REVIEW

Medicinal plants utilized in the management of epilepsy in Ethiopia: ethnobotany, pharmacology and phytochemistry

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Abstract
Epilepsy is a common central nervous system (CNS) disorder that affects 50 million people worldwide. Patients with status epilepticus (SE) suffer from devastating comorbidities and a high incidence of mortalities. Antiepileptic drugs (AEDs) are the mainstream treatment options for the symptomatic relief of epilepsy. The incidence of refractory epilepsy and the dose-dependent neurotoxicity of AEDs such as fatigue, cognitive impairment, dizziness, attention-deficit behavior, and other side effects are the major bottlenecks in epilepsy treatment. In low- and middle-income countries (LMICs), epilepsy patients failed to adhere to the AEDs regimens and consider other options such as complementary and alternative medicines (CAMs) to relieve pain due to status epilepticus (SE). Plant-based CAMs are widely employed for the treatment of epilepsy across the globe including Ethiopia. The current review documented around 96 plant species (PS) that are often used for the treatment of epilepsy in Ethiopia. It also described the in vivo anticonvulsant activities and toxicity profiles of the antiepileptic medicinal plants (MPs). Moreover, the phytochemical constituents of MPs with profound anticonvulsant effects were also assessed. The result reiterated that a lot has to be done to show the association between herbal-based epilepsy treatment and in vivo pharmacological activities of MPs regarding their mechanism of action (MOA), toxicity profiles, and bioactive constituents so that they can advance into the clinics and serve as a treatment option for epilepsy.

Keywords: Epilepsy, Medicinal plants, Anticonvulsant activity, Antiepileptic activity, Ethiopia

Introduction
Epilepsy is a common central nervous system (CNS) disorder and the fourth-largest cause of disease burden worldwide [1]. It is mainly characterized by recurrent, unprovoked seizures, which may trigger anxiety, depression, cognitive decline, schizophrenia, autism that can deteriorate the quality of life (QOL) and increase the incidence of mortality in patients [2, 3]. An imbalance instigated by inhibition of the excitatory γ-aminobutyric acid (GABA)-mediated neurotransmission and activation of inhibitory glutamatergic neurotransmission within the brain including hippocampal, neocortical, corticothalamic, and basal ganglia network is often implicated in the pathogenesis of epileptic seizures (ES) [4]. Epilepsy can emanate from a genetic predisposition of the brain to generate seizures or may be caused by brain damage due to tumor, injury, stroke, infection, etc. [5] that can elicit a wide array of abnormalities resulting in seizure generation [6]. According to WHO 2019 factsheet, approximately 50 million people around the globe are suffering from unpleasant symptoms and comorbidities resulting from ES [7]. It is reported that almost 80% of epilepsy cases are found in low—and middle-income countries (LMICs) [4] due to lack of sufficient antiepileptic drugs (AEDs), high cost if any AEDs available, and undesirable outcomes of the existing AEDs [8]. In the case of...
Ethiopia, epilepsy is one of the 20 leading causes of mortality, and 5.2 out of 1000 people are prone to ES in their lifetime [9, 10]. In general, epilepsy has substantial economic implications, predominantly in Africa, as it triggered a great burden on the underprivileged healthcare system of poor nations [11] as well as on patients owing to the epilepsy-bound poor QOL, stigma, and discrimination in patients and relatives [12] that could ominously increase healthcare expenditure and diminish overall productivity [10].

Modulating the activity of GABAergic, glutamatergic, purinergic neurotransmissions, cholinergic pathways and ATPases is a viable option for the treatment of epilepsy [13]. Attempts have been made to exploit the aforementioned neurotransmission pathways and enzymes implicated in epileptogenesis for the design of novel chemical agents to ameliorate the neurological deficits responsible for the progression of epilepsy. Thus far, more than 30 AEDs have been approved for clinical use [14]. However, the AEDs succeeded only in the symptomatic relief of epilepsy in patients without significantly correcting the underlying biochemical aberrations involved in epileptogenesis [15]. Currently, the treatment of epilepsy has mainly relied on such AEDs which can make patients free of seizures upon proper treatments regimens. Although the existing AEDs are effective in the suppression of seizures in the vast majority of epilepsy patients, 30% of them (15% of children and 34% adults) developed resistance towards AEDs, consequently, nonresponsive towards AEDs [16, 17]. Moreover, the dose-dependent neurotoxicity of AEDs such as fatigue, cognitive impairment, dizziness, attention-deficit behavior, and other side effects are the major bottlenecks in epilepsy treatment [8]. Patients with refractory ES are at increased risk of mortality and morbidity. Adjuvant therapies and AEDs along with ketogenic diet supplements are employed for the treatment of refractory ES [17]. Patients with untreated and/or refractory epilepsy are often desperate to seek nonconventional treatments including but not limited to complementary and alternative medicines (CAMs) [18]. The unaffordable price of newer AEDs and the wider treatment gaps have inspired researchers to focus on plants in the search for safe and effective drugs for the treatment of ES.

Current trends in the treatment of epileptic seizures
AEDs are pretty effective in the treatment of epilepsy if patients properly comply with treatment regimens. However, they are overpriced and seldom possess devastating and inevitable side effects resulting in poor patient compliance [19]. Treatment compliance or adherence is a major factor that can dictate the outcomes of AEDs in controlling the incidence of seizure attacks [20]. There is ample evidence suggesting the presence of a huge treatment gap among epilepsy patients in LMICs ranging from 25 to 100% [21]. In Africa, epilepsy is associated with fear, misunderstanding, witchcraft, discrimination and social stigmatization of patients and their families that can be considered as a driving force for the observed huge treatment gaps due to failure in several intervention mechanisms employed and persistent antiepileptic medications non-adherences (AEMNAs) [22]. Epileptic patients experiencing AEMNAs are more prone to have suboptimal treatment outcomes, recurrent seizure attacks, intermittent hospital admissions, increased healthcare expenditure, lowered level of productivity, and thereby deteriorated QOL [23]. For instance, in Ethiopia, the prevalence of AEMNAs was found to be in the range of 21.8–68%. Poor healthcare system and medical services, lack of medication access, economic constraints, antiepileptic medication side effects, and poor seizure control status are among the factors which significantly contributed to the high burden of AEMNAs in Ethiopia [24]. Moreover, the association of epilepsy with spiritual and predestined fate as well as the presence of different cultural and spiritual beliefs with potential impacts to enforce people to prefer CAMs for the treatment of “spiritual disease” such as epilepsy [25] have significantly contributed to the high incidence of AEMNAs in different parts of Ethiopia. Overall, AEMNAs resulted in treatment failure which in turn triggered devastating social consequences, life-threatening comorbidities, employment restriction, physical injuries, and increased mortality [23]. For instance, in sub-Saharan Africa, untreated ES are the common causes of death with status epilepticus (SE), drowning, falls, burns, and sudden death contributing to epilepsy-associated mortality [26]. A study conducted on 119 patients in Ethiopia revealed that about 58% of epileptic patients who acquired generalized tonic-clonic seizures (GTCS) at a baseline evaluation with a frequency of ≥ 8 times, 23.3% of them died [27]. Another study revealed that among 316 persons with epilepsy, 20 (6.3%) died within 2 year period mostly due to SE and burn [28]. Accordingly, improving the patient compliance towards the existing AEDs through novel intervention approaches and bringing CAMs, especially antiepileptic herbal formulation, into modern pharmacy shelves is an option in the long term to tackle seizure-related morbidity and mortality.

Importance of complementary and alternative medicine in Ethiopia
According to National Center for Complementary and Alternative Medicines (NCAM), CAMs are defined as a traditional healthcare system comprised of biological, spiritual, alternative, physical, and energy therapies...
A biological form of CAM that depends on natural products is commonly sought for the treatment of different diseases worldwide [29]. It uses medicinal herbs, medicinal animals, dietary supplements, antioxidants, minerals, vitamins, etc. alone or in combination to diagnose, prevent, treat different ailments [30]. Traditional medicines (TMs) of plant origin have become an integral part of the healthcare system of developed and developing countries [31] where 60% of the population entirely depend on them to relieve different types of ailments. Medicinal plants (MPs) have played a vital role in the treatment of human and livestock ailments since immemorial [32] partly due to the presence of bioactive secondary metabolites. Africa is the home of massive biodiversity rich in different types of animals and PS. The continent is likely to have approximately 45,000 PS of which 5000 species have medicinal importance [33]. Ethiopia is among the most diverse country located in East Africa containing approximately 6500–7000 PS (12% of them are endemic) in its flora [34]. It is also endowed with several languages, diverse cultures, and beliefs which are the driving force for the existence of traditional medical system plurality in the country [35]. Ethiopians have been using MPs and medicinal animals for the prevention, diagnosis, and treatment of different ailments since immemorial [36–40]. The healthcare demand of 80% of the people and 90% livestock in the country largely hinged on different PS [35]. Nearly 800 MPs are constantly employed to treat around 300 physical and mental diseases in the traditional healthcare system of Ethiopia [41]. The economic implication of MPs is noteworthy in Ethiopia. It is estimated that approximately 56,000 tons of wild MPs were collected per annum, which can potentially inject two billion Birr into the economy [42]. Such magnitude of MPs consumption is strongly associated with the accessibility, economic affordability, and cultural acceptability of MPs in different communities of Ethiopia [43].

**Data sources and search strategy**

The present review describes the ethnobotany of MPs used to treat epilepsy and related symptoms in Ethiopia. It also focuses on the in vivo experimental evidence about the pharmacological efficacy of MPs in attenuating seizures in different animal models and on the type of bioactive compounds with profound anticonvulsant outcomes from the phytochemical investigation of MPs to establish a solid foundation for future research to develop plant-based antiepileptic agents. For this purpose, ethnobotanical data about the antiepileptic MPs found in Ethiopia were searched and downloaded from online research databases (PubMed, Medline, Web of Science, Google Scholar, Science Direct, and other institutional repositories) written in English using specific keywords such as “medicinal plants”, “medicinal herbs”, “ethnobotanical study”, “traditional medicine”, “traditional medication”, “plant remedies”, “herbal remedies”, “traditional healers”, “indigenous knowledge”, “folk medicine”, “traditional healers” + “Ethiopia”. Plant use reports for epilepsy and related symptoms were compiled and examined in terms of the habit of the MPs, parts used, condition of remedy preparation, route of administration, number of use citation (by Districts), target groups, etc. Based on the ethnobotanical information, a combination of keywords such as “scientific name of MPs” + “convulsions”, “anticonvulsant”, “seizure”, “antiseizure”, “epilepsy”, “antiepileptic”, “epileptic seizure”, “phytochemical investigation”, “active compounds”, “phytochemical screening”, “phytocannabinoids”, “secondary metabolites”, “toxicity profiles”, etc. were used to search and collect relevant data on MPs with in vivo antiepileptic activities, toxicity profiles and to identify the phytochemicals (with already known anticonvulsant activities) present in the target MPs. The in vivo antiepileptic activities of MPs were analyzed based on the type of seizure-inducing agents, animal model, effective doses, and observed outcomes.

**Results and discussion**

**Ethnobotany of medicinal plants used for the treatment of epilepsy**

**Plant distribution across families and geography**

In this review, a total of 96 PS was found to have traditional healthcare prominence for the treatment of epilepsy and related symptoms in Ethiopia (Table 1). Of which 79 and 8 PS (*Agrocharis melanantha*, *Artemisia abyssinica*, *Crotalaria spinose*, *Cucurbita pepo*, *Erianthemum dregei*, *Myrica salicifolia*, *Solanum incanum*, and *Vigna membrancea*) were used to suppress ES in humans and animals, respectively. *Arundinaria alpina*, *Azadirachta indica*, *Croton macrostachyus*, *Echinops kebericho*, *Embelia schimperi*, *Nicotiana tabacum*, *Ocimum lamifolium*, *Satureja abyssinica* and *Vernonia amygdalina* were used to treat both human and livestock epilepsy cases. The reported MPs were distributed across 43 families and the highest occurrence belonged to Asteraceae (9, 20.93%), Fabaceae (8, 18.6%), Euphorbiaceae (7, 16.27%), Solanaceae (5, 11.63%), Lamiaceae (4, 9.3%) and Rutaceae (4, 9.3%). Apocynaceae, Celastraceae, and Rutaceae were represented by 3 (6.98%) PS each. In addition, Apiaceae, Cucurbitaceae, Verbenaceae, Malvaceae, Myrsinaceae, Myrtaceae, Oleaceae, Polygonaceae and Vitaceae families possessed 2 (4.65%) PS each. Other 26 families possessed a single PS effective against epilepsy in Ethiopia. Asteraceae, Fabaceae, Euphorbiaceae, and Solanaceae are the dominant families commonly found in the Ethiopian and Eritrean flora [44]. Thus, the
| No. | Scientific name | Family         | GF | PU | CP | ROA | TGs | Study areas                              | Refs.  |
|-----|----------------|----------------|----|----|----|-----|-----|------------------------------------------|--------|
| 1   | Acacia seyal    | Delile Fabaceae | T  | B  | D  | N   | Hu  | Amaro District, SNNPR                    | [62]   |
| 2   | Acalypha fruticosa | Forssk Euphorbiaceae | Sh | L  | F  | O   | Hu  | Yalo District, AF                       | [63]   |
| 3   | Aconitophyta schimperi (A. DC.) Benth. & Hook.f. ex Schweinf | Apocynaceae | Sh | R  | F/D– | Li  | Bale Mountain National Park, OR    | [65]   |
| 4   | Agrochris melanthera Hochst | Apiaceae | H  | R  | F  | N   | Li  | Ghimbi District, Selale Mountain Ridges, Jimma Zone, OR | [53, 66, 67] |
| 5   | Ajuga integrifolia, Buch.-Hamm | Lamiales | H  | L  | D  | O   | Hu  | Borecha District, OR                     | [68]   |
| 6   | Ampelocissus bombycina (Baker) Planch | Vitaceae | Cl | R  | F  | O   | Hu  | Hawassa Zuria District, SNNPR            | [59]   |
| 7   | Artemisia abyssica Sch. Bip. Ex A. Rich | Asteraceae | H  | R  | F  | N   | Li  | Bale Mountain National Park, OR         | [65]   |
| 8   | Artemisia afr a Jacq. Ex Wild | Asteraceae | H  | L, R, SB | F  | N   | Hu  | Bale Mountains National Park, OR       | [69]   |
| 9   | Anunnarina alpina K. Schum | Poaceae | T  | L  | Bu | F  | O   | Hu/Li Dawuro Zone, SNNPR               | [70]   |
| 10  | Asparagus africanus Lam | Asparagaceae | Sh | L, R, SB | F/D | N   | Hu  | Ankober & Enarj Enawga Districts, AR  | [71]   |
| 11  | Aspleniophyta aethiopicum (Kunth) mett | Apoapaeae | H  | L  | R  | F  | N   | Hu  | Ankober District, AR                    | [71]   |
| 12  | Azadirachta indica A. Juss | Mrieae | T  | L  | F  | O   | Hu/Li Adeva District, TR              | [72]   |
| 13  | Balanites aegyptica (L.) Del | Balanitaceae | T  | R  | –  | N   | Hu  | Chifia District, AR                     | [73]   |
| 14  | Biophytum umbraculum Welw | Oxliddaceae | H  | R  | F  | O   | Hu  | Dawuro Zone, SNNPR                    | [60]   |
| 15  | Brachylium brizantha (A. Rich.) Stapf | Poaceae | H  | R  | F  | O   | Hu  | Dawuro Zone, SNNPR                    | [60]   |
| 16  | Brucea antidysenterica J.F.Mill | Simaroubaceae | Sh | L  | F  | D   | Hu  | Adva District, TR                      | [74]   |
| 17  | Bredonia salicina (Vahl) Hepper & Wood | Rubiceae | T  | S  | F/D | O   | Hu  | Berta Ethnic Group, BGR                | [75]   |
| 18  | Buddleja polystachya | Luganiaceae | T  | L, R, B | D  | O, N | Hu  | Dawuro Zone, SNNPR                   | [60, 76] |
| 19  | Calpurnia aurea (Ait.) Benth | Fabaceae | Sh | R  | F/D | O   | Hu  | Berta Ethnic Group, BGR             | [75]   |
| 20  | Capparis tomentosa Lam | Capparidaceae | CI  | R  | D  | N   | Hu  | Enarj Enawga District, AR; Asgede Tsimbila District, TR | [77, 78] |
| 21  | Carissa edulis (Forssk). Vahl | Apoapaeae | Sh | R  | –  | –   | Hu  | Asgede Tsimbila District, TR     | [78]   |
| 22  | Causanthus auriculatus Forssk | Malpighiaceae | Cl | L  | F  | O   | Hu  | Gurage, Mareqo, Qebena, & Silti, SNNPR | [79]   |
| 23  | Caylusea abyssinica (Fresen.) Fisch. & C.A.Mey | Resedaceae | H  | L, R | F  | O   | Hu  | Hamar District, SNNPR                | [80]   |
| 24  | Chenopodium ambrosioides L | Chenopodiaceae | H  | L  | F  | O, Q | N   | Hu  | Dawuro Zone, SNNPR                    | [70]   |
| 25  | Cissus petiolata Hook. f | Vitaceae | Cl  | S  | –  | D   | Hu  | Tahtay Koraro, Medebay Zana & Asgede Tsimbila, TR | [81]   |
| 26  | Celosia polystachia (Forssk.) C.C. Towns | Aamaranthaceae | H  | L  | F  | O   | Hu  | Yalo District, AF                    | [63]   |
| 27  | Clerodendrum myricoides (Hochst.) R.Br. Ex Vatke | Verbenaceae | Sh | L  | F  | D   | Hu  | Bale Mountains National Park, OR, Asgede Tsimbila District, TR | [69, 78] |
| 28  | Clivia abyssinica Jaub | Euphorbiaceae | Sh | L  | F  | D   | Hu  | Aseko District, OR                  | [82]   |
| 29  | Croton spinosa Hochst. ex Benth | Fabaceae | H  | L  | F  | O   | Li  | Mana Angetu District, OR            | [83]   |
| 30  | Croton macrostachyus Del | Euphorbiaceae | T  | SB  | F/D | O   | Hu  | Mana Angetu District, OR        | [83]   |
| 31  | Cucumis ficifolius A. Rich | Cucumberaceae | Sh | L  | F  | O   | Hu  | Asendabo District, OR              | [84]   |
| 32  | Cucurbita pepo L | Cucurbitaceae | CI  | L  | F  | O   | Li  | Mana Angetu District & Jimma Zone, OR | [67, 83] |
| 33  | Desmodium repandum (Vahl) DC | Fabaceae | H  | R  | F/D | N   | Hu  | Ankober District, AR             | [71]   |
| 34  | Dicraneidra integrofili (L. f) Kuntze | Asteraceae | H  | L  | F  | N, D | Hu  | Dawuro Zone, SNNPR               | [60, 76] |
| 35  | Dregea schimperi (Decne.) Bullock | Apoapaeae | Cl | L  | F  | O   | Hu  | Gurage, Mareqo, Qebena & Silti, SNNPR | [79]   |
| 36  | Echinops Kebericho | Asteraceae | H  | R  | F  | N   | Hu  | Kembatta Tembaro Zone, SNNPR    | [85]   |
Table 1 (continued)

