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Bridging ethnobotany and neuro-pharmacology: exploring South Africa's indigenous plants for brain health

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South Africa's extensive floral biodiversity and ethnobotanical history represent a vast, underexplored resource for neurology, with over 300 species traditionally used for CNS ailments like epilepsy, anxiety, and cognitive decline. This paper advocates for a multi-targeted therapeutic strategy as an essential alternative to the insufficient "one drug, one target" conventional approach, given that complex neurological disorders are multifactorial, involving issues like neurotransmitter imbalance, neuroinflammation, and oxidative stress. Plant extracts, rich in bioactive compounds (alkaloids, flavonoids, phenols, and terpenoids), are uniquely suited for this approach, exemplified by *Sceletium tortuosum* alkaloids acting as serotonin reuptake inhibitors (SRIs) and *Boophone disticha* alkaloids showing acetylcholinesterase (AChE) inhibitory activity, with other species like *Sutherlandia frutescens* alleviating mitochondrial dysfunction. However, scientific translation is significantly impeded by a pervasive lack of human clinical trials (RCTs), considerable chemical variability in traditional remedies, and critical ethical and ecological challenges surrounding bioprospecting. To bridge this gap, future efforts must prioritize rigorous clinical validation, implement stringent Standardization and Quality Control (QC) using advanced analytical techniques, and strictly adhere to Access and Benefit-Sharing (ABS) principles to ensure sustainable and equitable commercial development.

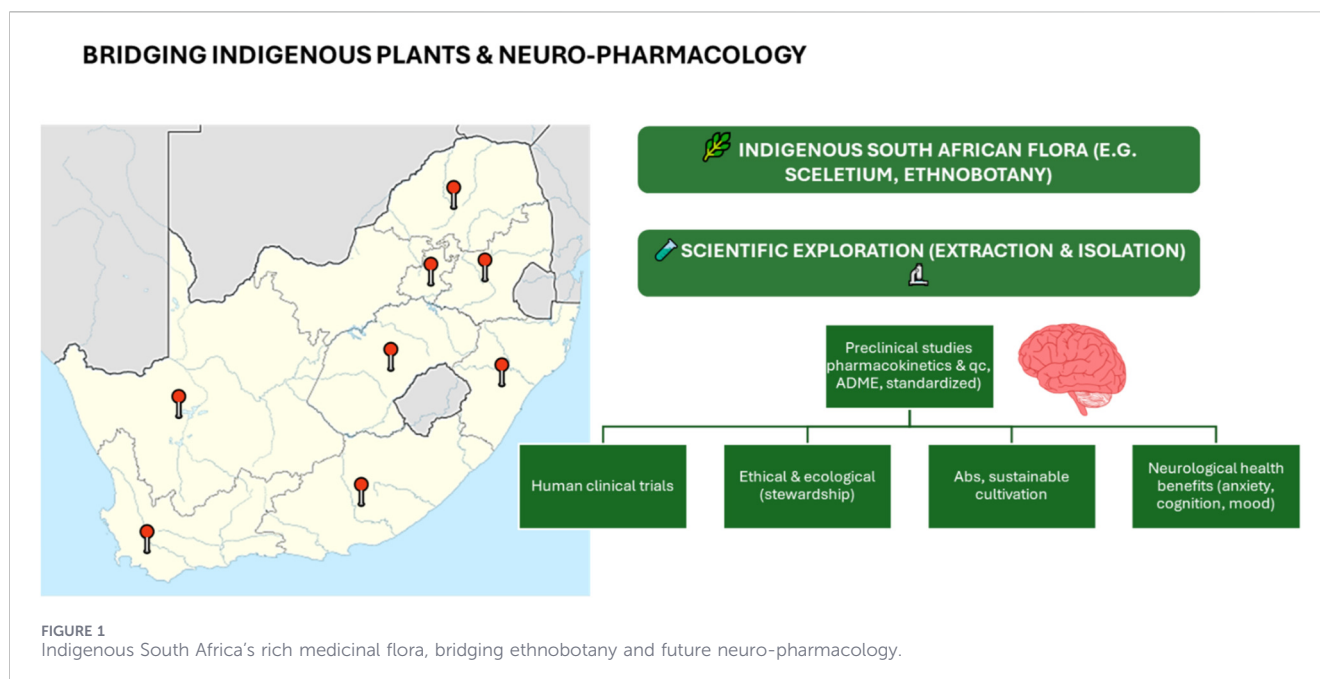
KEYWORDS

alkaloids, clinical validation, ethnobotany, multi-targeted therapy, neuro-pharmacology

1 Introduction

The rich floral biodiversity of South Africa, coupled with its profound history of indigenous medicine, presents an invaluable but underexplored resource for drug discovery in the field of neurology. Traditional South African healers have long employed plant remedies to address a spectrum of prevalent central nervous system (CNS) ailments, including epilepsy, anxiety, depression, and age-related cognitive decline (Stafford et al., 2008). While this ethnobotanical tradition is extensive, only a small fraction of the reported 300+ species with CNS effects have been subjected to rigorous scientific investigation, highlighting a critical gap between traditional knowledge and validated clinical application (Stafford et al., 2008; Sobiecki, 2002).

The imperative for scientific validation is further highlighted by a paradigm shift in neuropharmacology. Conventional "one drug, one target" strategies often fall short, as complex neurological and neuropsychiatric disorders are now recognized as multifactorial,



involving interconnected pathways such as neurotransmitter imbalance, chronic neuroinflammation, and oxidative stress (González et al., 2019; Raji et al., 2025). This necessitates a multi-targeted therapeutic approach.

Critically, the failure of many single-target synthetic compounds in late-stage clinical trials for complex neurodegenerative diseases stems from their inability to simultaneously address the multiple underlying pathological cascades. This limitation has propelled researchers to revisit nature's inherent combinatorial chemistry. Plant extracts, with their intrinsic cocktail of diverse bioactive compounds (including alkaloids, flavonoids, and terpenoids), are uniquely positioned to offer this superior multi-targeted strategy (Tan et al., 2022), enabling them to modulate several pathological hubs simultaneously for a more holistic and robust therapeutic effect.

Plant extracts, with their inherent cocktail of bioactive compounds, are uniquely positioned to offer this multi-targeted strategy (Tan et al., 2022). They can simultaneously modulate several pathological hubs, providing a more holistic and robust therapeutic effect than single-molecule synthetic drugs. This mini-review critically appraises the potential of South African flora to serve as multi-targeted neuro-therapeutics, focusing on two scientifically promising alkaloid classes that validate traditional use. For example, alkaloids were found in plants like *Sceletium tortuosum*, these alkaloids function as serotonin reuptake inhibitors (SRIs), a mechanism directly relevant to depression and anxiety (Coetzee et al., 2016). And amaryllidaceae alkaloids was isolated from species like *Boophone disticha*, these compounds exhibit potent acetylcholinesterase (AChE) inhibitory activity, providing a direct rationale for treating cognitive decline and neurodegeneration. By examining these specific compounds and their multifaceted mechanisms, this review aims to provide a scientifically grounded perspective on the future direction of neuro-herbalism in South Africa (Figure 1). In this review, ethnobotanical knowledge is treated as a hypothesis-generating framework that informs species selection,

traditional indication mapping, and interpretation of neuropharmacological mechanisms. Rather than listing traditional uses, we analyze how indigenous diagnostic categories, preparation methods, and cultural contexts of use align with experimentally validated neuroactive effects.

