A pilot study to compare the effects of Salicylic Acid 16.5% + Lactic Acid 16.5% Solution and *Melaleuca Alternifolia* (Tea Tree) oil on the Resolution Rates of Verruca Vulgaris

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Background: Verruca vulgaris is common in people of all ages and there is no gold standard of treatment at this time. Present treatment options are costly, painful or worse ineffective.

Objective: To establish if *Melaleuca alternifolia* oil has a value, or not, as a treatment for verruca vulgaris.

Methods: This was a randomized, single-blind, clinical trial wherein twenty patients with verruca vulgaris were included. Ten patients applied salicylic acid 16.5& + lactic acid 16.5% solution and another ten applied *Melaleuca alternifolia* (tea tree) oil on each lesion nightly. Patients were followed-up weekly for four weeks for assessment of resolution rates and adverse effects.

Results: A mean change in the size of the lesion of 2.90 + 1.97 and 3.70 + 5.33 in mm2 for the *Melaleuca alternifolia* oil and salicylic acid + lactic acid solution group, respectively, was observed. These results show that there is no statistically significant difference (p=0.661, t-test) between using *Melaleuca alternifolia* oil or salicylic acid + lactic acid solution for the treatment of verruca vulgaris. On the aspect of adverse reactions to the test substances, there was a statistically significant difference in both groups (p=0.0230, Fisher's test).

Conclusion: *Melaleuca alternifolia* may have a role as an alternative treatment for verruca vulgaris.

INTRODUCTION

The human papilloma virus (HPV) is the virus responsible for verruca vulgaris, or verrucae (singular: verruca verruca).[1] There are approximately 100 strains of human papilloma viruses wherein type 1, 2, and 3 causes most of the common verruca vulgaris.[2] Verrucae are benign growths on the skin that cause cosmetic problems, as well as pain and discomfort, seen on people of all ages but most commonly appear in children and teenagers.[3] The incubation period of a verruca vulgaris is 2 to 9 months following infection with the human papilloma virus, during which, an excessive proliferation of skin growth slowly develops.[4,5]

Verrucae commonly occur on hands and fingers of children and young adults with an incidence rate up to 12.9% in some countries and has been found to be more prevalent in 4-6 and 16-18 year olds with the girls outnumbering the boys.[6-9] It The virus is spread by contact, either directly from person to person, or indirectly via fomites left on surfaces.[10] Diagnosis is mainly made clinically, a skin biopsy is rarely needed nor warranted.[11] It is a common problem seen by the dermatologist everyday.

Verruca vulgaris (common warts) are hyperkeratotic, exophytic and dome-shaped papules or nodules especially located on the fingers, hands, knees, elbows or any other sites of trauma.[11] Lesions may be studded with black dots which represent thrombosed dermal capillary vessels.[11] On close inspection, normal skin lines over the surface of the lesion are typically disrupted, the surface hyperkeratotic with many small filamentous projections.[12]

Studies show that more than 50 percent may undergo spontaneous resolution within two years[13] most are bothered by its presence and opt to have it treated. Treatment of verruca vary from homemade topical concoctions to surgical procedures, each with its own reports of cure,[13-14] as no single therapy has been proven effective at achieving complete remission.[10] Several over-the-counter preparations are available for the self-treatment of verruca. One of these clinically employed treatments is the use of salicylic acid (SA) which, if correctly applied, will result to a cure of 70-80% of common verruca vulgaris.[13] However, the application of SA can have adverse effects such as local irritation.[13] Another common method of treatment is by electrocautery with curettage with pain being the most common complaint amongst the patients, even with the application of anesthesia.[15]

There are a lot of natural, herbal and home remedies available for the treatment of verruca, *Melaleuca alternifolia* oil being one of them. *Melaleuca alternifolia* oil has both antibacterial and antifungal properties.[16-18] It is recommended as a non-poisonous, nonirritant antiseptic of unusual strength even to sensitive tissues.[19] Although using Melaleuca alternifolia oil is not a new concept as treatment for common verruca, much of the evidence appears to be anecdotal as opposed to salicylic acid + lactic acid.

This study aims to assess the effectiveness of the topical application of Salicylic Acid 16.7% + Lactic Acid 16.7% (SA+LA) compared to that of *Melaleuca alternifolia* oil for the treatment of verruca vulgaris using a recommended course of treatment. It is of significance to investigate home treatments in an attempt to provide information for the profession and patients on possible alternative treatment options compared to mainstay treatments. This study aims to see if there is a role or not for *Melaleuca alternifolia* oil in the treatment of verruca, if there is, to compare the resolution rates with SA+LA solution and to compare the frequency of adverse effects between *Melaleuca alternifolia oil* and SA+LA solution.

