Journal of Experimental Pharmacology

Dovepress
Taylor & Francis Group

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REVIEW

Peperomia Pellucida (L.) Kunth: A Decade of Ethnopharmacological, Phytochemical, and Pharmacological Insights (2014–2025)

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Abstract: *Peperomia pellucida* (L.) Kunth, a tropical herb belonging to the Piperaceae family, is used in traditional medicine for various therapeutic applications. This review aims to comprehensively analyze preclinical evidence (in silico, in vitro, in vivo, cytotoxicity, and toxicity) supporting the pharmacological activities of *P. pellucida* and elucidate its mechanisms of action and therapeutic potential. Articles were searched in the PubMed and Scopus databases, filtered to those published between 2014 and 2025, to guarantee the most updated research on this plant. These findings indicate that *P. pellucida* should be explored globally. The bioactive compounds contained in this plant could interact with numerous proteins, such as estrogen receptors, NOS, NF-κB, PPAR-gamma, ACE, aldose reductase, alpha-glucosidase, alpha-amylase, DPP-IV, insulin receptor, and AChE. It was reported in vitro studies that the extracts and essential oils of this plant exerted their pharmacological effects through multiple pathways, such as inhibiting COX, NF-κB, and NOS, and scavenging free radicals, which are driven by terpenoids, phenolics, and flavonoids. The in silico and in vitro studies were in agreement with the in vivo studies, which delineated antihypertensive, anti-inflammatory, antinociceptive, antiplasmodial, and osteogenic activity. As expected, *P. pellucida* was not toxic towards normal cells or animal models, confirming its safety. Moreover, several articles describe ethnobotanical studies of this plant in Singapore, India, Myanmar, Nigeria, and Indonesia. However, despite promising pharmacological evidence, the clinical applications of *P. pellucida* remain limited owing to a lack of human studies and open challenges in determining its safety, dosage, and long-term effects. Further research for clinical validation is essential to assess its potential as a therapeutic agent.

Keywords: flavonoids, pellucidin A, Peperomia sp, pharmacology, phytotherapy, Piperaceae, terpenoids

Introduction

Plant-derived drug discovery has attracted considerable interest, and the development of phytopharmaceuticals pertains to an ethnopharmacological approach, which is a multidisciplinary field of inquiry exploring the anthropological perspectives and the pharmacological basis of medicinal plants. Various bioactive constituents present in a plant extract may exhibit the potential to modulate different proteins of certain signaling pathways, generating combined, preferred pharmacological effects. Moreover, the rapid development of herbal medicine, the publishing of papers focusing on complementary and alternative medicine, and the rising perception about how natural products alleviate diseases, particularly compared to conventional drugs with severe reported side effects, have added a stronger tendency to shift the pharmacotherapy paradigm to phytotherapy.

Of the megadiversity of medicinal plants, the Peperomia genus (Piperaceae), which comprises approximately 1,600 tropical species, has attracted many researchers to explore. *Peperomia* are annual or perennial herbs that grow on the surface of another plant (epiphytic), rocks (epilithic), or the soil (terrestrial). These herbs are often found in high and

Received: 18 April 2025
Accepted: 26 June 2025
Published: 3 July 2025

humid forests with plentiful rainfall. Many of the species show similar morphological characteristics; thus, their identification is challenging because the reproductive organs are tiny and easily fall off or are lost during harvesting. However, fewer than 50 species have been investigated for their chemical profiles, resulting in more than 200 isolated phytoconstituents.[1–5] Of those, gamma-sitosterol ($C_{29}H_{50}O$) was found in many Peperomia species, while linoelaidic acid ($C_{18}H_{32}O_2$), humulene ($C_{15}H_{24}$), and spathulenol ($C_{15}H_{24}O$) were mainly found in *P. tetraphylla*. Carotol ($C_{15}H_{26}O$) and apiole ($C_{12}H_{14}O_4$) were noticeably present in *P. pellucida*, and germacrene D ($C_{15}H_{24}$) was uniquely identified in *P. dindygulensis*.[2]

For initial study, we searched the PubMed database to find articles studying plants of the Peperomia genus, including those published between 1990 and 2025, resulting in 147 articles (summarized in Figure 1). PubMed is chosen for the resource of documents because this database supports the search and retrieval of biomedical, clinical, and life sciences references to improve health, both globally and personally, and covers more than 38 million citations and abstracts of biomedical and clinical literature. During the exploration we noted that a particular species namely *Peperomia pellucida* (depicted in Figure 2) was the most studied (49 articles), followed by, respectively, *P. dindygulensis* (15 articles), *P. obtusifolia* (11 articles), *P. tetraphylla* (9 articles), *P. blanda* (8 articles), *P. galioides* (6 articles), *P. duclouxii* (5 articles), while other species (in alphabetical order) such as *P. alata, P. campylotropa, P. cavaleriei, P. circinata, P. cymbifolia, P. dolabriformis, P. emarginulata, P. fernandopoioana, P. fraseri, P. haematolepis, P. heptaphylla, P. heyneana, P. hispidula, P. inaequalifolia, P. incana, P. jamesoniana, P. kotana, P. laevifolia, P. leptostachya, P. macrostachya, P. masuthoniana, P. metallica, P. moulmeiniana, P. multisurcula, P. nakaharai, P. palmiformis, P. pilocarpa, P. pseudopereskiifolia, P. ranongensis, P. retusa, P. ricardofernandezii, P. riosaniensis, P. rotundata, P. rotundifolia, P. sagasteguii, P. scandens, P. serpens, P. sirindhorniana, P. symmankii, P. sui, P. trinervis, P. tuisana, P. vivipar, P. villipetiola*, and *P. vulcanica*, were studied in only 1–2 articles. Most studies have described Brazil and China as locations where plant samples were collected.

Considering that *P. pellucida* became the center of attention of many authors, this review limits the search period of publication to the last decade (2014 to 2025), thus ensuring the most updated studies of this plant. *P. pellucida* is a tropical herb, predominantly found in South America, Africa, Australia, and Southeast Asia (including Indonesia). In Indonesia, *P. pellucida*, with the local names *sirih tumpang air* (Indonesian) or *suruhan* (Javanese), and *sasaladahan* (Sundanese), is commonly used to alleviate pain and pyrexia. A handful of the whole plant is simmered with a half-liter

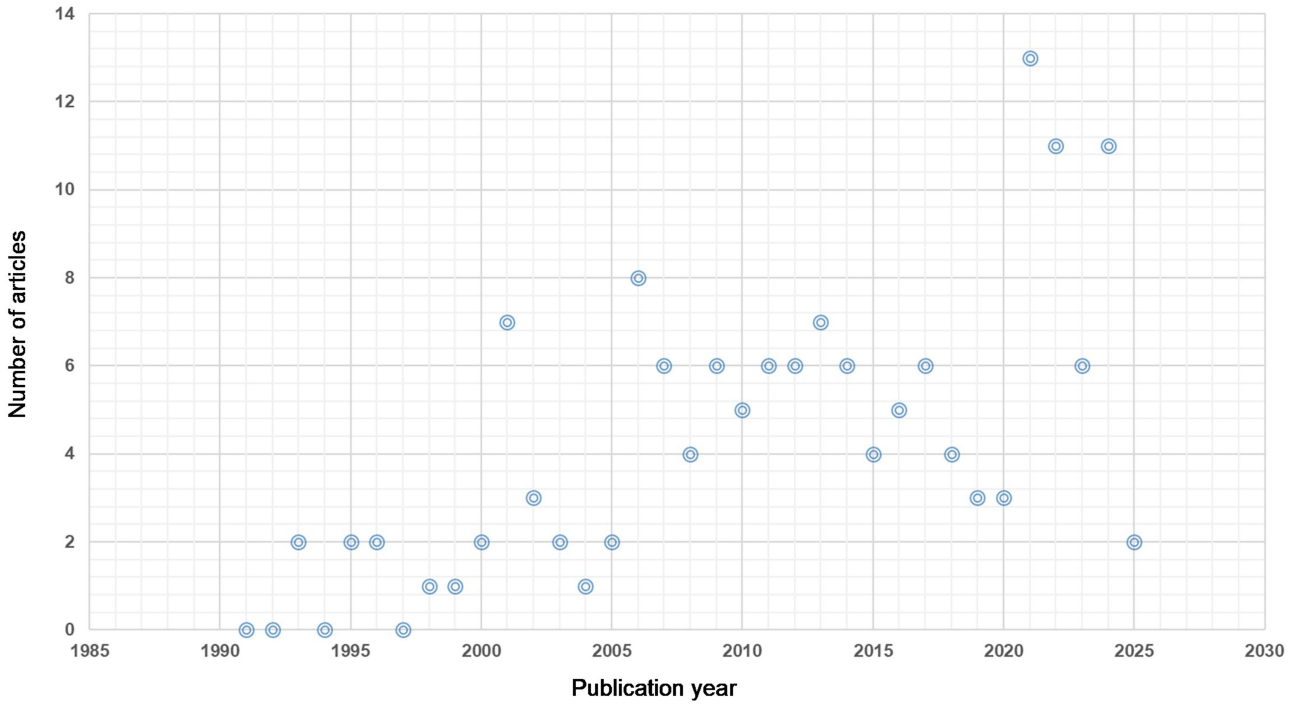


Figure 1 Scattered diagram showing the number of articles on Peperomia genus plants (Piperaceae) published from 1990 to 2025 plotted against the year of publication.

Figure 2 The leaves and aerial parts of the *Peperomia pellucida* plant (this image was taken by the first author).

of water and consumed daily until discomfort is resolved. To understand why this plant can suppress discomfort, we searched for relevant scientific information.

P. pellucida thrives in humid and shaded environments, and is distinguished by soft stems, trailing growth, and distinctive heart-shaped leaves with glossy and waxy surfaces. Numerous phytochemicals have been found in the leaves, stems, aerial parts, and roots of *P. pellucida*.[1–10] Therefore, this review aimed to identify the therapeutic potential, mechanisms of action, and toxicity studies of *P. pellucida*, assayed in cells and animal models, to provide a strong foundation for the clinical application of this plant in the future, bridging the gap between basic research and medical implementation. Furthermore, the ultimate goal is to offer recommendations for therapeutic development and to pave the way for clinical research to validate its therapeutic properties. Consequently, identifying the appropriate dosage and potential long-term side effects remains difficult, necessitating a comprehensive literature review to further explore the pharmacological activities of *P. pellucida* based on the existing preclinical evidence.

Methods

Relevant information regarding the pharmacological activities of *P. pellucida* was gathered through a search utilizing the PubMed and Scopus electronic databases. This search focused on studies that discussed the pharmacological activities of *P. pellucida*, including preclinical (in silico, in vitro, in vivo, cytotoxicity, and toxicity) and human studies, as well as its ethnopharmacological use.

The search on the PubMed database was filtered to 2014 to 2025 of the publication date, using the keywords "Peperomia pellucida AND pharmacology activity" resulted in 14 articles, "Peperomia pellucida AND molecular docking" resulted in 3 articles, "Peperomia pellucida AND in vitro" resulted in 8 articles, "Peperomia pellucida AND in vivo" resulted in 7 articles, and "Peperomia pellucida AND human studies" resulted in 7 articles. The collected articles were thoroughly screened based on their titles and abstracts by two authors. Duplicate articles, review articles, articles

not written in English, articles not open-access, and articles not related to the topic were excluded. Another search in Scopus using the same keywords enriched the review.

Phytochemical Aspects

Phytochemical analysis of *P. pellucida* has identified various bioactive compounds, each of which plays a pivotal role in multifaceted therapeutic applications. Multiple parts of *P. pellucida* were reported for their metabolite content, such as diterpenoids eg, phytol (leaves and stems),[1,9] monoterpenoids and monoterpenes, e.g., linalool, D-limonene, and alpha-terpineol (stems),[9] sesquiterpenes eg, beta-caryophyllene (leaves and stems),[2,9] sterols eg gamma-sitosterol (leaves and stems),[2] phenylpropanoids (leaves, stem, and roots),[3] sesquiterpene hydrocarbons (leaves, stem, and roots),[3] phenolics (aerial parts),[4] flavonoids (leaves and stems),[2] glycosylated-flavonoids (leaves, stem, and roots),[5] alkaloids (leaves, stem, and roots),[5] benzodioxols and amides (leaves, stem, and roots),[5] tannins (leaves),[6] reducing sugars (leaves, stem, and roots),[5] saponins (leaves, stem, and roots),[5,6] triterpenoids (leaves, stem, and roots),[5] azulenes (leaves),[7] carotenoids eg beta-carotene (leaves),[7] secolignans (leaves, stem, and roots),[8] tetrahydrofuran lignans (leaves, stem, and roots),[8] methoxylated dihydronaphthalenone (leaves, stem, and roots),[8] carbohydrates (leaves),[6] water soluble vitamins (leaves),[6] and minerals (leaves).[6] Moreover, 17 evaporative esters, acids, and alcohol compounds were also found in the leaves of this plant.[10]

Pharmacology Activities

With the advancement of ethnopharmacological research, increasing evidence supports the potential of this plant as a promising candidate for medical therapies using in silico, in vitro, and in vivo assays. The most studied effects were antibacterial and anti-inflammatory, followed by antidiabetic, antihypertensive, anticancer, and antidepressant activities, and their effect on sperm count, viability, motility, and morphology. However, despite substantial pharmacological evidence, most studies have been limited to preclinical stages, and clinical data remain scarce. This poses a significant challenge for confirming the efficacy and safety of the plant for human use.

The leaves and aerial parts of *P. pellucida* were broadly explored and confirmed as the active components, followed by the stems, entire plants, and seeds. Table 1 (in silico study), Table 2 (radical scavenging activity), Table 3 (in vitro study), and Table 4 (in vivo study) summarize the pharmacological activities of *P. pellucida* published from 2014 to 2025.

In vitro Radical Scavenging Capacity

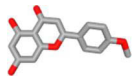
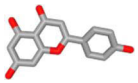
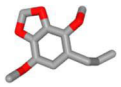
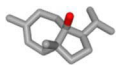
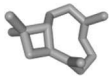
The radical scavenging capacity of *P. pellucida* has been verified using numerous reagents, such as 2,2- diphenyl-1-picrylhydrazyl (DPPH) radical,[6,9,10,18–21] 2,2′-azino-bis (3- ethylbenzothiazoline-6-sulphonic acid) diammonium salt (ABTS),[9,18,21] ferrous reducing antioxidant capacity (FRAC),[10] thiobarbituric acid assay (lipid peroxide radical),[9,18] inhibition of nitric oxide (NO) radical assay,[9] hydrogen peroxide scavenging activity,[18] reducing power (RP),[21] and total antioxidant capacity.[18,21]

The in vitro radical scavenging capacity of *P. pellucida* is summarized in Table 2, confirming a strong capacity of the leaves and the aerial parts of this plant in scavenging oxidant radicals. Although the location where the plants were collected was dissimilar, such as Nigeria,[6,9,18,20] Thailand,[10] Malaysia,[19] and Vietnam,[21] and the polarity of the extraction solvent was diverse eg, methanol,[10,19] butanol,[10] ethanol,[9] ethyl acetate,[10] and chloroform,[6] the IC_{50} obtained from various antioxidant assay techniques was reported to be similarly very low (ranging between 0.083 mg/mL and 2.83 mg/mL). This implies an intense radical scavenging capacity and confirms that antioxidants such as sterols, phenolic compounds, flavonoids, and carotenoids were present in an adequate amount in *P. pellucida*.

