



## **Wound Healing Efficacy of Guava Leaf Extract**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. Authors SBD is the principal investigator who designed the study. Authors MLO, KRR, MTAR, JIASV, MKST and ZBT performed the quantitative analysis of the study. All authors read and approved the final manuscript.*

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### **ABSTRACT**

A wound is a break in the continuity of the skin. The body's response to injury and the restoration of the same is healing. Wound healing is a biological process that is initiated by trauma and often terminated by scar formation. In this research, guava leaf extract was used as antiseptic and its efficacy was tested to commercially available products. The result revealed that all mice which received guava leaf extract formed scar earlier as compared to povidone iodine and PNSS. Since maturation phase which also refers to remodeling phase is responsible for the new epithelium and final scar tissue formation, and as the development of these completes the complex process of wound healing, the researchers suggest that the use of guava leaf extract in comparison with povidone iodine and PNSS when it comes to wound healing is the most affordable in treatment and promoting normal and more rapid wound healing.

**Keywords:** Wound healing; guava; leaf extract.

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## 1. INTRODUCTION

Biological based therapies consist primarily of herbal therapies or remedies, botanicals, and dietary supplements. Herbal remedies are a major component of all indigenous forms of medicine; prior to the development of pharmaceuticals at the end of the nineteenth century, people everywhere in the world relied on materials from nature for pain relief, wound healing, and treatments of a variety of ailments [1].

A wound is a break in the continuity of the skin. The body's response to injury and the restoration of the same is healing. Wound healing is a biological process that is initiated by trauma and often terminated by scar formation. Thus, healing is essentially a survival mechanism and represents an attempt to maintain normal anatomical structure and function [2].

Wound healing is a complex process involving many physiological events [3]. Healing of wound is a sign of growth and an important biological phenomenon. Whether acute or chronic, wounds can compromise an individual's wellbeing, self-image, workability and freedom. Skin wounds affect the quality of life of patients significantly and are considered as one of major causes of physical disability. The impact of wounds on physical, social and financial aspect of a person's life necessitate good wound management not only for the individual but for the community as well. For wounds to rapidly heal, complications from colonization of microorganisms must be avoided [4]. Topical disinfection and appropriate wound dressings are important to prevent wound infection. Systemic antibiotics are necessary only in systemic infections [5]. Antiseptics, with a broader spectrum of antimicrobial efficacy, lower risk of antibiotic resistance development, and minimal collateral damage to host tissues, are important alternatives to control the bioburden in wounds [6].

In rural communities, researchers observed that some therapies are usually initiated at health facilities for care and management of wound to promote healing and avoid infections and complications. In the health care centers, antisepsis and wound healing applications are done. Of the many antimicrobial agents available, iodophor-based formulations such as povidone iodine have remained popular of use [7]. Also, when used in daily regimen of ulcer care, Povidone-iodine can reduce the level of infection and promote healing [8]. Povidone-

iodine is promoted in wound care as a means of preventing and treating infection in a range of acute and chronic wounds [9]. The main effect of betadine solution is to eradicate bacterial seeding from the surgical wound and to achieve intraoperative disinfection [10].

Commercially available remains to be popular and commonly used due to its favorable efficacy and tolerability. It has a broad spectrum of activity, ability to penetrate biofilms, lack of associated resistance, anti-inflammatory properties, low cytotoxicity, good tolerability and no negative effect on wound healing. These factors have been observed and cited as important in clinical practice. However, there are cases and most often than not, patients prefer to simply stay at home and nurse themselves to care for their wounds. This is a common observation particularly when wounds are simply uninfected and do not require complicated and sophisticated treatments. Due to limited resources to buy medicines and sometimes access to medical treatments, they choose to stay at home and resort to local herbs and plants for treatments [7].

The wound healing effects of guava had been evaluated in several studies proving its effectiveness as supported by published reports. However, povidone iodine had been the most popularly used commercially-based antimicrobial formulation for wound healing. Local management of wounds that are considered to have poor potential for healing remains elusive [11]. Moreover, the researchers had come up with this study as they found out that comparing these two treatments is interesting to investigate. The present study is aimed at evaluating the antimicrobial potential of leaf extracts of guava as compared to povidone iodine for wound healing in mice.

