



***Phaleria macrocarpa* (scheff.) Boerl: A Phytochemical and Pharmacological Review**

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Abstract Herbs have always been the principal form of medicine in India. Medicinal plants have curative properties due to the presence of various complex chemical substances of different composition, which are found as secondary plant metabolites in one or more parts of these plants. Plants have been used for thousands of years to flavour and conserve food, to treat health disorders and to prevent diseases including epidemics. The knowledge of their healing properties has been transmitted over the centuries within and among human communities. Active compounds produced during secondary vegetal metabolism are usually responsible for the biological properties of some plant species used throughout the globe for various purposes, including treatment of infectious diseases. In recent years, the utilization of certain medicinal plants as therapeutic agents has drastically increased. *Phaleria macrocarpa* (Scheff.) Boerl is frequently used in traditional medicine. *Phaleria macrocarpa*, commonly known as Mahkota dewa is a medicinal plant that is indigenous to Indonesia and Malaysia. Extracts of *P. macrocarpa* have been used since years in traditional medicine that is evaluated scientifically as well. The extracts are reported for a number of valuable medicinal properties such as anti-cancer, anti-diabetic, anti-hyperlipidemic, anti-inflammatory, anti-bacterial, anti-fungal, anti-oxidant and vasorelaxant effect. The constituents isolated from different parts of *P. macrocarpa* include phalerin, gallic acid, icaricide C, mangiferin, mahkoside A, dodecanoic acid, palmitic acid, des-acetyl flavicordin-A, flavicordin-A, flavicordin-D, flavicordin-A glucoside, ethyl stearate, lignans, alkaloids and saponins. The present review is an up-to-date summary of occurrence, botanical description, ethnopharmacology, bioactivity and toxicological studies related to *Phaleria macrocarpa*.

Keywords *Phaleria macrocarpa* (Scheff.) Boerl, Mahkota dewa, phytochemicals, ethnopharmacology, vasorelaxant, phalerin

Introduction

Human beings have depended on nature for their simple requirements as being the sources for medicines, shelters, food stuffs, fragrances, clothing, flavours, fertilizers and means of transportation throughout the ages. For the large proportions of world's population medicinal plants continue to show a dominant role in the healthcare system and this is mainly true in developing countries, where herbal medicine has continuous history of long use. The



development and recognition of medicinal and financial aids of these plants are on rise in both industrialized and developing nations. The foundations of typical traditional systems of medicine for thousands of years that have been in existence have formed from plants. The plants remain to offer mankind with new medicines. Some of the beneficial properties ascribed to plants have recognised to be flawed and medicinal plant treatment is based on the experimental findings of hundreds to thousands of years. The earliest reports carved on clay tablets in cuneiform date from about 2600 BC are from Mesopotamia; among the materials that were used were oils of *Commiphora* species (Myrrh), *Cedrus* species (Cedar), *Glycyrrhiza glabra* (Liquorice), *Papaver somniferum* (Poppy juice) and *Cupressus sempervirens* (Cypress) are still used today for the cure of diseases extending from colds and coughs to inflammation and parasitic infections. The traditional medicine practice is widespread in China, India, Japan, Pakistan, Sri Lanka and Thailand. About 40% of the total medicinal consumption is attributed to traditional tribal medicines alone by China. In Thailand, herbal medicines make use of legumes encountered in the Caesalpiniaceae, the Fabaceae, and the Mimosaceae. It is estimated that in mid-90s, more than US\$2.5 billion have resulted from the sales of herbal medicines. The herbal medicinal preparations are more in demand than mainstream pharmaceutical products in Japan.

The use of plants for treating diseases is as old as the human species. Popular observations on the use and efficacy of medicinal plants significantly contribute to the disclosure of their therapeutic properties, so that they are frequently prescribed, even if their chemical constituents are not always completely known. All over the globe, especially in South American countries, the use of medicinal plants has significantly supported primary health care. From 250 to 500 thousand plant species are estimated to exist on the planet, and only between 1 and 10% are used as food by humans and other animals. Brazil has the world's highest biodiversity, accounting for over 20% of the total number of known species. This country presents the most diverse flora, with more than 55 thousand described species, which corresponds to 22% of the global total.

