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Traditional uses and phytopharmacology of *Cirsium arvense*: Bioprospecting potential of a weed from temperate biome

Acharya Balkrishna[1,2], Hemant Sharma[1], Ankita Kukreti[1], Amita Kumari[1], Priyanka Saini[1], Vedpriya Arya[1,2], Ashwani Kumar[1]*

[1]Patanjali Herbal Research Department, Patanjali Research Foundation, Haridwar, India.
[2]Centre of Excellence, Patanjali Ayurved Hospital, Haridwar, India.

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ABSTRACT

Cirsium arvense, a noxious weed of the Asteraceae family, has potential medicinal benefits. Traditionally, it has been used to cure ulcers, mouth infections, leukemia, dentalgia, canker sores, pharyngitis, and other ailments. Alkaloids, flavonoids, tannins, and diverse phytoconstituents are associated with its therapeutic potential. This review article sheds light on *C. arvense*'s taxonomy, geographical distribution, ethnomedicinal uses, and phytopharmacology. Despite its weedy nature, it has been a rich source of phytoconstituents, which is evident from its antimicrobial (against Gram positive and negative strains), antioxidant (2,2-diphenyl-1-picrylhydrazyl and others), and antiproliferative (HeLa, A43, and MCF7 cell lines) potential. Hispidulin, luteolin, and tracin, isolated from *C. arvense* were reported to be with antibacterial potential. Based on its bioactive components, a proposed mechanism for antibacterial action is also highlighted. A toxicity study revealed that the aerial parts of *C. arvense* are toxic (LC_{50} of 51 µg/ml). Bioprospecting of this weed after detailed follow-up studies will help manage *C. arvense* in the future.

INTRODUCTION

Emerging infections, drug resistance, and oxidative stress-mediated diseases have made it inevitable to search for new antioxidants and antimicrobials. In this context, plants could be used as safe and efficacious therapeutic options; several plants have been reported with diverse biological properties and therapeutic potential [1–6]. Among various plant families, Asteraceae is the most prominent family of the plant kingdom. It includes 1,701 accepted genera and over 24,000 species [7,8], comprising ~10% of the flowering plants. Most family members are annual or perennial herbs; some tropical forms include shrubs, vines, and trees [9]. These can be categorized into ornamental plants (*Tagetes*, *Chrysanthemum*, *Calendula, Ageratum*), wild plants (*Brachyscome, Arctium, Boltonia*), noxious weeds *(Taraxacum, Carduus*, *Cirsium*), and economically important plants (*Lactuca, Cynara, Helianthus, Artemisia*). The characteristic feature of this family is its inflorescence, called calathium or capitulum [10].

Asteraceae's genus *Cirsium* (thistle) is an annual, biennial or perennial herb. It comprises approximately 378 recognized species of spiny, perennial, biennial, or rarely yearly [8]. The species are found throughout the northern hemisphere (North America, North Africa, Asia, and Eurasia), from subtropical to boreal latitudes [11,12]. The plants of *Cirsium* genus are mainly utilized for the treatment of leukemia and peptic ulcer in folklore medicine [13], epistaxis, eye infections, metrorrhagia, syphilis [14], gonorrhea, skin sores, bleeding piles, diabetes, and hemostasis, therefore, making them safe and effective medicine [15–17]. Numerous phytochemicals such as flavonoids, phenolic acids, polyacetylenes, acetylenes, phenylpropanoids, sterols, and terpenoids contribute to these medicinal qualities of *Cersium* species [18]. Among various species, *Cirsium vulgare* and *Cirsium arvense* are considered noxious weeds [8,19].

Cirsium arvense (L.) Scop. is one of the world's most troublesome and persistent weeds. It is native to Europe and the northern hemisphere but was also introduced to North America

*Corresponding Author
Ashwani Kumar, Patanjali Herbal Research Department, Patanjali Research Foundation, Haridwar, India.
E-mail: dr.ashwanikumar @ patanjali.res.in

in the 1600s and the southern hemisphere [20]. It is often found in grasslands and riparian habitats. Even as a weed, *C. arvense* is known for its medicinal properties [21,22]. For example, plant decoction is a remedy for epistaxis, gastrointestinal disorders, hemorrhage, hypertension, metrorrhagia, pyogenic infections, scabies, ulcers, and skin diseases [23,24]. Additionally, *C. arvense* was reported as an antimicrobial and antioxidant agent, and its potential is attributed to the presence of flavonoids, alkaloids, steroids, and saponins [21,25–27].

