Review Article

International Journal of Research in Pharmaceutical Sciences

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

Ehretia amoena Klotzsch (Ehretiaceae): Review of its medicinal uses, phytochemistry and pharmacological properties

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Article History:

Received on: 07 Feb 2021
Revised on: 20 Mar 2021
Accepted on: 23 Mar 2021

Keywords:

Boraginaceae, Ehretia amoena, Ehretiaceae, herbal medicine, indigenous knowledge, traditional medicine

Abstract

Ehretia amoena is a deciduous shrub or small tree widely used as herbal medicine in tropical Africa. *Ehretia amoena* occurs naturally in Eswatini, Kenya, Malawi, Mozambique, Namibia, South Africa, Tanzania, Uganda, Zambia and Zimbabwe. The current study critically reviewed the medicinal uses, phytochemistry and pharmacological activities of *E. amoena*. Literature on medicinal uses, phytochemical and biological activities of *E. amoena* was collected from multiple internet sources such as Elsevier, Google Scholar, SciFinder, Web of Science, Pubmed, BMC, Science Direct and Scopus. Complementary information was collected from pre-electronic sources such as books, book chapters, theses, scientific reports and journal articles obtained from the university library. This study revealed that the bark, fruit, leaf, root, root bark, stem and stem bark decoction or infusion of *E. amoena* are mainly used as an anthelmintic or dewormer and herbal medicine for fever, typhoid, sleeping sickness, wounds, menstrual problems, abdominal pains, sexually transmitted infections, skin diseases, vomiting, pain, muscle pain and gastro-intestinal problems. Ethnopharmacological research identified chrysosplenetin, chrysosplenol D, emodins, polyose, polyuronoids, saponins, steroids, tannins, terpenoids and volatile oils from the leaves and roots of *E. amoena*. The crude extracts of *E. amoena* and the phytochemical compounds identified from the species exhibited antibacterial, antitrypanosomal and cytotoxicity activities. *Ehretia amoena* should be subjected to detailed phytochemical, pharmacological and toxicological studies.

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ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v12i2.4679

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INTRODUCTION

Ehretia amoena Klotzsch (Figure 1) is a shrub or small tree belonging to the Ehretiaceae. Recent molecular and phylogenetic studies based on nuclear (ITS) and plastid loci (rps16, trnL-trnF and trnS-trnG) supported the segregation of the family Ehretiaceae from Boraginaceae *sensu lato* (Gottschling *et al.*, 2016). The Ehretiaceae family comprise ten genera, that is, *Bourreria* P. Br., *Coldenia* L., *Cordia* L., *Cortesia* Cav., *Ehretia* P. Br., *Halgania* Gaudich., *Hoplestigma* Pierre, *Lepidocordia* Ducke, *Rochefortia* Sw. and *Tiquilia* Pers. With about 500 species and are pantropical in distribution, with centres of diversity in Central America and the Caribbean, Africa, and East Asia. The genus *Ehretia* consists of shrubs and trees with approximately 40 species (Gottschling *et al.*, 2016). The plant species belonging to the genus *Ehretia* have been recorded in the Old and New World tropics with a few species in tropical America and the West

Indies, with centres of diversity in tropical Africa and East Asia. Several *Ehretia* species are widely used as sources of traditional medicines in tropical Africa and these species are listed in the monograph "Plant Resources of Tropical Africa 11(1): Medicinal Plants 1". Such plant species include *E. amoena, E. bakeri* Britten, *E. cymosa* Thonn., *E. obtusifolia* DC., *E. rigida* (Thunb.) Druce and *E. trachyphylla* C.H. Wright. Shukla and Kaur (2018) argued that the medicinal uses of *Ehretia* species could be attributed to alkaloids, benzoquinones, cyanogenetic glycosides, fatty acids, phenolic acids, flavonoids and other phytochemical compounds identified from different species.

The pharmacological properties associated with crude extracts and phytochemical compounds isolated from the species include anti-inflammatory, antiarthritic, antibacterial, antitubercular, antioxidant, antiallergic, antitrypanosomal, antiprotozoal, antidiabetic, cardiotonic activities, as well as anti-snake venom properties.

Ehretia amoena occurs naturally in Eswatini, Kenya, Malawi, Mozambique, Namibia, South Africa, Tanzania, Uganda, Zambia and Zimbabwe (Martins *et al.*, 1990; Verdcourt, 1991). The genus name *Ehretia* is in honour of a German botanical artist and entomologist of the 18^{th} century known as Georg Dionysius Ehret (1708-1770). The species name *amoena* is a Latin word that means "charming" and "pleasant" in reference to showy and beautiful flowers (see Figure 1). The English common names of *E. amoena* include "sandpaper-bush" and "sandpaper stamperwood" (Van Wyk and Van Wyk, 2013; Schmidt *et al.*, 2017). Synonyms of *E. amoena* include *E. goetzei* Gürke, *E. mossambicensis* Klotzsch, *E. stuhlmannii* Gürke and *Ficus obovata* Sim (Verdcourt, 1991; Retief and Van Wyk, 2001).

