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NEW UPDATE: TRADITIONAL USES, PHYTOCHEMICAL, PHARMACOLOGICAL AND TOXICITY REVIEW OF *PEPEROMIA PELLUCIDA* (L.) KUNTH

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Abstract

Peperomia pellucida (L.) Kunth. (Fam. Piperaceae) has been used as traditional medicine worldwide, and some scientific data regarding this plant also exist. This report comprehensively reviews the ethnopharmacological, pharmacological, and toxicological studies of *P. pellucida* (L.) Kunth, as well as studies made regarding its chemical constituents. The pharmacological studies of extracts, fractions, or isolated compounds of this plant show such activities as analgesic, anti-inflammatory, antipyretic, antioxidant, antihyperglicemia, antihyperuricemia, burn healing, depressant effect, gastroprotective, hypotensive, cytotoxic, antimicrobial, antisickling cell, lipase inhibitory, fibrinolytic and thrombolytic, antidiarrhoeal, as well as antiosteoporotic. These activities are induced by the plant's many types of chemical compounds, including Patuloside A, Dillapiolle, and Pachypophyllin. In conclusion, *P. pellucida* (L.) Kunth has wide traditional and pharmacological uses in various pathophysiological conditions. Therefore, it is an attractive subject for further experimental and clinical investigations.

Keywords: *Peperomia pellucida* (L.) Kunth, Ethnopharmacology, Phytochemical, Pharmacological, Toxicity

Introduction

Peperomia pellucida (L.) Kunth. (Figure 1), of the Piperaceae family [1], is native to tropical Central and South America (as well as Hawaii and Fiji [2]), Asia (China, India, South East Asia) [3, 4, 5], and Africa from Senegal to Eritrea and Somalia, and also Angola, Zambia, Zimbabwe, and Mozambique, Madagascar, and Reunion [4]. It normally grows in damp and crowded places such as roadside ditches, yards, gardens, roadside, and other humid or aqueous locations [6]. It is often naturalized as herb, wild, or weed [7]. A study showed that the main environmental factors affecting the invasion risk of *P. pellucida* (L.) Kunth include precipitation in the wettest month, isothermality, mean temperature of the coldest quarter, precipitation of the coldest quarter, and altitude [8]. This plant is known by various local names. In North America, where this plant is believed to have originated, it is called Silverbush, Man-To-Man, Pepper Elder, Clearweed or Rat Ear; while in South America, it is called Lingua de Sapo, Herva-de-Vidro, Herva-de-Jaboti or Herva-de-Jabuti. In northeastern Brazil, this plant is named as "coraçãozinho" (little heart), "língua de sapo" (toad's tongue), "erva-de-vidro" (glass grass), and "erva-de-jaboti" (purpoise grass) [9]. In Indonesia, it is known as Kaca-kaca, Suruhan/Susuruhan (Jawa), Sasaladaan (Sunda), Ketumpangan Air/Tumpangan Air (Sumatera, Jakarta), Rangu-rangu, and Gofu Goroho (Ternate) [6, 7, 10]. *P. pellucida* (L.) Kunth has been used as a traditional medicine worldwide, and much research has been devoted to it. Therefore, it is interesting to perform an up-to-date, comprehensive review regarding the traditional uses, phytoconstituents, pharmacological activities, and toxicological studies of *P. pellucida* (L.) Kunth

Methods

Scientific datas were searched from books and journals published both in national and international journals. Journal search sites such as Scopus, Science Direct, Google Schoolar, Pubmed, Google using keywords *Peperomia pellucida* (L.) Kunth, extract, empirical, chemical compound, pharmacology, toxicity.

Results and Discussion

Traditional Uses

The empirical uses of *P. pellucida* (L.) Kunth are very diverse, depending on local traditions and location, from the use of its leaves and stems as vegetables [12] to acting as agents used in therapy and medicine since long [13]. In Africa, *P. pellucida* (L.) Kunth is occasionally cultivated for vegetables in cuisine, and is sometimes grown as an ornamental container plant [14]. Other examples of empirical uses of the plant include its use as an ingredient in infusions for treating convulsions in Nigeria and DR Congo. The warmed leaves are applied to sores and boils in Sierra Leone, DR Congo. In Nigeria, the leaves are applied as a poultice to treat breast cancer, while in DR Congo, an infusion or maceration of the plant, mixed with salt and palm oil, is taken to cure coughs [14]. In Cameroon, whole grains and plant parts were used for *treating fractures* [15, 16], while macerates or decoctions were administered orally or as a paste to the site of fracture after scarification [16].

Worldwide, and especially in Brazil, the plant is used to cure furuncles, conjunctivitis and skin sores [14], while in the northeastern part of Brazil, the plant is used to lower cholesterol levels [17]. In Guyana and the Amazon region, it is popular as a cough suppressant, emollient, diuretic, cardiac arrhythmia, and to treat proteinuria [17, 18, 19]. In Guyana, it is also eaten as a salad to cleanse the blood, or used in infusions to cure womb inflammations; juice is also squeezed from the leaves into a patient's eyes to treat cataracts, as well as being used in a strong tea for bronchitis and asthma [20]. Furthermore, in South America, fresh juice from the stems and leaves is used to treat eye *inflammations*, while the infusion and decoction of parts of the plant are used for gout and arthritis [21]. In Surinam, a solution of the fresh juice of stem and leaves is used against conjunctivitis. The leaves are used in a decoction to treat cough, fever and common cold, and are eaten fresh to treat headache, sore throat and kidney and prostate problems, high blood pressure, and also treat albuminuria [14, 22]. In addition, it is also used in Suriname for baby care as well as for the relief of pain in the body, epilepsy, eye infections, worm infections, and to improve general health and even supposedly to ward off evil spirits [23]. In Bolivia, Alteños Indians use the whole plant to stop hemorrhoids, the roots to treat fever, and parts of the plant above the ground (aerial) for wound healing [24]. In Asia, the ancient Indian medical system, Ayurveda, recommends the use of the whole Peperomia plant, described as –Rasa –Katu and Madhur; Guna- Lakhu, rooksha, Teekshna; and Virya-Ushna, as a medicinal herb. The plant is thought to relieve coughs, pitta, constipation, kidney disease, urinary retention, disuria, urinary tract infections, emaciations, edemas, and general weakness [13]. Besides its use in medicine, the plant is used as a condiment, and is eaten as a spicy, leafy vegetable, cooked, or used raw in salads in many parts of the

