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Siphonochilus aethiopicus: A Comprehensive Review of its Therapeutic Application for Alleviating Symptoms of Allergic and Infectious Respiratory Diseases

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Dedicated to Hans Vahrmejier who taught me the beauty of medicinal plants.

Abstract: *Siphonochilus aethiopicus*, is a medicinal plant traditionally used in South Africa to treat respiratory and inflammatory conditions. The plant species is endangered due to overharvesting, necessitating conservation and cultivation efforts. Scientific studies on *S. aethiopicus* led to the identification of key bioactive compounds, primarily furanoterpenoids, with demonstrated anti-inflammatory, bronchodilatory, and immunomodulatory effects. Laboratory and animal studies confirm its effectiveness in treating asthma and allergic airway diseases. Preclinical studies demonstrate the plant's effectiveness in models of allergic airway diseases, supporting its role in complementary medicine. This review consolidates ethnopharmacological knowledge, phytochemical composition and pharmacological properties related to *S. aethiopicus*, highlighting its potential therapeutic applications.

Keywords: *Siphonochilus aethiopicus, furanoterpenoids, respiratory diseases, phytochemistry*

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1. Introduction

Medicinal plants have been essential to traditional healing practices across worldwide, and their therapeutic significance continues to gain recognition in modern pharmacology.[1] In Africa, diverse plant species are employed as natural remedies against various ailments, which are often passed down through generations of traditional healers.[2] One such plant is *Siphonochilus aethiopicus* (Schweinf.) B. L. Burtt (British taxonomist that originally described the species), a plant species from the Zingiberaceae (ginger) family, renowned for its healing properties. *Siphonochilus aethiopicus* is unique to the African continent and has been used for centuries to alleviate respiratory conditions, inflammation, and various other ailments.[3] Geographically, it is widely distributed across Mozambique, Zimbabwe, and South Africa and in parts of Senegal, Ethiopia, and Malawi. Even the specific epithet of the scientific name points to the plant being primarily originated from southern Africa.

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The traditional knowledge surrounding *S. aethiopicus* has motivated scientific groups, leading to delve into its phytochemical composition and pharmacological activities.[4] Studies have shown that furanoterpenoids, one of the key bioactive constituents, is responsible for the plant's anti-inflammatory, bronchodilatory, and antimicrobial effects.[5] These findings support its traditional uses and indicate potential therapeutic applications in modern medicine.

Other research into the plant's biological activity and its constituents revealed the presence of a new identified diarylheptanoid, 2,3-diacetoxy-7-(3'',4''-dihydroxy-5''-methoxyphenyl)-1-(4'-hydroxy-3'-methoxyphenyl)-5-heptene with significant antiplasmodial activity against *Plasmodium falciparum*, the causative species of cerebral malaria.[6] Potent anti-leishmanial activity was also established for this diarylheptanoid.[7] Further phytochemical investigation yielded the presence of a novel eudesmane sesquiterpenoid (2, Figure

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2) from the rhizomes of the plant, which undoubtedly contributes to its biological activity.[8]

Despite its well-documented medicinal value, *S. aethiopicus* faces serious conservation threats due to overharvesting and habitat destruction.[9] The increasing demand for the plant in both local and global markets has led to its near-extinction in the wild. As a result, efforts are underway to cultivate and sustainably manage its growth to ensure its continued availability for medicinal use. Several research initiatives have focused on optimizing cultivation methods, including tissue culture propagation, to reduce the pressure on wild populations,[10] although there are some concerns regarding the chemistry of cultivated plants that are not exposed to their normal environmentral pressures.
Given the growing interest in natural remedies for respiratory and inflammatory diseases, there is a pressing need to bridge traditional knowledge with scientific validation.[11] This review intends to provide a comprehensive overview of the ethnopharmacological uses, phytochemistry and pharmacological properties of *S. aethiopicus*. By consolidating available research, this review emphasizes the potential for developing pharmaceutical and nutraceutical products based on *S. aethiopicus*.

2. Review Methodology

Information was gathered by searching for pertinent literature on *S. aethiopicus*. This review encompassed abstracts, full-text articles, MSc and PhD theses, research outputs, and books to provide succinct and comprehensive information about the plant's phytochemistry, indigenous medicinal uses, and pharmacological characteristics. Several online databases and search engines were also utilized, including ScienceDirect, Scopus, Google Scholar, Web of Science, PubMed, CAB Abstracts, SciFinder, and MEDLINE. Keywords used in the literature search included *Siphonochilus aethiopicus*, Zingiberaceae, siphonochilone, Natal ginger, medicinal plants, ginger, plant parts used, biological activity and indigenous knowledge. Only publications in the English language were considered for this review.