Traditionally, the locals have used *P. macrocarpa* as a herbal drink either on its own or mixed with other medicinal plants to treat illnesses such as cancer, hypertension and diabetes mellitus. The biological and pharmacological activities of the stem, leaves, fruit and seed parts have been examined by several researchers. The fruits can cure high blood pressure, gout, skin disease, liver, cancer and diabetes. The stems are used to treat bone cancer; the egg shells of the seeds are used as anti-dote for the breast cancer, cervix cancer, lung disease and heart disease, while the leaves contain constituents that treat impotence, allergies, blood disease and tumours. Regarding on the beneficial properties of this plant, it has been reported that *P. macrocarpa* has medicinal activities such as anti-tumour, anti-hyperglycemia, anti-hypertensive, anti-inflammation, anti-diarrheal, anti-oxidant, anti-viral, anti-bacterial, anti-fungal and vasorelaxant effects.

Botanical Descriptions

P. macrocarpa is a shrub or small tree that grows throughout the year. This plant usually reaches the height of 5 m but sometimes its height could also reach up to 18 m. It grows in areas of 10-1,200 m above the sea level and the most productive age of this plant is in between 10-20 years. The plant of *P. macrocarpa* has features of many-branched crown with 1 metre long straight root exuding sap, a brownish green bark and white wood. The leaves are green, sharp edge and tapering from 10 - 15 cm in length and 3 - 5 cm in wide. Its flowers appear in white colour with trumpet-like shape and produce pleasant smell. The fruits have an eclipse shape; occur in various sizes with diameter ranging from 3 - 5 cm. Its fruits have smooth surface and changing their colour from green when young into red or maroon when ripening. The pit is round, white and poisonous.

Taxonomy

Kingdom: Plantae
Division: Tracheophytes
Order: Malvales
Family: Thymelaeaceae
Genus: *Phaleria*
Species: *P. macrocarpa*



Binomial Name: *Phaleria macrocarpa* (Scheff.) Boerl



Figure 1: *Phaleria macrocarpa* tree



Figure 2: *Phaleria macrocarpa* leaves



Figure 3: *Phaleria macrocarpa* flowers

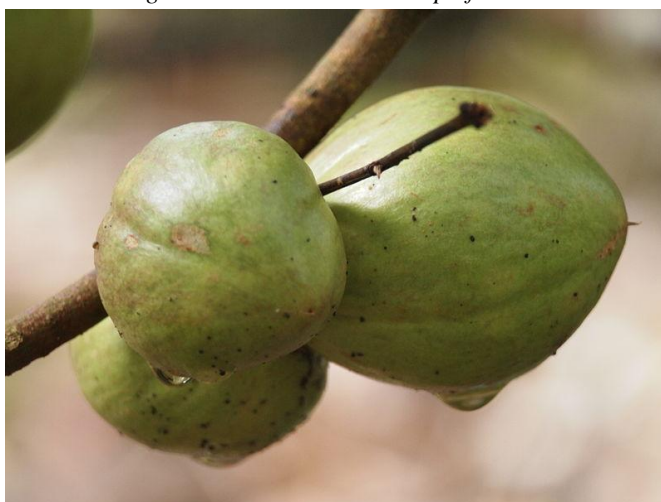


Figure 4: *Phaleria macrocarpa* young fruits



Figure 5: *Phaleria macrocarpa* fruits

Traditional Usage of Various Parts

P. macrocarpa is frequently used as a therapeutic healing alternative in health system of the Indonesians and lower course of Malaysia. All parts of this plant including fruits, seeds, stem and leaves have well known therapeutic properties and have been extensively used in traditional medicine. Specifically, the fruits of *P. macrocarpa* are used to treat flu, rheumatism, heart diseases and cancer; the leaves are used to treat dysentery, allergy, tumour and impotency while the stems are beneficial in the treatment of bone cancer. The eggshells of seeds are used to counter breast cancer, cervix cancer, lung disease, liver, and heart diseases. This plant especially the seed part cannot be consumed directly due to its high toxicity which can cause swelling, numbness and unconsciousness. However, the seeds can be used as an external medicine for the treatment of skin conditions and for ornamental cultivation purposes, which act as a traditional bio-pesticide.