In this study, it aimed to evaluate the ability of guava leaf extracts in comparison with povidone iodine solution to induce the wound healing in laboratory mice.

## 2. MATERIALS AND METHODS

All the materials needed for the study were brought into the facilities of the University of Eastern Philippines College of Veterinary Medicine (UEP-CVM). Commercially prepared povidone iodine (Betadine at 10% solution) and distilled water/plain NSS were procured from a drugstore. Processing of guava leaf extract and the induction and treatment of experimental

wound incision to laboratory mice was done at the UEP-CVM laboratory facility. The same procedure and process of wound application of the treatments was followed for all animals under study.

## 2.1 Collection and Preparation of Guava Leaf Extract

Young guava leaves were collected within the vicinity of the University of Eastern Philippines, Catarman, Northern Samar. The leaves were washed thoroughly in a running tap water and placed in a strainer to drain the water. The juice from the leaves were extracted and stored in a tight container until ready for use.

The Institutional Care and Use Research Committee, composed of diverse professionals in their respective fields concurred unanimously to proceed with the research. The committee reminded the researcher to follow the prescribed protocol in the conduct of the research. The committee is composed of the eight (8) professionals from different sectors, that is, academe, religious, research, and private sectors.

BALB/c laboratory mice of either sex having a homogenous characteristics weighing approximately 20-30 grams from 4-6 weeks' old were purchased from the University of the Philippines College of Public Health Central Animal House and were used for the study. They were taken from UP Manila animal research laboratory, housed in cages individually and maintained under standard conditions at the University of Eastern Philippines College of Veterinary Medicine Laboratory Room. They were fed on standard pellet with water *ad libitum* maintained at 12 hours of light and 12 hours dark cycle for 12 days in the departmental laboratory for acclimatization. All the mice were assessed for physiological parameters and only those apparently healthy were considered fit for surgical procedure, thus were considered in the study.

Animals were divided into three (3) groups, consisting of six (6) mice each. Every group were housed individually in the laboratory cages. They were given free access to standard feeds and drinking water and were maintained on a 12-hour light/dark cycle.

Group I: This were treated with pure guava leaves extract (100%).

Group II: This were treated with standard povidone iodine (Betadine 10% solution).

Group III: This were treated with normal saline solution, the control group.

## 2.2 Guava Leaf Extracts

Young leaves collected and washed with water were subjected for extraction. Extraction was carried out using an electric juicer to obtain a liquid form of extract. The extract was filtered using a mesh or muslin cloth. Extracted guava juice was placed in a sterile container and stored in the body of the refrigerator in order to preserve the freshness and the active particles present in it. In order to assure that the extract is fresh, as much as possible, a daily collection and extraction of leaves was done. Treatment was given once a day simultaneous with povidone iodine and distilled water solution.

## 2.3 Anesthesia and Wound Creation

Surgical procedure was aseptically performed in the animal facility operating room of the College of Veterinary Medicine. Eighteen (18) mice were divided into three (3) groups with six (6) laboratory animals in each. All animals in each group was anesthetized by intraperitoneal (IP) injection of Zoletil 50 at 0.01 mL dosage before the incision. A 2 cm full-thickness skin wound was incised from the dorsum of the laboratory mice. Incision was made through the skin and cutaneous muscle at a distance of 2 cm from the midline on one side of the depilated back of the mice aseptically. A single incision was made to each of the eighteen (18) mice. Using aseptic surgical technique, a 2 cm length and in full-thickness incision was made using a number 10 scalpel blade. On the other hand, a caliper was used as a guide on the incision length. Hemorrhage of wound was controlled by compression using sterile gauze. The wound incision was left unsutured for secondary intention healing for 24 hours. The day of wound creation marked the day 0 of the experiment. Application of the formulated test material commenced after 24 hours post-wounding.

