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REVIEW ARTICLE

Reproductive, antioxidant, anti-inflammatory, antimicrobial, protective and antidiabetic activities of *Helichrysum* Mill. species

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Abstract

South African *Helichrysum* species are known for their diverse medicinal use and treatment of different illnesses. Ethnopharmacological studies have revealed the potential use of *Helichrysum* plants in drug discovery. Although some of these species have been documented, there is still a paucity of information on most species. This review seeks to provide a compilation of documented traditional uses, reproductive potential, antioxidant, anti-inflammatory, antimicrobial, protective and antidiabetic activities and other therapeutic properties of some *Helichrysum* species of South Africa. Information on *Helichrysum cymosum*, *H. foetidum*, *H. odoratissimum*, *H. patulum* and *H. petiolare* were collected from such scientific databases as Google scholar, Scifinder, PubMed, Elsevier, Scopus, and Science Direct in the form of journal articles, scientific reports, theses and books from the Library of the Cape Peninsula University of Technology. Our findings show that these species have historic values in traditional medicine through their diverse use for the management and treatment of such illnesses as cold, diabetes, headaches, digestive problems, sores and wounds, HIV, cancer, etc. Additionally, the reported bioactive constituents isolated from these species have been shown to indicate several activities such as antimicrobial, antioxidant, antidiabetic, neuroprotection, reproductive potentials, etc. Thus, the current review highlights the phytochemical and bioactive constituents as well as some of the pharmacological properties of the five selected *Helichrysum* species with a view to providing validation for their use in the pharmaceutical drug development process.

Keywords

Ethnopharmacology, phytochemistry, therapeutic, biological activities, *Helichrysum*, traditional medicine

Introduction

Medicinal plant usage plays an integral role in the treatment of various diseases among ethnic communities, especially in developing countries. South Africa has a robust cultural identity of medicinal plants used for healing purposes (1, 2). The genus *Helichrysum* Mill. comprises of many medicinal herbs that have long been established across the world, and is grouped under the family Asteraceae, tribe Inuleae and subtribe Gnaphaliinae (3, 4). The genus derives its name from its golden yellow flowers known in Greek as helios 'sun' and chryos 'gold', which are common features exhibited by most of the species (4). About 500-600 species of *Helichrysum* are known across the

world, in countries such as Asia, Australia, Europe and Africa. However, the highest number of species has been recorded on the African continent (5). In South Africa, about 250 *Helichrysum* sp. are known and further divided into groups of 30, based on their differential morphological diversity (4, 6-8).

Generally, some species of the genus are remarkably scented and grow yearly while exhibiting different levels of polymorphism within the flowers, leaves and habitats. The presence of dense hair with attractive yellow flower heads of different varieties are common features within the genus (6, 9, 10). Secondary metabolites such as phenolic acids, flavonoids, diterpenes, coumarins, chalcones, polyacetylenes, sterols, pyrenes acylphloroglucinols, humulone derivatives, phthalides and sesquiterpenes have been isolated from the genus *Helichrysum*. These active compounds have exhibited the following activities in experimental studies: anti-oxidant, anti-allergic, anti-inflammatory, anti-microbial, hepatoprotective and protease-inhibition properties, among others (4, 11).

Herbal plant usage has yielded great therapeutic value against many illnesses in traditional medicine, necessitating the exploitation of indigenous South African medicinal plants (1). Many reviews on the traditional use, phytochemistry and biological activities of *Helichrysum cymosum* (L.) D. Don, *Helichrysum foetidum* (L.). Moench, *Helichrysum odoratissimum* (L.) Sweet, *Helichrysum patulum* (L.). Don and *Helichrysum petiolare* Hilliard & B. L Burtt have been published in recent literature, but studies are still ongoing on these plant species and their identified compounds to explore their diverse underscored biological activities, which has triggered the curiosity of several researchers. The current review is therefore aimed at elucidating and updating the documented medicinal uses, biological activities and phytochemical constituents of selected *Helichrysum* species of South African origin, with a view to assessing their suitability as sources of potential plant-derived pharmaceutical products.

Materials and Methods

An in-depth literature search on *Helichrysum cymosum*, *H. foetidum*, *H. odoratissimum*, *H. patulum* and *H. petiolare* was done using the following scientific databases: Google scholar, Scifinder, PubMed, Elsevier, Scopus and Science direct. Meanwhile, other information was sourced through online journal articles, dissertations, scientific reports and books from the Cape Peninsula University of Technology Library. The following keywords were inputted during the search: *Helichrysum*, phytochemistry, biological activities, ethnopharmacology, botanical description, traditional use and geographical distribution.

Results and Discussion

Morphological description of the five Helichrysum species

Helichrysum spp. are differentiated based on their morphological characteristics such as shape, size and flower heads (12). Each species of the plants exhibits distinct features as described in Table 1.

Traditional uses

A large number of South Africans living mostly in rural communities rely on herbal remedies because these are affordable, accessible and easy to prepare and administer (14, 20-22). These medicinal remedies are often used as complementary or alternative treatments to Western medication (23) and the genus *Helichrysum* is one of the many plants used extensively in traditional medicine for centuries across the world (4, 11, 17). These plants have been used for treating complications such as sores, wound dressing during circumcision, stress-related ailments, bruises, cuts, etc (4, 22, 24). Common traditional approaches of application include decoctions, infusions (using water), inhalation of smoke or vapour forms as well as the external application of leave extracts to wounds as shown in Table 2 (4, 10, 25-27).

