

Phytochemistry and medicinal properties of *Phaleria macrocarpa* (Scheff.) Boerl. extracts

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ABSTRACT

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 are 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, magniferin, mahkoside A, dodecanoic acid, palmitic acid, des-acetylflavicordin-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 *P. macrocarpa*.

Key words: Gallic acid, God's crown, magniferin, Mahkota dewa, phalerin, thymelaceae

OCCURRENCE, BOTANICAL DESCRIPTION AND ETHNOPHARMACOLOGY

Phaleria macrocarpa, commonly known as God's crown, Mahkota dewa or Pau is an Indonesian plant of family Thymelaceae that grows in tropical areas of Papua island. It is a complete tree, including stem, leaves, flowers and fruits [Figure 1]. Its height ranges from 1 m to 18 m with 1 m long straight root exuding sap, brownish green bark and white wood. It grows 10-1,200 m above sea level with a productive age that ranges from 10 to 20 years. The leaves are green and tapering with length and width ranging from 7 cm to 10 cm and 3-5 cm respectively. The flowers make a compound of 2-4, with color from green to maroon. Pit is round, white and poisonous^[1] and fruit is of eclipse shape with a diameter of 3 cm. Fruits are green when un-ripened

and become red on ripening.^[2] Seeds exist as 1-2 seeds per fruit and are brown, ovoid and anatropous. Although the herb is being used in both un-processed and processed form, however, the former can be poisonous and toxic.^[3] *P. macrocarpa* is being considered generally as a treatment of life style diseases.^[4] Extracts of *P. macrocarpa* are reported for a number of pharmacological activities, including anti-tumor, anti-hyperglycemia, anti-inflammation, anti-diarrhoeal, vasodilator, anti-oxidant, anti-viral, anti-bacterial and anti-fungal effect. Its stem is used to treat bone cancer; egg shells of seeds are used in treating breast cancer, cervix cancer,

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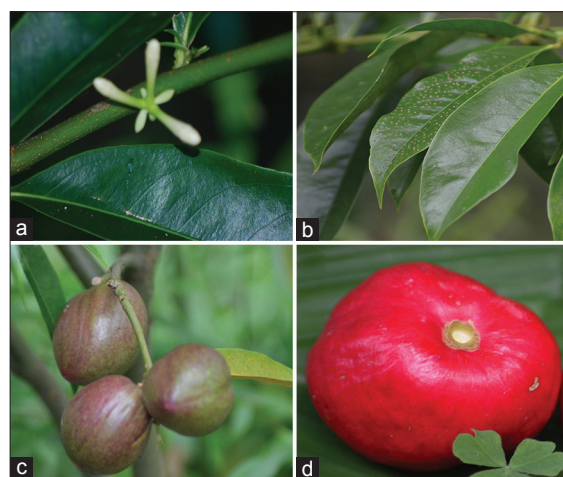


Figure 1: Botanical description of *Phaleria macrocarpa* showing a typical (a) small flower bud, (b) green tapering leaves, (c) un-ripened green fruit (c), and (d) fully grown red fruit

lung diseases, liver and heart diseases while leaves contain constituents that treat impotence, blood diseases, allergies, diabetes mellitus and tumors.^[5] In this review article, we have reviewed medicinal properties of *P. macrocarpa* extracts and chemical constituents that are isolated from its extracts to update current knowledge regarding this valuable plant and to provide guidelines for its future implications in the medical field.

PHYTOCHEMICAL STUDIES

Qualitative phytochemical studies

A variety of chemical constituents have been found in different parts of *P. macrocarpa* in varying concentrations. These include mahkoside A, dodecanoic acid, palmitic acid, des-acetyl flavicordin-A, flavicordin-A, flavicordin-D, flavicordin-A glucoside, ethyl stearate, lignans and sucrose.^[4] Yang and co-workers isolated mahkoside A (4,4-dihydroxy-2-methoxybenzophenone-6-O- β -D-glucopyranoside) for the first time from the pit of *P. macrocarpa* along with 6 known