| No. | Scientific name                  | Family              | GF | PU | CP | ROA | TGs | Study areas                                                                 | Refs. |
|-----|----------------------------------|---------------------|----|----|----|-----|-----|-------------------------------------------------------------------------------|-------|
| 37  | Embelia schimperi Vatke          | Myrsinaceae         | R, RB | F  | Q, N | Hu/Li | Dawuro Zone, SNNPR                                                  | (70)  |
| 38  | Erianthemum dregei (Eckl and Zeyh. V. Tiegh) | Loranthaceae            | T   | Fr | F  | O   | Hu | Debark Woreda, AR                                                                  | (87)  |
| 39  | Eucalyptus globulus Labull        | Myrtaceae           | T   | L, Se | F/D | O, N | Hu | Baso Liben & Debre Elias Districts, AR                                          | (86)  |
| 40  | Euphorbia tirucalli L            | Euphorbiaceae       | Sh  | R   | F/D | O   | Hu | Amaro District, SNNPR                                                          | (62)  |
| 41  | Fagaropsis angolensis (Engl.) Milne-Redh | Rutaceae            | T   | Se, L | F  | O   | Hu | Kochere District, SNNPR                                                        | (88)  |
| 42  | Ficus vasta Forssk               | Moraceae            | T   | B   | D  | N, D | Hu | Dega Damot District, AR                                                         | (52)  |
| 43  | Galphimia cocinea                | Rubiaceae           | Sh  | L, R | F  | O   | Hu | Dawuro Zone, SNNPR                                                              | (60, 76) |
| 44  | Gloriosa superba                 | Lamiaceae           | Sh  | L   | F  | O   | Hu | Harla & Dengego valleys, DDAC                                                   | (89)  |
| 45  | Guizotia scabra (Vis) Chiov      | Compositae          | H   | R   | D  | O   | Hu | Ada’a District, OR                                                              | (90)  |
| 46  | Hagenia abyssinica (Bruce) J.F. Gmel | Rosaceae            | T   | Fi  | –   | –   | Hu | Bale Rural Communities, OR                                                      | (91)  |
| 47  | Hypericum spinosum A. Rich       | Hypericaceae        | Sh  | L   | D  | D   | Hu | Around Fiche District, OR                                                       | (82)  |
| 48  | Indigofera articulata Gouan       | Fabaceae            | Sh  | L, R | F  | O   | Hu | Yalo District, AR                                                               | (63)  |
| 49  | Indigofera coerulesa Roxb         | Fabaceae            | Sh  | R   | F  | O   | Hu | Jeldesa Cluster, DDAC                                                           | (93)  |
| 50  | Inula confertifolia A. Rich      | Asteraceae          | Sh  | L   | F  | N   | Hu | Enarj Enawga District, AR                                                       | (77)  |
| 51  | Jatropha curcas L                 | Euphorbiaceae       | Sh  | Se  | F  | O   | Hu | Gurage, Mareqo, Qebena & Silti, SNNPR                                           | (79)  |
| 52  | Jasminum acutiflorum Hochst. ex DC | Oleaceae            | CI  | L   | F  | N   | Hu | Kembatta Tembaro Zone, SNNPR                                                    | (85)  |
| 53  | Justicia schimperiana Hochst. ex Nees Exell | Acanthaceae        | Sh  | L   | F  | O, D | Hu | Dawuro Zone, SNNPR                                                              | (70)  |
| 54  | Lagerstroemia abyssinica (Hoff. f) C. Jeffrey | Cucurbitaceae     | H   | L   | F  | N   | Hu | Asendabo District, OR                                                           | (84)  |
| 55  | Lagnera crispata (Vahl) Hepper & Wood | Asteraceae          | Sh  | R   | F  | O   | Hu | Yilmana Densa & Quarit Districts, AR                                            | (42)  |
| 56  | Labelia gibberosa Hermel          | Lobeliaceae         | T   | Se  | D  | O   | Hu | Gubalafto District, AR                                                           | (61)  |
| 57  | Maytenus gracilis (Welw.ex Oliv) Exell | Celastraceae       | Sh  | L   | D  | O   | Hu | Bale Mountains National Park, OR                                                | (69)  |
| 58  | Maytenus heterophylla (Eckl. & Zeyh.) Robson | Celastraceae      | Sh  | L   | F  | O   | Hu | Gurage, Mareqo, Qebena & Silti, SNNPR                                           | (79)  |
| 59  | Maytenus senegalensis (Lam.) Excell | Celastraceae       | Sh  | Se  | F/D | O   | Hu | Wonago District, SNNPR                                                          | (45)  |
| 60  | Myrsine coccifera Hochst. ex A. Rich | Myrtaceae          | T   | B   | D  | N   | Li | Hulet Eju Enese District, AR                                                    | (35)  |
| 61  | Nicotiana tabacum L               | Solanaceae          | Sh  | R   | D  | O, N | Hu | Mana Angetu District, OR, Ankerber District, AR                                 | (71, 83) |
| 62  | Ocimum canum Sims                 | Lamiaceae           | H   | L   | F  | O   | Li | Mana Angetu District, OR                                                        | (83)  |
| 63  | Ocimum conduleum L                | Lamiaceae           | H   | L   | F  | O, N, D | Hu/Li | Dawuro Zone, SNNPR                                                              | (70)  |
| 64  | Olea europaea L                   | Oleaceae            | T   | L   | D  | N   | Hu | Hulet Eju Enese District, AR                                                    | (35)  |
| 65  | Olnia rochetiana A. Juss          | Oliniaceae          | T   | R   | F/D | N   | Hu | Ankerber District, AR                                                           | (71)  |
| 66  | Opuntia ficus-indica (L) Miller   | Cactaceae           | H   | L   | F  | D   | Hu | Debark District, AR                                                             | (87)  |
| 67  | Pavetta abyssinica Fresen         | Rubiaceae           | Sh  | Bu, Se | F  | N   | Hu | Kembatta Tembaro Zone, SNNPR                                                    | (85)  |
| 68  | Pentas schimperiaria (A. Rich) Vatke | Rubiaceae          | Sh  | RB  | F/D | O   | Hu | Wonago District, SNNPR                                                          | (45)  |
| 69  | Plectranthus edulis Vatke         | Lamiaceae           | H   | L, R | -  | O   | Hu | Abay Chomen District, OR                                                        | (96)  |
| 70  | Pterolobium stellatum Forsk. Brenan | Fabaceae            | Sh  | R   | F/D | N   | Hu | Hulet Eju Enese District, AR                                                    | (35)  |
| 71  | Rhamnus stadda A. Rich            | Rhamnaceae          | Sh  | L   | F  | N   | Hu | Enarj Enawga District, AR                                                       | (77)  |
| 72  | Rhus vulgaris Meikle              | Anacardiaceae       | Sh  | L   | F  | O, N, D | Hu | Dawuro Zone, SNNPR                                                              | (70)  |
mire presence of such PS in a relatively higher number in the antiepileptic MPs list is not a surprise. Overall, the data showed the cultural significance and medicinal importance of Asteraceae, Fabaceae, Euphorbiaceae, and Solanaceae families in the management of ES in Ethiopia. The dominance of Asteraceae, Fabaceae, Euphorbiaceae, and Solanaceae families were also reported in several ethnobotanical surveys conducted to document the MPs and associated indigenous knowledge used to treat different ailments in Ethiopia [45, 46].

TMs, especially MPs are routinely used for the management of different diseases in the traditional healthcare system of the Regional States of Ethiopia [47–53]. Although these Regional States share some common entities, they have distinct biodiversities, agro-ecology, cultures, livelihood, values, beliefs, etc. which nurture the indigenous knowledge and traditional practices of dwellers. Hence, multifaceted treatment approaches and miscellaneous traditional remedies are prevalent in different cultural groups of Ethiopia [36, 44, 54, 55]. In line with this fact, the present literature review reiterated that the use citations of antiepileptic MPs are widely distributed across the different regional states of Ethiopia (Fig. 1): Oromia (29 PS), Amhara (25 PS), Southern Nations, Nationalities and Peoples (33 PS), Afar (4 PS), Tigray (8 PS), Benshangul-Gumuz (3 PS) and Dire Dawa Administration Council (2 PS). More than 70% of MP species prescribed for the treatment of seizure in Ethiopia belonged to the three most populous and diverse regions, namely Oromia, Amhara, and the SNNP Regional States. This may be attributed to the presence of different biodiversities, cultural pluralities, and thereby rich indigenous MPs knowledge and practice in the regions. Despite the cross-cultural connections and neighborhood manifested by the long common border between Oromia and Amhara regions as well as Oromia and SNNP regions, the consensus of THs on antiepileptic MPs was quite low, only a few MPs were commonly used across the regions.

### Table 1 (continued)

| No. | Scientific name          | Family            | GF | PU | CP | ROA | TGs | Study areas                                      | Refs. |
|-----|--------------------------|-------------------|----|----|----|-----|-----|-------------------------------------------------|-------|
| 73  | Rumex nepaensis Spreng   | Polygonaceae      | Sh | R  | F  | N   | Hu  | Boricha District, OR                            | 68    |
| 74  | Ruta chalepensis L        | Rutaceae          | Sh | L, Se | F | N   | Hu/Li | Hulet Eju Enese District, AR                   | 35    |
| 75  | Satureja abyssinica (Benth.) Briq | Lamiales | H | L  | F  | N   | Hu/Li | Dawro Zone, SNNP                               | 60, 76 |
| 76  | Securidaca longepedunculata Fries | Polygonaceae | T | R  | D  | N   | Hu  | Enemay District, AR                             | 39    |
| 77  | Solanum insularum L      | Solanaceae        | Sh | R  | F  | O   | Li   | Mana Angetu District, OR                        | 83    |
| 78  | Sida rhombifolia L       | Malvaceae         | H  | R  | –   | N   | Hu   | Tahtay Koraro, Medebay Zana & Asgede Tsimba, TR | 81    |
| 79  | Sida schimperiana Hochst. Ex A.Rich | Malvaceae  | Sh – | F | O   | Hu   | Wonago District, SNNP                          | 45    |
| 80  | Syzygium guineense (Willd.) DC | Myrtaceae       | T  | S  | D  | O, N | Hu   | Berta Ethnic Group, BGR                        | 75    |
| 81  | Traugia cinerea (Pax) Gilbert and Radcli-Smith | Euphorbiaceae | Cl | R  | D  | O   | Hu   | Menz Gera-Midir District, AR                   | 98    |
| 82  | Tyntura pseudochina L    | Compositae        | Sh  | L  | F  | O   | Hu   | Boricha District, OR                            | 68    |
| 83  | Urea hypselodendron (Hochst.) ex A. Rich | Urticaceae | Cl  | R  | D  | O   | Hu   | Hulet Eju Enese District, AR                   | 35    |
| 84  | Vangueria volkensii K.Schum | Rubiaceae       | Sh | L, R | F  | O   | Hu   | Hamar District, SNNP                           | 80    |
| 85  | Verbena bonariensis      | Verbenaceae       | H  | L  | D  | N   | Hu   | Mojana District, AR                             | 99    |
| 86  | Verronia amygdalina Del  | Asteraceae        | Sh | L, B | F  | O, D | Hu/Li | Dawro Zone, SNNP                               | 70    |
| 87  | Vigna membrancea (L.) A. Rich | Fabaceae        | Cl | L  | F/D | O   | Li   | Abay Chomen & Kersa Districts, OR              | 55, 96 |
| 88  | Withania somnifera (L.) Dun | Solanaceae     | Sh | R  | F/D | O   | Hu   | Mana Angetu District, OR                        | 83    |
| 89  | Xanthium stramonum L     | Solanaceae        | H  | L  | F  | D   | Hu   | Fadis District, OR                              | 95    |
| 90  | Zingiber officinale Rosco | Zingiberaceae    | H  | R  | F  | O   | Hu   | Amaro District, SNNPR                          | 62    |

GF: growth forms, T: Tree, Sh: shrub, H: herb and Cl: climber, Plant: PU parts used, L: leaf, S: stem, SB: stem bark, R: root, RB: root bark, Bd: buds, Ap: apex, Se: seed, Wh: whole plant, Ar: aerial part, Bu: bulbs, Lx: latex, Fr: fruit, Fl: flower and Rh: rhizome, CP: condition of preparation, F: fresh, and D: dry, ROA: routes of administration, O: Oral, N: nasal, D: dermal and Au: auricular, TGs: target groups, Hu: Human and Li: livestock, Regional states of Ethiopia: AR: amhara region, AF: Afar region, BGR: Benshangul-Gumuz region, DDAC: dire dawa administration council, OR: oromia region, TR: tigray region, SNNP: southern nations, nationalities and peoples region.
the preparation of remedies. They also often used roots (52, 34.14%) and seeds (10, 6.76%) for the formulation of medicinal recipes. In addition, bulbs, stembark, root-bark, apex, rhizome, flowers, fruits, the whole plant, and aerial part of MPs were also used for the extraction of effective medicines for seizure. The presence of bioactive compounds, both in therapeutic abundance and variety, in leaves and roots may be associated with the curative effects of such recipes against epilepsy [56, 57]. Fresh organs of plants (81, 64.8%) were often employed for the preparation of antiepileptic medications in Ethiopia. Dry forms of plant parts (23, 18.4%) were also used for the preparation of remedies. Nearly 17% of plant parts were used regardless of the condition they exist (either fresh or dry). As fresh plant parts are rich in bioactive metabolites, they are frequently sought for the formulation of remedies not only for epilepsy but also for other ailments in Ethiopia. In addition, fresh plant parts are convenient to prepare medications using crushing, squeezing, maceration, infusion, decoction, etc., and can be ready for use in a short period as compared to dry plant organs [44].

Diverse approaches and strict procedures are followed by the THs for the preparation of remedies: abstraction of pharmacologically relevant crude extract or essential oils from different plant organs in Ethiopia [47, 58, 59]. Depending on the perceived knowledge of the THs, some may prefer crushing for remedy preparation while others may use tying or burning of the same plant part for the same ailment. The antiepileptic medications in Ethiopia were most commonly prepared using crushing, squeezing, maceration, pounding, grinding, decoction, etc. techniques. Water was the main extraction solvent employed in most preparations to tailor the concentration of the recipe to the supposed level of therapeutic efficacy and to avoid dose-related toxicities in patients [45]. Additives such as milk, “tella” (local beer), “teff injera” (flat bread), sugar, etc. [60–62] were used to improve the taste of the recipe and to enhance patient compliance towards the formulations. Most of the antiepileptic herbal formulations were administered through the oral route (63, 51.64%) by drinking, chewing, etc. followed by nasal (41, 33.61%) in the form of sniffing, smoking, and fumigation. Dermal route of administration (ROA) (18, 14.75%)

Fig. 1 Location map of Ethiopia. The different colored areas represent the regional states in Ethiopia where the use of plant-based medicines are reported.

[Image of Ethiopia's location map]
(through fumigation and washing) was seldom employed for the delivery of antiseizure herbal medications in the Ethiopian context. Oral is described as the primary ROA in several ethnobotanical studies conducted elsewhere [48, 59] due to the fast onset of action and ease of application.

Multiple medicinal plants prescriptions for the treatment of epilepsy

Combinations of two or more PS are seldom used to formulate remedies for epilepsy and related symptoms in Ethiopia and elsewhere [100]. This is based on the fact that the consumption of multiple MPs could have potential synergistic outcomes and thereby enhanced pharmacological activities. For instance, the roots of four MPs including Guizotia scabra, Ajuga integrifolia, Foeniculum vulgare, and Withania somnifera have been used for the preparation of remedy that can be taken through the oral route in Ada’a District, Oromia Regional State, Ethiopia [90] that can potentially attenuate convulsions in humans (Table 2). On the other hand, leaves of Artemisia absy- sinica, Brucea antidysentrica, and Cucumis ficifolius were employed for the preparation of recipes effective against epilepsy, when taken orally, around Jimma, Oromia Regional State, Ethiopia [101]. Similarly, the leaves of Nicotiana tabacum, Ocimum lamii-folium, and Withania somnifera were also used for the preparation of remedies that can be applied externally (dermal route) to relieve seizure [102]. Herbalists living around Fiche District, Oromia Regional State, Ethiopia prepare a remedy for epilepsy from leaves of Hypericum quartinianum, Podocarpus falactus, and Teclea nobilis for external application through the nasal ROA [92]. The different classes of phytochemicals such as alkaloids, flavonoids, terpenoids, etc. present in these MPs and their combined effect in enhancing the relative abundance/concentration and amplifying the pharmacological efficacy through synergism may be associated with the preparation of efficient antiepileptic recipes from multiple MPs. Ocimum lamii-folium, Nicotiana tabacum, Ruta chalepensis and Withania somnifera were most frequently sought MPs for the preparation of antiseizure medications, each become part of two different formulations [35, 90, 94, 102]. The wide application of Ocimum lamii-folium, Nicotiana tabacum, Ruta chalepensis and Withania somnifera in different formulations might be due to the presence of

Table 2 Ethnobotanical data of multiple MPs prescriptions used to treat epilepsy and related symptoms in Ethiopia

| No. | Scientific name            | Family            | GF  | PU | CP | ROA  | Study area                | Refs. |
|-----|---------------------------|-------------------|-----|----|----|------|---------------------------|-------|
| 1   | Artemisia absy-sinica     | Asteraceae        | H   | L  | F  | O    | Jimma Area District, OR   | [101] |
| 2   | Brucea antidysenticra     | Simaroubaceae     | Sh  | L  | F  |      |                           |       |
| 3   | Cucumis ficifolus         | Solanaceae        | Cl  | L  | F  |      |                           |       |
| 1   | Embelia schimperi Vatke   | Myrsinaceae       | T   | Fr | F  | O    | Debark District, AR       | [87]  |
| 2   | Guizotia absy-sinica (L. f) | Cass | Asteraceae | H   | Se | D  |      |                           |       |
| 1   | Fagaropsis angolensis (Engl) Milne-Redh | Rutaceae | T   | Se | D  | O    | Kocbere District, SNNPR   | [88]  |
| 2   | Solanum spp.              | Solanaceae        | H   | L  | F  |      |                           |       |
| 1   | Guizotia scabra (Vis) Chiov | Compositae     | H   | R  | D  | O    | Ada’a District, OR        | [90]  |
| 2   | Ajuga integrifolia, Buch.-Hamn | Lamiaceae | H   | R  | F/D |      |                           |       |
| 3   | Foeniculum vulgare Mill  | Apiaceae          | H   | R  | F/D |      |                           |       |
| 4   | Withania somnifera (L.) Dun | Solanaceae | Sh  | R  | F/D |      |                           |       |
| 1   | Hypericum quartinianum A. Rich | Hypericaceae | Sh  | L  | D  | D    | Around Fiche District, OR | [92]  |
| 2   | Podocarpus falactus (Thunb.) R. B. ex Mirb | – | T   | L  | F  |      |                           |       |
| 3   | Teclea nobilis Del        | Rutaceae          | T   | L  | F  |      |                           |       |
| 1   | Nicotiana tabacum L       | Solanaceae        | H   | L  | F  | D    | Dugda District, OR        | [94]  |
| 2   | Ocimum lamii-folium Hochst | Lamiaceae        | H   | L  | F  |      |                           |       |
| 1   | Nicotiana tabacum L       | Solanaceae        | H   | L  | F  | D    | Seru District, OR         | [102] |
| 2   | Ocimum lamii-folium Hochst | Lamiaceae        | H   | L  | F  |      |                           |       |
| 3   | Withania somnifera (L.) Dun | Solanaceae | Sh  | L  | F  |      |                           |       |
| 1   | Pterolobium stellatum Forsk. Brenan | Fabaceae | Cl  | R  | F  | N    | Hulet Eju Enese District, AR | [35]  |
| 2   | Ruta chalepensis L        | Rutaceae          | Sh  | L  | F  |      |                           |       |
| 1   | Ruta chalepensis L        | Rutaceae          | Sh  | L  | Se | F  | N    | Hulet Eju Enese District, AR | [35]  |
| 2   | Allium sativum L          | Alliaceae         | H   | Bu | F/D |      |                           |       |

GF: growth forms, T: Tree, Sh: shrub, H: herb, CI: climber, PU: plant parts used, L: leaf, R: root, S: seed, Ar: aerial part, Bu: bulbs and Fr: fruit, CP: condition of preparation, F: Fresh and D dry, ROA: routes of administration, O: Oral, N: nasal and D: dermal, Reginal states of Ethiopia: AR: amhara region, AF: afar region, BGR: benshangul-gumuz region, DDAC: dire dawa administration council, OR: oromia region, TR: tigray region, SNNPR: southern nations, nationalities and peoples region.
convulsion-suppressive bioactive compounds in such MPs. For obvious reasons, the use of formulations of multiple MPs is a common practice in the treatment of epilepsy in different parts of the world [103].

