



Exploring *Euphorbia peplus* L. (Euphorbiaceae): Traditional uses, phytochemistry and therapeutic applications: A review

Noor Sabah Jaafar^{1*}, Iman Sabah Jaafar² & Qabas Sabah Aldahhan³

¹Department of Pharmacognosy and Medicinal plants, University of Baghdad, Baghdad 1001, Iraq

²Department of Pharmaceutics, College of Pharmacy, Mustansiriyah University, Baghdad 1001, Iraq

³Dermatology Centre, Medical City, Baghdad 1001, Iraq

*Correspondence: Noor Sabah Jaafar, nour.sadek@copharm.uobaghdad.edu.iq

Abstract

Euphorbia peplus L. (Euphorbiaceae), commonly known as petty spurge, is a cosmopolitan weed widely distributed across Iraq. Historically used in ethnomedicine, the species is recognised for the topical application of its milky latex to treat skin conditions, including warts, corns and cutaneous malignancies. Recent phytochemical profiling has identified an array of secondary metabolites, primarily complex diterpenoids, including ingenane and jatrophone esters, as well as triterpenoids, flavonoids, phenolic acids, tannins and alkaloids. Modern research has validated these traditional applications. Beyond oncology, recent preliminary studies demonstrated the probable anti-inflammatory, antimicrobial, antidiabetic and antileishmanial potential. This review systematically synthesises the ethnobotanical history, phytochemical profile and clinical milestones of *E. peplus* by investigating literature published from 1969 to 2026. Furthermore, it highlights recent research gaps, particularly those related to toxicological potential and non-oncological mechanisms and summarises future directions for standardised pharmaceutical formulation.

Keywords: anti-inflammatory; diterpenoids; *Euphorbia peplus*; ingenol mebutate; sap; skin cancer

Received: 04 May 2026. **Accepted:** 18 August 2026. **Published:** Version 1.0: 29 September 2026; Version 2.0: 01 October 2026.

Cite this article: Noor SJ, Iman SJ, Qabas SA. Exploring *Euphorbia peplus* L. (Euphorbiaceae): Traditional uses, phytochemistry and therapeutic applications: A review. Plant Science Today. 2026; 13(4): 1-13. <https://doi.org/10.14719/pst.15395>

1. Introduction

Euphorbia peplus L. (Euphorbiaceae), widely known as petty spurge or radium weed, is a small, erect, opportunistic annual herb native to the northern Mediterranean, northern and tropical Africa and temperate Asia (1–3). Locally known in Arabic as *widdeina*, this medicinal weed has successfully acclimated to diverse geographic zones, with established populations documented in the central, northern and southern regions of Iraq (4, 5). Structurally, the plant reaches approximately 25 cm in height, branching from the base with pale-green, oval leaves and inconspicuous, green cyathia that visually mimic emerging apical foliage (6–8). Like many members of its genus, *E. peplus* is chemically characterised by a dense, toxic milky latex exuded in response to mechanical tissue damage. This latex, yielding roughly 100–300 mg/kg of fresh biomass, serves an evolutionary defensive role as an animal deterrent and antifeedant (9, 10). From a pharmacognostic perspective, this sap constitutes a specialised biochemical reservoir abundant in complex diterpenoids and macrocyclic diterpenes (11). Ethnobotanical practices dictate varied preparation

methods; for instance, the crude latex is applied directly in traditional African medicine, whereas Australian practices conventionally favour crude polar extractions to isolate active constituents (12). The rigorous clinical validation of this traditional knowledge culminated in Food and Drug Administration (FDA) approval of ingenol mebutate, a diterpene ester obtained directly from *E. peplus* for the topical management of actinic keratosis (13).

Despite the clinical milestone of FDA approval of ingenol mebutate (IMt) in dermatology, the current literature remains largely descriptive and fragmented, primarily supporting localised botanical documentation or isolated phytochemical identification. There is a conspicuous paucity of comprehensive literature that displays the identified phytochemicals, particularly the diterpenoid type and content. Moreover, the molecular mechanisms mediating its recently approved non-oncological effects, such as its antidiabetic, antileishmanial and specific antimicrobial properties, have not yet been systematically recorded. This review addresses these limitations, delivering a rigorous, exhaustive overview of *E. peplus* literature published

over five decades from 1969 to 2026. Transcending mere descriptive data, this work creates a comparative framework correlating ethnobotanical applications and phytochemical maps directly to current clinical milestones. By highlighting overlooked secondary metabolites and ongoing clinical applications, this review provides a strategic, evidence-based roadmap for transforming crude *E. peplus* extracts into standardised pharmaceutical entities.

Methodology and literature search strategy

To synthesise a comprehensive and systematic overview of *E. peplus* (petty spurge), a rigorous search of peer-reviewed scientific literature was conducted across major electronic databases, including PubMed/MEDLINE, Web of Science, Scopus, ResearchGate and Google Scholar. The search strategy utilised specific keywords and Boolean operators, including: "*Euphorbia peplus* L.", "*E. peplus*", "botanical description", "traditional applications", "pharmacological properties", "diterpenoids", "ingenol mebutate", "sap", "skin cancer", "anti-inflammatory" and "toxicity". To ensure the reliability and validity of the retrieved data, explicit inclusion/exclusion criteria were established the inclusion criteria include: peer-reviewed research articles and comprehensive review papers focusing directly on the ethnopharmacology, phytochemistry, therapeutic applications and ecological roles of *E. peplus*, documented isolations of bioactive secondary metabolites (especially diterpenoid profiles) and pharmacological evaluations of its milky sap; and the availability of complete, peer-reviewed full-text publications published between 1968 to January 2026 to allow for exhaustive methodology verification and data abstraction. The exclusion criteria include manuscripts limited only to abstracts, conference proceedings without subsequent full-text publications, preprints, non-peer-reviewed works and publications written in languages other than English.

Traditional uses and follicular applications

Historically, *E. peplus* has also appeared in many classical herbals dating back to the early 16th century as a general remedy for various skin ailments, including

cancer, sunspots, corns and warts (14, 15). The traditional uses of *E. peplus* are listed in Table 1.

Phytochemistry

Diverse clinical properties are linked with the genus *Euphorbia*, driven by the wide diversity of constituent phytochemicals (21). Investigations into the methanolic extract of *E. peplus* have identified several major compound classes, including flavonoids, tannins, terpenoids, steroids, saponins, coumarins, quinones, glucosinolates, cyanogenic glycosides and alkaloids (22–24).

Phytochemical characterisation reveals that terpenoids constitute the majority of the identified compounds, with diterpenes and triterpenes predominant, while monoterpenes occur at notably lower abundances (25). The genus *Euphorbia* is particularly renowned for its diterpenoid content; to date, over 350 distinct diterpenoids spanning diverse carbon skeletons have been characterised. Furthermore, the characteristic milky exudate of these plants serves as a highly concentrated matrix for these diterpene structures (26). Peplusol, a triterpenic alcohol, is also a major component of *Euphorbia* latex (27).

Monoterpene glycosides have been isolated from both the leaves and stems (28). Lolilide-a monoterpene lactone derived from carotenoid degradation has been identified within the plant extract (22, 29). Three bisnor-squiterpenes (22) and humulene, a monocyclic sesquiterpene, were identified in the plant methanolic extract (30).

The isolated and identified diterpenes belong to various structural skeletons, including jatrophone, pepluane, ingenane, lathyrane, tigliane, paralianone, neo-clerodanes, abietane, ent-abietane, kauranes, atisanes, ingenes, clerodanes, paraliane, myrsinane, segetane (1, 22, 25, 31, 32) beside casbene (phytoalexine) a macrocyclic diterpene produced in response to fungal and bacterial attack (33). Ingenane, jatrophone and tigliane diterpenoids are derived from the intermediate lathyrane (34). The proposed biosynthetic relationship and cyclic structural classification of *Euphorbia* diterpenoids are illustrated in Fig. 1 (35, 36).

