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Review Article

Phaleria macrocarpa (Scheff.) Boerl. in Ethnopharmacology: Pharmacognosy, Safety, and Drug Development Perspectives

Anandarajagopal Kalusalingam[1]*, Kamaliah Kamal[1], Abdullah Khan[2], Bama Menon[1], Ching Siang Tan[1], Venkateshan Narayanan[3], Sattanathan Kumar[4], Khang Wen Goh[5], Kah Seng Lee[6], Jactty Chew[7]*, Long Chiau Ming[7]

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[1]School of Pharmacy, KPJ Healthcare University, 71800 Nilai, Malaysia; k4maliahkamal@gmail.com (KK); tcsiang@kpju.edu.my (CST); bamamenon@kpju.edu.my (BM)

[2]Faculty of Pharmacy, Quest International University, 30250 Ipoh, Malaysia; abdullah.khan@qiu.edu.my (AK)

[3]Arulmigu Kalasalingam College of Pharmacy, Krishan Koil 626126, Tamil Nadu, India; nv7776@gmail.com (VN)

[4]Sree Abiramy College of Pharmacy, Coimbatore 641021, Tamil Nadu, India; sattkumar7@yahoo.com (SK)

[5]Faculty of Data Science and Information Technology, INTI International University, 71800 Nilai, Malaysia; khangwen.goh@newinti.edu.my (KWG)

[6]Faculty of Pharmacy, University of Cyberjaya, Cyberjaya, Malaysia, ksl.pharm@gmail.com (KSL)

[7]School of Medical and Life Sciences, Sunway University, Sunway City, Malaysia, longchiauming@gmail.com (LCM)

*Corresponding author: Anandarajagopal Kalusalingam; School of Pharmacy, KPJ Healthcare University, 71800 Nilai, Malaysia; anand@kpju.edu.my (ARG); Jactty Chew; School of Medical and Life Sciences, Sunway University, Sunway City, Malaysia; jacttyc@sunway.edu.my (JC)

Abstract: *Phaleria macrocarpa*, a medicinal plant from the *Thymelaceae* family, is predominantly found in Malaysia and Indonesia. This review aims to comprehensively summarize the phytochemical, pharmacological, and toxicological aspects of *P. macrocarpa*, along with modern approaches and safety concerns. Data for the review were collected from various scientific databases and relevant literature on *P. macrocarpa*. The review discusses the plant's phytochemical composition and its diverse medicinal properties, including anti-inflammatory, antihypertensive, antidiabetic, antioxidant, antimicrobial, antipyretic, antiulcer, antiviral and anticancer activities. *P. macrocarpa* has also been used to treat various female health conditions. Additionally, combination therapies and advanced drug delivery systems such as nanoemulsion have been reviewed. These pharmacological activities are attributed to the plant's phytoconstituents. The review will be valuable for researchers

involved in medicinal plant research and drug discovery, offering potential for use alongside modern therapeutic agents. However, clinical studies are essential to validate its therapeutic applications. Further research is required to develop standardized herbal pharmaceuticals from *P. macrocarpa* that are effective, safe, and meet regulatory standards for quality assurance.

Keywords: natural product; biodiversity; *P. macrocarpa*; medicine; phytochemistry; pharmacology; toxicology; SDG 3 Good health and well-being

1. Introduction

Medicinal plants have been recognized and used extensively since ancient times by human beings as a source of curing various types of diseases and disorders [1]. Knowledge about the benefits of medicinal plants has been passed down from one generation to another, and even today's medicinal plants are the focus of interest in scientific investigations related to drug discovery and development [2, 3]. The discovery of bioactive compounds originating from medicinal plants has always been one of the major disciplines in pharmaceutical sciences [4, 5].

In Malaysia, trust in herbal medicines is based on practical experiences, observations, and rituals derived from socio-cultural and religious beliefs. About two hundred and thirteen species of plants have been reported as medicinal plants in Peninsular Malaysia in 2017 [6]. A cross-sectional study about Malaysian women's knowledge and practice revealed that parents are the major source of information about herbal medicines, as declared by 60.8% of the participants of the survey [7].

Phaleria. *macrocarpa* (Scheff.) Boerl. belongs to the *Thymelaceae* family. *C*ommonly known as Mahkota dewa, it is one of the most popular medicinal plants in Malaysia and Indonesia and is found abundantly in Papua Island. The name "Mahkota dewa" or "God's crown" given to its fruit indicates that it descends from heaven, from the divine powers of god to help humankind. The various parts of this plant including the stem, leaves and fruits are enriched with medicinal properties and are widely used in the treatment and prevention of diseases. *P. macrocarpa* is one of the medicinal plants that has gained interest in drug discovery investigations due to its extensive pharmacological activities and potential medicinal benefits [8].

The therapeutic effects of extracts of *P. macrocarpa* from its leaves, stems, flowers, fruits etc. have been known for more than a decade, and they have been used extensively to treat various ailments in human beings. It is essential to further investigate *P. macrocarpa* for its diverse medicinal properties and to further find out its effectiveness against specific diseases. Also, it is necessary to experimentally evaluate its safety and efficacy using optimized doses. Though *P. macrocarpa* has been reported to possess several medicinal

properties, the literature review suggests that there is ample scope to explore its effectiveness in many of the activities reported and proven in vitro and in vivo in animal models and also to validate its traditionally claimed therapeutic uses. Rizal et al. [9] have reported a study in an elderly hypertensive group to evaluate the antihypertensive effects of *P. macrocarpa*. It was reported that those who received *P. macrocarpa* demonstrated a decrease in their both systolic and diastolic blood pressure. Hence, this review aims to provide a comprehensive report on the phytochemical, pharmacological and toxicological profiles including the modern approaches and safety aspects of *P. macrocarpa* through a compilation of the literature, and also to provide guidelines for the development of standardized therapeutic options for *P. macrocarpa*.

2. Methods

Scientific data for this review was gathered from databases like PubMed, ScienceDirect, Springer, ResearchGate, Google Scholar, and relevant books on *P. macrocarpa*. Key journal articles were also reviewed, and references were manually screened for accuracy and reliability. Different combinations of keywords such as "Phaleriamacrocarpa / medicinal plants", "Mahkotadewa / pharmacological", "ethnobotany / Phaleriamacrocarpa", "phytoconstituent / Phaleriamacrocarpa", "Toxicity / Phaleriamacrocarpa", "Pharmacognostical / Phaleriamacrocarpa", "taxonomy / Phaleriamacrocarpa" were used to search for the relevant articles from the respective database.

3. Pharmacognosy of *P. macrocarpa*

3.1. Botany of P. macrocarpa

P. macrocarpa has various parts of plants such as stems, fruits, leaves and flowers with height ranges from 1-18 m with 1m straight long root exuding sap and brownish green bark. The length of life ranges from 10-20 years and can grow to 5-6 m in height but can reach a maximum height of 18 m [10].

3.1.1. Leaf

The leaves (Figure 1) are green, oppositely arranged, petiole 0.5 cm long, elliptic to oblong lanceolate with pointed apex with length and broad-ranging from 7-14 cm and 3-5 cm, respectively. Flowers can be seen as white trumpet-shaped in clusters of 2-4 which are produced throughout the year but mainly during the rainy season [10].

Figure 1. Leaves of *P. macrocarpa* (Scheff.) Boerl [11].

The microscopic observation of *P. macrocarpa* leaves powder at 40x magnification is described with adaxial epidermal cells with straight to wavy anticlinal walls. The fragment's epidermis is facing away from the stem with tetracytic stomata. The trichomes are simple and multicellular with pointed ends. Leaves of *P. macrocarpa* have abundant druse and solitary crystals, which are sometimes found isolated. *P. macrocarpa* leaf powder exhibited a green colour after treatment separately with concentrated hydrochloric acid and 5% sodium hydroxide solution.