compounds including magniferin (a C-glucosylxantone), kaempferol-3-O- β -D-glucoside, dodecanoic acid, palmitic acid, ethyl stearate, and sucrose.^[6] Lignans isolated from different parts of *P. macrocarpa*, when subjected to chiral column analysis, have been found to include pinosresinol ($79 \pm 4\%$ [-] -enantiomer excess), lariciresinol ($55 \pm 6\%$ [-] -enantiomer excess) and matairesinol (pure [+] -enantiomers).^[7] The bark and fruits are rich in saponins, alkaloids, polyphenolics, phenols, flavanoids, lignans and tannins.^[8-10] Isolated constituents of fruit include Icariside C3, magniferin, and gallic acid.^[1,11-13] Phalerin was first isolated from leaves of *P. macrocarpa* as a benzophenone glycoside (3,4,5, trihydroxy-4-methoxybenzophenone-3-O- β -D-glucoside) by Hartati *et al.*^[14] The same compound was isolated from fruits later by Oshimi *et al.*,^[11] however the proposed structure (2,4,6, trihydroxy-4-methoxybenzophenone-3-O- β -D-glucoside) was slightly different from the previous report. The pericarp of fruit contains kaempferol, myricetin, naringin and rutin.^[2] Naringin and quercetin are found in mesocarp and seeds^[2] while phorbosters, des-acetyl flavicordin-A and