Phytochemical Studies

Several research groups especially from Indonesia and China had extensively carried out studies to find chemical constituents from *P. macrocarpa*. The studies resulted in the isolation of several classes of compounds such as benzophenones, terpenoids, xanthenes, lignans, acids and sugars. Chemical investigation on the fruits leaves and barks of *P. macrocarpa* afforded eight benzophenone derivatives, identified as phalerin, isophalerin A, isophalerin B, Mahkoside A, Mahkoside B, 6,4'-dihydroxy 4-methoxy benzophenone-2-O- α -D-glucopyranoside, 6,4'-dihydroxy 4-methoxy benzophenone-2-O- β -D-glucopyranoside and 2,6,4'-trihydroxy 4-methoxy benzophenone. Several triterpenoids derivatives known as icariside C, phalerielide, β -sitosterol, stigmasterol and cyloargetanol were successfully isolated from the fruits of *P. macrocarpa*. Phytochemical studies on the fruits, reported a new 29-norcucurbitacin derivative named as desacetyl-fevicordin A, together with fevicordin A, fevicordin A-glucoside and fevicordin D-glucoside.

In addition, studies on chemical constituents from the fruits of *P. macrocarpa* revealed the isolation of an ester compound, ethyl stearate and acid derivatives including palmitic acid, oleic acid, linoleic acid, linolenic acid, dodecanoic acid and gallic acid. A novel lignin named as macronone and a known lignan, syringaresinol were obtained from the ethyl acetate extract of the bark and mesocarp of *P. macrocarpa*, respectively. The investigation on the chemical constituents of this plant yielded a xanthone and flavonoid compound identified as mangiferin and kaempferol-3-O- β -D-glucoside. Moreover, two sugar molecules known as glucose and sucrose were isolated from the aqueous extract of *P. macrocarpa* fruits. Furthermore, the quantitative analysis on various parts of *P. macrocarpa* fruits revealed the presence of five major flavonoids named as kaempferol, myricetin, quercetin, naringin, and rutin. Qualitative analysis of the flavonoids was carried out by reversed-phased high performance liquid chromatography (RP-HPLC) using an analytical column C18 60Å 4 μ m, 3.9 \times 150 mm, Waters, NANPA, MA (USA). The flavonoids were detected at 365 nm of UV-Vis photodiode array (DAD) detector.

Anti-insecticide, such as toluquinone, ethylquinone, octanoic acid, 1-nonene, 1-undecene, 1-pentadecene, 1-heptadene, and 6-alkyl-1-4-napthoquinone, have been found in the latex of seeds of *Phaleria macrocarpa*. It has been confirmed that the seeds extracts of *Phaleria macrocarpa* is highly toxic against the larva and adult stage of mosquito, *Aedes aegypti* Linn. Fruits and leaves of *Phaleria macrocarpa* have been known to contain Tannin, which is closely correlated with the induction of apoptosis and inter-nucleosomal DNA fragmentation in leukemia cells, HL-60.