2 Ethnobotanical frameworks for CNS disorders in South Africa

The conceptualization of central nervous system (CNS) disorders within South African indigenous knowledge systems (IKS) departs significantly from the Cartesian dualism inherent in Western biomedicine, which traditionally bisects the "mind" from the "body." Instead, the South African indigenous medical paradigm is constructed upon a holistic architecture that recognizes the inextricable link between biological, psychosocial, and ancestral-spiritual dimensions (Sobiecki, 2014). Within this framework, mental and neurological health is viewed as a state of equilibrium between the individual, the community, and the environment (Sorsdahl et al., 2009). For the Zulu, Xhosa, Sotho-Tswana, Venda, and Khoi-San peoples, CNS-related pathologies are categorized according to complex diagnostic etiologies. These frameworks distinguish between "natural" illnesses—those resulting from environmental factors or biological decay and "supernatural" or "ancestral" afflictions, which may stem from a breach of social taboos or a neglect of spiritual obligations (Puckree et al., 2002). In the Nguni traditions (Zulu and Xhosa), CNS disorders are interpreted through specific phenomenological lenses. For instance, isithuthwane (epilepsy) is frequently conceptualized as a physical manifestation of internal blockages or spiritual interference, requiring plants with both anticonvulsant properties and ritualistic cleansing functions (Stafford et al., 2008). Similarly, ukuphambana (psychosis or "madness") is addressed as a state of profound disharmony requiring deep-acting sedative or

psychoactive botanical agents (Cumes, 2013). The Khoi-San healers, recognized as the custodians of the region's oldest botanical knowledge, historically utilize a "shamanistic" approach to CNS health, employing psychoactive and sedative flora to navigate altered states of consciousness and mitigate cognitive stressors (Van Wyk, 2008).

The management of CNS disorders is facilitated by a specialized hierarchy of traditional health practitioners (THPs). The inyanga (predominantly Zulu/Xhosa) or ngaka (Sotho-Tswana) functions as an herbalist, possessing deep expertise in the phytochemistry and seasonal potency of the local biome to treat physical ailments. In contrast, the sangoma (diviner) addresses the psychospiritual dimensions of CNS disorders, often utilizing plants to enhance intuition or facilitate communication with ancestors (Hutchings and Scott, 1996). Among the Khoi-San, the distinction is often more fluid, with elder-healers acting as the primary repository for both the pharmacological "pharmacy" of the veld and the community's spiritual wellbeing (Bv and Gericke, 2000). The "bridge" between South African ethnobotany and neuropharmacology is anchored in a rigorous system of knowledge transmission that ensures the efficacy and safety of botanical treatments. This transmission occurs through three primary mechanisms: Apprenticeship (Ukuthwasa): The education of a healer is a protracted, disciplined process. For many, this begins with a spiritual "calling" (vocation), followed by years of intensive training under a mentor (uGogo). Apprentices learn to identify species, understand their seasonal potency, and master complex preparation methods (decoctions, infusions, or steam inhalations) specifically tailored for brain-related maladies (Cumes, 2013). Oral Tradition and Codification: In the absence of historical written texts, the "pharmacopoeia" of South Africa is preserved through a sophisticated oral archive. As noted by Dold and Cocks (2002), this system includes nuanced taxonomies of plant species and their specific applications for conditions ranging from anxiety and depression to age-related cognitive decline.

Indigenous botanical use is characterized by "experiential validation" a form of longitudinal empirical testing conducted over centuries. As highlighted by Street and Prinsloo (2013), the current indigenous pharmacopoeia represents a refined body of knowledge that has survived generations of trial and error. If a specific root or leaf consistently failed to alleviate the symptoms of isithuthwane or ukuphambana, its use would have been discarded. By recognizing these indigenous frameworks as a deliberate and structured system of medicine rather than mere folklore, the subsequent pharmacological analysis of these plants gains the necessary cultural and contextual depth required to truly "bridge" the two disciplines.

3 Integrated methodological framework for species for CNS disorders in South Africa

Plant selection in South African indigenous neurotherapeutics is predicated on observable physiological and behavioral responses rather than defined molecular pathways. Traditional health practitioners (THPs) identify botanical candidates for CNS-related disorders through their immediate, reproducible effects

on the human nervous system, such as sedation, trance induction, seizure suppression, or the modulation of cognitive states (Sobiecki, 2012). This selection process is often guided by a sophisticated system of sensory and organoleptic cues including the taste, smell, and physical morphology of the plant which healers correlate with specific therapeutic outcomes (Van Wyk, 2008). For example, plants utilized in the treatment of *isithuthwane* (epilepsy) or hyper-excitability are chosen specifically for their ability to visibly quieten the patient or restore behavioral equilibrium, reflecting a targeted, albeit non-molecular, diagnostic approach (Stafford et al., 2005).

The establishment of cultural validity for these indigenous neurotherapeutics occurs through a rigorous process of experiential validation conducted over centuries. Repeated clinical efficacy across generations creates a trusted botanical archive where the persistent use of a species serves as a proxy for its safety and therapeutic value (Stafford et al., 2008). This longitudinal empirical evidence, derived from community-level observation, often precedes and informs modern pharmacological confirmation. As a result, the ethnobotanical selection of CNS-active plants in South Africa functions as a pre-screened "leads" system, where the historical success of a treatment in a cultural framework provides the fundamental justification for subsequent bioprospecting and mechanistic investigation (Rasoanaivo et al., 2011).

The selection of botanical candidates for this review followed a stringent methodological funnel designed to prioritize plants with high indigenous traction and verified bioactivity. Only species with consistent ethnobotanical documentation for CNS-related indications across multiple South African cultural groups were included, ensuring cultural relevance before pharmacological validation. By requiring documented use across distinct cultural groups such as the Zulu, Xhosa, Sotho-Tswana, or Khoi-San, the selection process identifies plants that have achieved a form of regional consensus, thereby reducing the likelihood that a plant's usage is localized or idiosyncratic (Stafford et al., 2008). This cross-cultural convergence serves as a qualitative indicator of reliable bioactivity, specifically targeting species historically prioritized for managing symptoms of epilepsy (*isithuthwane*), anxiety, and age-related cognitive decline (Van Wyk, 2011). The integration process prioritized species where traditional preparation methods such as decoctions for sedation or steam inhalations for mood modulation—aligned with current mechanistic evidence involving neurotransmitter pathways (e.g., GABAergic or serotonergic systems) or neuroprotective markers (Street and Prinsloo, 2013). By filtering South African flora through this dual-validation lens, the methodology ensures that the discussed species represent not only established cultural heritage but also viable candidates for future neurotherapeutic drug discovery and clinical evaluation (Sobiecki, 2014).

4 Key plant species for major neurological challenges

Brain disorder is among the life-threatening health issues in South Africa. The human body has evolved antioxidant mechanisms to deal with brain-related oxidative stress; however, the endogenous antioxidant defence system showed to be overwhelmed in severe

cases (Guerra-Araiza et al., 2013). Attention has now shifted to exogenous antioxidant sources, such as plants, which showed to produce compounds that enhance the capacity of endogenous antioxidants (Grosso et al., 2023). Scientists have explored the potential of numerous plant species as sources of antioxidant compounds that can enhance brain activity and suppress disorders such as epilepsy, anxiety and depression, and neurodegenerative disorders.

