A comprehensive review of the ethnomedicine, phytochemistry, pharmacological activities of the genus *Kniphofia*

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**ABSTRACT**

**Context:** *Kniphofia* (Asphodelaceae) is found mainly in South Africa and Tropical Africa. Malaria, hepatitis B, blood purifier, cancer, eczema, and female infertility have all been traditionally treated using this genus.

**Objective:** The current review provides a complete and up-to-date compilation of documented traditional medicinal uses, phytochemicals, and pharmacological activities of the genus.

**Method:** Relevant literature was collected by searching the major electronic scientific databases including PubMed, Science Direct, Web of Science, and Google Scholar using appropriate keywords ethnomedical studies, phytochemical investigations, and pharmacological activities of *Kniphofia* species. The search strategy included all articles with descriptors that were available until November 30, 2021. Only published works in English were used for this study. The data were collected using textual descriptions of the studies, tabulation, grouping, and figures.

**Result:** At present, more than 40 compounds have been isolated from different parts of *Kniphofia* species. The major compounds isolated from the *Kniphofia* species are monomeric anthraquinones and dimeric anthraquinones. Pharmacologically the extracts and isolated compounds showed antioxidant, antimalarial, antiproliferative, anti-HIV-1, anti-leukotriene, and cytotoxic activity. The genus afforded exemplary drug leads such as knipholone and knipholone anthrone with anti-HIV-1, antimalarial and cytotoxicity activity.

**Conclusions:** *Kniphofia* species have traditionally been used to treat a variety of diseases. Pharmacological actions of phytochemicals were shown to be promising. Despite this, considering the genus’s inclusion on the red data list of South Africa, it deserves more attention. In order to find novel drug candidates, more studies on promising crude extracts and compounds are needed.

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**Introduction**

Plants, according to the locals, have nutritional, therapeutic, and mystical properties. Medicinal plants play an important role in local communities’ healthcare systems as major components of medicine, particularly among the rural population (Nigussie 2021). Plant knowledge and application are strongly linked to ethnic cultures. The distribution, taxonomic variety, and abundance of medicinal plants vary based on location and climatic circumstances, and ethnomedical healing systems vary between societies (Farooq et al. 2019). The World Health Organisation (WHO) report shows that over nearly 80% of the world’s population uses herbal plants to cure human ailments (WHO 2013). The report also demonstrates that medicinal plants are being studied as an alternative therapy and support for health-care activities. Traditional medicine incorporates medical parts of indigenous knowledge that have been passed down through generations prior to the development of modern medicine.

Traditional medicine is defined by the WHO as the sum of all skills, knowledge, and practices based on theories, beliefs, and indigenous experiences of various cultures and used in health care for the prevention, diagnosis, improvement, and treatment of mental and physical disease (WHO 2013). Traditional medicine which is mainly based on plants has been frequently confirmed by phytochemical investigations, pharmacological studies and clinical tests initiating further studies on medicinal plants in different parts of the world (Nigussie et al. 2021). Traditional medicines, on the other hand, can have adverse side effects, thus additional studies are needed to ensure the efficacy and safety of traditional medicine and methods employed by traditional medicine practitioners and consumers. WHO has launched a nine-year strategic plan to support member states in developing proactive strategies and implementing action plans that strengthen the role of traditional medicine in keeping populations healthy (WHO 2013).

*Kniphofia* is a genus of plants named after Johann Hieronymus Kniphof, a German botanist (1704-63) (Armitage 2011). The genus *Kniphofia* Moench, commonly known as ‘red hot pokers’, belongs to the family Asphodelaceae in the sub-family Asphodeloideae (Kubitzki et al. 1998). According to Codd (1968), the genus *Kniphofia* contains 70 species, 45 of which are found in South Africa, 1 in the Arab Republic of Yemen, 2 in Madagascar, and 23 in Tropical Africa, including 7 in Ethiopia. However, Ramdhani et al. (2006) later acknowledged that the
genus contains approximately 71 species by incorporating *Kniphofia monticola*, which was not previously included by Codd (1968). Several *Kniphofia* species have been utilised extensively and regularly by society and traditional healers for a variety of diseases. The leaves, stems, and roots are used in the formulation of traditional medicine. Various biological responses of *Kniphofia* indicate an extensive range of plant-derived compounds in various classes of chemical groups.

The World Health Organisation’s traditional medicine policy (WHO 2013) stated “traditional medicine and complementary products, practices, and practitioners will continue to be in high demand. In the meantime, there is a knowledge documentation gap. According to the current publication status, no comprehensive review study on the many features linked with the *Kniphofia* genus has been published. Therefore, the botanical description, reproduction, economic and ethnomedicinal usage, conservation, phytochemistry, and pharmacological applications of the *Kniphofia* genus are all covered in this review study.

**Review methodology**

This review adheres to the three-step review approach (Toyang and Verpoorte 2013). These include searching the literature, selecting relevant articles, and checking species names. The most widely used search tools or databases such as Google Scholar, PubMed, Scopus, Science Direct and Web of knowledge for the search terms: *Kniphofia* species, ethnomedicinal studies, phytochemical investigations, and pharmacological activities. The search strategy included all articles with descriptors that were available until November 30, 2021. Only published works in English have been used on this study. The data were collected using textual descriptions of the studies, tabulation, grouping, and figures. The worldwide plant name index ([https://www.ipni.org](https://www.ipni.org)) and the Kew Botanical Garden plant name database ([https://www.kew.org](https://www.kew.org)) were used to check species names.

**Botany and distribution of the genus Kniphofia**

*Kniphofia* is a perennial, acaulescent, and herbaceous genus with a single or branched thick rhizome and a thick well-developed stem that can be caespitose or solitary. The leaves are arranged in a basal rosette, generally in 4 or 5 ranks, but occasionally in 2, are linear, and taper gradually to the tip, and are frequently keeled. The leaf margin varies in texture from smooth to finely serrulate. Inflorescence peduncles are terminal, stout, erect, sub-equal to the leaves, simple or rarely branching, necked save for infrequent sterile bracts below the inflorescences, and inflorescences are sub-capitate racemes of usually numerous flowers, dense or lax. The bracts are scarlet or brown in colour, persistent, and longer than the pedicels. The pedicels are short to almost absent and articulated at the apex and flowers are spreading or pendulous with white, yellow or various shades of red. The perianth is tubular, campanulate to cylindrical or somewhat funnel-shaped and short, sub-equally lobed. The stamens are usually as long or longer than the perianth at anthesis and the ovary is sessile, ovoid, 3-locular with many ovules in each locule. The fruits are globose to ovoid often 3-angled with loculicidal dehiscence and seeds are somewhat flattened, acutely 3-angled or winged (Hedberg et al. 1997). The underground component of *Kniphofia* is made up of a strong rhizome and fibrous, meaty roots. The rhizome divides in certain species, generating groups of stems, while others have stems that are more or less solitary.