Phytochemistry

Previous studies have established the chemical components of large proportions of South African *Helichrysum* sp. (4, 30), and the occurrence of flavonoids, alpha pyrenes, coumanins, phoroglucinol and terpenoids compounds (29, 31), with some species known to contain an abundance of diterpenes and pyrenes derivatives (32). Despite, the wide variety of chemical compounds present in the *Helichrysum*, the presence of terpenoids appears to characterize this genus with a peculiar aromatic smell. Typically, all the species are also known to have hydroxylated/methylated flavonoids, as well as prenylated and O-prenylated flavonoids (29). Ring-A methoxylated flavonols have been described in European and South African *Helichrysum* species and sesquiterpenes with different alcohol and monoacid bicyclic derivatives, have also been documented in the South African and Australian species (29).

Flavonoids and other phenolic constituents are often associated with the medicinal potential exhibited by the *Helichrysum* plants especially for treating various infections (33), including their anti-oxidant, anti-bacterial, anti-inflammatory, anti-diabetic, anti-cancer, hepatoprotective and other effects (34). Likewise, phoroglucinol derivatives (arzanol) have indicated antibacterial and anti-viral potentials (10, 29).

The active compounds in the *Helichrysum* species are mostly responsible for the healing properties attributed to these plants (35), which also accounts for the bioactivity acclaim, medicinal value and general acknowledgement of this genus in traditional medicine (29, 34, 35).

Major classes of compounds isolated and characterized from five Helichrysum sp.

The bioactive compounds isolated from the *Helichrysum* species selected for this review have been well documented. *H. cymosum* contains flavone, 5-hydroxy-8 methoxy-7-prenyloxyflavonone helihumolone, helichromachalcone and phloroglucinol derivatives (4, 7, 14). *H. foetidum* contains chalcones (6-methoxy-2′, 4, 4’-trihydroxy-chalcone, 6-methoxy-2′, 4-dihydroxy-chalcone-4′-O-β-D-glucoside),

Table 1. Botanical description, common names and geographical origin of five South African *Helichrysum* sp.

Species	Common names	Botanical description and distribution	Sources
Helichrysum cymosum subsp. *cymosum*	Gold carpet (English), goute Tapyt/timie (Afrikaans), Impepho (isiXhosa and isiZulu).	**Botanical characteristics**: A well-branched, groundcover perennial shrubs, and grow up to 1m, having a small greyish-silver leaves and a greyish-white, woolly tinny branches. The plant consists of yellow flowers in flat-topped flower heads. Flowering occurs between September and April. **Geographical origin/habitat:** It is widely spread in South Africa, usually in damp and sandy slopes. They are distributed in the Eastern Cape, KwaZulu-Natal and Western Cape.	(7, 13- 16)
Helichrysum foetidum (L.) Moench	Yellow everlasting (English)	**Botanical characteristics:** Strong biennial shrublet and can grow up to 1 m. Leaves are aromatic, alternate, sticky, oblong-lanceolate, auriculate, sessile and clasping. Upper surface of the leaves is rough and hairy while the leave base is grey-woolly, clustering at the stem base and withers during flowering. The stems are simple, strong and straight with a cylindrical shape are habitually unbranched at the lower part. The flower heads have many florets with glossy, deep-yellow to cream color, Blossoming: October–May. **Geographical origin / habitat**: Naturally occurs in South Africa and other African countries. Also occurs as invasive weeds or naturalized in other parts of the world: Brazil, Crimea, Hawaii, Netherland, Portugal, and Spain, and the United Kingdom. Can grow in areas like; shrubby valleys, hill, mountain, damp areas and forest margins.	(17)
Helichrysum odoratissimum (L.) Sweet.	Imphepho (isiXhosa, isiZulu) Kooigoed (Afrikaans)	**Botanical characteristics**: The plant is a perennial shrub, scented, with woolly erect and straggling branches, can grow up to 20–200 cm. the surfaces are greyish white wooly on each side of the leaves. The shape of the leave is generally, linear, oblanceolate, having a thin base or wide and clasping. Has a bright yellow or golden yellow flowers head. Have two flowering season in South Africa based on the region: western and Eastern Cape from August to December while others like Kwazulu-Natal, Mpumalanga, Limpopo, Lesotho and Swaziland from January. **Geographical origin/habitat**: South Africa, Mozambique, Zimbabwe, Malawi. Commonly found in grassland areas, forest margins, and along roadsides reaching 5 m to 3050 m above the sea.	(7, 13, 18)
Helichrysum patulum (L.) D. Don (H. pat.)	Phefu (Sotho) Imphepho (Xhosa, Zulu) Kooigoed (Afrikaans)	**Botanical characteristics**: it is a well- branched subshrub and can attain a height of 1m, the leaves are small and hairy, the flower head is medium having Compact inflorescence Cream bracts, which blossom from September to February most especially between December-January. **Geographical origin/habitat**: Endemic to South Africa and grow on coastal dunes and mountain slopes reaching 600 m above sea level.	(17)
Helichrysum petiolare Hilliard & B. L. Burtt	Silver bush everlasting, (English), Hottentotskooigoed, Hottentotskruie, kooigoed, and Kruie (Afrikaans), Imphepho (Xhosa, Zulu)	**Botanical characteristics:** Aromatic, perennial shrub. The leaves are greenish-yellow or greyish, round to ovate form and covered by silver gray hairs on each side. The flower-heads is tiny having creamy or pale- yellow color. **Geographical origin/habitat**: The plant is prevalent in South Africa and other African countries like; Mozambique, Zimbabwe and Malawi. In South Africa, the species are distributed across Eastern Cape, Free State, Northern Cape and Western Cape Provinces.	(16, 19)

Table 2. Traditional uses of *H. cymosum*, *H. foetidum*, *H. odoratissimum*, *H. patulum* and *H. petiolare*.