Global importance of the medicinal plants in the treatment of Epilepsy
Among the reported MPs for the treatment of epilepsy and related symptoms in Ethiopia, 34 PS were also routinely used for the same indications in different parts of the world including Africa, Asia, the Middle East, and Latin America (Table 3). Among these, *Carissa edulis* was the most popular (cited in six countries) antiepileptic MP frequently used to control seizure in Ethiopia, Nigeria, South Africa, Uganda, Malawi, and Kenya [104–108]. Similarly, *Maytenus senegalensis* was another well-known (cited in five countries) anticonvulsant MP in Africa including Ethiopia, Uganda, Zimbabwe, South Africa, and Guinea-Bissau [100, 106, 107, 109]. *Withania somnifera* was another multipurpose MP (cited in four countries) used to control convulsions in Ethiopia, Lesotho, India, and in East African countries [107, 110, 111]. Moreover, *Acacia seyal*, *Acalypha fruticosa*, *Allium sativum*, *Balanites aegyptica*, *Biophytum umbraculum*,

| No. | Scientific name        | Family       | GF  | PU       | Country/region                      | Refs.        |
|-----|------------------------|--------------|-----|----------|-------------------------------------|--------------|
| 1   | *Acacia seyal*         | Fabaceae     | T   | R        | Tanzania and Uganda                 | [106, 112]   |
| 2   | *Acalypha fruticosa*   | Euphorbiaceae| Sh  | L, R     | Tanzania and Kenya                  | [113, 114]   |
| 3   | *Allium sativum*       | Alliaceae    | H   | Bu       | India and Cameroon                  | [103, 115]   |
| 4   | *Artemisia afra*       | Asteraceae   | H   | L        | South Africa                        | [105]        |
| 5   | *Arundinaria alpina*   | Poaceae      | T   | R        | Uganda                              | [138]        |
| 6   | *Asparagus africanus*   | Asparagaceae | Sh  | R        | Cameroon                            | [127]        |
| 7   | *Azadirachta indica*   | Meliaceae    | T   | L        | India                               | [128]        |
| 8   | *Balanites aegyptica*  | Balanitaceae | T   | L, B, R  | Mali and Saudi Arabia               | [116, 117]   |
| 9   | *Biophytum umbraclum*  | Oxalidaceae  | H   | L, Wh    | Cameron and Uganda                  | [115, 118]   |
| 10  | *Capparis tomentosa*   | Capparidaceae| Cl  | L        | Uganda                              | [106]        |
| 11  | *Carissa edulis*       | Apocynaceae  | Sh  | L, R, Fr | Nigeria, South Africa, Uganda, Malawi and Kenya | [104–108]   |
| 12  | *Chenopodium ambrosioides* | Chenopodiaceae | H   | L        | Democratic Republic of Congo        | [139]        |
| 13  | *Clerodendrum myricoides* | Verbenaceae   | Sh  | L, R     | South Africa and Kenya              | [100, 119]   |
| 14  | *Clutia abyssinica*    | Euphorbiaceae| Sh  | R        | Rwanda                              | [129]        |
| 15  | *Croton macrostachyus* | Euphorbiaceae| T   | B        | Cameroon                            | [140]        |
| 16  | *Cucurbita pepo*       | Cucurbitaceae| Cl  | –        | Nigeria                             | [130]        |
| 17  | *Eucalyptus globulus*  | Myrtaceae    | T   | L, B     | Kenya                               | [131]        |
| 18  | *Euphorbia tirucalli*  | Euphorbiaceae| S   | Lx, Ar   | Somalia and East Africa              | [120, 121]   |
| 19  | *Indigofera arrecta*   | Fabaceae     | Sh  | L, R     | South Africa and Nigeria            | [100, 122]   |
| 20  | *Indigofera articulata*| Fabaceae     | Sh  | Wh       | India                               | [132]        |
| 21  | *Indigofera coerulea*  | Fabaceae     | Sh  | L        | India                               | [133]        |
| 22  | *Jatropha curcas*      | Euphorbiaceae| Sh  | L        | Nigeria                             | [134]        |
| 23  | *Maytenus heterophylla*| Celastraceae | Sh  | R        | East Africa                         | [107]        |
| 24  | *Maytenus senegalensis*| Celastraceae | Sh  | L, R     | Uganda, Zimbabwe, South Africa and Guinea-Bissau | [100, 106, 107, 109] |
| 25  | *Mynta salicifolia*    | Myrsinaceae  | T   | B        | Uganda                              | [118]        |
| 26  | *Nicotiana tabacum*    | Solanaceae   | H   | L        | Nigeria and Cameroon                | [115, 123, 124] |
| 27  | *Olea europaea*        | Oleaceae     | T   | B, R, Fr | Kenya                               | [108]        |
| 28  | *Opuntia ficus-indica* | Cactaceae    | H   | Fl       | India                               | [135]        |
| 29  | *Ruta chalepensis*     | Rutaceae     | Sh  | Ar       | Morocco and Mexico                  | [125, 126]   |
| 30  | *Sida rhombifolia*     | Malvaceae    | H   | Wh       | India                               | [136]        |
| 31  | *Syzygium guineense*   | Myrtaceae    | T   | SB       | West Africa                         | [109]        |
| 32  | *Withania somnifera*   | Solanaceae   | H   | S, R     | Lesotho, East Africa and India      | [107, 110, 111] |
| 33  | *Xanthium stramonium*  | Solanaceae   | H   | Wh       | India                               | [141]        |
| 34  | *Zingiber officinale*  | Zingiberaceae| H   | Rh       | Japan                               | [137]        |

GF growth forms, T Tree, Sh shrub, H herb, Cl climber, PU plant parts used, L Leaf, S stem, SB stem bark, R root, RB root bark, Wh whole plant, Ar Aerial part, Bu bulbs, Lx latex, Fr fruit, and Rh rhizome
Capparis tomentosa, Artemisia afra, Asparagus africanus, Ruta chalepensis, Maytenus heterophylla, Nicotiana tabacum, and Clutia abyssinica were the other MPs reported for their usefulness against convulsions in at least three countries [100, 103, 106, 107, 112–126]. The remaining MPs: Artemisia arrecta, Asparagus africanus, Azadirachta indica, Capparis tomentosa, Clutia abyssinica, Croton macrostachyus, Cucurbita pepo, Eucalyptus globulus, Indigofera articulata, Indigofera coerulae, Jatropha curcas, Myrica salicifolia, Olea europaea, Opuntia ficus-indica, Sida rhombifolia, Xanthium stramonium, and Zingiber officinale were indicated for epilepsy in Ethiopia and at least one other country [105, 106, 108, 109, 118, 127–137]. The extensive use of MPs across different countries of the globe echoed the existence of shared ethnopharmacological knowledge among the THs, the importance of such MPs in the healthcare system of LMIC, especially in tropical and southern Africa, and more importantly, the pharmacological efficacy of the MPs in the treatment of epilepsy and related symptoms.

Pharmacological evidence of reported medicinal plants

Animal models for screening of anticonvulsant or antiepileptic agents

The anticonvulsant or antiseizure activity of MPs claimed by THs for the management of epilepsy could be verified by using different in vitro and in vivo experiments. In 1937, electrically-induced convulsions in cats were used to check the bioactivity of phenytoin, the first modern AED [142]. Later, this initiative paved the way for the discovery of other seizure models responsible for the discovery of more safe and efficacious second-generation AEDs such as lamotrigine, levetiracetam, topiramate, lacosamide, pregabalin, etc. [143]. The ability of crude extracts or bioactive compounds to suppress different forms of seizures can be examined by animal models by artificially induced convulsions using maximal electroshock (MES) or drugs such as pentylenetetrazol (PTZ), picrotoxin (PIC), strychnine (STR), pilocarpine (PLC), ionicoticin hydrazide acid (INH), Kainic acid (KA), 4-aminophylline (AMP), bicucculline (BIC), etc. [144]. The similarity in the pattern of seizure triggered by different stimuli in animal models with humans, simplicity upon execution, quick response rate, and most importantly, predictive clinical outcomes in humans [145] make the in vivo seizure models trustworthy in epilepsy research. In general, MES acute seizure tests characterized by tonic extensions of forelimbs in and hind limbs followed by all limb clonus in mice/rat; subcutaneous PTZ acute seizure tests manifested by myoclonic jerks followed by unilateral forelimb and bilateral clonus, vibrissae twitching in mice/rats and a Kindled rodent model of chronic hyperexcitability characterized by unilateral and bilateral forelimbs clonus that progresses to rearing and falling in rats are the most common and “clinically validated” models for early evaluation of AEDs [142]. Albeit, the aforementioned acute seizure models failed to trace bioactive compounds effective against refractory or drug-resistant seizures. Thus, there had been a pressing need for the discovery of alternative seizure models which can embrace the deviations observed in “clinically validated” models. More recently, several non-mammalian seizure models consisting of fruit flies (Drosophila melanogaster), medicinal leeches (Hirudo verbena), planaria, roundworms (Caenorhabditis elegans), tadpoles (Xenopus laevis), zebrafish (Danio rerio), etc. were recognized for their versatility to assess the anticonvulsant activities of synthesized compounds or plant extracts [146, 147]. Of which, the zebrafish larvae were the most frequently used seizure model because of its high fertility rate and development, similar CNS organization with mammals which can be observed in translucent egg and embryo make it ideal to study CNS disorders provoked by external stimuli [148]. PTZ, KA, PLC and electrical stimulation are employed to induce convulsions in in the aforesaid non-mammalian seizure models [147].

In vivo pharmacological activities of antiepileptic medicinal plants

CAMs, especially herbal remedies are extensively used for the treatment of epilepsy across the globe due to their desirable treatment outcomes and tolerable side effects [144]. Moreover, herbal therapies may yield a new horizon for treating patients seeking inexpensive treatments for untreated epilepsy and experiencing refractory seizures. Taking the popularity of the MPs prescribed for treatment and management of epilepsy in different cultural groups across the globe into account, preliminary in vitro and/or in vivo pharmacological evaluation of MPs and phytochemical isolation of bioactive compounds have been conducted to test the validity of the hypothesis made by THs found elsewhere. Researchers employed different animal models to quantify the extent of suppression of different forms of seizures induced via MES, PTZ, PIC, STR, PLC, BIC and phytochemical isolation of bioactive compounds or plant extracts [146, 147]. Of which, the zebrafish larvae were the most frequently used seizure model because of its high fertility rate and development, similar CNS organization with mammals which can be observed in translucent egg and embryo make it ideal to study CNS disorders provoked by external stimuli [148]. PTZ, KA, PLC and electrical stimulation are employed to induce convulsions in in the aforesaid non-mammalian seizure models [147].
| No. | Scientific name       | PU | Extract | Seizure-inducing stimuli | Animal models | Doses (mg/kg) | Treatment outcomes                                                                                     | Refs. |
|-----|----------------------|----|---------|--------------------------|---------------|---------------|-------------------------------------------------------------------------------------------------------|-------|
| 1   | Acalypha fruticosa   | Ar | CH      | PTZ, MES & INH           | Adult Swiss albino mice (25–30 g) | 30–300         | Protected the mice from PTZ and MES-induced convulsions. Delayed the latency of convulsions triggered by INH | [113] |
| 2   | Ajuga integrifolia   | L  | HME     | PTZ & MES                | Swiss albino mice (20–30 g)         | 100–400        | HME extract significantly delayed the latency onset of PTZ-induced convulsions at all doses (100, 200 & 400 mg/kg) and decreased the duration of tonic hind limb extension in the MES model. Unlike BU and CH fractions, the AQ fraction didn’t show any effect on latency and duration of convulsions at all doses | [149] |
| 3   | Allium sativum       | Bu | AQ      | PLC                      | Male adult Wistar rats (200–250 g)  | 100 & 300      | The AQ extract demonstrated neuroprotective potential in PLC-induced neurodegeneration, mitigated the prefrontal cortex (PFC) astrogliosis. However, it didn’t decrease GLU and other neurotransmitter levels | [150] |
| 4   | Artemisia afra       | Wh | HET     | PTZ                      | Male BALB/c mice (22–30 g)          | 250–1000       | Delay the mean onset of convulsion and decrease the mean duration of convulsions                      | [151] |
| 5   | Asparagus africanus  | R  | AQ      | PLC                      | Mus musculus Swiss mice (20–29 g)  | 63.5–254       | Decreased the duration and number of clonic and tonic convulsions. Increased the latency time of onset of clonic and tonic convulsions | [127] |
| 6   | Azadirachta indica  | –  | –       | PTZ                      | Sprague Dawley strain male rats     | 100            | Decrease in seizures severity by decreasing the mean onset time of jerks and protecting the brain against anoxic damage and oxidative stress (OS) due to prolonged seizures | [152] |
|     |                      | R  | HET     | PTZ & MES                | Albino rats of either sex (200–250 g) & Albino mice of either sex (30–50 g) | 200–800        | There was no significant increase in the mean duration of hind limb extension in the test groups at all doses (200, 400 & 800 mg/kg). The HET root extract was devoid of any anticonvulsant activity in rodents | [153] |
| 7   | Balanites aegyptica  | SB | CH & HME| PTZ, MES & PLC           | Male Albino Swiss mice (28–38 g) & Male Albino Swiss rats (200–225 g)  | 200 & 400      | Both solvent extracts significantly suppressed hind limb extension and delayed latency of myoclonic spasm and clonic convulsions of mice at all doses. Similarly, the CH (100 mg) and HME (100 & 200 mg) extracts delayed the latency to rearing with forelimb clonus in rats | [154] |
| No. | Scientific name       | PU | Extract | Seizure-inducing stimuli          | Animal models                        | Doses (mg/kg) | Treatment outcomes                                                                 | Refs. |
|-----|-----------------------|----|---------|-----------------------------------|--------------------------------------|---------------|------------------------------------------------------------------------------------|-------|
| 8   | Buddleja polystachya  | L  | HME     | PTZ & MES                        | Swiss albino mice (27–33 gm)         | 100–400       | The HME extract elicited a significant anticonvulsant effect in MES (all doses) and PTZ models (200 & 400 mg/kg). The BU fractions showed a significant anticonvulsant effect in both models. In addition, the CH fractions were active against seizure-induced by PTZ (200 & 400 mg/kg). While the AQ fractions were devoid of any anticonvulsant activities in both models | [155] |
| 9   | Carissa edulis        | RB | AQ      | PTZ, PIC, STR, NMDA, INH & AMP    | Swiss Albino mice (18–30 g) & Wistar albino male rats (130–220 g) | 150–600       | The AQ fractions protected PTZ, STR, and NMDA-induced seizures significantly at higher doses. But the AQ fractions and sub-fractions showed no effect on MES-induced seizures | [156] |
|     |                       | HET| PTZ & MES| Swiss Albino mice of either sex (15–24 g) & White ranger cockerels of either sex (30–41 g) | 5–20 | Delayed the mean onset of convulsions in mice and chicks. It exhibited a dose-dependent inhibition of the convulsion induced by MES (60% protection at 20 mg/kg) | [104] |
| 10  | Clerodendrum myricoides | L  | HET     | PTZ                               | Male BALB/c mice (22–30 g)           | 300–1200      | Unlike the solvent fractions, the crude extract demonstrated a significant delay in the mean latency to onset of seizures and decrease the duration of convulsions in a dose-dependent manner | [157] |
| 11  | Clutia abyssinica     | L  | HME     | PTZ & MES                        | Male BALB/c mice (20–30 g)           | 400 & 800     | Though the crude extract exhibited insignificant dose-dependent delay on the onset of a seizure, it improved the survival of mice | [158] |
| 12  | Croton macrostachyus  | SB | AQ      | PIC, STR, PTZ, INH & MES          | Adult male Mus musculus Swiss mice   | 13–135        | The crude extract prevented the mice from PIC, STR, PTZ, and MES-induced seizures. It also delayed the onset of INH-induced seizures | [140] |
| 13  | Indigofera arrecta    | L  | ME      | PTZ                               | Zebrafish with an AB or EK strain    | 30–300*       | The main constituent, idirubin, revealed reduction of epileptiform discharges in PTZ-treated zebrafish larvae | [144] |
| 14  | Jatropha curcas       | L  | AQ      | PTZ & MES                        | Male albino mice (25–30 g)           | 100–400       | Protected the mice against the MES-induced convulsion. While at 400 mg/kg, it significantly protected the mice against PTZ-induced seizures | [134] |
| No. | Scientific name               | PU    | Extract    | Seizure-inducing stimuli | Animal models                          | Doses (mg/kg) | Treatment outcomes                                                                                                                                                                                                 | Refs. |
|-----|-------------------------------|-------|------------|--------------------------|----------------------------------------|---------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|
| 15  | *Maytenus heterophylla*       | L, R & SB | ME         | PIC                      | White Swiss albino mice (20–24 g)     | 50–200        | The stembark extract significantly suppressed convulsions induced by PIC better than the leaf and root extracts. It also offered up to 62.5% protection against seizure at 200 mg/kg, which was significant (p < 0.05) as compared to diazepam | [159] |
| 16  | *Nicotiana tabacum*           | Ar    | AQ & HME   | PTZ                      | Random breed albino male mice (18–24 g) | 100           | Both extracts decreased the onset and severity of seizures (but it is statistically insignificant as compared to the negative control group). Both extracts decreased the mortality of PTZ-treated mice | [160] |
| 17  | *Olea europaea*               | –     | –          | PTZ                      | Mice weighing (25–30 g)                | 20            | The active constituent of *Olea europaea* leaf, oleuropein (20 mg/kg), caused a significant increase in seizure latency and a significant decrease in the whole body seizure | [161] |
| 18  | *Opuntia ficus-indica*        | Fl    | HME        | PTZ, MES & STR           | Swiss albino mice (20–25 g)            | 250 & 500     | Protect the mice against PTZ, MES, and STR-induced seizures                                                                                                                                                           | [135] |
| 19  | *Pentas schimperiana*         | RB    | HME        | PTZ & MES                | Swiss albino mice (20–30 g)            | 100–400       | The BU and ME fractions significantly inhibited the PTZ and MES-induced seizure at 400 mg/kg                                                                                                                        | [162] |
| 20  | *Pterolobium stellatum*       | L     | AQ & HME   | PTZ & MES                | Swiss albino mice (25–32 g)            | 100–400       | The HME extract exhibited a dose-dependent increase on the latency onset of seizure against PTZ. In addition, both HME and AQ fractions demonstrated a dose-dependent reduction in duration of hind limb tonic extensions in the MES model and myoclonic seizure in the PTZ model at 400 mg/kg | [163] |
| 21  | *Ruta chalepensis*            | Ar    | ET         | PTZ                      | Male Swiss albino mice (25–30 g)       | 10–1000       | Delayed the onset of seizures and a dose-dependent suppression in the tonic phase and mortality induced by PTZ was noticed                                                                                          | [164] |
| 22  | *Securidaca longipedunculata* | R     | AQ         | STR & PIC                | Albino mice of either sex (20–25 g)    | 100–400       | The extract elicited dose-dependent increase in onset of convulsion and prolongation of the cumulative time spent in the open arms of the elevated plus maze and Y maze compared with the control | [165] |
Table 4 (continued)

| No. | Scientific name          | PU | Extract | Seizure-inducing stimuli | Animal models                        | Doses (mg/kg) | Treatment outcomes                                                                 | Refs. |
|-----|--------------------------|----|---------|--------------------------|--------------------------------------|---------------|-------------------------------------------------------------------------------------|-------|
| SB  |                          | AQ |         | PTZ, MES & AMP           | Swiss albino mice of either sex      | 50–200        | The extract afforded significant protection against the mice treated with PTZ (50 & 100 mg/kg) and MES (50 mg/kg). It didn't attenuate AMP induced seizure though it prolonged the onset of convulsions at 100 and 200 mg/kg | [166] |
| 23  | Sida rhombifolia         | Wh | ME      | PTZ & MES                | Swiss albino mice of either sex      | 100–400       | The ME crude extract significantly reduced the duration of seizures at all doses     | [136] |
| 24  | Withania somnifera       | S & R | ET | PTZ & MES                | Albino Wistar rats of either sex    | 100–300       | The extracts significantly suppressed hind limb tonic extension and postictal depression in MES test groups at 300 mg/kg. Moreover, a significant reduction in the mean duration of hind limb tonic flexion, hind limb tonic extension, clonus, and stupor in PTZ test groups | [110] |
| 25  | Xanthium stramonium      | Wh | PE      | PTZ & MES                | Albino Wister albino rats (150–200 g) | 250 & 500     | The crude extract reduced the duration of convulsions. It also delayed the onset of myoclonic spasm and clonic convolution in albino Wister rats                                                                 | [167] |
| 26  | Zingiber officinale      | Rh | HET     | PTZ                      | Wild type adult zebras of the AB strain | 60           | The active constituent of the extract, 6-gingerol (6-GIN), effectively inhibited PTZ-induced seizures                                                                 | [168] |
|     |                          |    |         |                          | Adult male Swiss mice                | 25–200        | It significantly increased the onset time of myoclonic seizures at a dose of 25–100 mg/kg and significantly prevented generalized clonic seizures                                                                 | [169] |

PU: plant parts used, L: leaf, S: stem, SB: stem bark, R: root, RB: root bark, Wh: whole plant, Ar: Aerial part, Bu: bulbs, Fl: flower and Rh: rhizome Seizure-inducing agents: PIC: picrotoxin, STR: strychnine, PTZ: pentylenetetrazol, INH: isonicotinic hydrazide acid and MES: maximal electroshock, PLC: pilocarpine, AMP: 4-aminophylline, and NMDA: N-Methyl-D-aspartate. Extraction solvents: AQ: aqueous, CH: chloroform, Bu: butanol, ET: ethanolic, HET: hydroalcoholic/hydroethanolic, ME: methanolic, HME: hydromethanolic, and PE: petroleum ether.

