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Peperomia pellucida (L.) Kunth herbs: A comprehensive review on phytochemical, pharmacological, extraction engineering development, and economic promising perspectives

Islamudin Ahmad[1*], Baso Didik Hikmawan[1], Riski Sulistiarini[1], Abdul Mun'im[2]

[1]Department of Pharmaceutical Science and the Pharmaceutical Research and Development Laboratory, Faculty of Pharmacy, Universitas Mulawarman, Samarinda, Indonesia.
[2]Department of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Indonesia, Depok, Indonesia.

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ABSTRACT

Peperomia pellucida (L.) Kunth belongs to the Piperaceae family and has long been used empirically as a traditional medicine by the communities of Indonesia, the Philippines, India, Nigeria, Brazil, and other countries. The herb of *P. pellucida* has chemical constituents with potential activities such as analgesic, antipyretic, anti-inflammatory, antidiabetic, antigout, antihypertensive (angiotensin-converting enzyme inhibitors), antioxidant, and antibacterial, as well as activities such as a sunscreen. Unfortunately, this plant has not been utilized as a source of raw material for herbal medicines commercially. So far, this plant has been considered a weed by local farmers (mainly oil palm plantations in Indonesia). This narrative review aims to comprehensively overview *P. pellucida* herbs as a potential natural resource for herbal medicine by looking from different perspectives. This review article highlights some perspectives on this herb, including plant description and origins, phytochemistry, pharmacology and toxicology, extraction technique development, and its prospect as an economic natural resource of herbal medicines.

INTRODUCTION

Peperomia pellucida (L.) Kunth is a herbaceous plant that belongs to the Piperaceae family. In many countries, it has long been used traditionally to treat a wide range of diseases, including diabetes, muscle pain, aches, common cold, conjunctivitis, abscesses, boils and skin wounds, fever, headache, proteinuria, and convulsions, and it is also used as a diuretic and to lower blood cholesterol level, as well as its use in the Ayurvedic system of medicines. The plant is commonly found in several Asian and South American countries, is easy to find in yards and humid areas, and usually grows wild (Bojo *et al.*, 1994; Majumder, 2011; Susilawati *et al.*, 2017).

**Corresponding Author*
Islamudin Ahmad, Department of Pharmaceutical Science and the Pharmaceutical Research and Development Laboratory, Faculty of Pharmacy, Universitas Mulawarman, Samarinda, Indonesia.
E-mail: islamudinahmad @ farmasi.unmul.ac.id

Many biological activity studies have been successfully conducted to reveal the potential of *P. pellucida* in treating diseases, including antihypertensive, anti-inflammatory, antipyretic, analgesic, antibacterial, antiamoeba, antioxidant, gastroprotective, and other pharmacological activities (Ahmad *et al.*, 2019; Fakayode *et al.*, 2021; Idris *et al.*, 2016; Ng *et al.*, 2021; Rojas-Martínez *et al.*, 2013; Uwaya *et al.*, 2021). The results are also supported by the fact that this plant contains phytochemical compounds responsible for pharmacological activities. For instance, pellucidin A, isolated from *P. pellucida*, inhibits the angiotensin-converting enzyme (ACE), and patuloside A exhibits antibacterial activity. The herbs are also believed to possess polyphenolics, flavonoids, fatty acids, volatile oils, and other bioactive constituents (Ahmad *et al.*, 2019; Heinrich *et al.*, 1998; Khan *et al.*, 2010; Usman and Ismaeel, 2020).

Peperomia pellucida has great potential as it has been used empirically to treat diseases and is scientifically proven to possess biological activities related to its utilization in traditional medicine. However, currently, there is still limited data available about the use of this herb as a raw material for commercial herbal medicinal products. The plant is even considered a weed by some local farmers.

Recently, scientists have studied the development of the *P. pellucida* extraction method. These studies generally focus on increasing the yield obtained from the extraction process with a green chemistry approach. The results suggest that applying the suitable extraction method combined with optimal extraction parameters can produce more yields than those conventional techniques (Ahmad *et al.*, 2017a, 2017c; Gomes *et al.*, 2022; Hashim *et al.*, 2020; Mun'im *et al.*, 2017). Thus, it is possible to be applied to industrial-scale production. This current review aims to provide up-to-date information regarding the progress of research on *P. pellucida* herbs in terms of their phytochemical, pharmacological, and toxicological properties, as well as developments in the extraction technique. In addition, it also discussed the economic prospects of this plant.