Scientific name	Part and method of preparation	Traditional uses	Sources
H. cymosum	**Leaves:** Boiled as tea, burnt and smoke inhaled, wound dressing, boiled and vapour inhaled.	Treatment of cough and cold, pains, Infected wounds, headache, induces trances and goodwill to ancestors.	(4, 16)
H. foetidum	**Leaves:** Poultice, wound dressing, extract. **Roots:** Extract. Whole plant: Extract drunk, smoke inhaled**.**	Treatment of Sores, infected wounds, herpes, influenza, eye problem, sedative Induced trances, menstrual pain**.**	(11, 28, 29)
H. odoratissimum	**Leaves:** Tea, infusion, wound dressing, smoke inhaled, ointment, burnt as incense, eye drop **Stems:** Smoke inhaled **Ariel part**: extracts	Used in the treatment of, coughs and colds wounds and burns, headache, tonic for pregnant women, incense to invoke goodwill to ancestors, ointment for pimples, fumigate sickrooms.	(4, 11, 13)

diterpenoid (kaur-16-en-18-oic acid), flavonoids (apigenin-

H. patulum	Infusion	Treatment of, asthma, influenza, heart trouble, backache, kidney disease, bladder infections, gynaecological disorders, bedding and hyperpiesa.	(4, 11)
H. petiolare	**Leaves:** Taken as tea	Used to treat, coughs, colds, catarrh, headache, fever, menstrual disorders, urinary tract infections, bedding, wound dressing, heart conditions, stress, hypertension, anxiety.	(4)

7-O-β-D-glucoside), 7, 4' dihydroxy-5-methoxy-flavanone (28, 31), while *H. odoratissimum* contains numerous chalcone and flavanol compounds, diterpenes, phloroglucinol and pyrones (4, 7). The following compounds were isolated from *H. patulum*: carboxylic acids (hexadecanoic acid and tetradecanoic acid), glucosides (arbutin), several terpenoids, sesquiterpenes (viridiflorol, β-caryophyllene, (-)-alloaromadendrene, γ-gurjunene), monoterpenes (pinene), terpineol and limonene (36), while *H. petiolare* was found to contain the flavonoid derivatives, pyrenes and diterpenes (4). However, these are not the only compounds the present in *Helichrysum* sp., additional compounds pertaining to these plants are listed in Supplementary Table 1a to 1h.

Reproductive health potentials of Helichrysum spp.

Reproductive healthcare comprises of multiple processes involved in the sexual health functions and systems at all life stages in humans (48) and has been identified to be among the prevalent health challenges in Africa. However, the use of pharmaceutical drugs for the treatment and management of reproductive health challenges is known to be very costly or to have adverse side effects (49). As such, indigenous patients in most African countries opt for alternative forms of treatment mainly with plant-based products due to the fact that these are cheap, accessible and culturally acceptable alternatives (49, 50). Consequently, a variety of herbal remedies and their isolated bioactive compounds are used to treat infertility conditions and have demonstrated little or no side effects (51). Despite their effectiveness in traditional medicine, there is a lack of adequate pharmacological data relevant to the discovery of new therapeutic agents (50). Only a few studies have investigated the benefits of the genus *Helichrysum* for ameliorating reproductive health challenges. Some *Helichrysum* species of Southern African origin have been reported to be used traditionally to treat male and female infertility issues e.g. *Helichrysum caespititium* (DC.), *Helichrysum latifolium, Helichrysum nudifolium* var. *pilosellum, Helichrysum odoratissimum* (L.) Sweet, *Helichrysum platypterum* DC as well as *Helichrysum psilolepis* Harv. (38). There is limited information in literature, especially on the anti-infertility effects of *H. cymosum, H. foetidum, H. odoratissimum, H. patulum* and *H. petiolare*.

It was reported that the aqueous extract (AE) and the methanol extract (ME) of *H. odoratissimum* reduced cyclophosphamide (CP)-induced reproductive toxicity in male rats (52). Different doses of the extracts and CP were orally administered to seven animal groups, viz: 5 ml/kg of CP, 10 ml/kg of CP + distilled water (DW), 10 ml/kg of CP + 5% Tween 80, 0.25 mg/kg of CP + clomiphene citrate, 50 and 100 mg/kg of CP and AE, while 50 and 100 mg of CP and ME were administered to each of the groups (52). The results of the study indicated that there was a significant ($P < 0.001$) decrease in the weights of the seminal vesicles, testosterone levels, sperm count, motility and viability compared to the controls. All extracts and doses of *H. odoratissimum* treatment reversed the effects of CP and significantly ($P < 0.001$) increased sperm count, sperm viability and sperm motility ($P < 0.05$). Thus, *H. odoratissimum* could be considered as a potential alternative therapy in mitigating and preventing reproductive damage caused by cancer treatment (chemotherapy) with CP.

Anti-inflammatory activities

Potent bioactive compounds derived from the genus *Helichrysum* have indicated anti-inflammatory activities, often associated with the occurrence of different flavonoids. For instance, the compound kaempferol has been reported to be involved in the inflammatory process of experimental diabetes (53), while arzanol is known to be involved in the release of such pro-inflammatory mediators as IL-1β, IL-6, IL-8 (11, 54, 55). Therefore, the potential of freshly isolated bioactive compounds from the *Helichrysum* genus in the management of inflammatory responses has been reported and in one of such studies (56), the aqueous and methanol extracts of *H. cymosum* (whole plant) were investigated through the use of the cyclooxygenase (COX-1) inhibition technique and results showed values of 52.0% and 100% inhibition respectively. In another study, the 5-lipoxygenase inhibitory activities of the aqueous, methanol and essential oil extracts of *H. odoratissimum* were assessed using 3-fold stepwise dilution, and the positive and negative controls were nordihydroguaiaretic acid and Tween®20, respectively. The results showed that the essential oil produced a 5-lipoxygenase inhibitory activity of 50% (IC_{50} values of 22.5 ppm -35.9 ppm) (41).