Previously published review articles were primarily focused on the consequences of *C. arvense's* spread as a perennial weed in European countries, as well as control measures [28]. Further, reviews are available on medicinal properties, phytochemical and pharmacological studies of the genus *Cirsium,* and different species [29]. So, in this review, we endeavored to study *C. arvense's* ethnomedicinal uses, phytochemistry, and pharmacology. The primary goal of this review is to explore *C. arvense* as an economically significant plant that can provide a way to bioprospect this weed and open new doors for future research in different areas.

TAXONOMIC DESCRIPTION AND GEOGRAPHICAL DISTRIBUTION OF *C. ARVENSE*

Herb, dioecious, perennial, up to 160 cm tall. Stem erect, unwinged, branched above. Leaves petiolate, petioles narrowly winged, lamina 3–30 × 1–6 cm, oblong to elliptic, margins plane to revolute, entire, spinulose, main spines 1–7 mm, abaxial faces glabrous to densely grey-tomentose, adaxial green, glabrous to thinly tomentose. Inflorescence capitulum, terminal, corymbose; involucre narrowly ovoid. Phyllaries imbricate, in 5–7 rows, lacking wings and scarious appendage. Corolla reddish purple or rarely white; female florets 1.6–2.4 cm; male florets 1.5–1.8 cm. Fruits achene, yellowish. Pappus bristles dirty white, 2.5–3.5 cm [19,30,31]. Taxonomical features of *C. arvense* are shown in Figure 1.

Cirsium arvense grows in diverse habitats (ranging from moist places to grasslands, mountain slopes, flooded lands, disturbed sites, etc.) at 100–4,300 m [31]. Its native range is Temperate Eurasia, Northwest Africa. It has been introduced into North America, South America, Africa, Europe, Asia, Australia, and other regions, as shown in Figure 2 [8].

TRADITIONAL USES OF *C. ARVENSE*

In light of existing literature, several studies have reported the ethnomedicinal and culinary uses of *C. arvense*. A brief overview of the ethnomedicinal uses of *C. arvense* has been depicted in Table 1.

Ethnomedicinal uses

Various ethnobotanical studies have recognized the therapeutic and health-promoting uses of the whole plant of *C. arvense* [32]. In North America, *C. arvense* (whole plant) is used as a remedy against cirrhosis, lipoma, liver cancer, and gout [33,34]. Further, a decoction of the plant is used for the treatment of gastrointestinal disorders, hypertension, hemorrhage, lung troubles, epistaxis, hematemesis, ulcers, scabies, metrorrhagia, pyogenic infections, and various types of skin diseases [23,24,35–39]. The infusion or extract of the whole plant is used for the cure of mouth infections by North American Indian tribals and is considered to be useful as an astringent, diuretic, and health-promoting tonic [21,27,40].

Also, root decoction is used as an anthelmintic, astringent, diuretic, tonic, and remedy against hepatic disorders and intestinal worms [23,41,42]. David [41] documented the use of syrup from the roots to alleviate cough, while root juice is used to cure diabetes and jaundice and against snake bites [34,43–46]. The roots paste mixed with *Amaranthus spinosus* is given in case of indigestion [47]. Leaf juice and tea are employed for treating tuberculosis, piles, eye pain, skin-related problems, wounds, and urogenital diseases [41,44,45,48]. Subsequently, leaves paste is applied to heal boils [30]. Leaves are chewed to relieve toothache and sore throat because of their anti-inflammatory properties [21,27]. A mixture of the roots and leaves is used for oral disorders, toothache, diarrhea, dysentery, tuberculosis, and hepatic disorders [41,42,45,49]. The tincture of the leaves and flowers has been recommended against dermatitis [50].

Culinary uses

The foliage of *C. arvense* and aromatic seeds are used as food [37,53] due to their significant content of vitamins, minerals, and fibers [21,27]. The raw or cooked soft roots are eaten with other vegetables and used as drought food [54,55]. The peeled stem is cooked like *Asparagus,* while the leaves are used raw or cooked [54].

