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Ajuga iva L.: An Overview of Phytochemical Profile and Biological Functionalities

Laila Lahrizi[1], Faouzi Errachidi[1], Houria Nekhla[1], Lahsen El Ghadraoui[1]

[1]*Laboratory of Functional Ecology and Environmental Engineering, Department of Biology, Faculty of Science and Technology, Sidi Mohamed Ben Abdellah University, Fes, Morocco*

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ABSTRACT

Ajuga iva L. is a naturally growing plant in different locations around the world with multiple ethnopharmacological uses. The development of experimental research methods permits exploration and confirmation of the biological properties of *Ajuga iva*. These biological activities are highly affected by several factors, including the geographical origin of the plant, extraction method, and experimental model. This review collects traditional and modern knowledge regarding the phytochemical composition, pharmacological activities, and toxicological investigations of *Ajuga iva*. Different extracts prepared using several solvents and extraction methods have been proven to have considerable antioxidant, antidiabetic, antimicrobial, and anti-inflammatory activities in vitro and in vivo. Several bioactive compounds have been identified in *Ajuga iva* collected from different locations worldwide, including phenolic acids, flavonoids, steroids, terpenoids, and fatty acids, which show various pharmacological activities. The recorded toxicity studies revealed that *Ajuga iva* is safe and has many folk medicine uses for relieving symptoms of several diseases.

1. Introduction

Medicinal and aromatic plants constitute an important component of the human diet. They are widely appreciated by different populations worldwide. Before the discovery of industrial medication, herbs were and remain an exhaustible source of natural medicine for diverse human diseases [1,2]. In fact, many ethnopharmacological studies have confirmed the traditional use of aromatic and medicinal plants for treating diabetes, obesity, and inflammation [3–5]. Research on the active ingredients revealed different active compounds, including phenolic acids, flavonoids, terpenoids, organic acids, vitamins, and minerals in *Ajuga iva* [6,7]. The advantages of these chemicals extend beyond plant defense against biotic and abiotic threats to the regulation of some physiological traits in vivo [8–13]. Previous research results showed that the major pillars of active compounds have antioxidative and antiinflammatory activities, which afford ethnopharmacological activities to limit disease progression and pathogenesis [14].

Ajuga iva (L.) is one of the most well-known medicinal plants belonging to the Lamiaceae family. It has a long folk medicinal history and occupies an important position in the Moroccan traditional pharmacopeia because of its remarkable antidiabetic, antiobesity, antiinflammatory, and anticancer activities [15,16]. The use of homemade *A. iva* preparations for the treatment of hyperglycemia, hypertension, diabetes, headaches, fever, rheumatism, and other conditions dates back thousands of years [3,5]. Experimental studies have shown that the *A.iva* L. extract exhibited a remarkable antidiabetic effect [17–19]. It also enhances the antioxidant defense system by increasing the activities of glutathione peroxidase, glutathione reductase, and superoxide dismutase in diabetic subjects [20]. The beneficial effects of *A. iva* L. also include

∗ Corresponding author.; e-mail: lahrizilaila12@gmail.com
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antimicrobial effects against different pathogenic microorganisms [7], control of metabolic disorders in diabetic subjects [19], inhibitory effects against carbohydrate-hydrolyzing enzymes [21], and organ protective effects against toxic agents [22]. The biological functionalities of *A. iva* L. are highly related to its phytochemical composition, which is controlled by environmental conditions [7].

This review was designed to itemize the chemical composition of *A. iva* L. and its scientifically approved biological activities.

1. Methodology

Different electronic databases were checked to collect all references used to prepare the current review, such as Google Scholar, Springer, Science Direct, and MDPI. We assured our research using the following keywords: *Ajuga iva* chemical composition, and biological properties in vitro and in vivo. A total of 161 articles collected were examined for their relevance and scientific soundness, and 89 articles were selected to prepare this article review.

2. Plant description

Ajuga iva belongs to the Lamiaceae family. It is a herbaceous plant that is frequently encountered in forest clearings, pastures, uncultivated fields, and siliceous rocky areas of plains, and mountains [23]. Ajuga species are particularly abundant in the Moroccan Middle Atlas and more particularly in the Timahdite region (33°14'24" N 5°01'38" W) (Figure 1). AI can grow in arid places, stony hillsides, and at the edge of fields in the Mediterranean region in Southern Europe, North Africa, and the Canary Islands [24].

