AN INSIGHT INTO MALAY MEDICAL MANUSCRIPT MSS 4016 AND TYPHOID FEVER REMEDIES

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ABSTRACT

Records of traditional Malay medicine to treat various diseases, including typhoid fever, are contained in handwritten manuscripts. Typhoid, known in Malay as *kepialu*, is a bacterial infection caused by *Salmonella enterica* serovar Typhi (*S.* Typhi). The infection could be treated in the past using chloramphenicol, however chloramphenicol-resistant strain has emerged necessitating effort to find new drug candidates against typhoid fever. This study aims to extract and analyse the content of a Malay medical manuscript MSS 4016 pertaining to typhoid fever. The manuscript was first transliterated from *Jawi* to Roman alphabets using standard philological system. The formulations for typhoid fever were extracted and numbered. The ingredients were listed respective to each number. Then, comparative analysis against modern research was performed using Google Scholar journal database employing specific keywords such as the scientific names of plants and typhoid fever, combined using Boolean Operators, in any time frame. From 66 diseases and 248 differing formulations contained in the manuscript, 16 formulations were intended for typhoid fever involving the use of 63 types of plants. From the comparative analysis, 50 were reported in contemporary modern publications as having various pharmacological activities related to typhoid. Thirty-four plants possess antibacterial property and specifically 18 plants have been shown to inhibit the growth of *S.* Typhi such as *Allium cepa, Allium sativum and Nigella sativa*. MSS 4016 is indeed an ancient pharmacopoeia holding a lot of medicinal information on numerous diseases. The valuable information gathered from this study may preserve knowledge in the manuscript while at the same time help in discovering potential plants for typhoid treatments.

Keywords: Malay medicine, manuscript, MSS 4016, typhoid fever, *kepialu*, traditional medicine

INTRODUCTION

Malay medical manuscript (MMM) is one of the tangible heritages of Malay civilisation. The Malays produced their own manuscripts, "original, handwritten piece of writing that is unprinted." (Yahaya, 2016). After the arrival of Islam, *Jawi* is the main form of writing found in these Malay manuscripts. The earliest *Jawi* script discovered in Malaysia is the 1303 AD Terengganu Inscription (Al-Attas, 1970). One of the genres of Malay manuscripts is medical text or 'Kitab Tib'. These manuscripts, including the manuscript MSS 4016, record information about the medicinal uses of local natural resources to treat various diseases including typhoid fever. Typhoid fever is known to the Malays as *demam kepialu*. It is a bacterial infection caused by ingestion of food or drink contaminated with

Salmonella enterica serovar Typhi (*S.* Typhi). The signs and symptoms are highly variable including high fever, rash, diarrhoea and vomiting.

In Malaysia, typhoid fever remains a worry. The incidence rate of typhoid fever in Klang valley, Malaysia, was within 0.5 – 0.7 per 100 000 population from 2011 - 2014 but this has spiked to 1.42 in 2015. In addition, detected cases of multiple drug resistant (MDR) *S.* Typhi was also increasing from 10% in 2011 to 30% in 2015 (Muhammad et al., 2020). The infection could be previously treated with the antibiotic chloramphenicol but resistant to first-line antibiotics including methoxazole and ampicillin has since become a problem (Dyson et al. 2019). This was further aggravated by the large-scale emergence of extensively drug resistant (XDR) *S.* Typhi clone in 2016 in Pakistan, which are resistant to chloramphenicol, trimethoprim-sulfamethoxazole, ampicillin, fluoroquinolones and third-generation cephalosporin. Furthermore, XDR *S.* Typhi has also been reported in the United Kingdom. As only one oral antibiotic is currently able to treat the infection by XDR *S.* Typhi, treatment is rather difficult and costly (Klemm et al. 2018). Thus, the case of drug resistance of *S.* Typhi and possibility of its spread to other parts of the world is alarming and indicate an urgency in finding other alternative treatments.

MMM is seen as a pharmacopoeia that can provide some medicinal information regarding the treatment of typhoid fever, which is based on local resources. Therefore, the objective of this study is to extract and analyse the medicinal content pertaining to typhoid fever disease from manuscript MSS 4016. This is also in parallel with the Malaysian government's effort to establish traditional and complementary medicine (TCM) in Malaysia. By establishing the Traditional & Complementary Medicine Blueprint 2018-2027, the Malaysian Government, through the Ministry of Health Malaysia (2017), has introduced a strategy to enhance and control TCM to improve the national healthcare system. Thus, the knowledge in the manuscripts need to be preserved before these manuscripts degrade and become unreadable. Although there is a large collection of MMM gathered at Pusat Kebangsaan Manuskrip Melayu (PKMM), Kuala Lumpur, its existence is hardly known by the public, even among the scientists. If these manuscripts are not studied, the knowledge of medicine in this manuscript will be wasted and cannot be passed to the next generations.

METHODS

Selection and Identification of Malay Manuscript

Several visits to PKMM were made to search for a suitable manuscript. The centre provides catalogues that list all available manuscripts with a short summary for each manuscript. The beginning, middle and end parts of several manuscripts were pre-read to identify the best manuscript to be studied. The manuscript was selected based on several criteria which are completeness, physical state, readability, and content of the manuscripts.

