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Review Article

# PHYTOCHEMICAL AND ETHNOPHARMACOLOGICAL REVIEW OF *HETEROPYXIS NATALENSIS*

**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**

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**ABSTRACT**

The bark, leaves, roots, and twigs of *Heteropyxis natalensis* are widely used as herbal medicines in Southern Africa. The aim of this study was to review the phytochemical and ethnopharmacological properties of *H. natalensis* so as to provide baseline data required for evaluating the therapeutic potential of the species. Information on the botanical profile, medicinal uses, phytochemistry, and pharmacological properties of *H. natalensis* was undertaken using databases such as ScienceDirect, SciFinder, PubMed, Google Scholar, Medline, SCOPUS, EThOS, ProQuest, OATD, and open-thesis. Pre-electronic literature of conference papers, scientific articles, books, book chapters, dissertations, and theses were carried out at the university library. Literature search revealed that *H. natalensis* is used as an aphrodisiac, anti-infection, blood purifier, decongestant, for weaning, ethnoveterinary medicine and as herbal medicine for bleeding disorders, gums, nose, colds, gum infections, impotence, menorrhagia, respiratory disorders, toothache, and wounds. Phytochemical compounds identified from the species include essential oils, 3β-hydroxylup-20(29)-en-28-al, (E)-1-(2',4'-dihyroxy,5'-methoxy,3'-methylphenyl)-3-phenylprop-2-en-1-one, (2E)-2-[(2E)-1-hydroxy-3-phenylprop-2-en-1-ylidene]-5-methoxy-6,6-dimethylcyclohex-4-ene-1,3-dione, 2',4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone, 3',4',5'-tri-O-methyl-3,4-methylenedioxy ellagic acid, 3,5,7-trihydroxyflavan, 5-hydroxy-7-methoxy-6-methylflavanone, aurentiacin A, betulinic acid, cardamomin, lupenone, lupeol, quercetin, and sitost-4-en-3-one. Pharmacological studies revealed that *H. natalensis* extracts and compounds have antibacterial, antimycobacterial, antifungal, antioxidant, anti-inflammatory, cytotoxicity, and pro-inflammatory activities. Detailed studies are required to establish the efficacy, clinical relevance, safety and mechanisms of action of the plant extracts, and compounds of *H. natalensis*.

**Keywords:** *Heteropyxis natalensis*, Heteropyxidaceae, Southern Africa, Traditional medicine.

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## INTRODUCTION

*Heteropyxis natalensis* Harv. is a tree species which belongs to the Heteropyxidaceae family. Research by Cunningham [1] and Williams *et al*. [2] revealed that the bark of *H. natalensis* is widely used as herbal medicine in South Africa and therefore, traded in medicinal informal markets in Gauteng and KwaZulu-Natal Provinces in the country. The species is also included in the monographic treatment of "medicinal plants of South Africa" [3], a publication which provides details of how important medicinal plants in the country are utilized. Traditional, complementary, and alternative medicines are popular and widely used in tropical Africa with about 80% of the people in the continent relying on them for primary health care [4-28]. Mahomoodally [29] argued that the use of herbal medicines is a fundamental component of the African traditional health-care system with traditional healers prescribing herbal medicines because they are the most easily accessible and affordable health resources available to local communities. The same author also argued that Western or allopathic modern medicine is rooted in traditional, complementary, and alternative medicine, and currently, several new pharmaceutical drugs and health-promoting products are being produced and developed from plants traditionally used as herbal medicines [30,31]. Van Wyk [30,31] argued that the essential oils, leaves, and roots of *H. natalensis* are important in the development of new pharmaceutical and health products in Southern Africa for colds, weaning, nose bleeding, bleeding gums menorrhagia, aromatherapy, and topical products. This is not surprising since 25% of pharmaceutical drugs and products and 11% of prescription drugs which are regarded by the World Health Organization as essential to human health are prepared from herbal medicines [32]. It is, therefore, within this context that this study was undertaken aimed at summarizing the phytochemical and ethnopharmacological properties of *H. natalensis*, an important medicinal plant species in Southern Africa.

## BOTANICAL PROFILE OF *H. NATALENSIS*

The family Heteropyxidaceae consists of three species, *H. natalensis, Heteropyxis canescens* Oliv., and *Heteropyxis dehniae* Suess. [33,34]. These *Heteropyxis* species have previously been assigned to families Lythraceae, Myrtaceae, and Rutaceae [35]. *H. canescens* is confined to Swaziland and KwaZulu-Natal Province in South Africa, *H. dehniae* is confined to Zimbabwe and the Limpopo Province in South Africa while *H. natalensis* is more widespread, recorded in Botswana, Mozambique, South Africa, Swaziland, and Zimbabwe [33,34,36-42]. The genus name "*Heteropyxis*" is derived from the Greek word "*heteros*" which means "other" or "distinct" and the Latin word "*pyxidatus*" which means "a capsule with a box-like lid" [35,43]. The specific name "*Natalensis*" means "from Natal," which is now KwaZulu-Natal province in South Africa, where the type specimen of the species was collected from [44].

