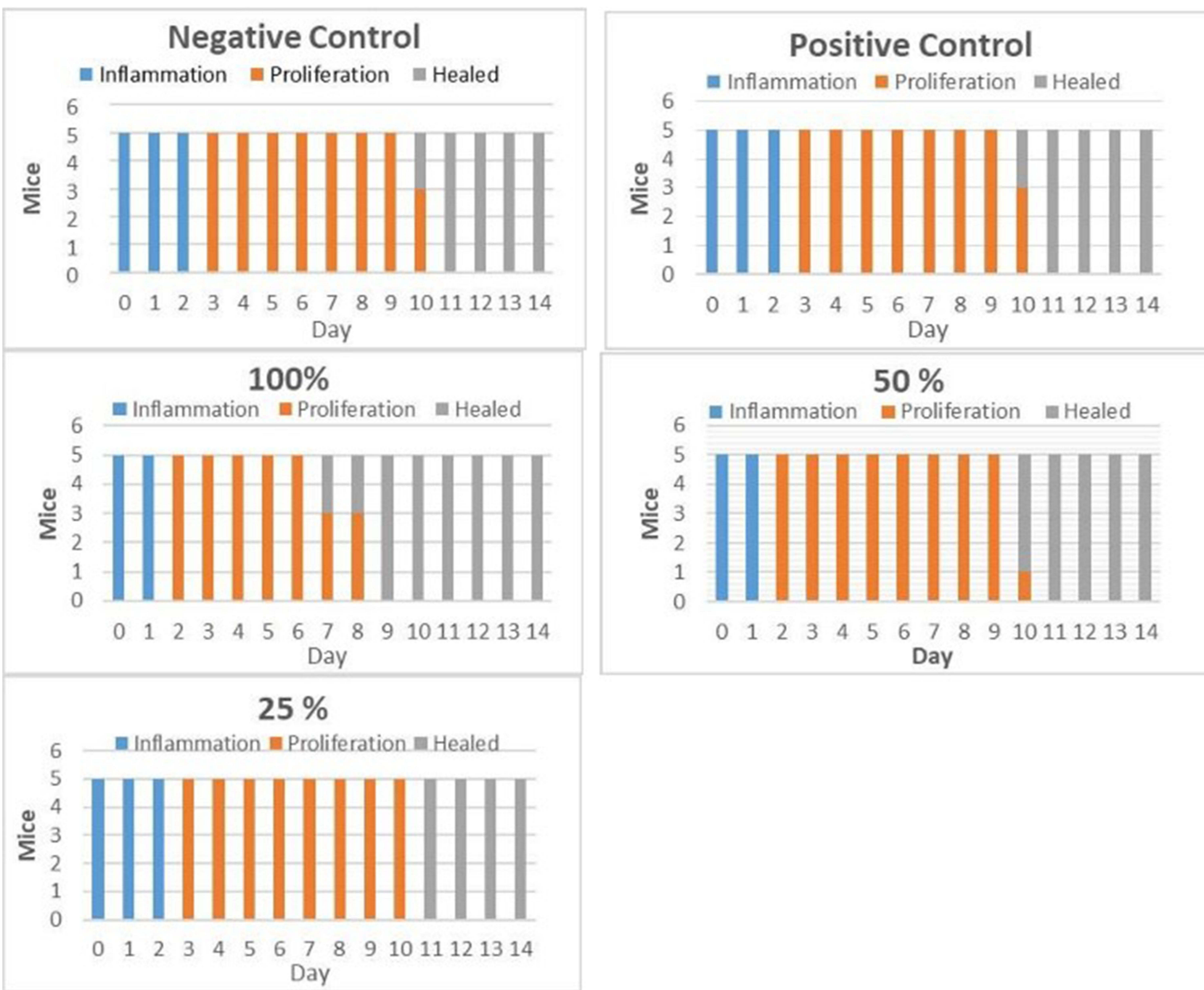


Figure 3 Showing the day of onset and duration of clinical stages of wound healing during the treatment period.