To ensure the completeness of a manuscript, page numbers and sentence continuity were observed to indicate the continuity of pages. The physical state of the manuscript should be relatively in a good condition to ensure the manuscript can be read easily without any missing words. The content of the selected manuscript also needs to be in medical theme to meet the objectives of this study. PKMM helped in preparing the photocopied version of the manuscript.

Transliteration and Data Extraction

The text in the manuscript was transliterated from *Jawi* into Roman alphabets using standard edition technique. The technique changes the types of alphabets with addition of punctuation marks, correction of spellings, and aligment with modern spelling, but strictly no additional words. An Android application, Speech Texter – Speech To Text (SpeechTexter, 2019) was also used to help the transliteration process as this application provides transcription of voice in real time. The transliteration process of MSS 4016 was conducted in two phases: individually and in a group of researchers to get as many opinions as possible. Furthermore, three online dictionaries were used, namely Majlis Bahasa Brunei-Indonesia-Malaysia (MABBIM), Pusat Rujukan Persuratan Melayu (PRPM) and Kamus Besar Bahasa Indonesia (KBBI), together with Google search engine and reference books (Mat Piah & Mustapha, 2019; Mat Piah & Baba, 2014) to recognise unfamiliar words and plants.

The formulations and diseases mentioned in the manuscript were extracted, tabulated and organised using a numbering system in the format of 4016.XXX.YYY, for which:

4016 refers to the name of the manuscript;

XXX refers to the disease sequence (Typhoid or *demam kepialu* has been assigned to number 030); and

YYY refers to the sequential number of formulations.

Analysis and Comparative Study

The identification of typhoid fever was done by searching the keyword of *demam kepialu* in the manuscript. The plants mentioned for the disease were extracted, analysed, and then classified into categories: name of the plant mentioned in the manuscript, plant's vernacular name, plant's scientific name, benefits of the plants discovered in modern studies. Since this study focused on typhoid fever, the analysis and comparative studies from modern research were done in relation to typhoid fever only. Google scholar journal database has been used in this study by searching the specific keywords such as "scientific name of plant" and "typhoid fever" in any time frame using Boolean operators.

RESULTS

Selection of Manuscript

Manuscript MSS 4016 is a manuscript written in traditional *Jawi* writing system, containing more than 200 pages. However, the real number of pages is vague because the manuscript seems to be mixed with other manuscripts, or at least other volumes of manuscripts written by the same author since the handwriting looks consistent. There is no information regarding the author of this manuscript because of missing pages at the beginning.

The physical state of this manuscript is relatively good that permits readability. Page number is indicated at the top of every page which consists of 21 lines of writing with approximately 11 to 12 words per line. The manuscript contains various fields including supplication, dream interpretation and medical. The latter is presented on 25 pages spanning from page 68 until 94 with a missing sheet (page 83 and 84). The pages exhibit the main text body in the middle of the pages with uniform margin throughout. Interestingly, some of the margin areas on most of the pages are filled with text, written in various directions, which is known as paratext. In this current study, the paratext was not transliterated but a quick observation on the text revealed that the paratext is also under medical theme.

The writing of this manuscript is systematic as the author arranged the chapters by diseases, indicated by red ink for the first word '*Bab ini*'. After the introduction of the disease name, it is usually followed by description of the disease and subsequently a few formulations which are divided by the word '*Sebagai lagi*' in red ink. Some words from this manuscript cannot be identified, or the meaning of the word cannot be deciphered.

A total of 66 diseases were identified including flu, sore eyes, toothache, bladder stone and dysmenorrhoea; and these constitute 248 formulations. These diseases cover all body systems, e.g., toothache (skeletal system), diarrhoea (gastrointestinal system), fungal infection (integumentary system), cough (respiratory system), back pain (muscular system), dysmenorrhoea (reproductive system), bladder stone (urinary system), headache (cardiovascular system/endocrine system), swelling (immune system) and quadriplegia (nervous system).

Transliteration and Data Extraction

There are 16 out of 248 formulations associated with typhoid fever, which is the highest number in the manuscript (6.45%). All the formulations are compounded which means multiple ingredients involved in one formulation. From 16 formulations, 63 types of plants and three minerals were identified while eight ingredients, potentially plant-based, could not be identified. Table 1 represents the list of plants intended to treat typhoid fever and Table 2 is the list of words that cannot be identified. The transliteration and translation together with formulation number of the 16 formulations are provided here:

4016.030.001 ***Bab ini pada menyatakan penawar kepialu. Ambil akar saga dan akar kepadang dan akar cengkian. Asah, minum.***
Meaning: This chapter presents the remedies for typhoid fever. Take jequirity bean root and *kepadang* root and purging croton root. Rub all onto a hard surface, then drink.

