

## HELICHRYSUM LONGIFOLIUM AND HELICHRYSUM PEDUNCULATUM: A COMPARATIVE ANALYSIS OF THEIR MEDICINAL USES, CHEMISTRY AND BIOLOGICAL ACTIVITIES

ALFRED MAROYI\*

Department of Botany, Medicinal Plants and Economic Development Research Centre, University of Fort Hare, Private Bag X1314, Alice 5700, South Africa. Email: amaroyi@ufh.ac.za

Received: 21 April 2019, Revised and Accepted: 28 May 2019

### ABSTRACT

*Helichrysum longifolium* and *Helichrysum pedunculatum* have a long history of medicinal use, particularly managing wounds acquired during male circumcision rites in South Africa. There is a need to evaluate the existence of any correlation between the ethnomedicinal applications, the phytochemistry and pharmacological properties of the species. Therefore, in this review, analyses of the botanical, medicinal, and chemical and biological activities of *H. longifolium* and *H. pedunculatum* are presented as well as exploring the potential of the two species as important sources of health and pharmaceutical products. Information on the botany, medicinal uses, and phytochemistry and biological activities of *H. longifolium* and *H. pedunculatum* was assembled from several internet sources which included Scopus, Google Scholar, Elsevier, Science Direct, Web of Science, PubMed, SciFinder, and BMC. Additional information was sourced from journal articles, scientific reports, theses, books, and book chapters obtained from the University library. This study showed that alkaloids, flavonoids, linoleic acid, oleic acid, phenol, proanthocyanidin, saponins, and tannins have been identified from the leaves of *H. longifolium* and *H. pedunculatum*. The pharmacological research showed that *H. longifolium* and *H. pedunculatum* extracts and compounds isolated from the species have antibacterial, antifungal, anti-inflammatory, antioxidant, antiparasitic, antiprotozoal, and cytotoxicity activities. For local communities to use *H. longifolium* and *H. pedunculatum* extracts with confidence as herbal medicines, there is a need for extensive phytochemical and pharmacological studies. Further research is required to establish the safety profiles of different *H. longifolium* and *H. pedunculatum* preparations.

**Keywords:** Asteraceae, Ethnopharmacology, *Helichrysum longifolium*, *Helichrysum pedunculatum*, Herbal medicine, South Africa.

© 2019 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>) DOI: <http://dx.doi.org/10.22159/ajpcr.2019.v12i7.33684>

### INTRODUCTION

The Asteraceae family continues to play an important role in the development of drugs used in modern medicine. For example, the discovery of artemisinin, an antimalarial drug from the leaves of *Artemisia annua* L., a member of the Asteraceae family [1-8] illustrated the importance of the family toward a role in the production of plant-derived medicines. The Asteraceae is one of the largest families of flowering plants in the world, with about 1600 genera and 23,000 species, found almost everywhere in the world except in Antarctica [9-14]. Several members of this family are characterized by phytochemical compounds such as acetophenones, caffeoylquinic acids, phloroglucinol, polyphenols, pyrrolizidine alkaloids, polyacetylenes, chalcone, flavonoids, and diterpenoids [15-19]. Several species of the family Asteraceae are characterized by analgesic, anti-allergic, antibacterial, antidiabetic, antifungal, antiviral, anti-inflammatory, antimigraine, antioxidant, antiproliferative, antipyretic, antitumor, antiulcer, cardiogenic, and neuroprotective and neurotoxicity activities [16,17,19-35]. The genus *Helichrysum* Mill. is one of the most important sources of herbal medicines among the Asteraceae genera [17,27,29-44]. *Helichrysum longifolium* DC. and *Helichrysum pedunculatum* Hilliard and B.L. Burtt. are among the species widely used as herbal medicines in South Africa [17]. Apart from used as herbal medicines for similar medicinal conditions, these two species have been recorded in overlapping geographical areas [17,31,45-60]. Therefore, in this review, analytical analyses of the botanical, medicinal, and chemical and biological activities of *H. longifolium* and *H. pedunculatum* are presented as well as exploring the potential of the two species as important sources of health and pharmaceutical products.

### BOTANICAL DESCRIPTION OF *H. LONGIFOLIUM* AND *H. PEDUNCULATUM*

Both *H. longifolium* and *H. pedunculatum* are perennial herbs growing up to 60 cm from a woody rootstock [46,50]. The leaves of *H. longifolium*

are linear-lanceolate to oblong-lanceolate in shape, 100 mm to 250 mm in length and 7 mm to 20 mm in width [60]. The leaves are rosetted, apex more or less acute, base broad, clasping and bicolored with white hairs below. The leaves of *H. pedunculatum* are broader but shorter in length than those of *H. longifolium*, 80 mm–130 mm in length and 20 mm–40 mm in width [51]. The leaves of *H. pedunculatum* are elliptic in shape, apex acute, tapering to a broad, clasping petiole-like base, and upper surface glabrous, while the lower surface has a white silky-woolly-felted skin-like indumentum. Flowers of *H. longifolium* are yellow in color while those of *H. pedunculatum* are reddish-brown in color [52]. *H. longifolium* has been recorded in sandy grassland biome at an altitude ranging from 10 m to 915 m above sea level in the Eastern Cape and KwaZulu Natal Provinces in South Africa [40] and Mozambique [52,53] (Fig. 1). *H. pedunculatum* has also been recorded in a grassland biome at an altitude ranging from 30 m to 1525 m above sea level in the Eastern Cape, Free State and the Western Cape Provinces in South Africa and Lesotho [46] (Fig. 1).

### MEDICINAL USES OF *H. LONGIFOLIUM* AND *H. PEDUNCULATUM*

In South Africa, *H. longifolium* and *H. pedunculatum* have a long history of medicinal usage, particularly managing wounds acquired during male circumcision rites in South Africa [45,47-49,55-75] (Table 1). Conventionally, the wound caused by circumcision is bandaged by crushed leaves of *H. longifolium* and *H. pedunculatum*, and hence these two species have been described by Watt and Breyer-Brandwijk [76] as “anti-septic” and “anti-inflammatory” agents. This argument was based on the usage of the two species as herbal medicines against microbial infections and infestations, thus directly or indirectly providing protection or inhibiting the growth of undesirable microbes. Leaf or root decoction or infusion of *H. pedunculatum* is also used as herbal medicine for colds [36,60,61,63,76-78], cough [36,60,61,63,76-78], respiratory problems [65], postpartum problems [64], skin infections [74], and stomach ailments [49,61,64].

