

Is It True That Some Herbs Are Effective Against Dengue Hemorrhagic Fever?

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Abstract

Some chemical compounds in plants such as papaya leaves, red yeast rice, dates, etc., are believed to be effective in increasing the number of platelets/thrombocytes in cases of dengue hemorrhagic fever. This literature review aims to determine the level of safety and effectiveness of herbal extracts in increasing platelet counts in patients with dengue fever. The method was done by searching the article database using the Medline search engine, Science direct, Google scholar, ProQuest, PNRI and found relevant articles totaling 11. From the articles examined it was found that: Papaya leaf extract or juice (*Carica papaya*. L) contains Papaine, Chymopapaine Cystatine, Tocopherol, Ascorbic Acid, and Glucocynoolates and flavonoids function as anti-inflammatory, anti-tumor activity and the formation of the immune system. Fermentation of brown rice (*Monascus purpureus*) contains flavonoids also commonly called isoflavones that functions by inhibiting the activity of the hyaluronidase enzyme in dengue virus. Guava leaf extract (*Psidium guajava*) contains quercetin flavonoid compounds functioning as anti-dengue and anti-thrombocytopenia by inhibiting mRNA enzyme formation in Dengue virus. Date palm juice containing flavonoid glycosides functions in the formation of platelets in the condition of thrombocytopenia due to heparin administration. Papaya leaf extract or juice, guava leaves, date palm juice and brown rice fermentation (*Monascus purpureus*) are effective in inhibiting the activity of the hyaluronidase enzyme in dengue virus.

Complementary therapy can be combined with the aim of preventing the severity of dengue virus which can lead to hypovolemic shock conditions and thrombocytopenia.

Introduction

The World Health Organization (WHO) says that the infectious disease dengue fever caused by a mosquito virus has spread 30 times worldwide in the last 50 years and is endemic in tropical and subtropical areas and it is often one of the main health problems in the general population [1]. Vyas (2013) [2] states that two types of mosquitoes, namely *Aedes aegypti* and *Aedes albopictus*, can be found in tropical and subtropical areas such as northern Australia, including the Indonesian archipelago [2]. The two types of mosquitoes carry one of the four types of Indonesian dengue virus which is the cause of Dengue Hemorrhagic Fever (DHF) infection.

In 2008, the number of dengue cases in America, the West Pacific and Southeast Asia had exceeded 1.2 million cases, and in 2015 there were 3.2 million cases of dengue fever. There were 10,200 with severe dengue cases and 1181 of them were declared dead from the 2.35 million cases in America alone that had been reported in 2015 [3]. Thanachartwet, *et al.*, (2016) [4] cited a statement coming from WHO whose saying that in 2020 early detection (early detection) and appropriate curative treatment is one of the methods to prevent patients with DHF from experiencing shock and organ dysfunction [4]. Thus, cases of DHF have decreased by 25% morbidity and 50% of mortality can be reduced.

Since 1968 until now (the last 47 years) DHF has become one of the health problems in Indonesia and has spread in various regions (34 provinces and from 497 districts / cities (88%). There are 436 districts / cities (85% in endemic areas) [5].

The number of DHF sufferers in Indonesia has increased from 2014-2015. In 2014 there were 100,347 cases and 907 of them were declared dead and in 2015 there were 126,675 dengue cases, 1,229 of whom were not helped (died). These cases are spread throughout Indonesia from 34 existing provinces [6]. The number of DHF sufferers in Indonesia per 100,000 population in 2015 were three major provinces, where Bali (257.75) was in first place, followed by East Kalimantan (188.46), then North Kalimantan (112.00), and in South Sulawesi province itself (46.64). If according to the Case Fatality Rate (CFR)>1%, there are five provinces which are quite high, namely Maluku (7.69%), Gorontalo (6.06%), West Papua (4.55%), North Sulawesi (2.33%), and Bengkulu (1.99%). While based on the mortality rate at the provincial level from the lowest to the highest: East Kalimantan (65 deaths), Central Java (255 deaths), and the highest was in the province of East Java (283 deaths) [5].

