BIOMEDICAL REPORTS 20: 47, 2024

Physalis angulata Linn. as a medicinal plant (Review)

ARIYANI NOVITASARI[1], ENNY ROHMAWATY[2] and AZIIZ M. ROSDIANTO[3]

[1]Magister Program of Biomedical Sciences; [2]Division of Pharmacology and Therapy, Department of Biomedical Sciences; [3]Veterinary Medicine Program, Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Sumedang, West Java 45363, Indonesia

Received May 18, 2023; Accepted January 5, 2024

DOI: 10.3892/br.2024.1735

Abstract. There are numerous medicinal benefits from herbal plants, with many herbal medicines being used as 'Jamu', 'standardized herbal medicines' and phytopharmaceuticals. *Physalis angulata* Linn. (*P. angulata* L.), a plant utilized for both medicinal and food consumption purposes in a number of tropical and subtropical nations, is widely studied for its beneficial properties. The present review summarized the scientific evidence which suggested that *P. angulata* L. possesses antibacterial, anticancer, antiparasitic, anti-inflammatory, antifibrotic and antidiabetic properties. Furthermore, the various pharmacological studies that have been conducted utilizing *in vivo* and *in vitro* models, as well as the identification of phytochemical components with therapeutic value are described. In addition, the present review explained the solvents and the toxicity tests that were used for the investigation of *P. angulata* L. The authors aspire that this literature review will provide an overview for researchers regarding the scientific progress of *P. angulata* L. over the past ten years and the potential areas of future research.

Contents

Correspondence to: Dr Enny Rohmawaty, Division of Pharmacology and Therapy, Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Jl. Raya Bandung-Sumedang km 21, Hegarmanah, Jatinangor, Sumedang, West Java 45363, Indonesia
E-mail: e.rohmawaty@unpad.ac.id

Key words: *Physalis angulata* Linn., *in vivo*, *in vitro*, medicinal uses, phytochemical, extraction

1. Introduction

According to the World Health Organization (WHO), 60% of individuals worldwide utilize herbal medicines and 80% of those living in developing countries rely almost solely on them to meet their basic medical needs (1). *Physalis angulata* Linn. (*P. angulata* L.) was first identified and noted in the flora of Libya. *P. angulata* L. is a member of the *Solanaceae* plant (or Nightshade) family and is widely found in both tropical and subtropical regions. The Greek word 'physalis', which translates to 'bladder', is used to describe the inflated calyx. Popular names for *P. angulata* L. include camapu, cutleaf groundcherry, wild tomato, winter cherry, cow pops, Chinese lantern, mullaca, koropo (in Western Africa), wild gooseberry and ciplukan (in Indonesia) (2). The extracts or infusions of this plant are used as antimalarial, anti-asthmatic and for dermatitis treatments. In addition, *in vitro* tests have demonstrated that the extracted phytoconstituents from *P. angulata* L. have an anticancer effect against numerous cancer cell lines (Y79, HeLa, DLD-1, MCF-7 and HGC-27). Furthermore, *P. angulata* L. has been employed for a long time as an antipyretic in Japan (3). In traditional Chinese medicine, *P. angulata* L., a species that is widely spread in the east and southwest areas of China, is frequently used for antipyretic, anti-inflammatory and diuretic purposes (4).

Tropical Indonesia is home to a large number of medicinal plants and *P. angulata* L. grows wild on the slopes of Mount Kelud in East Java, as well as commercially in Mersi, Purwokerto, Central Java and a few locations in West Java (5). Ciplukan (*P. angulata* L.) has long been used as a traditional medicine to treat a variety of ailments, including body aches, asthma, diabetes, chickenpox, cough medication, fever, diarrhea, hypertension and back pain (6).

Over the past 10 years, the benefits of *P. angulata* L. as a medicinal plant have been demonstrated both *in vitro* and *in vivo*, with research regarding the antibacterial, anticancer, antiparasitic, anti-inflammatory, antifibrotic and antidiabetic properties of *P. angulata* L. conducted (Table I).

2. Antibacterial properties

Finding innovative, safer and more cost-effective treatments that can address the issue of antibiotic resistance has driven research on the antibacterial properties of *P. angulata* L. and its components. Research is ongoing to determine the impacts of *P. angulata* L. against a variety of Gram-positive and Gram-negative bacteria.

P. angulata L. is widely used as a traditional medicine in Southeast Asian and North and South American countries, but studies related to *in vivo* antibacterial activity in mice and humans have not yet, to the best of our knowledge, been conducted (2). An ethanol extract of *P. angulata* L. calyces suppressed the growth of *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* (7). The growth of *S. aureus* was also suppressed by an ethanol extract of *P. angulata* L. fruit (8). In addition, *P. angulata* L. leaf aqueous extract demonstrated activity against *S. aureus* (9) and an aqueous extract of the aerial parts was effective [minimum inhibitory concentration (MIC) 2.5 mg/ml)] against *S. aureus* and *Listeria monocytogenes* (10). In 2020, Cuong *et al* (11) studied four secosteroids, namely physalin B, D, F and G, obtained from a *P. angulata* dichloromethane extract. Physalin B was found to have antibacterial activity against *S. aureus, Bacillus subtilis* and *Escherichia coli (E. coli)*, with MIC values ranging from 32 to 128. Physalin D exhibited antibacterial activity against *S. aureus*, *B. subtilis*, *Bacillus cereus* and *E. coli*, with MIC values ranging from 64 to 128. Physalin F had a MIC of 128 against *S. aureus*, *B. subtilis*, *B. cereus* and *E. coli*, whereas physalin G exhibited no antimicrobial activity against any of the microorganisms tested.

The unknown mechanism of action of *P. angulata* L. is a potential avenue for future research. In the future, *P. angulata* L. could be investigated for broad-spectrum or narrow-spectrum antibacterial activity. Preclinical tests are also required to evaluate the role of *P. angulata* L. as an antibacterial agent with a more complex mechanism. Secondary metabolites can alter bacterial cell membrane functions and structure, impact intermediary metabolism, disrupt DNA/RNA synthesis and function, interfere with normal cell communication (quorum sensing) and trigger cytoplasmic coagulation (12). *P. angulata* L. could be used in conjunction with standard drugs to achieve synergism, which may overcome drug resistance issues, minimize side effects and enhance drug pharmacokinetics (12).

3. Anticancer properties

Over the last 10 years, the role of *P. angulata* L. as an anticancer agent has been investigated using the Y79, HeLa, DLD-1, MCF-7 and HGC-27 cancer cell lines. In 2019, research was conducted in Indonesia on the activity of *P. angulata* L. on the Y79 (retinoblastoma) cell line. The ethanol extract of *P. angulata* L. leaves promoted apoptosis and lowered the number of live cells at doses of 25, 50 and 100 μg/ml, with 100 μg/ml causing the greatest increase in apoptosis level (12). Pillai *et al* (3) examined the effects of *P. angulata* L. leaf and fruit ethanol extracts on HeLa, DLD-1 and MCF-7 cells. The fruit extracts had lower median lethal dose (LD_{50}) values than the leaf extracts, but the leaf extracts had a stronger cytotoxic action against HeLa cells.

Physalin B, the active component in *P. angulata* L may become essential in anticancer therapy (14,15). There is evidence that physalin B has anticancer activity in a variety of human solid tumors, including lung, breast, colon, melanoma and prostate tumors (16). By altering mitochondrial function, physalin B causes G2/M cell cycle arrest and cell death in human non-small cell lung cancer cells (A549) and a cell line for human breast cancer (MCF-7) affects p53-dependent signaling. The survival and proliferation of the undifferentiated gastric cancer cell line, HGC-27, and the ability to produce clones were all inhibited by physalin B, which induces G0/G1 cell cycle arrest and caspase 8, 3, 7 and poly (ADP-ribose) polymerase cleavage (17). In 2006, Magalhães *et al* (18) conducted *in vivo* studies investigating the antitumor activity of *P. angulata* L. using mice bearing sarcoma 180 tumor cells, confirming the antitumor activity of physalin B and D.

The potential role of drug candidates in cell growth and death is the cornerstone of anticancer research. While cell proliferation is the process by which cells multiply by expanding and dividing into two, apoptosis is a mechanism for planned cell death. However, the effectiveness of *P. angulata* L. and its isolates as anticancer drugs must be further studied. Future research on *P. angulata* L. as an anticancer agent may focus on directly preventing cancer cell proliferation by stimulating phagocytic cells and enhancing natural killer cell activity, delaying the development of cancer cell appendages by increasing the production of interferons, interleukins and antibodies in the bloodstream, removing the tumor tissue from the body and preventing it from metastasizing by obstructing blood supply to the cancerous tissue, inducing the inverse transformation of tumor cells into normal cells, boosting metabolism and protecting normal cells from changing into cancer cells, increasing appetite, improving sleep quality and managing pain (19).

4. Antiparasitic properties

Trypanosoma cruzi (*T. cruzi*), *Leishmania amazonensis (L. amazonensis)* and *L. braziliensis* have all been studied using *P. angulata* L. as an antiparasitic agent. Meira *et al* (20) conducted *T. cruzi in vitro* research using physalin B, D, F and G from *P. angulata* L. ethanol extract as candidate agents. According to the results of an alamar Blue assay, after 24 h treatment, 3.7 g/ml extracts of the *P. angulata* L. stem markedly decreased the percentage of infected cells with *T. cruzi*. In addition, compared with the untreated control, the anti-leishmanial impact at 3.7 g/ml increased after 48 h, and the number of infected macrophages containing amastigotes of *L. amazonensis* parasites decreased by 91.8% (21).