3. Ethnomedicinal Uses

Many plant species within the Zingiberaceae family are frequently used as flavouring agents, spices and medicines because of their distinctive taste and health benefits.[12] The roots and rhizomes of *S. aethiopicus* are widely employed in traditional African medicine. The fresh rhizomes have a potent ginger aroma and are chewed to alleviate nasal congestion and treat coughs, asthma, flu, colds and several other ailments and cultural practices.[13] Traditionally, the Zulu people of South Africa use the plant for safeguard against lightning and snakes[12]. Chewing the fresh leaves and a decoction of the rhizomes are used for menstrual pain relief.[14]

In parts of East Africa and Senegal, *S. aethiopicus* rhizomes and roots are utilized to treat stomach infections, diarrhoea, and internal parasites, including schistosomiasis, and as a spice.[15] Traditionally, the combination of roots and rhizomes is used to treat hysteria and alleviate dysmenorrhea.[16] In Benin, a water decoction of the rhizomes and roots is used for treating endometriosis and female infertility.[17] In Swaziland (Kingdom of Eswatini), this plant species is used as a remedy for malaria and to relieve menstrual pain.[18] In Africa, various ethnic groups utilize *S. aethiopicus* for colds, coughs, asthma, pain-related conditions, headaches, and respiratory problems.[19] The published literature indicates a prevalent pattern in the traditional practice of *S. aethiopicus* rhizomes and roots, against respiratory problems (including cough, influenza), pain, and malaria across the different African regions where this plant is found.

4. Phytochemistry

The key chemical components of the plant species are sesquiterpenoids of the furanoid type and diarylheptanoids.[20] Organic extracts of *S. aethiopicus* prepared by extraction of the dried, ground roots and rhizomes of the plant mainly consist of a mixture of furanoterpenoids. HPLC UV/MS data identified the major constituent in both the diethyl ether and ethanol extracts as 4,4a,5,8a,9-tetrahydro-3,5,8a-trimethylnaptho[2,3-b]furan-8-one, also named as siphonochilone (Figure 1,2).[21] The major furanoterpenoid was purified from the diethyl ether extract of the plant *via* fractionation of the diethyl ether extract. Flash chromatography with silica gel was used, eluting with increasing polarity of a 5% ethyl acetate/hexane solution to 100% ethyl acetate.[21] The structure of the furanoterpenoid was confirmed using NMR and mass spectrometry.[21,22] Another method of obtaining the furanterpenoid is *via* steam distillation of the fresh rhizomes of the plant. The rhizomes are sliced and placed in a suitable vessel for steam distillation. This process produces a clear distillate containing crystals of the pure compound, which is retrieved after filtration, washing with cold water, and drying in a desiccator overnight.[21]

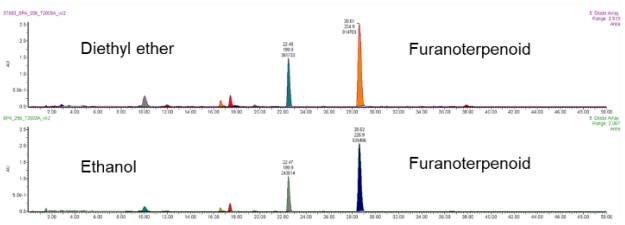

Figure 1. *HPLC UV chromatograms of the diethyl ether and ethanol extracts [Represented with permission from Ref [21].*

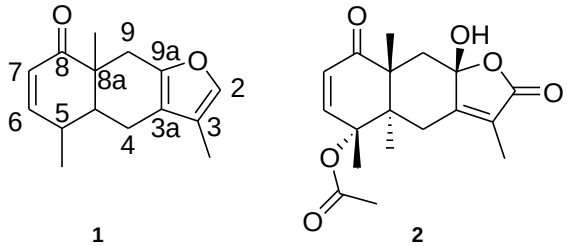

Figure 2. *Chemical structures of compounds isolated from Siphonochilus aethiopicus [Represented with permission from Ref [21].*

Other compounds were also isolated by Igoli[16] and Lategan[23] namely, epi-curzerenone, furanodienone, 16-oxo-8(17),12E-labdadiene-15-oic acid, 15-hydroxy-8(17), 12E-labdadiene-16-al, 8(17),12E-labdadiene-15,16-dial, 2-hydroxy-4aαH-3,5α,8aβ-trimethyl-4,4α,8α,9-tetrahydro-naphtho[2,3β]-furan-8(5H) and 8,12-epoxy-1(10),4,7,11-germacratetraen-6-one. Viljoen *et al.*[24] identified seventy compounds in the essential oil obtained by hydrodistillation of the roots of the plant. Siphonochilone was shown to be the major compound, comprising over 20%, and could be taxonomically significant for this plant species. The other key compounds identified in the roots included cis-alloocimene, 1,8-cineole, terpinen-4-ol, (E)-β-ocimene, kessane, sabinene, and β-pinene.