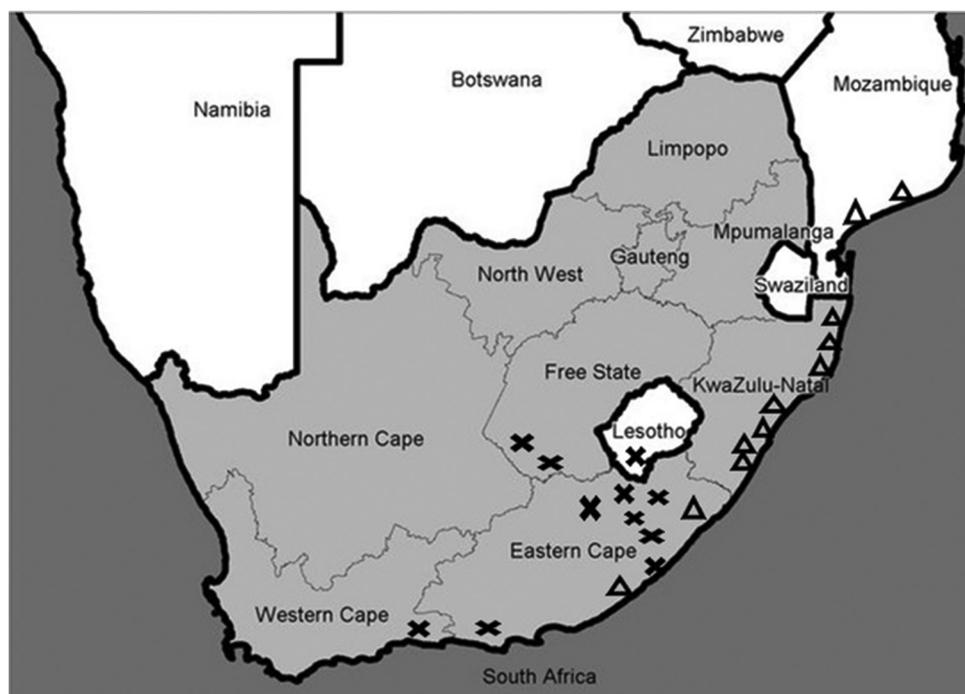


Fig. 1: Geographical distribution of *Helichrysum longifolium* (Δ) and *Helichrysum pedunculatum* (X)

#### PHARMACOLOGY OF *H. LONGIFOLIUM* AND *H. PEDUNCULATUM*

Some phytochemical constituents including alkaloids, flavonoids, linoleic acid, oleic acid, phenol, proanthocyanidin, saponins, and tannins (Table 2) which are considered important for some of the biological activities have been isolated from the leaves of *H. longifolium* and *H. pedunculatum*. There appear to be similarities in terms of the content of total flavonoids, phenol, and proanthocyanidin of *H. longifolium* and *H. pedunculatum* (Table 2). Research by Kumar and Pandey [79] and Marín and Máñez [80] showed that flavonoids and other phenolic compounds, in general, have antibacterial, antiprotozoal, antifungal, anti-inflammatory, antiviral, antioxidative activities, free radical scavenging capacity, coronary heart disease prevention, hepatoprotective, estrogenic, antidiabetic, or antithrombotic agents, and anticancer activities. Marín and Máñez [80] argued that flavonoids and other phenolic compounds in herbal medicines correlate with their activities as an antioxidant or anti-infectious agents. The observed flavonoids and phenolic compounds in leaf extracts of *H. longifolium* and *H. pedunculatum* are of importance since the current interest in the medicinal uses of these two species is focusing on their antimicrobial, anti-inflammatory, and antioxidant effects, particularly in the management and treatment of circumcision wounds, colds, coughs, skin infections, respiratory, and stomach problems (Table 1).

#### BIOLOGICAL ACTIVITIES OF *H. LONGIFOLIUM* AND *H. PEDUNCULATUM*

There is vast scientific literature on the biological activities of *H. longifolium* and *H. pedunculatum* based on *in vitro* studies. Current research has focused on antibacterial [44,47,48,56,57,67-70,78,81-85], antifungal [60], anti-inflammatory [61], antioxidant [49,81], antiplasmodial [86], antiprotozoal [86], and cytotoxicity [86] activities of the species.

##### Antibacterial activities

Dilika *et al.* [56] evaluated antibacterial activities of the methanol leaf extracts of *H. pedunculatum* against *Streptococcus pyogenes*, *Streptococcus viridans*, and *Escherichia coli* using the agar diffusion method. The extracts exhibited activities against all tested pathogens [56]. Meyer and Dilika [83] evaluated antibacterial activities of aqueous, dichloromethane, and methanol leaf extracts of

Table 1: Medicinal uses of *Helichrysum longifolium* and *Helichrysum pedunculatum*

Disease	Parts used	References
<i>Helichrysum longifolium</i>		
Wounds	Leaves	[45,47-49,60,61,65]
<i>Helichrysum pedunculatum</i>		
Colds	Roots	[36,60,61,63,76-78]
Coughs	Roots	[36,60,61,63,76-78]
Respiratory problems	Roots	[65]
Postpartum problems	Leaves	[64]
Skin infections	Leaves	[74]
Stomach ailments	Leaves	[49,61,64,65]
Wounds	Leaves	[45,55-75]

Table 2: Phytochemical composition of *Helichrysum longifolium* and *Helichrysum pedunculatum* leaf extracts