METHODOLOGY

Study Design and Subject Selection

This is a 4-week, randomized, single-blind, clinical trial conducted at the Dermatology Department – Out Patient of East Avenue Medical Center from February to April 2010 after being approved by the hospital's institutional review board committee. Patients included were a) aged 8 to 45 years old, b) male and female, c) able to follow simple instructions in English and d) diagnosed clinically by a dermatology resident to have verruca vulgaris, characterized by the presence of a hyperkeratotic papule with/

without visible thrombosed vessels, located on the trunk or extremities. Patients excluded from the study were a) those who have previously treated their verruca vulgaris, either with topical or oral medications within the past 4 weeks, b) those who have an inflammatory or infectious skin condition in the location of the verruca vulgaris, c) those who are immunocompromised (i.e. with known systemic illnesses such as diabetes mellitus and malignancy) and d) those who suffer from known allergies, especially to salicylic acid, lactic acid and/or *Melaleuca alternifolia* oil, or other skin conditions. Once eligibility criteria were met, the nature of the study was explained to the subject and an informed written consent was obtained.

Preparation of Test Substances

Test substances used in this study were obtained from Chemworld Philippines and Stiefel Philippines for the *Melaleuca alternifolia* oil and SA+LA solution respectively. The medications were placed in identical 10ml amber-colored glass bottles and labeled as A (Melaleuca alternifolia oil) and B (SA+LA) by a primary investigator, with codes assigned only known to the primary investigator. Computer-generated randomization was done using www.randomizer.org for the assignment of patients to the medications. The randomization codes were placed in sealed, opaque envelopes, opened as each patient was deemed eligible for the study.

Application of Test Substances and Follow-up

If the patient had more than one lesion, only one lesion was selected for the study. Baseline measurements of the lesion was taken using an acetate grid with a measurement of 1 mm2/square on weeks 0, 1, 2, 3 and 4 and recorded by a secondary investigator, who was blinded as to the allocation of the medications. Baseline photographs of the lesion under standardized setting (no flash, ISO400, macro mode) were taken using a Canon G9, 12.1 megapixel camera was taken.

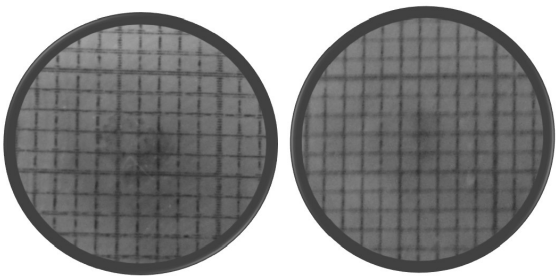


Fig. 1. Measurement of verruca using an acetate grid in mm2 were done on weeks 0, 1, 2, 3 and 4.

On entry, each patient, and guardian if the patient was a minor, was/were given the following materials: a 10ml amber glass bottle with the test substance labeled either A or B, wooden stick applicators, cotton balls and an emery board and an instruction sheet, explained at the start of the study. Method of application will direct participants to perform the following nightly: 1) clean the verruca with soap and water, 2) apply a piece of cotton dipped in tap water over the verruca and left on for 3 minutes, 3) remove cotton over the verruca and dry the area thoroughly with a paper towel, 4) use the emery board given and slide it over the verruca 4 times, as instructed on week 0, 5) apply the just enough amount of the test substance to cover the verruca using a wooden stick applicator which is to be discarded after each use, 6) let the test substance dry for ten minutes and 7) to check the corresponding box on the chart in the instruction sheet given. Patients were advised to adhere to the guidelines as shown in the enclosed instruction sheet, explained to the patient or guardian at the start of the study. If skin irritation does occur, patients were advised to discontinue use and follow-up at the soonest time possible.

Patients were asked to follow-up every week for 4 weeks, during which, measurements and photographs of the lesion were taken, supply of materials replenished and patients asked for any adverse reactions upon application of the test substance. Patients who failed to keep their weekly appointments were given an extra 72 hours in which to be seen by the secondary investigator.

At the end of the study period, patients were given the option to either continue with their corresponding test substance or to undergo

electrodessication and curettage, done by the primary investigator, free of cost.

Outcome Measures

The primary outcome measured in this study is the resolution rate (reduction in size) of the verruca after 4 weeks of treatment with either SA+LA solution or *Melaleuca alternifolia* oil. The secondary outcome measured is the type and frequency of adverse reactions to either SA+LA solution or *Melaleuca alternifolia* oil.

Statistical Analyses

Previous studies showed a cure rate of 75% with salicylic acid with or without lactic acid and no study were found as to the use of *Melaleuca alternifolia* oil for verruca vulgaris. In the absence of any preliminary quantitative data on the efficacy of *Melaleuca alternifolia* for verruca, no sample size calculations were possible. Any information gained from this pilot study may be used to plan a larger study.

Demographic and baseline characteristics of the study population were summarized and described by descriptive statistics. Paired t test was used to compare means and fisher test used to compare counts.

