










REVIEW

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# Ethnopharmacological uses, phytochemistry, pharmacology, and toxicology of *Olax subscorpioidea* Oliv (Olacaceae): a review

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## Abstract

**Background:** The plant *Olax subscorpioidea* Oliv (Olacaceae) is a shrub that is widely available in Africa. It has been used in traditional medicine to treat various diseases including asthma, pain, inflammation, gastrointestinal and central nervous system (CNS) disorders, cough, diabetes mellitus, cancer, infectious diseases, hepatic diseases, and many other diseases. Several phytochemical and pharmacological investigations were conducted on this plant. However, comprehensive information on this medicinally important plant is not available in the literature. Therefore, in this review, we aimed to provide comprehensive and critical information on all the reported ethnomedicinal uses, phytochemistry, pharmacological activities, and potential toxicity of *Olax subscorpioidea* to highlight its therapeutic potentials based on traditional usage and identify research gaps as a basis for further investigations to develop novel therapeutic compounds.

**Main body:** The available information about the plant was retrieved from the online bibliographic databases (PubMed and Google Scholar) and published PhD dissertation using the search terms *Olax subscorpioidea*, traditional uses, ethnomedicinal uses, phytochemistry, pharmacology, toxicology, and safety. Phytochemical studies have shown that the plant contains several bioactive compounds such as rutin, morin, quercetin, caffeic acid, santalbic acid, n-hexadecanoic acid, squalene, nonacosane, hentriacontane, and many more compounds. Also, pharmacological investigations revealed that *Olax subscorpioidea* has antidepressant, antiepileptic, anti-Alzheimer's, cytotoxic, antioxidant, antihyperlipidemic, analgesic, antiinflammatory, antiarthritic, antidiabetic, anticancer, antiulcer, antimicrobial, hepatoprotective, apoptotic, antiprotease, and other CNS effects.

**Conclusion:** Several pharmacological studies on *Olax subscorpioidea* have established its ethnopharmacological uses. However, there are limited phytochemical and pharmacological studies to validate other folkloric claims of the plant. Therefore, extensive phytochemical and further pre-clinical efficacy and safety evaluations to fully establish its therapeutic potentials and elucidate its mechanisms of pharmacological actions could be necessary.

**Keywords:** Bioactive compounds, Ethnomedicinal uses, Medicinal plants, *Olax subscorpioidea*, Pharmacology, Phytochemistry

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## Background

Medicinal plants have been used for many years to prevent and manage diseases [1]. These medicinal plants have gained attention in traditional medicine and remain the primary source of naturally occurring drugs used in many communities worldwide [2]. Approximately 30% of the currently available drugs contain bioactive compounds obtained from medicinal plants [3]. The World Health Organization (WHO) has reported that approximately 80% of the global population relies on medicinal plants for their primary health care needs [4]. Traditional knowledge of naturally occurring products from plant sources serves as a source of nutraceuticals and plays a vital role in drug discovery and development [5]. The use of natural products, including medicinal plants as therapeutic agents, faces numerous challenges, including lack of standardization, inadequate identification, and isolation of the bioactive compounds and lack of elucidation of mechanisms of pharmacological activities and clinical trials [6].

The plant *Olax subscorpioidea* Oliv is a shrub or tree that belongs to the family Olacaceae. It is up to 10 m or more in height. The plant is widely distributed in Nigeria, Zaire, Senegal, and other parts of Africa [7]. The plant is a woody shrub with leafy branches, its flowers are whitish, and the fruits are round and bright yellow when ripe. The plant is commonly known in different African languages as *Ifon* or *Ufon* in Yoruba; *Gwaanon kurmii* or *Gwaanon raafii* in Hausa; *Igbulu*, *Atu-ogili*, or *Osaja* in Igbo; *Ukpakon* in Edo; *Ocheja* in Igala; *Aziza* in Nsukka; and *Mtungapwezi* in Swahili [8, 9]. The plant *Olax subscorpioidea* in its natural habitat is illustrated in Fig. 1.

Several scientific studies were conducted to evaluate the bioactive compounds and therapeutic potentials of *Olax subscorpioidea*. However, there is no summarized information on the ethnomedicinal uses, phytochemistry, and pharmacological properties of the plant to our knowledge. Therefore, this review summarizes the ethnomedicinal

uses, phytochemical components, pharmacological properties, and toxicological studies of *O. subscorpioidea*. We have also identified research potentials of the plant that could be explored in the future.

## Botanical classification of *Olax subscorpioidea*

*Kingdom*: Plantae; *Subkingdom*: Tracheobionta; *Superdivision*: Spermatophyta; *Division*: Magnoliophyta; *Class*: Magnoliopsida; *Subclass*: Rosidae; *Order*: Santalales; *Family*: Olacaceae; *Genus*: *Olax*; *Species*: *subscorpioidea* [10].

## Main text

### Ethnopharmacological uses

The roots of *Olax subscorpioidea* have been used as an aphrodisiac and are topically applied to treat cutaneous and subcutaneous parasitic infections in Nigeria [11]. The roots or the stem bark of the plant are also used as a chewing stick and preparations of dento-oral herbal remedies in the Western part of Nigeria for oro-dental hygiene [12]. Additionally, the plant roots have been used to manage inflammatory and mental diseases, convulsion, pain, and cancer in Nigeria [13]. The roots are used as a decoction against diabetes mellitus and obesity [14, 15] and asthma in South-Western Nigeria and as a recipe for the management of cancer [11, 16], malaria [17], constipation, diarrhoea, and gastric ulcer [8].