Table 1. The traditional uses of Euphorbia peplus

Country / culture	Form used	Traditional applications	Reference
England and Australia	Sap application	Various skin conditions	(14, 15)
North America	Not specified	Wart removal	(16)
Mauritius	Leaf decoction	Diarrhea and dysentery	(8)
Nasa people	Hot extract	Malaria, wart removal, eye spots and as a febrifuge	(17)
Morocco	Leaves (Decoction or infusion), Seeds (Decoction or infusion)	Management of increased blood sugar Nutritional issues	(18, 19)
Saudi Arabia	Aerial parts infusion	Lowering blood pressure	(8)
Not specified	Aqueous plant extract	Liver disorder	(20)



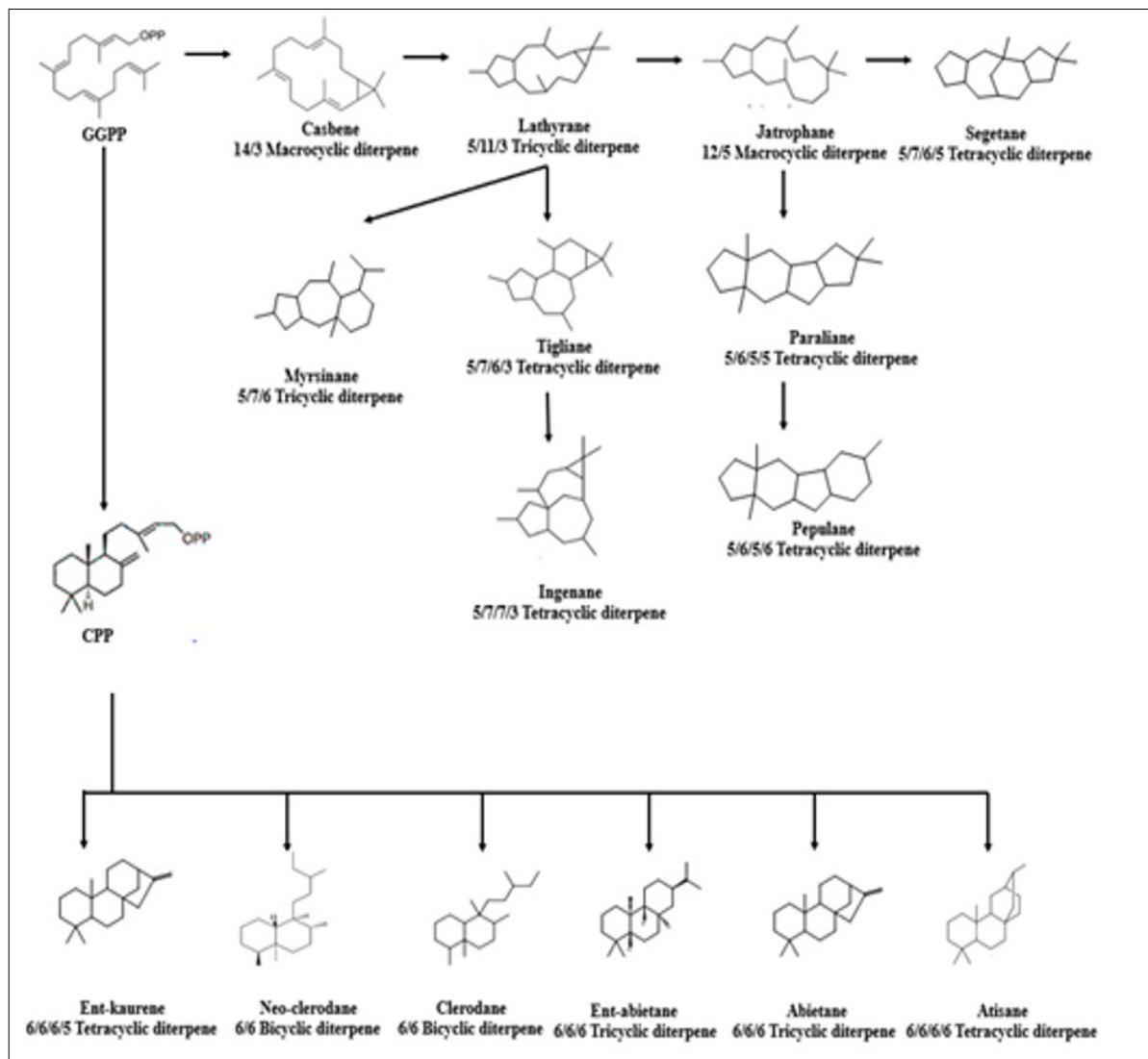


Fig. 1. The proposed biosynthetic relationship and cyclic structural classification of *Euphorbia* diterpenoids (35, 36).

Diterpenoids include 3-O benzoyl-20-deoxyingenol. Euphjatrophane H, Euphjatrophane I, Euphjatrophane K (jatrophone-type diterpenoids), Euphjatrophane L, euphepluones G, euphepluin, pepluanin C, euphepluone F and euphohelioscopin A were isolated from the ethyl acetate fraction of *E. peplus* methanolic extract (6). A diterpenoid, euphepluin A and peplusol were isolated from the latex. Peplusol has antifungal activity (27, 37). A mixture of diterpenoids composed of pepluanone, pepluanins A, euphepluin A and E, euphodendrophane E, D and nicaaenin G was isolated from an ethanolic extract (38). Pepluanol A, pepluanol B and pepluacetal, with a highly modified skeleton, were isolated and identified as minor extract components (39). Pepluanol, in addition to pepluacetal and paralianones and pepluanols are tetracyclic diterpenoids that have fused-ring systems (40, 41). Euphepluanone, ingenol-20-angelate, ingenol-3-angelate and 5-O-benzoyl-20-deoxyingenol were isolated from the seed extract (42).

Tetracyclic triterpenoids (phytosterols) include β -sitosterol and stigmasterol glycosides (22),

campesterol, lanosterol, obtusifoliol and 28-isofucosterol (8, 43). Gas chromatography-mass spectrometry (GC/MS) identified Δ^7 -isofucosterol and 28-isofucosterol in the sterol fraction (44). Stem latex extract contains a significant amount of pentacyclic triterpenoids. Pentacyclic triterpenoids simiarenol, oleanolic acid, α -amyrin, β -amyrin, lupeol, germanicol, fernenol, lupenone, β -amyrinone and lupeol acetate were identified in leaf wax (45).

Previous studies have reported substantial levels of flavonoids and phenolic compounds in *E. peplus*, with approximately 3889 $\mu\text{g/g}$ and 7465 $\mu\text{g/g}$, respectively, highlighting their potential contribution to the plant's bioactivity (23). The Iraqi species has a moderate phenolic content among the other *Euphorbia* species: *Euphorbia hirta* L., *Euphorbia macroclada* Boiss., *Euphorbia falcata* L., *Euphorbia helioscopia* L., *Euphorbia craspedia* Boiss. and *Euphorbia denticulata* Lam. (46). Tannins, 3,3'-di-O-methyl ellagic acid and pyrogallol and a coumarin esculetin, were isolated from the ethyl acetate extract of the plant (47, 48). Flavonoids: myricetin, kaempferol, astragalin, quercitrin,

quercetin, quercetin-3-O- β -D glucopyranoside, rutin, hyperoside, kaempferol-3-O-rutinoside and kaempferol-3-O- β -D-glucopyranoside, kaempferol-3-galactoside and rhamnetin-3-galactoside were isolated and identified in the previous studies (8, 22, 47–49). Luteolin 2 (luteolin di C-glycoside) was identified in the methanolic extract using GC/MS (30). Phenolic acids such as chlorogenic acid, neo-chlorogenic acid and crypto-chlorogenic acid were identified in the ethanolic extract (38). In previous study, identified 10 phenolic acids in this Egyptian weed: hydroxycinnamic acid, syringic acid, p-hydroxybenzoic acid, gallic acid, chlorogenic acid, caffeic acid, vanillic acid, coumaric acid, ferulic acid and salicylic acid (40, 48). Coumaric acid concentration was the highest, while vanillic acid was the lowest (40). High-performance liquid chromatography (HPLC) analysis of the Iraqi species revealed that 4-hydroxybenzoic acid (18 mg/g) was the major phenolic acid, whereas chlorogenic acid (0.33 mg/g) was present in much lower concentrations (50). However, in another study, benzoic acid, chlorogenic acid, resveratrol and ferulic acid were the main phenolics present in the Iraqi plant ethyl acetate extract (51). The HPLC analysis of the crude ethanolic extract of Iraqi *E. peplus* confirmed the presence of theobromine and scopolamine in substantial levels. Other identified alkaloids include methaqualone, atropine, quinidine, thebaine, benztropine and diphenhydramine (50). The phytochemical classes, representative compounds and their biological activity are listed in Table 2.

Pharmacological activities

Anti-inflammatory effect

Euphorbia peplus demonstrated a powerful anti-inflammatory effect that is related to its high diterpenoid content. Among various subclasses of diterpenoids, ingenane and jatropane are known for their anti-inflammatory action mediated by blocking the activation of certain transcription factors (NF- κ B) and mitogen-activated protein kinase (MAPK) signalling pathways that are involved in the production of proinflammatory mediators (25). The anti-inflammatory effect was demonstrated through several *in vitro* models; for instance, previous study clarifies the anti-inflammatory effect of certain types of euphjatrophanes H-R on lipopolysaccharide (LPS)-induced inflammation in RAW 264.7 cells through blocking nitric oxide production; meanwhile, the other euphjatrophanes act by mitigating the mRNA expression of IL-1 β , IL-6 and TNF α . Another mechanism is the suppression of FOXO1 transcription factor expression and the down-regulation of NF- κ B and p65 phosphorylation levels (31, 66). Similarly, another study confirmed the moderate anti-inflammatory activity of the diterpenoids paralipone and peplanol, which attenuated NO production in LPS-stimulated mouse macrophage models (39). Nitric oxide is a pro-inflammatory mediator (67). Enhanced levels of nitric oxide are linked to massive organ damage, such as joint cartilage degeneration in rheumatoid arthritis, mucosal lining injury in inflammatory bowel disease (IBD) and

neuronal degeneration in neurodegenerative diseases, such as Huntington's, Alzheimer's and Parkinson's diseases (68). Supporting these findings, *in vivo* studies have substantiated the therapeutic potential of *E. peplus* extracts. A previous study established the anti-inflammatory response of ethanolic extract through two experimental models: cotton pellet-induced granuloma and carrageenan-induced paw oedema in rats. Flavone and anthraquinone, besides terpenoids, are thought to be responsible for the anti-inflammatory effect (24). Peplunone a unique diterpene based on a rare pepluane skeleton. This compound possess a powerful anti-inflammatory activity *in vivo* as it was capable to suppress the carrageenin-induced rat paw oedema, an experimental model of acute inflammation, demonstrated an activity analogous to that of the standard drug dexamethasone (69). Furthermore, previous researchers utilised a yeast-induced paw edema model in male rats to confirm that ethyl acetate and methanolic extracts of *E. peplus* (at doses of 200 and 400 mg/kg) imparted an anti-inflammatory effect comparable to the standard indomethacin, whereas hexane and chloroform fractions yielded markedly weaker activity (70).