Standardization methods such as foreign matter, ash content, loss on drying, and extractive values for water-soluble and ethanol-soluble extracts have been conducted on *P. macrocarpa* leaves with a 0.355mm particle size. The tests on foreign matters found not more than (NMT) 2%, while loss on drying was NMT 9%. Meanwhile, the contents of ash value in total ash and acid-insoluble ash were found to be NMT 15% and 2%, respectively. Two methods used for the extraction of water-soluble and ethanol-soluble extracts are the hot method and the cold method. The hot method produced extractive values not less than (NLT) 27% in water-soluble extracts and NLT 19% in ethanol-soluble extracts. The cold method produced extractive values of NLT 22% in water-soluble extracts and NLT 15% in ethanol-soluble extracts. The presence of heavy metals such as arsenic, mercury, lead and cadmium has been evaluated on *P. macrocarpa* leaves. Cadmium showed the highest safety with a value NMT 0.3 mg/kg, followed by mercury NMT 0.5 mg/kg, arsenic NMT 5.0 mg/kg and lead NMT 10.0 mg/kg. The total aerobic microbial count produced in *P. macrocarpa* leaves was also determined and found to be NMT 10^5 cfu/g. Pathogens including *E. coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* are absent in 1g while *Salmonella* spp. is absent in 25g [12].

3.1.2. Flower

P. macrocarpa is a flowering plant. The development of the flower (Figure 2) takes place for seven days, and the flower is tubular in shape and white in colour. It consists of four main parts: sepals, petals, stamens and carpels. Early budding is green, which changes to white on the fourth day, with a length of 0.8 to 0.9 cm. The length increases on the sixth day to 1.6 to 1.7 cm. When it is in bloom, it consists of 4 sepals, 4 to 5 petals, 8 stamens and a carpel with a long and rounded stigma (Figure 3). The petals are fused together, which is

called gamopetalous or sympetalous. The arrangement of the *P. macrocarpa* flower is biradial symmetrical. The carpel, the female reproductive organ of *P. macrocarpa*, features a rounded sticky stigma, a long style, and an ovary enclosed by fused petals. The stamens, the male reproductive organs, consist of a brown, oval-shaped anther with a short filament attached to the petals wall. The flowers are produced throughout the year but mostly during the rainy season, with very few of the flowers successfully growing into mature fruits. Meanwhile, the rest of the flowers will drop off to the ground. The floral formula for *P. macrocarpa* is $K^4_{br}C^{(4[5])}_{br}A^8G^1$, indicating four free calyces with biradial symmetry, four (rarely five) fused corolla petals with biradial symmetry, eight stamens, a unicarpellate gynoecium, and a superior ovary [13].

Figure 2. Flowers of *P. macrocarpa* (Scheff.) Boerl [11].

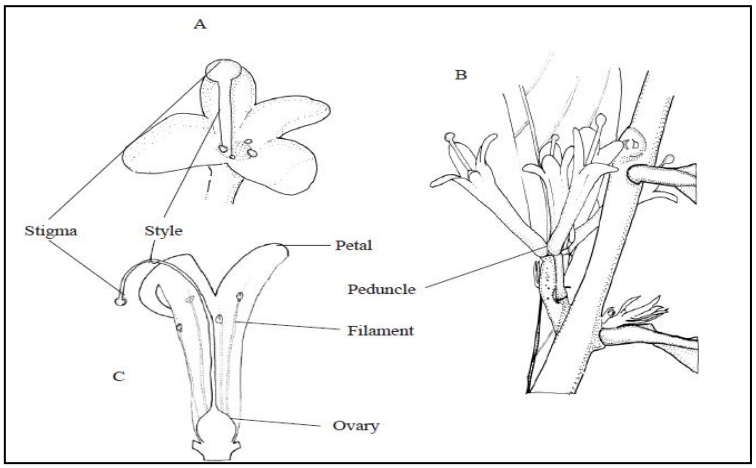


Figure 3. Illustration of *P. macrocarpa* flower: (**A**) fully opened, (**B**) inflorescence on a peduncle, (**C**) cross-section showing petals, style, and round stigma [13].

The colours of *P. macrocarpa* fruit powder with concentrated sulfuric acid and 5% sodium hydroxide solution were found to be brown and yellow, respectively. The standardization methods such as foreign matter, ash content, loss on drying, and extractive values for water-soluble and ethanol-soluble extracts have been conducted on *P. macrocarpa* flowers with 0.355mm particle size. The foreign matters found NMT 2% while the loss on drying was NMT 11%. Meanwhile, the total ash value and acid-insoluble ash value were

found to be NMT 10% and 1%, respectively. Hot extraction and cold extraction methods using water and ethanol were used to determine soluble extractive values. The hot extraction method was found to be NLT 25% in the water-soluble extractive value and NLT 12% in the ethanol-soluble extractive value. The cold extraction method found NLT of 17% in the water-soluble extractive value and NLT of 6% in the ethanol-soluble extractive value [12]

3.1.3. Fruit

The fruit of *P. macrocarpa* (Figure 4) develops from single or multiple fused carpels, with or without accessory parts, producing one fruit with one or two seeds. A single-seeded fruit is asymmetrical, while a two-seeded fruit shows bilateral symmetry. Fruit of *P. macrocarpa* at different stages of ripening exhibit different content of functional compounds. Fruit ripeness can be detected through a visual guide of the pericarp or the fruit skin at various stages of ripeness, which include the full size of unripe, half-ripe and fully ripe fruit. The unripe fruit is characterized by a totally green colour, half ripe has a greenish-red colour while full ripe is completely bright red. However, if the unripe fruits are plucked early, they will turn red after a few days at room temperature [10].

Figure 4. *Fruits of P. macrocarpa* (Scheff.) Boerl [11]

A fruit derived from a single ovary has three main parts: the pericarp, mesocarp, and endocarp. The pericarp forms the epicarp or outer skin. The mesocarp is fleshy, while the endocarp is hard and stony. The pulp is thick, white, fibrous, and watery. *P. macrocarpa's* fleshy fruit is a drupe with one or more chambers and seeds, developing from a monocarpellary or syncarpous pistil [13]. Antioxidants are present at a high percentage in unripe fruits, which indicates their roles in protecting the developing fruits. The functional properties of the fruit flesh vary at different levels of ripeness. For the development of medicinal products, it is suggested to harvest the fruit of *P. macrocarpa* at a stage of unripeness which has a high antioxidant content [14].

3.1.4. Seed

The seeds of *P. macrocarpa* (Figure 5) are coated with two free layers known as exalbuminous. The outer layer or testa consists of a thin, soft white coating, while the inner layer or tegmen is thicker, harder and dark brown in colour. Both layers are attached to the

hilum. The embryo part is lying within. This consists of an axis and two fleshy cotyledons filled with food material [13].

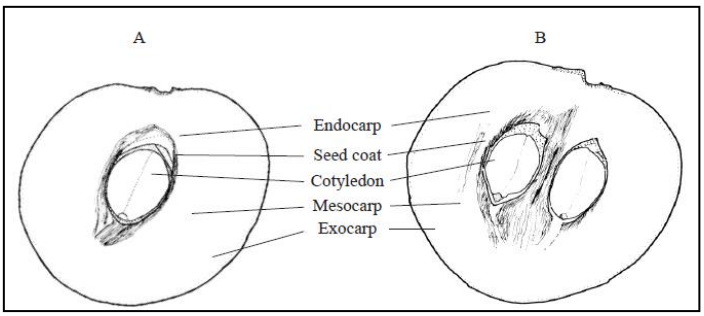


Figure 5. The cross-section of *P. macrocarpa* fruit with (A) one seed; (B) two seeds [13].

