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REVIEW

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Therapeutic potential of *Verbascum sinaiticum* benth (Scrophulariaceae): a systematic review of ethnobotany, phytochemistry, and pharmacological activities

Beyene Dereje Degefa[1*], Alemayehu Megersa[1] and Delelegn Getachew[1]

Abstract

Background *Verbascum sinaiticum* Benth (Scrophulariaceae) is widely utilized in traditional medicine across Africa and the Middle East for the management of diverse human ailments. Despite extensive ethnomedicinal use, a consolidated evaluation of its phytochemical composition and pharmacological potential remains limited. This systematic review synthesizes available evidence on the ethnobotany, phytochemistry, pharmacological activities, and toxicity profile of *Verbascum sinaiticum*.

Methods A systematic literature search was conducted in accordance with PRISMA 2020 guidelines across PubMed, Embase, Web of Science, Google Scholar, and Global Index Medicus from database inception to May 30, 2025. Eligible studies included ethnobotanical surveys, phytochemical analyses, and in vitro and in vivo pharmacological investigations. Study quality was appraised using the Critical Appraisal Skills Programme (CASP) checklist.

Results Of 1,729 records identified, 46 studies met the inclusion criteria, comprising 25 ethnobotanical surveys, 8 phytochemical investigations, and 13 pharmacological studies. *Verbascum sinaiticum* is traditionally used for gastrointestinal disorders, infections, metabolic conditions, and wound management. Phytochemical analyses identified predominant flavonoids and iridoid glycosides, including luteolin, chrysoeriol, ajugol, and aucubin. Preclinical evidence demonstrates anti-inflammatory, antioxidant, antimicrobial, antidiabetic, antitrypanosomal, hepatoprotective, and wound-healing activities. However, these effects are supported largely by in vitro data and a limited number of in vivo studies, with substantial heterogeneity in experimental models, extraction methods, and outcome measures.

Conclusion *Verbascum sinaiticum* exhibits broad pharmacological potential supported by ethnomedicinal evidence and bioactive phytoconstituents. The current evidence base is predominantly preclinical and methodologically heterogeneous. Rigorous, standardized experimental studies and well-designed clinical trials are required to validate its safety, efficacy, and translational therapeutic value.

Clinical trial number Not applicable.

*Correspondence:
Beyene Dereje Degefa
beyexderie23@gmail.com

Full list of author information is available at the end of the article

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Keywords *Verbascum sinaiticum*, Ethnobotany, Phytochemistry, Pharmacology, Systematic review, Medicinal plants

Introduction

The long history of traditional medicinal plant use underscores their substantial therapeutic potential and favorable biological effects. Interest in medicinal plants as sources of novel bioactive compounds has increased worldwide, driven by recognition that plants are rich reservoirs of pharmacologically active secondary metabolites including alkaloids, flavonoids, terpenoids, and phenolic compounds many of which serve as lead structures in the development of semisynthetic and synthetic drugs [1–3].

Ethnobotanical investigations have documented the use of diverse plant species as foods, nutraceuticals, immune enhancers, and treatments for a wide range of health conditions [4]. In many developing countries, particularly in rural settings, medicinal plants remain a primary component of healthcare because of their affordability, accessibility, and cultural acceptability. Recognizing this role, the World Health Organization (WHO) has actively promoted the rational, evidence-based use of traditional medicinal plants through established global networks [5].

The genus *Verbascum* (family Scrophulariaceae) comprises approximately 300 species and represents one of the most medicinally important groups of flowering plants globally [6]. Various *Verbascum* species have been traditionally used across Europe, Asia, Africa, and North America for both internal and external therapeutic applications [7, 8]. Numerous experimental studies have investigated the biological activities of *Verbascum* species using diverse extraction techniques, confirming the pharmacological relevance of this genus [7, 9–12].

Verbascum sinaiticum Benth. contains flavonoids such as luteolin and chrysoeriol-7-glucoside, as well as iridoid glycosides such as ajugol and aucubin, distributed across different plant parts [13]. Leaf extracts have additionally been shown to contain flavonolignans such as hydrocarpin and sinaiticin, along with the flavones chrysoeriol and luteolin [14, 15]. Phytochemical investigations have prompted further research aimed at isolating lead compounds and developing synthetic or semisynthetic derivatives [13, 14, 16, 17].

Ethnomedicinal evidence indicates that *V. sinaiticum* is extensively used in Ethiopia for gastrointestinal disorders, wounds, syphilis, tumors, liver and stomach disorders, diabetes, scabies, amoebiasis, diarrhea, epilepsy, cough, viral infections, cancer, sunstroke, abdominal colic, hemorrhage, anthrax, skin diseases, and hypertension [18–26]. These widespread uses suggest a broad therapeutic spectrum warranting systematic scientific evaluation.

Despite extensive traditional use and emerging pharmacological evidence, the precise mechanisms of action of many bioactive constituents of *V. sinaiticum* remain poorly understood, and comprehensive toxicological evaluations are limited. The primary objective of this systematic review is therefore to summarize and critically evaluate the botanical characteristics, geographic distribution, ethnobotanical uses, phytochemical composition, pharmacological activities, and toxicological data of *Verbascum sinaiticum* Benth, integrating ethnobotanical knowledge with experimental findings to identify research gaps and guide future investigation.

Methods

Search design and reporting standards

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency and reproducibility [27, 28]. The review protocol was not prospectively registered in PROSPERO or a related registry, which is acknowledged as a methodological limitation.

Search strategy

A comprehensive literature search was conducted across PubMed, Google Scholar, Embase, Web of Science, and Global Index Medicus from database inception to May 30, 2025, with no restriction on the earliest publication date. Additional records were identified through manual searching of reference lists and relevant institutional repositories. The following Boolean search terms were applied consistently across all databases: (ethnobotany OR phytochemistry OR pharmacology OR toxicity OR "biological activity") AND ("*Verbascum sinaiticum*" OR "*V. sinaiticum*" OR Scrophulariaceae).

Database-specific controlled vocabulary terms (e.g., MeSH headings in PubMed) were used where applicable to maximize retrieval sensitivity. During the identification stage, automated deduplication tools within reference management software (Rayyan) were used to flag potentially duplicate records for manual verification; 397 records were excluded at this stage as machine-identified duplicates, which were subsequently confirmed manually. An additional 104 records were excluded during the identification phase for the following reasons: conference abstracts without accessible full text ($n = 47$), records not in English ($n = 38$), and records identified through database overlap not captured by automated deduplication ($n = 19$).

