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Chemistry and biological activities of *Artemisia judaica:* A mini review

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Abstract

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Artemisia judaica L. is widely spread in the desert and coast of the Mediterranean region. Traditionally, it had been used as a vermifuge, stomachic, sedative, antispasmodic, diabetes, fungal infections and arthritis. It is strongly aromatic, with bushy herbs, woody bases and sturdy spreading branches, covered by woolly hairs, crowded and short leaves, heads are made of tubular florets. Recently, *A. judaica* gained attention around the world because of its therapeutic and biological activities such as anti-inflammatory, analgesic, anti-oxidant activity and high potential antiangiogenic activity. In this review, we summarize the most important chemical constituents and biological activities *A. judaica*.

Keywords: *Artemisia judaica*; chemical constituents; biological activities.

1. Introduction:

Artemisia judaica L. (Arabic name: Shih Balady) is a perennial small shrub belongs to family Asteraceae. It is strongly aromatic, with bushy herbs, woody bases and sturdy spreading branches, covered by woolly hairs, with grayish dissected, crowded and short leaves, heads are rounded, crowded and made of tubular florets (Figure 1). A. *judaica* L. is widely spread in the desert and coast of the Mediterranean region and some middle eastern counties like Jordan, Saudi Arabia, Algeria and Sinai Peninsula in Egypt. (Van Wyk & Wink, 2004; Dob & Chelghoum, 2006; Abu-Darwish et al., 2016).

It is widely used by Bedouins in the traditional medicine as a vermifuge, stomachic, sedative, antispasmodic (**Dob & Chelghoum, 2006**) and to relieve ear infections, coughing, and external wounding (**Moharram** *et al.*, **2021**). It is also recommended for enhancing eyesight and capillary

strength, also, in the treatment of skin disorders, weak immune systems, gastrointestinal disorders, diabetes, fungal infections, arthritis. Furthermore, it can be used for cardiovascular health and to decrease risk of atherosclerosis (Batanouny *et al.*, 1999; Liu *et al.*, 2004; Abd-Elhady, 2012; Abu-Darwish *et al.*, 2016).

A. judaica also showed many biological activities such as anti-blastocystis (Mokhtar et al., 2019), anti-inflammatory, analgesic, and antipyretic (Batanouny et al., 1999), anti-oxidative activity (El-Massry et al., 2002) and high potential and selective antiangiogenic activity (Zihlif et al., 2012).

Phytochemical investigation of *A. judaica* revealed presence of many bioactive compounds, such as flavonoids (**Saleh** *et al.*, **1987; Moharram** *et al.*, **2021**), sesquiterpene lactones (**Khafagy** *et al.*, **1988**), phenolic acids (**Allam** *et al.*, **2019**), sterols, triterpenes (**Abd-Alla** *et al.*, **2014**) and bitter principle (Saber & Khafagy, 1958).

2. Phytochemical constituents reported in *Artemisia judaica*

A review on the phytochemical compounds and the pharmacological activities of *Artemisia judaica* was done and it revealed that the chemical compounds

isolated and identified from the *A. judaica* belong to various chemical classes including sterols, triterpenes, sesquiterpenes, flavonoids, phenolic acids, and phenolic acids derivatives, phenolic glycosides, alkaloids along with many other miscellaneous compounds involved in *A. judaica*'s essential oils as summarized in the following tables (**1-6**).