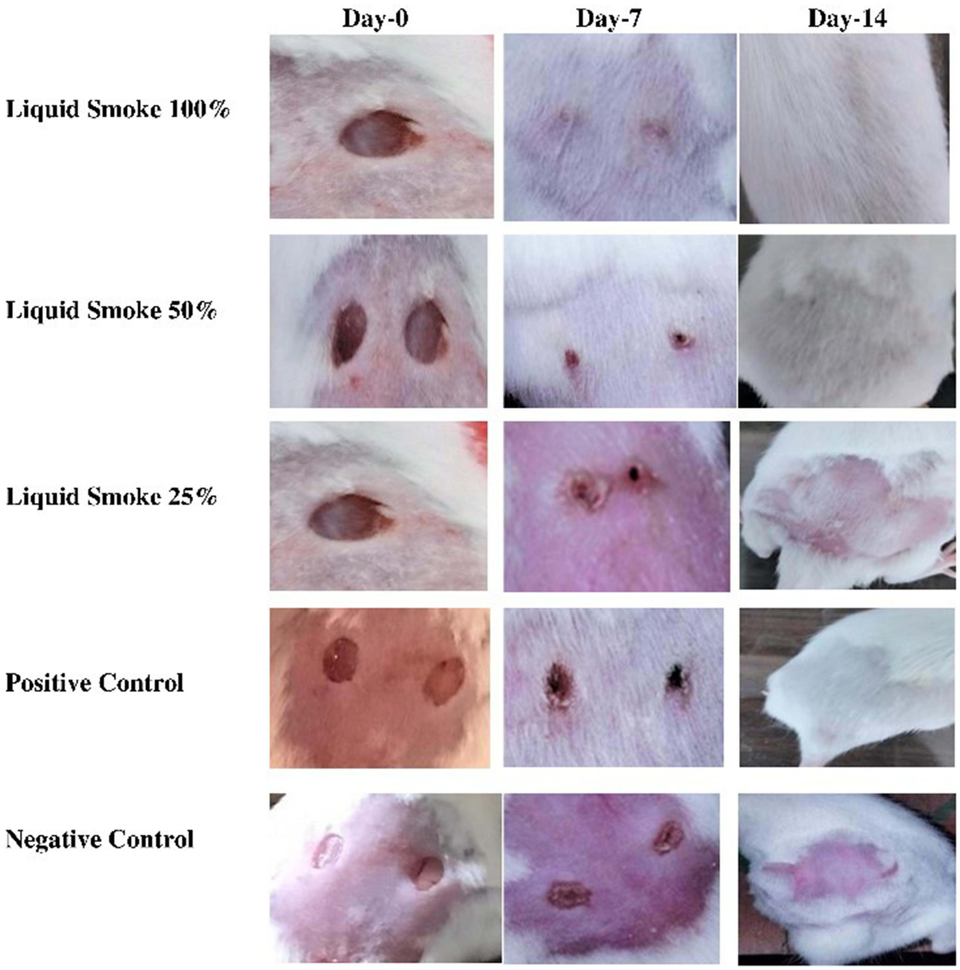


Figure 4 The wound diameter change at the onset, midway, and last day of treatment.

wound changes among the treatment groups. Wounds treated with 100% liquid smoke heal very quickly. The wound closes within 7 days, and new skin cells multiply and grow throughout the wound. Fibroblastic stage – collagen, the protein fibers that give skin its strength, begins to grow within the wound. The wounds heal completely within 2 weeks and have a complete covering of new hair growth. Meanwhile, the wounds for the treatment group of 50%, 25% liquid smoke, positive control, and negative control still looked a little red on day 7, and by day 14, the mice's skin had incomplete healing and hair growth.

