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Review

Phaleria macrocarpa (Scheff.) Boerl.: An updated review of pharmacological effects, toxicity studies, and separation techniques

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ABSTRACT

Phaleria macrocarpa (Scheff.) Boerl. is geographically distributed around Papua Island, Indonesia. Traditionally, *P. macrocarpa* is exercised to reduce pain, stomachache, diarrhea, tumor problems, blood glucose, cholesterol, and blood pressure. A growing interest in the medicinal values of *P. macrocarpa* especially in Asia reflects the usage of diverse extraction techniques, particularly modern approaches. In this review article, the extraction methods and solvents relevant to *P. macrocarpa* were discussed, with the extent of its pharmacological activities. Recent bibliographic databases such as Google Scholar, PubMed, and Elsevier between 2010 and 2022 were assessed. Based on the findings, the pharmacological studies of *P. macrocarpa* are still pertinent to its traditional uses but primarily emphasise anti-proliferative activity especially colon and breast cancer cells with low toxicity and fruit as the most studied plant part. The utilization of modern separation techniques has predominantly been aimed at extracting mangiferin and phenolic-rich compounds and evaluating their antioxidant capacity. However, the isolation of bioactive compounds remains a challenge, leading to the extensive utilization of the extracts in *in vivo* studies. This review endeavors to highlight modern extraction methods that could potentially be used as a point of reference in the future for exploring novel bioactive compounds and drug discovery on a multi-scale extraction level.

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1. Introduction

Phaleria macrocarpa (Scheff.) Boerl., widely known as Mahkota dewa or God's crown, is geographically distributed around Papua Island, Indonesia. It was first cultivated in Solo, Yogyakarta, and Jawa Tengah, then widely grown in Singapore and Malaysia due to its highly medicinal values (Harmanto, 2005; Quattrocchi, 2012). *P. macrocarpa* is a member of *Thymelaecaeae* family. It has various botanical names, including *Phaleria calantha* Gilg, *Phaleria papuana* Warb. Ex. K.Schum & Lauterb., *Phaleria papuana* var. *wichmannii* (Valeton) Backer, and *Phaleria wichmannii* Valeton (The Plant List, 2013). *P. macrocarpa* is classified as a shrub or an evergreen tree based on its morphology. The plant can range from 1 to 18 m in height. It can grow between 10 and 1200 m above sea level and has a productive life span of 10 to 20 years. It has a multi-branched crown, a one-meter-long straight root that exudes sap, an erect cylindrical trunk up to 15 cm in diameter, brownish-green bark, and white wood (Saufi, 2007).

P. macrocarpa has a long history of ethnomedicinal applications in Asian countries, especially Indonesia and the lower course of Malaysia (Ali et al., 2012). The majority parts of the plant are traditionally exercised in managing pain, stomachache, diarrhea, and tumor problems, as well as lowering blood glucose, cholesterol, and blood pressure (Mustapha et al., 2017). Phytochemical studies of *P. macrocarpa* revealed bioactive compounds such as acids, benzophenones, lignans, phenolics, sugars, terpenoids, and xanthones (Alara et al., 2016; Othman et al., 2014b). It is also well known in traditional Chinese medicine and can be found in local markets and specialty retailers in several Asian countries. An emerging interest in this plant leads to wide usage of *P. macrocarpa* in the production of food, herbal tea, cosmetics, and medicine as well as the emergence of its extensive pharmacological studies.

Considerable studies have been performed nowadays that determined the efficiency of extraction methods and solvents to obtain high-yield recoveries of the bioactive principles exerting potent biological effects. Often organic liquid solvents such as methanol and ethanol take a long extraction time, resulting in little extraction yields carrying toxic residual solvents. These impurities can affect the quality of the extracts and become harmful when consumed. Advanced processing technology nowadays makes extraction easier and shorter. Not only it gives better yield results, but also it can reduce toxicity caused by the residual solvents. *P. macrocarpa* is among the plants used in modern applications. A few studies were tailored in such the extraction methods were compared to obtain specific bioactive compounds, for example, mangiferin. In a study, the extraction yield of mangiferin using subcritical water improved proportionally with the increase in temperature and time (Kim et al., 2010). The optimum subcritical water condition showed almost similar extraction yield when using methanol. This study proposed that the environmentally friendly modern technique can also retain the pharmacological feature of the extracts using water.

In this review, the updated information on *P. macrocarpa* was characterised into a few major aspects: 1) pharmacological effect 2) phytoconstituent and 3) extraction technique. The conventional extraction techniques, modern extraction methods, as well as green solvents relevant to *P. macrocarpa* were discussed. This review aims to clarify the biological activities and techniques used to process *P. macrocarpa* with the extent of their current trends, limitations, and future directions. Therefore, a literature survey of *P. macrocarpa* was conducted via bibliographic databases assessment including PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), ScienceDirect (https://www.sciencedirect.com), and Google Scholar (https://www.google.scholar.com). Keywords "*Phaleria Macrocarpa*", "*P. macrocarpa*", "Mahkota dewa", "biological activity", "pharmacological activity", "bioactive compounds", "extraction", solvent", and their combinations were used for the search. Published ethnobotanical data and experimental studies about *Phaleria*

Fig. 1. *Phaleria macrocarpa.* (a) Plant (b) Leaf arrangement (c) Unripe fruit (d) Ripe fruit (e) Flower.

macrocarpa reported from 2010 to 2022 were included. Any published data lacking a scientific plant name, as well as data from predatory journals, were excluded. This review included and analysed peer-reviewed journal articles, theses, dissertations, research reports, and books (n = 54).

2. Botanical description

The **leaves** are simple, dark green, oppositely arranged, elliptic to oblong-lanceolate with pointed apex, 7–14 cm long and 3–5 cm broad, and coriaceous; the petiole is 0.5 cm long (Fig. 1) (Alimon et al., 2013; Altaf et al., 2018). *P. macrocarpa* produces tubular fragrance **flowers** that are white in colour. Flowers develop in the course of seven days. Early budding is green in colour and begins to turn white on the fourth day. The budding is 0.8–0.9 cm long on the fourth day. The length of the budding is 1.6–1.7 cm on the sixth day, one day before the bloom. *P. macrocarpa*'s flower comprises four parts: four sepals, four to five petals, eight stamens, and one carpel with a long style and rounded stigma. The flower is unique as its petals are fused together; this type of flower is known as sympetalous or gamopetalous (Alimon et al., 2013).

P. macrocarpa **fruits** are simple, fleshy drupes with one or two seeds, round or elliptical in shape, and 3–5 cm in diameter when mature. Fruit ripeness can be determined visually by the colour of the pericarp. The fruit is green when it is unripe and turns red when it ripens. Half-ripe fruit, which is usually a mix of green and red in colour, can be found about six weeks after the fruit set. Meanwhile, fully ripe fruits appear bright red and can last three to four days before falling from the trees (Asrity et al., 2018). *P. macrocarpa* has 1–2 **seeds** per fruit that are

dicotyledonous, exalbuminous, brown in colour, ovoid, and anatropous (Alimon et al., 2013) *P. macrocarpa's* **pit** is spherical, white, and exceedingly poisonous (Saufi, 2007).

3. Traditional uses

The ethnomedicinal uses of *P. macrocarpa* are appropriately documented based on the folk medicinal applications by local traditional healers in Malaysia (Mustapha et al., 2017). Leaves and fruits are the most common plant parts used to treat ailments traditionally. Their medicinal usages include treating indigestion, stomachache, diarrhea, high blood pressure, haemorrhoids, high blood glucose and cholesterol, urinary symptoms, back pain, and gouts. *P. macrocarpa* leaves are usually boiled together with coconut flowers, screw pine leaves, citronella (fragrant lemongrass), and Ngai camphor (sembung) (Mustapha et al., 2017). The boiled water is used as bath water for postpartum mothers. To treat indigestion, diarrhea, and haemorrhoids, one cup of boiled water extract of three to seven *P. macrocarpa* leaves is consumed two times a day. A few methods have been practiced among the local healers to control high blood pressure (Mustapha et al., 2017). *P. macrocarpa* fruits usually are cut into pieces, washed, and dried first. Then the dried fruits are boiled together with other herbal plant leaves or soaked in hot water and consumed one to three times per day. The same method is used to control blood glucose and cholesterol levels and other health problems according to Malaysian traditional practice. Additionally, the dried fruits can be fried first without oil and then boiled as herbal drinks. *P. macrocarpa* fruits are also used as complementary medicine to treat kidney, heart, and tumor problems by drinking the water extracts of the dried fruits that are usually boiled together with other medicinal plants (Mustapha et al., 2017). The dried-cut fruits are also eaten as capsules to alleviate symptoms.