The stem of *P. angulata* L. acts as an anti-leishmanial agent (22). The WHO lists leishmaniasis as a significant tropical disease, ranking it second only to malaria (23). The *Leishmania* parasites enter the digestive tract of sand flies (the vector) when it feeds on an infected host and multiply there as promastigotes. These promastigotes can then be transmitted to a mammalian host when the sand fly bites a healthy individual. The parasite multiplies in this mammalian host and settles inside the macrophages, where it survives and develops. *Leishmania* parasites can also persist in amastigote form in a phagolysosomal chamber. During

Table I. Research list of *Physalis angulata* Linn. as a herbal medicine from 2012 to 2022.

Type	No.	Author's/Year	Part	Solvent	Methods	Organism/ Organ test	Dosage	Results	(Refs.)
Antibacterial	1	Rivera *et al*, 2015	Calyces	Ethanol 96%	*In vitro*	*S. aureus* *K. pneumoniae* *P. aeruginosa*	50 μl (1,000 mcg/ml)	*Klebsiella pneumoniae* (MIC 94.05±1.94) *Staphylococcus aureus* (MIC 96.57±1.69) *Pseudomonas aeruginosa* (MIC 96.87±0.50)	(7)
	2	Hananto *et al*, 2021	Whole plant	Ethanol 70%	*In vitro*	*S. aureus*	20 mg/ml	*Staphylococcus aureus* (Zone of Inhibition 17.00±0.0 mm)	(8)
	3	Pillai *et al*, 2022	Leaves	Petroleum ether	*In vitro*	*E. coli* *S. aureus*	100 μl-25 mg/ml	*Escherichia coli* (MBC=5 mg/ml; MIC 10 mg/ml); *Staphylococcus aureus* (MBC=5 mg/ml; MIC 10 mg/ml)	(3)
				Ethyl acetoacetate				*Escherichia coli* (MBC=1.25 mg/ml; MIC 2.5 mg/ml); *Staphylococcus aureus* (MBC=1.25 mg/ml; MIC 2.5 mg/ml)	
				Ethanol				*Escherichia coli* (MBC=5 mg/ml; MIC 10 mg/ml); *Staphylococcus aureus* (MBC=2.5 mg/ml; MIC 5 mg/ml)	
			Fruits	Petroleum Ether			100 μl- 25 mg/ml	*Escherichia coli* (MBC=1.25 mg/ml; MIC 2.5 mg/ml) *Staphylococcus aureus* (MBC=5 mg/ml; MIC 10 mg/ml);	

Table I. Continued.

Type	No.	Author's/Year	Part	Solvent	Methods	Organism/ Organ test	Dosage	Results	(Refs.)
				Ethyl Acetoacetate				*Escherichia coli* (MBC=1.25 mg/ml; MIC 2.5 mg/ml) *Staphylococcus aureus* (MBC=5 mg/ml; MIC 10 mg/ml);	
				Ethanol				*Escherichia coli* (MBC=5 mg/ml; MIC 10 mg/ml) *Staphylococcus aureus* (MBC=5 mg/ml; MIC 10 mg/ml);	
	4	Dias *et al*, 2020	Leaves	Aqueous	*In vitro*	*S. aureus* *L. monocyto-genes*	50 µl (50 mg/ml)	Cultivated leaf extract obtained by decoction: *Staphylococcus aureus* (agar diffusion Inhibition zone 13 mm) *Listeria monocytogenes* (agar diffusion Inhibition zone 18 mm) Native leaf extract obtained by decoction: *Staphylococcus aureus* (agar diffusion Inhibition zone 8 mm) *Listeria monocytogenes* (agar diffusion Inhibition zone 14 mm)	(10)
	5	Gagare *et al*, 2021	Leaves	Water	*In vitro*	*S. aureus* *P. aeruginosa*	25 µl	*Staphylococcus aureus* (agar diffusion Inhibition zone 4 mm) *Pseudomonas aeruginosa* (agar diffusion Inhibition zone 2 mm) *Escherichia coli* (agar diffusion Inhibition zone 2 mm)	(9)

Table I. Continued.

Type	No.	Author's/Year	Part	Solvent	Methods	Organism/ Organ test	Dosage	Results	(Refs.)
	6	Cuong *et al*, 2020	Whole plant	Dichlorome-thane extract	*In vitro*	*S. aureus* *B. subtilis* *E. coli* *E. faecalis* *B. cereus*		Physalin B: *S. aureus*, *B. subtilis*, *E. coli* (MIC 128, 64, 32 µg/ml) Physalin D: *S. aureus*, *E. faecalis*, *B. subtilis*, *B. cereus*, *E. coli* (MIC 64, 64, 128, 128, 64 µg/ml) Physalin F: *S. aureus*, *B. subtilis*, *B. cereus*, *E. coli* (MIC @ 128 µg/ml) Physalin G : -	(11)
Anticancer	1	Pillai *et al*, 2022	Leaves	Ethanolic extract	*In vitro*	DLD-1, HeLa, and MCF-7 cell lines	100 mcg/ml	The percentage viability of *Physalis angulata* leaf extracts at 100 µg/ml was observed at 46.23, 33.66, and 51.54 for DLD-1, HeLa, and MCF-7 cell lines, respectively. The leaf extract LC50 values were 90, 44, and 100 µg/ml for DLD-1, Hela, and MCF-7 cell lines, respectively.	(3)
			Fruit		*In vitro*	DLD-1, HeLa, and MCF-7 cell lines		The percentage viability of *Physalis angulata* fruit extracts at 100 µg/ml was observed 70, 69.41, and 65.27 for DLD-1, HeLa, and MCF-7 cell lines, respectively. The fruit extracts LC50 values were 188, 167, and 157 µg/ml for DLD-1, HeLa, and MCF-7 cell lines, respectively.	

Table I. Continued.

Type	No.	Author's/Year	Part	Solvent	Methods	Organism/ Organ test	Dosage	Results	(Refs.)
	2	Chairissy *et al*, 2019	Leaves	Ethanol	*In vitro*	retinoblastoma cells	25 μg/ml, 50 μg/ml, 100 μg/ml	Apoptosis 25 μg/ml 1.06±0.31, 50 μg/ml 1.33±0.17, and 100 μg/ml 1.54±0.34 Proliferation 25 μg/ml 87.84±1.01, 50 μg/ml 86.77±1.75, and 100 μg/ml 84.80±1.01	(13)
	3	Fang *et al*, 2021	Whole plant	Ethanol	*In vitro*	HGC-27 cell	2 μM, 5 μM, 10 μM, 20 μM	IC_{50} 9 μM, G0/G1 phase ratio ↑, G2/M phase ↓, p-CHK2 ↑, cyclin D1 ↓, cyclin D3↓, CDK4↓, CDK6 ↓ and cyclin E ↓, p-Rb (Ser780) ↓, p-Rb (Ser795) ↓. Apoptosis 5 μM 18.0±1.0%, 10 μM 36.9±3.7%, and 20 *μM* 40.6% ±4.8% Caspase 8, 3, 7, PARP ↑	(17)
Antiparasitic	1	Silva *et al*, 2015	Roots	Aqueous extract	*In vitro*	*Leishmania amazonensis*	25 μg/ml, 50 μg/ml, 100 μg/ml	*L. amazonensis* amastigotes IC_{50}: 43.3±10.1 μg/ml *L. amazonensis* promastigotes IC_{50}: 39.5±5.1 μg/ml	(23)
	2	Meira *et al*, 2013	Whole plant	Ethanolic extracts	*In vitro*	*Trypanosoma cruzi*		*T. cruzi* epimastigotes IC_{50} 5.3-5.8±1.5-1.9 μM *T. cruzi* trypomastigotes IC_{50}: 0.68-0.84±0.001-0.004 μM	(20)
	3	Nogueira *et al*, 2013	Stem	Ethanolic extracts	*In vitro*	*Leismania amazonensis, Leishmania braziliensis*	1.2-100 μg/ml	*L. amazonensis* IC_{50}: 5.35±2.50 μg/ml *L. braziliensis* IC_{50}: 4.50±1.17 μg/ml	(21)
Anti-inflammatory	1	Santo *et al*, 2019	Whole plant	Ethanolic extracts	*In vivo*	Paw edema	50 mg/kg and 100 mg/kg	Paw edema ↓, TNF-α ↓, IL-1β↓, COX-2↓, iNOS ↓	(32)

Table I. Continued.

Type	No.	Author's/Year	Part	Solvent	Methods	Organism/ Organ test	Dosage	Results	(Refs.)
	2.	Rivera *et al*, 2020	Calyces	Dichloromethane fraction	*In vivo*	Intestinal inflammation	5 and 10 mg/kg	MPO ↓, IL-1β ↓, TNF-α↓, IL 10 ↑,	(7)
	3.	Arruda *et al*, 2021	Whole plant	Ethanolic extract	*In vivo* & *in vitro*	Acute lung injury & HEK293		IL-1β↓, TNF-α ↓ IC50 value IL-1β release: Physalin B 0.072±0.011, Physalin D 0.004±0.0008, Physalin F 0.023±0.001, Physalin G 0.015±0.017 IC_{50} value TNF-α release: Physalin B 0.089±0.019, Physalin D 0.068±0.09, Physalin F 0.085±0.16, Physalin G 0.138±0.025.	(34)
	4.	Junior *et al*, 2014	Stem	Ethanolic extract	*In vivo*	Intestinal inflammation	25, 50, 100 mg/kg	MPO↓, ALP activity ↓, IFN-γ ↓, IL-6 ↓, Hsp 70↓, Mapk 3↓, Mapk 9↓, Muc 1↓, Muc2↓, Hpse expression ↓, edema ↓	(33)
	5.	Rivera *et al*, 2018	Calyces	Ethanolic extracts	*In vivo*	Acute ear edema		MPO ↓, edema↓, NO↓, PGE2 ↓, IL-6 ↓, IL-1β ↓, TNF-α ↓, CCL-2↓	(7)
	6.	Pereda *et al*, 2018	Aerial Parts	Supercritical CO2 Extraction	*In vitro* & Clinical trial	Normal human epidermal keratinocytes, dermal fibroblast,		TNF α↓, IL-1α ↓, IL-6 ↓, COX-2 ↓, LOX ↓, Phospholipase A2 ↓, PGE2 ↓, LTB4↓, Histamin ↓, NF-kB ↓	(53)
	7.	Wang *et al*, 2021	Stem & Leaves	Ethanolic Extract	*In vitro*	RAW 264.7		NO ↓, PGE2 ↓, IL-6 ↓, TNF α ↓, iNOS↓, COX-2 ↓, NFkB↓	(16)
	8.	Yen *et al*, 2019	Whole plant	Methanolic extract (Dichloromethane fractioned)	*In vitro*	RAW 264.7		NO ↓	(27)
	9.	Ukwubile, 2016	Leaves	Methanolic extract	*In vivo*	Paw edema	400 mg/kg	Mean inhibition 62,71 %	(30)

Table I. Continued.