Most plants are commonly used in South Africa to treat specific conditions, without being aware of their additional benefits. *Sutherlandia frutescens* is used to treat illnesses such as stress, chronic diseases, cancer, and HIV/AIDS (Chuang et al., 2014), whereas it also has potential for a neuroprotective effect (Jiang et al., 2014; Darbinyan et al., 2025) observed that *S. frutescens* inhibits NMDA-induced reactive oxygen species (ROS) production in neurons, making it efficient in treating inflammatory diseases in the brain. Moreover, treatment with *S. frutescens* compounds was found to substantially preserve ATP levels in SH-SY5Y cells exposed to 1-methyl-4-phenylpyridinium, suggesting that they alleviate mitochondrial dysfunction (Enogieru et al., 2020; Ndjoubi et al., 2024).

Hypoxis hemerocallidea, African potato, is known for its wide range of pharmaceutical properties and has been widely used for numerous ailments (Bassey et al., 2023; Erasto et al., 2020). The species has been found to possess anticonvulsant activity, suggesting its potential use in the management and control of convulsions and epilepsy (Ojewole, 2008). This species is referred to as a “wonder herb” in the Zulu, Xhosa, and Sotho-Tswana communities across South Africa, locally *inongwe* or *ifubeni* is culturally revered as a potent restorative tonic. Its corms are well marketed commercially due to their wide range of medicinal properties (Potgieter et al., 2017). Nevertheless, their leaves and corms are not used interchangeably due to differences in pharmaceutical properties, with the latter being preferred (Asong et al., 2019). In the context of the central nervous system, it is frequently employed to manage isithuthwane (epilepsy or convulsions) and to strengthen the body against chronic wasting (Dold and Cocks, 2002; Street and Prinsloo, 2013; Stafford et al., 2005). Traditional practitioners maintain a strict distinction between the plant’s organs; the corms are the preferred medicinal part, and they are not used interchangeably with the leaves due to perceived differences in potency (Rasoanaivo et al., 2011). Modern pharmacological investigations support this indigenous preference, confirming that the corm extracts possess significant anticonvulsant activity, validating its centuries-old role in seizure management (Sobiecki, 2012).

Boophone haemanthoides is one of the popular medicinal plants used for treating Parkinson’s disease and other brain disorders (Ibrakaw et al., 2020a; Nair et al., 2013). The genus occupies a complex space in South African healing, traditionally utilized by the Zulu and Khoi-San for treating ukuphambana (psychosis) and facilitating trances or ancestral communication. Preparation involves precise decoctions or highly potent snuffs, but its administration is governed by strict dosing protocols and a profound cultural awareness of its lethal toxicity (Van Wyk, 2011). This “medicine of the shadows” is handled only by expert healers who recognize its narrow therapeutic window. Its extracts were found to enhance cell viability, ATP generation, and the inhibition of apoptosis induced by MPP⁺ in the Parkinson’s

disease neuronal cells (Ibrakaw et al., 2020a). Moreover, a study found that the *Boophone haemanthoides* extracts induced cytotoxicity in the glioblastoma cells, suggesting that they could be important in controlling the proliferation of these cells in the brain. Furthermore, its Amaryllidaceae alkaloids are potent Acetylcholinesterase (AChE) inhibitors, a mechanism central to treating Alzheimer’s Disease, while also exhibiting cytotoxic activity against glioblastoma cells (Sobiecki, 2014; Van Wyk, 2008).

Searsia species are known for their anticonvulsive properties in epileptic patients (Pedersen et al., 2010). Species of the *Searsia* genus are prominent in Zulu and Xhosa pharmacopoeias for treating neurological fits and febrile seizures. Healers typically prepare decoctions of the bark or leaves, though contemporary observations highlight the importance of traditional caution, as *S. chirindensis* can induce toxicity in the liver and kidneys. *Searsia chirindensis* has been reported to treat heart complications and neurological disorders, and it was found to enhance the reversal of febrile seizures resulting from prenatal stress (Qulu et al., 2016). Moreover, *Searsia dentata* and *Searsia pyroides* were also found to be effective in treating epilepsy by acting as antagonists of N-methyl-D-aspartate-type glutamate receptors (NRs) (Marchetti et al., 2011). Most medicinal plants were reported to have side effects by interacting with non-target sites, resulting in an indirect toxicity (Başaran et al., 2022). Nevertheless, Moosa and Mabandla (2017) observed side effects for *S. chirindensis* in the liver and kidneys. Pharmacological validation has shown that *S. dentata* and *S. pyroides* act as antagonists of N-methyl-D-aspartate (NMDA) glutamate receptors, a critical pathway in the suppression of epileptic activity (Darbinyan et al., 2025). Furthermore, *S. chirindensis* has been shown to reverse seizures resulting from prenatal stress, reinforcing its role in pediatric traditional medicine (Jiang et al., 2017).

Scelletium tortuosum, a succulent forb endemic to South Africa, is extensively utilized in traditional practice as a mood-elevator, anxiolytic, and stress reliever, with modern interest focusing on its potential to enhance cognitive function. Traditionally fermented and chewed as a masticatory, it is culturally valued for fostering social cohesion and relieving “sorrow” (Stafford et al., 2008). The plant’s psychoactive properties are primarily attributed to a group of mesembrine-type alkaloids. Preclinical and clinical studies suggest these compounds act as Selective Serotonin Reuptake Inhibitors (SSRIs) and possess phosphodiesterase 4 (PDE4) inhibitory activity, providing a dual mechanism that contributes to its therapeutic efficacy in managing symptoms of anxiety and depression and improving executive function in healthy individuals. This dual mechanism provides a clear scientific rationale for its traditional use in managing anxiety and depression, while current clinical interest highlights its potential for improving executive function and cognitive performance in healthy individuals (Olatunji et al., 2021).

Various species of the genus *Helichrysum*, widely known as Imphepho or Incense, are prominent in South African traditional medicine for treating neurological symptoms like headaches, nervousness, and hysteria (Lourens et al., 2004; Serabele et al., 2023). Culturally, the plant is burnt as a ritual incense; the inhalation of the smoke is believed to clear the mind and invite ancestral presence. Scientific investigation of the essential oils (EOs) of species like *H. odoratissimum* reveals a complex phytochemical

TABLE 1 Ethnobotanical use and neuropharmacological validation of selected South African medicinal plants used for CNS-related disorders.

