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Review of phytochemistry, biological activities and therapeutic potential of *Cleistochlamys kirkii*

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ABSTRACT

Cleistochlamys kirkii (Benth.) Oliv is a shrub or small tree widely used as a traditional medicine in the east and central Africa. *Cleistochlamys kirkii* is indigenous to Malawi, Mozambique, Tanzania, Zambia and Zimbabwe. This study is aimed at evaluating the phytochemistry, biological activities and therapeutic potential of *C. kirkii*. Results of the current study are based on data derived from several online databases such as Scopus, Google Scholar, PubMed and Science Direct, and pre-electronic sources such as scientific publications, books, dissertations, book chapters and journal articles. This study revealed that the leaf and root infusion, maceration and decoction of *C. kirkii* are mainly used as traditional medicines for haemorrhoid wounds, rheumatism and tuberculosis. Phytochemical compounds identified from the species include α,β-unsaturated lactone, acetogenin, benzyl benzoate derivatives, c-benzylated flavanone, heptanolide, an indole alkaloid, phenolics, polyoxygenated cyclohexene and derivatives, sesquiterpene and tetracyclic triterpenes. *In vitro* studies have confirmed the biological activities of *C. kirkii* crude extracts and compounds isolated from the species which include antibacterial, antifungal, antiplasmodial and cytotoxicity. Documentation of the medicinal uses, phytochemistry and pharmacological properties of *C. kirkii* is essential as this information provides baseline data required for future research and development of health-promoting and pharmaceutical products. *Cleistochlamys kirkii* should be subjected to detailed ethnopharmacological and toxicological evaluations aimed at correlating its medicinal uses with its phytochemistry and pharmacological properties.

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INTRODUCTION

Cleistochlamys kirkii (Benth.) Oliv is a shrub or small tree belonging to the Annonaceae, commonly known as the custard apple family. Annonaceae is one of the most diverse and primitive plant families consisting of about 108 genera and 2400 species worldwide (Chatrou *et al.*, 2012; Attiq *et al.*, 2017) argued that members of the Annonaceae family are used throughout the world as sources of traditional medicines used against arthritis, gastrointestinal problems, hypertension, inflammation, respiratory infections, rheumatism, skin infections, snake bites, sores and wounds. The extracts and phytochemical compounds isolated from Annonaceae species are characterized by analgesic, anthelmintic, antidia-

Table 1: Medicinal uses of Cleistochlamys kirkii

Medicinal uses	Plant part used	Reference
Cough	Leaf and root decoction taken orally	(Bruschi *et al.*, 2011)
General weakness	Leaf and root decoction taken orally	(Bruschi *et al.*, 2011)
Haemorrhoid wounds	Leaf decoction applied topically	(Nyandoro *et al.*, 2017; Kincses *et al.*, 2018)
Hernia	Leaf and root decoction taken orally	(Bruschi *et al.*, 2014; Monjane, 2017)
Muscular pains	Leaf and root maceration taken orally	(Bruschi *et al.*, 2011; Monjane, 2017)
Purgative	Leaf and root decoction taken orally	(Bruschi *et al.*, 2011)
Rheumatism	Leaf decoction applied topically	(Verzar and Petri, 1987; Nyandoro *et al.*, 2019)
Stomach ache	Leaf and root maceration taken orally	(Bruschi *et al.*, 2011; Monjane, 2017)
Tuberculosis	Leaf infusion and/or decoction taken orally	(Verzar and Petri, 1987; Samwel *et al.*, 2007)
Venereal diseases	Leaf and root decoction taken orally	(Bruschi *et al.*, 2011; Monjane, 2017)

betic, anti-inflammatory, antimicrobial, antioxidant, antipyretic, antiulcer, antinociceptive, antimalarial, antiprotozoal, antileishmanial, cytotoxicity and hepatoprotective properties (Bhardwaj *et al.*, 2019; Nugraha *et al.*, 2019). The genus *Cleistochlamys* Oliver is a monotypic genus confined to east and central tropical Africa (Verdcourt and Annonaceae, 1971; Van Wyk and Van Wyk, 2013). The genus name "*Cleistochlamys*" is a contraction of two Greek words "*kleistos*" or "*klistos*" meaning "closed" and "*chlamys*" or "*chlamydos*" meaning "cloak" (Quattrocchi, 1999). The specific name "*kirkii*" honours Sir John Kirk (1832 – 1922), a Scottish physician, naturalist and companion of the explorer David Livingstone, a British administrator in Zanzibar who recorded and collected the tree species in Sena district of Mozambique (Robson and Annonaceae, 1960).