MATERIALS AND METHOD

A literature search was conducted between mid-2021 and mid-2022 to find all published papers on *P. pellucida* L. Kunth In electronic databases such as Google Scholar, Directory of Open Access Journals, PubMed, and ScienceDirect. All the data included in the review were articles written in English.

DISCUSSION

Plant description and origins

Taxonomy

Kingdom: Plants
Subkingdom: Tracheobionta – vascular plants
Superdivision: Spermatophyta – seed plants
Division class: Magnoliophyta – flowering plants
Class: Magnoliopsida – Dicotyledons
Subclass: Magnoliidae
Order: Piperales
Family: Piperaceae
Genus: *Peperomia*
Species: *Peperomia pellucida* (L.) Kunth
(Anonim, 2015; Majumder, 2011)

Morphology

The *P. pellucida* herb (Fig. 1) is a plant that usually grows wild in damp clusters. This plant is easy to find in gardens and yards and on roadsides and edges of ditches and other watery places. This herb flowers throughout the year and is an annular herb; the leaves are bare and light green on the upper surface and green and white on the lower surface, thinly fleshy, ovoid or oval, with an area of +1.5–4 (−5) cm, width 1–3.3 cm, with fibrous roots, pale green translucent stems, erect or ascending, with a height of +15–45 cm (Abere and Okpalaonyagu, 2015; Majumder, 2012; Rahman *et al.*, 2014).

Habitat

This plant is widespread in South America and many Asian countries and grows at about 400 m above sea level as a weed along roadsides, in moist soil and in shady places around houses that are usually in clusters, and in plantations (mainly oil palm plantations in Indonesia). Most of these plants are in the tropics (Majumder, 2011; Rahman *et al.*, 2014). The herb of *P. pellucida* is widely distributed in many American and South Asian countries (Arrigoni-Blank *et al.*, 2004; Ho *et al.*, 2022).

Figure 1. *Peperomia pellucida* (L) Kunth in natural habitat.

Empirical uses

Ethnobotanical studies on the *P. pellucida* herb show that every part of this plant has long been used as a medicinal plant. Empirically, the herb is used by Indonesians to treat headaches accompanied by fever, and the leaves extract is used to treat stomach pain, gout, and hypertension (Heyne, 1988). In Bolivia, all parts of this plant are used to stop bleeding. The herbaceous root of *P. pellucida* is used to treat fever and wounds. In northeastern Brazil, this herb is used for blood pressure and lowering cholesterol levels, and this plant is used in religious activities (de Albuquerque *et al.*, 2007). In Guyana and the Amazon, it acts as a cough medicine, emollient, and diuretic and can be used to treat proteinuria (Nwokocha *et al.*, 2012). In the Philippines, the decoction of this plant is used to reduce uric acid levels and kidney disorders. In various areas of Bangladesh, the leaves of this plant are used by local people as a treatment for mental illness. In South America, the fresh juice of the stems and leaves of this plant can be used as a treatment for inflammation of the eyes (Majumder, 2011).

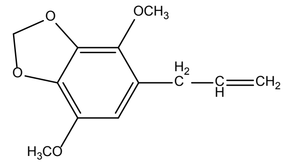
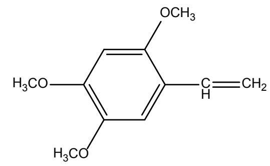
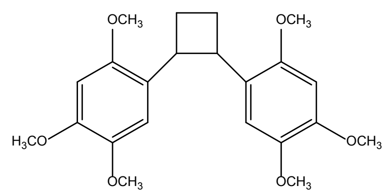
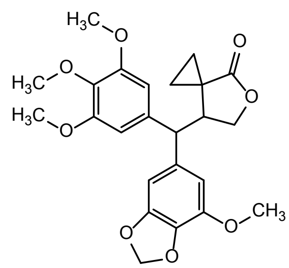
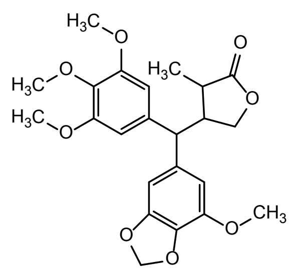
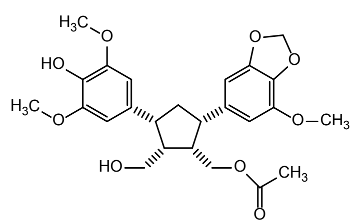
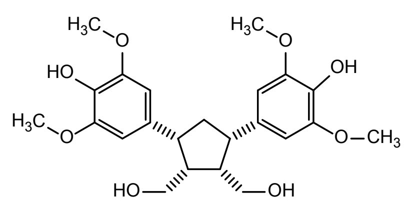
Phytochemistry