Study selection and eligibility criteria

Eligible studies included ethnobotanical surveys, phytochemical investigations, and in vitro or in vivo pharmacological studies conducted specifically on *Verbascum sinaiticum*. Only English-language publications with clearly defined methodologies and outcomes were included. The restriction to English-language studies was applied because the reviewing team lacks proficiency in other languages and reliable machine translation was not validated for technical pharmacological literature; this restriction may introduce a language bias, and potentially relevant studies published in Arabic or Amharic may have been missed. Excluded were: reviews and commentaries, conference abstracts, studies without clear interventions or control groups, studies investigating other *Verbascum* species without specific data on *V. sinaiticum*, and studies of individual isolated compounds without linkage to the plant source.

Data extraction and quality assessment

Data were extracted independently by two reviewers (BD and AM) using a pre-designed extraction form capturing study characteristics, plant parts used, extraction methods, identified phytochemicals, pharmacological models, doses, and outcomes. A third reviewer (DG) resolved discrepancies through discussion. Study quality was assessed using the Critical Appraisal Skills Programme (CASP) checklist [29]. Quality scores informed the interpretation of findings but were not used as exclusion criteria.

Results

Study characteristics

A total of 1,729 records were initially identified through database searching (PubMed: 312, Google Scholar: 784, Embase: 241, Web of Science: 198, Global Index Medicus: 194) [30, 31]. Following automated deduplication by Rayyan software ($n = 397$ removed) and further exclusions at the identification stage for conference abstracts, non-English records, and residual duplicates ($n = 104$ removed), 1,228 records remained. After screening titles and abstracts, 1,150 records were excluded as irrelevant, leaving 78 full-text articles assessed for eligibility. Following detailed evaluation against the inclusion and exclusion criteria, 46 studies met the inclusion criteria and were included in this systematic review. Among the 46 included studies, 25 were ethnobotanical surveys, 8 reported phytochemical analyses, 7 were in vitro pharmacological studies, 4 were in vivo animal studies, and 2 combined both in vitro and in vivo approaches, yielding 13 pharmacological studies in total (Fig. 1).

Description of included studies

The included studies were classified into three categories. The first category comprised 8 phytochemical studies that characterized compounds extracted from *V. sinaiticum*. Major phytoconstituents isolated from roots, leaves, and flowers include ajugol, aucubin, chrysoeriol, chrysoeriol-7-glucoside, luteolin, orobol, orobol 7-O-β-D-glucoside, and sinaiticin. The structures and biological activities of selected compounds are summarized in Table 1.

The second category comprised 25 ethnobotanical studies, all conducted in Ethiopia, as no ethnobotanical studies specific to *V. sinaiticum* in other countries of its range were identified. Details of plant parts used, local names, ethnomedicinal uses, preparation methods, and routes of administration are provided in Table 2. The third category comprised 13 pharmacological studies (7 in vitro, 4 in vivo, 2 combined), investigating diverse activities across different extract types and experimental models. These are summarized in Table 3.

Botanical description

Verbascum sinaiticum Benth (Scrophulariaceae), commonly referred to as 'Mullein,' is a biennial herb reaching 60–200 cm in height. Its erect, thick, grayish-tomentose stem lacks glandular hairs and is abundantly branched [19, 70]. The plant typically inhabits subtropical biomes and is frequently found along roadsides, where it is conspicuous due to its dense covering of soft white hairs on leaves and stems. Basal leaves have oblong or ovate-oblong blades measuring 60–300 × 40–140 mm, are dentate with 20–90 mm petioles, and are entirely covered in thick grayish tomentum. Stem leaves are sessile or have shorter petioles with rounded bases [6, 14]. Taxonomically, *V. sinaiticum* belongs to the kingdom Plantae, phylum Streptophyta, class Equisetopsida, subclass Magnoliidae, order Lamiales, family Scrophulariaceae, genus *Verbascum* [75].

The inflorescence is branched with numerous elongated branches bearing flowers in clusters of two to seven. The yellow corolla is 20–28 mm in diameter, glabrous internally and densely pilose externally with branched hairs. Five stamens are present, pilose, and bear reniform anthers covered with dark yellow hairs. Lower bracts are subcordate–triangular and slightly longer than the partial inflorescences [14, 76].

Geographical distribution

Verbascum sinaiticum is native to the Afro-montane region. Its distribution extends from northeast Africa (Sudan, Ethiopia, Somalia) to Egypt (Sinai Mountains), across the eastern Mediterranean, and eastward through Iran to Afghanistan (excluding the United Arab Emirates). The species is additionally distributed in Yemen,