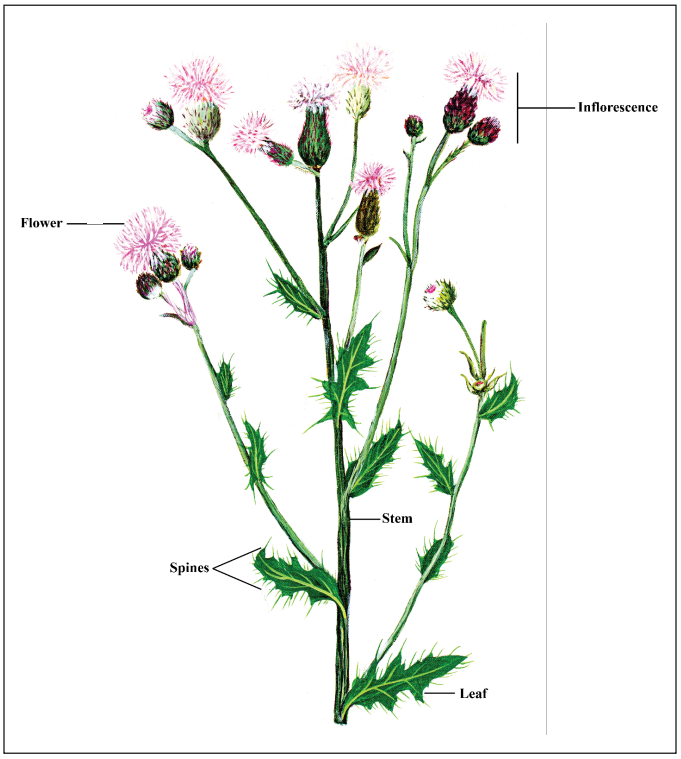

Figure 1. Salient botanical features of *C. arvense*. (Source: Patanjali Herbal Museum, Haridwar, India).

PHYTOCHEMISTRY OF *C. ARVENSE*

Cirsium arvense contains carotenoids, alkaloids, flavonoids, phenols, tannins, terpenoids, and glycosides [27,56]. Different flavonoids such as kaempferol-3-O-*β*-D-glucopyranoside, hispidulin-7-O-*β*-D-glucopyranoside, quercetin-3-O-*β*-D-glucopyranoside, luteolin-5-O-*β*-D-glucopyranoside and phenolic acid like caftaric, protocatechuic, and neochlorogenic acid have been reported in *C. arvense* by Popova [57], Khan *et al.* [58] and Ashmita *et al.* [59] observed the presence of α-tocopherol, 9,12,15-octadecatrienoic acid, hispidulin, and tracin *C. arvense*. The plant also contains flavones (acacetin and apigenin), caffeic acid, chlorogenic acid, enicin, protocatechualdehyde, rutin, stigmasterol, taraxasterol, and triterpenes [36,60,61]. The aerial parts and young inflorescence have alkaloids, choline, glucoside, and saponins [52,62]. Roots contain phytotoxic compounds, whereas leaves have flavones and cyanide-glycoside [60,61]. The *C. arvense* flower's methanolic extract contains triterpenoids (α and β-amyrin), sterols (γ-sitosterol, stigmasterol), and olean-12-en-3-ol, acetate [63]. Some other constituents like 1,2-benzenedicarboxylic acid; mono(2-ethylhexyl) ester; 10-octadecenoic acid, methyl ester; 2-pentadecanone; 6,10,14-trimethyl,2H-1-benzopyran, 6,7-dimethoxy-2-2-dimethyl,3,5-ditert-butyl-4-hydroxyacetophenone, 6,7-dimethoxycoumarin, 9,12-octadecadienoic acid (Z,Z)-,methyl ester, citronellol, acacetin, arvense A-B, camphor, ciryneol C, dihydroxy-6,7-dimethoxyflavone 4′-glucoside, ergoline-8-carboxylic acid, 10-methoxy-methyl-,methyl ester, heneicosane, heptadecanoic acid, 16-methyl-,methyl ester, hexadecanoic acid, nonadecane, pectolinarigenin-7-O-glucopyranoside, phytol, and scopoletin have also been reported in *C. arvense* [64]. The chemical structures of some of the representative phytoconstituents are highlighted in Figure 3.

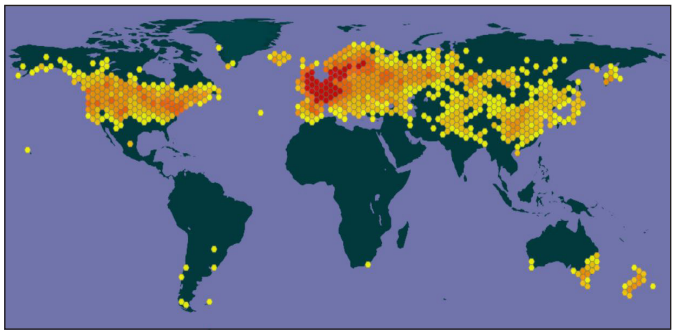

Figure 2. Map showing the geographical distribution of *C. arvense* (Source: https://www.gbif.org/).