Toxicological Studies

In spite of a number of medicinal properties claimed in traditional medicine for the extracts of *P. macrocarpa*, there are equally known poisonous tendencies of the extracts as well. However, we have not found a considerable supporting literature to evaluate the nature of the possible side effects. Even scientifically, there is a lack of credible and detailed report about the toxicity of *P. Macrocarpa* extracts. The only available literature consists of some preliminary toxicity reports. In tradition medicine, eating of unprocessed ripened fruits of *P. macrocarpa* is believed to cause oral ulcers, however, neither the possible mechanism of this toxicity has been evaluated scientifically, nor the responsible constituents of *P. macrocarpa* fruits that are responsible for this effect are identified and quantified



so far. Consumption of *P. macrocarpa* at a dose higher than 27 mg/kg is reported to show embryo-fetotoxicity in female mice. Butanol extracts of ripened fruits, when given to mice at doses of 0, 42.5, 85 and 170 mg/kg intraperitoneally, is reported to cause mild necrosis of proximal convoluted tubules in mice kidney at a dose higher than 85 mg/kg. Ethanol extracts of *P. macrocarpa*, when given to Javanese Quail in doses of 50, 100 and 200 mg/kg for two months are reported to cause mild hepatic hypertrophy and an increase in serum glutamate pyruvate transaminase activity at a dose of 100 mg/kg. Like fruits, seeds of *P. macrocarpa* are also reported for their toxicity. Des-acetyl fevicordin-A and its derivatives isolated from seeds of *P. macrocarpa* are reported to exert toxicity in brine shrimp (*Artemia Salina*) with a median lethal dose (LD50) of 3 ppm for desacetyl fevicordin-A and from 5 ppm to 12 ppm for its derivatives. The available literature until today is, however, not enough to evaluate the toxic profile of different extracts of this invaluable medicinal plant. This lack of toxicity data creates doubt about the success of employing *P. macrocarpa* extracts in treating different ailments.

Bio-activity

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. Therefore, many scientific evaluations on bioactivities of *P. macrocarpa* have been conducted in order to prove the traditional claims on the medicinal values of this plant. This review paper discusses the studies that have been undertaken on the pharmacological and phytochemical effects of *Phaleria macrocarpa*.

Anti-cancer activity

In recent years, the demand of potent and safer compounds for cancer therapy and chemoprevention has been increasing. Natural bioactive compounds derived from plants and their synthetic derivatives are expected to play an important role in the creation of novel and improved therapies for cancer management, both as monotherapy and in combination with conventional anticancer drugs. Cytotoxic activities of the methanolic extract from different parts of *P. macrocarpa* fruits were evaluated against the human colon adenocarcinoma cell line (HT-29), human breast adenocarcinoma cell line (MCF-7), human cervical cell line (HeLa) and normal human hepatocytes cell line (Chang liver cell). The viability of cells was measured using the MTT assay. The fruits were divided into pericarp, mesocarp and seed. Results obtained indicated that all parts had potential cytotoxic activity against the MCF-7 and HeLa cancer cell lines with IC₅₀ values ranging from 25.5 - 40.8 µg/ml. The results also showed that the seeds exhibited potential cytotoxic effect against HT-29 with an IC₅₀ value of 29.5 µg/ml while the pericarp and mesocarp exhibited mild cytotoxicity with IC₅₀ values between 63.8 - 70.1 µg/ml.

Anti-hyperglycemic activity

Hyperglycemia is a condition in which excessive amounts of glucose circulates in blood plasma. The extracts of *P. macrocarpa* fruits have been found to lower the post-prandial hyperglycemia. Highest activity is being shown by n-butanol extract of young and ripened fruits followed by ethyl acetate extract and then methanol extract. The α -glucosidase enzyme is present in the brush border of the small intestine, which breaks down oligosaccharides, trisaccharides and starch to glucose and other monosaccharides. The inhibition of α -glucosidase reduces rate of carbohydrates digestion, thus reducing the breakdown of carbohydrates into glucose. Glucose absorption, therefore, reduces and blood glucose level decreases contributing to hypoglycemic effect. *P. Macrocarpa* fruit competitively inhibits pancreatic α -amylase and membrane bound intestinal hydrolase as isomaltase, maltase and sucrose by inhibiting α -glucosidase. This delays glucose absorption and lowers post prandial hyperglycemia in short-term effect, while reduces HbA1c (glycated hemoglobin) in long term effect. Methanol extracts of pericarp is recently reported to decrease blood glucose on 12th day in diabetic rats by 56.25% and 58.33% when compared with diabetic control and pre-treatment value respectively. A further fractionation of n-butanol fraction of this pericarp methanol extract has revealed the presence of phalerin in the most active sub-fraction up to 22.50%.