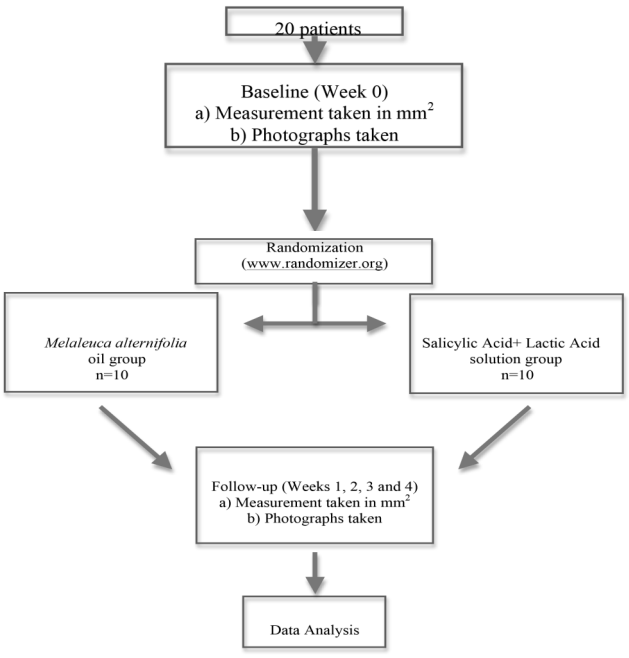


Fig.2. Methodology flow chart

RESULTS

Patient Demographics

The study assessed 20 subjects, 8-44 years of age, (mean of 24.6 + standard deviation 11.98) were included in the study. Test for homogeneity of the study population in all categories, using the paired t-test for means and fisher test for counts showed that there is no significant difference between the two groups in terms of their baseline characteristics (Table 1)

Table 1. Patient demographics and characteristics of lesion at baseline

	Melaleuca alternifolia oil N (Mean ± SD)	Salicylic Acid 16.5% + Lactic Acid 16.5% solution N (mean ± SD)	p value
Age (years)	8-44 (24.4±13.15	8-40 (24.8±11.39)	0.937*
Gender			1.00**
Male	5	6	
Female	5	5	
Location			1.00**
Upper Extremity	6	7	
Lower Extremity	4	3	
Duration of Lesion (Weeks)	1-10 (4.7±3.02)	4-10 (6.6±2.84)	0.201*
Size of Lesion (mm^2)	2-1 (8.60±5.34)	5-28 (12.00±8.25)	0.315*

**** paired t-test; ** Fisher's test***

Resolution Rates

In the TTO group, all of the lesions decreased in size wherein one had complete resolution of the lesion. In the SA+LA group, 7 decreased in size with two of these having complete resolution of the lesion and the other two increased in size while one remained the same size. There is no significant differences between the two groups in the resolution rates of verruca vulgaris. (Table 2)

Table 2. Change in size of lesion

	Week 0 Size in mm2 (mean + SD)	Week 4 Size in mm2 (mean + SD)	Change in Size Size in mm2 (mean + SD)
Melaleuca alternifolia oil	2-18 (8.60±5.34)	0-10 (5.70±3.86)	1-8 (2.90±1.97)
SA+LA Solution	5-28 (12.00±8.25)	0-30 (8.30±9.92)	-2-15 (3.70±5.33)
p value*	0.315	0.450	0.662

paired t-test

On a weekly basis, the mean size of change with the *Melaleuca alternifolia* group decreased continuously as compared to that of the SA+LA group wherein the lesions increased in size in the first week of application of the solution before decreasing in size. (Figure 1)

Figure 1. Change in size of the lesion of both treatment groups from baseline to week 4.

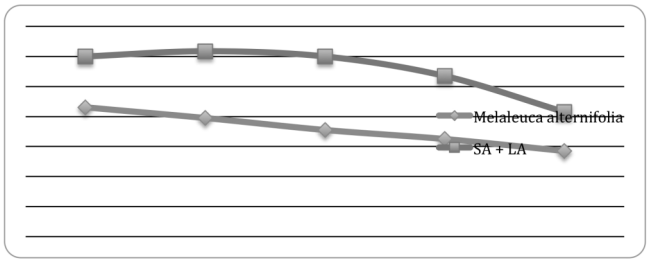
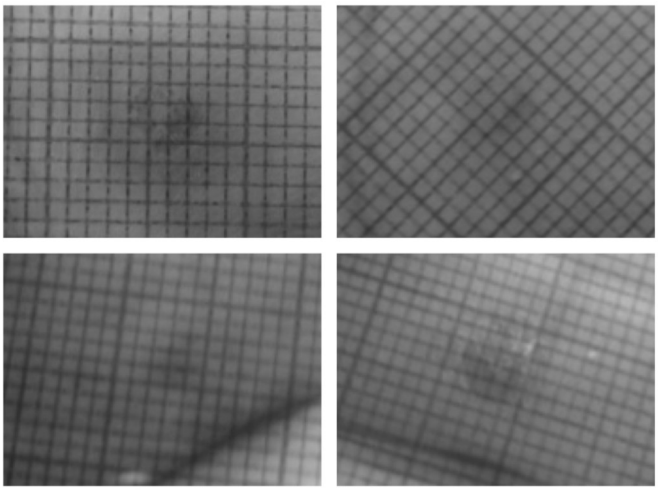


Table 3. Frequency of adverse effects

	Adverse Effects	No Adverse Effects	Total
Melaleuca alternifolia oil	2 (20%)	8 (80%)	10
Salicylic acid + Lactic Acid solution	8 (80%)	2 (20%)	10

p=0.0230, Fishers test

Figure 2. Images on top are before and after application of Melaleuca alternifolia oil. Images on the bottom are before and after application of Salicylic acid + Lactic acid



Safety and Tolerability

Adverse reactions to both test substances were recorded on each follow-up and were localized to the area around the verruca. Patients complained of erythema, pruritus, and stinging over and around the lesion. A total of 10 patients reported adverse reactions to the test substance, 8 from salicylic acid + lactic acid group and 2 from the *Melaleuca alternifolia* oil group. In the salicylic acid + lactic acid group, 2 (20%) complained of erythema, 2 (20%) experienced pruritus and 4 (40%) had a stinging sensation upon application of the solution. In the *Melaleuca alternifolia* oil group, 1 (10%) noticed erythema around the verruca vulgaris and 1 (10%) complained of pruritus upon application of the oil. There is a statistical difference between the ocurrence of adverse effects between the two groups.

