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Review Article

MEDICINAL USES, BIOLOGICAL AND PHYTOCHEMICAL PROPERTIES OF *HELICHRYSUM FOETIDUM* (L.) MOENCH. (ASTERACEAE)

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ABSTRACT

Helichrysum foetidum is a medicinal plant species with various medicinal applications among different ethnic groups in Africa, Asia, and Europe. This review was aimed at providing a critical appraisal of the existing medicinal uses, biological activities, and phytochemical components of *H. foetidum*. Literature search for information on medicinal uses, biological activities, and phytochemical components of *H. foetidum* was conducted using various online search engines such as Scopus, Google Scholar, Mendeley, and Web of Science. Additional information on these aspects was sourced from the university library. Literature studies revealed that *H. foetidum* is mainly used to induce trances and as herbal medicine against wounds, sores, dysmenorrhea, eye infections, influenza, and as a sedative. Phytochemical compounds identified from the species include chalcones, diterpenoids, flavanols, flavonoids, phenolics, phenols, and proanthocyanidins. Pharmacological studies revealed that *H. foetidum* extracts and compounds have antibacterial, antifungal, antiviral, antioxidant, protease-inhibiting, and cytotoxicity activities. There is a need for advanced phytochemical and pharmacological evaluations and clinical trials aimed at evaluating the therapeutic potential of *H. foetidum* in Africa, Asia, and Europe.

Keywords: Asteraceae, Ethnopharmacology, *Helichrysum foetidum*, Herbal medicine, Indigenous pharmacopoeias

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INTRODUCTION

In African traditional medicine, species of the genus *Helichrysum* Mill. (family Asteraceae or Compositae) are highly valued as sources of herbal medicines [1-15]. Some of the species which include *H. nudifolium* (L.) Less. and *H. odoratissimum* (L.) Sweet are reported to have commercial potential as ritual incense, sedative, and herbal medicine for colds and chest pains, with their essential oils having commercial potential as inhalant and aromatherapy [10-12]. The leaves, stems, and twigs of these two species are sold as herbal medicines in the informal herbal medicine markets in South Africa [14,16-18]. In tropical Africa, *Helichrysum foetidum* (L.) Moench., commonly called yellow everlasting or silvery lemon everlasting, is a valuable herbal medicine in the region [19,20]. Five synonyms, namely *Anaxeton foetidum* Gaertn., *Gnaphalium argenteum* Mill., *Gnaphalium buchingeri* Sch. Bip., *Gnaphalium foetidum* L., and *Gnaphalium fruticans* Schrank, are associated with the species [21-27]. The species is native to Burundi [28], Cameroon [29], Democratic Republic of Congo (DRC) [28,30], Equatorial Guinea [31], Eritrea [25], Ethiopia [25,28,32-39], Kenya [3,28], Malawi [5,26,28], Nigeria [28,40], Rwanda [41], São Tomé and Príncipe (Gulf of Guinea) [42], Somalia [27], South Africa [20,21,24,43,44], South Sudan [28,45], Sudan [28,45], Tanzania [28,46,47], Uganda [28,48], and Yemen [28,49]. *H. foetidum* has also been introduced in several countries throughout the world as an ornamental or medicinal plant species [50-62]. The species was introduced in Crimea [50], Hawaii [53,55,57,60], Spain [61], the Netherlands [51], and the UK [54] as an ornamental plant. *H. foetidum* was first recorded as naturalized in Portugal in 1868, and the species is currently categorized as a weed, established in natural or semi-natural communities [58]. In Spain, the species was introduced as an ornamental plant in Galicia and it was first recorded as naturalized in 1870 [59]. Research by Bujan [59] revealed that the species is now widespread as a weed and regarded as an important component of indigenous pharmacopoeia of several communities in the country [56]. Research by Wester [53] and Daehler [57] showed that *H. foetidum* was first recorded as naturalized in Hawaii in 1949. In Brazil, *H. foetidum* is naturalized in temperate grasslands, particularly swamp areas and on ecotone zones of thickets and semi-deciduous forests [62]. Based on literature records, *H. foetidum* is naturalized as a casual or invasive weed in Brazil, Hawaii, Portugal, and Spain [52,53,57,58-62].

