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Review on *Phaleria macrocarpa* Pharmacological and Phytochemical Properties

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Abstract

Phaleria macrocarpa or Mahkota Dewa has been a unique plant because of its antioxidant, anti-inflammatory and anti-cancer properties. The phytochemical studies of this plant have revealed the presence of bioactive compounds: phenolic compound, terpenes (isoprenoids) compounds, alkaloids compounds, and benzophenones compounds. Researches done on its have shown its ability to treat some diseases and serves as herbal medicines. The aim of this review is to summarize and evaluate the existing researches regarding the pharmacological effects, phytochemical properties, and toxicological studies of *Phaleria macrocarpa*. This review is expected to be useful for researchers working on the potential roles of Phaleria macrocarpa in the treatment of diseases or for product development.

Keywords: *Phaleria macrocarpa*; Mahkota Dewa; Antioxidant; Anti-inflammatory; Anti-cancer

Introduction

Medicinal plants have been recognized and utilized all through mankind's history. Mahkota Dewa plant scientifically known as *Phaleria macrocarpa* originates from Papua Island, Indonesia and grows in tropical areas. This plant belongs to Thymelaeaceae family and has been mostly used traditionally as an indispensable medicinal plant in Malaysia and Indonesia [1]. Several ailments such as cancer, impotence, haemorrhoids, Diabetes mellitus, allergies, liver and heart diseases, kidney disorders, blood diseases, rheumatism, high blood pressure, stroke, migraine, skin diseases, and acne has been treated with this plant [2–4].

Likewise, research had revealed that *Phaleria macrocarpa* fruit extracts can prevent arteriosclerosis and reduced cholesterol level in Japanese quails as well as primary culture of rat hepatocytes [5,6]. *Phaleria macrocarpa* has been used as a main ingredient in some healthy drink or tea, cosmetics and drugs [7].

The four major parts of this plant shown in Figure 1 are mostly enriched in medicine: the stems, the leaves, egg shell of the seeds and the fruits.

The stems has been used in treating bone cancer [8]; the leaves has been used for impotence, blood diseases, allergies, diabetes mellitus and tumor treatments [2,9]; the egg shell of seeds has been used for breast cancer, cervix cancer, lung diseases, liver and heart diseases treatments [10]; and the fruits consisting of alkaloid, saponin, flavonoid and polyphenol has been used as antioxidants [11].

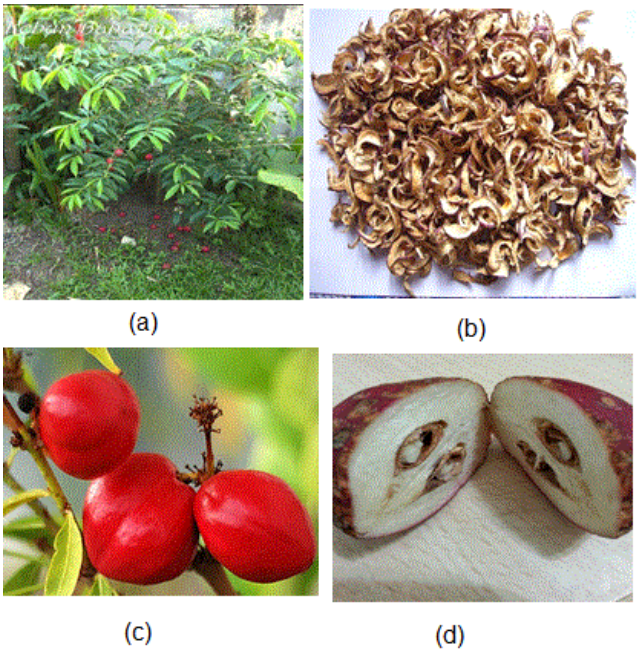

Figure 1: (a) the stems; (b) dried fruit peels; (c) fruits; and (d) seeds of *Phaleria macrocarpa*.

The use of this plant in traditional medicine has been documented in literatures. Research had been done on in-vivo and in-vitro hypercholesterolemia model to determine the effects of *Phaleria macrocarpa* fruit extracts on blood lipid profile (total cholesterol, triglyceride, high density lipoprotein, and low density lipoprotein) as well as LDL receptor, PCSK9 protein, and mRNA expression [12]. Meanwhile, the work performed on DLBS1245, a *Phaleria macrocarpa* standardized extract of fresh fruit, revealed the anticancer activities of

this plant [13]. Likewise, *Phaleria macrocarpa* fruits and seeds had shown the existence of important biological activities of the extract in term of anti-microbial, anti-inflammatory and its antioxidant activity [14].

