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A Situation Analysis on the Use of Standardized-Herbal Medicines as Supportive Therapies for Dengue Hemorrhagic Fever (DHF) patients in Indonesia

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ABSTRACT

Objective: To conduct a situation analysis on the use of standardized-herbal medicines as supportive therapies for the treatment of Dengue Hemorrhagic Fever (DHF) patients in Indonesia.
Method: Semi-structured interviews were conducted with health stakeholders (n=6) at the national and regional levels.
Results: There are lack of clinical trials for herbal medicines used in DHF therapy. Several challenges are faced by the herbal medicines industries (HMI) in the effort to improve the quality of herbal medicines. The government plays important role in stimulating the research conducted by HMI and generating policies that support the researchers and HMI to improve the quality of Indonesian herbal medicines and increase the number of registered phytopharmaceuticals. **Conclusion:** DHF continues to be major mosquito-borne disease that must be taken seriously by the stakeholders. Different efforts have been done to prevent the increased DHF case or treat DHF patients. One of them is by using SHM as supportive therapy based on its proven empirical use. Yet, more scientific proof and clinical data are required to prove the efficacy of SHM containing Psidii folium and/or *Monascus purpueus*. The synergy of Academy, Business, Community, and Government (ABCG) in improving the safety and quality of herbal medicines is one of the strategy to accelerate the researches and innovations in finding the best therapy and preventing the increased DHF cases in Indonesia.

Keywords: Dengue hemorrhagic fever, standardized-herbal medicine, phytopharmaceuticals, herbal medicine industries, Indonesia

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INTRODUCTION

Dengue is a mosquito-borne viral disease caused by infection of dengue virus (DENV-1, DENV-2, DENV-3, and DENV-4) transmitted by mosquitoes of the genus *Aedes*, mainly *Aedes aegypti* and *Aedes albopictus*. Dengue transmission rates often peaked during and after rainy seasons. (1,2) Dengue affects tropical and subtropical countries, mainly in urban and semi-urban areas, and influenced by local spatial variations of rainfall, temperature, relative humidity, degree of urbanization, and quality of vector control services in urban areas. (3) According to WHO, dengue infection cases increased over 15-fold over the last two decades with death increased from 960 in 2000 to more than 4032 in 2015. It has been estimated 390 million DENV infections annually with 96 million cases showed clinical manifestations. (4)

To date, there is no specific antiviral treatment for dengue infections. Medication for dengue treatment is symptomatic treatment such as fever reducers and pain killers. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided. The patient needs to take adequate bed rest and the body fluid volume is maintained. (5) Paracetamol is often prescribed to treat the fever. In addition, whole blood transfusion is required in small percentage of patients who experienced major haemorrhage. (6)

The availability of a safe, efficacious, and cost-effective vaccine would significantly alter the concept for dengue prevention. (1) Dengue vaccine must provide protection against all four dengue viruses, yet proof of concept of vaccine efficacy is currently still missing. (1) However, successful progression of ongoing efficacy trials could lead to the availability of a vaccine in 2–4 years. (1)

It is known that the principal burden of dengue epidemics is not the number of deaths, but the enormous number of hospitalization and days of illness. (6) Consequently, an increased number of dengue cases requires high number of trained physicians and nursing personnel, beds, supplies and equipment. (6)

The clinical manifestations of dengue may be asymptomatic, undifferentiated fever (viral syndrome), dengue fever (DF), potentially lethal complication called severe dengue or dengue hemorrhagic fever (DHF) with plasma leakage that may progress to shock (dengue shock syndrome, DSS). (6) DF symptoms frequently depend on the patient's age and most common in older children, adolescents, and adults. Commonly, it shows acute febrile illness, and sometimes biphasic fever typically for 2-7 days with severe headache, retro-orbital pain, myalgia, arthralgia, rash, or hemorrhagic manifestations without evidence of plasma leakage. DHF typically manifest high fever, hemorrhagic phenomena, hepatomegaly, and often circulatory disturbance and shock. (6)

Several clinical and laboratory characteristic of dengue patients have been studied on its association with the length of hospital stay. Thrombocytopenia and rising haematocrit/haemoconcentration are clinical manifestations in patients with either mild or severe cases of dengue infections. (7) Thrombocytopenia is a key prognostic factor in the immunopathogenesis of dengue. (8,9) Platelets are one of the major cell populations affected by direct and/or indirect dengue infection.

