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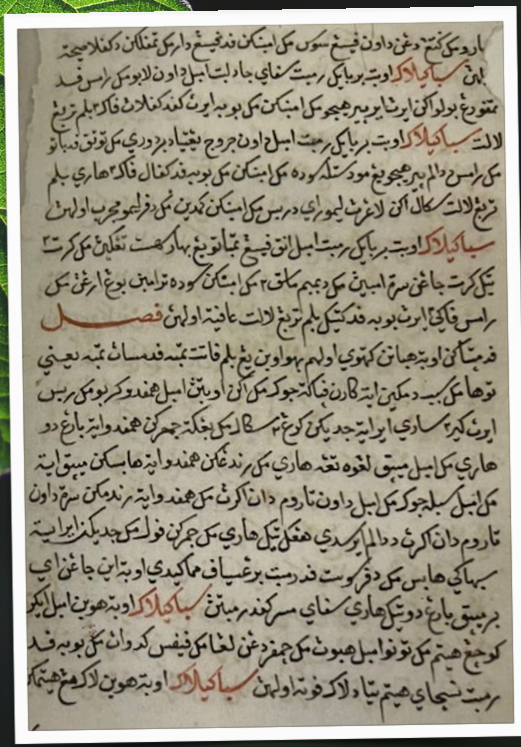

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# SHINGLES REMEDIES BASED ON ANALYSIS OF ACCORDION-FOLDED MALAY MEDICAL MANUSCRIPT MSS 3048

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## ABSTRACT

Shingles or herpes zoster (HZ) is a painful disease caused by reactivation of latent varicella zoster virus (VZV) in the sensory dorsal root ganglion cells of human body after the primary infection, chickenpox. Currently, there is no drug that can cure it besides for symptoms relief. Therefore, traditional remedies from credible sources such as the Malay medical manuscript MSS 3048 was referred to for getting various valuable medicinal information regarding cure and treatment of shingles disease. A transliterated Malay medical manuscript (MMM) containing remedies on shingles disease was selected, followed by data extraction and tabulation on its formulations and ingredients used. Subsequently, ingredients from the formulations were comparatively analysed against contemporary studies to discover scientific evidence and pharmacological properties that has high potential to be developed as new pharmaceutical products. After evaluation using SAKTI-iPharmaprospect index, the highly scored-formulations were assessed based on comparative analysis to determine the best formulations that can be recommended for further studies. In MSS 3048, 19 formulations were discovered for shingles disease. Data analysis and comparative study on shingles provided information on pharmacological properties of each plant and there were a few plants having high scientific evidences including *Annona* spp., *Piper betel* Linn, *Schima wallichii*, *Dipterocarpus* spp., *Areca catechu*, *Euphorbia hirta* and *Quercus infectoria*. The use of SAKTI-iPharmaprospect discovered eight Grade A formulations and after assessment with contemporary scientific evidence, three formulations which were F2, F4 and F15 were selected as the best formulations. In conclusion, grade A formulations, F2, F4 and F15 have high potential to be selected for further studies and developed into new pharmaceutical products. The findings from this study may contribute to future laboratory works and research for development of pharmaceutical products for shingles treatment and Traditional and Complementary Medicine (T&CM) in Malaysia.

## KEYWORDS

Shingles, Herpes zoster, *kayap*, Varicella-zoster virus (VZV), MSS 3048, Traditional Malay medicine

## INTRODUCTION

Shingles or herpes zoster (HZ) is a painful viral infection caused by reactivation of varicella zoster virus (VZV), a type of herpesvirus from family herpesviridae that able to induce persistent infection causing chickenpox and shingles (Freer, 2018). Signs and symptoms of shingles are burning or tingling pain in the skin, rash of fluid-filled blisters, numbness, itching, fever, fatigue and headache. Shingles can be treated using antiviral drugs such as acyclovir, valacyclovir or famycyclovir along with other symptom-based treatments.

Many current modern treatments are known to help alleviate shingles symptoms. However, they cannot effectively cure the patients after primary infection subsided because the virus stayed latent in the sensory dorsal root ganglion cells. Other than that, shingles also cause complications such as long-term nerve pain called postherpetic neuralgia (PHN), eye complications, hearing or balance problem and meningitis (National Institute of Neurological Disorders and Stroke, 2015). Therefore, traditional remedies against shingles are very interesting and beneficial to be studied as they might possess different treatments for the disease and its symptoms. To find credible source from traditional

remedies, a Malay medical manuscript was referred to as it contained valuable medical information that has been preserved from more than 100 years ago.

Malay medical manuscripts (MMMs), handwritten in *Jawi* scripts were produced in the early 16th century until the early 20th century in Malay language (National Library of Malaysia, 2018) and recorded more than 80% of medicinal contents (Mohd Shafri, 2021a) such as illnesses or health issues, formulations for treatment, materia medica, and various healing methods in their texts. In this study, manuscript MSS 3048 containing traditional remedies for shingles or '*kayap*' was obtained from the collection of National Centre for Malay Manuscripts (PKMM) of the National Library of Malaysia.

This study is important in conserving and analysing the medicinal information, their uses and benefits which may contribute to the new discovery and development of pharmaceutical products from naturally occurring ingredients. Additionally, these findings align with the establishment of Traditional and Complementary Medicine (T&CM), and could be beneficial for research and development of Malay medicine for T&CM, as well as modern medicine as supported by the Ministry of Health, Malaysia (MOH).

## MATERIALS & METHODS

### Manuscript Selection and Data Extraction

An accordion-folded MMM, MSS 3048 that have been transliterated from *Jawi* scripts into Roman alphabets containing formulations for treatment of shingles or '*kayap*' was selected to be studied based on Scientific Analysis of Kitab Tib Index- Index of Manuscript Selection (SAKTI-iMS) (Mohd. Shafri, 2021b). To enable a systematic and objective evaluation for the manuscript selection of MSS 3048, SAKTI-iMS used four major criteria which were: (i) author's profile, (ii) completeness of text, (iii) legibility of text and (iv) amount of medical content in the manuscript. Finally, the sum of scores given according to the four criteria were be graded accordingly. Manuscript with final score ($\Sigma x$ = 5-6) was graded A which indicates a strong candidate, or of high priority, B ($\Sigma x$ =3-4) indicates medium or intermediate priority, C ($\Sigma x$ = 1-2) indicates low priority and D ($\Sigma x$=0) denotes very low priority for manuscript selection.

