PHYTOCHEMICAL AND ETHNOPHARMACOLOGICAL REVIEW OF HETEROPYXIS NATALENSIS

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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 ethnomedical 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, DARY, and open-access. Pre-electronic literature of Africa and 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-inflammatory, blood purifier, decongestant, for weaning, ethnoveterinary medicine and as herbal medicine for bleeding disorders, gauze, nose, colds, gum infections, impotence, menorrhagia, respiratory disorders, toothache, and wounds. Phytochemical compounds identified from the species include essential oils, 3,6-dihydroxy-5-methoxy,3',4',5'-trihydroxyflavan, 3',5,7-trihydroxyflavan, 5-hydroxy-3,6-dimethoxy,3'-methylphenyl)-3-phenylprop-2-en-1-one, (2E)-2-[(2E)-1-hydroxy-3-phenylprop-2-en-1-ylidene]-5-methoxy-6,6-dimethylcylohex-4-ene-3,1,3-dione, 2',4'-dihydropyrazine-6-methoxy-3,5'-dimethoxychalcone, 3',4',5'-tri-O-methyl-3,4-methylenedioxy ellagic acid, 3,5,7-trihydroxyflavan, 5-hydroxy-7-methoxy-6-methylphenol, aurantiac, betulinic acid, cardamom, lupene, luteol, quercetin, and sitosterol-3-ene-3-o.

Pharmacological studies revealed that H. natalensis extracts and compounds have antifungal, antifungal, antioxidant, anti-inflammatory, cytotoxicity, and anti-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.

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 plans 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 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 ethnomedical 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, H. canescens Ohl., and H. dehniae Suess. [33,34]. These Heteropyxis species have previously been assigned to families Lythraceae and others. Mahomoodally [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 “pseudus” 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 branch 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-inflammatory 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 cadinol (17.1%), 1,8-cineole (0.2-41.2%), limonene (1.8-25.4%), linalool (0.1-42.7%), myrcene (0.5-10.7%), β-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 [6,0,6-3-65].

Adesanwo et al. [66] identified (E)-1,2',4'-dihydroxy-5'-methoxy-3',5'-dimethylphenyl-3-phenylprop-2-en-1-one while Shode et al. [67] identified (2E)-1-(2'-hydroxy-3',5'-dimethylcyclohexane-4-ene-1,3)-dione from leaves of *H. natalensis*. Mohammed et al. [68] identified 2',4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone, 3',5'-tri-O-methyl-3,4-methylenedioxy ellagic acid, betulinic acid, lupenone, and lupenofolin from the twigs of *H. natalensis* while the roots yielded 3β-hydroxy-3-oxo-5α-cholestane, 5-methoxy-6,6-dimethylcyclohexene-4-ene-1,3-dione.
## Table 2: Essential oils identified from aerial parts of *Heteropyxis natalensis* (Contd...)

| 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 isoalactarate           | 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<   | [63]       |
| Bornol                       | 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]       |
| β-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-calamarene                 | 0.1<–0.1| [62,63] |
| cis-calamene                 | 0.1<   | [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 (= caryophyllenol) | 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 (= caryophylladienol ii) | 0.1<| [62,63] |
| cis-carveol                  | 0.1<–0.2| [63]    |
| trans-carveol                | 0.1<–0.5| [62,63] |
| Camphene                     | 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                  | 0.2–4.12| [58-63] |
| Glovonal                     | 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    | [58]       |
| 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-dimethyl styrene        | 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...)
| Essential oil (%) wet weight | Values | References |
|-----------------------------|--------|------------|
| Geranyl butyrate            | 0.1<–0.2 | [62,63] |
| Glenol                      | 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] |
| Hexadecanal                 | 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                  | 0.05–0.9 | [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 calamene         | 0.1–0.4 | [63] |
| trans-2-hydroxy-1,8-cineole | 0.1     | [63] |
| (E)-1-β-ionone              | 0.1     | [63] |
| Isoaryophyllene 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                    | 0.1–4.27 | [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<–0.8 | [63] |
| Linyl acetate               | 0.05–0.5 | [61,63] |
| p-menth-2-en-1-ol           | 0.1<–0.1 | [62,63] |
| p-mentha-1,7 (8)-diene (= pseudolimonene) | 0.1<–7.1 | [63] |
| Methyl4-(4′-methyl-3′-pentenyl)-3-cyclohexenyl ketone | 0.1 | [63] |
| 2-methylbutyl acetate       | 0.1     | [63] |
| 3-methylbutyl butyrate      | 0.1<–0.4 | [62,63] |
| 3-methyl butyl hexanoate (= isovaleryl 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<    | [63] |
| p-mentha-1,8-dien-4-ol (= limonen-4-ol) | 0.1<–0.1 | [63] |
| p-methylacetophenone         | 0.1<    | [63] |
| Methylsalicylate             | 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-muurolone                 | 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] |
| Myrtanyl 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] |

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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 parastaticus*. The essential oil exhibited activities against all tested microbes [60]. Van Vuuren and Viljoen [64] evaluated the antifungal activities of the essential oil of

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### Table 2: (Continued)

| Essential oil (%) wet weight | Values | References |
|-----------------------------|--------|------------|
| Nonanol                      | 0.2    | [63]       |
| 2-nonenol                   | 0.1<0.4 | [62,63]    |
| 2-nonenone                  | 0.05–0.2 | [61-63]    |
| 2-nonyl acetate             | 0.3    | [62]       |
| (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]  |
| Pino carvone                 | 0.1<0.1 | [63]       |
| cis-piperitol                | 0.1<    | [62,63]    |
| Phytool                      | 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]       |
| Rosikkol                     | 0.1<0.3 | [62,63]    |
| Sabinene                     | 0.05–0.6 | [61-63]   |
| Salvial-4(14)-ene-1-one      | 0.1<0.2 | [62,63]    |
| Selin-11-ene-4-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-terpeneol                 | 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]       |

**Antimycobacterial activities**

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**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 parastaticus*. 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. natalensis, 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 minimal 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]. Brathwaite 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]. Ahammad 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-hexenynonanoate 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 ethanolic 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 0.09 ± 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 4.66 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-tetrazolium]-bis-[4 methoxy-6-nitro] benzene sulfonic acid hydrate) assay as described by Zheng et al. [77]. The extract showed a LC_{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 might 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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