*H. natalensis* is a small deciduous to the semi-deciduous tree of not more than 15 m in height [33,35,45]. The tree consists of a branched trunk, dense leafy branches, and highly aromatic foliage [33,35]. The crushed twigs and leaves are strongly aromatic, reminiscent of lavender, hence the English common name of the species, lavender-tree [33]. The bark is pale gray to almost white in color, flaking off on older stems in large pieces. The leaves are simple, alternate, narrowly elliptic, ovate to obovate, shiny dark green above, paler green below, and slightly hairy to hairless when mature, pleasantly aromatic when crushed [33]. The flowers are small, bisexual, occur in branched terminal clusters yellowish green in color. The fruit is a capsule, oval and brownish in color when mature [33]. *H. natalensis* has been recorded in Bushveld and along forest margins in riverine fringes and often in rocky places, from sea level to an altitude of about 1400 m above sea level [33,35,45].

## MEDICINAL USE OF *H. NATALENSIS*

The bark of *H. natalensis* is used as an aphrodisiac [46,47], the bark, leaves, and roots of the species are used as an anti-infection and

decongestant [3] while leaves are used as blood purifier [46] and for weaning [3,30,31,48] (Table 1). The bark, leaves, roots, and twigs of *H. natalensis* are used as herbal medicines for bleeding disorders, gums, nose, colds, gum infections, impotence, menorrhagia, respiratory disorders, toothache, and wounds [3,30,31,35,46-54]. The leaves of *H. natalensis* are used as ethnoveterinary medicine, mainly as drench for deworming purposes [3,46]. Leaves and twigs of *H. natalensis* are used as herbal tea or tisane [55,56], and this practice appears to be popular particularly in South Africa and Swaziland [3,33,35,46,50,51,53,57].

**PHYTOCHEMISTRY AND PHARMACOLOGICAL PROPERTIES**

More than 190 essential oils (Table 2) have been identified from the aerial parts of *H. natalensis*. The major essential oils appear to be cadinols (17.1%), 1.8-cineole (0.2–41.2%), limonene (1.8–25.4%), linalool (0.1–42.7%), myrcene (0.5–10.7%), (E)-nerolidol (0.1<–16.3%), (E)-ocimene (29.0%), (E)-β-ocimene (0.1<–12.4%), and β-pinene (0.05–25.2%) [58-63]. Previous research demonstrated seasonal and geographical variations in essential oil constituents of *H. natalensis* [58-63]. Previous studies by several researchers showed that essential oils isolated from *H. natalensis* have antibacterial and antifungal properties [60,63-65].

Adesanwo *et al*. [66] identified (E)-1-(2',4'-dihyroxy,5'-methoxy,3'-methylphenyl)-3-phenylprop-2-en-1-one while Shode *et al*. [67] identified (2E)-2-[(2E)-1-hydroxy-3-phenylprop-2-en-1-ylidene]-5-methoxy-6,6-dimethylcyclohex-4-ene-1,3-dione from leaves of *H. natalensis*. Mohammed *et a*l. [68] identified 2',4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone, 3',4',5'-tri-O-methyl-3,4-methylenedioxy ellagic acid, betulinic acid, lupenone, and lupeolfrom the twigs of *H. natalensis* while the roots yielded 3β-hydroxylup-20(29)-en-28-al and sitost-4-en-3-one. Henley-Smith *et al*. [54] identified cardamomin, aurentiacin A, 5-hydroxy-7-methoxy-6-methylflavanone, quercetin, and 3,5,7-trihydroxyflavan from the leaves and twigs of *H. natalensis*. The compounds cardamomin, aurentiacin A, quercetin, and 3,5,7-trihydroxyflavan showed antibacterial activities [54].

The extracts and phytochemical compounds of *H. natalensis* showed several pharmacological properties which include antibacterial [52,54,60,63-66,69-72], antimycobacterial [73], antifungal [52,54,60,63-65,69,72], antioxidant [74,75], anti-inflammatory [75,76], cytotoxicity [54,73,75], and pro-inflammatory [54] activities.