One of the most important parameters of dengue fever is "thrombocytopenia", this condition has an impact on the number of platelets (platelets) in the blood to be reduced. This is due to the dengue virus which attacks the bone marrow where plasma, platelets, and other blood cells are produced [7]. Failure of platelet production, increased platelet consumption, abnormal platelet distribution, and loss due to dilution are all contributing factors for the emergence of thrombocytopenia. Thrombocytopenia is caused by several things, including an abnormal decrease in the number of blood cells involved in the formation of blood clots. These cells are called platelets [8].

Conservative therapy in conditions of thrombocytopenia and plasma leakage due to increased vascular permeability is generally still supportive or symptomatic, such as: to replace lost body fluids due to plasma infiltration, fluid therapy is performed [9]. Achmadi, *et al* (2010) [10] said that to overcome this condition, until now there has been no curative treatment (vaccination) that can prevent the occurrence of dengue infection. Until now, chemical drugs are still questionable about their effectiveness on thrombocytopenia [10].

Herbal treatment is treatment using ingredients or ingredients from plants, animals, or minerals, presented in the form of extracts, or a mixture of these ingredients and is passed down from generation to generation and has been used for treatment and can be applied in accordance with the prevailing norms in society [11]. As an example of a study that tried to use herbal plants from papaya leaf extract (*Carica Papaya*), in which this study used a quantitative research design with an open random control system (randomly) with 80 patients, 40 patients as a control group and 40 patients. Other patients as the treatment group were given 24 capsules of papaya leaf extract, from the results of the study until the ninth day it was found that there was an increase in platelets in the treatment group that increased significantly (platelet count $200 \times 10^3 / \mu\text{L}$) [12].

Therefore, a literature study needs to be done to look further and find out whether it is true that several types of herbal plants can increase the platelet count in DHF sufferers and then to see which difference is more effective and faster in increasing the number/levels of platelets in the blood based on evidence based research that supports this.

Methods

Search for related articles was found through several academic journal searches such as: Pubmed/MedLine, Cengage, Google Scholar (Cendekia), and PNRI (ProQuest). In searching for journals / articles, access the ProQuest e-journal, then type in the keyword “Effectiveness of herbal plants” *Carica papaya. L*, *Monascus purpureus* yeast, *Psidium guava* leaf extract, and *Phoenix dactylifera* Extract “to increase the number of platelet in patients with Dengue haemorrhagic fever” found 14 results (2008-2019), but those relevant to the topic were only one journal. Three articles were found on the Pubmed link, then searched through ProQuest, Gale-Group/Cengage in the same way, and found two journals/articles relevant to the topic, then search by accessing Google Scholar publication year 2016-2019 there were 245 articles / journals and narrowed down the publication year 2019 to 99 articles related but only four full-text articles relevant to the topic.

Result and Discussion

Summarizing the results of several studies discussed in this literature study. Several types of herbal plants used as complementary or alternative therapies apart from medical treatment or therapy in cases of dengue fever with thrombocytopenia. Appear to be applicable because of the research results that these herbs contain substances or compounds that are very helpful in increasing the number of platelets in DHF sufferers. Process of preventing complications of DHF for several types of plants and their compounds. Some of them such as papaya leaf extract or juice (*Carica papaya. L*) which contains Papaine, Chymopapaine, Cystatine, Tocopherol, Ascorbic Acid, and Glucocynoolates and flavonoids function as anti-inflammatory, anti-tumor activity and the formation of immune system [13,14]. At this time as for other preparations in capsule form.

Fermentation from brown rice (*Monascus purpureus*) contains flavonoids or commonly called isoflavones which inhibit the activity of the hyaluronidase enzyme in the dengue virus (Sahasrabbudhe & Deodhar, 2010; Tisnadajaja, 2006; Wiyasihati *et al.*, 2013) [7,15,16]. In addition, papaya leaf extract also acts as anti-thrombocytopenia, anti-viral which functions to inhibit the meeting between the protease enzyme NS2b / NS3 and DENV-2 Dengue virus. Guava leaf extract (*Psidium guajava*) contains the flavonoid compound quercetin which functions as an anti-dengue, anti-thrombocytopenia by inhibiting the formation of the mRNA enzyme in Dengue virus [17]. Date palm juice contains flavonoids glycosides that function in the formation of platelets in conditions of thrombocytopenia due to heparin administration [18].