Type	No.	Author's/Year	Part	Solvent	Methods	Organism/ Organ test	Dosage	Results	(Refs.)
	10	Abdul-Nasir-Deen *et al*, 2020	Leaves	Methanolic extract	*In vivo*	Paw edema	30, 100, 300 mg/kg	Prophylactic (2H): Mean inhibition 64.08±1.75, 60.91±0.62, and 59.12±3.34% Therapeutic (6H): 89.93±2.47, 82.14±1.14, and 77.48±2.61%	(31)
	11	Yang *et al*, 2017	Stem and Aerial parts	Methanolic extract	*In vitro*	RAW 264.7		TNF-α ↓, IL-6 ↓, NFkB ↓,	(26)
	12	Anh *et al*, 2020	Whole plants	Methanolic extract	*In vitro*	RAW 264.7		INOS ↓, COX-2 ↓	(28)
Antifibrotic	1	Zhu *et al*, 2021	Calyces	Ethanolic extracts	*In vivo* & *in vitro*	Liver fibrosis HSC cell		COL1A1 ↓, αSMA ↓, TGFβ1 ↓, TIMP-1 ↓ ALT ↑, AST ↑, Fibrous collagen deposition ↓, fibroplasia ↓, bridging fibrosis ↓, Hydroxyproline ↑, GLI 1 ↓ HHIP ↓, Cyclin D ↓, Cyclin E ↓, C-MYC ↓	(37)
	2	Rohmawaty *et al*, 2021	Aerial parts	Ethanolic extract	*In vivo*	Liver fibrosis	1.11 mg & 2.22 mg	ALT ↓, Histological fibrosis score ↓,	(36)
	3	Dewi *et al*, 2019	Aerial parts	Ethanolic extract	Clinical trial	Skin fibrosis	3x250 mg	MRSS score ↓, PINP ↓	(38)
Antidiabetic	1	Raju *et al*, 2015	Fruits	Methanolic extract	*In vivo*	DM alloxan induced	25 & 50 mg/kg	Blood sugar level ↓	(40)
	2	Reddy *et al*, 2014	Roots	Methanolic extract	*In vivo*	DM streptozotocin induced		Serum glucose level ↓, Triglyceride ↓, Total Cholesterol ↓, VLDL ↓, LDL ↓, SGOT ↓, SGPT ↓, MDA ↓	(41)

P. angulata L. has antibacterial activity against *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Escherichia coli*, *Listeria monocytogenes*, *Bacillus subtilis*, *Bacillus cereus*, *Pseudomonas aeruginosa*; *P. angulata* L. acts as an anticancer in Y79, HeLa, DLD-1, MCF-7 and HGC-27 cancer cell lines; *P. angulata* L. acts as an antiparasitic against *Trypanosoma cruzi*, *Leishmania amazonensis* and *Leishmania braziliensis*; *P. angulata* L. significantly reduced proinflammatory cytokines *in vivo* and *in vitro* studies; *P. angulata* L. has been proven as a treatment for skin fibrosis in humans and liver fibrosis in rats; *P. angulata* L. is able to reduce blood glucose levels in rats induced by alloxan or Streptozotocin. *P. angulata* L., *Physalis angulata* Linn.; MIC, minimum inhibition concentration; MBC, minimum bactericidal concentration; LC_{50}, lethal concentration 50; IC_{50}, inhibition concentration 50; p-CHK2, phospho-CHK2; CDK4, cyclin-dependent kinase 4; CDK6, cyclin-dependent kinase 6; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin 1-beta; COX-2, cyclooxygenase-2; iNOS, inducible nitric oxide synthase; MPO, myeloperoxidase; ALP, alkaline phosphatase; IFN-γ, interferon gamma; MAPK, mitogen-activated protein kinase; NO, nitric oxide; PGE2, prostaglandin E2; TGFβ1, transforming growth factor-beta; LTB4, latent TGF β Binding Protein 4; NF-κB, nuclear factor kappa B; MMP, matrix metalloproteinase; COL1A1, collagen type 1 alpha 1; αSMA, alpha smooth muscle actin; TIMP-1, tissue inhibitor of metalloproteinase 1; ALT, alanine transaminase; AST, aspartate aminotransferase; MRSS, modified rodnan skin score; PINP, procollagen type I N-propeptide; DM, diabetes mellitus; VLDL, very low-density lipoprotein; LDL, low-density lipoprotein; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; MDA, malondialdehyde.

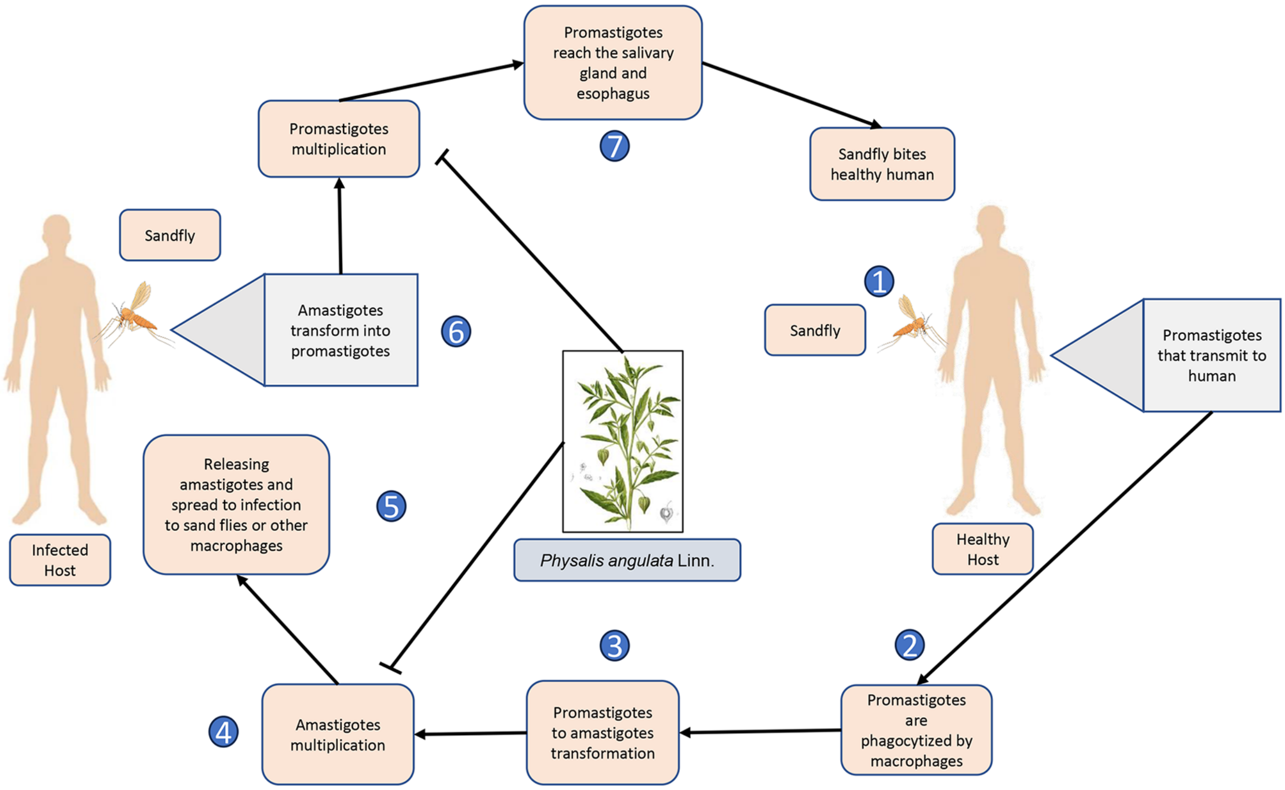

Figure 1. The life cycle of *Leishmania spp*., the causal agents of leishmaniasis are transmitted by the bite of female sandfly. Sandfly injects the infective stage, promastigotes, during blood meals (1). Promastigotes that reach the puncture wound are phagocytized by macrophages (2) and transform into amastigotes (3). Amastigotes multiply in infected cells and affect different tissues, depending in part on the *Leishmania* species (4). This originates the clinical manifestations of leishmaniasis. Sandfly become infected during blood meals on an infected host when they ingest macrophages infected with amastigotes (5). In the midgut of the sandfly, the parasites differentiate into promastigotes (6), which multiply and migrate to the proboscis (7). *Physalis angulata* Linn. acts as an anti-leishmania agent by inhibiting promastigotes multiplication in infected humans and inhibiting amastigotes multiplication in healthy host bitten by sandfly.

times of stress, macrophages lyse and are phagocytosed by new host cells (21). Physalin isolates A, B, D, E, F, G and H present in the aqueous extract of *P. angulata* L. roots induced 99.8% anti-leishmanial activity against *L. amazonensis* promastigotes and reduced parasite survival at a dose of 100 μg/ml extract. Furthermore, *P. angulata* L. participates in cell division, cytoskeleton disintegration and autophagy in promastigotes (23). *P. angulata* L. acts as an anti-*Leishmania* agent by inhibiting promastigotes multiplication in infected humans and inhibiting amastigotes multiplication in healthy humans bitten by sandfly (Fig. 1).