**Antibacterial activities**

Gundidza *et al*. [60] evaluated antibacterial activities of the essential oil isolated from *H. natalensis* against 25 bacterial species. The essential oil exhibited activities against all tested microbes showing good activities against pathogens *Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus,* and *Moraxella* species with lower sensitivities for *Pseudomonas aeruginosa* [60]. Van Vuuren and Viljoen [64] evaluated the antibacterial activities of the essential oil of *H. natalensis* against *S. aureus*, *Staphylococcus epidermidis*, *Bacillus cereus*, *Bacillus subtilis, E. coli*, *P. aeruginosa, Enterococcus faecalis,* and *K. pneumoniae* using the microtiter plate method with ciprofloxacin (0.01 mg/ml) as a positive control. The essential oil exhibited activities with while minimum inhibitory concentration (MIC) values ranging from 4.5 mg/mL to 32.0 mg/mL [64]. Van Vuuren and Viljoen [64] exposed the oil to *S. aureus,* and the cidal efficacy was plotted over time against the logarithm of viable colonies. The oil showed a rapid cidal effect against the tested pathogen [64]. Van Vuuren *et al*. [63] evaluated the antibacterial activities of the essential oil of *H. natalensis* against *B. cereus*, *E. faecalis*, *E. coli*, *K. pneumoniae*, *Moraxella catarrhalis*, *P. aeruginosa,* and *S. aureus* using the microtiter plate method with ciprofloxacin (0.01 mg/ml) as a positive control. The essential oil exhibited activities with MIC values ranging from 1.0 mg/ml to 16 mg/ml [63]. Braithwaite *et al*. [52] evaluated the antibacterial activities of methanol and acetone leaf extracts, essential oil and smoke fraction of *H. natalensis* against *S. aureus, B. cereus,* and *K. pneumoniae* using the microtiter plate technique with ciprofloxacin as a positive control. The extracts exhibited activities with MIC values ranging from 0.25 mg/ml to 32.0 mg/ml [52]. Henley-Smith *et al*. [69] evaluated the synergistic activities of *H. natalensis* mixed with *Melaleuca alternifolia* (Maiden and Betche) Cheel, *Mentha piperita* L., and the green tea extract known as TEAVIGO™ against *Streptococcus mutans* and *Prevotella intermedia*. The mixed extract successfully inhibited the growth of the pathogens [69]. Sharma and Lall [70] evaluated antimicrobial activities of leaf ethanol extracts of *H. natalensis* against pathogenic bacteria, *Propionibacterium acnes* using the broth dilution method with tetracycline as a positive control (0.2 mg/mL). The extracts showed weak activities with MIC value of 250 µg/mL in comparison to the MIC value of 3.1 µg/mL demonstrated by tetracycline, the positive control [70]. Cock and Van Vuuren [71] evaluated antibacterial activities of aqueous and methanol leaf extracts of *H. natalensis* against *Alcaligenes faecalis, Aeromonas hydrophila*, *B. cereus, B. subtilis, Citrobacter freundi, E. coli, K. pneumoniae, Proteus mirabilis, Proteus vulgaris, P. aeruginosa, Pseudomonas fluorescens, Salmonella typhimurium, Serratia marcescens, Shigella sonnei, S. aureus,* and *S. epidermidis* using a modified disk diffusion method with ampicillin (2 µg) and chloramphenicol (10 µg) as positive controls. Only methanol extract exhibited activities against *A. faecalis*, *A. hydrophilia*, *B. cereus*, *B. subtilis*, *P. mirabilis*, *P. vulgaris,* and *S. epidermidis* with a zone of inhibition ranging from 6.0 mm to 8.0 mm, and the MIC values ranged from 525 µg/ml to 6150 µg/ml [71]. Akhalwaya *et al*. [72] evaluated antibacterial activities of aqueous and dichloromethane:methanol (1:1) leaf and stem extracts of *H. natalensis* against *S. mutans, Streptococcus sanguis*, *Lactobacillus acidophilus, Lactobacillus casei, Porphyromonas gingivalis,* and *Fusobacterium nucleatum* using the microtiter plate dilution assay with ciprofloxacin (0.1 mg/mL) as a positive control. The extracts exhibited activities with MIC values ranging from 0.21 mg/mL to >8.0 mg/mL [72]. Henley-Smith *et al*. [54] evaluated antibacterial activities of ethanolic leaf and twig extracts of *H. natalensis* against pathogenic oral bacterial organisms, *Actinomyces israelii, P. intermedia, S. mutans,* and *Lactobacillus paracasei*, a commensal bacterium essential in plaque prevention using the microdilution technique with 5% chlorhexidine gluconate as a positive control. The extracts exhibited activities with MIC values ranging from 0.9 mg/ml to 12.5 mg/ml while minimum bactericidal concentration (MBC) values ranged from 3.3 mg/ml to >12.5 mg/ml [54].

Chakravorty *et al*. [65] evaluated antibacterial activities of essential oils (Z)-3-hexenyl nonanoate, (E)-3-hexenyl nonanoate, hexyl nonanoate, and (Z)-2-hexenylnonanoate isolated from *H. natalensis* against *E. coli, P. aeruginosa, Morexella cattarhalis, S. aureus, B. cereus,* and *Enterococcus facealis* using the microdilution method with ciprofloxacin (0.01 mg/mL) as a positive control. The essential oils showed activities