4016.030.002 ***Sebagai lagi, ambil pangkal benalu hijau dan akar betung dan akar saga petak dan akar seribu baik dan akar belalai puak.***
Meaning: Take Malayan mistletoe root, giant bamboo root, jequirity bean root, *seribu baik* root and *belalai puak* root.

4016.030.003 ***Sebagai lagi, ambil akar seribu bisa dan akar merpusi dan akar mertajam dan akar serapat dan akar temiang dan cendana janggi dan belerang bang.***
Meaning: Take *seribu bisa* root, freshwater mangrove root, kalayo root, *serapat* root, *temiang* root, red sandalwood and sulphur.

Bab ini pada menyatakan ubat kepialu tanah.
Meaning: This chapter presents the remedies for *kepialu tanah.*

4016.030.004 ***Ambil daun ribu-ribu seni dan daun susuk baju dan pucuk dan kanti, mesui. Giling lumat-lumat. Hancurkan dengan air, maka percikkan semua tubuhnya.***
Meaning: Take climbing fern leaves, *susuk baju* leaves, *pucuk*, *kanti* and masoy bark. Grind into smooth texture. Crush with water, then splash onto the whole body.

4016.030.005 ***Sebagai lagi, ambil daun gadung dan daun cekering dan jintan hitam dan cekur dan bawang merah.***
Meaning: Take *gadung* leaves, purple coral tree leaves, black cumin, aromatic ginger and onion.

4016.030.006 ***Sebagai lagi, ambil daun nilam dan beras kerisik dan beras mayang nyiur dan beras mayang pinang dan kulit mempelasari dan temu putih. Giling lumat-lumat. Hancurkan dengan air cendana.***
Meaning: Take patchouli leaves, fried coconut flesh, coconut flowers, betel palm flowers, alyxia cinnamon bark and zedoary. Grind into smooth texture. Crush with sandalwood water.

Bab ini pada menyatakan ubat kepialu air.
Meaning: This chapter presents the remedies for *kepialu air.*

4016.030.007 ***Ambil daun lada pahit dan ibu kunyit daun jintan hitam. Giling lumat-lumat. Hancurkan dengan air, maka percikkan semua tubuhnya.***
Meaning: Take macassar kernel leaves, turmeric and black cumin leaves. Grind into smooth texture. Crush with water, then splash onto the whole body.

4016.030.008 ***Sebagai lagi, ambil daun maman kuning dan daun benalu hijau dan sunti halia dan adas pedas dan jintan hitam.***
Meaning: Take tick weed leaves, Malayan mistletoe leaves, ginger buds, fennel and black cumin.

4016.030.009 ***Sebagai lagi, ambil akar birah hitam dan daun lakum dan lada sulah dan jabir dan daun delima dan bawang merah. Giling lumat-lumat. Hancurkan dengan air cendana.***
Meaning: Take *birah hitam* roots, cissus leaves, white pepper, *jabir,* pomegranate leaves and onion. Grind into smooth texture. Crush with sandalwood water.

Bab ini pada menyatakan ubat kepialu angin.
Meaning: This chapter presents the remedies for *kepialu angin.*

4016.030.010 ***Ambil cendana putih dan gaharu lampung dan kayu kelembak dan pucuk. Asah, maka percikkan semua tubuhnya.***
Meaning: Take sandalwood, agarwood, chinese rhubarb and costus. Rub all onto hard surface, then splash onto the whole body.

4016.030.011 ***Sebagai lagi, ambil temu lawak dan temu kuning dan temu iring dan lengkuas ranting dan sunti halia. Giling lumat-lumat. Hancurkan dengan air.***
Meaning: Take javanese turmeric, zedoary, pink and blue ginger, shell ginger and ginger buds. Grind into smooth texture. Crush with water.

4016.030.012 ***Sebagai lagi, ambil bunga melur dan bunga cempaka dan bunga kenanga dan bunga salu dan bunga pagar anak dan bunga pekan dan bunga campur aduk dan bunga kemuting dan bunga keduduk dan bunga leban dan bunga larak dan kulit mempelasari dan buah kulim dan bawang kedua dan beras kerisik. Giling lumat-lumat. Hancurkan dengan air cendana.***
Meaning: Take Arabian jasmine flowers, champak flowers, ylang-ylang flowers, *salu* flowers, *pagar anak* flowers, yesterday-today-tomorrow flowers, *campur aduk* flowers, rose myrtle flowers, malabar melastome flowers, Malayan teak flowers, large flower Uvaria, alyxia cinnamon bark, garlic nut, garlic, onion and fried coconut flesh. Grind into smooth texture. Crush with sandalwood water.

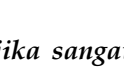
Bab ini pada menyatakan ubat kepialu api.
Meaning: This chapter presents the remedies for *kepialu api.*

4016.030.013 ***Ambil akar delima dan umbi serai dan kulit kelempayan dan buah kulim dan cendana putih. Asah, maka percikkan semua tubuhnya.***

Meaning: Take pomegranate root, lemongrass root, burflower-tree bark, garlic nut and sandalwood. Rub all onto hard surface, then splash onto the whole body.