The *in vitro* desiccation tolerance in *P. macrocarpa* embryonic axes was reported elsewhere [14]. The desiccation process of embryonic axes is important for germplasm conservation and seed storage. The results indicated that *P. macrocarpa* embryonic axes are able to retain viability for up to 8 hours in a relatively low moisture content of 13.6%. These findings showed marked differences in desiccation tolerance than whole seeds that are rapidly destroyed in moisture content below 20%. Hence, normal development of at least 60% of plantlet and 16.7% of callus tissue were observed and were more favourable with embryonic axes. However, the seeds are considered to be a toxic part of the plant and should not be consumed. The seed germinates easily in organic draining loam with a maintained humidity and a temperature of 25–28°C. *P. macrocarpa* is cultivated in tropical and humid subtropical climate regions on draining soils under direct sunlight or in partial shade [13].

3.2. Phytochemistry of P. macrocarpa

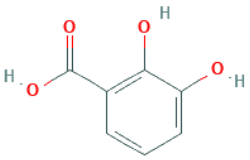
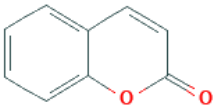
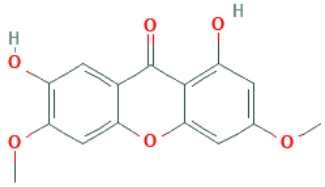
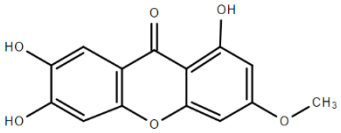
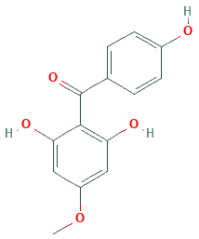
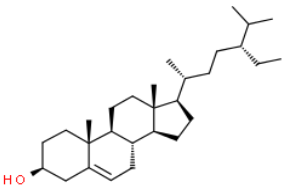
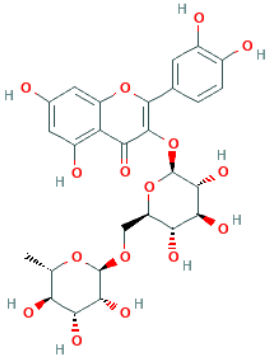
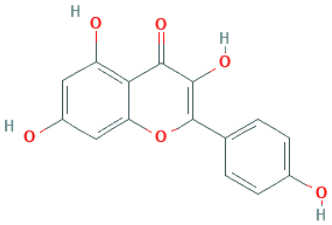
Phytochemicals are chemical substances isolated from the whole plant or parts of plants. Phytochemical screening is important to discover the secondary metabolites/ phytoconstituents present in plants. A study has demonstrated the presence of carbohydrates, flavonoids, glycosides, saponin glycosides, steroids, phenolic compounds, steroids, tannins, and terpenoids in the seeds of *P. macrocarpa*. In addition, alkaloids, α-amino acids, cyanogenic glycosides, organic acids, reducing sugars, and starches were also found in small quantities [15]. Flavonoids, glycosides, saponin glycosides, phenolic compounds, tannins, terpenoids and small amounts of alkaloids, proteins and carbohydrates were identified in *P. macrocarpa* fruits [16]. Another study reported the highest percentage of total phenolic and total flavonoid compounds in *P. macrocarpa* fruits [17], and Tedjo et al. [18] reported the presence of flavonoids. Another study by Ismaeel et al. [19] revealed the presence of terpenoids in the hexane fraction of *P. macrocarpa* fruits. Nevertheless, the same authors reported the presence of steroids, tannins, flavones aglycones, saponins, terpenoids and alkaloids in aqueous extracts of *P. macrocarpa* fruits [20].

The ethanol extract of *P. macrocarpa* stem and bark indicates the presence of tannins, flavonoids, glycoside, triterpenoid [21], saponins, alkaloids, polyphenolics, phenols and

lignans [18]. Many isolated constituents of *P. macrocarpa* are known for medicinal uses and some may cause toxicity when consumed. Ali, et al. [22] concluded that a flavonoid-rich sub-fraction from the fruit pericarp of *P. macrocarpa* demonstrated strong antidiabetic activity, primarily due to its 22.5% mangiferin content, as identified by LC-MS analysis. This fraction was more effective than acarbose in inhibiting glucose transport/absorption in a rat intestinal model, suggesting that *P. macrocarpa* exerts its antidiabetic effects through extra-pancreatic mechanisms. However, mangiferin is present in several other plants such as mango even in more quantities than *P. macrocarpa*, thus suggesting the exclusive antidiabetic potential of *P. macrocarpa* is not significant. However, identifying the presence of mangiferin is significant as it has several other benefits including antitumor, anti-neuropsychiatric and anti-neurodegenerative activities [23]. It is worth exploring the reported effects based on the *in vitro*, *in silico* and *in vivo* studies in animal models in human volunteers and controlled patient populations and finding the optimized ways to utilize the plant to achieve desired effects. Moreover, the reported activities seem mainly due to its antioxidant properties which are attributed to the presence of phenolic compounds. There may be several other secondary metabolites that may be responsible for the pharmacological effects of the plant. Application of computer aided drug design, molecular docking studies and studies on molecular dynamics could provide an in depth knowledge and will help in identifying the therapeutic phytoconstituents, markers and target binding sites responsible for the beneficial pharmacological effects of *P. macrocarpa.* One such study is recently published by Easmin et al. [24] that aimed at identifying the α-glucosidase inhibitors from the fruit extracts of *P. macrocarpa*.

The GC-MS metabolomics approach used by the researchers for the ethanolic extracts and it was noted that compounds such as isoquinoline, myo-inositol, palmitic acid methyl-α-D-glucopyranosidesqualene, and squalene could possibly be the potential inhibitors of α-glucosidase activity. Similarly, Habib and Ismail [25] performed LC-MS analysis for the identification of proteins present in *P. macrocarpa*. They reported the presence of various enzymatic proteins such as Transferases, Hydrolases, Lyases, Isomerases, Ligases, and Oxidoreductases, these enzymes are known to have various biological activities and produce therapeutic effects. However, this has to be tested to establish their effects upon the use of extracts of *P. macrocarpa* and also to establish the dose to be administered to achieve their therapeutic or desired effect. Mia et al. [26] studied the antiobesity effects of liquid carbon dioxide extracts of *P. macrocarpa*. This study highlighted the antihyperlipidemic potential of *P. macrocarpa* fruit using in vitro, in silico, and in vivo assays. The LCE-2 extract showed stronger antioxidant activity and functional groups compared to HRE and LCE-1. Compounds identified via GC–MS, especially 3-deoxyestradiol and phenol, demonstrated strong binding affinities for HMG-CoA reductase and pancreatic lipase, with the best docking scores. LCE-2 also demonstrated significant in vivo antiobesity and antihyperlipidemic effects, making it a promising candidate for developing new therapeutic agents. Tables 1–7 show the isolated bioactive compounds reported from various parts of *P. macrocarpa* plants.

Table 1. The isolated bioactive compounds from *P. macrocarpa* fruits.

