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REVIEW

Salvia africana-lutea L.: a review of ethnobotany, phytochemistry, pharmacology applications and future prospects

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Abstract

Plants are nature's reserve for vitality and health-boosting agents. Despite ever-rising interest and research on plant medicinal chemistry, many stones are still being left unturned. Moreover, many traditional medicinal plants are yet to be discovered or functionally characterized. This study presented an up-to-date review of a poorly explored member of the *Salvia* genus indigenous to Africa—*Salvia africana-lutea* L. (synonymous with *Salvia aurea* L.) with details on its geographical distribution, ethnobotany, and pharmacological applications. We reviewed all literature published on *Salvia africana-lutea* up to January 2023, retrieved from PubMed, Scopus, and ScienceDirect as primary databases and google scholar as the secondary source. From our literature search, we found 38 documents published on *S. africana-lutea*, despite the popularity of the *Salvia* genus as a medicinal plant (having over 15,000 articles published to date). From the retrieved literature, only a few studies focused on exploiting the ethnobotanical features of the plants, such as the morphology, flowering and existence, and nature of its trichomes. Some studies have reported *S. africana-lutea* as an excellent source of essential oils trapped within their leaf trichomes with numerous phytochemicals and bioactivities. Other studies have reported some interesting pharmacological activities of plant extracts and isolated phytochemicals, such as their antimicrobial, anti-oxidative, analgesic, antipyretic, anticancer, cytotoxic, and other bioactivities. We identified some limitations of the few published studies, highlighting future research needs that should draw more scientific interest to foster more study on this under-explored and valuable plant species of *Salvia*, to harness its medicinal and industrial potential fully.

Keywords *Salvia africana-lutea* L. · *Salvia aurea L.* · Ethnobotany · Phytochemical · Phytochemistry · Ethnopharmacology

Introduction

Since ancient times, one of the most common treatments has been the use of medicinal plants (Batiha et al. 2020). Due to their antioxidant, antimicrobial, and anticancer properties, as well as other biological potentials, a variety of plants are used in traditional and modern medicine (Iravani et al. 2020). The genus *Salvia* (Lamiaceae) includes nearly 900 species spread worldwide, with only a few species, such as *Salvia africana-lutea* L., being indigenous in Africa. In many African communities, *Salvia africana-lutea* L. is also referred to as "Sandsalie," "Strandsalie" and "Geelblomsalie" (Mozafarian 1996). The name "*Salvia*" is derived from the Italian word "salvare," which means "healer." These plant species have been employed as ornamentals in cooking and aromatherapy and the empirical treatment of many ailments. This name was later translated into Sauja (French) and then altered to Sawge (in Old English). However, Sage

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has become a popular name in recent years. There was a proverb in the Middle Ages that said, "*Cur moriatur homo cui Salvia crescit in horto*?" ("Why should a man die if his garden has sage?") (Dweck 2000). This demonstrates that plants in the *Salvia* genus have been used to treat various diseases for ages.

A recent study has shown different wild Salvia species from Iran to be economically significant because of their seeds' high fatty acid content and potential application as fragrance sources, flavoring agents, food, and cosmetic ingredients (Moazzami Farida et al. 2016). As such, numerous representatives of the *Salvia* genus, including *S. officinalis*, *S. verbenaca*, *S. fruticosa*, and *S. tomentosa*, are cultivated for commercial reasons (Akhtar and Swamy 2018).

Salvia africana-lutea L. is an African indigenous species of the *Salvia* genus. Although the plant is a very popular medicinal botanical drug in many African countries, especially in the coastal region of South Africa, only a few scientific studies have preliminary explored the plant's bioactivities as an antioxidant, anti-inflammatory, and antimicrobial activities (Shakeri et al. 2016). The plant is a shrubby evergreen plant with trichome projections in the leaves, which have been reported to trap valuable essential oils under its leaves. The plant has a yellow to conspicuous golden flowering that fosters its pollination by insects and hummingbirds. More information reported about the distribution, ethnobotany, and pharmacological activities of *S. africana-lutea* has been present in this review (Ayatollahi et al. 2009).

From a concise bibliometric analysis, only about 0.23% of reported literature on the *Salvia* genus is specific to *S. africana-lutea*. Although a few reports had information on the plant's distribution, morphology, and ethnobotany, most studies reported the plant's diverse phytochemical constituents and therapeutic activities such as antimicrobial, antioxidant, anti-inflammatory, cytotoxic, and others (Shakeri et al. 2016. Being the first classical review on *S. africana-lutea*, this paper aims to foster a more in-depth study and applied research into this medicinal plant). We aim to critically examine all the available evidence about the underexplored plants, highlighting limitations, problems in the design of the studies, and future research needs. Few studies on the plant were not so detailed in their pharmacological examination of different plant extracts. Although traditionally, plants have helped alleviate inflammatory-related health conditions, the only studies on anti-inflammation were preliminary and did not show significant bioactivities. More so, the *S. africana-lutea* plant has been reported in many societies as edible foliage; however, there are no scientific studies on its nutraceutical application of the plants. Because of the poor level of interest in the plant, the conservation status of the plants may become worrisome and change from 'least concern.' Advance studies of the plant may investigate methods for improving plant propagation through in vitro cultivation and other genetic breeding protocol for an optimal cultivar.

Methodology

Studies on *S. africana-lutea* L. were retrieved primarily from PubMed, Scopus, and ScienceDirect databases by searching the term "*Salvia africana-lutea* L." OR "*Salvia aurea*" OR "*Crolocos aurea*" OR "*Salvia colorata*" OR" *Salvia ecklo-niana*" (all synonymous to *Salvia africana-lutea* L.) across the title, abstract, and keywords published literature in the databases. Results obtained for literature specific on the *S. africana-lutea* were compared to a general search on reports published on other members of the *Salvia* genus so far, on the same databases with just the search term "*Salvia*." The Google scholar database was used as a secondary search engine to ensure the study covers broad findings on the plant species. For inclusion, selected studies must be research articles that focus mainly on *S. africana-lutea* or *Salvia aurea* and must be reported in English. We excluded studies on other *Salvia* species, review papers, and articles in other languages apart from English.

We obtained 10 documents from PubMed, 38 from Scopus, and 10 from ScienceDirect, which focused on *Salvia africana-lutea* L. After an inclusion and exclusion filter, only 35 non-redundant studies were obtained as the focus of this review. From our bibliometric analysis, only about 0.23% (35/15,000+) of the total literatures published on the genus *Salvia* was focused on the African Indigenous *Salvia africana-lutea* L. as of January 2023.

Finally, using the Boolean connector "OR" and "AND" to join other keywords (antimicrobial, antibacterial, antioxidant, flowering, trichomes, analgesic, nanoparticles), studies specifically on ethnobotanical, different biological and pharmacological activities on *S. africana-lutea* were easily retrieved.

Ethnobotanical classification and morphology of *Salvia africana-lutea* L.

Salvia africana-lutea L. is an evergreen shrubby plant up to 2 m in height, indigenous to South Africa, although it may be found in other African and Asian countries (Rattray and Van Wyk 2021). Generally, the plants have various common names based on their morphology as well as differences in vernacular. Some of these common names are golden *Salvia* (due to its yellowish golden petals), dune *Salvia* (due to its flower and leave shape), beach *Salvia* (due to its common coastal location), and wild sage and sand sage. Other vernacular names common with many South African societies

are Sandsalie, Geelblomsalie, Strandsalie, and Bruinsalie (Foden and Potter 2005a; Viljoen and Notten 2019a).

S. africana-lutea is classified under "least concern" to its conservation status due to its widespread nature, abundance, and lower risk of extinction (Foden and Potter 2005b). The plants grow in coastal and sandy areas and have shown excellent resistance to drought or limited water. The plants are very hardy, with aromatic grey-greenish leaves and unique clusters of brown funnel-shaped flowers (Fig. 1). The plant begins flowering in early spring with bright yellow flowers, which mature in June (having a rusty-orange color) and finally fade to reddish-brown in December. The conspicuous nature of the flowers producing nectar makes them attractive for insect/sunbird pollination (Wester and Claßen-Bockhoff 2006; Wester 2013). Faded flowers fall off., leaving a nicely purple-colored calyx (Strelin et al. 2017).

The name *Salvia. africana-lutea* is also synonymous with *Salvia. aurea* L., *Crolocos aurea* (L), *Salvia colorata* (L) and *Salvia eckloniana* Benth (Retrieved from Royal Botanical Garden, Kew Science). The plant belongs to the Lamiaceae (Labiatae) family, commonly referred to as the sage family, which are well-known for their square stems, aromatic and opposite leaves, bilaterally symmetrical flowers bearing four stamens, and ovaries with two fused carpels (Rattray and Van Wyk 2021). The plant name "*Salvia. africana-lutea*" or "*S. aurea*" is derived from the Latin description of its characteristics; for instance—*Salvia* is from the Latin word *Salvere* (which means to save or heal based on its medicinal properties) and *aurea,* which means golden (Latin words to describe its flower color). The new name, according to Linnaeus's system of taxonomy, "*S. africana-lutea*," describes the plant's origin in Africa (*africana*) and its characteristic golden flowers (*lutea*) (Viljoen and Notten 2019b). The modern taxonomical classification of *S. africana-lutea* is summarized below.

Fig. 1 A snapshot of *Salvia africana-lutea* L. whole plant. The plant is shrubby with grey-green leaves up to 2 m in height. It has golden petals (hence sometimes called "golden salvia") and a unique dune-shaped/funnel-shaped flower and leaves (dune salvia). Faded flowers fall off, leaving a nicely purple-colored calyx

Taxonomical classification of *S. africana-lutea*

Kingdom:Plantae
Phylum:Tracheophytes
Sub-phylum:Angiosperms
Class:Eudicots
Subclass:Asterids
Order:Lamiales
Family:Lamiaceae
Genus:Salvia
Species:*S. africana-lutea*

The *Salvia* genus is made up of plants with characteristic hair-like trichomes. A few studies have reported the presence of glandular and non-glandular trichomes (a form of outgrowths) on the leaves surface of different members of the *Salvia genus* from microscopy analysis. Specifically, Kamatou et al. (2006) reported that *S. africana-lutea* showed non-glandular trichomes on their leave surface, consisting of elongated, unbranched, and multicellular cells. However, another study identified two types of glandular trichomes: the peltate gland and the capitate trichome. The peltate gland is characterized by a short stalk and multiple large cell-head, whereas the capitate trichome shows two sub-type (type 1 and II) (Serrato-Valenti et al. 1997). Type I had a monocellular stalk and a bicellular head, while type II had a multicellular stalk, a neck cell, and a unicellular head. In the study, the peltate gland and the Type 1 trichome were more ubiquitous across *S. africana*, while Type 11 capitate trichomes were sparsely dispersed (Serrato-Valenti et al. 1997). This morphological feature (hair-like trichomes) is an interesting taxonomical distinguishing feature of different members of the *Salvia* genus (Kamatou 2006).

