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Euclea undulata Thunb.: Review of its botany, ethnomedicinal uses, phytochemistry and biological activities

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ABSTRACT

Euclea undulata (*E. undulata*) is traditionally used for the treatment of body pains, chest complaints, cough, diabetes, diarrhoea, headaches, heart diseases and toothaches in southern Africa. This study was aimed at reviewing the botany, ethnopharmacology and biological activities of *E. undulata* in southern Africa. Results presented in this study are based on review of literature using search engines such as Science Direct, Springerlink, Scopus, PubMed, Web of Science, BioMed Central and Google Scholar. Herbal medicine is prepared from the decoctions of the roots, bark and leaves, and extracts of these plant parts have demonstrated anticholinesterase, anti-inflammatory, antimicrobial, anti-mycobacterial, antiplasmodial, antioxidant and hypoglycaemic activities. Multiple classes of phytochemical compounds such alkaloids, diterpenes, fatty acids, flavonoids, glycosides, naphthoquinones, phenolics, phytosterols, reducing sugars, saponins and tannins have been isolated from the species. *E. undulata* has a lot of potential as herbal medicine in tropical Africa, and advanced research is required aimed at correlating its medicinal uses with the phytochemistry and pharmacological properties.

1. Introduction

Euclea undulata Thunb. (*E. undulata*) is one of the traditional medicines (TM) widely utilized in the tropics for various human diseases and ailments. Due to its popularity as TM in southern Africa, the roots of *E. undulata* are sold as herbal medicines in informal herbal medicine or Muthi shops in the Gauteng province in South Africa [1]. Traditional medicine is defined as the indigenous knowledge, skill, cultural beliefs and practices that are used to manage, treat, prevent, and diagnose illnesses [2]. The term TM is sometimes used interchangeably with “complementary medicine” or “alternative medicine” in some countries. The term CAM, that is, complementary and alternative medicine is used to refer to any other healthcare therapies that are different from conventional medical treatments [2]. Traditional medicines are important sources of natural products which serve as sources of pharmaceutical drugs and other health products [3]. According to Yeh *et al.* [4] current research is focussing on the use of TM and CAM mainly because these strategies are widely used in improving primary health care of local communities. This is particularly important in sub-Saharan Africa where rural communities and those people living in marginalized areas are reliant on TM as their basic source of health care [5]. Research by Mander *et al.* revealed that there is growing demand for consumers of TM in South Africa where about three quarters (72%) of the Black Africans are reliant on herbal medicines, accounting for 27 million people in the country [6]. Research by Mander *et al.* revealed that 97% of traditional healers' patients in South Africa prefer TMs [6]. Research done by van Wyk *et al.* revealed that 50% of pharmaceutical drugs and health products are derived from natural products isolated from plants [3]. Some of the examples include aspirin derived from a compound called salicin isolated from *Salix alba* L., paclitaxel from *Taxus brevifolia* Nutt., artemisin from *Artemisia annua* L. and silymarin from *Silybum marianum* (L.) Gaertn. [7].

It is within this context that the potential of *E. undulata* as herbal medicine and its associated botany, ethnomedicinal uses, phytochemistry and biological activities are reviewed. The utilization of *E. undulata* as herbal medicine generated a lot of interest over the years as demonstrated by research focussing on the species [3,8–14]. It is important to establish if there is

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correlation between the ethnomedicinal uses of *E. undulata*, its phytochemistry and pharmacological properties. This study therefore, was aimed at reviewing the botany, ethnopharmacology and biological activities of *E. undulata* in southern Africa. It is hoped that this information will highlight the important medicinal and ethnopharmacological properties of *E. undulata* and the necessary baseline data required for future research on the species.

2. Research methodology

Relevant literature about *E. undulata* were collected by searching the major scientific databases including Science Direct, Springerlink, Scopus, PubMed, Web of Science, BioMed Central and Google Scholar for the botany, ethnopharmacology and pharmacological properties of the species. Some articles were found through tracking citations from other publications or by directly accessing the journals' websites. The keyword combinations for the search were ethnobotany, ethnomedicinal uses, ethnopharmacology, pharmacology, phytochemistry, biological activities or properties and therapeutic value of *E. undulata*, *E. undulata* var. *myrtina* (Burch.) Hiern, *E. undulata* var. *undulata*, and historical name and synonym of the species *Euclea myrtina* Burch. were also used. Literature search also used common names such as “common guarri”, “fire-fighter's blessing”, “small-leaved guarri” and “thicket euclea”. The University of Fort Hare library, South Africa was used as source of additional literature such as books, dissertations, and other scientific papers.