Antibacterial activities

Most of the available information in the literature is focused on the antimicrobial effects of the genus *Helichrysum*, which is so far the predominantly studied activity (11). The 5 selected *Helichrysum* sp. have been reported to exhibit toxic effects against transformed human kidney epithelial (Graham) cells, (*H. cymosum* and *H. odoratissimum*) as well as growth inhibitory activities (*H. petiolare* and *H. nudifolium*) (26). Despite numerous documented antimicrobial activities, most of the compounds isolated from the *Helichrysum* spp. still need further investigation on their activities (26). The antibacterial activities of the 5 *Helichrysum* spp. are presented in Supplementary Table 2.

Antioxidant properties

Evaluation has been done on the antioxidant properties of whole plant extracts (acetone, ethanol, boiled and cold aqueous) of *Helichrysum petiolare* using 2, 2'- azino-bis (3-ethylbenzothiazoline-6-sulphonic acid (ABTS), diphenyl-1-picrylhydrazyl (DPPH), nitric oxide radical (NO) scavenging activities and total antioxidant capacity (TAC) assays (60).

The boiled aqueous extracts exhibited the highest phenolic content of 212.963 mg/g, which suggests that heating might have facilitated a higher extraction of this compound, while, the ethanol extract was high in flavonoids (172.393 mg/g) and proanthocyanidines (65.855 mg/g) contents, suggesting a higher extraction yield for these solvents and possible stronger antioxidant properties. The acetone extracts showed higher amounts of alkaloids, flavonols and saponins, while the cold aqueous extract had a relatively lower overall phytochemical content. The DPPH and ABTS radical scavenging activities were highest with the boiled aqueous extract at IC50 inhibition values of 0.02 mg/ml and 0.07 mg/ml respectively, while the highest NO inhibition and TAC effects were observed with the ethanol extract (IC50 0.41 and IC50 0.19) respectively. The findings from these studies proposed the use of ethanol and boiled aqueous extracts of *H. petiolare* for medicinal treatments which correlates with the mode of administration in traditional medicine. Investigations are on the acetone and methanol extracts as well as essential oils from the leaves of *H. petiolare,* using the DPPH assay found that both these extracts showed activities at IC50 values of 44.28 µg/ml and 28.70 µg/ml respectively (39). The findings of this study reveal that the extracts and essential oil exhibited antioxidant activity. However, the activities of extracts were enhanced compared to essential oil.

The antioxidant activity of the essential oil from the leaves of *H. cymosum* using the DPPH assay and butylated hydroxyl toluene as the positive control have also been studied (61). The radical scavenging potential demonstrated by *H. cymosum* was attained at a value of 6.3 g/l compared with butylated hydroxy toluene (BHT) at 7.0 mg/l. In addition, the antioxidant activity of the ethanol extracts from the leaves of *H. odoratissimum* using the DPPH assay have been documented (62). The plant extract showed a higher scavenging activity with IC50 value of 5.13 ± 0.07 pg/ml. Also, the antioxidant activities of the essential oil and methanol extract from the leaves of *H. odoratissimum*, using the DPPH assay have been reported (41). The results showed a decrease in activity for the essential oil with IC50 >100 parts per million (ppm).

Neuroprotective properties

Only a few studies have investigated the neurodegenerative properties of most *Helichrysum* species. *H. odoratissimum* has been listed among medicinal plants of Southern Africa used for memory and central nervous-related ailments (63), but their neuroprotective properties have not been elucidated. Neuroprotection is an approach used by scientists in managing neurodegenerative diseases, since treatments are mostly palliative (64). Additionally, antidepressant drugs have exhibited numerous side effects, thus hampering the usage of such medication for longer periods of time. Recently, herbal medicines have been acknowledged as alternative approaches to manage neurodegenerative diseases (NDD), seemingly because they are considered to be safer and can potentially be used over longer durations with minimal side effects (65). Studies have shown that plant dietary supplements and foods rich in antioxidant scavenging free radicals, could be used to modulate apoptotic effects and have been reported to exhibit neuroprotective properties (66). Pharmacological activities displayed by some compounds such as arzanol, pholoroglucinol α-pyrone isolated from some species within the genus *Helichrysum* are known to act as eicosanoid inhibitors on PGE2 synthesis, the NF-κB pathway, while other compounds such as caffeic and quercetin derivatives are known for their antioxidant and anti-inflammatory effects for managing NDD such as mood disorders. Therefore, exploration of these bioactive compounds could be useful in drug discovery and treatment of NDD (65).

Antidiabetic activities

Diabetes is a disease of global concern due to its high prevalence across the world (67), most especially in the developing countries where the management and treatment are still problematic (68). Based on the challenges associated with diabetic treatments, researchers and pharmaceutical industries are now focusing attention on alternative herbal remedies to treat and manage diabetes (68). However, only a few medicinal plants with hypoglycemic effects have been investigated extensively in both *in vitro* and *in vivo* studies. Some *Helichrysum* sp. like *H. gymnocomum, H. nudifolium, H. odoratissimum* and *H. petiolare* are well-known antidiabetic plants used by traditional healers in the Eastern Cape region of South Africa (67, 69).