Research opportunities for anti-*Leishmania* drug targets could explore several routes, such as effects on sterol biosynthesis enzymes, thiol metabolism enzymes, the hypusine pathway, the glycosylphosphatidylinositol pathway, the glycolytic pathway, the purine salvage pathway, nucleoside transporters, cyclin-dependent kinases, mitogen-activated protein kinase, polyamine biosynthesis enzymes, dihydrofolate reductase, peptidase, topoisomerase, metaspora and glyoxalase systems. Another unique strategy for directly controlling *Leishmania* parasites that dwell in macrophages is the use of macrophage key target drug delivery systems. Since delivering drugs into macrophages is difficult, drug carriers such as liposomes, microspheres, nanoparticles and carbon nanotubes are being investigated. Additionally, specific receptors expressed by macrophages are also used to actively deliver drugs (24).

5. Anti-inflammatory properties

Inflammation is a protective response to potentially harmful stimuli such as allergens and/or injury to tissues. Inflammation is a complex process that involves various cellular interactions and can be classified as acute or chronic. Acute inflammation protects the body by repairing wounds and fighting microbial invasion, whereas chronic inflammation is distinguished by the simultaneous destruction and repair of tissues. Macrophages and lymphocytes are the primary immune cells that infiltrate chronic inflammatory sites (25).

P. angulata L. has been studied as an anti-inflammatory agent *in vitro*, *in vivo* and in clinical studies. In the last 10 years, there have been four studies using RAW 264.7 cells to determine the anti-inflammatory properties of *P. angulata* L. and its isolates. Yang *et al* (26) isolated physalin E from the stem and aerial parts of *P. angulata* L. and demonstrated that physalin E significantly reduced TNF-α and IL-6 mRNA and protein expression at 12.5, 25.0 and 50.0 M (26,27). In addition, withaminimin, obtained from dichloromethane extract of the whole plant of *P. angulata* L., educed nitric oxide (NO) generation in RAW 264.7 macrophages stimulated with lipopolysaccharide (LPS) (27). Using NO production measurements following 1 lg/ml of LPS stimulation, the NO inhibition of each of the isolated compounds was assessed in RAW 246.7 cells. The IC_{50} values for physagulin B, physalin B and physagunin R were <1.0 μM, followed by physalin F (IC_{50} 1.06±0.68 μM),

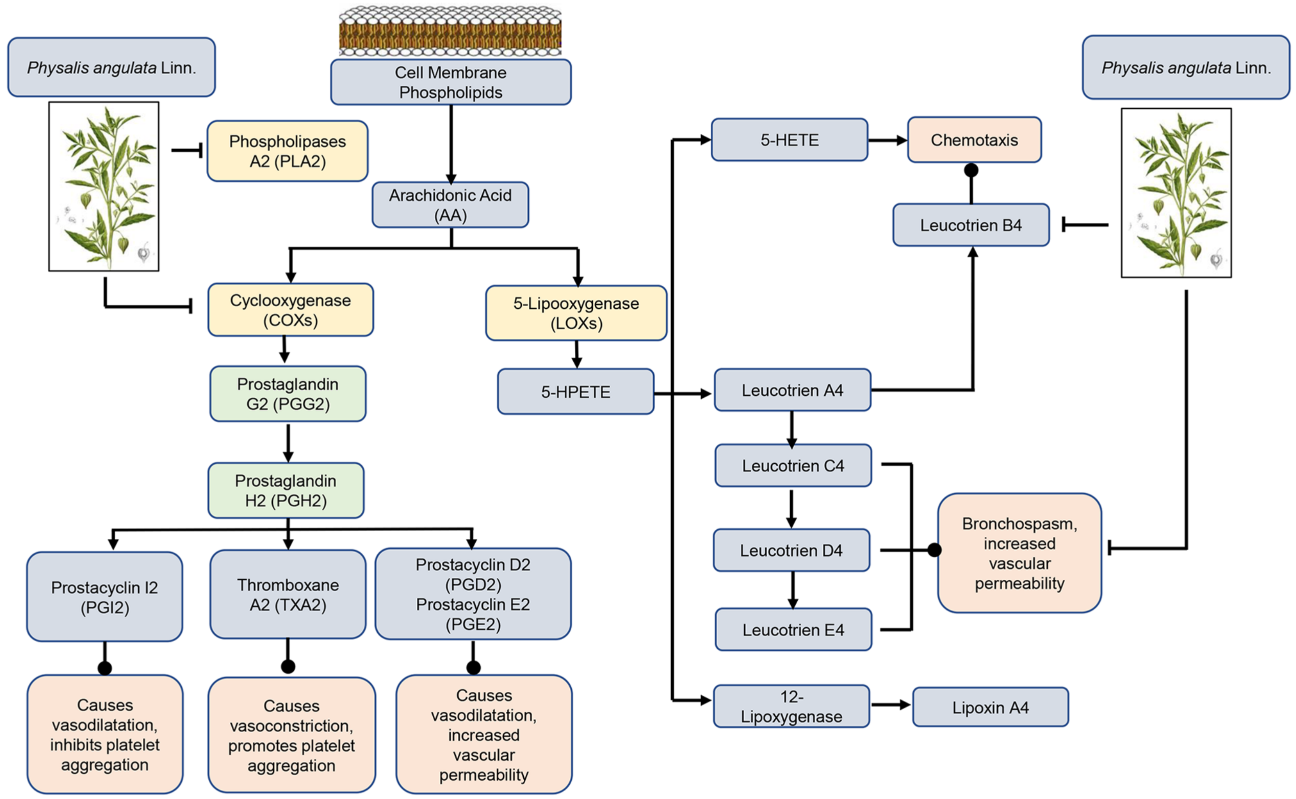

Figure 2. AA metabolism pathways. Esterified AA on the inner surface of the cell membrane is hydrolyzed to its free form by PLA2, which is in turn further metabolized by COXs and LOXs enzymes to a mediator that includes prostanoids, LTs, 5-HPETE, 5-HETE and LXs. *Physalis angulata* Linn. inhibits the action of the PLA2, COXs, and Leucotrien B4. AA, arachidonic acid; PLA2, phospholipase A2; COX, cyclooxygenase; LOX, 5-lipoxygenases; LT, leukotrienes; 5-HPETE, 5-hydroperoxyeicosatetraenoic acid; 5-HETE, 5-hydroxyeicosatraenoic axid; LX, lipoxin.

physalucoside A (IC_{50} 2.69±0.17 μM) and physalin G (IC_{50} 3.74±0.29 μM) (28). Furthermore, physagulins A, C and H inhibit NO, prostaglandin (PG) E2 and IL-6 production, as well as the expression of inducible NO synthase (iNOS) and cyclooxygenase-2 (COX-2) proteins and the translocation of NF-κBo in the nucleus (28,29).

The anti-inflammatory effect of *P. angulata* L. leaf methanol extract against carrageenan-induced paw edema was shown to be dose-dependent, with 62.71% inhibition at 400 mg/kg compared with 34.31% inhibition for the standard drug (ibuprofen 100 mg/kg) (30). To investigate the prophylactic anti-inflammatory effects of *P. angulata* L. extract, different extract concentrations (30, 100 and 300 mg/kg body weight) were administered before the paw edema was induced with carrageenan. The results demonstrated that the mean maximal swelling at 2 h was significantly (P<0.01) reduced from 69.77±3.83% in the inflamed control group to 64.08±1.75, 60.91±0.62 and 59.12±3.34% in the 30, 100 and 300 mg/kg treatment groups, respectively. The extracts significantly reduced the mean maximal swelling (P<0.001) when administered 2 and 6 h after carrageenan-induced paw edema (curative) (31).

P. angulata L. reduced TNF-α, IL-1β, COX-2 and iNOS mRNA expression and induced a significant reduction in TNF-α, IL-1β and PGE2 (Fig. 2) paw edema levels during inflammation (31). LPS-induced NF-κB activation was also inhibited by physalin E (25). NF-κB, a promoter-binding immediate early transcriptional activator, plays a role in immunological, inflammatory and acute phase responses by regulating the expression of immediate early inflammatory genes such as TNF-α, IFN-γ, NOS II and intercellular adhesion molecule (26).

In vivo anti-inflammatory research has also received attention in the last decade, in which paw edema, intestinal inflammation and acute lung injury were induced in experimental animal models. In intestinal inflammation, *P. angulata* L. aerial parts improved anti-inflammatory response throughout 2,4,6-trinitrobenzane sulfonic acid-induced intestinal damage, modulating oxidative stress, immune response and inflammatory gene expression (33). According to a study by Arruda *et al* (34), physalin D prevents the release of cytokines, protein accumulation and cell migration caused by ATP, reduces the edematogenic response and the LPS impact for an independent glucocorticoid receptor pathway. Furthermore, physalin D exhibits effective anti-inflammatory activity, low murine toxicity, good aqueous solubility, as well as pharmacokinetics of absorption, low liver conversion and high urine and fecal excretion.