Compound Name	Compound Structure	Reference
β-Setosterol	HO HO	(Abd-Alla <i>et al.</i> , 2014)
β-Amyrin		(Abd-Alla <i>et al.</i> , 2014)
Lupeol		(Abd-Alla <i>et al.</i> , 2014)
Taraxerol acetate		(Abd-Alla <i>et al.</i> , 2014)

Table 1: Sterols and triterpenoids:

Compound Name	Compound Structure	Reference
Vulgarin		(Abd-Alla <i>et al.</i> , 2014)
Judaicin		(Khafagy <i>et al.</i> , 1988)
1-epi-erivanin		(Khafagy <i>et al.</i> , 1988)
1-epi-isoerivanin	HOWING	(Khafagy <i>et al.</i> , 1988)
13-O desacetyl eudesma- afraglaucolide	AcO OH	(Khafagy <i>et al.</i> , 1988)
13-O-desacetyl-1α- hydroxy-afraglaucolide	HO ACO O O O O O O	(Khafagy <i>et al.</i> , 1988)

Table 2: Sesquiterpenes

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Table 3: Flavonoids:

Compound Name	Compound Structure	Reference
Luteolin	HO OH OH OH OH	(Saleh <i>et al.</i> , 1987; Moharram <i>et al.</i> ,2021)
Luteolin 3'-glucoside	HO OH O	(Saleh <i>et al.</i> , 1987)
Luteolin 4'-glucoside		(Saleh <i>et al.</i> , 1987)









Cirsimaritin	H ₃ CO H ₃ CO OH OH	(Saleh <i>et al.</i> , 1987; Moharram <i>et al.</i> ,2021)
Eupatilin	HO H ₃ CO OH OH OH	(Saleh <i>et al.</i> , 1987)
Cirsilineol	H ₃ CO H ₃ CO H ₃ CO OH OH	(Saleh <i>et al.</i> , 1987)
Kaempferol	НО ОН ОН	(Allam <i>et al.</i> , 2019)
Kaempferol 3-O- rutinoside		(Allam <i>et al.</i> , 2019)
Diosmetin	HO OH OH OH OH	(Moharram <i>et al.</i> ,2021)



Neoiso-schaftoside	(Saleh <i>et al.</i> , 1987)
Isovitexin	(Moharram <i>et al.</i> ,2021)

Table 4: Phenolic acids derivatives and glucosides

Compound Name	Compound Structure	Reference
Trans-cinnamic acid	ОН	(Allam <i>et al.</i> , 2019)
Trans-3- hydroxycinnamic acid	НО ОН	(Allam <i>et al.</i> , 2019)
<i>para-</i> coumaric acid	но	(Allam <i>et al.</i> , 2019)
Resveratrol	но ОН	(Allam <i>et al.</i> , 2019)
Resveratrol 3-O- glucoside	HO HOW OH OH	(Allam <i>et al.</i> , 2019)



Table 5: Alkaloids:

Compound Name	Compound Structure	Reference
Pterin-6-carboxylic acid	HO NH NH2 O O O	(Elsharkawy <i>et al.</i> , 2017)
Dasycarpidan-1- methanol acetate		(Elsharkawy <i>et al.</i> , 2017)
Aspidospermidin-17-ol	OH NH	(Elsharkawy <i>et al.</i> , 2017)
Pseudosolasodine diacetate		(Elsharkawy <i>et al.</i> , 2017)

Compound Name	Compound Structure	Reference
Spathulenol		(El-Massry <i>et al.</i> , 2002; Abdelgaleil <i>et al.</i> , 2008; Abu-Darwish <i>et al.</i> , 2016)
Piperitone		(El-Massry <i>et al.</i> , 2002; Abdelgaleil <i>et al.</i> , 2008; Abu-Darwish <i>et al.</i> , 2016)
β-eudesmol	ОН	(Al-Wahaibi <i>et al.</i> , 2020)
Trans-ethyl cinnamate		(El-Massry <i>et al.</i> , 2002; Abdelgaleil <i>et al.</i> , 2008; Abu-Darwish <i>et al.</i> , 2016)
Cis-ethyl cinnamate		(El-Massry <i>et al.</i> , 2002)
Camphor		(Abu-Darwish <i>et al.</i> , 2016)
Ethyl-3-phenyl propionate		(El-Massry <i>et al.</i> , 2002)

Table 6: Miscellaneous compounds in essential oils:



3- Biological activities reported in

Artemisia judaica:

Studies on *Artemisia judaica* revealed that it possesses a wide range of biological activities including anti-oxidant, antimicrobial, strong

repellent, antifeedant, anthelmintic anti-Blastocystis, anti-diabetic antihyperglycemic, antihyperlipidemic, anti-inflammatory, antiangiogenic and cytotoxic activities as summarized in **Table 7**.