3. Botanical profile and taxonomy of *E. undulata*

E. undulata belongs to the Ebenaceae or Ebony family. The family Ebenaceae is represented by two genera, namely *Euclea* Murray and *Diospyros* L. in southern Africa [15]. The genus *Euclea* is composed of 20 species, mostly shrubs, trees or suffrutices with 16 of them recorded in southern Africa [15,16]. The genus name “*Euclea*” is derived from a Greek word “*eukleia”*, derived from “*eu”* meaning ‘good’, and “*kleios”* meaning report [17]. This is possibly in reference to the good quality timber and wood derived from some *Euclea* species, such as *Euclea pseudebenus* E. Mey. ex A. DC. [17]. The specific name “*undulata*” is derived from “undulating” in reference to undulate or waxy leaf margins [16]. Two varieties of *E. undulata* are recognized, var. *undulata* and var. *myrtina* (Burch.) Hiern. [16,18]. The name of the variety “*myrtina*” was given by Burchell who knew the plant in the north west Cape and thought it resembled the leaves of genus *Myrtus* L., the myrtle [9,16].

E. undulata var. *myrtina* and *E. undulata* var. *undulata* are separated based on the shape of the leaves. The var. *undulata* has wider and more waxy leaves than var. *myrtina*. Both varieties make upright, multi-stemmed, dense twiggy evergreen dioecious shrubs or little trees up to about 6 m high, occasionally larger than 18 m with many-branched, twiggy and densely leafy crowns [16,18]. The bark is pale grey and covered in reddish-brown granules when young [16]. The leaves are alternate or arranged in pseudowhorls, crowded at the ends of the branches. The leaves are obovate, narrowly elliptic and small in size [16]. The leaves of var. *undulata* are egg-shaped to widely lance-shaped, the tips round or bluntly pointed, the margin not toothed but often waxy. Those of var. *myrtina* are narrower, taper both ends and are not as strongly waxy as those of var. *undulata*. Both varieties have small, white or yellow-green, fragrant flowers in short racemes in the axils of the leaves which are up to 2 cm long [18]. They are attractive to bees which make a good honey from them. The fruit of both varieties is spherical, globose fleshy berry 4–6 mm in diameter, reddish brown becoming purple or black when mature and single seeded [18]. Researchers rarely separate *E. undulata* into specific varieties, therefore, *E. undulata sensu lato* is recognized and used throughout this report.

E. undulata has been recorded in Botswana, Zimbabwe, Namibia, Swaziland, Mozambique and South Africa [18]. *E. undulata* has been recorded in a variety of environments in the semi-arid, tropical and subtropical areas [17]. The species is common in low hills with valleys, rocky places and slopes, *Colophospermum mopane* (Benth.) Leonard or acacia bushland or woodland, bushveld, grassland and semi-desert areas [17,18]. Several specimens of *E. undulata* commonly grow close to each other, and in such cases forming impenetrable thickets especially in the coastal regions [17]. The fruits of *E. undulata* are eaten by both humans and animals, while the leaves of the species are browsed by game and livestock [17].