4. Pharmacological activities

4.1. Antioxidant activity

Antioxidants play a fundamental role in oxidative stress due to their ability to donate hydrogen or electrons. They are commonly derived from the secondary metabolism of plants. It can provide protective effects for humans when the plants are consumed as supplementary food (Chaves et al., 2020). The most common methods for assessing antioxidant activity are phenyl-1-picrylhydrazyl (DPPH) radical scavenging assay, the ferric reducing (FRAP) test, trolox equivalent antioxidant capacity (TEAC or ABTS) assay, and oxygen radical absorbance capacity (ORAC) (Huang et al., 2005; Prior et al., 2005).

Phytochemical screening of aqueous methanol (70%) extracts and different fractions from the fruits of *P. macrocarpa* showed the presence of secondary metabolites such as flavonoids, phenols, saponin glycosides, and tannins. The presence of these compounds contributed to the highest antioxidant activity in methanol extract and ethyl acetate fractions with prominent IC_{50} values of 8.15–9.12 μg/mL in the DPPH assay. These IC_{50} values are much lower than gallic acid (10.8 μg/mL), indicating the fruit extracts of *P. macrocarpa* possess excellent antioxidant activity (Lay et al., 2014c).

Shwter and colleagues studied another antioxidant activity of *P. macrocarpa* fruits from ethanol extract (Shwter et al., 2016). In the FRAP assay, the extract had a moderate IC_{50} value of 2122 mmol/g compared to the butylated hydroxytoluene (BHT) standard of 6366 mmol/g. Phenolic compounds appeared to be the most abundant antioxidant components in ethanol extract, contributing to a potent free radical scavenging effect (Shwter et al., 2016). The optimal conditions for antioxidant extraction from *P. macrocarpa* fruit were determined using the response surface methodology (RSM) approach. The ethanol extract demonstrated the highest percentage yield of antioxidant activity, with a value of 86.85% in the DPPH assay and 7.47% in the FRAP assay (Mohamed Mahzir et al., 2018). The aqueous ethanol extract of *P. macrocarpa* fruits also exhibited fair antioxidant capacity with a percentage yield of 57% based on the DPPH assay. The utilisation of optimum conditions in Ultrasonic-Assisted Extraction (UAE) enabled the extraction of high mangiferin content, flavonoids, and phenolic compounds in the samples, which are believed to be the main factor contributing to the good antioxidant activity of *P. macrocarpa* (Lim et al., 2019).

In addition to fruits, fruit peels were observed to exert antioxidant activity. Different processing parameters in Microwave-Assisted Extraction (MAE), including irradiation time, microwave temperature, and power level, revealed varying antioxidant activity in dried *P. macrocarpa* fruit peels. At the optimum conditions of different extraction parameters, the extract recorded the total phenolic content (TPC) within the range of 97.88–102.6 mg GAE/g dry weight and antioxidant activity 55–58-61.15% based on the DPPH assay (Alara et al., 2019).

The seeds of *P. macrocarpa* were reported as the most poisonous part of the plant and highly toxic compared to the stems, roots, and leaves (Lay et al., 2014b). Despite the toxicity level, the water fraction of *P. macrocarpa* seeds exhibited a lower IC_{50} value (9.75 mg/mL) compared to ethyl acetate, chloroform, and hexane fractions via the DPPH assay due to higher phenolic and flavonoid contents (Lay et al., 2014b).

4.2. Anti-microbial activity

Fruits and leaves of *P. macrocarpa* exerted mild anti-bacterial activity against Gram-positive and Gram-negative bacteria. Two isolated triterpenoids compounds from *P. macrocarpa* fruits known as 24-methylenecycloartan-3-one and 24-methyl-9,19-cyclolanost-25-en-3-ol displayed a moderate inhibition against *Bacillus subtilis, Staphylococcus aureus, Escherichia coli,* and *Pseudomonas putida* with inhibition zone diameter (IZD) ranging from 8.0 to 9.01 mm when compared to the positive control streptomycin with IZD of 16.5–19.5 mm (Othman et al., 2014a). The ethanol extract combining silver nanoparticles from a green synthesis of *P. macrocarpa* leaves demonstrated weaker anti-bacterial activity against *Staphylococcus aureus* and *Escherichia coli* with an inhibition zone diameter of 9.17–10.10 mm when compared to positive control chloramphenicol and gentamicin with IZD of 18.13–18.43 mm (Lestari et al., 2019). The nanoparticle synthesis enhanced the anti-bacterial properties since the ethanol extract alone did not inhibit the bacteria growth (Lestari et al., 2019).

4.3. Anti-diabetic activity

Diabetes mellitus is a chronic metabolic disorder characterised by elevated blood glucose levels and increased risk of micro and macrovascular complications such as nephropathy, strokes, and coronary heart diseases (Baeyens et al., 2018). α-Amylase, α-glucosidase, and lipase are among the standard parameters evaluated in the in-vitro assay to determine anti-diabetic properties (Tian et al., 2016). The fruit extracts of *P. macrocarpa* with different polarity were tested for α-glucosidase inhibitory activity. Based on the observation, the ethanol extract revealed the highest inhibition of α-glucosidase activity with an IC_{50} of 7.4 μg/mL, compared to the positive control quercetin exhibiting an IC_{50} value of 4.3 μg/mL. The strong activity exerted by the ethanol extract might be due to the presence of more lipophilic compounds as well as

aldehyde and carboxylic acid groups that are responsible for α-glucosidase activity (Easmin et al., 2017).

The ethanol extract of *P. macrocarpa* (EEPM) fruits has shown a profound anti-diabetic activity through an *in vivo* study using Sprague-Dawley (SD) male rats (Azad and Sulaiman, 2020). Based on the oral glucose tolerance test, 200 mg/kg EEPM lowered the blood glucose level after oral administration of 2 g/kg glucose compared to the positive control, glibenclamide (0.5 mg/kg). Different doses of EEPM (50,100, and 200 mg/kg) were administered orally to streptozotocin (STZ)-induced SD rats daily for up to 35 days (Azad and Sulaiman, 2020). After 35 days of treatment, 200 mg/kg EEPM significantly reduced the blood glucose level compared to the drug control group, glibenclamide. The serum creatinine and urea level for 200 mg/kg EEPM and glibenclamide group were almost similar, suggesting no kidney failure due to the administration of extracts. The liver enzymes and protein profile results remarkably indicated no liver damage or dysfunction caused by the administration of the extract. Based on the findings, *P. macrocarpa* fruits could be a potential candidate for anti-diabetic drugs (Azad and Sulaiman, 2020).

4.4. Anti-hypercholesteremic activity

Elevated blood cholesterol (hypercholesterolemia) is a leading source of disease burden, accounting for one-third of ischemic heart disease and one-fifth of stroke (Adeloye et al., 2020). Hypercholesterolemia is also regarded as a risk factor for the development of cardiovascular diseases. One of the effective practices to prevent cardiovascular illnesses is to alter the serum cholesterol profile. Although lifestyle changes such as physical activity and a healthy diet are frequently used as the first steps toward lowering blood cholesterol, drug therapy is required when lifestyle changes are ineffective (Araya - Quintanilla et al., 2019).

The ability of *P. macrocarpa* to reduce cholesterol level were investigated through an in-vitro assay, observing the hepatic scavenger receptor class B type 1 (SR-B1) expression. In this assay, the ethyl acetate extract of *P. macrocarpa* leaves increased the SR-B1 expression comparable to the positive drug rosiglitazone at 12.5 μg/ml of concentration. It might be due to the synergistic effects of the phytoconstituents in the extracts that promoted the SR-B1 expression. The active fraction (CF6) and isolated compound (2,6,4′-trihydroxy-4-methoxybenzophenone) also showed moderate SR-B1 expression at 12.5 μg/ml with transcriptional activity of 90% and 60%, respectively (Andriani et al., 2015).

The ethyl acetate extracts of *P. macrocarpa* leaves (EEMD) were further investigated for their antihyperlipidemic ability via an in-vivo study using hypercholesterolemia-induced SD rats. EEMD at 0.5 g/kg body weight has been found to reduce the cholesterol level in the tested SD Rats for 28 days. The HDL level also increased throughout the experiment, which could be correlated to the enhancement of SR-B1 expression in the liver. Serum glutamate oxalate transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT) enzymes levels also appeared in the normal range throughout the whole experiment, indicating the administration of *P. macrocarpa* extract did not cause any toxicity and disturbance to the rat liver functions. This empirically suggests that *P. macrocarpa* could be a good candidate for antihyperlipidemic treatment, and SR-B1 could be a potential target for drug therapies (Andriani et al., 2015).