H. foetidum is an annual or short-lived perennial shrublet, about 30 cm–150 cm in height [21,24,44]. The stems are erect, simple, robust, cylindrical, striated, and rarely branched near base. Leaves are alternate, sticky and aromatic, sessile, oblong-lanceolate, auriculate and clasping, roughly hairy above, and grey-woolly beneath [44]. The leaves are grouped at the stem base and wither at the time of flowering. *H. foetidum* is characterized by glossy, deep yellow to cream flower heads with several florets [20,44]. The species is a fire ephemeral which grows rapidly, flowers profusely and produces many fruits which have pappus bristles and several tiny seeds which are easily dispersed by wind [20]. These seeds are capable of persisting in the soil until conditions are conducive for germination. The current study is focusing on the medicinal applications of the species and its contribution to primary health care of local communities. Therefore, this review aims to provide a critical appraisal of the existing ethnomedicinal value, phytochemistry, and biological activities of compounds isolated from the species including *H. foetidum* crude extracts as well as exploring the potential of the species as herbal medicine.

MEDICINAL USES OF *H. FOETIDUM*

Major medicinal applications of different plant parts of *H. foetidum* based on literature records include the following (in descending order of importance): wounds, sores, induce trances, dysmenorrhea, eye infections, influenza, and as a sedative (Table 1 and Fig. 1). Smoke of different plant parts of *H. foetidum* is regarded as a rapid and effective means of inducing trances or causing hallucinogenic effects in South Africa [6,8,63-68]. Other minor medicinal applications of different plant parts of *H. foetidum* include uses as herbal medicine for herpes in Rwanda [41], pneumonia in Tanzania [69], snakebite antidote in the DRC [30], and tonsillitis in Spain [56]. *H. foetidum* together with other *Helichrysum* species such as *H. aureonitens* Sch. Bip., *H. cymosum* (L.) D. Don, *H. nudifolium*, *H. odoratissimum*, *H. pedunculatum* Hilliard

Table 1: Medicinal uses of *Helichrysum foetidum*

Disease	Parts used	Country	References
Dysmenorrhea	Whole plant	South Africa	[1,4,20,65,74-76]
Eye infections	Roots	Kenya and South Africa	[3,4,20,76,77]
Herpes	Whole plant	Rwanda	[41]
Induce trances	Whole plant	South Africa	[6,8,20,63-68,76]
Influenza	Leaves	Kenya and South Africa	[3,4,20,76]
Pneumonia	Leaves	Tanzania	[69]
Sedative	Leaves and stems	South Africa	[7,78]
Snakebite	Whole plant	DRC	[30]
Sores	Leaves	South Africa	[1,4,20,63,76,79-87]
Tonsillitis	Whole plant	Spain	[56]
Wounds	Leaves	South Africa, Spain, and Yemen	[1,20,56,63,75,76,79-81,83,84,88-90]