The decrease in platelet counts in DHF patients is often caused by increased plasma membrane permeability resulting in plasma leakage, blood cells seeping out including platelets are also wasted from the blood plasma [19]. In addition, blood clotting factors such as thrombin, prothrombin, thrombokinase are also wasted, their effects can cause bleeding risks, a condition like this is a further manifestation of a decrease in the number of platelets in the blood (thrombocytopenia). Heavy bleeding and death can occur if the risk of bleeding from the start is not treated immediately. Platelet aggregation that activates the coagulation system is a condition caused by the dengue virus by forming anti-gene and antibody complexes then activating the complement system [20].

Platelet aggregation that activates the coagulation system stimulates the attachment of antigen-antibodies in the platelet membrane (platelet cells sticking together) then releases ADP (Adenosine Diphosphat). Furthermore, the reticuloendothelial system (Reticuloendotelial system-RES) destroys these platelet cells and triggers the risk of bleeding due to thrombocytopenia (loss of platelet counts in the blood) [20]. Regarding the condition of thrombocytopenia, the medical or pharmacological world states that there is no type of chemical drug to increase the platelet count. There are still anti-platelet cell aggregation drugs and there is also no type of drug or anti-viral to kill the dengue virus [10].

Therefore, to overcome this problem certain groups in society try to return to nature, in this case using herbal-based (traditional) healing sources known as “Complementary Therapies” as a complement to medical-based therapies. The number of studies using several types of herbal plants has also begun to appear to try to prove whether herbal plants such as: red yeast (angkak), guava leaf extract, papaya leaf extract, date juice, apple room, sweet potatoes, and so on, can increase the platelet count. in the blood in patients with DHF. One such study is a study using guava leaf extract, date juice, and red yeast rice.

They used a quantitative research design with an experimental study method on animals (28 male/wistar white rats) divided into four groups: Group (K1) treated with placebo extract with thrombocytopenia (control), Group 2 (K2) treatment + red yeast extract., group 3 (K3) thrombocytopenia treatment + date palm extract, group 4 (K4) thrombocytopenia treatment + guava leaf extract. Then, the sample was given a subcutaneous injection of heparin for 3 days, once daily with a dose of 0.1mg/100/body weight rats/day. The dose given is 2x the dose for adults and has been given to all animals that have experienced thrombocytopenia. Extracts of red yeast, guava leaves, and date juice are given in the form of liquid / suspension 0.5% CMC, Na 1m / 100g / BW rats / day through sonde tubes 2x / day, the dose used is 108mg / kg rats / day according to the adult dose and given for 3 days, a blood sample is taken via a vacutainer as much as 3ml + EDTA to check the platelet count [7,18]. The platelet count was calculated using an automated blood analysis machine

(automated hematologic analyzer) with a Sysmex KX-21 method. The findings of the study found that the three types of herbal plants were all stated to be able to increase the platelet count, but when compared between the three, which is more effective in increasing the number of platelets (platelets) is the administration of extract from red yeast rice at a dose of 108mg / kg rats / day for three days [7,14,16,18].

The results of a similar study who examined the effects of using guava leaf extract supplements (*Psidium guajava* Linn.) and Angkak /red yeast (*Monascus Purpureus* fermented rice) in increasing the platelet count in DHF sufferers. This study used a quantitative research design with a quasi-experimental research method (pre test & post test) with a total of 20 respondents with a non-randomized sampling method with a “consecutive sampling” approach. Then divided into two groups I totaling 10 people (DHF management according to WHO) and group II totaling 10 people (management of DHF according to WHO and giving extracts of guava and angkak leaves at a dose of 3x1 packs / day). The platelet count was measured every 12 hours [21].