According to Ramdhani et al. (2006), the genus *Kniphofia* has six centres of diversity, five of which are endemism centres. The South African Centre is the most important in terms of species diversity and endemism, and it is also the largest. According to Marais (1973), the genus *Kniphofia* varies in size depending on the location and availability of water, and it can be found in a variety of environments ranging from low and wet savannah grassland to montane and alpine vegetation. In tropical and East Africa, *Kniphofia* has a strong afromontane grassland affinity. In South Africa, it is found from high altitudes to coastal habitats, with the most species regions being afromontane grasslands. It is, thus, not considered to be an afromontane element, but rather an afromontane associate. Five major evolutionary lineages were identified using cpDNA sequence data (trnT-L spacer), four of which are southern African. The fifth lineage was represented by material from Madagascar, tropical and East Africa (Ramdhani et al. 2006). In Ethiopian flora, seven *Kniphofia* species, *Kniphofia foliosa* Hochst., *Kniphofia hildebrandtii* Cufod., *Kniphofia insignis* Rendle., *Kniphofia isoetifolia* Hochst., *Kniphofia pumila* (Ait) Kunth., *Kniphofia schimperi* Baker., and *Kniphofia thomsonii* Baker were identified (Hedberg et al. 1997). Of those *Kniphofia foliosa*, *Kniphofia hildebrandtii*, *Kniphofia insignis*, *Kniphofia isoetifolia*, and *Kniphofia schimperi* are all endemic to Ethiopia, whereas *Kniphofia pumila* and *Kniphofia thomsonii* are widely distributed from West Africa to Eastern and Central Africa. *Kniphofia thomsonii* is found in Kenya, Uganda, and Tanzania, particularly on Mount Kilimanjaro (Marais 1973). Some of the representative samples of *Kniphofia* species are presented in Figure 1 (Codd 1968; Whitehouse 2002; Brown et al. 2009).

**Reproduction**

*Kniphofia* can be sexually propagated by seed. However, in all species, the low number of sexually reproducing plants may have an impact on the number of seedlings produced from seeds, which may have a negative impact on the plants’ long-term survival. Furthermore, because all *Kniphofia* species are obligatory outcrossers, a decrease in new seedlings could lead to a decrease in seed production due to gametophytic self-incompatibility. It can also reproduce asexually by dividing underground stems known as short rhizomes into ramets, which have the ability to be physiologically independent. As a result, even though it generates all genets in an area with the same genetic makeup due to proliferation and later fragmentation into clones, the asexual form of reproduction known as vegetative reproduction contributes more to population expansion (Teklehaymanot 2001).

**Economic and ethnomedicinal importance**

The genus is well-known for its ornamental value due to its colourful flowers, and it is used in horticulture and is planted in both home and botanical gardens. *Kniphofia* species found in nature are major pollen and nectar sources for honeybees (Fichtl and Adi 1994). An infusion of the roots is used to relieve or treat chest disorder and *Kniphofia parvisflora* is reported to have been made into a traditional snake repellent (Bringmann et al. 2008). In Ethiopian traditional medicine, the roots of *Kniphofia foliosa* are used to relieve abdominal cramps (Wube et al. 2005). The use of the genus *Kniphofia* in traditional medicine is limited to few species which is summarised in Table 1.
Figure 1. Images of some representative samples of Kniphofia species.

Table 1. Botanical distribution and traditional medicinal uses of the genus Kniphofia.

| Species            | Disease treated                  | Plant organs used | Preparation and application                                      | Distribution   | Ref                        |
|--------------------|----------------------------------|-------------------|-----------------------------------------------------------------|----------------|----------------------------|
| Kniphofia foliosa  | Cervical and breast              | Roots             | Dry roots are pounded and the powder is mixed with honey.       | Ethiopia       | Tesfaye et al. 2020        |
| Kniphofia isoetifoli| Gonorrhoea                       | Roots             | Concoction, crushing and powdering and taken orally             | Ethiopia       | Bizuayehu and Garedew 2018 |
|                    | Hepatitis B                      | Roots             | Fresh or dried roots concocted, crushed, decocted              | Ethiopia       | Yineger et al. 2013        |
| Kniphofia caulescens| Headache, painful eyes           | Root bulb         | Crush & add water                                              | South Africa   | Mugomeri et al. 2016       |
|                    | Blood purifier                   |                   | Not Reported                                                    | South Africa   | Van Vuuren & Frank 2020    |
| Kniphofia northiae | Period pains; menorrhagia        | Stems             | Decoction taken orally                                          | South Africa   | Moteteetee and Kose 2016   |
| Kniphofia drepanophylla | Ringworm, wounds, pimples, acne | Rhizomes (root)   | Dry, grind and mix with red oak or use alone in water.         | South Africa   | Josia 2013                 |
| Kniphofia sumarae  | Malaria                          | Roots             | Not Reported                                                    | Yemen          | Al-Musayeib et al. 2012    |
| Kniphofia pumila   | Evil eye                         | Bulbs             | Soak it in water with leaves of Rumex nervosus and wash body    | Ethiopia       | Teklay et al. 2013         |
|                    |                                  |                   | with it                                                         |                |                            |
| Kniphofia reflexa  | High relapsing fever             | Rhizomes          | Not reported                                                    | Cameroon       | Sema et al. 2018           |
| Kniphofia uvaria   | Dysmenorrhoea                    | Rhizome           | Not reported                                                    | South Africa   | Steenkamp 2003             |
| Kniphofia linearifolia | To treat infertility in women    | Roots             | The powdered root is consumed by mixing it with food.           | Zimbabwe       | Bosch 2008                 |
Conservation

Many *Kniphofia* species are in urgent need of conservation because a high number of South African species are included in the red data list of Hilton-Taylor (1996). Scott-Shaw (1999), identified 17 *Kniphofia* taxa in KwaZulu Natal (South Africa) and surrounding areas that are considered endangered. The endemic *Kniphofia hildebrandtii* in Ethiopia likewise requires special attention due to its biologically limited distribution and location in very venerable grassland that is exploited for livestock grazing. Additionally, *Kniphofia insignis*, which is found in wetland habitats, requires special attention because the community is converting wetland ecosystems to agriculture, so that it will not have refuge places to escape (Teklehaymanot 2001).

Phytochemistry

The genus *Kniphofia* is comprehensively studied for its chemical constituents and till now, more than 40 compounds from different chemical classes have been identified. These phytochemicals mainly contain anthraquinones, naphthalene derivatives, organic acids, indane derivatives and miscellaneous group of compounds. Monomeric anthraquinone, dimeric anthraquinone and Phenyl anthraquinones and anthrones are the major constituents isolated from the majority of the *Kniphofia* species. Many of the isolated compounds were also evaluated for their bioefficiency. The methods used for isolating new compounds for the plants of *Kniphofia* species include serial extraction, bioassay guided extraction, high performance liquid chromatography (HPLC), apart from the successive fractionation using different polarity solvents and column chromatography. Activity guided bioactive compound isolation is currently gaining attention because of the increased demand for the use of traditional medicine as an alternative and complementary medicine (WHO 2013). The root of the plants in the genus was frequently considered for investigation. Indeed, *Kniphofia* species are mostly found in Tropical Africa and South Africa, which explains why there aren’t many compounds isolated from this genus. This could be due to a number of factors, including plant availability, material shortages, a lack of skilled manpower, and the tedious nature of the work. The summaries for the phytochemical investigation are presented in Table 2 and Figure 2 depicts the structures of those compounds.

Pre-anthraquinones

Pre-anthraquinones are precursors of anthraquinones, and when treated with a base, they readily convert to the equivalent anthraquinones (Yenesew et al. 1994). From the stem of *K. foliosa*, only two related pre-anthraquinones, aloeasaponol III (27) and aloeasaponol III-8-methyl ether (28), have been reported (Yenesew et al. 1994).