PHARMACOLOGICAL PROFILE OF *C. ARVENSE*

The plant contains many phytoconstituents that have shown potential towards various bacterial strains, cancer cells, fungi, and also against free radicals. The validation of ethnomedicinal information by utilizing evidence-based pharmacological studies is necessary. Toxicity studies should support biological activities to assure the safety and efficacy of herbal medicine. This weed is not much explored; only a few studies, like antimicrobial, antioxidant, and antiproliferative are available in light of existing literature.

Antioxidant activity

Antioxidants are the molecules that can scavenge free radicals or reactive oxygen species (ROS) like superoxide (O_2^{-}), hydroxyl radical ($^{\bullet}OH$), hydrogen peroxide (H_2O_2), and others. ROS are produced in a cell due to biochemical reactions and can adversely affect nucleic acids, lipids, and proteins, resulting

Table 1. Ethnomedicinal uses of *C. arvense.*

Diseases/Indications	Part used	Preparation	Country/Communities	Reference
Gastrointestinal diseases, lung troubles, sores, epistaxis, hypertension, hemorrhage, abscesses, hematemesis, traumatic bleeding, ulcers, hemoptysis, scabies, metrorrhagia, furuncles, carbuncles, pyogenic infections	Whole plant	Decoction	North America/Ojibwa and Montagnais people	[23,24,35–39]
Mouth sickness	Roots, leaves	Infusion	North America/Iroquois and Mohegan tribals	[23]
Hepatic disorders, intestinal worm infestation	Roots	Decoction	NA	[23,41,42]
Toothache	Roots, leaves	Raw	NA	[41,42]
Cough	Roots	Syrup	NA	[41]
Diarrhea, dysentery, hepatic disorders	Roots, leaves	NA	NA	[41,43–45]
Piles, tender eyes, irritable sores, skin eruptions, skin ulcers, poison ivy rash, wounds, urogenital diseases	Leaves	Juice/ointment	NA	[41,44,45,48]
Diabetes, jaundice, burning sensation, snake bites	Roots	Juice	NA	[34,43–46]
Liver cancer, cirrhosis, lipoma, gout, contraceptive, dyspnea, urinary tract infection, prostate disorders	Whole plant	NA	North America and Turkey/ Quinault Indians	[33,34,51]
Boils	Leaves	Paste	NA	[30]
Tuberculosis	Leaves	Tea	NA	[44]
Dermatitis	Leaves, Flowers	Tincture	NA	[50]
Dyspepsia	Leaves, inflorescence	NA	NA	[45,52]

NA = Not available.