Cleistochlamys kirkii (Figure 1) is a much-branched shrub or small straggling tree, seldom taller than 10 metres (Palgrave and Keith, 2002). The bark of *C. kirkii* is smooth, tough, pale grey to light brown in colour and flaking. The leaves are simple, alternate, narrowly oblong to obovate and thinly textured (Burrows *et al.*, 2018). The leaves are dark to bright shiny green above, blue-green and slightly paler below, apex rounded, often notched with a broadly tapering to the rounded base with entire and waxy margins (Strugnell, 2006). The flowers are axillary, sessile, with a heavy sweet scent, creamy-white with reddish-brown bracts below, appearing when trees are leafless. The fruit is a cluster of fleshy oval berries which are purple-black when ripe (Figure 1). *Cleistochlamys kirkii* has been recorded in alluvium soils in hot and dry bushveld, thickets and river valleys in Malawi, Mozambique, Tanzania, Zambia and Zimbabwe up to an altitude of 900 m above sea level (Drummond, 1975; Silva *et al.*, 2004). The fruit of *C. kirkii* is eaten fresh or left to stand in water to make a pleasant fruit drink (Tredgold, 1986; Chikuni, 1996). *Cleistochlamys kirkii* is an important medicinal plant species in southern Africa (Verzar and Petri, 1987; Bruschi *et al.*, 2011). Thus, this review aims to provide an integrated and detailed appraisal of the existing knowledge on the phytochemistry, biological activities and therapeutic potential of *C. kirkii*.

Medicinal uses of *Cleistochlamys kirkii*

The leaf and root infusion, maceration and decoction of *C. kirkii* are mainly used as traditional medicines for haemorrhoid wounds, rheumatism and tuberculosis (Samwel *et al.*, 2007; Pereira *et al.*, 2016) (Table 1).

Other medicinal applications of *C. kirkii* supported by at least two literature records include the use of leaf and root decoction against hernia, muscular pains, stomach ache and venereal diseases (Bruschi *et al.*, 2011; Monjane, 2017).