Monomeric anthraquinones

*Kniphofia* is known for producing monomeric anthraquinones. Monomeric anthraquinones were isolated in many parts of the *Kniphofia* species, including rhizomes, leaves, flowers, roots, and fruits. Seven monomeric anthraquinones (3–9) have been found in 11 different *Kniphofia* species so far. Only two monomeric anthraquinones were studied for their pharmacological properties. Helmantosporine (9) was isolated from the acetone fraction of *Kniphofia insignis* roots and tested for antibacterial and antifungal properties (Tadesse et al. 2021). The anti-inflammatory potential of the compound chrysophanol (5), which was obtained from the methanol crude extract fraction of *Kniphofia reflexa* rhizome, was also investigated (Sema et al. 2018).

Dimeric anthraquinones

*Kniphofia* has been shown to be an excellent source of dimeric anthraquinones. In this genus, phenol-oxidative coupling dimerisation of two identical anthraquinones as well as mixed dimerisation has been observed. Dimeric anthraquinones were discovered in several parts of the *Kniphofia* species, including rhizomes, leaves, roots, and whole plants. To date, 12 dimeric anthraquinones (10–22) have been found in 11 different *Kniphofia* species. Only 5 dimeric anthraquinones were studied for their pharmacological properties. The antibacterial and antifungal properties of asphodeline (10) derived from the acetone fraction of *Kniphofia insignis* roots were investigated (Tadesse et al. 2021). Microcarpin (11) was isolated from the rhizomes of a methanol extract of *Kniphofia reflexa* and tested for cytotoxicity on the LLC-MK2 Monkey Kidney Epithelial cell line using the MTT assay with Gleevec (Imatinib) as a positive control. It was found to be moderately cytotoxic with a CC₅₀ value of 11.24 μg/mL (Sema et al. 2018). The antimalarial and antiproliferative properties of chyslandicin (15), which was isolated from whole parts of an ethanolic crude extract of *Kniphofia ensifolia*, were investigated (Dai et al. 2014). The antiplasmodial activity of the compound 10-methoxy-10′, 7′-(chrysophanol anthrone)-chrysophanol (21) isolated from the methanol crude extract of *Kniphofia foliosa* roots was investigated, and it showed good activity with IC₅₀ values of 1.17 and 4.07 μg/mL, respectively, against chloroquine resistant (W2) and chloroquine sensitive (D6) *P. falciparum* strains (Abdissa et al. 2020). The compound, 10-(chrysophanol-7-yl)-10′-(5)-hydroxychrysophanol-9-anthrone (22) isolated from dichloromethane extract of *Kniphofia foliosa* roots was evaluated in vitro against the chloroquine-sensitive 3D7 strain of *P. falciparum*, and it significantly inhibited malaria parasite development with an ED₅₀ value of 0.26 μg/mL (Sema et al. 2018).

Phenyl anthraquinones and anthrones

The phenylanthraquinones and anthrones, which are made up of a 1, 8-dihydroxyanthraquinone and an acetylpheophoroglucin component linked by a biaryl axis, are another interesting and emerging class of secondary metabolites generated by the *Kniphofia* genus. Compounds 23, 24, and 25 were isolated from *Kniphofia foliosa* stem parts, whereas compound 26 was isolated from *Kniphofia foliosa* root parts. Khipholone (27) was found in practically all *Kniphofia* species in all parts of the plant, including leaves, rhizomes, stems, roots, and flowers. Only two compounds (25 and 27) were tested for their pharmacological properties. Khipholone anthrone (25) was tested for its antimalarial, antioxidant, and anti-HIV-1 properties (Habtemariam 2007; Felicke et al. 2019; Richard et al. 2020). Khipholone (27) has a variety of pharmacological properties, including antibacterial, antimalarial, anti-inflammatory, anti-HIV-1, anti-leukotriene, and cytotoxic properties (Wube et al. 2006; Habtemariam 2010; Sema et al. 2018; Felicke et al. 2019; Abdissa et al. 2020; Alebachew et al. 2021).

Oxanthrones

Two oxanthrone compounds (28 and 29) were isolated in the stem of *Kniphofia foliosa* by Yenesew et al. (1994). The pharmacological effects of both of these compounds have not been investigated.
### Table 2. Recently isolated compounds from *Kniphofia* species.

| Compound                              | Species                  | Plant organ investigated | Extraction method used | Ref |
|---------------------------------------|--------------------------|--------------------------|------------------------|-----|
| **Pre anthraquinones**                |                          |                          |                        |     |
| Aloesaponol III (1)                   | *Kniphofia foliosa*      | Ethiopia Stem             | SE, TLC and CC         | Yenesew et al. 1994 |
| Aloesaponol III-8-methyl ether (2)    | *Kniphofia foliosa*      | Ethiopia Stem             | SE, TLC and CC         | Yenesew et al. 1994 |
| Aloe-eminod (3)                       | *Kniphofia foliosa*      | Ethiopia Leaves, flowers, | SE, TLC and CC         | Berhanu et al. 1986 |
|                                       | *Kniphofia insignis*     | Flowers                  | SE, TLC and CC         | Berhanu et al. 1986 |
|                                       | *Kniphofia isoitofolia*  | Flowers                  | SE, TLC and CC         | Berhanu et al. 1986 |
|                                       | *Kniphofia schimperi*    | Flowers                  | SE, TLC and CC         | Berhanu et al. 1986 |
|                                       | *Kniphofia thomsonii*    | Kenya Roots              | SE, TLC and CC         | Achieng 2009       |
| Aloe-eminod acetate (4)               | *Kniphofia foliosa*      | South Africa Whole parts | BGE, SE, TLC and HPLC  | Berhanu and Dagne 1984; 1986 |}