Next, numbering system were generated for each medical formulation found in the manuscript. FXX system was used where F refers to 'formulation' and XX were given numbers that denoted the sequence of formulations for shingles remedies. FXX(a) or FXX(b) were designated to indicate the same formulation having two different drug delivery routes. Data from the formulations were extracted and tabulated.

### Comparative Analysis and Assessment of Ingredients with Contemporary Scientific Evidence

Comparative analysis was performed on all identified plant-based ingredients mentioned in the shingles formulations to find scientific evidence of their pharmacological properties that could be used for further research on treatment and prevention of shingles disease. Comparative study on the identified plants were conducted using online database Google Scholar and PubMed where related articles were searched using keywords such as "scientific name of plant", "disease", "medicinal importance" and "pharmacological properties", with relevant Boolean operators. Review papers of a particular plant were referred to for getting some ideas on the experimented therapeutic or pharmacological properties of the plant that related to the VZV infection or symptoms of shingles. The articles were selected based on a few criteria. The inclusion criteria include (i) English or Malay language, (ii) time ranging between 1980 and present, (iii) in-vivo, in-vitro, ex-vivo or clinical trial studies (v) related pharmacological action and (vi) full articles. Next, the exclusion criteria were articles of (i) different languages other than English and Malay language, (ii) not full paper (containing abstract only) and (iii) unrelated pharmacological action.

### Evaluation of Formulations Using SAKTI- iPharmaprospect

Lastly, systematic search bioprospect using Scientific Analysis of Kitab Tib Index- Index of Pharmaceutical Prospectivity (SAKTI-iPharmaprospect) (Mohd. Shafri, 2021b) was performed to discover the potential and useful application of a formulation. Several components including material

provenance, complexity of formulation, ease of use or drug delivery system and ease of preparation were summed up to get the final score between ∑x = 4 and Σx = 12. The component material provenance consisted of local material, foreign material and mix material from foreign and local source were scored 3, 2 and 1 respectively. Next, the type of formulation consisted of single ingredients was given score 2 and mixed ingredients, was given score 1. Drug delivery system by topical or external application was given the highest score, 3, followed by ear or eye drop, score 2 and oral route, score 1. As for ease of preparation, the formulation that could be immediately used was given the highest score, 4. Other than that, formulation that need one step in a day was scored 3 and formulation with more than 2 steps in a day was scored 2. Table 4 showed the final score graded between A (Σx = 10-12), B (Σx =7-9), and C (Σx = 4-6). Finally, comprehensive assessment of ingredients along with contemporary scientific evidence were performed across all formulations, focusing particularly on Grade A formulations to determine the best formulation with highest potential to be selected for further research.

## RESULTS

### Manuscript Selection and Evaluation Using SAKTI-iMS Index.

MSS 3048 was selected and graded based on SAKTI-iMS evaluation (Mohd Shafri, 2021b). The amount of medical content of MSS 3048 was evaluated and it was found that the manuscript had more than 80% amount of medical content. Next, evaluation of completeness and legibility of text was conducted. The text in MSS 3048 was legible and considered complete as it has more than 80% of the pages that are able to be read. Lastly, the author's profile was evaluated. There was no author's profile found from this manuscript. Table 1 recorded the evaluation of manuscript MSS 3048 based on the four major selection criteria.

**Table 1** Evaluation of MSS 3028 using Index of Manuscript Selection (SAKTI-IMS)

| Name of manuscript | Author's profile (x=score) | | Integrity of text (x=score) | | Legibility of text (x=score) | | Medical content (physical treatment) (x=score) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Unknown (0) | Known (1) | Incomplete (0) | Complete >80% (1) | Illegible (0) | Legibility >80% (1) | <5% (0) | 5-50% (1) | 50-80% (2) | >80% (3) | Σx Score | Grade |
| MSS 3048 | ✓ | | | ✓ | | ✓ | | | | ✓ | 5 | A |

As grading for MSS 3048 was carried out, the score was (∑x = 0+1+1+3) where the final score Σx = 5. Thus, MSS 3048 was graded as Grade A which indicates a strong candidate for manuscript selection and was selected for this study.

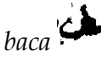
### Formulation and data extraction

MSS 3048 containing traditional remedies on shingles or *'kayap'* was found to have 19 formulations in the transliterated text. The formulations were described for different types of *'kayap'* including *'ubat kayap'*, *'ubat kayap ular dan kayap api'*, *'ubat kayap di dalam perut busuk bangar baunya lagi memulas perutnya'* and *'ubat kayap atau cercak'*. The formulations were presented in Table 2.

Table 2: Formulations related to shingles and *'kayap'* in MSS 3048.