* and † represented the plant extract doses given in µM and µg/mL, respectively.
**In vivo pharmacological activities of crude extracts and solvent fractions**

*Single stimuli-induced seizure model*  PTZ is routinely used as a stimulus to induce convulsions in different animal models by inhibiting the GABAAergic neurotransmission [170]. PTZ-induced seizures are characterized by an initial ‘absence-like’ immobility, followed by brief myoclonic jerks, sustained myoclonus, and finally GTCS with a loss of the righting reflex. The subcutaneous administration of PTZ is often used to induce a seizure in mice [171] that can be employed to assess the anticonvulsant activity of MPs. The whole plant and leaf extract of *Artemisia afra* are traditionally used for the treatment of epilepsy in Ethiopia and South Africa, respectively (Table 3) [105]. Kediso et al. [151] investigated the anticonvulsant effect of the HET and solvent fractions of *Artemisia afra* whole part against PTZ-induced seizure in mice. Unlike the solvent fractions, the HET crude extract triggered a significant delay in the mean onset of convulsions (504.833 ± 62.835 s, 551.833 ± 74.69 s, and 808.333 ± 64.8 s) and a decrease in the mean duration of convulsions (17.000 ± 1.88 s, 13.000 ± 1.8 s and 7.833 ± 1.07 s) at the respective doses of 250, 500 and 1000 mg/kg. The observed activity of the crude extract might be attributed to the presence of multiple secondary metabolites in the herb. *Clerodendrum myricoides* is another MP whose leaf extract is traditionally used as an anticonvulsant in Ethiopia, Kenya, and South Africa [100, 119]. Owing this, the anticonvulsant activity of the HET and solvent fractions of the leaf extract was assessed via mice experiencing PTZ-induced seizures [157]. The HET crude extract of *Clerodendrum myricoides* at 300, 600 and 1200 mg/kg significantly delayed the mean latency in the onset of seizures (299.33 ± 30.129 s, 387.167 ± 27.6 s and 417.833 ± 31.9 s, respectively) and decrease in the duration of convulsions (27.333 ± 1.585 s, 16.833 ± 1.537 s and 10.50 ± 0.671 s, respectively) in a dose dependent manner as compared to the control group. On the other hand, the solvent fractions of *Clerodendrum myricoides* didn’t show significant anticonvulsant effect in the model.

*Ruta chalepensis* is known for its antiepileptic activities in the traditional folklore of Ethiopia, Morocco, and Mexico [125, 126]. The ET extracts of the aerial parts of *Ruta chalepensis* were assessed by using PTZ-induced seizure and a dose-dependent suppression in the tonic phase was observed, moreover, it reduced the mortality triggered by PTZ in the experimental animals. *Azadirachta indica* is employed in the traditional healthcare system of Ethiopia and India to treat epilepsy [128]. Kumar et al. [152] compared the antiseizure activities of Valproic acid (VPA) and *Azadirachta indica* on PTZ-induced kindling in Sprague Dawley strain male rats at 200 mg/kg and 100 mg/kg, respectively. A decrease in the mean onset time of jerks, clonus, and extensor phases was observed in VPA and *Azadirachta indica* treated groups. Moreover, an increase in glutathione reductase activity and a decrease in the activity of lipid peroxidation enzymes, glutathione S-transferase activity, catalase, and nitric oxide was observed in the same group, asserting the protective effects of VPA and *Azadirachta indica* against anoxic damage and OS of the brain due to prolonged seizures. Overall, *Azadirachta indica* demonstrated better preventive effects than VPA on PTZ-induced chemical kindling in rats. *Asparagus africanus* is a widely used plant in TM as an anti-inflammatory, antioxidant, for the treatment of CNS disorders including epilepsy. The anticonvulsant activity of the root decoction of *Asparagus africanus* was evaluated in PLC-induced SE in *Mus musculus* Swiss mice. It increased the onset time of tonic–clonic convulsions and decreased the duration and number of tonic–clonic convulsions at doses of 63.5, 127, and 254 mg/kg. The anticonvulsant activity of *Asparagus africanus* emanated from modulation of GABA (increase), GABA-T, TNF-α (decrease) levels, and inhibition of OS in the brain [127].

**Dual stimuli-induced seizure models**  MES is the second most commonly used seizure-inducing stimuli in different animal models of epilepsy next to PTZ. It is convenient to assess GTCS that can be reproduced with reliable endpoints [172]. The use of two common stimuli, PTZ and MES, in different animal models will help to better understand the pharmacological effects and the MOA of anticonvulsant agents. *Carissa edulis* is commonly used for the treatment of epilepsy in Africa especially in Ethiopia, Nigeria, South Africa, Uganda, Malawi, and Kenya [104–108]. Owing to this, the anticonvulsant activity of the rootbark of *Carissa edulis* was investigated using PTZ-induced seizure in mice and the MES test in chicks. It exhibited a suboptimal level of inhibition against seizure as compared to benzodiazepine (BZP) (100%) in the mice model. Moreover, the crude extract elicited 90% protection as compared to phénytoïn (100%) at 20 mg/kg in convulsions induced by MES in chicks signifying the beneficial effect of *Carissa edulis* for the management of epilepsy and related symptoms [104]. *Clutia abyssinica* is claimed to have antiepileptic activity in traditional herbal medicine folklore of Ethiopia and Rwanda [129]. Although the HET leaf crude extract of *Clutia abyssinica* improved the mean survival time of epileptic mice, the recorded mean time of hind limb extension was not significant at 400 and 800 mg/kg as compared to the negative control group [158]. Leaves of *Jatropha curcas* have been used by TH of Ethiopia and Nigeria for the management of epilepsy. Bolanle et al. [134] examined the anticonvulsant activity of AQ leaf extract of *Jatropha curcas* in PTZ- and
MES-induced seizure models. The crude extract delayed the onset of tonic leg extension and the seizure-induced mortality was inhibited in mice. Moreover, it significantly ($p<0.05$) protected mice from MES-induced seizure at 100, 200, and 400 mg/kg; at a higher dose, 400 mg/kg, it also significantly inhibited PTZ-induced convulsions.

*Pentas schimperiana* is a MP used in Ethiopian TM for the treatment of epilepsy. Fisseha et al., [162] assessed the HME root bark crude extract and CH, BU, and AQ fractions of *Pentas schimperiana* using PTZ and MES-induced seizure models at doses of 200 and 400 mg/kg. As compared to the control group, the ME and BU fractions, at 400 mg/kg, demonstrated significant ($p<0.001$) anticonvulsant activities in both models. In addition, the CH fraction exerted significant ($p<0.001$) seizure control in PTZ treated mice whereas the aqueous fraction was devoid of significant antiepileptic activities in both models. In general, the alkaloids, flavonoids, saponins, tannins, phenols, steroids, and terpenoids present in the root bark may be ascribed to the observed seizure control in mice.

*Sida rhombifolia* is a plant commonly prescribed for the treatment of epilepsy by the THs of Ethiopia and India [136]. The ME crude extract of the whole part of *Sida rhombifolia* was examined PTZ and MES-induced seizure in mice at 100, 200, and 400 mg/kg. The result reiterated that the ME crude extract of 100, 200, and 400 mg/kg significantly suppressed the duration of seizure as compared to the control group in both models. *Xanthium stramonium* is a famous MP in China due to its widespread healthcare prominence. It is also used for the treatment of epilepsy in Ethiopia and India [141]. Owing to this, Kumar et al. [167] screened the anticonvulsant activity of the PE whole plant extract of *Xanthium stramonium* against PTZ and MES-induced seizure models in albino Wistar rats at a dose of 250 and 500 mg/kg. It increased the latency onset of myoclonic spasms and clonic convulsions in PTZ-treated groups. In addition, it also reduced the mean duration of the exterior phase significantly as compared to the control group in the MES test. The root of *Azadirachta indica* was used in herbal formulations prepared to treat epilepsy in different countries. The in vivo anticonvulsant assessment done on PTZ-induced seizure in mice and MES-induced seizure in Albio rats indicated that the ET root extract has no significant effect on the mean duration of limb extension, mean onset of convulsions and mean number of convulsions at a dose of 800 mg/kg as compared to the control group [153].

**Multiple stimuli-induced seizure models** Multiple stimuli-induced seizure models provide better information about the effect of drugs or a plant extract in the target experimental animals. The depth and breadth of data obtained in such multiple seizure models can shed light on the different aspects of the plant extract under consideration: MOA, potential targets for antiepileptic interventions, possible bioactive compounds, etc. In addition to PTZ and MES, one or more of the following stimuli such as INH, PIC, PLC, NMDA, STR, AMP, and BIC are used to induce convulsions (in experimental animals) in epilepsy research. Traditional herbalists of Ethiopia, Tanzania, and Kenya [113, 114] have faith in the curative effect of *Acalypha fruticosa* for the treatment of epilepsy. Govindu et al., [113] assessed the anticonvulsant activity of the CH crude extracts of the aerial parts of *Acalypha fruticosa* using PTZ, MES, and INH-induced seizures in Swiss albino mice at doses of 30, 100, and 300 mg/kg. The result confirmed the potential of the crude extract to suppress seizures triggered by MES in a dose-dependent pattern. At 300 mg/kg, as compared to diazepam (4 mg/kg) the extract demonstrated more pronounced anticonvulsant activity. It also inhibited the PTZ-induced seizures better than the positive control, phenobarbitone sodium. While in the INH model, it delayed the onset of convulsions in a dose-dependent manner but failed to protect the mice from seizure-induced mortality. *Balantides aegyptiaca* is used traditionally in Ethiopia, Mali, Saudi Arabia [116, 117], and India to treat epilepsy. Hence, HMET and CHL extract of stembark of *Balantides aegyptiaca* were assessed using PTZ, MES-induced convulsions, and PLC-induced SE in rats [154]. Both the HME and CH extract at 200 and 400 mg/kg significantly delayed the onset of myoclonic spasm and clonic convulsions as well as significantly reduced the duration of hind limb extension in PTZ and MES models. In the PLC model, the CH extract (100 mg) and HME extract (100 and 200 mg) delayed the latency to rearing with forelimb clonus significantly.

*Carissa edulis* is popular in African countries such as Ethiopia, Nigeria, South Africa, Uganda, Malawi, and Kenya [104–108] for its beneficial effect in the management of epilepsy by herbalists or TH. The anticonvulsant activity of the AQ fractions (150, 300, and 600 mg/kg) and sub-fractions (250, 500, 500, and 1000 mg/kg) of the root bark extract was examined using PTZ, PIC, NMDA, INH, STR, and AMP-induced seizures in mice. The AQ fraction and sub-fractions suppressed 50% and 16.67% of PTZ-induced convulsions. Similarly, the AQ fraction experienced 33.33% and 16.67% protection against strychnine and NMDA seizure models, respectively. Moreover, the AQ fractions elicited 66.67–33.33% protection against AMP-induced seizures at doses of 150 and 600 mg/kg. However, the AQ fractions and sub-fractions did not affect MES-induced seizures. *Croton macrostachyus* is a common tree used to treat epilepsy in Ethiopia and Cameroon [140]. Bum et al. [140] employed MES, STR, PTZ, PIC, and INH-induced seizure models
to evaluate the anticonvulsant activity of AQ stem bark extract of Croton macrostachyus in Mus musculus Swiss mice. The extract protected 60, 80, 80, and 80% of mice from MES, PTZ, PIC, and STR-induced convulsions, respectively even at an initial dose of 34 mg/kg. It also increased the latency onset of seizures in INH-treated mice. Overall, the result suggested that Croton macrostachyus may have a promising effect in secondary GTCS and primary generalized seizures in humans. Opuntia ficus-indica commonly known as cactus pear is used in the treatment of epilepsy in Ethiopia and India [135]. The in vivo anticonvulsant activity of the flower ME extract was assessed using Swiss Albino mice. The ME extract produced significant inhibition against PTZ, MES, and STR-induced convulsion at 250 and 500 mg/kg. There was an increase in noradrenaline and dopamine level in the mice’s brains due to the avoidance of MES-induced convulsions.

In vivo pharmacological activities of isolated compounds/constituents

Indigofera arrecta is a common MP used by the indigenous inhabitants of Ethiopia, Nigeria, Congo, and South Africa [100, 122]. Bioassay-guided fractionation of Indigofera arrecta in zebrafish model results in the identification of indirubin and 6-bromoirubin-3-oxime (BIO-acetoxime), compounds with glycogen synthase kinase (GSK)-3 inhibition activity demonstrated significant anticonvulsant activity in PTZ-induced seizure in zebrafish larvae. Moreover, they also showed significant antiseizure activity in the PLC rat model limbic seizure and the 6-Hz refractory seizure mouse model, demonstrating GSK-3 inhibition as a potential therapeutic target for epilepsy. Olea europaea is among the known MPs used for the management of epilepsy in Ethiopia and Kenya [108]. Oleuropin, a secondary metabolite extracted from the leaves of Olea europaea, elicited a significant increase in seizure latency and a significant decrease in total frequencies of head ticks, head and upper limbs seizures, frequent spinning and jumping, and tonic seizures in PTZ kindling of seizure in mice. Oleuropin treated groups (20 mg/kg) showed downregulation of genes responsible for the expression of IL-1 without change in GLT-1 levels. The significant antiepileptic activity of oleuropin may be attributed to its antioxidant and antiinflammatory activities making it an ideal pharmacophore for the synthesis of AEDs. Zingiber officinale is another most frequently used medicinal herb in different parts of the world. For instance, in Ethiopia and Japan Zingiber officinale is used for the management of epilepsy [137]. Its HET extract of rhizome has demonstrated anticonvulsant activity in rodent seizure models [169, 173]. Gawel et al., [168] also proved the anticonvulsant effect of ME crude extract using a PTZ-induced seizure in zebrafish larvae. Inspired by its activity, the group also isolated the major constituent of Zingiber officinale rhizome, 6-gingerol (6-GIN) that exerted dose-dependent antiseizure activity in PTZ-induced hyperlocomotion assay in zebrafish larvae. Rigorous experimental procedures and molecular docking analysis in human NR2B-containing NMDA receptors suggested that the antiepileptic activity of 6-GIN may be partly mediated by restoring the balance between GABA and GLU in the epileptic brains. In general, the in vivo anticonvulsant activity of the aforementioned MPs resonated the potentials of herbal formulations in the healthcare system of different countries. Although most of the antiepileptic MPs claimed by THs were not screened for their anticonvulsant effects through suitable seizure models, this review partly documented the strong association that exist between the indigenous knowledge of THs and pharmacological activities of MPs used to treat epilepsy and related symptoms in Ethiopia and other parts of the world.

Toxicity profiles of antiepileptic or anticonvulsant medicinal plants

Acute toxicity profiles of medicinal plants

Acute toxicity study of plant extracts is performed to assess the potential inherent toxicity that may be displayed in a short period of time upon a single dose exposure mostly via the oral route as it is considered as a viable route for accidental human exposure for hazardous substances and it allows for hazard classification of test substances [174]. The leaf part of Artemisia afra, Azadirachta indica, Brucea antidysenterica, Buddleja polystachya, Eucalyptus Globulus, Gloriosa superba, Maytenus heterophylla, Nicotiana tabacum, and Ocimum lamifolium are commonly used for the preparation of remedies used to treat epilepsy and related symptoms in Ethiopia. The acute toxicity studies conducted in the crude extracts, essential oils and bio-oils recapped the absence of gross behavioral, physical changes and signs of overt toxicity such as lacrimation, urination, muscle weakness and convulsions in different animal models [175–181]. As depicted in Table 5, relatively higher LD$_{50}$ value greater than 5000 mg/kg of body weight were recorded for Artemisia afra, Azadirachta indica, Gloriosa superba, and Nicotiana tabacum extracts. In addition, the EO of Eucalyptus Globulus, and HET extract of Maytenus heterophylla 2.5 mL/kg and >1200 mg/kg, respectively demonstrating the safety profiles of single dose of the plant extracts. Furthermore, the roots of Asparagus africanus, Biophytum umbraculum, Capparis tomentosa, and Withania somnifera are believed to be rich in bioactive chemicals characterized by attenuating convulsions. Their crude extracts and solvent fractions were devoid
| No. | Scientific name       | Extract | Animal models                  | Doses (mg/kg) | LD50 (mg/kg) | Treatment outcomes                                                                                                                                                                                                 |
|-----|------------------------|---------|---------------------------------|---------------|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1   | *Ajuga integrifolia*   | R       | HME Swiss albino male mice (20–30 g) | 2000          | >2000        | Neither mortality of mice nor any signs of toxicity (behavioral, neurological, autonomic, or physical changes) was observed at 2000 mg/kg of body weight                                                                 |
| 2   | *Allium sativum*       | Bu      | AQ Wistar rats (~115–126 g)      | 100, 1000, 2500 & 5000 | >5000        | No death was recorded at all doses. The rats treated with 5000 mg/kg of body weight experienced cardiac problem and disorientation                                                                                           |
| 3   | *Artemisia abyssinica* | Ar      | ET Swiss albino mice (25–30 g)   | 500, 1000 & 3000 | >3000        | The mice did not show visible toxicity, although at 3000 mg/kg a decreased in locomotor activity was observed                                                                                                         |
| 4   | *Artemisia afra*       | L       | AQ Female adult Swiss albino mice (25–30 g) | 200, 700, 1200, 2200, 3200, 4200 & 5000 | >5000        | Mild toxicities like anxiety and piloerection were observed at higher doses (≥3200 mg/kg) that disappear in the washout periods. No mortality in mice was recorded at all doses                                                  |
|     |                         | L       | ET, DCM & HX Swiss albino mice (20–22 g) | 1000, 2000 and 2500 | >2500        | Loss of appetite, hypoaactivity, lethargic, dizziness that disappeared in the washout period was noticed in mouse treated with DCM extract at 2500 mg/kg                                                                 |
| 5   | *Asparagus africanus*  | R       | HET & BU Swiss albino mice (20–25 g) | 1000, 3000 & 5000 | >5000        | There was no dose-dependent behavioral change, weight change and mortality in mice treated single dose BUT fraction orally                                                                                             |
| 6   | *Azadirachta indica*   | L       | AQ Female BALB/c mice (average mass of 30 g) | 1250, 2500 & 5000 | >5000        | The mice treated with the extract were devoid of weight/hair loss, allergy, or other symptoms of discomfort                                                                                                        |
| 7   | *Balanites aegyptiaca* | SB      | AQ Fishes                        | 17.5, 20, 22.5 & 25a | ~18.99–2072a | *B. nurse*, *L. intermedius* and *L. bynni* fish species treated with the extract suffered from the debilitating toxic effect                                                                                     |
| 8   | *Biophytum umbraculum* | R       | AQ, BU & CH Female Swiss Albion mice (22–30 g) | 2000          | >2000        | There was no behavioral change, weight change and mortality in mice treated single dose of all fractions                                                                                                         |
| No. | Scientific name          | PU  | Extract | Animal models                      | Acute toxicity studies | LD_{50} (mg/kg) | Treatment outcomes                                                                                                                                                                                                 | Refs. |
|-----|--------------------------|-----|---------|------------------------------------|------------------------|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|
| 9   | *Bricea antidysenterica* | L   | AQ, ME & CH | Swiss albino mice (27–36 g)       | 500, 1000 & 2000       | –              | The extracts lack visible signs of acute toxicity and mice fatality till the dose of 1000 mg/kg. But, at the dose of 2000 mg/kg it caused mortality in all mice with in 24 h | [194] |
| 10  | *Buddleja polystachya*  | L   | HME     | Female Sprague–Dawley rats (150–200 g) | 2000                   | –              | There was no visible sign of skin reaction, inflammation, erythema, irritation or redness, and any adverse reaction in rats                                                                                                  | [177] |
| 11  | *Calpurnia aurea*       | L   | AQ & HME | Female Swiss albino mice          | 5000                   | > 5000         | The mice were devoid of gross behavioral or physical changes and signs of overt toxicity such as lacrimation, urination, muscle weakness and convulsions                                                                 | [186] |
| 12  | *Capparis tomentosa*    | R   | HME     | Male Swiss Albino mice (25–38 g)  | 2000, 3000 & 5000      | > 2000         | The mice showed signs of slight rigidity and sleepy activity at higher doses of extract (3000 and 5000 mg/kg). No mortality was recorded at all doses                                                                        | [184] |
| 13  | *Carissa edulis*        | L   | AQ      | Wistar albino rats of either sex  | 2000                   | > 2000         | The rats showed no gross behavioral or physical changes and signs of overt toxicity                                                                                                                                 | [195] |
|     |                          |     | ET      | Wistar albino rats (124–220 g) &  | 10, 100 & 1000         | ~3808          | None of the mice and rats orally treated with the extract manifested signs of toxicity except death at the dose of 5000 mg/kg (in both species)                                                                                 | [187] |
| 14  | *Caylusea abyssinica*   | L   | HME     | Male Swiss albino mice (20–30 g)  | 2000                   | > 2000         | The mice didn’t experience any behavioral, neurological, autonomic or physical changes                                                                                                                                 | [196] |
| 15  | *Clerodendrum myricoides* | R  | AQ      | Swiss albino mice of either sex (25–30 g) | 1134                   | –              | Behavioral changes such as horripilation, difficulty in breathing, grooming, and asthenia followed by death was noticed in mice treated with 1134 mg/kg                                                                 | [197] |
| 16  | *Croton macrostachyus*  | R   | HME     | Female Swiss Albino mice (25–28 g) | 2000 & 5000           | > 5000         | The mice showed no visible signs of lacrimation, loss of appetite, tremors, hair erection, salivation, diarrhea and convulsion                                                                                           | [198] |
Table 5 (continued)