**Table 1: Medicinal applications of *Heteropyxis natalensis* in Southern Africa**

| Medicinal use | Parts of the plant used | References |
|---|---|---|
| Anti-infection | Bark, leaves, and roots | [3] |
| Aphrodisiac | Bark | [46,47] |
| Bleeding disorders | Bark, leaves, and roots | [46] |
| Bleeding gums | Roots | [3,30,35,46,53] |
| Blood purifier | Leaves | [46] |
| Colds | Leaves | [3,30,52] |
| Decongestant | Bark, leaves, and roots | [3] |
| Gum infections | Leaves and twigs | [51,54] |
| Impotence | Bark | [47] |
| Menorrhagia | Bark, leaves, and roots | [3,31,46,48,49,53] |
| Nose bleeding | Leaves and roots | [3,30,31,35,46,50,53] |
| Respiratory disorders | Bark, leaves, and roots | [3] |
| Toothache | Leaves and twigs | [51,54] |
| Weaning | Leaves | [3,30,31,48] |
| Wounds | Bark | [50] |
| Ethnoveterinary medicine | Leaves used as a drench (anthelmintic drug) for deworming | [3,46] |

**Table 2: Essential oils identified from aerial parts of *Heteropyxis natalensis***

| Essential oil (%) wet weight | Values | References |
|---|---|---|
| Acetophenone | 0.1<–0.1 | [63] |
| Agglomerone | 0.4 | [63] |
| Alismol | 0.1–0.7 | [63] |
| Alloaromadendrene | 0.3 | [63] |
| Amyl isovalerate | 0.1–1.2 | [63] |
| Aromadendrene | 0.1< | [63] |
| Benzaldehyde | 0.1<–0.1 | [63] |
| Benzyl butanoate | 0.1<–0.3 | [62,63] |
| *trans*-α-bergamotol | 0.1<–0.1 | [63] |
| Borneol | 0.05–0.2 | [61-63] |
| Bornyl acetate | 0.1–0.2 | [62,63] |
| Cadina-1,4-diene (= cubenene) | 0.1< | [62] |
| α-cadinene | 0.1 | [63] |
| δ-cadinene | 0.05–1.2 | [61-63] |
| γ-cadinene | 0.05–0.6 | [61-63] |
| Cadinol | 17.1 | [59] |
| α-cadinol | 0.1<–0.8 | [62,63] |
| *T*-cadinol | 0.1–1.4 | [62,63] |
| α-calacorene | 0.1<–0.1 | [62,63] |
| *cis*-calamenene | 0.1<–0.6 | [62,63] |
| Camphene | 0.1<–0.1 | [62,63] |
| Camphor | 0.05–0.1 | [61] |
| Carvacrol | 0.1< | [62] |
| Carvone hydrate (= aralone) | 0.2 | [63] |
| Caryophylla-2 (12),6-dien-5α-ol (= caryophyllenoli) | 0.1<–0.4 | [62,63] |
| Caryophylla-2 (12),6-dien-5β-ol (= caryophyllenol ii) | 0.1–0.5 | [62,63] |
| Caryophylla-2 (12),6 (13)-dien-5β-ol (= caryophylladienoli) | 0.1< | [62,63] |
| Caryophylla-2 (12),6 (13)-dien-5α-ol (= caryophylladienol ii) | 0.1–0.4 | [62,63] |
| *cis*-carveol | 0.1<–0.2 | [63] |
| *trans*-carveol | 0.1<–0.5 | [62,63] |
| Carvone | 0.1<–0.5 | [62,63] |
| β-caryophyllene | 0.05–1.9 | [62,63] |
| *p*-caryophyllene | 3.3 | [58] |
| Caryophyllene oxide | 0.05–9.9 | [59,61-63] |
| Cinnamyl acetate | 0.1<–7.6 | [59,63] |
| 1,8-cineole | 0.2–41.2 | [58-63] |
| Clovenol | 0.1<–0.1 | [62,63] |
| α-copaene | 0.1<–0.1 | [62,63] |
| β-copaene | 0.1<–0.2 | [63] |
| α-cubebene | 0.1 | [63] |
| Cubenol | 0.1<–0.5 | [62,63] |
| epi-cubenol | 4.5 | [59] |
| 1-epi-cubenol | 0.1–0.2 | [62,63] |
| 6-epi-cubenol | 0.1<–0.3 | [62,63] |
| *p*-cymen-8-ol | 0.05–0.5 | [61-63] |
| *p*-cymene | 0.1–5.8 | [61-63] |
| Decanal | 0.1 | [63] |
| 4,4-dimethyl but-2-enolide | 0.1 | [63] |
| 3,7-dimethyloct-1-en-3,6,7-triol | 0.5 | [63] |
| 2,6-dimethyl-3(E),5(E),7-octatriene-2-ol | 0.1<–0.1 | [63] |
| 3,7-dimethyl-1,7-octadien-3,6-diol | 3.4 | [63] |
| α, p-dimethylstyrene | 0.1< | [62] |
| Eicosane | 0.1< | [62] |
| β-elemene | 0.1 | [63] |
| Elemol | 0.4 | [63] |
| (E, E)-10,11-epoxyfarnesyl acetate | 0.4 | [63] |
| 1,5-epoxy-salvial (4) 14-ene | 0.1 | [62] |
| *cis*-1,2-epoxy-terpin-4-ol | 0.1<–0.2 | [63] |
| Eremoligenol | 0.1–1.7 | [62,63] |
| Eudesma-4 (15),7-dien-1-β-ol | 0.1<–0.5 | [62,63] |
| α-eudesmol | 0.4–7.5 | [62,63] |
| β-eudesmol | 0.8–3.1 | [63] |
| γ-eudesmol | 0.2–5.2 | [62,63] |
| (E, E)-α-farnesene | 0.1< | [62,63] |
| (2E,6E)-farnesol | 0.1–0.5 | [62,63] |
| (2E,6E)-farnesyl acetate | 0.1< | [62] |
| Fenchyl acetate | 0.1<–0.1 | [62,63] |
| Fenchyl alcohol | 0.1<–0.2 | [63] |
| Geraniol | 0.1<–0.3 | [62,63] |
| Geranyl acetate | 0.05–0.2 | [61-63] |