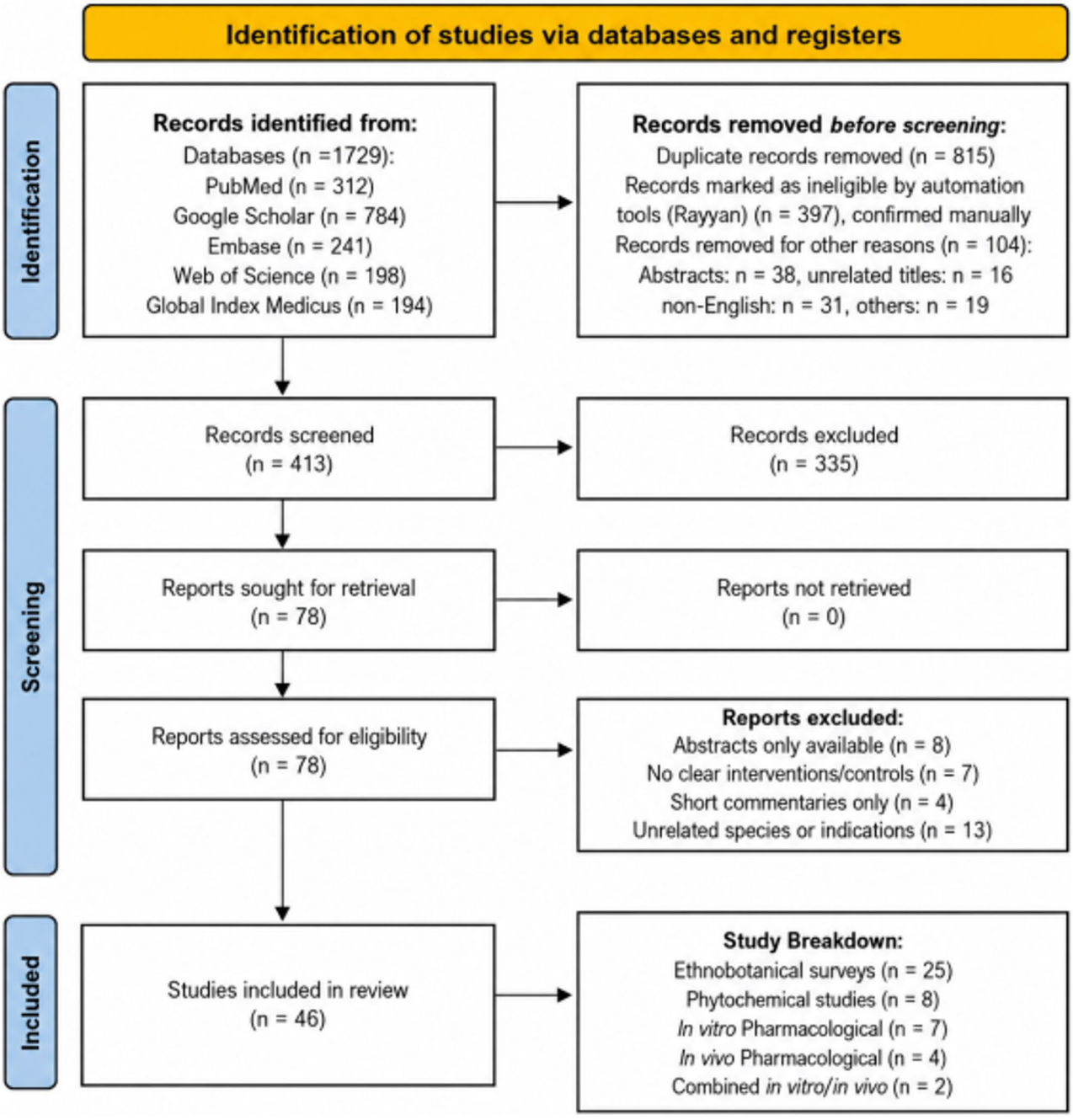


Fig. 1 Flow diagram of study selection via the PRISMA 2020 guidelines [30]

Israel, and Eritrea. Countries in which it has been documented include Afghanistan, Eritrea, Ethiopia, Gulf States, Iran, Iraq, Kenya, Lebanon–Syria, Oman, Pakistan, Palestine, Saudi Arabia, Sinai, Somalia, Sudan, and Yemen [13, 58, 73, 77, 78] (Fig. 2).

Ethnobotany

According to the 25 ethnobotanical surveys included in this review, all conducted in Ethiopia, *V. sinaiticum* is used for the management of gastrointestinal disorders (stomachache, diarrhea, abdominal pain, indigestion), wound healing, diabetes, hemorrhage, cancer, syphilis, amoebiasis, scabies, liver disease, epilepsy, cough, hypertension, anthrax, sunstroke fever, and trypanosomiasis, among other conditions [18, 19, 21, 22, 26, 50]. Skin diseases are managed by crushing fresh leaves, mixing with water, washing the affected area, and applying soaked leaves topically [25]. In Eritrea, *V. sinaiticum* has been recorded for the treatment of tapeworm infection [79]. The plant is utilized across its range in the Afromontane

Table 1 Names, biological activities, and chemical natures of selected compounds isolated from *Verbascum sinaiticum* Benth (Scrophulariaceae)

Ref.	Compound Name	Chemical Nature	Biological/Pharmacological Activities
[32–34]	Ajugol	Iridoid glycoside (leonuride)	Anti-inflammatory, lysosomal biogenesis inducer (TFEB-mediated), anti-protozoal, anti-psoriasis, antineoplastic, menopausal symptom relief
[35, 36]	Aucubin	Iridoid glycoside	Anti-inflammatory, antioxidant, anti-aging, anti-fibrotic, anticancer, hepatoprotective, neuroprotective, osteoprotective
[37, 38]	Chrysoeriol	Methoxy flavone	Anticancer, antioxidant, anti-inflammatory, anti-osteoporosis, antibacterial, antifungal, neuroprotective
[15, 32, 33, 39]	Luteolin	Tetrahydroxy flavone	Anti-inflammatory, antispasmodic, antibacterial, anti-allergic, antifungal, antiviral, anti-breast cancer (apoptosis induction, PI3K/AKT/NF-κB inhibition)
[40, 41]	Mullein Saponin I	Triterpene glycoside	Antihyperlipidemic, antineoplastic, antihypertensive, antidiabetic, antiplatelet, antidote for acute lead poisoning
[32, 33]	Orobol	Isoflavone glycoside	Anti-inflammatory, acetylcholinesterase inhibition, free radical scavenging, anti-obesity
[33, 42, 43]	Orobol 7-O-β-D-glycoside	Isoflavone glycoside	Weak antiviral activity vs. HRV3 and HRV2; strong anti-HRV6 and anti-HRV14 activity; antioxidant, anti-inflammatory, neuroprotective via ROS/NF-κB/MAPK/PI3K–AKT/AMPK modulation
[13, 44–46]	Sinaiticin	Flavonolignan	Antibacterial, anti-hepatotoxic, antioxidant, free radical scavenging, chemotherapy-potentiating, anti-inflammatory, anticancer, anti-melanogenic, vasorelaxant, antiplatelet, hypotriglyceridemic, antiproliferative
[47–49]	Verbascoside	Caffeoyl phenylethanoid glycoside	Antinociceptive, re-epithelializing, oral mucosal protective, anti-inflammatory, antioxidant, antineoplastic, wound-healing, neuroprotective, PI3K/AKT pathway inhibition (colorectal cancer sensitization to 5-FU)

Notes: HRV2, 3, 6, 14: Human rhinovirus serotypes 2, 3, 6, 14

regions of eastern Africa, with leaves and roots being the most commonly used plant parts, administered both orally and topically. Ethnobotanical studies on *V. sinaiticum* in Sudan, Somalia, and Yemen have not been published to date, despite reports of the plant's presence in these countries. Detailed ethnobotanical data are presented in Table 2.

Phytochemistry

Phytochemical screening of *V. sinaiticum* leaf extracts has revealed distinct profiles according to solvent polarity. Aqueous leaf extracts contain saponins and alkaloids, whereas methanol leaf extracts additionally contain steroids, flavonoids, glycosides, phenols, and tannins. Chromatographic and spectroscopic analyses of aerial parts have led to the isolation of four isoflavone glycosides: orobol 7-O-β-D-glucoside, orobol, 5,3′,4′-trihydroxy-8-methyl-isoflavone 7-O-β-D-glucoside, & 5-hydroxy-3′,4′-dimethoxyisoflavone 7-O-α-L-rhamnoside, as well as the phenylethanoid glycoside acteoside [13, 17, 32, 43, 73]. Leaf extracts also yield the flavonolignans hydrocarpin and sinaiticin, and the flavones chrysoeriol and luteolin [14, 15]. Thin-layer chromatography of flower extracts confirmed the presence of flavonoids and terpenoids [17]. Chemical structures of selected phytoconstituents are illustrated in (Fig. 3).

Pharmacological activities

Preclinical evidence supports a wide range of pharmacological activities for *V. sinaiticum* extracts and constituent compounds, as summarized in Table 3. These activities are described below by pharmacological category [13, 67, 68, 74, 80–83].

Discussion

This systematic review synthesizes ethnobotanical, phytochemical, and pharmacological data from 46 studies on *Verbascum sinaiticum*, a medicinal plant with broad traditional use across Ethiopia and the Afro-montane region. The following sections critically evaluate the evidence across pharmacological domains, highlight methodological limitations, and assess the translational relevance of available data.