Supplement



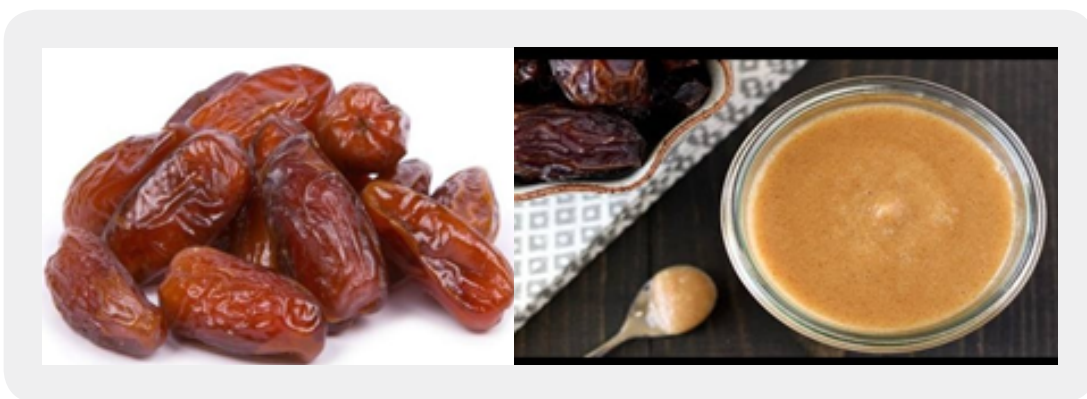
Papaya leaves extract (Carica Papaya Linn)



Angkak/Red yeast (Monascus Purpureus)



Guava leaves extract (Psidium guava leaf extract)



Date juice (Phoenix dactylifera Extract)

Furthermore, independent t-test analysis at the beginning and at the end of the study was carried out to test the difference in changes in the number of platelets between groups and the test to analyze the level of response between the two groups was carried out using the chi-square test. Results: the number of platelets in the treatment group was significant (p value = 0.0120) $p \leq 0.05$. Increased compared to the control group and the number of responses to increased platelet counts in the control group did not change significantly compared to the treatment group (p value = 0.0034) $p \leq 0.01$. That way, giving guava and angkak leaf extracts to DHF patients can increase the platelet count as evidenced by the results of this research study.

Stimulation of megakaryocyte proliferation and differentiation can be caused by an increase in the GM-CSF mechanism which first begins with an increase in the number of megakaryocytes in the bone marrow. The effect can increase the number of platelets in the blood, while the content in guava leaf extract is "Tannins and Flavonoids" thought to be able to increase megakaryocytes in the bone marrow. Another study that tried to combine three types of herbal plants (fruit) in DHF patients with thrombocytopenia found that the incidence and symptoms of shock in cases of dengue fever with thrombocytopenia conditions can be reduced by giving papaya leaf extract [22].

This study aims to see the process of the papaya leaf extract so that it can increase the number of platelets in the blood. The method used in this research study is a “prospective study” which was conducted in 2016 in October. The treatment was given for three days from 5/10/2016 to 07/10/2016 by providing several types of fruit such as: papaya, guava seeds, and apples and giving papaya leaf extract as much as one full spoon. DHF patients also continue to receive symptomatic treatment. The calculation of the respondent’s blood sample is very reliable and the cost is affordable because it uses an automatic blood analysis machine and the results can be immediately known. The results of this study say that DHF and the symptoms of shock that can appear at any time can be prevented by improving the increase in platelet count. Papaya leaf extract is proven from the results of this research study to increase the platelet count [22].

Research relevant to previous research was also found that Carica Papaya leaves extract (CPLE) as a complementary therapy can prevent complications associated with thrombocytopenia and can significantly increase the platelet count. The initial aim of this study was to evaluate the effectiveness of papaya leaf extract on the platelet count in DHF patients with thrombocytopenia. This study uses a method in which respondents and data processors or researchers do not know the status of each respondent whether they fall into the category of intervention or non-intervention groups of researchers or respondents, the sample is limited only to patients with grade I and II DHF [23].

Active components such as Papain, Chymopapain, Cystatin, Tocopherol, Ascorbic Acid, and Glucocynolates, are contained in papaya leaf extract and research results prove that these substances / components have functions as anti-inflammatory, anti-tumor activity, and also act as a regulator of the immune system [12-14,23]. Other studies on DHF with thrombocytopenia who received papaya leaf extract treatment therapy were reported to be effective in inhibiting dengue virus enzyme activity Other studies on DHF with thrombocytopenia receiving papaya leaf extract treatment therapy were reported to be effective in inhibiting dengue virus enzyme activity [24-26].