| No. | Scientific name     | PU | Extract     | Animal models                       | Acute toxicity studies                                                                 | Refs. |
|-----|---------------------|----|-------------|-------------------------------------|-----------------------------------------------------------------------------------------|-------|
|     |                     |    |             |                                     | Doses (mg/kg)                                                                 | LD₅₀ (mg/kg) | Treatment outcomes                                                                 |       |
| 17  | *Cucumis ficifolius*| R  | HME & CH    | Swiss albino mice (25–30 g)         | 125, 250, 500 & 2000                                                                     | > 2000 | There were no mortality and signs of overt toxicities at a dose of 2000 mg/kg of body weight | [200] |
| 18  | *Echinops kebericho*| Tu | EO          | Swiss albino mice (18–26 g)         | 300 & 2000                                                                               | > 2000 | Though the mice showed piloerection, muscle spasm and apathy immediately after administration, there were no significant treatment-related morbidities | [201] |
|     |                     | Tu | AQ          | Wistar albino rats (250–350 g)      | 300, 2000 & 5000                                                                         | > 5000 | The rats experienced piloerection, muscle twinge, and lethargy after the treatment with the extract (5000 mg/kg) which disappeared after 5 h. But, there were no treatment related morbidity and mortality at 5000 mg/kg | [202] |
| 19  | *Embelia schimperi* | Fr | HET         | Female Wistar rats (180–210 g)      | 400, 1000, 2000, 3000, 4000 & 5000                                                       | > 5000 | The extract didn’t elicit prominent signs of toxicity and any mortality in rats in the study period | [203] |
| 20  | *Eucalyptus Globulus* | L | EO         | Swiss albino mice of either sex (23–30 g) | 2, 2.5, 3 & 3.5ₕ                                                                 | 2.5ₕ | The mice treated with the essential oil showed restlessness, debilitation, reduced food and water intake and piloerection which disappeared in the washout period after treatment with ≥ 2.5 mL/kg | [178] |
| 21  | *Fagaropsis angolensis* | SB | HME, AQ, BU & CH | Adult male Swiss albino mice (25–30 g) | 2000                                                                                   | ≥ 2000 | Neither mortality nor any signs of toxicity were observed in mice treated with both extracts at 2000 mg/kg body weight | [204] |
| No. | Scientific name            | PU | Extract | Animal models                  | Acute toxicity studies | LD$_{50}$ (mg/kg) | Treatment outcomes                                                                                                                                                                                                 |
|-----|---------------------------|----|---------|--------------------------------|------------------------|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 22  | Foeniculum vulgare        | Fr | ET      | Swiss labial mice (25–28 g)   | 500, 1000 & 3000       | ≥ 3000            | The extract didn't trigger mortality of mice and overt toxicity except reduced locomotor activity and piloerection at 3000 mg/kg of body weight                                           |
| 23  | Gloriosa superba          | L  | AQ      | White male Wistar rats (200–250 g) | >121, 364, 1091 & 3274 | > 1500            | The rats experienced treated with colchicine of standardized Gloriosa superba extract showed no visible sign of overt toxicity                                                                                     |
|     |                           | L  | HME     | Non-pregnant Wistar rats (120–140 g) | 200 & 5000             | > 5000            | There were no visible overt signs of toxicity at 5000 mg/kg. No mortality or mortality was observed in the rats treated groups at both doses                                                                        |
| 24  | Justicia schimperiana     | L  | HME     | Swiss albino mice (18–30 g)    | 2000                   | > 2000            | The extract didn't trigger signs of overt toxicity. Moreover, no mortality of mice was recorded in the study period                                                                                                   |
|     |                           | L  | HME     | Female adult Wistar rats (180–200 g) | 2000                   | > 2000            | Rats showed no formation of edema or erythema. No signs of toxicity as well as no mortality were noted during the study period                                                                                     |
| 25  | Maytenus heterophylla     | L  | HET     | Male CD-6 mice (35–40 g)       | 1200                   | > 1200            | The mice treated with the extract were devoid of physical and behavioral changes at 1200 mg/kg                                                                                                                     |
| 26  | Maytenus senegalensis     | RB | ET      | Swiss albino mice (18–22 g)    | 200, 300, 400, 800 & 1600 | > 1600            | The mice treated with the extract were devoid of physical and behavioral changes at 1600 mg/kg                                                                                                                     |
|     |                           | SB | HET     | Theiller’s albino mice of either sex | 1000, 2000, 3000, 4000 & 5000 | > 5000            | The mice treated with the extract were devoid of physical and behavioral changes at 5000 mg/kg                                                                                                                     |
|     |                           | L & S | HET | Male CD-6 mice (35–40 g)      | 1200                   | –                 | The mice treated with leaf extract exhibited some signs of overt toxicity. In addition, the stem extract caused pronounced toxicity at 1200 mg/kg                                                                 |
| 27  | Myrica salicifolia        | R  | HME     | Non-pregnant female mice       | 2000                   | > 2000            | There are no visible signs of overt toxicity and mortality in mice treated with the extract at 2000 mg/kg                                                                                                       |
| No. | Scientific name              | PU | Extract | Animal models                        | Acute toxicity studies | Refs. |
|-----|------------------------------|----|---------|--------------------------------------|------------------------|-------|
|     |                              |    |         |                                      | Doses (mg/kg)          |       |
|     |                              |    |         |                                      | LD_{50} (mg/kg)        |       |
|     |                              |    |         |                                      | Treatment outcomes     |       |
| 28  | *Nicotiana tabacum*          | L  | Bio-oil | Female Wistar rats (130–140 g)       | 5000                   | > 5000 |
|     |                              |    |         |                                      | The rats exhibited no significant change in the body weight and behavior. In addition, there was no mortality of rats in the study period | [181] |
| 29  | *Ocimum lamifolium*          | L  | ME      | Swiss albino mice (27–36 g)          | 500, 1000 & 2000       | ≥ 2000 |
|     |                              |    |         |                                      | The crude extract didn’t trigger gross visible signs of acute toxicity such as urination, hair erection, lacrimation, and reduction in feeding activity | [194] |
| 30  | *Olea europaea*              | L  | ET      | Wistar rats of either sex (150–200 g)| 2000                   | ≥ 2000 |
|     |                              |    |         |                                      | Oral administration of the extract didn’t cause any mortality or sign of toxicity at 2000 mg/kg of body weight during the study period | [212] |
| 31  | *Opuntia ficus-indica*       | S  | HET     | White Sprague Dawley rats either sex | 500, 1000 & 2000       | –     |
|     |                              |    |         |                                      | The rats exhibited no genotoxicity at all treatments regimens even at the maximum dose of 2000 mg/kg | [213] |
|     |                              | Se | HX (fixed oil) | Mus musculus mice (20–30 g) | 10, 20, 30, 40, 50, 60 & 70^{b} | 43^{b} |
|     |                              |    |         |                                      | The mice suffered from immediate agitation and behavioral perturbations with temporary writhing, followed by a quiet attitude period and sedation | [214] |
| 32  | *Pentas schimperi ana*       | L  | AQ & HME| Swiss Albino mice of either sex      | 1000, 2000 & 5000      | >4000  |
|     |                              |    |         | (20–33 g)                            | The mice experienced no visible change in behavior such as restlessness, motor activity, breathing and diarrhea. Moreover, there was no mortality recorded at 5000 mg/kg | [215] |
| 33  | *Podocarpus falcatus*        | Ap | AQ      | Female Sprague Dawley rats           | 2000                   | > 2000 |
|     |                              |    |         | (260–300 g)                          | The rats showed neither mortality nor gross behavioral changes and mortality at 2000 mg/kg of body weight | [216] |
| 34  | *Ruta chalepensis*           | Ar | ET      | Male Swiss albino mice (25–30 g)    | 1600, 3000 & 5000      | > 5000 |
|     |                              |    |         |                                      | The extract didn’t trigger mortality nor macroscopic tissue injury or weight loss at 5000 mg/kg per body weight | [164] |
| 35  | *Rhus vulgaris*              | SB | AQ     | Female Swiss albino mice (18–26 g)  | 50, 300 & 2000         | > 2000 |
|     |                              |    |         |                                      | The mice were devoid of changes in general appearance and behavioral patterns. In addition, there was no mortality or gross pathology in any organ at necropsy | [217] |
| No. | Scientific name                  | PU | Extract       | Animal models                      | Acute toxicity studies | Refs. |
|-----|----------------------------------|----|---------------|------------------------------------|------------------------|-------|
|     |                                  |    |               |                                    |                        |       |
| 36  | Securidaca longipedunculata      | L  | S & R AQ & ME/CH (1:1) | Swiss female mice (20–22 g)       | 50, 300 & 2000         | >2000 | The AQ total extracts of leaves and stem bark did not show any change in behavior following administration of the crude extracts at 2000 mg/kg of body weight |
|     |                                  |    |               |                                    |                        |       |
| 37  | Sida rhombifolia                 | Ar | ET            | Adult male Wistar albino rats (180–220 g) | 2000                   | >2000 | There were no visible overt signs of toxicity and mortality in rats treated with 2000 mg/kg of the extract |
|     |                                  | Ar | HME           | Albino Wistar rats (102–134 g)     | 4000, 8000, 12000 & 1600 | >8000 | The rats exhibited slight changes in general behavior such as sow response to external stimuli, stretching and sluggishness |
|     |                                  | R  | AQ            | Sprague Dawley rats of either sex (130–190 g) | 5000                   | >5000 | The rats experienced neither overt toxicity signs nor mortality at a single dose of 5000 mg/kg |
| 38  | Syzygium guineense               | L  | HME           | Wistar rats of either sex (120–140 g) | 2000 & 5000            | >5000 | In the acute toxicity study, rats treated with 2000 mg/kg and 5000 mg/kg showed no toxicological signs observed on behavior, gross pathology, and body weight of rats |
|     |                                  |    |               |                                    |                        |       |
| 39  | Teclea nobilis                   | Wh | HME & AQ      | Male Swiss mice (~20 g)            | 1000, 2000, 3000, 4000 & 5000 | >5000 | The extract was devoid of any overt toxicities at 5000 mg/kg of body weight. Moreover, there was no mortality recorded in the study period |
|     |                                  |    |               |                                    |                        |       |
| 40  | Vernonia amygdalina              | L  | AQ & HME      | Female Swiss albino mice           | 5000                   | >5000 | The mice exhibited no signs of overt toxicity such as lacrimation, urination, muscle weakness, sedation and convulsions at 5000 mg/kg |
|     |                                  | L  | AQ & ET       | Albino Wistar rats (200–250 g)     | 2000                   | >2000 | The extract triggered no significant effect on the biochemical and hematological parameters of treated rats (no lesions were also observed in the liver and kidneys histologically) |
| 41  | Withania somnifera               | R  | ME            | Wistar rats                        | 5000, 1000 & 2000      | >2000 | The rats didn’t experience any organ atrophy, hypertrophy, and degenerative or infiltrative lesions even at 2000 mg/kg |
Table 5 (continued)

| No. | Scientific name  | PU | Extract | Animal models | Acute toxicity studies | LD₅₀ (mg/kg) | Treatment outcomes                                                                 |
|-----|------------------|----|---------|---------------|------------------------|-------------|-----------------------------------------------------------------------------------|
| 42. | Zingiber officinale | R  | HX (fixed oil), EO | Swiss albino mice (23–26 g) and Wistar rats (150–170 g) | 0.02, 0.04, 0.06, 0.08 and 0.1¹ mL/kg for fixed oil; 0.2, 0.4, 0.6, 0.8, 1.0, 2.0, 4, 6, 8 and 10² for EO | -           | Observed cardinal signs of toxicity for both oils were decreased motor activity, convulsion and paralysis. In addition, mortality of experimental animals was noticed in both fixed-oil (0.2 mL/kg) and EO treated group [224] |

PU: plant parts used; Ap: apex, L: leaf, S: stem, Se: seeds, SB: stem bark, R: root, RB: root bark, Ar: aerial part, Bu: bulbs, Tu: tuber and Rh: rhizome, Extraction solvents: AQ: aqueous, CH: chloroform, BU: butanol, DCM: dichloromethane, ET: ethanolic, ETAc: ethyl acetate, HX: hexane, HET: hydroalcoholic/hydroethanolic, ME: methanolic, HME: hydromethanolic, PE: petroleum ether and EO: essential oil.

¹ and ² represented the plant extract doses and LD₅₀ values are given in mg/L and mL/kg, respectively.
of any inherent acute toxicity symptoms at a single dose greater than 2000 mg/kg body weight [182–185]. The AQ and HME stem bark extract of *Croton macrostachyus* (LD$_{50}$ > 5000) and the ET root bark crude extract of *Carissa edulis*, (LD$_{50}$ ~3,808) were found to be safe [186, 187], consequently, the experimental animals manifested neither visible signs of lacrimation, loss of appetite, tremors, hair erection, salivation, diarrhea and convulsion nor mortality in the study period at the estimated doses equivalent to LD$_{50}$ values. According to Globally Harmonized Classification System (GHCS) for chemical substances and mixtures, synthetic chemicals and plant extracts having an LD$_{50}$ > 2000 mg/kg of body weight is considered as safe [188]. This reiterated the relative safety profiles of most MPs used to treat epilepsy and related symptoms in Ethiopia.

**Subacute toxicity profiles of medicinal plants**

Acute toxicity studies provide preliminary data about the safety profiles of a single dose of chemical agents [225], consequently, it is considered as shallow and sometimes misleading. Better information about the safety of chemicals of synthetic and natural origin can be obtained from the subacute toxicity studies, which involve repeated administration of the chemical agent under consideration. In subacute toxicity assessments, weight loss of experimental animals is an important variable that can be attributed to harmful effects of test substances [179]. A weight loss, that may be attributed to the anti-nutritive and malabsorption effect of chemicals, that amount to $\geq$ 10% can be considered a sign of toxicity even in the absence of other changes on target organs, haematological or biochemical effects [226]. The subacute toxicity of plant-based materials including crude extracts, solvent fractions, bio-oils, essential oils, etc. was evaluated through repeated administration a specific dose in different animal models with the intention of assessing its accumulation in the body with gradual effects on tissues and organs [188]. In this regard, Loha et al. [179] assessed the subacute toxicity of HME leaf extract of *Syzygium guineense* in rats at 500 and 1500 mg/kg of body weight. Herein, the rats were devoid of significant change on behavior, gross pathology, body weight, and hematological and biochemical parameters, asserting the safety profile of the leaf extract at a repeated dose of 1500 mg/kg. In addition, subacute toxicity study was conducted on EO obtained from *Echinops kebericho* tuber at the doses of 100, 200 and 400 mg/kg [201]. The EO treated groups did not experience significant dose-dependent alterations in body weight, clinical chemistry parameters and relative organ weights. Deyno et al. [202] confirmed that *Echinops kebericho* decoction was well tolerated up to the dose of 600 mg/kg body weight as food consumption, body weight, organ weight, hematology, clinical chemistry, and histopathology did not show significant alterations between control and treatment groups.

Moreover, subacute toxicity studies conducted on the different extracts of antiepileptic or anticonvulsant MPs such as *Allium sativum* (AQ bulb extract at 300 mg/kg) [190], *Artemisia abyssinica* (ET extract of the aerial part at 3000 mg/kg) [191], *Artemisia afra* (AQ leaf extract at 1800 mg/kg) [175], *Asparagus africanus* (HET and BU root extracts) [182], *Azadirachta indica* (AQ leaf extract at 1000 mg/kg) [176], *Capparis tomentosa* (HME root extract at 1000 mg/kg) [184], *Eucalyptus Globulus* (EO of leaf at 2 mL/kg) [178], *Olea europaea* (ET leaf extract at 400 mg/kg) [212], *Opuntia ficus-indica* (HET stem extract at 2000 mg/kg) [213], *Myrica salicifolia* (HME root extract at 400 mg/kg) [211], *Sida rhombifolia* (AQ root extract at 1200 mg/kg) [221], and *Withania somnifera* (ME root extract at 2000 mg/kg) [185] clearly asserted their safety profiles at the respective maximum doses per body weight as manifested by the absence of significant treatment related variations in clinical observations, ophthalmic examination, body weight gain, feed consumption, clinical pathology evaluation, organ weight, and so on. On the other hand, notable discomforts or mild signs of toxicities were observed on rats treated with some MPs utilized in the management of epilepsy and related symptoms. For instance, Zewdu et al. [203] conducted subacute toxicity study on the HET fruit extract of *Embelia Schimperi* in Wistar rats at doses of 400 and 1600 mg/kg body weight. The result revealed that chronic administration of the extract (1600 mg/kg) was not significantly associated with body weight loss and organ weights such as liver and kidney. Some haematological and biochemical parameters such as platelets and AST concentration were significantly increased which may be attributed to inflammation of liver and kidney tissue upon repeated dose exposure, stressing the mild toxicity of the fruit extract of *Embelia Schimperi* at a dose of 1600 mg/kg or higher. In addition, fixed oil of *Zingiber officinale* root was found to have inherent propensity to trigger a range of toxicities (0.4 mL/kg) including hypertrophy of the liver, kidneys, lungs and spleen, cellular toxicity and oxidative stress following 60-day subchronic toxicity study [224]. Similarly, repeated administration of *Clerodendrum myricoides* AQ root extracts in mice causes reduction in body weight gain, damage to the liver and kidney and changes in some hematological and biochemical parameters in mice. The research group also reported the significant body weight loss of the AQ leaf extract of *Croton macrostachyus* at 1000 mg/kg in the treated groups [227].
Developmental toxicity profiles of medicinal plants

Prenatal development is comprised of pre-embryonic, embryonic and fetal stages. The embryonic stage is a critical period where organs of the embryo as well as the placenta can be damaged if exposed to toxic agents directly or indirectly. At times, toxic agents may cross the compromised placental membrane and elicit debilitating effect on the developing embryonic/fetal tissues [228]. The developmental toxicity studies of crude extracts, solvent fractions and/or essential oils has paramount healthcare implications for PS consumed by pregnant women for therapeutic as well as nutritional purpose [229]. In this regard, the effect of some MPs that are frequently employed to relive seizure in patients with epilepsy on prenatal growth (developing embryos and fetuses) are assessed by using different animal models. For instance, the developmental effect HET fruit extract of *Embelia schimperi* on embryo and fetuses was investigated by using Wistar albino rats and the result echoed that the crude extract was devoid of a significant toxic effect on embryonic and fetal development indices (in the period of organogenesis) at a dose of 1000 mg/kg body weight [230]. Similarly, the HET leaf extract of *Syzygium guineense* was evaluated at a dose of 250, 500 & 1000 mg/kg in the same animal model and the extract didn’t compromise the number of implantations, fetal resorptions, live births, and stillbirths in the same animal model though there was dose-dependent decrease in the weight of the fetuses and the placentae [228]. Abebe et al., also assessed the teratogenic potentials of the HET leaf extract of *Gloriosa superba* on Wistar albino rats (220–240 g) at a dose of 250, 500 and 1000 mg/kg of body weight. The crude extract was devoid of any significant teratogenic effects on rat embryos/fetuses up to 500 mg/kg but influenced the growth of embryos at 1000 mg/kg of body weight as manifested by diminished crown-rump length, decreased number of somites and morphological scores [231]. Moreover, the teratogenic effect of the HME leaf extract of *Catha edulis* was investigated on pregnant Wistar albino rats at a dose of 250, 500 & 750 mg/kg of body weight. The result echoed that khat extract presented dose-dependent toxicity in rat embryo and fetuses such as cytolysis, decidual hypoplasia and atrophy [232]. Overall, the aforementioned acute, subacute and developmental toxicity results witnessed the safety of MPs utilized in the management of epilepsy and related symptoms in Ethiopia.

Flavonoids with anticonvulsant activities

Flavonoids, often synthesized by the phenylpropanoid pathway, belong to a class of phenolic compounds with a benzo-γ-pyrone structure that is ubiquitously distributed in plants [265, 266]. They are the first class of phytochemicals involved in the suppression of seizures in different animal models. Apigenin (Fig. 2) is one of the most common flavones found in *Ajuga integrifolia*, *Balanites aegyptica*, *Nicotiana tabacum*, and *Olea europaea* among others. It elicited pronounced anticonvulsant...
activity in PTC-induced seizures in SD rats as well as KA-induced seizure model through activation of GABA_A receptor and inhibition of glutamatergic neurotransmission. Moreover, apigenin possesses inhibitory activity against hydroxyl radical generation through upregulation of reduced glutathione (GSH), consequently, can inhibit neuronal damage in the hippocampal caused by oxidative glutamate toxicity (involved in neuronal death due to epilepsy) [267]. Rutin is a flavonoid glycoside and a constituent of Balanites aegyptica, Buddleja polystachya, Carissa edulis, Opuntia ficus-indica, Ruta chalepensis, and Xanthium stramonium that exhibited noticeable anticonvulsant activities in different seizure models. In the KA-induced seizure model involving BALB/c mice, quercetin recorded lower seizure scores as compared to the negative control group [269]. It also elicited significant anticonvulsant outcomes after 30 and 60 min of administration in psychomotor seizures induced by 6-Hz simulation. In addition, it also prolonged the onset of seizures and reduced the generalized seizure duration in PTZ-induced convulsions in the male Albino rat at a dose of 10 mg/kg. Furthermore, at 20 mg/kg, quercetin amplified the latency of PIC-induced seizures [6].

