Helichrysum nudifolium (L.) Less.: Review of its Medicinal Uses, Phytochemistry and Biological Activities

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Abstract: *Helichrysum nudifolium* is a valuable and well-known medicinal plant species in southern Africa. The current study critically reviewed the medicinal uses, phytochemistry and biological activities of *H. nudifolium*. Information on medicinal uses, phytochemistry and biological activities of *H. nudifolium* was collected from multiple internet sources which included Scopus, Google Scholar, Elsevier, Science Direct, Web of Science, Pubmed, SciFinder and BMC. Additional information was gathered from pre-electronic sources such as journal articles, scientific reports, theses, books and book chapters obtained from the University library. This study showed that *H. nudifolium* is mainly used as ethnoveterinary medicine, as colic and herbal medicine for fever, headache, swellings, infertility, pregnancy and postpartum problems. Pharmacological research revealed that *H. nudifolium* extracts have antibacterial, antimycobacterial, antifungal, anti-HIV, GABAA-benzodiazepine receptor-binding, anticancer, anti-inflammatory, antiplasmodial, antiprotozoal and cytotoxicity activities. There is need for experimental animal studies, randomized clinical trials and target-organ toxicity studies involving *H. nudifolium* crude extracts and compounds isolated from the species. Future should also focus on evaluation of pharmacological properties of compounds isolated from *H. nudifolium*.

Keywords: Asteraceae, *Helichrysum nudifolium*, ethnopharmacology, herbal medicine, southern Africa.

INTRODUCTION

Helichrysum nudifolium (L.) Less. is a perennial herb or small shrub which belongs to the Asteraceae or Compositae family. The species has been recorded in Angola, Botswana, Burundi, Cameroon, Democratic Republic of Congo (DRC), Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Rwanda, Sierra Leone, South Africa, South Sudan, Sudan, Swaziland, Tanzania, Uganda, Zambia, Zimbabwe and Yemen [1-3]. *Helichrysum nudifolium* shows enormous variation in terms of its growth form, with plants from different geographical areas often having different appearances. In the formal taxonomic revision of the species, Beentje [2] described three different varieties namely *H. nudifolium* var. *nudifolium, H. nudifolium* var. *oxyphyllum* (DC.) Beentje and *H. nudifolium* var. *pilosellum* (L.f.) Beentje. However, most ethnobotanical and ethnopharmacological literature do not separate *H. nudifolium* into specific varieties, but rather to *H. nudifolium sensu lato*, and this is the approach that has been adopted in this study. The height of *H. nudifolium* ranges from 10 to 150 cm, with annual stems emanating from stout, perennial underground, woody rootstock [1-3]. The leaves are long, thin, narrowly elliptic to ovate, glabrous or hairy, cauline, broad-based and clasping. The inflorescence is branched, consisting of loose flower heads which are pale yellow to pale brown in colour. *Helichrysum nudifolium* has been recorded in grassland, wooded grassland, thicket, disturbed areas and on roadsides at an altitude ranging from 5 m to 2810 m above sea level [1-3].

The leaves, roots, stems and twigs of *H. nudifolium* are primary sources of herbal medicines in tropical Africa. Due to the popularity of the species as herbal medicine, the leaves and stems of *H. nudifolium* are sold as herbal medicines in the herbal medicine informal markets in Gauteng and Mpumalanga provinces in South Africa [4,5]. *Helichrysum nudifolium* is also one of the important medicinal plants in South Africa, included in the book “medicinal plants of South Africa”, a photographic guide to the most commonly used plant medicines in the country, including their botany, main traditional uses, and active ingredients [6]. *Helichrysum nudifolium* is commonly known as hottentot's tea in southern Africa as the aromatic young leaves are used as a tea-substitute or herbal tea in Lesotho [7], South Africa [8] and Swaziland [9]. Research by Van Wyk and Gorelik [10] showed that the leaves of *H. nudifolium* are used as a substitute for common tea (that is, *Camellia sinensis* (L.) Kuntze) or as a hot beverage, that is herbal tea or tisane, primarily consumed as food but also as herbal medicine for colds and chest complaints. According to Van Wyk [11], the leaves of *H. nudifolium* have commercial potential as remedies for colds and chest complaints in South Africa. Therefore, *H. nudifolium* is an integral

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part of traditional pharmacopoeia in southern Africa with potential contribution to primary health care of local communities in the region. Therefore, this is the rationale behind the current study, aimed at providing a critical appraisal of the existing ethnomedicinal value, phytochemistry and biological activities of *H. nudifolium* as well as exploring the potential of the species as herbal medicine.