4.5. Inhibition of endometriosis development

Flavonoids (7.5 mg/day and 15 mg/day) isolated from the ethanol extract of *P. macrocarpa* were able to suppress the growth of granulomas in *Mus musculus* mice via two mechanisms: anti-proliferative and anti-apoptotic effects. Six active compounds (eriodictyol, glycitin, 5-O-methylgenistein, (+)-catechin 7-O-beta-D-xyloside, (-)-8-prenylnaringenin and (±)-naringenin) from the extract were observed to involve in the suppression mechanism. These flavonoid isolates from *P. macrocarpa* ethanol extract could potentially be used as an alternative remedy to inhibit the development of endometriosis (Maharani et al., 2021).

The bioactive fraction of *P. macrocarpa* fruits, designated as DLBS1442, showed inhibition toward angiogenesis and cell migration in a dose-dependent manner (Tandrasasmita et al., 2015). At 100 μg/mL, DLBS1442 increased the cell population in sub-G1 phase from 7% to 34%. DLBS1442 also significantly downregulated the oestrogen receptor level and upregulated the progesterone receptor level. Furthermore, it inhibited the eicosanoid signaling pathway by reducing the transcription level of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) and subsequent reduction of inducible nitric oxide synthase. A dose-dependent decrease in viability and increased apoptosis in RL95-2 cells were also evident after exposure to DLBS1442, where the IC_{50} value was obtained at around 100 μg/mL. These results demonstrated that DLBS1442 could be a potential agent for alleviating symptoms of endometriosis via its anti-angiogenic, anti-inflammatory, and proapoptotic activity (Tandrasasmita et al., 2015).

4.6. Anti-proliferative activity

Benzophenone glucopyranosides isolated from the nutshell part of *P. macrocarpa* were identified as Mahkoside A and Mahkoside B (Zhang et al., 2012). The series of benzophenone glucopyranosides derivatives were synthesised using various techniques, including alkylation, acylation, and etherification substitutions. Designated compound 18 gave significant cytotoxicity against four different cancer cell lines, with IC_{50} values less than 10 μM/L. The inhibitions of four different cancer cell growth were as follows: Oesophageal cancer cell line EC109: 5.139 ± 0.711 μM/L; oesophageal cancer cell line EC9706: 4.971 ± 0.696 μM/L; stomach cancer cell line MGC-803: 3.121 ± 0.494 μM/L, and prostate cancer cell line PC-3: 3.47 4 ± 0.541 μM/L (Zhang et al., 2012).

2, 6, 4′-trihydroxy-4-methoxybenzophenone compound was isolated from the ethyl acetate fraction of *P. macrocarpa* fruits (Lay et al., 2014a). This compound is a potent anti-proliferative agent for HT-29 human colon carcinoma cell line. Under a microscopic examination, HT-29 cells treated with the compound displayed morphological changes such as cell shrinkage, membrane blebbing, DNA fragmentation, and the presence of apoptotic nuclei. The p53 upregulated modulator of apoptosis (PUMA), Bak, Bcl-2, and Mcl-1 proteins were upregulated in the Western blots, suggesting the compound could induce apoptosis in HT-29 cells by regulating these proteins (Lay et al., 2014a).

The methanol extracts and different fractions of *P. macrocarpa* seeds were tested against human cervical carcinoma cells (Ca Ski), hormone-dependent breast carcinoma cells (MCF-7), human breast adenocarcinoma cells (MDAMB231), human ovarian carcinoma cells (SKOV-3), and human colon carcinoma cells (HT-29) to observe the cytotoxic effects. The ethyl acetate fractions (EEF) showed cytotoxic effects in all cell lines with low IC_{50} values ranging from 1.1 to 22.3 mg/mL when compared to doxorubicin as a positive control. After a 24-hour incubation period of the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay using HT29 as tested cell lines, EEF exhibited an excellent IC_{50} value of 1.1 ± 1.20 mg/mL, comparable to doxorubicin with an IC_{50} value of 0.92 ± 0.72 mg/mL. For Ca Ski cell line, EEF also showed a low IC_{50} value of 5.6 ± 1.17 mg/mL as compared to doxorubicin with an IC_{50} value of 0.92 ± 0.64 mg/mL (Lay et al., 2014b).

The aqueous methanol (70%) extracts and different fractions of *P. macrocarpa* fruits were tested against Ca Ski, MCF-7,

MDAMB231, SKOV-3, and HT-29 using the MTT assay to observe the cytotoxic effects (Lay et al., 2014c). The methanol extract exhibited good cytotoxicity toward SKOV-3 cell lines with an IC_{50} value of 7.75 ± 2.56 mg/mL at 72 h of incubation. For MCF-7, the ethyl acetate fraction revealed moderate cytotoxicity toward MCF-7 cell lines with an IC_{50} value of 16.5 ± 2.45 mg/mL at 24 h of incubation. The hexane fraction showed good cytotoxicity toward MDA-MB231 cell lines with an IC_{50} value of 5.8 ± 2.15 m g/mL at 24 h of incubation (Lay et al., 2014c).

The fractionated extract of fruit flesh (endocarp) of *P. macrocarpa* designated as DLBS1425 showed inhibitory activity toward human retinoblastoma Y-79 cell line proliferation (Trilaksana et al., 2017). DLBS1425 lowered the number of Y-79 human retinoblastoma tumor cells corresponding to the dosage levels. DLBS1425 was considered to inhibit the gene transcription of cyclin E human retinoblastoma tumor cell Y-79 at the level of messenger RNA (mRNA) without going through the p21 gene regulation line. It could be a potential scaffold for developing anti-cancer drug therapy (Trilaksana et al., 2017).

The ethanol extract of *P. macrocarpa* fruits was fed orally to azoxymethane (AOM)-induced aberrant crypt foci (ACF) SD adult male rats (Shwter et al., 2016). In the colon carcinogenetic model, aberrant crypt foci are considered the first detectable neoplastic lesions. The progression of ACF to polyp and, eventually, cancer is accompanied by several biochemical alterations and mutations, with a small proportion of ACF evolving into colon cancer (Alrawi et al., 2006). The induction of ACF was achieved by administering AOM subcutaneously for two weeks at a dosage of 15 mg/kg body weight per week. Then, the experimental groups received the ethanol extract of *P. macrocarpa* at dosages of 250 mg/kg body weight and 500 mg/kg body weight with continuous monitoring before the rats were sacrificed for examination. The number of ACF per rat in rats administered with *P. macrocarpa* was significantly lower than in other groups. About 72.2% and 71.8% decrease in the total crypts in the rats fed with 250 mg/kg and 500 mg/kg *P. macrocarpa* were observed (Shwter et al., 2016).

A study performed by Kusmardi and the team proved the ability of *P. macrocarpa* leaf ethanol extract (PMLEE) to upregulate the expression of Caspase-3 (Kusmardi et al., 2021a). It decreased the expression of Ki-67 (Kusmardi et al., 2021b) in induced dextran sodium sulfate (DSS) colon cells of Balb/c mice. Caspase-3 was used as an apoptosis marker, while Ki-67 was used as a proliferative marker in the ulcerative colitis study. Based on different doses of PMLEE, 300 mg/kg BW of PMLEE showed a significant outcome compared to aspirin as the positive control (Kusmardi et al., 2021a; Kusmardi et al., 2021b).

The ethanol extracts of *P. macrocarpa* stems and barks inhibited the expression of inducible nitric acid oxide synthase (iNOS) in colorectal cancer cell line HCT116 (Harmen et al., 2019). The results suggested that the extracts from stem and bark parts could also be a potential chemo preventive agent for colorectal cancer.

In comparison to the formulated probiotic or non-treated groups, treatment with *P. macrocarpa* leaves methanol extract (500 mg/kg) resulted in a remarkable recovery in the colon tissues of immunocompromised New Zealand rabbits based on the observed histopathological changes (Saleh et al., 2021). Samples of the immunocompromised rabbits treated with *P. macrocarpa* extract showed a distinct decrease in mucin secretion and goblet cell structured composition, as well as a significant recovery in body weight gain, physical activity, a reduction in pro-inflammatory immune markers, and abundant rates of neutrophils in plasma (Saleh et al., 2021).

The ethanol extract of *P. macrocarpa* leaves showed cytotoxicity toward T47D breast cancer cell lines with an IC_{50} value of 97 µg/ml using the WST-1 assay (Christina et al., 2021b). MCF7 cell lines are commonly employed as in-vitro tools in breast cancer research; however, this study showed that T47D cell lines could be a suitable experimental model for elucidating the progesterone-specific effects of a luminal A subtype of breast cancer (Yu et al., 2017).

Polyphenols extracted from *P. macrocarpa* fruits were administered to mice Balb/c strains to observe the inhibition of lung carcinogenesis growth. *P. macrocarpa* polyphenols influenced the expression of p53, pro-apoptosis Bax and anti-apoptosis Bcl-2, Caspase-3, −8, and −9 proteins in Balb/c mice. The chemo preventive properties of *P. macrocarpa* polyphenols are thought to be capable of inducing an apoptotic process manifested by cell blebbing and shrinkage, increased permeability, and decreased mitochondrial potential (Watuguly et al., 2020).