| Formulation number | Formulations | Ingredients/ Vernacular name | Scientific name |
|---|---|---|---|
| F01<br>*Ubat kayap* | *Bab ini ubat kayap ambil daun keruing, hujung lemukut, mata kunyit giling lumat-lumat bubuhkan. Jikalau pecah ambil daun benalu mayang dan daun cengkilan, hujung lemukut, mata kunyit giling lumat-lumat bubuhkan pada kayap itu.* | *Daun Keruing* | *Dipterocarpus* spp. |
| | | *Hujung Lemukut*/ Rice | *Oryza sativa L.* |
| | | *Mata Kunyit*/ Turmeric | *Curcuma longa* |
| | | *Daun Benalu Mayang* | - |
| | | *Daun Cengkilan*/ Purging Croton | *Croton tiglium* |
| F02 (b)<br>*Ubat kayap di dalam perut*/ Eruption of epithelial surface in gut lining | *Bab ini ubat kayap di dalam perut busuk baunya dan atau putus perutnya oleh sebab penyakit itu, maka ambil daun keremak betina dan daun lonang dan daun nyarang songsang dan sekaliannya itu ambil patinya minum* | *Daun Keremak Betina*/ False Daisy | *Eclipta alba hassk* |
| | | *Daun Lonang*/ Sugar Apple | *Annona* spp. |
| F02 (a) | *dan hampasnya bedakkan pada penyakit itu ā'fiyāt.* | *Daun Nyarang Songsang*/ Chaff-Flower | *Achyranthes aspera* |
| F03<br>*Ubat membantutkan kayap* | *Bab ini ubat membantutkan kayap maka ambil lada dan kulit tengar maka mamah-mamah semburkan dengan sirih pinang ā'fiyāt.* | *Lada* | *Capsicum* |
| | | *Kulit Tengar*/ Spurred Mangrove | *Ceriops tagal* |
| | | *Sirih*/ Betel | *Piper betel Linn* |

| | | | |
|---|---|---|---|
| | | *Pinang*/ Betel Nut | *Areca catechu* |
| F04<br>*Ubat membantutkan kayap* | *Sebagai lagi ubat membantutkan kayap maka ambil sirih yang masak tiga helai atau yang kuning maka semburkan pada kayap.* | *Sirih*/ Betel | *Piper betel Linn* |
| F05<br>*Ubat kayap* | *Sebagai lagi ubat kayap maka ambil akar lemah-lemah dengan daki buyung bubuh pada kayap itu mujarāb.* | *Akar Lemah-lemah* | - |
| | | *Daki Buyung* | - |
| F06 (b)<br>*Ubat kayap di dalam perut*/ Eruption of epithelial surface in gut lining | *Bab ini ubat kayap di dalam perut busuk bangar baunya lagi memulas perutnya. Maka daun tulang-tulang dan daun keremak betina, maka pipis ambil patinya minum* | *Daun Tulang-tulang*/ Indian Tree Spurge | *Euphorbia tirucalli* |
| F06 (a) | *dan hampasnya bedakkan sekalian tubuhnya* | *Daun Keremak Betina*/ False Daisy | *Eclipta alba hassk* |
| F07<br>*Ubat kayap atau cercak* | *Sebagai lagi ubat kayap atau cercak. Maka ambil karang dan beras dan akar cemperai dan ara tanah merah dan kunyit maka giling lumat-lumat tampalkan pada penyakit itu, basuh pagi dan petang. Sudah giling tutup, jangan kena angin kalau-kalau tawar bisanya.* | *Karang* | *Hedyotis phillippensis* |
| | | *Beras*/ Asian Rice Paddy | *Oryza sativa* |
| | | *Akar Cemperai*/ False Olive | *Champereia griffithii, Champereia manillana* |
| | | *Ara Tanah Merah*/ Hairy Spurge | *Euphorbia hirta* |
| | | *Kunyit*/ Turmeric | *Curcuma domestica, Curcuma longa* |
| F08 | | *Akar* [illegible] | - |

| | | | |
|---|---|---|---|
| *Ubat kayap atau cercak di mata* | *Sebagai lagi ubat kayap atau cercak di mata, keluar nanah dari mata*  *. Titis di dalam mata, ambil akar*  *yang menghadap matahari naik asah dengan air bermalam bubuh ke dalam mata itu ā'fiyāt.* | *Air Bermalam/* Day-old water | - |
| F09 *Ubat kayap* | *Sebagai lagi ubat kayap ambil akar*  *dan daun delima dan pucuk kemudu dan bunga*  *, lada tiga butir semburkan pada kayap itu ā'fiyāt.* | *Akar Melidang* | - |
| | | *Daun Delima/* Pomegranate | *Punica granatum* |
| | | *Pucuk Kemudu/* Lettuce Tree | *Pisonia grandis* |
| | | *Bunga Memeri* | - |
| | | *Lada* | *Capsicum* |
| F10 *Ubat kayap* | *Sebagai lagi ubat kayap maka ambil pucuk nipah, basuh. Maka kikis kulitnya jangan kena kulit daunnya. Maka ambil batangnya pipis, masuk, hujung lemukut, mata kunyit giling lumat-lumat hancurkan dengan air bermalam maka bubuh pada kayap itu maka baca*   *hingga akhirnya tiga kali senafas, bubuh dengan bulu ayam pada tempat yang sakit itu ā'fiyāt.* | *Pucuk Nipah/* Nipah Palm | *Nypa fruticans Wurmb* |
| | | *Hujung Lemukut /* Rice | *Oryza sativa L.* |
| | | *Mata Kunyit/* Turmeric | *Curcuma domestica, Curcuma longa* |
| | | *Air bermalam/* Day-old water | - |
| | | *Bulu Ayam/ Chicken* | *Gallus gallus domesticus* |
| F11 *Ubat kayap* | *Sebagai lagi ubat yang diminum dalamnya maka ambil akar lemah-lemah dan akar terung kemar dan buah pala dan manjakani dan cendana canggi asah beri minum ā'fiyāt.* | *Akar Lemah-lemah* | - |
| | | *Akar Terung Kemar* | *Cyclea laxiflora* |