4. Ethnomedicinal uses

The roots, bark and leaves of *E. undulata* are used as herbal medicines for several human diseases (Table 1). The bark of *E. undulata* is herbal medicine for body pains in South Africa [8,9,14,16], diabetes in South Africa [20–23], headaches in Swaziland [24], toothaches in South Africa [8,9,16] and Swaziland [24]. In South Africa, headache problems are treated by applying powdered bark of *E. undulata* to a strip of *Dombeya rotundifolia* leaf and the head bandaged until the headache subsidises [8,9,16]. An infusion of the leaves is herbal medicine for stomach problems or diarrhoea, and leaf decoction is gargled against tonsillitis in South Africa [21]. Root infusions are used as purgative in Swaziland [24], enemas and purgative, remedy for chest complaints, cough and heart diseases in South Africa [8,9,16,19,21] and remedy for stomach problems in Botswana [25]. *E. undulata* is used as remedy for tooathache in Botswana, root powder is rubbed on affected tooth or the root chewed [13] and root decoction is also taken for ailments thought to indicate an excess of blood in the body, sometimes symptomatized by fever and feelings of distension [10]. In South Africa, the root infusion of *E. undulata* is taken as a component of herbal concoction called *inembe* (herbal concoction taken by women during pregnancy), a mixed with roots of *Cyphostemma natalitium* (Szyszyl.) J.J.M. van der Merwe, *Rhoicissus tridentata* subsp. *cuneifolia* (Eckl. & Zeyh.) Urton, *Triumfetta rhomboidea* Jacq. and *Gunnera perpensa* L. [21]. Twigs and stems of *E. undulata* are used as chewing sticks, that is, for cleaning teeth in Botswana [26] and Zimbabwe [12].

5. Phytochemistry

Several researchers have investigated phytochemical and pharmacological properties of *E. undulata* aimed at identifying the compounds responsible for the traditional and

Table 1

Ethnomedicinal uses of *E. undulata*.

Medicinal uses	Different plant part(s) used as herbal medicines	Country	References
Body pains	Bark decoction taken orally	South Africa	[8,9,14,16]
Chest complaints	Root decoctions taken orally	South Africa	[19]
Cough	Root decoctions taken orally	South Africa	[19]
Diabetes	An aqueous infusion is being made with ground root bark and drank as a tea.	South Africa	[20–23]
Diarrhoea	Leaf infusion taken orally	South Africa	[21]
Enemata	Root infusions taken orally	South Africa	[21]
Excess of blood in the body	Root decoction taken orally	Botswana	[10]
Headache	Bark decoction taken orally	Swaziland	[24]
Headache	Powdered bark applied to a strip of *Dombeya rotundifolia* Planch. leaf and the head bandaged	South Africa	[8,9,16]
Heart disease	Powdered root taken orally	South Africa	[8,9,16]
Purgative	Root decoction taken orally	South Africa, Swaziland	[9,16,24]
Stomach problems	Leaf or roots decoction taken orally	Botswana, South Africa	[21,25]
Tonsillitis	Leaf infusion taken orally as a gargle	South Africa	[21]
Toothache	Bark or root powder rubbed on affected tooth or root chewed	Botswana, South Africa, Swaziland	[8,9,13,16,24]
To induce labour	Root infusions taken as an ingredient of *inembe*, i.e., roots of *Cyphostemma natalitium* (Szyszyl.) J.J.M. van der Merwe, *Rhoicissus tridentata* subsp. *cuneifolia* (Eckl. & Zeyh.) Urton, *Triumfetta rhomboidea* Jacq. and *Gunnera perpensa* L.	South Africa	[21]
Chewing stick	Stem	Botswana, Zimbabwe	[12,26]

ethnomedicinal uses of the species. Ndondo *et al.* isolated vitamin E (729 μg/g dry weight) and total fatty acid methyl esters content of 2.25 μg/g dry weight from twigs and leaves of *E. undulata* [27]. The fatty acid methyl esters consisted of both saturated (C14, C20) and unsaturated (C16, C18:0, C18:1, C18:2 and C18:3) fatty acids [27]. These findings are important since the leaves and twigs of *E. undulata* are used as chewing sticks in Botswana [26] and Zimbabwe [12], herbal medicines, browsed by both game and livestock throughout the distributional range of the species (Table 1). Vitamin E is a potent chain-breaking antioxidant that inhibits the production of reactive oxygen species molecules when fat undergoes oxidation and during the propagation of free radical reactions and therefore, vitamin E might help prevent or delay the chronic diseases associated with reactive oxygen species molecules [28]. Vitamin E has been found to be very effective in the prevention and reversal of various disease complications due to its function as an antioxidant, its role in anti-inflammatory processes, its inhibition of platelet aggregation and its immune-enhancing activity [28]. Similarly, research done by Elagbar *et al.* showed that fatty acids isolated from the oil of *Annona muricata* L. exhibited free radical scavenging activities and also inhibited the gastrointestinal motility [29].

