Biomedicine & Pharmacotherapy 165 (2023) 115205

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Anticancer properties and mechanism insights of α-hederin

Omar Belmehdi [a], Douae Taha [b], Jamal Abrini [a], Long Chiau Ming [c,d,e], Asaad Khalid [f,g], Ashraf N. Abdalla [h,*], Alanood S. Algarni [h], Andi Hermansyah [c,*], Abdelhakim Bouyahya [i,*]

[a] Biotechnology and Applied Microbiology Team, Department of Biology, Faculty of Sciences, Abdelmalek Essaadi University, Tetouan, Morocco
[b] Laboratory of Spectroscopy, Molecular Modelling Materials, Nanomaterials Water and Environment–CERNE2D, Faculty of Sciences, Mohammed V University in Rabat, Morocco
[c] Department of Pharmacy Practice, Faculty of Pharmacy, Universitas Airlangga, Surabaya 60115, Indonesia
[d] PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, BE1410 Gadong, Brunei Darussalam
[e] School of Medical and Life Sciences, Sunway University, Sunway City 47500, Malaysia
[f] Substance Abuse and Toxicology Research Center, Jazan University, P.O. Box: 114, Jazan 45142, Saudi Arabia
[g] Medicinal and Aromatic Plants and Traditional Medicine Research Institute, National Center for Research, P. O. Box 2404, Khartoum, the Sudan
[h] Department of Pharmacology and Toxicology, College of Pharmacy, Umm Al-Qura University, Makkah , Saudi Arabia
[i] Laboratory of Human Pathologies Biology, Faculty of Sciences, Mohammed V University in Rabat, Morocco

ARTICLE INFO

Keywords:
Cancer cell
Biological properties
Anticancer
Bioactive compound
Chemotherapy
Drug treatment

ABSTRACT

α-Hederin is a natural bioactive molecule very abundant in aromatic and medicinal plants (AMP). It was identified, characterized, and isolated using different extraction and characterization technologies, such as HPLC, LC-MS and NMR. Biological tests have revealed that this natural molecule possesses different biological properties, particularly anticancer activity. Indeed, this activity has been investigated against several cancers (*e.g.*, esophageal, hepatic, breast, colon, colorectal, lung, ovarian, and gastric). The underlying mechanisms are varied and include induction of apoptosis and cell cycle arrest, reduction of ATP generation, as well as inhibition of autophagy, cell proliferation, invasion, and metastasis. In fact, these anticancer mechanisms are considered the most targeted for new chemotherapeutic agents' development. In the light of all these data, α-hederin could be a very interesting candidate as an anticancer drug for chemotherapy, as well as it could be used in combination with other molecules already validated or possibly investigated as an agent sensitizing tumor cells to chemotherapeutic treatments.

1. Introduction

Natural products derived from medicinal plants have long been recognized as valuable sources of drugs [1–3]. Throughout history, traditional medicine has relied on the use of plant-based remedies for treating various ailments. These medicinal plants are rich in bioactive compounds such as alkaloids, flavonoids, terpenoids, and phenolic compounds, which possess therapeutic properties. The diverse chemical constituents present in these plants offer a wide range of biological activities, including antimicrobial, anti-inflammatory, anticancer, and antioxidant effects. Scientists and researchers continue to explore and harness the potential of natural products from medicinal plants to develop new drugs or as inspiration for drug development [4–6]. Their effectiveness, coupled with their relatively lower toxicity compared to synthetic drugs, makes them an attractive option in the search for novel therapeutic agents [7]. Moreover, the sustainable nature of plant-based sources makes them a valuable and environmentally friendly alternative in the field of drug discovery. Overall, natural products from medicinal plants represent a valuable reservoir of bioactive compounds that hold great promise for the development of effective and safe drugs for various diseases.

α-Hederin is a pentacyclic triterpene saponin detected in different plants such as *Hedera helix* L., *Nigella sativa* L., *Lens culinaris* Medik. and *Pulsatilla chinensis*, in different location [8–11]. The amount of this molecule can vary according to the type of species, the part used, the harvest season, as well as the geographical and climatic conditions. The

* Corresponding authors.
E-mail addresses: belmehdiomar@hotmail.fr (O. Belmehdi), douae.taha02@gmail.com (D. Taha), abrinij@hotmail.com (J. Abrini), longchiauming@gmail.com (L.C. Ming), akahmed@jazanu.edu.sa (A. Khalid), anabdrabo@uqu.edu.sa (A.N. Abdalla), aagarni@uqu.edu.sa (A.S. Algarni), andi-h@ff.unair.ac.id (A. Hermansyah), a.bouyahya@um5r.ac.ma (A. Bouyahya).

https://doi.org/10.1016/j.biopha.2023.115205
Received 5 June 2023; Received in revised form 15 July 2023; Accepted 18 July 2023
Available online 25 July 2023

identification and the chemical characterization of this natural molecule were carried out using several technologies, especially UPLC-ESI-MS and HPLC analysis, LC-EI/MS-MS, and MS, ^{1}H- and ^{13}C NMR methods [12–15].

Furthermore, the biological and pharmacological investigations demonstrated that this substance has diversified properties, such as anticancer [16], antifungal [17], antioxidant [18], antileishmanial [19], anthelminthic [20], and antibacterial [21] activities, which are related to different mechanisms that are poorly understood. Importantly, α-hederin has shown promising anticancer effects against a number of cancers, including gastric, ovarian, lung, colorectal, colon, breast, hepatic, and esophageal [22–29] *via* various mechanisms, namely induction of apoptosis and cell cycle arrest, reduction of ATP generation, as well as inhibition of autophagy, cell proliferation, invasion, and metastasis. This saponin could give rise to important downstream investigations and less highlighted pharmacodynamic investigations as well as other pharmacokinetic tests to validate its bioavailability and its safety.

In the light of all these data, this review is proposed which includes all the essential elements concerning α-hederin sources, extraction, identification, and isolation technologies, as well as the anticancer activity with the reported mechanisms of action.

2. Sources of α-hederin

α-Hederin (Fig. 1) is the major compound in leaf extracts of *Hedera helix* L., commonly known as ivy in many countries (Table 1) [10,13,14, 18,30–39] and the stem extract of the same species collected in Austria and France [40–42]. The richness of plants in this compound depends on several geographic factors as well as on the plant part used.

Seed parts of *Nigella sativa* L. collected in the regions of Israel, the United States, Iran, Singapore, and Germany were characterized by their richness in α-hederin [8,44,45,47,48]. Also, α-hederin was detected as the major compound of *Cephalaria genus*, namely *Cephalaria hirsute, Cephalaria elazigensis* var. elazigensis, and *Cephalaria procera*, collected in Turkey [51]. Other works mentioned the richness of Chinese plants such as *Pulsatilla chinensis* in this molecule [9,50]. In addition, it has been characterized as the major compound of hydroethanolic extract of *Lens culinaris* collected from Spain and Canada [49], and in the ethanolic and hexanic leaf extracts of *Polyscias fulva* (Hiern) Harms collected from Babanki Keku, Northwest Province of Cameroon [52].

This saponin was characterized as the major compound of hydromethanolic stem bark extract of *Kalopanax pictus* collected from Korean regions [54], methanolic leaf extracts of *Vigna unguiculata* L. Walp. (Cowpea) from India [55], *Fructus akebiae* from China [53], *Hedera Nepalensis* K.Koch collected in Vietnam, and hydromethanolic leaf extracts of *Maesa lanceolata* Forsskal var. gonlungensis Welw. In addition, it was detected in high amounts in many plants, such as *Trevesia palmata* collected in Korea [58], *Elattostachys apetala* from France [59], and *Anthyllis vulneraria* L. from Germany [15].

Moreover, α-hederin has been isolated from stem bark extracts of *Uncaria tomentosa* (Willd.) collected in Brazil [60], seeds of *Lupinus Angustifolius* and Chickpeas *Cicer arietinum* [49,62], and *Lysimachia thyrsiflora* from Poland. Two minor triterpene saponins, one of them has not been previously reported, were isolated from the underground parts of *Lysimachia thyrsiflora* L. The structures were determined based on a combination of one- and two-dimensional NMR techniques, and mass spectrometry, as 30- O-β-D-glucopyranosyl-3β,16α,30-trihydroxy-olean-12-en-28-yl acetate 3- O-β-D-glucopyranosyl-(1→4)-O-[β-D-glucopyranosyl-(1→2)-]- O-α-L-arabinopyranoside (denoted as thyrsiloside A), and davuricoside L. Quantitative determination of these two compounds, along with other saponins present in *L. thyrsiflora* underground parts, was performed by a developed UPLC-ESI-MS/MS method, validated according to the ICH guidelines. The relative total content of triterpene saponins amounted to 1.19 μg/mg dw. Both 4 and 5 were present in minor quantities, 0.031 and 0.077 μg/mg dw, respectively.