Additionally, polyphenols from *P. macrocarpa*, as well as cytostatic drugs like Paclitaxel and Cisplatin, have been shown to reduce the mitotic index of epidermoid carcinoma and inhibit tumor growth (Ekasaputra et al., 2020). As a result, *P. macrocarpa* could be used as an adjuvant therapy to cytostatic drugs in treating epidermoid carcinoma.

4.7. Anti-hypertensive and vasorelaxant activity

A quasy experiment design was used to assess hypertension in an elderly population in Blitar and Tulungagung, Indonesia, by giving ethnic food containing different parts of *P. macrocarpa* to 40 respondents over a 7-day period (Rizal et al., 2020). The tested group that consumed the ethnic food comprising 15 g of *P. macrocarpa* showed a positive result in reducing hypertension with decreasing systolic blood pressure, diastolic blood pressure, and mean arterial pressure (MAP). This finding is consistent with Altaf et al. (2018), which revealed that the water extracts of *P. macrocarpa* fruits showed a significant reduction in MAP and heart rate (HR) in spontaneous hypertensive rats as compared to reference drug verapamil (Altaf et al., 2018). In addition, SF2 subfraction from the water extract also demonstrated pronounce vasorelaxation effects on rat aortic explant due to the presence of polar components such as kaempferol-3-*O*-β-glucuronide, mangiferin, gallic acid and rutin (Altaf et al., 2018).

4.8. Wound healing activity

Wound is defined as damage to the integrity of biological tissues, which includes skin, mucous membranes, and organ tissues. Wound healing is a fascinating mechanism and a crucial phase in the wound closure process. The wound healing process is divided into three stages: inflammatory, proliferative, and maturation (Sorg et al., 2017). The ethanol extracts of *P. macrocarpa* seedless fruits were reported to possess a wound-healing effect (Abood et al., 2015). The 200 mg/ml dose of the extract showed a faster wound healing rate with signs of dermal healing and smaller wound enclosure in wounded Sprague Dawley rats compared to the control group. More collagen, fibroblasts, blood proliferating capillaries, and fewer inflammatory cells were observed in the granulation tissues. A significant decrease in the wound area was influenced by a significant rise in TGF β1 level in the treated groups. The reduced pro-inflammatory cytokine tumor necrosis factor-α (TNF α) level and increased collagen formation level were also observed in the treated groups. The topical application of *P. macrocarpa* fruit extract boosted the superoxide dismutase (SOD) and catalase (CAT) activities in healing wounds, lowering the malondialdehyde (MDA) levels considerably. The topical treatment with *P. macrocarpa* fruit extract had a substantial healing effect on excision wounds and played an essential role in the inflammatory process by enhancing antioxidant enzyme activities, which accelerated wound healing and reduced tissue damage (Abood et al., 2015).

In another study, the fruit extract of *P. macrocarpa* was also reported to induce a wound-healing effect. One mg/kg body weight of the extract increased the collagen density around the wounded area of *Rattus norvegicus* white rats (Sulistyoning Suharto et al., 2021). The extract was administered orally, and the wound observation was performed thrice. On the 10th day, the extract treatment group showed significant collagen density on the incision wound, with a value of 2.63, compared to the control group, with a value of 1.28 (Sulistyoning Suharto et al., 2021).

4.9. Analgesic activity

Pain is a psychological, sensory, and unpleasant experience caused by tissue damage. Analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) and opiates are widely used to relieve pain without altering consciousness, and they can cause various adverse effects. NSAIDs cause ulceration, bleeding, gastrointestinal discomfort, and other side effects, whereas opiates frequently cause addiction and tolerance (Kumar Paliwal et al., 2017). As a result, researchers have expressed a desire to discover analgesic drugs derived from natural sources with fewer side effects (Hossen et al., 2021).

P. macrocarpa leaves demonstrated a potent analgesic property using the stretching method. Different doses of the ethanol (70%) extracts of *P. macrocarpa* leaves (0.25 g/kg body weight (BW), 0.50 g/kg BW, and 0.75 g/kg BW) were administered orally to *M. Musculus* mice (Salman et al., 2021). Glacial acetic acid (1%) as a pain inducer was administered orally 5 min after the administration of the extract. The squirming of mice was calculated every 5 min for one and a half hours, and the analgesic rate was calculated based on the squirming results and translated into effectivity percentage. The ability of the extracts to inhibit and decrease the number of squirming in mice indicated analgesic activity. 0.75 g/kg BW of the extract exerted 92.65% of the analgesic rate, showing almost similar effectivity as mefenamic acid (positive control group) (Salman et al., 2021).

4.10. Anti-inflammatory activity

Inflammation is characterised as an adaptive body response that is triggered by harmful stimuli and conditions such as infections, injury of cells and tissues, and tissue stress and malfunctioning (Medzhitov, 2008). Steroids and non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat

Table 1
Summary of recent pharmacological activities based on different plant parts of *P. macrocarpa*.

Plant parts	Activity	Assay	References
Fruit	Antioxidant activity	DPPH assay	(Lay et al., 2014c)
		FRAP assay	(Shwter et al., 2016)
		DPPH & FRAP assay	(Mohamed Mahzir et al., 2018)
		DPPH assay	(Lim et al., 2019)
		DPPH assay	(Alara et al., 2019)
	Anti-microbial activity	Disc diffusion method	(Othman et al., 2014a)
	Anti-diabetic activity	α-Glucosidase inhibitory assay	(Easmin et al., 2017)
		In vivo study using STZ-induced SD rats	(Azad and Sulaiman, 2020)
	Inhibition of endometriosis development	*In vitro* assay using RL95-2 cell line	
	Anti-proliferative	*In vitro* assay using Ca Ski, MCF-7, MDAMB231, SKOV-3 and HT-29 cell lines	(Tandrasasmita et al., 2015)
		In vitro assay using HT-29 cell line	(Lay et al., 2014a)
		In vitro assay using Y-79 cell lines	(Trilaksana et al., 2017)
		In vivo study using azoxymethane-induced aberrant crypt foci SD rats	(Shwter et al., 2016)
		In vivo study for lung carcinogenesis growth in mice Balb/c	(Watuguly et al., 2020)
	Anti-hypertensive	Clinical trial based on 40 respondents for hypertension study in elderly population	(Rizal et al., 2020)
	Anti-hypertensive and vasorelaxant activity	*In vivo* study using hypertensive rats	(Altaf et al., 2018)
	Wound healing activity	*In vivo* study using wounded SD rats	(Abood et al., 2015)
		In vivo study using wounded *Rattus norvegicus* white rats	(Sulistyoning Suharto et al., 2021)
	Anti-inflammatory	*In vivo* study using carrageenan-induced male Swiss mice	(Tjandrawinata et al., 2015)
		In vivo study using ethanol-induced gastric ulcers in SD rats	(Abood, 2014)
	Aphrodisiac activity	*In vivo* study using male SD rats	(Parhizkar et al., 2013b)
		In vivo study using male SD rats	(Parhizkar et al., 2014)
Leaves	Anti-microbial activity	Disc diffusion method	(Othman et al., 2014a)
		Disc diffusion method	(Lestari et al., 2019)
	Anti-hypercholesteraemic activity	*In vitro* assay based on SR-B1 expression	(Andriani et al., 2015)
		in vivo study using hypercholesterolemia-induced SD rats	(Andriani et al., 2015)
	Anti-proliferative	*In vivo* study using DSS-induced Balb/c mice	(Kusmardi et al., 2021a), (Kusmardi et al., 2021b)
		In vivo study using immunocompromised New Zealand rabbits	(Saleh et al., 2021)
		In vitro assay using T47D cell line	(Christina et al., 2021b)
	Analgesic	*In vivo* study using glacial acetic acid-induced *M. Musculus* mice	(Salman et al., 2021)
Seed	Antioxidant activity	DPPH assay	(Lay et al., 2014b)
	Anti-proliferative	*In vitro* assay using Ca Ski, MCF-7, MDAMB231, SKOV-3 and HT-29 cell lines	(Lay et al., 2014b)
Nutshell	Anti-proliferative	*In vitro* assay using EC109, EC9706, MGC-803 and PC-3	(Zhang et al., 2012)
Stem & bark	Anti-proliferative	*In vitro* assay using HCT116 cell line	(Harmen et al., 2019)
Unknown part	Anti-proliferative	*In vivo* study using 18 epidermoid carcinoma induced Swiss mice	(Ekasaputra et al., 2020)

Ca Ski- Human cervical carcinoma cells; DPPH-1,1-diphenyl-2-picrylhydrazyl; DSS- Dextran sodium sulfate; EC109- Oesophageal cancer cell line; EC9706- Oesophageal cancer cell line; FRAP- Ferric reducing test; HT-29-Human colon carcinoma cells; HCT116- Colorectal cancer cell line; MCF-7-hormone-dependent breast carcinoma cells; MDAMB231- Human breast adenocarcinoma cells; MGC-803- Stomach cancer cell line; PC-3- Prostate cancer cell line; RL95-2- New human endometrial carcinoma cells; SD-Sprague Dawley; SR-B1- Scavenger receptor B1; SKOV-3- Human ovarian carcinoma cells; STZ-Streptozotocin; T47D- Breast cancer cell line; Y-79-Human retinoblastoma cells.