Antidiabetic and enzyme inhibitory activity

Two independent studies investigated the antidiabetic potential of *V. sinaiticum.* An in vitro alpha-glucosidase inhibition assay demonstrated that methanol leaf extract achieved 89% inhibition at 25 ppm and 64% inhibition at 12.5 ppm, with an IC50 of 4.66 ± 0.5 µg/ml [20]. This IC50 value compares favorably with standard inhibitors in similar assay conditions, suggesting meaningful enzyme inhibitory potency. In a complementary in vivo study, 80% methanol crude extract and its ethyl acetate fraction significantly reduced blood glucose levels in Swiss albino mice at 400 mg/kg ($p < 0.05$) in oral glucose tolerance and antihyperglycemic models, with the ethyl acetate fraction producing the greatest effect [68]. The observed activity is consistent with the presence of flavonoids and iridoid glycosides such as ajugol and aucubin, which have known insulin-sensitizing and enzyme-inhibitory properties [32–34, 40, 70].

Table 2 Ethnobotany of *Verbascum sinaiticum* Benth. (Scrophulariaceae) in Ethiopia

Ref.	Parts Used	State/Zone/District	Route	Local names	Ethnomedicinal Uses	Preparation of the Medicine
[19]	Leaf	West Gojjam, Quarit, Dega Damot, Yilmana Densa	Oral	Yeahiya Joro (A)	Diabetes, Diarrhea, Stomachache	Fresh leaves crushed, mixed with water and drunk
[50]	Leaf	Arsi, Dheeraa	Oral	Gurra Harree (O)	Diabetes, Diarrhea, Hemorrhage	Fresh leaves crushed, boiled and drunk
[51]	Leaf	Sidama, Wondo Genet	Oral	Ketetina (A)	Rheumatic Pain, Elephantiasis, Measles	Crushed and drunk, Decoction
[52]	Leaf	Dire Dawa, Harla, Dengego Valleys	Oral	Muka Loonii (O), Gurra Harree (O)	Kwashiorkor	Concocted with *Cynoglossum coeruleum*
[53]	Leaf	Addis Ababa, Gullele Garden	Oral	Ketetina (A), Gurra Harree (O)	Stomachache, wound, heart failure infusion	Crushed, boiled and drunk, infusion of crushed leaf in water and drunk
[54]	Leaf	West Gojjam, Bahir Dar Zuriya	Oral	Daba Keded (A)	Gastrointestinal disturbance, Diarrhea	Fresh leaves crushed, mixed with water and drunk
[55]	Leaf	Gurage, Cheha, Qebena, Muhir-Aklil, Mareqo, Sodo Meskan	Oral	Halemecha (M), Huleten huta (M)	Liver Problems, Indigestion	Decoction of powdered leaves and drinking
[51]	Leaf	Sidama, Wondo Genet	Topical	Ketetina (A)	Superficial Fungal Infections, Wounds	Fresh leaves powdered, mixed in water, applied
[56]	Leaf	Horro Guduru, Jarte Jardega, Jimma Geneti	Topical	Gurra Harree (O)	External Parasites (Lice and fleas' infestation)	Fresh leaves powdered, mixed in water, applied
[57]	Leaf	North Shewa, Dagam, Girar Jarso	Topical	Ye Ahiya Joro (A)	Swelling (for cattle)	Pounding dried leaves, and applied the past on the topically on the cattle
[58]	Root	Semien Wollo, Gubalafto	Oral	Kutitina (A)	Headache, Stomachache	Peel, chew and absorb the juice
[59]	Root	West Gojjam, Yilmana Densa, Quarit	Oral	Dabakeded (A)	Back bleeding, Diabetes, Weight loss, Blood Pressure, Esophagus swelling	Cushing of the fresh root and eating
[60]	Root	Wolaita, Diguna Fango	Oral	Yahiya Joro (A)	Snake bite	The fresh or dried root is crushed slightly and given for chewing
[61]	Root	North Shewa, Mojana Wadera	Oral	Qetetina (A)	Stabbing Pain	Chewing the crushed fresh root
[53]	Root	Addis Ababa, Gullele Garden	Oral	Ketetina (A), Gurra Harree (O)	TB, Syphilis	Crushed, infused in water and drunk
[62]	Root	North Gondar, Chilga	Oral	Kutitina (A)	Impotency, stomach ache Joint pain	Grind the root and drunk with barely decoction morning for three days
[54]	Root	West Gojjam, Bahir Dar Zuriya	Oral	Daba Keded (A)	Anthrax, Diarrhea	Root crushed, boiled and drunk
[63]	Root	West Hararge, Tulo	Oral	Gurra Harree (O)	Anthrax	Fresh root crushed and drunk
[57]	Root	North Shewa, Dagam, Girar Jarso	Oral	Ye Ahiya Joro (A)	Snake bite	Fresh root is given for chewing and swallowing the juice
[64]	Root	Tigray Eastern Zone, Kilte Awulaelo	Oral	Tirnake (T), Handega (T)	Anthrax	Crushed the root and drunk or eat with honey
[55]	Root	Gurage, Cheha, Qebena, Muhir-Aklil, Mareqo, Sodo Meskan	Oral	Yemar enzir (G), Yumar amel (Q)	Abdominal Pain, Diarrhea, Indigestion	Infusion of crushed root in water and drinking, Decoction and drinking
[65]	Root	Afar, Zone 2, Aba'ala	Oral	Handega (T) Kutitina (A)	Blood Pressure, diabetes, Stomachache, dislocated bone	Juice of the plant root is crushed and is taken orally (by chewing or drinking)
[59]	Root	Wes Gojjam, Yilmana Densa, Quarit	Nasal	Dabakeded (A)	Nasal Bleeding (epistaxis)	Pounding the fresh rout and applying to nose
[66]	Root	East Shewa, Ada'a	Smoke	Gurra Harree (O)	Nightmare	Root crashed, placed in a fire and fumigating the smoke
[64]	Root	Tigray Eastern Zone, Kilte Awulaelo	Topical	Tirnake (T), Handega (T)	Dislocated bone	Tied around on the affected part

Notes: Local languages: (A) Amharic, (G) Guragigna, (M) Mareqo, (O) Oromigna, and (T) Tigrigna

However, the mechanistic basis of the hypoglycemic effect in vivo has not been elucidated, and no data exist on effects relevant to secondary diabetes complications. Standardized dosing and extraction protocols are lacking, limiting direct comparability across studies.