The first group received pure guava leaf extract (100%), the second group with povidone iodine (Betadine at 10% solution), and the third group with placebo (distilled water). The mice were observed daily. The treated area was measured and observed for evidence of healing in terms of length and width of wound, presence or absence of inflammation (swelling and hyperemia),

presence or absence of clinical signs (weakness, in appetence, incoordination), presence or absence of pus and scab formation.

### 2.4 Gross Scoring of Wound Healing

Macroscopic characteristics of swelling, hyperemia, wound elevation, pus, scab and scar formation were scored from day 0 to 9 following the procedure of Chupeco et al., [12], as cited by Adao, [13]. The table below explained the gross scoring of wound healing.

Swelling was graded as seen above: + for slightly negative; ++ for moderate; and +++ for prominent. Scab formation was graded as + to +++: + for slightly negative; ++ for moderate; and +++ for prominent. Lastly, scar formation was also graded as + to +++: + for slightly negative; ++ for moderate; and +++ for prominent. All parametric data, including presence or absence of clinical signs (weakness, inappetence, incoordination) were observed and collected daily through actual observation and data recording. In this research, the parameter for swelling and scar formation was used. Observations on all parameters were noted by describing its characteristics based on the appearance of the mice. However, size of wound in terms of length and width were determined through mixed Analysis of Variance (ANOVA). Comparison on the effects of guava leaf extracts and povidone iodine in the wound healing of the incised wound of laboratory mice was done every after 3 days (day 3, day 6 and day 9) until the duration of the study.

### 3. RESULTS AND DISCUSSION

The results of the study which determined the macroscopic wound healing efficacy of guava leaf extracts and povidone iodine on the incised skin of laboratory mice in terms of time by describing its characteristics is presented.

Table 2 presents that all experimental mice were induced with 2 cm long induced wound at Day 0. During the 9-day observation, the data revealed that incised wounds have an average mean length of 10.90, 11.15 and 11.26 treated with GLE (100%), P1 (10% solution) and the controlled treatment of PNSS, respectively. Apparently laboratory mice treated with pure GLE (100%) had decreased length of wound measurement compared to other treatments.

As presented in the Table 2, the data revealed that the GLE exhibited property to contract the wound more than the PI at 10% and PNSS. This could describe that GLE could be utilized as an effective wound healing treatment rather than the costlier povidone iodine solution.

It can be gleaned in Table 3, that 100% or six (6) out of six (6) laboratory treated with pure GLE (100%) manifested moderate swelling from day 1 until day 2. However, from day 3 until day 9, six (6) out of six (6) mice had already manifested slight negative swelling.

For laboratory mice treated with PI solution (10%), six (6) out of six (6) or 100% exhibited moderate swelling. However, on the third day until the ninth day, six (6) mice exhibited slight negative swelling except for two. One of the test animal had moderate swelling on the third day while the other test animal had prominent swelling on the fifth day and a moderate swelling on Day 6 to Day 7 until slight negative on Day 8 and Day 9.

In the third group which received PNSS, the six (6) laboratory mice exhibited swelling on day 1 until day 2. On day 3, two of the test animal reportedly manifested swelling. One of the test animal had swelling again on day 6, scored as prominent, then moderate swelling on day 7 to day 8 until slight negative on day 9.

**Table 1. Gross scoring for wound healing [13]**

Gross scoring	Interpretation		
	Slightly negative	Moderate	Prominent
Swelling	+	++	+++
Scab formation	+	++	+++
Scar formation	+	++	+++