A histochemical study reported that the role of these multiclassed glandular trichomes is to trap and prevent the loss of *S. africana-lutea* essential oil (Serrato-Valenti et al. 1997). Moreover, the trichome was also implicated in secreting biomacromolecules such as polyphenols, polysaccharides, and other bioactive polypeptides. There is a need for more in-depth

studies on other morphological features of *S. africana-lutea* plants to fill the missing gaps in the body of knowledge.

Traditional uses

Salvia genus has been used in the treatment of different disorders such as sore throats, common cold, flu, night sweats, tuberculosis, menopause (against sweat flushes), and some cancers, and used to cure some heart diseases such as angina pectoris, myocardial infarction in China (Russo et al. 2016, 2018; Fotovvat et al. 2019). This genus has been used as a disinfectant for wounds, as a diuretic, stomach tonic, antiflatulent, and reconstituent, and for the treatment of eye disorders, diarrhea, dyspepsia, fever, rheumatism, excessive menstruation, coughing, pertussis, sinusitis (Moazzami Farida et al. 2016), psoriasis, seborrhoeic eczemas (Jantová et al. 2014), bronchitis, pyretic, rheumatoid arthritis, colds, wounds and skin infections, headache, cerebral ischemia, and memory disorders, including hepatitis (Fotovvat et al. 2019) and malaria, inflammation, loss of memory and disinfecting homes after sickness (Kamatou et al. 2008a, b, c). *Salvia* genus members were also employed to increase women's fertility, ward off evil spirits, and heal snake bites, among other things (Dweck 2000; Bakir et al. 2020).

S. Africana-lutea, also known as beach sage, golden sage, or *S. aurea*, is one of the most important species used by traditional healers. Leaf decoction is generally used to treat coughs, colds, and ailments related to women (Scott et al. 2008; Van Wyk and Gorelik 2017). The first European settlers used *S. africana-lutea* aqueous extracts of the leaves to treat colds, tuberculosis, and chronic bronchitis. Traditional indigenous healers use ethanol extracts (maceration in concentrated ethanol/dry gins) to treat respiratory problems, influenza, gynecological concerns, fever, headaches, and digestive disorders (Watt & Breyer-Brandwijk 1967; Kamatou et al. 2008a, b, c). The whole plants and sometimes the leaves of *S. africana-lutea* are traditionally used as an infusion (maceration in water at room temperature) in South Africa to treat colds, tuberculosis, chronic bronchitis, influenza, gynecological complaints, fever, headaches, and digestive disorders (Kamatou et al. 2010; Arief et al. 2018; Rattray and Van Wyk 2021). Focused information on the traditional uses of *S. africana-lutea* is sparse and still superficial. Therefore, we recommend a detailed ethnopharmacological study of the underexplored plant in different societies in Africa and the world.

Phytochemical constituents of *S. africana-lutea*

Phytochemical investigations on *S. africana-lutea* have shown the presence of different bioactive constituents, as summarized in Table 1. Researchers have isolated and characterized bioactive constituents from the aerial parts of this plant and systematically evaluated them for different pharmacological activities. These constituents include non-volatile and volatile metabolites from essential oils obtained from *S. africana*, analyzed by gas chromatography-mass spectrometry (GC–MS) and gas chromatography with a flame ionization detector (GC–FID) (Bisio et al. 1998a, b). This analysis shows that monoterpenes, diterpenes, triterpenes, and sesquiterpene were the primary active metabolites (Figs. 2, 3, 4 and 5) (Najar et al. 2021). Like other botanical drugs, the bioactive metabolites of *S. africana* varies depending on the part of the plant used, the collection zone, and environmental conditions such as water availability, altitude, and climate (Russo et al. 2013). Hence, future studies may opt to properly report phytochemical/bioactive metabolites from *S. africana* and the variation in their relative abundance. The metabolites isolated from *S. africana* forms valuable resources for designing new drugs and disease treatment (Calderón-Oropeza et al. 2021). The primary metabolites identified from *S. africana* and their class of metabolites are summarized in Table 1.

Pharmacological properties of *S. africana-lutea* extracts and phytochemicals

Most of the available studies on *Salvia africana-lutea* L. have reported some preliminary but interesting pharmacological bioactivities of its extracts and phytochemicals, such as its activities in suppressing inflammation, oxidation, microbial infection, and related disorders. We have discussed each of its biological activities in the following section (Fig. 6).

Suppression of inflammation by *S. africana-lutea* extracts and phytochemicals

S. africana-lutea has been demonstrated to possess phytochemicals that can modulate immune systems response (e.g., suppress the production of inflammatory mediators and suppress mast cells' infiltration) (Maione et al. 2017; Ahmed et al. 2021; Sina Içen et al. 2021). Mast cells play essential roles in the initiation and sustainment of inflammation (Yousef et al. 2020); leukotrienes, one of its granules' contents, contribute to the attraction of eosinophils into the airways where they cause/exacerbate chronic obstructive pulmonary diseases (Lee et al. 2021), while prostaglandins (another granules' content) have been implicated in tumorigenesis (Wang et al. 2021b) other neuropsychiatric and cardiovascular disorders, reviewed in (Famitafreshi and Karimian 2020; Wang et al. 2021a). In mammals, leukotrienes and prostaglandins are biosynthesized from arachidonic acid in a series of reactions initiated by 5-lipoxygenase

Table 1 Main Chemical metabolites isolated from *S. africana-lutea*

Main metabolites	Sources	References
Phenolic metabolites		
*Salvia*nolic acid K	Aqueous Extracts of aerial parts	Afonso et al. (2019)
Rosmadial	Aqueous and Ethanol Extracts of aerial parts	Hussein et al. (2007b), Arief et al. (2018)
Rosmarinic acid	Aqueous and methanol Extracts of aerial parts	Kamatou et al. (2012b); Scott et al. (2019), Afonso et al. 2019; Lim Ah Tock et al. (2020a)
*Salvia*nolic acid B	Aqueous Extracts of aerial parts	Afonso et al. (2019)
2,4-Dimethyl Benzenepropanoic acid	Aqueous Extracts of aerial parts	Afonso et al. (2019)
Quinic Acid	Aqueous Extracts of aerial parts	Afonso et al. (2019)
Danshensu	Aqueous Extracts of aerial parts	Afonso et al. (2019)
Caffeoyl Acid	Aqueous Extracts of aerial parts	Afonso et al. (2019)
Yunnaneic acid E (isomer 1–6)	Aqueous Extracts of aerial parts	Afonso et al. (2019)
Hydroxy-Luteolin-Glucuronide	Aqueous Extracts of aerial parts	Afonso et al. (2019)
Yunnaneic acid F	Aqueous Extracts of aerial parts	Afonso et al. (2019)
Yunnaneic acid D (isomer 1–2)	Aqueous Extracts of aerial parts	Afonso et al. (2019)
Luteolin-7-O-Glucuronide	Aqueous Extracts of aerial parts	Afonso et al. (2019)
Sagerinic acid (isomer 1)	Aqueous Extracts of aerial parts	Afonso et al. (2019)
Api-O-GlcA	Aqueous Extracts of aerial parts	Afonso et al. (2019)
Caffeoyl Rosmarinic acid (isomer 1–3)	Aqueous Extracts of aerial parts	Afonso et al. (2019)
Thymol	Essential oils of aerial parts	De Martino et al. (2010)
Carvacrol	Essential oils of aerial parts	De Martino et al. (2010)
(Z)-Isoeugenol	Essential oils of aerial parts	De Martino et al. (2010)
Diterpenes		
Carnosol	Methanol and ethanol extracts of aerial parts	Arief et al. (2018), Hussein et al. (2007)
Carnosic acid methyl ester	Methanol and ethanol extracts of aerial parts	Hussein et al. (2007b), Arief et al. (2018)
Methyl carnosate	Methanol extract of aerial parts	Lim Ah Tock et al. (2020b)
7-methoxyrosmanol	Methanol extract of aerial parts	Arief et al. (2018)
19-acetoxy-12-methoxycarnosic acid	Methanol extract of aerial parts	Etsassala et al. (2019)
3β-acetoxy-7α-methoxyrosmanol	Methanol extract of aerial parts	Etsassala et al. (2019)
19-acetoxy-7α-methoxyrosmanol	Methanol extract of aerial parts	Etsassala et al. (2019)
19-acetoxy-12-methoxy carnosol	Methanol extract of aerial parts	Etsassala et al. (2019)
Clinopodiolides A and B	Methanol extract of aerial parts	Etsassala et al. (2019)
Triterpenes		
Oleanolic	Methanol extract of aerial parts	Etsassala et al. (2019)
Ursolic acids	Methanol extract of aerial parts	Etsassala et al. (2019)
11,12-dehydroursolic acid lactone	Methanol extract of aerial parts	Etsassala et al. (2019)
β-amyrin	Methanol extract of aerial parts	Etsassala et al. (2019)
Propanoic acid	Methanol extract of aerial parts	Nkomo et al. (2014)
Rythronic acid	Methanol extract of aerial parts	Nkomo et al. (2014)
2- keto-1-gluconic acid	Methanol extract of aerial parts	Nkomo et al. (2014)
1,3-dibromobicyclon	Methanol extract of aerial parts	Nkomo et al. (2014)
Terpinene-4-ol + β-caryophyllene	Essential oils from aerial parts	Lim Ah Tock et al. (2020b)
Ursolic acid	Methanol extract of aerial parts	Arief et al. (2018)
Monoterpene hydrocarbons		
Tricyclene	Essential oils of aerial parts	De Martino et al. (2010)
α-Thujene	Essential oils of aerial parts	De Martino et al. (2010)
Sabinene	Essential oils of aerial parts	De Martino et al. (2010)
β-Pinene	Essential oils of aerial parts	De Martino et al. (2010)
Monoterpenes		
δ-3-Carene	Essential oils of aerial parts	De Martino et al. (2010)
α-Terpinene	Essential oils of aerial parts	De Martino et al. (2010)