In silico Molecular Docking Study

In silico molecular docking study is broadly employed in pharmacology to predict the molecular interactions between drugs or drug candidates and their biological targets (proteins). There are limited PubMed-indexed articles reporting in silico studies of phytoconstituents contained in *P. pellucida* (tabulated in Table 1), among others, were phenylpropanoids,[12] lignans,[12,16] pheophorbide esters,[13] polyphenols,[14] ellagic acid,[15] flavonoids,[11] and chromenes.[17]

Table 1 In silico Study of Bioactive Compounds Isolated from Peperomia *Pellucida* L. Kunth Reported in the Period from 2014 to 2025

Name of Bioactive Compound (In Alphabetical Order) and 3D Chemical Structure	Molecular Formula	Macromolecule Target (PDB ID, Resolution)	Molecular Docking Software and Algorithm Used	Hydrogen Bond and Amino Acid Residues Involved in the Interaction	Results (Docking Score or Binding Affinity in kcal/mol)	Pharmacological Activity	Reference
Acacetin 	$C_{16}H_{12}O_5$ (PubChem CID 5280442)	Human acetylcholinesterase (PDB ID 4M0E)	AutoDock Vina (the algorithm is not described)	The binding mode of acacetin to human acetylcholinesterase is not described in detail. No description of the amino acid residues involved in the interaction.	−7.70	Neuroprotective	[11]
Apigenin 	$C_{15}H_{10}O_5$ (PubChem CID 5280443)			The binding mode of apigenin to human acetylcholinesterase is not described in detail. No description of the amino acid residues involved in the interaction.	−7.80	Neuroprotective	
Apiole 	$C_{12}H_{14}O_4$ (PubChem CID 10659)	Estrogen receptor: ERα (PDB ID 1GWR, resolution 2.4 Å)	AutoDock 4.0 with Lamarckian genetic algorithm	Hydrogen bond to Arg394	−5.58	Anti-osteoporotic	[12]
		Estrogen receptor: ERβ (PDB ID 3OLS, resolution 2.2 Å)		Hydrogen bond to Arg346	−5.44		
Carotol 	$C_{15}H_{26}O$ (PubChem CID 442347)	NF-kappaB p65 (PDB ID 9BDW, resolution 1.87 Å)	AutoDock 4.2.6 with Lamarckian genetic algorithm	The binding mode of carotol to NF-kappaB p65 is not described in detail. No description of the amino acid residues involved in the interaction.	−5.89	Anti-inflammatory	[13]
		PPAR-gamma (PDB ID 3U9Q, resolution 1.52 Å)		The binding mode of carotol to PPAR-gamma is not described in detail. No description of the amino acid residues involved in the interaction.	−7.90		
Caryophyllene (Beta-caryophyllene) 	$C_{15}H_{24}$ (PubChem CID 5281515)	NF-kappaB p65 (PDB ID 9BDW, resolution 1.87 Å)	AutoDock 4.2.6 with Lamarckian genetic algorithm	The binding mode of caryophyllene to NF-kappaB p65 is not described in detail. No description of the amino acid residues involved in the interaction.	−6.14	Anti-inflammatory	[13]
		PPAR-gamma (PDB ID 3U9Q, resolution 1.52 Å)		The binding mode of caryophyllene to PPAR-gamma is not described in detail. No description of the amino acid residues involved in the interaction.	−7.68		

(*Continued*)

https://doi.org/10.2147/JEP.S532898

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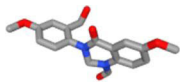
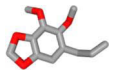
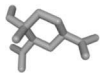
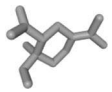
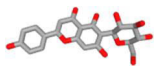
Table 1 (Continued).

Name of Bioactive Compound (In Alphabetical Order) and 3D Chemical Structure	Molecular Formula	Macromolecule Target (PDB ID, Resolution)	Molecular Docking Software and Algorithm Used	Hydrogen Bond and Amino Acid Residues Involved in the Interaction	Results (Docking Score or Binding Affinity in kcal/mol)	Pharmacological Activity	Reference
Dictyoquinazol C 	$C_{18}H_{18}N_2O_5$ (PubChem CID 11099949)	NF-kappaB p65 (PDB ID 9BDW, resolution 1.87 Å)	AutoDock 4.2.6 with Lamarckian genetic algorithm	The binding mode of dictyoquinazol C to NF-kappaB p65 is not described in detail. No description of the amino acid residues involved in the interaction.	−5.75	Anti-inflammatory	[13]
		PPAR-gamma (PDB ID 3U9Q, resolution 1.52 Å)		The binding mode of dictyoquinazol C to PPAR-gamma is not described in detail. No description of the amino acid residues involved in the interaction.	−6.44		
Dillapiole 	$C_{12}H_{14}O_4$ (PubChem CID 10231)	Estrogen receptor: ERα (PDB ID 1GWR, resolution 2.4 Å)	AutoDock 4.0 with Lamarckian genetic algorithm	No hydrogen bond	−5.14	Anti-osteoporotic	[12]
		Estrogen receptor: ERβ (PDB ID 3OLS, resolution 2.2 Å)		Hydrogen bond to Leu476	−5.26		
		NF-kappaB p65 (PDB ID 9BDW, resolution 1.87 Å)	AutoDock 4.2.6 with Lamarckian genetic algorithm	The binding mode of dillapiole to NF-kappaB p65 is not described in detail. No description of the amino acid residues involved in the interaction.	−3.69	Anti-inflammatory	[13]
		PPAR-gamma (PDB ID 3U9Q, resolution 1.52 Å)		The binding mode of dillapiole to PPAR-gamma is not described in detail. No description of the amino acid residues involved in the interaction.	−3.37		
		Angiotensin-converting enzyme (ACE) (PDB ID 1UZF, resolution 2.00 Å)	AutoDockZn with Lamarckian genetic algorithm	Hydrogen bonds to Gln281, Lys511, Tyr520, and Tyr523	−4.99	Antihypertension	[14]
Elemene (Beta-elemene) 	$C_{15}H_{24}$ (PubChem CID 6918391)	NF-kappaB p65 (PDB ID 9BDW, resolution 1.87 Å)	AutoDock 4.2.6 with Lamarckian genetic algorithm	The binding mode of beta-elemene to NF-kappaB p65 is not described in detail. No description of the amino acid residues involved in the interaction.	−5.47	Anti-inflammatory	[13]
		PPAR-gamma (PDB ID 3U9Q, resolution 1.52 Å)		The binding mode of beta-elemene to PPAR-gamma is not described in detail. No description of the amino acid residues involved in the interaction.	−7.45		

Elemene (Delta-elemene) 	$C_{15}H_{24}$ (PubChem CID 12309449)	NF-kappaB p65 (PDB ID 9BDW, resolution 1.87 Å)	AutoDock 4.2.6 with Lamarckian genetic algorithm	The binding mode of delta-elemene to NF-kappaB p65 is not described in detail. No description of the amino acid residues involved in the interaction.	−5.48	Anti-inflammatory	[13]
		PPAR-gamma (PDB ID 3U9Q, resolution 1.52 Å)		The binding mode of delta-elemene to PPAR-gamma is not described in detail. No description of the amino acid residues involved in the interaction.	−7.29		
Elemene (Gamma-elemene) 	$C_{15}H_{24}$ (PubChem CID 6432312)	NF-kappaB p65 (PDB ID 9BDW, resolution 1.87 Å)	AutoDock 4.2.6 with Lamarckian genetic algorithm	The binding mode of gamma-elemene to NF-kappaB p65 is not described in detail. No description of the amino acid residues involved in the interaction.	−5.57	Anti-inflammatory	[13]
		PPAR-gamma (PDB ID 3U9Q, resolution 1.52 Å)		The binding mode of gamma-elemene to PPAR-gamma is not described in detail. No description of the amino acid residues involved in the interaction.	−7.01		
Ellagic acid (Dimethoxy-ellagic acid)	Not available in the PubChem database	Aldose reductase (PDB ID 3S3G)	AutoDock Vina under PyRx 8.0 (the algorithm is not described)	Hydrogen bonds to Ala300, Leu301, leu302, and Ser303	−10.30	Antidiabetic	[15]
		Alpha-amylase (PDB ID 1B2Y)		Hydrogen bonds to Gln63 and His305	−7.80		
		Alpha-glucosidase (PDB ID 2QMJ)		Hydrogen bond to Arg526	−7.10		
		Dipeptidyl peptidase IV (PDB ID 3F8S)		No hydrogen bond	−6.90		
		Insulin receptor (PDB ID 1IR3)		No hydrogen bond			
Isovitexin 	$C_{21}H_{20}O_{10}$ (PubChem CID 162350)	Human acetylcholinesterase (PDB ID 4M0E)	AutoDock Vina (the algorithm is not described)	The binding mode of isovitexin to human acetylcholinesterase is not described in detail. No description of the amino acid residues involved in the interaction.	−8.70	Neuroprotective	[11]

(*Continued*)

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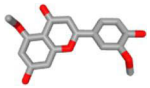
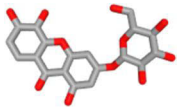
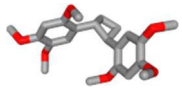
Table 1 (Continued).

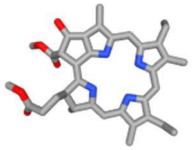
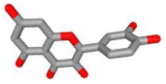
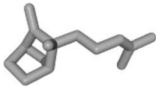
Name of Bioactive Compound (In Alphabetical Order) and 3D Chemical Structure	Molecular Formula	Macromolecule Target (PDB ID, Resolution)	Molecular Docking Software and Algorithm Used	Hydrogen Bond and Amino Acid Residues Involved in the Interaction	Results (Docking Score or Binding Affinity in kcal/mol)	Pharmacological Activity	Reference
Luteolin 5,3′-dimethyl ether (Chrysoeriol 5-methyl ether) 	$C_{17}H_{14}O_6$ (PubChem CID 13964549)	NF-kappaB p65 (PDB ID 9BDW, resolution 1.87 Å)	AutoDock 4.2.6 with Lamarckian genetic algorithm	The binding mode of gamma-elemene to NF-kappaB p65 is not described in detail. No description of the amino acid residues involved in the interaction.	−5.43	Anti-inflammatory	[13]
		PPAR-gamma (PDB ID 3U9Q, resolution 1.52 Å)		The binding mode of gamma-elemene to PPAR-gamma is not described in detail. No description of the amino acid residues involved in the interaction.	−6.54		
Pachypostaudin B	Not available in the PubChem database	Estrogen receptor: ERα (PDB ID 1GWR, resolution 2.4 Å)	AutoDock 4.0 with Lamarckian genetic algorithm	Hydrogen bond to His524	−8.17	Anti-osteoporotic	[12]
		Estrogen receptor: ERβ (PDB ID 3OLS, resolution 2.2 Å)		Hydrogen bonds to His475 and Leu476	−7.03		
Patuloside A (1,5,6-trihydroxy-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl] oxyxanthen-9-one) 	$C_{19}H_{18}O_{11}$ (PubChem CID 53883544)	Angiotensin-converting enzyme (ACE) (PDB ID 1UZF, resolution 2.00 Å)	AutoDockZn with Lamarckian genetic algorithm	Hydrogen bonds to Gln281, His353, Glu386, His513, and Tyr523	−7.65	Antihypertension	[14]

Pellucidin A 	$C_{22}H_{28}O_6$ (PubChem CID 637244)	Estrogen receptor: ERα (PDB ID 1GWR, resolution 2.4 Å)	AutoDock 4.0 with Lamarckian genetic algorithm	Hydrogen bond to His524	−8.20	Anti-osteoporotic	[12]
		Estrogen receptor: ERβ (PDB ID 3OLS, resolution 2.2 Å)		No hydrogen bond	−7.65		
		Inducible NOS (iNOS) (PDB ID 1M8D, resolution 2.35 Å)	Molegro Virtual Docker (MVD) with the MolDock SE (Simplex Evolution) algorithm	The binding mode of pellucidin A to iNOS is not described in detail. No description of the amino acid residues involved in the interaction.	−125.21	Anti-nociceptive	[16]
		Endothelial NOS (eNOS) (PDB ID 1M9J, resolution 1.90 Å)		The binding mode of pellucidin A to eNOS is not described in detail. No description of the amino acid residues involved in the interaction.	−124.87		
		Ancestral corticoid receptor (ACR) (PDB ID 2Q1V, resolution 1.95 Å)		The binding mode of pellucidin A to ACR is not described in detail. No description of the amino acid residues involved in the interaction.	−106.54		
		COX-2 (PDB ID 4COX, resolution 2.90 Å)		The binding mode of pellucidin A to COX2 is not described in detail. No description of the amino acid residues involved in the interaction.	−107.18		
Peperochromene A	Not available in the PubChem database	Aldose reductase (PDB ID 1Z8A, resolution 0.95 Å)	AutoDock 4.2 embedded in LigandScout (the algorithm is not described)	No hydrogen bond	Not described	Antidiabetic	[17]
		Alpha-amylase (PDB ID 2QV4, resolution 1.97 Å)		Hydrogen bond to Thr163	Not described		
		Alpha-glucosidase (PDB ID 3W37, resolution 1.70 Å)		No hydrogen bond	Not described		
		Dipeptidyl peptidase IV (PDB ID 4PNZ, resolution 1.90 Å)		No hydrogen bond			

(*Continued*)

https://doi.org/10.2147/JEP.S532898

Table 1 (Continued).

Name of Bioactive Compound (In Alphabetical Order) and 3D Chemical Structure	Molecular Formula	Macromolecule Target (PDB ID, Resolution)	Molecular Docking Software and Algorithm Used	Hydrogen Bond and Amino Acid Residues Involved in the Interaction	Results (Docking Score or Binding Affinity in kcal/mol)	Pharmacological Activity	Reference
Pheophorbide A-methyl ester 	$C_{36}H_{38}N_4O_5$ (PubChem CID 73074)	NF-kappaB p65 (PDB ID 9BDW, resolution 1.87 Å)	AutoDock 4.2.6 with Lamarckian genetic algorithm	The binding mode of pheophorbide A-methyl ester to NF-kappaB p65 is not described in detail. No description of the amino acid residues involved in the interaction.	−7.43	Anti-inflammatory	[13]
		PPAR-gamma (PDB ID 3U9Q, resolution 1.52 Å)		The binding mode of pheophorbide A-methyl ester to PPAR-gamma is not described in detail. No description of the amino acid residues involved in the interaction.	−10.57		
Quercetin 	$C_{15}H_{10}O_7$ (PubChem CID 5280343)	Angiotensin-converting enzyme (ACE) (PDB ID 1UZF, resolution 2.00 Å)	AutoDockZn with Lamarckian genetic algorithm	Hydrogen bonds to Gln281, His353, Glu386, His513, and Tyr523	−8.30	Antihypertension	[14]
Santalene (Beta-santalene) 	$C_{15}H_{24}$ (PubChem CID 10889018)	NF-kappaB p65 (PDB ID 9BDW, resolution 1.87 Å)	AutoDock 4.2.6 with Lamarckian genetic algorithm	The binding mode of beta-santalene to NF-kappaB p65 is not described in detail. No description of the amino acid residues involved in the interaction.	−5.72	Anti-inflammatory	[13]
		PPAR-gamma (PDB ID 3U9Q, resolution 1.52 Å)		The binding mode of beta-santalene to PPAR-gamma is not described in detail. No description of the amino acid residues involved in the interaction.	−7.60		

https://doi.org/10.2147/JEP.S532898

Table 2 In vitro Radical Scavenging Capacity of *Peperomia Pellucida* L. Kunth. Reported in the Period from 2014 to 2025

Part of the Plant, Collected in and Authenticated by	Extraction Method and Phytochemical Analysis	Oxidant Reagent	Control Used and Concentration	Data Analysis	Results	Ref
Using DPPH reagent						
The leaves were harvested at Umunomo Ihitteafokwu in Ahiazu Mbaise Local Government Area of Imo State, South Eastern Nigeria. The plant materials were identified by Mr. Ibe Ndukwe of the Taxonomy section, Forestry Department, Michael Okpara University of Agriculture, Umudike, Nigeria.	The leaves were handpicked and air dried for 30 d at room temperature, milled to a fine powder, and extracted using distilled water. Alkaloids, flavonoids, saponins, tannins, and phenols were determined by adapting the standard phytochemical analysis method. The levels of ascorbic acid, niacin, riboflavin, thiamine, β-carotene, minerals, and proximate composition in the extract were also determined.	The free radical scavenging activity was measured using the DPPH reagent	Ascorbic acid was used as a reference standard.	All experiments were performed in triplicate (n = 3). All results are expressed as means ± SD.	Phytochemicals in the extract were alkaloids (2.49%), saponins (0.64%), flavonoids (0.59%), tannins (0.08%), and phenols (0.05%). Minerals were nitrogen (3.14 ± 0.03 mg/100 g), phosphorus (0.49 ± 0.02 mg/100 g), potassium (0.63 ± 0.01 mg/100 g), calcium (2.82 ± 0 mg/100 g), magnesium (1.19 ± 0.06 mg/100 g), and sodium (0.38 ± 0.05 mg/100 g). Vitamins were ascorbic acid (8.74 ± 0.12 mg/100 g), riboflavin (0.34 ± 0.01 mg/100 g), thiamine (0.21±0.03 mg/100 g), niacin (0.57 ± 0.01 mg/100 g), β-carotene (2.33±0.15 mg/100 g) Proximate compositions were ash (9.71 ± 0.34 mg/100 g), proteins (19.58 ± 0.22 mg/100 g), fibres (11.45±1.7 mg/100 g), carbohydrates (53.43 ± 1.52 mg/100 g), lipids (5.83 ± 0.74 mg/100 g), and moisture content (7.90 ± 1.94 mg/100 g) The extract exhibited a DPPH radical scavenging activity at 2.0 and 12.0 mg/mL.	[6]
The leaves and stems were collected in August 2016 at the Forest Research Institute of Nigeria, Ibadan, Southwest Nigeria. The plant materials were identified by a plant taxonomist, and a voucher specimen (LUH 6956) was deposited at the Lagos University Herbarium (LUH).	The leaves were left to air-dry at an ambient room temperature for 5 d, while the stems were cut into smaller pieces and dried for 7 d. The dried plant materials were pulverized, and EOs were extracted for 3 h using a modified Clevenger-type apparatus, repeated 3x. The extracts were analyzed using high-resolution GC-MS. GC-MS data were identified by matching the mass spectra with the Wiley 275 library and comparing retention indices.	The free radical scavenging activity was measured using the DPPH reagent.	Ascorbic acid and β-carotene were used as a reference standard.	The IC_{50} (mg/mL) was calculated in a regression equation from a standard curve for each extract and reference compound. $p < 0.05$ was considered significant. Values are mean ± SD (n = 3).	The IC_{50} value of LEO was 1.67 ± 0.01 mg/mL, significantly lower ($p < 0.05$) than SEO (2.83 ± 0.02 mg/mL), ascorbic acid (2.86 ± 0.03 mg/mL), and comparable to β-carotene (2.02 ± 0.02 mg/mL), implying the strongest DPPH radical scavenging activity of LEO among the tested samples.	[9]

(*Continued*)

Table 2 (Continued).