Fig. 1. Image of *Ajuga iva*

It is a perennial plant of small size, ranging from 5 to 10 cm, usually hairy-whitish, having a bitter taste, often with musky odor, whose green stems are spread out and rambling, woody toward their base, with recumbent and rectified branches. Its green leaves are linear, their size varies from 14 to 25 mm in length and are dense and covered with down; they are 5 to 10 times longer than broad, have no petioles, and are whole or with some teeth upwards. Its purpuric flowers bloom from May to October. The plant perpetuates itself with buds that are born at the base of the woody stems. Sometimes, although its corolla and stamens do not develop, its flowers produce fruits with well-conformed seeds because their stigmas are pollinated by the pollen of other flowers. The flowering period is from May to June [24].

AI is commonly called in Arabic: Chendgoura, in Berber: Touftelba, and in English: Herb ivy, Musky bugle. The systematic of the species is as follows [25]:

Kingdom: Plant
Phylum: Spermaphytes
Subphylum: Angiosperms
Class: Dicotyledons
Order: Lamiaceae / Tubiflorae
Family: Lamiaceae
Genus: Ajuga
Species: *Ajuga iva* (L.) Schreb

3. Extraction techniques

Medicinal plants contain several biologically active compounds. The right extraction method for these active compounds is a determinant factor for predicting the biological activities of the selected extract [26]. Herbal extract preparation includes different extraction techniques, e.g., infusion, maceration, percolation, decoction, reflux extraction, soxhlet extraction, pressurized liquid extraction, supercritical fluid extraction, ultrasound-assisted extraction, microwave-assisted extraction, pulsed electric field extraction, enzyme-assisted extraction, and hydrodistillation [27]. This section of the current review presents different extraction techniques used to prepare *A. iva* extracts.

3.1. Classical methods

The extraction is the starting point for isolating the desired molecules from different vegetal matrices. The selection of the right extraction method and solvent is crucial for increasing the extraction yield. Numerous factors affect the extraction yield, including solvent, particle size, temperature, and extraction duration [27]. Conventional extraction techniques have been used to prepare *A. iva* L. extracts to determine their biochemical

attributes [21,22,28,29]. Different amounts of total phenolic content (TPC) and total flavonoid content (TFC) in the studied extracts were determined using numerous extractor solvents [7]. They also found that the water extract showed the highest extract yield (12.85 ± 1.40 %), whereas the methanol extract showed the highest values of TPC and TFC [7]. Furthermore, the Soxhlet method revealed that dichloromethane was the most appropriate solvent to extract the highest amounts of TPC compared with ethanol [30]. The decoction method revealed its ability to maximize the extraction yield but registered the lowest amounts of TPC and TFC than those found in aqueous and hydroethanolic macerated extracts (Saidi et al., 2023). Maceration is a very simple method that is widely used, but the long extraction time and yield of extraction were determinant factors for selecting other effective methods [27]. The impurities and degradation of thermolabile bioactive compounds were the main reasons for reorienting research interest toward greener methods.

3.2. Ecofriendly methods

Technological evolution has boosted the search for effective extraction techniques and avoided the negative consequences of classical techniques on the environment and operator. Greener methods have gained huge interest from the researcher community due to their advantages such as green extraction using ecological solvents, pressurized liquid extraction, supercritical fluid extraction, and microwave-assisted extraction [32,33]. A comparison of both greener techniques, supercritical dioxide extraction and pressurized liquid extraction, revealed that the second technique produced higher extraction yields of *Ajuga iva* L. than the first, but the percentage of both methods exceeded the extraction yield recorded for water extract [34]. Modern techniques present several advantages, including low cost, extract safety, selectivity, and low temperature [27].

4. Chemical composition

Ajuga iva has been the subject of several scientific researches because of its diverse phytochemical composition. The phytochemistry of *A. iva* plant revealed the presence of various bioactive compounds, including alkaloids, tannins, flavonoids, quinones, terpenoids, saponins, and reducing compounds (Bouyahya et al., 2016, 2020). In addition, some authors have noted the presence of anthocyanins, phenolic acids, diterpenoid neo-clerodane such as ajugarine and other substances [37].

4.1. Phenolic acids

Pharmacologically active compounds constitute an important quality criterion for predicting the beneficial effects of different vegetal matrices. Several analytical assays have been developed to determine the phenolic profile of *A. iva* L., including UHPLC, GC-MS, LC/UV/MS, HPLC-PDA-ESI-MS/MS, and HPLC/UV-vis-DAD/ESI-MS [7,17,31,38]. Different phenolic acids were determined in AI such as ferulic acid (19.06%), coumaric acid (9.63%), quinic acid (2.01%), Trans-p-coumaric acid (1.87%), ascorbic acid 1.37%), mucic acid (1.3%), cinnamic acid (1.06%), vanillic acid glucoside (0.31%), gallic acid (0.73%), myricetin (0.79%), and galacturonic acid (0.43%) [31].