The traditional preparation involved inhalation of the vapours from the steaming of *S. aethiopicus* rhizomes as a decongestant and for treating asthma.[25] Evidence was found by Naude *et al.*[26] that eucalyptol was the major component in the vapour phase of hot water infusions prepared from fresh and dried rhizomes. The authors observed a considerable reduction of eucalyptol and other compounds in the dried rhizomes. These results support the use of *S. aethiopicus* as a

decongestant, offering additional scientific support for the anecdotal claims of its effectiveness against coughs, flu, colds and allergic asthma.

5. Pharmacological Properties

5.1 *In vitro* biological assays

The aqueous extract, the diethyl ether extract, and the purified furanoterpenoid compound of *S. aethiopicus* were evaluated using the histamine receptor binding assay, the glucocorticoid receptor binding assay, and the phosphodiesterase IV inhibition assay at a single dose concentration and the data are shown in Table 1.[21] Dose-response studies were conducted for the diethyl ether extract and the furanoterpenoid compound only, as the water extract did not show any activity. The results are given in Table 2. The diethyl ether extract demonstrated good efficacy in both the glucocorticoid receptor binding assay (IC_{50} of 12.9 µg/ml) as well as the phosphodiesterase IV enzyme assay (IC_{50} of 26.6 µg/ml), suggesting that the plant may function similarly to corticosteroids in the treatment of allergies and asthma. The purified compound (Figure 2) demonstrated activity comparable to that of the diethyl ether extract.

These results showed that the diethyl ether extract and purified compound of *S. aethiopicus* have notable activity *in vitro* in systems associated with anti-inflammatory and anti-allergic effects.

Table 1. *Bioassay results of extracts and purified compound (1), furanoterpenoid*

Sample	PDE IV[a] %	Glu %[b]	H_1 %[c]
Ether	70	104	60
Water	15	11	-
Compound	78	91	80

a: PDE IV (Phosphodiesterase Inhibition. b: Glu (Glucocorticoid Inhibition). c: H_1 (Histamine Inhibition). Testing was conducted using the sample at a concentration of 100 µg/ml.

Table 2. *Bioassay results of the diethyl ether extract and compound (1), furanoterpenoid.*

Sample	Bioassay	IC_{50} (µg/ml)	K_i (µg/ml)	n_H
Ether	PDE IV	26.6	-	-
Ether	Glu	12.9	6.92	1.48
Ether	H1	89.0	42.50	1.75
Compound	PDE IV	43.6	-	-
Compound	Glu	11.4	6.12	0.91
Compound	H1	56.5	27.00	2.05

n_H: Hill coefficient. K_i: Inhibition constant. IC_{50}: Inhibition concentration. Reference compound data: Phosphodiesterase PDE IV: 4-(3-Butoxy-4-methoxybenzyl)-2-imidazolidinone, IC_{50} = 1.10 µM. Glucocorticoid: Dexamethasone, IC_{50} = 4.10 nM. Histimine H_1: Pyrilamine, IC_{50} = 3.30 nM.

In chronic inflammatory diseases, including rheumatoid arthritis, asthma, psoriasis, and inflammatory bowel diseases, several cytokines recruit activated immune and inflammatory cells to the site of lesions, thereby amplifying and perpetuating the inflammatory state. Transcription factors are essential in regulating immune and inflammatory responses, and nuclear factor-κB (NF-κB) is a particularly important and widespread transcription factor. NF-κB serves as a central mediator of the human immune response, regulating the transcription of a range of pro-inflammatory and inflammatory mediators such as the cytokines, interleukin-2, -1, -8 and TNF-α, as well as genes that encode nitric oxide synthase, cyclo-oxygenase II, cell adhesion molecules, immunoreceptors, or acute phase proteins. NF-κB acts as a master regulator of inflammation, making it a promising target for drug development. The diethyl ether extract was assessed for its anti-inflammatory properties in the NF-κB transcription assay where significant inhibition was observed with an estimated IC_{50} of 14.3 µg/mL and no cytotoxicity was observed at concentrations up to 100 µg/mL.[21] Cyclosporin A served as the reference compound in this assay (IC_{50} of 0.0608 µM). These results indicated that the diethyl ether extract effectively inhibited NF-κB, consequently reducing the release of various pro-inflammatory and inflammatory mediators involved in the inflammatory pathway of asthma.