Part of the Plant, Collected in and Authenticated by	Extraction Method and Phytochemical Analysis	Oxidant Reagent	Control Used and Concentration	Data Analysis	Results	Ref
The whole plant of *P. pellucida* L. Kunth was collected in Amphoe Sampran, Nakornpathom Province, Thailand, in April 2011. Details of authentication were not specified in the original article.	The samples were macerated for 24 h at room temperature, refluxed for 45 min using MeOH, BuOH, and EtOAc (400 mL for 20 g of dried sample), and concentrated using a rotary evaporator. The TPC was determined using the Folin–Ciocalteu method.	The free radical scavenging activity was measured using the DPPH reagent	Not described	All experiments were performed in triplicate (n = 3). Data are presented as mean ± SD. ANOVA was performed using SPSS, with significance set at $p < 0.05$.	The highest yield was obtained using MeOH under reflux conditions (20.00 ± 0.69%), followed by BuOH (8.63 ± 0.06%) and EtOAc (4.07 ± 0.40%). In maceration, MeOH produced the highest yield (10.28 ± 0.61%), while both BuOH (3.04 ± 0.59%) and EtOAc (3.06 ± 0.64%) yielded lower amounts, with no significant difference between them. The highest TPC was recorded in the EtOAc extract under reflux (121.47 ± 0.32 mg GAE/g extract), followed by BuOH (109.47 ± 0.98 mg GAE/g extract) and MeOH (35.79 ± 1.10 mg GAE/g extract). Similarly, in the macerated samples, the TPC values were EtOAc (93.64 ± 5.64 mg GAE/g), BuOH (42.73 ± 0.81 mg GAE/g), and MeOH (25.09 ± 0.53 mg GAE/g). Among all extracts, EtOAc under reflux exhibited the strongest activity with an IC_{50} value of 74.0 ± 0.52 μg/mL, followed by MeOH (79.0 ± 0.50 μg/mL) and BuOH (87.3 ± 0.11 μg/mL).	[10]
The whole plant of *P. pellucida* was collected in Ogbeson, Ikpoba Hill, Edo State, Nigeria. The plant was authenticated by Dr. H.A. Akinnibosun from the Department of Plant Biology and Biotechnology, University of Benin.	Maceration was performed using distilled water (aqueous), 100% MeOH, and 70% MeOH. Phytochemical screening was conducted qualitatively to detect alkaloids, flavonoids, tannins, saponins, phenolics, and terpenoids.	The free radical scavenging activity was measured using the DPPH reagent	Ascorbic acid (50–250 μg/mL) was used as a reference standard.	Results are expressed as mean ± SEM. Statistical significance was determined using one-way ANOVA followed by Tukey's post-hoc test. A *p*-value of < 0.05 was considered significant.	The MeOH and aqueous extracts tested positive for alkaloids, flavonoids, tannins, saponins, phenolics, and terpenoids. At a concentration of 0.2 μg/mL, the aqueous extract demonstrated a DPPH scavenging activity of 83.53%, which was comparable to that of ascorbic acid (83.58%), indicating a strong hydrogen-donating ability and effective free radical neutralization.	[18]

https://doi.org/10.2147/JEP.S532898

The plant, with flowers, was collected in March 2009. Taxonomic authentication was performed at the Department of Botany, School of Biological Sciences, Universiti Sains Malaysia, where the herbarium specimen is deposited. The herbarium voucher number is 11154.	The plant was dried at 45°C in an oven, ground into a powder, and serially extracted with 5 L of petroleum ether, chloroform, and MeOH using a Soxhlet extractor, each for 3 d. The extracts were concentrated and subsequently lyophilized. The yields of petroleum ether, chloroform, and MeOH extracts were found to be 11.1 g, 5.92 g, and 21.26 g, respectively.	The free radical scavenging activity was measured using the DPPH reagent	BHT was used as a reference standard.	The results are reported as mean ± SEM. For comparison, one-way ANOVA followed by two-tailed Dunnett's multiple comparison test was used. Statistical analysis was performed using SPSS version 10. $p < 0.01$ and < 0.05 was considered statistically significant.	The MeOH extract exhibited the strongest radical scavenging activity, with an IC_{50} value of 0.083 ± 0.008 mg/mL, followed by the chloroform extract (0.1633 ± 0.019 mg/mL) and the petroleum ether extract (0.8200 ± 0.314 mg/mL). BHT demonstrated the highest activity with an IC_{50} of 0.027 ± 0.004 mg/mL.	[19]
The whole plant of *P. pellucida* was collected in June 2010 from the vicinity of the Department of Botany and Microbiology, University of Ibadan, Oyo State, Nigeria. The plant was authenticated by Dr. L.S. Adebisi, Head of the Department of Forestry and Wildlife, Faculty of Agriculture, University of Ibadan.	The plant was air-dried for 23 d, powdered, and extracted with MeOH using cold maceration. Fractions were obtained using C_6H_{14}, EtOAc, BuOH, and water. Phytochemical screening was performed to detect alkaloids, flavonoids, steroids, saponins, phenols, tannins, glycosides, reducing sugars, anthraquinones, carbohydrates, resins, and cardiac glycosides.	The free radical scavenging activity was measured using the DPPH reagent	BHA, ascorbic acid, and α-tocopherol were used as reference standards.	Not described	The crude MeOH extract was found to contain alkaloids, tannins, resins, flavonoids, steroids, phenols, and carbohydrates. All fractions exhibited significant DPPH radical scavenging activity, with the BuOH fraction showing the highest activity. At the lowest concentration (0.0625 mg/mL), the BuOH fraction demonstrated 98.6% inhibition, outperforming the standards (ascorbic acid, BHA, and α-tocopherol).	[20]
Stems and leaves were collected in Can Tho City, Vietnam. The plant materials were identified by Dr. Nguyen Thi Kim Hue from the Department of Biology, College of Natural Sciences, Can Tho University.	Maceration was performed with 96% EtOH (1:30 w/v) for 24 h, repeated 5x. The EtOH was evaporated via vacuum distillation. Phytochemical screening was conducted for alkaloids, flavonoids, polyphenols, tannins, saponins, and steroids. TPCs were quantified using the Folin-Ciocalteu method, and flavonoids were quantified using the $AlCl_3$ method.	The free radical scavenging activity was measured using the DPPH reagent	Gallic acid (0.05 mg/mL) was used as a reference standard.	All experiments were performed in triplicate.	The extract tested positive for alkaloids, flavonoids, polyphenols, tannins, saponins, and steroids. The TPC and flavonoid contents of the extract were reported to be 359.91 ± 0.77 mg GAE/g and 200.28 ± 1.23 mg QE/g, respectively. The extract demonstrated a weaker DPPH radical scavenging activity with an EC_{50} value of 730.3 ± 0.7 μg/mL compared to gallic acid with an EC_{50} of 8.3 ± 0.3 μg/mL.	[21]
Using ABTS reagent						
The leaves and stems of the plant were collected in August 2016 at the Forest Research Institute of Nigeria, Ibadan, Southwest Nigeria. The plant materials were identified by a plant taxonomist, and a voucher specimen (LUH 6956) was deposited at the Lagos University Herbarium (LUH).	The leaves were left to air-dry at an ambient room temperature for 5 d, while the stems were cut into smaller pieces and dried for 7 d. The dried plant materials were then pulverized, and EOs were extracted for 3 h using a modified Clevenger-type apparatus, repeated 3x. The extracts were analyzed using high-resolution GC-MS. GC-MS data were identified by matching the mass spectra with the Wiley 275 library and comparing retention indices.	The free radical scavenging activity was measured using the ABTS reagent	Ascorbic acid and β-carotene were used as a reference standard.	The IC_{50} (mg/mL) was calculated in a regression equation from a standard curve for each extract and reference compound. $p < 0.05$ was considered significant. Values are mean ± SD (n=3).	LEO exhibited more potent ABTS scavenging activity than SEO and the reference compounds, with an IC_{50} value of 1.94 ± 0.03 mg/mL, compared to 2.34 ± 0.01 mg/mL for SEO, 2.70 ± 0.02 mg/mL for ascorbic acid, and 1.71 ± 0.01 mg/mL for β-carotene.	[9]

(*Continued*)

https://doi.org/10.2147/JEP.S532898

Table 2 (Continued).

Part of the Plant, Collected in and Authenticated by	Extraction Method and Phytochemical Analysis	Oxidant Reagent	Control Used and Concentration	Data Analysis	Results	Ref
The whole plant of Peperomia pellucida was collected in Ogbeson, Ikpoba Hill, Edo State, Nigeria. The plant was authenticated by Dr. H.A. Akinnibosun from the Department of Plant Biology and Biotechnology, University of Benin.	Maceration was performed using distilled water (aqueous), 100% MeOH, and 70% MeOH. Phytochemical screening was conducted qualitatively to detect alkaloids, flavonoids, tannins, saponins, phenolics, and terpenoids.	The free radical scavenging activity was measured using the ABTS reagent	Ascorbic acid (50–250 µg/mL) was used as a reference standard.	Results are expressed as mean ± SEM. Statistical significance was determined using one-way ANOVA followed by Tukey's post-hoc test. A *p*-value of < 0.05 was considered significant.	The MeOH and aqueous extracts tested positive for alkaloids, flavonoids, tannins, saponins, phenolics, and terpenoids. The MeOH extract exhibited a higher ABTS radical scavenging activity of 62.77% at 0.2 µg/mL, compared to ascorbic acid (52.96%), highlighting the superior TAC of the MeOH extract.	[18]
Stems and leaves were collected in Can Tho City, Vietnam. The plant materials were identified by Dr. Nguyen Thi Kim Hue from the Department of Biology, College of Natural Sciences, Can Tho University.	Maceration was performed with 96% EtOH (1:30 w/v) for 24 hours, repeated five times. The EtOH was evaporated via vacuum distillation. Phytochemical screening was conducted for alkaloids, flavonoids, polyphenols, tannins, saponins, and steroids. TPC was quantified using the Folin-Ciocalteu method, and TFC was quantified using the $AlCl_3$ method.	The free radical scavenging activity was measured using the ABTS reagent.	Gallic acid (0.05 mg/mL) was used as a reference standard.	All experiments were performed in triplicate (n = 3).	The TPC and TFC of the extract were reported to be 359.91 ± 0.77 mg GAE/g and 200.28 ± 1.23 mg QE/g, respectively. The extract demonstrated stronger ABTS radical scavenging activity (EC_{50} value of 84.3 ± 0.5 µg/mL) compared to gallic acid (EC_{50} of 4.7 ± 0.2 µg/mL).	[21]
Using FRAC reagent						
The whole plant of Peperomia pellucida L. Kunth was collected in Amphoe Sampran, Nakornpathom Province, Thailand, in April 2011. Details of authentication were not specified in the original article.	The samples were macerated for 24 h at room temperature and refluxed for 45 min using MeOH, BuOH, and EtOAc (400 mL for 20 g of dried sample). The extracts were then concentrated using a rotary evaporator. The TPC was determined using the Folin–Ciocalteu method.	The free radical scavenging activity was measured using the FRAC reagent.	Not described	All experiments were performed in triplicate (n = 3). Data are presented as mean ± SD. ANOVA was performed using SPSS, with significance set at $p < 0.05$.	The highest yield was obtained with MeOH under reflux conditions (20.00 ± 0.69%), followed by BuOH (8.63 ± 0.06%) and EtOAc (4.07 ± 0.40%). For maceration, MeOH still showed the highest yield (10.28 ± 0.61%), while both BuOH (3.04 ± 0.59%) and EtOAc (3.06 ± 0.64%) produced lower yields, with no significant difference between them. Statistically, both the type of solvent and the extraction method significantly influenced the yield ($p < 0.05$), with reflux extraction consistently producing higher yields compared to maceration. The highest TPC was recorded in the EtOAc extract under reflux (121.47 ± 0.32 mg GAE/g extract), followed by BuOH (109.47 ± 0.98 mg GAE/g extract), and MeOH (35.79 ± 1.10 mg GAE/g extract). The highest reducing ability was found in the MeOH extract obtained via reflux (1.164 ± 0.028 µmol $FeSO_4$/g extract), followed by the MeOH-macerated extract (0.651 ± 0.005 µmol $FeSO_4$/g). EtOAc and BuOH extracts exhibited lower FRAP values: 0.218 ± 0.001 and 0.163 ± 0.011 µmol $FeSO_4$/g (reflux), and 0.154 ± 0.001 and 0.139 ± 0.004 µmol $FeSO_4$/g (maceration).	[10]

Using the TBA assay (lipid peroxide radical) reagent						
The leaves and stems of the plant were collected in August 2016 at the Forest Research Institute of Nigeria, Ibadan, Southwest Nigeria. The plant materials were identified by a plant taxonomist, and a voucher specimen (LUH 6956) was deposited at the Lagos University Herbarium (LUH).	The leaves were left to air-dry at an ambient room temperature for 5 d, while the stems were cut into smaller pieces and dried for 7 d. The dried plant materials were then pulverized, and EOs were extracted for 3 h using a modified Clevenger-type apparatus, repeated 3x. The extracts were analyzed using high-resolution GC-MS. GC-MS data were identified by matching the mass spectra with the Wiley 275 library and comparing retention indices.	The free radical scavenging activity was measured using the TBA (lipid peroxide radical) reagent	Ascorbic acid and β-carotene were used as a reference standard.	The IC_{50} (mg/mL) was calculated in a regression equation from a standard curve for each extract and reference compound. $p<0.05$ was considered significant. Values are mean ± SD (n = 3).	Both LEO and SEO exhibited notable lipid peroxidation (LP) radical scavenging activity, with LEO showing a lower IC_{50} value of 1.61 ± 0.02 mg/mL compared to 1.88 ± 0.01 mg/mL for SEO. These values were significantly lower than those of the reference compounds, ascorbic acid (2.90 ± 0.00 mg/mL) and β-carotene (2.12 ± 0.02 mg/mL), indicating that the essential oils possess superior lipid peroxidation inhibitory potential.	[9]
The whole plant of *P. pellucida* was collected in Ogbeson, Ikpoba Hill, Edo State, Nigeria. The plant was authenticated by Dr. H.A. Akinnibosun from the Department of Plant Biology and Biotechnology, University of Benin.	Maceration was performed using distilled water (aqueous), 100% MeOH, and 70% MeOH. Phytochemical screening was conducted qualitatively to detect alkaloids, flavonoids, tannins, saponins, phenolics, and terpenoids.	The free radical scavenging activity was measured using the TBA assay (lipid peroxide radical) reagent	Ascorbic acid (50–250 µg/mL) was used as a reference standard.	Results are expressed as mean ± SEM. Statistical significance was determined using one-way ANOVA followed by Tukey's post-hoc test. $p < 0.05$ was considered significant.	MeOH and aqueous extracts showed positive reactions for alkaloids, flavonoids, tannins, saponins, phenolics, and terpenoids. The MeOH extract demonstrated a lipid peroxidation inhibition of 66.95% at 0.2 µg/mL, while ascorbic acid inhibited lipid peroxidation by 91.85%, thus suggesting the substantial membrane-protective antioxidant properties of the extract.	[18]
Using the inhibition of the NO radical assay						
The leaves and stems of the plant were collected in August 2016 at the Forest Research Institute of Nigeria, Ibadan, Southwest Nigeria. The plant materials were identified by a plant taxonomist, and a voucher specimen (LUH 6956) was deposited at the Lagos University Herbarium (LUH).	The leaves were left to air-dry at an ambient room temperature for 5 d, while the stems were cut into smaller pieces and dried for 7 d. The dried plant materials were then pulverized, and EOs were extracted for 3 h using a modified Clevenger-type apparatus, repeated 3x. The extracts were analyzed using high-resolution GC-MS. GC-MS data were identified by matching the mass spectra with the Wiley 275 library and comparing retention indices.	The free radical scavenging activity was measured using the NO method.	Ascorbic acid and β-carotene were used as a reference standard.	The IC_{50} (mg/mL) was calculated in a regression equation from a standard curve for each extract and reference compound. $p < 0.05$ was considered significant. Values are mean ± SD (n = 3).	The EOs demonstrated concentration-dependent NO scavenging activity, with LEO exhibiting significantly stronger effects (IC_{50} value of 2.10 ± 0.04 mg/mL) compared to SEO (2.40 ± 0.03 mg/mL) and the reference compounds (ascorbic acid at 2.83 ± 0.01 mg/mL and β-carotene at 2.39 ± 0.01 mg/mL).	[9]
Using H_2O_2 scavenging activity						
The whole plant of *P. pellucida* was collected in Ogbeson, Ikpoba Hill, Edo State, Nigeria. The plant was authenticated by Dr. H.A. Akinnibosun from the Department of Plant Biology and Biotechnology, University of Benin.	Maceration was performed using distilled water (aqueous), 100% MeOH, and 70% MeOH. Phytochemical screening was conducted qualitatively to detect alkaloids, flavonoids, tannins, saponins, phenolics, and terpenoids.	The free radical scavenging activity was measured using hydrogen peroxide.	Ascorbic acid (50–250 µg/mL) was used as a reference standard.	Results are expressed as mean ± SEM. Statistical significance was determined using one-way ANOVA followed by Tukey's post-hoc test. $p < 0.05$ was considered significant.	MeOH and aqueous extracts showed positive reactions for alkaloids, flavonoids, tannins, saponins, phenolics, and terpenoids. The MeOH extract exhibited H_2O_2 scavenging activity of 92.75% at 0.2 µg/mL, which was markedly higher than that of ascorbic acid (74.56%), indicating its high electron-donating ability to detoxify H_2O_2 and prevent oxidative cellular damage.	[18]

(*Continued*)

https://doi.org/10.2147/JEP.S532898

Table 2 (Continued).