Xanthine oxidase inhibitory effect

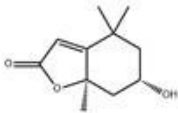
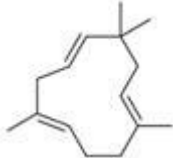
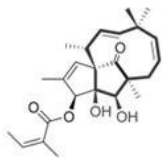
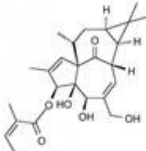
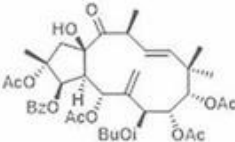
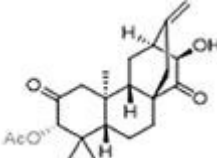
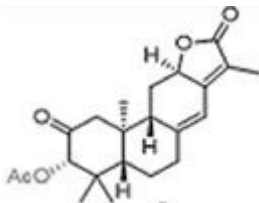
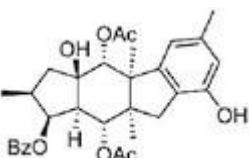
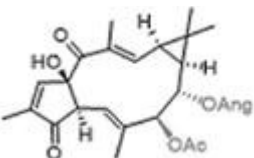
Xanthine oxidase plays a crucial role in purine metabolism by converting xanthine to uric acid and producing reactive oxygen species (ROS), in addition to reactive nitrogen species (71). Excessive ROS generation damages macromolecules and triggers further ROS production, which induces cell death and urate crystal accumulation in joints, ultimately causing joint inflammation and pain.

A recent study demonstrated in an *in vitro* enzymatic assay that *E. peplus* extract and its isolated phenolics (myricetin, esculetin and 3,3'-di-O-methyl ellagic acid) are potent xanthine oxidase inhibitors implicated in gout and hyperuricemia management (47). The ethyl acetate fraction and its phenolics showed potent *in vitro* inhibitory activity against xanthine oxidase. The three isolated phenolics showed stronger inhibitory profiles than the crude ethyl acetate fraction (IC₅₀= 87.35 μ g). Specifically, the IC₅₀ values were 32.11 μ g for myricetin, 48.73 μ g for 3,3'-di-O-methylellagic acid and 51.62 μ g for esculetin, compared with the standard positive control, allopurinol (IC₅₀= 10.51 μ g).

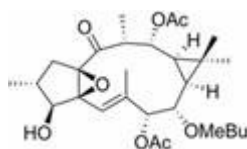
Furthermore, the *in vivo* hypouricemic activity was demonstrated in a rodent model of potassium oxonate-induced hyperuricemia. Oral administration of *E. peplus* extract at increasing doses (100, 250 and 500 mg/kg) effectively reduced xanthine oxidase activity and lowered serum uric acid level in a dose-dependent pattern. Thus, the clinical effect of *E. peplus* extract is exerted through direct action mediated by inhibition of xanthine oxidase and indirectly through reduction in reactive oxygen species that induce oxidative stress and macromolecular damage (47).



Table 2. Summary of *Euphorbia peplus* phytoconstituents and their associated biological activities

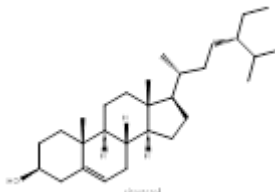
Chemical class and a representative compound	Chemical structure	Biological activity	Reference
Monoterpenes Lidiolid		anti-inflammatory, anticancer and neuroprotective.	(52)
Sesquiterpene Humulene		gastroprotective, analgesic and antioxidant.	(53)
Diterpene Ingenane-type Pepluanol C		Treatment of autoimmune disease and anti-inflammatory action.	(54)
Diterpene Ingenane-type Ingenol mebutate		For actinic keratosis and premalignant skin condition.	(55)
Diterpene Jatropha-type Euphopepluanone		Anti-inflammatory action.	-56
Diterpene <i>ent</i> -atisane-type Euphpeluane A		Might has anti-Alzheimer's action.	(57)
Diterpene <i>ent</i> -abietane Euphpeluane B		Might has anti-Alzheimer's action.	(57)
Diterpene Pepluane-type Peplunone		Anti-inflammatory action.	(58)
Diterpene Lathyrane-type Euphpeluane D		Might has anti-Alzheimer's action.	(57)

Diterpene
Lathyrane- type
Euphepluone S



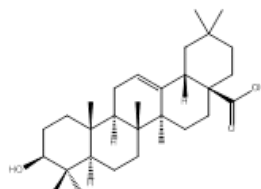
Anti-inflammatory action. (59)

Triterpene
Tetra cyclic Phytosterol-type
 β -sitosterol



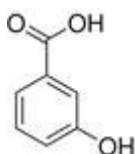
Cytotoxic activity. (60)

Triterpene
Penta cyclic
Oleanan-type
Oleanolic acid



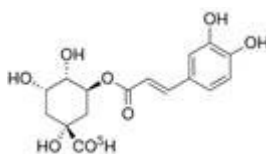
Cytotoxic and antimicrobial activity. (61)

Phenolic acid
Hydroxy benzoic acid- type
3-hydroxy benzoic acid



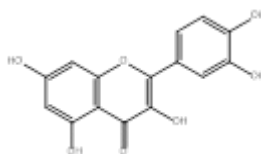
Antibacterial, antifungal and anticancer activities. (62)

Phenolic acid
Hydroxy cinnamic acid-type
Chlorogenic acid



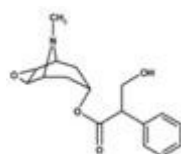
Neuroprotective and gastroprotective properties. (63)

Flavonoid
Flavonol-type
Quercetin



Antioxidant, immunosuppressant and antimicrobial activities. (64)

Alkaloid
Tropane-type
scopolamine



Antiemetic for motion sickness (65)

Cytotoxic effect

Traditionally, euphorbia sap was used to manage numerous cancers (72). The phytochemicals, especially diterpenoids, exert variable cytotoxic effects depending on the examined cell line and the extreme structural diversity of diterpenoids (1). Previous studies evaluated the clinical efficacy of topically applied *Euphorbia peplus* sap in patients with non-melanoma skin tumors and precancerous lesions, specifically intraepidermal carcinoma (IEC), basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) (72). The therapeutic response varied by tumor type; the optimum clearance rate was observed in patients with IEC, whereas the lowest response was recorded for SCC lesions. The main cytotoxic and chemo-curative properties of the sap were attributed to the lipophilic diterpene IMt, which is present in the crude sap at an approximate

concentration of 200 $\mu\text{g/mL}$ (72). Al-Emam's study demonstrated the cytotoxic and antiproliferative effect of *E. peplus* aqueous extract on the human breast adenocarcinoma cell line (MCF-7 cells) using sulphorhodamine B assay. The tested concentrations 0.01, 0.1, 1, 10 and 100 $\mu\text{g/mL}$ exhibit a concentration-dependent inhibition of cell proliferation by 2.79 %, 4.65 %, 10.30 %, 41.96 % and 96.09 % respectively. The morphological cytotoxic manifestations of MCF-7 treated at the IC_{50} value of 30.32 $\mu\text{g/ml}$ after 48 hr showed extensive cellular shrinkage, loss of distinctive epithelial morphology and massive detachment from the culture substrate compared to the control cells (2). In previous study, Simiarendiol was evaluated for its *in vitro* antiproliferative activity against four human cancer cell lines (HeLa, MDA-MB-231, MCF-7 and A549) using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. This triterpene showed

moderate-to-significant cytotoxic potential across the panel of the tested lines, with IC_{50} values ranging from 3.93 to 14.22 μ M. The highest cytotoxicity was observed against the HeLa cervical cancer line (IC_{50} = 3.93 μ M); at this concentration, simiarenol caused inhibition of cell viability, apoptosis induction and cell cycle arrest at S/G2 phases in a concentration-dependent pattern (73). Imgenol -3-angelate; a selective activator of protein kinase C capable of apoptosis induction at nanomolar concentrations in primary acute myeloid leukemia cells and myeloid leukemia cell lines (74).

Earlier studies synthesised gold nanoparticles in combination with *E. peplus* leaf extract and proved the significant inhibitory potential of the synthesised nanoparticles on HepG2 and HeLa cells (75). Another study established the antiproliferative potential of the ethyl acetate fraction against human prostate cancer cells (PC-3) using MTT assay. A concentration-dependent moderate cytotoxic potential with an IC_{50} value of 162.5 μ g/mL was displayed. The cytotoxic activity and associated morphological changes, including cellular shrinkage and detachment, observed in PC-3 cells are determined by the synergistic action of the prominent phenolic components, specifically chlorogenic acid and resveratrol (51).