| | | | |
|---|---|---|---|
| | | *Buah Pala*/ Nutmeg | *Myristica fragrans* |
| | | *Manjakani*/ Aleppo Oak | *Quercus infectoria* |
| | | *Cendana Canggi* | *Pterocarpus santalinus Blanco* |
| F12 *Ubat kayap* | *Sebagai lagi ubat kayap maka ambil daun delima dan daun cucuran atap dan lada maka semburkan pada kayap itu ā'fiyāt.* | *Daun Delima*/ Pomegranate | *Punica granatum* |
| | | *Daun Cucuran Atap*/ False Ru | *Baeckea frutescens* |
| | | *Lada* | *Capsicum* |
| F13 *Ubat kayap* | *Sebagai lagi ubat sakit kayap maka ambil sabuk dan sepah dan rambu tikar maka ambil abunya bubuh dengan air pinang ā'fiyāt.* | *Sabuk* | - |
| | | *Sepah* | - |
| | | *Rambu Tikar* | - |
| | | *Air Pinang*/ Betel Nut | *Areca catechu* |
| F14 *Ubat kayap* | *Sebagai lagi ubat kayap maka ambil butir macang dan lada semburkan pada kayap itu ā'fiyāt.* | *Butir Macang*/ Horse Mango | *Mangifera foetida* |
| | | *Lada* | *Capsicum* |
| F15 *Ubat kayap* | *Ini ubat bedaknya maka ambil daun cangkuk manis dan beras kunyit giling lumat-lumat bedakkan ā'fiyāt.* | *Daun Cangkuk Manis*/ Needlewood | *Schima wallichii* |
| | | *Beras Kunyit*/ Rice | *Oryza sativa* |
| F16 *Ubat kayap* | | *Isi* طاکیت | - |

| | | | |
|---|---|---|---|
| | *Sebagai lagi ubat kayap maka ambil isi* طالكيت *dan akar rotan tawar semburkan pada kayap itu ā'fiyāt.* | *Akar Rotan Tawar*/ Rattan | *Calamus aquatilis* |
| F17<br>*Ubat kayap* | *Fasal ini pada menyatakan ubat kayap. Sebermula kayap itu tiga pagi, pertamanya kayap api dan keduanya kayap ular, ketiganya kayap air. Adapun kayap api itu maka ambil timah hitam, asah bubuhkan. Kemudian maka ambil bawang dan daun kayu yang lendir dan yang sejuk maka giling dengan hujung lemukut, mata kunyit maka bubuh pada kayap itu.* | *Timah Hitam* | *Lead* |
| | | *Bawang* | *Allium sp.* |
| | | *Daun Kayu yang Lendir dan Sejuk* (Slime, From Plants) | - |
| | | *Hujung Lemukut*/ Rice | *Oryza sativa L.* |
| | | *Mata Kunyit*/ Turmeric | *Curcuma longa* |
| F18<br>*Ubat kayap* | *Sebagai lagi ubat kayap maka ambil sekalian perkara wangi dan jangan yang gatal tiada baik, maka bubuh pada kayap itu ā'fiyāt.* | *Perkara Wangi* (Aromatic) | - |
| F19<br>*Ubat kayap ular dan kayap api* | *Dan adapun kayap ular dan kayap api itu sangat-sangat mintak tolong orang tawar bisanya akan hal ubatnya kayap ular dan kayap api itu sekalian barang yang lendir insyā Allāh tawarlah bisanya.* | *Barang Yang Lendir* (Slime, might be from Plants or Animals) | - |

**Comparative analysis against contemporary scientific evidence**

To compare the identified plants in MSS 3048 against contemporary published studies, the pharmacological properties of each plant was presented in Table 3. Pharmacological actions found related to shingles were antiviral or antiherpetic, anti-inflammatory, wound healing, analgesic, antibacterial, and anti-neuroinflammatory properties.

*Keruing* found in F01 possess antibacterial, antiviral, anti-inflammatory and wound healing properties. Next, *keremak betina* mentioned in F02 and F06, *lada* or *Capsicum* spp. in F03, F09, F12 and F14, *nipah* in F10, *buah pala* or nutmeg in F11, *cendana canggi* in F11, and *macang* or horse mango in F14 possess antibacterial, analgesic and anti-inflammatory pharmacological properties. Other than that, analgesic, antibacterial, wound healing and anti-inflammatory properties were found for *lonang* in F02, *sirih* or betel leaves in F03 and F04, *pinang* or betel nut in F03 and F13, *ara tanah merah* in F07 and *manjakani* in F11. As for *delima* or pomegranate cited in F09 and F12, it comprises of anti-inflammatory, antibacterial, and antiviral properties while *cangkuk manis* noted in F15 held anti-inflammatory, analgesic, antipyretic, and antibacterial properties. As for *mata kunyit* or turmeric in F01, F07, F10 and F17, *kemudu in F09 and bawang or Allium* spp. *in F17*, they held anti-inflammatory, wound healing, and antibacterial properties. Wound healing and antibacterial properties were identified for *nyarang songsang* in F02 while antiviral and antibacterial properties was identified for *tulang-tulang* in F06. On the other hand, *cengkilan* in F01 had the analgesic and anti-neuroinflammatory properties that could reduce pain caused by shingles lesion and helped in the injury to peripheral as well as central nervous system caused by PHN complication. *Rotan tawar* written in F16 was observed to have anti-inflammatory and antibacterial properties. *Karang* in F07 and *Oryza sativa* mentioned in MSS 3048 as *hujung lemukut, beras,* and *beras kunyit* found in F01, F07, F10, F15 and F17 only had anti-inflammatory properties. Finally, *terung kemar* cited in F11 and *cucuran atap* mentioned in F12 consisted of antibacterial and wound healing properties respectively.

From the analysis of ingredients against contemporary published studies depicted in Table 4, the findings demonstrated that *keruing* (*Dipterocarpus* spp.), *lonang* (*Annona* spp.), *sirih (Piper betel Linn), pinang (Areca catechu), ara tanah merah (Euphorbia hirta), manjakani (Quercus infectoria)* and *cangkuk manis (Schima wallichii)* exhibited the highest number of pharmacological properties. Each ingredients possess a minimum of four distinct pharmacological properties and were most frequently cited in published articles in relation to treatments for symptoms associated with shingles infections.