**Table 2. Wound contraction based on length measurement**

Subject/ Treatment group	Day of observation										
	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Weighted Mean
<b>Group I- Guava leaf extract (GLE 100%)</b>	<b>Total(cm)</b>										
1	20.0	12.5	10.8	11.6	10.8	8.1	8.3	6.2	6.1	6.0	10.04
2	20.0	16.3	13.1	13.2	14.4	8.1	6.9	4.7	4.3	4.3	10.53
3	20.0	12.7	11.3	11.8	9.8	10.2	9.9	9.8	9.1	8.7	11.40
4	20.0	15.0	11.2	10.6	8.6	9.1	9.8	9.2	8.8	8.5	11.08
5	20.0	19.1	14.2	13.5	11.5	9.0	9.8	8.2	7.6	7.2	12.01
6	20.0	16.6	13.8	12.5	8.6	8.5	7.8	5.9	5.3	4.9	10.34
Total Mean	20.0	15.37	12.40	12.20	10.61	8.83	8.75	7.33	6.87	6.60	10.90
<b>Group II- Povidone iodine solution (PI 10%)</b>											
7	20.0	13.4	13.3	11.7	11.2	12.1	12.1	10.9	9.7	7.8	12.22
8	20.0	12.7	12.1	13.2	10.0	10.8	10.0	9.5	9.4	7.4	11.51
9	20.0	13.0	13.2	11.3	9.3	9.1	7.9	6.3	5.4	5.4	10.09
10	20.0	14.2	11.8	12.8	11.0	13.3	13.1	12.7	12.3	12.0	13.32
11	20.0	11.7	11.5	12.8	8.6	9.0	7.5	5.5	4.4	3.7	9.47
12	20.0	12.4	12.4	10.0	9.5	8.0	8.8	8.8	6.7	6.6	10.32
Total Mean	20.0	12.90	12.40	11.97	9.93	10.40	9.90	8.95	7.98	7.15	11.15
<b>Group III- Plain normal saline solution (PNSS)</b>											
13	20.0	15.0	13.5	13.0	10.3	11.8	11.1	9.8	9.3	9.3	12.31
14	20.0	13.4	13.3	14.0	9.8	9.2	8.9	6.3	9.1	7.4	11.14
15	20.0	11.6	11.7	13.3	10.1	9.8	12.1	9.7	8.2	6.9	11.34
16	20.0	14.9	14.1	13.0	9.7	10.9	11.5	9.2	8.4	8.4	12.01
17	20.0	13.9	14.1	12.0	9.8	8.7	9.0	6.9	6.8	6.8	10.80
18	20.0	14.3	14.3	14.5	11.0	11.7	9.5	8.8	8.3	8.2	12.06
Total Mean	20.0	13.85	13.50	13.30	10.12	10.35	10.35	8.45	8.35	7.83	11.61
Weighted Mean	20.0	14.04	12.77	12.49	10.22	9.86	9.67	8.24	7.73	7.19	11.22

**Table 3. Swelling of wound**

Subject/ Treatment group	Day of observation								
	1	2	3	4	5	6	7	8	9
<b>GROUP I- Guava leaf extract (GLE 100%)</b>									
Prominent	0	0	0	0	0	0	0	0	0
Moderate	6	6	0	0	0	0	0	0	0
Slightly negative	0	0	6	6	6	6	6	6	6
<b>GROUP II- Povidone iodine solution (PI 10%)</b>									
Prominent	0	0	0	0	1	0	0	0	0
Moderate	6	6	1	0	0	1	1	0	0
Slightly negative	0	0	5	6	5	5	5	6	6
<b>Group III- Plain normal saline solution (PNSS)</b>									
Prominent	0	0	0	0	0	1	0	0	0
Moderate	6	6	2	0	0	0	1	1	0
Slightly negative	0	0	4	6	6	5	5	5	6

As presented in the Table 3, the data revealed that the GLE after the third day generated effectiveness to the swelling of wounds of the test animals. It could be noted that this could be an alternative to the commonly used povidone iodine solution.

scar formation on Day 3 and Day 6 was not yet present for all the three (3) treatment groups. However, on the ninth day, scarring was apparent in Group 1 treated with GLE (100%). Three (3) out of six (6) test animals, scored to have prominent scars while the other three (3) test animals had moderate scars formation.

Table 4 determined the presence or absence of scar formation. Data shows that

**Table 4. Presence/absence of scar formation**

Subject/ treatment group	Day of observation								
	1	2	3	4	5	6	7	8	9
<b>Group I- Guava leaf extract (GLE 100%)</b>									
Prominent	0	0	0	0	0	0	0	0	3
Moderate	0	0	0	0	0	0	3	3	3
Slightly negative	6	6	6	6	6	6	3	3	0
<b>Group II- Povidone iodine solution (PI 10%)</b>									
Prominent	0	0	0	0	0	0	0	0	2
Moderate	0	0	0	0	0	0	1	2	2
Slightly negative	6	6	6	6	6	6	5	4	2
<b>Group III- Plain normal saline solution (PNSS)</b>									
Prominent	0	0	0	0	0	0	0	0	1
Moderate	0	0	0	0	0	0	1	1	2
Slightly negative	6	6	6	6	6	6	5	5	3

For Group II treated with PI (10%), two (2) mice, out of six (6), exhibited prominent scar formations while two (2) were scored moderate and the remaining two (2) had slightly negative scar formations.