4016.030.014 ***Sebagai lagi, ambil umbi anak pisang karuk dan anak pisang abu dan umbi anak pisang emas dan umbi anak pisang kelat. Maka tumbuk, ramas dengan air nyiur hijau. Maka tapis, ambil airnya. Maka, asah akar jarum gajah dan akar saga petak. Maka campurkan dengan air itu.***
Meaning: Take the root of wild banana pup, saba banana pup, lady finger banana pup and banana pup. Then, pound and squeeze with green coconut water. Afterwards, filter the water. Then rub *jarum gajah* root and jequirity bean root onto hard surface, and mix with the filtered water prepared previously.

4016.030.015 ***Sebagai lagi, ambil batang birah hitam dan daun kelemoyang dan daun kentut-kentut dan daun sirih masak dan isi pinang muda dan cekur, jerangau dan kanti, mesui dan bawang kedua dan ketumbar. Giling lumat-lumat. Hancurkan dengan air cendana.***
Meaning: Take *birah hitam* trunk, red-arrow leaf, skunk vine leaves, betel leaves, betel nut flesh, aromatic ginger, sweet flag, *kanti,* massoy bark, garlic, onion and coriander. Grind into smooth texture. Then crush with sandalwood water.

4016.030.016 ***Sebagai lagi, jika sangat sejuk kakinya, ambil daun***  ***dan ibu kunyit. Giling dengan kapur tohor. Maka bubuhkan pada kakinya.***

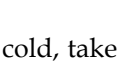
Meaning: If the feet are too cold, take  leaves and turmeric. Grind them with hydrated lime into smooth texture. Then paste it on the feet.

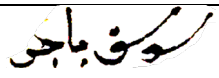
Table 1 List of plants identified for the treatment of typhoid fever.

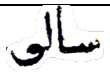
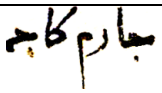
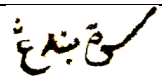
Vernacular name	Scientific Name	Formulation number (4016.030.xxx)	Part used
Adas pedas (Fennel)	*Foeniculum vulgare*	008	Seed
Bawang merah (Onion)	*Allium cepa*	005 009 012 015	Bulb
Bawang putih (Garlic)	*Allium sativum*	012 015	Clove
Belalai puak (Slay-berry tree)	*Pittosporum ferrugineum*	002	Root
Benalu hijau (Malayan mistletoe)	*Dendrophthoe pentandra (L.) Miq.*	005 008	Bottom Leaf
Betung (Giant bamboo)	*Dendrocalamus asper*	002	Root
Birah hitam	*Alocasia longiloba* Miq.	009 015	Root Trunk
Bunga melur (Arabian jasmine)	*Jasminum sambac*	012	Flower
Cekering (Purple coral tree)	*Erythrina fusca*	005	Leaves
Cekur (Aromatic ginger)	*Kaempferia galanga*	005 015	Rhizome
Cengkian (Purging croton)	*Croton tiglium*	001	Root
Cempaka (Champak)	*Michelia champaca*	012	Flower

Cendana/ Cendana kuning/ Cendana putih (Sandalwood)	*Santalum album*	006 009 012 015	Water extract
		010 013	Not stated
Cendana janggi (Red Sandalwood)	*Pterocarpus spp.*	003	Not stated
Delima (Pomegranate)	*Punica granatum*	009 013	Leaf Root
Gadung	*Dioscorea hispida*	005	Leaves
Gaharu (Agarwood)	*Aquilaria* spp.	010	Trunk
Halia (Ginger)	*Zingiber officinale*	008 011	Rhizome buds
Jerangau (Sweet flag)	*Acorus calamus*	015	Not stated
Jintan hitam (Black cumin)	*Nigella sativa*	005 007 008	Seed
Kanti	*Ligusticum acutilobum*	004 015	Not stated
Keduduk (Malabar melastome,)	*Melastoma malabathricum*	012	Flower
Kelembak (Chinese rhubarb)	*Rheum officinale*	010	Trunk
Kelemoyang (Red Arrow-leaf)	*Homalomena spp.,*	015	Flower
Kelempayan (Burflower-tree)	*Neolamarckia cadamba*	013	Bark
Kemuting (Rose myrtle)	*Rhodomyrtus Tomentosa*	012	Flower
Kenanga (Ylang-ylang)	*Cananga odorata*	012	Flower
Kentut-kentut (Skunk Vine)	*Paederia foetida*	015	Leaf
Ketumbar (Coriander)	*Coriandrum sativum*	015	Seed
Kulim (Garlic nut tree)	*Scorodocarpus borneensis*	012 013	Fruit Fruit
Kunyit (Turmeric)	*Curcuma longa*	007 016	Rhizome Rhizome
Lada pahit (Macassar kernels)	*Brucea amarissima, Brucea sumatrana*	007	Leaf
Lada sulah (White pepper)	*Piper nigrum*	009	Seed
Lakum (Cissus)	*Cissus repens*	009	Leaf
Larak (Large flower Uvaria)	*Uvaria grandiflora*	012	Flower
Leban (Malayan teak)	*Vitex pinnata*	012	Flower
Lengkuas ranting (Shell ginger)	*Alpinia conchigera*	011	Rhizome
Maman kuning (Tick weed)	*Cleome viscosa*	008	Leaf
Mempelasari (Alyxia cinnamon)	*Alyxia reinwardtii*	006 012	Bark Bark