**Table 3** Analysis and contemporary published articles for ingredients in shingles formulation.

| Scientific name/ Vernacular name | Formulation number | Properties of ingredients | References | Types of study |
|---|---|---|---|---|
| *Dipterocarpus* spp./ *Keruing* | F01 | Antibacterial | (Samad & Silva, 2021) | in vitro |
| | | | (Le et al., 2021) | in vitro |
| | | Antiviral | (Shen et al., 2017) | in vitro |
| | | Anti-inflammatory | (Yang et al., 2013) | in vivo |
| | | | (Fernandes & Maharani, 2019) | in vitro |
| | | Wound healing | (Biswas et al., 2004) | in vivo |
| *Oryza sativa*/ *Hujung lemukut, Beras, Beras kunyit* | F01<br>F07<br>F10<br>F15<br>F17 | Anti-inflammatory | (Limtrakul et al., 2016) | in vitro |

| | | | | |
|---|---|---|---|---|
| *Curcuma longa*/ *Mata kunyit* | F01<br>F07<br>F10<br>F17 | Anti-inflammatory | (Motterlini et al., 2000)<br>(Ramsewak et al., 2000) | in vitro<br>in vitro |
| | | Wound healing | (Kundu et al., 2014) | in vivo |
| | | Antibacterial | (Singh et al., 2002) | in vitro |
| *Croton tiglium*/ *Cengkilan* | F01 | Analgesic | (Liu et al., 2016) | in vivo & in vitro |
| | | Anti-neuroinflammatory | (Gupta et al., 2020) | in vitro |
| *Eclipta alba* hassk/ *Keremak betina* | F02<br>F06 | Antibacterial | (Pandey et al., 2011) | in vitro |
| | | Analgesic | (Sawant et al., 2004) | in vivo |
| | | Anti-inflammatory | (Leal et al., 2000) | in vivo |
| *Annona* spp./ *Lonang* | F02 | Analgesic | (Abd Hamid et al., 2012) | in vivo |
| | | Antibacterial | (Padhi et al., 2011) | in vitro |
| | | Wound healing | (Moghadamtousi et al., 2015) | in vivo |
| | | Anti-inflammatory | (De Sousa et al., 2010) | in vivo |
| *Achyranthes aspera*/ *Nyarang songsang* | F02 | Wound healing | (Edwin et al., 2008) | in vivo |
| | | Antibacterial | (Abi Beaulah et al., 2011) | in vitro |
| *Capsicum* spp./ *Lada* | F03<br>F09<br>F12<br>F14 | Analgesic | (Jolayemi & Ojewole, 2014) | in vivo |
| | | Anti-inflammatory | (Zimmer et al., 2012) | in vivo |
| | | Antibacterial | (Nascimento et al., 2014) | in vitro |
| *Piper betel Linn*/ *Sirih* | F03<br>F04 | Antibacterial | (Akter et al., 2014) | in vivo |
| | | Analgesic | (Reddy et al., 2016)<br>(Alam et al., 2021) | in vivo<br>in vivo |
| | | Anti-inflammatory | (reddy et al., 2016)<br>(Alam et al., 2021) | in vivo<br>in vivo |
| | | Wound healing | (Nilugal et al., 2014) | in vivo |
| *Areca catechu*/ *Pinang* | F03<br>F13 | Anti-inflammatory | (Khan et al., 2011) | in vivo |
| | | Wound healing | (Dewi & Fatonah, 2019) | in vivo |
| | | Analgesic | (Bhandare et al., 2010) | in vivo |
| | | Antibacterial | (Negi & Dave, 2010)<br>(Anupama et al., 2021) | in vitro<br>in vitro |

| | | | | |
|---|---|---|---|---|
| *Euphorbia tirucalli/ Tulang-tulang* | F06 | Antiviral | (Son et al., 2013) | in vitro |
| | | | (Betancur-Galvis, 2002) | in vitro |
| | | Antibacterial | (Upadhyay et al., 2013) | in vitro |
| *Hedyotis phillippensis/ Karang* | F07 | Anti-inflammatory | (Lin et al., 2002) | in vivo |
| | | | (Chen et al., 2015) | in vitro |
| *Euphorbia hirta/ Ara tanah merah* | F07 | Antibacterial | (Enerva et al., 2015) | in vitro |
| | | Wound healing | (Upadhyay et al., 2014) | in vivo |
| | | Anti-inflammatory | (Gunjan et al., 2021) | in vivo |
| | | Analgesic | (Lanhers et al., 1990) | in vivo |
| *Punica granatum/ Delima* | F09 F12 | Anti-inflammatory | (Lee et al., 2010) | in vitro & in vivo |
| | | Antibacterial | (Duman et al., 2009) | in vitro |
| | | Antiviral | (Angamuthu, 2019) | in vitro |
| *Pisonia grandis/ Kemudu* | F09 | Anti-inflammatory | (Radha, 2008) | in vivo |
| | | Antibacterial | (Prabu, 2015) | in vivo |
| | | Wound healing | (Prabu, 2015) | in vivo |
| *Nypa fruticans* Wurmb/ *Nipah* | F10 | Antibacterial | (Lovly & Marlee, 2018) | in vitro |
| | | Anti-inflammatory | (Kang & Hyun, 2020) | in vivo |
| | | Analgesic | (Reza et al., 2011) | in vivo |
| *Cyclea laxiflora/ Terung kemar* | F11 | Antibacterial | (George et al., 2017) | in vitro |
| | | | (Raja et al. 2011) | in vitro |
| *Myristica fragrans/ Buah pala* | F11 | Anti-inflammatory | (Jin et al., 2012) | in vitro |
| | | Antibacterial | (Ibrahim et al., 2011) | in vitro |
| | | Analgesic | (Hayfaa et al., 2013) | in vivo |
| *Quercus infectoria/ Manjakani* | F11 | Anti-inflammatory | (Kaur et al., 2004) | in vivo & in vitro |
| | | Wound healing | (Jalalpure et al., 2002) | in vivo |
| | | | (Umachigi et al., 2008) | in vivo |
| | | Analgesic | (Fan et al., 2014) | in vivo |
| | | Antibacterial | (Basri & Fan, 2004) | in vitro |
| *Pterocarpus santalinus* Blanco/ *Cendana canggi* | F11 | Analgesic | (Tippani et al., 2010) | in vivo |
| | | | | in vivo |