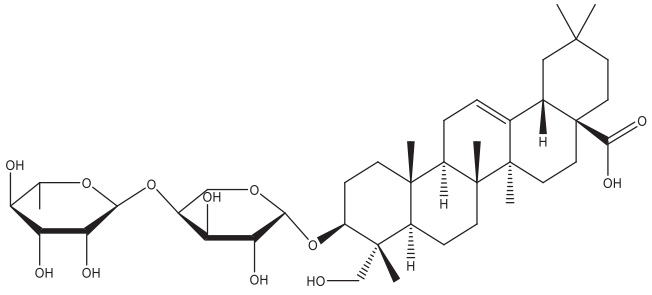

Fig. 1. Chemical structure of α-hederin.

3. Extraction, identification, and isolation processes of α-hederin

To extract, identify and isolate α-hederin different techniques has been sued. Indeed, UPLC-ESI-MS analysis, LC-EI/MS-MS, and MS, ^{1}H and ^{13}C NMR methods were used for the structural elucidation and purification of this molecule from the leaves of *Hedera helix* L. (Table 2) [12–14,30–35,37,39,56]. In addition, it was purified from the same plant (stems and whole plant) using HPLC-MS analysis [36,41].

Moreover, α-hederin was identified in of *Nigella sativa* L. seeds using UPLC-Q-TOF-MS, LC/MS, TLC, HPLC, ^{1}H and ^{13}C NMR analysis [8,44, 47,48], as well as from the leaves of this species [45]. Indeed, using UPLC-MS, ^{1}D, ^{2}D NMR, HR-ESI-MS, this bioactive compound was identified in the leaves of *Cephalaria hirsute*, *Cephalaria elazigensis* var. elazigensis, and *Cephalaria procera* [51], also with a combination of DQF-COSY, TOCSY, HMQC, and HMBC experiments,^{13} and C NMR it was identified in *Polyscias fulva* (Hiern) Harms [52].

α-Hederin has been eluted using one-dimensional (1D) and ^{2}D ^{1}H and ^{13}C NMR from the stem bark of *Kalopanax pictus* [54], by LC-ESI-Q-TOF MS analysis from the leaf extract of *Vigna unguiculata* L. Walp. (Cowpea) [55], and with HPLC analysis from *Hedera Nepalensis* K.Koch [56], *Maesa lanceolata* Forsskal var. gonlungensis Welw. [57], *Pulsatilla chinensis* [9], *Pulsatilla* genus [50], and *Trevesia palmata* [58]. In addition, using ^{1} H and ^{13}C NMR, HSQC and HMBC, it was identified in the leaves and stem bark of *Elattostachys apetala* [59], *Anthyllis vulneraria* L., [15], and, by HPLC-PDA UPLC/Q-TOF–MS, in the stem barks of *Uncaria tomentosa* (Willd.) [60].

4. Anticancer activity of α-hederin

The anticancer activity of α-hederin has been investigated by several studies (Table 3). The data collected from the literature show that this molecule has a high level of antitumor action against numerous cancer cell lines. In fact, its antitumor potential was proved *in vitro* (Adamska et al., 2019) as well as *in vivo* using animal models [16,29,65]. Moreover, the main mechanistic actions have been reported. α-Hederin exhibits anticancer action by altering some important biological functions in tumor cells such as apoptosis and ferroptosis induction, cell proliferation and metastasis inhibition, depletion of ATP generation, disruption of the antioxidant system, *etc.*(Fig. 2).

4.1. Induction of apoptosis

It has been shown that α-hederin induces pro-apoptotic proteins such as Bax (Bcl-2-associated protein) and inhibits anti-apoptotic proteins such as Bcl-2 (B-cell lymphoma 2), as well as induction of ROS (reactive oxygen species) accumulation. These latter are known to increase mitochondrial membrane permeability, which lead to cytochrome C, AIF (apoptosis inducing factor) and Apaf-1 (apoptotic peptidase activating factor 1) release from the mitochondria to cytosol. This release

Table 1
Sources of α-hederin.

Plants species/family	Country	Part	Type of extract	References
Hedera helix L.	Vietnam	Leaves	Not reported	[10]
Araliaceae	Romania		Not reported	[39]
	Lithuania, Ukraine, Hungary, Czech Republic, Austria, Slovakia, Poland, and Greece		Methanolic extract	[12]
	France		Hydromethanolic extract	[30]
	Belgium		Not reported	[31]
	Germany		Methanolic extract	[32]
	Italy		Not reported	[33]
	France		Not reported	[34]
	Bagdati region of West Georgia France		Not reported	[13]
	Germany		Not reported	[35]
	Not reported		Not reported	[43]
	Czech Republic		Hydromethanolic extract	[14]
	France		Ethyl acetate and methanol extracts	[20]
	Korea		Hydroethanolic extract	[37]
	Poland		DMSO extract	[38]
	Iraq		Methanolic extract	[36]
	Austria	Stems	Not reported	[41]
	France		Not reported	[40]
	France		Not reported	[42]
Nigella sativa L.	Israel	Seeds	Not reported	[44]
Ranunculaceae	United States		Aqueous extract	[8]
	Iran		Not reported	[45]
	Not reported		Not reported	[46]
	Singapore		Ethanolic extract	[47]
	Germany		Not reported	[48]
Lens culinaris Medik.	Canada	Not reported	Not reported	[11]
Fabaceae				
Lens culinaris	Spain	Not reported	Hydroethanolic extract	[49]
Fabaceae				
Pulsatilla chinensis	China	Not reported	Not reported	[9,50]
Ranunculaceae				
Cephalaria hirsuta	Turkey	Aerial parts	Not reported	[51]
Caprifoliaceae				
Cephalaria elazigensis var. elazigensis				
Caprifoliaceae				
Cephalaria procera				
Caprifoliaceae				
Polyscias fulva (Hiern) Harms Araliaceae	Cameroon	Leaves	Ethanolic and hexanic extracts	[52]
Fructus akebiae	China	Not reported	Not reported	[53]
Lardizabalaceae				
Kalopanax pictus	Korea	stem bark	Hydromethanolic extract	[54]
Araliaceae				
Vigna unguiculata L. Walp. (Cowpea)	India	Leaves	Methanolic extract	[55]
Fabaceae				
Hedera Nepalensis K.Koch	Vietnam	Not reported	Not reported	[56]
Araliaceae				
Maesa lanceolata Forsskal var. gonlungensis Welw.	Belgium	Leaves	Hydromethanolic extract	[57]
Primulaceae				
Pulsatilla cernua	China	Not reported	Not reported	[50]
Ranunculaceae				
Pulsatilla dahurica				
Ranunculaceae				
Pulsatilla turczaninovii				
Ranunculaceae				
Trevesia palmata	Korea	Not reported	Not reported	[58]
Araliaceae				
Elattostachys apetala	France	Stem bark	Hydromethanolic extract	[59]
Sapindaceae				
Anthyllis vulneraria L.	Germany	Not reported	Hydroethanolic extract	[15]
Fabaceae				
Uncaria tomentosa (Willd.)	Brazil	Stem barks	Not reported	[60]
Rubiaceae				
Lysimachia thyrsiflora	Poland	No reported	Not reported	[61]
Primulaceae				
Lupinus Angustifolius	Not reported	Seeds	Not reported	[62]
Fabaceae				
Chickpeas *Cicer arietinum*	Spain		Hydroethanolic extract	[49]
Fabaceae				
Clematis parviloba	China	Stems	Not reported	[63]
Ranunculaceae				
Clematis tangutica (Maxim.) Korsh		Aerial parts	Ethanolic extract	[64]
Ranunculaceae				

Table 2
Extraction, identification, and isolation process of α-hederin.