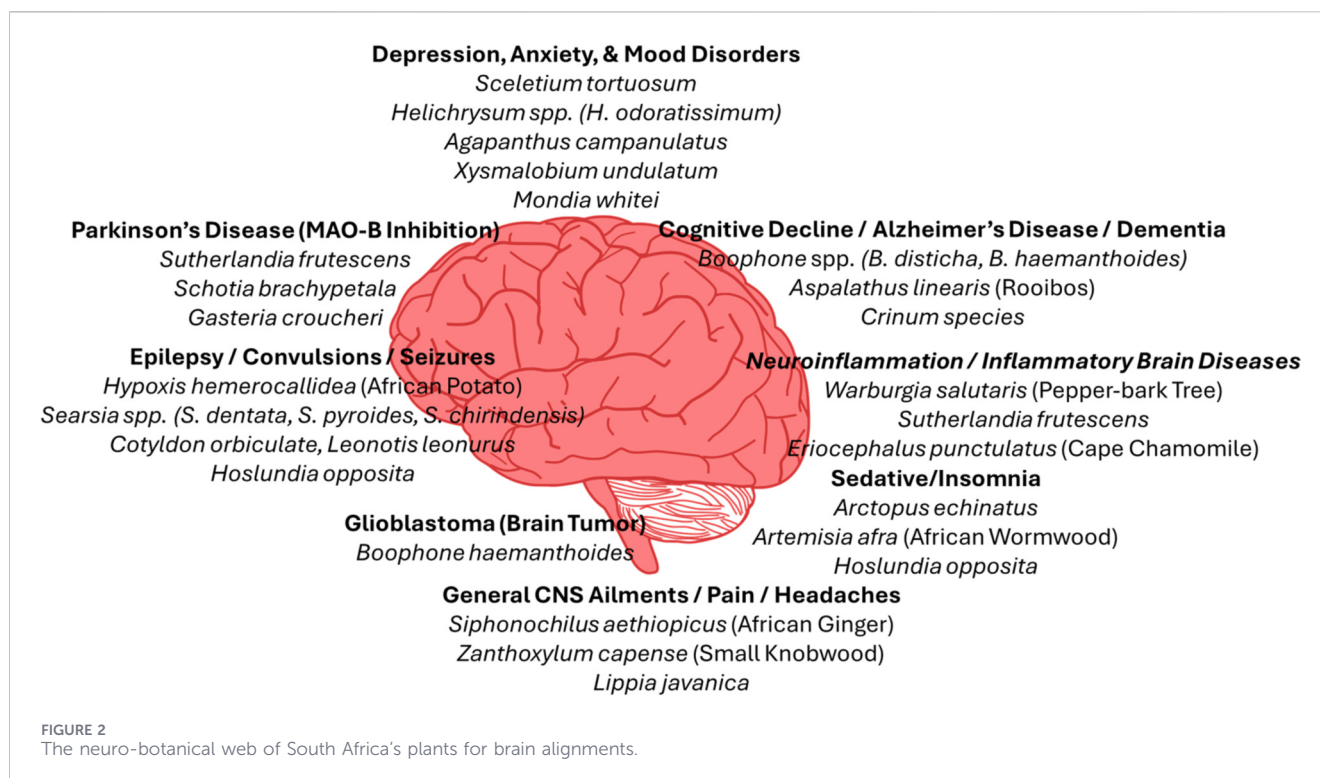
Plant species	Cultural group(s)	Indigenous indication/ diagnostic category	Plant part and preparation	Ethnobotanical rationale (observed effects)	Neuropharmacological evidence
<i>Sceletium tortuosum</i> (L.) N.E.Br.	Khoi-San	Anxiety, emotional distress, fatigue, altered mood states	Fermented aerial parts; chewed or taken as snuff	Mood elevation, calming effects, suppression of fear and hunger during hunting	Serotonin reuptake inhibition; PDE4 inhibition; anxiolytic and antidepressant activity
<i>Boophone disticha</i> (L.f.) Herb.	Zulu, Xhosa, Sotho-Tswana	Isithuthwane (epilepsy), trance induction, spirit disturbance	Bulb; powdered snuff or decoction under strict ritual control	Induction of altered states, seizure control; recognized high toxicity requiring precise dosing	Anticholinergic and neurotoxic Amaryllidaceae alkaloids affecting CNS excitability
<i>Hypoxis hemerocallidea</i> Fisch. et C.A.Mey.	Zulu, Xhosa, Sotho-Tswana	Nervous weakness, immune-related fatigue, general malaise	Corm; decoction or infusion	Restoration of strength and resilience; indirect support of mental health	Anti-inflammatory, antioxidant, neuroprotective effects via sterols and glycosides
<i>Searsia</i> spp.	Zulu, Venda	Headache, mental agitation, inflammation-related discomfort	Leaves and bark; decoctions	Relief of pain and calming effects	Anti-inflammatory, antioxidant, and neuromodulatory activities
<i>Leonotis leonurus</i> (L.) R.Br.	Zulu, Khoi-San	Epilepsy, headache, anxiety	Leaves; smoked or infused	Sedative and calming effects; reduction of convulsions	Interaction with GABAergic pathways; mild sedative properties
<i>Datura stramonium</i> L.	Multiple (ritual-restricted use)	Trance, divination, severe mental disturbance	Leaves/seeds; ritual inhalation or ingestion (restricted)	Powerful psychoactive effects used only under ceremonial contexts	Tropane alkaloids (anticholinergic), hallucinogenic CNS effects

profile dominated by monoterpenes and sesquiterpenes (Adewinogo et al., 2022). These compounds confer potent antioxidant and anti-inflammatory activities, indicated by activity in the 5-lipoxygenase assay (Lourens et al., 2004; Serabele et al., 2023). This anti-inflammatory action is crucial, as neuroinflammation is a central component of many neurological and psychiatric disorders (Borgonetti et al., 2020). Given that neuroinflammation is a primary driver of psychiatric and neurodegenerative disorders, the traditional use of *Imphepho* as a sedative and cognitive stabilizer is increasingly supported by its ability to modulate pro-inflammatory cytokine secretion.

Warburgia salutaris is highly regarded in traditional healing across Southern Africa for its broad anti-inflammatory and pain-relieving properties, which are often directed toward conditions manifesting as headaches, fever, and general body pains (Babandi, 2025). In the context of neurological wellness, it is frequently prescribed for conditions manifesting as chronic headaches, febrile episodes, and general somatic pains that often accompany CNS distress (Ibrakaw et al., 2020b). The primary bioactive compounds are drimane sesquiterpenoids (e.g., warburganal, polygodial), which confer strong antimicrobial and anti-inflammatory activity (Nkqenkqa and Mundembe, 2023). Modern research corroborates its traditional use, showing that *Warburgia salutaris* extracts possess significant antioxidant activity and exhibit a protective effect against inflammation-induced cellular injury by modulating pro-inflammatory cytokine secretion (Abdelfattah et al., 2022). Mechanistic studies show that the plant exerts a protective effect against inflammation-induced cellular injury by actively modulating the secretion of pro-inflammatory cytokines. This ability to mitigate systemic inflammation is particularly relevant for brain health, as neuroinflammatory pathways are increasingly recognized as secondary drivers of both neurodegenerative and neuropsychiatric disorders.

Aspalathus linearis, the source of Rooibos tea represents an indigenous Khoi-San beverage with significant neuroprotective potential. It is a caffeine-free beverage endemic to the Cederberg region and is of increasing interest in neuroprotection due to its high concentration of flavonoid C- and O-glycosides, notably aspalathin (Chaudhary et al., 2021; Kreuz et al., 2008). Scientific reviews suggest that Rooibos and its major flavonoids possess significant potential against neurodegenerative mechanisms, including those associated with Alzheimer's disease (AD) (Chipofya et al., 2025). Its efficacy stems from potent antioxidant activity that directly counters the oxidative stress and lipid peroxidation linked to AD pathogenesis, alongside a suggested ability to modulate tau protein and amyloid plaque formation (Chipofya et al., 2025). These findings suggest that the traditional South African diet and medicinal complex contain a diverse array of compounds capable of modulating major neurotransmitter systems and protecting against chronic neurodegeneration. Table 1 summarizes the convergence between indigenous ethnobotanical knowledge and experimentally validated neuropharmacological mechanisms, illustrating how traditional selection, preparation, and cultural control align with modern CNS science.