Numerous cytokines are recognized as mediators of inflammation and play a role in the development of asthma. When an allergen, for instance, is inhaled, bronchial epithelial cells become activated and produce specific pro-inflammatory cytokines (interleukins, abbreviated IL), particularly the chemokine IL-8. We showed that extracts of *S. aethiopicus* exhibited substantial suppression of IL-8 with the stimulation of PMA compared to the positive control.[25] Evidence also linked NF-κB activation to improved IL-8 production, which recruits specific immune cells called neutrophils (and other granulocytes) to the site of disruption/infection.[27] Manna and Ramesh[28] showed that NF-κB, which regulated IL-8 expression, was also induced further by this chemokine. The interrelationship between NF-κB and IL-8 indicates that they are closely connected and play a significant role in inflammation and immune responses associated with allergic airway reactions. It is highly probable that *S. aethiopicus* exerts its actions on IL-8 and other cytokines through its observed inhibition of NF-κB.

5.2 *In vivo* biological assays

Upon inhalation of a causative agent such as an allergen, bronchial epithelial cells are activated and release specific pro-inflammatory cytokines. To evaluate the efficacy of *S. aethiopicus* against allergic inflammation *in vivo*, mice were sensitized and exposed to the allergen ovalbumin while simultaneously receiving *S. aethiopicus* extracts (diethyl ether or ethanol) or the purified furanoterpenoid compound.[21] Airway hyperreactivity, assessed through whole body plethysmography, was heightened in ovalbumin-sensitized mice challenged with methacholine when compared to naïve controls, and there was no substantial reduction observed in any group following the administration of S. aethiopicus extracts (Figure 3). Results showed that *S. aethiopicus* extracts exhibited anti-inflammatory properties in the lung. When given intraperitoneally, the diethyl ether extract of *S. aethiopicus* reduced allergic inflammation in the lungs similarly to the dexamethasone control. This was observed by a significant decrease in the percentage of eosinophils in the bronchoalveolar lavage fluid (see Figure 3) and a reduction in immune cell infiltration around the airways and blood vessels (Figure 4). Oral administration of the powdered plant material and diethyl ether or ethanol extract also led to a significant reduction in eosinophil counts in the bronchoalveolar lavage fluid, along with a decrease in lung inflammation (Figure 3). Although neutrophils were found in lower numbers compared to eosinophils in the bronchoalveolar lavage fluid, their counts were also significantly diminished by intraperitoneal administration of dexamethasone or the diethyl ether extract.

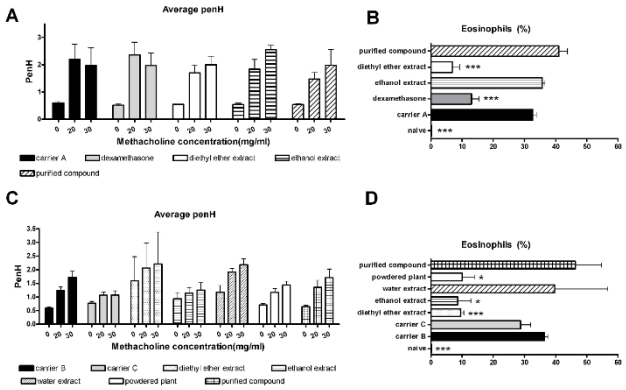

Figure 3. *Influence of S. aethiopicus on airway hyperreactivity and eosinophils in bronchoalveolar lavage fluid. Mice were sensitized and challenged with ovalbumin and treated with S. aethiopicus or control solutions intraperitoneally (A, B) or orally (C, D) twice daily for 3 days and 1 hour before methacholine challenge. A, C. PenH value as a measure of airway hyperreactivity. B, D. Percentage of eosinophils in the bronchoalveolar lavage fluid after challenge. Significance was calculated in comparison to the correlating carrier controls. *, P<0.05; ***, P<0.001. [Represented with permission from Ref [21].*