*(Contd...)*

**Table 2: (*Continued)***

| Essential oil (%) wet weight | Values | References |
|---|---|---|
| Geranyl butyrate | 0.1<–0.2 | [62,63] |
| Gleenol | 0.1< | [62,63] |
| Globulol | 0.1–0.8 | [62,63] |
| α-guaiol | 0.5 | [63] |
| Guaiyl acetate | 0.2 | [63] |
| 4,6-guaiadiene (= γ-guaiene) | 0.1< | [63] |
| Heneicosane | 0.1< | [63] |
| γ-heptalactone | 1.1 | [63] |
| *cis*-*p*-mentha-1 (7),8-dien-2-ol (= cis-2-hydroxy pseudolimonene) | 0.1 | [63] |
| Hexadecanol | 0.1< | [62] |
| 2-heptyl acetate | 0.1–0.2 | [62,63] |
| (Z)-3-hexen-1-yl benzoate | 0.1 | [63] |
| (Z)-3-hexenyl acetate | 0.1 | [62] |
| (Z)-3-hexenol | 0.1<–0.4 | [63] |
| (E)-2-hexenyl butyrate | 0.1<–0.2 | [62,63] |
| (Z)-3-hexenyl butyrate | 0.1–0.2 | [63] |
| (Z)-3-hexenyl nonanoate | 16.0 | [63] |
| Hinesol | 0.1< | [62] |
| Hotrienol | 0.3 | [63] |
| α-humulene | 0.05–0.8 | [61-63] |
| Humulene epoxide-i | 0.1<–0.1 | [62,63] |
| Humulene epoxide-ii | 0.2–1.6 | [62,63] |
| Humulene epoxide-iii | 0.1< | [62] |
| 10-hydroxy calamenene | 0.1–0.4 | [63] |
| *trans*-2-hydroxy-1,8-cineole | 0.1 | [63] |
| (E)-β-ionone | 0.1 | [63] |
| Isocaryophyllene oxide | 0.1<–0.5 | [63] |
| *cis*-jasmone | 0.1<–0.1 | [63] |
| Kaur-16-ene | 0.2 | [63] |
| Limonene | 1.8–25.4 | [58-63] |
| *cis*-1,2-limonene epoxide | 0.1<–0.3 | [63] |
| *trans*-1,2-limonene epoxide | 0.2 | [63] |
| 8,9-limonene epoxide-i | 0.1< | [63] |
| Linalool | 0.1–42.7 | [58-63] |
| *cis*-linalool oxide (furanoid) | 0.1<–8.0 | [63] |
| *cis*-linalool oxide (pyranoid) | 0.1–0.9 | [61,63] |
| *trans*-linalool oxide (pyranoid) | 0.05–0.5 | [61,63] |
| *trans*-linalool oxide (furanoid) | 0.1<–8.8 | [63] |
| Linalyl acetate | 0.05–0.5 | [61,63] |
| *trans*-*p*-menth-2-en-1-ol | 0.1<–0.1 | [62,63] |
| *p*-mentha-1,7 (8)-diene (= pseudolimonene) | 0.1<–7.1 | [63] |
| Methyl-4-(4′-methyl-3′-pentenyl)-3-cyclohexenyl ketone | 0.1 | [63] |
| 2-methylbutyl acetate | 0.1 | [63] |
| 2-methylbutyl butyrate | 0.1<–0.4 | [62,63] |
| 3-methyl butyl hexanoate (= isoamyl hexanoate) | 0.1 | [63] |
| *cis*-*p*-menth-2-en-1-ol | 0.1<–1.0 | [61,63] |
| *cis*-*p*-menth-3-en-1,2-diol | 0.1–0.5 | [63] |
| trans-p-mentha-2,8-dien-1-ol | 0.1<–0.2 | [63] |
| *cis*-*p*-mentha-2,8-dien-1-ol | 0.1 | [63] |
| *cis*-*p*-mentha-1 (7),8-dien-2-ol (= *cis*-2-hydroxy pseudolimonene) | 0.1< | [63] |
| *trans*-p-mentha-1 (7),8-dien-2-ol (= *trans*-2-hydroxy pseudolimonene) | 0.1< | [62,63] |
| *p*-mentha-1,8-dien-4-ol(= limonen-4-ol) | 0.1<–0.1 | [63] |
| *p*-methyl acetophenone | 0.1< | [63] |
| Methyl salicylate | 0.1< | [63] |
| 4-methyl-4-vinyl butyrolactone | 5.3 | [63] |
| 3-methyl-2-butenyl butyrate | 0.2–1.1 | [63] |
| 3-methyl-3-butenyl isovalerate | 0.1 | [62] |
| 3-methyl-2-butenyl hexanoate | 0.1<–0.1 | [63] |
| 6-methyl-3,5-heptadien-2-one | 0.1–0.2 | [63] |
| γ-muurolene | 0.3 | [62,63] |
| α-muurolene | 0.1–0.3 | [63] |
| *T*-muurolol | 0.1<–0.3 | [62,63] |
| Myrtenal | 0.1–0.3 | [63] |
| Myrtenol | 0.1–0.3 | [63] |
| Myrtenyl acetate | 0.1< | [63] |
| Myrcene | 0.5–10.7 | [59-63] |
| Neointermedeol | 0.1<–0.6 | [62,63] |
| (E)-nerolidol | 0.1<–16.3 | [59,62,63] |
| Nerol | 0.1 | [63] |
| Neryl acetate | 0.1< | [62,63] |