The decoction of the stem, bark, and leaves of the plant has been used in the Congo Republic against rheumatism and articular pains [18], venereal diseases, and guinea worms [19]. The whole plant of *Olax subscorpioidea* is used alone or in combination with *Eleusine indica* in the northern part of Nigeria to manage anxiety, mental disorders, and infectious diseases [13, 20]. The leaves, twig, and bark are used against arthritis, rheumatism, hepatic diseases, sexually transmitted diseases (STDs), and fever and as antidotes against venomous stings and bites [21]. The leaves of *Olax subscorpioidea* have been used in traditional medicine in Nigeria to manage Alzheimer's disease [22] and depression [23].

The Fruits, seeds, roots, bark, and leaves are used as a decoction in Nigeria and Cameroon to treat constipation, yellow fever, jaundice, venereal diseases, and guinea worm [19, 24]. Various parts of the plant are used in Nigeria to treat arthritis, constipation, cough, dermatosis, fever, headaches, jaundice, malaria, rheumatism, syphilis, ulcer, and many other diseases [25]. The herbal concoction of *Olax subscorpioidea* is used in the management of postpartum haemorrhage [26]. The plant is also used in combination with *Tetrapleura tetrapteru* and other plant material to manage infantile seizure [26]. The combined herbal concoction of *Olax subscorpioidea*, *Fagara zanthoxyloides*, and *T. tetraptera*, together with other plant material, is used to treat syphilis, stomach disorders, and gonorrhoea [26]. The summary



**Fig. 1** *Olax subscorpioidea* in its natural habitat

of the reported ethnopharmacological uses of different parts of *Olox subscorpioidea* is presented in Table 1.

### Phytochemistry

#### **Preliminary phytochemical contents of *Olox subscorpioidea***

Preliminary phytochemical screening of the methanol leaf extract of *Olox subscorpioidea* and its fractions (aqueous, butanol, hexane, and ethyl-acetate) revealed the presence of saponins, tannins, steroids, cardiac glycosides, flavonoids, alkaloids, terpenoids, phenols, and carbohydrates [35, 37, 38]. Kazeem et al. reported cardiac glycosides, flavonoids, phenols, phlobatannins, terpenoids, alkaloids, steroids, and tannins in the hexane, ethyl-acetate, and acetone leaf extract of *Olox subscorpioidea* [15]. The plant's ethanol leaf extract showed carbohydrates, flavonoids, phenol, steroids, tannins, and terpenoids [25]. Ishola et al. found tannins, saponins, anthraquinones, phlobatannins, steroids, cardiac glycoside, polyphenols, reducing sugars, deoxysugar, cardenolides, and flavonoids in the aqueous leaf extract of the plant [23].

The methanol root extract of the plant revealed the presence of glycosides, terpenoids, alkaloids, and steroids [8]. Additionally, Popoola et al. reported tannins, alkaloids, saponins, flavonoids, cardiac glycosides, phenols, terpenoids, and reducing sugars in the hydro-ethanolic root extract of the plant [33].

Ayandele and Adebisi (2007) reported the presence of tannins, glycosides, and saponins in the aqueous stem bark extract of *Olox subscorpioidea*, while tannins, alkaloids, glycosides, flavonoids, and steroids were present in the ethanol stem bark extract of the plant [7]. The methanol stem bark extract of *Olox subscorpioidea* was reported to contain alkaloids, saponins, tannins, cardiac glycosides, terpenoids, and phenols [12]. Fankam et al. reported alkaloids, anthraquinones, flavonoids, phenols, tannins, and triterpenes in the methanol fruit extract of the *Olox subscorpioidea* [39].

#### **Quantitative phytochemical analysis of *Olox subscorpioidea***

Quantitative phytochemical contents of *Olox subscorpioidea* are shown in Table 2.

#### **Elemental contents of *Olox subscorpioidea***

The mineral elements present in herbal medicines are essential supplements to the bioactive compounds and are closely related to the effectiveness and potential toxic effects of traditional remedies [43]. The elemental analysis of the root and leaf extract of *Olox subscorpioidea* revealed the presence of calcium, copper, manganese, magnesium, sodium, zinc, potassium, aluminium, silicon, phosphorus, sulphur, chlorine, iron, cobalt, nickel, bromine, rubidium, and strontium [25, 40].

#### **Chemical compounds isolated and identified from *Olox subscorpioidea***

The butanol leaves' fraction of *Olox subscorpioidea* revealed rutin, morin, quercetin, and caffeic acid [31]. Oladipupo et al. identified the presence of n-hexadecanoic acid (17.6%), 7,10,13-hexadecatrienoic acid, methyl ester (0.84%), 9,17-octadecadienal, (Z)- (2.87%), 9,12-octadecadienoic acid (Z,Z)- (18.0%), octadecanoic acid (4.05%), squalene (4.12%), nonacosane (5.54%), and hentriacontane (1.22%) in the n-hexane leaf extract of the plant [44]. Additionally, santalbic acid was isolated from the methanol seed fraction of *Olox subscorpioidea* [45]. The phytochemical constituents identified and isolated from *Olox subscorpioidea* are illustrated in Table 3. The chemical structures of the major isolated compounds from *Olox subscorpioidea* are presented in Fig. 2.

#### **Pharmacological activities of *Olox subscorpioidea***

The extracts and fractions of various parts of *Olox subscorpioidea* were screened for various pharmacological activities, namely antidepressant, anticonvulsant, sedative, anxiolytic, anti-Alzheimer's, cytotoxicity, antioxidant, hypolipidemic, analgesic, antiinflammatory, antiarthritic, hypoglycaemic, antiulcer, anticancer, antimicrobial, anthelmintic, hepatoprotective, apoptotic, and antiprotease activities. The summary of the reported pharmacological activities of different extracts and fractions obtained from various parts of *Olox subscorpioidea* are presented in Table 4.