Phytochemical composition	<i>Helichrysum longifolium</i>	<i>Helichrysum pedunculatum</i>	References
Alkaloids	+	-	[49]
Flavonoids	+	+	[49,81]
Linoleic acid (%)	-	<0.01	[82]
Oleic acid (%)	-	<0.01	[82]
Saponins	+	+	[49,81]
Steroids	+	+	[49,81]
Tannins	+	+	[49,81]
Total flavonoids (mg/g dry extract as Gallic acid)	0.7	0.6	[49,81]
Total phenol (mg/g dry extract as Gallic acid)	0.5	0.5	[49,81]
Total proanthocyanidin (mg/g dry extract as Gallic acid)	0.005	0.004	[49,81]

+ : Present, - : Absent

*H. pedunculatum* against *Bacillus cereus*, *Bacillus pumilus*, *Bacillus subtilis*, *Micrococcus kristinae*, *Staphylococcus aureus*, *Enterobacter cloacae*, *E. coli*, *Klebsiella pneumoniae*, and *Serratia marcescens* using

agar diffusion method. The dichloromethane extract was active against all tested pathogens with the exception of *E. coli* and *K. pneumoniae* with minimum inhibitory concentration (MIC) values ranging from 10.0 mg/ml to 50.0 mg/ml. The aqueous extract was only active against *B. cereus*, *M. kristinae*, and *S. aureus* with MIC value of 100.0 mg/ml [83]. Dilika *et al.* [45] evaluated the antibacterial activities of acetone leaf extracts of *H. pedunculatum* against *S. aureus* by direct bioautography on thin-layer chromatography (TLC). The extract inhibited the growth of *S. aureus* [45]. Dilika and Meyer [57] evaluated the antibacterial activities of homogenized dichloromethane extract of the callus of *H. pedunculatum* against *B. cereus*, *B. pumilus*, *B. subtilis*, *M. kristinae*, *S. aureus*, *E. cloacae*, *E. coli*, *K. pneumoniae*, *Pseudomonas aeruginosa*, and *S. marcescens* by direct bioautography on TLC. The extract inhibited the growth of *B. cereus*, *B. pumilus*, *B. subtilis*, *S. aureus*, and *S. marcescens* [57]. Eloff [84] evaluated the antibacterial activities of herbarium specimens of *H. pedunculatum* collected between 1893 and 1997. The MIC values were determined using two-fold serial dilution method against *S. aureus* with gentamycin as a positive control. The MIC values of acetone leaf extracts of the specimens ranged from 0.5 mg/ml to 8 mg/ml while gentamycin, the positive control exhibiting MIC value of 0.1 µg/ml [84]. Dilika *et al.* [82] evaluated the antibacterial activities of linoleic and oleic acids isolated from the leaves of *H. pedunculatum* against *B. cereus*, *B. pumilus*, *B. subtilis*, *M. kristinae*, *S. aureus*, *E. cloacae*, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and *S. marcescens* using agar diffusion method. Linoleic acid was active against *B. cereus*, *B. pumilus*, *B. subtilis*, *M. kristinae*, and *S. aureus* with MIC values ranging from 0.01 mg/ml to 1.0 mg/ml. Oleic acid was active against *B. subtilis*, *M. kristinae*, and *S. aureus* with MIC value of 1.0 mg/ml [82]. Dilika *et al.* [82] also evaluated the antibacterial activities of isolated linoleic and oleic acids in combination against *M. kristinae* and *S. aureus* aimed at assessing the possibility of synergistic effects. When administered in combination, linoleic and oleic acids exhibited MIC value of 0.05 mg/ml, indicating strong synergistic effects [82]. Aiyegoro *et al.* [67] evaluated antibacterial activities of acetone and aqueous leaf extracts of *H. pedunculatum* against *B. cereus*, *Proteus vulgaris*, *M. kristinae*, *Enterococcus faecalis*, *Staphylococcus epidermidis*, and *S. aureus* using agar dilution method. The acetone extract exhibited activities against *B. cereus* and *M. kristinae* with MIC values of 5.0 mg/ml and 0.5 mg/ml, respectively. The aqueous extracts exhibited activities against *S. epidermidis*, *E. faecalis*, *P. vulgaris*, and *S. aureus* with MIC values of 20.0 mg/ml, 25.0 mg/ml, 30.0 mg/ml, and 35.0 mg/ml, respectively [67]. Aiyegoro *et al.* [67] evaluated the rate of kill of *H. pedunculatum* by determining the bacterial cell-death time against *B. cereus*, *P. vulgaris*, *M. kristinae*, *E. faecalis*, *S. epidermidis*, and *S. aureus*. The effect of acetone and aqueous extracts on tested pathogens was time and concentration dependent [67]. Aiyegoro *et al.* [68] evaluated antibacterial activities of methanol leaf extracts of *H. pedunculatum* against *Acinetobacter calcoaceticus*, *Serratia marsecens*, *P. vulgaris*, *K. pneumoniae*, *P. aeruginosa*, *B. pumilus*, *S. aureus*, *P. aeruginosa*, *E. coli*, *S. aureus*, *Micrococcus luteus*, *M. kristinae*, *E. coli*, *E. faecalis*, *Salmonella* spp., *Shigella flexneri*, *B. subtilis*, and *K. pneumonia* using agar dilution method. The extract exhibited activities against *P. aeruginosa*, *S. aureus*, *B. pumilus*, *P. vulgaris*, *K. pneumoniae*, *B. subtilis*, *M. kristinae*, and *M. luteus* with MIC values ranging from 0.1 mg/ml to 5.0 mg/ml [68]. Aiyegoro *et al.* [68] evaluated the rate of kill of *H. pedunculatum* by determining the bacterial cell-death time against *P. aeruginosa*, *S. aureus*, *B. pumilus*, *P. vulgaris*, *K. pneumoniae*, *B. subtilis*, *M. luteus*, and *M. kristinae*. The effect of the extract on the tested pathogens was found to be time and concentration-dependent [68]. Ncube [78] evaluated antibacterial activities of the methanol leaf extracts of *H. pedunculatum* against *E. coli*, *S. aureus*, *Streptococcus faecalis*, *B. cereus*, *E. cloacae*, *Klebsiella pneumoniae*, *P. vulgaris*, *Acinetobacter calcoaceticus*, *S. epidermidis*, and *Staphylococcus sciuri* using the agar dilution method. The extract exhibited activities against *S. aureus*, *B. cereus*, *P. vulgaris*, *A. calcoaceticus*, and *S. epidermidis* with MIC values ranging from 1 mg/ml to 5 mg/ml [78]. Ncube [78] evaluated the rate of kill of *H. pedunculatum* extracts only or in combination with antibiotics chloramphenicol and penicillin by determining the bacterial cell-death time against *B. cereus*, *P. vulgaris*, and *S. aureus*. The effect of the extract