Table 2: Phytochemical composition of Cleistochlamys kirkii

Phytochemical compound	Plant part	Reference
(-)-1,6-desoxy-β-senepoxide	Fruits, leaves, roots and stems	(Samwel *et al.*, 2007)
(1S,4S,5S,6R)-5-[(benzyloxy)-methyl]-5,6-dihydroxycyclohex-2-ene-1,4-diyl diacetate	Leaves	(Nyandoro *et al.*, 2017)
2-Methoxybenzylbenzoate	Root bark	(Nyandoro *et al.*, 2019)
3-hydroxybenzaldehyde	Leaves	(Nyandoro *et al.*, 2017)
7-Methoxyisochamanetin	Root bark	(Nyandoro *et al.*, 2019)
Acetylmelodorinol	Bark, fruits, leaves, roots and stems	(Samwel *et al.*, 2007; Pereira *et al.*, 2016)
(E)-Acetylmelodorinol	Root bark	(Nyandoro *et al.*, 2019)
Benzophenone	Root bark	(Pereira *et al.*, 2016)
Benzoylmelodorinol	Fruits, leaves, roots and stems	(Samwel *et al.*, 2007)
Benzylbenzoate	Root bark	(Nyandoro *et al.*, 2019)
Butenolide cleistanolate	Leaves	(Nyandoro *et al.*, 2017)
Chamanetin	Root bark	(Pereira *et al.*, 2016; Nyandoro *et al.*, 2019)
cis-solamin	Root bark	(Pereira *et al.*, 2016)
Cleistonol	Root bark	(Nyandoro *et al.*, 2019)
Cleistenonal	Leaves	(Nyandoro *et al.*, 2017)
Cleistenolide	Bark, fruits, leaves, roots and stems	(Samwel *et al.*, 2007; Pereira *et al.*, 2016)
Cleistodienol	Fruits, leaves, roots and stems	(Samwel *et al.*, 2007)
Cleistodiendiol	Leaves	(Nyandoro *et al.*, 2017)
Cleistenediols A - F	Leaves	(Nyandoro *et al.*, 2017)
Cleistenechlorohydrins A - B	Leaves	(Nyandoro *et al.*, 2017)
Cleistophenolide	Leaves	(Nyandoro *et al.*, 2017)
Cleistodienol A - B	Leaves	(Nyandoro *et al.*, 2017)
Dichamanetin	Root bark	(Pereira *et al.*, 2016; Nyandoro *et al.*, 2019)
Echinulin	Root bark	(Pereira *et al.*, 2016)
ent-subglain C	Leaves	(Nyandoro *et al.*, 2017)
Guaiol	Root bark	(Nyandoro *et al.*, 2019)
Iso-acetyl melodorinol	Fruits, leaves roots and stems	(Samwel *et al.*, 2007)
Isochamanetin	Root bark	(Pereira *et al.*, 2016; Nyandoro *et al.*, 2019)
Melodorinol	Fruits, leaves roots and stems	(Samwel *et al.*, 2007)
Pinocembrin	Bark, fruits, leaves, roots and stems	(Samwel *et al.*, 2007; Nyandoro *et al.*, 2019)
Pinostrobin	Root bark	(Nyandoro *et al.*, 2019)
Polycarpol	Bark, fruits, leaves, roots and stems	(Pereira *et al.*, 2016; Nyandoro *et al.*, 2019)
Sootepenol B	Leaves	(Nyandoro *et al.*, 2017)
Tetramethylscutellarein	Leaves	(Nyandoro *et al.*, 2017)
(Z)-(+)-5-(2,3-dihydroxy-propylidene)-5H-furan-2-one	Fruits, leaves, roots and stems	(Samwel *et al.*, 2007)
Z-acetylmelodorinol	Leaves	(Nyandoro *et al.*, 2017)
Z-melodorinol	Leaves	(Nyandoro *et al.*, 2017)

Phytochemical composition and pharmacological properties of *Cleistochlamys kirkii*

Phytochemical compounds such as α,β-unsaturated lactone, acetogenin, benzyl benzoate derivatives, c-benzylated flavanone, heptanolide, an indole alkaloid, phenolics, polyoxygenated cyclohexene and derivatives, sesquiterpene and tetracyclic triterpenes have been identified from the bark, fruits, leaves, roots and stems of *C. kirkii* (Table 2). The following pharmacological activities have been documented from the crude extracts and phytochemical compounds isolated from *C. kirkii*: antibacterial, antifungal, antiplasmodial and cytotoxicity.