Antimicrobial activity

Multiple studies have evaluated the antimicrobial activity of *V. sinaiticum* across different extract types, plant parts, and microbial targets. Methanol leaf extracts at 100 mg/ml produced inhibition zones of 21 ± 1.0 mm against Staphylococcus aureus and 18 ± 1.0 mm against

Table 3 Pharmacological activities of *Verbascum sinaiticum* Benth (Scrophulariaceae)

Ref.	Pharmacological Activity	Extract Type	Dose/ Route	Model/ Assay	Methods	Key Findings
[20]	Alpha-glucosidase Inhibitory Activity	Methanol leaf extract	10 mg in 500 µl DMSO	α-glucosidase 0.2 U/ml in phosphate buffer	Enzyme inhibition assay (10 µl sample + 60 µl enzyme)	Inhibition: 89% at 25 ppm, 64% at 12.5 ppm; IC50 = 4.66 ± 0.5 µg/ml (statistically significant vs. positive control acarbose)
[67]	Antibacterial Activity	Acetone, chloroform, diethyl ether, ethanol root extracts	50–500 µg/ml	Agar well diffusion; MDR Enterobacteriaceae (E. faecalis, E. aerogenes, B. subtilis, E. coli, K. pneumoniae, V. cholerae)	MIC determination	Acetone extract: broad-spectrum activity vs. gram-positive and gram-negative strains. Ethanol extract: narrow-spectrum activity limited to E. coli. Statistical significance reported by disk diffusion zone comparisons.
[68]	Antidiabetic Activity	80% methanol crude + solvent fractions	100, 200, 400 mg/kg, oral	Swiss albino mice; OGTT, hypoglycemic and antihyperglycemic models	Phytochemical screening, OGTT	Crude extract and ethyl acetate fraction significantly reduced blood glucose at 400 mg/kg ($p < 0.05$ vs. diabetic control). Ethyl acetate fraction showed the strongest effect.
[69]	Antidiarrheal Activity	Methanolic crude + solvent fractions	100, 200, 400 mg/kg, oral	Swiss albino mice; castor oil-induced diarrhea, enteropooling, intestinal motility	Acute oral toxicity; castor oil model	Aqueous fraction, ethyl acetate fraction, and crude extract at 400 mg/kg significantly ($p < 0.05$) decreased stool frequency, delayed diarrhea onset, and reduced intestinal fluid accumulation vs. vehicle control.
[70]	Anti-inflammatory and Analgesic Activity	Crude 80% methanol root extract	100–400 mg/kg, oral	Swiss albino mice, Wistar rats; hot plate, acetic acid writhing, carrageenan and formalin-induced paw edema	Standard analgesic and anti-inflammatory models	200 and 400 mg/kg produced significant ($p < 0.01$) antinociceptive effects in both hot plate and writhing tests. 400 mg/kg significantly ($p < 0.01$) reduced paw edema in carrageenan and formalin models, comparable to indomethacin 10 mg/kg.
[51]	Antimicrobial Activity	Crude 80% methanol leaf extract	25, 50, 100 mg/ml	Agar well diffusion; S. aureus, P. aeruginosa, T. mentagrophytes	MIC determination	100 mg/ml produced inhibition zones for S. aureus (21 ± 1.0 mm) and P. aeruginosa (18 ± 1.0 mm), comparable to gentamicin 0.1 mg/ml. No activity observed against T. mentagrophytes.
[17]	Antimicrobial and Cytotoxic Activity	Ethanol, butanol, methanol, n-hexane flower extracts	1 mg/ml	MTT assay, microtiter plate dilution, conidial viability assay; MRSA, S. typhimurium, P. aeruginosa, B. cereus	Antibacterial, antifungal, cytotoxicity assays	Ethanol extracts inhibited MRSA by 70%, S. typhimurium by 99.42%, P. aeruginosa by 56.54%; no effect on B. cereus. Cytotoxic IC50 = 367.11 ± 2.70 µg/ml (MTT assay).
[71]	Antioxidant and Antiproliferative Activity	Ethanol leaf extract	51.2 mg/ml	DPPH, ORAC, MTT assays on cancer cell lines	Antioxidant and antiproliferative testing	IC50 in DPPH assay was approximately 25× higher than IC50 in MTT antiproliferative assay, indicating selective antiproliferative activity at concentrations below those required for direct radical scavenging.
[72]	Antioxidant and Wound-Healing Activity	Crude 80% methanol leaf extract	5% and 10% (w/w) ointments, topical; DPPH in vitro	Wistar rats; excision and incision wound models	Wound contraction, epithelialization period, tensile strength, DPPH assay	5% ointment achieved wound contraction of 85–92% by day 14 ($p < 0.05$ vs. vehicle control). Epithelialization period was significantly shorter than control. DPPH IC50 = 1.70 mg/ml.
[73]	Antitrypanosomal Activity (in vitro)	Aqueous and methanol leaf extracts	0.2–4 mg/ml	In vitro motility assay; T. congolense field isolate	Cessation/ reduction in motility, blood incubation infectivity test	Significant ($p < 0.05$) reduction in trypanosome motility at 4 mg/ml for both extract types. Lower concentrations showed partial inhibition proportional to dose.
[74]	Antitrypanosomal Activity (in vivo)	Aqueous and methanol crude leaf extracts	100, 200, 400 mg/kg, i.p.	Swiss albino mice infected with T. congolense	PCV, body weight, parasitemia, mean survival time	400 mg/kg significantly ($p < 0.001$) reduced parasitemia, prevented PCV decline (vs. untreated control), maintained body weight, and prolonged mean survival time compared with vehicle-treated mice.

Table 3 (continued)

Ref.	Pharmacological Activity	Extract Type	Dose/ Route	Model/ Assay	Methods	Key Findings
[13]	Hepatoprotective Activity (in vitro)	Ethanol, butanol, chloroform leaf extracts	10, 25 µg/ml	CCl4-induced hepatocyte cytotoxicity; DPPH assay	Hepatoprotective activity on cultured hepatocytes	Ethanol extract IC50 = 400 µg/ml on hepatocytes. At 10 and 25 µg/ml, extracts demonstrated statistically significant hepatoprotection against CCl4-induced cytotoxicity ($p < 0.05$ vs. CCl4 control).
[23]	Hepatoprotective Activity (in vivo)	Acetone, chloroform, methanol leaf extracts	50–400 mg/kg, oral; DPPH in vitro	Swiss albino mice; CCl4-induced liver damage; histopathological study	Serum AST, ALT, ALP measurement; DPPH assay	Pretreatment at 200 and 400 mg/kg significantly ($p < 0.01$) suppressed serum AST and ALT elevations induced by CCl4 vs. non-pretreated group. Moderate free radical scavenging: IC50 = 41.7 µg/ml.