For disorders such as Depression, Anxiety, and Cognitive Decline, pharmacological interest centres on modulating neurotransmitter systems. *Sceletium tortuosum* is the most highly investigated plant, whose mesembrine alkaloids have been rigorously confirmed to act as potent Serotonin Reuptake Inhibitors (SRIs), providing a clear mechanism for its traditional anxiolytic and antidepressant effects (Stafford et al., 2008). For cognitive disorders, the Amaryllidaceae alkaloids found in *Boophone* spp. and *Crinum* species are vital, exhibiting strong Acetylcholinesterase (AChE) inhibitory activity (Llalla-Cordova et al., 2025). This mechanism increases acetylcholine levels, which is a key symptomatic treatment strategy for Alzheimer's Disease (AD). Furthermore, the antioxidant capacity of species



like *Aspalathus linearis* (Rooibos) is crucial for combating the oxidative stress underlying chronic neurodegeneration (Stafford et al., 2007). Other plants like *Agapanthus*, *Xysmalobium*, and *Mondia whitei* have also shown evidence of antidepressant-like activity in preclinical models (Stafford et al., 2008).

In Parkinson's Disease (PD), therapeutic strategies aim to preserve dopamine and mitochondrial integrity. *Sutherlandia frutescens* is critical here for its ability to alleviate mitochondrial dysfunction and suppress the overproduction of Reactive Oxygen Species (ROS), thereby addressing the bioenergetic failure common in PD neurons (Darbinyan et al., 2025). Complementing this, species like *Schotia brachypetala* and *Gasteria croucheri* have demonstrated promising Monoamine Oxidase B (MAO-B) inhibitory activity in *in vitro* assays, a mechanism used in synthetic drugs to mitigate dopamine degradation (Stafford et al., 2008; Koki et al., 2022).

The management of Epilepsy and Seizures often involves reducing neuronal hyperexcitability. Plants such as *Hypoxis hemerocallidea* (African Potato) and the *Searsia* genus are utilised for their confirmed anticonvulsant activities (Olatunde et al., 2023). This efficacy is linked to compounds that act as N-methyl-D-aspartate (NMDA) receptor antagonists (*Searsia* spp.) or those that modulate inhibitory neurotransmission via the GABA-benzodiazepine receptor complex (*Leonotis leonurus*, *Hoslundia opposita*) (Stafford et al., 2008; Olatunde et al., 2023). The contribution to Neuroinflammation, a common feature across all neurological diseases, is addressed by potent anti-inflammatory agents like *Warburgia salutaris* (Khumalo, 2023) and *Eriocephalus punctulatus* (Haikal et al., 2024), which help temper the chronic inflammatory cascade (Cumes, 2013). Finally, the cytotoxic potential of Amaryllidaceae alkaloids from *Boophone haemanthoides* against Glioblastoma cells highlights the role of

these plants as sources for novel anti-cancer neuro-agents (Ibrakaw et al., 2020b).

Extracts from most plant species are dose-dependent; therefore, the integration of the dose-response aspect is recommended for medicinal plants efficacy studies. Moreover, traditional applications do not pay attention to technicalities, which result in shortcomings with regard to concentrations, target plant organ, and time of harvest. These shortcomings hinder the optimal utilisation of these resources. Therefore, collaborative efforts between tradition and science, which have the potential to address these shortcomings, remain the missing link. Some plant compounds counteract the role of endogenous anticonvulsants, resulting in toxic effects, whereas other traditional healers recommend extracts from more than one plant without understanding the interactions among them. With South Africa being rich in plant diversity, more species with anticonvulsive properties likely remain underexplored. Figure 2 visually encapsulates the critical link between traditional indigenous knowledge and neuropharmacology, illustrating how native South African communities employ specific medicinal plants to manage a spectrum of neurological ailments, ranging from mood disorders and epilepsy to cognitive decline.

5 Bioactive compounds and mechanisms of action

South Africa is home to a variety of indigenous plants such as incense (*Helichrysum odoratissimum* L.) (Serabele et al., 2021), nana-berry (*Searsia dentata* Thunb.) (Sibiya et al., 2021), kanna (*Mesembryanthemum tortuosum* L.) (Nižnik and Jurowski, 2025)

and Cape aloe (*Aloe ferox* Mill.) (Viljoen et al., 2023) that are recognized for their potential benefits to brain health (Serabele et al., 2021; Niznik and Jurowski, 2025). These plants are rich in bioactive compounds such as alkaloids, flavonoids, saponins, terpenoids and phenolic compounds as well as pharmacological properties including antioxidant, antimicrobial, anti-inflammatory, anticancer, antidiabetic and cardioprotective effects (Serabele et al., 2021; Sibiya et al., 2021; Niznik and Jurowski, 2025). A study by Matrose et al. (2022) showed that *Helichrysum patulum* contained γ -terpinene (0.1%), α -amorphene (0.6%) α -gurjunene (1.4%), β -selinene (3.2%), γ -gurjunene (3.3%), methyl cinnamate (20%), total phenolic content (19.30 g GA 100 g⁻¹) and antioxidant capacity (13.251.5 μ mol Trolox g⁻¹). Thus, indigenous plants are traditionally used to treat various diseases including colds, tuberculosis, diabetes, cancer, arthritis, mental health disorders (Cock et al., 2024) and neurodegenerative conditions such as Alzheimer and Parkinson's diseases, epilepsy and brain tumours (Tettevi et al., 2022). Although this review focuses on flavonoids, alkaloids, terpenoids, and phenolic compounds, South African indigenous plants are known to contain a wider range of bioactive constituents, including saponins, tannins, lignans, glycosides, coumarins, and steroids. These additional phytochemicals also contribute to neuropharmacological activity through antioxidant, anti-inflammatory, and neuromodulatory mechanisms, as reported by Hasan et al. (2024) and Tkaczenko et al. (2025). However, flavonoids, alkaloids, terpenoids, and phenols were prioritised in this review due to their higher abundance in medicinal plants, stronger ability to cross the blood-brain barrier, and the availability of extensive mechanistic, experimental, and clinical evidence supporting their roles in neuroprotection and cognitive enhancement (Singh et al., 2024).

5.1 Flavonoids

Flavonoids, a diverse group of polyphenolic compounds found in various medicinal plants, fruits and vegetables, play a significant role in promoting brain health through their neuroprotective properties (Cheng et al., 2025). They are classified in several categories including flavanols, flavonols, flavones, flavanones, isoflavones, anthocyanidins, and chalcones based on their chemical structure (Ysrafil et al., 2025). They possess multiple biological effects such as antiviral, anti-allergic, antiplatelet, anti-inflammatory, antitumor, and antioxidant activities which are crucial in mitigating neurodegenerative diseases such as Alzheimer's and Parkinson's (Cheng et al., 2025; Ysrafil et al., 2025). Furthermore, they can cross the blood-brain-barrier and may exhibit neuropharmacological activities at the molecular level, influencing the protein function and gene expression (Al-Shuhaib and Al-Shuhaib, 2025). Importantly, dietary intake of flavonoids exerts neuroprotective effects in the brain, including the protection of neurons against neurotoxin-induced injury, suppression of neuroinflammation, and also has a potential to promote cognitive, learning, and memory functions (Ysrafil et al., 2025; Al-Shuhaib and Al-Shuhaib, 2025). Flavonoids can modulate the immune system of brain, attenuate the neuroinflammation by inhibiting the production of nitric