Antibacterial activities

Odebode *et al.* (2004a) evaluated the antibacterial activities of crude dichloromethane extract of *C. kirkii* stem bark and the compounds cleistenolide and pinocembrin isolated from the stem bark of the species against *Pseudomonas phaseolicola* and *Staphyloccocus aureus* using the disc method. The crude extract exhibited activities at all concentrations, while the compounds showed moderate to weak activities at concentrations above 200.0 ppm (Odebode *et al.*, 2004b). Similarly, Odebode *et al.* (2004a) evaluated the antibacterial activities of crude dichloromethane extract of *C. kirkii* stem bark and the compounds cleistenolide and pinocembrin isolated from the stem bark of the species against *Pseudomonas syringae* PV. *phaseolicola* using the disc method with streptomycin as a positive control. The crude extract and the compounds exhibited activities against the tested pathogen with a diameter of inhibition zones ranging from 5.3 mm to 15.0 mm in comparison to the width of inhibition zone of 17.5 mm exhibited by the positive control Odebode *et al.* (2004b); Samwel *et al.* (2007) evaluated the antibacterial activities of the compounds cleistenolide, cleistodienol, (Z)-(+)-5-(2,3-dihydroxy-propylidene)-5H-furan-2-one, melodorinol, acetyl melodorinol, iso-acetyl melodorinol and benzoyl melodorinol isolated from the fruits, leaves, roots and stems of *C. kirkii* against *Staphylococcus aureus* and *Bacillus anthracis* using the hole plate method with chloramphenicol (10.0 μg/mL) as a positive control. The compounds exhibited activities Samwel *et al.* (2007); Pereira *et al.* (2014, 2015) evaluated the antibacterial activities of n-hexane, dichloromethane, ethyl acetate and methanol extracts and fractions of *C. kirkii* root bark and the compounds chamanetin, isochamanetin, dichamanetin, echinulin, cis-solamin, cleistenolide, acetylmelodorinol, polycarpol and benzophenone isolated from the species against *Salmonella typhymurium, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterococcus faecalis, Bacillus subtilis* and *Staphylococcus aureus* using broth microdilution method with amoxicillin, oxacillin and vancomycin as positive controls. The authors also evaluated the type of interaction of the compounds with the β-lactam antibiotics amoxicillin and oxacillin using a chemosensitization assay performed on the checkerboard method against *Staphylococcus aureus* resistant and susceptible strains. The best results were obtained for apolar and polar extracts with minimum inhibitory concentration (MIC) values of 7.5 μg/mL to 62.μg/mL against Gram-positive strains. The compounds chamanetin, isochamanetin, dichamanetin and cleistenolide exhibited activities against the tested pathogens. The compound polycarpol, in combination with antibiotics, exhibited substantial synergistic activities Pereira *et al.* (2014, 2016); Kincses *et al.* (2018) evaluated the antibacterial activities of the compounds polycarpol, chamanetin, isochamanetin, dichamanetin and acetylmelodorinol isolated from the root bark of *C. kirkii* against *Staphylococcus aureus, Escherichia coli, Chromobacterium violaceum* and *Enterobacter cloaceae* using the microdilution method. The authors also assessed the combined effects of antibiotics ciprofloxacin and tetracycline and the compounds chamanetin and dichamanetin by using the checkerboard microdilution method in *Staphylococcus aureus* strains. The compounds chamanetin and dichamanetin exhibited activities against *Staphylococcus aureus* with MIC values ranging from 0.8 μM to 25 μM. The combined effect of the antibiotics and the compounds chamanetin and dichamanetin on *Staphylococcus aureus* resulted in synergism (Kincses *et al.*, 2018) .

Antifungal activities

Odebode *et al.* (2004a) evaluated the antifungal activities of crude dichloromethane extract of *C. kirkii* stem bark and the compounds cleistenolide and pinocembrin isolated from the stem bark of the species against *Fusarium solani, Botryodiploida theobromae, Aspergillus niger* and *Aspergillus flavus* using the disc method with benomyl as a positive control. The crude extract and the compounds exhibited activities against *Botryodiploida theobromae, Aspergillus niger* and *Aspergillus flavus* with a diameter of inhibition zones ranging from 10.0% to 48.5% in comparison to the diameter of inhibition zone of 100% exhibited by the positive control (Odebode *et al.*, 2004a). Similarly, Samwel *et al.* (2007) evaluated the antifungal activities of the compounds cleistenolide, cleistodienol, (Z)-(+)-5-(2,3-dihydroxy-propylidene)-5H-furan-2-one, melodorinol, acetyl melodorinol, iso-acetyl melodorinol and benzoyl melodorinol isolated from the fruits, leaves,

Figure 1: Cleistochlamys kirkii: (A) branch showingleaves and fruits and (B) branch showingflower buds (photo: WT Wursten)

roots and stems of *C. kirkii* against *Candida albicans* using the disk diffusion method with ketoconazole as a positive control. The compounds exhibited activities against the tested pathogen (Samwel *et al.*, 2007).