The COX and 5-lipoxygenase pathways are two key arachidonic acid metabolic processes. The COX process generates the cyclo-endoperoxides, PGG2 and PGH2, as intermediates. These cyclo-endoperoxides are then converted into the physiologically active prostanoid by enzymes. PGs are produced by smooth muscle cells in blood arteries. PGD2 is a major metabolite of the cyclooxygenase pathway in mast cells, together with PGE2 causes vasodilation and promote edema formation. PGE2 is a vasodilator that stimulates the Gs-protein pathway, whereas PGF2 is a vasoconstrictor that stimulates the Gq-protein pathway. PGI2 is the principal arachidonic acid derivative produced by vascular endothelial cells, and is a strong vasodilator and platelet adhesion inhibitor that functions via the Gs-protein pathway (35).

Platelets produce thromboxane A2 (TXA2), a strong vasoconstrictor that functions via the Gq-protein pathway. TXA2 synthesis increases with inflammation, tissue injury and platelet activation. When an artery is cut and bleeding, TXA2 enhances vascular contraction (hemostatic function). In reaction to inflammation and tissue injury, leukocytes produce leukotrienes (LTs), such as LTC4. LTC4, like TXA2, is a powerful vasoconstrictor that functions via the Gq-protein pathway. LTs (and PGs) can also cause vascular endothelium 'leakage', promoting edema during inflammation. *P. angulata* L. acts as an anti-inflammatory by preventing the action of phospholipase, COX and LTB4 (35).

P. angulata L. acts as an anti-inflammatory by inhibiting the cyclooxygenase pathway, thus reducing PGE2. In addition, *P. angulata* L. also inhibits the lipo-oxygenase pathway by reducing LTB4, which is a chemotaxis agent (Fig. 2).

6. Antifibrotic properties

P. angulata L. is an effective acute anti-inflammatory agent and its potential action against chronic diseases, such as fibrosis, is also being investigated. Fibrosis is associated with diseases including the hepatitis virus, non-alcoholic fatty liver disease, chronic kidney diseases, idiopathic pulmonary fibrosis, pneumoconiosis and cystic fibrosis (36). Global disability-adjusted life-years in 2019 were significantly impacted by fibrosis-related disorders (36).

Physalin B derived from *P. angulata* L. has been proven to be an antifibrosis agent. Physalin B has a potent antifibrotic effect on activated hematopoietic stem cells (HSCs), as demonstrated in both *in vitro* and *in vivo* studies. The antifibrotic activity of physalin B on LX-2 cells was examined using the Cell Counting Kit-8 viability assay, and the results revealed that the IC_{50} was 5 μM. Transforming growth factor β-1 induced HSC proliferation was also inhibited by physalin B. Furthermore, *in vivo* studies revealed that physalin B reduces hepatic injury, as measured by decreased aspartate aminotransferase and alanine transaminase (ALT) levels (36). Histopathological examination also demonstrated that physalin B could repair liver fibrosis (37).

In 2019, Dewi *et al* (38) conducted a study on patients with scleroderma, which is a fibrosing disease of the skin. *P. angulata* L. was administered as an adjuvant therapy at a dose of 250, 3 times daily for 12 weeks, which reduced the modified Rodnan skin scores (MRSS) and procollagen type I N-pro-peptide serum levels of patients. Another study on CCL4-induced liver fibrosis demonstrated that, in the group that received CCL4, serum ALT levels were higher and, microscopically, hepatocyte architecture lost its typical appearance, transparent collagen was deposited and fiber segmentation formed (36). Significant variations in serum ALT concentration were observed at the 2.22 mg dose of ethyl acetate fraction of *P. angulata* L. along with microscopic histologic changes, where the Ishak and Metavir scores decreased indicating healing of the hepatocytes (36-38).

Research is still being conducted on the mechanism of action of *P. angulata* L. and its isolates, as well as on *in vitro* and *in vivo* fibrosis models for the heart, kidneys and lungs. Fibrosis-related *in vitro* studies may utilize epithelial cells, endothelial cells, immune cells and fibroblasts (39). Notable signaling pathways within *in vivo* or *in vitro* studies involved in fibrotic diseases are growth factors (e.g. fibroblast growth factors, platelet-derived growth factor, connective tissue growth factor, and TGF-βs) and related signaling pathways (39). Finding effective therapeutic drugs is difficult due to the complicated pathophysiology of fibrotic disorders, which involve several abnormal cells (for example, epithelial cells, endothelial cells, immune cells and fibroblasts) and signaling pathways during development of the disease (39).

7. Antidiabetic properties

Raju and Estari (40) demonstrated that fruits from *P. angulata* L. reduced blood sugar levels at doses of 25 and 50 mg/kg. The methanolic extract of *P. angulata* L. roots lowers blood glucose levels at a dose of 200-400 mg/kg body weight (40). In addition, withangulatin A isolated from *P. angulata* L. fruit has a hypolipidemic action and lowers blood sugar levels (41). However, further research is needed to determine the optimal dose of extracts with minimal side effects. The unclear mechanism of *P. angulata* L. in reducing blood sugar levels needs further research. Pharmacology-related anti-diabetes research could explore the mechanism of insulin synthesis stimulation and/or secretion, restoration of damaged pancreatic β cells, improved insulin sensitivity and increased glucose uptake by fat and muscle cells, insulin mimics, slowing carbohydrate absorption from the gut, altering glucose metabolizing enzymes or ameliorating oxidative stress (42).

8. Chemical components of *Physalis angulata* Linn (*P. angulata* L.)

P. angulata L. contains active ingredients that have medicinal properties. These active substances are: i) Physalin A in the roots, with antiparasitic properties (23), ii) physalin B in the whole plant, with anti-inflammatory, antiparasitic, antibacterial, anticancer and antifibrotic properties (10,16,17,27,29,31,37,43,), iii) physalin D, F, G in the whole plant, with anti-inflammatory, antiparasitic and antibacterial properties (11,20,23,32,34,43), iv) physalin E in the whole plant, with anti-inflammatory and antiparasitic properties (23), v) physalin H in the root, with antiparasitic properties (20,31), vi) withangulatin A in the fruit, with antidiabetic properties (35) and vii) physangulatin A in the leaves and stems, with anti-inflammatory properties (35). The active substances in *P. angulata* L. are also presented in Table II and Fig. 3.

Clinical study. Over the past 10 years, there has only been one study of the role of *P. angulata* L. with human subjects, namely the study of Dewi *et al* (38) (2019). The aforementioned study was about to evaluate the effect of the addition *P. angulata* L. extract as adjuvant to scleroderma standard therapy in suppressing inflammatory, immunological, and

Table II. The active compounds in *Physalis angulata* L.

Name of chemical	Plant part	Activities	(Refs.)
Physalin A	Roots	Anti-parasitic/antileishmanial	(23)
Physalin B	Stem	Immunomodulatory	(54)
		Anti-inflammatory	(28,32,43)
	Whole plant	Anti-inflammatory, antiparasitic	(28,32,43)
	Root	Antibacterial	(20,23,55)
		Anticancer/Antifibrosis	(11,17,37)
Physalin D	Stem	Immunomodulatory	(54,56)
	Whole plant	Anti-inflammatory	(32,34,43)
	Root	Antiparasitic	(23,55)
		Antibacterial	(11)
Physalin E	Root	Antiparasitic	(23)
	Whole plant	Immunomodulatory	(56)
		Anti-inflammatory	(26,57)
Physalin F	Stem	Immunomodulatory	54
	Whole plant	Anti-inflammatory	(28,32,43)
	Root	Antiparasitic	(20,23,55)
		Antibacterial	(11)
Physalin G	Stem	Immunomodulatory	(54,56)
	Whole plant	Anti-inflammatory	(28,32,43)
	Root	Antiparasitic	(23)
		Antibacterial	(11)
Physalin H	Root	Antiparasitic	(23)
Withangulatin A	Fruit	Antidiabetic	(40)
Physagulin A	Leaves and stems	Anti-inflammatory	(35)
Physagulin C	Leaves and stems	Anti-inflammatory	(35)
Physagulin H	Leaves and stems	Anti-inflammatory	(35)

fibrosis processes to accelerate clinical improvement of skin fibrosis based on MRSS in scleroderma patients. The the degree of disease activity was assessed using the following biomarkers: Erythrocyte sedimentation rate for inflammation; serum levels of soluble CD40 ligand (sCD40L) and B-cell activation factor (BAFF) for immunological biomarkers; and serum levels of procollagen Type I N-Terminal propeptide (P1NP) for fibrotic process biomarker (38).

During November 2015-March 2017, 59 scleroderma patients who met the selection criteria and remained receiving regular therapy at Cipto Mangunkusumo Hospital and Hasan Sadikin Hospital in Indonesia participated in a double-blind, randomized clinical trial. The subjects were randomly allocated into two groups: the study group (29 patients) received the *P. angulata* L. extract 3x250 mg/day for 12 weeks and the placebo group (30 patients). Examination of MRSS, ESR, P1NP, BAFF and sCD40L was performed every 4 weeks until the end of the study. After 12 weeks, MRSS decreased 35.9% in the *P. angulata* L. group and 6.3% in the placebo group. Serum P1NP levels were also decreased in the *P. angulata* L. group (17.8%) compared with the placebo group (0.7%). This indicated that *P. angulata* L. can therapeutically improve skin fibrosis. The result identified no correlation between MRSS and the result of ESR value, serum BAFF and CD40L levels in both groups. To demonstrate that *P. angulata* L. has anti-inflammatory properties, more research utilizing additional inflammatory indicators is required (38).