oxide and cytokines induced by activated microglia (Cheng et al., 2025). A clinical study by Sayeed et al. (Sayeed et al., 2014) showed that the administration of black caraway (*Nigella sativa* L.) capsules (500 mg) on healthy adolescent, 14–17 years old (n = 48) once daily for 1 month decreased anxiety, stabilized mood and modulated cognition. Another study by Silva et al. (2020) showed that spongweed (*Codium tomentosum* Stackhouse) extract (100 μ g/mL) rich in flavonoids was effective in managing the Parkinson's diseases by mitigating reactive oxygen species (ROS) generation, mitochondrial dysfunctions, and deoxyribonucleic acid damage and reducing Caspase-3 activity in 6-OHDA-induced SH-SY5Y human cells. Thus, flavonoids enriched foods such as medicinal plants, fruit and vegetables could reduce the risks of brain-related diseases. Recent studies further support the neuroprotective potential of flavonoids isolated from medicinal plants. For instance, Adnan et al. (2025) demonstrated that quercetin significantly attenuated amyloid- β -induced neurotoxicity by reducing oxidative stress and inhibiting neuronal apoptosis in both *in vitro* and *in vivo* Alzheimer's disease models. Similarly, Enogieru et al. (2018) reported that rutin improved memory deficits and reduced neuroinflammation by modulating acetylcholinesterase activity and suppressing pro-inflammatory cytokines in experimental Parkinson's disease models. In addition, dietary flavanols such as epicatechin have been shown to enhance synaptic plasticity and cerebral blood flow, leading to improved cognitive performance, as reported by Godos et al. (2025).

5.2 Alkaloids

Alkaloids, naturally occurring compounds found in plants, have shown significant potential in promoting brain health. Alkaloids can be primarily classified based on their origin and structure (Bhambhani et al., 2021). The most common alkaloids include piperidine, indole, quinoline and steroidal (Zhang et al., 2023). These compounds are known for their ability to modulate neurotransmitter pathways, reduce oxidative stress, and inhibit enzymes that contribute to neurodegenerative diseases (Kinsou, 2019). A study by Harvey et al. (2011) and Kinsou (2019) demonstrated that kanna (*Sceletium tortuosum* L.), grains of paradise (*Aframomum melegueta* K. Schum.), conkerberry (*Carissa spinarum* L.) and African corkwood (*Hymenocardia acida* Tul.) extracts, rich in mesembrine and mesembrenone alkaloids had neuroprotective effects against brain diseases such as Alzheimer's, Parkinson's, and Huntington's by targeting oxidative stress, mitochondrial dysfunction, and protein misfolding. Alkaloids function as antioxidants, anti-inflammatory agents, and modulators of calcium homeostasis, which are crucial in maintaining neuronal health (Bhambhani et al., 2021; Zhang et al., 2023). Beyond previously reported studies, emerging evidence indicates that several alkaloids exert strong neuroprotective effects through multiple mechanisms. Berberine, an isoquinoline alkaloid (Li et al., 2023), to reduce tau hyperphosphorylation and amyloid- β accumulation by regulating glycogen synthase kinase-3 β signaling in Alzheimer's disease models. Similarly, harmine, a β -carboline alkaloid, demonstrated antidepressant and neurogenic effects by enhancing brain-derived neurotrophic factor expression and

reducing neuroinflammation (Li et al., 2023). This strengthens the relevance of alkaloids from medicinal plants as therapeutic candidates for neurodegenerative and neuropsychiatric disorders.

5.3 Terpenoids

Terpenoids, a diverse group of secondary metabolites found in various medicinal plants, have shown significant potential in promoting brain health through their neuroprotective and cognitive-enhancing properties (Lai Shi Min et al., 2022). Terpenoids can be classified into hemiterpenoids, monoterpenoids, sesquiterpenoids, diterpenoids, sesterterpenoids, triterpenoids and tetraterpenoids according to the number of isoprene units or carbon atoms that form the parent terpene (Tetali, 2019). These compounds can alleviate symptoms associated with neurodegenerative diseases and improve cognitive functions, making them valuable in promoting brain health (Wang et al., 2023). Alam et al. (2023) stated that terpenoids exhibit neuroprotective effects, which are crucial in combating neurodegenerative diseases such as Alzheimer's and Parkinson's due to the presence of biological activities, such as antimicrobial, anti-inflammatory, antioxidant, antiparasitic, immunomodulatory and anti-cholinesterase activities (Lai Shi Min et al., 2022). A study by Park et al. (2014) and Kim et al. (2018) showed that common bean (*Phaseolus vulgaris* L.) and Asian ginseng (*Panax ginseng* C.A.Mey.) extracts, rich in terpenoids were effective in managing the Schizophrenic disorder. Recent investigations have expanded the evidence supporting the neuropharmacological significance of terpenoids. Ginkgolides and bilobalide, diterpenoid and sesquiterpenoid constituents of *Ginkgo biloba*, were shown to protect neurons against ischemic injury by improving mitochondrial function and suppressing neuroinflammation, according to Xia et al. (2024). Additionally, β -caryophyllene, a sesquiterpenoid, was reported by Ricardi et al. (2024) to exert anxiolytic and neuroprotective effects through cannabinoid receptor type-2 activation, leading to reduced oxidative stress and microglial activation. These studies highlight the broad therapeutic relevance of terpenoids in brain health.

5.4 Phenols

Phenols in medicinal plants have been shown to promote brain health through various mechanisms, primarily due to their polyphenolic content (Tirado-Kulieva et al., 2022). The most abundant phenolic compounds in medicinal plants include phenolic monoterpenes and diterpenes, hydroxybenzoic acids, phenylpropanoic acids, phenylpropenes and coumarins (Sun et al., 2022). These compounds exhibit neuroprotective effects by crossing the blood-brain barrier, eliminating ROS, which helps in reducing oxidative stress and preventing neuronal damage (Arias-Sánchez et al., 2023). They modulate neurotrophic factors such as nerve growth factor and brain-derived neurotrophic factor, enhancing neuronal plasticity, survival, and growth and cognitive functions (Fiore et al., 2025). Phenolic compounds also exhibit immunomodulatory and anti-inflammatory properties, which are crucial in reducing neuroinflammation associated with

neurodegenerative diseases (Tirado-Kulieva et al., 2022). A study by Lin (2011) and Aleksandrova et al. (2023) showed that Baikal skullcap (*Scutellaria baicalensis* Georgi), Veitch's peony (*Paeonia veitchii* L.), tree peony (*Paeonia* \times *suffruticosa* Andrews) and pomegranate (*Punica granatum* L.) extracts contained phenolic compounds such as baicalin, paeonol and ellagitannins demonstrated neuroprotective and antioxidant effects against ischemia and neurodegeneration. Ellagitannins support brain health by maintaining redox balance, enhancing blood flow, and protecting against mitochondrial damage (Tirado-Kulieva et al., 2022). Table 2 summarizes indigenous plant species, applications, and mechanisms in neuro-pharmacology. While Figures 3, 4 illustrates the primary mechanisms by which major bioactive compounds flavonoids, alkaloids, terpenoids, and phenols contribute to neuroprotection, modulation of neurotransmitters, reduction of oxidative stress, anti-inflammatory activity, and cognitive enhancement, providing a mechanistic link between traditional use of South African indigenous plants and their observed neuropharmacological effects. Recent studies have also reinforced the role of phenolic compounds in neuroprotection. Gallic acid was reported by Dastan et al. (2024) to attenuate neuroinflammation and improve memory by modulating nuclear factor kappa B signalling and enhancing antioxidant defense systems. Furthermore, resveratrol-related phenolic compounds have been shown to enhance mitochondrial biogenesis and cerebral blood flow, thereby improving cognitive function in aging and neurodegenerative models, as documented by Tu (2025). These findings support the inclusion of phenolic compounds as key contributors to the neuroprotective potential of medicinal plants.