tropics. In China, it is used against abscesses, boils, sores on the skin, trauma and bleeding, furuncles, conjunctivitis and skin sores [12, 14]. In the Philippines, a decoction or infusion of the Peperomia plant is taken to treat rheumatic pain, gout and kidney troubles, and applied externally to cure sores, boils, and other dermatology disease [14, 25]. In Lakshmipur, Bangladesh, leaves of the plant are used by locals to treat mental disorders and are used topically for the treatment of skin problems such as pimples and boils [26, 27]. In Assam, India, the plant is used to treat stomach problems, while the stems and leaves are mainly used for urinary tract disorders and fever [28]. Indonesian folk medicine uses the plant to treat fever, contused wounds and skin diseases [29]. This plant is also used for lowering blood cholesterol, uric acid, and as a cure for tetanus in Sulawesi [30, 31]. In Kalimantan, the local communities use it to treat gout [32].

Phytochemical Constituents

Studies regarding the phytochemical content of *P. pellucida* (L.) Kunth have been extensively conducted since the 1990's. Hundreds of chemical compounds were reported (Table 1 and Figure 2). Several studies have shown that some of the chemical compounds of the pepperomia plant exhibit pharmacological effects. For example, 2 - methylene - 3 - [(3', 4', 5'-trimethoxyphenyl) (5''-methoxy - 3'', 4''-methylenedioxyphenyl) methyl] butyrolactone and peperomin E showed growth inhibitory effects on breast cancer, leukemia, and cervical cancer cells, while 2 - methyl - 3 - [(3' - hydroxyl - 4', 5' - dimethoxyphenyl) (5'' - methoxy - 3'', 4'' - methlenedioxyphenyl) - [methyl] butyrolactone exhibited a weak suppressive activity on HL-60 cells [5]. Other chemical constituents of the peperomia plant with pharmacological activities include patuloside A as an antibacterial agent [40], dillapiolle as a gastroprotective and antifungal agent [39, 48], pachypophyllin as antifungal [48], and vitexin, a lignan compound, that can induce apoptosis and suppress tumor growth [49]. Narayanamoorthi *et al.* (2015) also documented the activities of 32 chemical compounds found in extract of whole plant of *P. pellucida* (L.) Kunth (Table 2).

Pharmacological Studies

Several studies have shown that *P. pellucida* (L.) Kunth exhibits various pharmacological activities, including analgesic, anti-inflammatory, antipyretic, antioxidant, antihyperglycemia antihyperuricemia, burn healing, depressant, gastroprotective, hypotensive, cytotoxic, antimicrobial, antisickling cell, lipase inhibitory, fibrinolytic and thrombolytic, antidiarrhoeal, as well as antiosteoporosis.

Analgesic

In studies regarding the analgesic activities of *P. pellucida* (L.) Kunth, the aqueous extract of the plant showed significantly higher activities compared to the control group, similar to that of Indomethacin at a dose of 400 mg/kg BW in mice, and has an effect approaching morphine at a dose of 100 mg/kg BW [9]. Also, in 2001, Aziba *et al.* demonstrated that the greatest activity of methanol extract of *P. pellucida* (L.) Kunth is at a dose of 210 mg/kg. In addition, the analgesic of *P. pellucida* (L.) Kunth was also proved by Mulyani (2011) through measurement of stretching episodes. Samples that contained 30%, 45%, and 60% methanol extract showed analgesic activity 10.58% (138 stretching episodes), 44.92% (85 stretching episodes), and 56.8% (67 stretching episodes), respectively. These activities were lower than the aspirin group (33 stretching episodes).

Anti-inflammatory

The anti-inflammatory effects of *P. pellucida* (L.) Kunth were studied by De Fatima *et al.* (2004). The results showed that the aqueous extract of the aerial part provided 51.09% inhibition of edema at a dose of 400 mg/kg, approaching the activity of Indomethacin 10 mg/kg (59.08%). Studies by Wijaya and Monica (2004) showed that orally administered extracts of *P. pellucida* (L.) Kunth with doses ranging from 1500 to 2500 mg/kg body weight had anti-inflammation effects that differ significantly with the control group. Another study proved that the petroleum ether extract of the plant at a dose of 1000 mg/kg showed significant anti-inflammatory activity, although this result was lower than that of Indomethacin 10 mg/kg [54]. Also, the aqueous extract of *P. pellucida* (L.) Kunth showed significant anti-inflammatory activity during phenophases 1 and 2 of winter and spring [55]. New research by Salim *et al*. (2014) showed that methanol extract of whole plant *P. pellucida* (L.) Kunth could inhibited released of various pro-inflammatory cytokines such as TNF-α (3.9±0.8%), IL-1α (29.5±2.31%), IL-1β (18.5±5.4%), IL-6 (19.6±1.2%), and IL-8 (6.4±1.0) but this activity still lower than standard Dexamethasone.

Antipyretic

The antipyretic activity of *P. pellucida* (L.) Kunth was proven by Khan *et al.* (2008b) who showed that fractions of the petroleum ether extract of leaves

with a dose of 80 mg/kg decreased body temperature significantly, almost as effectively as aspirin (10 mg/kg).