Isolated compounds	Chemical structure	References
2,3-dihydroxybenzoic acid		
Coumarin		
1,7-dihydroxy-3,6-dimethoxyxanthone		(Ramdani et al., 2017) [27]
1,6,7-trihydroxy-3-methoxyxanthone		
2,4′,6-trihydroxy-4-methoxybenzophenone		
β-sitosterol		(Ramdani et al., 2017) [27] (Othman, et al., 2014) [28]
Rutin		(Hendra et al., 2011) [29] (Rabia et al., 2017) [30]
Kaempferol		(Hendra et al., 2011) [29]

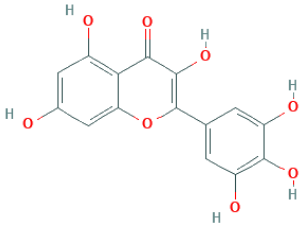
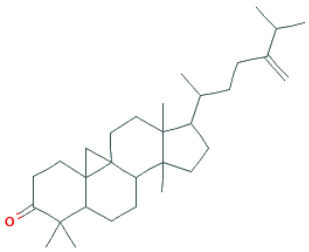
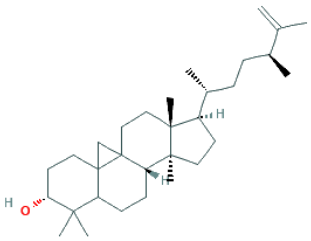
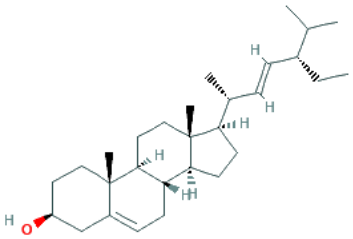
Myricetin		
24-methylenecycloartan-3-one		
24-methyl-9,19-cyclolanost-25-en-3-ol		(Othman et al., 2014) [28]
Stigmasterol		

Table 2. The isolated bioactive compounds from *P. macrocarpa* leaves.

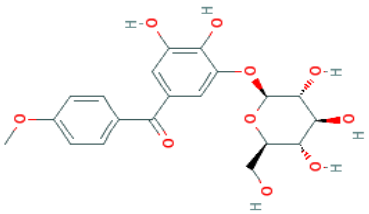
Isolated compounds	Chemical structure	References
4,5-dihydroxy,4'-methoxybenzophenone-3-0-β- ɒ -glucoside (Phalerin)		(Lay et al., 2014a) [15]

Table 3. The isolated bioactive compounds from *P. macrocarpa* seeds.

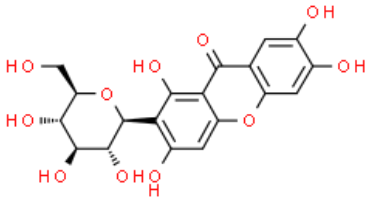
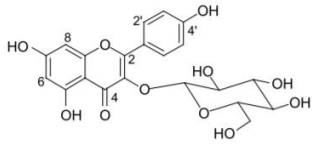
Isolated compounds	Chemical structure	References
Mangiferin		(Tedjo et al., 2019) [18]
kaempferol-3-o-β-D-glucoside		

Table 4. The isolated bioactive compounds from *P. macrocarpa* leaves and seeds.

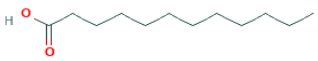
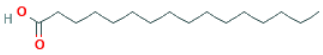
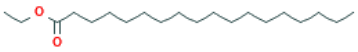
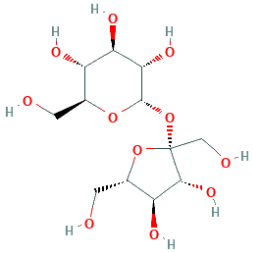
Isolated compounds	Chemical structure	References
Dodecanoic acid		
Palmitic acid		
Ethyl stearate		(Hendra et al., 2009) [31] (Zhang et al., 2006) [32]
Sucrose		

Table 5. The isolated bioactive compounds from *P. macrocarpa* fruits and seeds.

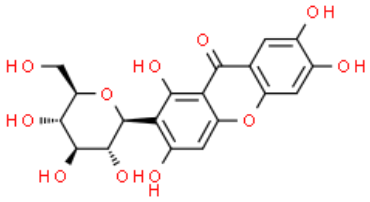
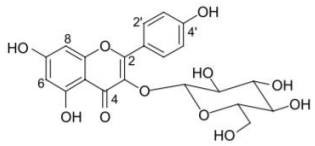
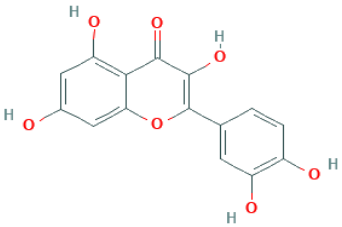
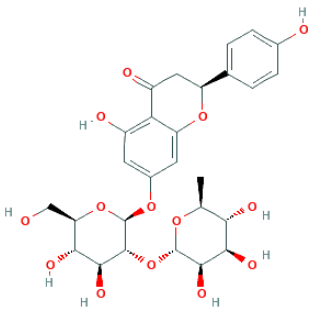
Isolated compounds	Chemical structure	References
Mangiferin		(Zhang et al., 2006) [32] (Rabia et al., 2017) [30]
kaempferol-3-o-β-D-glucoside		(Zhang et al., 2006) [32]
Quercetin		
Naringin		(Hendra et al., 2011) [29]

Table 6. The isolated bioactive compounds from *P. macrocarpa* leaves, fruits and seeds.

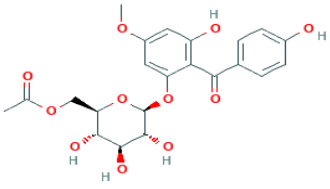
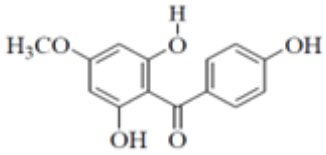
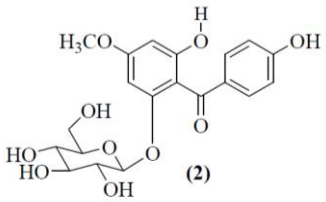
Isolated compounds	Chemical structure	References
2,4′,6-trihydroxy-4-methoxybenzophenone-2-O-β-D-glucoside (Mahkoside A) 2,4′,6-trihydroxy-4-methoxy-6”-acetylbenzophenone-2-O-β-D-glucoside (Mahkoside B)		(Hendra et al., 2009) [31] (Zhang & Liu, 2006) [32] (Ramdani et al., 2017) [27]

Table 7. The isolated bioactive compounds from *P. macrocarpa* leaves, fruits and stems.

Isolated compounds	Chemical structure	References
Aglycone benzophenone		(Othman et al., 2014) [28]
Benzophenone glycoside	 (2)	(Susilawati et al., 2011) [33]

3.3. Pharmacological profile of P. macrocarpa

Medicinal plants are a focus of ongoing research for contemporary treatments. Numerous studies have investigated the extracts and compounds of *P. macrocarpa* for their potential in addressing various illnesses. With an extensive literature survey, it is found that almost all the research articles published related to the medicinal applications and evaluation of activities of *P. macrocarpa*, the discussion ends with a conclusion stating that more comprehensive research or studies must be carried out to understand the underlying the mechanism of its beneficial effects. However, again the actual benefits could only be accepted if the clinical studies are performed whilst doses are established and compared with the currently available treatment. Various pharmacological activities have been reported from various parts of *P. macrocarpa* plants.