Peperomia pellucida plants have been known to have various types of chemical constituents, including amino acids, protein carbohydrates, minerals consisting of sodium, calcium, and iron (Ooi *et al.*, 2012), tannins, saponins, phenols, steroids, terpenoids, amino acids, alkaloids (Abere *et al.*, 2012; Abere and Okpalaonyagu, 2015; de Albuquerque *et al.*, 2007; Awe *et al.*, 2013; Gini and Jothi, 2013; Gomes *et al.*, 2022; Majumder and Majumder, 2013; Mengome *et al.*, 2010; Pappachen and Chacko, 2013), essential oils (Manalo *et al.*, 1983; Usman and Ismaeel, 2020; Verma *et al.*, 2015), and fatty acid (linoleic acid and α-linoleic acid) (Heinrich *et al.*, 1998). Some studies have succeeded in isolating and identifying the chemical compounds contained in the *P. pellucida* herb, and these studies have been carried out since 1983, as presented in Table 1.

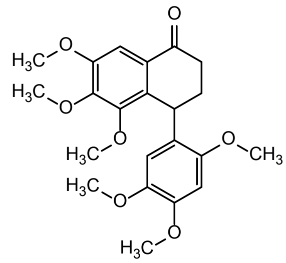
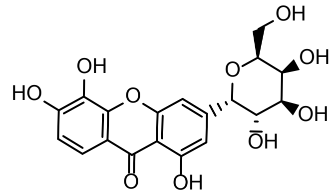
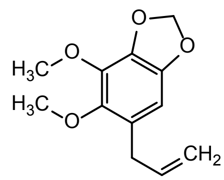
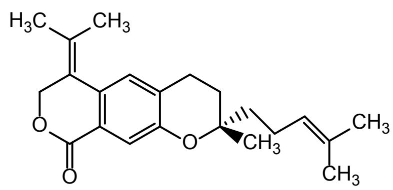
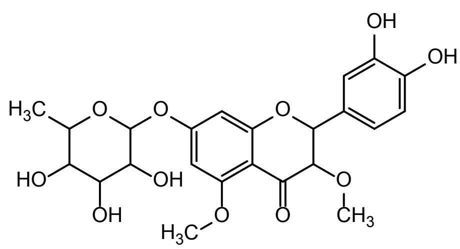
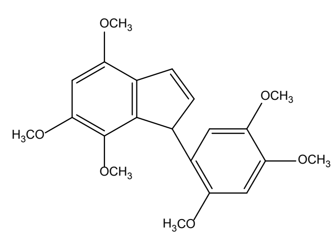
Pharmacology activity

A comprehensive study of pharmacological activities of *P. pellucida* has been discussed by Kartika *et al.* (2016). The

Table 1. Isolated bioactive compounds from *P. pellucida*.

Compounds	Structure formula	Ref.
4,7-Dimethoxy-5-(2-propenyl)-1,3-benzodioxole		Manalo *et al.* (1983)
2,4,5-Trimethoxy styrene		Manalo *et al.* (1983)
1,2-Bis(2,4,5-trimethoxyphenyl)-cyclobutane		Ahmad *et al.* (2019); Bayma *et al.* (2000)
7-((7-Methoxybenzo[d][1,3]dioxol-5-yl)(3,4,5-trimethoxyphenyl) methyl)-5-oxaspiro[2.4]heptan-4-one (secolignan)		Xu *et al.* (2006)
4-((7-Methoxybenzo[d][1,3]dioxol-5- yl)(3,4,5-trimethoxyphenyl) methyl)-3-methyldihydrofuran-2(3H)-one (secolignan)		Xu *et al.* (2006)
((1S,2R,3R,5S)-3-(4-Hydroxy-3,5-dimethoxyphenyl)-2-(hydroxymethyl)-5-(7-methoxybenzo[d][1,3]dioxol-5-yl)cyclopentyl) methyl acetate (tetrahydrofuran lignin)		Xu *et al.* (2006)
((1R,2S,3S,5R)-3,5-Bis(4-hydroxy-3,5-dimethoxyphenyl) cyclopentane-1,2-diyl)bis(methylene) diacetate (tetrahydrofuran lignin)		Xu *et al.* (2006)