Discussion

This study is the first to chemically characterize Rope bamboo liquid smoke and test for its wound-healing potential. The results show that Rope bamboo liquid smoke contains flavonoids alkaloid, phytosphingosine, oleic acid, benzoic acid, vitamins, and other compounds that are possibly responsible for the observed dose-dependent acceleration of the wound healing process in mice. The findings of this study aligned with earlier findings of studies looking at liquid smoke preparation from other plants or plant parts, which have indicated the presence of organic acids, phenolic compounds, flavonoids, alkaloids, and other compounds.[37,40–42]

Other studies have found similar wound healing effects when using liquid smoke preparations from plant materials such as rice husk and coconut shells.[43–46] One study found that plants extract liquid smoke containing alkaloids and flavonoids, which are natural antioxidants and can act as antibacterials to prevent infections caused by bacteria.[47] Another study also found that flavonoids and alkaloids can function as anti-inflammatory and therapeutic agents in tissue repair.[48] Alkaloids and flavonoids can also function as analgesics.[49,50] A review study stated that alkaloids can inhibit the phase of the cyclooxygenase pathway in the arachidonic acid metabolic pathway in prostaglandin biosynthesis.[51] Meanwhile, according to Ferraz et al (2020), the mechanism of flavonoid analgesia is by inhibiting the cyclooxygenase enzyme, which plays a role in pain-forming mediators in the synthesis of prostaglandins.[52] Flavonoids can also inhibit the production of cytokines, free radicals, and other enzymes that work in inflammation.[53] A separate study stated that flavonoids act as anti-inflammatories by inhibiting capillary permeability and inhibiting arachidonic acid metabolism and lysosomal enzyme secretion from endothelial cells and neutrophil cells.[48,53] This study has shown that liquid smoke from Rope bamboo has alkaloids and flavonoids that can help accelerate the wound healing process. Alkaloids function as anti-inflammatory by reducing the volume of oedema in the area of inflammation and affecting migration and leukocytes in the blood and exudate, alkaloids can inhibit the activity of enzymes that play a role in the inflammatory process so that inflammation does not progress.[54] A study in China found that alkaloids from Chinese medicinal herbs have anti-inflammatory, analgesic, antitumor, anticonvulsant, diuretic, and antiarrhythmic effects, among which the anti-inflammatory effect is very prominent and commonly used in the treatment of rheumatoid arthritis, ankylosing spondylitis, and other rheumatic immune diseases.[55] A study about plant wound healing conducted in Brazil using the bark of Mimosa tenuiflora (Wild). Poiret (*Leguminosae family*) found that extracted fractions of *M. tenuiflora* bark containing flavones (including sakuranetin) demonstrated great antinociceptive and anti-inflammatory activities.[56]