3.3.1. Anti-inflammatory activity

A study examined the anti-inflammatory impact of *P. macrocarpa* fruit pericarp extract on iNOS in the colons of DSS-induced Swiss Webster male mice. The anti-inflammatory activity was assessed through hematoxylin-eosin staining and iNOS assays at four different doses: 650, 1250, 2500 and 5000 mg/kg. Significant differences were observed in both the inflammatory activity score ($p=0.008$) and iNOS optical density score ($p=0.000$) compared to the DSS group across all doses. These findings suggest that *P. macrocarpa* fruit extract can suppress inflammatory cells and iNOS, likely due to its flavonoid and saponin content [34].

The anti-inflammatory and antioxidant properties of *P. macrocarpa* fruit extracts may aid in wound healing when used topically. A previous study examined the wound-healing effects of ethanol extracts from *P. macrocarpa* fruits in Sprague-Dawley rats. Over 15 days,

macroscopic evaluation showed significant improvement in wound healing for excision wounds. The reduction in inflammation and increased antioxidant enzyme activity facilitated wound healing by addressing oxidative stress. The mechanism may involve the plant extract's mitogenic activity, which accelerates cellular proliferation and reduces skin injury [35].

3.3.2. Antipyretic activity

P. macrocarpa has been clinically reported for its anti-inflammatory activity, suggesting it may also possess analgesic properties. Both activities may involve similar mechanisms, specifically through the inhibition of cyclooxygenases (COXs) and the reduction of prostaglandin synthesis, leading to pain relief. A study by Noval Halim et al. investigated the antipyretic effects of *P. macrocarpa* in mice using a heat-induced method with a pepton solvent. Mice were treated with extracts at concentrations of 3%, 6%, and 12%. All concentrations showed significant antipyretic activity, with the 12% concentration combined with crocodile leaf exhibiting the most effective antipyretic activity, characterized by the longest duration and fastest onset [36].

3.3.3. Antihypertensive activity

Chloroform, petroleum ether, methanol, and water extracts of *P. macrocarpa* fruits were evaluated for antihypertensive activity in rats. Blood pressure-lowering effects were observed in petroleum ether, methanol, and water extracts, with the water extract showing the most significant decrease in blood pressure, heart rate, and arterial stiffness. This efficacy may be attributed to the high polarity of the water extract, which contains more polar constituents. Additionally, the water extract exhibited the most potent vasorelaxant activity compared to the other extracts. Thus, the polar compounds in the water extract of *P. macrocarpa* fruits are particularly effective in lowering blood pressure and inducing vasorelaxation [30].

3.3.4. Antidiabetic activity

A study assessed the impact of *P. macrocarpa* dry fruit extract on blood glucose levels in healthy adults. Thirty volunteers ingested 75 g of glucose and then received *P. macrocarpa* extract at doses of 125 mg and 250 mg. The results demonstrated a significant reduction in the area under the curve (AUC) at the 125 mg dose ($p=0.000$), while the 250 mg dose did not show a significant reduction ($p=0.06$). The reduction in AUC was significantly greater at the 125 mg dose compared to the 250 mg dose ($p=0.011$). Thus, the 125 mg dose exhibited better hypoglycemic activity than the 250 mg dose [37].

Another study evaluated the in vitro α-glucosidase inhibitory activity of various parts of the *P. macrocarpa* plant, including fruit, leaves, and stems, using methanol and n-hexane extracts. α-Glucosidase inhibition helps suppress postprandial blood glucose levels by delaying carbohydrate digestion and absorption. Among the extracts, n-hexane extracts demonstrated stronger inhibitory activity than methanol extracts, with the highest effect observed in the stems. The n-hexane stem extract, which contained α-linolenic acid, tetracosanoic acid, and 1-(4-tbutylphenyl)-2, 3, 4, 5-tetraphenylcyclopenta-2, 4-diene, was particularly effective in inhibiting α-glucosidase, compounds not found in other extracts [38].

A study was conducted using ethanol extract of *P. macrocarpa* fruits at three doses (550, 1100 and 1650 mg/kg) in alloxan-induced diabetic rats over 7 days. The results found that all doses significantly reduced blood glucose levels, showing hypoglycemic activity comparable to Sitagliptin at a dose of 9 mg/kg. *P. macrocarpa* fruits contain phenolic compounds that may inhibit the enzyme, Dipeptidyl peptidase IV (DPP-IV) in diabetic animals [39].

3.3.5. Antioxidant activity

The optimal conditions for extracting antioxidant compounds from *P. macrocarpa* fruits were determined using Response Surface Methodology (RSM). The study evaluated four metrics: free radical scavenging activity (DPPH), ferric ion reducing power (FRAP), total phenolic content (TPC), and total flavonoid content (TFC). The highest yields were obtained with an extraction temperature of 64°C, a time of 66 minutes, and a solvent-to-feed ratio of 75% v/v. The RSM model confirmed that these factors, chosen based on preliminary studies, significantly influenced the results. This study demonstrated that *P. macrocarpa* fruits exhibit strong antioxidant activity when optimal extraction conditions are applied [17].

A study evaluated the free radical scavenging activity of a sunscreen gel formulated with methanolic extracts of ripened *P. macrocarpa* fruit pulp. Using the DPPH assay, the extracts demonstrated significant UV barrier potential due to their antioxidant activity and effective sun protection factor. The strong antioxidant activity is attributed to the presence of benzophenone compounds, specifically 4,5-dihydroxy-4'-methoxybensophenone-3-O-β-D-glycoside. The formulated sunscreen gel was found to be safe for use as a UV barrier. Further research is recommended to explore the potential of natural products in developing cosmeceuticals [16].

Polyphenol compounds derived from plants are known for their effective antioxidant properties and protection against free radical damage [40]. The in vitro antioxidant activity of

P. macrocarpa fruit was analyzed in relation to extraction time and temperature. Extraction for 60 minutes at temperatures between 60-80°C resulted in the highest yields of total flavonoid content (TFC), total phenolic content (TPC), and DPPH radical-scavenging activity (DPPH-RSA) (Rice-Evans, Miller, & Paganga, 1997). These findings are valuable for estimating the free radical scavenging activity of *P. macrocarpa* fruits, aligning with the research of Lim et al. [41].

3.3.6. Antimicrobial activity

P. macrocarpa fruits extract exhibited antimicrobial activity against eight Gram-negative and Gram-positive bacteria that were tested at a concentration of 0.3 mg/disc and it might be due to their flavonoid compounds The extracts displayed weak to moderate inhibitory activity, with inhibition zone diameters ranging from 0.93 to 2.33 cm. Gram-positive bacteria were more affected compared to Gram-negative bacteria, likely due to the latter's outer membrane permeability barrier, which makes them more resistant to antimicrobial agents. The extracts showed minimal to weak antifungal activity [29].

The fruit of *P. macrocarpa* and leaf extracts demonstrated weak activity against *Bacillus subtilis, Staphylococcus aureus, Escherichia coli,* and *Pseudomonas putida,* with inhibition zone diameters ranging from 6.1 to 7.3 mm using the disc diffusion method. The weak antibacterial activity is attributed to the absence of flavonoids and prenyl and geranyl substituents in benzophenones, as compared to previous studies. Additionally, the presence of triterpenoids in this study also contributed to the weak antibacterial activity observed against all tested bacteria [42].

A previous study demonstrated the effectiveness of methanolic *P. macrocarpa* leaf extract against pathogenic bacteria isolated from human diabetic wounds. The study showed that the extract inhibited the growth of *Pseudomonas mallei, Klebsiella pneumoniae, Escherichia coli, Klebsiella aerogenes,* and *Proteus* sp. The observed antimicrobial effect was attributed to shrinkage and degradation of the bacterial cell walls [43].