#### **Antidepressant activity**

The ethanol leaf extract of *Olox subscorpioidea* significantly reduced the immobility time in forced swimming test (FST) and tail suspension test (TST) and reduced the number of crossing activity in the open field test (OFT) [13]. The results also demonstrated a significant reduction in diarrhoea in the reserpine model of depression [13]. Adeoluwa et al. reported the possible involvement of adrenergic, dopaminergic, and serotonergic systems in the antidepressant activity of *Olox subscorpioidea* [31]. Several antidepressant drugs such as tricyclic antidepressants and monoamine oxidase inhibitors reduce immobility time [46]. Also, antidepressant drugs including imipramine blocked reserpine-induced diarrhoea [47]. Studies have shown a correlation between adrenergic dysfunction and pathophysiology of depression [48, 49]. The ( $\alpha$ 1 and  $\alpha$ 2)-adrenergic system serves as a target for the antidepressant drugs [50]. Previous research by Yamada et al. reported the antidepressant action of drugs via dopaminergic system [51]. The serotonin reuptake inhibitors increase the synaptic concentration of serotonin [52] Therefore, the results justified the traditional use of the *Olox subscorpioidea* in the management of mental illness, including depression.

**Table 1** Ethnopharmacological uses of *Olex subscorpioidea* and scientific confirmation of their pharmacological activity

Ethnomedicinal uses	Plant part	References	Confirmation of pharmacological activity
Alzheimer's disease	Leaves	[22]	Confirmed [22]
Antidote against venomous stings and bites	Leaves, twig, and bark	[21]	Not confirmed
Anxiety	Whole plant	[20]	Not confirmed
Aphrodisiac	Roots	[11]	Not confirmed
Arthritis	Leaves, twig, and bark	[21]	Confirmed [27]
Asthma	Roots	[16]	Not confirmed
Cancer	Roots	[18]	Confirmed [28]
Constipation	Fruit, seed, root, bark	[8, 19, 24]	Not confirmed
Convulsion	Roots and leaves	[13]	Confirmed [29, 30]
Cough	Whole plant	[25]	Not confirmed
Dental diseases	Stem or roots	[12]	Not confirmed
Depression	Leaves	[23]	Confirmed [13, 31]
Dermatosis	Whole plant	[25]	Not confirmed
Diabetes mellitus	Roots	[14, 15]	Confirmed [15, 32]
Diarrhoea	Roots	[8]	Not confirmed
Fever	Leaves, twig, and bark	[21]	Not confirmed
Gonorrhoea	Not specified	[26]	Not confirmed
Guinea worm	Bark or leaves	[19]	Not confirmed
Headache	Whole plant	[25]	Not confirmed
Hepatic diseases	Leaves, twig, and bark	[21]	Confirmed [21]
Inflammation	Roots	[18]	Confirmed [23, 30, 33]
Infectious diseases	Whole plant	[20]	Confirmed [7, 12, 24, 25, 34]
Jaundice	Whole plant	[24, 25]	Not confirmed
Malaria	Roots	[17, 25]	Not confirmed
Obesity	Roots	[14]	Confirmed [14]
Pain	Leaves	[21]	Confirmed [18, 23, 33, 35]
Parasitic infections	Roots	[11]	Confirmed [36]
Postpartum haemorrhage	Not specified	[26]	Not confirmed
Rheumatism	Stem and leaves	[18]	Not confirmed
Sexually transmitted diseases	Leaves, twig, and bark	[9, 21]	Not confirmed
Syphilis	Whole plant	[25]	Not confirmed
Typhoid	Roots	[14]	Not confirmed
Ulcer	Roots	[8]	Confirmed [8]
Yellow fever	Leaves	[9]	Not confirmed

**Anti-Alzheimer's activity**

The aqueous leaf extract of *Olex subscorpioidea* demonstrated promising inhibitory effects against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) [22]. Therefore, the plant can potentially manage Alzheimer's disease due to its inhibitory action on the key enzymes (AChE and BChE) associated with the disease [22].

**Anticonvulsant activity**

The ethanol and methanol leaf extracts of *Olex subscorpioidea* significantly delayed the onset of seizures and

death latency, which provided the scientific basis for using the plant in traditional medicine for the management of convulsion which could be due to the enhancement of gamma-aminobutyric acid (GABA) [29, 30].

**Sedative effects**

The ethanol leaf extract of *Olex subscorpioidea* produced a significant and dose-dependent reduction in rearing and grooming frequency, suggestive of its sedative and stress attenuating effects due to its interaction with  $\alpha_2$ -adrenergic pathway [29]. The extract at 25 mg/kg also significantly

**Table 2** Quantitative phytochemical contents of *Olox subscorpioidea*

Plant part	Solvent	Phytochemical	Reference
Root	Powdered form	Alkaloids (0.61%), anthraquinones (0.1%), cardiac glycosides (0.24%), saponins (0.27%), tannins (0.03%) and polyphenols (0.14%)	[40]
Root	Aqueous and ethanol	Tannins (4.72% and 4.91%), terpenoids (0.285% and 3.32%), steroids (2.12% and 3.58%), alkaloids (2.10% and 3.58%), saponins (4.22% and 0.02%), phenols (3.57% and 6.70%), flavonoids (2.35% and 3.45%), and carotenoids (1.12% and 2.23%) respectively	[27]
Roots	Ethanol	Saponins (865.00 mg/100 g), alkaloids (963.33 mg/100 g), tannins (863.33 mg/100 g), flavonoids (636.67 mg/100 g), anthraquinones (46.67 mg/100 g), Proanthocyanidins (2.67 mg/g), and total polyphenol content (TPC) (38.77 GAE/g)	[14]
Leaves	Aqueous	TPC (30 mg GAE/g) and total flavonoids content (4.26 mg QAE/g)	[22]
Leaves	Aqueous and ethanol	TPC (12.78 and 35.49 GAE/g), total flavonoids (4.01 and 22.69 QAE/g), flavonols (1.35 and 9.78 QAE/g), and proanthocyanidins (1.44 and 1.99 QAE/g)	[41]
	Methanol spice	phenols and triterpenes and a TPC (8.39 GAE/100 g of extract)	[42]

TPC total polyphenols content, GAE/g gallic acid equivalent per gram of the extract

reduced the locomotor activity in a similar manner to diazepam (2 mg/kg), indicative of its central nervous system (CNS) depressant effect [29]. Furthermore, the extract produced a significant and dose-dependent reduction in the number of head dip and prolonged the pentobarbitone-induced sleeping time [29]. The study supports the folkloric claim of the plant in the management of mental illness.