Merpusi (Freshwater mangrove)	*Carallia brachiata*	003	Root
Mertajam (Kalayo)	*Erioglossum rubiginosum*	003	Root
Mesui (Massoy bark)	*Massoia aromatica, Cryptocarya massoia*	004	Bark
Nilam (Patchouli)	*Pogostemon cablin*	006	Leaf
Nyiur hijau (Coconut)	*Cocos nucifera*	006	Flesh
Pagar anak	*Ixonanthes icosandra*	012	Flower
Pekan (Yesterday-today-tomorrow)	*Brunfelsia latifolia*	012	Flower
Pinang/ Pinang muda (Betel tree)	*Areca catechu*	015	Flesh
Pisang abu (Saba banana)	*Musa acuminata x balbisiana*	014	Root
Pisang emas (Lady finger banana)	*Musa acuminate Colla*	014	Root
Pisang karuk (Wild banana)	*Musa malaccensis*	014	Root
Pisang kelat (Banana)	*Musa paradisiaca*	014	Root
Pucuk (Costus)	*Saussurea lappa*	004	Not stated
*Ribu-ribu seni (*Climbing fern)	*Lygodium spp.*	004	Leaf
Seribu bisa	*Pittosporum ferrugineum*	003	Root
Saga petak (Jequirity bean)	*Abrus precatorius*	002 004	Root Root
Serai (Lemon grass)	*Cymbopogon citratus*	013	Root
Serapat	*Streptocaulon wallichii*	003	Root
Sirih (Betel)	*Piper betle*	015	Leaf
Temiang	*Lettsomia peguensis*	003	Root
Temu iring (Pink and blue ginger)	*Curcuma aeruginosa*	011	Rhizome
Temu kuning/ Temu putih (Zedoary)	*Curcuma zedoaria*	011 006	Rhizome Rhizome
Temu lawak (Javanese turmeric)	*Curcuma xanthorrhiza*	011	Rhizome

Table 2 List of words cannot be identified.

Formulation number (4016.030.xxx)	**Original text**	**Suggested word**	**Part used**
001		Kepadang	Root
002		Seribu baik	Root
004		Susuk bajar	Leaf
009		Jabir	Not stated

012		Salu	Flower
012		Campur aduk	Flower
014		Jarum gajah	Root
016		-	Leaf

Comparative analysis

Out of 63 plants, 50 have been researched and shown in contemporary studies to possess various pharmacological activities pertaining to typhoid fever. Table 3 shows pharmacological activities possessed by the plants, which had been indicated in *in vitro* or *in vivo* experiments. In this paper, plants that have antibacterial are of interest because typhoid fever is caused by the invasion of *S.* Typhi and the key for treating the disease is by killing the causative pathogen. Nonetheless, other pharmacological actions related to typhoid symptoms are also studied and tabulated in Table 3. The search revealed that 34 of the plants exhibited antibacterial effects. Out of that, 18 had been shown to inhibit the growth of *S.* Typhi. *A. cepa* was the most frequently mentioned plant for typhoid fever treatment (n=4), i.e., used in four formulations, and followed by *N. sativa* (n=3) and *A. sativum* (n=2).

Table 3 Pharmacological properties discovered in contemporary studies related to typhoid.

Scientific Name	**Pharmacological acitons**	**Reference/ Types of study**
Abrus precatorius	Antibacterial** Antiinflammatory Neuroprotective	Sunday et al. (2016)/ in vitro Georgewill & Georgewill (2009)/ in vivo Premanand & Ganesh (2010)/ in vivo
Acorus calamus	Analgesic	Jayaraman et al. (2010)/ in vivo
Allium cepa	Antibacterial**	Bakht et al. (2013)/ in vitro
Allium sativum	Antibacterial**	Abdou et al. (1972)/ in vitro
Alpinia conchigera	Antibacterial** Antidiarrhoeal,	Ibrahim et al. (2012)/ in vitro Ibrahim et al. (2012)/ in vivo
Alyxia reinwardtii,	Antibacterial* Gastroprotective effect	Sundari et al. (2001)/ in vitro Nugroho et al. (2016)/ in vivo
Aquilaria spp.	Antibacterial*	Apridamayanti et al. (2020)/ in vitro
Areca catechu	Antibacterial* Antinociceptive	Liu et al. (2016) Barman et al. (2011)/ in vivo
Brucea amarissima, *Brucea sumatrana*	Antiinflammation	Chen et al. (2012)/ in vitro
Cananga odorata	Antibacterial** Antioxidant	Syed Ismail et al. (2020)/ in vitro Kusuma et al. (2014)/ in vitro
Carallia brachiata	Analgesic Antiinflammatory	Islam et al. (2020)/ in vivo Islam et al. (2020)/ in vivo