| | | | | |
|---|---|---|---|---|
| | | | (Sikdar et al., 2013) | |
| | | Anti-inflammatory | (Wu et al., 2011) | in vitro |
| | | | (Mohammed Usman, 2012) | in vitro |
| | | Antibacterial | (Gayathri & Kannabiran, 2009) | in vitro |
| | | | (Donga et al., 2017) | in vitro |
| *Baeckea frutescens/ Cucuran atap* | F12 | Wound healing | (Kamarazaman et al., 2022) | In vitro |
| *Mangifera foetida/ Macang* | F14 | Analgesic | (Garrido et al., 2001) | in vivo |
| | | Anti-inflammatory | (Garrido et al., 2001) | in vivo |
| | | | (Garrido et al., 2004) | in vivo & in vitro |
| | | Antibacterial | (Engels et al., 2011) | in vitro |
| *Schima wallichii/ Cangkuk manis* | F15 | Anti-inflammatory | (Dewanjee et al., 2009) | in vivo |
| | | | (Dewanjee et al., 2011) | in vivo & in vitro |
| | | Analgesic | (Dewanjee et al., 2009) | in vivo |
| | | Antipyretic | (Dewanjee et al., 2009) | in vivo |
| | | Antibacterial | (Barma et al., 2015) | in vitro |
| *Calamus aquatilis/ Rotan tawar* | F16 | Anti-inflammatory | (Chang et al., 2010) | in vitro |
| | | Antibacterial | (Borah et al., 2015) | in vitro |
| *Allium* spp./ *Bawang* | F17 | Wound healing | (Jalali et al., 2009) | in vivo |
| | | Anti-inflammatory | (Jayanthi & Dhar, 2011) | in vivo |
| | | Antibacterial | (Daka, 2011) | in vitro |

**Evaluation of formulations using SAKTI- iPharmaprospect**

Subsequently, SAKTI-iPharmaprospect (Mohd Shafri, 2021b) was performed for grading of shingles formulations along with assessment of their contemporary scientific evidence to evaluate the best formulation that have high potential to be selected for further studies. The scoring and grading of the formulations were shown in Table 4. Grade A, which was regarded as easy formulations was given for F4 with final score ($\Sigma x = 12$) while F2(a), F3, F4, F7, F13, F15, F18 and F19 with ($\Sigma x = 11$). For grade B or intermediate formulations, the final score ($\Sigma x = 9$) was given for F2(b), F6(a), F10, F12, F14, and F17. Final score ($\Sigma x = 8$) was given for F1, F5, F9 and F16 while F6(b) scored ($\Sigma x = 7$)**.** Lastly, F8 ($\Sigma x = 5$) and F11 ($\Sigma x = 6$) that were graded as grade C observed as difficult formulations. F2(a) and F2(b) consisted of same material provenance, type of formulation and ease of preparation but different drug delivery system which had affected the grading of the formulations. F2(a) used the oral drug delivery system and graded as A while F2(b) utilized topical application and graded as B. As for F6(a) and F6(b), they also used different drug delivery system but were graded as B.

**Table 4** Scoring and grading of shingles formulations in MSS 3048 using SAKTI iPharmaprospect.

| FORMULATION NUMBER, F(Y) | Material Provenance | | | Type of Formulation | | Drug Delivery System | | | Ease of Preparation | | | | Σx Score | GRADE: Easy: A: 10-12 Intermediate: B: 7-9 Difficult: C: 4-6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Local material | Foreign material | Mix | Single ingredient | Mixed ingredients | Topical /external | Ear / Eye drop | Oral | Immediate use | 1 step, in a day | >2 steps, in a day | >1 day | | |
| SCORE | 3 | 2 | 1 | 2 | 1 | 3 | 2 | 1 | 4 | 3 | 2 | 1 | | |
| F1 | | | - | | ✓ | ✓ | | | ✓ | | | | 8 | B |
| F2 (a) | ✓ | | | | ✓ | ✓ | | | ✓ | | | | 11 | A |
| F2 (b) | ✓ | | | | ✓ | | | ✓ | ✓ | | | | 9 | B |
| F3 | ✓ | | | | ✓ | ✓ | | | ✓ | | | | 11 | A |
| F4 | ✓ | | | ✓ | | ✓ | | | ✓ | | | | 12 | A |
| F5 | | | - | | ✓ | ✓ | | | ✓ | | | | 8 | B |
| F6 (a) | | | ✓ | | ✓ | ✓ | | | ✓ | | | | 9 | B |
| F6 (b) | | | ✓ | | ✓ | | | ✓ | ✓ | | | | 7 | B |
| F7 | ✓ | | | | ✓ | ✓ | | | ✓ | | | | 11 | A |
| F8 | | | - | - | | | ✓ | | | ✓ | | | 5 | C |
| F9 | | | - | | ✓ | ✓ | | | ✓ | | | | 8 | B |
| F10 | ✓ | | | | ✓ | ✓ | | | | | ✓ | | 9 | B |
| F11 | | | - | | ✓ | | | ✓ | ✓ | | | | 6 | C |
| F12 | | | ✓ | | ✓ | ✓ | | | ✓ | | | | 9 | B |
| F13 | ✓ | | | | ✓ | ✓ | | | ✓ | | | | 11 | A |
| F14 | | | ✓ | | ✓ | ✓ | | | ✓ | | | | 9 | B |
| F15 | ✓ | | | | ✓ | ✓ | | | ✓ | | | | 11 | A |
| F16 | | | - | | ✓ | ✓ | | | ✓ | | | | 8 | B |
| F17 | | | ✓ | | ✓ | ✓ | | | ✓ | | | | 9 | B |
| F18 | ✓ | | | | ✓ | ✓ | | | ✓ | | | | 11 | A |
| F19 | ✓ | | | | ✓ | ✓ | | | ✓ | | | | 11 | A |

## DISCUSSION

Shingles treatment in Grade A MSS 3048 mentioned 19 formulations consisting of single and compounded ingredients. From the 44 ingredients mentioned, 29 plants were identified and analysed against contemporary published studies. From analysis of Table 3, three plants had been tested in vitro for their antiviral or antiherpetic properties against herpesviridae family. In a study by Betancur-Galvis et al. (2002), the capacity of *Euphorbia tirucalli* extract to inhibit herpes simplex virus type 2 (HSV-2) lytic activity was evaluated using end-point-titration technique and MTT antiviral colorimetric assay. The findings showed that *Euphorbia tirucalli* water-methanol extract exhibited antiherpetic action with highest therapeutic index >7.1 compared to other plants from genus Euphorbia and shows no cytotoxicity.