Reports are on the antidiabetic potentials of ethanol, the cold and boiled aqueous extracts of *H. petiolare,* on L6 myocytes and HepG2 (C3A) hepatocytes using the following the α-amylase, α-glucosidase and lipase inhibition assays (60). The ethanol extracts exhibited cytotoxic effects in the treated cells while the cold and boiled aqueous extracts enhanced glucose uptake in L6 and C3A cell lines. However, L6 myocytes indicated a higher glucose uptake compared to the C3A hepatocyte cell-line following treatment with cold aqueous extract. Also, the best inhibition of α-amylase and α-glucosidase was exhibited by the boiled aqueous extract compared with the cold aqueous extract, while the boiled aqueous extract exhibited a lower lipase inhibition than acarbose, an approved dietary treatment for type 2 diabetes mellitus used as the control, with no significant difference observed ($p<0.05$). Another study investigated the hypoglycemic activities of 50, 100 and 150 mg/kg body weight doses of *H. odoratissimum* aqueous leaf extract in alloxan-induced diabetic Swiss albino mice which showed a non-dose dependent response by decreasing the glucose levels (70).

Cytotoxicity

The cytotoxicity of the chloroform and methanol extracts (ratio 1:1), of the leaves and stems of *H. foetidum, H. odoratissimum, H. patulum* and *H. petiolare* which were amongst the 35 South African *Helichrysum* sp. investigated (26), using the sulforhodamine B (SRB) assay against transformed human kidney epithelial (Graham's) cells, MCF-7 breast adenocarcinoma and SF-268 glioblastoma cells, at a concentration of 0.1 mg/ml. The results were as follows*: H. foetidum* (% Graham cells = 32.7 ± 2.1, % SF-268 cells = 57.8 ± 2.1 and % MCF-7 cell = 24.9 ± 0.4), *H. odoratissimum* (%

Graham cells = 17.5 ± 0.4, % SF-268 cells = 48.2 ± 1.4 and % MCF-7 cell = 7.4 ± 0.7), *H. patulum* (% Graham cells = 63.8 ± 1.3, % SF-268 cells = 75.2 ± 2.0 and % MCF-7 cell = 37.8), *H. petiolare* (% Graham cells = 59.3 ± 3.4, % SF-268 cells = 76.6 ± 3.0 and % MCF-7 cell = 33.4). These results tend to suggest that the plant species investigated might be toxic against Graham cells at the concentration of 0.1 mg/ml. In another study, the cytotoxicities of the chloroform and water-methanol extracts of the aerial parts of *H. cymosum* were investigated against the Vero African green monkey kidney cells, using the XTT assay and zearalenone as positive control. The IC50 values of the extracts were 36.5 µg/ml (chloroform) and 59.7 µg/ml (methanol-water) and 1.3 µg/ml (control), respectively. These results suggest that both the aqueous and chloroform extracts of the tested species had more toxic effects on Vero African green monkey kidney cells compared to the control (7). Also, the cytotoxicity of essential oil of *H. odoratissimum* was investigated using the brine shrimp assay, with a median lethal concentration of 31.6 µg/ml recorded against the brine shrimp (45), indicating toxicity.

Conclusion

This review reveals important bioactive compounds, medicinal properties and some pharmacological activities of *H. cymosum, H. foetidum, H, odoratissimum, H. petiolare* and *H. patulum*. The diverse medicinal uses reported have shown that these plants have a potential as herbal remedies and necessitate further pharmacological evaluation of all the bioactive compounds isolated from these species. Therefore, exploring the phytochemical properties and pharmacological activities in correlation with the traditional uses of these plants in further studies, will improve upon available knowledge about their medicinal value and also enhance scientific validation of these medicinal plants in drug discovery.

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Authors contributions

Conceptualization was made by AQ Nkemzi and OO Oguntibeju, Writing of the original draft was by AQ Nkemzi, Writing review and editing by AQ Nkemzi, OE Ekpo and OO Oguntibeju, Supervision was by OE Ekpo and OO Oguntibeju. All authors have read and agreed to the published version of the manuscript.

Compliance with ethical standards

Conflict of interest: The authors declare no conflicts of interest.

Ethical issues: None.

Supplementary data

Supplementary Table 1. Phytochemical compound reported from five *Helichrysum* sp.