Plant species/family	Part used	Method of extraction	Method of identification	Yield	References
Hedera helix L. Araliaceae	Leaves	Sonication	UPLC-ESI-MS analysis	-	[12]
		Ultrasonic	Column liquid chromatographic, light-scattering detector	-	[30]
		Not reported	HPLC analysis	-	[31]
		Decoction	HPLC profiling		[32]
		Not reported	HPLC analysis	-	[33]
		Not reported	LC-EI/MS-MS	-	[34]
		Not reported	MS and ^{1}H and ^{13}C NMR methods	1 g	[13]
		Not reported	HPLC-MS analysis	-	[35]
		Not reported	HPLC analysis	-	[14]
		Sonication	UPLC–ESI–MS/MS	-	[37]
		Not reported	UHPLC-Q-TOF-MS/MS	-	[10]
		Not reported	HPLC-MS/MS	-	[39]
	Stems	Not reported	HPLC-MS analysis	-	[41]
	Whole plant	Maceration	HPLC-MS analysis		[36]
Nigella sativa L. Ranunculaceae	Seeds	Not reported	UPLC-Q-TOF-MS	-	[44]
		Maceration	LC/MS analysis	-	[8]
		Not reported	TLC, HPLC,^{1}H and ^{13}C NMR, and LC/MS	-	[47]
		Not reported	HPLC analysis	-	[48]
	Leaves	Not reported	UPLC-ESI–MS/MS	-	[45]
Cephalaria hirsuta Caprifoliaceae *Cephalaria elazigensis* var. elazigensis Caprifoliaceae *Cephalaria procera* Caprifoliaceae	Aerial parts	Not reported	UPLC-MS ^{1}D,^{2}D NMR, HR-ESI-MS chemical methods	-	[51]
Polyscias fulva (Hiern) Harms Araliaceae	Leaves	Maceration	Combination of DQF-COSY, TOCSY, HMQC, and HMBC experiments, ^{13}C NMR	628 mg	[52]
Kalopanax pictus Araliaceae	Stem bark	Not reported	One-dimensional (1D) and^{2}D^{1} H and^{13}C NMR	-	[54]
Vigna unguiculata L. Walp. (Cowpea) Fabaceae	Leaves	Soxhlet	LC-ESI-Q-TOF MS analysis	-	[55]
Hedera Nepalensis K.Koch Araliaceae	Not reported	Not reported	HPLC-UV analysis	-	[56]
Maesa lanceolata Forsskal var. gonlungensis Welw. Primulaceae	Leaves	Maceration	LC–MS/MS analysis	-	[57]
Pulsatilla chinensis Caprifoliaceae	Not reported	Not reported	UHPLC–ESI-MS/MS	-	[9]
Pulsatilla chinensis Caprifoliaceae	Not reported	Not reported	UPLC–ESI–MS/MS	-	[50]
Pulsatilla cernua Caprifoliaceae	Not reported	Not reported			
Pulsatilla dahurica Caprifoliaceae	Not reported	Not reported			
Pulsatilla turczaninovii Caprifoliaceae	Not reported	Not reported			
Trevesia palmata Araliaceae	Not reported	Not reported	HPLC analysis	-	[58]
Elattostachys apetala Sapindaceae	Leaves and stem bark	Not reported	^{1} H and^{13}C NMR, HSQC and HMBC	1,5 %	[59]
Anthyllis vulneraria L. Fabaceae	Not reported	Not reported	LC-MS MS	-	[15]
Uncaria tomentosa (Willd.) Rubiaceae	Stem barks	Not reported	HPLC-PDA UPLC/Q-TOF–MS	-	[60]

leads to caspase 9 and caspase 3/7 cleavage, which induces cell apoptosis. GSH (glutathione) plays an important role in protecting cells against oxidative stress, caused by exogenous and endogenous agents, including ROS. The main cause of ROS accumulation is the disruption of the redox system, mainly through GSH depletion. It has been shown that α-hederin could decrease the activity of GSH leading to ROS accumulation, which results in apoptosis and ferroptosis induction in some cancer cells [16,23,26,27,29,65,66,70,75].

4.2. Induction of cell cycle arrest

Cell proliferation is a highly controlled process in which several proteins interfere. The phases of a cell cycle are G1, S, G2 and M. Each phase is controlled by specific proteins, and any damage in the biological content of the cell can lead to the cycle arrest in order to initiate the mechanisms of repair. The main proteins involved in the cell cycle control are the cyclins and CDK. It is known that cancer cells depend on the G2 phase in order to protect against DNA damage. In this regard, the G2/M transition has been considered a target for cancer therapy, as this phase is controlled by the kinase protein, namely cyclin B1, that interferes with CDK1 to constitute a checkpoint for DNA repair. Interestingly, *in vitro* studies have shown that α-hederin could inhibit the CDK1 and cyclin B1, which results in cell cycle arrest in the G2/M phase. This inhibition was noticed at the protein and transcriptional levels [26].

Table 3
Anticancer activity of α-hederin.

Source of α-Hederin	Methods used	Cell lines/animal models	Key results	References
Purchased from Sigma-Aldrich, St. Louis, United States	Cytotoxicity assay 5–ethynyl-2′-deoxyuridine (EdU) retention assay Colony formation assay Hoechst 33258 staining for apoptosis cells Flow cytometric analysis of cell cycle and apoptosis GSH/glutathione disulfide (GSSG) Assay Mitochondrial and cytosolic protein fractionation and Western blot analysis Hematoxylin and eosin staining and TUNEL assay	Human gastric cancer cell lines (HGC-27 and SGC-7901) Xenografted tumor model	Inhibition of gastric cancer cells, with IC_{50} = 20.86 μM and 25.91 μM, against HGC-27 and SGC-7901, respectively.Induction of cell cycle arrest in G1. Induction of apoptosis by increasing protein levels of Bax, cleaved caspase-3, caspase 8, and caspase-9, and a decrease in Bcl-2 level. Induction of intracellular decrement of GSH of gastric cancer cells. Diminution of ATP level by disturbing the mitochondrial membrane potential *via* ROS accumulation. Inhibition of growth of xenografted gastric tumors Inhibition of metastasis *in vivo*	[16]
Purchased from igma-Aldrich, St. Louis, United States	Real-Time xCELLigence and MTT assays	human cancer ovarian cell line SKOV-3.	IC_{50} values equal to 2.62 ± 0.04 μg/mL and 2.48 ± 0.32 μg/mL, by Real-Time xCELLigence and MTT assays, respectivel y.Induction of apoptosis. Decrease of mitochondria membrane potential. Inactivation of anti-apoptotic protein bcl-2, and activation of caspase-9 and caspase-3/7 Induction of cancer cells cycle arrest in G0/G1.	[22]
provided by Cheng du PUSH BIO-TECHNOLOGY	CCK8 assay Colony formation assay	A549 lung cancer cells Xenograft mouse model	Inhibition of cell proliferation Inhibition of glucose uptake and ATP generation Reduction of lactate production Inhibition of hexokinase 2, GLUT1, pyruvate kinase M2, lactate dehydrogenase A, monocarboxylate transporter, c-Myc. Activation of Srtuin 6. Inhibition of lung cancer growth *via* glycolysis inhibition.	[24]
purchased from Sigma Aldrich Germany.	MTT	Normal fibroblasts cells Cervix ephitelial tumor cells (Hep-2)	α-hederin was biocompatible in normal fibroblasts cells. IC50 = 2 ug/mL on Hep-2 cells	[28]
provided by Chengdu Push Bio- Technology Co. Ltd. (Chengdu, China)	Cell Counting Kit 8 assay Colony formation assay	Human NSCLC A549 cells Human lung cancer cells NCI-H460 and NCI-H292 (lymph node metastasis) Male BALB/c nude mice	Inhibition of A549 (IC50 1⁄4 13.75lM), NCI-H460 (IC50 1⁄4 17.57lM), and NCI-H292 (IC50 1⁄4 18.04lM), proliferation. Inhibition of glucose uptake and ATP generation Reduction of lactate production Inhibition of hexokinase 2, glucose transporter 1, pyruvate kinase M2, lactate dehydrogenase A, monocarboxylate transporter, c-Myc, hypoxia-inducible factor-1aplha. Activation SIRT6 protein expression. Inhibition of glycolysis *via* SIRT 6 activation. Inhibition of lung cancer *in vivo* by glycolysis inhibition.	[25]
purchased from Sigma-Aldrich; Merck KGaA (Darmstadt, Germany).	Cell counting kit-8 and colony formation assays Flow cytometry Western blotting	human colorectal cancer cells	Inhibition of HCT116 and HCT8 proliferation. Induction of apoptosis *via* mitochondrial apoptosis pathway activation. Inhibition of autophagy *in vitro* and *in vivo via* activation of AMP-activated protein kinase (AMPK)/mechanistic target of rapamycin (mTOR) signaling.	[27]
provided by Shanghai Yuanye Biotechnology Co., Ltd. (Shanghai, China)	CellViabilityAssay. CellCycleAnalysisbyFlowCytometry Hoechst 33258 Staining. Flow Cytometry Analysis of MMP. Immunofluorescence Staining Real-Time PCR Western Blot Analyses	human colon cancer cells HCT116 and SW620	Reduction of SW620 viability. Arrest of cell cycle at G2/M phase. Reduction of mRNA and protein expression of cyclin B1 and CDK1. Induction apoptosis and loss of mitochondrial membrane potential Downregulation of Bcl-2 expression, Upregulation of Bax expression. Promotion of cytochrome c release from mitochondria into cytoplasm. Elevation of the levels of cleaved-caspase-9, cleaved- caspase-3, and cleaved-PARP	[26]