They could also fight human parasite Trypanosoma cruzi (Chagas's disease) [7] and displayed significant antioxidant activity [14,15]. There are a lot of products like cosmetics, teas and drugs in the market that had been formulated with *Phaleria macrocarpa* due to its outstanding health enhancing properties. Several patents have been done on *Phaleria macrocarpa* after extensive animal and human clinical evaluation had been done. Some of the patents are WO2009153692 A1, US20070203249 A1, CN102065879 B, EP2310027 A1, US8999404 B2 and WO2012143872 A1.

Wide spectrum of pharmacological activities of *Phaleria macrocarpa* is attributed to the presence of several classes of metabolites. The major metabolites in *P. macrocarpa* are phenolic compounds [14], terpenes (isoprenoids) compounds [15], alkaloids compounds [16], and benzophenone compounds [5,17].

Compounds such as kaempferol-3-O-β-D-glucoside [4], gallic acid [18], 29-norcucurbitacin, fevicordin A and fevicordin A glucosides [19], and Cucurbitacins have anticancer effects on cancer cells [20,21]. Some of these compounds exhibit a wide range of physiological properties, such as anti-allergenic, anti-artherogenic, anti-inflammatory, anti-microbial, antioxidant, anti-thrombotic, cardio-protective and vasodilator effects [2,9,14,22,23].

This review paper discusses the studies that have been undertaken on the pharmacological and phytochemical effects of *Phaleria macrocarpa*.

Pharmacological effect

Phaleria macrocarpa has been used for traditional medicine over the years but there should be scientific validations in order to verify the effectiveness of the ailment treatments. The pharmacological effects like anti-cancer, antioxidant, anti-inflammatory effect among others are discussed in the next section.

Anti-cancer effect

Cancer is a group of diseases involving the growth of abnormal cells with the potential to invade or spread to other parts of the body. The 70% ethanolic extract of *Phaleria macrocarpa* fruit pulp had shown anticancer activity on C3H mouse mammary tumor induced by transplantation [22].

Antioxidant effect

Antioxidants are molecules capable of slowing or inhibiting the oxidation of other molecules. Oxidation reaction involves transfer of electrons from a substance to an oxidizing agent whereby this reaction can leads to the formation of free radicals, and further reaction forms chain reactions which can damage body cells. Antioxidant acts as a principal agent that terminates the formation of chain reactions through the remover of free radical and inhibition of other oxidation reactions by oxidizing themselves. As a result, antioxidants are often acted as reducing agents such as thiols or polyphenols [24]. Polyphenolics, thiols, carotenoids, tocopherols and glucosinolates are commonly found in fruits, vegetables and grains that provide the chemo-protective effects [25]. Excess oxidants can lead to an imbalance of free radical cells that can cause oxidative stress. In addition, the DNA and protein sequences can be damaged resulting in high risk of degenerative diseases.

Consumption of fresh fruits and vegetables, as well as grains, has been associated with a reduction in risk of oxidative diseases. Antioxidants are substances that can prevent oxidative damage of lipids, proteins and nucleic acids by reactive oxygen species, which include reactive free radicals such as superoxide, hydroxyl, peroxyl, alkoxyl and non-radicals such as hydrogen peroxide and hypochlorous.

Isolated antioxidant compounds can prevent and treat the free radical-related disorders [26]. They are responsible for scavenging radicals through inhibition of the primary steps and breaking of formation chains. Based on the previous study, fruits are rich in antioxidant compounds like polyphenols and vitamin C, vitamins A, B and E, and carotenoids [25]. According to the research conducted by Hendra et al., the results showed that pericarp of *Phaleria macrocarpa* has highest scavenging activity which was 71.97% while that of the seed extract was 54.44% at concentration of 300µg/ml indicating the presence of antioxidant [27].

Anti-diabetic Effect

Diabetes has been described as a group of metabolic diseases whereby there are high blood sugar levels over a long period of time [28]. Study has been conducted on diabetic rats and the results showed that butanol extract of *Phaleria macrocarpa* had anti-diabetic effect in reducing plasma glucose levels by 66.67% ($p<0.05$) when compare with metformin (51.1%), glibenclamide (66.67%) and insulin (71.43%) after 12 days of treatment [9]. In addition, fruits of *Phaleria macrocarpa* has shown ACE inhibitory activity in which IC50 values was 122µg/ml in methanol extracts [29]. Phaleria macrocarpa (Scheff.) Boerl has also shown anti-diabetic effects that inhibit the enzymealpha-glukosidase and anti-diabetic effect in mice induced sterptozotosin [30].