For those treated with PNSS, it was found out that only one mouse, out of six (6), had prominent scar. Two (2) mice were found to have moderate scar and three (3) of them were still having slightly negative scar.

In this table, it can be noted that the GLE gave a scar formation better than the other treatment. With this, GLE could be an alternative to the commonly used povidone iodine solution as it has better result with regards to scar formation.

**3.1 Statistical Treatment of the Data**

In terms of length, Table 5 and 6 showed the average wound length in all mice within the three (3) treatment groups from day 1 of observation until day 9. A 3 (Treatment Group) x 3 (Day) mixed model analysis of variance (ANOVA) revealed that the main effect for Treatment was not significant  $F(2,15) = 1.629, p > 0.001$  (Table

8). Thus, there was no overall difference in the wound length in all three treatment groups (GLE 100%, PI 10%, and PNSS). A significant main effect for Day was obtained  $F(2,30) = 66.679, p < 0.001$  (Table 7), which indicated that there was an overall difference in the wound length in all three observation periods (Day 3, Day 6, and Day 9). No significant interaction between Treatment Groups and Day was obtained  $F(4,30) = 0.494, p > 0.001$  (Table 7). Bonferroni tests revealed that a significant difference in the wound length lies between Day 3 and Day 6, Day 3 and Day 9, and Day 6 and Day 9,  $p < 0.001$  (Table 9). For multiple comparisons, it was revealed that there was no significant difference between the three (3) treatments in terms of wound length in all mice.

Maturation phase, also known as the remodeling stage is the final phase of wound healing. It is responsible for the development of new epithelium and final scar tissue formation. Scar tissues are always expected to be observed earlier with PI (10%) than in PNSS or the control group. However, based on the result of this study, the use of GLE 100% exhibited more rapid progress in terms of scar formation.

**Table 5. Wound contraction in terms of length – effect of *Psidium guajava* extract, povidone iodine, and PNSS on wound length\***

Group	Day									
	0	1	2	3	4	5	6	7	8	9
Guava Extract	20 ± 0.00	2.60 ± 0.37	12.40 ± 0.60	12.20 ± 0.44	10.62 ± 0.89	8.83 ± 0.32	8.75 ± 0.52	7.33 ± 0.83	6.87 ± 0.79	6.60 ± 0.75
Povidone Iodine	20 ± 0.00	1.62 ± 0.43	12.38 ± 0.30	11.97 ± 0.49	9.93 ± 0.41	10.38 ± 0.83	9.90 ± 0.93	8.95 ± 1.11	7.98 ± 1.22	7.48 ± 1.21
PNSS	20 ± 0.00	1.37 ± 0.27	13.50 ± 0.39	13.30 ± 0.36	10.12 ± 0.20	10.35 ± 0.53	10.35 ± 0.57	8.45 ± 0.61	8.35 ± 0.36	7.83 ± 0.40

\*Values are mean length ± s.e. mean

**Table 6. Descriptive statistics**

	Group	Mean	Std. Deviation	N
Length on Day 3	Guava extract	12.200	1.0826	6
	Povidone Iodine	11.967	1.2078	6
	PNSS	13.300	.8718	6
	Total	12.489	1.1641	18
Length on Day 6	Guava extract	8.750000	1.2692517	6
	Povidone Iodine	9.900000	2.2829805	6
	PNSS	10.350000	1.3852798	6
	Total	9.666667	1.7469301	18
Length on Day 9	Guava extract	6.600000	1.8395652	6
	Povidone Iodine	7.483333	2.9532468	6
	PNSS	7.833333	.9729680	6
	Total	7.305556	2.0307843	18