DRC: Democratic Republic of Congo

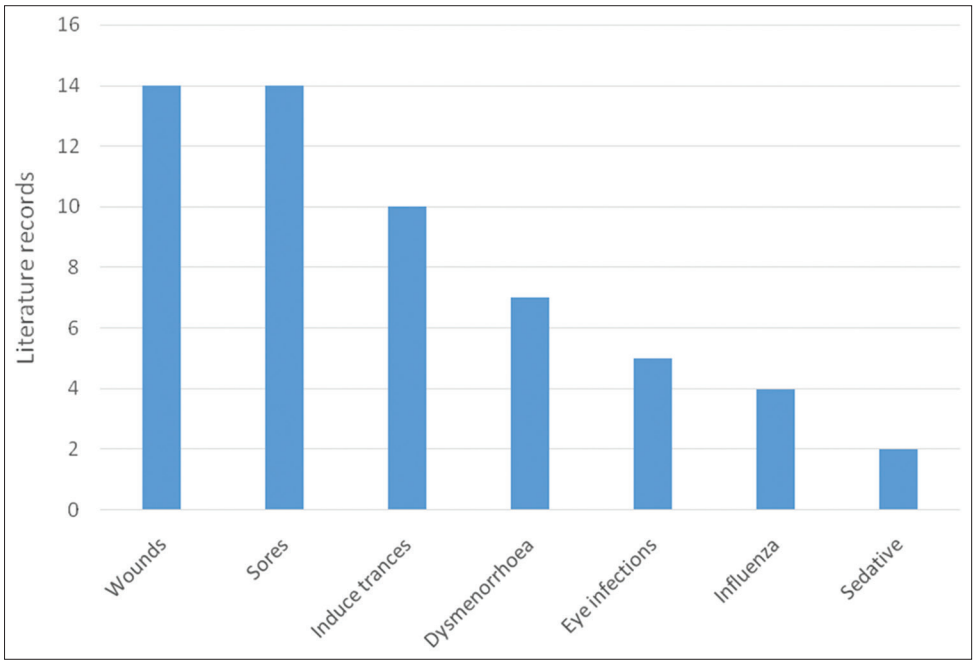

Fig. 1: Medicinal applications of *Helichrysum foetidum* derived from literature records

and B. L. Burtt, and *H. petiolare* Hilliard and B. L. Burtt are important medicinal plants used almost daily in South Africa [14]. Some of the *Helichrysum* species such as *H. nudifolium* and *H. odoratissimum* have recently become the focus of commercial development of health promoting and pharmaceutical products in South Africa [10-12]. The dynamic and adaptive usage of *H. foetidum* as herbal medicine is corroborated by the usage of different plant parts of the species as herbal medicine for tonsillitis and wounds in Spain [56]. These findings support the hypothesis that indigenous pharmacopoeias are influenced by the availability of exotic species in local communities as these systems are not static social institutions, but evolve overtime, with evidence of deletions and insertions of plants that compose it, with the addition of alien plants as sources of herbal medicines [70-73].

PHYTOCHEMISTRY

Many classes of nutritional and phytochemicals (Table 2) including flavanols, flavonoids, phenolics, phenols, and proanthocyanidins as well as classic nutrients and mineral elements have been identified and quantified [91,92]. Chalcones, flavonoids, and diterpenoids have so far been isolated and identified in *H. foetidum* flowers and leaves by Barrero *et al*. [93], Kakam *et al*. [94], and Malolo *et al*. [95] using gas chromatography–mass spectrometry, hydrogen nuclear magnetic resonance, and thin-layer chromatography (TLC) analyses (Table 3). Research by Fong *et al*. [96] revealed that 6′-methoxy-2′,4, 4′-trihydroxychalcone inhibited Ca Ski cells at half maximal inhibitory concentration (IC_{50}) of 30.6 µM, and therefore, the compound has the ability to induce DNA damage, mitochondrial membrane disruption, and loss of cell membrane integrity. The chemical structures of isolated compounds are shown in Fig. 2.

BIOLOGICAL ACTIVITIES

The following biological activities have been reported from *H. foetidum* crude extracts and compounds isolated from the species: antibacterial [41,95,97,98], antifungal [95,98,99], antiviral [41], antioxidant [92], protease-inhibiting [95], and cytotoxicity [97] activities.