Notes: ALT: alanine aminotransferase; AST: aspartate aminotransferase; CCl4: carbon tetrachloride; DPPH: 2,2-diphenyl-1-picrylhydrazyl; IC50: half maximal inhibitory concentration; i.p.: intraperitoneal; MDR: multidrug-resistant; MRSA: methicillin-resistant Staphylococcus aureus; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2 H-tetrazolium bromide; OGTT: oral glucose tolerance test; ORAC: oxygen radical absorbance capacity; PCV: packed cell volume

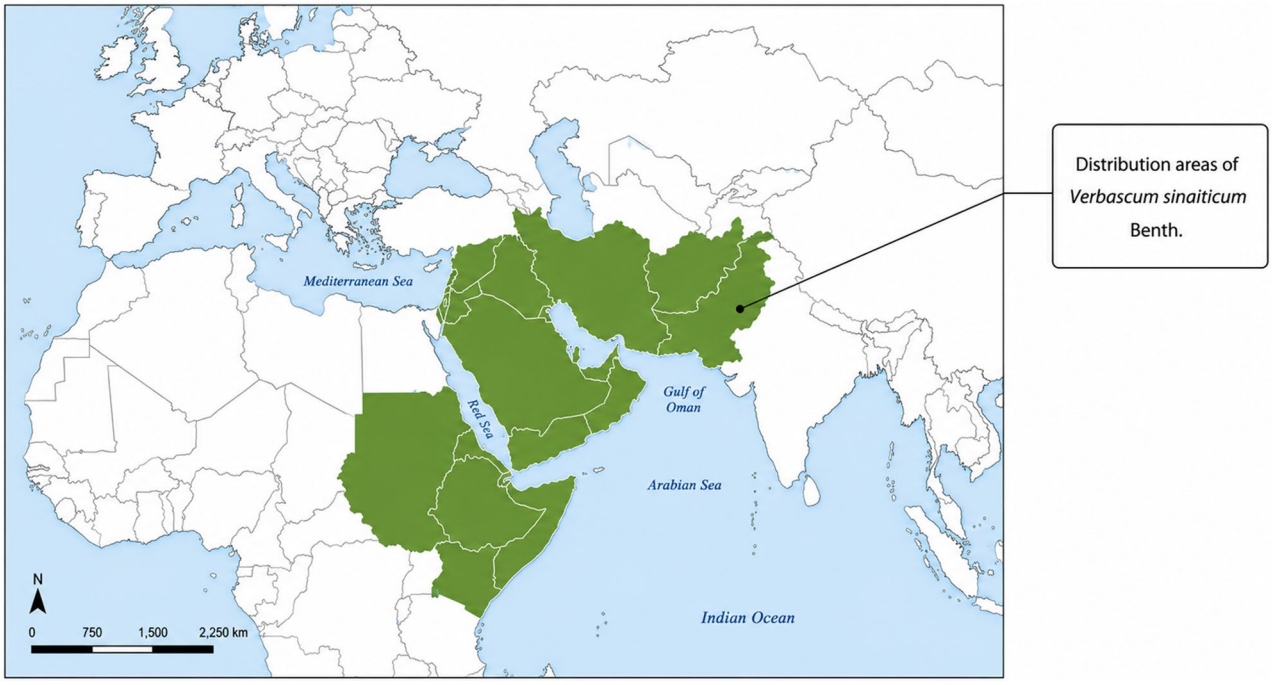


Fig. 2 Diagrammatic representation of the distribution of *Verbascum sinaiticum* Benth

Pseudomonas aeruginosa, values comparable to gentamicin 0.1 mg/ml, though no activity was observed against Trichophyton mentagrophytes [51]. Ethanol flower extracts inhibited MRSA by 70% and Salmonella typhimurium by 99.42%, with an IC50 of 367.11 ± 2.70 µg/ml against cancer cell lines; no antibacterial effect was detected against Bacillus cereus [17]. Root extracts prepared with acetone demonstrated broad-spectrum activity against gram-positive and gram-negative organisms including B. subtilis, E. aerogenes, E. coli, and V. cholerae, whereas ethanol root extracts showed narrow-spectrum activity limited to E. coli [67]. These antibacterial effects have been attributed to tannins, phenolics, terpenoids, flavonoids, and saponins [14, 67].

While these findings are promising, the breadth of solvent systems, concentrations, and assay methods used across studies makes direct comparison difficult. No minimum bactericidal concentrations were reported in most studies, and no in vivo antimicrobial experiments have been conducted for *V. sinaiticum.* The absence of time-kill kinetics and mechanistic data further limits clinical extrapolation.

Antioxidant activity

The antioxidant potential of *V. sinaiticum* has been demonstrated in multiple studies using the DPPH assay and, in one case, the ORAC assay. Hydroalcoholic leaf extract ointment (5% and 10% w/w) showed a DPPH