on tested pathogens was time and concentration-dependent, and synergistic interactions were observed at higher extract concentrations [78]. Aiyegoro *et al.* [69] evaluated the antibacterial activities of methanol leaf extracts of *H. pedunculatum* against *S. faecalis*, *S. aureus*, *B. pumilus*, *K. pneumoniae*, *P. vulgaris*, *M. kristinae*, *M. luteus*, *P. vulgaris*, *B. subtilis*, and *S. epidermidis* using the agar-well diffusion method with tetracycline (0.1 mg/ml) and ampicillin (10 µg/ml) as positive controls. The extract was active against all tested pathogens with a zone of inhibition ranging from 18 mm to 27 mm, which was comparable to 10 mm to 30 mm exhibited by the positive controls. The MIC values exhibited by the extracts against all the tested pathogens ranged from 0.1 mg/ml to 5.0 mg/ml which was higher than 0.001 mg/ml to 0.4 mg/ml exhibited by the positive controls [69]. Aiyegoro *et al.* [69] evaluated the effect of combining methanolic leaf extract of *H. pedunculatum* and first-line antibiotics which included penicillin G sodium, amoxicillin, chloramphenicol, oxytetracycline, ampicillin sodium salt, tetracycline hydrochloride, erythromycin, and ciprofloxacin using time-kill assays against *S. faecalis*, *S. aureus*, *B. pumilus*, *K. pneumoniae*, *P. vulgaris*, *M. kristinae*, *M. luteus*, *P. vulgaris*, *K. pneumonia*, *B. subtilis*, and *S. epidermidis*. The time-kill assay revealed synergy against tested pathogens [69]. Aiyegoro *et al.* [70] evaluated the effect of combining acetone, methanol and waterleaf extracts of *H. pedunculatum* and first-line antibiotics which included penicillin G sodium, amoxicillin, chloramphenicol, oxytetracycline, ampicillin sodium salt, tetracycline hydrochloride, erythromycin, and ciprofloxacin against *S. faecalis*, *S. aureus*, *B. pumilus*, *K. pneumoniae*, *P. vulgaris*, *M. kristinae*, *M. luteus*, *P. vulgaris*, *K. pneumonia*, *B. subtilis*, and *S. epidermidis* by means of fractional inhibitory concentration (FIC) indices as well as by the use of time-kill assays. The FIC indices and time-kill assay revealed synergy against tested pathogens [70]. Aiyegoro *et al.* [85] evaluated the antibacterial activities of acetone and waterleaf extracts of *H. pedunculatum* against *B. cereus*, *P. vulgaris*, *M. kristinae*, *S. aureus*, *P. aeruginosa*, and *Salmonella* spp. using agar dilution method with penicillin G sodium salt, amoxicillin, chloramphenicol, oxytetracycline, tetracycline hydrochloride, erythromycin, ampicillin sodium salt, and ciprofloxacin as positive controls. The extracts exhibited MIC values ranging from 500 mg/L to 35,000 mg/L, which were higher than MIC value of 1 mg/L to 412 mg/L exhibited by the antibiotics. Aiyegoro *et al.* [85] also evaluated the effect of combining acetone and waterleaf extracts of *H. pedunculatum* and first-line antibiotics which included penicillin G sodium salt, amoxicillin, chloramphenicol, oxytetracycline, tetracycline hydrochloride, erythromycin, ampicillin sodium salt, and ciprofloxacin against *B. cereus*, *P. vulgaris*, *M. kristinae*, *S. aureus*, *P. aeruginosa*, and *Salmonella* spp. by means of checkerboard and time-kill methods. In the checkerboard method, the synergy of 45.8% was observed while time-kill assay resulted in the synergy of 45.8% [85].

Dilika *et al.* [56] evaluated antibacterial activities of methanol leaf extracts of *H. longifolium* against *S. pyogenes*, *S. viridans*, and *E. coli* using the agar diffusion method. The extracts exhibited activities against all tested pathogens [56]. Dilika *et al.* [45] evaluated the antibacterial activities of acetone leaf extracts of *H. longifolium* against *S. aureus* by direct bioautography on TLC. The extract inhibited the growth of *S. aureus* and activities decreased with an increase in temperature [45]. Aiyegoro *et al.* [47] evaluated the antibacterial activities of aqueous, acetone, chloroform, ethyl acetate, and methanol leaf extracts of *H. longifolium* against *P. aeruginosa*, *S. aureus*, *S. faecalis*, *B. cereus*, *B. pumilus*, *P. vulgaris*, *S. marsecens*, *A. calcoaceticus*, *A. calcoaceticus anitratus*, *K. pneumoniae*, *S. flexneri*, *Salmonella* spp., *E. coli*, *M. luteus*, and *M. kristinae* using the agar-well diffusion method. All the extracts with the exception of aqueous extract were active against all tested pathogens with MIC and minimum bactericidal concentration values ranging from 0.1 mg/ml to >5.0 mg/ml [47]. Aiyegoro *et al.* [47] also evaluated the rate of kill of acetone, chloroform, ethyl acetate, and methanol leaf extracts of *H. longifolium* by determining the bacterial cell-death time against *P. aeruginosa*, *S. aureus*, *S. faecalis*, *B. cereus*, *B. pumilus*, *P. vulgaris*, *S. marsecens*, *A. calcoaceticus*, *A. calcoaceticus anitratus*, *K. pneumoniae*, *S. flexneri*, *Salmonella* spp., *E. coli*, *M. luteus*, and