Table 2
Toxicity studies of different plant parts from *P. macrocarpa*.

No	Plant part	Plant extract	Type of toxicity study	Animal and Dose	Duration	Observation	Reference
1	Ripe fruits (Mesocarp & pericarp)	Ethanol	Acute toxicity	Brine shrimp naupli (*Artemia salina*) 0.78 ug/ml – 800 ug/ml	24 h	Safe and non-toxic. LC_{50} > 800 ug/ml	(Azad, 2016)
2	Fruits	Ethanol	Acute toxicity	Adult SD rats 2000, 5000 mg/kg BW	14 days	No mortality, no hepatoxic and no nephrotoxic	(Shwter et al., 2016)
3	Fruits (Mesocarp & pericarp)	Ethanol	Acute toxicity	Healthy male SD rats 5000 mg/kg BW	7 days	No mortality, no sign of toxicity; physical behavior, central nervous system, and autonomic nervous system working well	(Azad and Sulaiman, 2020)
4	Fruits	Petroleum ether Chloroform Methanol Water	Acute toxicity	Healthy adult female SD rats 2000 mg/kg BW	14 days	No sign of toxicity and no changes in animal behavioral pattern. No sign of toxicity and no changes in animal behavioral pattern. No sign of toxicity and no changes in animal behavioral pattern. No sign of toxicity and no changes in animal behavioral pattern.	(Altaf et al., 2018)
5	Fruits (Mesocarp & pericarp)	70% ethanol	Acute toxicity	Healthy adult male SD rats 500, 1000, 2000, 5000 mg/kg BW	28 days	No body weight changes, no mortality, no diseases, and no significant changes in animal behavior. However, at dose 5000 mg/kg, serum creatinine and urea levels are reduced compared to normal control	(Azad et al., 2021)
6	Leaves	Ethanol	Subchronic toxicity	Male and female Wistar rats 100, 500, 1000 mg/kg BW	90 days	No toxic effect, AST and ALT level did not increase. No effect in blood hematology. However, liver tissue necrosis observed at dose 1000 mg/kg BW, but it was reversible.	(Hanif, 2021)
7	Leaves	Ethanol	Teratogenic toxicity	Female rats (Day 6 to day 15 pregnancy) 100, 500, 1000 mg/kg BW	19 days	No abnormalities, however, 3 fetuses with incomplete sternum at dose 1000 mg/kg BW were observed.	(Hanif, 2021)
8	Unknown part	Methanol	Teratogenic toxicity	Zebra fish embryos 10, 100, 1000 ug/ml	96-hour post fertilisation	No teratogenic effects	(Omar et al., 2020)

AST-Aspartate aminotransferase; ALT-Alanine transaminase; BW-Body weight; LC_{50}-Lethal concentration at 50%; SD- Sprague Dawley.

inflammation. They primarily work by inhibiting the cyclooxygenase (COX) pathway. They specifically inhibit the conversion of arachidonic acids into prostaglandins. Diclofenac potassium is a non-selective NSAID that inhibits COX-1 and COX-2 (Carinci and Rathmell, 2012).

Mixtures of *P. macrocarpa* fruits and *Nigella sativa* seeds, namely DLBS0533, were reported to exert anti-inflammatory properties (Tjandrawinata et al., 2015). At doses of 156 mg/kg of body weight, DLBS0533 demonstrated strong anti-inflammatory activity by reducing oedema thickness in carrageenan-induced male Swiss mice. The reduction effect was comparable to 9.1 mg/kg BW of diclofenac potassium (Tjandrawinata et al., 2015).

The ethanol extract of *P. macrocarpa* seedless fruits was found to have a protective effect against ethanol-induced gastric ulcers in SD rats (Abood, 2014). The effect of 1000 mg/kg extract on the ulcer lesion area was 23 mm, and gastric stomach pH was 7.0, which was comparable to the effect of omeprazole as a positive control. The *P. macrocarpa* extract also caused a significant increase in prostaglandin E2 (PGE2) levels as compared to the ulcer control group. It suggests that *P. macrocarpa* exhibits anti-ulcer mechanisms. Interestingly, the level of TNF-α was dramatically reduced, while the anti-inflammatory cytokine transforming growth factor (TGF-β1) level was significantly elevated in the extract-treated group (Abood, 2014).

4.11. Aphrodisiac activity

Infertility is one of the most severe problems that some people encounter worldwide, and men account for half of all cases of infertility. Androgen deficiency or a low testosterone level can lead to infertility. The history, physical examination, and sperm analysis can all be used to perform diagnostic tests (Lindsay and Vitrikas, 2015; Stahl et al., 2012). When clinical complaints are accompanied by a decrease in testosterone, the doctor will begin Testosterone Replacement Therapy (TRT). However, if TRT is used excessively, side effects such as nausea, acne, headache, fluid retention, liver toxicity, sleep apnoea, and prostate hyperplasia may occur. Herbal medicines have been gaining wide attention in recent decades because of the various side effects of hormone therapy (Parhizkar et al., 2013a).

Traditionally, *P. macrocarpa* was reported to enhance sexual strength and libido behaviour in men (Parhizkar et al., 2013b). Based on research by Parhizkar and the team, the aqueous extract of *P. macrocarpa* fruits significantly increased the number of cells and the thickness of seminiferous tubules of male SD rats (Parhizkar et al., 2014). The mean thickness of seminiferous tubules in treated *P. macrocarpa* groups was 80.66 μm, which is significantly greater than the positive control commercial testosterone drug (Andriol® Testocap™) that showed a mean thickness of 50 μm (Parhizkar et al., 2014). In addition, the aqueous extract of *P. macrocarpa* fruits with a dose of 240 mg/kg also elevated the sperm viability of male SD rats in seven weeks compared to the testosterone hormone Andriol® Testocap™ (Parhizkar et al., 2013a). A study also revealed the oral administration of 240 mg/kg of *P. macrocarpa* aqueous extract for seven weeks in the SD male rats preceded the enhancement of fertility as evidenced by a significant increment of serum testosterone level and mounting frequency (Parhizkar et al., 2013b).

The following table (Table 1) summarises recent pharmacological effects reported from different plant parts of *P. macrocarpa*.