**Table 7. Tests of between-subjects effects transformed variable: Average**

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	5207.742	1	5207.742	1094.276	.000	.986
Group	15.508	2	7.754	1.629	.229	.178
Error	71.386	15	4.759			

**Table 8. Pairwise comparisons**

(I)Day	(J)Day	Mean Difference (I-J)	Std. Error	Sig. <sup>a</sup>	99.9% Confidence Interval for Difference <sup>a</sup>	
					Lower Bound	Upper Bound
3	6	2.822 <sup>*</sup>	.472	.000	.640	5.005
	9	5.183 <sup>*</sup>	.543	.000	2.676	7.691
6	3	-2.822 <sup>*</sup>	.472	.000	-5.005	-.640
	9	2.361 <sup>*</sup>	.297	.000	.988	3.734
9	3	-5.183 <sup>*</sup>	.543	.000	-7.691	-2.676
	6	-2.361 <sup>*</sup>	.297	.000	-3.734	-.988

Based on estimated marginal means

\*. The mean difference is significant at the .001 level.

a. Adjustment for multiple comparisons: Bonferroni

**Table 9. Multiple comparisons**

(I)Group	(J)Group	Mean Difference (I-J)	Std. Error	Sig.	99.9% Confidence Interval	
					Lower Bound	Upper Bound
Guava extract	Povidone Iodine	-.600000	.7271767	1.000	-3.959738	2.759738
	PNSS	-1.311111	.7271767	.275	-4.670849	2.048626
Povidone Iodine	Guava extract	.600000	.7271767	1.000	-2.759738	3.959738
	PNSS	-.711111	.7271767	1.000	-4.070849	2.648626
PNSS	Guava extract	1.311111	.7271767	.275	-2.048626	4.670849
	Povidone Iodine	.711111	.7271767	1.000	-2.648626	4.070849

**Table 10. Statistical analysis of the scar formation**

PARAMETER	GROUP I (GLE 100%)	GROUP II (PI 10%)	GROUP III (PNSS)
Scar Formation	effective	less effective	least effective

Treatment with PI (10%) was less effective and the control group or placebo using PNSS was found to be the least effective. Therefore, in terms of scar formation, pure GLE (100%) was revealed to be the most effective compared to the other two (2) treatment groups.

#### 4. CONCLUSION

Generally, in terms of wound contraction (length and width) findings showed no significant difference in all three treatments used (GLE (100%), PI (10% solution) and PNSS. This implies that although guava leaves have earlier wound contraction compared to povidone iodine it is not superior to povidone iodine and plain normal saline solution.

In terms of swelling and wound elevation, results revealed that guava leaf extract showed no prolonged swelling and elevation of wound compared to povidone iodine and plain normal saline solution. Furthermore, guava leaf extract is more effective than povidone iodine, while PNSS was found to be the least effective.

Observations done for scab and scar formation showed that guava leaf extract dominated the two treatments with all mice seen with scab and scar formation. In povidone iodine there were three (3) which already developed scar tissue and only one (1) mouse from those treated with PNSS was observed to form scar.

The result revealed that all mice which received guava leaf extract formed scar earlier as compared to povidone iodine and PNSS. Since maturation phase which also refers to remodeling phase is responsible for the new epithelium and final scar tissue formation, and as the development of these completes the complex process of wound healing, the researchers suggest that the use of guava leaf extract in comparison with povidone iodine and PNSS when it comes to wound healing is the most effective treatment in promoting normal and more rapid wound healing. For further analysis, the chemical component of guava leaf extract must be studied to further know the compounds causing the wound healing, after that, it could be compared to the commercially available antiseptic solution, the povidone iodine solution.

#### CONSENT

It is not applicable.

#### ETHICAL CONSIDERATION

This study was carried out in strict accordance with the recommendations and approved Protocol in the Guide for the Care and Use of Laboratory Animals of the UEP-CVM's Institutional Care and Use Committee. All animals were treated under sedation with minimal pain upon incision.

#### COMPETING INTERESTS

Author has declared that no competing interests exist.

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