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Article · January 2017

DOI: 10.9734/JAMPS/2016/30431

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Journal of Advances in Medical and Pharmaceutical Sciences
11(4): 1-10, 2016; Article no.JAMPS.30431
ISSN: 2394-1111

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A Review: Ethnomedicinal, Phytochemical and Pharmacological Investigations of *Lannea welwitschii* (Hiern) Engl.

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Authors' contributions

This work was carried out in collaboration between both authors. Authors NO and YDB designed the study, wrote the protocol and wrote the first draft of the manuscript. Author NO managed the literature searches and author YDB proof read the manuscript. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMPS/2016/30431
Editor(s):
(1) Esam Z. Dajani, President, IDDC Corporation, USA and Adjunct Professor of Medicine, Loyola University Chicago, USA.
(2) Alexander E. Berezin, Department of Internal Medicine, Zaporozhye State Medical University, Ukraine.
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Reviewers:
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(2) María Margarita Canales Martínez, UNAM, Mexico.
Complete Peer review History: http://www.sciencedomain.org/review-history/17554

Review Article

Received 8th November 2016
Accepted 14th January 2017
Published 18th January 2017

ABSTRACT

Ethnopharmacological Relevance: *Lannea welwitschii* (Hiern) Engl. (Synonyms: *Calesiam welwitschii*, *Lannea acidissima*, *Lannea amaniensis*), of the family Anacardiaceae is a woody plant that is employed in African traditional medicine to treat various diseases. The study aimed to highlight the folkloric importance, phytochemical composition and reported pharmacological activities of *L. welwitschii*.
Materials and Methods: Google Scholar, Excerpta Medica database and PubMed Central, were the electronic databases used to search for and filter published research on *Lannea welwitschii*.
Results: The review comprehensively summarizes relevant data from published literature on the ethno-botanical uses of *L. welwitschii* within the last five decades. This comprehensive review on

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the phytochemical, pharmacological as well as the toxicological studies conducted has given an indication of the potential of this plant as phytotherapeutic agent or a source of lead compound(s).
Conclusion: This review might be helpful in identifying future research prospects aimed at isolation, purification, and characterization of bioactive compounds present in the plant as well as exploring the underlying pharmacological mechanisms of action.

Keywords: Lannea welwitschii; ethnomedicine; phytochemistry; pharmacology.

1. INTRODUCTION

Lannea welwitschii (Hiern) Engl. (Synonyms: *Calesiam welwitschii* Hiern, *Lannea acidissima* A. Chew., *Lannea amaniensis* Engl. & K.Krause) belongs to the family Anacardiaceae. It is a medium sized woody tree which is commonly found in tropical regions of the world especially in deciduous and secondary forests [1]. *L. welwitschii* is used in most traditional medicine systems in West Africa to manage diverse forms of infections and chronic diseases [1-3]. Aside its traditional medicinal uses, it also has a wide range of significant non-medicinal uses [1].

L. welwitschii in the past few decades has become the focal point of research for newer and potent therapeutic agents in some parts of the world especially the tropical regions due to its vast traditional medicinal uses. The increasing interest in *L. welwitschii* is also attributed to the upsurge in the search for newer and active therapeutic agents from nature of which medicinal plants have played a major role within the past century [4,5]. *L. welwitschii* has been reported in different studies to possess pharmacological activities such as antimicrobial [6], antioxidant [7], anti-inflammatory [8], analgesic [8], antidiabetic [9], antiallergic [8], antidiarrhoeal [10] and cytotoxic activities [11].

Hence the present review seeks to highlight the folkloric importance, phytochemical composition and reported pharmacological activities of *L. welwilschii* which has short- as well as long-term potential to be developed as future phytotherapeutic agents to treat and/or manage diseases and their associated complications that afflict man. The review might facilitate identification of future research prospects aimed at isolation, purification, and characterization of bioactive compounds present in the plant as well as exploring the underlying pharmacological mechanisms of action.

2. HISTORICAL PERSPECTIVE

L. welwitschii is traditionally employed in a wide range of afflictions of man. Some of the non-medicinal uses of the wood of the plant include light joinery, boxes, crates, utensils such as cups, plates, pots and mortars and for veneer and plywood. The boles are also used to make canoes. The wood is also suitable for flooring, interior trimming, vehicle bodies, furniture, hardboard, particle board and pulpwood. In homes, it is used as firewood and for charcoal production [1].

