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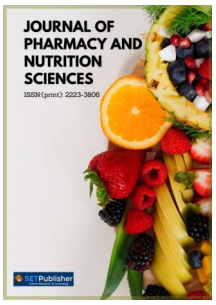

Kniphofia foliosa Hochst, (Asphodelaceae): Medicinal Uses, Phytochemistry and Pharmacological Properties

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Abstract:

This review gives the first comprehensive appraisal of *Kniphofia foliosa* Hochst, from the plant family Asphodelaceae: its botany, ethnomedicinal (with particular emphasis on the African communities), phytochemistry, and pharmacological potential. Particular emphasis is given to the biological and chemical properties. Peer review and literature search were done by conducting a logical and inclusive review. Indigenous cultures have used the plant among different ethnic groups in tropical Africa for medicinal and other purposes. The chemical compounds that have been isolated from *K. foliosa* include monomeric anthraquinones such as chrysophanol, islandicin, laccaic acid, aloe-emodin, and aloe-emodin acetate, which contain antileukaemic properties; dimeric anthraquinones such as asphodelin, knipholone, and chryslandicin; phenyl anthraquinones and anthrones, including knipholone anthrone, isoknipholone anthrone, knipholone, phenylanthrone knipholone anthrone and anthraquinone isoknipholone; oxanthrones such as isofoliosone and foliosone; and rare dimeric phenylanthraqunones joziknipholones A and B. The pharmacological studies on *K. foliosa* exhibited antimalarial, antioxidant, antibacterial, anti-HIV-1, and anti-leukotriene activities. From the above, it can be deduced that *K. foliosa* contains chemical constituents of pharmacological importance, contributing significantly to the development of new medicines.

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INTRODUCTION

The genus Kniphofia Moench is a member of the subfamily Asphodeloidea. The family Asphodelaceae and was named in honor of the German botanist Johann Hieronymus Kniphof (1704-63) [1]. The local name of the plant is “Lella” (in affaanoromiffaa). The genus is common among horticulturists and is almost entirely confined to the continent of Africa, with only three species, namely *Kniphofia pallidiflora*, *Kniphofia ankaratrensis,* and *Kniphofia sumarae* occurring outside Africa [2], with the first two being indigenous to Madagascar and the later to Yemen [3]. The genus includes the plants called Redhot Pokers due to the vibrant inflorescences evident in its various species. The genus comprises 70 species, which are mainly found in Africa, and a large diversity of the species is found in South Africa [3-4]. Approximately fifteen species of Kniphofia have been identified in Eastern Africa, seven of which are found in Ethiopia, including *Kniphofia foliosa* Hochst, which is the focus of this study [4-7]. In Africa, most people rely more on indigenous medicine as a primary source of health care because it is culturally entrenched, accessible, and affordable. This study, therefore, documents the medicinal, phytochemistry, and pharmacological properties of *K. foliosa* and its use by local communities to manage ailments across Africa and the world at large. Documentation of such plants creates a database of information that stores and preserve indigenous knowledge about the medicinal and food uses of plants for future generations. In addition, such databases store important information on the identities of plant species, which can be further developed through pharmacological and phytochemical research.

BOTANICAL DESCRIPTIONS

Kniphofia foliosa Hochst (Asphodelaceae) is a robust, perennial herb, which is stemless with thick erect rhizomes forming dense clumps of growth up to 175 cm tall [4, 8]. The herb produces a basal rosette of sword-shaped leaves, which can grow to a height of 100 cm and a width of 4-7 cm [8]. The simple, linear to lanceolate leaves usually kneel with finely toothed margins that narrow gradually to the apex [4-5]. *K. foliosa* has elongated inflorescences with a dense raceme on a simple erect peduncle [4-5]. The hermaphrodite small tubular flowers have tantalizing colors, and the apex is usually more conspicuous as the inflorescence can have a bicolored appearance [4, 5, 9]. The flowers bloom from May to October and from December to January [4]. The fruits are ovoid capsule-shaped, brown to black in color, and house few seeds that have fleshy endosperm, usually slightly flattened; acutely three angled or winged are grey-black in color [4-6].