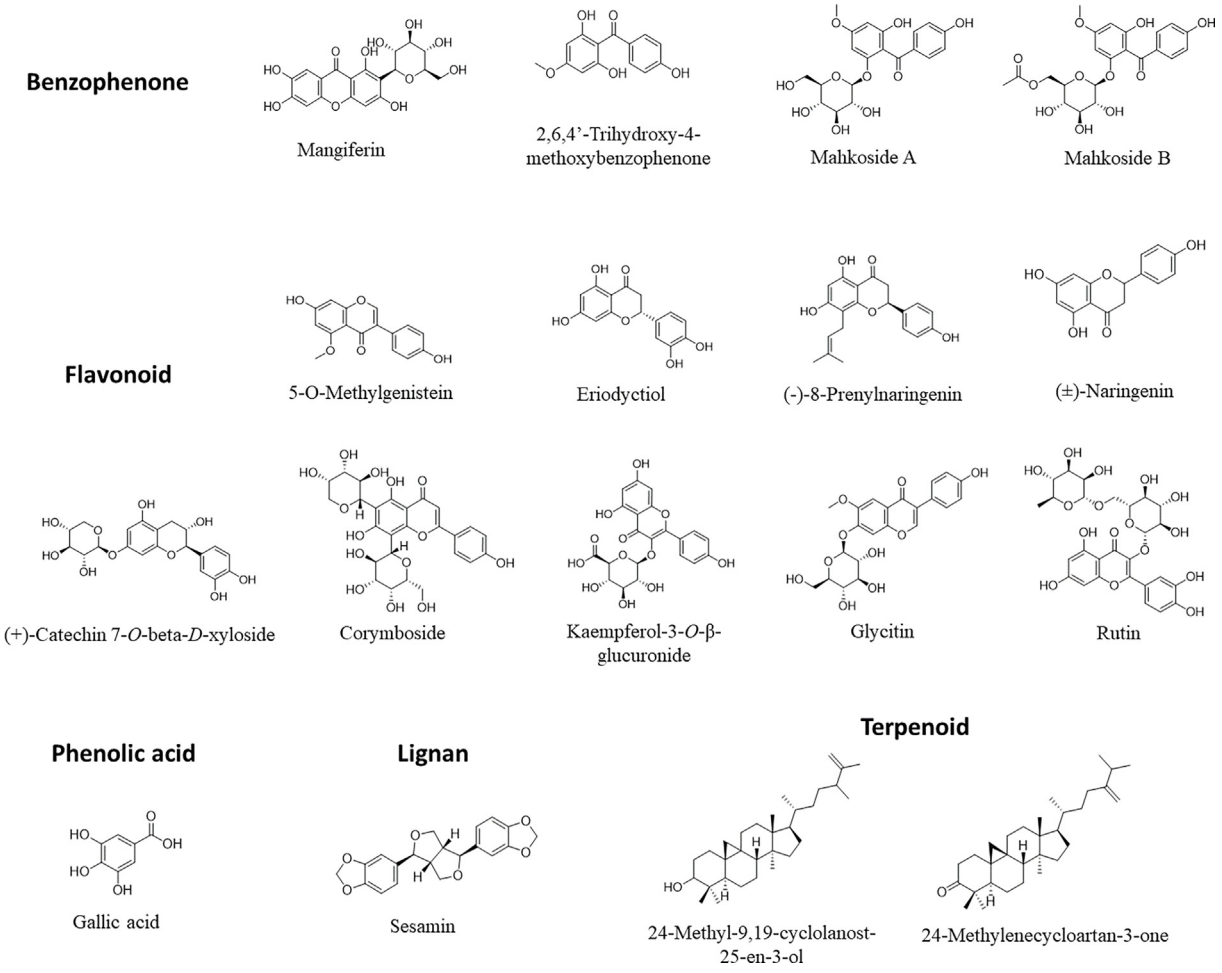

Fig. 2. Several bioactive compounds identified from *P. macrocarpa* with reported biological activities and extraction methods.

5. Toxicity studies

The main concern in the toxicity of herbal remedies is their capacity to produce lethality and antagonistic impacts when consumed (Azad et al., 2021). The main uniqueness of herbal plants is the presence of secondary metabolites as a natural defence toward plant growth. They can offer significant benefits but can also be harmful when consumed excessively (Wyk and Prinsloo, 2020). An acute toxicity study evaluates any adverse effects that occur when the organisms are exposed to single or multiple doses of test substance within 24 h by a known route such as oral, dermal, or inhalation (Saganuwan, 2017). During the study, the median lethal dose (LD_{50}) will be determined, and the mortality and any signs of toxicity will be closely monitored. The data obtained during the acute toxicity study will be used as a dosage selection guideline for long-term toxicity studies as well as other studies that involve the use of animals (Erhirhie et al., 2018). Recent toxicity studies of *P. macrocarpa* were summarised in Table 2.

6. Bioactive compounds

Several classes of compounds have been identified from *P. macrocarpa* (Fig. 2), especially benzophenones, terpenoids, and flavonoids. Mangiferin remains the major compound of interest that has led to the optimisation of many extraction techniques attributed to its capacity as an antioxidant agent. Flavonoids (eriodictyol, glycitin, 5-O-methylgenistein, (+)-catechin 7-O-beta-D-xyloside, (-)-8-prenylnaringenin, and (±)-naringenin) from the ethanol extract suppressed the growth of granulomas by inhibiting the development of endometriosis in *M. musculus* mice (Maharani et al., 2021). Two triterpenoids compounds known as 24-methylenecycloartan-3-one and 24-methyl-9,19-cyclolanost-25-en-3-ol exhibited moderate inhibition against microbes such as *B. subtilis, S. aureus, E. coli*, and *P. putida* (Othman et al., 2014a). 2,6,4′-trihydroxy-4-methoxybenzophenone isolated from the ethyl acetate extract of *P. macrocarpa* leaves showed moderate SR-B1 expression to reduce the cholesterol level (Andriani et al., 2015). Mahkoside A and Mahkoside B were used as scaffolds to design the series of benzophenone glucopyranosides derivatives that showed growth inhibition against various cancer lines (Zhang et al., 2012).

The maceration technique performed to extract *P. macrocarpa* leaves resulted in the identification of 14 bioactive compounds by liquid chromatography-high resolution mass spectrometry (LC-HRMS) analysis against breast cancer activity (Djati, 2021). Further *in silico* molecular docking study revealed that 12 of them showed anti-cancer properties that might be involved with p53 and PI3K/Akt signalling pathways related to cancer. Sesamin (-9.5 kcal/mol; −7.8 kcal/mol) exhibited the best binding affinity to Caspaces-3 and Bax, respectively, as compared to control drugs, Venetoclax (-10.2 kcal/mol; −8.8 kcal/mol). Corymboside demonstrated −7.3 kcal/mol binding affinity value toward Bcl-2 compared to the control drug with a binding affinity value of

−9.4 kcal/mol (Christina et al., 2021a). Kaempferol-3-*O*-β-glucuronide, mangiferin, gallic acid, and rutin were identified to have vasorelaxant activity (Altaf et al., 2018).

7. Extraction techniques

7.1. Conventional approaches

7.1.1. Maceration

Maceration is the most basic extraction technique commonly used among researchers worldwide since it only requires basic laboratory apparatus and is suitable for both small and large extraction setups. It is also exhaustive and suitable for thermosensitive compounds since it does not involve heat (Senica and Mikulic-Petkovsek, 2020; Vieitez et al., 2018). However, there are several disadvantages of using this technique such as long extraction time, a huge amount of solvent consumption, and low extraction efficiency (Zhang et al., 2018). In this process, the whole or coarsely powdered herbal material or plant is placed in a closed container with the solvent and allowed to stand at room temperature for at least three days with frequent agitation until the soluble matter has dissolved. Then the mixture is then filtered and collected.

The general belief in the maceration technique is the longer the extraction time, the higher the extraction yield. However, it is not always true. For example, the extraction of pinoresinol diglucoside from *Cortex eucommiae* decreases with increasing maceration time. It is due to pinoresinol diglucoside undergoing hydrolysis during the maceration process (Chen et al., 2016).

7.1.2. Reflux extraction

Reflux extraction is a solid–liquid extraction process at a constant temperature with continuous solvent evaporation and condensation for a specific time without solvent loss. The system is commonly used in herbal industries as it is efficient, easy to operate, and cost-effective (Wang et al., 2013). A study by Tongyen and colleagues showed that reflux extraction gives a comparable result with maceration in term of extraction yield (Tongyen et al., 2019). But the extraction time was reduced significantly from 14 days by maceration to 1 day by reflux extraction. However, in term of biological activity such as antioxidant activity, maceration has demonstrated a better result than reflux extraction. It is noteworthy that thermal degradation can occur in reflux extraction since it usually uses mild/high temperature (50–90 °C) (Moreira et al., 2019).

7.1.3. Soxhlet extraction

Soxhlet extraction has mostly been the standard technique for herbs among researchers. Compared to other conventional methods, it involves low operating cost and simple operation suitable for small- or large-scale extraction with a good yield recovery. In the soxhlet extraction, the sample is placed in a thimble that is gradually filled with fresh condensed solvent from the distillation flask. When the liquid reaches the overflow level, it will unload the solvent back to the distillation flask, together with extracted analytes into the solvent in the distillation flask. This process is repeated until complete extraction is achieved. This process allows the soxhlet extraction to be more effective since the fresh condensed solvent is recirculated through the samples continuously unlike the reflux and maceration techniques. However, a few drawbacks of using this technique are discovered such as (López-Bascón and de Castro, 2020):

(1) The long time required for extraction
(2) Massive amount of solvent waste that is expensive to dispose and harmful to the environment
(3) Thermal decomposition of thermolabile compounds is a concern during the extraction process because samples are usually extracted at the solvent's boiling point for a long time
(4) The technique is restricted to solvent selectivity and is not easily automated

7.2. Modern extraction techniques

7.2.1. Supercritical fluid extraction (SFE)

Supercritical fluid extraction (SFE) is an environmentally friendly and selective extraction technique that has been utilised widely to obtain valuable compounds from natural sources (Herrero et al., 2015). Carbon dioxide (CO_2) extraction is the most used technique in SFE and is occasionally modified with co-solvents such as ethanol and methanol. The critical point of CO_2 is at 31.1 °C and 73 atm. At this point, CO_2 behaves like both gas and liquid. In that state, CO_2 possesses high density like liquid, diffusivity like gas, and viscosity like gas–liquid (Arumugham et al., 2021). Unlike other extraction techniques, the SFE process does not produce any solvent residue. Since CO_2 is non-toxic, non-flammable, odourless, tasteless, inert, and inexpensive, it has been widely adapted in food, aromas, essential oils, and nutraceutical industries. Plants that have been recently extracted by SFE for their bioactive compounds include Manjakani (*Queris infectoria)* (Mohd-Nasir et al., 2021), Feijoa leaves (*Acca sellowiana*) (Santos et al., 2021), sugarcane (Albarelli et al., 2018), *Cannabis sativa* (Gallo-Molina et al., 2019), daisy flower (*Helichrysum italicum*) (Maksimovic et al., 2021), *Moringa oleifera* (Guzmán-Albores et al., 2021), coconut oil (Torres-Ramón et al., 2021), rice bran (Kayathi et al., 2021), tiger nut (*Cyperus esculentus L.*) (Lasekan and Mohammed, 2012), chia seed (*Salvia hispanica L.*) (Ishak et al., 2021), *Andrographis paniculate* (Kaushik et al., 2021), rosemary (Lefebvre et al., 2021), sweet paprika (*Capsicum annum*) and sage (Pavlić et al., 2018).