Anti-inflammatory activity

P. macrocarpa is found to have potent anti-inflammatory activity due to its contents, including terpenoids, saponins, tannins, flavonoids and phenols such as rutin and catechol. During the process of inflammation, lipopolysaccharides of invading bacteria (for instance) bind to the toll like receptors (TLRs) on the dendritic cells, macrophages or antigen presenting cells (APCs). The cytoplasmic domains of TLRs on surface of APCs change and they cause activation of inactive protein kinase in the cytoplasm as PI3-kinase or Akt. This activation brings about cascade of changes that involve gene transcription factors including nuclear factor kappa-B (NF- κ B). Tail of NF- κ B has nuclear localization signals (NLS) that remains inactive as long as it remains attached with inhibitory kappa-B (I κ B). Cascade of changes causes phosphorylation of I κ B, which gets separated from NLS resulting into its activation. Activated NLS finds a way into the nucleus where it induces transcription of pro-inflammatory genes and production of COX 1, COX 2, leukotrienes and cytokines starts, which form prostaglandins and TNF- α from arachidonic acid. These act on endothelial cells of post-capillary venules and stimulate synthesis of adhesion molecules as intracellular adhesive molecules and vascular adhesive molecules. Lymphocytes are attached with these adhesion molecules, invade the surrounding tissue and cause inflammation.

Anti-microbial effects

Anti-bacterial activity of various parts of *P. macrocarpa* fruits was studied using the disc diffusion method against eight bacterial strains, i.e., *Bacillus cereus*, *Bacillus subtilis*, *Enterobacter aerogenes*, *Escherichia coli*, *Klebsiella pneumonia*, *Micrococcus luteus*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. All parts including the pericarp, mesocarp and seeds exhibited weak to moderate anti-bacterial activity against all pathogenic bacteria strains with inhibition zones ranging from 9.3 - 23.3 mm. 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 *Aspergillus niger* at a concentration of 0.3 mg/well.

Vasorelaxant activity

The vasorelaxant activity of the extracts and compounds isolated from the fruits of *P. macrocarpa* was evaluated against noradrenaline-induced contraction of isolated rat aorta. The results demonstrated the moderate vasorelaxant activity of the chloroform extract, while icaraside C showed a slow vasorelaxant activity. Phalerin and mangiferin did not show any vasorelaxant effect.

Anti-oxidant activity

Free radicals or reactive oxygen species have deleterious effects on human body, foodstuffs and fats, which developed an urge to find antioxidant substances from natural sources, which either delay or inhibit oxidation. The anti-oxidant activity of an extract is associated with its free radical scavenging activity. Different types of assays are developed to determine the anti-oxidant properties of plant extracts as ferric thiocyanate assay, thiobarbituric acid assay, ferric reducing anti-oxidant power assay and DPPH (2,2-diphenyl-1-picryl-hydroxyl) assay. DPPH, discovered 50 years ago, is a violet coloured free radical used to determine antioxidant properties of plant extracts and is a strong indicator for measuring antioxidant capacity in human plasma too. Reactive oxygen creates oxidative stress in the body and along with other damages can also mediate alloxan-induced liver damage.

Anti-hypertensive effect

Study on the anti-hypertensive activity of nine medicinal plants from Indonesia was conducted against angiotensin converting enzyme. The nine tested plants were *Scurrula atropurpurea*, *Catharanthus roseus*, *Swietenia mahogany*, *Persea americana*, *Oxalis corniculata*, *P. macrocarpa*, *Gynura procumbens*, *Melia azedarach* and *Hibiscus rosa sinensis*. Interestingly, all extracts from the fruits and leaves of *P. macrocarpa* displayed the highest level of inhibitory activity against acetylcholine esterase with IC₅₀ ranging between 102-189 μ g/ml.