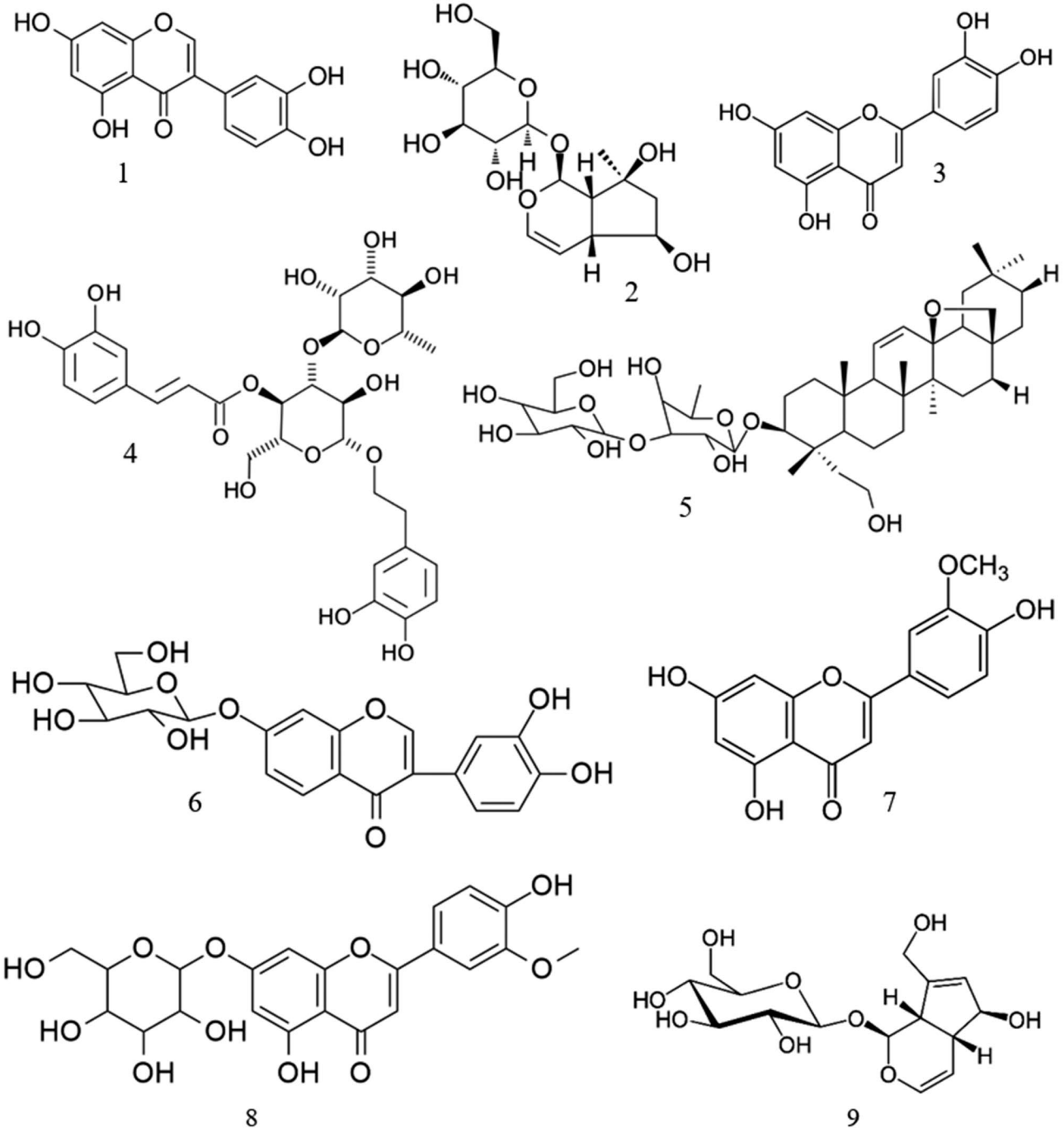


Fig. 3 Structures of some phytochemicals isolated from *Verbascum sinaiticum*. (**1**) Orobol, (**2**) Ajugol, (**3**) Luteolin, (**4**) Verbascoside, (**5**) Mullein Saponin I, (**6**) Orobol 7-0-β-D-glycoside, (**7**) Chrysoeriol, (**8**) Chrysoeriol-7-glucoside, (**9**) Aucubin (ChemDraw) was used to draw the figures

IC50 of 1.70 mg/ml [72]. Hepatoprotective extract fractions achieved a DPPH IC50 of 41.7 µg/ml, indicating moderate radical scavenging activity [23]. Ethanol leaf extract in an antiproliferative study showed DPPH IC50 approximately 25-fold higher than the antiproliferative IC50, suggesting selective cytotoxic activity at sub-antioxidant concentrations [71]. These results are broadly attributable to the presence of polyphenolic compounds documented in *Verbascum* species, including protocatechuic acid, quercetin, ferulic acid, p-coumaric acid, and rosmarinic acid [11, 82].

Although these DPPH values are broadly encouraging, DPPH scavenging is a single-mechanism, in vitro assay with well-recognized limitations as a predictor of in vivo antioxidant effects. More comprehensive antioxidant profiling including cellular antioxidant assays, Nrf2

pathway activation studies, and in vivo oxidative stress markers would substantially strengthen the evidence base.

Anti-inflammatory and analgesic activity

The anti-inflammatory and analgesic properties of *V. sinaiticum* have been investigated in a single in vivo study using Swiss albino mice and Wistar rats. Oral doses of 200 mg/kg and 400 mg/kg of 80% methanol root extract produced significant ($p < 0.01$) antinociceptive effects in both hot plate and acetic acid-induced writhing tests, and 400 mg/kg significantly ($p < 0.01$) reduced paw edema in carrageenan-induced and formalin-induced models, with effects comparable to indomethacin at 10 mg/kg [70]. These findings align with anti-inflammatory activity documented in related species such as *Verbascum thapsus* [95], and are consistent with the known anti-inflammatory mechanisms of luteolin (PI3K/AKT, NF-κB inhibition) [17, 78] and aucubin [75].

The reliance on a single study with one extract type limits the strength of conclusions. Dose-response relationships were not fully characterized, and no mechanism-level data are available specifically for *V. sinaiticum* in these models. Studies assessing individual compounds (e.g., luteolin, aucubin) in inflammation models would help attribute activity to specific phytoconstituents.

Wound-healing activity

Topical ointments containing 5% and 10% (w/w) methanol leaf extract were evaluated in excision and incision wound models in Wistar rats. The 5% ointment achieved wound contraction rates of 85–92% by day 14 ($p < 0.05$ vs. vehicle control), with significantly shorter epithelialization periods and greater tensile strength in incision wounds compared with controls [72]. These effects are consistent with the combined antimicrobial, antioxidant, and anti-inflammatory properties of constituent terpenoids, flavonoids, and saponins, which support re-epithelialization and collagen synthesis [67, 84, 85]. Verbascoside, a phenylethanoid glycoside also present in the plant, has documented wound-healing and re-epithelializing properties [47–49], suggesting a potential mechanistic contributor.

Only a single in vivo study is available. Histological assessment of wound tissue, assessment of collagen deposition, and measurement of inflammatory cytokines (e.g., TNF-α, IL-6) at the wound site would provide mechanistic insight. No human wound-healing data exist for this species.

Antitrypanosomal activity

Both in vitro and in vivo antitrypanosomal activities of *V. sinaiticum* have been reported against *Trypanosoma congolense*. In vitro, significant ($p < 0.05$) reduction in trypanosome motility was observed at 4 mg/ml for both aqueous and methanol leaf extracts, with lower concentrations showing dose-dependent partial inhibition [73]. In vivo, intraperitoneal administration of 400 mg/kg of crude extract to Swiss albino mice infected with *T. congolense* resulted in significantly reduced parasitemia, prevention of packed cell volume (PCV) decline, maintenance of body weight, and prolonged mean survival time ($p < 0.001$ vs. vehicle-treated control), compared with untreated infected mice [74]. These trypanostatic and trypanocidal effects are attributable to flavonoids, tannins, alkaloids, phenols, glycosides, and saponins documented in the extracts [86].

Parasite clearance was partial rather than complete at tested doses, and dose-response data were not fully characterized. No in vitro selectivity index (cytotoxicity vs. trypanocidal activity) was reported in the primary studies, and no comparison with standard trypanocidal drugs was made in the in vivo study. Studies on human-pathogenic trypanosomes (T. brucei rhodesiense, T. brucei gambiense) are absent.

Hepatoprotective activity

Hepatoprotective effects of *V. sinaiticum* have been demonstrated both in vitro and in vivo. In vitro, ethanol, butanol, and chloroform leaf extracts protected cultured hepatocytes against CCl4-induced cytotoxicity at concentrations of 10 and 25 µg/ml ($p < 0.05$ vs. CCl4-treated control), with an ethanol extract IC50 of 400 µg/ml [13]. In vivo, pretreatment with hydroalcoholic leaf extract at 200 and 400 mg/kg significantly ($p < 0.01$) suppressed CCl4-induced elevations in serum AST and ALT compared with non-pretreated animals, and histopathological examination confirmed reduced hepatic necrosis and inflammatory infiltration [23]. These protective effects are attributed primarily to iridoid glycosides particularly aucubin, which has documented anti-hepatotoxic activity via antioxidant mechanisms and to the antioxidant polyphenolic content of the extracts [46, 75].