Medicinal Uses

The leaves, roots, stems, twigs and the whole plant parts of *H. nudifolium* are used as herbal medicines against 29 human and animal diseases in tropical Africa (Table **1**). *Helichrysum nudifolium* is mainly used to treat fever (six citations in three countries), colic and headache (five citations in two countries each), swellings (four citations in two countries), infertility

Table 1: Medicinal Uses of *Helichrysum nudifolium*

Disease	Parts used	Country	References
Allergies	Leaves	South Africa	[14]
Antipyretic	Roots	South Africa	[8,12]
Aphrodisiac	Whole plant	Lesotho and South Africa	[7]
Burns	Leaves	Swaziland	[9]
Burnt as incense	Leaves	Lesotho and Swaziland	[7,9]
Catarrh	Leaves and roots	South Africa	[8,12,15]
Chest problems	Leaves and roots	South Africa	[6,8-10,12,16-21]
Colds	Leaves, roots, stems and whole plant	South Africa	[6,8,10,15-18,20-23]
Colic	Leaves, roots and whole plant	Lesotho and South Africa	[12,13,16,23,24]
Cough	Leaves, roots and whole plant	South Africa	[6,15-17,21,25,26]
Diabetes	Leaves, roots and whole plant	South Africa	[26-30]
Fever	Leaves and roots	Lesotho, South Africa and Swaziland	[6,9,12,13,16,17]
Flu	Leaves	South Africa	[22]
Headache	Leaves and whole plant	South Africa and Swaziland	[6,9,16,31-33]
HIV/AIDS	Roots	Uganda	[34]
Infections	Leaves and twigs	South Africa	[6]
Infertility	Whole plant	Malawi and South Africa	[24,35]
Infertility in women	Whole plant mixed with *Commelina africana* L. and *Salvia triangularis* Thunb.	South Africa	[12]
Internal sores	Leaves and roots	South Africa	[16]
Pregnancy and postpartum problems	Whole plant	Malawi and South Africa	[24,35]
Menstrual pain	Whole plant	South Africa	[6,26]
Otitis	Leaves	Swaziland	[9]
Pain	Leaves and twigs	South Africa	[6]
Pulmonary infections	Leaves	South Africa	[8,12,15,25]
Rectal prolapse	Whole plant	South Africa	[23]
Skin infections	Leaves	South Africa	[14]
Swellings	Leaves	Lesotho and South Africa	[7,12,13,17]
Weaning	Roots	South Africa	[36]
Wounds	Leaves, roots and whole plant	South Africa	[6,14-16,23,26,37,38]
Ethnoveterinary medicine (black leg)	Leaves	Lesotho	[7,12,13]

(three citations in two countries), pregnancy and postpartum problems (two citations in two countries) (Table **1**). In South Africa, the whole plant parts of *H. nudifolium* are mixed with those of *Commelina africana* L. and *Salvia triangularis* Thunb. as herbal medicine for infertility in women [12]. In Lesotho, the leaves of *H. nudifolium* are used as ethnoveterinary medicine for black leg [7,12,13].

Phytochemistry

Bohlmann *et al*. [39], Jakupovic *et al*. [40] and Reidel *et al*. [41] isolated (-)-5α-acetoxy-α-gurjunene, (-)-5β-acetoxy-α-gurjunene, cadinene, δ-cadinene, caryophyllene, β-caryophyllene, 9-geranyl-α-terpineol, helicerestripyrone-6-O-methyl ether, helinudichromene quinone, helinudiquinone-6-O-methyl ether, helinudifolin, 5α-hydroxy-α-gurjunene, 8α-hydroxygnaphala-13(16),14-dien, isoabienol, isocomene, isocomene-5,6-epoxide, β-isocomene, modhephene, 5-oxo-5,6α-h-isocomene, silphinene and squalene from aerial parts, flowers and leaves of *H. nudifolium* (Table **2**). Future research should focus on the isolation and identification of bioactive compounds in the utilized plant parts, particularly aerials parts, stems and roots and evaluate the biological activities of these compounds.

Table 2: Phytochemical Composition of *Helichrysum nudifolium* after Bohlmann *et al.* [39], Jakupovic *et al*. [40] and Reidel *et al*. [41]

Phytochemical composition	Plant parts
(-)-5α-acetoxy-α-gurjunene	Aerial parts
(-)-5β-acetoxy-α-gurjunene	Aerial parts
Cadinene	Aerial parts
δ-cadinene	Aerial parts
Caryophyllene	Aerial parts
β-Caryophyllene	Flowers and leaves
9-Geranyl-α-terpineol	Aerial parts
Helicerestripyrone-6-O-methyl ether	Aerial parts
Helinudichromene quinone	Aerial parts
Helinudiquinone-6-O-methyl ether	Aerial parts
Helinudifolin	Aerial parts
5α-hydroxy-α-gurjunene	Aerial parts
8α-Hydroxygnaphala-13(16),14-dien	Aerial parts
Isoabienol	Aerial parts
Isocomene	Aerial parts
Isocomene-5,6-epoxide	Aerial parts
β-isocomene	Aerial parts
Modhephene	Aerial parts
5-Oxo-5,6α-H-isocomene	Aerial parts
Silphinene	Aerial parts
Squalene	Aerial parts