As shingles was caused by VZV, studies on plants that were conducted on other herpesviruses such as HSV-1 and HSV-2 might have potential to exhibit same antiherpetic effect against the virus because all three viruses had been categorised as alphaherpesviruses (Baines & Pellett, 2007) and neurotropic that infected nervous system tissue (Roizman & Thayer, 2001). These viruses had same characteristics of unique four-layered structure which were a core with large, double-stranded DNA genome, enclosed by icosapentahedral capsid composed of capsomers and capsid surrounded by tegument amorphous protein coat. It was encased in a glycoprotein-bearing lipid bilayer envelope (Whitley, 1996). They also had 120 to 230 kbp length, base composition ranging from 31% to 75% G+C content and contained 60 to 120 genes (Roizman & Thayer, 2001). These common characteristics among the viruses might have potential for the plants to express same antiviral effect against them.

Shingles disease associated with pain, skin lesion, inflammation, and acute neuritis that causes burning or tingling sensation of the skin (Bolton et al., 2021). From Table 3, 13 plants possessed analgesic pharmacological properties and one of them was *Nypa fruticans* Wurmb. According to Reza et al. (2011), an in-vivo study for analgesic activity was performed using methanolic extract of leaf and stem of *Nypa fruticans* Wurmb(MENF) in experimental animals. The experiment used acetic acid induced writhing test in mice model to detect central and peripheral analgesia where they were treated with MENF of different doses and standard drug, aspirin. The mice were injected with acetic acid to cause pain by releasing endogenous mediators and production of prostaglandin, mainly prostacyclines (PGI2) and prostaglandin-E (PG-E) that was liable for pain sensation. Analgesic properties in the plant inhibited endogenous mediator prostaglandin synthesis observed through the results on maximum inhibition of writhing. The findings demonstrated significant analgesic activity which was better than the result obtained with aspirin indicating MENF have high potential to be developed as analgesia derived from local products.

Next, 20 plants had been studied in vivo and in vitro for their anti-inflammatory properties. One of the plants, *Myristica fragrans* mentioned by Jin et al. (2012) contained myrislignan, a compound that could attenuate lipopolysaccharide-induced inflammation in macrophages. As inflammation could occur due to inflammatory mediators, myrislignan were able to exhibit anti-inflammatory properties by inhibiting nitric oxide production in a dose-dependent manner, suppressed mRNA expression and inhibited the release of interleukin-6 (IL-6) and tumour necrosis factor-a (TNF-a). Myrislignan also decreased the cytoplasmic loss of inhibitor kB-α (IkB-α) protein and the translocation of NF-kB from cytoplasm to the nucleus, hence exhibited anti-inflammatory effects in LPS-stimulated macrophages cells by inhibiting the NF-kB signalling pathway activation.

Wound healing property of plants also important for healing of skin lesion after infection. 11 plants mentioned in the formulations possessed this property. An in vitro study of *Baeckea frutescens* by Kamarazaman et al. (2022) evaluated wound healing property by observing the increased rate of cytotoxicity proliferation and migration rate on keratinocytes and fibroblasts that were parts of complex wound healing process. In this study, cells viability of immortalized human keratinocyte and human dermal fibroblast against *Baeckea frutescens* leaves extract (BFLE) were performed using MTT assay. It was discovered that migratory effect BFLE on both fibroblast and keratinocyte displayed good response on speeding the proliferative phase of wound healing and toward the closing of wound gaps during wound contraction. Other than that, BFLE contained condensed tannins, flavonoids, steroids and saponins that also contributed to wound healing.

According to Bassukas and Kiorpelidou (2006), another complication of shingles was secondary invasive cutaneous and extracutaneous bacterial superinfection commonly caused by *Staphylococcus aureus* and Group A β hemolytic Streptococcus. Based on Table 3, in vitro studies for antibacterial properties were found on 21 plants. Anupama et al. (2021) demonstrated in vitro antibacterial study for evaluation of antibacterial properties of *Areca catechu* against two common bacterial pathogens, *Staphylococcus aureus* and *Escherichia coli*. The bacterial strains were inoculated into nutrient broth and incubated overnight with increasing concentration of *Areca catechu* extract. The absorbance at 530nm were recorded and bacterial growth inhibition were calculated. It was discovered that aqueous extract of *Areca catechu* exhibited antibacterial activity against both *Staphylococcus aureus* and *Escherichia coli* being tested. In conclusion, the plant that exhibited antibacterial action against *Staphylococcus aureus* could potentially treat and prevent bacterial superinfection due to VZV infection.

Other pharmacological property found was anti-neuroinflammatory property of *Croton tiglium*. As infection of VZV causing shingles would lead to unilateral, painful vesicular rash at a single dermatome due to reactivation of virus at the sensory root ganglion cells, it might cause injury to peripheral and central nervous system (Koshy et al., 2018). With anti-neuroinflammatory property, the consequences and complications of the infection could be prevented. Gupta et al. (2020) described an investigation on neuroprotective and anti-inflammatory effect of *Croton tiglium* extract (CTE). It was found that CTE significantly suppressed neurotoxic inflammatory factors production and increased neurotrophic factor and microglia production. In addition, CTE improved protection of neurons against neurotoxic factors released from LPS-stimulated microglia. This indicated the neuroprotective effect of CTE and had high potential as anti-neuroinflammatory agent.