Table 1 (continued)

Main metabolites	Sources	References
p-Cymene	Essential oils of aerial parts	De Martino et al. (2010)
Limonene	Essential oils of aerial parts	De Martino et al. (2010)
(Z)-β-Ocimene	Essential oils of aerial parts	De Martino et al. (2010)
γ-Terpinene	Essential oils of aerial parts	De Martino et al. (2010)
Oxygenated monoterpenes		
1,8-Cineole	Essential oils of aerial parts	De Martino et al. (2010)
Cis-Sabinene hydrate	Essential oils of aerial parts	De Martino et al. (2010)
Hydrate	Essential oils of aerial parts	De Martino et al. (2010)
Cis-Thujone	Essential oils of aerial parts	De Martino et al. (2010)
2-Phenyl ethyl alcool	Essential oils of aerial parts	De Martino et al. (2010)
Trans-Thujone	Essential oils of aerial parts	De Martino et al. (2010)
Cis-p -Menth-2-en-1-ol	Essential oils of aerial parts	De Martino et al. (2010)
Camphor	Essential oils of aerial parts	De Martino et al. (2010)
Pinocarvone	Essential oils of aerial parts	De Martino et al. (2010)
Borneol	Essential oils of aerial parts	De Martino et al. (2010)
Terpinen -4-ol	Essential oils of aerial parts	De Martino et al. (2010)
p-Cymen-8-ol	Essential oils of aerial parts	De Martino et al. (2010)
α-Terpineol	Essential oils of aerial parts	De Martino et al. (2010)
Verbenone	Essential oils of aerial parts	De Martino et al. (2010)
Trans-Carveol	Essential oils of aerial parts	De Martino et al. (2010)
Bornyl acetate	Essential oils of aerial parts	De Martino et al. (2010)
Sesquiterpene hydrocarbons		
α-Cubebene	Essential oils of aerial parts	De Martino et al. (2010)
α-Gurjunene	Essential oils of aerial parts	De Martino et al. (2010)
β-Caryophyllene	Essential oils of aerial parts	De Martino et al. (2010)
Aromadendrene	Essential oils of aerial parts	De Martino et al. (2010)
β-Gurjunene	Essential oils of aerial parts	De Martino et al. (2010)
α-Guaiene	Essential oils of aerial parts	De Martino et al. (2010)
α-Humulene	Essential oils of aerial parts	De Martino et al. (2010)
γ-Gurjunene	Essential oils of aerial parts	De Martino et al. (2010)
Germacrene D	Essential oils of aerial parts	De Martino et al. (2010)
Cis-β-Guaiene	Essential oils of aerial parts	De Martino et al. (2010)
Valencene	Essential oils of aerial parts	De Martino et al. (2010)
α-Muurolene	Essential oils of aerial parts	De Martino et al. (2010)
β-Himachalene	Essential oils of aerial parts	De Martino et al. (2010)
γ-Cadinene	Essential oils of aerial parts	De Martino et al. (2010)
Selina-3,7(11)-diene	Essential oils of aerial parts	De Martino et al. (2010)
δ-Cadinene	Essential oils of aerial parts	De Martino et al. (2010)
T-cadinol	Essential oils of aerial parts	Lim Ah Tock et al. (2020)
Oxygenated sesquiterpenes		
Germacrene B	Essential oils of aerial parts	De Martino et al. (2010)
Cubebol	Essential oils of aerial parts	De Martino et al. (2010)
Germacrene D-4-ol	Essential oils of aerial parts	De Martino et al. (2010)
Caryophyllene oxide	Essential oils of aerial parts	De Martino et al. (2010)
Globulol	Essential oils of aerial parts	De Martino et al. (2010)
Viridiflorol	Essential oils of aerial parts	De Martino et al. (2010)
1-epi-Cubenol	Essential oils of aerial parts	De Martino et al. (2010)
τ-Cadinol	Essential oils of aerial parts	De Martino et al. (2010)
α-Eudesmol	Essential oils of aerial parts	De Martino et al. (2010), Lim Ah Tock et al. (2020)
β-eudesmol	Essential oils of aerial parts	(Lim Ah Tock et al. 2021)

Table 1 (continued)

Main metabolites	Sources	References
Flavonoid		
Dihydroxydimethoxyflavone derivative	Essential oils of aerial parts	Lim Ah Tock et al. (2021)

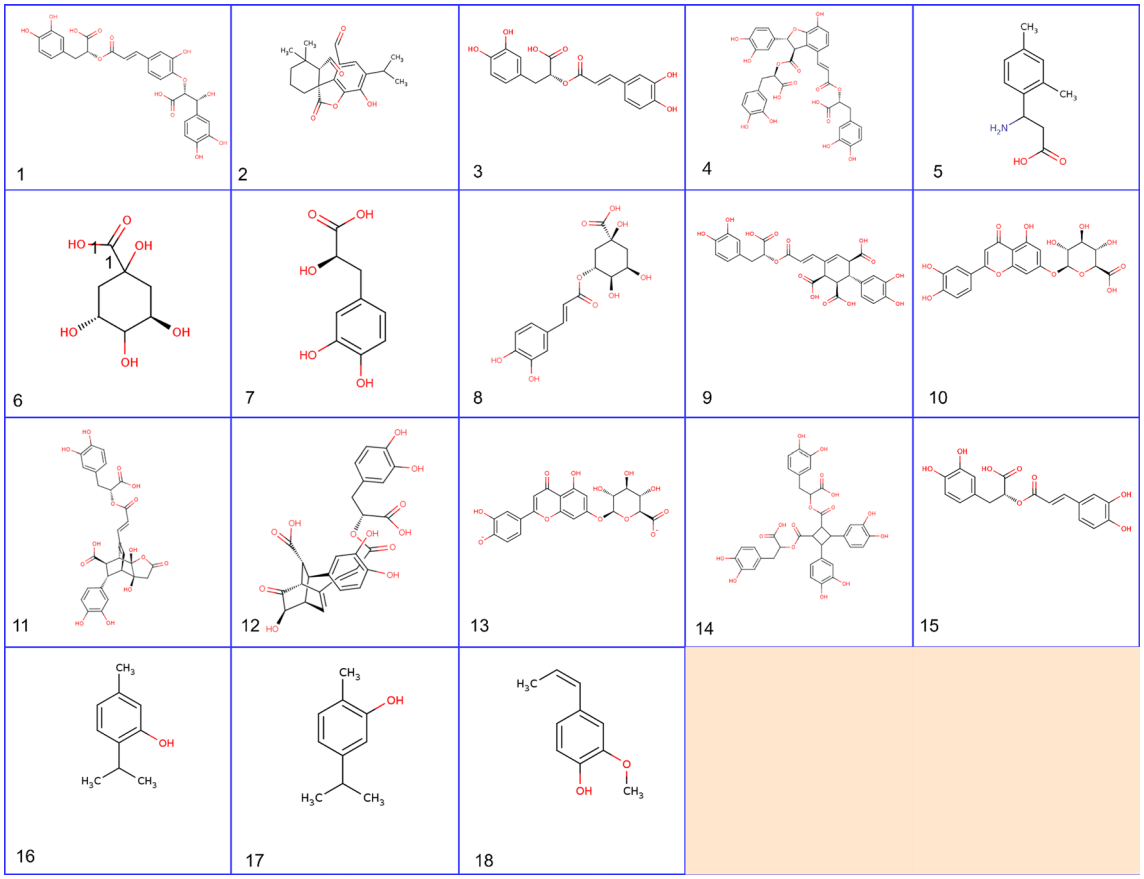

Fig. 2 Phenolics present *in S. africana-lutea*. (1) *Salvia*nolic acid K; (2) Rosmadial; (3) Rosmarinic acid; (4) *Salvia*nolic acid B; (5) 2,4-Dimethyl Benzenepropanoic acid; (6) Quinic Acid; (7) Danshensu; (8) Caffeoyl Acid; (9) Yunnaneic acid E (isomer 1–6); (10) Hydroxy-Luteolin–Glucuronide; (11) Yunnaneic acid F; (12) Yunnaneic acid D (isomer 1–2) (13) Luteolin-7-O-Glucuronide (14) Sagerinic Acid (isomer 1) (15) Caffeoyl Rosmarinic acid (isomer 1–3); (16) Thymol; (17) Carvacrol; (18) (Z)-Isoeugenol;

(5-LO) and cyclooxygenases(COX)-1/COX-2 respectively, reviewed in (Wang et al. 2021a, b; Giménez-Bastida et al. 2021); and inhibiting these key enzymes are the mechanisms of action of many anti-inflammatory agents, including aspirin, ibuprofen, nordihydroguaiaretic acid (NDGA) and zileuton (Famitafreshi and Karimian 2020; Wang et al. 2021a; Altinbas et al. 2021; Drago et al. 2021). Because of some of these drugs (Turpeinen et al. 2021; Bouchette and Preuss 2021), there is a need to discover other and more suitable anti-inflammatory agents, and some constituents of *S. africana-lutea* have potential. Essential oil from *S. africana-lutea* aerial parts inhibited 5-lipoxygenase activity (IC_{50} = 77.3 µg/ml). However, it has very low therapeutic potential as it is very toxic to transformed human kidney epithelial cells (IC_{50} < 7 µg/ml), and its effectiveness at inhibiting 5-lipoxygenase also pales when compared to that of the reference anti-inflammatory drug NDGA (IC_{50} = 5.0 µg/ml) (Kamatou et al. 2006). A similar poor inhibitory effect on 5-lipoxygenase (IC_{50} > 100 µg/ml) by the methanol: chloroform extract of *S. Africana-lutea* aerial parts was also observed by the same research group (Kamatou et al. 2010). Apart from the preliminary anti-inflammatory studies on the plant conducted by Kamatou et al. (2010), there has been limited information on the key bioactivities necessary for some of the most mentioned traditional usage. Other deductions on the anti-inflammatory activities can be