K. foliosa species grow on roadsides, in mountainous grasslands, in moist and swampy grounds, alongside tributaries, in areas with sparse vegetation and is commonly found in central and northern Ethiopia and Eritrea [3, 7, 11]. It favours altitudes between 2050 and 4000 m particularly in the Bale Mountains in Ethiopia [9].

Figure 1: *Kniphofia foliosa*: Source: africanplants.senckenberg [10].

METHODOLOGY

A comprehensive literature search on *K. foliosa* was generated from peer-reviewed publications and grey literature from databases such as Elsevier, JStor, Scopus, Science Direct, Cab Direct and BioMed Central (BMC), and PubMed.

Ethnomedicinal uses of *K. foliosa*

Traditional herbal remedies are used as alternative medicine in the treatment and management of various medical conditions. The genus Kniphofia has only a few species that are used in traditional medicine, and *K. foliosa* is one of them. *K. foliosa* has been reportedly used to treat wounds and abdominal cramps [12]. Traditionally, it is used to treat menstrual pains, infertility, malaria, chest complaint, gonorrhea, hepatitis B, cervical and breast cancer/tumor [13-15]. It is edible and also used as an ornamental in Europe, as well as eradicating endoparasites in cattle [7].

Phytochemistry of *K. foliosa*

The chemical constituents identified in different parts of *K. foliosa* are shown in Table **1**, and their structures are shown in Figure **2**. *K. foliosa* is known to elaborate monomeric [16], dimeric anthraquinones [12], and phenyl-anthraquinones [3, 17], some of which have exhibited diverse biological activities [3, 12, 18, 19].

Pharmacological Properties of *K. foliosa*

Antimalarial Activity

Extract from the dichloromethane roots of *K. foliosa* was evaluated for its antimalarial properties against *P. falciparum* [12]. With an IC_{50} value of 3.8 µg/mL, the

Table 1: Chemical Constituents Present in *K. foliosa*

Plant parts	Extract	Chemical constituents	Reference
Rhizomes	Acetone	Knipholone, islandicin, chrysophanol and bisanthraquinone pigments.	[20]
	Dichloromethane/ methanol (1:1)	Chrysophanol, islandicin, laccaic acid, chryslandicin, knipholone, jozikniphoIone A, jozikniphoIone B, Jozi-jozikniphoIone anthrone and 3,4-dihydroxybenzoic acid.	[21]
	Methanol	10-acetonylknipholone cyclooxanthrone, chryslandicin 10-methyl ether, jozikniphoIones A and B, chrysophanol, islandicin, laccaic acid D, aloe-emodin acetate and deoxyerythrolaccin. Others are anthraquinone dimers asphodelin and chryslandicin, knipholone, knipholone anthrone and a minor phenolic 3,4-dihydroxybenzoic acid.	[22]
Leaves	Acetone	Knipholone, chrysophanol, aloe-emodin, islandicin, and aloe-emodin acetate (which contains antileukaemic properties).	[16, 20]
Flowers	Acetone	Aloe-emodin, aloe-emodin acetate, chrysophanol and knipholone.	[20]
Stem	Ethyl acetate	Isoknipholone anthrone, isoknipholone, isofoliosone, foliosone, aloesaponol III, 4,6-dihydroxy-2-methoxyacetophenone and aloesaponol III-8-methyl ether.	[17]
	Acetone	Knipholone anthrone.	[23]
Fruit	Acetone	Aloe-emodin, aloe-emodin acetate and knipholone.	[20]
Roots	Acetone	Chrysophanol, knipholone, in which an anthraquinone moiety is attached to an acetylphloroglucinol methyl ether unit.	[24]
	Ethyl acetate	Knipholone cyclooxanthrone, dimeric anthraquinone, 10-methoxy-10,7'-(chrysophanol anthrone)-chrysophanol, 10-hydroxy-10,7'-(chrysophanol anthrone)-chrysophanol) and a naphthalene glycoside, dianellin.	[25]
	Chloroform/methanol (1:1)	Chrysophanol, asphodeline, 10-Hydroxy-10,7'-(chrysophanol anthrone) chrysophanol and 3,5,8-trihydroxy-2-methylnaphthalene-1,4-dione.	[13]
	Dichloromethane	Knipholone, 2-acetyl-1-hydroxy-8-methoxy-3-methylnaphthalene,10-(chrysophanol-7′-yl)-10-(ξ)-hydroxychrysophanol-9-anthrone, chryslandicin, and chrysophanol.	[12]
Whole plant	Ethanol	Kniphofiones A and B, two strongly active anthraquinones (10-(chrysophanol-7′-yl)-10-hydroxychrysophanol-9-anthrone and chryslandicin) and five other known anthraquinones (chrysophanol, aloe-emodin, knipholone, asphodeline and microcarpin).	[26]