DISCUSSION

Verruca vulgaris is a common, relatively benign skin lesion that plague people of all ages all around the world. But just like the common cold, there is no standard treatment for this infection. Lesions may be self-limited but may take up to two years for its spontaneous resolution 15 making the patient want to have the verruca removed as soon as possible due to its increase in size and number, associated pain, pruritus and social stigma brought about by its presence.

Numerous treatments are available for the treatment of verruca vulgaris, both as over the counter medications or those with the help of physicians yet no single therapy has been proven effective at achieving complete remission in every patient.[10] Amongst the over the counter medications available is salicylic acid.

Salicylic acid in concentrations from 15-60 % with or without the addition of lactic acid have shown a cure rate of 75%.[13] Common side effects observed in salicylic acid is contact dermatitis and a potential risk of systemic toxicity in children. [11]

Melaleuca alternifolia oil has been studied well for its antibacterial and antifungal properties, however much has yet to be investigated on its antiviral properties. 19 Reports on its efficacy as treatment for verruca are lacking and mostly anecdotal. It is more cost effective than SA+LA solution and even if it may cause allergic reactions, it has less side effects.

The spontaneous regression of verruca should not be forgotten in assessing the efficacy of any treatment modality used.[14] This regression has been attributed to the induced T-cell mediated tumor cell destruction.[20] The mechanism by which SA+LA solution works is that of being a keratolytic. It slowly destructs the virus-infected epidermis resulting in a mild irritation that may stimulate an immune response.[10] As for the proposed mechanism for *Melaleuca alternifolia* oil, it may be due to a direct effect on the extracellular virus particle, prior to penetration into a host cell by its proposed active components,terpinen-4-ol, alpha-terpineol and 1,8-cineole.[19]

This pilot study was done to provide preliminary data on the use of *Melaleuca alternifolia* oil in the treatment of verruca vulgaris. The outcome of the study showed no statistical difference in the resolution rates of verruca vulgaris in both groups and a statistical difference in the frequency of adverse reactions. Though these results are favorable to the *Melaleuca alternifolia* group, these may be due to the small sample size, hence a larger study group is recommended in the future. Another factor that is of importance is that of the time amount given in the study for follow-ups. Four weeks is a relatively short period of time given for the complete cure of verruca vulgaris with the use of topical agents. The reason for this is to decrease the amount of drop-outs from the study, hence the computation for the resolution rates instead of cure rate.

Melaleuca alternifolia oil holds promise on being a useful alternative treatment for verruca vulgaris. It is relatively inexpensive when compared to other treatment available and tolerability, in both pediatric and adult age groups, may be of higher value when considering treatment options.

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Appendix

Appendix A - Informed Consent Information

PATIENT INFORMATION SHEET (KAALAMAN PARA SA PASYENTE)

Verruca vulgaris or warts are caused by the human papilloma virus and is a very common problem which we, dermatologists see and treat regularly. No gold standard has been set for the treatment of warts hence the many different treatments available, both over the counter and those offered by dermatologists. *(Ang kulugo ay sanhi ng isang virus na ang pangalan ay human papilloma. Ito ay isang pangkaraniwang sakit na nakikita at ginagamot naming mga dermatologist sa araw-araw naming trabaho. Maraming paraan para magamot ito ngunit walang makakapagsabi na ito ay makakapagbigay ng lunas ng lubusan. Dahil dito, maraming gamot ang mabibili sa tindahan at paraan ginagamit ng mga dermatologist para maalis ang kulugo.)*

A study is being carried out at the Department of Dermatology of East Avenue Medical Center to investigate the effectiveness of the use two home treatments for warts. The study will involve applying a treatment of Melaleuca alternifolia (tea tree) oil and a mixture of Salicylic Acid and Lactic Acid solution directly onto the wart. *(Isang pag-aaral ang ginagawa sa Department of Dermatology ng East Avenue Medical Center para matukoy ang epektibo ng dalawang gamot na pangkaraniwang nabibili sa mga tindahan para sa paggaling ng kulugo. Ang isa ay Melaleuca alternifolia (tea tree) oil at ang isa ay halo ng Salicylic Acid at Lactic Acid na ipapahid sa kulugo.)*