Continued

Compounds	**Structure formula**	**Ref.**
5,6,7-Trimethoxy-4-(2,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one (methoxylated dihydronaphthalenone)		Xu *et al.* (2006)
1,5,6-Trihydroxy-3-((2S,3S,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)-9H-xanthen-9-one (Patuloside A)		Khan *et al.* (2010)
6-Allyl-4,5-dimethoxybenzo[d][1,3]dioxole (dillapiole)		Rojas-Martínez *et al.* (2013)
(S)-2-Methyl-2-(4-methylpent-3-en-1-yl)-6-(propan-2-ylidene)-3,4,6,7-tetrahydropyrano[4,3-g]chromen-9(2H)-one (chromene)		Susilawati *et al.* (2017)
2-(3,4-Dihydroxyphenyl)-3,5-dimethoxy-7-((3,4,5-trihydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)chroman-4-one (quercetin)		Kurniawan *et al.* (2016)
2,3,5-Trimethoxy-9-(12,14,15-trimethoxybenzyl)-1I-indene		Ahmad *et al.* (2019)

review describes *P. pellucida* herbs (in the form of pure compound isolates, fractions, or extracts) for their pharmacological activities such as cytotoxic, lipase inhibitory, fibrinolytic, and thrombolytic, hypotensive, gastroprotective, depressant, burn healing, analgesic, antioxidant, antipyretic, anti-inflammatory, antiosteoporotic, antidiarrheal, antisickling, antimicrobial, antihyperuricemic, and antihyperglycemic. However, in this subsection, we discuss some of the updated potential activities in detail.

Antihypertension

Peperomia pellucida herb has activity as an antihypertensive, mainly as an ACE inhibitor, based on several studies that have been reported (Ahmad *et al.*, 2019; Kurniawan *et al.*, 2016; Saputri *et al.*, 2021, 2015). An antihypertensive activity assay has been reported by Saputri *et al.* (2015), where the ethyl acetate fraction of the *P. pellucida* herb extract has activity as an ACE inhibitor (*in vitro* method) with an IC_{50} value of 7.17 µg/ml, and an *in vivo* assay method has also been carried out which shows that at the dose of 50 mg/kg body weight (BW) it has an ACE inhibitory effect similar to that of captopril. These results align with the research conducted by Nwokocha *et al.* (2012). The extract of the *P. pellucida* herb exhibited dose-dependent antihypertensive, vasodilating, and bradycardic effects by targeting nitric oxide-dependent signaling pathways in mice. ACE inhibitory compounds from the *P. pellucida* herb have been isolated and identified, including quercetin (Kurniawan *et al.*, 2016), pellucidin A, and 2,3,5-trimethoxy-9-(12,14,15-trimethoxybenzyl)-1H-indene (Ahmad *et al.*, 2019). In addition, an *in silico* molecular docking study has also been carried out on several other phenylpropanoid compounds against the ACE receptor, showing that most of these compounds have strong binding energy interactions with the receptor (Ahmad *et al.*, 2019).

Anti-inflammatory, antipyretic, and analgesic

The aqueous extract of the *P. pellucida* herb was tested as an anti-inflammatory (carrageenan and arachidonic acid induction method) and analgesic (acetic acid induction and heat induction using hot plates) in rats and mice orally, with anti-inflammatory activity at doses of 200 and 400 mg/kg, respectively, based on the effect of prostaglandin synthesis (Arrigoni-Blank *et al.*, 2004). In addition, anti-inflammatory activity has also been demonstrated by Ng *et al.* (2021), who showed that the fermentation and drying processes affected the effectiveness of the anti-inflammatory activity of the *P. pellucida* herb extracts, where the anti-inflammatory potential of *P. pellucida* increased significantly with the drying process compared to the results of the fermentation process. Furthermore, the fresh and dried leaf extracts of *P. pellucida* exhibited various antioxidant and anti-inflammatory potentials comparable to those obtained in the standard (Fakayode *et al.*, 2021).