Antioxidants

Essential oils from *P. pellucida* (L.) Kunth have been shown to have antioxidant activity with a total phenolic content in methanol extract of 48.3±3.1 EAG/g [34]. Mutee *et al.* (2010) reported that the highest total phenolic content in 20 mL of 4 mg/mL *P. pellucida* (L.) Kunth methanol extract is 6.93%, and that the free radical scavenging activity was highest with an IC_{50} value of 0.083±0.008 mg/mL, while Wei *et al.* (2011) reported that the highest inhibitory effect was 30% at a concentration of 0.625 ppt. The ethylacetate extract of *P. pellucida* (L.) Kunth had the highest total phenolic content and a higher antioxidant activity than that of the methanol extract and buthanol extract, with an IC_{50} value of 74.0±0.52 µg/mL [58]. However, this IC_{50} value differs with the results of new research conducted by Mohamad et al. (2015). They showed that the methanol extract of a freeze-dried sample exhibited the highest antioxidant activity with an IC_{50} value of 2.45±0.20 mg/mL. The antioxidant activity test of *P. pellucida* (L.) Kunth proved by Oloyede *et al*. (2011) showed a high antioxidant activity of more than 98% at a concentration of 0.065 mg/mL by the methanol extract. The IC_{50} value of methanolic extract of *P. pellucida* (L.) Kunth was found to be 351.56±0.21 µg/mL, 76.51±0.19 µg/mL and 282.30±0.42 µg/mL in DPPH (2, 2-diphenyl-1-picryl hydrazyl), ABTS (2,2'-azino-bis (3-ethylbenzthiazoline-6-sulphonic acid) and nitric oxide scavenging assays, respectively [60]. The methanol extract showed increased levels of antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT) at a dose of 400 mg/kg, but decreased levels at a dose of 800 mg/kg [61]. The total antioxidant content of dry extracts was higher than that of fresh extracts, and heating at a temperature of 100°C for 15 minutes increased this value [31].

Antihyperglycemia

A study by Salma *et al.* (2013) showed that *P. pellucida* (L.) Kunth extract with a dose of 40 mg/kg decreased rat blood glucose levels by 58.15% after 120 minutes. This supported the results of previous studies that showed that the ethyl acetate fraction of *P. pellucida* (L.) Kunth extract also showed antihyperglycemic activity as high as 53.44% [63]. The antihyperglycemia activities of the extract at a dose of 40 mg/kg were greater than at a dose of 20 and 80 mg/kg. Furthermore, a study by Togubu *et al.* (2013) concluded that ethanol and hexane extracts of *P. pellucida* (L.) Kunth with a dose of 40 mg/kg can decreased rat blood glucose levels by 54,57% dan 51.25% after 120 minutes and almost similar to that of glibenclamide 0.45 mg/kg. Meanwhile, the ethyl acetate extract showed an antihyperglycemic activity with the highest percentage decrease in mice blood glucose levels of 56.23%, followed by n-butanol extract (45.58%). The antihyperglycemic effects of both extracts were not significantly different compared to the effect of glibenclamide 0.5 mg/kg [10]. Futhermore another study conducted by Hamzah *et al*. (2012) showed administration diets supplemented with 10%w/w and 20%w/w of *P. pellucida* (L.) Kunth for 28 days in diabetic rats resulted 64% and 68% reduction in blood glucose level respectively. This result higher than reduction by 600 µg/kg body weight glibenclamide as standard drug (62%).

Antihyperuricemia

The antihyperuricemia effects of *P. pellucida* (L.) Kunth were studied by Tarigan *et al.* (2012), who showed that the ethanol extract at a dose of 50 mg/kg decreased uric acid levels by 24.35%, while a dose of 200 mg/kg decreased the levels by 31.52%, and a dose of 100 mg/kg by 32.20%. Research conducted by Yunarto (2013) also proved that water extracts at a dose of 200 mg/kg lowered cock uric acid levels by 62.49 ± 2.80%.

Burn Healing

P. pellucida (L.) Kunth burn healing activity was studied by Mappa *et al.* (2013), who showed that the effectiveness of the plant extract gel administered three times a day with varying concentrations of 5%, 10%, and 15% on burns was greater than the effect of the positive control Bioplacenton.

Depressant

Khan *et al.* (2008a) tested the neuropharmacological effects of *P. pellucida* (L.) Kunth in mice. The results showed that administration of the petroleum ether and ethyl acetate soluble fractions extended the duration of diazepam-induced sleep, delayed the death time induced by nikethamide, and showed diazepam-type effects in the light-dark and force swimming tests. Both fractions of *P. pellucida* (L.) Kunth showed dose-dependent depressant effects, with the petroleum ether fraction at a dose of 200 mg/kg showing a higher depressant effect than the ethyl acetate fraction.

Gastroprotective

The gastroprotective effect of *P. pellucida* (L.) Kunth was studied by Roslida and Noor (2009). The ethanol extract of the whole plant, except for the roots, was proven to be able to inhibit 84.8% of ulcers because of Indomethacin administration at the lowest dose of 10 mg/kg, and this value is comparable with the effect of Cimetidine at a dose of 50 mg/kg. Subsequent experiments carried out by Martinez *et al.* (2013) showed that the gastroprotective activities of dillapiole which is isolated from *P. pellucida* (L.) Kunth, are dose-dependent, with the maximum activity (85.7 ± 4.3%) at a dose of 100 mg/kg, and that they are larger than the activities of Carbenoxolone.

Hypotensive

A study conducted by Nwokocha *et al*. (2012) regarding the hypotensive activity of *P. pellucida* (L.) Kunth found that intravenous administration of the aqueous extract of the whole plant with a dose of 10-30 mg/kg showed dose-dependent reduction in systolic blood pressure, diastolic blood pressure, HR (heart rate), and MABP (Mean Arterial Blood Pressure) in rats. In addition, this study suggested a dose-dependent hypotensive effect of *P. pellucida* (L.) Kunth via enhancement of endothelial nitric oxide-dependent vasorelaxation. Furthermore, experiments conducted by Fasola and Adeboye (2015) showed that intravenous administration of the extract produced a marked fall in MABP and HR, which lasted for about 10 minutes, and the pressor response to adrenaline was reduced by 48.7% by the 6.25 mg/kg methanol extract.