Anti-hyperlipidemic activity

The increased body mass index causes increased level of total cholesterol and low-density lipoproteins (LDL) while reduce the levels of high-density lipoproteins. Increased cholesterol level in the body is termed as hypercholesterolemia. Imbalance in cholesterol homeostasis can create certain health problems as arteriosclerosis and heart diseases. The fruit of *P. macrocarpa* contains many active compounds as alkaloids, saponins and polyphenols, one of them is gallic acid that is found to regulate cholesterol homeostasis. Gallic acid decreases the cholesterol level in the body by up-regulating LDL-R (low-density lipoprotein receptors) and proprotein convertase subtilisin/kexin type-9 (PCSK-9) via sterol regulatory element binding protein transcription factor (SREBP-2-TF) up-regulation.

Sexual function

Eighteen male adult Sprague Dawley rats were divided into three groups and designated as treatment (240 mg/kg *P. macrocarpa* aqueous extract), negative control (distilled water), and positive control (4 mg/kg testosterone) which were supplemented through intragastric gavage for seven weeks. On the seventh week of supplementation, each of the male rats was introduced to five female rats at five different days to allow mating and observed the libido behaviour. The mounting latency and mounting frequency were recorded for each mating. *P. macrocarpa* aqueous extract significantly increased ($p < 0.05$) the serum testosterone level and mounting frequency of male rats. However, there was no significant effect on mounting latency. Body weight was significantly lower in rats supplemented with *Phaleria macrocarpa* aqueous extract compared with the control groups ($p < 0.05$).

Table 1: Ethnopharmacology of *Phaleria macrocarpa* (Scheff.) Boerl

S. No.	Tissue	Activity
1	Pericarp, mesocarp, seed, fruit, fruit pulp, leaves, irradiated leaves	Cytotoxic activity
2	Fruits, fruit powder, fruits pericarp	Anti-diabetic activity
3	Fruits	Ant-inflammatory activity
4	Different parts of young and old fruits, pericarp, mesocarp and seed	Anti-oxidant activity
5	Pericarp, mesocarp, seed, leaves	Anti-bacterial activity
6	Pericarp, mesocarp and seed	Anti-fungal activity
7	Fruits	Vasorelaxant activity
8	Fruits and leaves	Anti-hypertensive activity

Conclusion

Herbal medicine also called botanical medicine or phytomedicine refers to using a plant's seeds, berries, roots, leaves, bark, or flowers for medicinal purposes. Herbalism has a long tradition of use outside of conventional medicine. It is becoming more mainstream as improvements in analysis and quality control along with advances in clinical research show the value of herbal medicine in the treating and preventing disease over conventional medicines. Phytochemicals plays an important role in pharmacological activity.

In this review, we have reviewed the relevant literature to assemble the ethnomedicinal, phytochemical and pharmacological properties of *P. macrocarpa* (Scheff.) Boerl. This plant is used as folk remedies in both traditional as well as modern system of medicine to treat various diseases and illnesses. Various types of compounds with diverse chemical structures present in this plant are responsible for varied pharmacological and medicinal properties. The scientific research has suggested a significant biological potential of *P. macrocarpa* extracts. The phytoconstituents and the bioactivities associated with these constituents as presented in this short but concise review is strongly believed to be helpful for those researchers who are already working, or planning to start evaluating a particular biological aspect of this precious herb. There is an utmost need to evaluate toxicity of its fruit, seeds and other extracts with a special focus on the estimation of LD50 of the extracts and the identification of



the responsible constituents. Biologically active extracts of the plant can be further exploited in the future for the pharmaceutical and nutraceutical industry as well.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article the writing of this article.

Disclosure

The authors report no conflicts of interest in this work.

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