4.2. Flavonoids

Flavonoids are a class of secondary metabolites widely distributed in the plant kingdom. Known for their antioxidant properties and ability to fight cancer and cardiovascular diseases. Different flavonoid compounds were identified in *A. iva*, including quercetin (10.19%), pigenin-7-(2-O-apiosylglucoside) (6.8%), luteolin (4.53%), kaempferide (4.25%), epigallocatechin gallate (3.94%), vanillin (3.17%), catechin (2.43%), catechin-7-O-glucoside (2.04%), harpagid (1.39%), rhamnetin (1.3%) (Saidi et al., 2023). Seven flavonoids were detected in *Ajuga iva*, including apigenin and apigenin-7-O-neohesperidoside, quercetin, luteolin, naringenin, chrysoeriol, 5,5'-dihydroxy 4',7-dimethoxy flavone, and 5,7-dihydroxy 4',5'-dimethoxy flavone [39]. One flavonoid compound named naringenin-7-O-α-L-rhamnopyranosyl (1– > 42)-β-D-glucopyranoside was found in *Ajuga iva* [40].

In addition, quercetin and luteolin were both flavonoid compounds detected in the areal part of Algerian *A. iva*, with a total flavonoid content that did not exceed 51.18±1.03 mg CE/g [41]. The phytochemistry of *A. iva* L. requires further investigations to reveal different biologically active compounds that provide their pharmacological properties.

4.3. Steroids:

Steroids constitute an interesting kind of biologically active compound widely found in AI in different amounts. In fact, the major steroids of *A. iva* detected and isolated for the first time since 1971 were ecdysone and cyasterone [42]. Three major ecdysteroids (Makisterone A, 20-hydroxyecdysone, and cyasterone) and other compounds with the lowest amounts were recorded [38]. Other six steroids, such as 20-hydroxyecdysone (14.63%), unknown sterol (6.85%),

cyasterone (5.82%), makisterone A (4.92%), 7,8-dihydroajugasterone C (4.37%), 24-dehydroprecyasterone (0.88%), β-ecdysone (0.8%) were also determined [7]. Recently, ajugasterone (4.29%) and cyasterone (0.77%) were considered the most abundant steroids in *A. iva* L. leaf extract (Figure 2) [31]. The ecdysteroids identified in *A. iva* L. showed a significant reducing effect on the fecundity, fertility, and survival of *Bemisia tabaci,* and *Oligonychus perseae* [43].

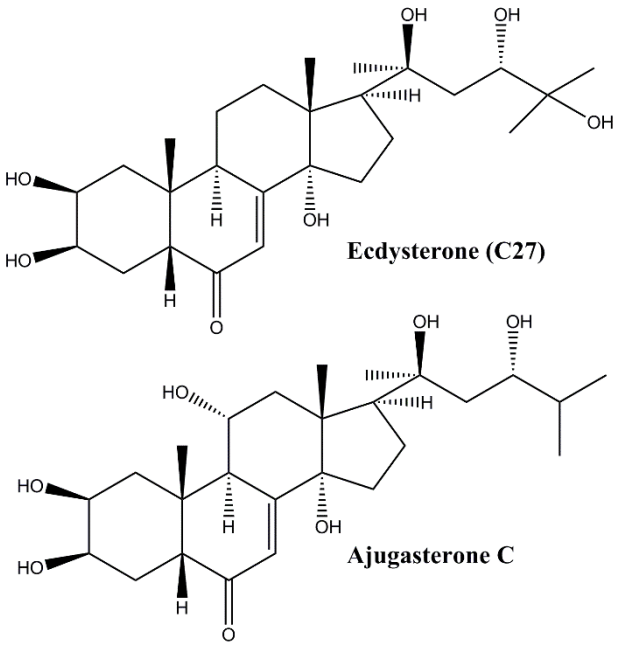

Fig. 2. The 2 steroids identified in *Ajuga iva*: Ecdysterone (C27) and Ajugasterone C.

4.4. Terpenoids

Terpenoids are a group of plant secondary metabolites formed from active isoprene [44]. These chemical compounds can exert specific functional effects in vivo. The phytochemical screening of *Ajuga iva* terpenoids indicated the presence of terpenoids in acetone, chloroform, and water extracts [45]. Within this framework, numerous researchers have performed various techniques to detect and isolate the terpenoids of *A. iva.* Four terpenoids, including ivan I, ivain II, ivain III, and ivain IV (Figure 3), were detected for the first time in *A. iva* using diethyl extract (camps) [46]. These are isolated especially from dichloromethane or acetone extracts [47]. In addition, other terpenoid compounds have been isolated from essential oils extracted from *A. iva,* including methyl chavicol, carvacrol, spathulenol, n-octadecane, and phytol [48]. The leaf essential oil of *A. iva* contains several volatile compounds in different proportions, including dienestrol (54.04 %), eucalyptol (27 %), o-xylene (7.98%), 1-octadecanol (5.80 %); 3-carene (4.46 %), (E)-2,3,6- trimethoxypentafulvene-1-carbonitrile (4.34 %), (-)-spathulenol (1.77 %), and nonanal (1.24 %) [49]. The predominant terpenoids found in the areal parts of Tunisian *A. iva* were β-pinene (70 ± 5%) and α-pinene (20 ± 2%) [50].