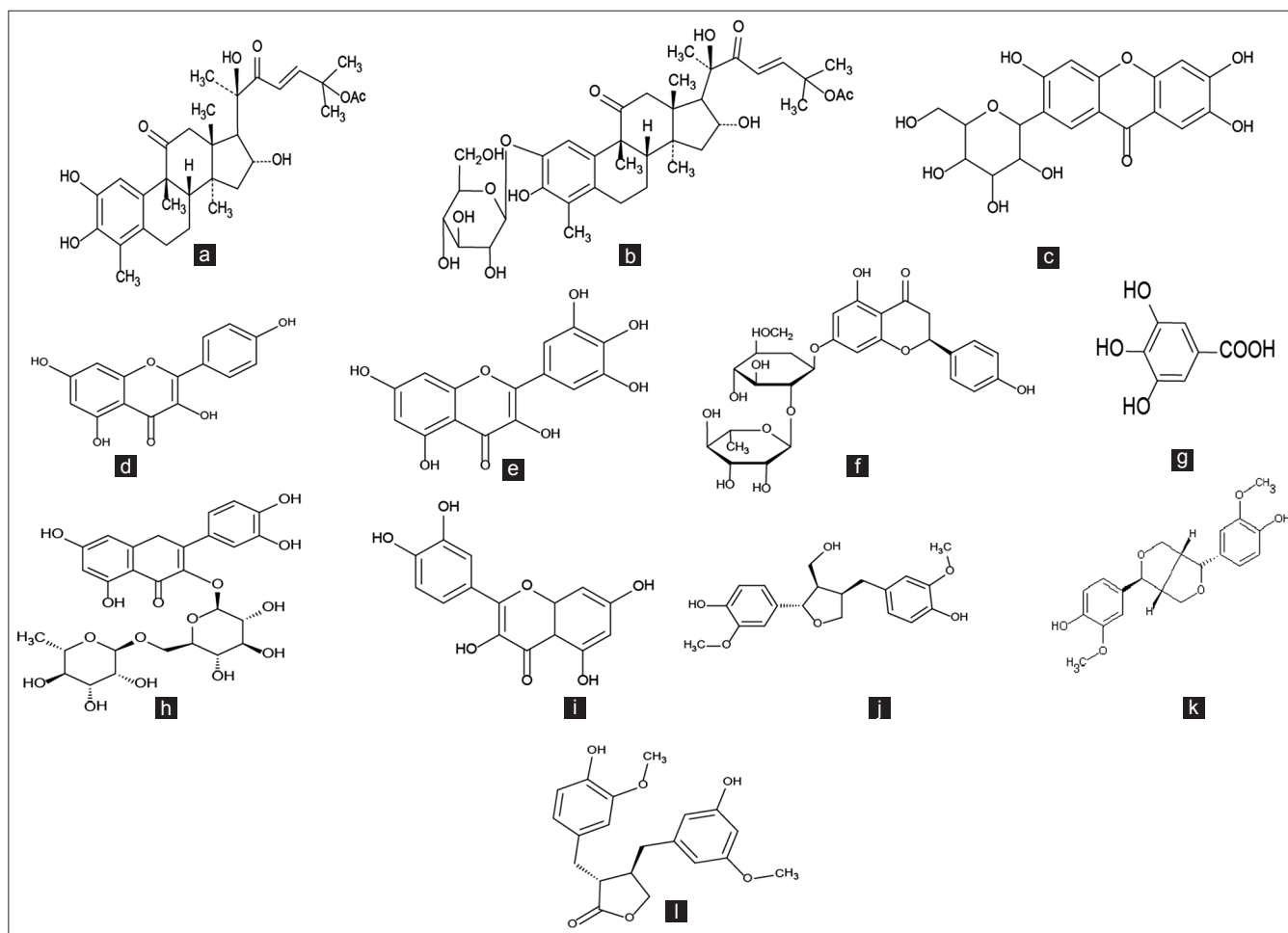


Figure 2: Chemical structures of constituents isolated from *Phaleria macrocarpa* extracts: (a) fevicordin-A, (b) fevicordin-D, (c) magniferin, (d) kaempferol, (e) myricetin, (f) naringin, (g) gallic acid, (h) rutin, (i) quercetin, (j) lariciresinol, (k) pinosresinol, (l) matairesinol. The structures are drawn by using ChemBio Draw 12.0

29-norcucurbitacin derivatives have been isolated from seeds.^[15] The chemical structures of the vital constituents isolated from *P. macrocarpa* are shown in Figure 2.

P. macrocarpa extracts are reported to contain alkaloids and saponins as well.^[4] There is, however, a need of investigating the extracts thoroughly for the identification of these alkaloids and saponins and to relate them with the reported biological properties of *P. macrocarpa* extracts.

Quantification of isolated phytoconstituents

The extracts of *P. macrocarpa* are not yet standardized fully to give a detailed percent quantity of its isolated constituents. However, the concentration of few of its constituents in a particular fraction of *P. macrocarpa* extracts are reported. For instance, methanol extracts of fruits of *P. macrocarpa* (when serially extracted in petroleum ether, chloroform, methanol and water) is reported to have phalerin content up to 9.52%.^[16] The crude paste (32 g) obtained from 3.2 kg of *P. macrocarpa* pit was found to consist of 9.1% Mahkoside A, 0.21% kaempferol and 0.1% magniferin, whereas 60% of this crude paste was consisted of sucrose.^[6] More recently, Kim *et al.* has advised an extraction method that has as much as 2.1% yield of magniferin by using pressurized hot water (subcritical water) as solvent.^[17] This high yield of magniferin was found to be dependent strongly on extraction temperature and weakly on pressure. The yield of magniferin with subcritical water was found to be lesser than that with methanol (2.5%) but higher than that with water (1.8%).

The total phenolic content of mesocarp, pericarp and seeds was found to be 60.5 ± 0.17 , 59.2 ± 0.04 and 47.7 ± 1.04 mg galic acid equivalent/gram of dry weight (GAE/gDW) respectively.^[18] The total flavonoid content of pericarp was found to be maximum (161.3 ± 1.58 mg RE (rutin equivalent)/g DW) when compared to that of mesocarp and seeds (131.7 ± 1.66 and 35.9 ± 2.47 mg RE/g DW respectively).^[18]

A detailed phytochemical study of *P. macrocarpa* extracts is imperative to get a more accurate estimation of its constituents. There is an utmost need of establishing chemical methods for the isolation of the already identified pharmacologically active constituents such as magniferin, phalerin, icaraside and gallic acid with maximum possible yield.

BIOACTIVITY

Anticancer activity

Leaves and fruits of *P. macrocarpa* are being used since years in treatment of different types of cancer^[9] especially against breast cancer^[5,19] and brain tumor.^[20] *P. macrocarpa* supplementation with adriamycin cyclophosphamide (AC) is reported for its synergistic effect in reducing tumor growth in

breast cells by inducing apoptosis, but also for its protective effect on liver and kidney damage caused by AC.^[21] Two of its constituents, phalerin and gallic acid, are proven to pay a major contribution to its cytotoxic properties.^[1,22]

Methanolic semipolar extract of *P. macrocarpa* (designated as DLBS1425) was proved to manifest its anticancer activity in breast cancer cells by acting as an anti-proliferative, anti-angiogenic and apoptotic inducer.^[23] This extract contained 20.26% phalerin and it induced apoptosis by DNA fragmentation, caspase-9 activation and by regulation of B-cell lymphoma 2 protein (Bcl-2) and Bcl-2 associated X proteins (BAX) at mRNA level. Bcl-2 are anti-apoptotic proteins encoded by Bcl-2 genes that act as check points in apoptosis regulation, while BAX are pro-apoptotic proteins of Bcl-2 gene family. Phalerin and gallic acid up-regulate BAX protein in a dose dependent manner while down-regulate the expression of Bcl-2 mRNA,^[22,24] which causes sustained elevation of calcium levels in mitochondria [Figure 3]. This induces opening of voltage dependent anion channels and cause release of a small amount of (Cytochrome-c, an inter-membrane space protein) from mitochondria.