Cytotoxic

In 2006, Xu *et al.* studied the cytotoxic activity of *P. pellucida* (L.) Kunth, and proved that compound 1 (2 – methylene – 3 - [(3', 4', 5' - trimethoxyphenyl) (5'' - methoxy - 3'', 4'' - methylenedioxyphenyl) methyl] butyrolactone) and peperomin E showed growth inhibitory effects on human promyelocytic leukemia cells (HL-60), human breast adenocarcinoma cells (MCF-7), and human cervical cancer cells (HeLa) with IC_{50} values ranging between 1.4 and 9.1 μM for compound 1 and between 1.8 and 11.1 μM for peperomin E. The study also showed that compound 2 (2 – methyl - 3 - [(3' - hydroxyl - 4', 5' - dimethoxyphenyl) (5'' - methoxy - 3'', 4''- methlenedioxyphenyl) - methyl] butyrolactone) has a weak suppressive activity on HL-60 cells (IC_{50} of 10.8 mM). This result differs with that of Widowati *et al.* (2013), who showed that the anticancer activity (IC_{50} value) of *P. pellucida* (L.) Kunth extract on cervical cancer cells after 24 h incubation was 2.85 μg/mL. In addition, a test conducted by Wei *et al.* (2011) using methanol extracts of leaves against MCF-7 showed a significant decrease in the viability of the cells with an extract concentration of 0.5 μg/mL, but the effect did not follow a dose-dependent activity pattern. The IC_{50} value of the extract was found to be 10.4 ± 0.06 μg/mL.

Antimicrobial

Methanolic crude extracts of *P. pellucida* (L.) Kunth have been reported to show antimicrobial activity against *Pseudomonas aeruginosa* [36]. Another study, conducted by Wei *et al.* (2011), showed that the MIC of methanol leaves extract is in the range of 31.25 to 125 mg/L, and the greatest activity is against *Edwardsiella tarda*, *Escherichia coli*, *Flavobacterium sp*., *P. aeruginosa,* and *Vibrio cholerae* with the same MIC values of 31.25 mg/L. Antimicrobial tests were also carried out by Abere *et al.* (2012) using methanol and chloroform extracts from *P. pellucida* (L.) Kunth leaves formulated in syrup. They showed that at a concentration of 100 mg/mL, *P. pellucida* (L.) Kunth exhibits antimicrobial activity against *Staphylococcus aureus*, *E. coli*, *P. aeruginosa*, *Klebsiella pneumoniae*, and *Bacillus subtilis*. The highest antimicrobial activity was against *P. aeruginosa* with an MIC value of 25 μg/mL. From studies conducted by Akinnibosun *et al.* (2008), it is known that the aqueous extract of *P. pellucida* (L.) Kunth is more potent against *E. coli*, followed by *P. mirabilis* and *P. aeruginosa*. However, the ethanol extract is more potent against *P. aeruginosa*, followed by *Proteus mirabilis* and *E. coli* [74]. Igwe *et al*. (2014) also found that ethanol extract of *P. pellucida* (L.) Kunth leaves can against *S. aureus, Enterococcus faecalis, Bacillus cereus, and Salmonella typhi.* A study conducted by Oloyede *et al.* (2011) showed that crude methanol fraction from the leaves were active against all test bacteria such as *S. aureus, E. coli, B. subtilis, P. aeruginosa, K. pneumonae, S. typhi* at concentration of 200 mg/mL and at concentration of 100 mg/mL only active against *P. aeruginosa.* The n-hexane fraction inhibits all bacteria at concentrations of 25-200 mg/mL and at concentrations of 12.5 mg/mL only active against *P. aeruginosa* and *S. typhi* [58]. Another study by Zubair *et al.* (2015) showed that n-hexane fraction also active against *Bacillus cereus* at concentration 5 mg/mL/disc, as well as *Proteus mirabilis* and *Pseudomonas fluroescens* at concentration 1 mg/mL/disc. Compared than ethyl acetate, chloroform, ethanol and aqueous fraction from

aqueous ethanol leaves extract, hexane fraction was also appeared to be the most effective extract especially against *P. mirabilis*. Furthermore, air dried-freeze dried Dihloromethane crude extract of *P. pellucida* (L.) Kunth displayed antimicrobial activity against *P. aeruginosa* (L.) Kunth, at concentration 12.5-200 µg/disc [36]. Based on a study conducted by Oloyede *et al.* (2011), the butanol fraction at a concentration of 100-200 mg/mL had a broad-spectrum activity. Another study by Khan *et al*. (2002) showed the butanol fraction also showed the greatest activity than other fractions. Ethyl acetate fraction at a concentration of 100-200 mg/mL also had a broad-spectrum activity except against *E. coli*. While, at the same concentration, the aqueous fraction had broad-spectrum antibacteria activity except against *B. subtilis* [59]. Finally, an isolated compound from *P. pellucida* (L.) Kunth, Patuloside A, showed antimicrobial activity equivalent to Kanamycin against *S. aureus* (MIC 8 µg/mL), *Streptococcus β-haemolyticus* (MIC 8 µg/mL), and *Shigella flexneri* (MIC 16 µg/mL) [40]. As for antifungal activity, acetone extracts of roots, stem, and leaves have an antifungal effect against *Aspergillus niger*, *Penicillium sp*. (white), *Penicillium sp*. (grey), and *Rhizopus sp*., with the highest being against *A. niger* for extract of roots and leaves, while being against *Penicillium sp*., (white) for extract of stem [77]. Methanol, n-hexane, butanol, and aqueous fractions of *P. pellucida* (L.) Kunth is also active against *Candida albicans*, *Rhizopus stolon*, *Aspergillus niger*, and *Penicillum notatum*. However, the methanol extract was more selective against *C. albicans* and *R. stolon* at concentrations of 25-200 mg/mL, while the n-hexane fraction at the same concentration more selective against *C. albicans* and *Aspergillus niger*. Also, the ethyl acetate fraction has lower activity against *C. albicans*; the butanol fraction at concentrations of 25-200 mg/mL was more active against *C. albicans*, *Rhizopus stolon*, and *Penicillum notatum*, and the activity of the aqueous fraction was highest at a concentration of 25-200 mg/mL against *Aspergillus niger* [59]. This results also supported by Abere *et al*. (2012) that metanol extract of leaves formulated in syrup active against *C. albicans* with an MIC value of 25 µg/mL. Patuloside A, the isolate compound from *P. pellucida* (L.) Kunth, also showed antifungal activities against *Aspergillus flavus* and *C. albicans* at a dose of 80 and 160 µg/disc, although at a level lower than the standard compound Nystatin with a dose of 30 µg/disc [40]. There are also dill-apiol and pachypophyllin which was proven to be effective against *Trichophyton metagrophyte* [48], *P. pellucida* (L.) Kunth was also found to inhibit the growth of *Plasmodium falciparum* chloroquine-resistant (Indo) strain. A whole plant ethanolic extract exhibited 95% inhibition effect *in vitro* at a concentration of 100 µg/mL. *P. pellucida* (L.) Kunth also showed 78% inhibition effect *in vivo* against rodent malaria *Plasmodium vinckei petteri* at 1,000 mg/kg/day [24]. As for antiamoeboic activity, the methanol fractions of *P. pellucida* (L.) Kunth from dried plants was proven effective against Acanthamoeba spp. The fractions can damage morphology and change structural of *Acanthamoeba cyst*, the opportunistic pathogen of human that causes Acanthamoeba keratitis which results in blindness. The IC_{50} is 29,28±3,64% [46]