Gap

In some of the literature that has been presented above, starting from the research conducted by Wiyasihati (2013) [7] using the object of research on male Wistar rats as the subjectivity of the results, if the sample in humans, there could be differences or bias [7]. Then in the other research only wanted to see the effect of red yeast and guava extracts in increasing platelets without doing a comparison / comparison test. The two types of complementary therapy compared the first group who received treatment only based on WHO standards with the second group who received the intervention “giving red yeast & guava leaf extract”. WHO standard treatment, where it is likely that the second group has a faster chance of increasing its platelet count. compared to group one [21]. Then the respondent was only in patients with grade I and II dengue fever, meaning that they could not generalize to all dengue sufferers by reason of the severity of dengue to grade IV and shock / shock [21,23]. Likewise, with other studies where the characteristics of the respondents were not homogeneous (varies from all ages).

The next research has less objectivity if seen from the results, it cannot represent that the extract from papaya leaves objectively increases the platelet count because besides being given papaya leaf extract. It is also given several other types of fruit such as guava, fruit from papaya itself, and also apples simultaneously. While it is

known that several studies have also proven, guava and apples also function to restore the function of red blood cells in maintaining and maintaining platelets (platelets) in the blood from being wasted [22].

The element of less homogeneity of respondents is taken from various types of ages ranging from the age of children to adulthood, by looking at the characteristics of respondents like that, the results may be different for each individual because many other factors influence the healing process of a disease besides age, for example nutritional status, medical history, physical condition, lifestyle, history of drug consumption, alcohol or smoking, is not really explained in the literature study. As for other research who conducted research using papaya leaf juice, it is almost the same as previous research studies (experiments) regarding the characteristics of the respondents who are not homogeneous, the abstract structure has not met the requirements of an article / journal: does not include objectives, research method / design, results of data analysis, and conclusions [25].

Opinion

By looking at the research that has been carried out and discussed in the discussion, broadly speaking it fulfills the elements (cohesiveness, terms relevant to the research study, the results of research objectivity and data are presented in statistical form. As for journal articles whose objectivity and originality are lacking). However, the findings are the same as other journals / articles on the topic of discussion, namely the types of herbal plants used as research instruments are proven to increase the number of platelets after intervention. There are four sections in each article in the abstract after the title: Introduction (background), Methods, Results, and Discussion (discussion) accompanied by keywords and bibliography in accordance with the reference [27].

Looking at the validity element (PI / ECOT), the research articles used have these elements: P (Population) all articles used have a population and sample, I / E (Intervention / Exposure) there are research objects that are intervened (exposed) in this case DHF sufferers who experience thrombocytopenia, C (Control / Comparison) groups / objects that are controlled or compared, O (Outcome) results of research studies: complementary therapies (herbal medicine) such as: papaya leaf extract, palm extract, guava leaf extract, fermentation of Red yeast is proven by the findings that have been done to have an effect in increasing the platelet count in DHF sufferers.

Accompanied by the sampling method, there was follow up and analysis, blinding was carried out, there was single blinding and double blinding. Research results are reported using the methodology by presenting complete and clear information starting from methods, descriptions, and other important information (Consolidated standards of reporting trials). The homogeneity element in some articles is still lacking but other articles have fulfilled it by selecting a uniform sample. The treatment of the control group in the related article does not explain whether the control group after the study was completed was also given therapy / intervention given to the intervention / treatment group.

From the point of view of reliability, the significance values of the articles discussed are all included in the discussion topic or in the research results / abstract. The article being reviewed also shows the accuracy and thoroughness of the research results and the research can be repeated with the characteristics of the respondent and with the same reliable results.