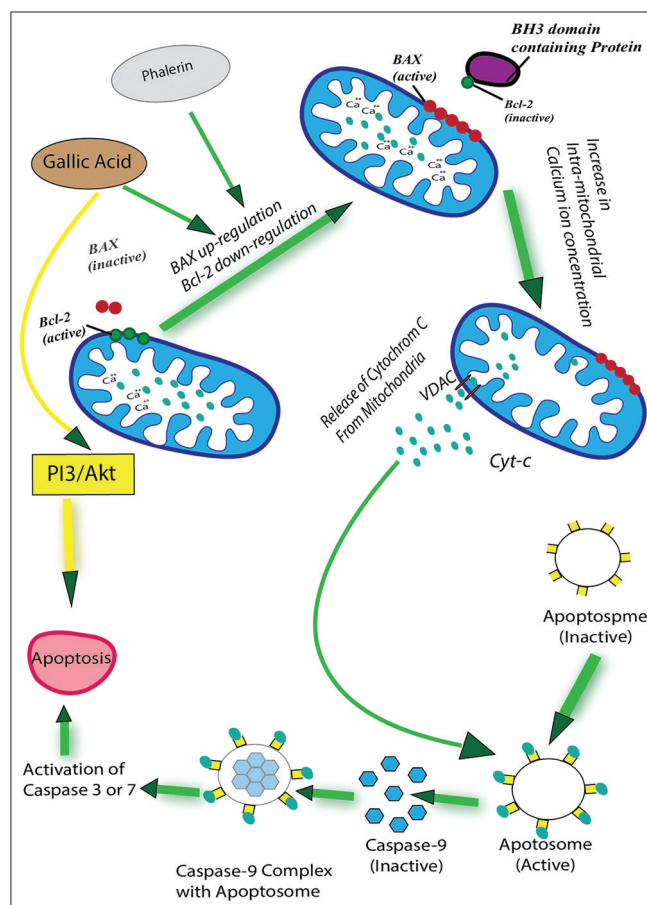


Figure 3: Mechanism of pro-apoptotic effect of gallic acid and phalerin isolated from *Phaleria macrocarpa* extracts. Bcl-2: B-cell lymphoma 2 protein, BAX: Bcl-2 associated X proteins, Cyt-c: Cytochrome C, VDAC: Voltage dependent anion channels, PI3/Akt: Phosphoinositide 3/protein kinase B pathway

Cyt-c interacts with inositol triphosphate receptor on endoplasmic reticulum causing the release of endoplasmic reticulum-calcium, enhancing overall level of calcium ions, which further triggers massive release of cyt-c. This cyt-c binds to WD-40 domain of C-terminus of apoptotic protease activating factor-1 (APAF-1) and ceases auto-inhibition of this domain while other two domains of APAF-1 as caspase activation and recruitment domain (CARD) and Nucleotide binding adaptor shared by APAF-1, R and CED-4 (NB-ARC) adenosine tri phosphatase domain (ATPase domain) remains in autoinhibited state. Cyt-c binding to APAF-1 triggers stable binding of ATP/dATP at nucleotide binding site of APAF-1. In the presence of seven cyt-c molecules and seven APAF-1 proteins, oligomerisation of APAF-1 into wheel-like heptagonal structure occurs and causes activation of apoptosome. The apoptosome causes cleavage and recruitment of inactive procaspase-9 (APAF-3) to activated caspase-9 molecules. Caspases are cysteine-aspartic-proteases consisting of initiator caspases as 2, 8, 9, 10 and effector caspases as 3, 6 and 7. The activated initiator caspase-9 further activates effector caspases, which triggers cascade of caspases 3, 6, 7. This activates DNAase to cause DNA fragmentation thus inducing apoptosis.^[23]