Anti-inflammatory Effect

Anti-inflammatory can be defined as the property of a substance or treatment in order to reduce inflammation or swelling. *Phaleria macrocarpa* fruit extracts has shown this effect due to the presence of phenolic and flavonoid compounds or other phytochemicals such as terpenoid compound in the study that has been conducted by some group of researchers [27].

Anti-microbial Effect

Antibacterial activity of various parts of *Phaleria macrocarpa* fruits was studied using the disc diffusion method against eight bacterial strains, i.e., *Bacillus cereus*, *Bacillus subtilis*, *Enterobacter aerogenes*, *Escherichia coli*, *Klebsiela pneumonie*, *Micrococcus luteus*, *Pseodomonas aeruginosa* and *Staphylococcus aureus*. All parts including the pericarp, mesocarp and seeds exhibited weak to moderate antibacterial activity against all pathogenic bacteria strains with inhibition zones ranging from 9.3–23.3 mm [30]. In the same study, the antifungal activity was evaluated using the agar well diffusion assay against *Aspergillus niger*, *Fusarium oxysporum*, *Ganoderma lucidum* and *Mucor indicus*, the results showed that only seed extract was active against *A. niger* at a concentration of 0.3 mg/well [30]. Different polarities of extracts from the leaves of *Phaleria macrocarpa* including the n-hexane, chloroform, ethyl acetate and methanol extracts were evaluated for their antibacterial activity against

E. coli, *K. pneumonia*, *P. aeruginosa*, *Streptococcus ubellis*, *Streptococcus aureus* and *B. cereus*. Mueller Hinton agar well diffusion method was used to determine the susceptibility of bacteria tests. The highest activity was shown by ethyl acetate and methanol extracts against B. cereus and S. aureus with inhibition zone diameter ranging between 15-27 mm [31,32].

Mechanism of Actions of *Phaleria macrocarpa* Extract

There are two kinds of mechanism of actions for flavonoids: antimicrobial mechanism and immunological mechanism. Routes like nucleic acid synthesis, cytoplasmic membrane function, and energy metabolism leading to pathogens direct elimination refers to the antimicrobial mechanism [33]. The immunological mechanism indicates functions of flavonoids that effect gene expression, cytokines and cytokine receptors. How all these effects are mediated is not yet clear, but one important mechanism may be capacity of flavonoids to stimulate or inhibit protein phosphorylation and thereby regulate cell function [33,34].

A study-conducted administration of the *Phaleria macrocarpa* leaf extract significantly increased killing activity of splenic NK 1.1 cells against targets. The effects are based on the secretion of IFN-γ from NK 1.1 cells, and expression of surface molecules. During infections, NK cells will produce IFN-γ rapidly before the development of adaptive immune response, approximately 4 hours after stimulation with Phaleria extract. And after 24 hours almost majority of NK cells are IFN-γ positive. IFN-γ is a potent activator of monocytes that allow macrophages to kill tumor cells and ingest microbes [35]. Another suggested mechanism is by flavonoid binding to the TNF family receptor triggering the IκB kinases complex to phosphorylate IκB. The NF-κB proteins translocate to the nucleus and bind the DNA binding sites inducing transcription of gene for the IFN-γ, TH1 immune response is activated and cellular mediated immunity orchestrated [35].

Toxicity

Toxicity can be defined as the degree to which a substance can cause damage to an organism like an animal, bacterium, or plant, as well as their effects on a substructure of the organism, such as a cell (cytotoxicity) or an organ such as the liver (hepatotoxicity). Research done to determine the toxicity of ethanolic extract of fruits, seeds and leaves of *Phaleria macrocarpa* using *Brine Shrimp Lethality Test* show a non-toxic substance against the brine shrimp nauplii. Therefore, the positive response obtained in this assay suggests that the plant fruits are non-toxic and it could be used as a traditional herbal remedy [36].

Phytochemical Test

Phenolic compounds are secondary metabolites that are derivatives from pentose phosphate, shikimate, and phenylpropanoid pathways in plants [14]. They are most widely occurring groups of phytochemicals that have considerable physiological and morphological importance in plants. These compounds play an important role in growth and reproduction, providing protection against pathogens, and predators [37]. Phenolic compounds exhibit a wide range of physiological properties, such as anti-allergenic, anti-artherogenic, anti-inflammatory, anti-microbial, antioxidant, anti-thrombotic, cardio-protective and vasodilator effects [2,9,14,22,23].