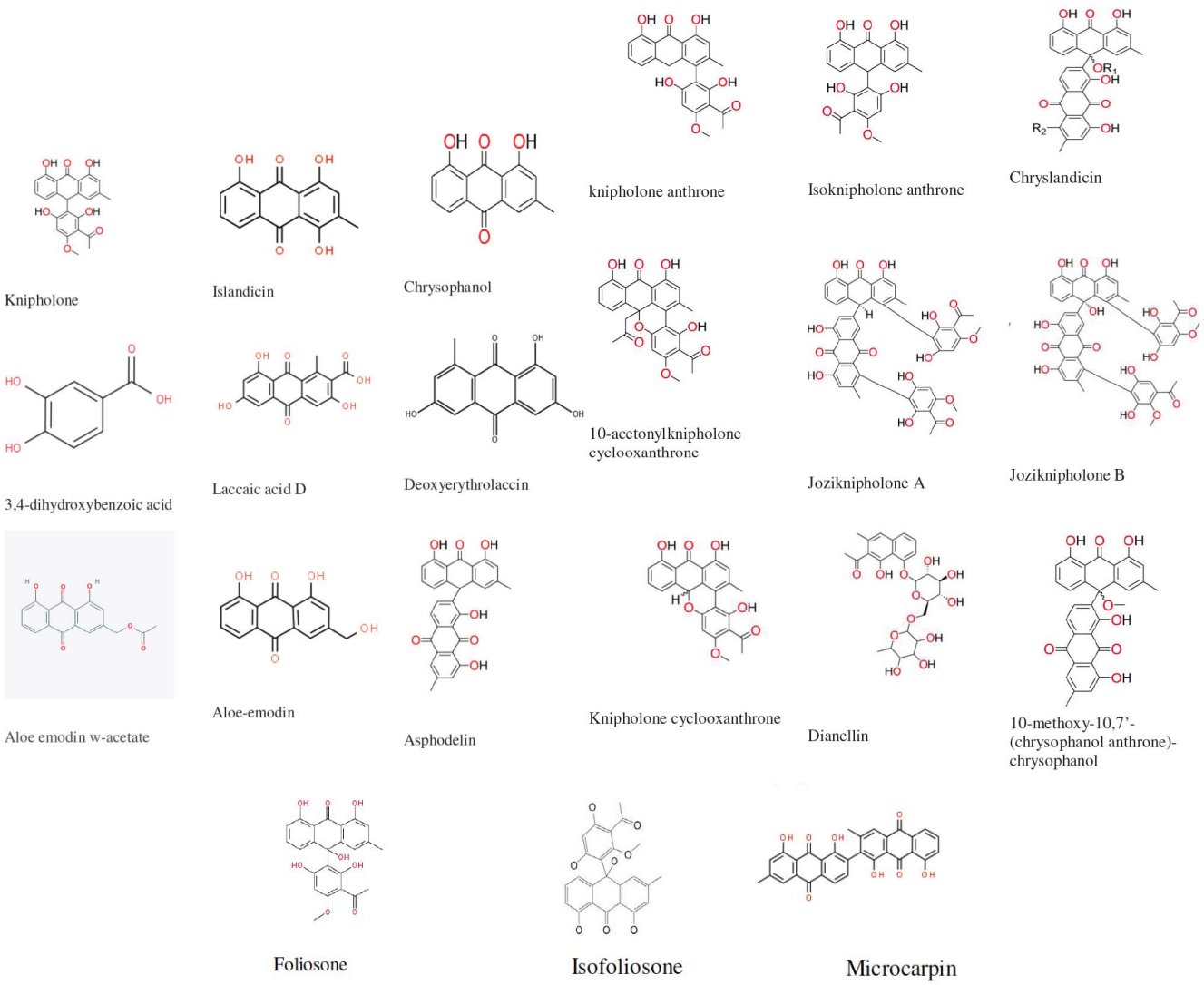

Figure 2: Chemical structure of compounds isolated from *K. foliosa*.