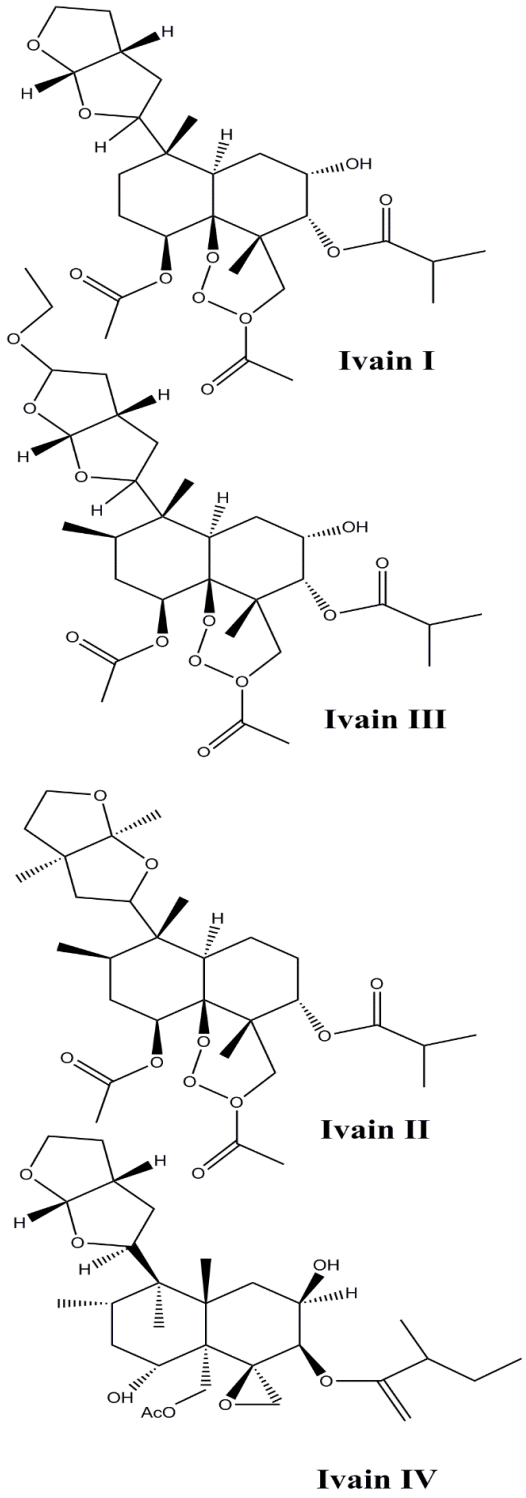

Fig. 3. The 4 terpenoids identified in *Ajuga iva (*Ivain I, II, III and Ivain IV).

4.5. Fatty acids

Fatty acids play a crucial role in human physiological functions as precursors of several hormones. Most essential fatty acids are obtained from the daily diet, such as omega-3 and omega-6 fatty acids, which are implicated in different physiological functions, including antiinflammation and cardiovascular diseases (Bouyahya et al., 2020; Saidi et al., 2023). Indeed, *Ajuga iva* is an excellent source of fatty acids [7]. The lipid profile of *A. iva* has been investigated and revealed the presence of fatty acids, which include palmitic (16.82±0.48%), palmitoleic (0.6±0.02%), stearic (2.18±0.06%), oleic (15.91±1.28%), linoleic (26.29±0.76%), linolenic (37.66±2.35%), arachidonic (0.54±0.02%), saturated fatty acids (19.54±1.22%), and unsaturated fatty acids (80.46±2.64%) [7]. Furthermore, different fatty acids with different proportions were recorded such as hexadecanoic acid, methyl ester, methyl palmitate (6.51%), hexadecanoic acid, trimethylsilyl ester, palmitic acid, trimethylsilyl ester (5.66%), octadecanoic acid, methyl ester, methyl stearate (3.82%), octadecanoic acid, trimethylsilyl ester, stearic acid, and trimethylsilyl ester (2.91%) [52]. These fatty acid methyl esters were found to be effective against several pathogenic microbes [52,53].