The methanol extract of the *P. pellucida* herb was administered orally at a dose range of 70–210 mg/kg and showed significant analgesic activity in mice induced with acetic acid (Aziba *et al.*, 2001; Sheikh *et al.*, 2013). The analgesic activity dose with the highest activity at a dose of 400 mg/kg is induced with acetic acid, and a dose of 100 mg/kg is the best dose in the heat induction method using a hot plate (Arrigoni-Blank *et al.*, 2004).

Antibacterial and antiamoeba

The n-butanol fraction of the *P. pellucida* herb extract has antibacterial activity (Khan and Omoloso, 2002), and there are also reported antibacterial tests on four Gram-positive bacteria (*Bacillus megaterium, Bacillus subtilis, Streptococcus β-haemolyticus,* and *Staphylococcus aureus*) and six Gram-negative bacteria (*Escherichia coli, Salmonella typhi, Pseudomonas aeruginosa, Shigella dysenteriae, Shigella sonnei,* and *Shigella flexneri*), with minimal inhibitory concentration (MIC) values against all these bacteria in the concentration range from 8 to 64 g/ml, and antifungal tests on *Aspergillus flavus* and *Candida albicans* (Khan *et al.*, 2010). *Peperomia pellucida* has broad-spectrum antimicrobial activity on *Penicillium notatum*, *Aspergillus niger*, *Rhizopus stolon*, *Candida albicans*, *Salmonella typhi*, *Klebsiella pneumonae*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* (Oloyede *et al.*, 2011), *Vibrio* sp., *Flavobacterium* sp., and *Edwardsiella tarda* (Wei *et al.*, 2011). Idris *et al.* (2016) also proved the antibacterial activity of the n-hexane extract of *P. pellucida* herb with a MIC value of 25 µg/ml. Khan *et al.* (2010) succeeded in isolating and identifying the compound patuloside A, which has antibacterial activity, from this herb. Another study revealed that *P. pellucida* has an antiamoebic activity where the methanol fraction can damage the morphology and change the structure of *Acanthamoeba* cysts (IC_{50} = 29.28% ± 3.64%) detected using toluidine dye and observed using a light microscope (Sangsuwon *et al.*, 2015).

Antidiabetic and antioxidant

The antidiabetic activity of the *P. pellucida* extract was observed in diabetic rats where doses of 10% and 20% w/w given for 6 days can reduce blood glucose levels (Hamzah *et al.*, 2012). Sheikh *et al.* (2013) also proved the hypoglycemic effect of the ethyl acetate extract of the herbs at a dose of 300 mg/kg *in vivo*. Then, Susilawati *et al.* (2017) isolated a new active compound (8,9-dimethoxy ellagic acid) from the plant, which exhibited antidiabetic properties in experimental animals.

On the other hand, the antioxidant properties of the *P. pellucida* herbs have been widely studied (Adhitia *et al.*, 2017; Mun'im *et al.*, 2017; Oloyede *et al.*, 2011; Uwaya *et al.*, 2021; Wei *et al.*, 2011; Yunarto *et al.*, 2018). The methanol extract of the herbs possesses higher free radical scavenging activity than petroleum ether and chloroform extract (Uwaya *et al.*, 2021; Wei *et al.*, 2011). The high antioxidant activity of the plant at low concentrations indicates that it could be beneficial for treating ailments resulting from oxidative stress (Oloyede *et al.*, 2011). Meanwhile, the ethanol extract has antioxidant activity with an IC_{50} value of 32.94 µg/ml (Yunarto *et al.*, 2018). This result is relatively weaker than the methanol extract. However, there was an increase in the activity of the ethanol extract combined with the microwave-assisted extraction (MAE) method (Mun'im *et al.*, 2017) and the effect of gamma irradiation (Yusuf *et al.*, 2017).