Antisickling

The antisickling cell activity of *P. pellucida* (L.) Kunth was evaluated by Abere and Okpalaonyagu (2015) by measuring the inhibition of sodium metabisulphite-induced sickling of homozygous (HbSS) red blood cells obtained from confirmed sickle cell patients who were not in crises. The maximum inhibition measured was 57.5% after 90 min of incubation, produced by a aqueous methanol extract of *P. pellucida* (L.) Kunth leaves with a dose of 500 mg/mL.

Lipase Inhibitory

Pancreatic lipase (PL) inhibitory activity test was conducted by Ong et al. (2014) using the substrate p-nitrophenyl butyrate. Crude methanolic extracts of leaves showed %inhibition 8.62 ± 1.79 lower than standard drug Orlistat of 34.49 ± 5.39%.

Fibrinolytic and Thrombolytic

A study conducted by Ebenezer *et al.* (2014) measured the levels of trace elements and fibrinolytic activity of several plant extracts, including extracts of *P. pellucida.* (L.) Kunth Trace element measurements were carried out because they are involved in the process of fibrinolysis. A crude methanolic extract of *P. pellucida* (L.) Kunth(1.09 mg/L) has a very high level of iron, but insignificant fibrinolytic activity by percentage of the clot that lysed was under 20%, lower than Streptokinase by 60.200% ± 4.303%, as measured with an *in vitro* clot lysis method. Thus, this suggests that the fibrinolytic activity is inversely proportional to the concentration of the iron. Different with fibrinolytic test result, through the in vitro test which was conducted by Zubair *et al*. (2015), *P. pellucida* (L.) Kunth was proved to have thrombolytic activity. Ethanolic soluble fractions of leaves of *P. pellucida* (L.) Kunth

showed maximum activity of 50.65% lysis of clot in comparison with standard drug Streptokinase 65%.

Antidiarrhoeal

The antidiarrhoeal activities from ethanolic extract of leaves of *P. pellucida* (L.) Kunth was evaluated by Zubair *et al.* (2015). As results, at a dose of 250 mg/kg & 500 mg/kg the extract inhibited the mean number of defecation by 41.81% and 60.18% respectively by inhibiting castor oil induced intestinal accumulation of fluid. The latent period for the extract treated group was increased as compared to control group. Although % inhibition of sampel was lower than standard Loperamide 70,38%.

Antiosteoporosis

The antiosteoporosis activity of *P. pellucida* (L.) Kunth was discovered serendipitously when one isolate, 7, 8 - trans - 8, 8′ - trans - 7′, 8′ - cis - 7, 7′ - bis (5 – methoxy -3, 4 - methylenedioxyphenyl) - 8 - acetoxymethyl - 8′ - hydroxymethyltetrahydrofuran, was found to be able to increase the proliferation of MCF-7 breast cancer cells in a cytotoxic activity assay, with an EC_{50} value of 142 nM [5]. The same study also proved that the compound has an activity similar to estrogen or estrogen agonist with an EC_{50} value of 3.1 µm. Subsequently, the antiosteoporosis activity of the plant was evaluated by Ngueguim *et al.* (2013) using a drill hole model of injury. From this test, an ethanol extract can induce bone regeneration at the fracture site. At a dose of 200 mg/kg, the extract can significantly increase bone mineral deposition, improve bone microarchitecture, and increase osteogenic gene expression, including mRNA levels of bone morphogenetic protein-2, type-1 collagen, and osteocalcin, by as much as 25-30 times greater than the negative control the negative control. A recent study using ovariectomy-induced osteoporotic rat model proved that ethanolic extract of *Peperomia pellucida* (L.) Kunth herbs at a dose of 100 mg/kg showed preventive effect for osteoporosis. The extract can reduced serum ALP (Alkaline Phosphatase) level and excretion of urine calcium. It also can improved three-dimensional image of trabecular bone [82].

Toxicological Studies

Several researchers have investigated the toxicological profiles of *P. pellucida* (L.) Kunth in mice and rats. In a study by Susie *et al.* (2001), an freeze-dried aqueous extract of the plant grown in the Philippines was administered orally to male and female mice for 14 days, and resulted in an LD_{50} value of 11.78 g/kg. From this research, it was also discovered that the incidence of side effects in the major organs, such as the integument, musculo-skeletal, nervous, respiratory, digestive organs, as well as the urinary tract, increased with increasing dose, which ranged from 6 g to 32 g per kg of mice body weight. In another study, Arrigoni-Blank *et al.* (2004) tested the toxicity of water extracts of the aerial parts of *P. pellucida* (L.) Kunth with a dose of 5000 mg/kg in Swiss mice for 14 days. There were no indication of any changes in the behavior and weight of the mice, which suggests low toxicity of the extract. Results of other acute toxicity studies also showed that no deaths occurred after administering a petroleum ether fraction of *P. pellucida* (L.) Kunth extract at a dose of 1200 mg/kg and an ethyl acetate fraction at a dose of 1000 mg/kg [26]. A study by Dewijanti *et al.* (2014) showed that *P. pellucida* (L.) Kunth ethanol extract was categorized as mildly toxic in mice with LD_{50} values of 15.13 g/kg for male and 11.87 g/kg for female. Furthermore, the acute toxicity of *P. pellucida* (L.) Kunth was tested by Khan *et al.* (2008b), and was found to be low for petroleum ether and ethyl acetate fractions, which resulted in no deaths at a dose of 1000 mg/kg. In addition, the use of a dose of 1000 mg/kg body weight of male and female rat for 30 days showed no toxic effects on the liver of rat based on alkaline phosphatase and alanine phosphatase activities, as well as liver centralis vein diameter and damage level of hepatocytes [86]. A further study by Benjamin *et al.* (2013) showed that intraperitoneal administration of 400 mg/kg crude extract daily for 14 days showed accumulation of slight injuries in the liver sample, which include mild fibrosis, minor blood congestion in the sinusoids and portal vein, and ballooning and microvesicularsteatosis in 2-3 layers of centrolobular hepatocytes. Cytotoxic tests done by de Lira *et al*. (2009) showed that the LC_{50} of *P. pellucida* (L.) Kunth methanol extract was LC_{50} 2.4±0.5 µg/mL and oil was 8.3±0.2 µg/mL. Another study stated that the LC_{50} of this plant is 81.28 mg/L [85]. Tests on the leaves showed that the methanol fraction has LC_{50} 260.89 µg/mL, hexane fraction LC_{50} 333.91 µg/mL, and ethyl acetate fraction has LC_{50} 45.85 µg/mL, but butanol and water fraction is not toxic with LC_{50} values greater than 1000 µg/ml [59]. Cytotoxic test conducted by Khan *et al*. (2010) showed that Patuloside A is known to have a LC_{50} value 18.24 µg/mL. Another study conducted by Chan *et al*. (2014), showed dillapiole 2.5-10 µM have activity increases apoptosis and reduce the total number of cells. There are post implantation embryo resorption