5. Biological properties

In vitro antioxidant studies have shown that *A. iva* exhibits antioxidant properties [57]. One of the main major pillars of natural products is antioxidants [14]. This property affords *A. iva* a broad spectrum of therapeutic applications. Diverse bioactive compounds were found in *A. iva*, including phenolic acids, flavonoids, terpenoids, sterols, and fatty acids, which are well known for their ability to counteract the deleterious effects of oxidants [7,31,58,59]. A panel of assays and animal models was used to determine the antioxidant activity of *A. iva*. Administration of *Ajuga iva* extract for three weeks promoted amelioration of enzymatic antioxidants (superoxide dismutase, catalase, and glutathione peroxidase), and metal antioxidants (copper, iron, magnesium and calcium) in alloxan-induced diabetic rats [60]. In contrast, *A. iva* revealed its activity to decrease the lipid peroxidation level [60]. In the same context, Bahi and coworkers found that the administration of *A. iva* extract ameliorated the levels of GSH, GPx, and GST, while a significant reduction in the lipid peroxidation level was observed in mercuric chloride-intoxicated rats [61]. A recently published study demonstrated that the aqueous extract of *Ajuga iva* leaves exhibited an interesting antioxidant activity against the deleterious effects of Castrol oil by controlling the elevation of different parameters of antioxidant status, including glutathione peroxidase, carbonyl protein, and malondialdehyde [62]. The manufacture of nanoparticles using *Ajuga iva* is an effective alternative to traditional methods. Al Moudani et al. found that *Ajuga iva* nanoparticles are promising candidates for combating various oxidants well-known for their deleterious effects [63]. The scarcity of experimental studies on the protective effect of *A. iva* L. constitutes a promising research subject for future studies.

5.1. Antioxidant abilities

Ajuga iva is an interesting source of antioxidant bioactive compounds investigated using different complementary assays, including total antioxidant capacity (TAC), 2,2 diphenyl 1-picrylhydrazyle (DPPH), ferric reducing antioxidant power (FRAP), 2;2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS), cupric reducing antioxidant capacity (CUPRAC), nitric oxide (NO), and ß-carotene assays [7,40,52,54,55]. The extraction solvent, method used, and geographical origin affect the antioxidant activity of *A. iva*. The in vitro antioxidant activities of different extracts prepared with different methods (decoction, infusion, and maceration) were evaluated and the obtained results showed the following values: H_2O_2 scavenging activity (0.42±0.25 %, 0.85±0.46%, and 4.08±0.02% for aqueous decocted, infusion and macerated extract, respectively), DPPH (616.57±44.21 µg/ml, 26128±00 µg/ml, and 403.5±10.94 µg/ml for decoction, infusion and macerated extract, respectively), ABTS (3.78±0.01 µg TE/g, 3.86±0.04 µg TE/g, and 3.81±0.02 µg TE/g for aqueous decoction, infusion and macerated extracts, respectively), FRAP (6.86±0.00 µg TE/g, 3.41±0.04 µg TE/g, and 5.45±0.04 µg TE/g for decoction, infusion and macerated extract, respectively), and PR(8.19±0.02 µg AAE/g, 2.85±0.03 µg AAE/g, and 4.97±0.09 µg AAE/g for decoction, infusion and macerated extract, respectively) [56].

5.2. Antidiabetic effect

Diabetes is a metabolic disorder that continues to expand in the affected population. Natural resources were and still are the primary source of medication for different animal and human pathologies [64,65]. In fact, several studies have indicated that *A. iva* is traditionally used to treat and control diabetes and its complications [16]. *A. iva* leaves infusion is used orally against diabetes, cancer, asthma, and rheumatism [16]. Within this framework, experimental studies have been undertaken to confirm the activity of *A. iva* as a diabetes

medication [17–19,21]. Carbohydrate hydrolyzing enzymes constitute the first line of diabetes control [66]. Different extracts of *A. iva* exhibited an interesting enzyme inhibitory effect on α-amylase, α-glucosidase, and ß-galactosidase [21]. Similarly, the highest inhibitory effect of methanol extract on α-amylase, α-glucosidase was recorded [55]. These effects were ascribed to the phytochemicals found *in A. iva,* including ferulic acid, quercetin, coumaric acid, and apeginin-7-(2-O-apiosylglucoside) [31]. Phenolic compounds inhibited the carbohydrates hydrolyzing enzymes and diminish carbohydrates absorption [67,68]. Furthermore, oral administration of *A. iva* extract at doses of 100, 200, and 300 mg/kg bw for 2 weeks, showed a significant reduction in blood glucose levels in diabetic rats [17]. Lyophilized aqueous extract of *A. iva* at a dose of 10 mg/kg decreased the blood sugar level in streptozotocin-diabetic rats [18].