Other pharmacology activities

Scientists also successfully revealed the potency of the *P. pellucida* herbs in other pharmacological activities, including gastroprotection, antimalaria, ultraviolet (UV) filter, and antihyperuricemia. Dillapiole, a chemical compound isolated from these herbs, showed gastroprotective activity in gastric ulcer experiment rats (Rojas-Martínez *et al.*, 2013). The study of antimalaria properties on *P. pellucida* fractions (n-hexane, ethyl acetate, and methanol) suggested that all tested fractions were active against malaria culture with IC_{50} of 12.80, 2.90, and 10.74 µg/ml, respectively (Bialangi *et al.*, 2016). Besides that, this plant also possesses UV protection activity (Ahmad, 2015). The ethanolic extract of *P. pellucida* demonstrated antihyperuricemia in rats and mice (Tarigan *et al.*, 2012). In addition to the pharmacological activity of *P. pellucida* herbs, it has also been reported that the extracts are rich in carbohydrates, proteins, and total ash content (31.22%), whose composition consists of main elements including sodium, calcium, and iron. This indicates that the plant can benefit humans in terms of protein and energy supplements (Ooi *et al.*, 2012). Moreover, the administration of the *P. pellucida* ethanol extract at a certain dose (200 mg/kg) can stimulate bone regeneration in the fractured part (Ngueguim *et al.*, 2013).

Toxicity activity

In some countries, *P. pellucida* has been eaten as salads, cooked as greens, and brewed as tea by the local communities (Wakhidah *et al.*, 2020). Moreover, the plant has historical data about its utilization as a herb to treat some diseases. This implies that this plant is safe to be consumed as food for humans. Several toxicological studies of this herb have been carried out to evaluate the safety of the extracts. An acute toxicity test on mice (*Mus musculus*) reported that the lethal dose 50% (LD_{50}) of the herb extract was 5,000 mg/kg BW, which suggested that the extract was relatively safe or exhibited low toxicity (Abere *et al.*, 2012; Arrigoni-Blank *et al.*, 2004). Similarly, acute toxicity tests performed by Waty *et al.* (2017) found that the LD_{50} of the methanol extract of the plant was more significant than 4,000 mg/kg BW in Deutsch Denken Yoken mice and there was no sign of toxicity on the skin and hair, respiration system, defecation, feed intake, and behavior. In addition, the highest tested dose (4,000 mg/kg BW) did not cause mortality. The safety of the *P. pellucida* herbs is also supported by the findings of a histopathological study on white rats, which statistically declared that the tested extract was nontoxic in the biological system tested (Beltran-Be *et al.*, 2013). Cytotoxicity effects on human embryonic kidney 293 cells (HEK 293) have also been observed by Pappachen and Chacko (2013). The results showed that there was no sign of toxicity at the lowest (6.25 µg/ml) to the highest (100 µg/ml) tested dose. Further research was done by Hsuuw and Chan (2015) to distinguish the apoptotic effects of dillapiole isolated from *P. pellucida* on rats' oocyte maturation, *in vitro* fertilization (IVF), and development before and after implantation. Dillapiole significantly impaired rat oocyte maturation, lowered the IVF rate, and inhibited the development of embryos in tested animals. The findings implied that *P. pellucida*-based products are not suggested for pregnant women and need further research. *In vitro* toxicity tests have been carried out on monkey kidney cells with an lethal concentration 50% of 70 µg/ml (Mengome *et al.*, 2010).

Extraction technique development

Designing environmentally friendly and sustainable natural product extraction processes is a research topic currently attracting attention in the interdisciplinary fields of applied pharmaceutical sciences, chemistry, biology, and technology (Ahmad *et al.*, 2017a; Mediani *et al.*, 2022; Mun'im *et al.*, 2017). Three main approaches have been identified to design and demonstrate green extraction on a laboratory and industrial scale to reach an optimal consumption of raw materials, solvents, and energy: (1) improving and optimizing existing processes; (2) using nondedicated equipment; and (3) innovation in processes and procedures as well as the discovery of alternative solvents (Chemat *et al.*, 2012).

The application of "green extraction" on the *P. pellucida* herb has been reported in a few studies. Gomes *et al.* (2022) extracted this herb with 99.8% ethanol using indirect ultrasounds assisted technique for 40 minutes to obtain crude extract. The extraction time was relatively low compared to the conventional methods that usually need longer time (Ahmad *et al*., 2017b).

Moreover, ultrasound-assisted extraction does not involve high temperatures that can cause degradation of desired bioactive compounds in the extracts, decreasing the bioactivity (Kumar *et al.*, 2021). Therefore, using ultrasounds to extract thermolabile compounds in *P. pellucida* could be an alternative method for the chemical, cosmetics, and pharmaceutical industries to obtain the compounds of interest.