I- Anticancer activity		
Active Compounds / extracts	Details	Reference
Ethanolic extract	<i>In-vitro</i> potent selective antiangiogenic activity against HUVEC cells.	(Zihlif et al., 2012)
Thujone, a monoterpene in <i>A. judaica</i> essential oil	Decreases tumor cell viability and shows a potent <i>in-vitro</i> anti- proliferative, proapoptotic and anti-angiogenic effects and promotes the regression of neoplasia and inhibits the angiogenic markers <i>in-vivo</i> .	(Elansary <i>et al.</i> , 2018; Torres <i>et al.</i> , 2016)
Cirsimaritin flavonoid	Potentially useful as an anti-metastatic agent and can <i>in-vitro</i> inhibit angiogenesis via downregulation of VEGF, p-Akt and p-ERK in MDA-MB-231 breast cancer cells.	(Park et al., 2017)
β-Eudesmol, a sesquiterpene in A. judaica essential oil	<i>In-vitro</i> inhibit proliferation of HeLa, SGC-7901, and BEL-7402 cell lines in a time- and dose-dependent manner. <i>In-vivo</i> significantly inhibit H22 and S180 mouse tumor growth via angiogenesis inhibition.	(Ma et al., 2008; Nigam et al., 2019;

Table 7: Biological activities reported in Artemisia judaica:

The ethanolic extract and essential oil	Improve <i>in-vivo</i> experimentally-induced prostatic hyperplasia progression in rats via inhibiting prostatic cell proliferation, angiogenesis and inflammation.	(Al-Trad <i>et al.</i> , 2020)
Methanolic extract	Remarkable <i>in-vitro</i> cytotoxic activity against HepG2, MCF-7 and LoVo cell lines.	(Nasr <i>et al.</i> , 2020)
Methanolic extract	Strong <i>in-vitro</i> cytotoxicity and antiproliferative effect in HepG2 cell line via induction of apoptotic process modulated by different tumor suppressor genes.	(Al-Senosy <i>et al.</i> , 2021)
Cirsimaritin flavonoid	Significantly can inhibit the proliferation of squamous lung cancer cells (NCIH-520) via apoptosis and inhibition of (ODC and CATD), the targeted enzymes involved in cancer cell proliferation and metastasis.	(Pathak <i>et al.</i> , 2021)
Methanolic extract of leaves	Can cause <i>in-vitro</i> cell death via activating tumor suppressor proteins that mediates several antiproliferative processes including apoptosis in HepG2 and A549 cell line.	(Younes <i>et al.</i> , 2022)
Methanolic extract of stem	High <i>in-vitro</i> cytotoxic activity against HepG2, moderate cytotoxic activity against HCT116 cell lines via activating tumor suppressor proteins that mediates several antiproliferative processes including apoptosis.	(Younes et al., 2022)
II- Antimicrobial	activity	
Artemisinin sesquiterpene lactone	Antimicrobial effectiveness against gram-positive bacteria (<i>Staphylococcus aureus</i> , <i>Bacillus thuringiensis</i> and <i>Bacillus subtilis</i>) and Gram-negative strain (<i>Salmonella sp.</i>).	(Appalasamy <i>et al.</i> , 2014)
The essential oil	High antibacterial activity against Gram-positive bacteria; Micrococcus flavus (ATCC 10240), Listeria monocytogenes (NCTC 7973)	(Janacković <i>et al.</i> , 2015)
The essential oil	High antifungal potential against <i>Aspergillus versicolor</i> (ATCC 11730), <i>Aspergillus ochraceus</i> (ATCC 12066) <i>Aspergillus niger</i> (ATCC 6275) <i>Penicillium funiculosum</i> (ATCC 36839) and <i>Penicillium ochrochloron</i> (ATCC 9112)	(Janacković <i>et al.</i> , 2015)
The essential oil	Antifungal activity against yeast (<i>Cryptococcus neoformans</i>), Aspergillus species: <i>Aspergillus niger</i> , <i>Aspergillus fumigatus</i> and Dermatophytes: (<i>Trichophyton rubrum</i> , <i>T. verrucosum</i> , <i>Microsporum canis FF1</i> , <i>M. gypseum</i> , and <i>Epidermophyton</i> <i>floccosum</i>).	(Abu-Darwish <i>et al.</i> , 2016)
The essential oil	Strong antibacterial activity against Gram-positive bacteria (Staphylococcus aureus, Methycillin resistant staphylococcus aureus (MRSA), Enterococcus faecalis ATCC 29212, Bacillus subtilis ATCC 6633, coagulase negative staphylococcus) and Gram-negative bacteria (Acinetobacter baumannii).	(Benmansour <i>et al.</i> , 2016)
Piperitone a monoterpene in <i>A. judaica</i> essential oil	AntibacterialactivityagainstGram-positivebacteria(Staphylococcus aureus).Antifungal activity against Aspergillus flavus.	(Mahboubi <i>et al.</i> , 2008; Benmansour <i>et al.</i> , 2016)
The essential oil	Antimicrobial effectiveness against gram-positive bacteria <i>Streptococcus agalactiae</i> and <i>Staphylococcus aureus</i> .	(Guetat <i>et al.</i> , 2017)
The aqueous extract Methanol and ethyl acetate extracts	Effective against <i>Escherichia coli</i> and <i>Proteus vulgaris</i> . Effective against <i>Escherichia coli</i> and <i>Pseudomonas aeruginosa</i> .	(Allam <i>et al.</i> , 2019)
The essential oil	Antibacterial activity against Gram-positive bacteria Streptococcus pneumoniae, Bacillis subtilis and Gram-negative bacteria Escherichia coli. Anti-fungal activity against some human pathogens (Aspergillus fumigates, Syncephalastrum racemosum, Geotricum candidum, Candidaalbicans).	(Al-Wahaibi <i>et al.</i> , 2020)