Part of the Plant, Collected in and Authenticated by	Extraction Method and Phytochemical Analysis	Oxidant Reagent	Control Used and Concentration	Data Analysis	Results	Ref
The whole plant of *P. pellucida* was collected in June 2010 from the vicinity of the Department of Botany and Microbiology, University of Ibadan, Oyo State, Nigeria. The plant was authenticated by Dr. L.S. Adebisi, Head of the Department of Forestry and Wildlife, Faculty of Agriculture, University of Ibadan.	The plant was air-dried for 23 d, then powdered and extracted with MeOH using cold maceration. Fractions were obtained using C_6H_{14}, EtOAc, BuOH, and water. Phytochemical screening was performed to detect alkaloids, flavonoids, steroids, saponins, phenols, tannins, glycosides, reducing sugars, anthraquinones, carbohydrates, resins, and cardiac glycosides.	The free radical scavenging activity was measured using H_2O_2.	BHA, ascorbic acid, and α-tocopherol were used as reference standards.	Not described	The crude MeOH extract contained alkaloids, tannins, resins, flavonoids, steroids, phenols, and carbohydrates. The fractions demonstrated significant H_2O_2 scavenging activity in a concentration-dependent manner. The BuOH fraction exhibited the strongest activity, followed by the crude MeOH extract and EtOAc fraction.	[20]
Using the FRP method						
Stems and leaves were collected in Can Tho City, Vietnam. The plant materials were identified by Dr. Nguyen Thi Kim Hue from the Department of Biology, College of Natural Sciences, Can Tho University.	Maceration was performed with 96% EtOH (1:30 w/v) for 24 h, repeated 5x. The EtOH was evaporated via vacuum distillation. Phytochemical screening was conducted for alkaloids, flavonoids, polyphenols, tannins, saponins, and steroids. TPCs were quantified using the Folin-Ciocalteu method, and flavonoids were quantified using the $AlCl_3$ method.	The free radical scavenging activity was measured using the FRP method.	Gallic acid (0.05 mg/mL) was used as a reference standard.	All experiments were performed in triplicate (n = 3).	The extract tested positive for alkaloids, flavonoids, polyphenols, tannins, saponins, and steroids. The TPC and TFC contents of the extract were reported to be 359.91 ± 0.77 mg GAE/g and 200.28 ± 1.23 mg QE/g, respectively. The extract also exhibited ferric reducing ability, with an EC_{50} value of 95.3 ± 1.2 μg/mL. This value was notably higher than that of gallic acid, which had an EC_{50} of 3.3 ± 0.5 μg/mL, indicating a lower reducing power.	[21]
Using the TAC method						
The whole plant of *P. pellucida* was collected in Ogbeson, Ikpoba Hill, Edo State, Nigeria. The plant was authenticated by Dr. H.A. Akinnibosun from the Department of Plant Biology and Biotechnology, University of Benin.	Maceration was performed using distilled water (aqueous), 100% MeOH, and 70% MeOH. Phytochemical screening was conducted qualitatively to detect alkaloids, flavonoids, tannins, saponins, phenolics, and terpenoids.	The free radical scavenging activity was measured using the TAC method.	Ascorbic acid (50–250 μg/mL) was used as a reference standard.	Results are expressed as mean ± SEM. Statistical significance was determined using one-way ANOVA followed by Tukey's post-hoc test. $p < 0.05$ was considered significant.	MeOH and aqueous extracts showed positive reactions for alkaloids, flavonoids, tannins, saponins, phenolics, and terpenoids. The MeOH extract exhibited the highest TAC (95.63%) at 0.2 μg/mL, which is closely similar to that of ascorbic acid (97.3%).	[18]
Stems and leaves were collected in Can Tho City, Vietnam. The plant materials were identified by Dr. Nguyen Thi Kim Hue from the Department of Biology, College of Natural Sciences, Can Tho University.	Maceration was performed with 96% EtOH (1:30 w/v) for 24 h, repeated 5x. The EtOH was evaporated via vacuum distillation.	The free radical scavenging activity was measured using the TAC method.	Gallic acid (0.05 mg/mL) was used as a reference standard.	All experiments were performed in triplicate (n = 3).	The antioxidant capacity of the extract (114.7 ± 1.7 μg/mL) was weaker than gallic acid (4.0 ± 0.1 μg/mL).	[21]

Abbreviations: ABTS, 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid) diammonium salt; $AlCl_3$, aluminum chloride; ANOVA, analysis of variance; BHA, butylated hydroxyl anisole; BHT, butyl hydroxytoluene; BuOH, butanol; C_6H_{14}. Hexane; DPPH, 2,2-diphenyl-1-picrylhydrazyl; EC_{50}, half maximum effective concentration; EO, essential oils; EtOAc, ethyl acetate; EtOH, ethanol; FRAC, ferrous reducing antioxidant capacity; FRP, ferric reducing power; GAE, gallic acid equivalence; GC-MS, gas chromatography-mass spectroscopy; IC_{50}, half maximum inhibitory concentration; H_2O_2, hydrogen peroxide; LEO, leaves essential oils; MeOH, methanol; Na_2SO_4, sodium sulfate; NO, nitric oxide; QE, quercetin equivalence; SEM, standard error of the mean; SEO, stem essential oils; TAC, total antioxidant capacity; TBA, thiobarbituric acid; TFC, total flavonoid content; TPC, total phenolic content;

https://doi.org/10.2147/JEP.S532898

The protein targets reported were those involved in estrogenic activities,[12] inflammation and pain,[13,16] hypertension,[14] glucose metabolism,[15,17] and neuroprotection.[11]

In one study, three phenylpropanoids and two lignan derivatives were molecular-docked to estrogen receptors (Erα with PDB ID: 1GWR and Erβ with PDB ID: 3OLS), and the binding energy resulting from the interaction was compared to that of 17β-estradiol. These phytoconstituents revealed similar capabilities to interact with both proteins, revealing their estrogenic activity.[12] Pellucidin A, a lignan compound, was reported by Queiroz et al (2020) for its strong binding to the active site of inducible NOS (iNOS) (PDB ID: 1M8D, endothelial NOS (eNOS) (PDB ID: 1M9J), and in the allosteric binding site of COX-2 (PDB ID: 4COX), which is similar to indomethacin, a known non-steroidal anti-inflammatory drug.[16] The strong binding affinities of the *P. pellucida* phytoconstituents towards NF-κB p65 (PDB ID 9BDW) and PPAR-γ (PDB ID 3U9Q) have confirmed their anti-inflammatory activity. In this paper, Queiroz et al (2020) validated the in silico results with an in vitro study.[13]

A further search in the Scopus database using the same keywords ("Peperomia pellucida AND molecular docking") and the publication period of 2014 to 2025 was performed, resulting in eight articles. Of those, three articles were excluded due to duplication with results in the PubMed database, and one article was published before 2014. The results are as follows:

Polyphenolic compounds from *P. pellucida* were molecular-docked towards angiotensin-converting enzyme (ACE) (PDB ID 1UZF) in complex with captopril, revealing the best binding affinity of tetrahydrofuran lignin with a value of −8.66 kcal/mol, which is better than captopril (−6.36 kcal/mol), thus revealing its potential as an antihypertensive agent.[14] Dimethoxy ellagic acid obtained from the ethanol extract of the same plant interacted with aldose reductase (PDB ID 3S3G) and with alpha-amylase (PDB ID 1B2Y) and the DEA-enzyme complexes were stable for more than 100 ns, thus evidencing its role in modulating glucose metabolism.[15] Similarly, peperochromene A obtained from *P. pellucida* has been shown to interact with four essential enzymes in carbohydrate metabolism, indicating its antidiabetic properties.[17] The flavonoids acacetin, isovitexin, and apigenin of *P. pellucida* were molecular-docked towards human AChE (acetylcholinesterase) in complex with dihydrotanshinone I (PDB ID 4M0E), revealing that all the flavonoids interacted with the enzyme in similar binding mode with the standard drugs (donepezil; PubChem CID 3152 and rivastigmine; PubChem CID 77991), proclaiming their neuroprotective activity.[11]

In vitro Pharmacological Activity Study

In silico studies need to be validated with in vitro and in vivo techniques, which have been reported in several papers. A search on the PubMed database using the keywords "Peperomia pellucida AND in vitro" resulted in eight articles;[9,11,13,21–32] of those, two were excluded because they were not original articles. A further search in the Scopus database using the same keywords ("Peperomia pellucida AND in vitro") and publication period of 2014 to 2025 was performed, resulting in 35 articles, of those, 26 articles were excluded either due to duplication with results in the PubMed database, articles were reviews/not original research, articles were short communications, articles were in silico or in vivo, articles were not related to the topic or only studying isolation technique of compounds, or articles did not discussing *P. pellucida* extract. The included articles portrayed assays of antibacterial,[9,22–28] anti-inflammatory,[13,29,] neuroprotective,[11] repellent,[30] and antidiabetic activity,[21,32] as presented in Table 3.

Antibacterial, antifungal, and antiplasmodial activities of *P. pellucida* were reported in 8 articles in inhibiting *Escherichia coli*,[9,22,24,26] *Enterobacter cloacae*,[9] *Enterococcus faecalis*,[23] *Lactobacillus casei*,[23] *Listeria ivanovii*,[9] *Mycobacterium smegmatis*,[9] *Proteus mirabilis*,[25] *Pseudomonas aeruginosa*,[22,24] *P. fluorescens*,[25] *Staphylococcus aureus*,[9,22,24,25] *Streptococcus uberis*,[9] *S. mutans*,[23] *S. mitis*,[23] *S. sanguinis*,[23] *S. salivarius*,[23] *S. sobrinus*,[23] *S. pneumoniae*,[26] *Salmonella typhi*,[24] *Bacillus subtilis*,[25] *Vibrio parahaemolyticus*,[9] *Candida albicans*,[28] and *Plasmodium falciparum*.[25]

Anti-inflammatory activities were confirmed in human retinal pigment epithelial cell line (ARPE-19) exposed to high glucose and advanced glycation end product (AGE) under different glucose environments, as reported by Ho et al (2024). In this study, the methanol extract of *P. pellucida* collected in Selangor, Malaysia, and the ethyl acetate fraction significantly downregulated ($p < 0.05$) the expression of the pro-inflammatory and angiogenic markers, thus confirming their potential anti-inflammatory activity,[13] and markedly suppressed the expression of IL-8 ($p < 0.05$), indicating its anti-inflammatory activity by altering the Janus kinase (JAK)-STAT3 pathway, as described by the same authors.[29]

Table 3 In vitro Pharmacological Activity and Cytotoxicity of *Peperomia Pellucida* L. Kunth. Reported in the Period from 2014 to 2025

Part of the Plant, Collected in and Authenticated by	Extraction Method	Phytochemical Analysis and the Bioactive Compounds	Type of Cell or Bacteria	Model Category, Methods, Inducer, and Parameter Assessed	Control Drug Used and Concentration	Statistical Analysis	Results	Ref
Antibacterial/Antiplasmodial/Antifungal Activity								
The leaves and stems of the plant were collected in August 2016 at the Forest Research Institute of Nigeria, Ibadan, Southwest Nigeria. The plant materials were identified by a plant taxonomist, and a voucher specimen (LUH 6956) was deposited at the Lagos University Herbarium (LUH).	The leaves were left to air-dry at an ambient room temperature for 5 d, while the stems were cut into smaller pieces and dried for 7 d. The dried plant materials were then pulverized, and EOs were extracted for 3 h using a modified Clevenger-type apparatus, repeated 3×.	EOs obtained from the leaves and stems were analyzed using high-resolution GC-MS. The main bioactive terpenoids identified were linalool (17.09%), limonene (14.25%), β-caryophyllene (12.52%), and linalyl acetate (10.15%).	*S. aureus*, *L. ivanovii*, *M. smegmatis*, *S. uberis*, *E. cloacae*, *E. coli*, *V. parahaemolyticus*	Antibacterial activity was assessed using the microdilution method. The parameters determined were the MIC and MBC.	Ciprofloxacin was used as the positive control, and DMSO as the negative control.	All experiments were performed in triplicate (n = 3). All results are expressed as means ± SD. Analysis was carried out using SPSS 15.0 for Windows. $p < 0.05$ was considered significantly different.	EOs exhibited strong antibacterial activities against six bacterial strains with MICs ranging between 0.15 and 0.20 mg/mL EOs were bactericidal at MBC 0.20 mg/mL against *S. aureus*.	[9]
The leaves, bark, aerial parts, and seeds of the plant were collected in Suchdol, Czech Republic. The plant materials were identified by Prof. Kokoska, and voucher specimens were deposited in the herbarium of the Department of Botany and Plant Physiology, Faculty of Agrobiology, Food and Natural Resources, Czech University of Life Sciences, Prague.	Each dried plant sample was finely ground into powder, extracted with 80% EtOH for 24 h at room temperature, and concentrated under reduced pressure using a rotary evaporator at 40 °C. The dried residues were finally dissolved in 100% DMSO to prepare stock solutions at a final concentration of 51.2 mg/mL.	Not described	*S. aureus* (ATCC 25923, 29,213, 33,591, 33,592, 43300, BAA 976) *E. coli* (ATCC 25922) *P. aeruginosa* (ATCC 27853) *C. acnes* (ATCC 11827) *B. fragilis* (ATCC 25285) *C. difficile* (DSMZ 12056) *C. perfringens* (DSMZ 11778) *F. magna* (DSMZ 2974)	The broth microdilution method was used to determine the MIC of the tested compounds.	Gentamicin and oxacillin were used as positive controls.	MIC values were obtained from 3 independent experiments, each performed in triplicate.	*The extracts* inhibited the growth of *S. aureus*, *E. coli, and P. aeruginosa* with a MIC ≥ 4 μg/mL.	[22]
Leaves of the plant were collected in March 2019 in Itacoatiara, Amazonas, Brazil (S 03°08′ 28.800″, W 58°26′54.300″). The plant materials were identified by Prof. Dr. Ari de Freitas Hidalgo, and a voucher specimen (No. 8264) was deposited in the Herbarium of the Federal University of Amazonas.	Fresh leaves were hydro-distilled for 3 h using a Clevenger-type apparatus. The EO was separated by freezing and stored at −20 °C until further use.	EOs were dissolved in ET_2O and analyzed using GC-FID and GC-MS. Separation was carried out on an Rtx-5 capillary column with a temperature program ranging from 60°C to 240°C. Helium (1.0 mL/min) was used as the carrier gas, with a split ratio of 1:10 and an injection volume of 0.1 μL. The EOs contained phenylpropanoids (41.7%), monoterpenes (0.7%), and sesquiterpenes (52.4%). The major compounds identified were 3,4-(methylenedioxy) propiophenone (11.3%), α-pinene (19.2%), and dillapiole (40.6%).	Gram-positive bacterial strains (ATCC): *S.mutans*, *S. mitis*, *S. sanguinis*, *S. salivarius*, *S. sobrinus*, *E. faecalis*, *L. casei*	Antibacterial activity was assessed using the broth microdilution method in 96-well plates. EO concentrations ranging from 4000 to 3.9 μg/mL. The MIC was determined based on the resazurin colorimetric change after 24 h of incubation at 37 °C.	Chlorhexidine dihydrochloride (59.0 to 0.115 μg/mL) was used as the positive control.	All experiments were performed in triplicate (n = 3). Microbial activity was assessed based on visual color changes using resazurin as an indicator.	The EO exhibited antibacterial activity against *S. mutans*, *L. casei*, and *E. faecalis*.	[23]