Studies showed that low platelet count is one of the major causes of bleeding in DHF patients. According to the WHO guidelines for 2009, a rapid decline or platelet count below 150,000 cells/mm^3 of blood are one of the indicators of clinal dengue worsening. (6) A drop in platelet count to below 100,000 cells/mm^3 is usually found between the 3rd and 10th days of illness. A rise in haematocrit occurs in all DHF cases, particularly in shock cases. Haemoconcentration with haematocrit increases by 20% or more is objective evidence of plasma leakage. The platelet counts are normal during the early febrile phase. A mild decrease could be observed thereafter. A sudden drop in platelet count to below 100,000 occurs by the end of the febrile phase before the onset of shock or subsidence of fever. (6) Peripheral destruction of platelets can occur directly through interaction with the virus and indirectly from the formation of aggregates platelet-endothelial cells and platelet leukocytes or the secretion of anti-platelet antibodies and production of factors detrimental to platelets. (10)

The level of platelet count is correlated with severity of DHF and has been associated with the length of hospital stay. (9,11,12) A study involving 225 dengue patients showed that bleeding occurred more in patients with profound thrombocytopenia (platelet count ≤ 20,000/mm^3). (1,2) In addition, lower level of platelet count has been shown to correlate with increased rate of nonhemorrhagic complications. (9) Patients with lower platelet count have higher chances of nonhemorrhagic complications including acute respiratory distress syndrome (ARDS) and encephalophaty. (9)

Indonesia is in tropical monsoon and equatorial zone where main dengue vectors (*Aedes aegypti* and *Aedes albopictus*) are spread in almost all regions. According to WHO, DF/DHF in Indonesia is a major public health problem and a leading cause of hospitalization and death among child. (13) In Indonesia, DHF incidence rate in 2018 was 24.76 per 100,000 population with case fatality rate of 0.71% in 440 infected cities (Figure 1). According to Ministry of Health (MoH) of the Republic of Indonesia through Directorate of Vector-Borne and Zoonotic Disease Control, DHF cases in January-April 2020 amounted to 49,931 cases. This is already one third of the incidence in year 2019. It was postulated that dengue outbreaks in 2020 was due to mandatory lockdown to reduce COVID-19 cases. (14)

Indonesia has high biodiversity and rich natural resources which encourages the use of traditional medicine in treating disease. Herbal medicine is defined as preparations manufactured industrially consisting of active ingredient(s) which is/are purely and naturally original, not chemically altered plant substance(s), and is/are responsible for the overall therapeutic effect of the product. (15) The National Agency of Drug and Food Control (NADFC, BPOM) Indonesia categorized Indonesian traditional medicine into three types for product development positioning: *Jamu* (Indonesian indigenous herbal medicine), standardized-herbal medicine (SHM), and phytopharmaceuticals (phytomedicines; regulation nr. HK.00.05.4.2411, 2004). The efficacy claims of *Jamu* are based on empirical approach, while SHM are based on preclinical trials, and phytopharmaceuticals are based on clinical trials.

To date, there are three SHM products registered as supportive therapy in DHF treatment. The products contain guava leave extract (*Psidium guajava* Linn.) in combination with or without red yeast rice extract (*Monascus purpureus*). There have been some studies on the mechanism of action of *Psidium guajava* and *Monascus purpureus* in the treatmen of DHF. (16-20) Tannin and flavonoid compounds in a form of quercetin in guava leave extract inhibited virus replication as they inhibited reverse transcriptase enzyme. (16-19) The compounds also increased the number of megakaryocytes in the bone marrow, so the number of platelets increased. (19,20) The registered SHM in Indonesia claimed that the active ingredients can help increasing the platelet count. However, these medicines were only categorized as SHM and not yet upgraded into phytopharmaceuticals. Consequently, the health professionals especially physicians still doubted to prescribe SHM to DHF patient. This was conflicting with the belief of a lot of Indonesian people that *Psidium guajava* leaf (Psidii folium) extract and *Monascus purpureus* can be used in the treatment of DHF empirically. There have been some cases where the patient's family gave the herbal medicines to DHF patients without the knowledge of the physician, which could create problems in the treatment.