Biological Activities

The following biological activities have been reported from *H.* nudifolium crude extracts: anti-bacterial [15,18,42], antimycobacterial [18], antifungal [15,18], anti-HIV [43,44], GABAA-benzodiazepine receptor-binding [45], anticancer [19], anti-inflammatory [32], antiplasmodial [46], antiprotozoal [47] and cytotoxicity [42,43,44,47] activities.

Antibacterial Activities

Mathekga [15] evaluated the antibacterial activities of acetone extracts of aerial parts of H. nudifolium against Bacillus cereus, Bacillus pumilus, Bacillus subtilis, Micrococcus kristinae, Staphylococcus aureus, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa and Serratia marcescens using agar dilution method. The extract exhibited activities against all tested pathogens with the exception of Klebsiella pneumoniae and Serratia marcescens with minimum inhibitory concentration (MIC) value of 1.0 mg/ml [15]. Seaman [18] evaluated the antibacterial activities of acetone and methanol leaf and root extracts of H. nudifolium against Staphylococcus aureus, Enterococcus faecalis, Bacillus cereus, Pseudomonas aeruginosa, Klebsiella pneumoniae, Serratia odorifera and Moraxella catarrhalis using disc diffusion and broth micro-dilution methods with neomycin and ciprofloxacin as positive controls. The extracts showed activities against Staphylococcus aureus, Enterococcus faecalis and Bacillus cereus with MIC values ranging from 0.5 mg/ml to >8.0 mg/ml [18]. Lourens et al. [42] evaluated antibacterial activities of chloroform: methanol (1:1) leaf and stem extracts of H. nudifolium against Staphylococcus aureus, Staphylococcus epidermidis, Bacillus cereus, Klebsiella pneumoniae and Pseudomonas aeruginosa using the 96-well microplate method with ciprofloxacin as the positive control. The extracts exhibited activities against Staphylococcus aureus, Staphylococcus epidermidis, Bacillus cereus and Klebsiella pneumoniae with MIC values ranging from 0.02 mg/ml to 4.0 mg/ml [42].

Antimycobacterial Activities

Seaman [18] evaluated the antimycobacterial activities of acetone and water leaf and root extracts *of*

H. nudifolium against *Mycobacterium smegmatis* and *Mycobacterium* aurum using broth micro-dilution technique and *Mycobacterium tuberculosis* using BACTEC susceptibility testing with rifampicin and ciprofloxacin as positive controls. The extracts exhibited activities with MIC values ranging from 1.0 mg/ml to 16.0 mg/ml [18].

Antifungal Activities

Mathekga [15] evaluated the antifungal activities of acetone extracts of aerial parts of H. nudifolium against Aspergillus flavus, Aspergillus niger, Cladosporium cladosporioides, Cladosporium cucumerinum, Cladosporium sphaerospermum and Phytophthora capsici using agar dilution method. The extract exhibited activities against all tested pathogens with MIC values of 0.1 mg/ml [15]. Seaman [18] evaluated the antibacterial activities of acetone and methanol leaf and root extracts of H. nudifolium against Candida albicans using disc diffusion and broth micro-dilution methods with neomycin and ciprofloxacin as positive controls. The extract showed activities with MIC values ranging from >2.0 mg/ml to 8.0 mg/ml [18].

Anti-HIV Activities

Heyman [43] evaluated anti-HIV activities of methanol: water and chloroform extracts of aerial parts of *H. nudifolium* on vero African green monkey kidney cells using the cytopathic effect (CPE) inhibition assay with acyclovir (0.75 µg/ml) as a positive control. The methanol: water extract showed slight toxicity with cytopathic effect of 100.0 µg/ml in comparison to 0.8 µg/ml exhibited by the positive control [43]. Heyman *et al*. [44] evaluated anti-HIV activities of dichloromethane and methanol: water extracts of aerial parts of *H. nudifolium* using the DeCIPhR method. The dichloromethane extract exhibited activities with the median lethal concentration (LC_{50}) value of 48.0 µg/mL [44].

GABAA-Benzodiazepine Receptor-Binding Activities

Stafford *et al*. [45] evaluated GABAA-benzodiazepine receptor-binding activities of ethanol leaf extracts of *H. nudifolium* using the GABAA-benzodiazepine receptor-binding assay. The extract showed dose-dependent activities [45].