Based on Dewi's research that *P. angulata* L. can therapeutically improve skin fibrosis, research was continued on other organs. Rohmawaty *et al* (36) conducted the research on liver of male adult Wistar rats that induced by carbon tetrachloride (CCl4) to perform liver fibrosis model.

The aim of the aforementioned study was to determine if the ethyl acetate fraction of *P. angulata* L. had an antifibrotic effect on liver fibrosis. Liver fibrosis was induced by oral injection of 20% CCl4 twice a week for eight weeks. A total of four weeks following fibrosis induction, *P. angulata* L. ethyl acetate fractions of 1.11 mg (CPL-1) and 2.22 mg (CPL-2) were administered orally. As a positive control group, vitamin E was used (36).

The ethyl acetate component of 2.22 mg (CPL-2) decreased serum alanine aminotransaminase levels (83.95±27.675 vs. 175.23±5.641, P-value <0.05) as compared with the negative control. Microscopic histopathological changes based on the better Metavir score (CPL-2 vs. negative control=1.25±1.893 vs. 3.50±0.577; $P<0.05$) and Ishak score (CPL-2 vs. negative control=1.50±1.000 vs. 4.75±0.957 $P<0.05$) were demonstrated. These findings suggested that the ethyl acetate fraction of *P. angulata* L. has an antifibrotic effect (36).

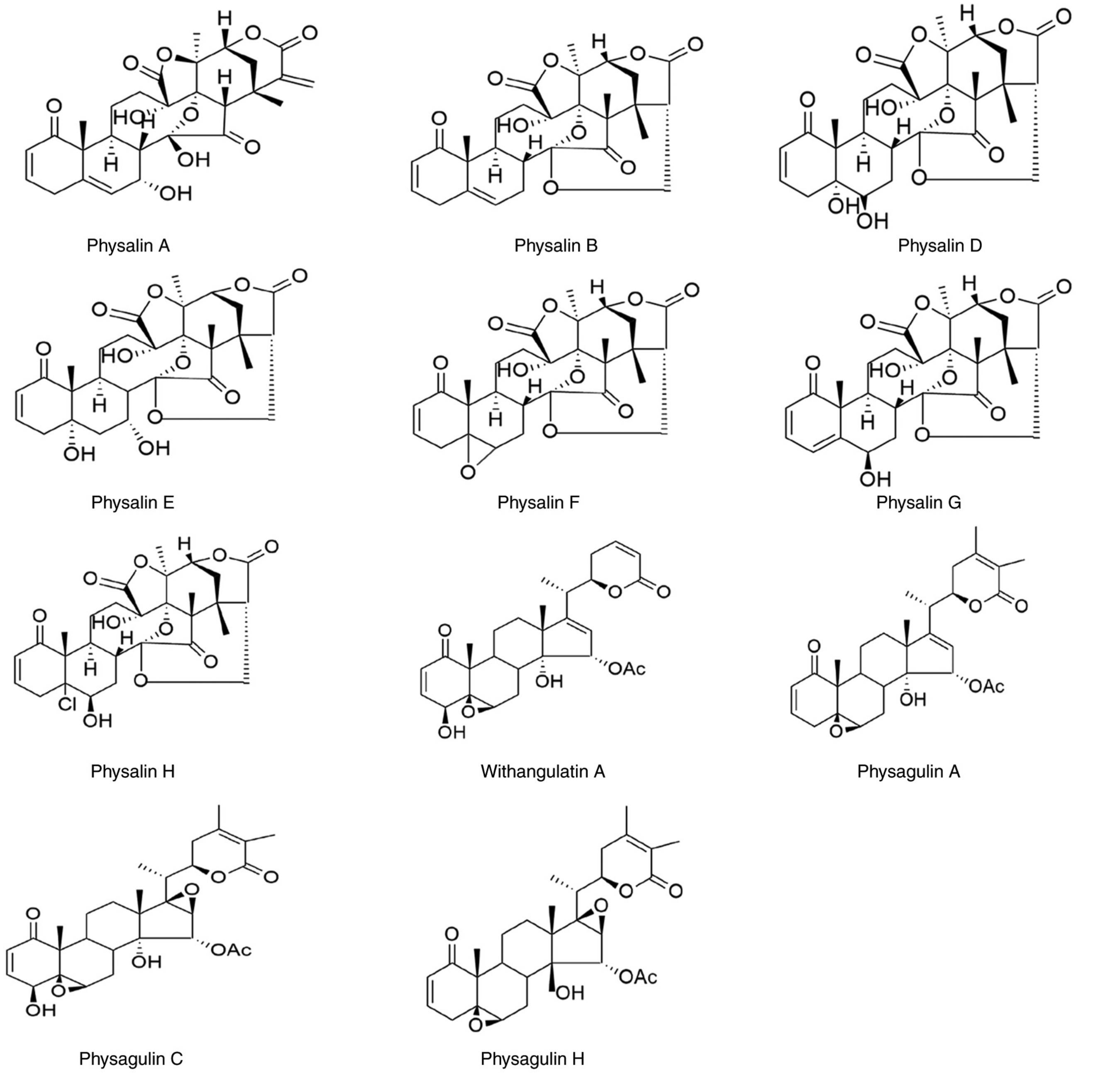

Figure 3. Chemical components of *Physalis angulata* Linn.

The use of *P. angulata* L. as an adjuvant therapy in humans can be provided by calculating the dose. The dose of *P. angulata* L. for humans is obtained by calculating the dose in animals with Laurence Bacharach's coefficient and the yield of the fraction (36).

9. Extraction process

In the present context, extraction is the process of separating the parts of a plant that are medicinally active, whilst utilizing certain solvents and accepted practices. All extraction procedures have the goal of separating the soluble metabolites of the plant from its insoluble cellular marc (residue). Preparing plant samples to preserve the constituent biomolecules before extraction is the first step in investigating therapeutic plants. Fresh or dried plant material can be used to extract samples such as from the leaves, bark, roots, fruits and flowers (44). Parts of *P. angulata* L. that can be utilized include: Whole plants (25%), leaves (25%), stems (19%), aerial parts (13%), roots (9%) and fruit (9%) (Fig. 4). Sulaiman *et al* (45) restricted the time between collecting the medicinal plant and experimental work to a maximum of 3 h to preserve sample freshness. In most situations, dried samples are preferred since they require less time to prepare for experiments (46).

The surface contact between samples and extraction solvents is increased when the particle size is reduced. Grinding produces coarser, lower sample sizes whereas pulverized samples have smaller, more homogeneous particles, which improve the surface contact with extraction solvents. The

Table III. List of solutions and polarities.

No.	Solvent	Polarity
1.	n-Hexane	0.009
2.	Petroleum ether	0.117
3.	Diethyl ether	0.117
4.	Ethyl acetate	0.228
5.	Chloroform	0.259
6.	Dichloromethane	0.309
7.	Acetone	0.335
8.	n-Buthanol	0.586
9.	Ethanol	0.654
10.	Methanol	0.762
11.	Water	1.000

optimum particle size for good extraction is <0.5 mm (44). The particle size has a significant impact on the use of pectinolytic enzymes that break down cell wall polysaccharides, as smaller particles increase the activity of these enzymes (44).

The type of plant, the plant component being extracted, the makeup of the bioactive chemicals and solvent accessibility all influence the choice of extraction solvent (46). In general, non-polar solvents such as hexane and dichloromethane are used to extract non-polar substances, while polar solvents such as water, methanol and ethanol are used to extract polar substances (47-49). Solvents with increasing polarity are introduced during fractionation, beginning with n-hexane, the least polar, and ending with water, the most polar (46,47,50). The solvents and their polarity are demonstrated in Table III. During fractionation, it is customary to select five solvents: Two solvents with low polarity (such as n-hexane and chloroform), two solvents with medium polarity (such as dichloromethane and n-butanol) and one solvent with the highest polarity (such as water) (Fig. 5) (46). Water is the 'greenest' solvent and is not only affordable and safe for the environment, but it also offers the potential for clean processing and pollution avoidance since it is non-toxic and non-flammable (48,50).

When selecting an extraction solvent, the following factors should be considered: i) Selectivity, the capacity of a given solvent to separate the inert material from the active component; ii) safety, the ideal extraction solvent is non-toxic and non-flammable; iii) price, it should be as affordable as possible; iv) reactivity, an appropriate extraction solvent should not react with the extract; v) recovery, it is important to be able to promptly recover and separate the extraction solvent from the extract; vi) viscosity, low viscosity is necessary for easy penetration and vii) the boiling temperature, to avoid heat-related degradation, the solvent boiling temperature should be as low as possible (46,47,50).

10. Toxicity studies

Research conducted by Sukandar and Sheba (51) demonstrated that *P. angulata* L. extract does not affect the behavior of rats in a single-dose therapy of up to 5 g/kg body weight and had an

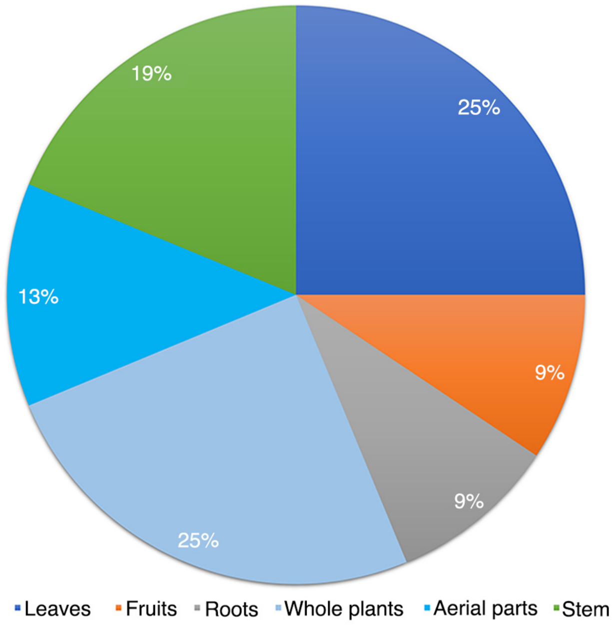

Figure 4. Percentage of *Physalis angulata* Linn. parts.