3.3.7. Antiviral activity

A study found that the aqueous extract of *P. macrocarpa* fruits exhibited antiviral activity against herpes simplex virus type 1 (HSV-1) in a plaque reduction assay. This strong antiviral activity was supported by a selective index (SI) of 17.9 and a CC50 of 5 mg/ml, indicating safety and non-cytotoxicity against Vero cells. In contrast, a previous study using a hexane fraction reported a lower SI (2.6) and CC50 (0.48 mg/ml), suggesting weak to

moderate antiviral activity. The higher polarity of the aqueous fraction likely extracts more secondary metabolites from *P. macrocarpa* fruits, which contributes to its greater antiviral efficacy compared to the hexane fraction, which contains fewer secondary metabolites [19].

3.3.8. Anticancer activity

Ethanol extract of *P. macrocarpa* fruits was tested for anti-cancer activity in C3H mouse mammary tumours induced by transplantation over 30 days at doses equivalent to 20, 40, and 80 times the human dose. The results showed no significant differences in tumour volumes, weights, AgNOR values, or necrotic areas between the control and the treated groups ($p>0.05$). However, the apoptosis index was significantly higher in the group receiving the 80-fold human dose ($p<0.05$) [44].

3.3.9. Antihyperlipidemic activity

A study on *P. macrocarpa* leaves has shown potential as an alternative treatment for hypercholesterolemia in Sprague Dawley rats. This effect is linked to enhanced SR-BI expression, achieved with ethyl acetate extract (EMD) and its component, 2',6',4-trihydroxy-4'-methoxybenzophenone. Increased SR-BI expression in the liver reduces cholesterol levels by decreasing plasma HDL cholesterol transport into bile, thus protecting against atherosclerosis by boosting the catabolism of HDL and atherogenic lipoproteins. In vivo studies showed a 157% increase in HDL cholesterol and a 224.9% reduction in total cholesterol after 28 days of treatment. Measurements of SGOT and SGPT confirmed that a dose of 0.5 g/kg body weight of EMD extract was safe and non-toxic [45].

A study explored the effects of Forhidrol, a bioactive compound from *P. macrocarpa* fruit extract, on Cholesteryl Ester Transfer Protein (CETP). Forhidrol, extracted from dried fruits using 96% ethanol, acts as a CETP inhibitor. CETP reduces plasma HDL cholesterol levels by exchanging neutral lipids between HDL and other lipoproteins. CETP deficiency results in higher HDL cholesterol levels, which may help prevent atherosclerosis. In vitro, Forhidrol was found to reduce CETP activity in a dose-dependent manner and slightly suppress triglyceride synthesis by activating PPARs. The in vivo study, conducted on New Zealand white rabbits, demonstrated that Forhidrol treatment increased HDL levels and decreased LDL and triglyceride levels at a dose of 37.5 mg/1.5 kg body weight, correlating with reduced CETP activity [46].

3.3.10. Antiulcer activity

A study investigated the gastroprotective effects of *P. macrocarpa* ethanolic extracts on gastric ulcers induced by acetosal and ethanol in rats. The results showed that the extract reduced ulcer numbers, improved epithelial repair, increased pH, and decreased total gastric acidity. In ethanol-induced ulcers, the highest dose (400 mg/kg BW) achieved 91.91% ulcer inhibition, while in acetosal-induced ulcers, the inhibition was 59%. These findings suggest that *P. macrocarpa* ethanolic extract has significant gastroprotective effects, particularly in acetosal-induced ulcers [47].

3.3.11. Women pathological conditions

A study found that *P. macrocarpa* fruit extract is effective in treating various gynaecological conditions, including premenstrual syndrome (PMS), dysmenorrhea, endometriosis, breast cancer, and cervical cancer. PMS symptoms, which occur before menstruation, include depression, mood swings, sleep disorders, and pain, often due to hormonal imbalances, such as progesterone deficiency and estrogen dominance, as well as inflammation from prostaglandin imbalances [48].

The study evaluated a standardized semi-polar bioactive extract of *P. macrocarpa* fruit. It was found to be safe and well-tolerated in alleviating PMS and primary dysmenorrhea symptoms. Participants received 100 mg of the standardized extract two to three times daily for an average of six days. Results showed a significant reduction in pain and inflammation through prostaglandin suppression, with only a few mild adverse events, such as dyspepsia, reported [49].

Further research on a standardized extract of *P. macrocarpa* fruit using the RL95-2 cell line, a model for endometriosis, has shown that it has potential as a treatment for the condition. It exerts antiangiogenic, anti-inflammatory, and pro-apoptotic effects by reducing NFκB and inhibiting the eicosanoid pathway [50].

A pilot clinical study also demonstrated the effectiveness of the standardized extract of *P. macrocarpa* fruit in alleviating pain related to endometriosis and/or adenomyosis. Patients with symptoms such as PMS pain, dysmenorrhea, dyschezia, and dysuria were given 100 mg of extract three times daily for 12 weeks. Significant reductions in pain intensity were observed for all symptoms, with continuous improvement noted across menstrual cycles [48, 51].

3.4. Combinatory Approaches and Targeted Drug Delivery Systems

A study evaluated the effects of combining *P. macrocarpa* extract with soybean extract on fibroblasts, VEGF, IL-6, and TNF-alpha expression, as well as serum IL-6 and TNF-alpha levels in UV-B-exposed mice. Mice were divided into a control group, three treatment groups, and a combination group (1:1 ratio of extracts). On days 5 and 21, mice were euthanized for histological analysis. Fibroblasts were counted, and VEGF, IL-6, and TNF-alpha expression were assessed via immunohistochemistry. IL-6 and TNF-alpha levels were measured using ELISA. Results indicated that the combination group had significantly higher fibroblast counts and increased VEGF, IL-6, and TNF-alpha expression compared to other groups. However, no significant changes in serum IL-6 and TNF-alpha levels were observed [52].

A study investigated the effects of combining *Elephantopus scaber* with different parts of *P. macrocarpa* (leaves, mesocarp, seed, and pericarp) on T47D breast cancer cells. The cells were treated with three ratios (1:1, 2:1, and 1:2) for 24, 48, and 72 hours. Cell viability was assessed using the WST-1 assay, apoptosis through FITC Annexin V-PI staining and DNA fragmentation, and cell proliferation and cycle progression with CFSE and Propidium Iodide flow cytometry assays. Key signalling proteins (p-ERα, p-Nrf2, p-PI3K, p-AKT, p-mTOR) were quantified by flow cytometry, and molecular docking was used to confirm the mechanism. The combination of *E. scaber* and *P. macrocarpa* leaves showed significant cytotoxic activity ($p < 0.05$) against T47D cells, with minimal effects on normal TIG-1 cells. The 2:1 ratio of EL reduced cell viability, inhibited cell division, induced apoptosis, and arrested the cell cycle by targeting the p-Nrf2, p-ERα, and p-PI3K/AKT/mTOR pathways. Molecular docking confirmed that EL inhibited the ERα and Nrf2 complex, disrupting crosstalk between the Nrf2, ERα, and PI3K/AKT/mTOR pathways. This suggests that the *E. scaber* and *P. macrocarpa* leaf combination has potential as an anticancer treatment for T47D breast cancer cells [53].

A clinical study found that the standardized extract of *P. macrocarpa* administered at a human-equivalent dose of 300 mg three times daily, showed no harmful effects on the heart, haematological profile, or general safety in mice with breast cancer, with the animals surviving the entire therapy and considered safe as adjuvant therapy for breast cancer, offering protection against cardiac damage caused by reduced dose ($1/8^{th}$) of chemotherapeutic regimen, 5-fluorouracil, doxorubicin, and cyclophosphamide. Previous studies demonstrated that the extract protected cardiac muscle and improved haemoglobin levels, mitigating side effects from chemotherapy [54].