https://doi.org/10.2147/JEP.S532898

Aerial parts of the plant were collected in 2017 at the garden of the Institute of Biological Sciences, University of Malaya (UM), Kuala Lumpur, Malaysia. The plant materials were identified, and a voucher specimen was deposited in the UM Herbarium.	The dried plant materials were Soxhlet-extracted with MeOH or EtOH for 48 h. The extracts were then concentrated using a rotary evaporator and stored at −20°C.	The chemical composition was analyzed using GC-MS. GC-MS data were interpreted using the National Institute of Standards and Technology (NIST) Version 2011 library. The MeOH extract contained 13 constituents, with the most abundant being 1,2-dimethoxy-4-(2-methoxyethenyl) benzene, octadecane, dodecane, hexadecane, eicosane, and caryophyllene. The EtOH extract contained 13 constituents, with the most abundant being pentanedioic acid, heneicosane, heptadecane, octasiloxane, dodecane, apiol, and phytol.	*S. typhi*, *P. aeruginosa*, *E. coli*, *S. aureus*	Antibacterial activity was assessed using the disk diffusion assay (modified Bauer method). The parameter assessed was the diameter of the inhibition zone.	Chloramphenicol was used as the positive control at 10 µg/mL.	Statistical differences were determined using Duncan's Multiple Range Test at a significance level of $p < 0.05$.	The extracts showed antimicrobial activity against *S. aureus, S. typhi, E. coli*, and *P. aeruginosa*. The highest activity was observed in the MeOH extract against *S. aureus* (inhibition zone 12.5 mm). The EtOH extract exhibited antibacterial activity against *S. typhi* and *P. aeruginosa* (inhibition zone 12 mm).	[24]
Leaves were collected in May 2014 at the National Botanical Garden, Dhaka, Bangladesh. The plant materials were identified by a botanist at the Bangladesh National Herbarium, Mirpur, Dhaka, and a voucher specimen was deposited in the herbarium.	The leaves were extracted with 90% EtOH at room temperature for 10 d. The extract was filtered and concentrated using a rotary evaporator, then partitioned via the Kupchan method into C_6H_{14}, EtOAc, $CHCl_3$, and aqueous fractions.	Preliminary phytochemical screening of the organic extracts revealed the presence of carbohydrates, steroids, alkaloids, tannins, and flavonoids. The C_6H_{14}-soluble fraction contained all secondary metabolites except carbohydrates, while the $CHCl_3$ and EtOH-soluble fractions contained non-reducing carbohydrates but lacked steroids.	Bacterial strains: 3 Gram-positive: *S. aureus*, *B. subtilis*, *B. cereus* and 5 Gram-negative: *E. coli*, *P. mirabilis*, *P. fluorescens*, *P. aeruginosa*, *S. typhi.*	Antibacterial activity was assessed using the disc diffusion method. The parameter assessed was the diameter of the inhibition zones (in mm).	Penicillin was used as the positive control at 10 mg/mL.	All results are expressed as means ± SD. Statistical analysis was performed using Student's paired *t*-test. A *p*-value of < 0.01 was considered statistically significant.	The extract showed antibacterial activity against various Gram-positive and Gram-negative bacteria at concentrations of 1.0, 2.0, 5.0, and 10.0 mg/mL, compared to penicillin (10 mg/mL). The EtOH extract showed higher inhibitory action against *S. aureus, B. subtilis, P. mirabilis*, and *P. fluorescens*. Among the fractions, the C_6H_{14} fraction exhibited the highest activity, with a maximum inhibition zone of 18.4 mm against *P. mirabilis*.	[25]
The whole plant was collected in August 2020 in Kerala, India. The plant materials were identified by Dr. Dhanapal V. from Sri Sastha College of Pharmacy, Chennai, India.	The plant was extracted with MeOH using a modified Clevenger-type apparatus for 5 h.	Not described	*S. pneumoniae*, *E. coli*	Antibacterial activity was tested using the agar well diffusion method. The parameters measured were the diameter of the inhibition zone, MIC, and MBC.	Amikacin was used as the standard drug, at 10 µg.	Statistical analysis was performed using one-way ANOVA followed by Duncan's Multiple Range Test (SPSS version 12.0). $p < 0.05$ was considered statistically significant.	The extract exhibited antibacterial activity against *S. pneumoniae* and *E. coli*, with inhibition zones of 16 ± 5 mm and 15 ± 3 mm, respectively. The MIC and MBC tests revealed that the extract had a MIC value of 2000 µg/mL and an MBC of 1000 µg/mL for both bacteria. In comparison, Amikacin demonstrated a MIC of 62.5 µg/mL and an MBC of 31.25 µg/mL.	[26]

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https://doi.org/10.2147/JEP.S532898

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Table 3 (Continued).

Leaves and stems were collected in North Gorontalo, Indonesia. The plant materials were identified by a botanist at the Herbarium Biology Laboratory, Universitas Negeri Gorontalo, and a voucher specimen was deposited in the herbarium.	The leaves and stems were extracted with MeOH at room temperature for 2 d, followed by partitioning with n-C_6H_{14} and EtOAc.	The EtOAc extract was purified using silica gel G60 column chromatography with n-C_6H_{14}/EtOAc elution, employing a linear gradient from 10% to 100% EtOAc, resulting in 11 fractions (A1–A11). The compounds identified were 3-hydroxy-24-ethyl-5,22-cholestadiene (a steroid) and 3-hydroxy-9-lanosta-7,24E-dien-26-oic acid (a triterpenoid).	*P. falciparum* 3D7	Antiplasmodial activity was assessed using the Desjardins method. The assay was initiated at 1% parasitemia and incubated for 48 h. Parasitemia levels were assessed using Giemsa staining, and the percentage of infected erythrocytes was determined by counting parasitized RBCs/ 500 total RBCs under a microscope.	Chloroquine diphosphate was used at 25 mg/kg BW.	*Statistical analysis was performed using an unpaired two-tailed t-test with GraphPad Prism.* Differences were considered statistically significant at $p < 0.05$.	The MeOH crude extract at concentrations ranging from 0.1 to 100 µg/mL exhibited significant antiplasmodial activity, with an IC_{50} value of 4.0 µg/mL.	[27]
Fresh leaves were collected in Malang, East Java, Indonesia.	Fresh leaves were extracted with 95% EtOH at room temperature for 3 d, each for 24 h.	Not described	*C. albicans* isolate	Antifungal activity was assessed using the agar diffusion method on SDA plates inoculated with *C. albicans* standardized to 0.5 McFarland. The parameter determined was the diameter of the inhibition zone.	Nystatin was used as the positive control.	Data were analyzed using one-way ANOVA followed by the LSD test at a significance level of 1% ($p < 0.01$).	The extract demonstrated significant antifungal activity against *C. albicans* with the highest inhibition zone of 5.48 mm at 70% and 80% concentrations, which was significantly larger than that of Nystatin (1.39 mm).	[28]
Anti-inflammatory/Antidiabetic/Anticancer Activity								
Aerial parts of the plant were collected in Selangor, Malaysia. The plant materials were identified by a botanist, with validation confirmed on 1st December 2023 through the International Plant Names Index (IPNI). A voucher specimen (KLU50130) was deposited at the Rimba Ilmu Botanic Garden, University of Malaya.	The plant was macerated in MeOH at 10% (w/v) for 72 h at 25°C, followed by filtration and solvent removal under reduced pressure. The extract was then fractionated using C_6H_{14}, $CHCl_3$, EtOAc, and n-BuOH.	Phytochemical analysis was conducted using various techniques to identify and characterize the bioactive compounds in *P. pellucida*. TLC was performed on aluminum plates coated with fluorescent indicator F254, using a $CHCl_3$-C_6H_{14} (1:1) mobile phase, and visualized under ultraviolet light at 254 nm. *GC-MS analysis* was carried out, and compound identification was based on the NIST database. A range of bioactive compounds were identified, including non-polar phytochemicals (β-santalene, dillapiole, β-caryophyllene, β-elemene) and polar constituents (pheophorbide A-methyl ester, N-cyclohexanecarbonylpentadecylamine, dictyoquinazol, 2,4,5-trimethoxystyrene, and 9-octadecenoic acid methyl ester).	ARPE-19 (human retinal pigment epithelial cell line)	Anti-inflammatory activity relevant to diabetic retinopathy induced by high glucose concentrations (17, 34, and 68 mM) and products AGEs. SDS-PAGE, Western blotting, and ELISA were employed to assess the expression of key inflammatory and oxidative stress markers, including p-NF-κB p65, PPAR-γ, p-PPAR-γ, IL-8, MCP-1, MMP-2, VEGF, RAGE, and GPx. sRAGE levels were quantified in the culture supernatant via ELISA.	Not described	Statistical analysis was performed using GraphPad Prism version 9.5.1. Data were analyzed using one-way ANOVA followed by Tukey's post hoc test. A *p*-value of < 0.05 was considered statistically significant.	The MeOH extract (1.5 and 3 mg/mL) and the EtOAc fraction (4 mg/mL) were non-toxic to ARPE-19 cells. Treatment significantly ($p < 0.05$) reduced the levels of phosphorylated NF-κB p65, IL-8, MCP-1, MMP-2, VEGF, and RAGE, while upregulating PPAR-γ, GPx, and sRAGE expression. These findings indicate protective effects against high glucose and AGE-induced cellular stress.	[13]

Aerial parts of the plant were collected in Selangor, Malaysia. The plant materials were identified by a botanist, with validation confirmed on 1st December 2023 through the International Plant Names Index (IPNI). A voucher specimen (KLU50130) was deposited at the Rimba Ilmu Botanic Garden, University of Malaya.	The plant was macerated in MeOH at 10% (w/v) for 72 h at 25°C, followed by filtration and solvent removal under reduced pressure. The extract was then fractionated using C_6H_{14}, $CHCl_3$, EtOAc, and n-BuOH.	Phytochemical analysis was conducted using various techniques to identify and characterize the bioactive compounds in *P. pellucida*. *GC-MS analysis* was carried out, and compound identification was based on the NIST database. The identified phytochemicals include phenylpropanoids, terpenes, and fatty acids.	ARPE-19 cell line	Anti-inflammatory activity was assessed through a model of AGE-induced inflammation associated with diabetic retinopathy. Furthermore, IL-8 suppression and restoration of cell viability were assessed to determine the anti-inflammatory potential of the tested extracts.	Not described	A p-value of < 0.05 was considered statistically significant.	AGE stimulation significantly increased the expression of STAT3, IL-8, MCP-1, MMP-2, and VEGF at both the gene (2.4–5.8-fold) and protein (1.4–2.3-fold) levels. Treatment with the MeOH extract at 1.5 mg/mL effectively suppressed IL-8 expression ($p < 0.05$) and restored cell viability under AGE-induced stress conditions. The MeOH extract and EtOAc fraction exhibited no cytotoxicity, with IC_{50} values of 8.70 mg/mL and 7.34 mg/mL, respectively. The anti-inflammatory activity was attributed to modulation of the JAK-STAT3 signaling pathway.	[29]
Fresh (and some dried) leaves and/or bark were collected in the Departments of Atlántico and Sucre, Colombia. The plant materials were identified by a botanist from the Instituto de Ciencias Naturales, Universidad Nacional de Colombia.	Hydrodistillation was assisted by microwave heating (4 cycles of 15 min each, for a total of 1 h) using a modified apparatus with a Dean–Stark reservoir.	EOs were isolated from 200–300 g of fresh or dried plant material by hydrodistillation, assisted by microwave heating for 1 h in four 15-min cycles. After isolation, the EOs were decanted, dehydrated with anhydrous Na_2SO_4, and analyzed by GC-MS. Chromatographic and mass spectrometry data were processed with Thermo Xcalibur™ v. 2.2 SP1.48 and AMDIS v. 2.70. Linear retention indices were calculated using a C7-C35 hydrocarbon mixture. The EOs leaves were primarily composed of carotol (44%) and dillapiole (21%)	Not using cells or bacteria	AChE inhibitory activity was assessed using a microplate-based assay, with absorbance measured at 412 nm following a 6-min incubation period. The half-maximal inhibitory concentration (IC_{50}) value was subsequently calculated to quantify the potency of enzyme inhibition.	Chlorpyrifos (0.3–4.8 µg/mL) was used as the positive control.	Statistical analyses were conducted using IBM SPSS Statistics version 27, Statgraphics Centurion 18, and R Core version 4.0.3. One-way and two-way ANOVA with Tukey's HSD and Dunnett's post hoc tests, as well as the Kolmogorov–Smirnov test, Levene's test, and Spearman correlation analysis. Multivariate methods such as PCA, CA, and KmCA were also applied.	The inhibitory activity against the AChE enzyme was lower compared to chlorpyrifos (IC_{50} = 0.59 µg/mL).	[30]

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https://doi.org/10.2147/JEP.S532898

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Table 3 (Continued).

The whole plant was collected in April 2022 from the southwestern region of Thiruvananthapuram District, Kerala, India. Authentication details were not specified in the source.	Soxhlet extraction was performed on 100 g of powdered plant material using 500 mL of EtOH at 65°C for 72 h. The extract was then concentrated using a rotary vacuum evaporator at 50°C, followed by further extraction with EtOH, PE, and EtOAc (3× 11 mL each). The resulting extracts were evaporated under reduced pressure.	The EtOH extract contains acacetin, isovitexin, and apigenin	Not using cells or bacteria	AChE inhibitory activity was assessed using Ellman's colorimetric method, adapted to a 96-well microplate format. The reaction mixture contained DTNB, AChE enzyme, Tris buffer, and plant extracts at varying concentrations (25–400 µg/mL). The enzymatic reaction was initiated by the addition of ATCI, and absorbance was recorded at 412 nm after 5 and 20 min of incubation. AChE inhibition was expressed as a percentage, and the IC_{50} value was calculated to determine inhibitory potency.	Galantamine was used as the positive control.	Not described	The extract demonstrated potential as an AChE inhibitor, targeting the enzyme responsible for the breakdown of acetylcholine, a neurotransmitter essential for cognitive processes. Among the tested extracts, the EtOH fraction exhibited the strongest AChE inhibitory activity (IC_{50} = 175.12 µg/mL), outperforming the EtOAc and PE extracts (IC_{50} = 279.67 and 313.54 µg/mL, respectively). Although the inhibitory effect was dose-dependent, it remained less potent than the reference compound galantamine (IC_{50} = 130.79 µg/mL).	[11]
Aerial parts of the plant were collected from the Manoko Experimental Garden, Medicinal Plants Center, Forestry Department, Lembang, West Java, Indonesia. The plant materials were identified by a botanist from the Taxonomy Laboratory, Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Padjadjaran.	Cold maceration was performed with 70% EtOH for 3 d, with 3 extraction cycles. The extract was then evaporated at 50°C using a rotary evaporator.	Phytochemical screening was conducted to identify secondary metabolites in the plant, resulting in the presence of flavonoids, polyphenols, monoterpenoids, sesquiterpenoids, steroids, and quinones.	*Not using cells or bacteria*	XO inhibitory activity was assessed using a spectrophotometric assay, in which the enzymatic conversion of xanthine (0.15 mmol) to uric acid was monitored by measuring absorbance at 290 nm. The percentage of enzyme inhibition and the IC_{50} value were calculated based on the reduction in uric acid formation	Allopurinol was used as the positive control, with a final concentration of 0.1–2 µg/mL.	IC_{50} values were calculated using linear regression analysis. All experiments were performed in triplicate (n = 3), data are presented as mean ± SD) Statistical analysis was performed using one-way ANOVA, and a p-value < 0.05 was considered statistically significant.	The extract exhibited XO inhibitory activity with an IC_{50} value of 43.11 µg/mL. Although this potency is lower than that of the reference compound allopurinol (IC_{50} = 1.24 µg/mL), the extract demonstrates a promising potential as a natural alternative for managing hyperuricemia-related conditions.	[31]