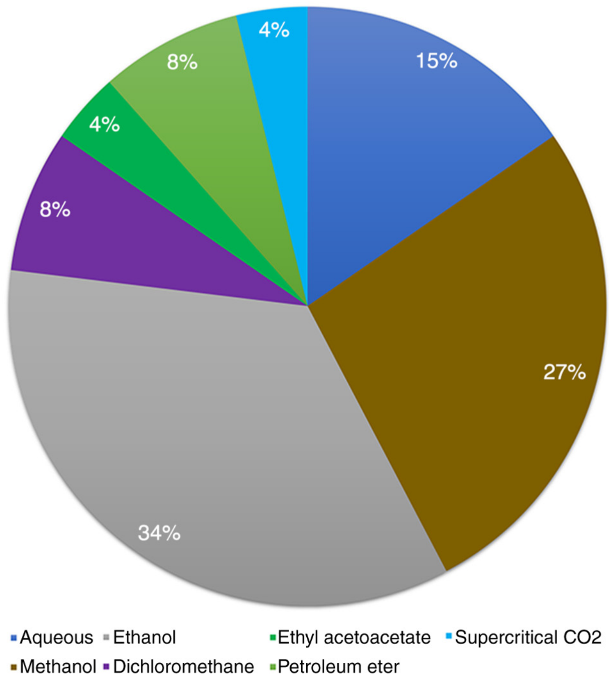

Figure 5. Percentage solvent selection.

LD_{50} of >5 g/kg body weight, which is regarded as non-toxic. Sub-chronic toxicity studies revealed that up to 1 g/kg body weight of *P. angulata* L. extract administered for 90 days did not cause mortality, was not poisonous to organs and had no effect on the blood cell count, blood biochemistry or urinalysis.

Guideline no. 420 of the Organization for Economic Co-operation and Development (1997) was used to calculate the acute toxicity test (LD_{50}) of *P. angulata* L. methanolic extracts (51). *P. angulata* L. at a dose of 2,000 mg/kg was administered to four groups of 6 albino mice (20-25 g, either sex), and the mortality and general behavior of the treated animals were observed for 14 days. At the conclusion of the trial, no fatalities were recorded. The extract was therefore confirmed to be safe up to a dose of 2,000 mg/kg (52).

11. Conclusion

P. angulata L. exhibits antibacterial, anticancer, antiparasitic, anti-inflammatory, antifibrotic and antidiabetic effects. *P. angulata* L. extract is safe based on acute and sub-chronic toxicity data. However, to further evaluate the safety of *P. angulata* L. extract, a chronic toxicity study is required, examining repeated doses or lifetime exposure.

In the study of medicinal plants, all extraction stages, including pre-extraction and extraction, are crucial. The sample preparation steps, such as grinding and drying, have an impact on the effectiveness and phytochemical components of the final extractions.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

AN, ER and AMR performed the literature search and assisted in drafting and revising the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Kasali FM, Tusiimire J, Kadima JN, Tolo CU, Weisheit A and Agaba AG: Ethnotherapeutic uses and phytochemical composition of *Physalis peruviana* L.: An overview. ScientificWorldJournal 2021: 5212348, 2021.
2. Mahklouf MH: The first record of *Physalis angulata* L. (*Solanaceae*) for the flora of Libya. Biodiv Res Conserv 53: 67-71, 2019.
3. Ramakrishna Pillai J, Wali AF, Menezes GA, Rehman MU, Wani TA, Arafah A, Zargar S and Mir TM: Chemical composition analysis, cytotoxic, antimicrobial and antioxidant activities of *Physalis angulata* L.: A comparative study of leaves and fruit. Molecules 27: 1480, 2022.
4. Gao CY, Ma T, Luo J and Kong LY: Three new cytotoxic withanolides from the Chinese folk medicine *Physalis angulata*. Nat Prod Commun 10: 2059-2062, 2015.
5. Hadiyanti N, SupriyadiS and PardonoP: Keragaman beberapa tumbuhan ciplukan (Physalis spp.) di lereng gunung kelud, jawa timur. Berita Biologi 17: 135-146, 2018.
6. Fadhli H, Ruska Sl, Furi M, Suhery WN, Susanti E and Nasution MR: Ciplukan (*Physalis angulata* L.): Review tanaman liar yang berpotensi sebagai tanaman obat. J Farm Indones 15: 134-141, 2023.
7. Rivera DE, Ocampo YC, Castro JP, Caro D and Franco LA: Antibacterial activity of *Physalis angulata* L., Merremia umbellataL., and Cryptostegia grandiflora Roxb. Ex R.Br. -medicinal plants of the Colombian Northern Coast. Orient Pharm Exp Med 15: 95-102, 2015.
8. Hananto H, Rahman A and Fahmi M: Antibacterial activity of ethanolic extract of morel berry (*Physalis angulata* L.) towards *Staphylococcus aureus*. Malays J Med Health Sci 17: 132-135, 2021.
9. Gagare SB, Chavan SL and Sagade AB: Antibacterial potential and phytochemical screening of *Physalis angulata* and solanum virgianum. Int J Res Biosci Agric Technol 1: 36-40, 2021.
10. Dias FGB, Ferreira MJG, da Silva LMR, de Sousa Menezes RC and de Figueiredo EAT: Bioaccessibility of the bioactive compounds and antimicrobial activity of aqueous extracts of *Physalis angulata* L. Rev Cienc Agron 51: e20196619, 2020.
11. Cuong LCV, Dat TTH, Nhiem NX, Cuc NT, Yen DTH and Anh HLT: The anti-microbial activities of secosteroids isolated from *Physalis angulata*. Vietnam J Chem 58: 321-326, 2020.
12. Anand U, Jacobo-Herrera N, Altemimi A and Lakhssassi N: A comprehensive review on medicinal plants as antimicrobial therapeutics: Potential avenues of biocompatible drug discovery. Metabolites 9: 258, 2019.
13. Chairissy MD, Wulandari LR and Sujuti H: Pro-apoptotic and anti-proliferative effects of *Physalis angulata* leaf extract on retinoblastoma cells. Int J Ophthalmol 12: 1402-1407, 2019.
14. Yang Y, Yi L, Wang Q, Xie B, Sha C and Dong Y: Physalin B suppresses inflammatory response to lipopolysaccharide in RAW264.7 cells by inhibiting NF-κB signaling. J Chem 4: 7943140, 2018.
15. Guimarães ET, Lima MS, Santos LA, Ribeiro IM, Tomassini TBC, Ribeiro dos Santos R, dos Santos WLC and Soares MBP: Activity of physalins purified from *Physalis angulata* in in vitro and in vivo models of cutaneous leishmaniasis. J Antimicrob Chemother 64: 84-87, 2009.
16. Wang A, Wang S, Zhou F, Li P, Wang Y, Gan L and Lin L: Physalin B induces cell cycle arrest and triggers apoptosis in breast cancer cells through modulating p53-dependent apoptotic pathway. Biomed Pharmacother 101: 334-341, 2018.
17. Fang C, Chen C, Yang Y, Li K, Gao R, Xu D, Huang Y, Chen Z, Liu Z, Chen S, *et al*: Physalin B inhibits cell proliferation and induces apoptosis in undifferentiated human gastric cancer HGC-27 cells. Asia Pac J Clin Oncol 18: 224-231, 2022.
18. Magalhães HI, Veras ML, Torres MR, Alves AP, Pessoa OD, Silveira ER, Costa-Lotufo LV, de Moraes MO and Pessoa C: In-vitro and in-vivo antitumour activity of physalins B and D from *Physalis angulata*. J Pharm Pharmacol 58: 235-241, 2006.
19. Abdulridha MK, Al-Marzoqi AH, Al-Awsi GRL, Mubarak SMH, Heidarifard M and Ghasemian A: Anticancer Effects of herbal medicine compounds and novel formulations: A literature review. J Gastrointest Cancer 51: 765-773, 2020.
20. Meira CS, Guimarães ET, Bastos TM, Moreira DR, Tomassini TC, Ribeiro IM, Dos Santos RR and Soares MB: Physalins B and F, seco-steroids isolated from *Physalis angulata* L., strongly inhibit proliferation, ultrastructure and infectivity of *Trypanosoma cruzi*. Parasitology 140: 1811-1821, 2013.
21. Nogueira RC, Rocha VPC, Nonato FR, Tomassini TC, Ribeiro IM, dos Santos RR and Soares MB: Genotoxicity and antileishmanial activity evaluation of *Physalis angulata* concentrated ethanolic extract. Environ Toxicol Pharmacol 36: 1304-1311, 2013.
22. Sangshetti JN, Khan FAK, Kulkarni AA, Arote R and Patil RH: Antileishmanial drug discovery: Comprehensive review of the last 10 years. RSC Adv 5: 32376-32415, 2015.
23. da Silva RR, da Silva BJ, Rodrigues AP, Farias LH, da Silva MN, Alves DT, Bastos GN, do Nascimento JL and Silva EO: In vitro biological action of aqueous extract from roots of *Physalis angulata* against *Leishmania* (*Leishmania*) amazonensis. BMC Complement Altern Med 15: 249, 2015.