#### Anxiolytic effect

The leaves of *Olox subscorpioidea* did not significantly alter the frequency of open arm entries and the percentage of open arm duration, which indicated its lack of anxiolytic effect [29]. Therefore, based on the reported traditional use of *Olox subscorpioidea* in the management of anxiety, other parts of the plant are recommended to be thoroughly screened for the folkloric claimed anxiolytic activity with other extracts or fractions that may contain potential anxiolytic compounds.

#### Antihyperlipidemic activity

The ethanol root extract of *Olox subscorpioidea* at 200 and 400 mg/kg significantly reduced the total cholesterol, triglycerides, and low-density lipoprotein and increased the high-density lipoprotein [14]. The result validated the lipid-lowering effect of the plant in the management of obesity in traditional medicine

#### Cytotoxic activity

Cantrell et al. reported the cytotoxicity effect of the methanol seed extract of *Olox subscorpioidea*. In the same study, santalbic acid isolated from the plant also showed remarkable cytotoxicity [45].

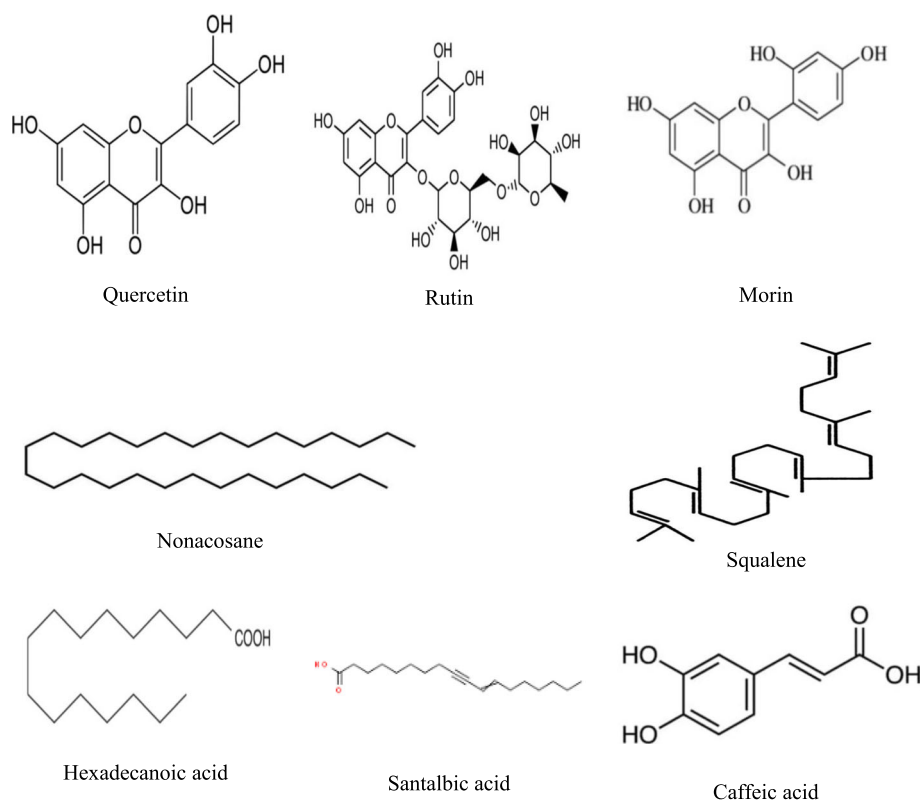
#### Antioxidant activity

The aqueous leaf extract of *Olox subscorpioidea* exerted 2, 2-azino-bis-3-ethylbenzothiazoline-6-sulphonic acid (ABTS) scavenging activity, iron chelating and reducing effects, and iron-induced lipid peroxidation due to the presence

**Table 3** Chemical compounds isolated and identified from *Olox subscorpioidea* and their reported pharmacological activities

Compound	Plant part	Solvent	Activity	References
Rutin	Leaves	Butanol	NP	[31]
Morin	Leaves	Butanol	NP	[31]
Quercetin	Leaves	Butanol	NP	[31]
Caffeic acid	Leaves	Butanol	NP	[31]
n-Hexadecanoic acid	Leaves	n-hexane	NP	[44]
7,10,13-Hexadecatrienoic acid, methyl ester	Leaves	n-hexane	NP	[44]
9,17-Octadecadienal, (Z)-	Leaves	n-hexane	NP	[44]
9,12-Octadecadienoic acid (Z,Z)-	Leaves	n-hexane	NP	[44]
Octadecanoic acid	Leaves	n-hexane	NP	[44]
Squalene	Leaves	n-hexane	NP	[44]
Nonacosane	Leaves	n-hexane	NP	[44]
Hentriacontane	Leaves	n-hexane	NP	[44]
Santalbic acid	Seed	Methanol	Cytotoxicity	[45]

NP no pharmacological screening reported



**Fig. 2** Chemical structures of isolated compounds from *Olax subscorpioidea*

of high TPC [22]. The hydroethanolic leaf extract of *Olax subscorpioidea* produced a dose-dependent reduction in the levels of thiobarbituric acid reactive substances (TBARS) and increased the antioxidant power as well as 1, 1-diphenyl-2-picryl-hydrazyl (DPPH) radical scavenging activity [21]. In another study conducted by Konan et al., the plant's ethanol and aqueous leaf extracts produced a significant radical scavenging activity, inhibitory effect on lipid peroxidation, and ferric ion chelating activity and reducing power [41].