The flavonoids found in Rope bamboo liquid smoke in this study were cotarnine, hydrocotarnine, pseudojervine and harmine. Cotarnine has been shown to have local haemostatic activity in vivo, and hydrocortisone has been found to increase the chemotactic factor interleukin 8 IL_8 in animal colitis models, having anti-inflammatory, sedative, anti-tussive and analgesic actions.[57–59] Pseudojervine has potential application in hypertension, diabetes, cancer and rheumatic pain and is thought to act through its interaction with ion channels, inhibition of enzymes, cytotoxicity and antimitotic activity,[60–63] these activities also have potential for pseudojervine to act as an antiseptic that prevents microbial contamination and growth on wounds. Studies have illustrated the potential of Harmine in promoting wound healing through anti-inflammatory actions and enhancement of tissue regeneration.[64] Cianadiaol has antimicrobial, anti-inflammatory, anti-oxidant and endothelial cell-protecting properties, and 3'-O-methylcatechin inhibits inflammatory modulators such as; interleukin-6 (IL-6), inducible nitric oxide synthase (iNOs), and cyclooxygenase 2 (COX-2).[65–68] It has also been established that benzoic acid can inhibit the synthesis of fungal folic acid so that it functions as an antifungal that can reduce inflammation and tissue damage so that the task of neutrophil cells is lighter in phagocytosing foreign microorganisms and enable wounds to heal quickly.[69] According to Wohlrab J, Kreft D (2014), niacinamide has antimicrobial, antipruritic, sebostatic, photo-protective, and vasoactive functions, in addition to its skin brightening properties.[70] Oleic acid also exhibits anti-inflammatory through AMPK/MAPK/PI3K, MAPK/Nrf2/PPARγ, oxidative phosphorylation, histone acetylated and Lys 310 acetylated/SIRT1 pathway, and tissue-protecting effects through a reduction in apoptosis, reduction in reactive oxygen species (ROS), interleukins (IL-8, IL-6), tissue necrotic factor alpha (TNFα), increases in PPARγ pathway activities and by the increased presence of oleic acid in the cell wall of both immunocompetent and epithelial cell wall enhances cell survival.[71] Therefore, oleic acid plays a role in reducing inflammation and maintaining healthy cells in wounds that accelerate wound healing.[72] Ferulic acid can accelerate wound healing, reduce inflammation through similar intracellular pathways, enhance angiogenesis and protect skin structures.[73] Phytosphingosine is a potential treatment for acne vulgaris due to its anti-inflammatory, antibacterial, antifungal and skin-protecting effects. It has been shown to exert its anti-inflammatory action by inhibiting the activation of the NF-κB and NLRP3 signalling pathways. Phytosphingosine also increases the expression of the classic Tight-junctions (TJs) proteins including ZO1, Occludin and Claudin-3, thereby enhancing the effectiveness of the tight junction barrier.[74–76] Thus phytosphingosine can play a role in wound healing by reducing inflammation, preventing microbial growth and enhancing epithelial tissue regeneration and integrity. Gentiopicroside possesses anti-inflammatory, anti-oxidant and anti-microbial activity, and promotes the proliferation of fibroblasts by increasing basic fibroblast growth factor receptor 1 (bFGFR1) and proliferating cell nuclear antigen (PCNA) (Gentiopicroside injection promotes the healing of pressure injury wounds by upregulating the expression of bFGFR1).[77] The various mechanisms by which alkaloids, flavonoids and other compounds found in rope bamboo liquid smoke explain the wound healing acceleration in mice. The constituents acted by shortening the inflammation phase, enhancing epithelialization, increasing vascularization, and protecting wounds from microbial and oxidative stress, resulting in faster wound healing.[78,79]

The wound-healing acceleration activity by Rope bamboo liquid smoke shown in this study is supported by the potential mechanisms of the phytochemical constituent found in other studies, and the dose-dependent nature of these wound-healing effects indicates a stronger association between the chemical components and wound-healing effects. The fact that diluted treatments showed lesser effects than the undiluted underscores the role these constituents played in the shortening of the wound healing process.

This study did not involve histological and biochemical evaluations of wound healing and the phytochemical profiling was not followed by structural confirmation. Future studies are needed to confirm the phytochemicals and mechanisms involved in wound healing acceleration activity of Rope bamboo liquid smoke.

Conclusion

The results from the wound diameter measurement and visual clinical staging of the wound healing process illustrate the dose-dependent wound-healing acceleration of wound healing by Rope bamboo (*Gigantochloa apus*) liquid smoke in mice. The liquid smoke from Rope bamboo was found to contain several alkaloids, flavonoids and other compounds that can promote and accelerate the healing process of external wounds. These wound healing effects are achieved through the anti-inflammatory, antioxidant, antimicrobial, tissue protection, promotion of angiogenesis and epithelialization of wounds of Rope bamboo liquid smoke constituents. The most effective liquid smoke concentration in helping and speeding up the wound healing process in mice is 100% undiluted liquid smoke. Further studies need to look into the side effects of topically administered rope bamboo liquid smoke by performing histopathological and other tests. In addition, there is a need to study the effectiveness of Rope bamboo liquid smoke in accelerating healing in different types of wounds.

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Disclosure

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