Ehretia amoena is a deciduous shrub or small tree with somewhat arching branches and can grow up to five metres in height. *Ehretia amoena* has been recorded in medium to low altitudes, at the margins of coastal forests, riverine forest, in riparian thickets, bushveld, woodland, termite mounds, along watercourses and in alluvial and sandy soils. The bark of *E. amoena* is smooth but flaking in older trees, light grey-brown to dark grey in colour. The leaves are simple, alternate and entire, broadly ovate to elliptic in shape, both surfaces with short hairs lying flat against the surface, dark green above and paler dull green below with midrib and lateral veins prominent and net-veining conspicuous. Flowers of *E. amoena* are white to pale mauve in colour, sweetly scented occurring in large terminal heads. The fruit is a drupe, ovoid to globose in shape, fleshy, hairless, red in colour when ripe.

The fruits of *E. amoena* are edible but not very tasty, widely used as a snack (Fox *et al.*, 1982; Welcome and Van Wyk, 2019). The leaves and young shoots of *E. amoena* are browsed by game and livestock (Peters *et al.*, 1992; Mtengeti and Mhelela, 2006). The leaves of *E. amoena* are sold as traditional medicines in informal herbal medicine markets in Tanzania (Posthouwer, 2015; Posthouwer *et al.*, 2018). It is therefore, within this context that the current study was undertaken aimed at documenting the medicinal uses, phytochemistry and pharmacological properties of *E. amoena* so as to provide baseline data required in evaluating the therapeutic potential of the species.

Figure 1: *Ehretia amoena*: Branch showing leaves, flowers and fruits (photo: BT Wursten)

MATERIALS AND METHODS

An extensive literature survey related to *E. amoena* was conducted using various search engines such as Elsevier, Pubmed, Google Scholar, Springer, Science Direct, Taylor and Francis, and pre-electronic sources such as books, book chapters, scientific journals and other grey literature. The literature search was conducted using keywords such as *"Ehretia amoena"*, "medicinal uses of *Ehretia amoena"*, "phytochemicals of *Ehretia amoena"*, "biological activities of *Ehretia amoena"*, "ethnobotany

Table 1: Medicinal applications of *Ehretia amoena*

Medicinal use	Parts used	Country	References
Abdominal pains	Root decoction is taken orally	Tanzania and Zimbabwe	(Gelfand *et al.*, 1985; Newmark, 2002)
Anthelmintic	Leaf and root decoction are taken orally	Tanzania	(Luoga *et al.*, 2000; Posthouwer *et al.*, 2018)
Bilharzia	Root infusion is taken orally	Tanzania	(Chhabra *et al.*, 1987)
Bleeding from ears, mouth and nose	Roots boiled and the resultant stem inhaled	Tanzania	(Chhabra *et al.*, 1987)
Convulsions and epilepsy	Root infusion is taken orally	Tanzania	(Chhabra *et al.*, 1987; Moshi *et al.*, 2005)
Diabetes mellitus	Root infusion is taken orally	Tanzania	(Moshi and Mbwambo, 2002)
Eye problems	Root maceration applied topically	Tanzania	(Nahashon, 2013)
Fever and typhoid	Leaf and root decoction are taken orally	Tanzania	(Chhabra *et al.*, 1987; Posthouwer *et al.*, 2018)
Gastro-intestinal problems (blood diarrhoea, diarrhoea, dysentery, stomach ache and stomach problems)	Leaf, root and stem decoction are taken orally	Mozambique, Tanzania and South Africa	(Hedberg *et al.*, 1982; Bruschi *et al.*, 2011)
Hernia	Root decoction is taken orally	Tanzania	(Chhabra *et al.*, 1987)
Hypertension	Leaf infusion is taken orally	Tanzania	(Posthouwer, 2015; Posthouwer *et al.*, 2018)
Infertility	Root infusion is taken orally	Tanzania	(Chhabra *et al.*, 1987)
Internal swellings	Root decoction is taken orally	Tanzania	(Chhabra *et al.*, 1987)
Malaria	Root decoction is taken orally	Mozambique	(Manuel *et al.*, 2020)
Menstrual problems	Bark, fruit, leaf and root decoction are taken orally	Tanzania	(Hedberg *et al.*, 1982; Kokwaro, 2009)