Phytoecdysteroid is one of the bioactive compounds isolated from *Ajuga iva* and is used to counteract the harmful effect of alloxan on glycemia status and pancreatic histological tissues [69]. The authors found that phytoecdysteroid administration markedly attenuated the atrophic alterations of acinar cells and regenerated whole pancreatic islets in diabetic rats [69]. Furthermore, phytoecdysteroid was found to be able to upregulate hesokinase-1 mRNA expression and hexokinase-1 protein expression in a dose-dependent manner [69]. Phytoedysteroids control glycaemia levels directly by enhancing insulin release by pancreatic ß-cells [69–71]. In addition, these compounds suppress glucogenic and lipogenic enzyme activity [69,71]. Ferulic acid is another active compound found in *A. iva*, which has demonstrated its ability to reactive nucleotide sugars, starch and sucrose, rostenedione, estrone, androgen and estrogen, porphyrin, and purine metabolism pathways [72]. In addition, it restores dysregulated redox balance in ferric-induced pancreatic oxidative injury [72]. The phytochemicals of *A. iva* act synergistically to control different pathways implicated in the pathogenesis of diabetes.

5.3. Antimicrobial ability

Pathogenic microbes constitute a real challenge for human health and healthcare systems. Medicinal plants are considered natural medications for diseases such as infection. Recently, the emergence of resistance has afforded pathogenic microbes the ability to resist multiple chemical antimicrobial agents [73,73]. *A. iva* has effective antibacterial activity against multiple pathogenic microorganisms [7,31,53,74–77]. The antimicrobial effect of *Ajuga iva*, has been investigated against several microorganisms, including *Staphylococcus aureus* and *Enterococcus faecalis*, *Paracoccus paratrophus*, *Staphylococcus aureus, Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa,* and *Staphylococcus aureus* [7,21,31,53,74,77]. This antibacterial activity appears to be influenced by many factors, including the nature of the extract and the type of microorganisms studied.

The table below summarizes the results of antibacterial activities, considering the part of the plant used, extraction technique and the type of microorganisms under study.

Table 1. Antibacterial activity of *Ajuga iva*

Parts used	Tested extract/compound	Tested strains	Diameter of inhibition	Minimal inhibitiotory concentration	References
Sheets	Essential oil	*Escherichia coli* (ATCC 25922)	15.5 ± 10.20 mm	0.18 µg/mL	[49]
		Salmonella typhimurium (ATCC14028)	16.0 ± 0.33 mm	14.6 µg/mL	
		Staphylococcus aureus (ATCC-29213)	12 ± 0.03 mm	14.50 µg/mL	
		Bacillus subtilis (ATCC-6633)	3.5 ± 0.8 mm	15 µg/mL	
		Escherichia coli (ATCC 35218)	15.3 ± 0.1 mm	12.50 µg/mL	

		Pseudomonas aeruginosa (ATCC 27853)	14.5 ± 0.14	19.5 µg/mL	
Sheets	Essential oil	*Staphylococcus aureus* (ATCC 25923)	30 ± 1 mm	MIC= 0.5% MBC = 1% (v/v)	[75]
		Enterococcus faecalis (ATCC 29212)	38 ± 05 mm	MIC = 0.25% (v/v), MBC = 0.5%	
		Salmonella typhimurium (NCTC 6017)	19 ± 1 mm	MIC = 1% (v/v) MBC = 2%	
		Escherichia coli (ATCC 25922)	22 ± 0.5 mm	MIC = 1% (v/v) MBC = 1.6%	
Sheets	Methanolic extract	*Escherichia coli* (ATCC25922)	13 ± 0.7 mm	MIC = 17.1 mg/mL	[78]
		Staphylococcus aureus (ATCC6538)	13.25 ± 0.98 mm	MIC > 50 mg/ml	
Sheets	Methanolic extract	*Bacillus cereus*	15 mm	-	[79]
		Escherichia coli	27 mm		
		Pseudomonas aeruginosa	05 mm		
		Staphylococcus aureus	20 mm		
Areal parts	Methanolic extract	*E. coli* (ATTC 35218)	5mm	-	[52]
		S. *enteritidis* (DMB 560)	4 mm		
		Pseudomonas aeruginosa (ATTC 2134)	4 mm	-	
		L. monocytogenes (ATTC 1919)	3 mm		
		B. cereus (ATTC 14759)	11 mm		
		Methicillin Resistant *S. aureus*	20 mm		
		L. monocytogenes (ATTC 1919)	12 mm		
Whole plant	Methanolic extract	*Bacillus subtilis*	0 mm	-	[80]
		Escherichia coli MC 4100	0 mm		
		Escherichia coli MC 4100	0 mm		
		Paracoccus pantotrophus	2 mm		
		Pseudomonas diminutus	0 mm		
Sheets	Aqueous Extract	*Bacillus cereus*	4 mm	-	[79]
		Escherichia coli	7 mm		
		Pseudomonas aeruginosa	2 mm		
		Staphylococcus aureus	4 mm		
Aerial		*Escherichia coli* (ATTC 35218)	-	8625 < MIC < 1250	[52]
		S. enteritidis (DMB 560)	-	6625 < MIC < 1250	