MSS 3048 demonstrated 19 formulations for shingles remedies with 4 formulations consisting of single ingredients and 15 formulations encompassing mixed ingredients. Individual formulations were evaluated by utilizing SAKTI-iPharmaprospect, hence determined the grade of each formulation. In addition, as this evaluation was formulation-centred, the SAKTI-iPharmaprospect scores must also be assessed together with results from the comparative analysis. The combination of SAKTI-iPharmaprospect and scientific evidence from contemporary studies on plants found during the analysis further helped and contributed in evaluation and selection of the best formulation to treat this disease. In this study, SAKTI-iPharmaprospect was used to identify the formulations with the highest final score, especially those graded as A as these formulations had highest potential to be utilised for new treatments and development of drugs. Next, the re-assessment of contemporary scientific evidence from the former methodology was performed on ingredients used in the Grade A formulations to finally determine the best formulation that can be recommended for further study.
From Table 4, Grade A formulations including F2(a), F3, F4, F7, F13, F15, F18 and F19 used combination of two or more ingredients from local source, employed external drug delivery system and could be used immediately. Subsequently, the contemporary scientific evidence on the ingredients mentioned in Grade A formulations were assessed and the best formulations were described by the author as below:

F02:
"*Bab ini ubat kayap di dalam perut busuk baunya dan atau putus perutnya oleh sebab penyakit itu, maka ambil daun keremak betina dan daun lonang dan daun nyarang songsang dan sekaliannya itu ambil patinya minum dan hampasnya bedakkan pada penyakit itu ā'fiyāt.*"

Meaning: This chapter is a remedy for eruption of epithelial surface in gut lining, the smell is bad, and or the stomach breaks due to the disease. Take *keremak betina* leaves and *lonang* leaves and *nyarang songsang* leaves, take their extract and drink and grind (any leftover) the residues finely. Apply it on the disease. It will heal.

F02(a), a Grade A formulation with final score of ($\Sigma x = 11$) cited the usage of mixture of three ingredients and all the ingredients which were *keremak betina* (*Eclipta alba* hassk), *lonang (Annona* spp.) and *nyarang songsang* (*Achyranthes aspera)* showed scientific evidence of pharmacological properties including antibacterial, analgesic, anti-inflammatory, and wound healing. These ingredients were local ingredients that could be easily found and the formulation could be immediately used by applying it topically on the disease.

F04:
"*Sebagai lagi ubat membantutkan kayap maka ambil sirih yang masak tiga helai atau yang kuning maka semburkan pada kayap.*"

Meaning: Also, remedy to curb shingles. Take three ripe betel leaves or the yellow one, then spray on the shingles.

Grade A formulation, F04 had the highest final score of ($\Sigma x = 12$). It used only one ingredient, *betel* leaves (*Piper betel Linn)* that was be easily found and could be sourced locally. The *Piper betel* Linn presented evidence on antibacterial, analgesic, anti-inflammatory and wound healing properties. The

formulation was also easy to prepare, could be immediately used and the delivery system of the drug was also less complex as it can be applied externally. This indicated the benefit of using one local ingredient with many pharmacological properties that has potential for further studies to be developed as treatment for shingles infection.

F15: elaborate
"*Ini ubat bedaknya, maka ambil daun cangkuk manis dan beras kunyit giling lumat-lumat bedakkan ā'fiyāt.*"

Meaning: This is the powder medicine. Take *cangkuk manis* leaves and turmeric rice, grind them finely, apply. It will heal.

Lastly, grade A formulation F15 with final score of ($\Sigma x = 11$) containing *cangkuk manis* (*Schima wallichii*) and *beras kunyit (Oryza sativa)* were revealed to be having anti-inflammatory, analgesic, antipyretic and antibacterial effects based on the contemporary scientific evidence. These mixed ingredients could be easily sourced locally, utilized external application and immediately used after preparation. The formulation suggested its potential to be considered for further studies related to shingles infection.

Meanwhile, for other Grade A formulations, scientific evidence on their pharmacological properties against contemporary studies on some of the ingredients were not found. This could be attributed to the decreased usage of ingredients, stemming from scarcity of the plants, which lead to challenges in their acquisition. Consequently, there was a decrease or no research conducted on these ingredients.

Following assessment and evaluation using both SAKTI-iPharmaprospect and contemporary scientific evidence criteria, F2, F4 and F15 which exhibited various important pharmacological properties essential for treatment of shingles could be shortlisted for further laboratory works and studies. With proper research supported by modern scientific empirical data, these formulations utilizing available local resources from the Malay Archipelago would demonstrate significant potential to be developed into pharmaceutical products for treatment of shingles diseases.

## CONCLUSIONS

MSS 3048 is a unique accordion-folded manuscript, handwritten in *Jawi* scripts that recorded 19 formulations for shingles remedies mentioning 44 ingredients with 29 plants identified with their scientific names. The plants had various pharmacological properties related to shingles where 3 plants possessed antiviral properties against the alphaherpesviruses, 13 plants showed analgesic pharmacological properties, 20 plants with anti-inflammatory properties and 1 plant exhibited anti-neuroinflammatory properties. Other than that, 21 plants possessed antibacterial properties that could fight against shingles complication of bacterial superinfection and 11 plants presented wound healing properties that could be used to heal the wound due to lesion during infection. In addition, evaluation of shingles formulations using SAKTI-iPharmaprospect had found that three Grade A formulations, F2, F4 and F15 could be selected as the best formulations using assessment based on contemporary scientific evidence. These findings revealed high potential of formulations to be developed as commercially valuable and viable pharmaceutical products that able to contribute to further research and laboratory works for treatment and prevention of shingles disease other than help in the development of Traditional and Complementary Medicine (T&CM) in Malaysia.

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