Continued on next page

Table 1 continued

Medicinal use	Parts used	Country	References
Mental illness	Leaf infusion is taken orally	Tanzania	(Chhabra *et al.*, 1987)
Miscarriage	Root infusion is taken orally	Tanzania	(Hedberg *et al.*, 1982)
Pain and muscle pain	Root, root bark and stem powder applied topically	Mozambique, South Africa and Tanzania	(Watt and Breyer-Brandwijk, 1962; Wentzel and Van Ginkel, 2012)
Rectal prolapse	Root decoction is taken orally	Tanzania	(Chhabra *et al.*, 1987)
Respiratory infections (pneumonia and tuberculosis)	Root decoction is taken orally	Tanzania	(Chhabra *et al.*, 1987)
Rheumatism	Root decoction applied topically	Tanzania	(Chhabra *et al.*, 1984)
Sexually transmitted infections (genital ulcers, gonorrhoea and venereal diseases)	Root decoction is taken orally	Mozambique and Tanzania	(Hedberg *et al.*, 1982; Bruschi *et al.*, 2011)
Skin diseases (fungal infections and rash)	Leaf, root, stem and stem bark powder applied topically	South Africa and Tanzania	(Cosam *et al.*, 2004; Runyoro *et al.*, 2006)
Sleeping sickness	Leaf decoction is taken orally	Uganda	(Freiburghaus *et al.*, 1996; Räz *et al.*, 1996)
Tonic	Root decoction is taken orally	Tanzania	(Moshi and Mbwambo, 2002)
Vomiting	Leaf, root and stem bark decoction are taken orally	Eswatini, Mozambique and Tanzania	(Long *et al.*, 2005; Manuel *et al.*, 2020)
Wounds	Leaf powder applied topically	Tanzania	(Hedberg *et al.*, 1982; Cosam *et al.*, 2004)

of *Ehretia amoena",* and various other synonyms and common names of the plant species.

RESULT AND DISCUSSION

Medicinal uses of *Ehretia amoena*

The bark, fruit, leaf, root, root bark, stem and stem bark decoction or infusion of *E. amoena* are mainly used as anthelmintic and traditional medicine for fever, typhoid, sleeping sickness, wounds, menstrual problems, abdominal pains, sexually transmitted infections, skin diseases, vomiting, pain, muscle pain and gastro-intestinal problems (Table 1, Figure 2). Other medicinal applications of *E. amoena* supported by at least two literature sources include the use of root infusions against convulsions and epilepsy (Chhabra *et al.*, 1987; Moshi *et al.*, 2005) and use of leaf infusions against hypertension (Posthouwer, 2015; Posthouwer *et al.*, 2018).

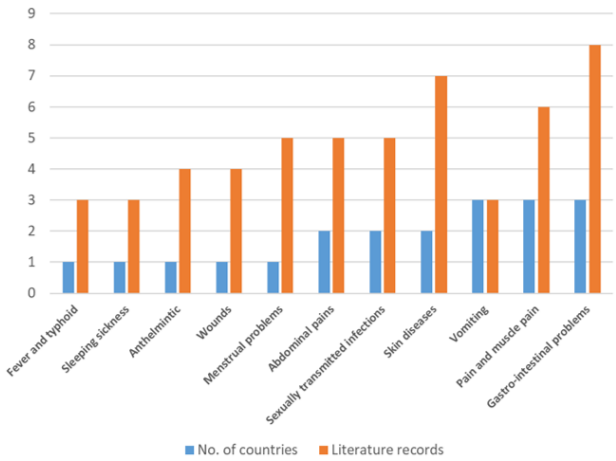

Figure 2: Medicinal uses of *Ehretia amoena* based on literature records

Phytochemical composition of *Ehretia amoena*

Researchers such as Chhabra *et al.* (1984) and Räz *et al.* (1996) identified phytochemical compounds such as chrysosplenetin, chrysosplenol D, emodins, polyose, polyuronoids, saponins, steroids, tannins, terpenoids and volatile oils from the leaves and roots of *E. amoena* (Table 2).

Some of these phytochemical compounds identified from *E. amoena* could be responsible for the pharmacological properties associated with the species.

Pharmacological properties of *Ehretia amoena*

Pharmacological research revealed that aerial parts, leaves, root bark, roots and stem bark of *E. amoena* and compounds isolated from the species have various biological activities such as antibacterial, antitrypanosomal and cytotoxicity activities.

Antibacterial activities

Khan and Nkunya (1990) evaluated the antibacterial activities of crude extracts of *E. amoena* root bark against *Staphylococcus aureus* and *Escherichia coli* using agar diffusion method. The extracts exhibited activities against tested pathogens with a zone of inhibition ranging from 10.0 mm to 25.0 mm (Khan and Nkunya, 1990). Preliminary studies evaluating the antibacterial activities of the aerial parts and root bark extracts of *E. amoena* showed that the extracts were active against *Staphylococcus aureus* (Khan *et al.*, 1980; Chhabra *et al.*, 1981). These findings could be used to corroborate traditional uses of *E. amoena* extracts as traditional medicines for gastrointestinal problems such as blood diarrhoea, diarrhoea, dysentery, stomach ache and stomach problems and sexually transmitted infections such as genital ulcers, gonorrhoea and venereal diseases (Hedberg *et al.*, 1982; Bruschi *et al.*, 2011).