An investigator will measure your wart and record any pain or discomfort it may be causing. The first treatment will be done in the clinic to teach you how to put the medicine properly onto the wart. You will receive a bottle of one of the medicines to use daily at home for the next 3 weeks, together with written instructions on how to use the them properly. It will also be necessary for you to return to the clinic after 7, 14 and 21 days for the assessment and monitoring of the wart. *(Isang imbestigador ang magsusukat ng laki ng iyong kulugo at ikaw ay tatanungin tungkol sa sakit na nararamdaman dahil dito. Ang unang gamutan ay gagawin sa OPD upang maituro ang wastong paglagay ng gamot sa kulugo. Pagkatapos nito at bibigyan ka ng isang bote na naglalaman ng gamot na iyong gagamitin sa bahay kasama ang instruksyon sa wastong paggamit ng gamot na naayon sa pag-aaral. Ikaw ay inaasahang bumalik sa klinik pagkatapos ng 7, 14, 21 at 28 na araw ng gamutan para masubaybayan ang gamutan.)*

It is unlikely that you will have any adverse reactions to the medications used as there are minimal adverse side effects reported to both treatments used in the study. However, if there are any adverse reactions such as the area becoming red and swollen or undue pain or discomfort is felt, please discontinue use of the medications and go back to the clinic to notify the investigators. Please keep the medication given to you in a place where it may be used in any other means. In case the medication given to you gets to the eyes or skin other than the wart, please wash the area as soon as possible. *(Kakaunti ang nagkakaroon ng "allergy" sa mga gamot na gamit sa pag-aaral na ito. Subalit kung ikaw ay nakaramdam ng hindi pangkaraniwang sakit, namula o namaga ang iyong kulugo, itigil agad ang paggamit nito at pumunta sa klinik sa lalong madaling panahon. Kung maari, itago ang gamot ni binigay sa iyo upang maiwasan na gamitin ito sa maling paraan. Ang gamot na ito ay pinapahid at hindi dapat kailanman inumin ng isang tao. Kung sakaling malagyan ang ibang parte ng katawan ng gamot, hugasan itong maigi lalo na kung ito ay mapunta sa mga mata.)*

All personal information gained is strictly confidential and will only be used for the purposes of this study. At any time you may withdraw from the study and this will not prejudice further treatment.

(Lahat ng impormasyon na makukuha sa pag-aaral na ito ay confidential at ang mga imbestigador lang ang makakaalam nito. Kung may pagkakataon na gusto mong tumigil ng gamutan, bumalik lamang sa klinik para ipaalam sa mga imbestigador.)

Thank you for agreeing to participate in this study. *(Salamat ng marami sa paglahok sa pag-aaral na ito.)*

Maria Rhea B. Lombos-Serondo, MD
Dermatology Resident

Appendix B – Informed Consent Form

Patient Identification Number: _____

CONSENT FORM

Title of Study:
"A Pilot Study to Compare the Effects of Salicylic Acid 16.5% + Lactic Acid 16.5% solution vs *Melaleuca alternifolia* (tea tree) oil on the Resolution rates of Verruca vulgaris"

Name of Researcher: Maria Rhea B. Lombos-Serondo, MD

Please check each box to confirm.
Markahan ng check ang box kung ikaw ay sumasang-ayon sa sinasaad nito.

❑I confirm that I have read and understand the information sheet dated January 25,2010:version 1 for the above study and have had the opportunity to ask questions.
Nabasa at naintindihan ko ang papeles tungkol sa kaalaman para sa pasyente (January 25, 2010:version 1) para sa pag-aaral na ito at binigyan ako ng pagkakaton na magtanong tungkol dito.

❑I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
Naiintindihan ko na ang paglahok ko sa pag-aaral na ito ay boluntaryo at maari akong tumigil kung gusto ko, ng walang paglabag sa ano mang kasulatan.

❑I understand that any record from the study may be looked at by responsible individuals from the Department of Dermatology of East Avenue Medical Center or from regulatory authorities where it is relevant to my taking part in research and give them access to the said records.
Naiintindihan ko na ang mga dokyumento na gagamitin sa pag-aaral na ito ay maaring tingnan o basahin ng mga taong bumubuo ng Department of Dermatology ng East Avenue Medical Center o ng sino man na mangangailangan nito. Dahil dito, binibigyan ko sila ng permiso para gawin ito.

❑I agree to have pictures of my warts to be taken.
Ako ay sumasang-ayon sa pagkuha ng litrato sa aking mga kulugo.

❑I agree to take part in the above study.
Ako ay sumasang-ayon sa paglahok sa pag-aaral na ito.

Name and Signature of Patient: _____
Name and Signature of Person taking consent: _____
Date: _____

Total of 3 copies: 1 for the patient; 1 for the researcher; 1 to be kept with clinical trial

Appendix C – Patient Data Sheet

PATIENT DATA SHEET

STRICTLY CONFIDENTIAL

MEDICAL HISTORY:

Pangalan: _____ Edad: _____ Kasarian: _____

1. Gaano na katagal ang iyong kulugo? _____
   Ilan ang iyong kulugo?_____
   Ito ba ay dumadami o kumukonti ng bilang?_____

2. Nagamot na ba ang iyong kulugo? _____
   Kung oo ang sagot, sagutan ang mga sumusunod na tanong, kung hindi ay lumaktaw na sa pangatlong tanong.
   Sino ang gumamot nito? _____
   Gaano katagal ito ginamot? _____
   Ito ba ay gumaling ng lubusan? _____