### Monomeric anthraquinones

| **Chrysophanic acid (5)**             | *Kniphofia foliosa*      | Ethiopia Rhizomes, leaves, flowers, Roots | SE, TLC and CC         | Berhanu et al. 1986 |
|                                       | *Kniphofia thomsonii*    | Kenya Roots               | SE, TLC and CC         | Achieng 2009       |
|                                       | *Kniphofia insignis*     | Ethiopia Rhizomes         | SE, TLC and CC         | Berhanu et al. 1986 |
|                                       | *Kniphofia isoitofolia*  | Ethiopia Rhizomes, leaves, flowers, Roots | SE, TLC and CC         | Berhanu et al. 1986 |
|                                       | *Kniphofia pwnila*       | Ethiopia Rhizomes         | SE, TLC and CC         | Berhanu et al. 1986 |
|                                       | *Kniphofia schimperi*    | Ethiopia Rhizomes, flowers | SE, TLC and CC         | Berhanu et al. 1986 |
|                                       | *Kniphofia thomsonii*    | Kenya Roots               | SE, TLC and CC         | Achieng 2009       |
|                                       | *Kniphofia reflexa*      | South Africa Rhizomes     | FC, CC, HPLC and PTLC  | Dai et al. 2014    |
|                                       | *Kniphofia ensifolia*    | South Africa Whole parts  | BGE, SE, TLC and HPLC  | Dai et al. 2014    |
| Physcion (6)                          | *Kniphofia thomsonii*    | Kenya Roots               | SE, TLC and CC         | Achieng 2009       |
| Chrystophanic acid (7)                | *Kniphofia cauliscens*   | Roots                    | SE, TLC and CC         | Berhanu et al. 1986 |
|                                       | *Kniphofia foliosa*      | Ethiopia Leaves, rhizomes, roots and fruits | SE, TLC and CC         | Berhanu et al. 1986 |
|                                       | *Kniphofia insignis*     | Ethiopia Rhizomes         | SE, TLC and CC         | Berhanu et al. 1986 |
|                                       | *Kniphofia isoitofilia*  | Ethiopia Rhizomes         | SE, TLC and CC         | Berhanu et al. 1986 |
|                                       | *Kniphofia linearifolia* | Ethiopia Roots            | SE, TLC and CC         | Berhanu et al. 1986 |
| Islandicin (8)                        | *Kniphofia foliosa*      | Ethiopia Roots, leaves, and flowers | SE, TLC and CC         | Berhanu et al. 1986 |
|                                       | *Kniphofia insignis*     | Ethiopia Rhizomes         | SE, TLC and CC         | Berhanu et al. 1986 |
|                                       | *Kniphofia isoitofilia*  | Ethiopia Rhizomes         | SE, TLC and CC         | Berhanu et al. 1986 |
|                                       | *Kniphofia schimperi*    | Ethiopia Rhizomes         | SE, TLC and CC         | Berhanu et al. 1986 |
|                                       | *Kniphofia linearifolia* | Ethiopia Roots            | SE, TLC and CC         | Berhanu et al. 1986 |
| Islandicin (8)                        | *Kniphofia reynolds*     | Ethiopia Roots            | SE, TLC and CC         | Yenesew et al. 1988 |
|                                       | *Kniphofia thomsonii*    | Kenya Roots               | SE, TLC and CC         | Achieng 2009       |
| Helmithosporin (9)                    | *Kniphofia insignis*     | Ethiopia Roots            | BGE, TLC and CC        | Tadesse et al. 2021 |
| **Dimeric anthraquinones**            |                          |                          |                        |     |
| Asphodelin (10)                       | *Kniphofia albescens*    | South Africa Roots       | SE, TLC and CC         | Van Wyk et al. 1995 |
|                                       | *Kniphofia insignis*     | Ethiopia Roots            | BGE, TLC and CC        | Tadesse et al. 2021 |
|                                       | *Kniphofia isoitofilia*  | Ethiopia Roots            | SE, TLC and CC         | Meshesha et al. 2017 |
|                                       | *Kniphofia ensifolia*    | South Africa Whole parts | BGE, SE, TLC and HPLC  | Dai et al. 2014 |
| Microcarpin (11)                      | *Kniphofia ensifolia*    | South Africa Whole parts | BGE, SE, TLC and HPLC  | Dai et al. 2014 |
|                                       | *Kniphofia reflexa*      | Ethiopia Leaves           | FC, CC, HPLC and PTLC  | Sema et al. 2018   |
| Chrysolinol (12)                      | *Kniphofia foliosa*      | Ethiopia Rhizomes         | SE, TLC and CC         | Dagne et al. 1987  |
| Kniphofine (13)                       | *Kniphofia insignis*     | Ethiopia Rhizomes         | SE, TLC and CC         | Berhanu et al. 1985 |
|                                       | *Kniphofia isoitofilia*  | Ethiopia Rhizomes         | SE, TLC and CC         | Berhanu et al. 1985 |
|                                       | *Kniphofia pwnila*       | Ethiopia Rhizomes         | SE, TLC and CC         | Berhanu et al. 1985 |
|                                       | *Kniphofia schimperi*    | Ethiopia Rhizomes         | SE, TLC and CC         | Berhanu et al. 1985 |
|                                       | *Kniphofia reflexa*      | Ethiopia Leaves           | SE, TLC and CC         | Dagine et al. 1987 |
|                                       | *Kniphofia ensifolia*    | South Africa Whole parts  | SE, TLC and CC         | Dai et al. 2014    |

(continued)
| Compound | Species | Collection area | Plant organ investigated | Extraction method used | Ref |
|----------|---------|----------------|-------------------------|----------------------|-----|
| Kniphofione B (17) | *Kniphofia ensifolia* | Ethiopia | Whole parts | BGE, SE, TLC, and HPLC | Dagne et al. 1987 |
| 10,10'-Bichrysophanolanthrone (18) | *Kniphofia thomsonii* | Kenya | Roots | SE, TLC and CC | Achieng 2009 |
| 10-Hydroxy-10-(chrysophanol-7'-yl)-aloe-emodin anthrone (19) | *Kniphofia thomsonii* | Kenya | Roots | SE, TLC and CC | Achieng 2009 |
| 10-Hydroxy-10-(islandicin-7'-yl)-aloe-emodin anthrone (20) | *Kniphofia thomsonii* | Kenya | Roots | SE, TLC and CC | Achieng 2009 |
| 10-Methoxy-10,7'-chrysophanol anthrone-chrysophanol (21) | *Kniphofia foliosa* | Ethiopia | Roots | SE, TLC and CC | Abdissa et al. 2013 |
| 10-(Chrysophanol-7'-yl)-10,10'-Kniphofione B (22) | *Kniphofia foliosa* | Ethiopia | Roots | SE, TLC and CC | Abdissa et al. 2013 |
| Isoknipholone (23) | *Kniphofia foliosa* | Ethiopia | Stems | SE, TLC and CC | Yenesew et al. 1994 |
| Isoknipholone anthrone (24) | *Kniphofia foliosa* | Ethiopia | Stems | SE, TLC and CC | Yenesew et al. 1994 |
| Kniphofone cyclooxyanthrone (26) | *Kniphofia foliosa* | Ethiopia | Roots | SE, TLC and CC | Dagne and Steglich 1984; Yenesew et al. 1988; Dagne and Yenesew 1993; Yenesew et al. 1994; Adebachew et al. 2021 |
| Kniphofone (27) | *Kniphofia foliosa* | Ethiopia | Roots, leaves, stems, flowers, rhizomes and fruits | SE, TLC, CC and PTLC | Yenesew et al. 1994; Dagne and Steglich 1984; Yenesew et al. 1988; Dagne and Yenesew 1993; Yenesew et al. 1994; Adebachew et al. 2021 |
| Kniphofone (28) | *Kniphofia foliosa* | Ethiopia | Stems | SE, TLC and CC | Yenesew et al. 1994 |
| Kofiolosone (29) | *Kniphofia foliosa* | Ethiopia | Stem | SE, TLC and CC | Yenesew et al. 1994 |
| Organic acids | Citric acid (30) | *Kniphofia burchellii* | South Africa | Leaves | SE, TLC and CC | Van Oudtshoorn 1964 |
| Malic acid (31) | *Kniphofia burchellii* | South Africa | Leaves | SE, TLC and CC | Van Oudtshoorn 1964 |
| Quinic acid (32) | *Kniphofia uvaria* | Tokyo, Japan | Leaves | SE, TLC and CC | Yoshida et al. 1975 |
| Shikimic acid (33) | *Kniphofia uvaria* | Tokyo, Japan | Leaves | SE, TLC and CC | Yoshida et al. 1975 |
| Naphthalene Derivatives | 2- Acetil-1 -hydroxy-8-methoxy-3-methyl-naphthalene (34) | *Kniphofia foliosa* | Ethiopia | Roots | SE, CC and HPLC | Wube et al. 2005 |
| 2- Acetil-1 -hydroxy-8-methoxy-3-methyl-naphthalene (35) | *Kniphofia reflexa* | Ethiopia | Rhizomes | FC, CC, HPLC and PTLC | Sema et al. 2018 |
| Hydroxydeoseron (3,5,8-tri-hydroxy-2-methyl-naphthalenedione) (36) | *Kniphofia isofoliola* | Ethiopia | Rhizomes | SE, TLC and CC | Meshesha et al. 2017 |
| Dianellin (37) | *Kniphofia foliosa* | Ethiopia | Roots, rhizomes | SE, TLC, CC and PTLC | Abdissa et al. 2013; Alebachew et al. 2021 |
| Kniphofiarinsene (38) | *Kniphofia reflexa* | Ethiopia | Rhizomes | FC, CC, HPLC and PTLC | Sema et al. 2018 |
| Indane Derivatives | Kniphofiarindane (39) | *Kniphofia reflexa* | Ethiopia | Rhizomes | FC, CC, HPLC and PTLC | Sema et al. 2018 |
| Miscellaneous compounds | Flavoglucin (40) | *Kniphofia thomsonii* | Kenya | Roots | SE, TLC and CC | Yenesew et al. 1994 |
| 3'β,4'β-Dideoxyflavoglucin (41) | *Kniphofia thomsonii* | Kenya | Roots | SE, TLC and CC | Yenesew et al. 1994 |
| 4,6-Dihydroxy-2- methoxycetophenone (42) | *Kniphofia reflexa* | Ethiopia | Rhizomes | FC, CC, HPLC and PTLC | Sema et al. 2018 |
| 2',4',6'-Trimethoxycetophenone (43) | *Kniphofia reflexa* | Ethiopia | Rhizomes | FC, CC, HPLC and PTLC | Sema et al. 2018 |
| 3,4-Dihydrobenzoic acid (44) | *Kniphofia reflexa* | Ethiopia | Rhizomes | FC, CC, HPLC and PTLC | Sema et al. 2018 |