The ethanol root extract of *Olax subscorpioidea* demonstrated a significant antioxidant effect against DPPH radicals [14, 28]. The hydro-alcoholic root extract of the plant also showed a significant effect against nitric oxide (NO) radicals in a similar manner to ascorbic acid but higher than gallic acid [28]. In the same study, the extract significantly increased the levels of glutathione (GSH) and superoxide dismutase (SOD) and reduced the levels of malondialdehydes (MDA) [28]. The findings suggested that the plant can enhance the antioxidant activities of GSH and SOD and inhibit lipid peroxidation [28]. The methanol leaves and spice extract of *Olax subscorpioidea* elicited DPPH radical and hydroxyl radical scavenging activities and remarkable ferric reducing antioxidant power (FRAP) and total antioxidant capacity [32, 42].

#### Analgesic activity

The leaf extracts of *Olax subscorpioidea* showed a significant and dose-dependent reduction in the number of abdominal writhes and reduced pain responses [18, 37] suggestive of its central and peripheral analgesic activity [53]. Similarly, the extracts produced a significant increase in the pain latency in the hot plate test, which affirms its central analgesic property [10, 18]. It was concluded that the analgesic action of the extract involves its interaction with the opioidergic system [10, 18].

In another study by Odoma et al., the hexane, butanol, and aqueous leaf fractions of *Olax subscorpioidea* produced a significant and dose-dependent reduction in the number of abdominal writhes and pain perception in formalin-induced paw licking [37]. The aqueous and butanol fractions also demonstrated a significant and dose- and time-dependent increase in pain latency in hot plate test [37]. The mechanism of analgesic action of the butanol fraction was suggested to be due to its interaction with serotonergic and nitric oxide l-arginine pathways [9].

The aqueous leaf extract of *Olax subscorpioidea* showed a significant and non-dose-dependent reduction in the mean number of abdominal constrictions [23]. The extract at 50 mg/kg produced the highest activity (68.28%) in a similar manner to the standard drug, ibuprofen (67.74%). Also, at the dose of 200 mg/kg, the

**Table 4** Reported pharmacological activities of *Olox subscorpioidea*

Activity	Solvent	Plant part	Assay	References
Antiarthritic	Aqueous, ethanol	Roots	In vivo	[42]
Antidepressant	Ethanol and butanol	Leaves	In vivo	[13]
Anticonvulsant	Ethanol and methanol	Leaves	In vivo	[29, 30]
Sedative	Ethanol	Leaves	In vivo	[29]
Anti-Alzheimer	Aqueous	Leaves	In vitro	[22]
Cytotoxicity	Methanol	Seeds	In vivo	[45]
Antioxidant	Ethanol	Roots	In vitro	[14]
	Aqueous	Leaves	In vitro	[22, 41]
	Hydroalcoholic	Roots	In vivo	[28]
	Hydroethanolic	Leaves	In vivo	[21]
	Methanol	Spices	In vivo	[42]
	Ethanol	Leaves	In vitro	[41]
	Methanol	Leaves	In vitro	[32]
Antihyperlipidemic	Ethanol	Roots	In vivo	[14]
Analgesic	Ethanol	Leaves	In vivo	[18]
	Methanol	Leaves	In vivo	[35]
	Hexane	Leaves	In vivo	[37]
	Butanol	Leaves	In vivo	[37]
	Aqueous	Leaves	In vivo	[23, 37]
	Hydroethanolic	Roots	In vivo	[33]
Antiinflammatory	Butanol	Leaves	In vivo	[9]
	Methanol	Leaves	In vivo	[35]
	Hexane	Leaves	In vivo	[37]
	Butanol	Leaves	In vivo	[37]
Antihyperglycaemic	Aqueous	Leaves	In vivo	[23, 37]
	Acetone	Leaves	In vitro	[15]
	Ethylacetate	Leaves	In vitro	[15]
	Hexane	Leaves	In vitro	[15]
	Hexane	Leaves	In vivo	[15]
Antiulcer	Methanol	Leaves	In vivo	[32]
	Methanol	Roots	In vivo	[8]
Anticancer	Hydroalcoholic	Roots	In vitro and in vivo	[28]
Antimicrobial	Methanol-dichloromethane	Fruit	In vivo and in vitro	[24]
	Ethanol	Leaves	In vitro	[25]
	Aqueous and ethanol	Stem	In vitro	[7]
	Methanol	Stem bark	In vitro	[12]
	Methanol	Seeds	In vitro	[34]
Antihelmintic	Ethanol	Roots	In vitro	[36]
Hepatoprotective	Hydroethanolic	Leaves	In vivo	[21]
Apoptotic	Methanol	Leaves	In vitro	[38]

extract significantly reduced paw licking duration and biting in formalin-induced pain [23]. The extract at the doses of 50 and 400 mg/kg significantly and time-dependently increased the pain latency [23].

The authors concluded that the extract's probable mechanisms of analgesic activity involve its interaction with serotonergic,  $K_{ATP}$  channels, and dopaminergic systems [23].