Antileishmanial effect

Leishmaniasis is a vector-borne parasitic disease caused by the protozoan *Leishmania* and it infects humans via a sand fly bite. This disease is endemic to the Middle East, Asia, parts of America and Europe (76). Leishmaniasis could be cutaneous, mucocutaneous, or visceral leishmaniasis (77). A study demonstrated in an *in vitro* study the powerful antileishmanial activity of the methanolic extract of *E. peplus* aerial parts, displaying an inhibitory effect comparable to that of the positive control, amphotericin (100 % inhibition). The methanolic extract was fractionated sequentially, among the obtained fractions (n-hexane, dichloromethane and ethyl acetate), the n-hexane portion displayed the most pronounced efficacy, eliciting 75 % inhibition of parasitic growth. Additional fractionation of this active extract yielded four subfractions. Upon assessment, three of these subfractions established prominent antileishmanial activity, while the fourth was regarded as inactive (IC_{50} > 40 μ g/mL). The active subfractions produced IC_{50} values of 20.24, 32.05 and 34.87 μ g/mL, compared to the reference drugs amphotericin B (IC_{50} = 0.47 μ g/mL) and pentamidine (IC_{50} = 1.01 μ g/mL). This antileishmanial efficacy is ascribed to non-polar phytochemicals particularly simiarenol, 1-hexacosanol, β -sitosterol and its 3-O-glucoside which direct the inhibitory activity against *Leishmania donovani*. Eventually, the maximum inhibitory potential of the crude methanolic extract is probably due to the synergistic interaction of these phytochemicals alongside other active constituents existing in the extract (78).

Antidiabetic effect

Plants of the genus *Euphorbia* have shown antidiabetic efficacy across several experimental models, including

streptozotocin (STZ)-, alloxan- and sucrose-induced diabetic rats. Specifically, previously demonstrated in an *in vivo* study the effect of a phenolics-rich ethyl acetate fraction of the *E. peplus* extract on insulin resistance in high-fat diet (HFD)/STZ-induced diabetic rats (48). The tested doses were 100, 200 and 400 mg/kg of the extract, given daily for 4 weeks; pioglitazone was the standard antidiabetic agent used in the study. The extract at all doses ameliorates insulin resistance, improves glucose tolerance, reduces fasting glucose levels, exhibits potent insulin-sensitising effects, boosts insulin secretion and glucose clearance from blood, effectively reversing and normalising metabolic disturbances in diabetic animals without altering baseline insulin kinetics or basal blood glucose levels in healthy standard control animals.

Mechanistically, the extract modulates key enzymes governing glycemic regulation by up-regulating hexokinase activity to stimulate glycolysis. All the tested doses trigger dose-dependent activation of hexokinase. Simultaneously down-regulating glucose-6-phosphatase (G-6-Pase) and fructose-1,6-bisphosphatase (F-1,6-BPase), particularly at the dose of 400 mg/kg, produces statistically significantly superior suppression when compared to the 100 mg/kg dose.

Furthermore, all three doses effectively restored glycogen phosphorylase activity to near normal levels. Thus, this action constrains both gluconeogenesis and glycogenolysis, eventually lowering circulating blood glucose levels. Furthermore, by stimulating insulin secretion and enhancing sensitivity, the extract efficiently mitigates peripheral lipolysis and hepatic lipid accumulation, thereby reducing the risk of diabetic atherogenicity and associated cardiovascular complications (48).

Antimicrobial effect

Various classes of secondary metabolites, including terpenoids, are known to exert antimicrobial effects. In previous studies, diterpenes of *E. peplus* latex, particularly peplusol, exhibit robust antifungal potential against some agricultural phytopathogenic fungi: *Colletotrichum litchi*, *Rhizoctonia solani* and *Fusarium oxysporum* f. sp. *niveum*. Zones of inhibition produced by peplusol were (15.75 $\pm$ 0.81, 19.18 $\pm$ 0.35 and 16.63 $\pm$ 3.50 mm respectively) and they were marginally lower than those of nystatin (20.59 $\pm$ 0.61, 21.90 $\pm$ 1.50 and 22.42 $\pm$ 4.13 mm, respectively) highlighting the importance of this compound as a natural scaffold for the production of an eco-friendly biocontrol agent (27). In another study, the *E. peplus* ethyl acetate fraction demonstrated a potent, concentration-dependent phytotoxic effect against the plant-pathogenic fungi *Sclerotinia sclerotiorum*, *Alternaria alternata* and *Fusarium oxysporum*, exhibited as mycelial growth suppression. Among the evaluated concentrations (250, 500, 1000 and 2000 μ g/mL), the maximum dose was remarkably effective against all fungal strains, inhibiting *A. alternata* by 63.1 %, *F. oxysporum* by 63.0 % and *S. sclerotiorum* by 57.2 %. Phenolic acids, particularly p-coumaric acid, caffeic acid and citric acid, are present



at high concentrations and may be implicated in the extract's phytotoxic effect (40). A methanolic extract of *E. peplus* exhibits stronger antifungal potential on *Saccharomyces cerevisiae* than on *Aspergillus flavus*, as compared to *Euphorbia maculata* L. (23).

Findings from previous study highlighted the importance of *E. peplus* as a valuable candidate for combating bacterial infection, particularly those involving resistant strains (51). Utilising the agar well diffusion method, the broad antibacterial spectrum of *E. peplus*, as well as *Vitis vinifera* L., *Cornus sanguinea* L., *Ecballium elaterium* (L.) A.Rich., *Punica granatum* L., *Liquidambar orientalis* Mill., *Inula viscosa* (L.) Aiton and *Eucalyptus camaldulensis* Dehnh., against some multidrug-resistant human pathogens was established. The ethanolic plant extract yielded peak activity and the maximum inhibition zone against *Pseudomonas aeruginosa*, achieved at a concentration of 10.2 mg/mL; in contrast, *Corynebacterium* sp. displayed the lowest sensitivity as compared to other strains. *Escherichia coli*, *Klebsiella pneumoniae* and methicillin-resistant *Staphylococcus aureus* responded equally and produced uniform zones of inhibition (79). Aziz et al. demonstrated the antimicrobial effect of the methanolic extract of *Euphorbia peplus* and *E. maculata* against numerous bacteria, including Gram-positive (*Bacillus subtilis*, *S. aureus*) and Gram-negative (*Salmonella typhimurium*, *E. coli*) (71). Using the agar diffusion method, both species exhibited comparable antimicrobial inhibitory activity on *Salmonella typhimurium* and *B. subtilis*. At a concentration of 10.2 mg/mL, the ethanolic extract exhibited optimum antibacterial action, producing a maximum zone of inhibition against *P. aeruginosa*.

In a previous study, green-synthesised gold nanoparticles showed powerful activity against a panel of pathogenic bacteria (*E. coli*, *Proteus mirabilis*, *Shigella flexneri* and *S. aureus*) (75). Zones of inhibition ranged from a minimum of 11.67mm for *Escherichia coli* to a maximum of 14.33 mm for *P. mirabilis*. In contrast, the crude ethanolic leaf extract yielded negligible zones and antibacterial potential (75).

Analgesic and antipyretic effects

In vivo assessment revealed that the plant extracts (methanol, hexane, chloroform and ethyl acetate) have substantial analgesic and antipyretic actions. When evaluated by the acetic acid-induced writhing method, given extracts at a dose of 400 mg/kg body weight inhibit writhing imparted significant antinociceptive property. This therapeutic effect was analogous to the standard analgesic; acetylsalicylic acid administered at 150 mg/kg. Moreover, the extracts produce a notable, dose-dependent antipyretic effect when assessed at both 200 and 400 mg/kg establishing their ability for pain and fever management (70).

Other effects

Euphorbia peplus extract and its phenolics, isoquercetin, astragalin, quercitrin, quercetin, myricitrin, kaempferol and methyl gallate, inhibit fatty acid

synthase, with the maximum inhibitory effect exerted by myricitrin (11). This enzyme is involved in fatty acid metabolism and plays a crucial role in the growth, development and survival of cells, especially in phenotypic lipogenic tumor cells. Thus, inhibition of this enzyme might play a role in cancer treatment and management of obesity (80). Previous studies showed the genus *Euphorbia* might be effective for treating neurodegenerative diseases such as Alzheimer's. Members of the gastropane type of diterpenoids in the sap of this plant stimulate autophagy and activate lysosome biogenesis, which helps in the removal of amyloid- β in the mice's brains (6). β -amyloid peptide deposits and protein tau tangles are two key pathological markers for Alzheimer's diagnosis (81). Additionally, this herb probably has a therapeutic role in some immune diseases, such as asthma and psoriasis. A diterpene, pepluanol B, blocks a certain type of potassium channel (Kv1.3), which is the main channel in the activated effector memory T cells that plays an important role in their activation, proliferation and, therefore, cytokine secretion. Thus, Kv1.3 channel blockers are immunosuppressing agents for autoimmune diseases, such as asthma, multiple sclerosis and psoriasis, affecting effector memory T (TEM)-cell-specific responses without repressing native immunological responses (39). Antifeedant activity is another action reported for *E. peplus* (27).