*M. kristinae*. The effect of the extracts on tested pathogens was time- and concentration-dependent, eliminating most of the test organisms within 12 h of exposure time [47]. Aiyegoro *et al.* [48] evaluated the effect of combining acetone, chloroform, ethyl acetate, and methanol leaf extracts of *H. longifolium* against first-line antibiotics which included penicillin G sodium, amoxicillin, chloramphenicol, oxytetracycline, erythromycin, and ciprofloxacin using the time-kill and the Chequerboard methods against *P. aeruginosa*, *S. aureus*, *B. cereus*, *B. pumilus*, *P. vulgaris*, *A. calcaoceticus* anitratus, *S. flexneri*, *Salmonella* spp., and *M. kristinae*. In the time-kill assay, a synergistic response constituted about 65.0%, while indifference and antagonism constituted about 28.3% and 6.7%, respectively. In the Chequerboard method, the synergistic response was 61.7%, indifference and antagonistic interactions were 26.7% and 11.76%, respectively [48].

#### Antifungal activities

Mathekga [60] evaluated the antifungal activities of acetone extracts of aerial parts of *H. longifolium* against *Aspergillus niger*, *Aspergillus flavus*, *Cladosporium sphaerospermum*, *Cladosporium cladosporioides*, *Microsporium canis*, and *Cladosporium cucumerinum* using agar dilution method. The extract showed activities against all tested pathogens with the MIC values ranging from 0.1 mg/ml to 1.0 mg/ml [60].

#### Anti-inflammatory activities

Bilika [61] evaluated the anti-inflammatory activities of aqueous leaf extracts of *H. pedunculatum* using adenosine and opiate receptor binding assays. The extract was found to be active on both adenosine and opiate receptors with >70.0% inhibition [61].

#### Antioxidant activities

Aiyegoro and Okoh [81] evaluated the antioxidant activities of aqueous leaf extracts of *H. pedunculatum* using 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging, 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid (ABTS) scavenging, scavenging activity of nitric oxide (NO), scavenging activity of superoxide anion and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) scavenging activity assays. The superoxide anion, NO, DPPH, H<sub>2</sub>O<sub>2</sub>, and ABTS radical scavenging activities of the extract at 0.8 mg/mL (the highest concentration of the extract tested) were 79.0%, 68.0%, 69.3%, 77.1%, and 77.8%, respectively [81]. Similarly, Aiyegoro and Okoh [49] evaluated the antioxidant activities of aqueous leaf extracts of *H. longifolium* using DPPH free radical scavenging, ABTS scavenging, scavenging activity of NO, scavenging activity of superoxide anion and scavenging activities of H<sub>2</sub>O<sub>2</sub>. The superoxide anion, NO, DPPH, H<sub>2</sub>O<sub>2</sub>, and ABTS radical scavenging activities of the extract at 0.8 mg/mL were 75.0%, 65.0%, 76.0%, 72.4%, and 75.1%, respectively [49].

#### Antiplasmodial activities

Mokoka *et al.* [86] evaluated antiplasmodial activities of dichloromethane:methanol (1:1) whole plant extracts of *H. pedunculatum* using the (G<sup>-3</sup>H) hypoxanthine incorporation assay using *Plasmodium falciparum* as the test organism with chloroquine (IC<sub>50</sub>=0.05 µM) as the positive control. The extract exhibited weak antiplasmodial activities with half maximal inhibitory concentration (IC<sub>50</sub>) value of 6.5 µg/mL which was higher than 0.003 µg/mL exhibited by the positive control [86].

#### Antiprotozoal activities

Mokoka *et al.* [86] evaluated antiprotozoal activities of dichloromethane:methanol (1:1) whole plant extracts of *H. pedunculatum* using the resazurin assay against axenically grown *Leishmania donovani* with miltefosine (IC<sub>50</sub>=0.24 µg/mL) as the positive control. The extract exhibited weak antiprotozoal activities with IC<sub>50</sub> value of 13.5 µg/mL which was higher than 0.18 µg/mL exhibited by the positive control [86].

#### Cytotoxicity activities

Mokoka *et al.* [86] evaluated cytotoxicity activities of dichloromethane:methanol (1:1) whole plant extracts of *H. pedunculatum* against rat myoblast (L6-cells) using the Alamar Blue

assay with podophyllotoxin (IC<sub>50</sub>=0.05 µM) as the positive control. The extract exhibited very weak cytotoxicity activities with IC<sub>50</sub> value of 57.9 µg/mL with selectivity index value of 9.0. The observed IC<sub>50</sub> value was higher than 0.008 µg/mL exhibited by the positive control [86].

#### CONCLUSION

The present review summarizes the botanical, medicinal, and chemical and biological activities of *H. longifolium* and *H. pedunculatum*. Based on the presented information, these two species are closely related and deemed as highly potent traditional medicines for treating wounds acquired during male circumcision rites in South Africa. *H. longifolium* and *H. pedunculatum* have an overlapping distributional range in the Eastern Cape Province in South Africa and morphologically, the two species are quite similar, therefore, often confused when growing together. There are similarities and overlaps in terms of phytochemistry and biological activities of the two species. Therefore, these preliminary findings call for advanced phytochemical and pharmacological studies aimed at evaluating the variation of these aspects in the two species. Future studies should establish whether there are phytochemical compounds and pharmacological properties that could be used to distinguish these two species, and also supplement the currently known ethnomedicinal uses and taxonomical characters used to distinguish *H. longifolium* and *H. pedunculatum*. There is a lack of *in vivo* and clinical research on *H. longifolium* and *H. pedunculatum* extracts and compounds isolated from the species. Further research is required to establish the safety profiles of different *H. longifolium* and *H. pedunculatum* preparations.

#### ACKNOWLEDGMENTS

The author would like to express his gratitude to the National Research Foundation, South Africa and Govan Mbeki Research and Development Centre, University of Fort Hare for financial support to conduct this study.