**Table 2.** Continued.

BGE = bioassay guided extraction, CC = column chromatography, FC = flash chromatography, SE = successive extraction, HPLC = high column chromatography, PTLC = preparative thin layer chromatography, TLC = thin layer chromatograph
Organic acids

Another essential component of the _Kniphofia_ genus is organic acids. Compounds (30 and 31) were isolated in the leaves of _Kniphofia burchelli_ and (32 and 33) in the leaves of _Kniphofia uvarica_, respectively (Van Oudtshoorn 1964; Yoshida et al. 1975). The pharmacological actions of the compounds have not been studied.

**Naphthalene derivatives**

Naphthalene, commonly known as naphthene, naphthalin, camphor tar, and white tar, is an organic compound having the formula C10H8. A fused pair of benzene rings makes up the structure of naphthalene. Naphthalene shows various antagonistic activities including anticancer, antimicrobial, anti-inflammatory, antiviral, antihypertensive, antidiabetic, anti-neurodegenerative, antipsychotic, anticonvulsant and antidepressant (Makar et al. 2019). _Kniphofia_ species roots and rhizomes were used to isolate naphthalene derivatives. Three different _Kniphofia_ species have been reported to contain five naphthalene derivatives (34–38). The pharmacological activities of three of these compounds (34, 36, and 37) were investigated. On the LLC-MK2 Monkey Kidney Epithelial Cell Line, the cytotoxic activity of the compound isolated from methanolic crude extract of _Kniphofia reflexa_ rhizomes was tested against Gleevec (Imatinib) as the positive control using the MTT assay. The compound (34) was extremely cytotoxic, with a CC50 of 4.43 μg/mL (Sema et al. 2018). The antimalarial activity of a compound (36) isolated from 80% methanol rhizome extracts of _Kniphofia foliosa_ was evaluated in mice against the chloroquine (CQ) sensitive ANKA strain of _Plasmodium berghei_. At a dose of 200 mg/kg body weight, the compound dianellin (36) exhibited a substantial suppression value of 60.16%, and it extended the treatment group’s mean survival time (Alebachew et al. 2021). Kniphofiarexin (37) was isolated from crude methanol extracts of _Kniphofia reflexa_ rhizome and evaluated for anti-inflammatory effects on phagocyte oxidative burst. After activation, phagocytic cells released free reactive oxygen species (ROS) radicals, which were quantified using a luminal-enhanced chemiluminescence assay with ibuprofen as a positive control. Kniphofiarexin (37) was less effective than the reference drug ibuprofen in inhibiting monocyte activity, with just 42.2% compared to 73.2% for ibuprofen (Sema et al. 2018).

**Indane derivative**

Kniphofiarindane (39) is the only indane derivative that has been isolated from _Knifolia_ species so far. On the LLC-MK2 Monkey Kidney Epithelial Cell Line, the cytotoxic activity of the compound isolated from methanol crude extract of _Kniphofia reflexa_ rhizomes was evaluated against Gleevec (Imatinib) as the positive control using the MTT assay. The compound (39) was moderately cytotoxic, with a CC50 of 16.35 μg/mL (Sema et al. 2018).

**Miscellaneous compounds**

So far, four miscellaneous compounds (40–44) have been isolated from three _Kniphofia_ species: _Kniphofia thomsonii_, _Kniphofia foliosa_, and _Kniphofia reflexa_. These compounds’ biological activities have not been studied.

**Pharmacological activities**

Modern and traditional approaches to healthcare frequently coexist and complement one another. Ethnomedicinal practices are now widely used in the search for novel pharmaceuticals (Gurib-Fakim 2006). Recent interest in examining plant constituents for their pharmacological activity and screening for useful
and safe phytochemicals has renewed (Nigussie et al. 2021). Dysmenorrhoea, eczema, malaria, gonorrhoea, Hepatitis B, Blood purifier, gout, and cervical and breast cancer are just a few of the ailments for which *Kniphofia* species have been used in traditional medicine (Table 1). Various *in vitro* and *in vivo* pharmacological activities of *Kniphofia* species such as antibacterial, antifungal, antimalarial, antioxidant, anti-inflammatory, anti-HIV-1, anti-leukotriene, antiproliferative and cytotoxic activity are showed in Figure 3 and mentioned below.