Phytochemical analysis of the methanol leaf and stem extracts *E. undulata* showed the presence of alkaloids, diterpenes, glycosides, phytosterols, reducing sugars, saponins and tannins [12]. Dzoyem and Eloff found total flavonoids content of *E. undulata* to be (35.2 ± 2.5) mg QE/g and total phenolic content to be (129.8 ± 32.6) mg GAE/g [14]. Earlier research by Van der Vijver and Gerritsma showed naphthoquinones diospyrin and 7-methyljuglone as major constituents of the fruit, root and stems of *E. undulata* roots [30,31]. Deutschländer *et al.* isolated α-amyrin-3*O*-β-(5-hydroxy) ferulic acid, betulin, lupeol and epicatechin from a crude acetone extract of the root bark of *E. undulata* var. *myrtina* [32]. Botha isolated 7-methyljuglone from leaves and roots of *E. undulata* [33]. Existing literature indicates an increase in the number of phytochemical investigations of the species and this interest is mainly because of its numerous ethnomedicinal uses and reported pharmacological properties.

6. Biological activities

A number of biological activities of *E. undulata* have been reported in literature corroborating some of the ethnomedicinal uses of the species. Among the reported biological activities include anticholinesterase [14], anti-inflammatory [14], antimicrobial [12], antimycobacterial [24,34–36], antiplasmodial [37], antioxidant [14], hypoglycaemic [20,22,32], toxicity and cytotoxicity [20,38–40].

6.1. Anticholinesterase activities

Dzoyem and Eloff determined anticholinesterase activities of *E. undulata* extracts by using the acetylcholinesterase inhibition assay [14]. At a concentration of 500 μg/mL, the *E. undulata* had the AChE inhibitory activity of 55% and a dose-dependent inhibition with AChE activity with 50% inhibitory concentration (IC_{50}) value of (450.3 ± 18.7) μg/mL. Eserine used as a positive control AChE inhibitor in this study inhibited 50% of AChE activity (IC_{50}) at a concentration of (4.94 ± 0.05) μg/mL [14]. Observed anticholinesterase activities of *E. undulata* may be due to the presence of alkaloids which have been isolated from the species by Mbanga *et al.* [12]. Alkaloids are naturally occurring compounds that are known to have the ability of inhibiting the enzyme AChE, which, according to the cholinergic hypothesis, increases the levels of the neurotransmitter acetylcholine in the brain, thus improving cholinergic functions in patients with Alzheimer's disease and alleviating the symptoms of this neurological disorder [41].

6.2. Anti-inflammatory activities

Dzoyem and Eloff [14] evaluated anti-inflammatory activities of *E. undulata* extracts through nitric oxide production in LPSactivated RAW 264.7 macrophages and 15-lipoxygenase inhibitory assay. *E. undulata* showed weak anti-15-lipoxygenase activity with 33.9% inhibition at 100 μg/mL. *E. undulata* showed dose dependent inhibition of nitric oxide production at the concentration of 6.25, 12.5, 25 and 50 μg/mL. At the highest concentration of 50 μg/mL, *E. undulata* had a potent inhibition of 90.6% and cell viability of 85.0% [14]. These results corroborate ethnomedicinal uses of *E. undulata* in various inflammatory ailments and general body pains in South Africa [8,9,14,16].

6.3. Antimicrobial activities

Mbanga *et al.* evaluated antimicrobial activities of aqueous, methanol, acetone and diethyl ether stem extracts of *E. undulata* against *Streptococcus mutans* using disc diffusion and broth macro-dilution assays with ampicillin as control [13]. The largest inhibition zones were exhibited by methanol extracts ranging from 40 to 60 mm, acetone extracts demonstrated 1–11 mm, and aqueous extracts showed a range of 1–14 mm against a range of 6–25 mm demonstrated by ampicillin control. The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of aqueous, methanol and acetone extracts ranged from 2.4–9.8 mg/mL and 2.4–17.6 mg/mL respectively. The antimicrobial activities of *E. undulata* documented by Mbanga *et al.* [12] support traditional use of the species against dental caries and toothache in Botswana, South Africa and Zimbabwe [8,9,12,13,16,24,26]. Therefore, results obtained by Mbanga *et al.* [12] suggest that *E. undulata* extracts may have potential use as anticarcinogenic agents.