Conclusion

Conservative therapy in conditions of thrombocytopenia and plasma leakage due to increased vascular permeability is generally still supportive or symptomatic, such as: replacement of body fluids lost due to plasma infiltration, then given fluid therapy. Nowadays herbal treatment methods are increasingly developing, using various types of plants that contain various functions (healing factors) such as anti-inflammatory, anti-tumor activity, boosting the immune system, increasing platelets, anti-pyretic, anti-microbial, anti-biotic, anti-bacterial / fungal and others. Papaya leaf extract and red yeast rice which contain several bioactive compounds are believed to have various functions that have been mentioned previously and one of them is the level of effectiveness in handling thrombocytopenia conditions in cases of dengue hemorrhagic fever. In addition, the extract or juice of papaya leaves, guava leaves, date palm juice and fermented brown rice or red yeast (*Monascus purpureus*) effectively inhibits the activity of the hyaluronidase enzyme in dengue virus. Complementary therapy can be combined with the aim of preventing the severity of the dengue virus which can lead to hypovolemic shock and thrombocytopenia.

Table 1: Synthesis Grid

| No. | Authors | Year | Types of plants studied | Research results (medicinal content of plants) |
|-----|---|------|--|--|
| 1 | Otsuki, dkk. | 2010 | <ul style="list-style-type: none"> Papaya leaf extract or juice (<i>Carica papaya. L</i>) | <ul style="list-style-type: none"> <i>Papaine, Chymopapaine, Cystatine, Tocopherol, Asam askorbat, and Glucocynoolates</i> (anti-inflammatory, anti-tumor activity) |
| 2 | Owoyele, Adebukola, Funmilayo, & Soladoye | 2008 | <ul style="list-style-type: none"> Papaya leaf extract or juice (<i>Carica papaya. L</i>) | <ul style="list-style-type: none"> <i>Papaine, Chymopapaine, Cystatine, Tocopherol, Asam askorbat, dan Glucocynoolates and flavonoids</i> (anti-inflammatory, anti-tumor activity and immune formation) |
| 3 | Sahasrabudhe A, Deodhar | 2010 | <ul style="list-style-type: none"> Red yeast or brown rice (<i>Monascus purpureus</i>) | <ul style="list-style-type: none"> Senyawa/zat <i>Flavonoids (Isoflavon)</i> (Inhibits hyaluronidase enzyme activity in dengue virus) |
| 4 | Wiyasihati, Wigiati, & Wardani | 2013 | <ul style="list-style-type: none"> Red yeast or brown rice (<i>Monascus purpureus</i>) Guava leaf extract (<i>Psidium guajava</i>) Extract date palm (<i>Date palm</i>) | <ul style="list-style-type: none"> <i>Isoflavon/Flavonoid quercetin</i> (Interfere with the enzyme hyaluronidase / RNA Dengue Virus), Flavonoid glikosida (platelet formation) |