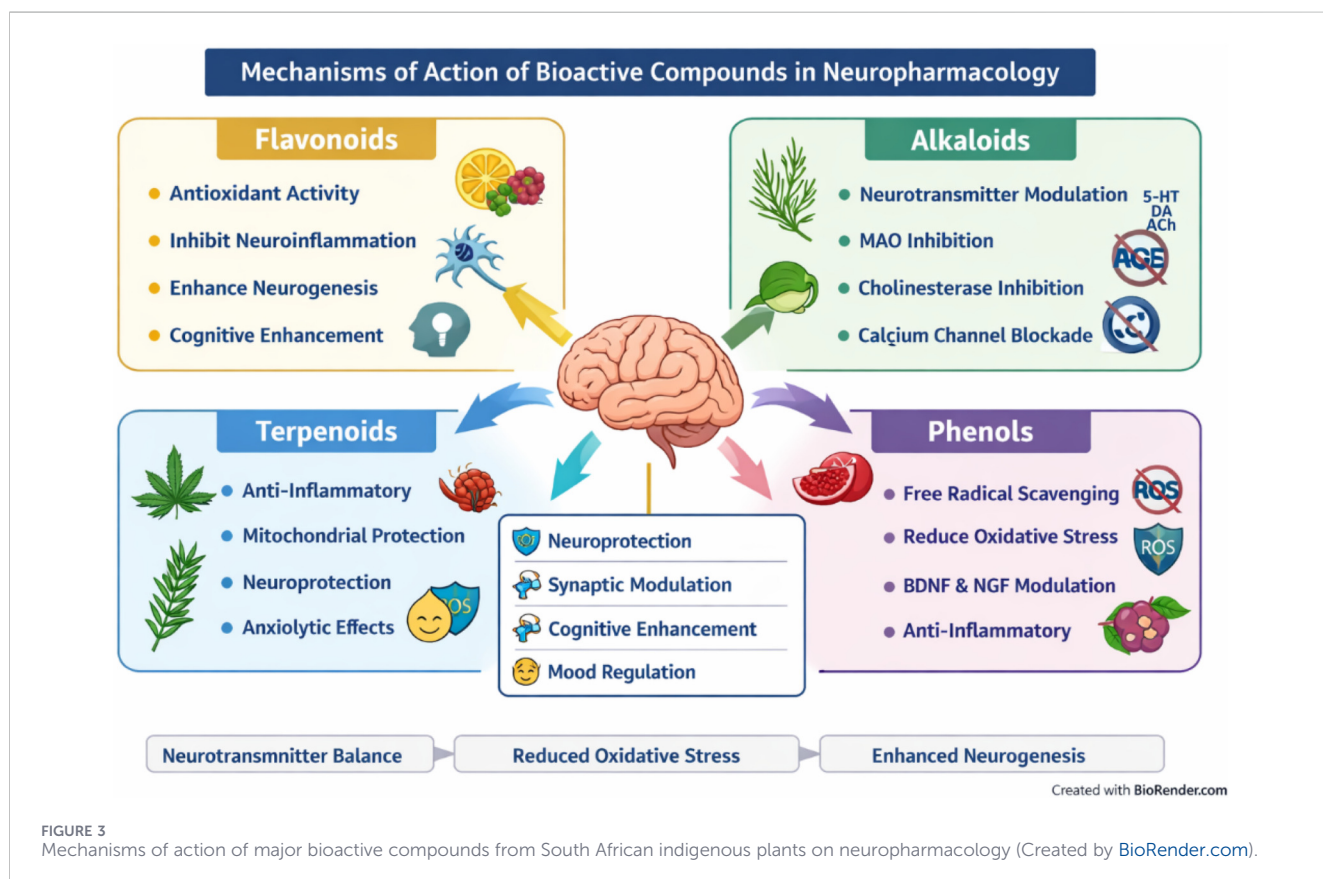
6 Challenges and future directions

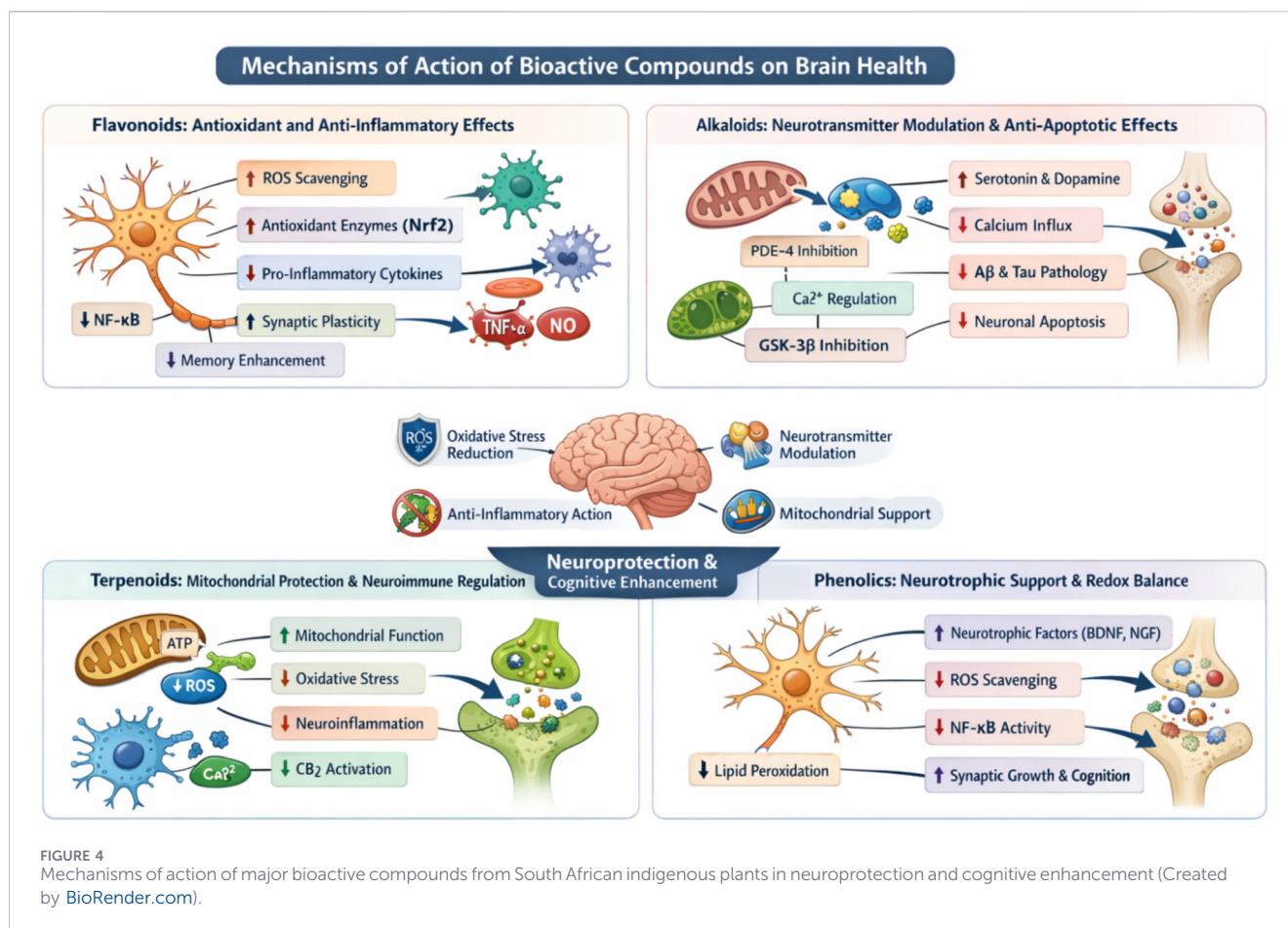
The most significant hurdle is the pervasive lack of human clinical trials. Currently, the compelling evidence of multi-targeted action such as the serotonin reuptake inhibition by mesembrine alkaloids or the acetylcholinesterase inhibition by Amaryllidaceae alkaloids is confined almost entirely to preclinical (*in vitro* or animal) studies (Stafford et al., 2008). Moving these extracts from the bench to the bedside requires substantial investment in rigorous randomized, placebo-controlled trials (RCTs) to validate the efficacy, establish optimal dosage, and conclusively determine the long-term safety profile of the extracts in patients (Ullah et al., 2025). Without this robust evidence, clinical adoption and regulatory approval remain impossible. Traditional plant remedies suffer from inherent chemical variability, a challenge compounded by the multi-compound nature of plant extracts. Factors like harvest time, climate, and processing methods lead to inconsistent alkaloid ratios, undermining reliable dosing and therapeutic predictability (Karthikeyan et al., 2025). The lack of uniform Standardization and Quality Control (QC) protocols is a major issue. Researchers must employ advanced analytical techniques (HPLC, GC-MS) to define chemical biomarkers within the extracts, such as specific ratios of mesembrine and mesembrenone, to ensure consistent therapeutic delivery across all commercial products (Patnala and Kanfer, 2017).