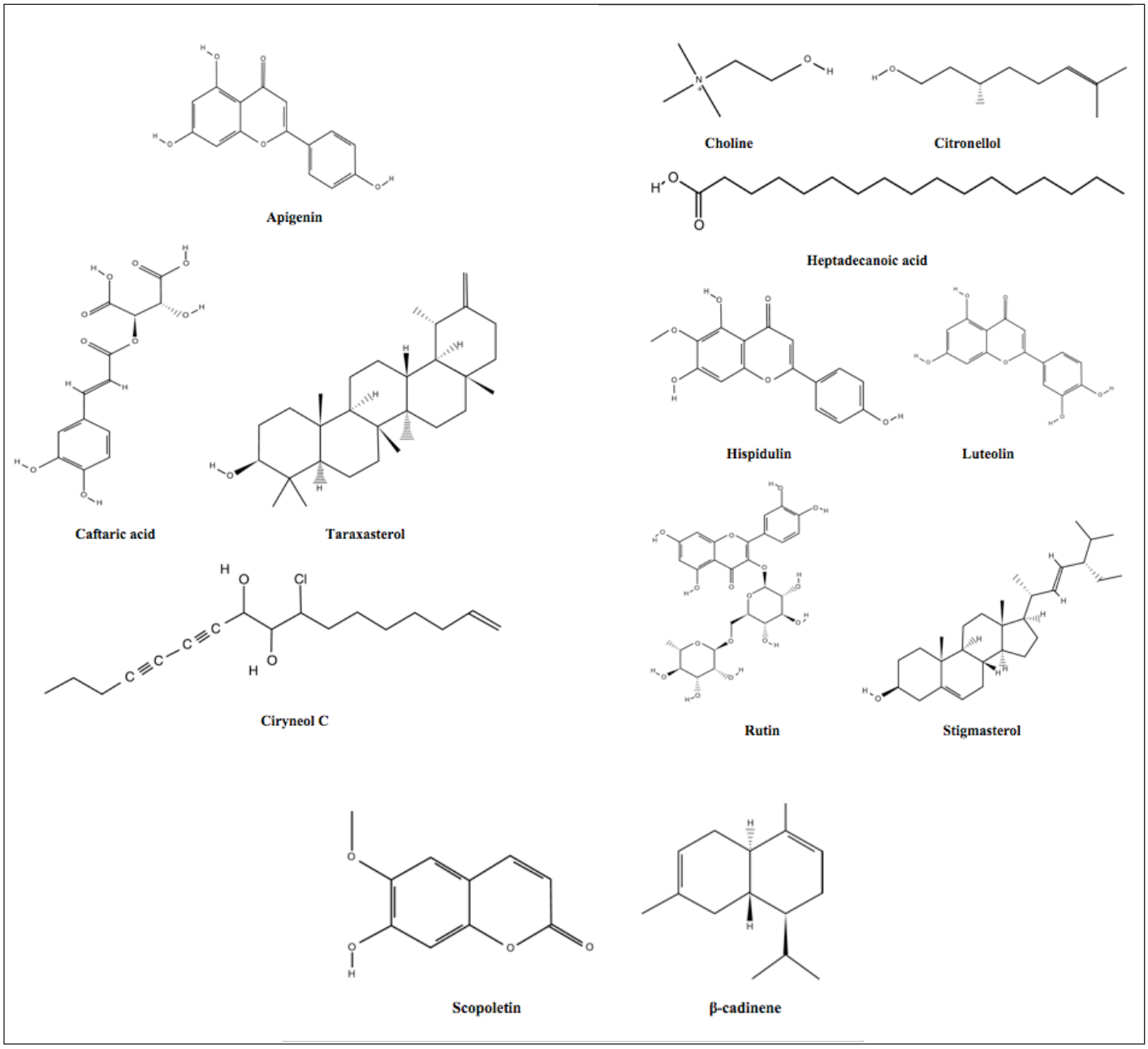

Figure 3. Representative chemical composition of *C. arvense.*

in oxidative stress and multiple diseases [65]. Antioxidants are crucial for inhibiting oxidative reactions and removing ROS or neutralizing harmful effects of ROS in the body [66]. In this context, the crude extract from leaves, flowers, and roots of *C. arvense* displayed *in vitro* antioxidant activity against 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical, superoxide anion radical, and also in ferric reducing antioxidant power assay [67]. The ethanol extract of *C. arvense* aerial parts exhibited antioxidant activity in ferrous ion (Fe^{++}) chelating assay, DPPH, H_2O_2, O_2^- and nitric oxide radical scavenging assays with IC_{50} values of 92, 118, 142, 110, and 100 µg/ml, respectively [27]. On the other hand, the aqueous extract from *C. arvense* leaves exhibited antioxidant activity with total antioxidant status of 2.74 m/ml [68]. The crude methanol extract of *C. arvense* inflorescence and leaves and its fractions (chloroform, diethyl ether, ethyl acetate, and n-butanol) were also evaluated for antioxidant activity. With a total antioxidant status of 1.76–2.69 mM/l, all fractions demonstrated antioxidant activity. The inflorescences' butanol and leaves' ethyl acetate fractions were observed to be the most active [69]. *Cirsium arvense* is reported to have antioxidant potential, but further studies (*in vitro* and *in vivo*) are warranted to validate this potential.

Antiproliferative activity

In vitro antiproliferative activity of different extracts (chloroform, n-hexane, aqueous methanol, and

water) of *C. arvense* herb and roots (10 µg/ml) was evaluated against A431 (skin epidermoid carcinoma), HeLa (cervix epithelial adenocarcinoma), and MCF7 (breast epithelial adenocarcinoma) cells using 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyltetrazolium bromide assay. All fractions exhibited antiproliferative activity with 2.88%–21.15% inhibition against all tested cell lines [70].