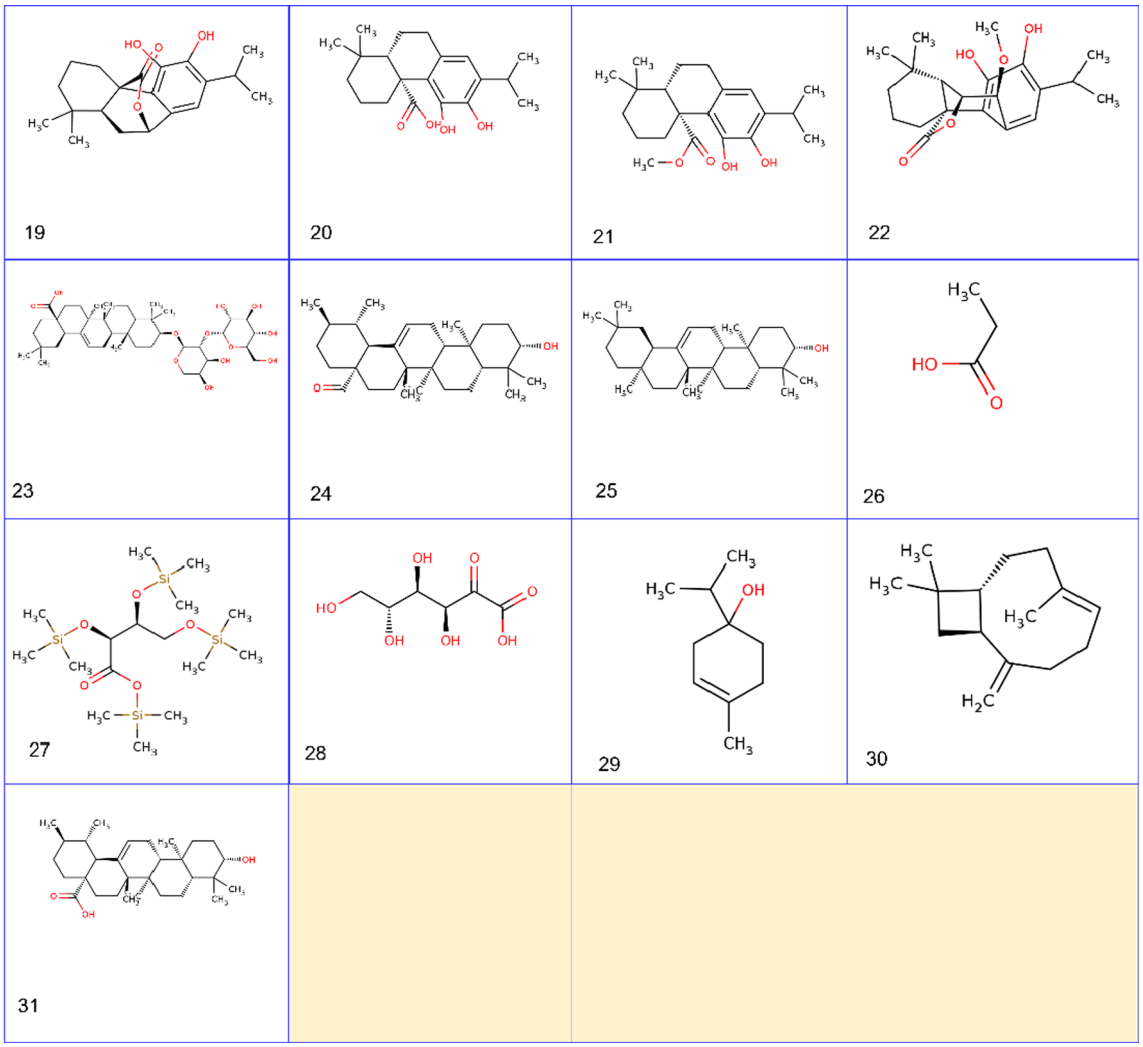

Fig. 3 Di and triterpenes of *S. africana-lutea.* (19) Carnosol; (20) Carnosic acid methyl ester; (21) Methyl carnosate; (22) 7-methoxy-rosmanol; (23) Oleanolic; (24) Ursolic acids; (25) β-amyrin; (26) Propanoic acid; (27) Rythronic acid; (28) 2-keto-1-gluconic acid; (29) Terpinene-4-ol; (30) β-caryophyllene; (31) Ursolic acid

made from a few anti-inflammatory studies on its specific and abundant phytochemicals. For instance, the phytochemical rosmarinic acid methyl ester (syn. methyl rosmarinate) abundant in *S. africana-lutea* (Arief et al. 2018) and some other *Salvia* species (Kamatou et al. 2012a; Sina Içen et al. 2021) showed interesting in-vitro lipoxygenase inhibitory activity (IC_{50} = 0.02 µM = 8.23 µg/mL) that is similar to that of NDGA (IC_{50} = 0.03 µM = 11.62 µg/mL) (Sina Içen et al. 2021).

The enzyme microsomal prostaglandin E synthase-1 (mPGES-1) is involved in the production of prostaglandin E, a pro-inflammatory molecule. Carnosol (CS) and carnosic acid (CA), both present in *S. africana-lutea* (Kamatou et al. 2010; Arief et al. 2018), inhibited mPGES-1 activity in cell-free microsomes (IC_{50} of both = 5 µM) while CA (but not CS) inhibited the lipopolysaccharide-induced formation of PGE_2 in whole blood (IC_{50} = 9.3 µM) (Bauer et al. 2012). The effectiveness of CA is comparable to that of mPGES-1 reference inhibitor MD-52 (3 µM of CA reduced PGE_2 synthesis in whole blood by 35%, while 2 µM of MD-52 inhibited PGE_2 synthesis by 44%). 10 µM indomethacin (reference COX inhibitor), on the other hand, reduced PGE_2 synthesis by 81% (Bauer et al. 2012). In another study, both CA and CS in cell-free assays inhibited the formation of 5-LO products (IC_{50} = 0.8 and 0.3 µM respectively) and also inhibited mPGES-1 activity (IC_{50} = 14.0 and 10.9 µM respectively) (Maione et al. 2017). Rosmarinic acid (RA), a popular *S. africana-lutea* phytochemical (Kamatou et al. 2010; Lim Ah Tock et al. 2021), on the other hand, had a poor inhibitory effect on lipoxygenase (IC_{50} = 0.21 µM = 76 µg/mL), when compared to reference drug NDGA (IC_{50} = 0.03 µM = 11.62 µg/mL) (Sina Içen

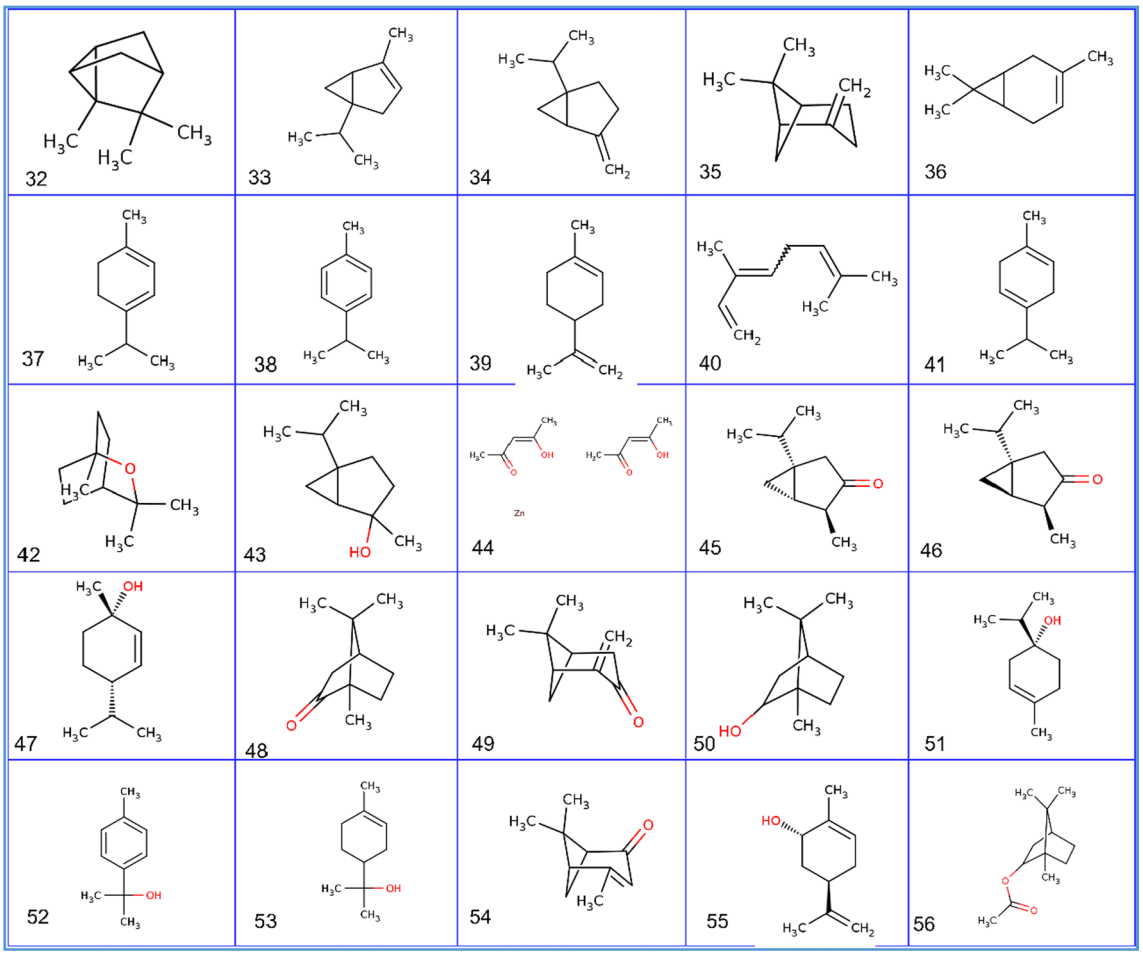

Fig. 4 Monoterpene of *S. africana-lutea*. (32) Tricyclene; (33) α-Thujene; (34) Sabinene; (35) β-Pinene; (36) δ-3-Carene; (37) α-Terpinene; (38) p-Cymene; (39) Limonene; (40) (Z)-β-Ocimene; (41) γ-Terpinene; (42) 1,8-Cineole; (43) Cis-Sabinene hydrate; (44) Hydrate; (45) Cis-Thujone; (46) Trans-Thujone; (47) Cis-p-Menth-2-en-1-ol; (48) Camphor; (49) Pinocarvone; (50) Borneol; (51) Terpinen-4-ol; (52) p-Cymen-8-ol; (53) α-Terpineol; (54) Verbenone; (55) Trans-Carveol; (56) Bornyl acetate

et al. 2021), and was unable to inhibit PGE_2 formation in whole blood (Bauer et al. 2012).