Cissus repens	Antiinflammatory Analgesic Antiulcer	Chang et al. (2012)/ in vivo Chang et al. (2012)/ in vivo Umbare et al. (2011)/ in vivo
Cleome viscosa	Antibacterial** Antinociceptive	Bose et al. (2011)/ in vitro Bose et al. (2011)/ in vivo
Coriandrum sativum	Antibacterial** Anticonvulsant Antioxidant	Oudah & Ali (2010)/ in vitro Karami et al. (2015)/ in vivo Karami et al. (2015)/ in vivo
Croton tiglium	Antibacterial Analgesic	Shahid et al. (2008)/ in vitro Wu et al. (2005)/ in vivo
Curcuma aeruginosa	Antibacterial* Antiinflammatory	Kamazeri et al. (2012)/ in vitro Paramita et al. (2019)/ in vivo
Curcuma longa	Antibacterial** Antioxidant Antiinflammatory Hepatoprotective	Kodjio et al. (2016)/ in vivo, Naz et al. (2020)/ in vitro Kodjio et al. (2016)/ in vivo Ramsewak et al. (2000)/ in vitro Krup et al. (2013)/ in vitro
Curcuma xanthorrhiza	Antibacterial** Hepatoprotective	Mary et al. (2012)/ in vitro Devaraj et al. (2010)/ in vivo
Curcuma zeodoria	Antibacterial** Analgesic Hepatoprotective	Islam et al. (2017)/ in vitro Navarro et al. (2002)/ in vivo Matsuda et al. (1998)/ in vivo
Cymbopogon citratus	Antibacterial** Antidiarrhoeal	Ewansiha et al. (2012)/ in vitro Tangpu & Yadav (2006)/ in vivo
Dendrophthoe pentandra (L.) Miq.	Antioxidant	Artanti et al. (2012)/ in vitro
Dendrocalamus asper	Antibacterial*	Mulyono et al. (2012)/ in vitro
Erioglossum rubiginosum	Antibacterial**	Barua et al. (2013)/ in vitro
Foeniculum vulgare	Antibacterial* Antiinflammatory Hepatoprotective	Beyazen et al. (2017)/ in vitro Choi & Huang (2004)/ in vivo Özbek et al. (2003)/ in vivo
Homalomena spp.,	Hepatoprotective	Dutta et al. (2013)/ in vivo
Jasminum sambac	Antibacterial**	Senbagam et al. (2016)/ in vitro
Kaempferia galanga	Antibacterial** Antiinflammatory Analgesic, Antidiarrhoeal	Kochuthressia et al. (2012)/ in vitro Vittalrao et al. (2011)/ in vivo Vittalrao et al. (2011)/ in vivo Ali et al. (2014)/ in vivo
Lygodium spp.	Antioxidant Hepatoprotective	Kuncoro and Rijai (2019)/ in vitro Gnanaraj et al. (2017)/ in vivo
Massoia aromatica/ Cryptocarya massoia	Antibacterial*	Pratiwi et al. (2015)/ in vitro
Melastoma malabathricum	Antinociceptive Antiinflammatory Antipyretic	Zakaria et al. (2006)/ in vivo Zakaria et al. (2006)/ in vivo Zakaria et al. (2006)/ in vivo
Michelia champaca	Antibacterial** Antiinflammatory	Wei et al. (2011)/ in vitro Ananthi & Chitra (2013)/ in vitro

Musa acuminata x *balbisiana* *Musa acuminate Colla* *Musa malaccensis* *Musa paradisiaca*	Antibacterial* Antioxidant Antiulcer	Ahmed et al. (2016)/ in vitro Vijayakumar et al. (2008)/ in vivo Rao et al. (2016)/ in vivo
Nigella sativa	Antibacterial** Hepatoprotective Antiinflammatory Analgesic	Sarwar & Latif (2015)/ in vitro Hagag et al. (2013)/ clinical trial Umar et al. (2012)/ in vivo Alemi et al. (2013)/ in vitro
Paedderia foetida	Antidiarrheal Antioxidant Antiinflammatory	Afroz et al. (2005)/ in vivo Osman et al. (2009)/ in vitro De et al. (1994)/ in vivo
Piper betle	Antibacterial* Antioxidant	Datta et al. (2011)/ in vitro Kanjwani et al. (2008)/ in vitro
Piper nigrum	Antibacterial** Anticonvulsant Analgesic Antioxidant Antidiarrhoeal Hepatoprotective	Khan & Siddiqui (2007)/ in vivo Bukhari et al. (2013)/ in vivo Bukhari et al. (2013)/ in vivo Ahmad et al. (2010)/ in vitro Shamkuwar et al. (2012)/ in vivo Nirwane & Bapat (2012)/ in vivo
Pittosporum ferrugineum	Antibacterial*	Ainil Farhan et al. (2013)/ in vitro
Pogostemon cablin	Antibacterial* Antioxidant, Antiinflammatory Analgesic	Hammer et al. (2009)/ in vitro Kim et al. (2010)/ in vitro Lu et al. (2011)/ in vivo Lu et al. (2011)/ in vivo
Pterocarpus spp.	Antiinflammatory Analgesic	Noufou et al. (2012)/ in vivo Noufou et al. (2012)/ in vivo
Rheum officinale	Hepatoprotective	Qin et al. (2014)/ in vivo
Rhodomyrtus Tomentosa	Antibacterial Antioxidant Antiinflammatory	Limsuwan et al. (2011)/ in vitro Wu et al. (2015)/ in vivo Jeong et al. (2013)/ in vivo
Santalum album	Antibacterial** Hepatoprotective Antiulcer	Hire & Dhale (2012)/ in vitro Hegde et al. (2014)/ in vivo Ahmed et al. (2013)/ in vivo
Saussurea lappa	Antibacterial* Antiinflammatory Antiulcer Hepatoprotective	Hasson et al. (2013)/ in vitro Damre et al. (2003)/ in vivo Niranjan et al. (2011)/ in vivo Yaeesh et al. (2010)/ in vivo
Scorodocarpus borneensis	Antibacterial Antioxidant	Kuspradini et al. (2016)/ in vitro Kuspradini et al. (2016)/ in vitro
Zingiber officinale	Antiinflammatory Analgesic	Ojewole (2006)/ in vivo Ojewole (2006)/ in vivo
Uvaria grandiflora	Antiinflammatory	Seangphakdeea et al. (2013)/ in vivo
Vitex pinnata	Antibacterial Antioxidant	Shafie et al. (2020)/ in vitro Shafie et al. (2020)/ in vitro