6.4. Antimycobacterial activities

McGaw *et al.* evaluated antimycobacterial activities of *E. undulata* against *Mycobacterium bovis*, *Mycobacterium fortuitum* and *Mycobacterium smegmatis* using a twofold serial dilution assay with anti-tuberculosis (TB) drug isoniazid as positive control [19]. *E. undulata* extracts demonstrated activity with MIC values ranging from 5.7 to 16.3 μg/mL against *M. bovis*, and MIC value of 300 μg/mL against *M. fortuitum* and *M. smegmatis* [19]. Similarly, McGaw *et al.* evaluated antimycobacterial activities of *E. undulata* acetone root extracts against *M. bovis*, *M. fortuitum* and *M. smegmatis* using a twofold serial dilution assay with anti-TB drug isoniazid as positive control [36]. *E. undulata* acetone root extracts demonstrated activity with MIC values ranging from 126.8 to 625.0 μg/mL against *M. bovis*, *M. fortuitum* and *M. smegmatis* [36]. The MBC ranged from 1 250 to >2 500 μg/mL against *M. bovis*, *M. fortuitum* and *M. smegmatis* [36]. McGaw *et al.* evaluated antimycobacterial activities of diospyrin compound isolated from *E. undulata* against *M. bovis*, *M. fortuitum* and *M. smegmatis* using a twofold serial dilution assay with anti-TB drug isoniazid as positive control [19]. Compound diospyrin demonstrated activity with MIC values ranging from 5.7 μg/mL to 16.3 μg/mL against *M. bovis*, and MIC value of 15.6 μg/mL to 62.5 μg/mL against *M. fortuitum* and *M. smegmatis* [19]. McGaw *et al.* evaluated antimycobacterial activities of diospyrin, lupeol and 7-methyljuglone compounds isolated from *E. undulata* against *M. bovis*, *M. fortuitum* and *M. smegmatis* using a twofold serial dilution assay with anti-TB drug isoniazid as positive control [36]. Compound diospyrin demonstrated activity with MIC values ranging from 1.7 to 41.7 μg/mL while MBC values ranged from 31.3 to 250.0 μg/mL against *M. bovis*, *M. fortuitum* and *M. smegmatis* [36]. Compound 7-methyljuglone demonstrated activity with MIC values ranging from 1.7 to 22.1 μg/mL while MBC values ranged from 15.6 to >250.0 μg/mL against *M. bovis*, *M. fortuitum* and *M. smegmatis* [36]. Minimal inhibitory concentration values of diospyrin and 7-methyljuglone compounds against *Mycobacterium tuberculosis* were 8.0 and 0.5 μg/mL respectively [36]. Compound 7-methyljuglone isolated from *Euclea natalensis* A. DC. roots was found to have superior intracellular (in a macrophage cell line) and extracellular inhibition of *M. tuberculosis* relative to the anti-TB drugs streptomycin and ethambutol [34]. According to these authors, diospyrin and 7-methyljuglone exhibited potent activities with MIC values of 8.0 and 0.5 mg/mL respectively against drug-sensitive *M. tuberculosis*. Similarly, van der Kooy *et al.* evaluated antimycobacterial activities of diospyrin and 7-methyljuglone isolated from *Euclea natalensis* roots against *M. tuberculosis* [35]. The two compounds, diospyrin and 7-methyljuglone showed potent activities with MIC values of 8.0 and 0.5 mg/mL respectively [35]. These pharmacological evaluations serve as scientific validation for the use of *E. undulata* in traditional medicine for the treatment of respiratory systems such as chest complaints and cough in South Africa [19].