The whole herb was collected from Curahkalong, Jember, East Java, Indonesia. Authentication details were not specified in the source.	Ultrasonication was performed with 96% EtOH at a ratio of 1:7.5, followed by fractionation using EtOAc.	Phytochemical screening of *P. pellucida* was performed to identify flavonoids, alkaloids, polyphenols, and saponins. Patuloside A, isovitexin, isoswertisin, pellucidatin, and caryatin-7-O-β-rhamnoside were identified as bioactive compounds.	Enzyme α-*glucosidase*	The antidiabetic potential of the extract was assessed through an α-glucosidase inhibition assay, where 10 μL of the test sample was incubated with α-glucosidase (0.1 U/mL) and PNPG as the substrate. Enzymatic activity was assessed by measuring absorbance at 415 nm, and the percentage of inhibition was used to determine the extract's efficacy.	Acarbose was used as the positive control.	Linear regression analysis was used to determine the IC_{50} by plotting the percentage of inhibition against the logarithm of the concentration. All experiments were conducted in triplicate (n = 3), and all results are expressed as mean ± SD.	Both the EtOH extract and EtOAc fraction demonstrated inhibitory activity, with IC_{50} values of 13.43 mg/mL and 9.73 mg/mL, respectively. Although slightly less potent than the standard drug acarbose (IC_{50} = 8.11 mg/mL), the results suggest a promising potential for postprandial glucose regulation.	[32]
Stems and leaves were collected in Can Tho City, Vietnam. The plant materials were identified by Dr. Nguyen Thi Kim Hue from the Department of Biology, College of Natural Sciences, Can Tho University.	Maceration was performed using 96% EtOH at a ratio of 1:30 (w/v) for 24 h, repeated 5x. The extract was then concentrated by vacuum distillation.	Preliminary chemical composition characterization of *P. pellucida* identified biologically active compounds, including alkaloids, flavonoids, saponins, polyphenols, tannins, and steroids. Polyphenol content was quantified using the Folin-Ciocalteu reagent. Flavonoid content was quantified using the $AlCl_3$ reagent. The extract was rich in polyphenols (359.91 mg GAE/g) and flavonoids (200.28 mg QE/g).	Enzyme α-amylase	An α-amylase inhibition assay was conducted using a reaction mixture containing plant extract, buffer, α-amylase enzyme (3 U), and starch substrate (2 mg/mL). The mixture was incubated at 37°C, and the reaction was terminated with HCl, followed by color development with iodine solution. Absorbance was measured at 660 nm to determine residual starch content. Inhibitory activity was expressed as a percentage of α-amylase inhibition, with an IC_{50} value of 12.52 ± 0.68 mg/mL for the EtOH extract.	Acarbose was used as the positive control.	All experiments were performed in triplicate (n = 3), and results are expressed as mean ± SD. Statistical differences were analyzed using appropriate tests based on data distribution and experimental design.	The EtOH extract exhibited α-amylase inhibitory activity with an EC_{50} value of 115.32 ± 2.65 μg/mL, although this was weaker than acarbose (EC_{50} = 18.67 ± 0.01 μg/mL), suggesting moderate antidiabetic potential.	[21]

(*Continued*)

https://doi.org/10.2147/JEP.S532898

https://doi.org/10.2147/JEP.S532898

Table 3 (Continued).

Cytotoxicity Study								
Part of the Plant, Collected in and Authenticated by	**Extraction Method**	**Phytochemical Analysis and the Bioactive Compounds**	**Type of Cell**	**Model Category, Methods, Inducer, and Parameter Assessed**	**Control Drug Used and Concentration**	**Statistical Analysis**	**Results**	**Ref**
Aerial parts of the plant were collected in Selangor, Malaysia. The plant materials were identified by a botanist, with validation confirmed on 1st December 2023 through the International Plant Names Index (IPNI). A voucher specimen (KLU50130) was deposited at the Rimba Ilmu Botanic Garden, University of Malaya.	The plant was macerated in MeOH at 10% (w/v) for 72 h at 25°C, followed by filtration and solvent removal under reduced pressure. The extract was then fractionated using C_6H_{14}, $CHCl_3$, EtOAc, and n-BuOH.	Phytochemical analysis was conducted using various techniques to identify and characterize the bioactive compounds in *P. pellucida*. A range of bioactive compounds were identified, including non-polar phytochemicals (β-santalene, dillapiole, β-caryophyllene, β-elemene) and polar constituents (pheophorbide A-methyl ester, N-cyclohexanecarbonylpentadecylamine, dictyoquinazol, 2,4,5-trimethoxystyrene, and 9-octadecenoic acid methyl ester).	ARPE-19 cells	*Cytotoxic activity was evaluated with the MTT assay.*	Not described	Data are presented as mean ± SD (n = 3). Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test in GraphPad Prism version 9.5.1, with $p < 0.05$ considered statistically significant.	The cytotoxic activity of extracts was assessed using the MTT assay on ARPE-19 cells. The extracts were tested under high glucose (68 mM) and product AGE-induced stress conditions. The IC_{50} values, calculated based on cell viability, were 8.70 mg/mL for the crude MeOH extract and 7.34 mg/mL for the EtOAc extract, both exceeding the National Cancer Institute's cytotoxicity threshold of 30 μg/mL, indicating a non-toxic profile. Mild cytotoxicity was observed only at higher concentrations (≥ 4 mg/mL for MeOH extract; ≥ 5 mg/mL for EtOAc extract. At lower doses MeOH extract: 1.5–3 mg/mL; EtOAc extract: 1–4 mg/mL), both extracts significantly enhanced cell viability, demonstrating cytoprotective effects.	[13]
The leaves, bark, aerial parts, and seeds of the plant were collected in Suchdol, Czech Republic. The plant materials were identified by Prof. Kokoska, and voucher specimens were deposited in the herbarium of the Department of Botany and Plant Physiology, Faculty of Agrobiology, Food and Natural Resources, Czech University of Life Sciences, Prague.	Each dried plant sample was finely ground into powder and extracted with 80% EtOH for 24 h at room temperature using an orbital shaker. The extracts were then filtered and concentrated under reduced pressure using a rotary evaporator at 40 °C. The dried residues were finally dissolved in 100% DMSO to prepare stock solutions at a final concentration of 51.2 mg/mL.	Not described	NHDF-Ad cells	*Cytotoxic activity was assessed with the MTT assay.* Cell viability was evaluated after 72 h of treatment with serially diluted plant extracts (4–128 μg/mL), using mitochondrial dehydrogenase activity as an indicator. IC_{50} and IC_{80} values were calculated. Cytotoxicity was classified according criteria: <2.00 μg/mL = cytotoxic, 2.00–89.00 μg/mL = moderately cytotoxic, >90.00 μg/mL = not cytotoxic.	Fluorouracil was administered at concentrations ranging from 0.0625 to 128 μg/mL.	Data are presented as mean ± SD (n = 3 independent experiments, each in duplicate).	The extract exhibited moderate cytotoxicity against NHDF-Ad cells with an IC_{50} value of 63.52 ± 18.51 μg/mL and an IC_{80} > 128 μg/mL.	[22]

P. pellucida leaves collected in Banten, Indonesia.	*P. pellucida* were dissolved in MeOH.	Not described	MCF-7 and Vero cells (Elabscience®). The growth medium consists of DMEM high glucose, 10% FBS for MCF-7 cells or 20% FBS for Vero cells, and 1% penicillin-streptomycin. MCF-7 and Vero cells are cultured at 37°C with 5% CO_2.	Cytotoxic activity was assessed with the MTT assay.	Doxorubicin 10,000 ppm	The data were analysed using correlation and linear regression tests at a 95% confidence level. The synergistic cytotoxic effect of the combination was analysed by calculating the CI value. The SI calculation was performed to determine that the n-C_6H_{14} fraction is non-toxic to normal cells.	The n-C_6H_{14} fraction of *P. pellucida* leaves was confirmed to possess cytotoxic effects towards both cells. Doxorubicin (the control drug) showed an IC_{50} of 2.10 μg/mL. The combination of 24.2 μg/mL of the n-C_6H_{14} fraction and 0.26 μg/mL of doxorubicin revealed a synergistic cytotoxic effect.	[33]
The fresh leaves and stems were collected and authenticated, and voucher specimens (Nos. 7391, 7392, and 7393) were deposited at the Applied Thai Traditional Medicine Department, Faculty of Medicine, as well as at the Faculty of Science, Mahasarakham University, Thailand.	The plant samples were washed with tap water, chopped, air-dried, and oven-dried at 50°C for 2 d, and pulverized into a fine powder. Maceration was performed using 95% EtOH. After filtration, the solvent was removed from the filtrate using a rotary evaporator at 50°C.	The phytochemical composition of the extracts was analyzed to assess specific chemical reactions indicative of secondary metabolites, resulting in the presence of flavonoids, alkaloids. TPC and TFC were quantified as part of the analysis and resulted in a TPC of 97.30 ± 28.20 mg GAE/g) and *TFC* 335.20 ± 49.40 mg RE/g.	MCF-7 cells	*Cytotoxic activity was evaluated using the SRB assay.* Cells were exposed to the extract (0–500 μg/mL) for 24–48 h, and cytotoxicity was assessed based on the percentage of cell viability.	Not described	Data are presented as mean ± SD. Statistical analysis was conducted using SigmaStat software version 3.5. One-way ANOVA was performed, followed by the LSD post hoc test. $p < 0.05$ was considered statistically significant.	The extract of leaves and stems exhibited significant cytotoxic activity against MCF-7 cells, with an IC_{50} value of 139.3 ± 11.3 μg/mL at 24 h, which decreased to 46.0 ± 2.1 μg/mL at 48 h, indicating a time-dependent cytotoxic response. The extract also induced apoptosis, increased intracellular ROS production, suppressed colony formation, and inhibited cell migration in a dose-dependent manner (0–500 μg/mL).	[34]

Abbreviations: AChE, acetylcholinesterase; AGE_S, advanced glycation end products; ARPE-19, human retinal pigment epithelial cell line; ATCI, acetylthiocholine iodide; CA, cluster analysis; $CHCl_3$, chloroform; C_6H_{14}, hexane; DMEM, Dulbecco's modified eagle medium; CI, combination index; DMSO, dimethylsulfoxide; EO, essential oil; Et_2O, diethyl ether; EtOAc, ethyl acetate; EtOH, ethanol; ET_2O, ethyl ether; FBS, fetal bovine serum; FC, Folin-Ciocalteu; FTIR, Fourier-transform infrared; GAE, gallic acid equivalence; GC-FID, gas chromatography-flame ionization detector; GC-MS, gas chromatography-mass spectrometry; GPx, glutathione peroxidase; IL-8, interleukin-8; KmCA, K-means cluster analysis; LC-QToF-MS, liquid chromatography quadrupole time-of-flight mass spectrometry; MBC, minimum bactericidal concentration; MCF-7, human breast cancer cell line; MCP-1, monocyte chemoattractant protein-1; MeOH, methanol; MIC, minimum inhibitory concentration; MMP2, matrix metalloproteinase 2; NF-κB p65, Nuclear factor-kappa B subunit p65; NHDF-Ad cells, normal human dermal fibroblasts-adult; NMR, Nuclear magnetic resonance; n-BuOH, n-butanol; n-C_6H_{14}, n-hexane; Na_2SO_4, sodium sulfate; NHDF-Ad, Normal Human Dermal Fibroblasts – Adult; ODS, octa decyl silane; PCA, principal component analysis; PE, petroleum ether; PNPG, p-nitrophenyl-α-D-glucopyranoside; PPAR-γ, peroxisome proliferator-activated receptor-gamma; PRC, preparative radial chromatography; RAGE, receptor for advanced glycation end-products; RBCs, red blood cells; RE, rutin equivalence; sRAGE, soluble RAGE; ROS, reactive oxygen species; SDA, sabouraud dextrose agar; SD, standard deviation; SI, selectivity index; SRB, sulforhodamine B; TFC, Total flavonoid content; TLC, thin-layer chromatography; TPC, total phenolic content; UV-Vis, ultraviolet-visible; VEGF, vascular endothelial growth factor; Vero cells, derived from kidney tissue of the African green monkey (*Cercopithecus aethiops*); XO, xanthine oxidase.

Inhibition of acetylcholine esterase (AChE) by *P. pellucida* plants was evidenced in two papers.[11,30] In the first study, the ethanol extract of *P. pellucida* plants collected from the Southwestern region of Thiruvananthapuram, Kerala, India, exhibited a weak neuroprotective activity by inhibiting AChE with an IC_{50} value of 175.12 µg/mL.[11] This weak inhibition was consistent with the results of the authors' in silico pharmacology study, revealing the molecular interaction of flavonoids contained in the plant with human AChE (PDB ID 4M0E).[11] The second article delineated that the hydrodistilled extract of the fresh leaves of this plant, collected from the Northern Caribbean Region, Colombia, could inhibit AChE, although weaker than chlorpyrifos, an organophosphate pesticide.[30]

Other pharmacological activity assays of *P. pellucida* were reported by inhibiting the activity of alpha-amylase,[21] alpha-glucosidase,[32,] and xanthine oxidase,[31] indicating the potential of this plant in alleviating various disorders.

In vivo Pharmacological Activity Study

Considering that studies of living organisms can be separated into in vitro (using parts of living organisms combined in tubes or plates) and in vivo (using animals), in conjunction with the rapid advancement of computational technologies (in silico),[39] a combination of the three approaches will provide comprehensive information. An in vivo study is usually conducted concerning the results derived from in vitro studies.

To better comprehend the in silico and in vitro studies of *P. pellucida*, a search of the PubMed database using the keywords "Peperomia pellucida AND in vivo" was performed, resulting in seven articles, of those, five articles were excluded because one article was not original research, one article studied hepatotoxicity (toxicity and cytotoxicity are discussed in different subsections), one article studied cytotoxicity and molecular docking, one article discussed the isolation of compounds with estrogenic activity, and one article was not related to the topic. A further search in the Scopus database using the same keywords ("Peperomia pellucida AND in vivo") and publication period of 2014 to 2025 was performed, resulting in 21 articles, of which, 17 were excluded due to duplication with results in the PubMed database, articles were reviews/not original research, articles were in silico or in vitro although in their titles describing in vivo, articles were not related to the topic or only studying isolation technique of compounds, and articles did not discussing *P. pellucida* extract but synthetic compound.

The total of six articles included reported antihypertensive activity,[4] antinociceptive,[16] antiplasmodial,[27] anti-inflammatory,[35,36] and wound healing activity[37] of *P. pellucida* extracts, fraction, or metabolites (tabulated in Table 4).

Antihypertensive activity was explored by Saputri et al (2021), revealing that the ethyl acetate fraction of the aerial parts of *P. pellucida* collected at Bogor, West Java, Indonesia, decreased blood pressure and biomarkers associated with the renin–angiotensin–aldosterone systems (RAAS) in two-kidney, one-clip (2K1C) hypertensive model rats, comparable to that of captopril.[4] The antihypertensive activity in hypertensive model rats is in line with the in silico results of polyphenols towards angiotensin-converting enzyme (ACE) reported by Ahmad et al (2019).[14] Regrettably, we found no related in vitro study during the intended publication period.

Antinociceptive,[16] anti-inflammatory,[35,36] and wound healing activity[37] of *P. pellucida* or its metabolite, pellucidin A, have been confirmed, which were in agreement with the results of the in silico study, describing the molecular interaction of *P. pellucida* metabolites with iNOS, eNOS, COX-2, NF-κB p65, and PPAR-γ,[13,16] and the in vitro study, delineating a significant downregulation of the pro-inflammatory cytokines, angiogenic markers, and altering the Janus kinase (JAK)-STAT3 pathway.[13,29]

Cytotoxicity Study

It should be mandatory to guarantee the safety of a drug, whether it is a pure synthetic chemical or a plant-based drug; therefore, a search of the PubMed database using the keywords "Peperomia pellucida AND cytotoxicity" was carried out, resulting in three articles. Of these, one article was excluded because it was a review. A further search in the Scopus database using the same keywords ("Peperomia pellucida AND in vivo") and the publication period of 2014 to 2025 was performed, resulting in eleven articles, of which only two were included. Articles were excluded due to duplication with results in the PubMed database, not related to cytotoxicity, published in 2011, and reviews/not original research.