3. Mayroon ka bang mga allergy sa ano mang bagay, gamot o pagkain?_____
   Kung oo, saan ka nag-allergy? _____ at kailan nangyari ito? _____

4. Mayroon bang sakit, kati o iba pang hindi magandang karamdaman na idinudulot sa iyo ang iyong kulugo? _____
   Ito ba ay nagiging sagabal sa iyong pang-arawaraw na gawain o trabaho?_____
   Kung oo ang sagot, katulad ng ano ang mga ito?_____
   _____

RECORD OF LESION:

Day 0:
Size: _____ VAS: _____
Description of wart: (presence of hyperkeratosis, black dots, bleeding, etc)
_____

Day 7:
Size: _____ VAS: _____
Description of wart: (presence of hyperkeratosis, black dots, bleeding, etc)
_____

Day 14:
Size: _____ VAS: _____
Description of wart: (presence of hyperkeratosis, black dots, bleeding, etc)
_____

Day 21:
Size: _____ VAS: _____
Description of wart: (presence of hyperkeratosis, black dots, bleeding, etc)
_____

Day 28:
Size: _____ VAS: _____
Description of wart: (presence of hyperkeratosis, black dots, bleeding, etc)
_____

Appendix D – Study Treatment Guidelines

STUDY TREATMENT GUIDELINES

The medication should be applied on the wart on a daily basis, preferably at night.
Nararapat na pahiran ng gamot ang iyong kulugo araw-araw, kung maari ay sa gabi ito gawin.

No other medications for the wart may and should be used at the time of the study other than the one supplied by the investigator. If there is more than one wart, please put the medication on the one indicated by the investigator.
Walang ibang gamot para sa kulugo ang maaring gamitin habang ikaw ay kalahok sa pag-aaral na ito. Kung sakaling lagpas sa isa ang iyong kulugo, ipahid lamang ang gamot na binigay sa kulugo na sinaad ng imbestigador.

1. Clean the wart with soap and water.
   Linisin ang kulugo gamit ang tubig at sabon.
2. Apply a piece of cotton dipped in tap water over the wart and leave for 3 minutes.
   Maglagay ng bulak na binasa ng tubig sa ibabaw ng kulugo at iwanan ito ng 3 minuto.
3 Remove cotton over the wart and dry the area thoroughly with a paper towel.
   Tanggalin ang bulak at tuyuin ng mabuti ang kulugo gamit ang "paper towel".
4. Using the emery board provided, slide it over the wart 4 times as instructed.
   Gamit ang nail file na binigay, ikaskas ito sa ibabaw ng kulugo ng 4 na beses gaya ng itinuro.
5. Using the applicator supplied, carefully apply two drops over the wart. Avoid getting the medication to the surrounding normal skin.
   Gamit ang stick na binigay, maglagay ng 2 patak ng gamot sa ibabaw ng kulugo. Ingatan na hindi malagyan ng gamot ang nakapalibot na balat.
7. Let the solution dry for around ten minutes.
   Hayaang matuyo ang gamot sa balat ng mga sampung minuto.
8. Check the corresponding box on the chart below after doing the steps above.
   Markahan ng check ang box sa ilalim pagkatapos maglagay ng gamot.

	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY	SUNDAY
WEEK 1							
WEEK 2							
WEEK 3							
WEEK 4							

A slight tingling sensation, mild tenderness or redness may be felt during the treatment period and this is normal temporary. However, if any undue pain or irritation occurs, discontinue use of the medication and wash the area immediately. Notify the investigator as soon as possible. Please use the medication given only as prescribed by the investigator.
Maaring makaramdam na kaunting kirot o pamumula sa bahagi ng kulugo sa panahon ng gamutan, ito ay normal lamang at hindi magtatagal. Subalit kung labis na sakit o pamumula ang mararamdaman, itigil kaagad ang pagpahid ng gamot at hugasan ito ng tubig. Ipaalam ito sa imbestigador sa lalong madaling panahon. Pakiusap lamang na gamitin lang ang gamot na binigay sa paraan na sinabi ng imbestigador.

Appendix E – Certificate of Analysis of *Melaleuca alternifolia*

CERTIFICATE OF ANALYSIS

PRODUCT NAME……. TEA TREE OIL WATER SOLUBLE
TYPE OF EXTRACT…… WATER-SOLUBLE
PRODUCT CODE……. TTH-10
BATCH NO……. 186 FF 9 030
MANUFACTURING DATE…… December 11, 2009
EXPIRY DATE……. December 11, 2010
CERTIFICATE NUMBER…… 270609-254

ORGANOLEPTIC & PHYSICAL PROPERTIES:
COLOR…….. COLORLESS
ODOR…… characteristic smell
APPEARANCE……. CLEAR LQUID
SPECIFIC GRAVITY……. 0.9675
INDEX OF REFRACTION……: 1.3840
pH Value…… 5.8
SOLUBILITY…….. Soluble in water.
STORAGE:

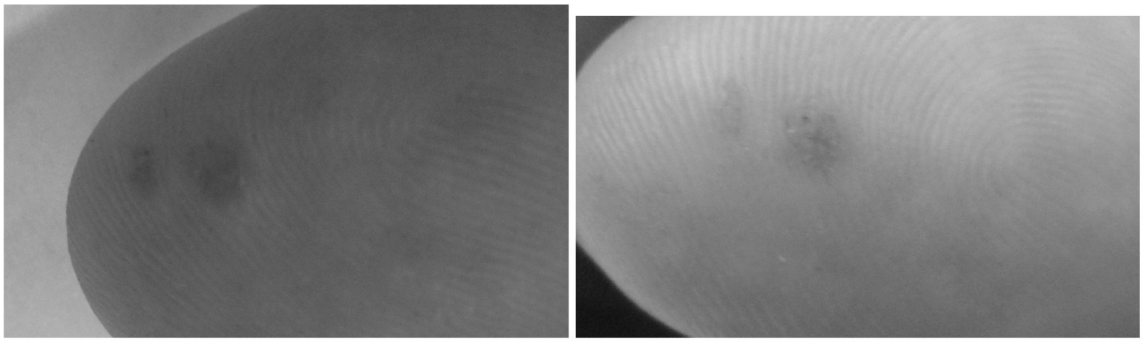
This product will last for at least 12 months at room temperature when stored in a full tightly sealed container.