Antibacterial activities

Sindambiwe *et al*. [41] evaluated antibacterial activities of 80% ethanol whole plant extracts of *H. foetidum* using the liquid dilution method against *Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella paratyphi, Bacillus cereus, Mycobacterium fortuitum, Staphylococcus aureus,* and *Streptococcus pyogenes.* The extract was active against *Streptococcus pyogenes* with minimum inhibitory concentration (MIC) value of 5 mg/ml [41]. Lourens *et al*. [97] evaluated antibacterial activities of leaf and stem chloroform: methanol (1:1) extracts of *H. foetidum* against *Bacillus cereus, Staphylococcus aureus, Staphylococcus epidermidis, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* using microdilution technique with ciprofloxacin as a positive control. The extract exhibited

Table 2: Nutritional composition and other phytochemical of *Helichrysum foetidum*

Composition	Values	Plant parts	References
Acid detergent fiber (%)	38.2	Leaves	[91]
Calcium (%)	1.3	Leaves	[91]
Cellulose digestibility (%)	51.2	Leaves	[91]
Flavanols	13 ± 2 mg/g dry extract as (-) epicatechin	Whole plant	[92]
Flavonoids	460 ± 69 mg/g dry extract as rutin	Whole plant	[92]
Magnesium (%)	0.4	Leaves	[91]
Moisture content (%)	86.0	Leaves	[91]
Oligomeric proanthocyanidins	5 ± 1 mg/g dry extract as cyaniding chlorhydrate	Whole plant	[92]
Phosphorus (%)	0.4	Leaves	[91]
Potassium (%)	3.4	Leaves	[91]
Protein content (%)	18.7	Leaves	[91]
Total phenolics (%)	6.7	Leaves	[91]
Total phenols	580 ± 87 mg/g dry extract as gallic acid	Whole plant	[92]

Table 3: Phytochemicals isolated and characterized from *Helichrysum foetidum*

Phytochemical	Extract	Method of characterization	Plant part	References
Chalcones				
6′-methoxy-2′,4, 4′-trihydroxychalcone	Methanol	GC–MS and H NMR	Flowers and leaves	[94,95]
6′-methoxy-2′,4-dihydroxychalcone -4′-O-β-D-glucoside	Methanol	GC–MS and H NMR	Flowers and leaves	[94,95]
Diterpenoid				
Kaur-16-en-18-oic acid	Chloroform and methanol	GC–MS, H NMR, and TLC	Flowers	[93-95]
Flavonoids				
Apigenin	Methanol	GC–MS and H NMR	Flowers and leaves	[94,95]
Apigenin-7-O-β-D-glucoside	Chloroform and methanol	GC–MS and H NMR	Flowers and leaves	[94,95]
7, 4′-dihydroxy-5-methoxy-flavanone	Methanol	GC–MS and H NMR	Flowers	[94,95]

GC–MS: Gas chromatography–mass spectrometry, TLC: Thin-layer chromatography, H NMR: Hydrogen nuclear magnetic resonance

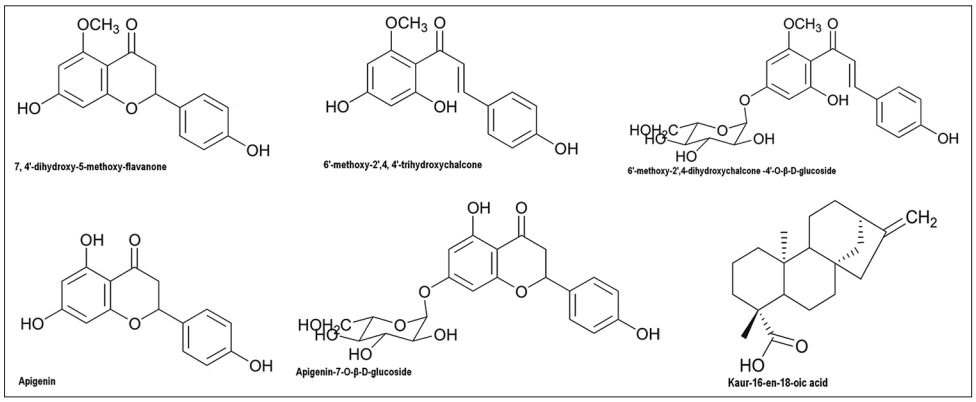

Fig 2: Chemical structures of compounds isolated from flowers and leaves of *Helichrysum foetidum*