Antimicrobial activity

Different extracts of *C. arvense* plant parts have been evaluated by various researchers for antimicrobial activity. The aqueous extract of *C. arvense* leaves exhibited antimicrobial activity against *Staphylococcus aureus* with minimum inhibitory concentration (MIC) 12.5 mg/ml), *Bacillus subtilis* (MIC 50 mg/ml), *Pseudomonas aeruginosa* (MIC 50 mg/ml), and *Candida albicans* (MIC 1.56 mg/ml) [68]. Similarly, chloroform, n-butanol, n-hexane, and ethyl acetate fractions (100 µl) of *C. arvense* methanol extract were evaluated against Gram positive (*S. aureus* and *Micrococcus luteus*), Gram negative bacterial strains (*Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* sp. and *P. aeruginosa*) and fungus (*Aspergillus niger*). The chloroform fraction was observed to be most active against *S. aureus* with an inhibition zone diameter (IZD)15 mm, followed by *Enterobacter* sp. (IZD 14 mm), *M. luteus* (IZD 13 mm), *E. coli* (IZD 10 mm), and others [21]. The ethanolic extract (200, 250, and 500 µg/disc) from *C. arvense* aerial parts was evaluated against *Streptococcus pyogenes*, *S. aureus*, *Staphylococcus epidermidis*, *Shigella boydii*, *Shigella sonnei*, *Shigella flexneri*, *Streptococcus agalactiae*, *E. coli* and *Enterococcus faecalis*. The extract at 500 µg/disc inhibited all bacterial strains except *S. epidermidis*, *S. agalactiae,* and *E. faecalis*, where maximum activity was observed towards *S. pyogenes* (13.6 mm) [71].

The compounds hispidulin, tracin, 9,12,15-octadecatrienoic acid, α-tocopherol, and luteolin (1,000 µg/ml) from the *C. arvense* were screened for antimicrobial activity against bacteria (*E. coli*, *B. subtilis*, *S. flexneri*, *S. aureus*, *Salmonella typhi*, and *P. aeruginosa*) and fungi (*C. albicans*, *C. glabrata, Trichophyton longifusus*, *Aspergillus flavus*, *Fusarium solani,* and *Microsporum canis*). All tested compounds showed activity against tested microbial strains with IZD ranging between 9 and 34 mm. Tracin was observed to be most effective against *B. subtilis*. In contrast, luteolin and α-tocopherol were effective against *M. canis* with IZD 13–36 mm, whereas hispidulin was highly active against *F. solani*. Ashmita *et al.* [59] also observed the antimicrobial activity of compounds arvense A-B. All these studies support the antimicrobial potential *C. arvense*; however, most studies have only presented qualitative data, and quantitative studies with MIC are still required.

Mechanistic insights into antibacterial potential

Antibiotic resistance has grown to be a serious global concern. Drug-resistant infections are mainly brought on by the improper use and overuse of antibiotics [72]. Antibacterial drugs disrupt bacterial membranes and inhibit DNA, RNA, and protein synthesis [73]. Bacterial strains are constantly devising new mechanisms through many processes to adapt and withstand antibiotics' lethal or biostatic effects [74]. Efflux pump (groups of transporter proteins) hyperactivity contributes to drug resistance; it extrudes drugs from cells to the external environment and reduces the antibiotic concentration inside [75–78]. Figure 4 displays antibiotic resistance mechanisms and a suggested strategy (based on existing literature) accentuating the antibacterial activity of *C. arvense*'s phytoconstituents.

The enzymatic resistance mechanism involves a range of bacterial enzymes generated against distinct antibiotics, which cause structural modifications of antibiotics by hydrolysis or transferring functional groups, decreasing their efficiency [78]. In addition, bacteria acquire resistance via porin channel impairment (outer membrane protein alteration), thereby reducing the uptake of antibiotics [76,78]. The mutation in bacterial DNA and biofilm formation can also confer antimicrobial resistance [73,76,78,79].

The utilization of herbal remedies against bacterial strains resistant to antibiotics has recently grown. Many plants possess antibacterial chemicals that can work alone or with antibiotics [80]. Likewise, to other medicinal plants, *C. arvense* aerial parts contain antibacterial compounds like hispidulin, luteolin, and tracin, which might help manage antibiotic resistance. Additionally, acacetin, apigenin, and citronellol are the active constituents observed in *C. arvense*, have already been reported in the literature as antimicrobials [81–83]. Therefore, these compounds from *C. arvense*, alone or in combination with antibiotics, can manage drug resistance by inhibiting hyperactivity of the efflux pump, drug-inactivating enzymes, cell wall protein alteration, DNA, RNA, and protein synthesis.