parts	Aqueous Extract	*Pseudomonas aeruginosa* (ATTC 2134)	-	7625 < MIC < 1250	
		L. monocytogenes (ATTC 1919)	-	6625 < MIC < 1250	
		L. monocytogenes (ATTC 1919)	-	14.145 < MIC < 200	
		B. cereus (ATTC 14759)	-	14.145 < MIC < 200	
		Methicillin Resistant S. *aureus*	-	14.145 < MIC < 200	
Aerial parts	Freeze-dried aqueous extract	*E. coli*	8.46 ± 0.51 mm	-	[77]
		Pseudomonas aeruginosa	0 mm		
		Salmonella spp.	8.88 ± 1.23 mm		
		Bacillus subtilis	0 mm		
		Staphylococcus aureus	8.58 ± 0.02 mm		

Phytochemical compounds found in *A. iva* possess antimicrobial activities by different mechanisms of action. Essential oils act as antimicrobial agents by affecting membrane stability, interacting with proteins, inhibiting biofilm installation, perturbing quorum sensing communication, and inhibiting gene transcription [81]. Terpenoids are important phytochemicals found in *A. iva*. These molecules are found to be able to perturb ion homeostasis of both Gram-positive and Gram-negative cells upon ion leakage as the main key antimicrobial effect of terpenoids [82]. The treatment of *Shigella flexneri* with ferulic acid dramatically affected gene expression implicated in the pathways of ribosomes, ABC transporters, and citrate cycle by upregulating of 169 differentially expressed genes and downregulating of 533 differentially expressed genes compared with the untreated *S. flexneri* biofilm [83]. In the same context, the application of ferulic acid amplified by quinolones to *Acinetobacter boumannii* markedly affected the redox balance by elevating the production of superoxide ions and ADP/ATP and NAD+/NADH ratios [84]. Furthermore, molecular docking showed promising results using ferulic acid as a potential inhibitor candidate of the NorA efflux pump [85].

6.1. Anti-inflammatory effect

In this section of this review, we discuss the relevant findings on the anti-inflammatory effect of *Ajuga iva*. The inflammatory process is a key factor in the prognosis of several human diseases. Anti-inflammatory chemical drug use is may be accompanied by harmful effects, which imposes the wicker in the vegetable kingdom for safer and effective active natural molecules [76]. Ethnopharmacological studies are the keystone of several modern investigations, that documented the activity of *Ajuga iva* as a natural anti-inflammatory agent [5,16,86–88]. The examined analgesic effect of *A. iva* aqueous extract showed a remarkable decrease in abdominal cramps and exhibited an important analgesic effect in a dose-dependent manner [89]. A decrease in the number of writhes was observed in animals treated with *A. iva* at doses of 500 and 1000 mg/kg with a percentage of 62.75% [77]. The anti-inflammatory effect of Egyptian *A. iva* has been studied against the carrageenan-induced rat pat edema technique [90]. They found that *A. iva* at doses of 50 and 200 mg/kg prevented the elevation in the volume of paw edema in a dose-dependent manner mice [90]. Furthermore, Romanian Ajuga was found to be able to decrease total leukocyte counts, phagocytosis, PMN, and oxidative stress [28]. Pleiotropic effect of AI makes it a promising source of bioactive compounds, that act synergistically at different levels of the pathogenesis process.

Several studies have investigated the anti-inflammatory properties of *Ajuga iva*. In one study, the methanol extract of the plant was found to inhibit the production of inflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), in human immune cells (Bouyahya et al., 2020). Another study found that the ethyl acetate extract of this plant exhibited anti-inflammatory activity in a mouse model of acute inflammation [57].

6.2. Hepatoprotective activity

Ajuga iva possesses hepatoprotective properties, which may help to protect the liver against damage. In one study, the methanol extract of the plant was found to protect against liver damage induced by carbon tetrachloride in rats [91].