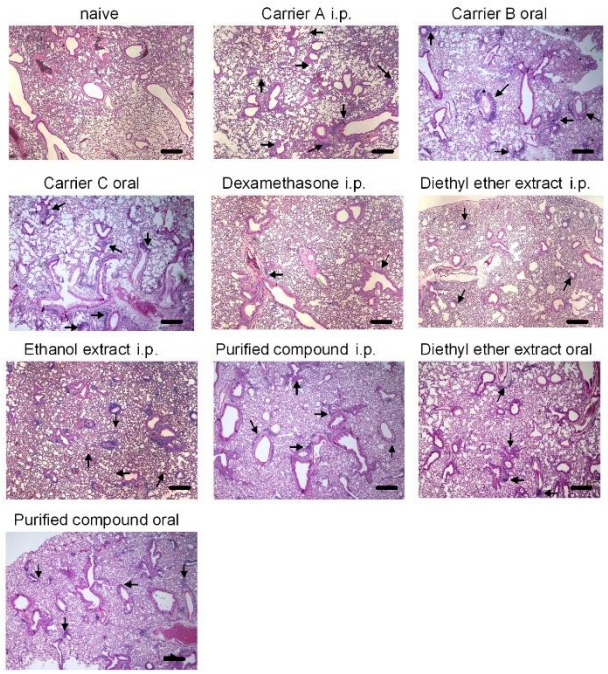

Figure 4. *Effect of S. aethiopicus on airway inflammation. Mice were sensitized and challenged with ovalbumin and treated with S. aethiopicus or control solutions twice daily for 3 days and 1 hour before methacholine challenge. Lung tissue sections were stained with haemotoxylin and eosin and examined at 100x magnification. Cellular inflammation around airways and blood vessels is indicated by black arrows. Scale bar = 200µm. [Represented with permission from Ref [21].*

The ethanol extract of *S. aethiopicus* was also assessed in a different *in vivo* animal model to evaluate its anti-asthmatic and anti-allergic/inflammatory properties. Ethanol and diethyl ether extracts of the plant were prepared and chemical constituents were analyzed using HPLC MS instrumentation. The extract was suspended in 1% ETOH/PEG solution. The test substance at a dose of 1000 mg/kg was given orally once daily for 6 consecutive days, one hour before the challenge of ovalbumin. The results of the anti-asthmatic activity are summarized in Figure 5, indicating that the ethanol extract (coded as BP4-256-72015A) demonstrated enhanced Penh values in the OVA-sensitized mice assay.

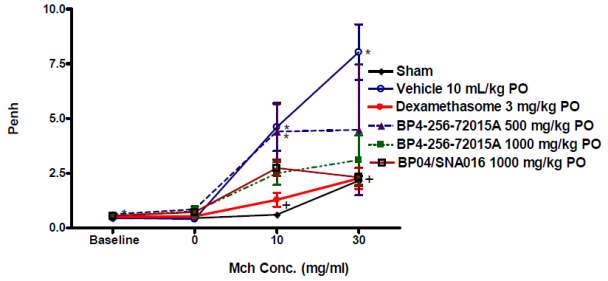

Figure 5. *Anti-asthmatic measurements [Represented with permission from Ref [21].*

Bronchoalveolar lavage fluid (BALF) samples were analyzed, and significant inhibition was observed in total WBC, lymphocytes, and eosinophils versus respective sham controls (Figure 6). One-way ANOVA, with subsequent Dunnett's test was performed to access the comparison between sham control, vehicle control, and test compound-treated groups ($P<0.05$ is considered significant).

The ethanol extract significantly suppressed the increase of inflammatory cells in bronchoalveolar lavage fluid (BALF) when measured in an *in vivo* anti-asthmatic ovalbumin-sensitized mice assay. In conclusion, biological assays performed on the extracts of *S. aethiopicus* and the purified furanoterpenoid compound demonstrated beneficial effects in the *in vitro* histamine H1, glucocorticoid receptor binding, phosphodiesterase IV, and NF-κB assays, indicating that this plant has anti-inflammatory, anti-allergic, immune and bronchodilatory effects. When the extracts were further tested *in vivo*, significant anti-inflammatory effects were observed, and the inflammatory cells were also significantly suppressed in BALF.

6. Toxicology

6.1 *In vitro* cytotoxicity, mutagenicity, and cardiac toxicity

The cytotoxicity of the diethyl ether extract, obtained from the liquid-liquid partitioning of the aqueous extract of the rhizomes was determined on Chinese Hamster Ovarian (CHO) cells using the MTT colorimetric assay. Emetine dihydrochloride (IC_{50} 0.07 µg/ml) was used as the standard reference compound and an IC_{50} value of 48.5 µg/ml was determined for the diethyl ether extract. The ethanol extract was evaluated against a cytotoxicity panel and genetic toxicity tests were also conducted, focusing on bacterial cytotoxicity and the Ames test. Four different bacterial strains were used; TA1537–S9, TA1535–S9, TA100–S9 and TA98–S9. No cytotoxicity was observed for concentrations up to 125 µg/ml.