Toxicity study

The ethanol extract of aerial parts of *C. arvense* showed toxicity against brine shrimp (*Artemia salina*) with LC_{50} 51 µg/ml in comparison to standard vincristine sulfate

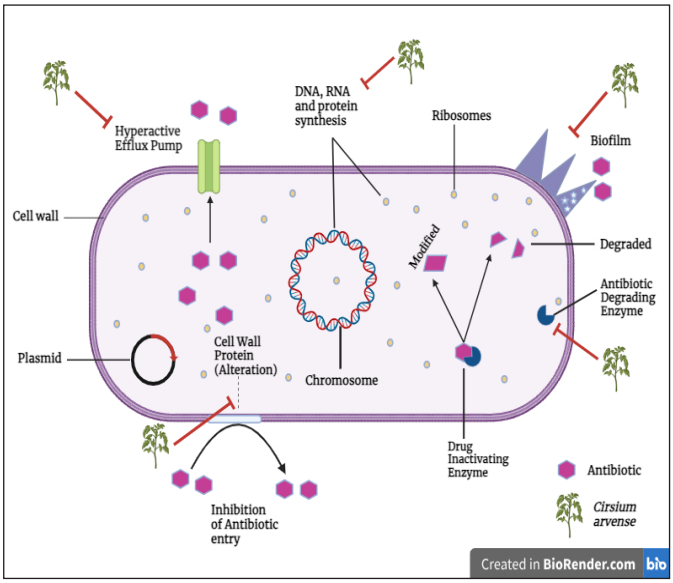

Figure 4. Mechanistic basis of antibacterial action of *C. arvense* (Created using Biorender.com).

(LC_{50} 0.44 µg/ml) [71]. More *in vitro*, *in vivo*, and clinical studies are required to assess the toxicity of this weed, as it is critical to focus research on the plant's safety and efficacy to use it adequately.

BIOPROSPECTING OF *C. ARVENSE*

Cirsium arvense is a widespread weed, but its potential for bioprospecting was not explicitly addressed. Despite being seen as an invasive plant in agricultural fields, *C. arvense* extracts have strong antioxidant properties, making them a viable source of antioxidants [67]. Its antimicrobial activity has also been investigated; tracin, hispidulin, and luteolin have antibacterial and antifungal effects [58]. Iranian *C. arvense* extracts displayed antibacterial efficacy against various bacterial strains [40]. *Cirsium arvense* was employed to generate silver nanoparticles with a high biological value and better *E. coli* inhibition activity [84]. Diverse phytoconstituents were responsible for the synthesis and biological activity of plant-mediated nanoparticles, as evidenced by several reports [85–89]. Therefore, *C. arvense*'s varied phytocomposition can be used in the future. However, in Tasmania, *C. arvense* root and foliage extracts prevented the germination and growth of several plant species, which may make it difficult for pasture and crop species to establish in *C. arvense*-infested environments [90]. Although its weeding potential may restrict its uses, but the biological potential of this opens up a new avenue for bioprospecting.

CONCLUSION AND FUTURE PERSPECTIVES

Cirsium arvense is a globally distributed weed that grows in various habitats. Ethnomedicinally, the plant is employed against gastrointestinal ailments, hypertension, bleeding, metrorrhagia, scabies, pyogenic infections, ulcers, and skin infections. Kaempferol-3-O-*β*-D-glucopyranoside, quercetin-3-O-*β*-D-glucopyranoside, hispidulin-7-O-*β*-D-glucopyranoside, luteolin-5-O-*β*-D-glucopyranoside, caffeic acid, chlorogenic acid, enicin, rutin, stigmasterol, and acacetin represent diverse phytocomposition of this weed. The current review study highlighted antioxidant, antibacterial, and antiproliferative activities. The major limitation of the antimicrobial studies is that researchers did not reported MIC, as IZD evaluation is only a preliminary study. *Cirsium arvense* extracts' antiproliferative ability against HeLa, A43, and MCF7 cell lines was evaluated, but vast research is still necessary. Although *C. arvense* has been utilized in various ethnomedicines, its pharmacological potential has yet to be thoroughly investigated, especially its toxicity (LC_{50} 51 µg/ml).

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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