A study explored a new method for managing Oral Squamous Cell Carcinoma (OSCC) by using nanotechnology with herbal treatments, focusing on *Bischofia javanica* leaves and *P. macrocarpa* fruits. BaP-induced OSCC rats were treated with nano herbal formulations of these plants, their combination, and Vitamin C as a control. Blood and organ analyses were compared to controls. OSCC induction caused significant cell changes, as confirmed by Papanicolaou staining and altered Complete Blood Count (CBC) and lipid profiles. Nano herbal treatments showed promise in reducing haematological and lipid damage while improving white blood cell, red blood cell, haemoglobin, and platelet counts. The combined nano herbals effectively reduced LDL and total cholesterol levels while increasing HDL levels, similar to Vitamin C. Nano herbals also helped normalize albumin levels and improve liver enzyme activity, mitigating the impact on liver and kidney function. Overall, nano herbal formulations from *B. javanica* and *P. macrocarpa* show potential as effective OSCC treatments [55].

A study investigated the therapeutic potential of nano-herbal *P. macrocarpa* in a rat model of preeclampsia, focusing on its anti-inflammatory and antioxidant properties. Pregnant rats were divided into five groups: C- (negative control), C+ (positive control), C1 (nifedipine-treated), and three treatment groups (T1, T2, T3) receiving various doses of the nano-herbal formulation. Preeclampsia was induced using prednisone and 6% NaCl, elevating blood pressure to 140/90 mmHg. Blood pressure was measured on days 5, 13, and 20, and blood counts and organ weights were assessed on the final day. The T3 group (720 mg/kg body weight) showed the most promising results, with improvements in diastolic blood pressure, organ weight, and haematological parameters comparable to nifedipine. These findings suggest that *P. macrocarpa* has the potential as an antihypertensive and organ-protective agent for preeclampsia [56].

A study assessed the antifibrotic effects of curcumin-loaded nanoemulsion and its combination with *P. macrocarpa* extract (PM) by evaluating collagen expression in NIH/3T3 fibroblast cells. The cytotoxicity of the blank nanoemulsion was first tested using the MTS assay. Collagen gene expression was measured with quantitative real-time PCR, and collagen protein levels were assessed with the Sirius Red/Fast Green Collagen Staining Kit. The stability of the curcumin-loaded nanoemulsion against hepatic metabolism was also evaluated. Results showed that both curcumin and curcumin-PM nanoemulsions maintained cell viability and significantly reduced procollagen α1(1) and collagen IV gene expression, as well as overall collagen protein levels. The nanoemulsion also protected curcumin from hepatic metabolism, indicating its potential as an effective antifibrotic agent [57].

3.5. Toxicological Assessment of P. macrocarpa

Assessment of plant toxicity is important in terms of safety, quality, and efficacy prior to the use of medicinal products. An appropriate dose of medicinal plants should be determined to prevent any side effects and toxicity associated with the use of herbal products

[58]. Toxicological studies are classified as acute, subacute or chronic. The source of toxicity could be determined by several factors, including the type and dose of the extract or phytoconstituent used and the route of administration [59]. *P. macrocarpa* has been proven to be a medicinal product due to its abundance of valuable medicinal properties. However, a toxicity study on *P. macrocarpa* is required to determine the exact concentration needed in the treatment of the disease [8]. A toxicological profile has been reported from various parts of *P. macrocarpa* plants. A study revealed the liver toxicity of the ethanol extracts of fruits of *P. macrocarpa* was assessed on Sprague-Dawley rats using an MTT assay with MCF-7 cell lines. An absence of periportal necrosis of the hepatocytes and inflammation of cells in the animals treated with ethanol extracts at the maximum dose of 5000 mg/kg/b.w were observed [60]. In another study, the brine shrimp lethality test method showed that the ethanol extracts of fruits, seeds, and leaves of *P. macrocarpa* were toxic to brine shrimp, with the Artemia saline leach with seed methanol extract fraction showing the highest toxicity profile [61]. A recent study on haematological parameters reported the absence of haematological changes in the experimental Wistar rats treated with *P. macrocarpa* leaf extracts [62]. Another study found that methanol extracts of *P. macrocarpa* leaves exhibited cytotoxic activity against MCF-7 cell lines using the MTT assay. However, the study also observed a weak antagonistic effect among the chemical constituents in the extracts, which negatively impacted cell viability and absorbance [63].

4. Discussion

Recent technological updates have provided an opportunity to obtain highly purified bioactive compounds from medicinal plant extracts, including *P. macrocarpa* extract for their prospective treatment and prevention of human diseases. Numerous experimental studies investigated the pharmacological properties of various plant-derived bioactive compounds to validate their therapeutic potential [64-67]. Nevertheless, herbal medicines have been used for a long time, and most Malay women in Malaysia use them [68]. Strong beliefs about the role of herbal medicines, including *P. macrocarpa,* in serving public health-related issues make it essential to provide the general public, including healthcare professionals, with adequate information regarding the safety of herbal medicines.

The optimisation of extraction methods is paramount to enhancing the efficacy of herbal medicines [69]. By fine-tuning and developing standardised modern extraction processes, the yield and potency of *P. macrocarpa* extract can be maximised for the consistent production of medicinal-grade compounds. This could then be integrated into formulations like conventional dosage forms such as capsules, tablets, topical applications etc and novel drug delivery systems such as nanoemulsion, liposomes, phytosomes, hydrogels etc for various therapeutic applications and cosmeceuticals [70]. Developing advanced drug delivery systems can ensure sustained release of *P. macrocarpa's* compounds over time, improving patient compliance and ensuring longer-lasting therapeutic effects [16, 57, 71, 72].

Traditionally, *P. macrocarpa* has been widely used for its anti-inflammatory, antidiabetic, and cytotoxic activities. Incorporating *P. macrocarpa* into modern therapeutics offers a rich avenue for novel drug development, particularly for chronic diseases, cancer therapy, and immune-related disorders. The bioactive components of *P. macrocarpa* and practicality in modern therapeutics lies in its broad spectrum of bioactive compounds such as flavonoids, alkaloids, tannins, and saponins that are relevant for modern therapeutics offer multiple pharmacological effects, including antioxidant, anti-inflammatory, anticancer, antidiabetic, and antiviral properties. These promising bioactive compounds in *P. macrocarpa* might be used in treating chronic diseases like cardiovascular, diabetes, neurodegenerative disorders and potentially offering alternatives to NSAIDs.

In this review of the *P. macrocarpa* plant, some of the pharmacological uses that have been reported, such as for its antiinflammatory, antihypertensive, antidiabetic, antioxidant, antimicrobial, antiulcer, antipyretic, and cytotoxic properties, and for the treatment of various female pathological conditions. This indicates that *P. macrocarpa* is considered one of the important candidates for the development of novel herbal drugs. In addition to that, *P. macrocarpa* could be integrated into skincare products for treating skin conditions like ageing, acting as both a therapeutic and preventive measure due to its antioxidant properties [16]. Due to the potential advantages of the antioxidant activity of *P. macrocarpa*, it has a vital role in the cosmetic field, including the development of sunscreen gel and antiaging cream. It received positive feedback when it came to promoting the use of natural products in the cosmetics industry [71].

P. macrocarpa has the potential for development into functional foods or nutraceuticals for health maintenance and disease prevention. Its extracts could be incorporated into beverages or supplements aimed at enhancing immunity, reducing inflammation, or managing blood sugar levels. A study successfully formulated and optimized tablets containing *P. macrocarpa* fruit extract as dietary supplements, offering potential health benefits. The extract was evaluated for its antioxidant, cytotoxicity, antidiabetic, and antimicrobial effects, supporting its potential use in the prevention and treatment of various diseases [72].