In another study conducted by Popoola et al. in 2016, the hydro-ethanolic root extract of *Olax subscorpioidea* significantly and dose-dependently reduced the number of abdominal constrictions [33]. Similarly, the extract at 200 and 400 mg/kg significantly reduced the paw licking in formalin-induced pain [33]. These findings validated the use of the plant in traditional medicine for the management of pain.

#### **Antiinflammatory activity**

The methanol leaf extract of *Olax subscorpioidea* and fractions (hexane, aqueous, and butanol) produced remarkable antiinflammatory effects [23, 37]. Moreover, the aqueous leaf extract of *Olax subscorpioidea* produced a significant and time-dependent reduction in the complete Freund's adjuvant (CFA)-induced chronic inflammation. The extract showed its maximum inhibitory effect (85.30%) at 400 mg/kg similar to the standard antiinflammatory agent, celecoxib [23]. In a study conducted by Popoola et al. in 2016, the hydro-ethanolic root extract of *Olax subscorpioidea* showed a significant and dose-dependent antiinflammatory effect [33].

Research by Odoma et al. has shown that the aqueous and butanol leaf fractions of *Olax subscorpioidea* significantly reduced the concentrations of the proinflammatory cytokines, including interleukin-1 $\alpha$  (IL-1 $\alpha$ ), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF); with no effect on tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) and IL-2 [54]. In contrast, the fractions stimulate the synthesis of antiinflammatory cytokines such as IL-5, IL-6, and interferon- $\gamma$  (IFN- $\gamma$ ) [54]. These findings validated the use of the plant in traditional medicine for the management of inflammatory disorders.

#### **Antiarthritic activity**

The aqueous and ethanol root extracts of *Olax subscorpioidea* significantly reduced the paw size, C-reactive protein, rheumatoid factor, erythrocyte sedimentation rate (ESR), and cytokines in a dose- and time-dependent manner compared to the arthritis-induced group [27]. The extracts also significantly reduced the synovial hyperplasia in a similar manner to indomethacin used as a standard agent [27]. The study validated the folkloric use of the plant in the management of rheumatoid arthritis.

#### **Antihyperglycaemic activity**

The hexane, ethyl-acetate, and acetone leaf extract of *Olax subscorpioidea* produced remarkable inhibitory effects on  $\alpha$ -amylase and  $\alpha$ -glucosidase, the critical enzymes associated with diabetes mellitus [15]. The hexane and ethyl-acetate extracts demonstrated higher inhibitory effects on  $\alpha$ -amylase than the standard hypoglycaemic

agent, acarbose [27]. The hexane extract produced higher  $\alpha$ -glucosidase inhibitory activity than the acarbose [27]. In the same study, the hexane extract significantly reduced the postprandial blood glucose level [27].

Based on the study conducted by Ayoola et al., the methanol leaf extract of *Olax subscorpioidea* showed a non-significant hypoglycaemic effect in normoglycaemic rats, suggestive of its lack of hypoglycaemic effect on non-diabetic subjects [32]. The extract demonstrated a significant and dose- and time-dependent antihyperglycaemic effect higher than that of the glibenclamide [32]. Also, the aqueous fraction of the extract (400 mg/kg) demonstrated a similar antihyperglycaemic effect (36.87%) to the glibenclamide (38.97%) [32]. These findings validated the use of the plant in traditional medicine for the management of diabetes mellitus.

#### **Antiulcer activity**

The methanol root extract of *Olax subscorpioidea* produced dose-dependent ulcer protection, which was significant at the dose of 600 mg/kg in a similar manner to the standard drug sucralfate [8]. Therefore, the roots of the plant could have antiulcer activity as claimed in traditional medicine.

#### **Anticancer activity**

The hydro-alcoholic root extract of *Olax subscorpioidea* significantly and dose-dependently inhibited the growth of *Allium cepa* root [28]. The extract also produced a significant mito-depressive effect on the onion bulb similar to the standard anticancer drug, cyclophosphamide [28]. Additionally, the extract significantly increased the deoxyribonucleic acid (DNA)-damaging effect [28]. The result provided the potential chemopreventive and chemotherapeutic effect of the plant in traditional medicine against cancers [28].

#### **Antimicrobial activity**

The aqueous stem extract of *Olax subscorpioidea* demonstrated narrow-spectrum antimicrobial activity against *Pseudomonas aeruginosa* and *Proteus vulgaris*. In contrast, the plant's ethanol stem extract showed broad-spectrum antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Salmonella* spp., *Aspergillus niger*, and *Aspergillus tamari* [7].

The methanol seeds and stem bark extracts of *Olax subscorpioidea* produced remarkable antimicrobial activity against *Aspergillus fumigatus* and *Staphylococcus aureus* [34]. In other studies, the fruit extract of *Olax subscorpioidea* demonstrated remarkable antimicrobial activity against *Candida albican*, *Cryptococcus neoformans*, *Candida tropicalis*, *Candida parapsilosis*, *Candida lusitaniae*, *Escherichia coli*, *Enterobacter aerogenes*,



*Klebsiella pneumoniae*, and *Providencia stuartii* [24, 39]. Furthermore, the extract at 2000 mg/kg significantly decreased the fungal load in the blood and kidneys of the yeast-infected rats [24].

The ethanol leaf extract of *Olox subscorpioidea* produced significant and concentration-dependent inhibitory effect against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Aspergillus niger*, and *Penicillium* sp. [25]. The extract at 500 mg/ml showed better antifungal activity against *Aspergillus niger* and *Penicillium* sp. than the standard antifungal drug, fluconazole [25]. A previous research by Idowu et al. has shown that the methanol root extract of *Olox subscorpioidea* produced a concentration-dependent inhibitory effect against *Bacillus anthracis*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Staphylococcus aureus*, and multi-drug resistant *Escherichia coli* implicated in urinary tract infection [55]. The roots of *Olox subscorpioidea* produced inhibitory effects against *Shigella* spp., *Escherichia coli*, and *Proteus* spp. [56].