The Ames test, which was performed using *Salmonella typhimurium*, is a commonly employed bacterial assay for identifying compounds capable of inducing gene mutations. This assay has a strong predictive value in relation to rodent carcinogenicity tests. The standard Ames test typically involves five strains of *Salmonella* that have pre-existing mutations preventing the bacteria from synthesizing the essential amino

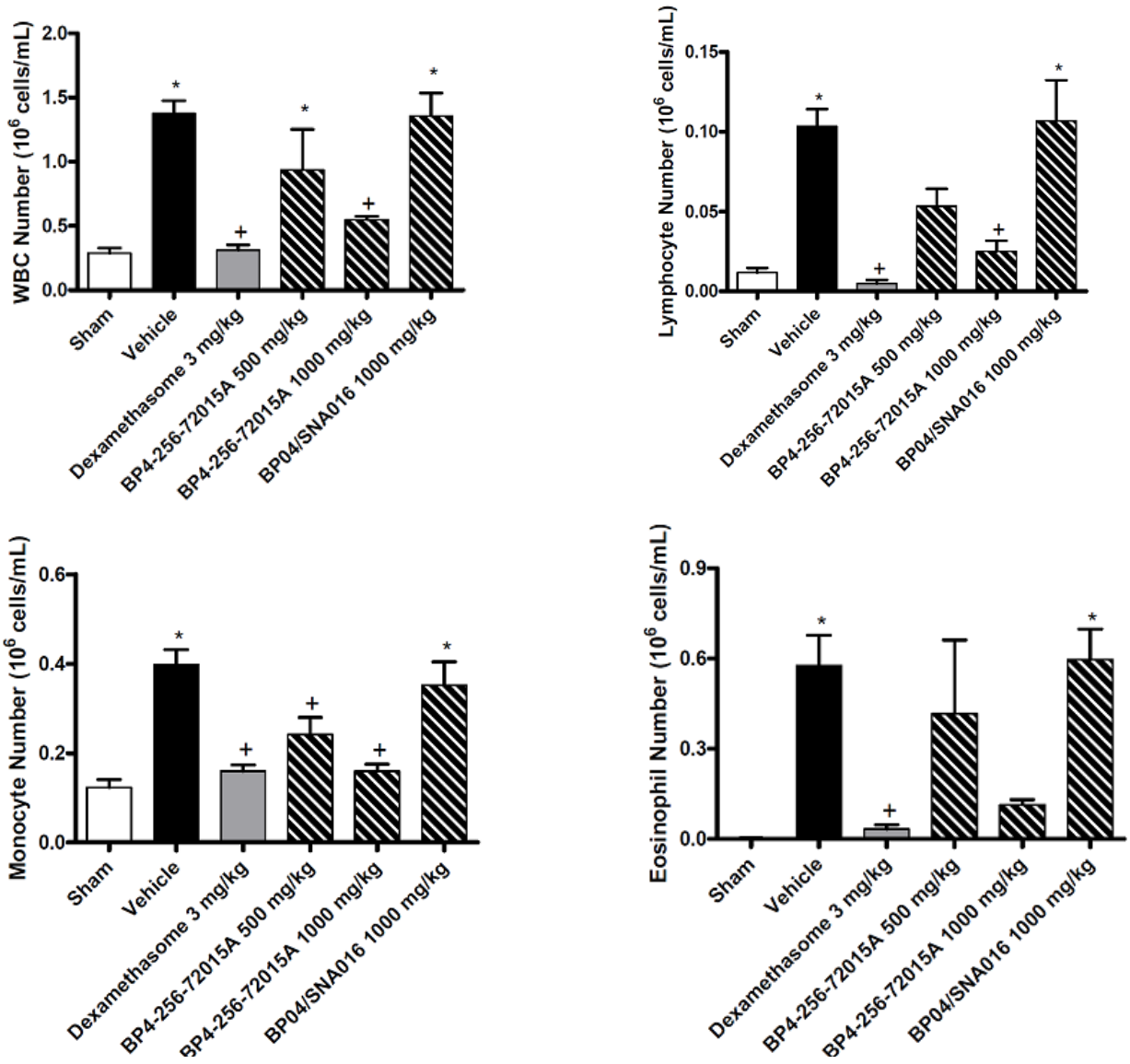

Figure 6. *Anti-allergic and inflammatory measurements BP4-256-72015A: ethanol extract; BP04/SNA016: dry, ground plant material. [Represented with permission from Ref [21].*