* indicates antibacterial action against Gram-negative bacteria excluding *S.* Typhi

** indicates antibacterial action against Gram-negative bacteria including *S.* Typhi.

DISCUSSION

Manuscript MSS 3136 presents 66 diseases with a total of 248 formulations for treatment using plants, animal parts or products, and minerals. With regards to typhoid fever, there are 16 formulations provided which are all compounded, i.e., comprises multiple ingredients. In addition, there are four types of typhoid fever mentioned in the manuscript, which are *kepialu tanah*, *kepialu air*, *kepialu api* and *kepialu angin*. However, only the first three were further described by the author. The description of the types is shown below:

"*Bab ini pada menyatakan mengenal kepialu. Adapun kepialu tanah itu tubuhnya berat, dan mukanya suci. Dan kepialu air itu tubuhnya sebentar panas sebentar sejuk. Dan kepialu api itu kaki tangannya sejuk, mukanya kuning, matanya merah*".

Meaning: This chapter is about the types of typhoid. *Kepialu tanah* is when the body is lethargic and the face is pale. *Kepialu air* is when the body is alternately feverish and *kepialu api* is when the feet and hands are cold, the face is yellowish, and the eyes are red.

The classifications and symptoms explanation are in agreement with another manuscript, MSS 2515 (Mat Piah & Baba, 2014). Better still, MSS 2515 provides more elaborated symptoms for each type of *kepialu*. In addition, MSS 2515 describes several symptoms for *kepialu angin* including constipation, sensation of feeling cold on the skin and sensation of feeling hot on the chest. These different types of typhoid may represent groups of highly variable symptoms arising from the disease. Kingsley & Dougan (2009) elucidated the symptoms of typhoid include alternate fever which can last up to four weeks, of which similar to the symptoms of *kepialu air*. Subsequently, the infected one will recover from the fever but it comes together with malaise and lethargy for a few weeks, of which similar to the symptoms of *kepialu tanah*. Diseased person also exhibits hepatomegaly which may be represented by *kepialu api* because the enlarged liver can result in jaundice, marked by yellowish skin. Constipation or diarrhoea is also a symptom of typhoid fever, which may be classified into *kepialu angin*. Different types of typhoid fever depicted in the manuscript may represent groups of symptoms rather than stages according to timeline.

Next, 50 plants mentioned in the manuscript for typhoid fever treatment have been investigated in contemporary studies and found to possess pharmacological actions that may benefit for treating typhoid fever or alleviating its symptoms. The main focus of comparative analysis was to find antibacterial activity of the 63 plants mentioned in the manuscript because the aetiology of typhoid fever is an infection of Gram-negative *S.* Typhi. Interestingly, 18 of the plants have been demonstrated in vitro to inhibit the growth of *S.* Typhi, and this could be the key to remedial effect of the formulations. Twelve of the plants show antibacterial action on both Gram-positive and negative bacteria but they are either not yet tested or ineffective against *S.* Typhi. Lastly, four plants have been indicated to show antibacterial effect on Gram-positive bacteria only. Nevertheless, other pharmacological actions are also important, which may help relieve the symptoms. Pain on abdomen is a symptom of typhoid fever (Colomba, 2008), thus analgesic or antinociceptive property could help in reducing the pain. Antipyretic property of *M. malabathricum*, for instance, may benefit feverish condition (Kingsley & Dougan, 2009).