6.3. Antidiarrheal effect

Diarrhea is a common disorder of gut function characterized by the presence of liquid feces [92]. This trouble is due to the perturbation of liquid homeostasis, leading to a water loss [93]. Various traditional mixtures have been made to treat diarrhea, including Banhasasim-tang [94]. Administration of an aqueous extract of *Ajuga iva* revealed a significant increase in the intestinal contents of minerals such as magnesium and calcium in Castrol-oil-intoxicated rats [62].

6.4. Toxicological studies

Medicinal herbs are ubiquitous and constitute a primary source of medication for approximately 80% of the population around the world [95]. Across centuries, several experimental studies have been undertaken to investigate the beneficial and toxicological effects of medical herbs to determine the safety and efficacy of different herbal mixtures used in folkloric medicine [5,16]. Oral administration of an aqueous extract of *A. iva* at a dose of 14 mg/kg did not induce any adverse effect while using the intraperitoneal route, however the signs of toxicity appeared in a dose-dependent manner and increased to 100% at a dose of 1500 mg/kg [96]. The acute and chronic toxicity of the methanol extract of *A. iva* has been investigated in rodents [97]. The authors found that the methanol extract administered at different doses (2-14 g/kg) did not induce any signs of toxicity or mortality, while using the intraperitoneal route at doses of 2-6 g/kg, rodents expressed significant changes in general behavior and mortality in a dose-dependent manner [98]. The histoarchitecture of the brain, liver, and kidneys of the study animals did not change after oral administration of various doses (100, 300, and 600 mg/kg) of *Ajuga iva* extract for 13 weeks [96,98]. The same findings are evoked by [55]. Female Swiss mice were administered a 2 g/kg dose of the methanol extract of Ajuga iva over a 2-week period without exhibiting any toxicity, behavioral abnormalities, or harmful biochemical alterations [55]. Medicinal plant toxicity is very complex because of the synergistic interaction between a cocktail of phytochemicals found in the vegetal matrix [99,100]. Overall, the determination of poisonous plants constitutes a crucial step in verifying the safety and efficacy of medicinal herbs. Table 2 displays the different findings of several studies designed to determine *A. iva* acute and chronic toxicity. In addition, it is important to consider that toxicity can vary depending on the dose and duration of exposure, as well as individual factors such as age, health status, and genetic predisposition.

Table 2: Toxicological investigations on *Ajuga iva*.

Excerpt/Component	Doses	Route of administration	Model	Main findings	References
Aqueous extract	2-14 g/l	Oral administration	Acute toxicity	No deaths and no observed signs of toxicity	[96,101]
	0, 100, 300 and 600 mg/kg		Chronic toxicity	Normal evolution of body weight. No significant change in blood parameters of treated animals. Histopathological examination of the different organs revealed no significant changes induced by the extract.	
	1.5-5.5 g/kg	Intraperitoneal injection	Acute toxicity	Mortality rate is dose-dependent Hypoactivity, weight loss and death of animals (LD50 = 3600 mg/kg).	

Methanol extract	0-6 g/kg	Oral administration		Mortality rate is dose-dependent Hypoactivity, weight loss and death of animals aux (LD50 = 3980 mg/kg).	[97]
	0-14 g/kg			No deaths and no observed signs of toxicity	
	0-600 mg/kg		Subacute toxicity	Normal evolution of body weight. No significant change in blood parameters of treated animals. Histopathological examination of the different organs revealed no significant changes induced by the extract.	
Aqueous extract	2000 mg/kg		Acute toxicity Acute	No deaths and no observed signs of toxicity	[55]
Methanol extract	2000 mg/kg			No deaths and no observed signs of toxicity	
Aqueous extract	800 mg/kg	Oral administration		Absence of any signs of mortality or visible toxicity	[62]

7. Limitations and future recommendations

Ajuga iva is a chemical-rich vegetal matrix with a distinct pharmacological effect on human health. It constitutes an exhaustible source of phytocompounds that can be used in different fields, including pharmaceutical, cosmetic, and food industries. Conducting clinical trials is the main challenge in studying how this plant works in humans. Ethanopharmacology research has shown a plethora of folkloric uses of *A.iva*, such as antidiabetic, anti-inflammatory, and immunostimulatory. However, it is of pivotal importance to determine the exact mechanism of action underlying *A. iva*.

8. Conclusion

The main source of natural medicine for numerous civilizations around the world has been *Ajuga iva,* a vegetal matrix frequently employed in folklore medicine. The existence of a wide variety of phenolic acids, flavonoids, steroids, terpenoids, and fatty acids has been investigated using various methodologies. The bioactive compounds of *Ajuga iva* acted synergistically to provide different physiological functionalities, including antioxidant, antidiabetic, anti-inflammatory, and antimicrobial effects.

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