The studies conducted on *Olox subscorpioidea* validated its use for the treatment of infectious diseases in traditional medicine. However, most of the studies concentrated on in vitro investigations. Therefore, more antimicrobial evaluations using in vivo assays should be conducted with specific microbial strains to validate these results. Furthermore, investigations are required to determine the plant's effects against multi-drug resistant microorganisms and evaluate its mechanisms of antimicrobial actions to develop novel antimicrobial agents.

#### **Antihelmintic activity**

Kone et al. reported the antihelmintic activity of the ethanol root extract of *Olox subscorpioidea* against *Echinostoma caproni*, *Schistosoma mansoni*, *Trichuris muris*, and *Heligmosomoides bakeri* [36]. The extract non-significantly reduced the total and female worm burden against *Schistosoma mansoni* [36]. Therefore, the result validated the use of the plant as a herbal remedy in the treatment of parasitic diseases such as helminthiasis.

#### **Hepatoprotective activity**

The hydro-ethanolic leaf extract of *Olox subscorpioidea* significantly reduced the levels of serum glutamate oxaloacetate transaminase (SGOT), glutamate pyruvate transaminase (SGPT), and alkaline phosphatase (ALP) compared with the carbon tetrachloride (CCl<sub>4</sub>) intoxicated group [21]. The extract at the doses of 25 and 100 mg/kg reduced the level of gamma-glutamyl transferase (GGT) and total bilirubin [21]. Also, the extract dose-dependently increased the level of (α<sub>1</sub>, α<sub>2</sub>, β, and γ)-globulin [21]. The extract at the dose of 100 mg/kg revealed near-normal hepatic cells with a mild degree of inflammation and lesser fatty infiltration without

necrosis compared to the CCl<sub>4</sub>-intoxicated animals [21]. The result validated the folkloric use of the plant for the management of liver diseases in traditional medicine.

#### **Apoptosis-induced activity**

The methanol leaf extract of *Olox subscorpioidea* induced mitochondrial membrane permeability transition pore opening [38]. The extract also significantly increased mitochondrial adenosine triphosphate (ATP) hydrolysis and produced significant mitochondrial membrane lipid peroxidation [38]. Therefore, the plant may contain bio-active components that could help manage diseases that require an enhanced rate of apoptosis, such as cancer [57].

#### **Antiprotease and membrane stabilizing activities**

The saline and alkaline extracts of *Olox subscorpioidea* demonstrated remarkable antitryptic and dose-dependent membrane stabilizing activities [26]. These findings justify the use of the plant in the treatment of inflammatory-related diseases.

#### **Phytotoxic activity**

Olubode et al. reported the inhibitory effect of the aqueous extracts of *Olox subscorpioidea* parts (leaf, seed, bark, stem, and root) on maize germination. The extract remarkably reduced seed germination, and significantly increased the number of leaves, plant height, and root and shoot dry weight. The finding revealed that the plant possesses allelopathic activity on seed maize that could be useful as bioherbicide [58].

#### **Toxicological studies on *Olox subscorpioidea***

There has been an upsurge in the use of herbal medicines to treat many diseases. However, some naturally occurring chemical substances have potential toxicity effects, and their safety is an essential point of health concern [59]. In the process of drug development, there are various pre-clinical toxicity studies needed, including acute toxicity study, repeated dose toxicity study, genetic toxicity study, reproductive toxicity study, carcinogenicity study, and toxicokinetic evaluations [60]. Safety information on traditional herbal medicines consumed is vital as part of a response to public health concerns [4]. Yuet Ping et al. suggested the need to document experimental information on medicinal plants' safety profile and their extracts used in drug development [61]. Therefore, reports and data on medicinal plants' potentially toxic effects are vital in their development for therapeutic use [4].

#### **Acute toxicity on *Olox subscorpioidea***

The intraperitoneal (i.p) median lethal dose (LD<sub>50</sub>) of the methanol and ethanol leaf extract of *Olox subscorpioidea* was estimated to be 3800 mg/kg [30] and 300 mg/kg [29]

respectively, while the oral LD<sub>50</sub> of the methanol leaf extract of *Olox subscorpioidea* was estimated to be higher than 5000 mg/kg [35]. The acute toxicity study of the methanol root extract of *Olox subscorpioidea* showed an LD<sub>50</sub> of 2154 mg/kg [8].

The hydro-ethanolic leaf extract of *Olox subscorpioidea* (500, 1000, 2000, and 4000 mg/kg) caused some behavioural changes and mortality in mice [21]. The extract also produced signs of acute toxicity, including agitation, aggression, body twisting, convulsion, and diarrhoea at 2000 and 4000 mg/kg. Also, the LD<sub>50</sub> of the extract was estimated to be 1000 mg/kg in mice [21].

The acute oral administration of the aqueous leaf extract of *Olox subscorpioidea* (500, 2500, and 5000 mg/kg) did not cause mortality in mice at all doses [23]. However, the extract produced abdominal constrictions, sedation, diarrhoea, and decreased motor activity [23]. The oral LD<sub>50</sub> of Hepacare (a herbal formulation consist of *Olox subscorpioidea* and *Capsicum frutescens*) was 3807.89 mg/kg [62].