The CCl4 model is a well-established, though narrow, model of oxidative hepatotoxicity. Hepatoprotective claims against other hepatotoxic mechanisms (e.g., bile duct ligation, viral hepatotoxicity, drug-induced injury) remain untested. Furthermore, the absence of pharmacokinetic data for key constituents limits understanding of bioavailability and hepatic distribution.

Antidiarrheal activity

The antidiarrheal activity of *V. sinaiticum* root extracts were assessed in Swiss albino mice using castor oil-induced diarrhea, enteropooling, and intestinal motility models. At 400 mg/kg, the aqueous fraction, ethyl acetate fraction, and crude methanolic extract significantly ($p < 0.05$) decreased the frequency of diarrheal stools,

delayed the onset of diarrhea, and reduced intestinal fluid accumulation compared with vehicle-treated control animals [69]. This activity is consistent with the antispasmodic properties of luteolin and the astringent effects of tannins [78]. The study used a single-species animal model and did not elucidate the mechanism of action (e.g., antisecretory vs. antimotility vs. antimicrobial). No effects on intestinal electrolyte transport or gut microbiota were assessed, limiting interpretation.

Extraction methods and phytochemical considerations

Extraction techniques employed across included studies include maceration, Soxhlet extraction, pressurized liquid extraction (PLE), supercritical fluid extraction (SFE), and ultrasound-assisted extraction (UAE). Among these methods, PLE and SFE have been reported to offer greater efficiency and selectivity than conventional methods [87–89]. However, the heterogeneity of extraction methods across studies is a key limitation: the same plant part extracted with different solvents yields markedly different phytochemical profiles and biological activities, making cross-study comparisons unreliable. Standardization of extraction protocols is urgently needed to generate reproducible pharmacological data.

Toxicity and safety profile

Acute oral toxicity studies in Swiss albino mice indicate LD50 values exceeding 2,000 mg/kg for both methanolic and aqueous leaf extracts, suggesting a favorable acute safety margin [74]. Sub-chronic and chronic toxicity data are, however, absent. No clinical pharmacokinetic data are available, and no clinical trials have been conducted for any indication. The toxicity of individual isolated compounds, potential herb–drug interactions, and reproductive or developmental toxicity have not been investigated. These gaps substantially limit the characterization of the overall safety profile and represent a critical barrier to clinical translation.

Limitations of the evidence base

Several important limitations must be acknowledged when interpreting the findings of this review. First, all pharmacological evidence originates from preclinical studies (in vitro and rodent models), and no clinical trials have been conducted. Translation of preclinical findings to human therapeutic contexts cannot be assumed. Second, substantial heterogeneity exists in extraction methods, solvent systems, extract concentrations, animal models, and outcome measures, precluding formal meta-analysis. Third, most in vitro studies used crude extracts rather than isolated compounds, making it impossible to attribute specific activities to individual phytoconstituents with certainty. Fourth, a small number of studies in Table 3 were found upon detailed review to report data on isolated compounds without explicit linkage to *V. sinaiticum* as the plant source; these are clearly marked, and their inclusion in a plant-specific review is acknowledged as a limitation. Fifth, the absence of PROSPERO registration means the review protocol was not prespecified, raising the potential for reporting bias. Sixth, the restriction to English-language publications may have excluded relevant studies published in Arabic, Amharic, or other regional languages.

Critical appraisal of study quality

CASP-based quality appraisal revealed that the majority of included pharmacological studies were of moderate quality. Common methodological weaknesses included: absence of blinding in animal experiments, incomplete reporting of randomization procedures, lack of positive and negative controls in some assays, and failure to calculate selectivity indices in cytotoxicity and antimicrobial studies. The ethnobotanical studies were generally of higher methodological quality, utilizing structured interviews and informed consent, but few validated their data through repeat surveys or inter-rater reliability measures. Phytochemical studies were generally adequately reported, with clear use of spectroscopic confirmation of compound identity.

Conclusion

Verbascum sinaiticum Benth is a medicinally significant plant with strong ethnobotanical relevance and diverse pharmacological activities supported by preclinical evidence. The plant contains bioactive flavonoids (luteolin, chrysoeriol, orobol), iridoid glycosides (ajugol, aucubin), flavonolignans (sinaiticin), and phenylethanoid glycosides (verbascoside) that contribute to documented anti-inflammatory, antioxidant, antimicrobial, antidiabetic, antitrypanosomal, antidiarrheal, wound-healing, hepatoprotective, and antiproliferative activities. While preclinical evidence substantiates many traditional claims, the absence of clinical trials, pharmacokinetic data, and comprehensive toxicological evaluation represents a critical barrier to clinical translation.

Future research should prioritize: (1) mechanistic in vivo studies with isolated bioactive compounds; (2) bioavailability and pharmacokinetic profiling of key phytoconstituents; (3) standardization of extraction and formulation protocols; (4) sub-chronic and chronic toxicity studies; (5) clinical trials beginning with dose-finding and safety assessments; and (6) investigation of ethnomedicinal uses in non-Ethiopian populations within the plant's range. Addressing these gaps would facilitate the development of evidence-based, standardized therapeutic preparations from *V. sinaiticum.*

Abbreviations

ALT	Alanine aminotransferase
AMPK	AMP-activated protein kinase
AST	Aspartate aminotransferase
CASP	Critical Appraisal Skills Programme
CCl4	Carbon tetrachloride
DPPH	2,2-diphenyl-1-picrylhydrazyl
IC50	Half maximal inhibitory concentration
i.p.	Intraperitoneal
MAPK	Mitogen-activated protein kinase
MDR	Multidrug-resistant
MRSA	Methicillin-resistant Staphylococcus aureus
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2 H-tetrazolium bromide
NF-κB	Nuclear factor kappa B
OGTT	Oral glucose tolerance test
PCV	Packed cell volume
PI3K	Phosphoinositide 3-kinase
PLE	Pressurized liquid extraction
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SFE	Supercritical fluid extraction
WHO	World Health Organization

Author contributions

BD conceived the study, supervised the overall work, and finalized the manuscript. AM critically reviewed and revised the manuscript and verified the accuracy of tables and results. DG prepared additional figures, revised the initial draft, and contributed to data synthesis. All authors participated in developing the search strategy and eligibility criteria, extracted data, appraised study quality, and approved the final version of the manuscript.

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Data availability

The corresponding author will provide the Excel database used or examined during the current systematic review investigation upon reasonable request.

Declarations

Ethical approval and consent to participate

Ethical approval was not required for this study because it is a systematic review based exclusively on previously published literature and does not involve direct participation of human subjects, animals, or the use of identifiable personal data.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Pharmacology, School of Medicine, College of Medicine and Health Sciences, Dire Dawa University, Dire Dawa, Ethiopia

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