The four papers included in this review reported that the extract of *P. pellucida*, collected from different sources, was confirmed to be non-toxic towards normal cells, namely, human retinal pigment epithelial cell line ARPE-19,[13] and

Table 4 In vivo Pharmacological Activity and Toxicity of *Peperomia Pellucida* L. Kunth Reported in the Period from 2014 to 2025

Part of the Plant, Collected in and Authenticated by	Extraction Method	Phytochemical Analysis and the Bioactive Compounds	Animals, Ethical Approval Committee	Model Category, Methods, Inducer, and Parameter Assessed	Control Drug and Dosage	Statistical Analysis	Results and Statistical Differences	Ref
Antihypertensive/Anti-inflammatory/Antinociceptive/Antiplasmodial/Osteogenic Activity								
Aerial parts of the plant were collected from the Bogor Botanical Gardens, West Java, Indonesia. The plant materials were identified by a botanist from the Research Center for Biology, Indonesian Institute of Sciences.	The powdered plant material 4600 g was macerated in a mixture of EtOH and H_2O (80:20, v/v) at room temperature for 48 h. The extraction process was repeated 3× to ensure optimal yield. The combined extracts were then concentrated under reduced pressure to obtain a crude extract weighing 830.2 g. Liquid-liquid partitioning was subsequently performed using n-C_6H_{14}, CH_2Cl_2, and EtOAc. This process yielded an EtOAc fraction, representing 2.5% of the total extract, which was stored at 4°C for further analysis.	The total flavonoid content was 2.91% (w/w). One major compound, 30,40-dihydroxy-3,5-dimethoxyflavone-7-O-β-rhamnose, was isolated using column chromatography and preparative TLC, and characterized by spectroscopy.	36 male Sprague–Dawley rats (180–200 g) were obtained from the Animal Laboratory of Bogor Agricultural Institute. All procedures were approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Indonesia (No. 539/UN2.F1/ETIK/2014).	The 2K1C RHR model was induced by clipping the renal artery. Parameters assessed included SBP, DBP, AII levels, and PRC.	Captopril (25 mg/kg BW) was used as the positive control.	All results are expressed as mean ± SD. Statistical analysis was performed using SPSS version 17.0. One-way ANOVA followed by a post hoc test was used to assess statistical differences. $p < 0.05$ was considered statistically significant.	After 6 weeks, RHR model rats had elevated BP, AII, and PRC. Treatment with PPF (50 mg/kg BW) significantly reduced these parameters, comparable to captopril. Histological analysis showed dose-dependent renal protection by the EtOAc fraction. Significant differences ($p < 0.05$) in SBP and DBP between the EtOAc fraction-treated and model groups; renal damage improved with the EtOAc fraction.	[4]
The aerial parts of the dried plant were collected from the Icoaraci district of Belém, Brazil. The plant materials were identified by the Emílio Goeldi Museum, and a voucher specimen (No. 190136 IAN) was deposited.	A total of 450 g of plant material was macerated at room temperature (25 ± 2°C) with 96% EtOH (8 L) for 3 extraction cycles, each lasting 3 d. The resulting H_2O-EtOH solution was concentrated under reduced pressure at 50–60°C to obtain 32 g of crude extract. A portion of this extract (15 g) was subjected to silica gel column chromatography using a solvent gradient of increasing polarity.	A 10 mg aliquot of the F5 fraction was analyzed using HPLC, solubilized in 1 mL of CH_3CN, and filtered through a 0.25 μm membrane. Chromatographic analysis was performed using a Gemini C18 column (5 μm, 250×4.6 mm), with a flow rate of 1 mL/min and an isocratic mobile phase of H_2O/CH_3CN (45:55) over 25 min. Pellucidin A (57.3 mg) was isolated through preparative HPLC.	Swiss albino mice (8–12 weeks old, 20–35 g, n = 180) were obtained from the Evandro Chagas Institute (Belém, Brazil). All experimental procedures were approved by the Federal University of Pará Animal Ethics Committee (CEUA-UFPA No. 5671030216).	Peripheral and central antinociceptive models included the acetic acid-induced writhing, formalin test, hot-plate test, and open-field test. Parameters assessed included writhing count, licking time, latency, and locomotor activity.	Indomethacin (5 mg/kg) was used as the positive control.	All results are expressed as mean ± SEM. Data were analyzed using one-way ANOVA followed by Tukey's post hoc test for individual pairwise comparisons. A **p**-value < 0.05 was considered statistically significant.	Pellucidin A (1 and 5 mg/kg) significantly reduced the number of writhes by 43% and 65% ($p < 0.05$) and decreased the licking time in the inflammatory phase of the formalin test by 68% ($p < 0.05$), without affecting locomotor activity ($p > 0.05$). No effect was observed in the neurogenic phase or hot plate test ($p > 0.05$). The mechanism likely involves peripheral pathways, including COX and NO, with a synergistic effect when combined with L-NAME (96% inhibition, $p < 0.05$).	[16]

(*Continued*)

Table 4 (Continued).

Part of the Plant, Collected in and Authenticated by	Extraction Method	Phytochemical Analysis and the Bioactive Compounds	Animals, Ethical Approval Committee	Model Category, Methods, Inducer, and Parameter Assessed	Control Drug and Dosage	Statistical Analysis	Results and Statistical Differences	Ref
The leaves were collected from West Java, Indonesia. The plant materials were identified by a botanist at the Faculty of Medicine, Jenderal Achmad Yani University.	A total of 1.000 g of plant material was accurately weighed, thoroughly washed, and oven-dried. The dried leaves were then ground into a fine powder and placed in a round-bottom flask. The powdered material was macerated in 96% EtOH, and the flask was equipped with a reflux condenser. The mixture was heated under reflux for 1 h. After extraction, the solution was filtered through filter paper, and the solvent was evaporated. The resulting extract was further concentrated using a water bath and diluted with DMSO to obtain a 50% solution for subsequent analysis.	Phytochemical screening of the extract confirmed the presence of alkaloids, polyphenols, tannins, flavonoids, quinones, saponins, monoterpenoids, sesquiterpenoids, steroids, and triterpenoids. The compounds identified were 3-hydroxy-24-ethyl-5,22-cholestadiene (a steroid) and 3-hydroxy-9-lanosta-7,24E-dien-26-oic acid (a triterpenoid)	Male *Rattus norvegicus* Wistar rats, aged 2–3 months, weighing 200–250 g, were used in this study. The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Jenderal Achmad Yani University, West Java, Indonesia (No: 032/UH4.11/2023).	A periodontitis model was established through ligature placement, human plaque insertion, and nicotine injection. The parameters assessed included the PBI, GI, and histological assessment of macrophages, neutrophils, osteoclasts, osteoblasts, and fibroblasts.	0.2% chlorhexidine was used as the positive control.	All results are expressed as mean ± SD. The Shapiro–Wilk test was used to assess data normality, and Levene's test was applied to evaluate the homogeneity of variances. For normally distributed data, one-way ANOVA followed by Tukey's HSD post hoc test was performed. For non-normally distributed data, the Kruskal–Wallis test followed by the Mann–Whitney *U*-test was used. $p < 0.05$ was considered statistically significant.	The extract exhibited antibacterial activity against *P. gingivalis* in a dose-dependent manner, with the highest inhibition zone observed at a 100% concentration (15.52 ± 0.104 mm). A significant reduction in the PBI and GI was observed on day 7 compared to the untreated group ($p < 0.05$). Histological analysis showed an increase in osteoblast and fibroblast counts, while macrophages and PMNs were significantly reduced ($p < 0.05$) in the extract-treated group compared to the periodontitis control group.	[35]

https://doi.org/10.2147/JEP.S532898

P. pellucida herbs were collected at Padang Pariaman, West Sumatra, Indonesia. The plant samples were identified by Dr. Nurainas, a botanist at the Herbarium of Andalas University, West Sumatra, Indonesia.	Extraction was carried out using 70% EtOH for 24 h at room temperature.	Not described	Male Wistar rats, 180–220 g in weight, and aged 2–3 months. The rats were housed in standard conditions with a 12h light/dark cycle and were fed with a standard pellet diet and water ad libitum. All the rats were acclimatized for 1 week before the experiment, and were randomly selected for different experimental groups (3 animals/ group). The protocol of this experiment was approved by the Committee of the Research Ethics of the Faculty of Medicine, Andalas University (permit No. 326/KEP/FK/2020).	The extract was evaluated on carrageenan-induced paw edema in rats, by injecting 0.1 mL of 1% carrageenan in 0.9% saline onto the right hind paw of the rat. Edema volume was determined every 1 h for up to 6 h after carrageenan injection using a plethysmometer. Evaluation of COX-2 inhibitory activity was carried out by preparing the rat serum at the 3rd h after carrageenan injection. The extracts (100, 200, and 400 mg/kg BW) were used for inhibition studies, and their ability to inhibit COX-2 was determined by using the ELISA kit assay.	Celecoxib 9 mg/kg BW	The statistical software SPSS version 25 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. Data were analyzed using one-way ANOVA followed by Duncan's multiple range test. p <0.05 was considered significant.	The extracts (100, 200, and 400 mg/kg BW) were effective in reducing the carrageenan-induced paw edema, with the % inhibition of paw edema being 34.93%, 46.61%, and 64.04%, respectively. The extracts (100, 200, and 400 mg/kg BW) decreased serum COX-2 levels after 3 h, with the percentage of COX-2 inhibition being 10.87%, 47.04%, and 56%, respectively.	[36]

(*Continued*)

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Table 4 (Continued).

Part of the Plant, Collected in and Authenticated by	Extraction Method	Phytochemical Analysis and the Bioactive Compounds	Animals, Ethical Approval Committee	Model Category, Methods, Inducer, and Parameter Assessed	Control Drug and Dosage	Statistical Analysis	Results and Statistical Differences	Ref
Leaves and stems were collected in North Gorontalo, Gorontalo Province, Indonesia. The plant materials were identified by a botanist from the Herbarium Biology Laboratory, Universitas Negeri Gorontalo, and a voucher specimen (No. 130/H47.B4.Bio.Lab Bio/LL/2016) was deposited.	Maceration was performed with MeOH at room temperature for 2 d, followed by partitioning with C_6H_{14} and EtOAc.	The EtOAc extract was purified using silica gel G60 column chromatography (132 g) with n-C_6H_{14}/EtOAc (200 mL) elution, employing a linear gradient from 10% to 100% EtOAc, resulting in eleven fractions (A1–A11). Fraction A6 was further purified by silica column chromatography with isocratic elution of n-C_6H_{14}/EtOAc (90:10–0:100), yielding 40 fractions. Fraction B9 was recrystallized using n-C_6H_{14} and $CHCl_3$ to obtain compound 1 (18 mg) as needle-shaped crystals. Fraction A7 was purified by silica chromatography using n-C_6H_{14}/EtOAc/MeOH (7:2:1) elution, generating 25 fractions. Fractions C13–C15 were combined and further purified using silica column chromatography on ODS with MeOH/H_2O (4:1) elution, resulting in compound 2 (12 mg) as a white powder. The compounds identified were 3-hydroxy-24-ethyl-5,22-cholestadiene (a steroid) and 3-hydroxy-9-lanosta-7,24E-dien-26-oic acid (a triterpenoid).	30 male BALB/c mice (25–28 g, 6–8 wk old) were obtained from the Animal Experimental Unit, Universitas Gadjah Mada (UGM), and housed at Universitas Airlangga. Ethical oversight was provided through institutional involvement and adherence to standard animal care protocols.	The *Plasmodium berghei* ANKA infection model was established by infecting mice i.p. with 10^6 parasitized erythrocytes. Treatment was administered for 4 d with the extract at doses of 1, 10, and 100 mg/kg BW. Parameters assessed included parasitemia, percentage of inhibition, and survival rate (on day 21).	The positive control group received chloroquine diphosphate (25 mg/kg BW) I.P once a day for 4 d.	An unpaired two-tailed **t**-test was performed using GraphPad Prism. Differences were considered statistically significant at $\mathbf{p} < 0.05$, $\mathbf{p} < 0.01$, and $\mathbf{p} < 0.001$.	Extract exhibited a proportion-dependent increase in antiplasmodial activity, with the highest inhibitory effect observed when the extract composition was predominantly 80%. Experiments in *P. berghei*-infected BALB/c mice confirmed its efficacy, with an ED_{50} value of 12.86 mg/kg and increased survival rates post-treatment.	[27]

https://doi.org/10.2147/JEP.S532898

A fresh plant was harvested in May 2014 at damp areas in Limbe, Cameroon. The plant materials were identified by botanist at the National Herbarium of Cameroon by comparison with voucher specimen No. 19,555/SRFCam.	The whole fresh plant was cleaned, cut into pieces, and dried in the shade at room temperature. Decoction was performed by boiling 100 g of the powder in 1.5 L of tap H_2O for 10 min. The resulting mixture was filtered, frozen at −20°C, and lyophilized, yielding 28.79% (w/w).	The aqueous extract contains minerals such as calcium, phosphorus, magnesium, sodium, and potassium.	3-month-old female Wistar rats, weighing between 150 and 200 g, were used in this study. All experimental procedures were approved by the Cameroon National Ethical Committee (Ref. No. Fw-IRb00001954).	Drill hole injury was induced in the mid-femur. Parameters assessed included bone calcium, phosphorus, and alkaline phosphatase levels in both bone homogenates and serum.	Distilled water (10 mL/kg) was used as the normal control.	One-way ANOVA followed by Dunnett's post hoc test was performed using GraphPad Prism version 5.03. A **p**-value < 0.05 was considered statistically significant.	Serum calcium concentration did not change significantly in all groups, but fracture increased bone calcium levels by 63.39% compared to normal controls ($p < 0.05$). Extract doses of 100 and 200 mg/kg increased this level significantly ($p < 0.01$), while 400 mg/kg decreased it by 36.48% compared to fracture controls ($p < 0.05$). Serum phosphorus decreased by 26.78% in fracture rats compared to normal controls ($p < 0.05$), while 400 mg/kg extract further decreased it by 59.30% compared to fracture controls ($p < 0.01$). In bone, 100 mg/kg extract increased phosphorus by 33.52% compared to normal controls and 40.41% compared to fracture controls ($p < 0.05$), whereas 400 mg/kg decreased it by 60.19% compared to fracture controls ($p < 0.001$). Serum AP activity decreased by 42.23% in the fracture group given a dose of 400 mg/kg ($p < 0.01$). In bone tissue, the same dose decreased AP activity by 57.61% in non-fractured rats compared to normal controls ($p < 0.05$).	[37]
Toxicity study								
The whole plant was collected from Can Tho City, Vietnam. The plant materials were identified by a member of the species in the laboratory.	The collected samples were washed, and damaged parts were removed. The samples were ground, dried at 35°C, and soaked in 96% **EtOH** at a ratio of 1:10 (m/v) for 24 h. The mixture was filtered, and the resulting solution was concentrated under reduced pressure. The extracts were collected.	Phytochemical analysis revealed the presence of polyphenols, tannins, flavonoids, saponins, alkaloids, and terpenoids, with high TPC (273.33 ± 4.91 mg GAE/g) and TFC (199.8 ± 0.346 mg QE/g).	**Mus musculus** (Linnaeus) were supplied by the Pasteur Institute of Ho Chi Minh City and maintained at the Animal Physiology Laboratory, College of Education, Can Tho University. All procedures involving animals were approved by the Animal Ethics Committee of Can Tho University (CTU-AEC24010).	**Acute toxicity** involved a single oral dose of 5000 mg/kg BW, with behavioral and physical signs monitored over 7 d. Liver and blood samples were collected post-treatment for further analysis. **Subchronic toxicity** was assessed through oral administration of 500 mg/kg/d for 28 d, followed by a 30-day post-exposure observation period. Tissue collection was conducted similarly to the acute toxicity protocol.	The control group received standard feed and water ad libitum without any extract exposure.	Data were analyzed using one-way ANOVA followed by Tukey's post hoc test in Minitab version 16 and GraphPad Prism. Statistical significance was set at $p < 0.05$. Results are expressed as mean ± SD from triplicate experiments.	No mortality or clinical signs of toxicity were observed after acute administration or subchronic exposure to the extract. Hematological and biochemical parameters did not differ significantly between treated and control groups ($p > 0.05$), except for a significant reduction in RBC count in the subchronic group ($p < 0.05$). Liver enzymes remained within normal limits. BW in treated animals increased significantly from 29.57 ± 1.74 g to 34.52 ± 3.06 g ($p < 0.05$), while controls experienced a decrease ($p < 0.05$).	[10]

(*Continued*)

https://doi.org/10.2147/JEP.S532898

Table 4 (Continued).