activity and fetal loss which are expected to have teratogenic effects but which still needs further study. Mutagenic test by Thepouyporn *et al*., (2006) proved samples taken from the stems and leaves of *P. pellucida* (L.) Kunth, which is made into distilled water and absolute ethanol extracts, do not show any mutagenic activity. Studies conducted by Nwokocha *et al*. (2013) tested the inhibitory effects of *P. pellucida* (L.) Kunth extract on CYP3A4 enzymes. CYPs are enzymes responsible for the metabolism of various antihypertensive drugs. From this study, an aqueous extract of the whole *P. pellucida* plant showed moderate inhibition of CYP3A4 in both heterogenously expressed CYP3A4 and human liver microsomes, with IC50 values of 0.466 ± 0.126 mg/mL and 0.153 ± 0.054 mg/mL, respectively. These values proved that *P. pellucida* (L.) Kunth has a low inhibitory effect on CYP3A4, especially compared to the IC_{50} value of $3.1x10^5$ mg/mL of ketoconazole, its known potent inhibitor. Therefore, when taken along with other medications that are metabolized by CYPs, *P. pellucida* (L.) Kunth extract will not affect their metabolism.

Conclusions

Empirically, the *P. pellucida* (L.) Kunth plant has been reported to have various pharmacological activities. However, according to the results of several studies, only some pharmacological effects of the plant such as antioxidants, burn healing, gastroprotective, cytotoxic, and antimicrobial. have been proven scientifically as the potential pharmacological effects, along with its toxicological profile, while its other activities remain undetermined due to lack of data. Therefore, there is still a high potential for further studies concerning the pharmacological profiles of the *P. pellucida* (L.) Kunth plant. In the next research, authors will further investigate the potential of Peperomia pellucida (L.) Kunth and its chemical compounds as antiosteoporotic.

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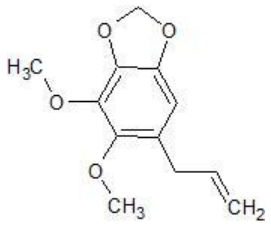
Figure 1. *Peperomia pellucida* (L.) Kunth [11]

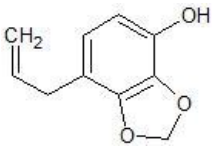
Table 1. Chemical Constituents Present in *Peperomia pellucida* (L.) Kunth

No.	Chemical Constituents	Sources	References
1.	peperomin A	whole plant	[5]
2.	peperomin B	whole plant	[5]
3.	peperomin C	whole plant	[5]
4.	peperomin E	whole plant	[5]
5.	sesamin	whole plant	[5]
6.	isoswertisin	whole plant	[5]
7.	2-methylene-3-[(3',4',5'-trimethoxyphenyl)(5"-methoxy-3",4"-methylenedioxyphenyl)methyl] butyrolactone	whole plant	[5]
8.	2-methyl-3-[(3'-hydroxyl-4',5'-dimethoxyphenyl)(5"-methoxy-3",4"-methlenedioxyphenyl)methyl]butyrolactone	whole plant	[5]
9.	7-(5-methoxy-3,4-methylenedioxyphenyl)-7'-(4-hydroxy-3,5-dimethoxyphenyl)-8-acetoxymethyl-8'-hydroxymethyltetrahydrofuran	whole plant	[5]
10.	7,8-trans-8,8'-trans-7',8'-cis-7,7'-bis(5-methoxy-3,4-methylenedioxyphenyl)-8-acetoxymethyl-8'-hydroxymethyltetrahydrofuran	whole plant	[5]
11.	apiols	undefined	[33, 34]
12.	(*E*)-caryophyllene	undefined	[34]
13.	elemicin	undefined	[34]
14.	myristicin	undefined	[34]
15.	safrole.	undefined	[34]
16.	α-Pinene	undefined	[34]
17.	Limonene	undefined	[34]
18.	(E)-β-Ocimene	undefined	[34]
19.	Undecane	undefined	[34]
20.	Methyl chavicol	undefined	[34]
21.	Decanal	undefined	[34]
22.	Octanol acetate	undefined	[34]
23.	δ-Elemene	undefined	[34]
24.	Daucene	undefined	[34]
25.	β-Bourbonene	undefined	[34]
26.	β-Elemene	undefined	[34]
27.	Decyl acetate	undefined	[34]
28.	Dodecanal	undefined	[34]
29.	β-Copaene	undefined	[34]
30.	trans-α-Bergamotene	undefined	[34]
31.	Aromadendrene	undefined	[34]
32.	epi-β-Santalene	undefined	[34]
33.	α-Himachalene	undefined	[34]
34.	α-Humulene	undefined	[34]
35.	(E)-β-Farnesene	undefined	[34]
36.	γ-Muurolene	undefined	[34]
37.	Germacrene D	undefined	[34]
38.	Pentadecane	undefined	[34]
39.	Bicyclogermacrene	undefined	[34]
40.	(E,E)α-Farnesene	undefined	[34]
41.	Myristicin	undefined	[34]
42.	β-Sesquiphellandrene	undefined	[34]
43.	δ-Cadinene	undefined	[34]
44.	(E)-Nerolidol	undefined	[34]
45.	Spathulenol	undefined	[34]