#### AUTHORS' CONTRIBUTIONS

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

#### CONFLICTS OF INTEREST

No conflicts of interest are associated with this work.

#### REFERENCES

- Liao F. Discovery of artemisinin (qinghaosu). *Molecules* 2009;14:5362-6.
- Miller LH, Su X. Artemisinin: Discovery from the Chinese herbal garden. *Cell* 2011;146:855-8.
- Udaykumar P. Discovery of artemisinin: The Chinese wonder drug. *Muller J Med Sci Res* 2014;5:191-2.
- Weathers PJ, Towler M, Hassanali A, Lutgen P, Engeu PO. Dried-leaf *Artemisia annua*: A practical malaria therapeutic for developing countries? *World J Pharmacol* 2014;3:39-55.
- Chang Z. The discovery of qinghaosu (artemisinin) as an effective anti-malaria drug: A unique China story. *Sci China Life Sci* 2016;59:81-8.
- Elfawal MA, Towler MJ, Reich NG, Weathers PJ, Rich SM. Dried whole-plant *Artemisia annua* slows evolution of malaria drug resistance and overcomes resistance to artemisinin. *Proc Natl Acad Sci U S A* 2015;112:821-6.
- Pulice G, Pelaz S, Matías-Hernández L. Molecular farming in *Artemisia annua*, a promising approach to improve anti-malarial drug production. *Front Plant Sci* 2016;7:329.
- Liu CX. Discovery and development of artemisinin and related compounds. *Chin Herb Med* 2017;9:101-14.
- Abdolkarim C, Atri M, Yousefi S, Jalali F. Polyploidy variation in some species of the genus *Artemisia* L. (*Asteraceae*) in Iran. *Caryologia* 2010;63:168-75.
- Gao T, Yao H, Song J, Zhu Y, Liu C, Chen S, *et al.* Evaluating the feasibility of using candidate DNA barcodes in discriminating species of the large *Asteraceae* family. *BMC Evol Biol* 2010;10:324.