*(Contd...)*

**Table 2: (*Continued)***

| Essential oil (%) wet weight | Values | References |
|---|---|---|
| Nonanol | 0.2 | [63] |
| 2-nonanol | 0.1<–0.4 | [62,63] |
| 2-nonanone | 0.05–2.4 | [61-63] |
| 2-nonyl acetate | 0.3 | [63] |
| (E)-β-ocimene | 0.1<–12.4 | [61-63] |
| (Z)-β-ocimene | 0.1<–3.8 | [61-63] |
| (E)-*p*-ocimene | 29.0 | [59] |
| (E)-β-ocimene epoxide | 0.1< | [63] |
| (Z)-β-ocimene epoxide | 0.1 | [63] |
| Octyl acetate | 0.1< | [63] |
| 4-pentenyl butyrate | 0.1<–1.2 | [63] |
| Perilla alcohol | 0.1<–0.1 | [62,63] |
| Perillen | 0.1<–0.1 | [63] |
| Phytol acetate | 1.1 | [63] |
| *trans*-pinocarveol | 0.1<–4 | [62,63] |
| α-pinene | 0.1<–6.1 | [61-63] |
| β-pinene | 0.05–25.2 | [60-63] |
| Pinocarvone | 0.1<–0.1 | [63] |
| *cis*-piperitol | 0.1< | [62,63] |
| Phytol | 0.1<–2.7 | [62,63] |
| *trans*-pinocarvyl acetate | 0.1< | [62] |
| *trans*-piperitol (= *trans*-p-menth-1-en-3-ol) | 0.1< | [62] |
| Rose furan | 0.1–0.2 | [63] |
| Rosifoliol | 0.1<–0.3 | [62,63] |
| Sabinene | 0.05–0.6 | [61-63] |
| Salvial-4 (14)-en-1-one | 0.1<–0.2 | [62,63] |
| Selin-11-en-4α-ol | 0.1<–0.3 | [62,63] |
| Selina-4,11-diene(= 4,11-eudesmadiene) | 0.2 | [63] |
| α-selinene | 0.1<–0.6 | [62,63] |
| β-selinene | 0.1–0.2 | [62,63] |
| δ-selinene | 0.1 | [63] |
| *trans*-sabinene hydrate | 0.1 | [63] |
| Spathulenol | 0.1–1.0 | [63] |
| Terpinen-4-ol | 0.1–3.2 | [61,63] |
| Terpinen-4-yl acetate (= 4-terpinenyl acetate) | 0.1< | [62,63] |
| α-terpinene | 0.05–3.6 | [61-63] |
| γ-terpinene | 0.1<–3.8 | [61-63] |
| α-terpineol | 1.0 – 9.6 | [59,61-63] |
| *cis*-β-terpineol | 0.1<–0.1 | [63] |
| δ-terpineol | 0.1–0.5 | [61-63] |
| Terpinolene | 0.1–0.6 | [61-63] |
| α-terpinyl acetate | 0.1<–0.1 | [63] |
| α-thujene | 0.05–5.2 | [61-63] |
| Torreyol | 0.1<–0.6 | [63] |
| 3,7,11-trimethyl-10,11-epoxy-2,6-dodecadien-1-yl acetate (= 10,11-epoxyfarnesyl acetate) | 1.0 | [63] |
| 2,6,10-trimethyl-7,10-epoxy-2,11-dodecadien-6-ol (= nerolidol oxide) | 0.4 | [63] |
| 2,6,10-trimethyl-7,10-epoxy-2,11-dodecadien-6-ol isomer (= nerolidol oxide isomer) | 0.6 | [63] |
| 2-undecanone | 0.1–0.8 | [62,63] |
| Valencene | 0.1–0.2 | [63] |
| Vinyl benzene (= styrene) | 0.1 | [62] |
| Viridiflorol | 0.1<–0.8 | [63] |
| β-ylangene | 0.1 | [63] |