This computerized document is not signed

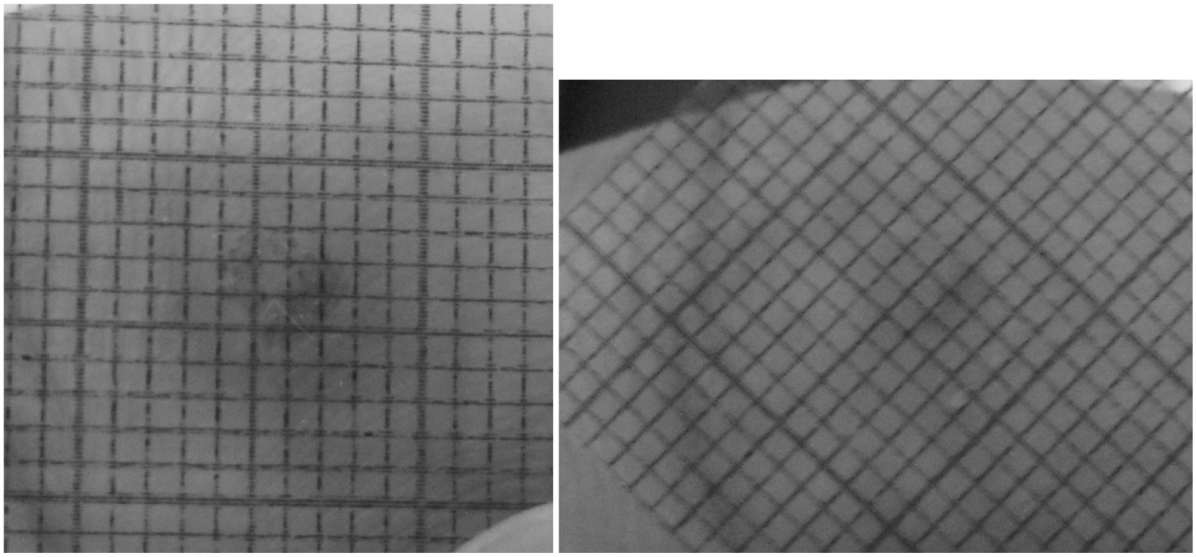
Appendix F

Melaleuca alternifolia

Baseline Week 4

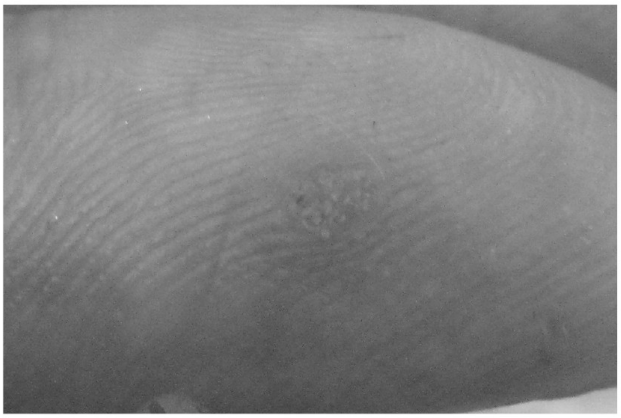


Baseline Week 4

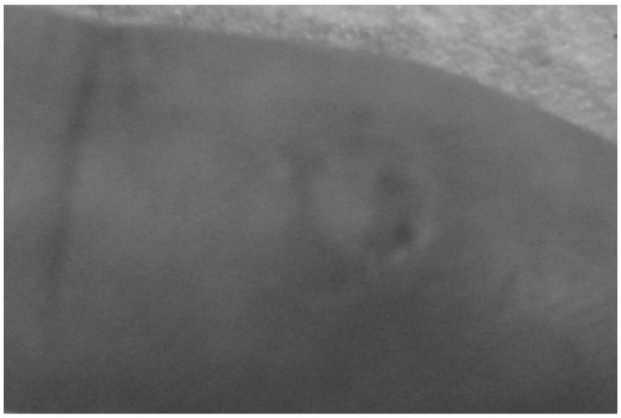


Salicylic Acid 16.5% + Lactic Acid 16.5% solution

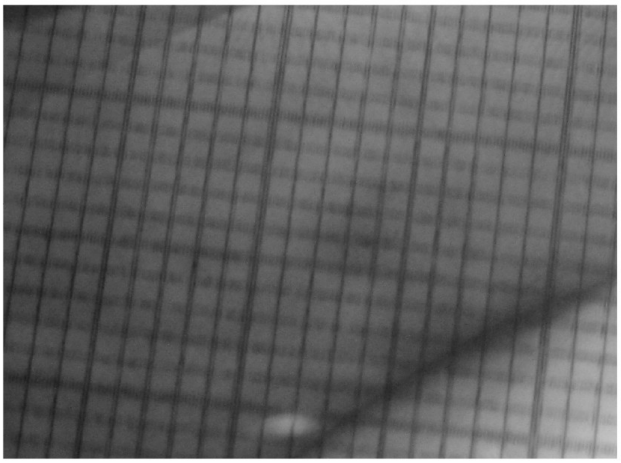
Baseline



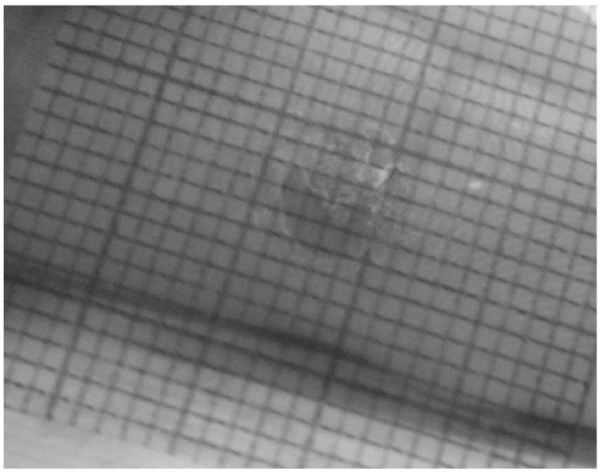
Week 4



Baseline



Week 4



Appendix G - *Melaleuca alternifolia* oil group

Patient Number	Age (yr)/ Sex	Duration of lesion (weeks)	Location of Lesion	Week 0 AR	Week 1 AR	Week 2 AR	Week 3 AR	Week 4 AR
1	14 M	8	UE	12 n	11 Slight pruritus	11 n	10 n	9 n
4	20 F	2	UE	4 n	3 n	3 n	2 n	2 n
5	24 F	4	LE	13 n	13 n	11 n	11 n	9 n
7	16 M	3	UE	6 4 n	5 slight erythema	5 n	4 n	4 n
9	9 M	2	LE	3 2 n	3 n	2 n	2 n	2 n
11	8 M	5	LE	5 n	4 n	4 n	3 n	3 n
12	36 F	8	LE	10 n	8 n	8 n	8 n	8 n
15	41 F	1	UE	2 n	1 n	1 n	1 n	0 n
18	32 M	4	UE	13 n	13 n	12 n	11 n	10 n
19	44 F	10	UE	18 n n	18 n	14 n	13 n	10 n

Appendix H - Salicylic Acid 16.5% + Lactic Acid 16.5% Solution Group

Patient Number	Age (yr)/ Sex	Duration of lesion (weeks)	Location of Lesion	Week 0 AR	Week 1 AR	Week 2 AR	Week 3 AR	Week 4 AR
2	21 M	10	UE	18 n	17 n	17 n	14 n	3 n
3	10 F	8	UE	7 n	11 slight stinging	11 n	7 n	4 n
6	17 M	8	LE	10 n	9.5 pruritus	9 n	7 n	0 n
8	8 M	4	UE	5 n	3 slight stinging	0 n	0 n	0 n
10	31 F	12	UE	12 n	14 stinging	14 stinging	14 slight erythema	14 slight erythema
13	40 F	16	LE	28 n	30 erythema	30 slight erythema	30 slight erythema	30 n
14	39 M	16	LE	23 n	21 pruritus	20 n	20 n	20 n
16	26 M	4	UE	5 n	5 slight stinging	5 pruritus	5 n	5 n
17	21 F	4	UE	6 n	8 erythema	9 pruritus	5 n	2 n
20	35 M	4	UE	6 n	5 n	5 n	5 n	5 n

Appendix I – Cost Analysis/Comparison

For the *Melaleuca alternifolia* oil

Melaleuca alternifoloia	P 38.40
Container	P 15.00
Wooden stick	P 0.40
Sticker Label	P 0.30
Cotton Balls	P 8.40
Forms	P 3.00
TOTAL	**P 65.50**

For the Salicylic Acid 16.5% + Lactic Acid 16.5% solution

SA + LA	P 205.87
Container	P 15.00
Wooden stick	P 0.40
Sticker Label	P 0.30
Cotton Balls	P 8.40
Forms	P 3.00
TOTAL	**P 232.97**