Antiplasmodial activities

Nyandoro *et al.* (2017) evaluated the antiplasmodial activities of the ethanolic crude extract of *C. kirkii* leaves. The compounds cleistodienediol, cleistodienol A, cleistodienol B, cleistenechlorohydrin A, cleistenechlorohydrin B, cleistenediol F, cleistenonal, cleistophenolide, ent-subglain C, melodorinol, acetylmelodorinol, tetramethylscutellarein and 2-hydroxybenzaldehyde isolated from the species against the chloroquine-sensitive strain of *Plasmodium falciparum* 3D7 and Dd2 using an imaging-based assay method. The compounds cleistodienediol, cleistodienol A, cleistodienol B and acetylmelodorinol exhibited activities against both 3D7 and Dd2 with half-maximal inhibitory concentration (IC_{50}) values ranging from 0.2 μM to 40.0 μM (Nyandoro *et al.*, 2017). Similarly, Nyandoro *et al.* (2019) evaluated the antiplasmodial activities of ethanolic crude extract of *C. kirkii* root bark and the compounds cleistonol, chamanetin, isochamanetin, dichamanetin, 7-methoxyisochamanetin, pinostrobin, pinocembrin, benzyl benzoate, 2-methoxybenzyl benzoate, guaiol, polycarpol, (E)-acetylmelodorinol and cleistenolide isolated from the species against the chloroquine-sensitive strain of *Plasmodium falciparum* 3D7 using an imaging-based assay method with artesunate as the reference drug. The crude extract gave 72.0% inhibition against the 3D7 strain at 0.01 μg/mL, while the compounds dichamanetin, (E)-acetylmelodorinol and cleistenolide exhibited IC_{50} values of 9.3 μM, 7.6 μM and 15.2 μM, respectively, against 3D7 (Nyandoro *et al.*, 2019).

Cytotoxicity activities

Samwel *et al.* (2007) evaluated the cytotoxicity activities of the compounds cleistodienol, (Z)-(+)-5-(2,3-dihydroxy-propylidene)-5H-furan-2-one, melodorinol, acetyl melodorinol, iso-acetyl melodorinol and benzoyl melodorinol isolated from the fruits, leaves, roots and stems of *C. kirkii* using the brine shrimp assay. The compounds exhibited activities with half-maximal lethal dose (LD_{50}) value of 0.09 μg/mL (Samwel *et al.*, 2007). Similarly, Nyandoro *et al.* (2017) evaluated the cytotoxicity activities of the ethanolic crude extract of *C. kirkii* leaves. The compounds cleistodienediol, cleistodienol A, cleistodienol B, cleistenechlorohydrin A, cleistenechlorohydrin B, cleistenediol F, cleistenonal, cleistophenolide, ent-subglain C, melodorinol, acetylmelodorinol, tetramethylscutellarein and 2-hydroxybenzaldehyde isolated from the species against HEK-293 cells and MDA-MB-231, triple-negative, aggressive breast cancer cell line. All the compounds exhibited activities with IC_{50} values ranging from 0.03 μM to 8.2 μM (Nyandoro *et al.*, 2019). Nyandoro *et al.* (2019) also evaluated the cytotoxicity activities of ethanolic crude extract of *C. kirkii* root bark and the compounds cleistonol, chamanetin, isochamanetin, dichamanetin, 7-methoxyisochamanetin, pinostrobin, pinocembrin, benzyl benzoate, 2-methoxybenzyl benzoate, guaiol, polycarpol, (E)-acetylmelodorinol and cleistenolide isolated from the species against the triple-negative aggressive breast cancer cell line MDA-MB-231 using Alamar Blue assay with lupeol as the reference drug. The crude extract exhibited activities with an IC_{50} value of 42.0 μg/mL. In contrast, the compounds chamanetin, isochamanetin, dichamanetin, pinocembrin, (E)-acetylmelodorinol and cleistenolide exhibited activities with IC_{50} values ranging from 9.6 μM to 30.7 μM (Nyandoro

et al., 2019).

CONCLUSIONS

The current scientific evidence, as illustrated by biological activities demonstrated by *C. kirkii*, indicates its potential as traditional medicine. The biological activities exhibited by the extracts and compounds isolated from the species directly or indirectly support a wide range of physiological processes, which offers protection against the growth of undesirable microbes and cytotoxicity properties which could trigger antitumor activities. The present study showed that there are still some research gaps in the phytochemistry, pharmacological and toxicological properties of the species. Therefore, further rigorous research is required aimed at evaluating the phytochemical properties of the different plant parts used as sources of traditional medicines as well as clinical trials and in vivo experiments.

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Conflict of Interest

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