(*continued on next page*)

Table 3 (*continued*)

Source of α-Hederin	Methods used	Cell lines/animal models	Key results	References
			Prevention of the nuclear translocation of nuclear factor- κB (NF-κB) and reduced the phosphorylation of IκBα and IKKα, suggesting the blockade of NF-κB signaling. Inhibition of the phosphorylation of ERK	
purchased from Shanghai Yuanye Biotechnology Co., Ltd. (Shanghai, Chona).	Cell viability assay	human SW620 colon cancer cells stimulated with interleukin 6 (IL-6)	Inhibition cell viability, migration and invasion in IL-6-treated SW620 cells Restore IL-6-induced decrease in E-cadherin expression and abolished IL-6-induced increase in N-cadherin, vimentin, fi- bronectin, twist and snail at both mRNA and protein levels in SW620 cells. Suppression of IL-6-indcued EMT in colon cancer cells. Phosphorylation Inhibition of Janus Kinase 2 (JAK2) and Signal Transducer and Activator of Transcription 3 (STAT3). Inhibition of the nuclear translocation of phosphorylated STAT3 in IL-6-treated SW620 cells.	[66]
	Proteomics, metabolomics, and high-throughput sequencing detection	non-small-cell lung cancer (NSCLC) cisplatin-resistant A549 cell line (A549-DDP), and PC9 cells BALB/c nude mice	Downregulation of glutathione peroxidase 2 (GPX2), and glutathione synthase (GSS) expression suppressed the synthesis of glutathione (GSH), which destroyed the GSH redox system. Induction of ferroptosis, apoptosis, and membrane permeabilization in NSCLC.	[67]
purchased from Sigma (Sigma-Aldrich, St. Louis, USA)	Cell Counting Kit-8, flow cytom- etry, Hoechst 33258 staining, enhanced ATP assay kit, 2′,7′-dichlorofluorescin diacetate, JC-1 kit, and Western bolt	Human esophageal carcinoma cell (ESCC) line (Eca-109)	Inhibition of proliferation, and induction of apoptosis of ESCC. Cell cycle arrest in G1 phase. Induction of ROS accumulation. Decrement of ATP levels. Disruption of MMP. Release of AIF, Apaf-1, and Cyt C. Increase of caspase-3, caspase-9, and Bax. Decrease of Bcl-2 level. α-hederin significantly inhibited the growth of xenografted tumors with favorable safety.	[29]
obtained from Sigma (Sigma-Aldrich, St. Louis, MO, USA)	Cell Counting Kit-8 Transwell invasion assay and wound healing assay Hoechst 33258 Staining Kit and an Annexin V-PE apoptosis kit GSH Assay Kit DCFH-DA and JC-1 Kit Western blot analysis	human gastric cancer cell line (HGC27) male BALB/c nude mice	Inhibition of HGC27/DDP proliferation and induction of obvious apoptosis compared with the control. Suppression of invasion and migration. Induction of GSH depletion and intracellular ROS accumulation. Disruption of mitochondrial membrane potential. Elevation of Bax, Apaf-1, AIF, Cyt C, cleaved caspase-3 and cleaved caspase-9 expression and depletion protein level of Bcl-2, survivin, MMP-9 and MMP-2. Inhibition of xenograft tumor growth *in vivo*	[68]
	Molecular docking	hepatocellular carcinoma (HCC) hepatoma cell lines HepG2, Hep3B, Huh7 and Hcclm3	Inhibitio of cell migration and invasion induced by PAF in HCC cells, as well as lung metastasis *in vivo*. Reduction the PAF-induced matrix metalloproteinase-2 expression through inhibiting the activation of STAT3 in PAF stimulated HCC cells	[69]
	5-ethynyl-2′- deoxyuridine staining, colony formation, flow cytometry. RT-qPCR and immunoblotting	human SMMC-7721, HepG2, and Huh-7 HCC cell lines female BALB/c nude mice	Promotion of apoptosis and inhibition of SMMC-7721 and HepG2 proliferation of *in vitro*. Inhibition of tumor size and weight in the xenograft mouse model a-hederin increased the expression of pro-apoptosis proteins and suppressed the expression of anti-apoptosis proteins. Upregulation of Hippo signaling pathway-related proteins and genes expression. Reduction the nuclear YAP level, Inhibition of proliferation and induction of apoptosis of HCC cells.hibitor in vitro.	[70] 1
Clematis ganpiniana	MTT	human breast cancer cell lines MCF-7 and MDA-MB-231	Strong inhibitory activity on the growth of breast cancer cells Induction of apoptosis Depolarization of mitochondrial membrane	[23]

(*continued on next page*)

Table 3 (*continued*)

Source of α-Hederin	Methods used	Cell lines/animal models	Key results	References
			potential and released Apaf-1 and cytochrome *c* from the intermembrane space into the cytosol, where they promoted caspase-3 and caspase-9 activation	
Hedera colchica	Cytotoxicity assay Calcein–AM assay	Human lung carcinoma (A549), human colorectal adenocarcinoma (DLD-1) and human normal skin fibroblasts (WS1) cell lines	Permeabilizing the cellular membranes.	[71]
purchased from Chengdu Must Bio-Technology (Chengdu, China)	Cell Viability Assay GFP-LC3B or mCherry-GFP-LC3B Assay Western Blotting AO Staining LysoTracker Red Staining Measurement of Intracellular ROS	human NSCLC cell lines NCI-H1299 and NCI-H1650	Inhibition of autophagy. Synergistic effect between α-hederin and Tax in NSCLC cell proliferation reduction and apoptosis induction. α-Hederin induced ROS accumulation in NSCLC cells.	[72]
α-hederin (Aldrich Chemical Co.)	Cell viability Nitrite assay Endotoxin assay RNA preparation and iNOS mRNA analysis by RT-PCR Transfection and luciferase and b-galactosidase assays	Peritoneal macrophages from pathogen free-BALB/C mice (female, 5 ± 7 weeks old)	Stimulation of NO release and upregulatation of nitric oxide synthase iNOS expression through NF-kB transactivation.	[73]
	Cell apoptosis assays *Measurement of intracellular glutathione and adenosine triphosphate* *ROS detection* *Western blot analysis*	Human SMMC-7721, HepG-2 and Huh-7 HCC cell lines xenograft tumor model. Male BALB/ c-nu/nu nude mice (4–6 wk old)	Induction of apoptosis of HCC cells Reduction of intracellular GSH and ATP levels. Induction of ROS accumulation. Disruption of mitochondrial membrane potential. Elevation of protein levels of Bax, cleaved caspase-3, cleaved caspase-9, apoptosis-inducing factor and cytochrome C, and deletion of Bcl-2 expression Inhibition of xenograft tumor growth *in vivo*.	[65]
Hedera helix	Cytotoxicity assay	human colon adenocarcinoma HT-29 cells	α-hederin at sub-IC_{50} cytotoxic concentrations enhanced 5-FU cytotoxicity about 3.3-fold. (widely prescribed 5-fluorouracil (5-FU) in a human colon adenocarcinoma model)	[74]
	CCK8 and colony formation assays	non-small cell lung cancer A549 cells A549 tumor xenograft mouse model of lung cancer	Cell proliferation inhibition Inhibition of glucose uptake and ATP generation and reduction of lactate production. Inhibition of hexokinase 2(HK2), glucose transporters 1(GLUT1), pyruvate kinase M2 (PKM2), lactate dehydrogenase A(LDHA), monocarboxylate transporter (MCT4), c-Myc, and hypoxia inducible factor-la(HIF-1x) protein expression. Inhibition of glycolysis by inhibiting glycolytic regulators. Inhibition of lung cancer growth *via* inhibiting glycolysis *in vivo*. The mechanism of glycolysis inhibition includes a-hederin inhibiting the expression of the glycolytic regulatory factors HIF-1α and c-Myc.	