A situation analysis was conducted to investigate the problems and challenges embraced by physicians, herbal medicine industries (HMI), and policy makers in ensuring the safety and efficacy of herbal medicines as supportive therapy for DHF patients in Indonesia.

METHODS

Six interviews were held with policy maker (NADFC), physicians, and herbal medicine industries (HMI) practitioners in Indonesia. Semi-structured interview guides were tailored according to the specific individual being interviewed. Topics covered including DHF incidence in Indonesia, SHM for DHF patients, herbal medicine regulation, and challenges in ensuring the safety and efficacy of herbal medicine in general and specifically SHM for DHF patients from all the stakeholders' perspectives. Interviews were digitally recorded with participants' consent and transcribed verbatim. The names and other identifying features of respondents were removed from the transcripts in order to ensure the confidentiality.

RESULTS AND DISCUSSION

To date, there have been more than 100,000 *Jamu* products, 62 SHM, and 25 phytopharmaceuticals (NADFC official website). Of all the products, three SHM and 2 *Jamu* claimed to help in increasing the platelet count, maintain the immune system and rehydration for dengue patient (NADFC official website). The contents of these products were Psidii folium extract and/or *Monascus purpueus*. None of the herbal medicines for DHF patients was registered as phytopharmaceuticals. This implies that the clinical trials have not been carried out for herbal medicines for DHF patients. However, there have been several studies showing the clinical trials result for these herbal medicines. Two of these researches showed that Psidii folium extract and *Monascus purpueus* could increase the platelet count significantly in DHF patients grade 1 and 2. (21,22) Nevertheless, Diansyah et al showed that there was no statistically significant difference in thrombopoietin level and platelet count of DHF patients after treated with *Monascus purpueus* and control DHF patients. (23)

There were various reasons why there was no available phytopharmaceutical products for DHF patient to date. According to the practitioners in the HMI interviewed in

the study, one of the reasons was due to the costly investment required for the clinical studies of phytopharmaceuticals. Especially in the treatment of DHF where herbal medicines were used only to support the WHO standard therapy. Besides, the commercialized SHM have already had an established market. The physicians interviewed in this study have prescribed SHM to their DHF patients grade 1 and 2. It means that although the herbal medicines were yet to be registered as phytopharmaceuticals, the physicians trusted the safety of these herbal medicines. Nevertheless, all the physicians interviewed in this study still doubted the efficacy of the registered herbal medicines for their DHF patients. One of the physicians mentioned that the prescription of SHM for their patients was to prevent the patient's family giving herbal medicines from untrusted sources without the knowledge of the physician. There have been several cases where the patient had acute diarrhea probably due to the unhygienic preparation of the unregistered herbal medicines. Obviously, this could worsen the severity of the DHF disease since dehydration is one of the dangerous clinical manifestations in DHF patients. Herbal medicines have been widely used by Indonesian to maintain their health and to cure the diseases since many centuries ago. (24) Indeed, some studies showed increased platelet counts in patient treated with WHO standard treatment accompanied with SHM. From the economic perspective, however, the additional treatment cost from SHM was not effective because both WHO standard treatment with or without SHM showed similar effectivity in increasing platelet levels. (25)

Aside from the product claims, HMI also faced problems in obtaining qualified herbal raw materials that fulfil the requirements from Indonesian Herbal Pharmacopoeia and NADFC regulations on standardization. This was because the sources of the herbal raw materials might be obtained from the farmers who have not applied the Good Agricultural Practices. In addition, some of the required markers stated in the Indonesian Herbal Pharmacopoeia for standardization is not available in the market or difficult to get. To the best of our knowledge, there is also no control on the price of herbal raw materials by the government, so the HMI have difficulties in estimating production cost that might vary greatly from batch to batch.