Part of the Plant, Collected in and Authenticated by	Extraction Method	Phytochemical Analysis and the Bioactive Compounds	Animals, Ethical Approval Committee	Model Category, Methods, Inducer, and Parameter Assessed	Control Drug and Dosage	Statistical Analysis	Results and Statistical Differences	Ref
The whole plant (excluding roots) was collected at Claveria, Misamis Oriental, Philippines. The plant materials were identified by Dr. Edwino S. Fernando at the Institute of Biology, Jose Vera Santos Memorial Herbarium (PUH), University of the Philippines Diliman.	Two different aqueous extraction methods were utilized to obtain bioactive compounds from dried leaf samples. In the first method, 24.06 g of dried leaves were soaked in 420 mL of distilled water and heated overnight at 50° C. The mixture was then filtered, and the resulting solution was subjected to lyophilization, yielding a freeze-dried extract weighing 1.28 g (equivalent to 5.33% yield). In the second method, a decoction was prepared by boiling 25 g of dried leaves in 420 mL of distilled water at 100°C for 20 min. The boiled extract was subsequently lyophilized, resulting in a final yield of 2.15 g (8.62%).	Not described	30 BALB/c mice were obtained from the Philippine FDA. The animals were acclimatized for 1 week and maintained under standard laboratory conditions. The study was approved by the Department of Agriculture Administrative Order No. 40, the Philippine Association for Laboratory Animal Science (PALAS) Code of Practice, and the De La Salle University-Manila Code of Research Ethics.	Toxicity and genotoxicity were evaluated. Mice were treated orally with either decoction or freeze-dried extracts at doses of 30 and 60 mg/kg/d for 9 weeks. Parameters assessed included serum ALT and AST levels as biochemical markers, and mutagenicity was evaluated using the micronucleus test on tail blood every 2 weeks. Blood samples were collected post-treatment for biochemical and cytological analysis.	The control group was administered distilled water via oral gavage.	Data were analyzed using PHStat4. Outliers were identified and removed using the Q test at a significance level of $\alpha = 0.05$. One-way ANOVA was performed, followed by Tukey's post hoc test. A **p**-value < 0.05 was considered statistically significant.	Subchronic oral administration of extracts (30 and 60 mg/kg/d for 9 weeks) showed no BW changes at 30 mg/kg, but a significant decrease was observed with 60 mg/kg freeze-dried extract ($p < 0.05$), possibly due to high tannin content. The micronucleus test showed no genotoxic effect until week 6. By 8 weeks, a significant increase in MPCEs was observed in the 60 mg/kg groups, especially with the freeze-dried extract, indicating dose-dependent genotoxicity. ALT and AST levels remained within normal limits across all groups ($p > 0.05$), suggesting no hepatocellular damage despite the observed genotoxic potential at higher doses.	[38]

Abbreviations: AII, angiotensin II; AP, alkaline phosphatase; C_6H_{14}, hexane; CH_2Cl_2, dichloromethane; $CHCl_3$, chloroform; DBP, diastolic blood pressure; ELISA, enzyme-linked immunosorbent assay; EtOH, ethanol; EtOAc, ethyl acetate; GI, Gingival Index; H_2O, water; H_2O-EtOH, hydroethanolic; HCl, hydrochloric acid; HPLC, high-performance liquid chromatography; IP, intraperitoneally; MeOH, methanol; C_6H_{14}, n-hexane; ODS, octa decyl silane; PBI, Papillary Bleeding Index; PRC, plasma renin concentration; RHR, renal hypertension; SBP, systolic blood pressure.

normal adult human dermal fibroblasts standard cell line,[22] however, it inhibited the growth of cancerous cells, such as human breast adenocarcinoma (MCF-7),[33,34] and Vero cells.[33]

Toxicity Study

Moreover, a search on the PubMed database using the keywords "Peperomia pellucida AND toxicity" resulted in nine articles; of these, only two articles were included because the others were either reviews or unrelated to a toxicity study, as follows:

Wild-type *P. pellucida* collected from Can Tho City, Vietnam, was extracted using 96% ethanol and subjected to acute and subchronic toxicity assays in mice. The extract at a dose of 5000 mg/kg body weight resulted in no acute toxicity in mice after seven days of consumption, as evidenced by the absence of mortality or abnormalities, such as convulsions, ruffled hair, diarrhea, or vomiting. The 28-day subchronic toxicity observation revealed that a dose of 500 mg/kg body weight did not cause any adverse reactions or clinical signs of toxicity. Hematological parameters, including MCV (mean corpuscular volume), HGB (hemoglobin), HCT (hematocrit), MCH (mean corpuscular hemoglobin), and MCHC (mean corpuscular hemoglobin concentration), remained unaltered when exposed to the extract.[10]

The aerial parts of *P. pellucida* obtained from Claveria, Misamis Oriental, Philippines, extracted with water (decoction and freeze-dried extracts), were tested for subchronic toxicity in BALB/c mice for 9 weeks. This study revealed that the 60 mg/kg body weight of freeze-dried extract contributed to a decrease in appetite. Long-term administration of the extracts did not alter the levels of serum alanine aminotransferase (ALT) (the liver enzyme), thus confirming their safety to the liver. However, the extracts were mutagenic at high concentrations.[38]

Ethnopharmacological/Ethnobotanical Survey

Although many studies have reported the in silico, in vitro, and in vivo approach of *P. pellucida*, in the form of extracts, fractions, or metabolites, it is regrettable that no human studies were recorded in the PubMed database in the publication period of 2014 to 2025, while the search in the Scopus database for open-access articles, after thorough screening by title and abstract, resulted in seven ethnopharmacological/ethnobotanical studies,[40–46] which described the use of *P. pellucida* for general health purpose,[40] to treat respiratory disorders,[40] to cure cancer,[40] hepatoprotector,[41] to treat numerous infections,[43,44] and other diseases. These ethnopharmacological surveys are closely related to the in silico, in vitro, and in vivo pharmacological assays of *P. pellucida* in the last decade. Polyphenols, flavonoids, lignans, and sterols contained in the aerial parts of this plant are considered to contribute greatly to the pharmacological activities. The detailed descriptions of the ethnopharmacological surveys are as follows:

In the first article published in 2014, information on demographic data and plant use methods was recorded through direct interviews with 200 participants. The study protocol was approved by the National University of Singapore Institutional Review Board, and informed consent was obtained from all the participants. This study documented 414 medicinal plants, grown in Singapore and used by the participants from 2009 to 2014, including *P. pellucida*. The herbs were mostly consumed in dried form for general health purposes or to treat respiratory-related disorders, although some were purchased as products. Indigenous knowledge was verbally transferred from older generations residing in many kampong villages in Singapore.[40] The second article, published in 2020, describes the use of medicinal plants to treat jaundice by the tribes of the Morigaon District, Assam, India. The survey was conducted from June 2016 to July 2017. Data were collected using a semi-structured questionnaire and evaluated using quantitative ethno-botanical indices: fidelity level (FL), use value (UV), and family use value (FUV). This study portrayed 27 plant families, with the highest use being Lamiaceae, Leguminosae, Acanthaceae, Oxalidaceae, Phyllanthaceae, Piperaceae, Poaceae, and Rutaceae. Among these, *P. pellucida* (Piperaceae) has been documented and noticed for its hepatoprotective activity.[41] A quantitative ethnobotanical study of medicinal plants in Ile-Ife, Osun State, Nigeria, was conducted through semi-structured interviews with 70 participants. Data were analyzed using the ethnobotanical knowledge index (EKI), species popularity index (SPI), relative frequency of citation (RFC), cultural importance index (CII), informant consensus factor (FIC), FL, and species therapeutic index (STI). This study identified 87 plant species belonging to 43 families, with the Euphorbiaceae family and leaves being the most used. Some of the recorded medicinal plants include *Rauvolfia vomitoria, Senna alata, Crinum jagus, Kigelia africana, P. pellucida, Solanum verbascifolium, Cnestis ferruginea,*

Ageratum conyzoides, and *Jatropha multifida*.[42] An ethnobotanical survey and interview were conducted in ten villages in Myanmar in 2018. Data were collected from interviews with 131 participants, recruited using the snowball sampling method. The therapeutic applications of the plants were categorized according to the ICPC-2 standard. Voucher plant specimens were collected and identified by experts. The data were evaluated by applying the use report (UR) per species in the EthnobotanyR (https://cran.r-project.org/web/packages/ethnobotanyR/vignettes/ethnobotanyr_vignette.html). A total of 158 species belonging to 64 families, including *P. pellucida*, were used in Myanmar. The participants listed 78 therapeutic uses of these plants, which were classified into 16 ICPC-2 disease categories. Digestive, urological, and respiratory diseases ranked first. Fabaceae was the most represented family. The leaves were the most commonly used plant part, while boiling and oral administration were the most preferred consumption techniques.[43] Another ethnopharmacological study of the medicinal plants in the central part and the Northern district of Bangladesh has been carried out, involving 127 face-to-face participants, including Ayurvedic practitioners, patients, and local people. Data were analyzed using quantitative indices including UV, informant consensus factor (ICF), FL, and rank order priority (ROP). The survey documented 71 species of 44 families, including *P. pellucida*, which have been used to treat numerous infections. The most cited plant families were, in respective order, Lamiaceae, Meliaceae, and Leguminosae. Leaves were the most frequently used plant part in preparation. Pneumonia bacteria were recorded for their highest FIC value.[44] Plants contribute an essential role in the indigenous medicine of the Nias tribe in North Sumatra, Indonesia. Knowledge was transferred from the older generation to the younger generation; thus, this ethnopharmacological survey was carried out through questionnaires, interviews, and observations to collect and document the knowledge. Participants were recruited using the snowball sampling method. Taxonomical identification was carried out at the Medanense Herbarium. Quantitative analysis was performed by calculating the frequency of quotations (FOQ), the ratio of informant agreement, and the citation frequency (CF). The survey resulted in 50 plant species of 26 families being used by the people of Nias, among which was *P. pellucida*, local name *tima-tima*, with a CF value of 56.49%.[45] Furthermore, an ethnobotanical study of plants used by local people in the upper region of Bengawan Solo River, Central Java, Indonesia, was performed using qualitative and quantitative data obtained by conducting open, semi-structured, and structured interviews with 90 adult participants. Quantitative data was analyzed to produce UV and informant consensus factor (ICF). This study concluded that the community used 49 species of 32 families, and the most consumed were *Leucaena leucocephala, Carica papaya, Dendrocalamus asper, Muntingia calabura, P. pellucida, Gnetum gnemon, Moringa oleifera*, and *Portulaca oleracea*, with an ICF value ranging from 0.645 to 1.[46]

Despite the lack of recent studies on *P. pellucida* in humans, in an article published in 1999, a 20% decoction of *P. pellucida* at a dose of 2 mL/kg body weight given orally was described to reduce the intraocular pressure (IOP) by 18% within 4 h in 40 glaucoma patients.[47]

Moreover, as a promising plant-derived drug, *P. pellucida* in spray-dried powder form (spray-dried at atomization temperatures of 140, 160, and 180°C), developed using the diluent Flowlac, was reported to meet physicochemical quality control parameters, thus confirming its readiness for technological development for pharmaceutical applications.[48]

Discussion on the Mechanism of Action of Bioactive Compounds

The multifaceted impact of bioactive compounds on different signaling proteins in the body suggests a complex network of interactions. *P. pellucida* is known for its numerous phytochemical contents or bioactive compounds; therefore, the mechanism of action of the main constituents is considered noteworthy.

Diterpenoids such as phytol have been reported to be present in the leaves and stems of *P. pellucida*.[1,9] In a review by Islam et al, phytol as a single compound was shown to activate apoptosis and autophagy in human gastric adenocarcinoma AGS cells, and downregulate protein kinase B (Akt), mTOR (mechanistic target of rapamycin), and p70S6K phosphorylation. Phytol exhibits anxiolytic, metabolism-modulating, cytotoxic, antioxidant, antinociceptive, anti-inflammatory, immune-modulating, and antimicrobial activities.[49] Other researchers, Ko and Cho (2018), delineated that phytol suppressed the expression of microphthalmia-associated transcription factor (MITF) by phosphorylating extracellular signal-regulated protein kinase (ERK) in B16F10 cells, thus suggesting its potential as a therapy for skin

hyperpigmentation.[50] Moreover, phytol is also involved in the NF-κB signaling pathway, hence reducing the pro-inflammatory cytokines TNF-α and IL-6.[51]

Monoterpenoids and monoterpenes such as linalool, D-limonene, and alpha-terpineol are present in the stems, while sesquiterpenes, such as beta-caryophyllene, are found in the leaves and stems of *P. pellucida*.[2,9]

Linalool (a monoterpene acyclic tertiary alcohol), as a single compound, has been studied for its antibacterial activity and mechanism of action against *P. fluorescens*. This monoterpene reduces the bacteria's membrane potential, changes the alkaline phosphatase levels, and releases DNA, RNA, and protein of the cell wall membrane structure, and disrupts the cytoplasmic contents.[52] Linalool increases the levels of histidine and methionine, which are involved in the structural phenotype of the bacterial biofilm.[53,54] Moreover, linalool exhibits antidepressant effects by targeting numerous systems in the body, such as in the monoaminergic transmission, where it interacts with the serotonergic and noradrenergic pathways. In the hypothalamus-pituitary-adrenal axis, linalool modulates the expression of stress-related genes, elevates oxytocin and neuropeptide Y levels, and reduces salivary cortisol.[55] In a study on the triple transgenic model of Alzheimer's disease mice, linalool showed improvement in learning, spatial memory, and behavior of the mice. Linalool significantly reduced extracellular beta-amyloidosis, tauopathy, astrogliosis, and microgliosis in the hippocampus and amygdala of mice, and suppressed the levels of p38 MAPK, NOS2, COX-2, and IL-1β.[56]

Limonene (1-methyl-4-isopropenylcyclohex-1-ene) is a natural monocyclic monoterpene, which has been reported for its antibacterial and anti-inflammatory activities.[57] D-Limonene increased the permeability of the cell membrane, altered membrane potential, and reduced heat resistance, thus leading to the leakage of intracellular substances and cell lysis.[58,59] In preclinical studies, d-limonene exhibited anti-inflammatory activity by suppressing the production of TNF-α, IL-6, IL-1β, and NF-κB, and elevating the level of IL-10 and glutathione peroxidase (GPX), thus maintaining the integrity of the inflammation site.[60] Furthermore, the anti-inflammatory activity of D-limonene in COVID-19 pulmonary fibrosis was confirmed that this compound could block the PI3K/Akt/IKK-α/NF-κB p65 signaling pathway.[61]

Alpha-terpineol inhibited the activity and translocation of NF-κB to the nucleus, thus restricting the transcription of NF-κB-related pro-inflammatory gene expression.[62] In another study, alpha-terpineol inhibited the activity of bovine COX-1 and COX-2 with an IC_{50} value of 5.14 mM and 0.69 mM, respectively.[63]

Beta-caryophyllene induces apoptosis via ROS-mediated MAPKs and inhibition of the AKT/PI3K /mTOR/S6K1 pathways. It also inhibits invasion and induces apoptosis via suppression of the NF-κB pathway. The anti-inflammatory activity was achieved via downregulation of TLR-4, IL-1ß, and TNF-α levels.[64] It was also reported for its neuroprotective activity in a review article.[65]

Other bioactive compounds, such as gamma-sitosterol, were found in the leaves and stems,[2] phenolics in the aerial parts,[4] and flavonoids in the leaves and stems.[2] Gamma-sitosterol was cytotoxic against Caco-2, HepG2, and MCF-7 with IC_{50}-values of 8.3, 21.8, and 28.8 µg/mL, respectively,[66] and in another study, it inhibited the cell proliferation by 42.18 ± 3.9% for MCF-7 and 44.36 ± 3.05% for A549 cells.[67] Phenolics were widely recognized for their strong radical scavenging capacity. In accordance with the Trolox equivalent antioxidant capacity (TEAC), FRAP, and hypochlorite scavenging activity, the order was procyanidin dimer > flavanol > flavonol > hydroxycinnamic acids > simple phenolic acids. Quercetin exhibited stronger radical scavenging capacity compared with myricetin and kaempferol. Moreover, among simple phenolics and hydroxycinnamic acids, gallic acid and rosmarinic acid are the strongest radical scavengers, respectively.[68]

Conclusion

Our study of the articles published between 2014 and 2025 confirms that *P. pellucida* is still being explored globally. The most explored parts of the *P. pellucida* plant in numerous in vitro and in vivo studies are the leaves and the aerial parts, which are considered the active parts. Methanol and ethanol are the commonly employed solvents for extraction, and the extraction at room temperature is the popular choice. Considering the notable findings of the in silico, in vitro, and in vivo studies, *P. pellucida* may have the potential to be further developed as a plant-based antimicrobial, anti-inflammatory, antihypertension, or hypoglycemic agent. These activities are supported by their bioactive compounds, in particular, polyphenols, flavonoids, lignans, and sterols. Moreover, this plant did not show toxicity towards numerous normal cells or animal models, but was reported to be toxic towards cancer cells, such as MCF-7 and Vero cells, implying the

potential as anticancer. During the study period, we did not find studies in humans, however, several articles describing ethnopharmacological surveys of medicinal plants in Singapore, India, Myanmar, Nigeria, and Indonesia were found, among which *P. pellucida* was mentioned, to treat respiratory disorders, to cure cancer, to treat numerous infections, and for general health purpose, thus agree with the results of pharmacological activity assays. Despite its promising pharmacological evidence, the clinical applications of *P. pellucida* remain limited due to a lack of human studies, presenting challenges in determining its safety, dosage, and long-term effects. Further research for clinical validation is essential to determine its potential as a therapeutic agent.

Acknowledgments

The authors thank the Rector of Universitas Padjadjaran via the Directorate of Research and Community Engagement of Universitas Padjadjaran for funding the APC. This study is the initial project within the framework of the first author's dissertation in the Doctoral Program in Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran.

Disclosure

The authors declare no potential conflicts of interest regarding the research, authorship, or publication of this manuscript.

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