4.3. Autophagy suppression

Autophagy is an important process in cell development, and it can have two opposite actions in tumor growth. In normal cells, autophagy participates as a survival mechanism to protect cells against damage factors such as the accumulation of oncogenic proteins, non-functional and damaged proteins and organelles, by facilitating their extracellular secretion. On the other hand, autophagy can promote tumor development by maintaining mitochondrial functions through the promotion of some essential metabolic substrates, as it is known that cancer cells face high pressure due to a lack of nutrients such as glucose. In this step, autophagy is involved in restoring cancer cells' development and metabolism through some processes such as the stabilization of mitochondrial functions and organelles and reusing substances. In this regard, the inhibition of autophagy is an important strategy to fight against cancer. But this approach can only be used with patients that reach a level in which autophagy is not involved in tumor inhibition. The data from the literature show that α-hederin could inhibit autophagy in some cancer cells. This inhibition is achieved by the alteration of lysosomal pH and the inhibition of cathepsin maturation [[27,66,72].

4.4. Inhibition of cell proliferation, migration, invasion, and metastasis

Migration, invasion, and metastasis play major roles in cancer progression. The main pathway involved in these phenomena is the STAT3 (signal transducer and activator of transcription 3), by activating MMP2. STAT3 can be activated by PAF and JAK-2. In addition, the ratio between E-cadherin and N-cadherin controls the metastasis of cancer cells. Decreased E-cadherin and increased N-cadherin, at the transcriptional and protein levels, promote metastasis. Interestingly, the data from the

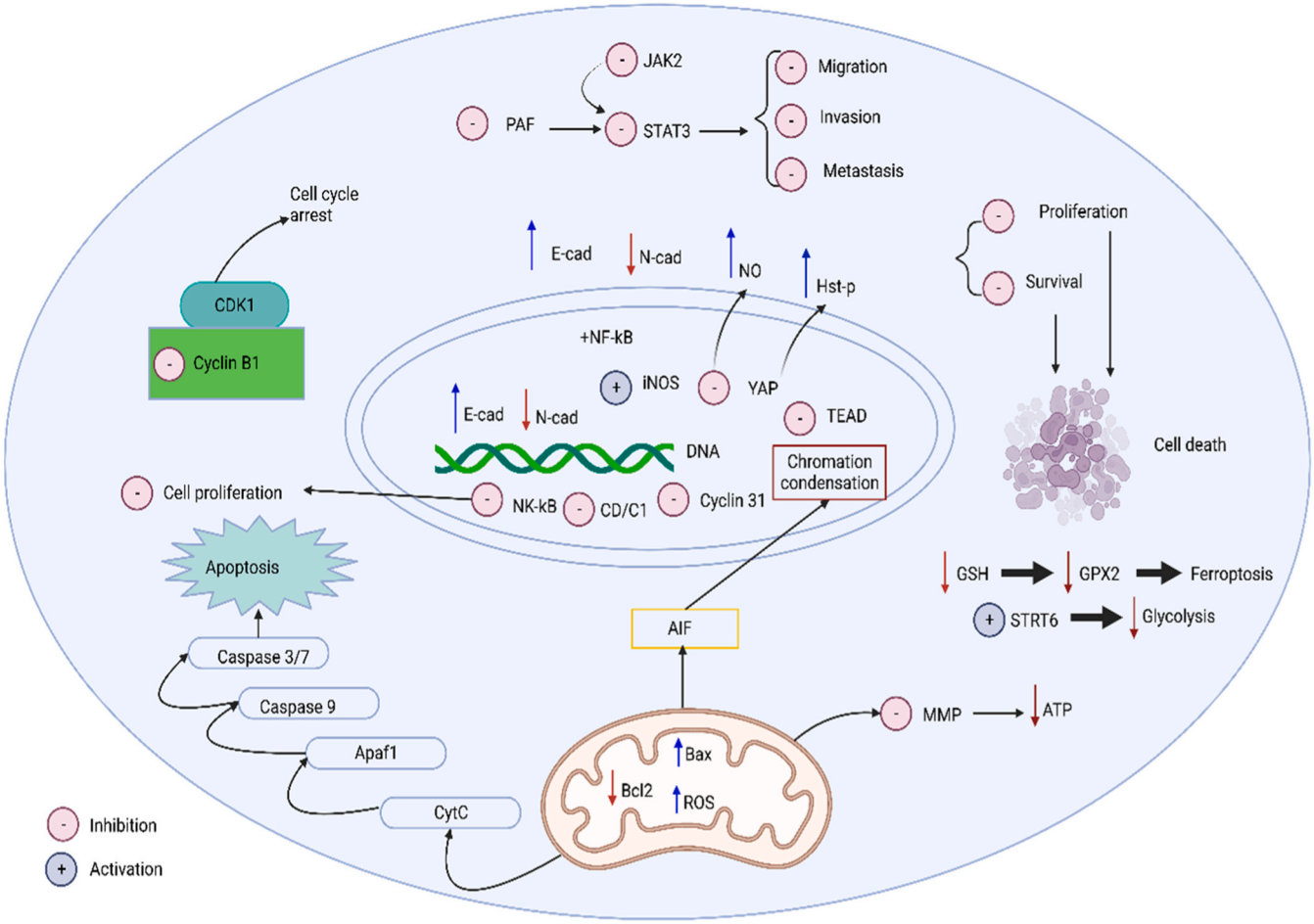

Fig. 2. Anticancer mechanisms of α-hederin. *JAK2: Janus kinase 2; STAT3: Signal transducer and activator of transcription 3; PAF: Platelet-activating factor; MMP2: mitochondrial membrane potentia; E-cad: E-cadherin; N-cad: N- cadherin; ERK: extracellular signal-regulated kinase; NF-kB:* Nuclear factor-kappa B*; YAP: yes-associated protein; Mst: mercaptopyruvate sulfurtransferase; TEAD: Transcriptional enhanced associate domain; Bcl-2:B-cell lymphoma 2: Bax: Bcl-2-*associated X *protein; ROS: Reactive oxygen species; Cyt C: Cytochrome C: Apaf-1: Apoptotic peptidase activating factor 1; AIF:* Apoptosis*-inducing factor; GSH:Glutathione;GPX2: glutathione peroxidase 2; GLUT1: Glucose transporter 1: iNOS: Inducible nitric oxide synthase; NO: Nitric oxide; MMP: Mitochondrial membrane potential.*

literature show that α-hederin inhibits cancer cell migration, invasion, and metastasis through PAF and JAK-2 inhibition, E-cadherin elevation, and N-cadherin depletion [66,68,69]. Cell proliferation is normally stimulated by the activation of transcriptional factor TEAD by YAP. This latter is activated when there is a low amount of Mst protein. α-Hederin has been shown to increase this protein, which causes YAP inhibition and as a result stops cancer cell proliferation [25,27,29,68,70].

4.5. Reduction of ATP generation

Cancer cells demand a high amount of energy due to their rapid growth. In this regard, targeting ATP production is a promising approach for cancer treatment. The main source of energy for cancer cells is glycolysis, which is controlled by some key enzymes and regulators such as HK2, PKM2, LDH, MCT4, GLUT1, cMyc, HIF1alpha, p53, Akt, and SIRT6. GLUT1 is involved in glucose uptake into the cell. HK is the essential and the initial catalytic enzyme of glycolysis which is highly expressed in tumor cells. Another key enzyme in glycolysis pathway is PKM2. It has been shown that this enzyme is overexpressed in tumor cells. MCT play an important role in the transport of pyruvate and lactate through the cell membrane. LDH catalyzes the reaction of pyruvate to lactate. With the intervention of the membrane protein MCT, lactate transported out of the cell, creating an acidic environment for tumor development. The data from the literature show that α-hederin can reduce the activity of glycolytic enzymes HK2, PKM2, and LDH, and membrane proteins GLUT1 and MCT4 in cancer cells. In addition, it was reported that α-hederin could inhibit the regulator of glycolysis HIF-1alpha, c-Myc, and SIRT6 [25,75].