This review has also highlighted the benefits of *P. macrocarpa* in treating several female pathological conditions. *P. macrocarpa* is known to alleviate symptoms of gynaecological problems such as premenstrual syndrome (PMS), dysmenorrhea, endometriosis, breast cancer, and cervical cancer. However, there is still elusive information regarding the safety of *P. macrocarpa,* especially for pregnant women [62].

In addition, there are a few reported toxicological evaluations that have been discussed in this study. Despite the positive response towards *P. macrocarpa*, some of the toxicity studies still lack information regarding the effects of toxicity on organs [62], meaning further research on the activity of organs is essential. The most important parameters in toxicity evaluation are changes in body weight and organ weight, haematological assessment, and serum biochemical testing [73]. A case report from Rahim et al. [74] indicated that *P.*

macrocarpa extracts in the form of premixed coffee consumed over the course of one year were associated with the adverse effects of cholestatic jaundice in a young, healthy man with no previous medical illness, who did not drink alcohol or smoke, and took no regular prescribed or over-the-counter medications. He stated that the use of *P. macrocarpa* coffee was only for supplementary purposes because the product was claimed to be liver-protective. Consequently, the patient was treated with oral ursodeoxycholic acid 250 mg three times daily and oral chlorphenamine 4mg as needed. The patient's conditions were resolved after the withdrawal of *P. macrocarpa* extracts, and he was discharged well, but regular clinic visits will continue to monitor his liver function. Therefore, validation regarding the safety of *P. macrocarpa* for long-term use should be confirmed to minimise the risk of adverse effects. Nevertheless, evidence in toxicity evaluation should be performed to qualify the standard of herbal products in order to be compatible with standards of safety, quality, and efficacy.

Given its wide range of bioactivities, *P. macrocarpa* could be incorporated into combination therapies to improve efficacy and reduce resistance. Modern studies reveal the therapeutic potential of *P. macrocarpa* across various health conditions through combination therapies and advanced drug delivery systems. For instance, combining its bioactive compounds with current anticancer drugs may enhance outcomes by targeting multiple pathways [75]. In UV-B-exposed mice, a combination of *P. macrocarpa* and soybean extract increased fibroblast counts and the expression of key inflammatory markers [52]. In breast cancer cells, combining *E. scaber* and *P. macrocarpa* leaves showed cytotoxic effects, inducing apoptosis and targeting the PI3K/AKT/mTOR pathway. A clinical study found *P. macrocarpa* safe for mice undergoing chemotherapy, protecting against cardiac damage [53].

P. macrocarpa's compounds could be engineered into nanoparticle systems for precise delivery to specific tissues, improving drug efficiency and reducing side effects. *P. macrocarpa's* bioactive compounds could be encapsulated into nanoparticle-based drug delivery systems for targeted therapies. This would enhance the precision of treatment, reduce dosage, and minimize side effects. Using this nanotechnology, the anticancer compounds from *P. macrocarpa* could be delivered directly to tumour cells, improving efficacy. In oral squamous cell carcinoma models, nano-herbal formulations of *B. javanica* and *P. macrocarpa* improved lipid profiles and liver function [55]. In a preeclampsia rat model, *P. macrocarpa* reduced blood pressure and improved organ health [56]. Additionally, a nanoemulsion of curcumin and *P. macrocarpa* showed antifibrotic effects by lowering collagen expression. These findings suggest *P. macrocarpa's* potential in cancer, fibrosis, cardiovascular, and inflammatory conditions [57].

P. macrocarpa's anticancer effects could be explored as an adjunct therapy in conventional cancer treatments like chemotherapy or immunotherapy, targeting cancer cells through complementary mechanisms. Its compatibility with conventional medications offers opportunities for developing combination therapies that enhance efficacy, reduce drug resistance, and lower required doses of synthetic drugs, reducing adverse effects [54]. These targeted drug therapy approaches could lead to personalized treatments, especially in cancer,

diabetes, and inflammatory conditions, by matching the right extract or formulation to patient profiles. In addition, advances in pharmacogenomics could be applied to assess how individual genetic variations affect responses to *P. macrocarpa's* compounds.

Findings from this review have shown that *P. macrocarpa* has many therapeutic values, which open the pathway to the discovery of new herbal products. Even though it has been known for a long time that *P. macrocarpa* has been used traditionally to treat many diseases, its use has become more popular as more people know about it and accept it. Moreover, with the extensive research and development in nanotechnology and other drug delivery systems, there exist extensive opportunities for researchers to develop optimized delivery systems achieving maximum benefits for the most useful phytoconstituents obtained from *P. macrocarpa* to target the specific sites in the body. As this plant is grown extensively in Southeast Asian countries and available comparatively cheaper, it will provide a sustainable source of medicinally important secondary metabolites [55-57].

P. macrocarpa's ability to target several biological pathways makes it a potential treatment for various conditions, including chronic diseases like cancer, diabetes, and inflammatory disorders. Systematic clinical trials are essential to integrate *P. macrocarpa* into modern medicine. Trials could focus on its efficacy and safety in managing chronic diseases, cancer, or immune disorders. Its multi-target approach aligns with modern medicine's shift toward holistic treatments that address the complexity of diseases. The wide range of pharmacological activities of *P. macrocarpa* makes the plant serve as a multifunctional drug candidate targeting conditions and a versatile candidate for drug development and complementary therapies. Following clinical validation, regulatory approvals could pave the way for its inclusion in official pharmacopoeias, allowing for its use as a complementary or alternative medicine in hospitals and clinics. These approaches would allow *P. macrocarpa* to transition from traditional uses into modern therapeutics, creating innovative treatments across a wide range of medical fields by validating its bioactive compounds through scientific research. These findings can be translated into innovative formulations that address chronic diseases, inflammatory conditions, cancer, diabetes, skin disorders, and immune health. Integrating this traditional knowledge into contemporary medicine offers natural, effective, and potentially safer alternatives or complements to existing treatments [76].

However, *P. macrocarpa's* traditional use in herbal medicine, combined with modern scientific studies, creates a bridge for its acceptance in regulated pharmaceutical markets. As a plant-based source of diverse bioactive compounds, *P. macrocarpa* could be more cost-effective to produce and standardize compared to synthesizing complex chemical drugs. This makes it accessible for wider use, especially in low-resource healthcare settings. In addition, the plant's compounds can be developed into modern drug delivery systems like nanoparticles and controlled-release formulations, enhancing bioavailability and precision in targeting diseases [77]. Regulatory approval through clinical validation is essential to realize its full potential, the critical component of *P. macrocarpa's* value in modern therapeutics is its broad pharmacological potential, synergy with existing treatments, and its adaptability to

innovative drug delivery systems, making it a valuable candidate for future therapeutic applications.

5. Conclusions

Herbal products receive much attention nowadays due to their numerous advantages over modern drugs. Through *in vivo* and *in vitro* studies, the use of *P. macrocarpa* in a variety of therapeutic agents to cure illness has been proven. It has been found that phytochemicals isolated from *P. macrocarpa* possess large therapeutic potential, including antiinflammatory, antipyretic, antihypertensive, antidiabetic, antioxidant, antimicrobial, antiulcer, antiviral and anticancer activities, and use for the treatment of various female pathological conditions. However, further study in isolation of any hindering compounds and responsible activity is required to develop standardized novel herbal pharmaceuticals from *P. macrocarpa*. Moreover, additional research is needed to prove that these herbal medicines work, are safe, and are of good quality to meet regulatory standards.

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