Supplementary Table 2. Antibacterial activities of five *Helichrysum* species

References

1. Street R, Prinsloo G. Commercially important medicinal plants of South Africa: a review. Journal of chemistry. 2013 Jan 1;2013. https://doi.org/10.1155/2013/205048
2. Olaokun OO, McGaw LJ, van Rensburg IJ, Eloff JN, Naidoo V. Antidiabetic activity of the ethyl acetate fraction of *Ficus lutea* (Moraceae) leaf extract: comparison of an *in vitro* assay with an *in vivo* obese mouse model. BMC Complementary and Alternative Medicine. 2016;16(1):1-12. https://doi.org/10.1186/s12906-016-1087-z
3. Ruberto G, Biondi DM, Barbagallo C, Meli R, Savoca F. Constituents of stem and flower oils of *Helichrysum litoreum* Guss. Flavour and Fragrance Journal. 2002;17(1):46-48. https://doi.org/10.1002/ffj.1037
4. Lourens A, Viljoen AM, Van Heerden F. South African *Helichrysum* species: a review of the traditional uses, biological activity and phytochemistry. Journal of Ethnopharmacology. 2008;119 (3):630-52. https://doi.org/10.1016/j.jep.2008.06.011
5. Manning J, Goldblatt P. Plants of the Greater Cape Floristic Region. 1: The Core Cape flora: South African National Biodiversity Institute; 2012.
6. Van Wyk B-E, Oudtshoorn Bv, Gericke N. Medicinal Plants of South Africa: Briza; 1997.
7. Heyman HM. Identification of anti-HIV compounds in *Helichrysum* sp. (Asteraceae) by means of NMR-based metabolomic guided fractionation: University of Pretoria; 2013.
8. Akinyede KA, Cupido CN, Hughes GD, Oguntibeju OO, Ekpo OE. Medicinal properties and *in vitro* biological activities of selected *Helichrysum* species from South Africa: A Review. Plants. 2021 Aug;10(8):1566. https://doi.org/10.3390/plants10081566
9. Matanzima Y. Quantitative and qualitative optimization of antimicrobial bioactive constituents of *Helichrysum cymosum* using hydroponics technology: Cape Peninsula University of Technology; 2014.
10. Leonardi M, Giovanelli S, Ambryszewska KE, Ruffoni B, Cervelli C, Pistelli L et al. Essential oil composition of six *Helichrysum* species grown in Italy. Biochemical Systematics and Ecology. 2018;79:15-20. https://doi.org/10.1016/j.bse.2018.04.014
11. Akaberi M, Sahebkar A, Azizi N, Emami SA. Everlasting flowers: Phytochemistry and pharmacology of the genus *Helichrysum*. Industrial Crops and Products. 2019;138:111471. https://doi.org/10.1016/j.indcrop.2019.111471
12. Najar B, Nardi V, Cervelli C, Mecacci G, Mancianti F, Ebani VV et al. Volatilome analyses and *in vitro* antimicrobial activity of the essential oils from five South African *Helichrysum* species. Molecules. 2020;25(14):3196. https://doi.org/10.3390/molecules25143196
13. Reddy D. The phytochemistry and antimicrobial activity of selected indigenous *Helichrysum* species: University of the Witwatersrand; 2007.
14. Van Vuuren S, Viljoen A, Van Zyl R, Van Heerden F, Başer KHC. The antimicrobial, antimalarial and toxicity profiles of helihumulone, leaf essential oil and extracts of *Helichrysum cymosum* (L.) D. Don subsp. *cymosum*. South African Journal of Botany. 2006;72(2):287-90. https://doi.org/10.1016/j.sajb.2005.07.007
15. Philander LA. An ethnobotany of Western Cape Rasta bush medicine. Journal of Ethnopharmacology. 2011;138(2):578-94. https://doi.org/10.1016/j.jep.2011.10.004
16. Giovanelli S, De Leo M, Cervelli C, Ruffoni B, Ciccarelli D, Pistelli

L. Essential oil composition and volatile profile of seven *Helichrysum* species grown in Italy. Chemistry & Biodiversity. 2018;15(5):e1700545. https://doi.org/10.1002/cbdv.201700545