Another technique studied for extracting the *P. pellucida* herbs was MAE. Extraction of phenolic constituents from this plant using MAE with solvent 95% ethanol was carried out to determine the impact of extraction duration (5–25 minutes) and temperature (65°C–145°C) on the extraction yield and the total phenolic content (TPC). The optimum condition reached 15 minutes at 145°C (Hashim *et al.*, 2020). A similar study was conducted by Mun'im *et al.* (2017). They investigated the efficiency of some parameters, including sample ratio, extraction time, ethanol concentration, and microwave power for extracting phenolic and flavonoid compounds. The ideal MAE parameters for TPC [49.78 mg gallic acid equivalent (GAE)/g extract] were 80% ethanol as solvent, 1:12 solid-to-solvent ratio, extraction time of 2 minutes, and microwave power of 30% watts, while for total flavonoid content these were 80% ethanol as solvent, 1:12 solid-to-solvent ratio, time of 2 minutes, and microwave power of 70% watts.

In terms of solvent optimization, ionic liquid-based microwave-assisted methods (IL-MAE) were studied to extract the *P. pellucida* herbs. The use of 1-ethyl-3-methylimidazolium bromide (EMIMBr) as a solvent for attracting optimum polyphenolic compounds has been demonstrated by Ahmad *et al.* (2017c). The study showed that using EMIMBr MAE on the following parameters, a microwave power of 30% watts, 10 minutes of extraction time, 14:1 (ml/g) liquid-to-solid ratio, and EMIMBr concentration of 0.7 mol/l yielded the highest TPC (13.750 µg GAE/g) compared to conventional organic solvent *n*-hexane and ethyl acetate (3.408 and 7.823 µg GAE/g, respectively). The application of ionic liquids, including 1-butyl-3-methyl imidazolium bromide ([BMIM]Br) and 1-butyl-3-methyl imidazolium chloride ([BMIM]Cl), on polyphenolic compounds extraction from the *P. pellucida* herbs was also demonstrated. The yield of TPC obtained using [BMIM]Cl as solvent was 18.287 µg GAE/g with parameter concentration of solvent 0.7 mol/l, 14 ml/l liquid–solid ratio, and 270-watt microwave power for 10 minutes. For the [BMIM]Br solvent, the highest TPC measurement was 15.734 µg GAE/g obtained from parameter concentration of solvent 0.7 mol/l, 14 ml/l liquid–solid ratio, and 270-watt microwave power for 15 minutes (Ahmad *et al*., 2017c).

Metabolite profiling analysis of the *P. pellucida* herbs was conducted by comparing the metabolite profile of extracts obtained from IL-MAE and maceration with 1-butyl-3-methylimidazolium tetrafluoroborate ($[BMIM]BF_4$) and ethyl acetate as a solvent, respectively. The total ion chromatogram from ultra high-performance liquid chromatography with quadrupole time-of-flight mass spectrometry/mass spectrometry suggested that there were differences between organic and ionic liquid solvents $[BMIM]BF_4$ in their metabolite profiles (Ahmad *et al.*, 2018). This may imply that using ionic liquids such as $[BMIM]BF_4$ can be opted to attract a class of compounds like polyphenols or to get some kinds of enriched *P. pellucida* extract.

Modern extraction techniques like MAE can efficiently extract valuable phytochemicals. MAE is thought to be more environmentally friendly and consumes less time and solvent since there is minimal to no carbon dioxide (CO_2) emission. This method has successfully demonstrated the extraction of flavonoid and phenolic compounds from the *P. pellucida* herbs and other plants (Ahmad *et al.*, 2018; Chemat *et al.*, 2019; Zhang *et al.*, 2018). Dipole rotation (reversal of dipoles) and ionic conduction (movement of charged ions present in the solute and solvent) are the two methods by which MAE transfers energy (Kubrakova and Toropchenova, 2008). In terms of microwave extraction, polar solvents are thought to be more efficient in absorbing electrical energy. The effectiveness of a solvent in a microwave environment, however, depends on the dielectric constant and the dissipation factor, both of which are expected to be high for solvents used to effectively influence microwaves. The efficiency of the process is further increased by the careful selection of an appropriate solvent to interact with the metabolite constituents to be extracted. Microwave energy absorbed by biological materials causes the build-up of pressure within the cellular material, eventually leading to the splitting of the cellular structure with the release of its chemical constituents (Kratchanova *et al.*, 2004; Routray and Orsat, 2012).