activities against *Bacillus cereus* and *Staphylococcus aureus* with MIC values of 0.01 mg/ml and 0.5 mg/ml, respectively, which were higher than 0.0003 mg/ml exhibited by the positive control [97]. Samie *et al*. [98] evaluated antibacterial activities of essential oils isolated from *H. foetidum* against *Acinetobacter calcoaceticus, Bacillus cereus, Escherichia coli, Klebsiella pneumoniae,* Micrococcus kristinae, *Proteus vulgaris, Pseudomonas aeruginosa, Salmonella* spp., *Salmonella typhi, Serratia marcescens, Staphylococcus aureu*s, *Staphylococcus epidermidis*, and *Streptococcus faecalis* using the agar diffusion method and microdilution technique. The essential oils showed activities with MIC and minimum bactericidal concentration (MBC) values ranging from 3.8 mg/ml to > 7.5 mg/ml [98]. Samie *et al*. [98] evaluated the killing kinetics of *Bacillus cereus, Proteus vulgaris, Staphylococcus aureus, Staphylococcus epidermidis,* and *Pseudomonas aeruginosa* by the essential oils of *H. foetidum.* The essential oils were able to significantly reduce the number of bacterial cells after 3 h [98]. Malolo *et al*. [95] evaluated antibacterial activities of methanol flower and leaf extracts and compounds 7, 4′-dihydroxy-5-methoxy-flavanone, 6′-methoxy-2′,4, 4′-trihydroxychalcone, 6′-methoxy-2′,4-dihydroxychalcone-4′-O-β-D-glucoside, apigenin, apigenin-7-O-β-D-glucoside, and Kaur-16-en-18-oic acid isolated from *H. foetidum* against *Bacillus subtilis* using a fluorescence-based antibacterial growth inhibition assay with erythromycin as a positive control. The extracts showed significant and concentration-dependent growth inhibition of 85.4% at a concentration of 1 mg/ml and 21.8% at a concentration of 0.1 mg/ml. All the compounds exhibited notable growth inhibition range of 75.0%–85.0% against *Bacillus subtilis* at a concentration of 1 mg/ml [95].

Antifungal activities

Samie and Nefefe [99] evaluated antifungal activities of essential oils isolated from *H. foetidum* against *Fusarium oxysporum,*

F. nygamai, F. proliferatum, F. verticillioides, and *F. graminearum* using the agar diffusion method and microdilution technique. The essential oils showed activities with zone of inhibition of 10 mm against *F. graminearum and F. nygamai, and* zone of inhibition of 15 mm against *F. oxysporum.* The MIC values against tested fungi ranged from 0.5 mg/ml to > 7.5 mg/ml while minimum fungicidal concentration (MFC) values against all tested fungi ranged from 1.0 mg/ml to > 7.5 mg/ml [99]. Samie and Nefefe [99] evaluated the rate of kill of *H. foetidum* essential oils by determining the fungal cell death time against *F. oxysporum, F. nygamai, F. proliferatum, F. verticillioides,* and *F. graminearum*. The essential oils were able to kill the cells at different rates varying from 48% to 100% after 2 days of experimentation [99]. Samie *et al*. [98] evaluated antifungal activities of essential oils isolated from *H. foetidum* against *Candida albicans, Candida glabrata, Candida krusei, Candida parapsilosis, Candida tropicalis,* and *Cryptococcus neoformans* using the agar diffusion method and microdilution technique. The essential oils showed activities with MIC values ranging from 0.06 mg/ml to 7.5 mg/ml and MFC values ranging from 1.9 mg/ml to > 7.5 mg/ml [98]. Samie *et al*. [98] evaluated the killing kinetics of *Candida albicans, Candida krusei, Candida parapsilosis,* and *Cryptococcus neoformans* by the essential oils of *H. foetidum.* The essential oils were able to substantially decrease the number of fungi cells within a day [98]. Malolo *et al*. [95] evaluated antifungal activities of methanol flower and leaf extracts and compounds 7, 4′-dihydroxy-5-methoxy-flavanone, 6′-methoxy-2′,4, 4′-trihydroxychalcone, 6′-methoxy-2′,4-dihydroxychalcone-4′-O-β-D-glucoside, apigenin, apigenin-7-O-β-D-glucoside, and Kaur-16-en-18-oic acid isolated from *H. foetidum* against *Cladosporium cucumerinum* using bioautography on silica gel plates with amphotericin B as a positive control. The extracts exhibited activities by showing the development of inhibition zones on the bioautography plates. All the compounds exhibited notable growth inhibition ranging from 56.0% to 70.0% against *C. cucumerinum* at a concentration of 1 mg/ml [95].