### Antibacterial activity

The acetone crude extracts of *Kniphofia pumila* roots were tested for antibacterial activity against *E. coli*, *K. pneumonia*, and *S. aureus* using the agar disc diffusion method with gentamycin as a positive control. The extract demonstrated inhibition zones of 12.6, 11.8 and 10.7 mm, which are very similar to the positive control gentamycin, which has inhibition zones of 16, 18 and 13 mm, respectively (Abdissa et al. 2020). The reported compound kniphoflone (27) also exhibited against *E. coli*, *S. aureus* and *S. typhimurium* with zones of inhibition 14, 16 and 12 mm, respectively. Whereas, the combined crude extracts with ZnCl₂, as well as the reported compound with ZnCl₂, had much higher antibacterial activity against *E. coli* and *S. aureus* bacterial strains than the crude extract and isolated compound, which could be attributed to a synergetic effect (Abdissa et al. 2020). The antibacterial activity of acetone crude extracts of *Kniphofia insignis* roots was examined using the agar disc diffusion method with gentamycin as a positive control against *E. coli*, *P. aeruginosa*, *S. aureus*, and *B. subtilis*. The inhibition zones of the crude extract were 18, 14, 15, and 18 mm, which are fewer activities than the inhibition zones of the positive control gentamycin, which were 32, 22, 33, and 31 mm, correspondingly. The reported compounds helmantosporine (9) and asphodeline (10) were found to inhibit Gram-positive and Gram-negative bacteria with zones of inhibition ranging from 11 to 15 mm, with helmantosporine (9) having the maximum activity (15 mm) against *P. aeruginosa* (Tadesse et al. 2021). Using the agar disc diffusion method and gentamicin as a positive control, Meshesha et al. (2017) investigated the antibacterial activity of methanol-chloroform (1:1 v/v) and ethyl acetate extracts of *Kniphofia isettofotia* roots against *S. aureus*, *E. faecalis*, *P. aeruginosa*, and *E. coli*. The results showed that the crude extracts had significant activity on both Gram-positive and Gram-negative bacterial strains, with zones of inhibition ranging from 21 to 28 mm and potencies that were closely related between the two crude extracts. However, the ethyl acetate extract exhibited highest zone of growth inhibition (28 mm) on *E. coli* and *E. faecalis* (Meshesha et al. 2017). The reported compounds asphodeline (10) and 10-hydroxy-10, 7′-(chrysophanolanthrone) chrysophanol (14) had strong inhibitory activities against the examined bacterial strains (inhibition zone diameters ranging from 18 to 30 mm), with asphodeline, 10-hydroxy-10,7′-(chrysophanolanthrone) chrysophanol having the best inhibitory capacity 30 and 28 mm respectively, that is extra comparable with standard drug having 31 mm inhibition zone (Meshesha et al. 2017).

### Antifungal activity

Using the agar disc diffusion method and chlortrimazole as a positive control, the antifungal activity of acetone crude extracts of *Kniphofia insignis* roots was investigated against *Fusarium* spp. The inhibition zones of the crude extract were 18 mm, which are quite similar to the inhibition zones of the positive control chlortrimazole, which were 20 mm. Helmantosporine (9) and asphodeline (10) were also shown to be effective against *Fusarium*.
spp., with zones of inhibition of 12 and 13 mm, respectively (Tadesse et al. 2021).

**Antimalarial activity**

Using malaria SYBR Green I-based *in vitro* assay techniques with reference drugs chloroquine and mefloquine, study examined antiplasmodial activity of methanol root extracts of *Kniphofia foliosa* against chloroquine resistant (W2) and chloroquine sensitive (D6) strains of *P. falciparum*. The crude extract showed IC₅₀ values of 11.28 and 8.92 μg/mL, which were weaker than the reference drugs chloroquine (0.22 and 0.01 μg/mL) and mefloquine (0.03 and 0.003 μg/mL respectively). However, compound 10-methoxy-10,2,7’-(chrysophanol anthrone)-chrysophanol (21) demonstrated good activity, with IC₅₀ values of 1.17 and 4.07 μg/mL, respectively (Abdissa et al. 2013). *Kniphofia foliosa* 80% methanol rhizome extracts were tested in mice for antimalarial activity against the chloroquine (CQ) sensitive ANKA strain of *Plasmodium berghei*. At dosages of 400 and 200 mg/kg body weight, respectively, the highest activities were suppressed with 61.52 and 51.39% suppression. Furthermore, when compared to the negative controls, the extract considerably increased the survival days of the treated groups at those levels. The reported compound, knipholone (27) and dianellin (36) were likewise shown to have significant suppression values of 55.14 and 60.16% at doses of 100 and 200 mg/kg, respectively, and they extended the treatment groups’ mean survival days (Alebachew et al. 2021).

Using chloroquine as a positive control, the antiplasmodial activity of dichloromethane extracts of *Kniphofia foliosa* roots were tested *in vitro* against the chloroquine-sensitive 3D7 strain of *P. falciparum*. The crude extract showed antiplasmodial action with an ED₅₀ of 3.8 μg/mL, which is a low level of activity when compared to the reference drug, which had an ED₅₀ of 0.0075 μg/mL (Wube et al. 2005). Also, the compound 10-(chrysophanol-7’-yl)-10-(2’)-hydroxychrysoanol-9-anthrone (22) which was isolated from the roots and tested for antimalarial activity *in vitro*, inhibited the malaria parasite *P. falciparum*’s development significantly, with ED₀₅₀ values of 0.260 μg/mL (Wube et al. 2005). The antiplasmodial activity of the compound chryslandin-15, reported from the whole parts of ethanol extract of *Kniphofia ensifolia*, was tested using the SYBR Green I assay. When compared to the positive control actinomycin/taxol, the compound demonstrated modest antiproliferative action with IC₅₀ values of 4 μM (Dai et al. 2014).

**Antioxidant activity**

An *in vitro* assay was used to test the antioxidant activity of the knipholone anthrone (25) reported from *Kniphofia foliosa* against 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radicals, the compound has a concentration-dependent scavenging effect. In the DPPH assay, the compound and the positive control (-)-epicatechin (EC) had IC₅₀ values of 22 and 8.7 μM, respectively. It was also more effective than EC at scavenging superoxide anions and inhibiting hydroxyl radical degradation of deoxyribose. The compound appeared to form a complex with Fe²⁺, had a concentration-dependent reducing power, and protected isolated DNA from damage induced by Fenton reaction-generated hydroxyl radicals (at concentrations of 4.4 μM and higher) (Habtemariam 2007).

**Anti-inflammatory activity**

The anti-inflammatory effects of crude methanol extracts of *Kniphofia reflexa* rhizome and its reported compounds kniphofiarexine (37), knipholone (27), and chrysophanol (5) on phagocyte oxidative burst were investigated. Phagocytic cells released free reactive oxygen species (ROS) radicals (oxidative burst) after activation, which was measured using a luminal-enhanced chemiluminescence assay with ibuprofen as a positive control. Compounds knipholone (27), and chrysophanol (5) (concentration 100.10 μg/mL) reduced the zymosan-induced oxidative burst in polymorpho-neutrophils (PMNs) moderately, with CC₅₀ values of 38.7 μg/mL and 20.0 μg/mL, respectively, as compared to the positive control, which had a CC₅₀ value of 27.16 μg/mL. The crude extract and compound kniphofiarexine (37) were less effective in inhibiting monocyte activity, with just 42.4% and 42.2%, respectively, compared to 73.2% for the reference drug ibuprofen (Sema et al. 2018).

**Antiproliferative activity**

The antiproliferative activity of the compound chryslandin (15), which were isolated from the whole parts of the ethanol extract of *Kniphofia ensifolia*, was tested using the Alamar blue assay. When compared to the positive control actinomycin/taxol, the compound demonstrated modest antiproliferative action with IC₅₀ values of 4 μM (Dai et al. 2014).