Close insight into ingenol mebutate

Ingenol mebutate, also known as ingenol-3-angelate or PEP005, is a plant-derived extract obtained from an active part of the sap of the *E. peplus* (82). Chemically, it is a macrocyclic diterpene ester weighing 430 Da, having a chemical formula of $C_{25}H_{34}O_6$ and is lipophilic (83). For centuries, the white, sticky, irritating latex sap has been traditionally used as a topical herbal remedy for skin diseases, such as skin lesions, warts and cancers, including actinic keratoses (AKs) (84). Actinic keratosis, which is also known as solar keratosis, is a common epidermal cutaneous skin condition that results from exposure to chronic ultraviolet (UV) radiation and its accumulation through life causes DNA damage (85). Consequently, it has the potential for skin cancer development, as documented since AK is identified as a precursor of squamous cell carcinoma and Bowen's disease (squamous cell carcinoma in situ) (86). The AK is characterised by visible, rough, scaly patches; sub-clinical lesions may also exist within areas of sun-exposed skin. The AK is most observed in young and older individuals, with a predominance of photo types I (very light skin tone) and II (light skin tone), which are not capable of producing much melanin. Over the past few decades, the worldwide prevalence of AK has continuously increased (11–25 %) and reached up to 79 % in individuals aged 60–69 years (87, 88). Ingenol mebutate was approved for AK treatment by the FDA in the USA in 2012 (89) and was produced by LEO Pharma (Ballerup, Denmark) and marketed as Picato® topical gel (90). It offers a short-duration treatment schedule (2–3 days), providing an efficient and



continuous AK lesion clearance with a predetermined onset and short duration of skin responses (91). The therapeutic activity of IMt has been partially elucidated with a dual mode of action; it induces rapid necrosis for transformed keratinocytes within 1–2 hr after administration by subsequent mitochondrial swelling and plasma membrane disruption (92). Besides its pro-apoptotic activity on dysplastic cells, IMt also has an immunostimulatory effect by activating a directed immune response in the lesion by stimulating a neutrophil-mediated form of antibody-dependent cytotoxicity that eradicates residual tumor cells (93). Various clinical studies have indicated that topical administration of IMt for a short-term duration is superior to other active ingredients, safe, well-tolerated and has minimal local adverse effects, consequently enhancing patient compliance and adherence (94–96). However, due to serious concerns about increased risk of skin carcinoma (especially squamous cell carcinomas) associated with IMt use, the manufacturer withdrew IMt from the market in January 2020 and provisionally suspended it in the European Union. In its safety assessment, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) concluded, based on results of a three-year two-arm safety study, that the drug may carry a higher risk of skin carcinoma, which outweighs any latent advantages (97).

Toxicity of *Euphorbia peplus*

The toxic principle of *E. peplus* is the sap and cyanogenic glycosides (98). *Euphorbia* sap is known as

a slightly toxic and irritating substance to the mucous membrane, skin and eyes (4, 8), as evidenced by the high LD50 of most species estimated to exceed 5000 mg/kg (48). The sap is toxic to humans and herbivores, while cyanogenic glycosides are toxic to herbivores (98). Accidental topical eye exposure causes mild to moderate keratoconjunctivitis and uveitis. This condition is characterised by tearing, photophobia, conjunctival burning, epithelial sloughing and corneal ulceration, which may take up to nine days to heal. The local irritation of sap is managed through supportive measures, mainly including the removal of irritant materials, from the mouth; skin cleansing and irrigation reduce the risk of minor irritation.

Systemic toxicity following ingestion of the spurge family plant is rare, but mild gastrointestinal disturbances, including self-limited spontaneous vomiting, might occur following ingestion (3).

The toxic effect could be related to the inflammatory and apoptotic action produced by the plant's constituents (30). Due to the sap's toxicity, it is advisable to use the plant only topically. Calves fed on this plant exhibited extreme salivation and blood-stained stool. General toxicity symptoms in lactating goats nourished with *E. peplus* aerial portions with their green hay: The main affected organs are the heart, liver and lungs. Degenerative manifestations are seen in the endothelial and parenchymal cells. Intoxication and even death in offspring nursing milk from their lactating mother fed on *E. peplus* (8). The reported toxic effects, doses and experimental models are listed in Table 3.

Table 3. *Euphorbia peplus* reported toxic effects, doses and experimental models

Doses	Reported toxic effect	Experimental model	Reference
500 mg/kg methanolic plant extract given orally twice weekly for 65 days	Reduction of the testis and seminal vesicle weight. Decreased sperm motility and concentration. Reductions in luteinising hormone and testosterone levels DNA damage and fragmentation in testicular tissue. Antioxidant enzymes catalase, superoxide dismutase and glutathione reductase were greatly reduced. DNA damage and fragmentation in hepatic tissue.	Adult albino Wistar rats Reproductive toxicity Hepatic toxicity	(99)
500 mg/Kg methanolic plant extract given orally twice weekly for 65 days	Myocardial necrosis and tissue damage evidenced by increased level of troponin, CPK-MB, LDH, AST and ALP. Renal blood vessels congestion, moderate perivascular fibrosis and accumulation of hyalin casts in renal tubules. Also, there is an increase in renal damage byproducts.	Rodent model Cardiovascular and renal	(30)
100 and 200 µg/mL for hexane chloroform, ethyl acetate and methanolic extracts	Hexane fraction mortality rate 20 % at 100 µg/mL and 40 % at 200 µg/mL Chloroform fraction mortality rate 40 % at 100 µg/mL and 88 % at 200 µg/mL Ethyl acetate fraction mortality rate 10 % at both concentrations Methanolic fraction mortality rate 25 % at 100 µg/mL and 35 % at 200 µg/mL.	Brine shrimp lethality test	(69)
0.5 kg of fresh aerial parts of plant /goat/day for 5 days /week for 4 weeks	Watery diarrhea, loss of appetite, general weakness and emaciation were the main symptoms of intoxication observed in this first week of the experiment.	Experimental lactating goat model	(100)

LDH: lactate dehydrogenase; CPK: creatinine phosphokinase; CK-MB: creatine kinase-MB; ALP: alkaline phosphatase.

4. Conclusion

Euphorbia peplus is a widely distributed weed that has gained significant attention due to its traditional uses and

its diverse phytochemical profile. This review offers detailed insights into its ethnomedical applications, supported by existing and ongoing scientific evidence. An array of bioactive entities has been successfully isolated



and identified, with diterpenoids being the most prominent therapeutic components. However, the present literature deeply favours this type of terpenoids, ignoring to some extent other potentially bioactive phytochemical classes such as glucosinolates, quinones and cyanogenic glycosides largely uninvestigated. Also, there is an absence of comparative studies individualised the therapeutic value of isolated single compound from that of the crude extract or original sap. The withdrawal of the ingenol mebutate (IMt) due to its association to skin carcinomas, specifically squamous cell carcinoma highlights the importance for ongoing studying and careful assessment of IMt's risks and benefits and the importance of long-term safety studies. At the end the future research should focus on enhancing phytochemical screening for isolation and characterisation of novel compounds and performing comparative studies between the isolated compounds and raw extracts to fully elucidate the multi-target synergistic potential.

Acknowledgements

The authors thank the University of Baghdad, College of Pharmacy and Mustansiriyah University, College of Pharmacy for providing us with the facilities necessary to accomplish this work.

Authors' contributions

NSJ and ISJ contributed equally to the initial drafting and critical revision of the manuscript. QSA provided technical editing and refinement. All authors have read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest

Authors do not have any conflict of interests to declare.