Another challenge in the development of phytopharmaceuticals was the design of clinical trials of herbal medicines for DHF patient. This was due the complexity of the disease. Dengue infections can be caused by different serotypes (DENV-1, DENV-2, DENV-3 and DENV-4) and each has different interactions with the antibodies in human blood serum. (26) Consequently, the clinical manifestations and laboratory parameters were also different. There were significant differences for platelet count with DENV-2 cases having the lowest platelet count compared to DENV-1 and DENV-3. (26) The disease complexity was also one of the reasons why dengue vaccination has not been included in the Indonesian national program. (27) Another reason on the delayed vaccination program was the scarcity of local cost-effectiveness studies. (28) Nevertheless, the recent study on the analysis of the cost-effectiveness of dengue vaccine showed that vaccination would reduce dengue fever, dengue hemorrhagic fever, and dengue shock syndrome cases. Besides, it would save millions of dollar treatment cost from the healthcare and payer perspective. (29)

Indonesian government through NADFC and MoH have introduced several programs to improve the quality of Indonesian herbal medicines. One of the programs is by providing financial and non-financial supports for HMI to upgrade their herbal medicines products from *Jamu* to SHM or from SHM to phytopharmaceuticals. The upgraded product would significantly increase the trust from health professionals especially physicians. NADFC provides coaching clinic for HMI before, during and after product registration. This policy was to ensure that the HMI do not lose their investment in unnecessary or incorrect protocols and documents required for herbal medicine product registration. Another strategy from the NADFC and MoH is a plan to include the SHM and phytopharmaceuticals in the national formularium. If both types of herbal medicines are included in the national formularium, there will be increased usage of the herbal medicines prescribed by the physicians because the medicine cost will be paid by the Indonesian National Healthcare Insurance (NHI/JKN). In return, the HMI will have confidence in investing for clinical trials to upgrade the status of the herbal medicines into phytopharmaceuticals.

Indonesian government also stimulates the HMI to produce qualified herbal medicines by providing research grant which can be utilized by the HMI to do clinical trials for phytopharmaceuticals registration. The grant is provided by the Indonesian Ministry of Research and Technology. Another thing that should be considered by the government in the efforts to improve the use and quality of herbal medicines in Indonesia is by generating the herbal medicines distribution policy. If the government aims to enhance the number of phytopharmaceuticals, then the policy should be the herbal medicine that can be used in the healthcare facility is only the phytopharmaceuticals with clinical proof.

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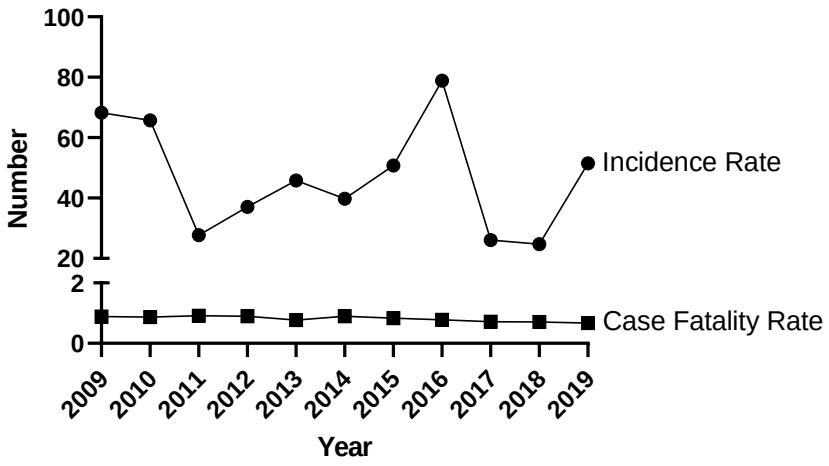

Figure 1: Incidence and case fatality rate of DHF in Indonesia (Data obtained from Ministry of Health of the Republic of Indonesia)