Daily consumption of human beings contains a complex mixture of plant polyphenols which is flavonoids, as much as one gram of plant phenols per day is consumed in their diets [5]. A research group in China isolated and identified kaempferol-3-O-β-D-glucoside from *Phaleria macrocarpa* fruit [4]. Kaempferol was also isolated from *jamu* (traditional Indonesian medicine from plants) and was found to protect H4IIE rat hepatoma cells against oxidative stress [38]. The ability of kaempferol to inhibit the breakage of DNA strands from oxidative stress supports its role as a protective agent against cancer [38]. Kaempferol increased the number of cells in the G2/M phase and sub-G1 among leukemia cells and enhanced the activation of caspase-3 expression.

Phenolic compounds have been classified into six subgroups: Flavones (luteonin, apigenin, tangeritin); Flavonols (quercetin, kaempferol, myricetin, isorhamnetin, pachypodol); Flavanones (hesteretin, naringenin, eriodictyol); Flavan-3-ols: catechins and epicatechins, Isoflavones (genistein, daidzein, glycitein); and Anthocyanidins compounds (cyanidin, delphinidin, malvidin, pelargonidin, peonidin, petunidin). Other common flavonoid groups include aurones, xanthones, and condensed tannins. The catechins and leucoanthocyanidins are structurally similar and only rarely exist as their glycosides [39].

Some researchers had isolated gallic acid from *Phaleria macrocarpa* fruit and found that gallic acid, a natural phenolic acid isolated from fruits and vegetables, had a more potent growth inhibitory effect on two ovarian cancer cell lines [18]. Tannins are present in the plants and according to the study by Matsjeh et al., fruits and leaves of *Phaleria macrocarpa* contain tannin which is closely correlated with the induction of apoptosis and inter-nucleosomal DNA fragmentation in leukemia cells [40]. Pinoresinol has been isolated and identified by Faried et al. [5] from wood methanol extract of *Phaleria macrocarpa* using semi-preparative HPLC. Pinoresinol has a cytotoxic effect in human cervix carcinoma, the KB cell line (derivative of HeLa) [32]. Lariciresinol is a dietary lignan that accounts for a significant portion of the total phytoestrogen intake from Western foods. Human serum and urine contain lariciresinol, when ingested, it can be metabolized first to secoisolariciresinol, and then further to enterolignans, for example, enterodiol and enterolactone. According to Jungestro et al. [41], these three compounds have been shown to attenuate breast cancer growth in different estrogenresponsive experimental cancer model in vivo. Also, recent epidemiological studies by Touillaud et al. [42] suggest that high dietary intake of lignans and lariciresinol is associated with reduced breast cancer risk. Matairesinol was isolated from the roots and callus extracts of *Phaleria macrocarpa* using HPLC with a C18 column, it was identified by its UV and MS spectra analysis that the roots contain ~0.3-0.5 mg/g dry weight matairesinol and the callus contains ~0.2 mg/g [5].

Levita et al. had isolated fevicordin A which is an active compound from the seeds extracts of *Phaleria macrocarpa* [43]. In addition, isolation and identification of other active compounds from the seeds extracts of *Phaleria macrocarpa*, which were: 29- norcucurbitacin, deacethyl fevicordin A, fevicordin A glucoside, and fevicordin D glucoside has been done [19]. Cucurbitacins and fevicordin family have anticancer effects in cancer cells [20, 21]. Saponins are glycoside groups of steroids, steroid alkaloids (steroids with a nitrogen function), or triterpenes found in plants, especially in plant skins, where they form a waxy protective coating. Saponins are found in the fruits and leaves extracts of *Phaleria macrocarpa* [5]. They have been shown to provide protection to humans against cancer [44].

Anti-insecticide, such as toluquinone, ethylquinone, octanoic acid, 1-nonene, 1-undecene, 1-pentadecene, 1-heptadene and 6-alkyl-1-4-naphtoquinone have been found in the latex of seeds of *Phaleria macrocarpa* [17]. Also, it has been confirmed that the seeds extracts of *Phaleria macrocarpa* are highly toxic against the larva and adult stage of mosquito, Aedes aegypti Linn in vivo [45]. Alkaloids are naturally occurring amines produced by some plants, and they are found in the fruits and leaves extracts of *Phaleria macrocarpa* [16]. Alkaloids are strongly suggested to have anticancer activity [46]. They were dodecanoic acid, palmitic acid, ethyl stearate, sucrose, vasorelaxant icariside C3, and mangiferin [4,47,48]. One study reported that *Phaleria macrocarpa* shown the potential effect in improving the male fertility [44].

Conclusions

This review has shown the pharmacological and phytochemical properties of *Phaleria macrocarpa*. However, these have shown the benefits of these plants to the nature.

Disclosure

The authors report no conflicts of interest in this work.

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