7.2.2. Pressurised liquid extraction (PLE)

Pressurised liquid extraction (PLE) is an extraction technique that involves extraction at an elevated temperature and pressure, which will increase its efficiency compared to room temperature and atmospheric pressure. In theory, at higher temperature and pressure, the solvent surface tension will decrease, hence increasing the mass transfer rate and solubility. PLE is a versatile technique for extraction with a wide range of solvents incorporating polar to non-polar compounds with several factors to be optimised such as type of solvents, extraction time, temperature, particle size, and water content of the sample (Harris et al., 2020). Among plants that have been extracted using the PLE technique for their bioactive compounds are *Eucalyptus* tree barks (Andrew et al., 2020), pepper fruits (*Capsicum annum L.*) (Ahmad et al., 2021b), olive fruit (*Olea europaea*) (Ahmad et al., 2021a), black seeds (*Nigella sativa*), and thistle (*Carthamus caeruleus*) roots (Toubane et al., 2017).

7.2.3. Microwave-Assisted extraction (MAE)

Microwave-assisted extraction (MAE) is an innovative extraction system to extract high yielded bioactive compounds in a shorter time and lower solvent and energy consumption. It utilises non-ionising electromagnetic waves between 300 MHz and 300 GHz and usually 2,450 MHz for extraction purposes, with a wide range of commercial units designed for analytical chemistry purposes (Routray and Orsat, 2012). Compared to conventional heating, microwave heating enhances the process, which makes it more energy-saving. Due to the heating up of the sample, excluding the apparatus by microwave, less energy is consumed (Chaturvedi, 2018).

Table 3
Recent studies of *P. macrocarpa* employing conventional and modern extraction techniques to obtain bioactive extracts and compounds.

No.	Extraction method	Solvent	Plant part/ compound	Extraction condition	Yield result or biological assay	Reference
Conventional						
1	Maceration	Ethanol	Fruits	2.5 kg of *P. macrocarpa* fruits were soaked in 30 L of 96% ethanol for 120 h (5 days), then filtered to obtain flavonoid-rich filtrate	The flavonoid-rich extract suppressed the growth of endometriosis lesions through normalisation of proliferation and apoptosis	(Maharani et al., 2021)
2	Reflux	Methanol	Pericarps, mesocarps, and seeds	Each part of *P. macrocarpa* fruit (0.5 g) was added with 40 ml of solvent, followed by 10 ml and 6 M HCl solution, attached to reflux, heated for 2 h at 90 °C, and then filtered	The pericarps and mesocarps inhibited inducible nitric oxide synthesis at 63.4 ± 2.7% and 69.5 ± 1.4%, respectively, in macrophage RAW 264.7 cell lines, indicating their potential for anti-inflammatory activity	(Hendra et al., 2011)
3	Soxhlet	Ethyl acetate	Fruits	*P. macrocarpa* fruit (0.5 g) was added with 40 ml of solvent, followed by 10 ml and 6 M HCl solution, heated for 2 h at 90 °C using soxhlet extractor, and then filtered	The pericarps showed higher DPPH antioxidant activity (IC_{50} = 122.4 ± 1.14 µg/ml) compared to mesocarps (IC_{50} = 175.48 ± 1.75 µg/ml).	(Hendra and Haryani, 2018)
Modern						
4	SFE	Supercritical carbon dioxide	Seed oil	Optimised conditions were used: temperature of 72 °C, a pressure of 42 MPa, and a CO_2 flow rate of 4.5 ml/min	52.9 g of oil yield per 100 g of dry sample and 0.99 of coefficient of determination (R^2) were obtained. The amount of oleic acid (18:1) was found to be highest (43.56%) among all the fatty acids. The total unsaturated fatty acid and saturated fatty acid were obtained as 73.62% and 26.38%, respectively in the *P. macrocarpa* seed oil.	(Azmir et al., 2014)
5	SFE	Supercritical carbon dioxide	Mangiferin	The extraction conditions were set at 40 MPa, 353 K, and a CO_2 flow rate of 41 g/min	No yield of mangiferin was obtained	(Kim et al., 2010)
6	PLE	Subcritical water	Mangiferin	2.5 g of *P. macrocarpa* sample of 25 g was mixed with 1 L of distilled water, poured into the extraction reactor with a 6-hour extraction time and an optimum temperature of 105 °C.	38.7 mg/g yield of mangiferin was obtained	(Alara et al., 2017)
7	PLE	Subcritical water	Mangiferin	The optimal condition was achieved at 373 K, 4.0 MPa, 100 °C of temperature and 5 h of extraction time	21.7 mg/g of extraction yield of mangiferin was obtained, which was close to the extraction yield with methanol (25.0 mg/g) and higher than those with water (18.6 mg/g) or ethanol (13.2 mg/g) at their boiling points.	(Kim et al., 2010)
8	MAE	Water	Fruit peels	The best condition was achieved at 1 min, 80 °C and 300 W.	The highest amount of antioxidant activity and TPC yield were observed at 61.15 ± 0.93% and 102.60 ± 1.17 mg GAE/g dry weight, respectively	(Alara et al., 2019)
9	MAE	Ethanol	Fruit pulp	Optimum extraction was achieved with 65% ethanol, in 1 min under 30% microwave power, and a 1:12 sample solvent ratio.	Optimum extraction yielded a TPC and antioxidant activity of 62.79 ± 0.74 mg GAE/g powder and 30.48 ± 0.32%, respectively. MAE showed better selectivity in extracting polar compounds compared to the conventional methods	(Handayani et al., 2020)
10	IL-MAE	$[BMIM]BF_4$	Fruit pulp	Optimum extraction parameters were used: 10% microwave power, 2.5 M $[BMIM]BF_4$ as a solvent, 0.01 M KH_2PO_4 as a salt solution, 2.5 min extraction time, and a solvent to sample ratio of 17.5:1	A TPC value of 191.72 ± 1.27 mg GAE/g powder, and radical-scavenging activity of 12.1 ± 0.003% using DPPH were acquired	(Handayani et al., 2021)
11	UAE-NADES	Choline chloride NADES	Fruit pulp	Optimum extraction parameters for *P. macrocarpa* incorporated choline chloride to a lactic acid ratio of 1:4 with 50% water at 20 min	The extract showed 65.25 mg GAE/g powder of TPC and antioxidant activity of 26.45 ± 0.02%	(Handayani et al., 2020)

$[BMIM]BF_4$- 1-Butyl-3-methylimidazolium tetrafluoroborate; CO_2-Carbon dioxide; DPPH-1,1-diphenyl-2-picrylhydrazyl; GAE-Gallic acid equivalent; HCl-Hydrochloric acid; IC_{50}-Inhibition concentration at 50%; IL-MAE- Ionic liquid-microwave-assisted extraction; KH_2PO_4-Potassium dihydrogen phosphate; MAE- Microwave-assisted extraction; PLE- Pressurized liquid extraction; SFE- Supercritical fluid extraction; TPC-Total phenolic content; UAE-NADES- Natural deep eutectic solvent-ultrasonic-assisted extraction.

8. Green solvent

8.1. Supercritical fluid

A supercritical fluid is the first generation of environmentally friendly or green solvent (Choi and Verpoorte, 2019). It is a substance above its critical pressure and temperature and has characteristics of both gas and liquid. Compared to liquid, supercritical fluid offers superior transport characteristics through solid materials due to its low viscosity and relatively rapid diffusion rate. Additionally, modifying the pressure and temperature can alter the properties of supercritical fluid transport. The high solvation power of supercritical fluids may result in a high selectivity with an excellent extraction yield (Jornitz et al., 2011; Mussatto, 2015). Additionally, CO_2 can be conveniently separated from the extract to obtain a solvent-free extract since it becomes gas at an ambient temperature. However, supercritical CO_2 is non-polar, making it less efficient to extract polar components from plant materials (Abhari and Mousavi Khaneghah, 2020; Al Jitan et al., 2018; Lorenzo et al., 2020). Fatty acids (Bitencourt et al., 2014), phytosterols (Narváez-Cuenca et al., 2020), carotenoids (Patel et al., 2019), triglycerides (Chen et al., 2010), and tocopherols (Lorenzo et al., 2020; Vardanega et al., 2019) are among the most commonly obtained compounds by using supercritical CO_2.