6.5. Antiplasmodial activities

Clarkson *et al.* evaluated antiplasmodial activities of *E. undulata* aqueous, dichloromethane, dichloromethane and methanol (1:1) leaf and twig extracts against *Plasmodium falciparum* using the parasite lactate dehydrogenase assay [37]. *E. undulata* dichloromethane and methanol (1:1) leaf and twig extracts showed weak and high activities with IC_{50} values of 11 and 4.6 μg/mL, respectively [37]. The antiplasmodial properties demonstrated by *E. undulata* imply that the species could be a promising candidate for further investigation as plant-based antimalarial agent. Historically, some of the antimalarial drugs have been derived from herbal medicines or from structures modelled on medicinal plant lead compounds and these include the quinoline-based antimalarials as well as artemisinin and its derivatives [37].

6.6. Antioxidant activities

Dzoyem and Eloff evaluated antioxidant activities of *E. undulata* extracts using the DPPH (1,1-diphenyl-1-picrylhydrazyl), ABTS radical scavenging and ferric reducing antioxidant power (FRAP) assays [14]. *E. undulata* demonstrated antioxidant activities with IC_{50} values of (31.7 ± 0.6) μg/mL in DPPH, (32.7 ± 0.5) μg/mL in ABTS and (274.2 ± 29.4) μg/mL in FRAP [14]. These antioxidant activities demonstrated by *E. undulata* are probably due to the presence of fatty acids [29], flavonoids and phenolics [42], since these phytochemical compounds have been isolated from the species by Ndombo *et al.* [27] and Dzoyem and Eloff [14].

6.7. Hypoglycaemic activities

Deutschländer *et al.* investigated hypoglycaemic activities of *E. undulata* by evaluating inhibiting effects of acetone root bark extracts on carbohydrate-hydrolising enzymes, alphaglucosidase and alpha-amylase [20]. Acetone extracts of *E. undulata* were screened against C2C12 myocytes, 3T3-L1 preadipocytes and Chang liver cells by measuring the glucose uptake. Acetone root bark extracts of *E. undulata* exhibited hypoglycaemic activity by displaying a glucose uptake of 162.2% by Chang liver cells at 50 μg/mL [20]. The *in vitro* assay in 3T3-L1 preadipocytes indicated that *E. undulata* (126.0%) had some potential to lower blood glucose levels at a concentration of 50 μg/mL [20]. The *in-vitro* assay in Chang liver cells indicated that *E. undulata* extract has some hypoglycaemic activities as the species extract displayed a glucose uptake of 119.7% by Chang liver cells at 50 μg/mL. The IC_{50} of the acetone extract of *E. undulata* was found to be 49.95 and 2.8 μg/mL for alpha-glucosidase and alpha-amylase enzymes respectively [20]. Similarly, Deutschländer *et al.* evaluated the hypoglycemic activities of crude acetone extracts of the root bark of *E. undulata* using streptozotocin-nicotinamide induced type 2 diabetes Wistar rat model [22]. Type 2 diabetes was induced by a single intraperitoneal injection of streptozotocin and administration of nicotinamide 15 min after and animals exhibiting fasting glucose levels of 140–200 mg/dL after 7 d were screened as type 2 diabetes [22]. *E. undulata* extract was administered for 21 d orally at a concentration of 50 and 100 mg/kg respectively with glibenclamide (1 mg/kg) as a positive control. On day 21, blood lipid profiles and body weight were determined by using standard enzymatic colourimetric kits before the rats were sacrificed by cervical decapitation. The crude acetone extract of *E. undulata* root bark at a concentration of 100 mg/kg body weight significantly lowered fasting blood glucose levels as well as elevated cholesterol and triglyceride levels to near normal without any weight gain [22]. The results indicate that the crude acetone root bark extract of *E. undulata* exhibit antidiabetic activity in type 2 induced diabetic rats [22].