The missing information regarding Pharmacokinetics and Bioavailability constitutes a severe translational limitation, as

TABLE 2 Key South African indigenous plant species, applications, and verified mechanisms in neuro-pharmacology.

Plant name (scientific name)	CNS-related application	Key bioactive compound class	Primary mechanism of action (MOA)
<i>Sceletium tortuosum</i>	Depression and anxiety, mental health disorders	Mesembrine alkaloids	Functions as a Serotonin Reuptake Inhibitor (SRI) (Coetzee et al., 2016).
<i>Boophone</i> spp. (<i>B. disticha</i> , <i>B. haemanthoides</i>)	Cognitive decline, neurodegeneration, Parkinson's disease, glioblastoma	Amaryllidaceae alkaloids	Exhibits potent Acetylcholinesterase (AChE) Inhibitory Activity; Enhances cell viability and ATP generation; Induces cytotoxicity in glioblastoma cells (Coetzee et al., 2016; Ibrakaw et al., 2020a; Omoruyi et al., 2025).
<i>Sutherlandia frutescens</i>	Neuroprotection, inflammatory brain diseases	L-canavanine, GABA (γ -aminobutyric acid)	Inhibits NMDA-induced Reactive Oxygen Species (ROS) production in neurons; Alleviates Mitochondrial Dysfunction (preserves ATP levels) (Jiang et al., 2014; Enogieru et al., 2020; Ndjoubi et al., 2024).
<i>Hypoxis hemerocallidea</i>	Convulsions and epilepsy	Hypoxoside, β -sitosterol	Possesses Anticonvulsant Activity (used for management and control of convulsions) (Ojewole, 2008).
<i>Searsia</i> spp. (<i>S. dentata</i> , <i>S. pyroides</i>)	Epilepsy, febrile seizures	Quercetin, myricetin, phenolic acids	Acts as Antagonists of N-methyl-d-aspartate-type glutamate receptors (NMRs), relevant to seizure control (Marchetti et al., 2011).
<i>Aspalathus linearis</i> (Rooibos)	Neuroprotection, Alzheimer's Disease	Flavonoid C- and O-Glycosides (e.g., Aspalathin)	Provides potent Antioxidant Activity to counter oxidative stress; Modulates mechanisms linked to tau protein and amyloid plaques (Chaudhary et al., 2021).
<i>Warburgia salutaris</i> (Pepper-bark Tree)	Headaches, pain relief, anti-inflammatory	Drimane sesquiterpenoids (e.g., polygodial)	Provides significant Antioxidant Activity; Exhibits a protective effect against inflammation-induced cellular injury (Nkqenkqa and Mundembe, 2023; Abdelfattah et al., 2022).
<i>Helichrysum</i> spp. (<i>H. odoratissimum</i> - Imphepho)	Headaches, nervousness, hysteria	Monoterpenes and Sesquiterpenes	Exhibits significant Antioxidant and Anti-inflammatory activity (via 5-lipoxygenase inhibition) (Serabele et al., 2023; Matrose et al., 2022).





the efficacy of South African neuro-herbal extracts is fundamentally dependent on understanding the fate of their compounds within the body. Specifically, the almost complete absence of data on Blood-Brain Barrier (BBB) permeability means that even compelling *in vitro* mechanisms of action are scientifically unproven, as the active molecules must cross this highly selective barrier to reach CNS targets (Ullah et al., 2025). Furthermore, the lack of data on the metabolic fate, half-life, and systemic bioavailability of the complex extracts introduces substantial uncertainty regarding predictable and reliable dosing. Without these critical ADME (Absorption, Distribution, Metabolism, and Excretion) metrics, clinical adoption and regulatory approval are scientifically impossible, as safety and therapeutic consistency cannot be guaranteed (Ullah et al., 2025; Karthikeyan et al., 2025). The commercialization of indigenous flora creates severe ethical and ecological challenges. Rising global demand threatens valuable species with over-harvesting and subsequent genetic erosion (Williams et al., 2000). Furthermore, there is a critical need to comply with the South African Bioprospecting, Access and Benefit-Sharing (ABS) framework, ensuring that the indigenous communities, whose knowledge underpins these discoveries, receive equitable benefits (Mawere and Mukonza, 2025). The path forward requires a fundamental shift from unsustainable wild collection to controlled, ethical, and

sustainable cultivation to protect biodiversity while securing a consistent supply.

7 Concluding remarks

The rich ethnobotanical history of South Africa offers a critical, yet currently under-validated, resource for the future of neuropharmacology. The conventional “one drug, one target” strategy is increasingly insufficient for complex, multifactorial neurological and neuropsychiatric disorders. In contrast, indigenous plant extracts present a unique, inherent multi-targeted strategy. Bioactive compounds, including alkaloids, flavonoids, terpenoids, and phenolic compounds, are scientifically proven to modulate several pathological hubs simultaneously, addressing issues like oxidative stress, neuroinflammation, and neurotransmitter pathways.

Author contributions

MM: Writing – review and editing, Writing – original draft, Conceptualization, Investigation. JL: Conceptualization, Writing – review and editing, Writing – original draft, Investigation. NB: Writing – original draft, Investigation, Writing – review and editing, Conceptualization.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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