11. Chehregani-Rad A, Mohsenzadeh F, Moazen F. Variation of chromosome numbers in *Tanacetum parthenium* Schultz Bip. (*Asteraceae*) in Iran. *Chromosome Bot* 2012;7:97-100.
12. Garcia S, Hidalgo O, Jakovljević I, Siljak-Yakovlev S, Vigo J, Garnatje T, *et al.* New data on genome size in 128 *Asteraceae* species and subspecies, with first assessments for 40 genera, 3 tribes and 2 subfamilies. *Plant Biosyst* 2013;147:1219-27.
13. Jana BK, Mukherjee SK. Exomorphic and histological characters of fruits in some taxa of the tribe Lactuceae-(*Asteraceae*). *J Econ Taxon Bot* 2013;37:372-8.
14. Barreda VD, Palazzesi L, Tellería MC, Olivero EB, Raine JI, Forest F. Early evolution of the angiosperm clade *Asteraceae* in the cretaceous of Antarctica. *Proc Natl Acad Sci U S A* 2015;112:10989-94.
15. Van Puyvelde L, De Kimpe N, Costa J, Munyjabo V, Nyirankuliza S, Hakizamungu E, *et al.* Isolation of flavonoids and a chalcone from *Helichrysum odoratissimum* and synthesis of helichrysetin. *J Nat Prod* 1989;52:629-33.
16. Heinrich M, Robles M, West JE, Ortiz de Montellano BR, Rodriguez E. Ethnopharmacology of Mexican *Asteraceae* (Compositae). *Annu Rev Pharmacol Toxicol* 1998;38:539-65.
17. Lourens AC, Viljoen AM, van Heerden FR. South African *Helichrysum* species: A review of the traditional uses, biological activity and phytochemistry. *J Ethnopharmacol* 2008;119:630-52.
18. Gouveia SC, Castilho PC. Validation of a HPLC-DAD-ESI/MS<sup>n</sup> method for caffeoylquinic acids separation, quantification and identification in medicinal *Helichrysum* species from Macaronesia. *Food Res Int* 2012;45:362-8.
19. Koc S, Isgor BS, Isgor YG, Moghaddam NS, Yildirim O. The potential medicinal value of plants from *Asteraceae* family with antioxidant defense enzymes as biological targets. *Pharm Biol* 2015;53:746-51.
20. Meyer JJ, Afolayan AJ, Taylor MB, Engelbrecht L. Inhibition of herpes simplex virus Type 1 by aqueous extracts from shoots of *Helichrysum aureonitens* (*Asteraceae*). *J Ethnopharmacol* 1996;52:41-3.
21. Meyer JJ, Afolayan AJ, Taylor MB, Erasmus D. Antiviral activity of galangin isolated from the aerial parts of *Helichrysum aureonitens*. *J Ethnopharmacol* 1997;56:165-9.
22. Afolayan AJ, Meyer JJ. The antimicrobial activity of 3,5,7-trihydroxyflavone isolated from the shoots of *Helichrysum aureonitens*. *J Ethnopharmacol* 1997;57:177-81.
23. Drewes SE, Mudau KE, van Vuuren SF, Viljoen AM. Antimicrobial monomeric and dimeric diterpenes from the leaves of *Helichrysum tenax* var *tenax*. *Phytochemistry* 2006;67:716-22.
24. van Vuuren SF, Viljoen AM, van Zyl RL, van Heerden FR, Hüsnü K, Başer C. The antimicrobial and toxicity profiles of helihumulone, leaf essential oil and extracts of *Helichrysum cymosum* (L.) D. Don subsp. *cymosum*. *S Afr J Bot* 2006;72:287-90.
25. Drewes SE, van Vuuren SF. Antimicrobial acylphloroglucinols and dibenzylxy flavonoids from flowers of *Helichrysum gymnocomum*. *Phytochemistry* 2008;69:1745-9.
26. Kenny O, Smyth TJ, Walsh D, Kelleher CT, Hewage CM, Brunton NP, *et al.* Investigating the potential of under-utilised plants from the *Asteraceae* family as a source of natural antimicrobial and antioxidant extracts. *Food Chem* 2014;161:79-86.
27. Antunes Viegas D, Palmeira-de-Oliveira A, Salgueiro L, Martinez-de-Oliveira J, Palmeira-de-Oliveira R. *Helichrysum italicum*: From traditional use to scientific data. *J Ethnopharmacol* 2014;151:54-65.
28. Bessada SM, Barreira JC, Oliveira MB. *Asteraceae* species with most prominent bioactivity and their potential applications: A review. *Ind Crops Prod* 2015;76:604-15.
29. Les F, Venditti A, Cásedas G, Frezza C, Guiso M, Sciubba F, *et al.* Everlasting flower (*Helichrysum stoechas* Moench) as a potential source of bioactive molecules with antiproliferative, antioxidant, antidiabetic and neuroprotective properties. *Ind Crops Prod* 2017;108:295-302.
30. Kanase V, Shaikh S. A pharmacognostic and pharmacological review on *Chromolaena odorata* (Siam weed). *Asian J Pharm Clin Res* 2018;11:34-8.
31. Amuthan A, Devi V, Shreedhara CS, Rao V, Puri K, Jasphin S. *Vernonia cinerea* (neichittikeerai) regenerates proximal tubules in cisplatin induced renal damage in mice. *Asian J Pharm Clin Res* 2019;12:332-5.
32. Ashraf K. An updated phytochemical and pharmacological review on *Gynura procumbens*. *Asian J Pharm Clin Res* 2019;12:9-14.
33. Maharana L, Sethi MK, Dash RN, Pattnaik S. Evaluation of antidiabetic and antihyperlipidemic effect of *Vernonia divergens* in streptozotocin-induced diabetic rats. *Asian J Pharm Clin Res* 2019;12:104-10.
34. Malik AY, Singh DP. Ethnobotanical and ethnoveterinary importance of plants of scrub areas of Dachigam national park, Jammu and Kashmir, India. *Asian J Pharm Clin Res* 2019;12:582-6.
35. Radha A, Puri S, Kumar S. An ethnobotanical study of wild medicinal plants used by migratory shepherds: A tribal community of Western Himalayas. *Asian J Pharm Clin Res* 2019;12:137-44.
36. Hutchings A, Scott AH, Lewis G, Cunningham AB. *Zulu Medicinal Plants: An Inventory*. Pietermaritzburg: University of Natal Press; 1996.
37. Swanepoel DP. *The Medicinal Value of the Southern African Asteraceae*. MSc Dissertation. Pretoria: University of Pretoria; 1997.
38. Neuwinger HD. *African Ethnobotany: Poisons and Drugs*. Weinheim: Chapman and Hall; 1996.
39. Williams VL, Balkwill K, Witkowski ET. Unraveling the commercial market for medicinal plants and plant parts on the Witwatersrand, South Africa. *Econ Bot* 2000;54:310-27.
40. Williams VL, Balkwill K, Witkowski ET. A lexicon of plants traded in the Witwatersrand umuthi shops. *Bothalia* 2001;31:71-98.
41. Arnold TH, Prentice CA, Hawker LC, Snyman EE, Tomalin M, Crouch NR, *et al.* *Medicinal and Magical Plants of Southern Africa: An Annotated Checklist*. Pretoria: National Botanical Institute; 2002.
42. Eroğlu HE, Aksoy A, Hamzaoğlu E, Budak U, Albayrak S. Cytogenetic effects of nine *Helichrysum* taxa in human lymphocytes culture. *Cytotechnology* 2009;59:65-72.
43. Drewes SE. Natural products research in South Africa: 1890-2010. *S Afr J Sci* 2012;108:1-8.
44. Van Wyk BE, Oudtshoorn BV, Gericke N. *Medicinal Plants of South Africa*. Pretoria: Briza Publications; 2013.
45. Dilika F, Afolayan AJ, Meyer JJ. Comparative antibacterial activity of two *Helichrysum* species used in male circumcision in South Africa. *S Afr J Bot* 1997;63:158-9.
46. Germishuizen G, Meyer NL. *Plants of Southern Africa: An Annotated Checklist*. Strelitzia 14. Pretoria: National Botanical Institute; 2003.
47. Aiyegoro OA, Afolayan AJ, Okoh AI. *In vitro* antibacterial time kill studies of leaves extracts of *Helichrysum longifolium*. *J Med Plant Res* 2009;3:462-7.
48. Aiyegoro OA, Afolayan AJ, Okoh AI. *In vitro* antibacterial activities of crude extracts of the leaves of *Helichrysum longifolium* in combination with selected antibiotics. *Afr J Pharm Pharmacol* 2009;3:293-300.
49. Aiyegoro OA, Okoh AI. Preliminary phytochemical screening and *in vitro* antioxidant activities of the aqueous extract of *Helichrysum longifolium* DC. *BMC Complement Alternat Med* 2010;10:21.
50. Hilliard OM. *Compositae in Natal*. Pietermaritzburg: University of Natal Press; 1977.
51. Hilliard OM. *Asteraceae*. In: Leistner OA, editor. *Flora of Southern Africa. Part 7. (Inuleae)*. Vol. 33. Pretoria: Botanical Research Institute; 1983. p. 1-325.
52. Manning JC, Goldblatt P. *Plants of the Greater Cape Floristic Region 1: The Core Cape Flora*. Cape Town: Strelitzia 29, South African National Biodiversity Institute; 2012.
53. Bandeira S, Bolnick D, Barbosa F. *Wild Flowers of Southern Mozambique*. Maputo: Universidade Eduardo Mondlane; 2007.
54. Hyde MA, Wursten BT, Ballings P, Palgrave MC. *Flora of Mozambique: Species Information: Helichrysum longifolium* DC; 2019. Available from: [https://www.mozambiqueflora.com/speciesdata/species.php?species\\_id=168540](https://www.mozambiqueflora.com/speciesdata/species.php?species_id=168540). [Last accessed on 2019 March 16].
55. Bhat RB, Jacobs TV. Traditional herbal medicine in Transkei. *J Ethnopharmacol* 1995;48:7-12.
56. Dilika NF, Nikolova RV, Jacobs TV. Plants used in the circumcision rites of the Xhosa tribe in South Africa. *Acta Hort* 1995;426:165-70.
57. Dilika F, Meyer JJ. Antibacterial activity of *Helichrysum pedunculatum* callus cultures. *S Afr J Bot* 1998;64:312-3.
58. Grierson DS, Afolayan AJ. An ethnobotanical study of plants used for the treatment of wounds in the Eastern Cape, South Africa. *J Ethnopharmacol* 1999;67:327-32.
59. Van Vuuren CJ, De Jongh M. Rituals of manhood in South Africa: Circumcision at the cutting edge of critical intervention. *S Afr J Ethnol* 1999;22:142-56.
60. Matheka AD. Antimicrobial Activity of *Helichrysum* species and the Isolation of a New Phloroglucinol from *Helichrysum caespititium*. PhD Dissertation. Pretoria: University of Pretoria; 2001.
61. Dilika NF. *The Medicinal Value of Amarylidiaceae and Asteraceae species used in Male Circumcision*. PhD Thesis. Pretoria: University of Pretoria; 2002.
62. Swartz VG. *Phytochemical Studies of Helichrysum patulum*. MSc Dissertation. Cape Town: University of the Western Cape; 2006.
63. Reddy D. *The Phytochemistry and Antimicrobial Activity of Selected Indigenous Helichrysum species*. MSc Dissertation. Johannesburg: University of the Witwatersrand; 2007.