In in-vivo models, however, the anti-inflammatory effects of RA, through different mechanisms, were more pronounced, though not without reservations. Wistar rats treated with rosmarinic acid (RA) showed fewer signs of inflammatory damage when exposed to the toxic pesticide malathion (MA) (Ahmed et al. 2021). RA (50 mg/kg b.w./day) was co-administered by gavage with MA (100 mg/kg b.w./day) for 3 weeks. It resulted in a 90% lower histopathological scoring of the lungs, 83.5% lower mast cell infiltration, 64.4% reduction in survivin expression, and 400% increase in pulmonary surfactant protein D (SP-D) expression in the treated group compared to those that received only MA. Mast cells activation has been implicated in acute lung injuries (Chen et al. 2021); survivin expression level has been positively correlated with acute lung injuries (Ahmed et al. 2019), while SP-D level has been negatively correlated with the number of apoptotic pneumocytes (Du et al. 2018; Cañadas et al. 2020). The ability of RA to suppress mast cell infiltration and survivin level while upregulating SP-D level proves that RA has anti-apoptotic effects and potential that can be harnessed for developing anti-inflammatory agents. However, its effectiveness in the in-vivo study by Ahmed et al. (2021) was not compared to that of any anti-inflammatory drug; and it has been demonstrated that RA, in a different study, decreased the viability of mast cells to 73.5% of the control (Yousef et al. 2020). Thus, the application of RA as an anti-inflammatory agent should be encouraged only after confirming that its suppression of mast cells' viability does not predispose the body to greater danger.

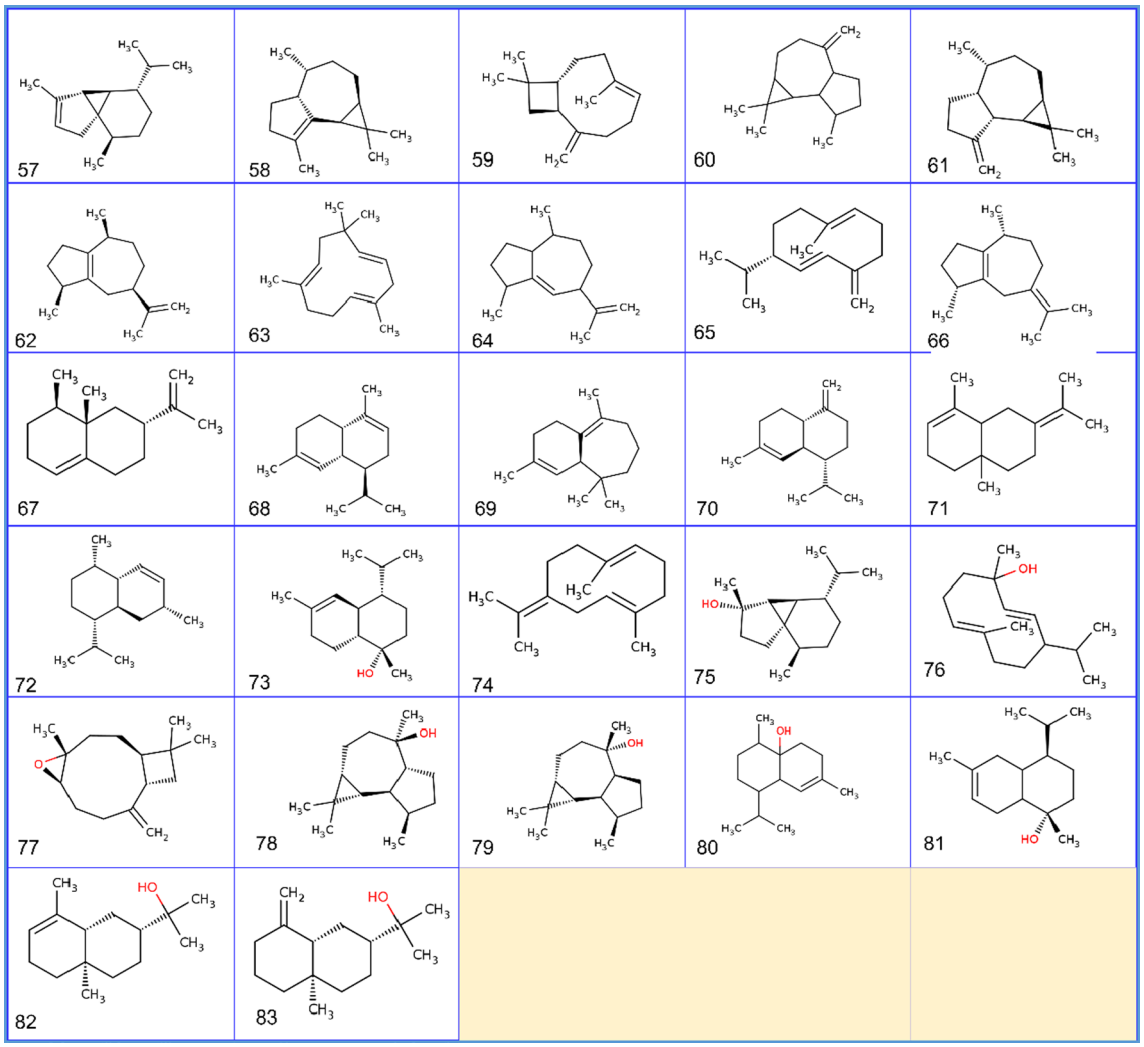

Fig. 5 Sesquiterpene of *S. africana-lutea*. (57) α-Cubebene; (58) α-Gurjunene; (59) β-Caryophyllene; (60) Aromadendrene; (61) β-Gurjunene; (62) α-Guaiene; (63) α-Humulene; (64) γ-Gurjunene; (65) Germacrene D; (66) Cis-β-Guaiene; (67) Valencene; (68) α-Muurolene; (69) β-Himachalene; (70) γ-Cadinene; (71) Selina-3,7(11)-diene; (72) δ-Cadinene; (73) T-cadinol; (74) Germacrene B; (75) Cubebol; (76) Germacrene D-4-ol; (77) Caryophyllene oxide; (78) Globulol; (79) Viridifloro; (80) 1-epi-Cubenol; (81) τ-Cadinol; (82) α-Eudesmol; (83) β-eudesmol

Antioxidant effects of *S. africana-lutea* extracts/phytochemicals and potentials for preventing melanin-related disorders

Salvia africana-lutea L. extracts and phytochemicals have been credited with alleviating oxidative stress by suppressing radicals' production or scavenging already-produced ones. Aqueous extract of *S. africana* aerial parts, through the unstudied mechanism, inhibited lipopolysaccharide-induced nitric oxide production in macrophages (EC_{50} = 47.8 µg/mL). However, it was not as effective as dexamethasone's reference product (EC_{50} = 16.0 µg/mL) (Afonso et al. 2019). The solvent extracts of *S. africana-lutea* also showed good potential to different radicals such as DPPH and ABTS scavenge radicals with IC_{50} or EC_{50} values ranging from 6.6 to 62.0 µg/mL, depending on the assay method (Kamatou et al. 2008c, b, 2010; Afonso et al. 2019), the composition of the extract (with or without the essential oil) (Kamatou et al. 2008b) and the season of plants collection (Kamatou et al. 2008c) (see Table 2). The extracts all displayed significantly lower activity than the positive controls (Kamatou et al. 2008b, 2008c, 2010; Afonso et al. 2019). In some of these studies, the antioxidant activities were accessed only by some checking out in vitro chemical analyses such as DPPH and ABTS radical scavenging activities. For instance, Kamatou et al. (2010) investigated the radical scavenging activities of chlorofoam/methanol extract (1:1) of 16 South African indigenous Salvia species, of which *S. Africana* is inclusive, using the DPPH and ABTS assays. This study merely compared their IC_{50} of the different plant extract, without