Methanolic extract	Antimicrobial effectiveness against gram-positive bacteria Staphylococcus aureus (ATCC 25923) and Enterococcus. faecalis (ATCC 29212)	(Nasr <i>et al.</i> , 2020)
The essential oil	Antibacterial activity against Gram-positive bacteria (<i>Bacillus cereus</i> ATCC 10876) and Gram-negative bacteria (<i>Salmonella Typhimurium</i> ATCC 13311).	(Mohammed <i>et al.</i> , 2022)
The essential oil	Antifungal activity was observed against <i>Candida albicans</i> ATCC 10231 and <i>Aspergillus niger</i> ATCC 6275.	(Mohammed <i>et al.</i> , 2022)
Leaves and stem methanolic extracts	Good antimicrobial activity against the Gram-positive bacteria (<i>Staphylococcus aureus</i>) and the Gram-negative bacteria (<i>Proteus vulgaris</i>)	(Younes et al., 2022)
III- Insecticidal a	ctivity	
The essential oil	Strong repellent effect on against the cowpea weevil, <i>Callosobruchus maculatus</i> (Fab.) (Coleoptera: Bruchidae).	(Abd-Elhady, 2012)
IV- Antioxidant a	ctivity	
The volatile oil (high content of trans-ethyl cinnamate & ethyl-3- phenyl propionate)	Significant antioxidant activity observed via decreasing peroxidation in <i>in-vitro</i> in linoleic acid assay. Significant radical scavenging activity in DPPH assay.	(El-Massry <i>et al.</i> , 2002)
Ethyl acetate extract	Strong <i>in-vitro</i> radical scavenging activity in DPPH (2,2-Diphenyl-1-Picrylhydrazyl) Scavenging Activity assay.	(Abd-Alla et al., 2014)
Methanolic extract	Powerful <i>in-vivo</i> free radical scavenging and protective activity against Doxorubicin-Induced toxicity in Mice with significant decrease in DNA damage and the histopathological lesions.	(Ahmed <i>et al.</i> , 2017)
Methanolic extract	Significant reduction in the rate of DNA fragmentation and lipid peroxidation levels in liver tissues. Significant reduction in all types of chromosomal aberrations in both bone marrow and spermatocyte cells as a protective effect as antioxidant in Doxorubicin-Induced toxicity in Mice <i>in-vivo</i> .	(Ahmed <i>et al.</i> , 2018)
The essential oil	Notable antioxidant activity in a time and concentration dependent manner <i>in-vitro</i> measured by DPPH (2,2-Diphenyl-1-Picrylhydrazyl) Scavenging Activity.	(Geesi <i>et al.</i> , 2018)
Methanolic extract Ethyl acetate extract Aqueous extract	 Methanolic extract showed the highest total antioxidant capacity (TAC). Methanolic and ethyl acetate extracts showed high scavenging activity in a concentration-dependent manner by DPPH• Radical Scavenging Activity. Methanolic and ethyl acetate extracts showed the highest activity to quench ABTS•+ was concentration dependent manner. Methanolic extract showed highest reducing power activity in the RPA assay. Ethyl acetate extract showed highest antioxidant activity in β-carotene/linoleic acid bleaching activity assay. 	(Allam <i>et al.</i> , 2019)
Hydro- methanolic extract	Remarkable antioxidant activity in- vitro by scavenging DPPH radicals in a dose-dependent manner.	(Bhat et al., 2019)
Ethanolic extract	Significant increase in the activities of antioxidant enzymes (glutathione peroxidase (GPx) and glutathione reductase (GR)) in renal and hepatic tissues. Significant decline in Nitric oxide (NO) levels in hepatic and renal tissues. Significant decrease in lipid peroxidation (LPO) with elevated glutathione (GSH) in renal tissue in high-fat diet/streptozotocine-induced diabetic rats <i>in-vivo</i> model.	(Albasher <i>et al.</i> , 2020)