extract showed a strong antimalarial activity; however, low cytotoxicity was observed against KB cells with an IC_{50} value of 35.2 µg/mL. Furthermore, the study also identified five compounds and investigated their antimalarial potential against the 3D7 strain of *P. falciparum*. All the test compounds showed good antiplasmodial activity with 10-(chrysophanol-7′-yl)-10-(ξ)-hydroxy chrysophanol-9-anthrone exhibiting a strong antimalarial activity at the IC_{50} value of 0.260 µg/mL and 0.537 µg/mL for chryslandicin. The author deduced that compounds with anthraquinone and anthrone dimer structure could be considered promising antimalarial agents [12].

In addition, strong antimalarial activity with IC_{50} values between 3-5 µg/mL was demonstrated by the crude rhizome extract of *K. foliosa* against chloroquine-sensitive (D6) and chloroquine-resistant (W2) *P. falciparum* strains [21]. Some compounds isolated from rhizomes of *K. foliosa* namely; phenylanthraquinones, anthraquinone-anthrone dimers, dimeric phenylanthraquinones, and joziknipholone A exhibited strong antimalarial activities against *P. falciparum* strain W2 and D6. Also, 10-acetonylknipholone cyclooxanthrone showed significant activity against the W2 strain of *P. falciparum* with an IC_{50} value of 3.1 mg/mL. Knipholone anthrone has also exhibited marginal antimalarial activity in an *in vivo* assay [22].

Feilcke *et al*. [27] equally revealed that knipholone and knipholone anthrone isolated from *K. foliosa* possesses strong antimalarial potential with IC_{50} values of 1.9 and 0.7 µM, respectively, against *P. falciparum*.

The knipholone and knipholone anthrone, constituents of the roots and stem of *K. foliosa*, respectively, showed considerable antiplasmodial activity against *P. falciparum* K1 and chloroquine-sensitive NF 54 strains.

In addition, the chemical compounds have shown a low level of cytotoxicity when tested against rat skeletal muscle myoblast (L-6) cells and mouse peritoneal macrophage [28].

Demissew and Nordan, [7] investigated the *in vitro* antiplasmodial activity of three chemical constituents isolated from *K. foliosa*. All the tested compounds showed significant antiplasmodial activities with 10-methoxy-10, 7'-(chrysophanol anthrone)-chrysophanol depicting the best activity with an IC_{50} value of 1.17 mg/mL against chloroquine-resistant strain of *P. falciparum*.

The study of Gebru [21] showed that the crude extract of *K. foliosa* and the isolated compounds exhibited good antimalarial potential. Phenylanthraquinones and anthraquinone dimers found in the plant could lead to the development of antimalarial drugs.

K. ensifolia extract showed promising antimalarial potential against *P. falciparum* and antiproliferative activity against the A2780 human ovarian cancer cell line [26].

Cytotoxicity

The cytotoxic activities of five compounds were evaluated against the KB cell line by Wube *et al.* [12]. The result showed that knipholone exhibited significant cytotoxicity with an IC_{50} value of 7.3 µg/mL, whereas 10-(chrysophanol-7′-yl)-10-(ξ)-hydroxyhrysopanol-9-anthrone depicted a low toxic effect with IC_{50} values of 104 µg/mL and 90 µg/mL for chryslandicin.

The cytotoxic activity of knipholone and knipholone anthrone isolated from *K. foliosa* against four human cell lines was studied by Feilcke *et al*. [27]. The results showed that knipholone exhibited significant cytotoxicity at 50 µM concentration against three cell lines, namely Jurkat, HEK293, and SH-SY5Y, with growth inhibition ranging from 62% to 95%. On the other hand, Knipholone anthrone demonstrated weak to high activity with 26, 48, and 70% cell growth inhibition, respectively.