with MIC values ranging from 0.5 mg/mL to 3.5 mg/mL [65]. Henley-Smith *et al*. [54] evaluated antibacterial activities of the compounds cardamomin, aurentiacin A, 5-hydroxy-7-methoxy-6-methylflavanone, quercetin, and 3,5,7-trihydroxyflavan isolated from *H. natalensis* against *A. israelii* using the microdilution technique with 5% chlorhexidine gluconate as a positive control. Only cardamomin, aurentiacin A, quercetin, and 3,5,7-trihydroxyflavan were active against the pathogen with MIC values ranging from 0.06 mg/ml to >1 mg/ml, while MBC values for aurentiacin A and quercetin were 0.06 mg/ml to 1 mg/ml, respectively [54]. An enzymatic bioanalysis of lactic and acetic acid production from *S. mutans* and *L. paracasei* was carried out after 24-h incubation with the ethanolic leaf and twig extract of *H. natalensis*. A reduction in the acid production from each bacterium was observed on exposure to the extract, and this consequently increased the pH, which could possibly reduce the demineralization of enamel which may help prevent the formation of dental caries [54].

**Antimycobacterial activities**

Dzoyem *et al*. [73] evaluated the antimycobacterial activities of acetone leaf extracts of *H. natalensis* against *Mycobacterium smegmatis*, *Mycobacterium aurum, Mycobacterium fortuitum,* and *Mycobacterium tuberculosis* using a tetrazolium violet based broth microdilution method with isoniazid (µg/mL) and rifampicin (µg/mL) as positive controls. The extracts exhibited activities with MIC values ranging from 0.08 mg/mL to 0.62 mg/mL and the total activities ranged from 147.2 mL/g to 1150 mL/g [73].

**Antifungal activities**

Gundidza *et al*. [60] evaluated antifungal activities of the essential oil isolated from *H. natalensis* against *Aspergillus flavus, Aspergillus niger, Aspergillus ochraceus,* and *Aspergillus parasiticus*. The essential oil exhibited activities against all tested microbes [60]. Van Vuuren and Viljoen [64] evaluated the antifungal activities of the essential oil of

*H. natalensis* against *Candida albicans* and *Cryptococcus neoformans* using the microtiter plate method with amphotericin B (0.01 mg/ml) as a positive control. The essential oil exhibited activities with MIC value of 4.5 mg/mL and 5.7 mg/mL against *C. albicans* and *C. neoformans*, respectively [64]. To demonstrate the time-kill efficacy of the essential oil of *H. nalalensis*, Van Vuuren and Viljoen [64] exposed the essential oil to *C. albicans,* and cidal efficacy plotted over time against the logarithm of viable colonies. The oil showed a rapid cidal effect against the tested pathogens [64]. Van Vuuren *et al*. [63] evaluated antifungal activities of the essential oil of *H. natalensis* collected from various geographical regions in South Africa against *C. neoformans* using the microtiter plate method with amphotericin B (0.01 mg/ml) as a positive control. The essential oil exhibited activities with MIC values ranging from 0.5 mg/ml to 3.0 mg/ml [63]. Braithwaite *et al*. [52] evaluated the antifungal activities of methanol and acetone leaf extracts, essential oil and a smoke fraction of *H. natalensis* against *C. neoformans* using the microtiter plate technique with amphotericin B as a positive control. The extracts exhibited activities with MIC values ranging from 0.93 mg/ml to 8.0 mg/ml [52]. Henley-Smith *et al*. [69] evaluated the synergistic activities of *H. natalensis* mixed with *M. alternifolia, M. piperita* and the green tea extract known as TEAVIGO™ against *C. albicans* and the mixed extract successfully inhibited the growth of the pathogen [69]. Akhalwaya *et al*. [72] evaluated antifungal activities of aqueous and dichloromethane:methanol (1:1) leaf and stem extracts of *H. natalensis* against *C. albicans*, *Candida glabrata,* and *Candida krusei* using the microtiter plate dilution assay with amphotericin B (0.01 mg/mL) as a positive control. The extracts exhibited activities with MIC values ranging from 0.25 mg/mL to >8.0 mg/mL [72]. Henley-Smith *et al*. [54] evaluated antifungal activities of ethanolic leaf and twig extracts of *H. natalensis* against pathogenic oral fungal species, *C. albicans* and polyene and azole-resistant *C. albicans* using the microdilution technique with amphotericin B as the positive control. The extracts exhibited activities with MIC value of 8.3 mg/ml and 12.5 mg/ml against *C. albicans* and polyene and azole-resistant *C. albicans*, respectively, while minimum fungicidal concentration values were 10.4 mg/ml and >12.5 mg/ml against *C. albicans* and polyene and azole-resistant *C. albicans*, respectively [54]. Chakravorty *et al*. [65] evaluated antifungal activities of essential oils (Z)-3-hexenyl nonanoate, (E)-3-hexenyl nonanoate, hexyl nonanoate, and (Z)-2-hexenylnonanoate isolated from *H. natalensis* against *C. albicans* and *C. neoformans* using the microdilution method with amphotericin B (0.01 mg/mL) as a positive control. The essential oils showed activities with MIC values ranging from 0.5 mg/mL to 1.5 mg/mL [65].