**Cytotoxic activity**

Habtemariam (2010) evaluated the cytotoxicity activity of knipholone (27) and knipholone anthrone (25) reported from *Kniphofia foliosa* in leukemic and melanocyte cancer cell lines using the annexin V-FITC apoptosis assay. Both compounds had anticancer action, with knipholone anthrone generating a quick onset of cytotoxicity with IC₅₀ values ranging from 0.5 to 3.3 μg/mL. When comparing the cytotoxicity of both compounds, knipholone was 70–480 times less harmful to cancer cells. The cytotoxicity of knipholone anthrone was also linked to a rapid loss of membrane integrity, resulting in necrotic cell death, according to morphological and biochemical analyses (Habtemariam 2010). The cytotoxicity of 80% methanol root extracts of *Kniphofia foliosa* against ten human cancer cell lines MCF-7, A427, RT-4, SiSo, LCLC-103H, DANG, A2780, KYSE-70, HL-60, and U-937 was evaluated using crystal violet cell proliferation and MTT cell viability assays. *Kniphofia foliosa* root extracts reduced cell growth in all cell lines tested, with IC₅₀ values ranging from 14.54 to 27.06 μg/mL (Tesfaye et al. 2021). The acute toxicity of *Kniphofia foliosa* methanol rhizome extracts and its reported compounds knipholone (27) and dianellin (36) was investigated. The LD₅₀ of extracts and reported compounds were found to be greater than 2000 mg/kg in the study (Alebachew et al. 2021). The MTT technique was used to test the cytotoxic activity of the methanolic crude extract of *Kniphofia reflexa* rhizomes and their chemical constituents against Gleevec (Imatinib) as the positive control on the LLC-MK2 Monkey Kidney Epithelial Cell Line. With a CC₅₀ of 4.43 μg/mL, 2-acetyl-1-hydroxy-8-methoxy-3-methylnaphthalene (34) was highly cytotoxic. Compounds kniphofiarindane (39) and microcarpin (11) were moderately cytotoxic as well, with CC₅₀ values of 16.35 μg/mL and
| Activity  | Plant species       | Plant part | Extract     | Isolated compound                  | Method (mode of action) | Effect                                                                 | Ref                      |
|----------|---------------------|------------|-------------|------------------------------------|-------------------------|----------------------------------------------------------------------|--------------------------|
| Antibacterial | *Kniphofia pumila* | Root       | Acetone     | Knipholone (27)                    | Agar disc diffusion/in vitro | The compound knipholone showed inhibition zones of 14, 16 and 12 mm against E. coli, S. aureus, and S. typhimurium, which are very similar to the positive control gentamycin, which has inhibition zones of 16, 18 and 13 mm, respectively. | Abdissa et al. 2020     |
| Antibacterial | *Kniphofia insignis* | Root       | Acetone     | Helmantosporine (9) and Asphodeline (10) | Agar disc diffusion/in vitro | The compounds helmantosporine and asphodeline were found to have zones of inhibition ranging from 11 to 15 mm against E. coli, P. aeruginosa, S. aureus, and S. subtilis, which are lower activities than the inhibition zones of the positive control gentamycin, which were 32, 22, 33, and 31 mm, respectively. | Tadesse et al. 2021     |
| Antibacterial | *Kniphofia isoetifolia* | Root       | Ethyl acetate | Asphodeline (10) 10-hydroxy-10,7'- (chrysophanolanthrone) chrysophanol (14) | Agar disc diffusion/in vitro | Asphodeline and 10-hydroxy-10, 7’-(chrysophanolanthrone) chrysophanol are effective against S. aureus, E. coli, E. faecalis and P. aeruginosa, with inhibition zones ranging from 18 to 30 mm, which is comparable to gentamicin has 31 mm inhibition zone. | Meshesha et al. 2017    |
| Antifungal | *Kniphofia insignis* | Root       | Acetone     | Helmantosporine (9) and Asphodeline (10) | Agar disc diffusion/in vitro | Helmantosporine and asphodeline have inhibition zones of 12 and 13 mm, respectively, against Fusarium spp., which are less effective than the positive control trichloromethane, which has an inhibition zone of 20 mm. | Tadesse et al. 2021     |
| Antimalarial | *Kniphofia foliosa* | Root       | Methanol    | 10-methoxy-10,7’- (chrysophanol anthrone)-chrysophanol (21) | SYBR Green I/in vitro | The compounds demonstrated good activity against chloroquine resistant (W2) and chloroquine sensitive (D6) strains of P. falciparum, with IC50 values of 1.17 and 4.0/lg/mL, respectively | Abdissa et al. 2013     |
| Antimalarial | *Kniphofia foliosa* | Root       | Methanol    | Knipholone (27) and Dianellin (36) | Blood-induced CQ resistant rodent parasite in mice/in vivo | The compound had significant suppression values of 55.14 and 60.16 % against the chloroquine sensitive ANKA strain of Plasmodium berghei at dosages of 100 and 200 mg/kg, respectively. | Alebachew et al. 2021   |
| Antimalarial | *Kniphofia foliosa* | Root       | Dichloromethane | 10-(chrysophanol-7’-yl)-10- (E)-hydroxychrysophanol-9-anthrone (22) | SYBR Green I/in vitro | The compound 10-(chrysophanol-7’-yl)-10- (E)-hydroxychrysophanol-9-anthrone inhibited chloroquine-sensitive 3D7 strain of P. falciparum development significantly, with ED50 values of 0.260 lg/mL. | Wube et al. 2005        |
| Antimalarial | *Kniphofia ensifolia* | Whole parts | Ethanol     | Chryslandicin (15) | SYBR Green I/in vitro | The compound had IC50 values of 0.2 µM against D62 chloroquine-resistant P. falciparum, which was comparable to the reference drug artemisinin, which has an IC50 value of 0.007 µM. | Dai et al. 2014          |
| Antimalarial | *Kniphofia foliosa* | Root       | Ethyl acetate | Knipholone (27) and Knipholone anthrone (25) | P. falciparum maintained in continuous culture in human erythrocytes/in vitro | The compound IC50 values of 1.9 and 0.7 µM, respectively, against P. falciparum 3D7 strain using chloroquine as a reference drug, which has an IC50 value of 0.005 µM. | Felicke et al. 2019     |
| Antioxidant | *Kniphofia foliosa* | Root       | Methanol    | Knipholone anthrone (25) | DPPH radical assay/in vitro | The compound and the positive control (-)-epicatechin (EC) had IC50 values of 22 and 8.7 µM, respectively | Habetemariam 2007        |