5. Conclusion and future perspectives

Here, we have discussed the natural resources, anticancer activities, and mechanism insights of α-Hederin. The reported studies show that this bioactive compound can be found in different natural sources, particularly in medicinal plants. Moreover, biological and pharmacological investigations have shown that α-hederin has potential anticancer properties against several human cancers. Indeed, α-hederin exhibits different pharmacodynamic anticancer mechanisms, which make it an important drug candidate. However, other pharmacodynamic actions as well as pharmacokinetic parameters should be investigated in further studies. In addition, *in vivo* anticancer studies are required to validate the effects of α-hederin on animal models as well as to validate the safety of this compound.

Funding

The study was supported by the deputyship for research and innovation, Ministry of Education in Saudi Arabia for funding this research work through the project number: IFP22UQU4331128DSR166.

Ethical disclosures

The authors declare that no experiments were performed on humans for this study.

Confidentiality of data

The authors declare that they have no patient data used in this study and declare they have followed the protocols of their work center on the publication of data.

CRediT authorship contribution statement

Conceptualization: **Andi Hermansyah, Long Chiau Ming, Abdelhakim Bouyahya.** Methodology: **Andi Hermansyah, Long Chiau Ming, Abdelhakim Bouyahya.** Formal analysis: **Omar Belmehdi, Douae Taha, Jamal Abrini, Asaad Khalid, Andi Hermansyah, Long Chiau Ming, Abdelhakim Bouyahya, Alanood S. Algarni.** Original Draft Preparation: **Omar Belmehdi, Douae Taha, Jamal Abrini, Asaad Khalid, Ashraf N. Abdalla.** Writing – review & editing: **Andi Hermansyah, Long Chiau Ming, Abdelhakim Bouyahya.** Supervision: **Andi Hermansyah, Long Chiau Ming, Abdelhakim Bouyahya.** Project administration: **Omar Belmehdi, Douae Taha, Jamal Abrini, Asaad Khalid, Ashraf N. Abdalla, Alanood S. Algarni.** Funding acquisition: **Andi Hermansyah, Long Chiau Ming.** All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest..

Data availability

The data used to support the findings of this study are included within the article.

Acknowledgements

The authors extend their appreciation to the deputyship for research and innovation, Ministry of Education in Saudi Arabia for funding this research work through the project number: IFP22UQU4331128DSR166.

References

[1] A. Bouyahya, O. Belmehdi, A. Benjouad, R.A. El Hassani, S. Amzazi, N. Dakka, Y. Bakri, Pharmacological properties and mechanism insights of Moroccan anticancer medicinal plants: what are the next steps? Ind. Crops Prod. 147 (2020), 112198.
[2] A. Bouyahya, J. Abrini, Y. Bakri, N. Dakka, Screening phytochimique et évaluation de l'activité antioxydante et antibactérienne des extraits d'Origanum compactum, Phytothérapie 15 (6) (2017) 379–383.
[3] M. Butnariu, C. Quispe, J. Herrera-Bravo, J. Sharifi-Rad, L. Singh, N.M. Aborehab, A. Bouyahya, A. Venditti, S. Sen, K. Acharya, The pharmacological activities of Crocus sativus L.: a review based on the mechanisms and therapeutic opportunities of its phytoconstituents, Oxid. Med. Cell. Longev. 2022 (2022).
[4] T. Benali, K. Habbadi, A. Khabbach, I. Marmouzi, G. Zengin, A. Bouyahya, I. Chamkhi, H. Chtibi, T. Aanniz, E.H. Achbani, GC–MS analysis, antioxidant and antimicrobial activities of Achillea odorata subsp. pectinata and Ruta montana essential oils and their potential use as food preservatives, Foods 9 (5) (2020) 668.
[5] A. Bouyahya, O. Belmehdi, J. Abrini, N. Dakka, Y. Bakri, Chemical composition of Mentha suaveolens and Pinus halepensis essential oils and their antibacterial and antioxidant activities, Asian Pac. J. Trop. Med. 12 (3) (2019) 117–122.
[6] T. Benali, A. Bouyahya, K. Habbadi, G. Zengin, A. Khabbach, K. Hammani, Chemical composition and antibacterial activity of the essential oil and extracts of Cistus ladaniferus subsp. ladanifer and Mentha suaveolens against phytopathogenic bacteria and their ecofriendly management of phytopathogenic bacteria, Biocatal. Agric. Biotechnol. 28 (2020), 101696.
[7] I. Marmouzi, A. Bouyahya, S.M. Ezzat, M. El Jemli, M. Kharbach, The food plant Silybum marianum (L.) Gaertn.: phytochemistry, ethnopharmacology and clinical evidence, J. Ethnopharmacol. 265 (2021), 113303.
[8] A.S. Dagtas, R.J. Griffin, Nigella sativa extract kills pre-malignant and malignant oral squamous cell carcinoma cells, J. Herb. Med. 29 (2021), 100473.
[9] M. Jin, W. Zhang, Y. Xu, Y. Du, Q. Sun, W. Guo, L. Cao, H. Xu, Simultaneous determination of 12 active components in the roots of Pulsatilla chinensis using tissue-smashing extraction with liquid chromatography and mass spectrometry, J. Sep. Sci. 40 (6) (2017) 1283–1292.
[10] H.N. Pham, C.A. Tran, T.D. Trinh, N. Lan, N. Thi, H. Nhu, T. Phan, V.N. Le, N.H. Le, V.T. Phung, UHPLC-Q-TOF-MS / MS dereplication to identify chemical constituents of Hedera helix leaves in Vietnam 2022 (2022).
[11] W.G. Taylor, P.G. Fields, D.H. Sutherland, Fractionation of lentil seeds (Lens culinaris Medik.) for insecticidal and flavonol tetraglycoside components, J. Agric. Food Chem. 55 (14) (2007) 5491–5498.