DLBS1425 also suppressed cyclo-oxygenase 2 mRNA expression and vascular endothelial growth factor-C (VGEF-C) mRNA expression. It caused a reduction in vascular permeability which further reduced endothelial cell proliferation and migration, resulting into anti-angiogenesis. Protein kinase-C was also inhibited by this extract causing down-regulation of transcriptional factors as activator protein-1, contributing further to its anti-proliferative activity.^[23] Gallic acid along with acting on BAX and Bcl-2 genes, also acts on PI3K/Akt/mammalian target of rapamycin (mTOR) pathway.^[20] In addition to these two pro-apoptotic mechanisms, gallic acid is also reported to increase reactive oxygen species in cancer cell lines *in vitro*.^[25]

Phosphatidyl-inositol-3-kinase (PI3K) activates Akt (protein kinase-B) that regulates cell survival. This further activates mTOR, which regulates cell growth and proliferation. In cancerous cells, this pathway becomes overactive and decreases apoptosis, which allows proliferation. Gallic acid exerts its anti-proliferative effect by down-regulating survival of Akt/mTOR.^[24] Gallic acid also down-regulates phosphorylation of Ras/mitogen activated protein kinase pathway, thus suppressing A disintegrin and Metalloproteinase (ADAM)-metallopeptidase domain 17 (tumor necrosis factor alpha converting enzyme) therefore, decreasing cell invasion and proliferation.^[26] Gallic acid has been found to interfere with interaction of C-X-C chemokine receptor type-4 and C-X-C chemokine ligand-12 which inhibits PI3K activation. This inhibition further inhibits phosphorylation of Akt thus down-regulating VGEF at both protein and mRNA level, combating progression of angiogenesis and tumor.^[27,28] Gallic acid

has been found to inhibit growth of Hela cells and human umbilical vein endothelial cells (HUVEC) cells *in vitro* with median inhibitory concentration (IC_{50}) of 80 μ M and 400 μ M for Hela and HUVEC cells respectively.^[25]

Ethanollic leaf extracts of *P. macrocarpa* is reported for its ability to increase expression of NKG2D (type-II integral membrane protein) and CD-122 (a subunit of interleukin-2), the surface molecules which enhances the activity of killer triggering receptors on natural killer cells (NKC) of spleen thus enhancing their killing activity. It increases interferon-gamma production, which is a glycoprotein that activates immune cells, macrophages and NKC, ultimately increasing recognition of infection or tumor by up-regulating T-lymphocytes.^[29,30]

Antihyperglycemic 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.^[31,32] 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.^[31] 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.^[33] 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%.^[16]

We have already mentioned about the presence of rutin in mesocarp and pericarp of *P. macrocarpa* fruits. Rutin is reported to have a significant anti-diabetic effect in rats,^[34] however, the anti-diabetic effect of *P. macrocarpa* fruit has not been linked with the presence of rutin so far.

Antihyperlipidemic activity

The increased body mass index causes increased level of total cholesterol and low-density lipoproteins (LDL) while reduces the levels of high-density lipoproteins. Increased cholesterol level in the body is termed as hypercholesterolemia. Imbalance in cholesterol hemostasis 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 hemostasis. Gallic acid decreases the cholesterol level in the body by up-regulating LDL-R (low-density lipoprotein receptors) and pro-protein convertase subtilisin/kexin type-9 (PCSK9) via sterol regulatory element binding protein transcription factor (SREBP-2-TF) up-regulation.^[8] High-levels of cholesterol in cells inhibit transcription of LDL-R and PCSK-9, which decreases intake of plasma cholesterol into cells. Gallic acid present in fruit of *P. macrocarpa* increases the number of LDL-R, which enhances binding of LDL particles in the blood to LDL-R. This further triggers LDL-R mediated endocytosis causing internalization into the peripheral cells decreasing circulating LDL-level, thus, reducing cholesterol level in cells. Gallic acid also up-regulates PCSK-9-mRNA expression. PCSK-9 binds to EGF-A (epidermal growth factor like repeat A) domain of cell surface LDL-R. Receptor-mediated endocytosis is initiated. PCSK-9-LDLR complex is formed and goes inside the cell and routed to lysosomes and degraded. This causes regulation of cell surface LDLR and thus decreases cholesterol levels.^[35] SREBPs activates expression of 30 genes involved in synthesis of cholesterol, fatty acids and triglycerides.^[36] SREBP up-regulates expression of 3-hydroxyl-3-methyl gentaryl-coenzyme A reductase. If cellular cholesterol level is high, SREBP exists as a membrane bound precursor and SREBP-cleavage activating protein (SCAP) remains inactivated, but if cellular cholesterol level decreases, SCAP becomes activated and escorts SREBP to golgi bodies. Proteolytic cleavage of SREBP occurs by site-1-protease and site-2-protease, which activates transcription factor of SREBP named as nuclear SREBP that translocates into nucleus. Inside the nucleus, SREBP binds to sterol regulatory elements activating genes involved in lipid hemostasis, thus controlling cholesterol balance.^[8,37,38]