17. Najar B, Cervelli C, Ferri B, Cioni P, Pistelli L. Essential oils and volatile emission of eight South African species of *Helichrysum* grown in uniform environmental conditions. South African Journal of Botany. 2019;124:178-87. https://doi.org/10.1016/j.sajb.2019.05.015
18. Pooley E. Mountain flowers: A field guide to the flora of the Drakensberg and Lesotho: Flora Publ. Trust; 2003.
19. Maroyi A. *Helichrysum longifolium* and *Helichrysum*: A comparative analysis of their medicinal uses, chemistry and biological. Asian J Pharm Clin Res. 2019;12(7):41-46. https://doi.org/10.22159/ajpcr.2019.v12i7.33684
20. Shaikh MM. Synthesis and biological activities of natural homoisoflavanones. 2011. (Doctoral dissertation).
21. Seoposengwe K, Van Tonder JJ, Steenkamp V. *In vitro* neuroprotective potential of four medicinal plants against rotenone-induced toxicity in SH-SY5Y neuroblastoma cells. BMC complementary and alternative medicine. 2013;13(1):1-11. https://doi.org/10.1186/1472-6882-13-353
22. Mzindle NB. Anti-inflammatory, anti-oxidant and wound-healing properties of selected South Africa Medicinal Plants. 2017.
23. Thring T, Weitz F. Medicinal plant use in the Bredasdorp/Elim region of the Southern Overberg in the Western Cape Province of South Africa. Journal of Ethnopharmacology. 2006;103(2):261-75. https://doi.org/10.1016/j.jep.2005.08.013
24. Aiyegoro OA, Okoh AI. Preliminary phytochemical screening and *in vitro* antioxidant activities of the aqueous extract of *Helichrysum longifolium* DC. BMC complementary and alternative medicine. 2010;10(1):1-8. https://doi.org/10.1186/1472-6882-10-21
25. Van Wyk B-E, Heerden FV, Oudtshoorn BV. Poisonous plants of South Africa: Briza Publications; 2002.
26. Lourens A, Van Vuuren S, Viljoen A, Davids H, Van Heerden F. Antimicrobial activity and *in vitro* cytotoxicity of selected South African *Helichrysum* species. South African Journal of Botany. 2011;77(1):229-35. https://doi.org/10.1016/j.sajb.2010.05.006
27. Viegas DA, Palmeira-de-Oliveira A, Salgueiro L, Martinez-de-Oliveira J, Palmeira-de-Oliveira R. *Helichrysum italicum*: From traditional use to scientific data. Journal of ethnopharmacology. 2014;151(1):54-65. https://doi.org/10.1016/j.jep.2013.11.005
28. Kakam AMZ, Franke K, Ndom JC, Dongo E, Mpondo TN, Wessjohann LA. Secondary metabolites from *Helichrysum foetidum* and their chemotaxonomic significance. Biochemical Systematics and Ecology. 2011;2(39):166-7. https://doi.org/10.1016/j.bse.2011.02.005
29. Popoola OK. The chemical and biological characterization of South African *Helichrysum* species. 2015.
30. Drewes SE, van Vuuren SF. Antimicrobial acylphloroglucinols and dibenzyloxy flavonoids from flowers of *Helichrysum gymnocomum*. Phytochemistry. 2008;69(8):1745-49. https://doi.org/10.1016/j.phytochem.2008.02.022
31. Malolo F-AE, Nouga AB, Kakam A, Franke K, Ngah L, Flausino O et al. Protease-inhibiting, molecular modeling and antimicrobial activities of extracts and constituents from *Helichrysum foetidum* and *Helichrysum mechowianum* (compositae). Chemistry Central Journal. 2015;9(1):1-11. https://doi.org/10.1186/s13065-015-0108-1
32. Scott G, Springfield E, Coldrey N. A pharmacognostical study of 26 South African plant species used as traditional medicines. Pharmaceutical Biology. 2004;42(3):186-213. https://doi.org/10.1080/13880200490514032
33. Marín M, Máñez S. Recent trends in the pharmacological activity of isoprenyl phenolics. Current Medicinal Chemistry. 2013;20(2):272-79. https://doi.org/10.2174/0929867311320020007 https://doi.org/10.2174/092986713804806676
34. Maroyi A. *Helichrysum petiolare* hilliard and BL burtt: A review of its medicinal uses, phytochemistry and biological activities. Asian J Pharm Clin Res. 2019;12(6):69-71. https://doi.org/10.22159/ajpcr.2018.v11i11.28813
35. Mabaleha MB, Zietsman PC, Wilhelm A, Bonnet SL. Ethnobotanical survey of medicinal plants used to treat mental illnesses in the Berea, Leribe and Maseru Districts of Lesotho. Natural Product Communications. 2019;14(7):1934578X19864215. https://doi.org/10.1177/1934578X19864215
36. Swartz VG. Phytochemical studies of *Helichrysum patulum*: University of the Western Cape; 2006.
37. Alfred M. *Helichrysum cymosum* (L.) D.Don (Asteraceae): Medicinal uses, chemistry and biological activities. Asian Journal of Pharmaceutical and Clinical Research. 2019:19-26. https://doi.org/10.22159/ajpcr.2019.v12i7.33771
38. Twilley D, Kishore N, Meyer D, Moodley I, Kumar V, Lall N. The effect of *Helichrysum odoratissimum* (L.) sweet on cancer cell proliferation and cytokine production.
39. Lourens A, Reddy D, Başer K, Viljoen A, Van Vuuren S. *In vitro* biological activity and essential oil composition of four indigenous South African *Helichrysum* species. Journal of Ethnopharmacology. 2004;95(2-3):253-58. https://doi.org/10.1016/j.jep.2004.07.027
40. Asekun OT, Grierson DS, Afolayan AJ. Characterization of essential oils from *Helichrysum odoratissimum* using different drying methods.
41. Frum Y, Viljoen AM. *In vitro* 5-lipoxygenase activity of three indigenous South African aromatic plants used in traditional healing and the stereospecific activity of limonene in the 5-lipoxygenase assay. Journal of Essential Oil Research. 2006;18(sup1):85-88. https://doi.org/10.1080/10412905.2006.12067127
42. Van Vuuren S. Antimicrobial activity of South African medicinal plants. Journal of Ethnopharmacology. 2008;119(3):462-72. https://doi.org/10.1016/j.jep.2008.05.038
43. Ocheng F, Bwanga F, Joloba M, Softrata A, Azeem M, Pütsep K, Borg-Karlson AK, Obua C, Gustafsson A. Essential oils from ugandan aromatic medicinal plants: chemical composition and growth inhibitory effects on oral pathogens. Evidence-Based Complementary and Alternative Medicine. 2015 Jan 1;2015. https://doi.org/10.1155/2015/230832
44. Kuiate JR, Amvam Zollo PH, Nguefa EH, Bessière JM, Lamaty G, Menut C. Composition of the essential oils from the leaves of *Microglossa pyrifolia* (Lam.) O. Kuntze and *Helichrysum odoratissimum* (L.) Less. growing in Cameroon. Flavour and fragrance journal. 1999 Mar;14(2):82-84. https://doi.org/10.1002/(SICI)1099-1026(199903/04)14:2%3C82::AID-FFJ780%3E3.0.CO;2-Z
45. Lawal OA, Ogunwande IA, Kasali AA, Opoku AR, Oyedeji AO. Chemical composition, antibacterial and cytotoxic activities of essential oil from the leaves of *Helichrysum odoratissimum* grown in South Africa. Journal of Essential Oil Bearing Plants. 2015;18(1):236-41. https://doi.org/10.1080/0972060X.2014.901618
46. Kajangwe V, Tomani JC, Mukazayire MJ, Chalchat JC, Duez P. Chemical composition and antibacterial activity of essential oils of 3 *Helichrysum* species. Planta Medica. 2008 Jul;74(09):117. https://doi.org/10.1055/s-0028-1084925
47. Gundidza MG, Zwaving JH. The chemical composition of the essential leaf oil of *Helichrysum odoratissimum* sweet from Zimbabwe. Journal of Essential Oil Research. 1993 May 1;5(3):341-43. https://doi.org/10.1080/10412905.1993.9698235
48. Abdillahi H, Van Staden J. South African plants and male reproductive healthcare: conception and contraception. Journal of Ethnopharmacology. 2012;143(2):475-80. https://doi.org/10.1016/j.jep.2012.06.047