### Terpenoids with anticonvulsant activities

**Monoterpenes**

Terpenoids, also known as terpenes or isoprenoids, are naturally occurring compounds derived from isoprene units and predominantly found in all classes of living organisms [270]. Terpenoids are often classified based on the number of carbon atoms or isoprene units (IPU) they possess: monoterpenes (C10, 2 IPU), sesquiterpenes (C15, 3 IPU), diterpenes (C20, 4 IPU), triterpenes (C30, 6 IPU), etc. [271]. Terpenoids in general and monoterpenes specifically are used for the management of CNS disorders including epilepsy. α-Terpineol is monoterpenic alcohol obtained from Artemisia afra, Buddleja polystachya, Croton macrostachyus, Ruta chalepensis, and Zingiber officinale. It has shown significant anticonvulsant activity in PTZ and MES-induced seizure models. Albeit, the exact seizure suppression mechanism of α-terpineol is not known yet [268]. Menthol is a monoterpenic alcohol found in Ruta chalepensis shown to have profound anticonvulsant effects in different animal models. It elicited its antiseizure activity by delaying the onset of clonic and tonic seizures against PTZ-induced

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**Table 6** Phytoconstituents of MPs with in vivo antiepileptic/anticonvulsant activities

| No. | Scientific name       | Active compounds                                                                                                                                  | Refs.                        |
|-----|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| 1   | *Ajuga integrifolia*  | Apigenin and quercetin                                                                                                                             | [236]                        |
| 2   | *Allium sativum*      | Quercetin                                                                                                                                          | [237]                        |
| 3   | *Artemisia afra*      | Borneol, camphor, eucalyptol, Eugenol, p-cymene, phytol, α-terpineol, and β-caryophyllene                                                        | [238, 239]                   |
| 4   | *Azadirachta indica*  | Phytol                                                                                                                                             | [240]                        |
| 5   | *Balanites aegyptica* | Apigenin, quercetin and rutin                                                                                                                    | [241]                        |
| 6   | *Buddleja polystachya*| Camphor, phytol, rutin, ursolic acid and α-terpineol                                                                                              | [242–244]                   |
| 7   | *Carissa edulis*      | Lupeol and rutin                                                                                                                                     | [245, 246]                   |
| 8   | *Croton macrostachyus*| Lupeol, linalool, p-cymene, α-terpineol, and β-caryophyllene                                                                                      | [247–249]                   |
| 9   | *Jatropha curcas*      | Lupeol, phytol and rutin                                                                                                                          | [250–252]                   |
| 10  | *Maytenus heterophylla*| Lupeol                                                                                                                                           | [253]                        |
| 11  | *Nicotiana tabacum*   | Apigenin, lupeol and quercetin                                                                                                                     | [254, 255]                   |
| 12  | *Olea europaea*       | Apigenin, oleuropein and quercetin                                                                                                                | [256]                        |
| 13  | *Opuntia ficus-indica*| Quercetin and rutin                                                                                                                               | [257]                        |
| 14  | *Ruta chalepensis*    | Borneol, camphor, carvacrol, linalool, menthol, pulegone, quercetin, rutin and α-terpineol                                                       | [258–260]                   |
| 15  | *Sida rhombifolia*    | Lupeol                                                                                                                                             | [261]                        |
| 16  | *Xanthium stramonium* | Borneol, lupeol, p-cymene, quercetin, β-caryophyllene                                                                                               | [262, 263]                   |
| 17  | *Zingiber officinale* | 6-gingerol, borneol, camphor, citral, citronellol, linalool, p-cymene, α-terpineol and β-caryophyllene                                              | [168, 264]                   |
convulsions. Moreover, it also suppressed seizures in hippocampal kindled rats. GABA$_A$ receptor activation in the hippocampal neurons and thereby inhibition of neuronal excitation (tonic GABAergic inhibition) is believed for the beneficiary effect of menthol against epileptiform [170]. Camphor is monoterpenes predominantly found in PMs such as Artemisia afra, Buddleja polystachya, Ruta chalepensis, and Zingiber officinale among others showed significant anticonvulsant activity in different models. Moreover, it served as a pharmacophore for the synthesis of different anticonvulsant agents. In this regard, benzylidene camphor derivatives containing hydrazones, semicarbazones and thiosemicarbazones exhibited significant antiepileptic activity against MES-induced seizures at 30 mg/kg (comparable to phenytoin) with low neurotoxicity [272]. $p$-cymene is a constituent of Artemisia afra, Croton macrostachyus, Xanthium stramonium and Zingiber officinale possess anticonvulsant activities. It suppressed convulsions induced by PTZ and MES in mice through modulation of GABAergic neurotransmission via GABA$_A$ receptor [273, 274]. Citral is another monoterpenes found in Zingiber officinale with biological importance for the treatment of CNS malfunction such as epilepsy. It increased the latency time in PTZ-induced seizure in zebrafish larvae model. Its effect is compromised in flumazenil (FMZ) pretreated groups suggesting the contribution of GABA$_A$ receptors. Moreover, down-regulation of malondialdehyde (MDA)/NO and upregulation of reduced GSH/catalase (CAT) in brain of citral treated groups reiterated its neuroprotective effect [275].
Pulegone is another monoterpene found in *Ruta chalepensis* that significantly increased the latency of convulsions in PTZ-induced seizure models [276]. Oleuropein is a glycosylated Seco-iridoids that can be predominantly found in *Olea europaea* [256]. It unveiled substantial anticonvulsant activity against PTZ-induced seizure through avoidance of neuronal damage via attenuation of generation of reactive oxygen species (ROS) in the epileptic brain [161].

**Sesquiterpenes and diterpenes**

Sesquiterpenes are the other class of terpenoids with potential anticonvulsant activities. β-caryophyllene is a natural sesquiterpene obtained from *Artemisia afra, Croton macrostachyus, Xanthium stramoniun,* and *Zingiber officinale*. Contrary to its outcome in PTZ-induced convulsions, β-caryophyllene has reduced seizure severity and OS in the KA-induced seizure model. The result revealed the potential of β-caryophyllene to suppress seizure by inhibiting thiobarbituric acid reactive species and elevating non-protein thiol levels in the KA model [277]. Diterpenes and their derivatives are among the single compounds that demonstrated relevant anti-seizure activities in animal models. Phytol is a component of *Artemisia afra, Buddleja polystachya, Jatropha curcas,* etc. It reduced SE and PLC-induced convulsions by targeting neurotransmitters other than the GABAergic system [268]. 6-GIN, major constituent of *Zingiber officinale* rhizome, is a diterpenoid with potent anticonvulsant activity. It exerted dose-dependent antiepileptic activity against PTZ-induced hyperlocomotion seizure in the zebrafish larvae model. Its anticonvulsant activity is partly associated with the restoration balance between GABA & GLU neurotransmission in the epileptic brain [168].

**Triterpenes**

Triterpenoids are a diverse class of phytochemicals with potential CNS effects such as memory enhancement, ameliorating of depression, suppression of epilepsy, etc. Borneol is a triterpenoid found in *Artemisia afra, Ruta chalepensis, Xanthium stramoniun,* and *Zingiber officinale* with the ability to alleviate ES in different and by targeting neurotransmitters other than the GABAergic system [280]. Citronellol is also another class of triterpenoid found in different MPs including *Zingiber officinale*. Inhibition of neuronal excitability through voltage-dependent Na⁺ channels is the proposed mechanism for the antiepileptic activity of citronellol. Moreover, it also activates the GABA_A receptor and thereby foster GABA neurotransmission in the rat brain [280].

Eugenol is a triterpenoid obtained from *Artemisia afra*. At 100 mg/kg, eugenol suppressed SE and related mortality in PLC-induced SD rats. The involvement of voltage-gated Na⁺ channel in the anticonvulsant activity of eugenol was proved by its weakened effect upon pre-administration of the Na⁺ channel antagonist, riluzole [281]. Linalool is found in *Croton macrostachyus, Ruta chalepensis* and *Zingiber officinale*. It suppressed quinolinic acid (QA)-induced seizure (via NMDA antagonism), delayed NMDA-induced convulsions, increase latency onset and duration of clonic seizures in the PTZ-kindling model. The later seizure model also proved the involvement of a wide array of mechanisms despite glutamate blockage [268]. Ursolic acid is a pentacyclic triterpenoid obtained found in *Buddleja polystachya*. It has a profound anticonvulsant activity possibly by modulating the non-BZP sites of the GABA_A receptor. In addition, it also showed an anticonvulsant effect in MES- and 6 Hz-induced seizure models through activation of the GABAergic pathway [282]. Lupeol is a triterpenoid found in *Carissa edulis, Croton macrostachyus, Jatropha curcas, Maytenus heterophylla, Nicotiana tabacum, Sida rhombifolia, Xanthium stramoniun,* etc. It has shown anticonvulsant activities against PTZ and MES-induced seizure models. Lupeol has increased the mean onset of myoclonic jerks/spasms and differentially protected the mice against mortality [172].

**Proconvulsive phytoconstituents of medicinal plants**

At this point, it is worthy to mention that some phytoconstituents have convulsive activity (vigorous jerking of the body and loss of consciousness). Crude extracts or essential oils of some MPs can induce seizure upon systemic or topical administration. Phytoconstituents such as eucalyptol and camphor have shown a significant convulsive effect [283]. For instance, one teaspoon of camphor oil taken orally (by a 3 year child) induced GTCS and respiratory depression within 20 min. On the other hand, eucalyptol induced convulsions characterized by the development of long-term SE and showed developmental delay for at least four years following the event [284]. Thus, attention should be given to antiepileptic MPs which contain camphor (*Artemisia afra, Buddleja polystachya, Ruta chalepensis,* and *Zingiber officinale*)
and eucalyptol (Artemisia afra) when used by THs to manage the convulsive effect and long-term side-effects. Extensive research could be conducted to determine the tolerable dose which can delimit the protective and convulsive outcomes of camphor and eucalyptol. Overall, the anticonvulsant activities of phytoconstituents included in Table 5 signifies the therapeutic potential of the antiepileptic MPs and the importance of evidence-based phytochemical screening to maximize the benefit of MPs and bring about new AEDs of plant origin.

Conclusion
Plants have a central role in the traditional medicinal folklore of Ethiopia. Around 96 PS which belong to 43 families were reported for the treatment of epilepsy and related symptoms in different parts of Ethiopia. A portion of these PS was also used for the same purpose in Africa, the Middle East, Asia, and Latin America. The pharmacological activities of nearly one-third of the MPs claimed by the THs for attenuation of seizure in Ethiopia and other parts of the globe were verified by in vivo experiments using different animal and seizure models. The experimentally proved anticonvulsant activities of MPs have presented the importance of indigenous knowledge and the existing traditional healthcare system in the management of epilepsy in different countries, especially in Ethiopia. A strong association between traditional herbal formulations and pharmacological activities of antiepileptic MPs has been established. Yet, the vast majority of the MPs documented in the present review were not screened for their anticonvulsant activities. In addition, the in vivo experiments conducted elsewhere on the target MPs are shallow and not insightful as far as the MOA of crude extracts, solvent fractions, and EOs are concerned. Furthermore, the in vivo pharmacological experiments (anticonvulsant activities) were not accompanied by isolation and characterization of bioactive phytoconstituents responsible for the antiepileptic MPs. Overall, the majority of the PS documented in this review require additional investigation on pharmacological activities, potential targets and mechanism of seizure attenuation, isolation and characterization of bioactive compounds, and toxicological analysis to validate the significance of MPs to tackle epilepsy-associated comorbidities and mortalities.

Abbreviations
AMP: Aminophylline; AEDs: Antiepileptic drugs; AEMNAs: Antiepileptic medications non-adherences; AQ: Aqueous; BIC: Bicuculline; BU: Butanol; CAT: Catalase; CNS: Central nervous system; CH: Chloroform; CAs: Complementary and alternative medicines; ET: Ethanolic; ES: Epileptic seizures; FMZ: Flumazenil; GTCS: Generalized tonic clonic seizures; GLU: Glutamine; GSK-3: Glycogen synthase kinase-3; HET: Hydroalcoholic/hydroethanolic; HME: Hydromethanolic; IP: Intraperitoneal; INH: Isonicotinic hydrazide acid; IPU: Isoprene units; KA: Kaanic acid; LPO: Lipid peroxidation; LMICs: Low- and middle-income countries; MDA: Malondialdehyde; ME: Methanolic; MFR: Methanol free residue; MGL: Malathion-glutathione; MIOA: Mechanism of action; MPs: Medicinal plants; ME: Methanolic; NCAM: National center for complementary and alternative medicines; NMDA: N-methyl-D-aspartate; OS: Oxidative stress; PE: Petroleum ether; PCT: Picrotoxin; PLC: Pilocarpine; PS: Plant species; PTZ: Pentylentetrazol; QOL: Quality of life; QA: Quinic acid; ROS: Reactive oxygen species; GSH: Reduced glutathione; SNNP: Southern nations nationalities and peoples; SE: Status epilepticus; STR: Strychnine; SOD: Superoxide dismutase; THS: Traditional healers; FDA: United States Food and Drug Administration; TM: Traditional medicine; VPA: Valproic acid; WHO: World Health Organization and GABA, γ-aminobutyric acid.

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References
1. Chippiti T, Viljoen AM, Cordero-Maldonado ML, Weale CGL, Van Heerden FR, Sandasi M, Chen W, Crawford AD, Enslin GM. Anti-seizure activity of African medicinal plants: the identification of bioactive alkaloids from the stem bark of Rauvolfia caffra using an in vivo zebrafish model. J Ethnopharmacol. 2021;279:114282.
2. Muhigwa A, Preux P-M, Gérard D, Marin B, Boumediène F, Ntamwira C, Tsai C-H. Comorbidities of epilepsy in low and middle-income countries: systematic review and meta-analysis. Sci Rep. 2020;10(1):9015.
3. Tao G, Auvrez C, Nightscapes R, Barnard S, McCartney L, Malpas CB, Perucca P, Chen Z, Adams S, McIntosh A, et al. Association between psychiatric comorbidities and mortality in epilepsy. Neurol Clin Pract. 2021;11(5):429–37.
4. Lin C-H, Hsieh C-L. Chinese herbal medicine for treating epilepsy. Front Neurosci. 2021;15(798):195.
5. Obese E, Biney RP, Henneh IT, Adakudugu EA, Anokwah D, Agyemang LS, Woode E, Ameyaw EO. The anticonvulsant effect of hydroethanolic leaf extract of Calotropis procera (Ait) R Br (Apocynaceae). Neural Plast. 2021;2021:5566890.
6. Akyuz E, Paudel YN, Polat AK, Dundar HE, Angelopoulos E. Enlightening the neuroprotective effect of quercetin in epilepsy: from mechanism to therapeutic opportunities. Epilepsy Behav. 2021;115:107701.
7. Kumar R, Arora R, Sarangi SC, Ganeshes NS, Agarwal A, Kaleekal T, Gupta VK. Pharmacodynamic and pharmacokinetic interactions of hydroalcoholic leaf extract of Centella asiatica with valproate and pentylenetetrazol in experimental models of epilepsy in rats. J Ethnopharmacol. 2021;270:113784.
8. Kaur J, Famta P, Famta M, Mehta M, Satija S, Sharma N, Vyas M, Khatik G, Chellappan DK, Dua K, et al. Potential anti-epileptic phytoconstituents: an updated review. J Ethnopharmacol. 2021;268:113565.

9. Yazeie TS, Kefale B, Molla EL. Treatment outcome of epileptic patients receiving antiepileptic drugs in Ethiopia: a systematic review and meta-analysis. Behav Neurol. 2021;2021:5586041.

10. Melkamu P, Animy Y, Mihiyun A, Atanauf A, Yitayal M. Cost of illness and associated factors in patients attending adult outpatient department of University of Gondar referral hospital Northwest Ethiopia. Risk Manag Healthc Policy. 2021;14:2385.

11. Allers K, Eussen BM, Hackett M, Anderson CS, Pickles K, Schiebel J, Jan S. The economic impact of epilepsy: a systematic review. BMC Neurol. 2015;15(1):245.

12. Fokoua AR, Ndjenda MK, Kaptué Wuyt A, Tatsinkou Bomba FD, Dongmo AK, Chouna P, Nguelefack TB. Anticonvulsant effects of the aqueous and methanol extracts from the stem bark of Psychotria comptopus verdc (Rubiacaeae) in rats. J Ethnopharmacol. 2021;272:113935.

13. Kambli L, Bhatt LK, Oza M, Prabhavalkar K. Novel therapeutic targets for epilepsy intervention. Seizure. 2017;51:27–34.

14. Perucca E. The pharmacological treatment of epilepsy: recent advances and future perspectives. Acta Epileptol. 2021;3(1):122.

15. Mishra P, Sinha JK, Rajput SK. Efficacy of cicuta virosa medicinal preparations against pentylenetetrazole-induced seizures. Epilepsy Behav. 2021;115:107653.

16. Aourz N, Serruy S-AK, Chabwaine JN, Baleagimire PB, Afikannova T, Edrada-Ebel R, Grey AI, Kamuhawba AR, Walrave L, Esguerra CV, et al. Identification of a potential therapeutic entry point for epilepsy. ACS Chem Neuosci. 2019;10(4):1992–2003.

17. Guery D, Rheims S. Clinical management of drug resistant epilepsy: a review on current strategies. Neuropsychiatr Dis Treat. 2021;17:2229.

18. Farrukh MJ, Makmor-Bakry M, Hatah E, Tan HJ. Use of complementary and alternative medicine and adherence to antiepileptic drug therapy among epilepsy patients: a systematic review. Patient Prefer Adherence. 2018;12:2111.

19. Faheem M, Ameer S, Khan AIW, Hasseeb M, Raza Q, Ali Shah F, Khusro A, Aarti C, Umar Khayam Sahibzada M, El-Saber Batha G, et al. Comprehensive review on antiepileptic properties of medicinal plants. Arabian J Chem. 2022;15(1):103478.

20. Hassio TY, Desse TA. Adherence to treatment and factors affecting adherence of epileptic patients at Yirgalem general hospital, Southern Ethiopia: a prospective cross-sectional study. PLoS ONE. 2016;11(9):e0163040.

21. Catalao R, Eshetu T, Tsigebrhan R, Medhin G, Fekadu A, Hanlon C. Implementation of a pictorial educational strategy for adherence of Epileptic patients in Ethiopia. BMC Med. 2021;2021:665845.

22. Kebedew M, Mohamed E, Meyer-Rochow V. Knowledge and use of traditional medicinal plants in Ethiopia, 2017. BMC Res Notes. 2018;11(1):652.

23. Kefelegen GA, Desta B. Xenimia americana: economic importance, medicinal value, and current status in Ethiopia. Sci World J. 2021;2021:8880021–8880021.

24. Abebe BA, Chane Teletien S. Ethnobotanical Study of medicinal plants used to treat human and livestock ailments in hulet Ene Ewese Woreda, East Gojam Zone of Amhara Region. Ethiopia. Evid Based Compl Alter Med 2021;2021:6668541.

25. Birhan YS. Traditional zootherapeutic prescriptions employed in the management of neurological and related disorders in Ethiopia. Acta Ecol Sinica 2022. https://doi.org/10.1007/j.cnjournals.2022.09.007. (In Press)

26. Birhan YS, Kitaw SL, Alemayehu YA, Mengesha NM: Medicinal plants with traditional healthcare importance to manage human and livestock ailments in Enemay District, Amhara Region, Ethiopia. Acta Ecol. In Press 2022. https://doi.org/10.1007/j.cnjournals.2022.05.004.

27. Birhan Y, Kitaw S, Alemayehu Y, Mengesha N. Ethnoveterinary medicinal plants and practices in Enar Enaagwa district, East Gojam zone, Amhara region, Ethiopia. Int J Anim Sci. 2018;14(1):1014.

28. Teklehaymanot T. Ethnobotanical study of knowledge and medicinal plants use by the people in Dek Island in Ethiopia. J Ethnopharmacol. 2009;124(1):69–78.

29. Alemneh D. Ethnobotanical study of plants used for human ailments in Yilmana Densa and quartz districts of West Gojam Zone, Amhara Region Ethiopia. J Ethnopharmacol. 2018;2018:617459.

30. Tekelehaymanot T. Ethnobotanical study of medicinal plants used to treat the erection dysfunction in Ethiopia: a systematic review. BioMed Res Int. 2021;2021:6656406.

31. Assen Y, Woldearegay M, Haile A. An ethnobotanical study of medicinal plants in Kelala District, south wollo zone of Amhara region, Northeastern Ethiopia. J Ethnopharmacol. 2021;2021:6651922.