Anticancer Activities

Fouche *et al*. [19] evaluated anticancer activities of dichloromethane root extracts of *H. nudifolium* against a panel of three human cell lines (breast MCF7, renal TK10 and melanoma UACC62). The extract showed moderate activities with total growth inhibition (TGI) values ranging from 8.4 µg/ml to 33.5 µg/ml [19].

Anti-Inflammatory Activities

Jäger *et al*. [32] evaluated aqueous and ethanolic leaf extracts of *H. nudifolium* in an *in vitro* assay for cyclooxygenase (COX) inhibitors with indomethacin (0.5µg) as the positive control. The ethanolic extract of *H. nudifolium* showed inhibition of 96% which was higher than 66.5% inhibition exhibited by the indomethacin control. Based on these results, there might be a rationale for the ethnopharmacological claim that *H. nudifolium* possess anti-inflammatory properties.

Antiplasmodial Activities

Clarkson *et al*. [46] evaluated the antiplasmodial activities of dichloromethane: methanol (1:1) and water extracts of whole plant parts of *H. nudifolium* against *Plasmodium falciparum* using the parasite lactate dehydrogenase assay. The dichloromethane: methanol (1:1) extract showed promising activities with half maximal inhibitory concentration (IC_{50}) value of 6.8 µg/ml. The promising antiplasmodial activities exhibited by *H. nudifolium* show that the plant could serve as an antimalarial agent as the species is used as a remedy for fever in Lesotho, South Africa and Swaziland [6,9,12,13,16,17].

Antiprotozoal Activities

Mokoka *et al*. [47] evaluated antiprotozoal activities of dichloromethane: methanol (1:1) whole plant part extracts of *H. nudifolium* against *Plasmodium falciparum, Trypanosoma cruzi, Trypanosoma brucei rhodesiense* and *Leishmania donovani* with benznidazole (IC_{50} = 0.5 µg/mL), chloroquine (IC_{50} = 0.05 µM), melarsoprol (IC_{50} = 0.03 µM) and miltfosine (IC_{50} = 0.2 µg/mL) as reference drugs. The extract exhibited activities with IC_{50} values ranging from 9.4 µg/mL to 43.9 µg/mL [47].

Cytotoxicity Activities

Heyman [43] evaluated cytotoxicity activities of chloroform and methanol: water extracts of aerial parts of *H. nudifolium* on Vero African green monkey kidney cells using the XTT (sodium 3'-[1-(phenyl amino-carbonyl)-3,4-tetrazolium]-bis-[4-methoxy-6-nitro] benzene sulfonic acid hydrate) method with

zearalenone as a positive control. The chloroform extract exhibited IC_{50} value of <3.1 µg/ml which was comparable to 1.3 µg/ml exhibited by the positive control, while methanol: water extract exhibited IC_{50} value of 138.4 µg/ml [43]. Lourens *et al*. [42] evaluated *in vitro* cytotoxicity activities of chloroform: methanol (1:1) leaf and stem extracts of *H. nudifolium* [against transformed human kidney epithelial (Graham) cells, MCF-7 breast adenocarcinoma and SF-268 glioblastoma cells] at a concentration of 0.1 mg/ml using the sulforhodamine B (SRB) assay. The extract exhibited Graham cell growth ranging from 35.3% to 83.9% at the tested concentration [42], implying that the species maybe toxic against Graham cells. Mokoka *et al*. [47] evaluated the cytotoxicity activities of dichloromethane: methanol (1:1) whole plant extracts of *H. nudifolium* against rat myoblast L6 cells with podophyllotoxin (IC_{50} = 0.05 µM) as a reference drug. The extract exhibited very little toxicity towards the myoblasts L-6 cells with IC_{50} value of 47.7 µg/mL [47]. Heyman *et al*. [44] evaluated cytotoxicity activities of dichloromethane and methanol: water extracts of aerial parts of *H. nudifolium* using the DeCIPhR method. The dichloromethane extract exhibited activities with median lethal dose (LD_{50}) value of >50.0 µg/mL [44].

CONCLUSION

The diverse medicinal uses of *H. nudifolium* and the preliminary phytochemical and pharmacological evaluations carried so far indicates its potential as herbal medicine. The documented preliminary diverse pharmacological activities are directly or indirectly involved in a range of physiological processes which offers protection against growth of undesirable microbes and free radicals. Although contemporary ethnopharmacological research involving *H. nudifolium* is promising, it is too preliminary and sometimes too general to be used to explain and support some of the medicinal uses of the species. There is need for evaluation of the clinical significance of the antioxidant properties, cytotoxicity and toxicity using *in vivo* models.

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

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