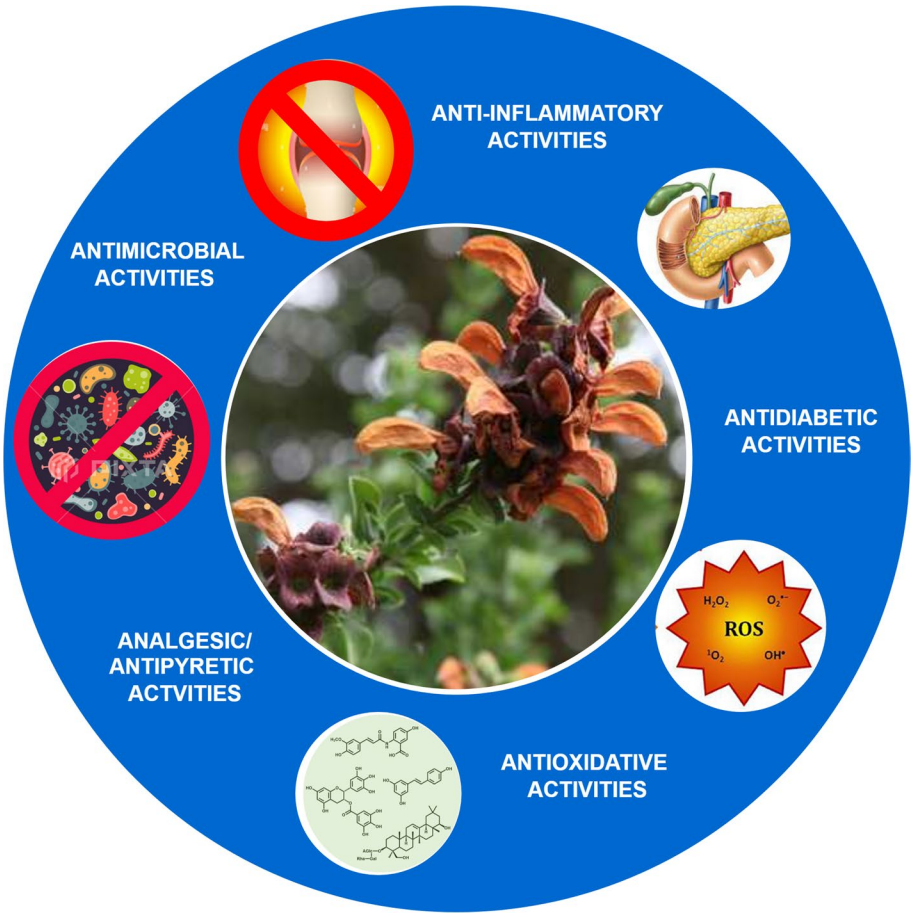

Fig. 6 An overview of some biological activities of *Salvia africana-lutea* L. and its phytoconstituents. A few studies on S. africana-*lutea* and its phytoconstituents show different bioactivities such as antioxidant, anti-inflammatory, antimicrobial, and others

critically evaluating if these activities are of clinical or pharmacological relevance. There have been recent debates on these analyses' insufficiencies in giving reliable and credible evidence on the antioxidant capacity of the plant extracts (de Menezes et al. 2021). However, these analyses could give a possible clue to the antioxidant capacity. There is a need for other in vivo or multiple in vitro analyses to give more robust evidence of an extract's antioxidant capacity, which can be of more pharmacological relevance.

The phytochemicals: 19-acetoxy-12-methoxycarnosic acid, 3β-acetoxy-7α-methoxyrosmanol, and clinopodiolides A isolated from the methanol extract of *S. africana-lutea* aerial parts exhibited high antioxidant activities (2588.2, 2233.9 and 2357.2 µmole TE/g respectively, as determined by Oxygen Radical Absorbance Capacity assay), which were comparable to that (3976.8 µmole TE/g) of epigallocatechin gallate, the reference product (Etsassala et al. 2019).

The antioxidant potentials of *S. africana-lutea* extracts and phytochemicals, however, are not limited to their abilities to scavenge radicals but also extend to their abilities to inhibit oxidizing enzymes, which has good potential for preventing/managing melanin-related disorders. Melanin is a heterogenous light-absorbing polymer containing indoles and other intermediate products of tyrosine oxidation, which plays a role in thermoregulation and protects human skin by absorbing/reflecting UV radiation; and scavenging reactive oxygen species (ROS), toxic drugs, and chemicals (Momtaz et al. 2008; Maranduca et al. 2019; Cao et al. 2021; McNamara et al. 2021). Its formation is radical-dependent and can be facilitated by exposure to UV radiation and iron (Momtaz et al. 2008; Hedges et al. 2020). Hyper-accumulation, especially in specific skin parts, as more pigmented patches (e.g., melasma, freckles, ephelides, etc.) becomes an aesthetic problem (Momtaz et al. 2008). Reducing the production of melanin by melanocytes has found applications in the cosmetics industry for skin-lightening effects, which can be achieved by, among other means, inhibiting the activities of tyrosinase, which catalyzes the hydroxylation of monophenols (L-tyrosine) to O-diphenols (DOPA) and the oxidation of the O-diphenols to O-quinones (DOPA quinone), essential steps in melanin biosynthesis (Momtaz et al. 2008; Ha et al. 2012; Asghari et al. 2019). Also, hyperactivity of tyrosinase has been implicated in Parkinson's disease, a neural disorder whereby the accumulation of neuromelanin, reactive oxygen species (ROS), and other tyrosinase catalyzed- dopamine oxidation products promote aging and death of dopaminergic neurons (Zhang et al. 2019; Maranduca et al. 2019). *S. africana-lutea* extracts and phytochemicals inhibit tyrosinase

Table 2 summary of the antioxidant, anti-inflammatory, anti-diabetic and analgelsic effects of *S. africana-lutea* extracts and phytochemicals

Salvia africana-lutea L. extract or phytochemical	Concentration tested/dose administered	Study model	Treatment duration	Pharmacological effects	References
Rosmarinic acid	50 mg/kg/b.w./day	Wistar rats	3 wks	90% lower histopathological scoring of the lungs, 83.5% lower mast cells infiltration, 64.4% reduction in survivin expression and 400% increase in pulmonary SP-D	Ahmed et al. (2021)
Abietane diterpenes, clinopodiolides and triterpenes isolated from methanol extract of *Salvia africana-lutea* L. aerial parts	n.d	In-vitro study	n.a	ursolic acid inhibited alpha-glucosidase activity (IC_{50} = 11.3 µg/mL), while oleanolic acid inhibited alpha-amylase activity (IC50 = 12.5 µg/mL) 19-acetoxy-12-methoxycarnosic acid, 3β-acetoxy-7α-methoxyrosmanol, and clinopodiolides A exhibited antioxidant activities (2588.2, 2233.9 and 2357.2 µmole TE/g respectively, as determined by ORAC)	Etsassala et al. (2019)
Water extracts of *Salvia africana-lutea* L. leaves	50–400 mg/kg; i.p.)	Male albino mice and male albino rats	15–30 min prophylaxis	200 and 400 mg/kg of extract reduced acetic acid-induced writhing by 61.45 and 58% respectively, compared to those that received only acetic acid At 55 °C: 15 and 30 min prophylaxis with 200 mg/kg increased time to pain threshold by 84.1 and 91.7% respectively; while 400 mg/kg increased that by 99.1 and 100% respectively. 15 min prophylaxis with 100, 200 and 400 mg/kg reduced LP-induced temperature increases by 1.75, 2.31 and 2.08 ºC respectively	Amabeoku et al. (2001)
methanol:chloroform extract of *Salvia africana-lutea* L. aerial parts	n.d	In-vitro study	n.a	Displayed antioxidant capacity (IC_{50} = 30.4 and 47.6 µg/ml by ABTS and DPPH assays respectively)	Kamatou et al. (2010)
Essential oil from *Salvia africana-lutea* L. aerial parts	n.d	Transformed human kidney epithelium cells for toxicity study	n.a	Inhibited 5-lipoxygenase (IC_{50} = 77.3 µg/ml) Toxic to kidney epithelial cells (IC_{50} < 7 µg/ml)	Kamatou et al. (2006)

Table 2 (continued)

Salvia africana-lutea L. extract or phytochemical	Concentration tested/dose administered	Study model	Treatment duration	Pharmacological effects	References
Methanol extract of *Salvia africana-lutea* L. aerial parts	500 µg/ml	In-vitro study	n.a	500 µg/ml inhibited tyrosinase by 48% and DOPA auto-oxidation by 36%	Momtaz et al. (2008)
Abietane diterpenes and triterpenes isolated from methanol extract of *Salvia africana-lutea* L. aerial parts	100 µg/mL for glucose uptake assay and 250 µg/mL for cytotoxicity assay	embryonic kidney (HEK293) cells	n.a	19-acetoxy-12-methoxycarnosic acid, clinopodiolides B and ursolic acid increased glucose uptake by 62.5, 55 and 45% respectively	Etsassala et al. (2020)
Aqeous extract of *Salvia africana* aerial parts	0.002– 0.625 mg/mL for antioxidant tests 25—100 µg/mL for NO production	RAW 264.7 macrophages	1 h prophylaxis before LP stimulation	High anti oxidant activity (EC_{50} = 6.6, 21.2 and 21.0 µg/mL in DPPH, Ferric reducing power and TBARS inhibition assays Inhibited LP-induced NO production in macrophages (EC_{50} = 47.8 µg/mL)	Afonso et al. (2019)
methanol:chloroform extract of *Salvia africana-lutea* L. aerial parts	n.d	In-vitro study	n.a	High anti oxidant activity by DPPH assay. IC_{50} ranged from 10.1 to 33.4 µg/ml depending on period of plants collection harvest	Kamatou et al. (2008c)
methanol:chloroform extract of *Salvia africana-lutea* L	n.d	In-vitro study	n.a	The extract (without the EO) has higher antioxidant activity (IC_{50} = 32.9 µg/ml) than with the EO (IC_{50} = 62.0 µg/ml) by DPPH assay	Kamatou et al. (2008b)

TE trolox equivalents; *ORAC* oxygen radical absorbance capacity; *LP* lipopolysaccharide; *ABTS* 2,20-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid); *DPPH* 2,2-diphenyl-1-picrylhydrazyl; *TBARS* thiobarbituric acid reactive substances; *EO* essential oil; *DOPA* 3,4-dihydroxyphenylalanine; *n.d* not defined; *n.a* not applicable

activity, and some have the potential for therapeutic applications. Methanol extract of *S. africana-lutea* aerial parts at 500 µg/ml in an in-vitro study inhibited tyrosinase activity by 48% and DOPA auto-oxidation by 36% (Momtaz et al. 2008). Its activity was, however significantly less than that of the reference products arbutin (tyrosinase IC_{50} = 149 µg/ml) and kojic acid (tyrosinase IC_{50} = 2.145 µg/ml and DOPA IC_{50} = 26.66 µg/ml). In a study that measured the ability of RA and methyl rosmarinate to inhibit tyrosinase oxidation of L-DOPA, 0.4 mM each of RA and methyl rosmarinate reduced activity by 19.8 and 37.1%, respectively (Lin et al. 2011). In another study, RA inhibited L-DOPA oxidation with an IC_{50} value of 6.67 µM (Zuo et al. 2018), which is close to the reported IC_{50} value of 4.0 µM, when RA was used as a substrate for tyrosinase reaction (Ha et al. 2012). In the above studies, the inhibitory effects of the phytochemicals were not compared to those of any reference antioxidant agents. In an earlier study that used L-tyrosine as the substrate, RA and methyl rosmarinate inhibited tyrosinase oxidation of L-tyrosine with IC_{50} values of 16.8 and 21.5 µM, respectively, which were similar to or marginally better than the activity of reference tyrosinase inhibitor kojic acid (IC_{50} = 22.4 µM) (Kang et al. 2004). We thus suggest that these two phytochemicals should be considered for therapeutic applications. We could also see that the reported IC_{50} values from different researchers varied widely (e.g., 4.0 µM to 16.8 µM for RA). This may be due to the differences in the choice of substrates.