32. Mesfin E, Demissew S. An ethnobotanical study of medicinal plants in Wonago Woreda, SNPR, Ethiopia. J Ethnopharmacol. 2009;51(1):28.

33. Hassen A, Mucbe M, Muaasya AM, Tesgay BA. Exploration of traditional plant-based medicines used for livestock ailments in northeastern Ethiopia. S Afr J Bot. 2022;146:230–42.

34. Kassa Z, Asfaw Z, Demissew S. An ethnobotanical study of medicinal plants in Sheka zone of Southern Nations Nationalities and Peoples regional state, Ethiopia. J Ethnopharmacol. 2020;161(1):7.

35. Mengsttu M, Kebede D, Atomsa D, Abebe A, Alemne D. Status and utilization of medicinal and aromatic plants in eastern Hararghe, Ethiopia. Cogent Food Agric. 2019;5(1):701349.

36. Kidane L, Gebremedhin G, Beyene T. Ethnobotanical study of medicinal plants in Ganta Afeshum District, Eastern zone of tigray, northern Ethiopia. J Ethnopharmacol. 2018;141(1):64.
50. Kebede E, Mengistu M, Serda B. Ethnobotanical knowledge of pastoral community for treating livestock diseases in Somali regional state, eastern Ethiopia. Trop Anim Health Prod. 2018;50(6):1379–86.

51. Demie G, Negash M, Awias T. Ethnobotanical study of medicinal plants used by indigenous people in and around Dire Sheikh Hussein heritage site of South-eastern Ethiopia. J Ethnopharmacol. 2018;220:87–93.

52. Wubetu M, Abula T, Dejenu G. Ethnopharmacologic survey of medicinal plants used to treat human diseases by traditional medical practitioners in Deega Damot district, Amhara, Northwestern Ethiopia. BMC Res Notes. 2017;10(1):1157.

53. Attnu’H, Awias T, Alemu S, Wube S. Ethnobotanical study of medicinal plants in Selale mountain ridges, North Shoa. Ethiopia Int J Biodiver. 2018;2(6):567–77.

54. Abhaley A, Leta S. Medicinal value of camel milk and meat. J Appl Anim Res. 2018;46(1):552–8.

55. Gemetchu EC. Assessment of indigenous knowledge of medicinal plants used for livestock treatment in five selected kebeles of Kerra District, Jimma Zone South Western Ethiopia. J Sci Agri. 2015;3:40–54.

56. Osman A, Sibhatu DB, Giday M. Medicinal plants used to manage human and livestock ailments in Raya Kobo District of Amhara regional state Ethiopia. Evid Based Compl Altern Med. 2020;2020:1329170.

57. Muluye AB, Aycieh MW. Medicinal plants utilized for hepatic disorders in Ethiopian traditional medical practices: a review. Clin Phytosci. 2020;6(1):52.

58. Berhanu M, Tintagiu T, Fentahun S, Giday M. Ethnoveterinary survey of medicinal plants used for treatment of animal diseases in Ambo district of Oromia regional state of Ethiopia. Evid Based Compl Altern Med. 2020;2020:8816227.

59. Tafera BN, Kim Y-D. Ethnobotanical study of medicinal plants in the Hawarsha Zura District, Sidama zone, Southern Ethiopia. J Ethnobot Ethnomed. 2019;15(1):25.

60. Andarge E, Shonga A, Agize M, Tora A. Utilization and conservation of medicinal plants and their associated indigenous knowledge (IK) in Dawuro Zone: An ethnobotanical approach. Int J Med Plant Res. 2015;4:330–7.

61. Chekole G. Ethnobotanical study of medicinal plants used against human ailments in Gubalabo District, Northern Ethiopia. J Ethnobot Ethnomed. 2017;13(1):55.

62. Mesfin F, Seta T, Assefa T. An ethnobotanical study of medicinal plants in Amaro Woreda. Ethiopia Ethnobot Res Appl. 2014;12:341–54.

63. Teklehaymanot T. An ethnobotanical survey of medicinal and edible plants of Yalo Woreda in Afar regional state, Ethiopia. J Ethnobot Ethnomed. 2017;13(1):40.

64. Asfaw A, Lulekal E, Bekele T, Debella A, Abebe A, Degu S. Ethnobotanical investigation on medicinal plants traditionally used against human ailments in Ensaro District, North Shewa Zone, Amhara regional state. Ethiopia. 2021. https://doi.org/10.21203/rs.3.rs-720404/v1.

65. Yiniger H, Kelbessa E, Bekele T, Lulekal E. Ethnoveterinary medicinal plants at Bale mountains national park. Ethiopia J Ethnopharmacol. 2007;112(1):55–70.

66. Abeera B. Medicinal plants used in traditional medicine by Oromo people, G limbsi District, Southwest Ethiopia. J Ethnobot Ethnomed. 2014;10(1):40.

67. Siraj J, Belaw SY, Suleman S. Ethnobotanical assessment and physico-chemical properties of commonly used medicinal plants in Jimma zone, Southwest Ethiopia: traditional healers based cross-sectional study. J Ethn Pharmacol. 2020;12665–81.

68. Tassew G. Ethnobotanical study of medicinal plants in Borecha Woreda, Buno Bedele Zone Southwestern Ethiopia. Int J Sci Res. 2019;8(9):1484–98.

69. Yiniger H, Kelbessa E, Bekele T, Lulekal E. Plants used in traditional management of human ailments at bale mountains national park Southeastern Ethiopia. J Med Plants Res. 2013;2(2):132–53.

70. Agize M, Asfaw Z, Nemomissa S, Gebre T. Ethnobotany of traditional medicinal plants and associated indigenous knowledge in Dawuro Zone of southwestern Ethiopia. J Ethnobot Ethnomed. 2022;18(1):48.

71. Lulekal E, Asfaw Z, Kelbessa E, Van Damme P. Ethnomedical study of plants used for human ailments in Ankober District, North Shewa Zone, Amhara Region, Ethiopia. J Ethnobot Ethnomed. 2013;9(1):63.

72. Assefa T, Nigussie N, Mullaleurad D, Sinshav G, Adimasu Y. The role of medicinal plants in traditional medicine in Adwa District, tigray northern Ethiopia Asian. J Plant Sci. 2019;8(3):4–11.

73. Seifu T, Aresk K, Gebre-Marom T. Ethnobotanical and ethnopharmacological studies on medicinal plants of Chifra District, Afar region north eastern Ethiopia. Ethiop Pharm J. 2006;24:41–58.

74. Tahir M, Gebrermichael L, Beyein T, Van Damme P. Ethnobotanical study of medicinal plants in Adwa District, central zone of tigray regional state, Northern Ethiopia. J Ethnobot Ethnomed. 2021;7(1):71.

75. Flate T, Gedif T, Aresk K, Gebre-Marom T. Ethnomedical survey of Berta ethnic group Assosa Zone, Benishangul-Gumuz regional state, mid-west Ethiopia. J Ethnobot Ethnomed. 2009;5(1):14.

76. Khan MA, Agize M, Shonga A, Tora A. The utilization and conservation of plants of medicinal value by local traditional medical practitioners and the associated indigenous knowledge in dawuro zone of Ethiopia: Northeast Africa—An Ethnobotanical Approach. In: Ozturk M, Hakeem KR, editors. Plant and human health ethnobotany and physiology. Cham: Springer International Publishing, 2018. p. 267–321.

77. Birhan YS, Kitaw SL, Alemayehu YA, Mengesha NM. Ethnobotanical study of medicinal plants used to treat human diseases in Enat Enawga district, East Gojam region, Amhara region Ethiopia. J Ethnobot Res Appl. 2012;10:305–20.

78. Teka A, Asfaw Z, Demissew S, Van Damme P. Medicinal plant use practice in four ethnic communities (Gurage, Mareqo, Qebena, and Siilti), south central Ethiopia. J Ethnobot Ethnomed. 2020;16(1):27.

79. Bekele M, Woldeyes F, Lulekal E, Bekele T, Demissew S. Ethnobotanical investigation of medicinal plants in bursa mountain range, Harar district, Southwestern Ethiopia. J Ethnobot Ethnomed. 2022;18(1):60.

80. Gebre MG, Lulekal E, Bekele T, Demissew S. Use and management practices of medicinal plants in and around mixed woodland vegetation, tigray regional state Northern Ethiopia. Ethnobot Res Appl. 2021;21:1–26.

81. Jara JS, Girma Z, Selamo MM. Ethnemedicinal study of plants used against human ailments in Aseko District. South East Ethiopia. 2020. https://doi.org/10.21203/rs.3.rs-23592/v1.

82. Lulekal E, Kelbessa E, Bekele T, Yineger H. An ethnobotanical study of medicinal plants in Mana Angetu District, southeastern Ethiopia. J Ethnobot Ethnomed. 2008;4(1):10.

83. Parvez N, Yadav S. Ethnopharmacology of single herbal preparations of medicinal plants in Asendabo district, Jimma Ethiopia Indian. J Tradit Knowl. 2010;9(4):724–9.

84. Maryo M, Nemomissa S, Bekele T. An ethnobotanical study of medicinal plants of the Kembatta ethnic group in Enset-based agricultural landscape of Kembatta Tembaro (KT) Zone, Southern Ethiopia. Asian J Plant Sci Res. 2015;5(7):42–61.

85. Abele NA. Vascular plant diversity and ethnobotany of medicinal and wild edible plants in Baso Liben and Debris Elias Districts, East Gojam Zone of Amhara Region, Northwestern, Ethiopia. PhD Dissertation, Addis Ababa University. 2020. http://213.55.95.56/handle/123456789/22266.

86. Abebe E. Ethnobotanical Study on Medicinal Plants Used by Local Communities in Debark Wereda, North-Goenar Zone, Amhara Regional State, Ethiopia. M.Sc. Thesis, Addis Ababa University. 2011. http://etd.aaau.edu/etd/handle/123456789/4244.

87. Tamrat S. Study of useful plants in and around GATE UDUMA (Traditional Gedeo Homegardens) in Kochere Wereda of Gedeo Zone, SNINPR, Ethiopia: an Ethnobotanical Approach. M.Sc. Thesis, Addis Ababa University. 2011. http://213.55.95.56/handle/123456789/9329.

88. Belayneh A, Bussa NF. Ethnobotanical plants used to treat human ailments in the prehistoric place of Harla and Dengego valleys, eastern Ethiopia. J Ethnobot Ethnomed. 2014;10(1):18.

89. Kefalew A, Asfaw Z, Kelbessa E. Ethnobotany of medicinal plants in Ad’A District, East Shewa zone of Oromia regional state, Ethiopia. J Ethnobot Ethnomed. 2015;11(1):25.

90. Assefa B, Glaztel G, Buchmann C. Ethnemedicinal uses of Hagenia abyssinica (Bruce) JF Gmel among rural communities of Ethiopia. J Ethnobot Ethnomed. 2010;6(1):20.
92. Enyew A, Asfaw Z, Kelbessa E, Nagappan R. Ethnobotanical study of tradi-
tional medicinal plants in and around Fiche District, central Ethiopia. Curr Res J Biol Sci. 2014;6(4):1154–67.
93. Ayalew S, Kebede A, Mesfin A, Mululeme G. Ethnobotanical study of medicinal plants used by agro pastoralist Somali people for the manage-
ment of human ailments in jeldesa cluster, Dire Dawa administra-
tion eastern Ethiopia. J Med Plants Res. 2017;11(9):171–87.
94. Belay M. Ethnobotanical investigation of traditional medicinal plants in Dugda District, Oromia Region. SM J Med Plant Stud. 2018;2(1):1007.
95. Kindie B, Tamiru C, Abdala T. 2021 Ethnobotanical study of medicinal plants and conservation status used to treat human and livestock ailments in Fadis District, Eastern Ethiopia. Int J Homeopath Nat Med. 2021;7(1):7–17.
96. Kebebew M. Diversity, knowledge and use of medicinal plants in Abay Chomen district, Horo Guduru Wollega zone, Oromia region of Ethiopia. J Med Plants Res. 2017;11(31):480–500.
97. Ragunathan M, Abay SM. 2009 Ethnomedicinal survey of folk drugs used in Bahir Dar Zuria district northwestern Ethiopia Indian. J Trad Knowl. 2009;8(2):281–4.
98. Yohannis SW, Asfaw Z, Kelbessa E. Ethnobotanical study of medicinal plants used by local people in menz gera midir district, north shewa zone, amhara regional state Ethiopia. J Med Plants Res. 2018;12(1):296–314.
99. Abebe M. The ethnomedicinal plants used for human ailments at Mojana Wodera District, central Ethiopia. Biodiversitas. 2021;22(10):4676–86.
100. Mazondo NA, Stafford GI, Aremu AO, Makunga NP. Acetylcholinesterase inhibitors from southern African plants: An overview of ethno-
botanical, pharmacological potential and phytochemical research including and beyond Alzheimer’s disease treatment. S Afr J Bot. 2019;120:39–64.
101. Wubetu M, Sintayehu M, Aeta MA. Ethnobotany of medicinal plants grown in and around Fiche District, central Ethiopia. J Med Plants Res. 2017;11(9):171–87.
102. Gebrehiwot M: An Ethnobotanical study of medicinal plants in and around Fiche District, central Ethiopia. J Med Plants Res. 2017;11(9):171–87.
103. Yao J, Yaro AH, Abubakar MS, Anuka JA, Hussaini IM. Anticonvulsant activity of Carissa edulis (Vahl) (Apocynaceae) root bark extract. J Ethnopharmacol. 2008;120(2):219–31.
104. Ya’u J, Yaro AH, Abubakar MS, Anuka JA, Hussaini IM. Anticonvulsant activity. J Ethnopharmacol. 2001;81(3):199–204.
105. Dong X, Qian G, Qian F, Zhang L, Lan W, Zeng X. Anticonvulsant activity of Noni (Morinda citrifolia L.) extract against pentylenetetrazole-induced seizures in rats. J Ethnopharmacol. 2019;234:73–80.
106. Tabuti JR, Lye KA, Dhillion S. Traditional herbal drugs of Bulamogi, Cameroon. S Afr J Bot. 2019;120:39–64.
107. Maria MR, Maria Cristina D, Bucar I, Luís C. Medicinal plants used to treat psychiatric illnesses. World J Adv Res Rev. 2020;8(2):296–306.
108. Feng G, Zhao Y, Deng J, Wang J, Chen X, Liu J, et al. Anticonvulsant activity of Withania somnifera (Dunal) in mice. Pharmacognosy Res. 2017;9(10):146–56.
109. Chauhan AK, Dobbal MP, Joshi BC. A review of research papers showing anticonvulsant activity. J Ethnopharmacol. 1998;61(2):11–23.
110. Wächter M. Ethnobotanical study of some aromatic and medicinal plants in the middle Atlas mountains of Morocco. Nat Prod Commun. 2011;6(10):1934578X1100601011.
111. Elisabeth T, Esther N, Stéphanie NKi, Gisèle NNC, Vedeko, J, Elisabeth NB. Anticonvulsant effect of asparagus africanus lam root decoction on pilocarpine-induced temporal lobe epilepsy in white mice (Mus musculus.) Swiss. World J Adv Res Rev. 2020;8(2):296–306.
112. Ramachandran NR, Muthukumaran V. Anticonvulsant activity. J Neurosci Res. 1996;44:173–180.
113. Govindu S, Adikay S. Evaluation of antiepileptic activity of chloro-
form extract of Acalypha fruticosa in mice. Pharmacognosy Res. 2014;6(2):108–12.
114. Gopalakrishnan S, Saroja K, Elizabeth JD. Chemical investigation of aerial parts of Acalypha fruticosa Forsk. Der Pharma Chemica. 2010;2(3):383–9.
115. Fito D, Ndam W, Fonge B. Medicinal plants of aqambam-bambum in the Lebaimal highlands, southwest province of Cameroon. Afr J Pharm Pharmacol. 2009;3(1):1–13.
116. Diallo D, Hveem B, Mahmoud MA, Berge G, Paulsen BS, Maiga A. An ethnobotanical survey of herbal drugs of Gourma district Mali. Pharm Biol. 1999;37(1):80–91.
117. Arnott MM. Ethnobotanical study of medicinal plants of Jazan region, Saudi Arabia. Evid Based Compl Altern Med. 2019;2019:3190670.
118. Gunja N, Vishnor G, Wal A, Wal P. Medicinal value of Euphorbia tirucalli. Syst Rev Pharm. 2013;4(1):40.
119. Ior L, Otienyin S, Oluwori V, Umar D, Azila J. Ethnobotanical survey of plants used in the management of mental illnesses in some selected local government areas of plateau state Nigeria. J Pharmacogn Phyto-
thecol. 2017;9(10):146–56.
120. Chauhan AK, Dobbal MP, Joshi BC. A review of research papers showing anticonvulsant activity. J Ethnopharmacol. 1998;61(2):11–23.
121. Wächter M. Ethnobotanical study of some aromatic and medicinal plants in the middle Atlas mountains of Morocco. Nat Prod Commun. 2011;6(10):1934578X1100601011.
122. Elisabeth T, Esther N, Stéphanie NKi, Gisèle NNC, Vedeko, J, Elisabeth NB. Anticonvulsant effect of asparagus africanus lam root decoction on pilocarpine-induced temporal lobe epilepsy in white mice (Mus musculus.) Swiss. World J Adv Res Rev. 2020;8(2):296–306.
123. Henry A, Hosagoudar V, Ravikumar K. Ethno-medicobotany of the Southern Western Ghats of India. Ethnobiol. Human Welfare 1996;173–180.
124. Ramachandran NR, Muthukumaran V. Anticonvulsant activity. J Neurosci Res. 1996;44:173–180.
125. Maria MR, Maria Cristina D, Bucar I, Luís C. Medicinal plants used to treat psychiatric illnesses. World J Adv Res Rev. 2020;8(2):296–306.
126. Maria MR, Maria Cristina D, Bucar I, Luís C. Medicinal plants used to treat psychiatric illnesses. World J Adv Res Review. 2020;8(2):296–306.
127. Adesina S. Studies on some plants used as anticonvulsant in Amein-
dian and African traditional medicine. Fitoterapia. 1982;53:147–62.
128. Kamau LN, Mtbaaibu PM, Mbiria JM, Gathumbi PK, Kiama SG. Ethnobot-
ological survey and threats to medicinal plants traditionally used for the management of human diseases in Nyeri County. Kenya: CELLMED; 2016.
129. Singh B, Singh S, Kishor A, Singh B. Traditional usage of medicinal plants in humans and animals health care and their chemical constituents from hills and valleys of Jammu province, Western Himalaya Indian. J Nat Prod Resour. 2021;12(1):94–100.
130. Geometz, G, Grondin I, Smadja J, Frederich M, Gauvin-Bialecki A. A review of traditional uses, phytochemistry and pharmacology of the genus Indigofera. J Ethnopharmacol. 2020;253:112608.
131. Bolanle O, Oviasogie O, Owolabi O, Akhigbemen A, Obarisiagbon P, Osagiebo C. Evaluation of the anti-convulsant activity of aqueous leaf extract of jatropha curcas (Euphorbiaceae) in mice. Trop J Nat Prod Res. 2018;2(11):489–93.
135. Kumar K, Shankhedar PK, Chauhan R. Evaluation of antiepileptic activity of ethanolic extract of populus deltoides leaf in mice. World J Pharma Res. 2017;6(8):923–40.

136. Sharma V, Sinoyna P, Mehta S. Anticonvulsant and CNS Depressant Activity of Methanolic Extracts of Whole Plant of Sida acuta and Sida rhombifolia in Mice. Curr. Res. Pharm Sci. 2013;03(04):148–53.

137. Sugaya A, Tsuda T, Makommen E, Seifu D. Evaluation of hydro-alcoholic extract of Cleodendrum myricoides (hochst Vatke) leaves and its solvent fraction in pentylentetrazole-induced convulsion in mice. J. Compl. Altern Med Res. 2020;10(3):31–16.

138. Saile A, Chauhan R. Anticonvulsant activity of 80% methanolic root bark extract and solvent fractions of Pentas schimperiana (A Rich) Vatke (Bauhiniaee) in Swiss albino mice. Adv Pharmacol. 2021;2021:6689978.

139. Tsyvunin V, Shtrygol S, Prokopenko Y, Georgiyants V, Blyznyuk N. Therapeutic effects of oleuropein in improving seizure, oxidative stress and cognitive disorder in pentylentetrazole kindling model of epilepsy in mice. Iran. J Pharm Res. 2020;19(1):98–110.

140. Tugume P, Kakudidi EK, Buyinza M, Namaalwa J, Kamatenesi MR, Mucunguzi P, Kalema J. Ethnobotanical survey of medicinal plant species used by communities around Mabira central forest reserve Uganda. J Ethnobiol. 2016;12(1):5.

141. Bassoueka DJ, Loufooua BE, Etou-Obisivi AW, Nsone-Ntandou GF, Ondélé R, Icin-Itou RDQ, Ouamba JM, Abubakar U, Danmallam U, Ibrahim H. Anticonvulsant activity of extracts and solvents fractions of Carissa edulis in mice. J Compl. Altern Med. 2020;10(3):1–10.