Apart from that, hepatomegaly is a common symptom of typhoid fever often detected during the second or third week of typhoid fever. It is characterised with jaundice and clinically increased level of alkaline phosphatase, alanine aminotransferase and alanine transaminase (Morgenstern & Hayes, 1991). In relation to this, hepatoprotective activity possessed by 11 plants mentioned in the manuscript may have the potential to protect the liver from hepatomegaly. Meanwhile, according to Kodjio et al.

(2016), the infection causes the production of a strong oxidant, peroxynitrite which leads to more pathological conditions because of the oxidative stress. Their study showed that *C. longa* can increase endogenous enzymatic antioxidants in typhoid fever induced rats. Typhoid fever is also associated with gastrointestinal bleeding due to ulceration in the ileum (Sonavane et al., 2020; Ezzat et al. 2010), and this may potentially be improved by plants that have antiulcer and gastroprotective activities. The bacterial penetration into epithelial cells of the intestine (top layer of the intestinal tissue) makes the intestinal wall more vulnerable and that enables bacteria to further invade the wall and proliferate, which will then cause diarrhoea (ETH Zurich, 2009). Hence, plants with antidiarrhoeal activity can possibly help in treating diarrhoea. The infection also provokes systemic inflammation reaction against the bacteria and this leads to the death of host cells, and eventually clinical signs appear (Andrade & Junior, 2003). Plants that have anti-inflammatory action may theoretically reduce the inflammation and subsequently clinical signs from typhoid fever.

From the 63 plants, *A. cepa* is the most frequently mentioned plant for typhoid fever treatment. In modern studies, the plant was reported to demonstrate various pharmacological effects and most importantly is antibacterial. Abdou et al. (1972) tested crude juice and multiple solvent extracts of *A. cepa* on both Gram-positive and negative bacteria including *S.* Typhi. They found that all the juice and extracts are able to inhibit the growth of the bacteria in vitro and the best to inhibit *S.* Typhi is ethyl acetate extract. Bakht et al. (2013) also reported similar results when multiple solvent extracts of *A. cepa* are tested on several Gram-positive and negative bacteria in vitro, whereby only ethyl acetate and chloroform extract inhibit the growth of *S.* Typhi. According to Kim & Kim (2006), the bioactive ingredient responsible for its antibacterial activity is quercetin.

The second most repeatedly indicated for typhoid fever is black cumin (*N. sativa*). Sarwar and Latif (2015) demonstrated in an in vitro study that 100% black cumin oil can inhibit the growth *S.* Typhi on agar plates, and the zone of inhibition is comparable to 100 µg/ml ciprofloxacin and better than 100 µg/ml ceftriaxone. Minimum inhibitory concentration of black cumin oil was found to be lower than the crude extract, indicating that black cumin oil is a better antibacterial agent against *S.* Typhi than crude extract. The finding from Ashraf et al. (2017) is also in agreement with previous findings. Black cumin oil used in the in vitro study is able to inhibit the growth of 10 *S. enterica* isolates of human and poultry origin whereas the crude extract does not show any inhibition. This indicates that black cumin needs to be solvent extracted to get the active ingredients for antibacterial, which are thymoquinone and thymohydroquinone (Halawani, 2009).

Two of the formulations mentioned in the manuscript combined the usage of *A. cepa* and *A. sativum*, which are for *kepialu angin* and *kepialu api.* According to Hamza (2014), water and oil extracts of *A. sativum* provide higher antibacterial effect than *A. cepa* alone. Moreover, the combination of both *Allium* spp. exerts a synergistic effect when the antimicrobial test showed that *S.* Typhi is more sensitive to the combined compared to single formulation.

CONCLUSION

MSS 4016 is indeed an ancient pharmacopoeia holding a lot of medicinal information on numerous diseases. A total of 66 diseases and 248 formulations were identified and extracted from the manuscript. There are 63 plants found in the manuscript, intended to treat typhoid fever, of which 50 have been demonstrated in contemporary studies to possess various pharmacological activities related to typhoid fever. In specific, antibacterial is considered the most important property that can treat typhoid fever. Out of 50 plants, 34 have antibacterial effect. Eighteen of them have been demonstrated to inhibit the growth of *S.* Typhi, 12 inhibit other Gram-positive and negative bacteria and four inhibit Gram-positive bacteria only. Other than antibacterial activity, other pharmacological actions may also

play roles in alleviating the symptoms of typhoid fever. Even so, further researches need to be done to observe the effects of the plants specifically on typhoid. *A. cepa*, *N. sativa* and *A. sativum* are the most frequented plants in the manuscript for the treatment of typhoid fever. All of them have been demonstrated in contemporary studies to show antibacterial effect against *S.* Typhi when tested in vitro. Overall, further experimental studies need to be followed up to test the formulations listed in the manuscript so that it can serve as alternative treatments to the existing medication, of which the pathogen is developing resistance gradually.

ACKNOWLEDGEMENT

A debt of gratitude goes to Pusat Kebangsaan Manuskrip Melayu for providing us the space and guide to browse through the manuscripts, and also the copy of the manuscript. Without the help, we could never achieve our goals and objectives to complete this study.

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