Ethical issues

None

References

- Chen YN, Lu QY, Li DM, Li YY, Pu XX, Li BT, et al. Three new diterpenoids from *Euphorbia peplus*. *Nat. Prod. Res.* 2021;35(21):3901–7. <https://doi.org/10.1080/14786419.2020.1749609>
- Al-Emam A, Al-Shraim M, Eid RA, Jamil AM, Moustafa MF, Radad K. Cytotoxicity of *Euphorbia peplus* Extract on MCF7 Breast Cancer Cells. *Folia Biol (krakow)*. 2019;67(3):127–39. https://doi.org/10.3409/fb_67-3.13
- Barceloux DG. *Medical Toxicology of Natural Substances: Foods, Fungi, Medicinal Herbs, Plants, and Venomous Animals*. 1st ed. Wiley; 2008. p. 757.
- Quattrocchi U. *CRC World Dictionary of Medicinal and Poisonous Plants*. CRC Press; 2016. P. 1690.
- Ismaeel ZA, Aliwy SA. Study the indumentum for some species of *Euphorbia* L. (*Euphorbiaceae*) in Iraq. *Iraqi J Agric Sci.* 2023;54(4):906–13. <https://doi.org/10.36103/ijas.v54i4.1780>
- Chen L, Liu L, Li Y, Guan S, Fan L, Qin X, et al. Macrocyclic Diterpenoids from *Euphorbia peplus* Possessing Activity Towards Autophagic Flux. *IJMS.* 2024;26(1):299. <https://doi.org/10.3390/ijms26010299>
- Christenhusz MJM, Fay MF, Leitch IJ. The genome sequence of petty spurge, *Euphorbia peplus* L. (*Euphorbiaceae*). *Wellcome Open Res.* 2025;10:219. <https://doi.org/10.12688/wellcomeopenres.24030.1>
- Schemezer GH, GÜeibFakin. *Plant resources of tropical Africa* 11(1). Medicinal plant. Netherland; 2008. P. 279.
- Ali A, Sayed H, Mohamed S, Zaher A. Macro- and micromorphology of the root, stem, leaf, inflorescence and fruit of *Euphorbia peplus* L. growing in Egypt. *Bull. Pharm. Sci. Assiut.* 2012;35(2):109–26. <https://doi.org/10.21608/bfsa.2012.64610>
- Herrera MeV. *The front yard forager: identifying, collecting, and cooking the 30 most common urban weeds*. Seattle, Wash.: Skipstone; 2013.
- Bin-Ammar A. Fatty Acid Synthase Inhibitory Activity of *Euphorbia peplus* and its Secondary Metabolites. *Adv Pharmacol Pharm.* 2024;12(4):367–79. <https://doi.org/10.13189/app.2024.120409>
- Huerta A, Chiffelle Í, Arias C, Curkovic T, Araya JE. Bio efficacy of *Euphorbia peplus* latex as an antifeedant and insecticide against *Gonipterus platensis* larvae on *Eucalyptus globulus*. *NZ J Forestry Sci.* 2022;53. <https://orcid.org/0000-0003-1142-4186>
- Hu D, Gao H, Yao X sheng. Biosynthesis of Triterpenoid Natural Products. In: *Comprehensive Natural Products III* p. 577–612. <https://doi.org/10.1016/B978-0-12-409547-2.14678-5>
- Braun SA, Homey B, Gerber PA. Successful treatment of Bowen disease with ingenol mebutate. *DerHautarzt.* 2014;65(10):848–50. <https://doi.org/10.1007/s00105-014-3509-5>
- Akhtar MS, Swamy MK. *Anticancer Plants: Clinical Trials and Nanotechnolog.* Singapore: Springer Singapore; 2017. p 123–125. <https://doi.org/10.1007/978-981-10-8216-0>
- Khodaie L, Sharma A, Bhatia S, Al-Harrasi A. *Introduction to plant-based latex: phytochemistry, ethnopharmacology, biological, and pharmacological activities*. 1st ed. New York: Jenny Stanford Publishing; 2025. <https://doi.org/10.1201/9781003570714>
- Martinez JL, Maroyi A, Wagner ML. *Ethnobotany: from the traditional to ethnopharmacology*. 1st ed. Boca Raton: CRC Press; 2023.
- Bussmann RW, Elachouri M, Kikvidze Z. *Ethnobotany of Northern Africa and Levant Cham: Springer Nature Switzerland*; 2024.
- Bussmann RW, Paniagua-Zambrana NY, Kikvidze Z, editors. *Ethnobotany of the Mountain Regions of Eastern Europe: Carpathians Cham: Springer Nature Switzerland*; 2025. p. 1119.
- Ghazanfar SA. *Handbook of Arabian Medicinal Plants*. 0 ed. CRC Press; 1994. p. 104.
- Mavundza EJ, Street R, Bajinath H. A review of the ethnomedicinal, pharmacology, cytotoxicity and phytochemistry of the genus *Euphorbia* in southern Africa. *S Afr J Bot.* 2022;144:403–18. <https://doi.org/10.1016/j.sajb.2021.08.029>
- Min XY, Chen YN, Li DM, Mu QY, Zhang ZT, Fang X. Chemical constituents of *Euphorbia peplus*. *Biochem Syst*



- Ecol.2021;98:104307.
<https://doi.org/10.1016/j.bse.2021.104307>
23. Nagah A, Aly S. Physiological approaches to evaluate the antioxidant and antimicrobial activities of two wild Euphorbiaceous species of the Egyptian flora. Egypt. Acad. J. Biol. Sci., H. Botany. 2021;12(2):191–205. <https://doi.org/10.21608/eajbsh.2021.298891>
 24. Parmar NS, Mossa JS, Al-Yahya MA, Al-Said MS, Tariq M, Ageel AM. Anti-inflammatory and Antipyretic Activity of *Euphorbia peplus* L. Int J. Crude Drug Res. 1989;27(1):9–13. <https://doi.org/10.3109/13880208909053929>
 25. Li Y, Yu ZP, Li YP, Yu JH, Yue JM. Diterpenoids from *Euphorbia peplus* possessing cytotoxic and anti-inflammatory activities. Bioorg Chem.2024.;145:107194. <https://doi.org/10.1016/j.bioorg.2024.107194>
 26. Kemboi D, Siwe-Noundou X, Krause RWM, Langat MK, Tembu VJ. Euphorbia diterpenes: An update of isolation, structure, pharmacological activities and structure–activity relationship. molecules. 2021;26(16):5055. <https://doi.org/10.3390/molecules26165055>
 27. Hua J, Liu Y, Xiao CJ, Jing SX, Luo SH, Li SH. Chemical profile and defensive function of the latex of *Euphorbia peplus*. Phytochemistry.2017;136:56–64. <https://doi.org/10.1016/j.phytochem.2016.12.021>
 28. Soni M, Singh IP, Ranjan Lal U. Naturally occurring monoterpene glycosides of plant origin. flavour & fragrance J. 2025;40(4):613–37. <https://doi.org/10.1002/ffj.3862>
 29. Murata M, Nakai Y, Kawazu K, Ishizaka M, Kajiwara H, Abe H, et al. Loliolide, a carotenoid metabolite, is a potential endogenous inducer of herbivore resistance. Plant Physiol. 2019;179(4):1822–33. <https://doi.org/10.1104/pp.18.00837>
 30. Abd-Elhakim YM, Abdo Nassan M, Salem GA, Sasi A, Aldahrani A, Ben Issa K, et al. Investigation of the *in-vivo* cytotoxicity and the *in silico*-prediction of MDM2-p53 inhibitor potential of *Euphorbia peplus* methanolic extract in rats. Toxins. 2019;11(11):642. <https://doi.org/10.3390/toxins11110642>
 31. Yan Y, Peng MY, Yang Y, Zhang ZB, Zhang LL, Tang L, et al. Highly oxygenated ent-abietane diterpenoid lactones from *Euphorbia peplus* and their anti-inflammatory activity. Bioorg Chem. 2025;154:1079. <https://doi.org/10.1016/j.bioorg.2024.107989>
 32. Ran X, Lu QY, Li YY, Pu XX, Guo Y, Yuan MR, et al. Euphejolkinolide A, a new ent-abietane lactone from *Euphorbia peplus* L. with promising biological activity in activating the autophagy-lysosomal pathway. Heliyon. 2023;9(2):e13691. <https://doi.org/10.1016/j.heliyon.2023.e13691>
 33. Hasanuzzaman M. Climate-Resilient Agriculture, Vol 1: Crop responses and agroecological perspectives. Cham: Springer International Publishing; 2023.
 34. King AJ, Brown GD, Gilday AD, Forestier E, Larson TR, Graham IA. A cytochrome P450-mediated intramolecular carbon–carbon ring closure in the biosynthesis of multidrug-resistance-reversing lathyrane diterpenoids. ChemBioChem. 2016;17(17):1593–7. <https://doi.org/10.1002/cbic.201600316>
 35. Fattahian M, Ghanadian M, Ali Z, Khan IA. Jatrophone and rearranged jatrophone-type diterpenes: biogenesis, structure, isolation, biological activity and SARs (1984–2019). Phytochem Rev. 2020;19(2):265–336. <https://doi.org/10.1007/s11101-020-09667-8>
 36. Xiao Y, Zhang Y, Ji WS, Jia XN, Shan LH, Li X, et al. Discovery of myrsinane-type Euphorbia diterpene derivatives through a skeleton conversion strategy from lathyrane diterpene for the treatment of Alzheimer's disease. Bioorg Chem. 2023;138:106595. <https://doi.org/10.1016/j.bioorg.2023.106595>
 37. Czechowski T, Li Y, Gilday A D et al. Evolution of linear triterpenoid biosynthesis within the *Euphorbia* genus. Nat Commun. 2025;16:1–14. <https://doi.org/10.1038/s41467-025-60708-2>
 38. Frezza C, Venditti A, Sciubba F, Tomai P, Antonetti M, Franceschin M, et al. Phytochemical profile of *Euphorbia peplus* L. collected in Central Italy and NMR semi-quantitative analysis of the diterpenoid fraction. J Pharm Biomed Anal. 2018;160:152–9. <https://doi.org/10.1016/j.jpba.2018.07.059>
 39. Wan LS, Nian Y, Ye CJ, Shao LD, Peng XR, Geng CA, et al. Three minor diterpenoids with three carbon skeletons from *Euphorbia peplus*. Org Lett. 2016;18(9):2166–9. <https://doi.org/10.1021/acs.orglett.6b00787>
 40. El-Sakhawy MA, El-Sherbiny Ateya AA, Balah MA. Implications of *Euphorbia peplus* and *Euphorbia geniculata* allelopathy on some plant species and phytopathogenic fungi. BioRes. 2025;20(3):5633–49. <https://doi.org/10.15376/biores.20.3.5633-5649>
 41. Wan LS, Chu R, Peng XR, Zhu GL, Yu MY, Li L, et al. Pepluane and paralane diterpenoids from *Euphorbia peplus* with potential anti-inflammatory activity. J Nat Prod. 2016 ;79(6):1628–34. <https://doi.org/10.1021/acs.jnatprod.6b00206>
 42. Chen YN, Ding X, Li DM, Lu QY, Liu S, Li YY, et al. Jatrophone diterpenoids from the seeds of *Euphorbia peplus* with potential bioactivities in lysosomal-autophagy pathway. Nat Prod Bioprospect. 2021;11(3):357–64. <https://doi.org/10.1007/s13659-021-00301-4>
 43. Gabr D G, AlQahtani R. A Review on: morphological, phytochemical and medical important of some wild euphorbiaceae poisonous plants. haya: Saudi J Life Sci. 2022;7(11):299–313. <https://doi.org/10.36348/sjls.2022.v07i11.001>
 44. Baisted DJ. Sterols of *Euphorbia peplus*: The fate of 28-isofucosterol in phytosterol biosynthesis. Phytochemistry. 1969;8(9):1697–703. [https://doi.org/10.1016/S0031-9422\(00\)85956-7](https://doi.org/10.1016/S0031-9422(00)85956-7)
 45. Hemmers H, Gülz PG, Marner FJ. Triterpenoids in epicuticular waxes of three European *Euphorbia* species. Z Naturfor C. 1988;43(11–12):799–805. <https://doi.org/10.1515/znc-1988-11-1202>
 46. Taib T, AlSamara R, Al-Sofi AAW. Chemical classification of some species *Euphorbia* in central and northern Iraq. Egypt Acad J Biol Sci H Botany. 2022;13(2):245–51. <https://doi.org/10.21608/eajbsh.2022.281341>
 47. Kamel EM, Ahmed NA, El-Bassuony AA, Hussein OE, Alrashdi B, Ahmed SA, et al. Xanthine oxidase inhibitory activity of *Euphorbia peplus* L. Phenolics. CCHTS. 2022 ;25(8):1336–44. <https://doi.org/10.2174/1386207324666210609104456>
 48. Alruhaimi RS, Mostafa-Hedeab G, Abduh MS, Bin-Ammar A, Hassanein EHM, Kamel EM, et al. A flavonoid-rich fraction of *Euphorbia peplus* attenuates hyperglycemia, insulin resistance, and oxidative stress in a type 2 diabetes rat model. Front Pharmacol. 2023 ;14:1204641. <https://doi.org/10.3389/fphar.2023.1204641>
 49. Khafagy S, Gharbo S, Salam N. Phytochemical study of *Euphorbia peplus*. Planta Med. 1975;27(04):387–94. <https://doi.org/10.1055/s-0028-1097820>
 50. Enas Rafaa Qasim, Jehan Al-Hatem, Lubna Abbas. Separation and identification of a number of alkaloids and some phenols from two species of plants of the genus *Euphorbia* grown in Nineveh Governorate. J Electrochem Soc. 2023;32(3):123–34. <https://doi.org/10.33899/edusj.2023.140578.1367>
 51. Mustafa MH, Thukaa ZAJ. Phytochemical profiling and evaluation of the anticancer activity of *Euphorbia peplus* ethyl