The essential oil	The oils obtained from natural drying methods (Shade drying and Sun drying) exhibited higher DPPH and ABTS radical scavenging effect than the obtained from the artificial drying methods due to their high content of Oxygenated monoterpenes in their essential oils.	(Al-Qudah <i>et al.</i> , 2021)
Piperitone Ethyl cinnamate Camphor Components of <i>A. judaica</i> essential oil	Noticeable reducing power and antioxidant activity due to presence in relatively high concentrations.	(El-Massry <i>et al.</i> , 2002; Cheraif <i>et al.</i> , 2020; Mohammed <i>et al.</i> , 2022)
The essential oil	Antioxidative activity measured <i>in-vitro</i> by Total Antioxidant Capacity (TAC), DPPH (2,2-Diphenyl-1-Picrylhydrazyl) Scavenging Activity (DPPH-SA), Ferric Reducing Antioxidant Power (FRAP), Metal Chelating Activity Assay (MCA) assays. <i>In-vivo</i> Antioxidative activity measured in induced second-degree burn on female rats with significant increase in Superoxide dismutase and Catalase antioxidant markers levels. This action attributed to high proportion of oxygenated monoterpenes and cinnamate derivatives.	(Mohammed <i>et al.</i> , 2022)
V- Anti-Inflamma	atory activity	
The essential oil	Significant anti-inflammatory potential by inhibition of nitric oxide (NO) production stimulated by lipopolysaccharides (LPS) in macrophage cell line (Raw 264.7).	(Abu-Darwish <i>et al.</i> , 2016)
Ethanolic extract	Reverse the inflammatory reactions by significant decrease in Tumor necrosis factor- α (TNF- α) levels in the liver and kidney tissues of high-fat diet/streptozotocine-induced diabetic rats <i>invivo</i> model.	(Albasher <i>et al.</i> , 2020)
Aqueous methanol extract	Inhibition of the paw edema as an anti-inflammatory effect in carrageenan-induced paw edema in rats <i>in-vivo</i> .	(Moharram <i>et al.</i> ,2021)
The essential oil	Remarkable anti-inflammatory effect measured in-vivo in induced second-degree burn on female rats with significant reduced in the pro-inflammatory marker TNF- α and augmented pro-angiogenic/anti-inflammatory TGF-b1 and IL-10 levels. This action attributed to high proportion of oxygenated monoterpenes and cinnamate derivatives.	(Mohammed <i>et al.</i> , 2022)
VI- Antidiabetic a	activity	
Hydro- methanolic extract	Remarkable <i>in-vitro</i> hypoglycemic effect by its ability of inhibition of pancreatic α -amylase, intestinal α -glucosidase and dipeptidyl peptidase IV (DPP IV) in a dose dependent manner which can attribute to manage type 2 diabetes.	(Bhat et al., 2019)
Ethanolic extract	Remarkable decrease in the glucose level with notable increase in the insulin level in high-fat diet/streptozotocine-induced diabetic rats <i>in-vivo</i> model.	(Albasher <i>et al.</i> , 2020)
Aqueous	Significant decrease in serum glucose level of diabetic rats	(Moharram et al.,2021)
VII- Henatorenal	notective activity	l
Ethanolic extract	Remarkable decrease in serum ALT, creatinine, urea, and uric acid levels as serum markers of hepatorenal dysfunction in high-fat diet/streptozotocine-induced diabetic rats <i>in-vivo</i> model.	(Albasher <i>et al.</i> , 2020)
VIII- Renal prote	ctive activity	
Ethyl acetate extract Petroleum ether extract Methanolic extract	Remarkable <i>in-vivo</i> renal protective activity in renal hyperlipidemic (fed a high fat diet) and hyperglycemic rats (induced by high fat diet and low doses of streptozotocin (STZ)).	(Abd-Alla <i>et al.</i> , 2014)