(continued)
| Activity       | Plant species | Plant part | Extract  | Isolated compound                                      | Method (mode of action)                                      | Effect                                                                 | Ref                  |
|----------------|---------------|------------|----------|--------------------------------------------------------|-------------------------------------------------------------|------------------------------------------------------------------------|----------------------|
| Antioxidant    | *Kniphofia foliosa* | Root       | Methanol | Knipholone anthrone (25)                               | DPPH radical assay/in vitro                                  | The compound and the positive control (-)-epicatechin (EC) had IC50 values of 22 and 8.7 μM, respectively | Habtemariam 2007     |
| Anti-inflammatory | *Kniphofia reflexa* | Rhizome    | Methanol | Knipholone (27), and Chrysophanol (5)                   | Luminal-enhanced chemiluminescence assay/in vitro            | Compounds knipholone (27), and chrysophanol (5) (concentration 100.10 μg/mL) reduced the zymosan-induced oxidative burst in polymorpho-neutrophils (PMNs) moderately, with CC50 values of 38.7 μg/mL and 20.0 μg/mL, respectively, as compared to the positive control ibuprofen, which had a CC50 value of 27.16 μg/mL | Sema et al. 2018     |
| Antiproliferative | *Kniphofia ensifolia* | Whole part | Ethanol  | Chrylsandicin (15)                                     | Alamar blue assay/in vitro                                   | The compound demonstrated modest antiproliferative action with IC50 values of 4 μM | Dai et al. 2014      |
| Anti-Leukotriene | *Kniphofia foliosa* | Root       | Dichloromethane | Knipholone (27)                                         | COX-1, and COX-2 tests/in vitro                             | With an IC50 value of 4.2 μM, knipholone demonstrated the ability to be a selective inhibitor of leukotriene biosynthesis when compared to the positive control, zileuton, which had an IC50 value of 10.4 μM | Wube et al. 2006     |
| Anti-HIV-1     | *Kniphofia foliosa* | Root       | Ethyl acetate | Knipholone anthrone (25)                               | HIV-1c infected peripheral blood mononuclear cells/in vitro  | At concentrations of 0.5, 5, 15, and 50 μg/mL, knipholone anthrone demonstrated considerable growth inhibition of more than 60 % | Felicke et al. 2019  |
| Cytotoxic      | *Kniphofia foliosa* | Root       | Methanol | Knipholone anthrone (25) and knipholone (27)            | Annexin V-FITC apoptosis assay/in vitro                      | Both compounds had anticancer action, with knipholone anthrone generating a quick onset of cytotoxicity with IC50 values ranging from 0.5 to 3.3 μg/mL | Habtemariam 2010     |
| Cytotoxic      | *Kniphofia foliosa* | Rhizome    | Methanol | Knipholone (27) and diarellin (36)                     | Wistar rats/in vivo                                           | The LD50 of compounds were found to be greater than 2000 mg/kg          | Aleybachew et al. 2021|
| Cytotoxic      | *Kniphofia reflexa* | Rhizome    | Methanol | Microcarpin (11), Knipholifarexine (37), Knipholone (27), Chrysophanol (5), 2-acetyl-1-hydroxy-8-methoxy-3-methyl naphthalene (34) and knipholifarindane (39) | MTT assay/in vitro                                           | With a CC50 of 4.43 μg/mL, 2-acetyl-1-hydroxy-8-methoxy-3-methyl naphthalene (34) was highly cytotoxic. Compounds knipholifarindane (39) and microcarpin (11) were moderately cytotoxic as well, with CC50 values of 16.35 μg/mL and 11.24 μg/mL, respectively, other compounds knipholifarexine, knipholone and chrysophanol (37, 27 and 5) were non-cytotoxic | Sema et al. 2018     |
| Cytotoxic      | *Kniphofia foliosa* | Root       | Dichloromethane | 10-(chrysophanol-7-yl)-10-[(E)-hydroxychrysophanol-9-anthrone (22) | Alamar blue assay/in vitro                                   | The compound showed very low toxicity with an ED50 of 104 μg/mL as compared to the reference drug podophyllotoxin, which had an ED50 value of 0.0123 μg/mL | Wube et al. 2005     |
11.24 µg/mL, respectively. The crude extract as well as the other compounds knipholiarexine, knipholone and chrysophanol (37, 27 and 5) were non-cytotoxic (Sema et al. 2018). Using the Alamar blue assay, the dichloromethane extract of *Kniphofia foliosa* roots was tested for cytotoxic action on KB cells against podophyllotoxin as the reference drug. The crude extract had an ED_{50} value of 35.2 µg/mL, which indicates low cytotoxic activity when compared to the reference drug, which had an ED_{50} value of 0.0123 µg/mL (Wube et al. 2005). In addition, the compound 10-(chrysophanol-7'-yl)-10-(z)-hydroxycr jysopanol-9-anthrone (22) which was isolated from the roots and tested for cytotoxicity, has a very low toxicity with an ED_{50} of 104 µg/mL (Wube et al. 2005).

**Anti-HIV-1 activity**
The anti-HIV-1 capability of knipholone (27) and knipholone anthrone (25) derived from *Kniphofia foliosa* was tested in HIV-1c infected peripheral blood mononuclear cells. At concentrations of 0.5, 5, 15, and 50 µg/mL, knipholone anthrone demonstrated considerable growth inhibition (HIV-1c replication suppression) of more than 60%, according to the study (Feilcke et al. 2019). Also, study showed that knipholone anthrone (25), induces both HIV-RNA and HIV-protein in primary cells from HIV infected donors (Richard et al. 2020).

**Anti-Leukotriene activity**
Activated human neutrophil granulocytes, as well as 12-LO, COX-1, and COX-2 tests, were used to study the leukotriene inhibitory action of knipholone (27) obtained from the root dichloromethane extract of *Kniphofia foliosa*. With an IC_{50} value of 4.2 µM, knipholone demonstrated the ability to be a selective inhibitor of leukotriene biosynthesis when compared to the positive control, zileuton, which had an IC_{50} value of 10.4 µM (Wube et al. 2006) (Table 3).

**Future perspective**
Natural-source drugs are gaining popularity because they are less expensive, have fewer or no side effects, and are better tolerated by patients. Plants provide an alternate source of active secondary metabolites for drug development (Beshah et al. 2020). *Kniphofia* species have multiple ranges of ethnmedicine uses in the treatment of different diseases. The pharmacological activities and toxicological consequences of the extracts from these plants have also been reported. Few members of this genus, however, have been studied. Secondary metabolites generated from plants have limited biological activity. As a result, a revival of interest in the *Kniphofia* species phytochemistry and pharmacology could lead to the development of lead drugs. In this regard, a random clinical trial as well as the pharmacokinetics of these plants could provide the possibility of developing effective curative agents. This requires isolating bioactive metabolites and pharmacological activities from plant extracts, as well as conducting clinical trials, pharmacokinetics, and toxicological analyses.

**Conclusions**
In this review, we outline what we know about botany, ethnomedical uses, reproduction, conservation, phytochemistry, and pharmacological activity of *Kniphofia* species. *Kniphofia* species were traditionally used to treat gonorrhoea, malaria, hepatitis B, blood purifier, wounds, cervical and breast cancer, and many other ailments, according to the findings. In addition, the *Kniphofia* species has been utilised as an ornamental plant, pollen and nectar sources for honeybees, and a pollution indicator. It is used in horticulture and is grown in both home and botanical gardens. It has been noticed that all studied plants belong to the same genus, they have a number of common pharmacological actions, such as antibacterial, antimalarial, and cytotoxic activity. The major compounds isolated from the majority of *Kniphofia* species are monomeric anthraquinone, dimeric anthraquinone, and phenyl anthraquinones and anthrones. The genus afforded exemplary drug leads such as knipholone (27) and knipholone anthrone (25) with anti-HIV-1, anti-leukotriene, anti-inflammatory, antimalarial and cytotoxicity activity. Nevertheless, given the presence of the genus in the red data list of South Africa and its broad range of pharmacological activities, greater attention should be dedicated to it. Further investigation should be conducted to evaluate promising crude extracts as well as compounds in search for new drug candidates.

**Author contributions**
Gashaw Nigussie developed the concept, conducted literature search while Metasebia Tegegn, Desalegn Abeje and Haregu Melak participated in manuscript writing, review, and correction.

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