Antitrypanosomal activity

Freiburghaus *et al.* (1996) evaluated the antitrypanosomal activities of dichloromethane, methanol and water extracts of *E. amoena* leaves, root and stem bark against *Trypanosoma hrucei rhodesiense* using *in vitro* assays with commercial drugs, pentamidine isethionate and suramin as positive controls. The extracts exhibited activities against the tested pathogen with minimum inhibitory concentration (MIC) values ranging from $\leq$19.0 μg/ml to $\geq$167.0 μg/ml (Freiburghaus *et al.*, 1996).

Similarly, Räz *et al.* (1996) evaluated the antitrypanosomal activities of dichloromethane extracts of *E. amoena* leave and the compound chrysosplenetin isolated from the species against the bloodstream forms of *Trypanosoma brucei rhodesiense* using *in vitro* assays. Both the extract and the compound exhibited activities with half-maximal inhibitory concentration (IC_{50}) values of 7.0 μg/ml and 1.1 μg/ml, respectively. This pharmacological evaluation is of importance in the traditional uses of *E. amoena* against sleeping sickness in Uganda and future research focusing on control and management of sleeping sickness and related vector-borne parasitic diseases in the tropics (Freiburghaus *et al.*, 1996; Räz *et al.*, 1996).

Cytotoxicity activities

Freiburghaus *et al.* (1996) evaluated the cytotoxicity activities of dichloromethane and methanol extracts of *E. amoena* leaves, root and stem bark on a human fibroblast cell line (W1-38) with pentamidine isethionate and suramin as positive controls. The extracts exhibited activities with IC_{50} and maximum tolerated concentration (MTC) values ranging from $\leq$0.9 μg/ml to 9.6 μg/ml and 19.0 μg/ml

Table 2: Phytochemical composition of *Ehretia amoena*

Phytochemical compound	Plant part	References
Chrysosplenetin	Leaves	(Räz *et al.*, 1996)
Chrysosplenol D	Leaves	(Räz *et al.*, 1996)
Emodins	Roots	(Chhabra *et al.*, 1984)
Polyoses	Roots	(Chhabra *et al.*, 1984)
Polyuronoids	Roots	(Chhabra *et al.*, 1984)
Saponins	Roots	(Chhabra *et al.*, 1984)
Steroids	Roots	(Chhabra *et al.*, 1984)
Tannins	Roots	(Chhabra *et al.*, 1984)
Terpenoids	Roots	(Chhabra *et al.*, 1984)
Volatile oils	Roots	(Chhabra *et al.*, 1984)

to 112.0 μg/ml, respectively (Freiburghaus *et al.*, 1996).

Cosam *et al.* (2004) assessed the cytotoxicity activities of 20% aqueous ethanol extract of *E. amoena* stem bark using the brine shrimp lethality test. The concentrations killing 50% of the brine shrimps (LC_{50}) was 65.0 μg/ml (Cosam *et al.*, 2004).

Sempombe *et al.* (2014) evaluated the cytotoxicity activities of ethanol and petroleum ether extracts of *E. amoena* leaves and root bark against a 3-cell line panel consisting of TK10 (renal), UACC62 (melanoma) and MCF7 (breast) cancer cells using the sulforhodamine B assay with etoposide as a reference standard.

The extracts exhibited activities with half-maximal growth inhibition concentration (GI_{50}), total growth inhibition (TGI) and LC_{50} values ranging from 9.3 μg/ml to 13.0 μg/ml, 22.3 μg/ml to 26.5 μg/ml and 40.3 μg/ml to 86.1 μg/ml, respectively (Sempombe *et al.*, 2014).

These findings imply that *E. amoena* extracts may have deleterious health implications and detailed toxicological evaluations are required to determine toxicity and/or any side effects associated with consumption of the species as herbal medicine.

CONCLUSION

This review showed that *E. amoena* is characterized by several phytochemicals and the species exhibited antibacterial, antitrypanosomal and cytotoxicity activities. However, the majority of these biological activities lack of bio guided isolation strategies and mechanisms of action. Therefore, future research should focus on pharmacokinetics, mechanisms of action and structural activity relationships of phytochemical compounds of the species. Future research should also focus on animal experiments aimed at assessing the toxicity and clinical efficacy of species extracts.

ACKNOWLEDGEMENT

I am grateful to the reviewers who kindly commented on my manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

Funding Support

The authors declare that they have no funding support for this study.

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