64. Bolofo RN, Johnson CT. The identification of 'isicakathi' and its medicinal use in Transkei. *Bothalia* 1988;18:125-30.
65. Lourens AC. Structural and Synthetic Studies of Sesquiterpenoids and Flavonoids isolated from *Helichrysum* species. PhD Thesis. Pietermaritzburg: KwaZulu-Natal University; 2008.
66. Nqeketo A. Xhosa Male Circumcision at the Crossroads: Responses by Government, Traditional Authorities and Communities to Circumcision Related Injuries and Deaths in Eastern Cape Province. MSc Dissertation. Cape Town: University of the Western Cape; 2008.
67. Aiyegoro OA, Afolayan AJ, Okoh AI. Studies on the *in vitro* time-kill assessment of crude aqueous and acetone extracts of *Helichrysum pedunculatum* leaves. *Afr J Biotechnol* 2008;7:3721-5.
68. Aiyegoro OA, Afolayan AJ, Okoh AI. *In vitro* time-kill assessment of crude methanol extract of *Helichrysum pedunculatum* leaves. *Afr J Biotechnol* 2008;7:1684-8.
69. Aiyegoro OA, Afolayan AJ, Okoh AI. Synergistic interaction of *Helichrysum pedunculatum* leaf extracts with antibiotics against wound infection associated bacteria. *Biol Res* 2009;42:327-38.
70. Aiyegoro OA, Afolayan AJ, Okoh AI. *In vitro* evaluation of the interactions between crude leaf extracts of *Helichrysum pedunculatum* and some antibiotics. *Afr J Tradit Complement Alternat Med* 2009;6:408.
71. Fearon JJ. Population Assessments of Priority Plant Species used by Local Communities in and around Three Wild Coast Reserves, Eastern Cape, South Africa. MSc Dissertation. Grahamstown: Rhodes University; 2010.
72. Venter MA. Some views of Xhosa women regarding the initiation of their sons. *Koers* 2011;76:559-75.
73. Bhat RB. Medicinal plants and traditional practices of Xhosa people in the Transkei region of Eastern Cape, South Africa. *Indian J Tradit Knowl* 2014;13:292-8.
74. Sewani-Rusike CR, Mammen M. Medicinal plants used as home remedies: A family survey by first year medical students. *Afr J Tradit Complement Altern Med* 2014;11:67-72.
75. Suntar I. The medicinal value of *Asteraceae* family plants in terms of wound healing activity. *FABAD J Pharm Sci* 2014;39:21-31.
76. Watt JM, Breyer-Brandwijk MG. *The Medicinal and Poisonous Plants of Southern and Eastern Africa*. Edinburgh: E and S Livingstone; 1962.
77. Hutchings A. *Zulu Medicinal Plants*. Pietermaritzburg: University of Natal Press; 1996.
78. Ncube NS. Anti-bacterial Properties of the Methanol Extract of *Helichrysum pedunculatum*. MSc Dissertation. Alice: University of Fort Hare; 2008.
79. Kumar S, Pandey AK. Chemistry and biological activities of flavonoids: An overview. *ScientificWorldJournal* 2013;2013:162750.
80. Marín M, Máñez S. Recent trends in the pharmacological activity of isoprenyl phenolics. *Curr Med Chem* 2013;20:272-9.
81. Aiyegoro OA, Okoh AI. Phytochemical screening and polyphenolic antioxidant activity of aqueous crude leaf extract of *Helichrysum pedunculatum*. *Int J Mol Sci* 2009;10:4990-5001.
82. Dilika F, Bremner PD, Meyer JJ. Antibacterial activity of linoleic and oleic acids isolated from *Helichrysum pedunculatum*: A plant used during circumcision rites. *Fitoterapia* 2000;71:450-2.
83. Meyer JJ, Dilika F. Antibacterial activity of *Helichrysum pedunculatum* used in circumcision rites. *J Ethnopharmacol* 1996;53:51-4.
84. Eloff JN. It is possible to use herbarium specimens to screen for antibacterial components in some plants. *J Ethnopharmacol* 1999;67:355-60.
85. Aiyegoro OA, Afolayan AJ, Okoh AI. Interactions of antibiotics and extracts of *Helichrysum pedunculatum* against bacteria implicated in wound infections. *Folia Microbiol (Praha)* 2010;55:176-80.
86. Mokoka TA, Xolani PK, Zimmermann S, Hata Y, Adams M, Kaiser M, et al. Antiprotozoal screening of 60 South African plants, and the identification of the antitrypanosomal germacranolides schkuhrin I and II. *Planta Med* 2013;79:1380-4.