24. Hassan AA, Khalid HE, Abdalla AH, Mukhtar MM, Osman WJ and Efferth T: Antileishmanial activities of medicinal herbs and phytochemicals in vitro and in vivo: An update for the years 2015 to 2021. Molecules 27: 7579, 2022.
25. Ghasemian M, Owlia S and Owlia MB: Review of anti-inflammatory herbal medicines. Adv Pharmacol Sci 2016: 9130979, 2016.
26. Yang YJ, Yi L, Wang Q, Xie BB, Dong Y and Sha CW: Anti-inflammatory effects of physalin E from *Physalis angulata* on lipopolysaccharide-stimulated RAW 264.7 cells through inhibition of NF-κB pathway. Immunopharmacol Immunotoxicol 39: 74-79, 2017.
27. Yen PH, Cuong LCV, Dat TTH, Thuy DTQ, Hoa DTN, Cuc NT, Yen DTH, Thao DT and Anh HLT: Withanolides from the whole plant of *Physalis angulata* and their anti-inflammatory activities. Vietnam J Chem 57: 334-338, 2019.
28. Tuan Anh HL, Le Ba V, Do TT, Phan VK, Pham Thi HY, Bach LG, Tran MH, Tran Thi PA and Kim YH: Bioactive compounds from *Physalis angulata* and their anti-inflammatory and cytotoxic activities. J Asian Nat Prod Res 23: 809-817, 2021.
29. Wang L, Lu S, Wang L, Xin M, Xu Y, Wang G, Chen D, Chen L, Liu S and Zhao F: Anti-inflammatory effects of three withanolides isolated from *Physalis angulata* L. in LPS-activated RAW 264.7 cells through blocking NF-κB signaling pathway. J Ethnopharmacol 276: 114186, 2021.
30. Ukwubile CA and Oise IE: Analgesic and anti-inflammatory activity of *Physalis angulata* Linn. (*Solanaceae*) Leaf methanolic extract in swiss albino mice. Int Biol Biomed J Autumn 2: 167-70, 2016.
31. Abdul-Nasir-Deen AY, Boakye YD, Osafo N, Agyare C, Boamah D, Boamah VE and Agyei EK: Anti-inflammatory and wound healing properties of methanol leaf extract of *Physalis angulata* L. S Afr J Bot 133: 124-131, 2020.
32. do Espírito Santo RF, Lima MDS, Juiz PJL, Opretzka LCF, Nogueira RC, Ribeiro IM, Tomassini TCB, Soares MBP and Villarreal CF: *Physalis angulata* concentrated ethanolic extract suppresses nociception and inflammation by modulating cytokines and prostanoid pathways. Nat Prod Res 35: 4675-4679, 2021.
33. Almeida Junior LD, Quaglio AEV, de Almeida Costa CAR and Di Stasi LC: Intestinal anti-inflammatory activity of Ground Cherry (*Physalis angulata* L.) standardized CO_2 phytopharmaceutical preparation. World J Gastroenterol 23: 4369-4380, 2017.
34. Arruda JCC, Rocha NC, Santos EG, Ferreira LGB, Bello ML, Penido C, Costa TEMM, Santos JAA, Ribeiro IM, Tomassini TCB and Faria RX: Physalin pool from *Physalis angulata* L. leaves and physalin D inhibit P2X7 receptor function in vitro and acute lung injury in vivo. Biomed Pharmacother 142: 112006, 2021.
35. Wang B, Wu L, Chen J, Dong L, Chen C, Wen Z, Hu J, Fleming I and Wang DW: Metabolism pathways of arachidonic acids: Mechanisms and potential therapeutic targets. Signal Transduct Target Ther 6: 94, 2021.
36. Rohmawaty E, Rosdianto AM, Usman HA, Saragih WAM, Zuhrotun A, Hendriani R, Wardhana YW, Ekawardhani S, Wiraswati HL, Agustanti N, *et al*: Antifibrotic effect of the ethyl acetate fraction of ciplukan (*Physalis angulate Linn*.) in rat liver fibrosis induced by CCl_4. J Appl Pharm Sci 11: 175-182, 2021.
37. Zhu X, Ye S, Yu D, Zhang Y, Li J, Zhang M, Leng Y, Yang T, Luo J, Chen X, *et al*: Physalin B attenuates liver fibrosis via suppressing LAP2α-HDAC1-mediated deacetylation of the transcription factor GLI1 and hepatic stellate cell activation. Br J Pharmacol 178: 3428-3437, 2021.
38. Dewi S, Isbagio H, Purwaningsih EH, Kertia N, Setiabudy R and Setiati S: A double-blind, randomized controlled trial of ciplukan (*Physalis angulata* Linn) extract on skin fibrosis, inflammatory, immunology, and fibrosis biomarkers in scleroderma patients. Acta Med Indones 51: 303-310, 2019.
39. Zhao M, Wang L, Wang M, Zhou S, Lu Y, Cui H, Racanelli AC, Zhang L, Ye T, Ding B, *et al*: Targeting fibrosis, mechanisms and cilinical trials. Signal Transduct Target Ther 7: 206, 2022.
40. Raju P and Estari M: Anti-diabetic activity of compound isolated from *Physalis angulata* fruit extracts in alloxan-induced diabetic rats. Am J Sci Med Res 1: 40-43, 2015.
41. Reddy PA, Vijay KR, Reddy GV, Reddy MK and Reddy YN: Anti-diabetic and hypolipidemic effect of aqueous and methanolic root extracts of *Physalis angulata* in streptozotocin (STZ) induced diabetic rats. Int J Pharm Res Scholars 3: 402-409, 2014.
42. Kibiti CM and Afolayan AJ: Herbal therapy: A review of emerging pharmacological tools in the management of diabetes mellitus in Africa. Pharmacogn Mag 11 (Suppl 2): S258-S274, 2015.
43. Daltro SRT, Santos IP, Barros PL, Moreira DRM, Tomassini TCB, Ribeiro IM, Ribeiro Dos Santos R, Meira CS and Soares MBP: In vitro and in vivo immunomodulatory activity of *Physalis angulata* concentrated ethanolic extract. Planta Med 87: 160-168, 2021.
44. Azwanida NN: A review on the extraction methods use in medicinal plants, principle, strength, and limitation. Med Aromat Plants 4: 1-6, 2015.
45. Sulaiman SF, Sajak AAB, Ooi KL, Supriatno and Seow EM: Effect of solvents in extracting polyphenols and antioxidants of selected raw vegetables. J Food Compos Anal 24: 506-515, 2011.
46. Abubakar AR and Haque M: Preparation of medicinal plants: Basic extraction and fractionation procedures for experimental purposes. J Pharm Bioallied Sci 12: 1-10, 2020.
47. Pandey A and Tripathi S: Concept of standardization, extraction and pre-phytochemical screening strategies for herbal drug. J Pharmacogn Phytochem 2: 115-119, 2014.
48. Sasidharan S, Chen Y, Saravanan D, Sundram KM and Yoga Latha L: Extraction, isolation and characterization of bioactive compounds from plants' extracts. Afr J Tradit Complement Altern Med 8: 1-10, 2011.
49. Altemimi A, Lakhssassi N, Baharlouei A, Watson DG and Lightfoot DA: Phytochemicals: Extraction, isolation, and identification of bioactive compounds from plant extracts. Plants (Basel) 6: 42, 2017.
50. Das K, Tiwari RKS and Shrivastava DK: Techniques for evaluation of medicinal plant products as antimicrobial agent: Current methods and future trends. J Med Plants Res 4: 104-111, 2010.
51. Sukandar EY and Sheba SH: Acute and Sub-chronic toxicity studies of combination of *Physalis angulata* L. (Cecendet) extract and methylprednisolone on animals. Int J Integr Health Sci 7: 48-55, 2019.
52. Rathore C, Dutt KR, Sahu S and Deb L: Antiasthmatic activity of the methanolic extract of *Physalis angulate* Linn.. J Med Plants Res 5: 5351-5355, 2011.
53. Pereda MDCV, Dieamant G, Nogueira C, Eberlin S, Facchini G, Mussi L, Polezel MA, Martins-Oliveira D, Rosa PTV and Di Stasi LC: Sterol-standardized phytopharmaceutical from ground cherry: Corticoid-like properties on human keratinocytes and fibroblasts and its effects in a randomized double-blind placebo-controlled clinical trial. J Cosmet Dermatol 18: 1516-1528, 2019.
54. Vieceli PS, Juiz PJL, Lauria PSS, Couto RD, Tomassini TCB, Ribeiro IM, Soares MBP and Villarreal CF: *Physalis angulata* reduces the progression of chronic experimental periodontitis by immunomodulatory mechanisms. J Ethnopharmacol 273: 113986, 2021.
55. Meira CS, Guimarães ET, Dos Santos JA, Moreira DR, Nogueira RC, Tomassini TC, Ribeiro IM, de Souza CV, Ribeiro Dos Santos R and Soares MB: In vitro and in vivo antiparasitic activity of *Physalis angulata* L. concentrated ethanolic extract against *Trypanosoma cruzi*. Phytomedicine 22: 969-974, 2015.
56. da Silva BJM, Rodrigues APD, Farias LHS, Hage AAP, Do Nascimento JL and Silva EO: *Physalis angulata* induces in vitro differentiation of murine bone marrow cells into macrophages. BMC Cell Biol 15: 37, 2014.
57. Pinto NB, Morais TC, Carvalho KMB, Silva CR, Andrade GM, Brito GAC, Veras ML, Pessoa ODL, Rao VS and Santos FA: Topical anti-inflammatory potential of Physalin E from *Physalis angulata* on experimental dermatitis in mice. Phytomedicine 17: 740-743, 2010.