acid histidine, rendering them unable to grow in a histidine-free medium. The *Salmonella* strains used have different mutations in various genes in the histidine operon and are designed to be responsive to mutagenic compounds that act through different mechanisms. No cytotoxicity was observed in the Ames test for the ethanol extract up to a concentration of 125 µg/ml. A cardiac toxicity test (hERG, automated patch-clamp) was also conducted. Patch-clamp is an electrophysiological technique performed on cells recombinantly expressing the channel of interest (in this case hERG) and capable of detecting any change in its physiological properties. An IC_{50} of 50 µg/ml was obtained.

6.2 *In vivo* acute toxicological evaluation

Two separate acute *in vivo* toxicological studies were conducted. The first study assessed the acute oral toxicity of a diethyl ether extract of the plant in Sprague Dawely rats and was carried out according to Guideline 420 (fixed dose procedure). The diethyl ether extract was sequentially administered to three rats until signs of evident toxicity were observed. From the results of the study no evident toxicological symptoms were recorded during the sighting study at the 300-2000 mg/kg dosage levels. There was also no evident effect of the substance on the weight of the animals. The diethyl ether extract was classified in category 5 of the Global Harmonized System for chemicals.

The objective of the second study was to characterize the toxicity of the ethanol extract as well as finely, ground plant material of *S. aethiopicus* in rats following a single oral dose. The *in vivo* toxicology study consisted of two Phases according to the Food and Drug Administration's International Conference on Harmonization (ICH) and the Organisation for Economic Co-operation and Development (OECD) guidelines. Animals were dosed with either the crude plant extract or the ethanol extract dissolved in propylene glycol and 5% ethanol. The animals were dosed in two sub-groups of three animals each, two days apart, and monitored for 14 full days. Following the monitoring period, the animals were terminated by an isoflurane overdose and submitted for gross necropsy.

Histological evaluation from the acute toxicity study did not demonstrate any specific morphological pathology. From the

observed clinical signs, the most prominent effect was mild sleepiness that was induced within about 15 to 30 minutes from dose administration. This clinical effect was resolved within 5-6 hours post-drug administration. Based on the clinical signs of sedation and recovery in the absence of pathology or weight related effects, these clinical signs are assigned to sedative-like effects induced by dosing. While it is possible that the extract produced this mild sedative effect, it is more likely that these clinical signs were a result of the 5% alcohol solvent. The clinical signs seen are very similar to the signs seen by Chuck *et al.*[29] in which rats were exposed to various concentrations of ethanol and evaluated over a period of 30 minutes. In this study, most of the animals demonstrated some form of depression within 5 minutes of administration. The major difference between this study and that of Chuck *et al.*,[29] was that the effects seen were minor at 0.25 mg/kg. For this study, the animals received approximately 0.8ml of a 5% ethanol solution which converts to approximately 0.160 mg/kg. There were no histological findings to indicate toxic tissue damage. Based on the reversible clinical signs of mild sedation that lasted approximately 6 hours, normal habitus for > 99% of the study, absence of weight-related effects, and lack of gross pathological changes the product is believed to have a LD_{50} of > 5000 mg/kg when administered by the oral route (category 5).

6.3 *In vivo* sub-chronic toxicological evaluation

The objective of this study was to further characterize the toxicity of the plant species in rats following repeated oral dosages. The study consisted of a follow-up Phase 3 according to the Food and Drug Administration's International Conference on Harmonization (ICH) and the Organisation for Economic Co-operation and Development (OECD) guidelines. Data was obtained in 80 rats over a three-month period at three different dosages administered, namely 3, 30 and 300 mg/kg. A repeated dose 90-day oral toxicity study in rodents as per OECD guideline 408 was followed. 40 female and 40 male outbred rats of 6-8 weeks were used at the start of the study, 10 animals of each sex per dosage group. The *S. aethiopicus* ethanol extract was dissolved in 1% ethanol and polyethylene glycol (PEG) for oral administration. The following monitoring parameters were included in the study: Individual Habitus, Cage feed intake, Change in weight, Basic ophthalmology, Terminal clinical pathology, Terminal haematology, Full pathology, Full histopathology, Actual and relative organ weights and Terminal urine analysis.