[12] I. Bezruk, M. Marksa, V. Georgiyants, L. Ivanauskas, L. Raudone, Phytogeographical profiling of ivy leaf (Hedera helix L.), Ind. Crops Prod. 154 (July) (2020), 112713.
[13] A. Gepdiremen, V. Mshvildadze, H. Süleyman, R. Elias, Acute anti-inflammatory activity of four saponins isolated from ivy: alpha-hederin, hederasaponin-C, hederacolchiside-E and hederacolchiside-F in carrageenan-induced rat paw edema, Phytomedicine 12 (6–7) (2005) 440–444.
[14] L. Havlíková, K. Macáková, L. Opletal, P. Solich, Rapid determination of α-Hederin and Hederacoside C in extracts of hedera helix leaves available in the Czech Republic and Poland (1934578×1501000). Nat. Prod. Commun. 10 (9) (2015), 1934578×1501000
[15] P. Lorenz, M. Bunse, I. Klaiber, J. Conrad, T. Laumann-Lipp, F.C. Stintzing, D. R. Kammerer, Comprehensive phytochemical characterization of herbal parts from kidney vetch (Anthyllis vulneraria L.) by LC/MS n and GC/MS, Chem. Biodivers. 17 (10) (2020).
[16] J. Wang, H. Deng, J. Zhang, D. Wu, J. Li, J. Ma, W. Dong, α-Hederin induces the apoptosis of gastric cancer cells accompanied by glutathione decrement and reactive oxygen species generation via activating mitochondrial dependent pathway, Phytother. Res. 34 (3) (2020) 601–611.
[17] Q. Hu, Y.-Y. Chen, Q.-Y. Jiao, A. Khan, F. Li, D.-F. Han, G.-D. Cao, H.-X. Lou, Triterpenoid saponins from the pulp of Sapindus mukorossi and their antifungal activities, Phytochemistry 147 (2018) 1–8.
[18] İ. Gülçin, V. Mshvildadze, A. Gepdiremen, R. Elias, Antioxidant activity of saponins isolated from ivy: α-hederin, hederasaponin-C, hederacolchiside-E and hederacolchiside-F, Planta Med. 70 (06) (2004) 561–563.
[19] B. Majester-Savornin, R. Elias, A.M. Diaz-Lanza, G. Balansard, M. Gasquet, F. Delmas, Saponins of the ivy plant, Hedera helix, and their leishmanicidic activity, Planta Med. 57 (03) (1991) 260–262.
[20] J. Julien, M. Gasquet, C. Maillard, G. Balansard, P. Timon-David, Extracts of the ivy plant, hedera helix, and their anthelminthic activity on liver flukes, Planta Med. 51 (03) (1985) 205–208.
[21] S. Passi, N. Aligiannis, H. Pratsinis, A.L. Skaltsounis, I.B. Chinou, Biologically active Triterpenoids of Cephalaria ambrosioides roots, Planta Med. 75 (2009) 163–167.
[22] A. Adamska, J. Stefanowicz-Hajduk, J.R. Ochocka, Alpha-Hederin, the active Saponin of Nigella sativa, as an anticancer agent inducing apoptosis in the SKOV-3 cell line, Molecules 24 (16) (2019) 2958.
[23] L. Cheng, T.-S. Xia, Y.-F. Wang, W. Zhou, X.-Q. Liang, J.-Q. Xue, L. Shi, Y. Wang, Q. Ding, M. Wang, The anticancer effect and mechanism of α-hederin on breast cancer cells, Int. J. Oncol. 45 (2) (2014) 757–763.
[24] (cong fang) Y. Liu, L. Chen, Y. Luo, Y. Cui, N. Zhang, P. Liu, M. Zhou, Y. Xie, α-Hederin inhibits the growth of lung cancer A549 cells in vitro and in vivo by increasing SIRT6 dependent glycolysis, Review (2020).
[25] C. Fang, Y. Liu, L. Chen, Y. Luo, Y. Cui, N. Zhang, P. Liu, M. Zhou, Y. Xie, α-Hederin inhibits the growth of lung cancer A549 cells *in vitro* and *in vivo* by decreasing SIRT6 dependent glycolysis, Pharm. Biol. 59 (1) (2021) 11–20.
[26] D. Sun, W. Shen, F. Zhang, H. Fan, J. Tan, L. Li, C. Xu, H. Zhang, Y. Yang, H. Cheng, α -Hederin arrests cell cycle at G2/M checkpoint and promotes mitochondrial apoptosis by blocking nuclear factor- κ B signaling in colon cancer cells, BioMed. Res. Int. 2018 (2018) 1–11.
[27] J. Sun, Y. Feng, Y. Wang, Q. Ji, G. Cai, L. Shi, Y. Wang, Y. Huang, J. Zhang, Q. Li, α-hederin induces autophagic cell death in colorectal cancer cells through reactive oxygen species dependent AMPK/mTOR signaling pathway activation, Int J. Oncol. (2019).
[28] R. Tatia, C. Zalaru, O. Craciunescu, L. Moldovan, A. Oancea, I. Calinescu, Optimization of Triterpene saponins mixture with antiproliferative activity, Appl. Sci. 9 (23) (2019) 5160.
[29] J. Wang, D. Wu, J. Zhang, H. Liu, J. Wu, W. Dong, α-HederiN Induces Apoptosis of Esophageal Squamous Cell Carcinoma Via an Oxidative and Mitochondrial-dependent pathway, Dig. Dis. Sci. 64 (12) (2019) 3528–3538.
[30] F. Crespin, M. Calmes, R. Elias, C. Maillard, G. Balansard, High-performance liquid chromatographic determination of saponins fromHedera helix L. using a light-scattering detector, Chromatographia 38 (3–4) (1994) 183–186.
[31] S. Danloy, J. Quetin-Leclercq, P. Coucke, M.-Cl De Pauw-Gillet, R. Elias, G. Balansard, L. Angenot, R. Bassleer, "Effects of α-Hederin, a saponin extracted from hedera helix, on cells cultured in vitro, Planta Med. 60 (01) (1994) 45–49.
[32] B. Demirci, M. Goppel, F. Demirci, G. Franz, HPLC profiling and quantification of active principles in leaves of Hedera helix L. Pharmazie 59 (10) (2004) 770–774.
[33] R.M. Facino, M. Carini, P. Traldi, B. Pelli, B. Gioia, E. Arlandini, Confirmative assay and quantitative determination of 14 (1987) 187–194.
[34] Y. Gaillard, P. Blaise, A. Darré, T. Barbier, G. Pépin, An unusual case of death: suffocation caused by leaves of common ivy (Hedera helix). Detection of Hederacoside C, α-Hederin, and Hederagenin by LC—EI/MS-MS, J. Anal. Toxicol. 27 (4) (2003) 257–262.
[35] C. Greunke, A. Hage-Hülsmann, T. Sorkalla, N. Keksel, F. Häberlein, H. Häberlein, A systematic study on the influence of the main ingredients of an ivy leaves dry