Deutschländer *et al.* evaluated the hypoglycaemic activities of compounds α-amyrin-3*O*-β-(5-hydroxy) ferulic acid, betulin, lupeol and epicatechin isolated from a crude acetone extract of the root bark of *E. undulata* var. *myrtina* by determining *in vitro* screening of glucose utilization by C2C12 myocytes at a concentration of 25 or 50 μg/mL [32]. The inhibition of carbohydrate-hydrolysing enzymes were also established at concentrations ranging from 0.02 to 200.00 μg/mL. The *in vitro* assay on C2C12 myocytes revealed that epicatechin was active (266.3%) in lowering blood glucose levels at a concentration of 25 μg/mL and betulin was active to a lesser extent (121.4%) at a concentration of 50 μg/mL [32]. Results obtained from the alpha-glucosidase assays showed that an inhibition of 68%, 39% and 40% on exposure of compounds α-amyrin-3O-β-(5-hydroxy) ferulic acid, lupeol and epicatechin respectively at a concentration of 200.0 μg/mL, and IC_{50} values for compounds α-amyrin-3O-β-(5-hydroxy) ferulic acid, lupeol and epicatechin were found to be (4.79 ± 2.54), (6.27 ± 4.75) and (5.86 ± 4.28) μg/mL respectively [32]. The screening of plant extracts and associated compounds scientifically validated traditional use of *E. undulata* for treatment of diabetes in South Africa [20,23].

6.8. Toxicity and cytotoxicity

Deutschländer *et al.* investigated cytotoxicity activities of *E. undulata* acetone root bark by evaluating its effects on pre-adipocytes and hepatocytes cell lines [20]. The crude acetone extract of *E. undulata* root bark gave positive results (hypoglycaemic activity) in the *in vitro* assays done on C2C12 myocytes, 3T3-L1 preadipocytes and in Chang liver cells without displaying any toxicity effects [20]. The carbohydrate-hydrolysing enzymes alpha-amylase and alpha-glucosidase were also inhibited to some extent [20]. But the compound 7-methyljuglone which has been isolated from the roots of *E. undulata* [33] was tested for cytotoxic activity (ED_{50} < 20 mg/mL) against a panel of cell lines using cell culture systems as described by Kigodi *et al.* [38]. The results indicate that 7-methyljuglone displayed cytotoxic activity against all cell lines and its most intense responses were observed with KB (human nasopharyngeal carcinoma), P-388 (murine lymphocytic leukaemia), LNCaP (human prostate cancer), ZR-75-1 (human breast cancer) and U373 (human glioblastoma) cells at 4.8, 0.1, 0.8, 2.2 and 2.7 μg/mL, respectively [38]. The cytotoxicity of 7-methyljuglone was also reported on several cancer cell lines including human oral epidermoid carcinoma (KB) with IC_{50} value of 4.1 μmol/L, the human lung cancer cells (Lu1) with IC_{50} value of 13.2 μmol/L and hormone-dependent human prostate cancer cells (LNCaP) with IC_{50} value of 3.7 μmol/L [39]. The toxicity of diospyrin and 7-methyljuglone toward the Vero cells was found to be high with IC_{50} values of 17.8 and 15.1 μg/mL, respectively [40]. At 10 μmol/L, 7-methyljuglone induced apoptosis against leukaemia HL60 cells with the percentage of sub-G1 phase ranging from 10.3% to 27.5% whilst the IC_{50} value of 8.75 μmol/L was reported on this cell line [43]. Due to its cytotoxic nature, 7-methyljuglone poses potential toxicological effects when *E. undulata* is used as herbal medicine.

7. Conclusion

The ethnomedicinal applications of *E. undulata* were shown to be quite broad, but it is clear that several areas of the species' usage in traditional medicine still require pharmacological validation. Preliminary phytochemical research conducted by Mbanga *et al.* showed that *E. undulata* is characterized by alkaloid compounds [12]. Detailed research is required aimed at characterizing the alkaloids associated with the species and the pharmacological activities of such compounds. Future research on the species should also identify other bioactive compounds, details of their molecular modes or mechanisms of action, pharmacokinetics and physiological pathways for specific bioactives of *E. undulata*. Some of the compounds isolated from *E. undulata*, for example diospyrin and 7-methyljuglone have been shown to be cytotoxic. Therefore, there is need for rigorous toxicological and clinical studies aimed at identification of poisonous compounds, associated pharmacological activities and the side effects that are likely to be caused when *E. undulata* is used as herbal medicine. Future research should focus on dosage range that is safe for humans and evaluation of target-organ toxicity.

Conflict of interest statement

We have no conflict of interest related to this work.

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