The comparative cytotoxicity of knipholone and knipholone anthrone isolated from *K. foliosa* in leukaemic and melanocyte cancer cell lines was investigated by Habtemariam [29]. The study revealed that both compounds possess anticancer activity with knipholone anthrone inducing a rapid onset of cytotoxicity with IC_{50} values between 0.5-3.3 µg/mL. When comparing the cytotoxicity of both compounds, knipholone was 70–480-times less toxic to cancer cells [29].

Antioxidant Activity

The knipholone anthrone isolated from *K. foliosa* was evaluated for its antioxidant activity. The compound showed a potent and concentration-dependent free radical scavenging effect against 2,2-diphenyl-1-picrylhydrazyl radicals with an IC_{50} value of 22 µM when compared with (-) epicatechin at the IC_{50} value of 8.7 µM. It has also demonstrated a stronger scavenging effect on superoxide anions and substantially prevents hydroxyl radicals from degrading deoxyribose. It forms a complex with ferrous ion, hence, showed a concentration-dependent reducing power and protecting isolated DNA from Fenton reaction-generated hydroxyl radical damage [29]. Further studies found that knipholone, isolated from *K. foliosa* demonstrated a poor dose-independent capacity to scavenge free radicals and prevent lipid peroxidation. In addition, the iron-chelating test carried out on knipholone revealed that it is not a metal chelator. Thus, the author suggested that the inhibition of 5-LO by knipholone was possibly due to its ability to suppress the 5-lipoxygenase activating protein (FLAP) or as a competitive enzyme inhibitor. The cytotoxicity assay has shown that knipholone has a low toxic effect on mammalian cells [18, 30].

Anti-HIV-1 Activity

The knipholone and knipholone anthrone isolated from *K. foliosa* were evaluated for their anti-HIV-1 potential in HIV-1c infected peripheral blood mononuclear cells. The study depicted that knipholone anthrone significantly showed growth inhibition (HIV-1c replication inhibition) higher than 60% at the concentrations of 0.5, 5, 15, and 50 µg/mL [27].

Antibacterial Activity

Crude extracts and chemical compounds isolated from *K. foliosa* exhibited antibacterial activity by inhibiting the growth of *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Enterococcus faecalis*. The dimeric anthraquinones (Asphodeline and 10-Hydroxy-10,7' (chrysophanol anthrone) chrysophanol) exhibited stronger activities, with Asphodeline having the highest zone of inhibition against *E. faecalis*. The observed antibacterial activities are an indication that *K. foliosa* may be a possible source of antibacterial drugs [13].

Anti-Leukotriene Activity

The leukotriene inhibitory activity of knipholone isolated from the roots of *K. foliosa* was investigated using activated human neutrophil granulocytes, alongside a 12-LO, COX-1, and COX-2 assays [18]. Anthraquinone knipholone depicted the ability to be a selective inhibitor of leukotriene biosynthesis with an IC_{50} value of 4.2 µM compared to the positive control: zileuton, IC_{50}=10.4 µM; other compounds isolated, 2-Acetyl-1-hydroxy-8-methoxy-3-methylnaphtalene, chrysophanol, and chryslandicin were not active [18].

CONCLUSION

K. foliosa is a valuable plant that possesses some anti-leukotriene, antioxidant, antimalarial, and antimicrobial properties. The medicinal and pharmacological importance of *K. foliosa* plant may be as a result of its chemical constituents such as dimeric anthraquinones, phenyl anthraquinones and anthrones, oxanthrones, and rare dimeric phenylanthraquinones joziknipholones A and B in the plant; hence this justifies its extensive use as traditional medicine for animals and human beings in developing countries. The herb plays a vital role in the primary healthcare of local communities in most parts of Africa as they are used traditionally to treat various human diseases and illnesses. The documentation of this plant would create a database of information that could help to preserve the indigenous knowledge and medicinal importance of the plant as baseline data for future research in pharmacological studies. The cytotoxic activity of the compounds isolated from *K. foliosa* has shown significant cytotoxic effect against the KB, Jurkat, HEK293, SH-SY5Y cell lines, leukemic and melanocyte cancer cell lines. However, there is a need for supplementary *in vivo* studies to assess *K. foliosa* toxicological properties and elucidate the mechanisms of action of the active compounds isolated from the plant.

CONFLICT OF INTEREST

The authors do not declare any conflict of interest.

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