Prospect and economic promising

Peperomia pellucida-based medicines have been used empirically by the communities in Indonesia, Bolivia, Brazil, Guyana, the Amazon, the Philippines, Bangladesh, and South America to treat many kinds of diseases (de Albuquerque *et al.*, 2007; Heyne, 1988; Majumder, 2011; Nwokocha *et al.*, 2012). Even though it has great economic potential, there is very limited data available about this plant's commercial products, at least until now. The previous section of this review has described the current development of extraction methods to increase the yield of polyphenolic content and flavonoid content of this herb using IL-MAE. Such a technique has a high possibility of being transferred to an industrial scale. It is because the time, energy use, high extraction yield, small amount of solvent, low economic costs, and eco-friendliness meet the criteria of the green extraction concept.

From the pharmaceutical industry perspective, *P. pellucida* has a high potential to be developed into herbal medicines with indications related to its pharmacological activities, as discussed in the previous section of this review. The most likely product to be produced with the currently available data (effective extraction method, pharmacological activity, and toxicity data) is health supplements. The health supplements could be used as a complementary therapy for hypertension, diabetes, or inflammation patients. Health supplements are regulated as food by the United States Food and Drug Administration, making it more feasible to be manufactured since the regulation for food is not as strict as the regulation for drugs (Commissioner, 2022). However, future development of *P. pellucida* as a herbal medicine should probe deeply into the formulation and clinical data trial so that the herbal medicine could be used in primary healthcare.

Regarding raw material supply, this plant is abundant in nature and is even considered a weed by local farmers. Utilizing this plant as a basic material in herbal medicine has several advantages. Firstly, concerning its nature that it can grow easily, it will not be challenging to cultivate so the reproducibility of the products can be maintained. Secondly, it can be cultivated with several modification methods, from hydroponic techniques, which can overcome the limited land issue, to biotechnology techniques to increase the yield of the compounds of interest. For instance, the polyphenolic content and the volatile oils are the compounds responsible for biological activities in the extract that can be improved by inoculating *P. pellucida* with *Enterobacter asburiae* and *Klebsiella variicola* (Alves *et al.*, 2022). Nevertheless, postharvest management for this plant would be challenging since the herb contains a lot of water, so it is easy to rot if not handled properly.

Interestingly, the Philippine Patent has been granted to the National Integrated Research Program on Medicinal Plants, Institute of Herbal Medicine, the University of the Philippines Manila, for *ulasimang bato*, the local name for *P. pellucida*, as an antihyperuricemic agent. The use of this plant as an antihyperuricemic agent has successfully passed clinical trials phases 1–3, and it is now available for commercial production and ready for public consumption as a medicine (Sanchez, 2020). This initial information rationalizes that the use of *P. pellucida* as a therapeutic agent in the treatment of hyperuricemia and the treatment of other various diseases is very possible.

CONCLUSION

The data presented in the review indicate that the herbs of *P. pellucida* are highly likely to be developed into herbal medicines. The research progress on the developments of extraction techniques for the plant in terms of yield improvement with green extraction approaches raises its chance of being produced on large scale. Combining the right extraction technique with available data on the phytochemical, pharmacology, and toxicity properties of *P. pellucida* could increase the economic value of this plant to become a commercial herbal medicinal product. In addition, utilizing this weed plant as a herbal medicine, apart from increasing self-reliance in terms of drug supply, can also improve the economy of the farmers in the future as well as enhance the value of the plant.

LIST OF ABBREVIATIONS

ACE: Angiotensin-converting enzyme; [BMIM]BF_4: 1-Butyl-3-metylimidazolium tetrafluoroborate; [BMIM]Br: 1-Butyl-3-metylimidazolium bromide; [BMIM]Cl: 1-Butyl-3-methylimidazolium chloride; BW: Body weight; EMIMBr: 1-Ethyl-3-methylimidazolium bromide; GAE: Gallic acid equivalent; IL-MAE: Ionic liquid-based microwave-assisted extraction; IVF: In vitro fertilization; LD_{50}: Lethal dose fifty percent; MAE: Microwave-assisted extraction; MIC: Minimal inhibitory concentration; *P. pellucida*: *Peperomia pellucida* L. Kunth; TPC: Total polyphenolic content; UV: Ultraviolet.

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All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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