**Antioxidant activities**

Muchuweti *et al*. [74] evaluated the antioxidant activities of ethanol leaf and stem extracts of *H. natalensis* using the 2,2-diphenyl-1-picrylhydrazyl hydrate (DPPH) radical scavenging assay. The percentage inhibition exhibited by the extracts was 29.7% for the standard β-carotene, and the amount of total phenolics was 0.096 ± 0.02 milligrams tannic acid per 100 mg of plant sample [74]. Mzindle [75] evaluated antioxidant activities of aqueous and methanol extracts of *H. natalensis* using the DPPH radical scavenging assay with rutin as a positive control. The extracts showed free radical scavenging abilities ranging from 42.9 ± 2.8% to 101.1 ± 2.1%, while rutin exhibited free radical scavenging abilities ranging from 27.4 ± 1.4% to 95.3 ± 0.5% [75].

**Anti-inflammatory activities**

Frum and Viljoen [76] evaluated anti-inflammatory activities of the essential oils 1.8-cineole, linalool, limonene, and β-pinene isolated from *H. natalensis* using the 5-lipoxygenase inhibitory assay. All oils tested exhibited promising 5-lipoxygenase inhibitory activities with half maximal $IC_{50}$ value of 46.6 ppm [76]. Mzindle [75] evaluated anti-inflammatory activities of aqueous and methanol leaf extracts of *H. natalensis* using the lipoxygenase inhibitor screening assay with nordihydroguaiaretic acid as a positive control. The aqueous and methanol extracts inhibited lipoxygenase enzyme by 101.6% ± 3.8% and 58.2 ± 12.3, respectively, which was lower than 122% and 129% inhibition demonstrated by nordihydroguaiaretic acid, the control [75].

Mzindle [74] also evaluated the wound healing activities of aqueous and methanol extracts of *H. natalensis* using the scratch wound assay. The migration rate of the extracts ranged from 24.9% ± 3.5% to 38.7% ± 2.7% when compared to the untreated cells with a percentage migration rate of 24% [75].

**Cytotoxicity activities**

Dzoyem *et al*. [73] evaluated the cytotoxicity activities acetone of leaf extracts of *H. natalensis* using the colorimetric tetrazolium-based 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay on Vero monkey kidney cells with doxorubicin as a positive control. Compared to doxorubicin which exhibited median lethal concentration ($LC_{50}$) value of 4.51 µg/mL, the extract could be considered as relatively safe with $LC_{50}$ value of 264.1 µg/mL with selectivity index (SI) value of 0.4–3.3 [73]. Henley-Smith et al. [54] used human monocyte (U937), kidney epithelial cells of the African green monkey (Vero) and human laryngeal epidermoid carcinoma (HEp-2) cells to assess cytotoxicity activities of ethanolic leaf and twig extract of *H. natalensis* using the XTT (Sodium 3'-[1-(phenyl amino-carbonyl)-3,4-tetrazolim]-bis-[4 methoxy-6-nitro] benzene sulfonic acid hydrate) assay as described by Zheng *et al*. [77]. The extract showed a $IC_{50}$ value of 35.6 µg/ml, 147.0 µg/ml, and 33.7 µg/ml on macrophage U937 cells, Vero, and HEp-2 cells, respectively. Therefore, on Vero cells, the extract might be potentially harmful, but on HEp-2 and U937 cells, the extract could be potentially toxic. Mzindle [75] evaluated the cytotoxicity of aqueous and methanol leaf extracts of *H. natalensis* using MTT assay on 3T3 NIH fibroblast cells by treating them with various concentrations of the extracts. The extracts exhibited >100% viability, indicating that the extracts were not toxic to the cells [75].

**Pro-inflammatory activities**

Henley-Smith *et al*. [54] evaluated the pro-inflammatory activities of ethanolic leaf and twig extracts of *H. natalensis* using *C. albicans* and *P. intermedia*. A significant reduction of interleukin-8 production by macrophage cells was observed when exposed to the extract. It is possible that *H. natalensis* can prevent excessive tissue damage in periodontal diseases through its reduction of inflammation [54].

## CONCLUSION

*H. natalensis* is an important herbal medicine in Southern Africa, and significant breakthrough has been made in the past 40 years elucidating the phytochemical and pharmacological properties of the species. However, there are still some research gaps regarding correlating the medicinal uses of *H. natalensis* with its chemical compounds and associated pharmacological properties of the compounds and extracts of the species. Detailed studies on the pharmacokinetics, *in vivo* and clinical research involving compounds isolated from the species and its extracts, are required.

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## AUTHOR'S CONTRIBUTIONS

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

## CONFLICTS OF INTEREST

No conflicts of interest are associated with this work.

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