- acetate extract against prostate cancer cells. *Plant Sci Today*. 2025;13(1):1-5. <https://doi.org/10.14719/pst.11675>
52. Han EJ, Fernando IPS, Kim HS, Lee DS, Kim A, Je JG, et al. (-)-Loliolide Isolated from *Sargassum horneri* Suppressed Oxidative Stress and Inflammation by Activating Nrf2/HO-1 Signaling in IFN- γ /TNF- α -Stimulated HaCaT Keratinocytes. *Antioxidants*. 2021;10(6):856. <https://doi.org/10.3390/antiox10060856>
 53. Mendes De Lacerda Leite G, De Oliveira Barbosa M, Pereira Lopes MJ, De Araújo Delmondes G, et al. Pharmacological and toxicological activities of α -humulene and its isomers: A systematic review. *Trends Food Sci. Technol.* 2021;115:255–74. <https://doi.org/10.1016/j.tifs.2021.06.049>
 54. Wan LS, Nian Y, Peng XR, Shao LD, Li XN, Yang J, et al. Pepluanols C–D, Two diterpenoids with two skeletons from *Euphorbia peplus*. *Org Lett*. 2018;20(10):3074–8. <https://doi.org/10.1021/acs.orglett.8b01114>
 55. Hammadi R, Kúsz N, Dávid CZ, Behány Z, Papp L, Kemény L, et al. Ingol and Ingenol-Type Diterpenes from *Euphorbia trigona* Miller with Keratinocyte Inhibitory Activity. *Plants*. 2021;10(6):1206. <https://doi.org/10.3390/plants10061206>
 56. Li YY, Yang Y, Sun M, Lu QY, Pu XX, Ran X, et al. Jatrophane polyesters from the leaves of *Euphorbia peplus* with anti-inflammatory activity. *Phytochem Lett*. 2022:114–9. <https://doi.org/10.1016/j.phytol.2022.03.017>
 57. Yang Y, He S, Lin Y, Chen J, Yang R, Li X, et al. *Euphorbia* diterpenoids from *Euphorbia peplus* possessing anti-Alzheimer's activity via targeting PPAR γ and upregulating the level of ABCA1. *Phytochemistry*. 2026;242:114712. <https://doi.org/10.1016/j.phytochem.2025.114712>
 58. Huang JY, Yang Y, Liang H, Pu XX, Li YY, Cai M, et al. Pepluenone, a new pepluane-type diterpenoid with inhibitory activity on the release of NO from the whole plant of *Euphorbia peplus* L. *Tetrahedron Lett*. 2023;123:154550. <https://doi.org/10.1016/j.tetlet.2023.154550>
 59. Guan SP, Yang Y, Sun M, Cai M, Pu XX, Huang JY, et al. Euphepepluone S, a new lathyrane diterpenoid with anti-inflammatory activity from *Euphorbia peplus* L. *Phytochem Lett*. 2023:61–6. <https://doi.org/10.1016/j.phytol.2023.03.011>
 60. Jaafar NS, Jaafar IS, Noori ZS. *Cressa cretica* pharmacognosy, and pharmacology (a review). *Iraqi J Pharm Sci*. 2021;30(2):31–40. <https://doi.org/10.31351/vol30iss2pp31-40>
 61. Bolleddu R, Mangal AK, Abdullah S, G B, Narasimhaji ChV, Nagayya S, et al. The role of Ursolic acid, a pharmacologically active compound from *Ocimum sanctum* L. as a potential chemotherapeutic agent. *Curr Pharm Anal*. 2025;21(2):77–87. <https://doi.org/10.1016/j.cpan.2025.02.001>
 62. Garg P, Awasthi S, Horne D, Salgia R, Singhal SS. The innate effects of plant secondary metabolites in preclusion of gynecologic cancers: Inflammatory response and therapeutic action. *Biochim. Biophys. Acta - Rev. Cancer* 2023;1878(4):188929. <https://doi.org/10.1016/j.bbcan.2023.188929>
 63. Yuan Q, Liu C, Zhang Z, Chen F, Xiao Q, Zhang L, et al. Pharmacological advances of the chlorogenic acids family: current insights and future research directions. *Front Pharmacol*. 2025;16:1613048. <https://doi.org/10.3389/fphar.2025.1613048>
 64. Jaafar NS, Enas J, Kadhim. A comprehensive pharmacognostic, phytochemical description, and clinical implementation of *Amaranthus viridis*. *Iraqi J Pharm Sci*. 2025;34(3):18–28. <https://doi.org/10.31351/vol34iss3pp18-28>
 65. Cherchi M. Scopalamine. In: *Otoneurology and vestibular medicine*. Cham: Springer Nature Switzerland; 2025. p. 1093–93.
 66. Ran X, Lu Q-Y, Li Y-Y, Pu X-X, Guo Y, Yuan M-R, et al. Euphejolkinolide A, a new ent-abietane lactone from *Euphorbia peplus* L. with promising biological activity in activating the autophagy-lysosomal pathway. *Heliyon*. 2023;9(2): e13691. <https://doi.org/10.1016/j.heliyon.2023.e13691>
 67. Iwata M, Inoue T, Asai Y, Hori K, Fujiwara M, Matsuo S, et al. The protective role of localized nitric oxide production during inflammation may be mediated by the heme oxygenase-1 /carbon monoxide pathway. *Biochem Biophys Rep*. 2020;23:100790. <https://doi.org/10.1016/j.bbrep.2020.100790>
 68. Marcinkiewicz E, Chlopicki S, Marcinkiewicz J. Nitric oxide - A pro-inflammatory and anti-inflammatory mediator. *Cent Eur J Immunol*. 2003;28(2):74–8.
 69. Barile E, Fattorusso E, Ialenti A, Iannaro A, Lanzotti V. Paraliane and pepluane diterpenes as anti-inflammatory agents: First insights in structure–activity relationships. *Bioorg Med Chem Lett*. 2007;17(15):4196–200. <https://doi.org/10.1016/j.bmcl.2007.05.072>
 70. Ali, AA, Sayed, HM, Ibrahim* SRM, Zaher AM. Chemical constituents, antimicrobial, analgesic, antipyretic, and anti-inflammatory activities of *Euphorbia peplus* L. *Phytopharmacology* 2013;4(1):69–80.
 71. Aziz N, Jamil R. *Biochemistry, Xanthine Oxidase*. StatPearls Publishing LLC; 2023.
 72. Ramsay JR, Suhrbier A, Aylward JH, Ogbourne S, Cozzi SJ, Poulsen MG, et al. The sap from *Euphorbia peplus* is effective against human nonmelanoma skin cancers: *Euphorbia peplus* sap is effective against skin cancers. *Br J Dermatol*. 2011;164(3):633–36 <https://doi.org/10.1111/j.1365-2133.2010.10184.x>
 73. Yu JH, Wu DX, Yu ZP, Li YP, Wang YY, Yu SJ, et al. New e:b-friedo-hopane type triterpenoids from *Euphorbia peplus* with simiarendiol possessing significant cytostatic activity against HeLa cells by induction of apoptosis and S/G2 cell cycle arrest. *Molecules*. 2019;24(17):3106. <https://doi.org/10.3390/molecules24173106>
 74. Öztürk MA, Egamberdieva D, Pesić M. Biodiversity and biomedicine: our future. San Diego: Elsevier Science & Technology; 2020. p.1.
 75. Ghramh HA, Khan KA, Ibrahim EH. Biological activities of *Euphorbia peplus* leaves ethanolic extract and the extract fabricated gold nanoparticles (AuNPs). *Molecules*. 2019 Apr 11;24(7):1431. <https://doi.org/10.3390/molecules24071431>
 76. Torres-Guerrero E, Quintanilla-Cedillo MR, Ruiz-Esmenjaud J, Arenas R. Leishmaniasis: a review. *F1000Res*. 2017;6:750. <https://doi.org/10.12688/f1000research.11120.1>
 77. Masne T, Kumar D, Bansode D. A review of leishmaniasis: current knowledge and future directions of heterocyclic molecules. *Explor Drug Sci*. 2024;508–39. <https://doi.org/10.37349/eds.2024.00059>
 78. Amin E, Moawad A, Hassan H. Biologically-guided isolation of leishmanicidal secondary metabolites from *Euphorbia peplus* L. *Saudi Pharm J*. 2017;25(2):236–40. <https://doi.org/10.1016/j.jsps.2016.06.003>
 79. Oskay M, Oskay D, Kalyoncu F. Activity of some plant extracts against multi-drug resistant human pathogens. *IJPR*. 2009;8(4):293-300. <https://doi.org/10.22037/ijpr.2010.825>
 80. Fhu CW, Ali A. fatty acid synthase: an emerging target in cancer. *Molecules*. 2020 Aug 28;25(17):3935. <https://doi.org/10.3390/molecules25173935>
 81. Gouras GK, Olsson TT, Hansson O. β -amyloid peptides and amyloid plaques in Alzheimer's disease. *Neurotherapeutics*. 2015;12(1):3–11. <https://doi.org/10.1007/s13311-014-0313-y>
 82. Liu M, Chen F, Yu R, Zhang W, Han M, Liu F, et al. Synthesis and cytotoxicity against K562 cells of 3-O-angeloyl-20-O-acetyl Ingenol, a derivative of ingenol mebutate. *Int J Mol*.