Anti-diabetic effects of *S. africana-lutea* extracts and phytochemicals

Diabetes, a disease characterized by chronic blood hyperglycemia due to inefficiencies in insulin production and/or utilization (Ezeorba et al. 2022), accounts for about 1.5 million deaths annually; is currently affecting about 422 million individuals (World Health Organization 2021) and is expected to affect about 700 million individuals by the year 2045 (Kaur et al. 2021). During type 2 diabetes, caused by insulin resistance, the body cannot use glucose as a source of energy. Hyperglycemia predisposes the body to stroke (Hill 2014), heart failure (Tochiya et al. 2020), obesity (Bentley et al. 2020), foot ulcers (Awasthi et al. 2020), diabetic retinopathy (Antonetti et al. 2021), diabetic nephropathy (Cheng et al. 2020), diabetic neuropathy (Jensen et al. 2021), etc. Reducing postprandial blood glucose levels and increasing glucose uptake into muscle, adipose, or liver cells reduces complications of type 2 diabetes (Etsassala et al. 2019, 2020). Ursolic and oleanolic acids isolated from methanol extract of *S. africana-lutea* aerial parts respectively inhibited alpha-glucosidase (IC_{50} = 11.3 µg/mL) and alpha-amylase (IC_{50} = 12.5 µg/mL) activities (Etsassala et al. 2019). They were non-toxic to human cells even at 250 µg/mL (Etsassala et al. 2020). Their enzymes' inhibitory effects were comparable to or even better than that of the reference agent, acarbose (alpha-glucosidase IC_{50} = 610.4 µg/mL; alpha-amylase IC_{50} = 10.2 µg/mL), highlighting their potential as anti-diabetic agents. Alpha-amylase breaks down complex polysaccharides to produce oligosaccharides and disaccharides, which are further hydrolyzed by alpha-glucosidase to absorb monomeric units (Etsassala et al. 2019; Zhang et al. 2020). These enzymes are unique targets for the prevention and treatment of type 2 diabetes (Zhang et al. 2020; Kaur et al. 2021), and by inhibiting them, the phytochemicals of *S. africana-lutea* delay carbohydrates absorption and reduce postprandial blood glucose levels. In another study, 100 µg/mL of 19-acetoxy-12-methoxycarnosic acid, clinopodiolides B, and ursolic acid, also isolated from methanol extract of *S. africana-lutea* aerial parts, increased glucose uptake into mammalian cells (thereby reducing insulin resistance) by 62.5, 55 and 45% respectively, compared to untreated cells (Etsassala et al. 2020). 19-acetoxy-12-methoxycarnosic acid and clinopodiolides B, however, had lower therapeutic potentials when compared to ursolic acid as they, unlike ursolic acid, reduced the viability of human embryonic kidney (HEK293) cells by 62 and 48% respectively at 250 µg/mL, compared to untreated cells (Etsassala et al. 2020). The toxicity of 19-acetoxy-12-methoxycarnosic acid and clinopodiolides B do not adversely limit their potential since their maximum tested concentration that increased glucose uptake (100 µg/mL) is still significantly lower than the tested toxic dose of 250 µg/mL. However, the glucose uptake efficiencies of these phytochemicals were not compared to any referenced product.

Analgesic/anti-nociceptive and antipyretic effects of *S. africana-lutea* extracts and phytochemicals

Pain is a distressing sensory or emotional occurrence correlating to existing or potential tissue damage (Raja et al. 2020). It can be physiological (nociceptive and/or inflammatory) or pathological (neuropathic and central nervous system dysfunctional) pain (Fong and Schug 2014). Nociceptive and inflammatory pains are protective and adaptive, encouraging withdrawal from noxious mechanical, thermal and chemical stimuli or protecting damaged but healing body tissues (Gangadharan and Kuner 2013; Fong and Schug 2014; Baral et al. 2019; Liu et al. 2021). Pathological pain, on the other hand, is chronic, non-protective, and maladaptive, serving as a life-impacting symptom of a disease or nervous system damage (Gangadharan and Kuner 2013; De Goeij et al. 2013; Fong and Schug 2014; Baral et al. 2019; Liu et al. 2021). Prostaglandins have been implicated in lowering the firing threshold of sensory neurons, promoting hyperexcitability, and increasing the number of action potentials generated by a stimulus (Jang et al. 2020; Liu

et al. 2021; Kwon et al. 2021). This is probably by increasing the expression of Nav1.7 (Zhang and Gan 2017), the master Na^+ channels, which relay nociceptive signals to the central nervous system (Gangadharan and Kuner 2013), making usually painless stimuli painful. The deletion of mPGES-1 has been associated with an increase in pain threshold (Jang et al. 2020). Thus, reducing the levels of prostaglandins will be a good analgesic strategy, and it will help in ameliorating the conditions of many patients in a study that measured the frequency of intraperitoneally-injected acetic acid-induced writhing in mice (Amabeoku et al. 2001), 15 min of prophylactic intraperitoneal (i.p). Injection with 200 and 400 mg/kg water extracts of *S. africana-lutea* leaves reduced the writhing frequency by 61.45 and 58%, respectively, compared to those that received only acetic acid. Paracetamol, the reference product, was more effective at reducing the number of writhes (96.7% compared to those that received only acetic acid). At 55 °C, 15 and 30 min i.p. prophylaxis with 200 mg/kg extracts, in the same study, increased the time to thermally induced pain threshold by 84.1 and 91.7%, respectively; while 400 mg/kg increased that by 99.1 and 100% respectively, compared to those treated i.p. with normal saline. This was unlike paracetamol (300–500 mg/kg, i.p.) which did not affect thermally induced pain. 15 min of prophylaxis with 100, 200, and 400 mg/kg reduced lipopolysaccharide-induced temperature increases by 1.75, 2.31, and 2.08 °C, respectively, unlike 500 mg/kg (i.p) paracetamol that did not affect lipopolysaccharide-induced fever. However, the above-described studyr, did not study the mechanism through which the extracts exerted their effects. In another study, by inhibiting the formation of 5-LO products by CA and CS (IC_{50} = 0.8 and 0.3 µM respectively) and also by inhibiting mPGES-1 activity (IC_{50} = 14.0 and 10.9 µM respectively), 100 g/l subcutaneously (s.c)-injected CA and CS were able to reduce 50 µl 1% s.c. Carrageenan-induced hyperalgesia in mice by 43.7 and 47%, respectively, compared to mice treated with only the vehicle (50 µl saline s.c.) (Maione et al. 2017). These indicate that *S. africana-lutea* extracts and phytochemicals have potentials that may be exploited for the development of analgesics.

Antimicrobial and anti-parasitic activities of *S. Africana-lutea*

Microbes are double-edged, as they can benefit humans and could become a source of severe trouble and health challenges (Weiman and Fox 2015). Pathogenic microbial groups represent all disease-causing bacteria, fungi, and parasitic protozoans known to cause physiological or metabolic distortion to the normal state of the human body (Najar et al. 2021). The battle for survival between these pathogenic organisms and humans has existed for many decades. Humans have constantly searched for effective antimicrobial (antibacterial, antifungal, anti-protozoan, or anti-parasitic) agents. In contrast, pathogens constantly evolve new mechanisms to resist these agents (Imperial and Ibana 2016). Plants have been reported as a reservoir for interesting metabolites and phytochemicals, which have proven effective antimicrobials (Savoia 2012). Traditionally, these metabolites and phytochemicals are enriched in different plant parts and are concentrated by different extraction solvents (yielding crude extract). Moreover, scientific advances have led to the development of protocols for the selective enrichment or purification of a single plant metabolite with known antimicrobial functions (Atanasov et al. 2015, 2021). *Salvia* species is one of those few plant genera showing interesting antimicrobial activities (Sharifi-Rad et al. 2018; Shirinda et al. 2019; Zaccardelli et al. 2020; Ezema et al. 2022). From our literature search, more than 1000 recent studies have focused on characterizing the antimicrobial activities as well as other bioactivities of different *Salvia* species. In contrast, only a few (about five articles) have focused on the indigenous African species—*S. Africana-lutea* (Table 3). The section extensively reviewed all the studies on the antimicrobial activities of *S. africana* to project its potential for exciting bioactivities to the global scientific community and draw attention to the need for more studies on this African indigenous *Salvia sp.* to harness other unraveled benefits fully.

Antibacterial activities

A few studies on *S. Africana-lutea* have shown its antibacterial potencies on pathogenic strains (Table 3). A recent study by Afonso et al. (2019) reported that 100 µL aqueous extract of *S. africana-lutea* at 1:400 dilution caused significant inhibition of *S. aureus* and *S. epidermis*. The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) were estimated to be 0.63 and 1.25, respectively (Afonso et al. 2019). Recently, Dube et al. (2020) reported improved antibacterial activities against *Staphylococcus epidermidis* and *Pseudomonas aeruginosa* when the aqueous extract of *S. africana* was delivered with silver nanoparticles (MIC: 0.1875 mg/ml and 0.375 mg/ml, respectively) (Dube et al. 2020).