IX- Hepatoprotective activity		
Aqueous methanol extract	Significant reduction in serum levels of ALT, AST and nitrite as a hepatoprotective effects in a CCl4-induced chronic hepatic damage model in rats <i>in-vivo</i> .	(Moharram <i>et al.</i> ,2021)
X- Hypolipidemic effect		
Ethanolic extract	Significant reduction in serum triglycerides ang low density lipoprotein levels in high-fat diet/streptozotocine-induced diabetic rats <i>in-vivo</i> model.	(Albasher et al., 2020)
XI- Antispasmodic activity		
Cirsimaritin flavonoid	Remarkable inhibitory effect against spasmogens (Histamine-, barium chloride- and acetyicholine-) induced contractions in isolated Guinea-pig ileum.	(Abdalla & Zarga, 1987)
XII- In-Vivo Skin Burn Wound Healing		
The essential oil	Healing of burn wound measured morphologically and histologically <i>in-vivo</i> in induced second-degree burn on female rats with disappearance of edema, increased collagen, fibroblast, neovascularization and decreased inflammation. This action attributed to high proportion of oxygenated monoterpenes and cinnamate derivatives.	(Mohammed <i>et al.</i> , 2022)
XIII- Anti-Blastocystis activity		
Ethanolic extract <i>n</i> -hexane fraction Dichloromethane fraction Ethyl acetate fraction	Promising anti-Blastocystis potential against Different subtypes of Blastocystis.	(Mokhtar <i>et al.</i> , 2019)
XIV- Anti-nociceptive and Antipyretic activity		
Aqueous methanol extract	Significant analgesic activity observed by decrease of number of writhes using acetic acid-induced writhing method <i>in-vivo</i> in rats. Significant decrease in the rats' body temperature as the hyperpyrexia was induced via i.m. injection of yeast suspension.	(Moharram <i>et al.</i> ,2021)

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