49. Moteetee A, Kose LS. Medicinal plants used in Lesotho for treatment of reproductive and post reproductive problems. Journal of Ethnopharmacology. 2016;194:827-49. https://doi.org/10.1016/j.jep.2016.10.062
50. Lembè DM, Bend EF, Oundoum PCO, Domkam J, Njila MN, Koloko B *et al*. Antifertility potential of *Helichrysum cameroonense* (Asteraceae). 2013.
51. Opuwari C. Effect of *Basella alba* and *Hibiscus macranthus* on tm4 sertoli cell functions. 2009.
52. Watcho P, Mpeck IR, Defo PBD, Wankeu-Nya M, Ngadjui E, Fozin GRB et al. Cyclophosphamide-induced reproductive toxicity: Beneficial effects of *Helichrysum odoratissimum* (Asteraceae) in male Wistar rats. Journal of integrative medicine. 2019;17(5):366-73. https://doi.org/10.1016/j.joim.2019.07.002
53. de la Garza AL, Etxeberria U, Palacios-Ortega S, Haslberger AG, Aumueller E, Milagro FI et al. Modulation of hyperglycemia and TNFα-mediated inflammation by *Helichrysum* and grapefruit extracts in diabetic db/db mice. Food and function. 2014;5(9):2120-28. https://doi.org/10.1039/C4FO00154K
54. Guinoiseau E, Lorenzi V, Luciani A, Muselli A, Costa J, Casanova J et al. Biological properties and resistance reversal effect of *Helichrysum italicum* (Roth) G. Don. Microbial pathogens and strategies for combating them: Science, Technology and Education. 2013;2:1073-80.
55. Kothavade PS, Nagmoti DM, Bulani VD, Juvekar AR. Arzanol, a potent mPGES-1 inhibitor: novel anti-inflammatory agent. The Scientific World Journal. 2013;2013. https://doi.org/10.1155/2013/986429
56. Stafford G, Jäger A, Van Staden J. Effect of storage on the chemical composition and biological activity of several popular South African medicinal plants. Journal of Ethnopharmacology. 2005;97(1):107-15. https://doi.org/10.1016/j.jep.2004.10.021
57. Samie A, Nefefe T, Gundidza M, Mmbengwa V, Magwa M, Mtshali M. Antimicrobial activities and time kill profiles of five essential oils from Southern Africa against selected bacterial and fungal organisms. African Journal of Pharmacy and Pharmacology. 2012;6(44):3086-95. https://doi.org/10.5897/AJPP12.1162
58. Seaman T. The antimicrobial and antimycobacterial activity of plants used for the treatment of respiratory ailments in Southern Africa and the isolation of anacardic acid from *Ozoroa paniculosa.* 2005.
59. Mathekga ADM. Antimicrobial activity of *Helichrysum* sp. and the isolation of a new phloroglucinol from *Helichrysum caespititium*: University of Pretoria; 2004.
60. Aladejana AE, Bradley G, Afolayan AJ. Phytochemical screening and *in-vitro* antioxidant activities of various extracts of *Helichrysum petiolare* Hilliard & BL Burtt used for the treatment of diabetes mellitus in the Eastern cape province of South Africa. Journal of Pharmacy and Nutrition Sciences. 2020;10:331-40. https://doi.org/10.29169/1927-5951.2020.10.06.3
61. Franccedil T, Lambert SM, Michel JDP, Gaby NME, Fabrice FB, Zaché N et al. Composition, radical scavenging and antifungal activities of essential oils from 3 *Helichrysum* species growing in Cameroon against *Penicillium oxalicum* a yam rot fungi. African Journal of Agricultural Research. 2010;5(2):121-27.
62. Twilley D, Lall N. Extracts and compositions of *Helichrysum odoratissimum* for preventing and treating skin cancers. Google Patents; 2015.
63. Masondo NA, Stafford GI, Aremu AO, Makunga NP. Acetylcholinesterase inhibitors from southern African plants: An overview of ethnobotanical, pharmacological potential and phytochemical research including and beyond Alzheimer's disease treatment. South African journal of botany. 2019;120:39-64. https://doi.org/10.1016/j.sajb.2018.09.011
64. Angeloni C, Vauzour D. Natural products and neuroprotection. Multidisciplinary Digital Publishing Institute; 2019. https://doi.org/10.3390/ijms20225570
65. Borgonetti V, Les F, López V, Galeotti N. Attenuation of anxiety-like behavior by *Helichrysum stoechas* (L.) moench methanolic extract through up-regulation of erk signaling pathways in noradrenergic neurons. Pharmaceuticals. 2020;13(12):472. https://doi.org/10.3390/ph13120472
66. Lobo V, Patil A, Phatak A, Chandra N. Free radicals, antioxidants and functional foods: Impact on human health. Pharmacognosy Reviews. 2010;4(8):118. https://doi.org/10.4103/0973-7847.70902
67. Odeyemi S, Bradley G. Medicinal plants used for the traditional management of diabetes in the Eastern Cape, South Africa: pharmacology and toxicology. Molecules. 2018;23(11):2759. https://doi.org/10.3390/molecules23112759
68. Oguntibeju OO, Meyer S, Aboua YG, Goboza M. *Hypoxis hemerocallidea* significantly reduced hyperglycaemia and hyperglycaemic-induced oxidative stress in the liver and kidney tissues of streptozotocin-induced diabetic male wistar rats. Evidence-Based Complementary and Alternative Medicine. 2016;2016. https://doi.org/10.1155/2016/8934362
69. Erasto P, Adebola P, Grierson D, Afolayan A. An ethnobotanical study of plants used for the treatment of diabetes in the Eastern Cape Province, South Africa. African Journal of Biotechnology. 2005;4(12).
70. Njagi JM, Ngugi MP, Kibiti CM, Ngeranwa J, Njue W, Gathumbi P et al. Hypoglycemic effect of *Helichrysum odoratissimum* in alloxan induced diabetic mice. 2015. https://doi.org/10.31254/phyto.2015.4106

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