In another study, the methanol extract of the whole *S. africana* plant (comprising its leaves, stems, and flowers) was reported to cause inhibition of the growth of pathogenic bacteria, *Escherichia coli*, and *Staphylococcus aureus,* as well as the fungi, *Microsporum audouinii,* all having a minimum inhibitory concentration (MIC) of 39.06 µg/ml (Nielsen et al. 2012). An extract or bioactive molecule is an effective antimicrobial agent if the MIC falls below 1 mg/mL or 1000 µg/ml. Judging from this standard, the antibacterial and antifungal activities reported by Nielsen et al. (2012), extract of *S. africana-lutea* are effective antibiotics. They

Table 3 Antimicrobial activities of *S. Africana-lutea*

Biological activities	Organisms	Plant preparation (Extract/Fraction or characterized metabolite)	Cell culture/media/study model	Assay	Dose and treatment time	Activities (IC50/EC50/MIC)	References
Antibacterial	*Staphylococcus epidermidis* and *P. aeruginosa*	Aqueous extract of SAL delivered with biogenic Ag Nanoparticles	Microtitre plate methods	MIC	1.5 to 0.012 mg ml^{-1} for 24 h. at 37 °C	*S. epidermidis*—0.1875 mg ml^{-1} *P. aeruginosa*—0.375 mg ml^{-1}	Dube et al. /92020)
Antibacterial	S. aureus and S. epidermis	Aqueous extract of SAL	Microdilution method	MIC and MBC	100 µL serially diluted 4 times, incubated for 24 h and 37 oC	MIC—0.63—1.25 mg/mL MBC—1.25 mg/mL	Afonso et al. (2019)
Antibacterial	(1) Brevibacillus agri (2) B. epidermidis (3) B. *linens*	Essential oil of SAL extracted through hydro distillation	Micro dilution method	MIC	100 µL of 1:100 dilution of essential oil	(1) 0.13 (2) 0.50 (3) 1.00	Kamatou et al. (2006)
Antibacterial	*E. coli* *S. aureus*	Methanol extract of SAL	Micro-broth dilution	MIC	19.53 to 2500 µg/ml at 37 oC for 24 h	39.06 µg/ml	Nielsen et al. (2012)
Antibacterial	*Mycobacterium smegmatis biofilm*	Ethanolic extracts of SAL	microplate Alamar Blue assay & Microbial infection of U937 human macrophage cells	Cytotoxic effect and MIC via ADTNB-coupled Glutathione/ Mycothiol disulfide reductase assay	3.12–400 µg/ml for 72 h	MIC—31.25 µg/ml EC_{50} Biofilm inhibition—95.8 µg/ml	Oosthuizen et al. (2019)
Antibacterial	*Mycobacterium tuberculosis*	Metabolites isolated from Ethanolic extracts of SAL (a derivative of carnosic acid)	Rapid radiometric method	MIC and cytotoxicity on MCF-7	0.004 and 0.006 mg/mL	MIC—28 µM	Hussein et al. (2007)
Antifungal	*Microsporum audouinii*	Methanol extract of SAL	Micro-broth dilution	MIC	19.53 to 2500 µg/ml at 37 oC for 24 h	39.06 µg/ml	Nielsen et al. (2012)
Antifungal	(1) Fusarium verticillioides (2) Fusarium proliferatum	DCM: methanol (1:1; v/v) extract of SAL	Microdilution method (Microtitre assay)	MIC	1–0.002 mg/ml	(1) 0.031 mg/ml (2) 0.063 mg/ml	Nkomo et al. (2014)

MIC minimum inhibitory concentration, *MBC* Minimum bactericidal concentration, *SAL Salvia africana-lutea* L

can be developed for treating and managing debilitating conditions caused by those microbial agents.

The essential oil of *Salvia Africana* L. was recently extracted through hydro-distillation and characterized using gas chromatography coupled with Mass Spectrometry (Kamatou et al. 2006). The abundance of the constituents of the essential oils, as well as the antimicrobial activities, was reported. An aliquot of 100 µL of 1:100 dilution of essential oil showed enjoyable inhibitory activities against spore-forming gram-positive bacteria (*Brevibacillus* sp.), which are frequently implicated in the foot odor disorder (bromodosis) (Kamatou et al. 2006). The MIC result for *B. agri, B. epidermi*s, and *B. linens* was reported to be 0.13, 0.50, and 1.00 mg/mL, respectively, showing the efficacy of S. *africana* essential oil-rich fraction in managing the foot odor disorder (Kamatou et al. 2006).

Finally, it was recently shown that the ethanolic extract of *S. africana-lutea* was potent against *mycobacterium sp.* for managing tuberculosis (Oosthuizen et al. 2019). Tuberculosis is ranked as the second leading source of death globally due to the invasiveness of its causative agent. *S. africana-lutea* was among the three plants screened out to possess significant anti-mycobacterium activities. The study reported that *S. africana-lutea* ethanolic extract gave a minimal inhibitory concentration (MIC) of 31.25 µg/ml against *Mycobacterium smegmatis* from a "microplate Alamar Blue assay" and EC_{50} of 95.8 µg/ml against the initiation of biofilm (Oosthuizen et al. 2019). An older study isolated and characterized a derivative of carnosic acid from the ethanoic extract of *S. africana-lutea*, which showed a MIC of 28 µM against *Mycobacterium tuberculosis* using the rapid radiometric method (Hussein et al. 2007). Both studies showing anti-mycobacterium activities also showed cytotoxic, apoptotic, and anticancer activities against human breast cancer (MCF-7) and U937 human macrophage cell lines (Hussein et al. 2007; Oosthuizen et al. 2019). Details report of the anticancer activities of *S. africana-lutea* and other *Salvia* sp. was recently reported in a review by Ezema et al. (2022).

Antifungal activities

There are only a few studies on the antifungal activities of *S. africana-lutea*. As aforementioned, Nielsen et al. (2012) studies reported a potent inhibition of *Microsporum audouinii* by the methanol extract of S. *africana*. Using the micro broth dilution method over a test concentration of 19.53 to 2500 µg/ml, an MIC of 39.06 µg/ml was obtained (Nielsen et al. 2012). Another study by (Nkomo et al. 2014) reported that Dichloromethane: methanol (1:1; v/v) extract of *S. africana lutea* at a test concentration between 0.002 and 1 mg/ml showed antifungal activities against *Fusarium verticillioides* and *Fusarium proliferatum* at a minimum inhibitory concentration of 0.031 mg/ml and 0.063 mg/ml respectively (Nkomo et al. 2014). These two studies have shown the promising antifungal activities of *S. africana-lutea*. Ever since the last study in 2014; there have been no other reports on the antifungal activities of S. *africana*. Hence, future studies could further investigate the inhibitory effects of different solvent extracts or purified phytochemicals of S. *africana* on other pathogenic fungal strains.

Prospects for anti-parasitic activities and future studies

Despite the global awareness of the health, nutritional and therapeutic benefits of *S. africana-lutea*, no studies have investigated the anti-parasitic activities of *S. africana.* Moreover, a number of studies have shown the efficacies of other varieties of *Salvia Sp.* to inhibit many parasites and protozoan, including *Trypanosoma* sp., *Schistosoma* sp., *Leishmania* sp., *Plasmodium* sp., and others (Akkawi et al. 2012; Amirmohammadi et al. 2014; Tariq et al. 2016; Montesino and Schmidt 2018; Tabefam et al. 2018). Therefore, studies need to investigate the efficacies of the *S. africana-lutea* strain on parasites and protozoans, especially against Plasmodium *sp.,* causing malaria infection, which is predominant in Africa.

Going a step further, studies should also be directed toward investigating the potential of this Africa-indigenous *Salvia sp.* on ameliorating or curbing the increase of antibiotic resistance microbial strains and superbugs causing the rise in microbial infection mortality rate. Similarly, modern analytical and computation tools could be applied to purify and characterize the bioactive component from *S. africana* responsible for its exciting bioactivities.

Conclusion and prospect for future research

Salvia africana-lutea L. is an indigenous African member of the *Salvia* genus, which has been poorly explored research-wise. We have reviewed all studies published on the plants with the most focus on their ethnobotanical features, phytochemical composition, and pharmacological activities. There is a need for more research focus to be redirected towards this plant species for better characterization of its bioactive metabolites for medicinal purposes and drug discovery.

Scientific literatures on the traditional usage of the plant are superfluous. More detailed ethnopharmacological reports are needed in the future on the usage of the different parts of the plants (their preparation and concentration) for alleviating health challenges by different societies of the world. More so, despite pieces of information about the plant's edible nature, there are sno astute scientific studies detailing the nutraceutical application of the plants, although this may be closely related to their pharmacological application. It is also worth mentioning that there are

no studies on bioavailability and toxicity. This is another future research that needs a more holistic understanding of the plant's true pharmacological bioactivities.

It is also surprising that despite the antimicrobial activities as well as cytotoxic activities of the plant, there have not been any studies to investigate the anti-COVID potential of the plant since the onset of the last pandemic. In silico and in vitro approaches can be adopted for future investigation of the potencies of *S. Africana-lutea* against Coronaviruses (COVID-19).

More so, future studies could investigate more into the potencies of green synthesized nanoparticle from the *S. africana-lutea*, as plant-derived nano-materials promises a lot in modern medicinal research. One available study by Dube et al. (2020) reported improved antibacterial activities against *Staphylococcus epidermidis* and *P. aeruginosa* of silver and gold biogenic nanoparticles from *S. africana-lutea*. Future research can investigate other biological activities, such as these plant-derived nanoparticles' cytotoxic, apoptotic, and anticancer activities.

Although reports from 2005 classified *S. africana-lutea* as a Least Concern, based on conservation status analysis, these may change as information on the biological potency broadens with more intense research. Going forward, there is a need for improved cultivation strategies for the plant to prevent its extinction. An old study by Makunga and Van Staden (2008) documented an in vitro cultivation *of S. africana-lutea* to produce clonal plantlets for more efficient propagation. More research efforts can be directed towards developing improved cultivation strategies as well as understanding its quantitative trait loci and genomics composition for improved breeding.

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Conflict of interest Chinonso Anthony Ezema has no conflict of interest. Rita Ngozi Aguchem has no conflict of interest. Emmanuel Chigozie Aham has no conflict of interest. Wisdom Favour Chinedu Ezeorba has no conflict of interest. Innocent Uzochukwu Okagu has no conflict of interest. Timothy Prince Chidike Ezeorba has no conflict of interest.

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