extract on the β2-adrenergic responsiveness of human airway smooth muscle cells, Pulm. Pharmacol. Ther. 31 (2015) 92–98.
[36] S.A. Hussien, Z.J. Awad, Isolation and characterization of triterpenoid saponin hederacoside c. present in the leaves of Hedera helix L. cultivated in Iraq, Iraqi J. Pharm. Sci. 23 (2) (2014) 33–41.
[37] N. Kim, Y.J. Shin, S. Park, G. Yoo, Y. Kim, H.H. Yoo, S.H. Kim, Simultaneous determination of six compounds in Hedera helix L. using UPLC-ESI–MS/MS, Chromatographia 80 (7) (2017) 1025–1033.
[38] M. Mendel, M. Chłopecka, N. Dziekan, M. Wiechetek, The effect of the whole extract of common ivy (Hedera helix) leaves and selected active substances on the motoric activity of rat isolated stomach strips, J. Ethnopharmacol. 134 (3) (2011) 796–802.
[39] R. Tatia, L. Moldovan, I. Tarcomnicu, A.D. Raiciu, A. Gavrila, I. Calinescu, C. Zalaru, Methods of obtaining extracts from Hedera helix L. leaves and evaluation of the total saponins content, Priochem, Basel Switzerland, 2021, 56. MDPI, (2022).
[40] F. Delmas, C. Di Giorgio, R. Elias, M. Gasquet, N. Azas, V. Mshvildadze, G. Dekanosidze, E. Kemertelidze, P. Timon-David, Antileishmanial activity of three saponins isolated from Ivy, α-Hederin, β-Hederin and Hederacolchiside A 1, as compared to their action on mammalian cells cultured in vitro, Planta Med. 66 (04) (2000) 343–347.
[41] M. Himmelsbach, A. Weth, C. Böhme, M. Schwarz, P. Bräunig, W. Baumgartner, The plant hopper Issus coleoptratus can detoxify phloem sap saponins including the degradation of the terpene core, Biol. Open 5 (3) (2016) 252–255.
[42] O. Ridoux, C. Di Giorgio, F. Delmas, R. Elias, V. Mshvildadze, G. Dekanosidze, E. Kemertelidze, G. Balansard, P. Timon-David, In vitro antileishmanial activity of three saponins isolated from ivy, ?-hederin, ?-hederin and hederacolchiside A1, in association with pentamidine and amphotericin B, Phytother. Res. 15 (4) (2001) 298–301.
[43] İ. Gülçin, V. Mshvildadze, A. Gepdiremen, R. Elias, Antioxidant activity of saponins isolated from ivy: α-Hederin, Hederasaponin-C, Hederacolchiside-E and Hederacolchiside-F, Planta Med. 70 (6) (2004) 561–563.
[44] I. Botnick, W. Xue, E. Bar, M. Ibdah, A. Schwartz, D.M. Joel, E. Lev, A. Fait, E. Lewinsohn, Distribution of primary and specialized metabolites in Nigella sativa seeds, a spice with vast traditional and historical uses, Molecules 17 (9) (2012) 10159–10177.
[45] R. Keyhanmanesh, S. Saadat, M. Mohammadi, A.-A. Shahbazfar, M. Fallahi, The protective effect of α-Hederin, the active constituent of Nigella sativa, on lung inflammation and blood cytokines in ovalbumin sensitized Guinea pigs, Phytother. Res. 29 (11) (2015) 1761–1767.
[46] M.F.-A. Kulyar, R. Li, K. Mehmood, M. Waqas, K. Li, J. Li, Potential influence of Nagella sativa (Black cumin) in reinforcing immune system: a hope to decelerate the COVID-19 pandemic, Phytomedicine 85 (July 2020) (2021), 153277.
[47] S.S. Muthu Kumara, B.T.K. Huat, Extraction, isolation and characterisation of antitumor principle, α-Hederin, from the seeds of Nigella sativa, Planta Med. 67 (1) (2001) 29–32.
[48] M. Scholz, M. Lipinski, M. Leupold, H. Luftmann, L. Harig, R. Ofir, R. Fischer, D. Prüfer, K.J. Müller, Methyl jasmonate induced accumulation of kalopanaxsaponin I in Nigella sativa, Phytochemistry 70 (4) (2009) 517–522.
[49] R.G. Ruiz, K.R. Price, A.E. Arthur, M.E. Rose, M.J.C. Rhodes, R.G. Fenwick, Effect of soaking and cooking on the saponin content and composition of chickpeas (Cicer arietinum) and lentils (Lens culinaris), J. Agric. Food Chem. 44 (6) (1996) 1526–1530.
[50] M. Jin, W. Zhang, H. Jiang, Y. Du, W. Guo, L. Cao, H. Xu, UPLC-Q-TOF-MS/MS-guided dereplication of Pulsatilla chinensis to identify triterpenoid saponins, Phytochem. Anal. 29 (5) (2018) 516–527.
[51] V.U. Celenk, N.B. Sarikahya, S. Kirmizigul, Isolation and structural studies on saponins from three cephalaria species from Anatolia, Chem. Nat. Compd. 56 (1) (2020) 180–182.
[52] E. Bedir, N.J. Toyang, I.A. Khan, L.A. Walker, A.M. Clark, A new dammarane-type triterpene glycoside from Polyscias fulva, J. Nat. Prod. 64 (1) (2001) 95–97.
[53] T. Chen, D. Sun, Q. Wang, T. Zhou, J. Tan, C. Xu, H. Cheng, W. Shen, α-Hederin inhibits the proliferation of hepatocellular carcinoma cells via Hippo-Yes-Associated protein signaling pathway, Front. Oncol. 12 (2022) 1–12.
[54] D.W. Li, J.E. Hyun, C.S. Jeong, Y.S. Kim, E.B. Lee, Antiinflammatory activity of. ALPHA.-Hederin methyl ester from the alkaline hydrolysate of the butanol fraction of Kalopanax pictus Bark extract, Biol. Pharm. Bull. 26 (4) (2003) 429–433.
[55] J.M. Dinore, H.S. Patil, B.S. Dobhal, M. Farooqui, Phytochemical analysis by GC-MS, LC-MS complementary approaches and antimicrobial activity investigation of Vigna unguiculata (L.) Walp. leaves, Nat. Prod. Res. (2021) 1–7.
[56] D. Thi Thuy Linh, H. Thanh Duong, N. Tuan Hiep, P. Thanh Huyen, N. Minh Khoi, D. Doan Long, Simultaneous quantification of Hederacoside C and α-hederin in Hedera Nepalensis K.Koch using HPLC-UV, VNU J. Sci. Med. Pharm. Sci. 36 (3) (2020) 17–23.
[57] K. Foubert, F. Cuyckens, K. Vleeschouwer, M. Theunis, A. Vlietinck, L. Pieters, S. Apers, Rapid quantification of 14 saponins of Maesa lanceolata by UPLC–MS/MS, Talanta 81 (4–5) (2010) 1258–1263.
[58] B. Kim, J.W. Han, M. Thi Ngo, Q. Le Dang, J.-C. Kim, H. Kim, G.J. Choi, Identification of novel compounds, oleanane- and ursane-type triterpene glycosides, from Trevesia palmata: their biocontrol activity against phytopathogenic fungi, Sci. Rep. 8 (1) (2018) 14522.
[59] C. Lavaud, M.-L. Crublet, I. Pouny, M. Litaudon, T. Sévenet, Triterpenoid saponins from the stem bark of Elattostachys apetala, Phytochemistry 57 (3) (2001) 469–478.
[60] C. Pavei, S. Kaiser, S.G. Verza, G.L. Borre, G.G. Ortega, HPLC-PDA method for quinovic acid glycosides assay in Cat's claw (Uncaria tomentosa) associated with UPLC/Q-TOF–MS analysis, J. Pharm. Biomed. Anal. 62 (2012) 250–257.
[61] I. Podolak, P. Żmudzki, P. Koczurkiewicz, M. Michalik, P. Zajdel, A. Galanty, Minor triterpene saponins from underground parts of Lysimachia thyrsiflora: structure elucidation, LC-ESI-MS/MS quantification, and biological activity, 1934578×1300801, Nat. Prod. Commun. 8 (12) (2013), 1934578×1300801.
[62] R.G. Ruiz, K.R. Price, M.E. Rose, M.J.C. Rhodes, G.R. Fenwick, Determination of saponins in lupin seed (Lupinus Angustifolius) using high-performance liquid chromatography: comparison with a gas chromatographic method, J. Liq. Chromatogr. 18 (14) (1995) 2843–2853.
[63] L.-H. Yan, L.-Z. Xu, J. Lin, S.-L. Yang, Y.-L. Feng, Triterpenoid saponins from the stems of Clematis parviloba, J. Asian Nat. Prod. Res. 11 (4) (2009) 332–338.
[64] H.M. Zhong, C.X. Chen, X. Tian, Y.X. Chui, Y.Z. Chen: Clematis tangutica, 67, 484–488, 2001.
[65] J. Li, D.-D. Wu, J.-X. Zhang, J. Wang, J.-J. Ma, X. Hu, W.-G. Dong, Mitochondrial pathway mediated by reactive oxygen species involvement in α-hederin-induced apoptosis in hepatocellular carcinoma cells, WJG 24 (17) (2018) 1901–1910.
[66] D. Sun, W. Shen, F. Zhang, H. Fan, C. Xu, L. Li, J. Tan, Y. Miao, H. Zhang, Y. Yang, H. Cheng, α-Hederin inhibits interleukin 6-induced epithelial-to-mesenchymal transition associated with disruption of JAK2/STAT3 signaling in colon cancer cells, Biomed. Pharmacother. 101 (2018) 107–114.
[67] Y. Wu, D. Wang, Y. Lou, X. Liu, P. Huang, M. Jin, G. Huang, Regulatory mechanism of α-hederin upon cisplatin sensibility in NSCLC at safe dose by destroying GSS/GSH/GPX2 axis–mediated glutathione oxidation-reduction system, Biomed. Pharmacother. 150 (2022), 112927.
[68] Y. Liu, H. Lei, J. Ma, H. Deng, P. He, W. Dong, α-Hederin increases the apoptosis of cisplatin-resistant gastric cancer cells by activating mitochondrial pathway in vivo and vitro, OTT 12 (2019) 8737–8750.
[69] L. Cao, Y. Zhang, J. Mi, Z. Shi, Z. Fang, D. Jia, Z. Pan, P. Peng, α-Hederin inhibits the platelet activating factor-induced metastasis of HCC cells through disruption of PAF/PTAFR axis cascaded STAT3/MMP-2 expression, Pharmacol. Res. 178 (2022), 106180.
[70] T. Chen, D. Sun, Q. Wang, T. Zhou, J. Tan, C. Xu, H. Cheng, W. Shen, α-Hederin inhibits the proliferation of hepatocellular carcinoma cells via Hippo-Yes-Associated protein signaling pathway, Front. Oncol. 12 (2022), 839603.
[71] C. Gauthier, J. Legault, K. Girard-Lalancette, V. Mshvildadze, A. Pichette, Haemolytic activity, cytotoxicity and membrane cell permeabilization of semi-synthetic and natural lupane- and oleanane-type saponins, Bioorg. Med. Chem. 17 (5) (2009) 2002–2008.
[72] Y. Zhan, K. Wang, Q. Li, Y. Zou, B. Chen, Q. Gong, H. Ho, T. Yin, F. Zhang, Y. Lu, W. Wu, Y. Zhang, Y. Tan, B. Du, X. Liu, J. Xiao, The novel autophagy inhibitor alpha-Hederin promoted paclitaxel cytotoxicity by increasing reactive oxygen species accumulation in non-small cell lung cancer cells, IJMS 19 (10) (2018) 3221.
[73] H.G. Jeong , C.Y. Choi: Expression of inducible nitric oxide synthase by a-Hederin in macrophages. Planta Med.
[74] S.-S. Bun, R. Elias, B. Baghdikian, J. Ciccolini, E. Ollivier, G. Balansard, "α -hederin potentiates 5-FU antitumor activity in human colon adenocarcinoma cells, Phytother. Res. 22 (10) (2008) 1299–1302.
[75] H. Wang, B. Wu, H. Wang, Alpha-hederin induces the apoptosis of oral cancer SCC-25 cells by regulating PI3K/Akt/mTOR signaling pathway, Electron. J. Biotechnol. 38 (2019) 27–31.