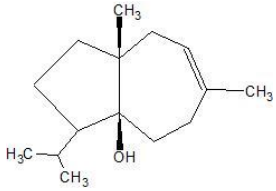
46.	Caryophyllene oxide	undefined	[34]
47.	Globulol	undefined	[34]
48.	Humulene II epoxide	undefined	[34]
49.	Alloaromadendrene epoxide	undefined	[34]
50.	Caryophylla-4(14),8(15)-dien-5-α-ol	undefined	[34]
51.	14-Hydroxy-9-epi-(E)-caryophyllene	undefined	[34]
52.	Carotol	aerial part	[34, 38]
53.	Dillapiole	aerial part	[34, 36, 38, 39, 48]
54.	Pellucidin A	aerial part	[35]
55.	Caryophyllene oxide	undefined	[36]
56.	Stigmasterol	undefined	[36, 44, 46]
57.	Sitosterol	undefined	[36, 46]
58.	Campesterol	undefined	[36]
59.	5,8-Dihydroxy-3,6,7,4'-tetramethoxyflavone-8-Neohesperidoside	undefined	[37]
60.	β-farnesene	aerial part	[38]
61.	Germacrene D	aerial part	[38]
62.	α-farnesene	aerial part	[38]
63.	5-hydroxy-3,4-methylenedioxy allylbenzene	aerial part	[38]
64.	cis-nerolidol	aerial part	[38]
65.	trans-nerolidol	aerial part	[38]
66.	patuloside A (3-β-D-glucopyranosyloxy-1,5,6-trihydroxy-9H-xanthene-9-one)	leaf	[40]
67.	Phytol	leaf	[41]
68.	2-Naphthalenol, decahydro-	leaf	[41]
69.	Hexadecanoic acid, methyl ester	leaf	[41]
70.	9,12-Octadecadienoic acid (Z,Z)-,methyl ester	leaf	[41]
71.	3 ',4',7-tri-methoxyflavone	undefined	[42]
72.	Vitexin	whole plant	[43]
73.	Analog pheophytin	herb	[44]
74.	β-sitosterol-D-glucopyranoside.	herb	[44]
75.	(S)-2-methyl-2-(4-methylpent-3-enyl)-6-(propan-2-ylidene)- 3,4,6,7-tetrahydropyrano[4,3-g]chromen-9(2H)-one (1)	leaf	[45]
76.	friedeline	undefined	[46]
77.	7-methoxy coumarin (herniarin),	undefined	[46]
78.	6-methoxy-7-hydroxy-coumarin (scopoletin)	undefined	[46]
79.	Bicyclo[7.2.0]undec-4-ene, 4,11,11-trimethyl-8-methylene (leaves)	leaf	[47]
80.	10,12-octadecadiynoic acid	leaf	[47]
81.	3,7,11,11-tetramethylbicyclo [8.1.0] undeca-2,6-diene	leaf	[47]
82.	2,6-bis (1,1-dimethylethyl)-4-methyl phenol	leaf	[47]
83.	1,2-dimethoxy-4-(2-methoxyethenyl benzene	leaf	[47]
84.	1,3-benzodioxole, 4,7-dimethoxy-5-(2-propenyl)	leaf	[47]
85.	Oxalic acid, cyclohexylmethyl tridecyl ester	leaf	[47]
86.	Ethyl alpha-d-glucopyranoside	leaf	[47]
87.	Hexadecanoic acid methyl ester	leaf	[47]
88.	Hexadecanoic acid ethyl ester	leaf	[47]
89.	10-octadecenoic acid methyl ester	leaf	[47]
90.	3,7,11,15-tetramethyl-2-hexadecen-1-ol	leaf	[47]
91.	(Z)6,(Z)9-pentadecadien-1-ol	leaf	[47]
92.	9,12,15-octadecatrienoic acid ethyl ester	leaf	[47]
93.	N,N-dimethyldodecanamide	leaf	[47]
94.	Pachypophyllin	leaf	[48]
95.	Aurantiamide acetate	leaf	[48]



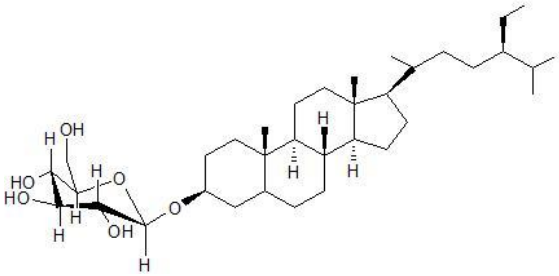
Dillapiole



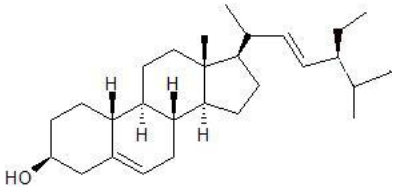
5-hydroxy-3,4-methylenedioxy allylbenzene



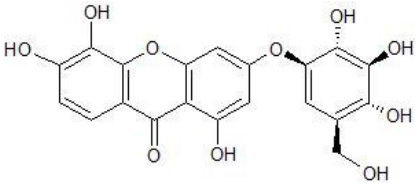
Carotol



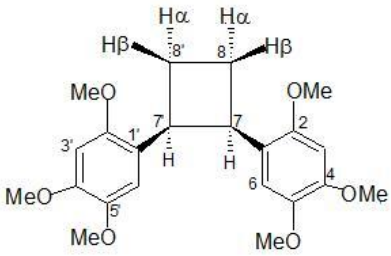
β-sitosterol-D-glucopyranoside



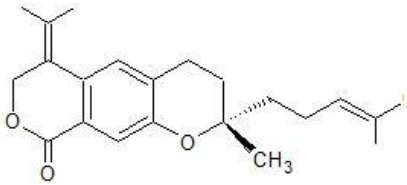
Stigmasterol



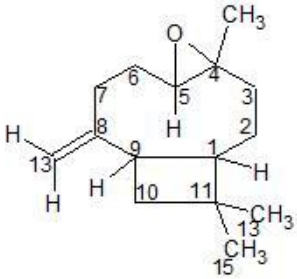
Patuloside A



Pellucidin A



(*S*)-2-methyl-2-(4-methylpent-3-enyl)-6-(propan-2-ylidene)-3,4,6,7-tetrahydropyrano[4,3-*g*]chromen-9(2*H*)-one