Antiviral activities

Sindambiwe *et al*. [41] evaluated antiviral activities of aqueous and 80% ethanol whole plant part extracts of *H. foetidum* using the method of 50% end point titration technique (50% EPPT) assay against herpes simplex virus type 1 (HSV 1), measles virus strain Edmonston A (MV-EA), Semliki Forest virus A7 (SF A7), and vesicular stomatitis virus T2 (VSV T2). The extract exhibited virucidal activities against HSV 1 and SF A7 [41].

Antioxidant activities

Tirillini *et al*. [92] evaluated the antioxidant activities of methanol whole plant part extracts of *H. foetidum* using 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid assay, 1,1-diphenyl-2-picrylhydrazyl free radical scavenging, ß-carotene/linoleic acid assay, scavenging of hydrogen peroxide (HRPO test), superoxide anion scavenging test, and hypochlorous acid scavenging (taurine test). The extract exhibited activities with IC_{50} values ranging from 0.5 µg to 34.0 µg [92].

Protease-inhibiting activities

Malolo *et al*. [95] evaluated the protease-inhibiting activities of methanol leaf extracts and compounds 7, 4′-dihydroxy-5-methoxy-flavanone, 6′-methoxy-2′,4, 4′-trihydroxychalcone, 6′-methoxy-2′,4-dihydroxychalcone-4′-O-β-D-glucoside, apigenin, apigenin-7-O-β-D-glucoside, and Kaur-16-en-18-oic acid isolated from *H. foetidum* using a fluorescence resonance energy transfer protease pepsin inhibition assay. The extract exhibited pepsin protease inhibition of 37.4% and 35.6% at 50 µg/ml and 25 µg/ml, respectively. The compounds 6′-methoxy-2′,4-dihydroxychalcone-4′-O-β-D-glucoside and apigenin-7-O-β-D-glucoside exhibited pepsin protease inhibition of 37.4% and 46.3% at 50 µg/ml, respectively [95].

Cytotoxicity activities

Lourens *et al*. [97] evaluated cytotoxicity activities of leaf and stem chloroform: methanol (1:1) extracts of *H. foetidum* using the sulforhodamine B assay against transformed human kidney epithelial (Graham) cells, MCF-7 breast adenocarcinoma, and SF-268 glioblastoma cells. The MCF-7 cells were more sensitive toward the extracts than either the Graham or SF-268 cells exhibiting 24.9% cell growth at a concentration of 0.1 mg/ml, implying potential cytotoxicity [97].

CONCLUSION

The current review highlighted the medicinal uses, phytochemistry, and pharmacological activities of *H. foetidum.* The most studied pharmacological activities are antibacterial and antifungal activities. Correlating the pharmacological studies of *H. foetidum* with its medicinal uses, it is clear that the diverse biological activities identified so far are directly or indirectly associated with a wide range of physiological processes which offer protection against both growth of undesirable bacterial, fungal, and free radicals. There is no doubt that there are still some gaps where current knowledge could be improved, focusing on validating ethnomedicinal uses of *H. foetidum* through detailed phytochemical and pharmacological studies. There is also a need for experimental animal studies, randomized clinical trials, and target organ toxicity studies involving *H. foetidum* and its compounds.

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AUTHOR'S CONTRIBUTIONS

The author declares that this work was done by the author named in this article.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest.

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