8.2. Ionic liquid

The ionic liquid is salt with a melting point below 100 °C (Bernardino and Ribeiro, 2022). At temperatures below 100 °C, it consists of an organic cation (e.g., imidazolium, pyrrolidinium,

pyridinium tetraalkyl ammonium, and tetraalkyl phosphonium) (Ahmad et al., 2017) and an organic or inorganic anion (e.g., bromide, chloride, hexafluorophosphate, and tetrafluoroborate) (Ahmad et al., 2017; Wang et al., 2009). The unique properties of this type of solvent include tunable viscosity, excellent chemical and thermal stability, non-flammability, low vapor pressure, and favorable solvating properties for a wide variety of polar and non-polar compounds (Dai et al., 2013; Green and Long, 2009; Tang et al., 2012; Wang et al., 2009). Nonetheless, previously reported data revealed that ionic liquid is cost-ineffective and may negatively impact the environment due to its relatively high toxicity and low biodegradability (Bubalo et al., 2017; Häckl and Kunz, 2018).

8.3. Deep eutectic solvent

Additionally, deep eutectic solvents (DESs) may be an alternative to conventional organic solvents. The synthesis of DESs is simple, requires just stirring at ambient temperature or heating to 100 °C, and is relatively inexpensive compared to the synthesis of ionic liquids (Häckl and Kunz, 2018). It comprises a combination of solid chemicals that transform into liquids under specific conditions (Dai et al., 2013). In terms of physical properties, they are similar. However, their chemical properties are significantly different, where DESs can donate and accept protons and electrons, which allow them to form hydrogen bonds. Conversely, ionic liquids are characterised by the formation of strong ionic bonds (Bubalo et al., 2017). They are referred as natural deep eutectic solvents (NADES) when each component that makes up the DES is natural, such as amino acids, organic acids, organic bases, and sugar (Vanda et al., 2018). Both DESs and NADESs are relatively non-toxic compared to the majority of organic solvents, and NADESs are ‘‘greener” than DESs (Yang, 2019).

Recent conventional and modern extraction techniques utilising green solvents to obtain *P. macrocarpa* extracts and compounds were summed up in Table 3.

9. Review perspective

The antioxidant capacity of *P. macrocarpa* has been well studied with the incorporation of modern extraction approaches to get better yields and stronger activity. Compared to the other pharmacological studies, its antioxidant activity was assessed with the utilisations of MAE and UAE that enabled high yields of flavonoids and phenolic compounds. Of the pharmacological effects exerted by *P. macrocarpa*, a good proportion of anti-proliferative studies has allowed the identification of a few anti-cancer compounds that include benzophenone glucopyranosides and polyphenols from fruits and nutshells. It is noteworthy that flavonoids from *P. macrocarpa* contribute to endometriosis inhibition and vasorelaxant activity as well, apart from their known antioxidant and anti-inflammatory properties. Djati and the team took a further step to study its anti-cancer activity using an in-silico study (Djati, 2021). Additional in-silico work on *P. macrocarpa* involving molecular docking and molecular dynamics in the future would be imperative to predict the molecular mechanisms of the plant.

The toxicity studies have proved that the leaves and fruits of *P. macrocarpa* are safe for consumption based on the toxic dose level, but further studies are needed to measure the toxicity for other plant parts. As mentioned before, the seeds of *P. macrocarpa* are considered the most toxic part of the plant, despite its potent antioxidant effect. A study of a proper treatment adopting advanced processing technology to lower its toxicity is necessary. In traditional Chinese medicine, Fuzi (*Aconitum carmichaelii* Debeaux.) is processed by preserving Fuzi with bile prior to fire and water processing to reduce aconitine and other toxic components (Wang et al., 2023). It is noteworthy to see if the seeds of *P. macrocarpa* can be treated to lower toxicity, which may increase the medicinal value of this plant.

Concerning the phytoconstituents of *P. macrocarpa*, it would be noteworthy to observe if the bioactive components especially benzophenones exhibit other pharmacological effects as well besides their reported activities. Additionally, the plant extracts were broadly used instead of the plant compounds. More bioactive compound isolation is recommended to increase the understanding of their pharmacological values. Phytochemical studies of different plant parts may give a new insight into the distributions of the phytoconstituents and their activity strength.

The modern extraction techniques of *P. macrocarpa* have incorporated SFE, PLE, MAE, and UAE with the utilisation of green solvents such as NADES and supercritical fluid. SFE is effective at acquiring a good quality essential oil, while PLE can obtain a good yield of mangiferin using subcritical water. The PLE technique is consistent with the need not only to reduce solvent toxicity but also to become relevant to the traditional uses of *P. macrocarpa* using water extract. MAE and UAE are more suitable for obtaining phenolic compounds exerting antioxidant activity that may also save more energy. Reflux and Soxhlet extractions are utilised to separate flavonoids and other antioxidant compounds conventionally.

Handayani et al. (2020) compared the yields obtained from MAE, Soxhlet, and reflux techniques that showed higher TPC when using MAE. MAE using ethanol also proved to work as efficient as UAE-NADES in term of TPC. It clearly ascertains that MAE and UAE would be the appropriate alternatives over conventional techniques for phenolic compounds extraction. Despite the outcomes, it would be beneficial to see if the team could perform the ‘green’ comparison between MAE using $[BMIM]BF_4$ (Handayani et al., 2021) and UAE using NADES (Handayani et al., 2020) in a single study. However, the optimisation of the MAE technique to obtain high TPC clearly has been improved, substituting the organic solvent for a greener solvent.

Kim et al. (2010) evidently compared the mangiferin yield using different extraction solvents and methods. The study showed that SFE yielded 0% mangiferin due to its polar nature that is mainly insoluble in the non-polar supercritical CO_2 medium. But mangiferin can be efficiently extracted with an increase in temperature when using subcritical water, which is almost close to the extraction yield using methanol and higher than those using water and ethanol at their boiling points. The study was also supported by Alara and team, suggesting subcritical water is a suitable solvent toward a greener approach to extract mangiferin. In short, the uses of modern approaches and green solvents are deemed to be slowly increasing. It would be desired to see if these green techniques are also applied to plant parts other than fruits. Rather than targeting specific groups of bioactive constituents using modern approaches, it would be valuable to obtain the whole plant extract, which will then be subjected to various biological activity studies (other than antioxidant effect) and compound isolation.

10. Conclusion

P. macrocarpa exhibits various biological activities, with extensive toxicity and anti-proliferative studies performed to discover its potential as an alternative therapeutic drug. The therapeutic effects of *P. macrocarpa* include antioxidant, anti-microbial, anti-diabetic, anti-hypercholesterolemic, anti-angiogenic, anti-cancer, anti-hypertensive, wound healing, analgesic, anti-inflammatory, and aphrodisiac properties. Its molecular mechanisms are attributed to its abilities to inhibit α-glucosidase, increase NFKB

transcription level, upregulate proteins that induce apoptosis, inhibit Y-79 gene transcription, upregulate Caspacase-3, increase TGF-B1, TNF- α, and collagen formation, elevate SOD and CAT levels but reduce MDA level, and improve PGE2 level. Therefore, *P. macrocarpa* is likely to be a promising functional food or a health supplement; therefore, advancing its capacity into clinical trials is recommended.

P. macrocarpa has been involved with diverse extraction techniques that include both conventional and modern methods. However, the utilisation of conventional methods is still demanded due to their low cost. Especially its fruits and leaves, *P. macrocarpa* has been vastly examined for its potential in the form of extracts. However, the bioactive principles are somewhat undetermined due to the lack of compound isolation. Future research to address these gaps is essential to exploit the medicinal values of *P. macrocarpa* effectively. This review highlighted modern extraction techniques that could be employed as a guide for multi-scale extraction, thereby facilitating the exploration of new bioactive compounds and drug discovery.

CRediT authorship contribution statement

Rosliza Ahmad: Writing – original draft, Visualization. **Mohd Khairul Nizam Mazlan:** Writing – original draft, Visualization. **Amir Firdaus Abdul Aziz:** Writing – original draft, Visualization. **Amirah Mohd Gazzali:** Writing – review & editing. **Mira Syahfriena Amir Rawa:** Writing – original draft, Visualization. **Habibah A. Wahab:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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