142. Bertoncello KT, Bonan CD. Zebrafish as a tool for the discovery of antiepileptic drugs (ASD): advantages and potential pitfalls in ASD screening. Neuropharmacology. 2020;167:107750.

143. Bucht, Ham (Lamiaceae) leaves in mice. Ethiop. J Health Sci. 2020;30(6):981–90.

144. Chauhan R, Shankhedar PK, Chauhan R. Evaluation of antiepileptic activity of ethanolic extract of populus deltoides leaf in mice. World J Pharma Res. 2017;6(8):923–40.

145. Dixit R, Patil PR. Alcoholic extract of Buddleja abyssinica in mice. Curr. Res. Pharm Sci. 2013;03(04):148–53.

146. Garba K, Yaro AH, Yusu J. Anticonvulsant activity of ethanolic stem bark extract of Lannea barteri (Anacardiaceae) in mice and chicks. J Ethnopharmacol. 2015;153(5):298–305.

147. Guria B, Nigam I, Nigam A. Anticonvulsant activity of methanolic extract and its solvent fractions of Scurrula parasitica (L) L. (Asteraceae). Toxicon 2018;148:455–65.

148. Hossain A, Mura N, Tungjuk T, Wrae MA, Chittaphong P. Evaluation of antiepileptic activity of extracts and isolated compounds from leaves of Curcuma longa L. (Zingiberaceae). J Ethnopharmacol. 2015;172:227–31.

149. Hosseini A, Mirazi N. Alteration of pentylenetetrazol-induced seizure model in larval zebrafish. Int J Mol Sci. 2021;22(14):7745.

150. Kasture SB, Gupta SC, Kotecha M. Anticonvulsant activity of Zingiber officinale rhizome, exerts anticonvulsant activity in the Pentylenetetrazol-induced seizure model in larval zebrafish. Int J Mol Sci. 2021;22(14):7745.

151. Kumar KS, Rajkapoor B. Evaluation of anti-epileptic activity of Xanthium strumarium L. Pharmacologyonline. 2010;25:850–5.

152. Ng’uni T, Klaasen JA, Fielding BC. Acute toxicity studies of the South African medicinal plant Galenia africana. Toxicol. Rep. 2018;5:813–8.

153. Olatunji SY, Ogunnaike PO, Owolabi JO, Abijo AZ, Alabi A, Adelodun ST, Kediso TE, Tolessa T, Getachew T, Togumelowu P, Nkwenou M, Talla E, Moto W, Wu C. Traditional uses, botany, phytochemistry, pharmacology, pharmacokinetics and toxicology of Xanthium strumarium L. a review. Molecules. 2019;24(2):359.

154. Ondélé R, Elion-Itou RDG, Ouamba JM, Abena AA. Plantes anticonvulsantes: examination de l'influence de la quantité d'eau d'extrait de Clutia abyssinica. Ethnobiol Ethnomed. 2016;12(1):5.

155. Ogbom D, Oga M, Ogunrinade OA, Adekunle AA. Anticonvulsant activity of methanol leaf extract and solvent fractions of Azadirachta indica (Bougainvillaea). J Ethnopharmacol. 2015;13(5):298–305.

156. Olatunji SY, Azubuike C, Okwuonwu F, Okereke C. Evaluation of anti-epileptic activity of extracts and solvents fractions of Buddleja abyssinica in mice. Ethiop. J Health Sci. 2020;30(6):981–90.

157. Tsyvunin V, Shtrygol S, Prokopenko Y, Georgiyants V, Blyznyuk N. Therapeutic effects of oleuropein in improving seizure, oxidative stress and cognitive disorder in pentylentetrazole kindling model of epilepsy in mice. Iran. J Pharm Res. 2020;19(1):98–110.

158. Viswanath BS, Chauhan R. Anticonvulsant activity of 80% methanolic root bark extract and solvent fractions of Pentas schimperiana (A Rich) Vatke (Bauhiniae) in Swiss albino mice. Adv. Pharm. 2021;2021:6689978.

159. Viswanath BS, Chauhan R. Anticonvulsant activity of 80% methanolic root bark extract and solvent fractions of Pentas schimperiana (A Rich) Vatke (Bauhiniae) in Swiss albino mice. Adv. Pharm. 2021;2021:6689978.

160. Xie J, Kim J, Wang W, Wu C. Traditional uses, botany, phytochemistry, pharmacology, pharmacokinetics and toxicology of Xanthium strumarium L. a review. Molecules. 2019;24(2):359.

161. Xue J, Kim J, Wang W, Wu C. Traditional uses, botany, phytochemistry, pharmacology, pharmacokinetics and toxicology of Xanthium strumarium L. a review. Molecules. 2019;24(2):359.

162. Yip X, Zhou J, Wang W, Wu C. Traditional uses, botany, phytochemistry, pharmacology, pharmacokinetics and toxicology of Xanthium strumarium L. a review. Molecules. 2019;24(2):359.

163. Zeng Q, Pan Y, Wang W, Wu C. Traditional uses, botany, phytochemistry, pharmacology, pharmacokinetics and toxicology of Xanthium strumarium L. a review. Molecules. 2019;24(2):359.
177. Getahun A, Kifle ZD, Ambikar D, Atnafie SA. In vivo evaluation of 80% methanolic leaves crude extract and solvent fractions of bundleja polystachya fiesen (bundlejaaceae) for wound healing activity in normal and diabetic mice. Metabo Open. 2021;11:100110.

180. Hu Z, Feng R, Xiang F, Song X, Yin Z, Zhang C, Zhao X, Jia R, Chen Z, Li L. Acute and subchronic toxicity as well as evaluation of safety pharmacology of Eucalyptus oil-water emulsions. Int J Clin Exp Med. 2014;7(12):4835.

181. Andjani HN, Sentosa Y, Yati K, Fauzantoro A, Gozan M, Yoo YJ. Acute oral toxicity test of Nicotiana tabacum L. bio-oil against female wistar rats. IOP Conf Ser Earth Environ Sci. 2019;33(1):012047.

183. Kebede S, Afework M, Debella A, Ergete W, Makonnen E. Toxicological study of the butanol fractionated root extract of Asparagus africanus Lam on some blood parameter and histopathology of liver and kidney in mice. BMC Res Notes. 2016;9(1):49.

201. Deyno S, Tola MA, Bazira J, Makonnen E, Alele PE. Acute and repeated-dose toxicity of Echinops kebenci Mesfin essential oil. Toxicol Rep. 2021;8:131–8.

202. Deyno S, Abebe A, Tola MA, Hymeete A, Bazira J, Makonnen E, Alele PE. Acute and sub-acute toxicity of Echinops kebenci decoction in rats. BMC Compl Med Therapies. 2020;20(1):2.

205. Tanira MOM, Shah AH, Moshin A, Ageel AM, Qureshi S. Pharmacological and toxicological investigations on Foeniculum vulgare dried fruit extract in experimental animals. Phytother Res. 1996;10(1):33–6.

206. Widiastuti H, Primaharinastiti P, Prihatiningtyas S. Toxicity test from Glo- riosa superba leaves extract in rats (rattus novegicus). Int J Pharm Sci. 2016;4(5):183–7.

207. Mekonnen B, Asrie AB, Wubneh Z. Antidiarrheal activity of 80% methanolic leaf extract of Justicia schimperiana. Evid Based Compl Med. 2020;2019:3037120.

208. Ambikar D, Tsegaw A, Belayneh YM. Wound healing activity of 80% alcoholic extract of Carissa tomentosa Lam in swiss albino mice. J Sci Innov Res. 2018;7(15):60–3.

209. Patel SB, Rau NJ, Hingorani LL. Safety assessment of Withania somnifera extract standardized for withaferin a: acute and sub-acute toxicity study. J Ayurveda Integr Med. 2016;7(1):30–7.

213. Dinku T, Tadesse S, Asres K. Antidiabetic activity of the leaf extracts of Pentas schimperiana in mice. J Exp Pharmacol. 2020;12:683.

214. Halae EE, Mosti MJ, Nondo RSO, Mwangomo DT, Mahunah RLA. A study of antimicrobial activity, acute toxicity and cytotoxic protective effect of a polyherbal extract in a rat ethanol-HCl gastric ulcer model. BMC Res Notes. 2012;5(1):546.

215. Gosht BT. Evaluation of toxic effect of hydro-methanolic root extract of Myrica salicifolia A. Rich (Myrica-ceea) on brain, heart, spleen and blood parameters in swiss albino mice. EC Pharmacol Toxicol. 2020;8:01–11.

216. Guex CG, Reginato FZ, Figueredo KC, da Silva ARHdC, Pires FB, Jesus RD, Lhamas CL, Lopes GHH, Bauermann LdF. Safety assessment of ethanolic crude extract of Olea europea L. leaves after acute and subacute administration to Wistar rats. Regul Toxicol Pharmacol. 2018;85:395–9.

217. Alameem E, Abbege G. Acute toxicity evaluation of water extract stem barks of Balanites aegyptica on adults of three different fish species. J Toxicol Environ Health Sci. 2019;12(9):9–15.

218. Kane NF, Kyama MC, Nganga JK, Hassanali A, Dallol M, Kimani FT. Acute toxicity effect of Artemisia afra plant extracts on the liver, kidney, spleen and in vivo antimarial assay on swiss albino mice. Adv Biosci Biotechn. 2019;7(4):64.

219. Chong H, Lim MK, Lee SH, Rahman MM, Lim Y-H. An oral toxicity test in rats and a genotoxicity study of extracts from the stems of Opuntia ficus-indica var saboten. BMC Compl Med Therapies. 2019;19(1):31.

220. Boukeloua A, Belkhiri A, Djerrou Z, Bahri L, Boulebda N, Pacha YH. Acute toxicity of Opuntia ficus indica and Pustecia lemniscis seed oils in mice. Afr J Tradit Compl Altern Med. 2012;9(4):607–11.

221. Bantle L, Gebeeyehu E. Antidiabetic activity of hydroalcoholic extract of the root of Croton macrostachyus in streptozotocin induced diabetic mice. World J Pharm Sci. 2015;3(2):185–91.

222. Azza MA, Rajakpoor B, Wondafrash DZ, Berhe AH. Protective effect of Croton macrostachyus (euphorbiaceae) stem bark on cyclophospha-mide-induced nephrotoxicity in rats. J Exp Pharmacol. 2020;12:275.

223. Araya EM, Adamu BA, Periasamy G, Sintayehu B, Gebrehiwot Hiben M. In vivo hepatoprotective and In vitro radical scavenging activities of Cucumis ficifolius a rich root extract. J Ethnopharmacol. 2019;242:112031.

224. Deyo S, Tola MA, Bazira J, Makonnen E, Alele PE. Acute and repeated-dose toxicity of Echinops kebenci Mesfin essential oil. Toxicol Rep. 2021;8:131–8.

225. Deyo S, Abebe A, Tola MA, Hymeete A, Bazira J, Makonnen E, Alele PE. Acute and sub-acute toxicity of Echinops kebenci decoction in rats. BMC Compl Med Therapies. 2020;20(1):2.

226. Kane NF, Kyama MC, Nganga JK, Hassanali A, Dallol M, Kimani FT. Acute toxicity effect of Artemisia afra plant extracts on the liver, kidney, spleen and in vivo antimarial assay on swiss albino mice. Adv Biosci Biotechn. 2019;7(4):64.

227. Alameem E, Abbege G. Acute toxicity evaluation of water extract stem barks of Balanites aegyptica on adults of three different fish species. J Toxicol Environ Health Sci. 2019;12(9):9–15.

228. Kefie A, Giday M, Mamo H, Erko B. Antimarial properties of crude extracts of seeds of Brucea antidysenterica and leaves of Oicinum lamia- filum. BMC Compl Altern Med. 2016;16(1):118.

229. Osseni R, Akoha S, Adjagba M, Azonbakin S, Lagnika L, Awedde B, Bigot A, Doua A, Darboux R, Layele A. In vivo toxicological assessment of the aqueous extracts of the leaves of Canisa adulps (Apocynaceae) in wistar rats. Eur J Med Plants. 2016;15(1):10–11.

230. Tamiru W, Engidawork E, Ares K. Evaluation of the effects of 80% methanolic leaf extract of Caylusea abyssinica (fresen) Fisch & Mey on glucose handling in normal glucose loaded and diabetic rodents. BMC Compl Altern Med. 2012;12(1):151.
of *Rhus vulgaris* (Anacardiaceae) extracts. BMC Compl Med Therap. 2020;20(1):272.

218. Nguta JM. In vivo antimalarial activity, toxicity, and phytochemical composition of total extracts from *Securidaca longepedunculata* Fresen (polypalaeaceae). Biomed Biotechnol Res. J. 2019;9(3):196.

219. Luciana DSNR, Gabriela TD, Edna JRCG, Micaelly DOS, Andrea BL, Kardilindo MDO, Otemberg SC, Josu DAR, Alexandre RDR, Janine AP. Acute toxicity evaluation of ethanolic extract of the air parts of *Sida rhombifolia* Linn in wistar rats Afr. J. Pharm. Pharmacol. 2019;13(14):181–7.

220. Assam Jp A, Dzoyem JP, Pieme CA, Penlap VB. In vitro antibacterial activity and acute toxicity studies of aqueous-methanol extract of *Sida rhombifolia* Linn (Malvaceae). BMC Compl Med Therap. 2016;10(1):40.

221. Sireeratawong S, Lertpratsatkun N, Sirsawat U, Thuppha A, Ngamjari-yavat A, Suwanlikhit N, Jaiky J. Acute and subchronic toxicity study of the water extract from root of *Sida rhombifolia* Linn in rats Songklanakarin J. Sci. Technol. 2008;30(6):729–737.

222. Nyangacha R, Gathirwa J, Muthaura C, Mungai G, Mwikwabe N, Orndicho J, Moind E, Omar S, Rukunga G, Maranga R. Antimalarial activity and toxicity evaluation of *Kenyan Hugiona castaneifolia* Engl *Telea nobilis* Del and *Turnera mombassana* C DC. Afr J Health Sci. 2012;23(4):305–15.

223. Legba B, Dougnou V, Deeguenon E, Agbankpe J, Senou M, Aniambossou A, Gbaguidi C, Sintondji K, Baba-Moussa L, Dougnou J. Toxicological characterization of six plants of the Beninese pharmacopoeia used in the treatment of Salmonellosis. J. Toxicol. 2019;2019:3530659.

224. Idang EO, Yemitan OK, Mbagwu HO, Udom GJ, Ogbuagu EO, Udobang L. *Zingiber officinalis* Rosc (Ginger) root oil extracts in Albino rats. Toxicol Digest. 2019;4(1):108–19.

225. Bhide RM, Bethapudi B, Chalichem NSS, Nithyanantham M, Murugan SK, Mundkinajeddu D. Acute and subchronic toxicity study of flavonoid rich extract of *Psidium guajava* methanolic leaf extract in rats. J Toxicol. 2022;2022:8517603.

226. Manekeng HT, Mbaveng AT, Pieme CA, Penlap VB. In vitro evaluaton of 80% methanolic leaves crude extract and solvent fractions of *Buddleja polysacyna* fenes (buddlejidae) for wound healing activity in normal and diabetic mice. Metab Open. 2021;11:10010–100110.

227. Abera T, Ashebir R, Basha H, Debebe A, Debebe E, Samuel W. Kidan Tadele A Ethno medicinal uses, phytochemistry and anti-malarial effect of *Croton macrostachyus* (Bisana): a review. J Med Plants Stud. 2019;7:79–88.

228. Tariku Y, Hymete A, Aihla A, Rolf Hoff. J Constituents, antileishmanial activity and toxicity profile of volatile oil from berries of *Croton macrostachyus*. J Nat Prod Commun. 2012;2012:252758.

229. El-Gamal A, Al-Massarani S, Fawzy G, Ahi H, Al-Rehaily A, Basudan O, Abdel-Kader M, Tabanca N, Becnel J. Chemical composition of *Buddleja polysacyna* aerial parts and its biactivity against *Anesegyptica*. Nat Prod. Res. 2018;32(23):2775–82.

230. Ali HYA, Gamal AAU, Fawzy GA. Chemical composition, in vitro antimicrobial and cytotoxic activities of *Buddleja polysacyna* essential oils. J Essent Oil-Bear Plants. 2014;17(6):1112–9.

231. Belete S, Asres K, Bekuretsion Y, Ashebir R, Abebe MS, Seyoum G. *Carissa edulis* growing in Saudi Arabia. Biosci Biotechnol Res Asia. 2016;7(2):635–46.

232. Zayri A, Nouir S, Zarrouk A, Haddad H, Khélifa A, Achour L. Phytochemical and pharmacological review. Nat Prod Bioprospect. 2021(6):25361–71.

233. Vega-Ruiz YC, Hayano-Kanashiro C, Gámez-Meza N, Medina-Juárez LÁ. *Ajuga integrifolia* Linn (Lamiaceae): a review. J Ethnopharmacol. 2020;234:820–7.

234. Birhan MS, Belay A, Yimer M, Messele B. Determination of chemical components and antioxidant activities of *Ajuga integrifolia* Linn. J Food Biochem. 2020;44(6):e13229.
258. Alotaibi SM, Saleem MS, Al-Humaidi JG. Phytochemical contents and biological evaluation of *Ruta chalepensis* L growing in three Palestinian regions. BioMed Res Int. 2017;2017:2672689.

259. jaradat n, adwan l, k’aibni s, zaid an, shtaya mjy, shraim n, assali m. Variability of chemical compositions and antimicrobial and antioxidant activities of *Ruta chalepensis* L growing in three Palestinian regions. BioMed Res Int. 2017;2017:2672689.

260. nahar l, el-seedi hr, khalfia sam, mohammedhosseini m, sarker sd. *Ruta* essential oil properties composition and bioactivities. Molecules. 2021;26(10):4766.

261. mah sh, teh ss, ee gcl. Anti-inflammatory, anti-cholinergic and cytotoxic effects of *Sidra hombobifolia*. Pharma Biol. 2017;55(1):920–8.

262. khan y, shah s,ullah s. Ethnomedicinal, pharmacological and phytochemical evaluation of *Xanthium strumarium* L. Int J Biol Sci. 2020;11(7):587.

263. Kamboj a, saluja aK. Phytopharmacological review of *Xanthium strumarium* L (Cocklebur). Int J Green Pharm. 2019;4(4):129–39.

264. liu y, liu j, zhanga y. Research progress on chemical constituents of *Zingiber officinale* roscoe. BioMed Res Int. 2019;2019:5370823.

265. panche an, diwan ad, chandra sr. Flavonoids: an overview. J Nutr Sci. 2016;5:67–467.

266. kumar s, pandey ak. Chemistry and biological activities of flavonoids: an overview. Sci World J. 2013;2013:162750.

267. diniz tc, silva jc, lima-saraiva srgd, ribeiro fpFAd, pacheco agm, de freitas mw, quintans-júnior lj. The role of flavonoids on oxidative stress in epilepsy. Oxid Med Cell Longev. 2015;2015:171766.

268. zhu h-l, wan j-b, wang y-t, li b-c, xiang c, he j, li l, pi medicinal compounds with antiepileptic/anticonvulsant activities. Epilepsia. 2014;55(1):3–16.

269. carmona-aparicio l, cádiznas-rodriquez n, delgado-lamas g, pedraza-chaverri j, montesinos-correa h, rivera-espíndola l, torres-espíndola lm, hernández me, lópez-acées t, pérez-lozano dl, et al. Dose-dependent behavioral and antioxidant effects of quercetin and methanol and acetonic extracts from *Heterotheca inuloides* on several rat tissues following kainic acid-induced status epilepticus. Oxid Med Cell Longev. 2019;2019:5287507.

270. pichersky e, raguso ra. Why do plants produce so many terpenoid compounds? New Phyto. 2018;2020(3):692–702.

271. reyes bas, dufourt ec, ross j, warner mw, tanqullit nc, leung ab. Chapter 4—selected phyto and marine bioactive compounds: alternatives for the treatment of type 2 diabetes. In: Atta r, editor. Studies: Natural Products Chemistry. Amsterdam: Elsevier; 2018.

272. angelova v, karabelov v, andreeva-gateva pa, tchekalarova j. recent developments of hydrazide/hydrazone derivatives and their analogs as anticonvulsant agents in animal models. Drug Dev Res. 2016;77(7):379–92.

273. raza m, alghasham aa, alorainy ms, el-hadiyah tm. Potentiation of valproate-induced anticonvulsant response by *Nigella sativa* seed constituents: the role of GABA-agonists. Int J Health Sci. 2008;2(1):15–25.

274. wang z-j, he x, lin h, zhang y, song x, miao c. Essential oils on epilepsy and acute seizure: a systematic review. Evid Based Compl Med Altern. 2019. https://doi.org/10.1155/2019/6216745.