Caryophyllene oxide

Figure 2. Chemical Structures of Compounds Isolated from *Peperomia pellucida* (L.) Kunth

Table 2. Chemical Constituents and Their Activities of *Peperomia pellucida* (L.) Kunth Extract

No.	Chemical Constituents	Activities
1	Propane, 1,1,3-triethoxy-	No activity reported
2	Cyclohexane,1-ethenyl-1-methyl-2,4-bis(1-methylethenyl)-	Anti-tumor, Analgesic, Anti-bacterial, Anti-inflammatory, Sedative, Fungicide
3	Caryophyllene	Anti-tumor, Analgesic, Anti-bacterial, Anti-inflammatory, Sedative, Fungicide
4	1H-Cyclopenta[1,3]cyclopropa[1,2]benzene, octahydro-7-methyl-3-methylene-4-(1-methylethyl)-,[3aS-(3aà,3bá,4á,7à,7aS*)]-	Anti-tumor, Analgesic, Antibacterial, Anti-inflammatory, Sedative, Fungicide
5	ç-Elemene	Anti-tumor, Analgesic, Antibacterial, Antiinflammatory, Sedative, Fungicide
6	Naphthalene,1,2,3,4,4a,5,6,8aoctahydro-4a,8-dimethyl-2-(1-methylethenyl)-,[2R-(2à,4aà,8aá)]-	Anti-tumor, Analgesic, Antibacterial, Anti-inflammatory, Sedative, Fungicide
7	(3-Methoxy-2-nitrophenyl)acetic acid, methyl ester	No activity reported
8	1H-Cycloprop[e]azulen-7-ol, decahydro-1,1,7-trimethyl-4-methylene-,[1ar-(1aà,4aà,7á,7aá,7bà)]-	Anti-tumor, Analgesic, Antibacterial, Antiinflammatory, Sedative, Fungicide
9	Carotol	Anti-tumor, Analgesic, Antibacterial, Anti-inflammatory, Sedative, Fungicide
10	Apiol	Used in abortion
11	1,4-Benzenediol,2,6-bis(1,1-dimethylethyl)-	Antimicrobial
12	E-2-Tetradecen-1-ol	No activity reported
13	Z,Z-2,5-Pentadecadien-1-ol	No activity reported
14	3,7,11,15-Tetramethyl-2-hexadecen-1-ol	Antimicrobial, Anti-inflammatory
15	n-Hexadecanoic acid	Antioxidant, Hypocholesterolemic Nematicide, Pesticide, Lubricant, Antiandrogenic, Flavor, Hemolytic, 5-Alpha reductase inhibitor
16	2,6,10-Dodecatrien-1-ol,3,7,11-trimethyl-, (Z,E)-	Anti-tumor,Analgesic, Antibacterial, Anti-inflammatory, Sedative, Fungicide
17	Phytol	Antimicrobial, Antiinflammatory, Anticancer, Diuretic
18	9,12-Octadecadienoic acid (Z,Z)-	Anti-inflammatory, Hypocholesterolemic, Cancer preventive, Hepatoprotective, Nematicide, Insectifuge, Antihistaminic, Antieczemic, Antiacne, 5-Alpha reductase inhibitor, Antiandrogenic, Antiarthritic, Insectifuge
19	9,12,15-Octadecatrienoic acid, (Z,Z,Z)-	Anti-inflammatory, Hypocholesterolemic, Cancer preventive, Hepatoprotective, Nematicide, Insectifuge, Antihistaminic, Antieczemic, Antiacne, 5- Alpha reductase inhibitor, Antiandrogenic, Antiarthritic, Anticoronary, Insectifuge
20	1-Hexadecanol, 2-methyl-	Antimicrobial
21	10-Undecenoic acid, octyl ester	No activity reported
22	1,4-Dioxaspiro[4.5]decane, 8-(methylthio)-	Antimicrobial
23	7-Methyl-Ztetradecen-1-ol acetate	No activity reported
24	6,9,12,15-Docosatetra-enoic acid, methyl ester	Cardio protective, Hypocholesterolemic
25	5HCyclopropa[3,4]benz[1,2-e]azulen-5-one, 4,9,9atris(acetyloxy)-3-[(acetyloxy)methyl]- ,1a,1b,4,4a,7a,7b,8,9, 9a-decahydro-4a,7bdihydroxy-1,1,6,8-tetramethyl	No activity reported
26	á-D Mannofuranoside, farnesyl	Preservative
27	3-Hydroxy-4-methoxycinnamic acid	Antimicrobial, Antioxidant, Anti-inflammatory
28	Vitamin E	Antiageing,Analgesic, Antidiabetic, Anti-inflammatory, Antioxidant, Antidermatitic, Antileukemic, Antitumor, Anticancer, Hepatoprotective, Hypocholesterolemic, Antiulcerogenic, Vasodilator, Antispasmodic, Anticoronary
29	12-Methyl-E,E-2,13-octadecadien-1-ol	No activity reported
30	Campesterol	Antiarthritic, Hepatoprotective, Antiasthma, Anti-inflammatory, Diuretic, Cancer preventive, Antioxidant, Hypocholesterolemic
31	Stigmasterol	Hypocholesterolemic, Sedative, Antiviral, Antioxidant, Antihepatotoxic, Anti-inflammatory, Diuretic, Cancer preventive
32	á-Sitosterol	Antiarthritic, Hepatoprotective, Antiasthma, Anti-inflammatory, Diuretic, Cancer preventive, Antioxidant, Hypocholesterolemic