Antibacterial and anti-fungal activity

Leaves and seeds of *P. macrocarpa* are found to have profound antibacterial activity.^[39] Flavanoids, saponins, polyphenols and tannins present in the fruit highly inhibit gram positive bacteria as compared to gram-negative bacteria^[40] due to the outer permeability barrier in gram-negative bacteria. These bacteria include *Bacillus cereus*, *Bacillus subtilis*, *Enterobacter aerogenes*, *Escherichia coli*, *Klebsiella pneumonia*, *Micrococcus luteus*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*. It exhibits its antimicrobial activity by different mechanisms as inhibiting nucleic acid synthesis, energy metabolism or cytoplasmic membrane function.^[41] Kaempferols are found to inhibit *S. aureus*, *Enterococcus faecalis*, *Escherichia coli* and *P. aeruginosa*. The methanol extracts of fruit of *P. macrocarpa* is found to have good activity against *P. aeruginosa* and strong activity against *E. coli*,^[42] *B. cereus* and *Streptococcus aureus* with the diameter of the inhibitory zone (DIZ) as 15-18 mm. Ethyl acetate extract has shown

good activity against *E. coli*, *Klebsiella pneumoniae* and *Streptococcus ubellis* while strong activity against *P. aeruginosa*, *Streptococcus aureus* and *B. cereus* with DIZ as 15-27 mm. The hexane and chloroform extract have found lowest activity with DIZ less than 10 mm.^[41] Phorbol esters in *P. macrocarpa* seeds inhibit growth of certain fungi as *Aspergillus niger*, *Fusarium oxysporum*, *Ganoderma lucidum*, and *Mucor indicus*.^[2]

Anti-inflammatory activity

P. macrocarpa is found to have potent anti-inflammatory activity^[2] due to its contents, including terpenoids, saponins, tannins, flavanoids 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 have 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 COX1, COX2, 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.

Semipolar methanolic extract of fruit of *P. macrocarpa* DLBS1425 (containing 20.26% phalerin) is reported to inhibit inflammation.^[23] It suppresses COX2-mRNA expression even in the presence of phorbol ester 12-O-tetradecanoylphorbol-13-acetate. This inhibition of COX2-mRNA causes a decrease in prostaglandin E2 (PGE2) synthesis thus inhibiting inflammation. More recently, phalerin is reported to have mild inhibitory effect on xanthine oxidase and lipo-oxygenase (34.83 ± 4.64 and $23.47 \pm 9.43\%$ inhibition respectively). However its inhibitory effect on Hyaluronidase was found to be non-significant ($1.34 \pm 0.57\%$ inhibition).^[43] *P. macrocarpa* is also found to treat primary dysmenorrhea in which the production of leukotrienes and prostaglandins F2- α and E2 is enhanced at a large level and may cause increased uterine smooth muscles tone and contractions causing abdominal cramps.^[10] The pericarp and mesocarp extract of fruit have shown moderate anti-inflammatory activity while seed extract has shown weak activity.^[2] Cytokines by binding with macrophages up-regulate nitric oxide synthase enzyme

which forms NO (nitric oxide) from l-arginine. NO plays an important role in inflammation.^[44] Extracts of *P. macrocarpa* inhibit NO production in a dose dependent manner thus inhibiting inflammation.

Antioxidant 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.^[45] The antioxidant activity of an extract is associated with its free radical scavenging activity. Different types of assays are developed to determine the antioxidant properties of plant extracts as ferric thiocyanate assay, thiobarbituric acid assay, ferric reducing antioxidant power assay and DPPH (2,2-diphenyl-1-picryl-hydroxyl) assay.^[9,41] DPPH, discovered 50 years ago, is a violet colored free radical used to determine antioxidant properties of plant extracts and is a strong indicator for measuring antioxidant capacity in human plasma too.^[46] Reactive oxygen creates oxidative stress in the body and along with other damages can also mediate alloxan-induced liver damage.^[47]