| | | | | |
|----|---|----------------------|--|---|
| 5 | Kadir, Yaakob, & Zulkifli | 2013 | <ul style="list-style-type: none"> • Guava leaf extract (<i>Psidium guajava</i>) | <ul style="list-style-type: none"> • Senyawa <i>Flavonoid quercetin</i> (Anti-dengue, anti-thrombocytopenia by inhibiting the formation of the mRNA enzyme in the dengue virus) |
| 6 | Zahroh, JM, Khotib, Rahmawati, & Riami | 2013 | <ul style="list-style-type: none"> • Date juice (<i>Date palm</i>) | <ul style="list-style-type: none"> • <i>Flavonoid glikosida</i> (Platelet formation in thrombocytopenia results from heparin administration) |
| 7 | Muharni, Almahdy, & Martini | 2013 | <ul style="list-style-type: none"> • Guava leaf extract (<i>Psidium guajava</i> Linn.) • Angkak/red yeast (fermented rice <i>Monascus Purpureus</i>) | <ul style="list-style-type: none"> • <i>Isoflavon quercetin</i> dan glikosida (anti-dengue and platelet aggregate formation) |
| 8 | Krishna, Myreddy, & Uppara; Mochizuki M., <i>et al</i> (2004) | 2016 | <ul style="list-style-type: none"> • Papaya leaf extract or juice and papaya fruit (<i>Carica papaya. L</i>) • Guava leaf extract (<i>Psidium guajava</i>) • Apple extract (<i>Malus Domestica</i>) | <ul style="list-style-type: none"> • <i>Papaine, Chymopapaine, Cystatine, Tocopherol, Asam askorbat, dan Glucocynoolates</i> and <i>flavonoids</i> (anti-inflammatory, anti-tumor activity and immune formation) • <i>Isoflavon quercetin</i> dan <i>glikosida</i> (anti-dengue and platelet aggregate formation) • <i>Kuersetin</i> 17-55 mg and The average concentration of phytochemical compounds per 100 g of apples was 13.2 mg of quercetin glycosia. Apple peel ethanol extract (decreased vascular permeability) |
| 9 | Adarsh V, Doddamane, & Kumar | 2017 | <ul style="list-style-type: none"> • <i>Carica Papaya</i> leaves extract (CPLE) | <ul style="list-style-type: none"> • <i>Papaine, Chymopapaine, Cystatine, Tocopherol, Asam askorbat, dan Glucocynoolates</i> (anti-inflammatory, anti-tumor activity) |
| 10 | Kala Subhentiran Ahmad, dkk | 2012 2013 2011 | <ul style="list-style-type: none"> • <i>Carica Papaya</i> leaves extract (CPLE) | <ul style="list-style-type: none"> • <i>Papaine, Chymopapaine, Cystatine, Tocopherol, Asam askorbat, dan Glucocynoolates</i> dan <i>flavonoids</i> (anti-inflammatory, anti-tumor activity and the formation of body resistance and inhibits the work of the dengue virus enzymes) |
| 11 | Yunita, Hanani, & Kristianto | 2012 | <ul style="list-style-type: none"> • Papaya leaf extract or juice and papaya fruit (<i>Carica papaya. L</i>) | <ul style="list-style-type: none"> • <i>Papaine, Chymopapaine, Cystatine, Tocopherol, Asam askorbat, dan Glucocynoolates</i> dan <i>flavonoids</i> (anti-inflammatory, anti-tumor activity and the formation of body resistance and inhibits the work of the dengue virus enzymes) |

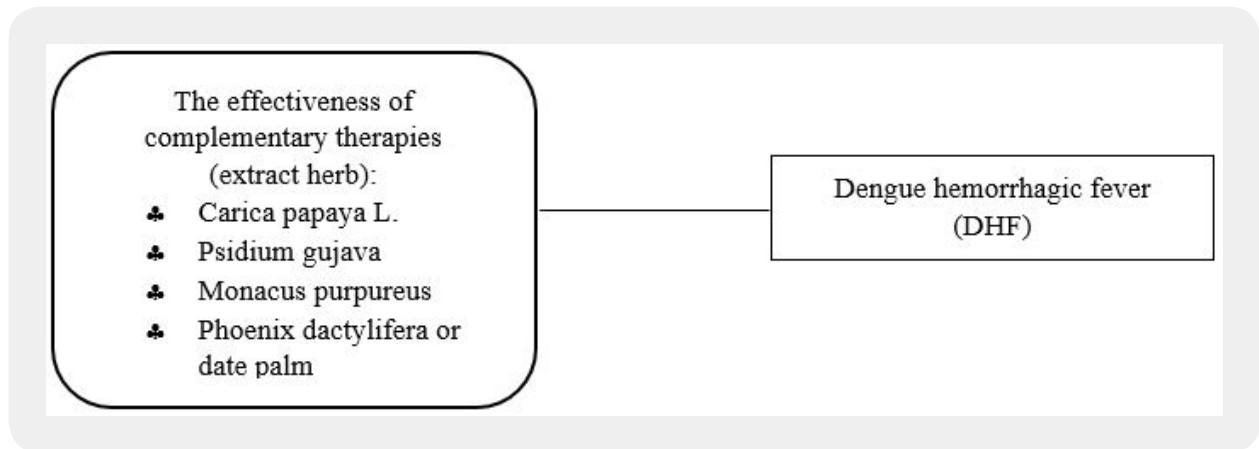


Figure 1: The effectiveness of *Carica papaya L.*, *Psidium guajava*, *Monascus purpureus*, Dates in people with dengue hemorrhagic fever

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