- Sci. 2016;19;17(8):1348. <https://doi.org/10.3390/ijms17081348>
83. Aditya S, Gupta S. Ingenol mebutate: A novel topical drug for actinic keratosis. *Indian Dermatol Online J.* 2013;4(3):246. <https://doi.org/10.4103/2229-5178.115538>
 84. Silva VAO, Rosa MN, Martinho O, Tanuri A, Lima JP, Pianowski LF, et al. Modified ingenol semi-synthetic derivatives from *Euphorbia tirucalli* induce cytotoxicity on a large panel of human cancer cell lines. *Invest New Drugs.* 2019;37(5):1029–35. <https://doi.org/10.1007/s10637-019-00728-0>
 85. Stockfleth E, Bastian M. Pharmacokinetic and pharmacodynamic evaluation of ingenol mebutate for the treatment of actinic keratosis. *Expert Opin. Drug Metab. Toxicol.* 2018;14(9):911–8. <https://doi.org/10.1080/17425255.2018.1508449>
 86. Dodds A, Chia A, Shumack S. Actinic Keratosis: Rationale and management. *Dermatol Ther (Heidelb).* 2014;4(1):11–31. <https://doi.org/10.1007/s13555-014-0049-y>
 87. Figueras Nart I, Cerio R, Dirschka T, Dréno B, Lear JT, Pellacani G, et al. Defining the actinic keratosis field: a literature review and discussion. *Acad Dermatol Venereol.* 2018;32(4):544–63. <https://doi.org/10.1111/jdv.14652>
 88. Skroza N, Bernardini N, Proietti I, Potenza C. Clinical utility of ingenol mebutate in the management of actinic keratosis: perspectives from clinical practice. *TCRM.* 2018;14:1879–85. <https://doi.org/10.2147/tcrm.s145779>
 89. Alves ALV, Da Silva LS, Faleiros CA, Silva VAO, Reis RM. The Role of ingenane diterpenes in cancer therapy: from bioactive secondary compounds to small molecules. *Nat Prod Commun.* 2022;17(7):1934578X221105691. <https://doi.org/10.1177/1934578X221105691>
 90. Collier NJ, Ali FR, Lear JT. Ingenol mebutate: a novel treatment for actinic keratosis. *Clinical Practice.* 2014;11(3):295–306. <https://doi.org/10.2217/cpr.14.13>
 91. Liang X, Grue-Sørensen G, Månsson K, Vedsø P, Soor A, Stahlhut M, et al. Syntheses, biological evaluation and SAR of ingenol mebutate analogues for treatment of actinic keratosis and non-melanoma skin cancer. *Bioorg Med Chem Lett.* 2013;23(20):5624–9. <https://doi.org/10.1016/j.bmcl.2013.08.038>
 92. Fidler B, Golgberg T. Ingenol mebutate gel (picato): a novel agent for the treatment of actinic keratoses. *P & T J* 2014;39(1):40–6. <https://pubmed.ncbi.nlm.nih.gov/24672213/>
 93. Rosen R, Gupta A, Tying S. Dual mechanism of action of ingenol mebutate gel for topical treatment of actinic keratoses: Rapid lesion necrosis followed by lesion-specific immune response. *J. Am. Acad. Dermatol.* 2011;66:486–89. <https://doi.org/10.1016/j.jaad.2010.12.038>
 94. Shafombabi NF, Knott M, Kapewangolo P, Sharifi-Rad J, Calina D. Ingenol mebutate in cancer therapy: mechanisms, clinical applications and future directions. *Med Oncol.* 2025;42(3):69. <https://doi.org/10.1007/s12032-025-02615-6>
 95. Grada A, Feldman SR, Bragazzi NL, Damiani G. Patient-reported outcomes of topical therapies in actinic keratosis: A systematic review. *Dermatol Ther.* 2021;34(2):e14833. <https://doi.org/10.1111/dth.14833>
 96. Lesiak A, Maćkowska A, Bednarski I, Kolano P, Olejniczak-Staruch I, Woźniacka A, et al. Ingenol mebutate treatment in actinic keratosis – clinical effectiveness and potential side effects. *Postępy Dermatol Alergol.* 2019;36(4):468–71. <https://doi.org/10.5114/ada.2019.87450>
 97. Heron C, Feldman S. Ingenol mebutate and the treatment of actinic keratosis. *J Drugs Dermatol.* 2021;20(1):102–4. <https://doi.org/10.36849/jdd.5328>
 98. Ross M. Australia's poisonous plants, fungi and cyanobacteria: A guide to species of medical and veterinary importance CSIRO Publishing Locked Bag 10, Clayton South VIC 3169, Australia; 2020. <https://doi.org/10.1071/9781486313877>
 99. Moustafa GG, Mohammed AT, Hadeed AHA, Kandil FH, El Kelsh EKM. Estimation of toxic hazards caused by methanolic extract of *Euphorbia peplus* in male albino rats. *Adv Anim Vet Sci.* 2015;4(1):5–11. <https://doi.org/10.14737/journal.aavs/2016/4.1.5.11>
 100. Nawito M, Ahmed YF, Zayed SMAD, Hecker E. Dietary cancer risk from conditional cancerogens in produce of livestock fed on species of spurge (Euphorbiaceae). *J Cancer Res Clin Oncol.* 1998;22;124(3–4):179–85. <https://doi.org/10.1007/s004320050152>

Additional information

Peer review: Publisher thanks the Sectional Editor and anonymous reviewers for their contribution to the peer review of this work.

Reprints & permissions information: Available at https://horizonpublishing.com/journals/index.php/PST/open_access_policy.

Publisher's Note: Horizon e-Publishing Group remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Indexing: See https://horizonpublishing.com/journals/index.php/PST/indexing_abstracting.

Copyright: © The Author(s). This is an open-access article distributed under the Creative Commons Attribution License CC BY 4.0.

Publisher information: Plant Science Today is published by Horizon e-Publishing Group with support from Empirion Publishers Private Limited, Thiruvananthapuram, India.