Fruit and leaves of *P. macrocarpa* are found to possess flavanoids and phenolics^[41] which make it a potent antioxidant. The constituents present in mesocarp, pericarp and seed extract of *P. macrocarpa* are responsible for antioxidant activity such as gallic acid^[24] and 6-dihydroxy-4-methoxybenzophenone-2-o- β -D-glucoside which shows activity on DPPH.^[48] Fruit extracts of *P. macrocarpa* has been found to increase the level of SOD (superoxide dismutase),^[47,48] which are enzymes of three types, SOD1, 2 and 3, that catalyze the dismutation of superoxide into oxygen and hydrogen peroxide thus acting as an antioxidant. Pericarp extract has found to possess highest activity as an antioxidant while seed extract the lowest.^[9]

Vasorelaxant activity

For centuries, the leaves and fruit of *P. macrocarpa* have been used to counter a number of diseases, including vascular problems and high blood pressure.^[1,8] Dried flesh fruit powder^[19] and egg shells of seeds^[5] have been empirically considered potent cure of hypertension and heart diseases.^[2] Epidemiological studies have shown that its two major constituents have effect on cardiovascular system, the kaempferol, a flavanoid that reduces the risk of cardiovascular diseases^[49] and icaricide, that is a moderate vasorelaxant reducing hypertension.^[11] Icaricide which is being isolated from chloroform extracts of *P. macrocarpa* fruit enhances vasorelaxant responses of isoproterenol and inhibits noradrenaline induced contractions contributing to the increase of second messengers as cyclic adenosine monophosphate and cyclic guanosine mono phosphate, phosphodiesterase inhibition and adenylatecyclase activation.^[11]

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,^[3] 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.^[50] 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.^[51] 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

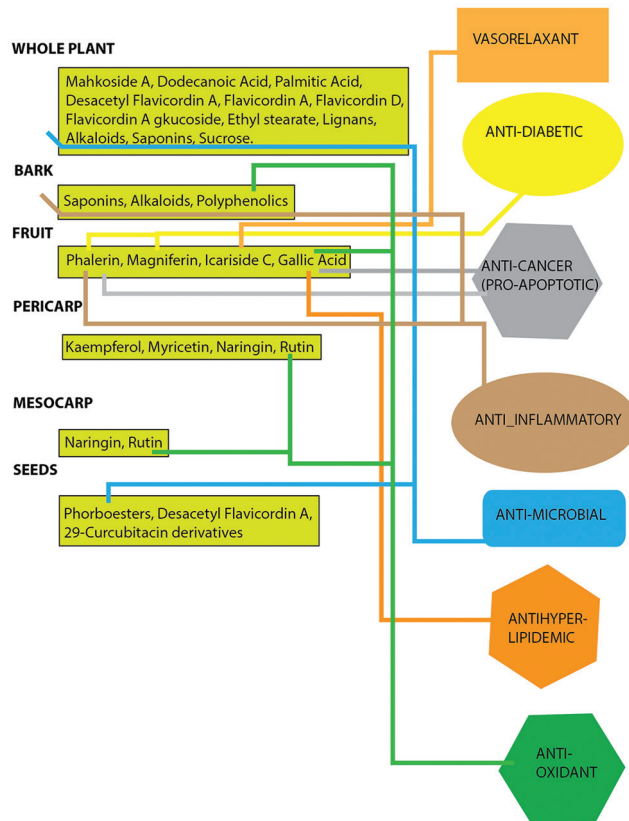


Figure 4: Phytoconstituents isolated from *Phaleria macrocarpa* with their respective biological activity

pyruvate transaminase activity at a dose of 100 mg/kg.^[52] Like fruits, seeds of *P. macrocarpa* are also reported for their toxicity. Des-acetylfevicordin-A and its derivatives isolated from seeds of *P. macrocarpa* are reported to exert toxicity in brine shrimp (*Artemiasalina*) with a median lethal dose (LD₅₀) of 3 ppm for des-acetylfevicordin-A and from 5 ppm to 12 ppm for its derivatives.^[15] 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.

CONCLUSION

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 [Figure 4] 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. Anti-cancer effect of fruit extracts is already well-established, but the activity report is based only on the *in-vitro* assay. There is still no report of the evaluation of this otherwise tremendous *in vitro* cytotoxic effect of *P. macrocarpa* extracts in an *in-vivo* tumor model, insisting further clinical trials first in animals and then in human. Biologically active extracts of the plant can be further exploited in the future for the pharmaceutical and nutraceutical industry as well.

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