No significant changes were evident on clinical signs, necropsy, histopathology or clinical pathology when the groups were evaluated independent of sex. When evaluated by sex, the animals had minor changes evident in some of the organ weight parameters, especially testicular weight, albeit in the absence of histopathological changes. Based on the results, it is assumed that the product is non-toxic. However, based on the organ weights and urine analysis, there appeared to be a physiological effect which may be due to the pharmacodynamics mechanisms of the extract viz steroid-like mechanism coupled with the ability to interfere with smooth muscle functionality.

7. Conclusion

Siphonochilus aethiopicus as one of the most commonly used medicinal plants in South Africa, holds significant promise in complementary medicine for treating respiratory and inflammatory conditions. Traditionally, it is primarily used for mild asthma, colds, influenza, and sinus issues. Preparations include both cold and hot infusions of the rhizomes and roots, steaming the rhizomes and inhaling the vapour, as well as chewing on the fresh rhizomes. Unlike many other widely used international medicinal plants e.g. *Ginko biloba* and *Echinacea*, there is currently no scientifically validated product based on *S. aethiopicus* on the market both locally and internationally. Only a few South African medicinal plants are now on international markets (e.g. Devil's Claw and *Pelargonium*); these plants have been extensively researched internationally and their claims scientifically validated.

Literature studies on *S. aethiopicus* provided anecdotal information but little scientifically assessed biological data. Scientific research conducted on *S. aethiopicus* led to the identification of extracts/compound (s) from the plant that can be developed for the management of allergic diseases, infectious respiratory diseases, and asthma. Biological assaying of the extracts of the plant and the purified non-steroidal metabolite showed a very interesting pharmacological profile supporting the beneficial effects of the plant extract in allergic and infectious respiratory diseases. The plant extract and/or the purified non-steroidal metabolite showed activity in the glucocorticoid receptor binding, histamine receptor binding, and phosphodiesterase IV inhibition assays. All these systems have a crucial role in respiratory diseases and inflammation and support a soothing and supporting effect in the treatment of allergic and infectious respiratory diseases. These activities were also supported by activities on IL-8, 5-lipoxygenase and nuclear factor-κB assays. The organic extracts and dried ground plant material demonstrated reduced infiltration of inflammatory cells in the lung tissue of animals and lowered production of inflammatory mediators in these animal models of asthma.

The plant extract of this widely used medicinal plant has been tested both *in vitro* and *in vivo* for toxicity. *In vitro* cytotoxicity studies in Chinese Hamster Ovarian (CHO) cells showed that the cytotoxicity (IC_{50}) of the diethyl ether extract using the MTT colorimetric assay is 48.5 µg/ml. The *in vivo* acute toxicity studies in rats have been completed using the diethyl ether and ethanol extracts as well as the finely, ground plant material and are based on OECD (The Organisation for Economic Cooperation and Development) Guideline 420 (fixed dose procedure) and Guideline 423 (single dose procedure). The results are encouraging, as the oral administration of organic extracts and ground plant material to rats exhibited no visible signs of toxicity. Additionally, histological evaluations revealed no specific morphological abnormalities or noticeable weight differences at the test concentrations of 300-2000 mg/kg. Based on the absence of toxicity at the limit dose of 2000 mg/kg, the finely ground rhizomes as well as the diethyl ether and ethanol extracts are considered category 5 compounds, according to OECD guideline 423.

Based on research results, data, and the conservation status of the plant, it is evident that commercial quantities of plant material can be supplied more cost-effectively and sustainably by using cultivation sites rather than harvesting from the wild. Areas in the Limpopo, Mpumalanga, and KwaZulu-Natal provinces should be identified as potential cultivation sites. *Siphonochilus aethiopicus* is well adapted to the climates of these provinces and is relatively easy to cultivate, as it grows from cuttings of the rhizomes during the winter when they are dormant. The plant may also be propagated from seeds, although this process may take up to a year for germination. Tissue culture is another method for propagating the plant. Cultivation is a critical aspect of any future development program for this species, which is critically threatened in the wild. Collectively, these findings demonstrate the beneficial properties of *S. aethiopicus* in alleviating symptoms associated with allergic and infectious respiratory diseases, providing scientific evidence that supports its traditional use and inclusion in complementary medicine products. Further research should focus on clinical trials to establish standardized dosing and assess long-term safety. Sustainable

cultivation remains a priority to ensure its availability for medicinal use, as extensive harvesting has led to near extinction in its natural habitat.

Author Contribution Declaration

Schalk van Rooyen: engaged in editing, data curation and writing.

Gerda Fouche: engaged in data curation, writing, conceptualization and editing.

Data Availability Declaration

New data were included for the toxicology evaluation of the extracts and purified compound, furanoterpenoid of *S. aethiopicus*.

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