#### **Sub-acute toxicity on *Olox subscorpioidea***

The sub-acute oral administration of the ethanol leaf extract of *Olox subscorpioidea* (250, 500, 750, and 1000 mg/kg) caused a significant decrease in the serum levels of alanine aminotransferase (ALT) and total bilirubin at 250 and 500 mg/kg, respectively [63]. The extract caused a significant increase in ALP at 500, 750, and 1000 mg/kg and increased plasma albumin levels at 1000 mg/kg [63]. There was also a significant reduction in mean corpuscular haemoglobin (MCH), lymphocyte (LYMP), white blood cell (WBC), and haemoglobin (HB). However, the neutrophils (NEU) significantly increased at 1000 mg/kg. The extract did not significantly change the levels of red blood cells (RBC), packed cell volume (PCV), mean corpuscular volume (MCV), platelet (PLT), and mean corpuscular haemoglobin concentration (MCHC). Similarly, there were no histopathological changes in the livers and kidney at all doses [63].

Abiodon et al. also reported the sub-acute toxicity effects of Hepacare (a herbal formulation consisting of *Olox subscorpioidea* and *Capsicum frutescens*) [62]. The herbal product has no effect on the body weight, relative heart, liver, kidney, spleen, and lung weights [62]. The ALP remarkably elevated at the dose of 750 mg/kg. Besides, ALT, AST, ALP, bilirubin, and total protein significantly increased at the dose 2500 mg/kg. The effects of the herbal combination on haematological parameters showed a significant elevation in monocytes counts with no effects on PCV, WBC, neutrophils, and lymphocytes [62]. The herbal product also revealed an evidence of hepatic and renal damage after 28-day period of administration. In contrast, Adebayo et al. reported a lack of

hepatotoxicity and renal toxicity of *Olox subscorpioidea* following the 28-day treatment [63].

#### **Genotoxicity study on *Olox subscorpioidea***

The n-hexane leaf extract of *O. Olox subscorpioidea* (50 mg/kg) significantly reduced the DNA fragmentation in both the liver and testis compared with the control group [44]. Additionally, the extract produced a significant reduction in the levels of HB, PCV, RBC, NEU, and monocytes (MID), suggestive of deleterious effects of the extract on blood production, which may result in anaemia. However, the extract significantly increased WBC, LYMP, MCV, MCH, and MCHC compared with the control group [44].

#### **Conclusion**

Studies on *Olox subscorpioidea* have established some of the plant's ethnopharmacological uses and provided its therapeutic potentials against many diseases. However, there are limited studies on its pharmacological activities that could further validate many reported folkloric claims. Therefore, detailed pharmacological investigations are required in the future on different parts of the plant to validate their traditional uses. Few studies were conducted to identify and isolate the phytochemical compounds present in different parts of the plant. Besides, detailed pharmacological investigations to explore their biological effects were lacking. Therefore, there is a need for more research in the future on bioassay-guided fractionation, isolation, and characterization of the extracts and fractions of *Olox subscorpioidea* to determine the active compounds responsible for the pharmacological activities. Moreover, the available isolated compounds could be screened for detailed pharmacological activities in animal models to explore their mechanisms of actions and molecular targets that would enable the discovery of lead compounds to develop novel therapeutic agents. Human clinical trials should also be performed to establish the clinical safety and efficacy of *Olox subscorpioidea* for use in the treatment of various diseases. However, the plant has the potential of causing toxicity through interfering with haematological parameters. Therefore, it should be used cautiously in patients at high risk of blood-related disorders such as anaemia. Also, further toxicity evaluations (chronic, mutagenicity, carcinogenicity, teratogenicity, reproductive toxicity) of all parts of this plant are needed. Besides, more researches are required to standardize the appropriate dosage of *Olox subscorpioidea* for the claimed therapeutic use in traditional medicine.

#### **Abbreviations**

ABTS: 2,2-Azino-bis-3-ethylbenzothiazoline-6-sulphonic acid; AChE: Acetylcholinesterase; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; ATP: Adenosine triphosphate; BChE: Butyrylcholinesterase;

CCl<sub>4</sub>: Carbon tetrachloride; CFA: Complete Freund's adjuvant; CNS: Central nervous system; DNA: Deoxyribonucleic acid; DPPH: 1,1-Diphenyl-2-picrylhydrazyl; EGF: Epidermal growth factor; ESR: Erythrocyte sedimentation rate; FRAP: Ferric reducing antioxidant power; FST: Forced swimming test; GABA: Gamma-amino-butyric acid; GAE/g: Gallic acid equivalent per gram of the extract; GGT: Gamma-glutamyl transferase; GSH: Glutathione; HB: Haemoglobin; IFN- $\gamma$ : Interferon- $\gamma$ ; IL: Interleukin; K<sub>ATP</sub>: Potassium adenosine triphosphate; LD<sub>50</sub>: Median lethal dose; LYMP: Lymphocytes; MDA: Malondialdehydes; MCH: Mean corpuscular haemoglobin; MCHC: Mean corpuscular haemoglobin concentration; MCV: Mean corpuscular volume; MID: Monocytes; MRSA: Methicillin-resistant *S. aureus*; NEU: Neutrophils; NO: Nitric oxide; OFT: Open field test; PCV: Packed cell volume; PLT: Platelet; QAE/g: Quercetin equivalent per gram of dried extract; RBC: Red blood cell; SGOT: Serum glutamate oxaloacetate transaminase; SGPT: Serum glutamate pyruvate transaminase; SOD: Superoxide dismutase; STDs: Sexually transmitted diseases; TBARS: Thiobarbituric acid reactive substances; TNF: Tumour necrosis factor; TPC: Total polyphenol content; TST: Tail suspension test; VEGF: Vascular endothelial growth factor; WBC: White blood cells; WHO: World Health Organization

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#### Authors' contributions

MHA: conceptualization, designing of the work, writing of the original draft, and editing. AU: critically reviewed the whole manuscript. OYA: writing and review. JMS: writing and review. MM: writing and review. SM: writing and review. SM: writing and review. AAB: writing and review. ASW: writing and review. MA: writing. AMU: writing. All the authors have read and approved the manuscript.

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