In Ghana, orange-yellow to reddish brown dye from the bark is used for dyeing traditional mourning cloth. The bark is also used in the manufacture of sandals. The tree is occasionally planted as shade tree in coffee and cocoa plantations. Leaves are fed to livestock and mulch from the leaves used as manure [1,2]. The ethnopharmacological use of the plant is tabulated below (Table 1).

Table 1. Medicinal uses of *Lannea welwitschii*

Part of the plant	Use	References
Bark	Antisickling	[3,12]
Root	impetigo	[1-3]
Bark (powdered)	Snakebite treatment, wounds	[1,2]
Leaf	Oedema, epilepsy, Ophthalmia, Toothache	[1,2,13]
Seeds	purgative	[1,2,14]
Root (decoction)	Expectorant, emetic, pulmonary infection, mouth infections, antidote in some poisonings	[1,2]
Bark mixture (with other plant parts)	Diabetes	[2]
Bark (decoction)	Diarrhoea, haemorrhoids, sterility of women, menstrual troubles, pain after childbirth, gonorrhoea, epilepsy, oedema, palpitation, skin infections and ulcers	[1-3]

3. PLANT PROFILING AND LOCAL NAMES IN DIFFERENT CULTURES

Classification

Kingdom: Plantae
Phylum: Tracheophyta
Class: Magnoliopsida
Order: Sapindales
Family: Anacardiaceae
Genus: *Lannea*
Species: *Lannea welwitschii*
Chromosome number: 2n = 28

It is known in vernacular across cultures worldwide some of which have been noted in this review (Table 2).

Table 2. Vernacular names of *Lannea welwitschii*

S. no	People	Vernacular name	Reference
1	Fante	Kakoro	[15,16]
2	Asante	Kuntunkuri	[15,16]
3	Wasa	Kumenini	[15,16]
4	Anyi-Sehwi	Bopire	[15,16]
5	Nzema	Abalapuli	[15,16]
6	Edo	Ewínwán	[16,17]
7	Yoruba	Ekika	[16,17]
8	Abe	Loloti	[16,17]
9	Akye	Tchiwo	[16,17]
10	Anyi	Baiséguma	[16,17]
11	Baule	Trongba	[16,17]
12	Gagu	Tobero	[16,17]
13	Kru-guere	Tétégné	[16,17]
14	Kulango	Duko	[16,17]
15	Kyama	Adubruhia	[16,17]

4. ECOLOGY AND BIOGEOGRAPHY

L. welwitschii is documented to be present in Liberia, east to western Ethiopia and Kenya, southern Tanzania and northern Angola; possibly also in northern Mozambique. It occurs in lowland rainforest and riverine forest up to 1100–1250 m altitude. It is often found in swampy areas in the forest. In West Africa, it shows little preference for different forest zones, but in Cameroon it occurs most abundantly in semi-deciduous forest [1,18,19]. In Ethiopia it is found in regions with a mean annual rainfall of 1500–2000 mm [20]. It is especially common in secondary forest and is considered a pioneer species.

5. PHARMACOGNOSTIC DATA

L. welwitschii is a deciduous or evergreen, dioecious, medium-sized tree which grows up to 30–35 m tall with a straight and cylindrical bole. It is branchless for up to 15–26 m, up to 100–120 cm in diameter, without buttresses. The bark surface is grey to greyish brown, initially nearly smooth but becoming scaly and developing roundish pits, inner bark reddish with white wavy lines, fibrous, with a clear and sticky exudate. The crown consists of large, spreading branches and twigs with numerous lenticels. Leaves are arranged spirally and cluster at the ends of branchlets. They are imparipinnately compound with 3–13 leaflets; stipules absent; petiole and rachis together up to 25–40 cm long and grooved above. The petiolules are up to 2 cm long but petiolule of terminal leaflet are up to 5 cm long. The leaflets are opposite, oblongovate or ovate-lanceolate with dimensions of 10–20 cm × 5–12 cm, cuneate to obtuse at base, long-acuminate at apex, papery, entire and glabrous. They are pinnately veined with 9–15 pairs of lateral veins (Fig. 1) [1,14].

Fig. 1. Aerial part of *Lannea welwitschii* (Adapted from protabase records)

L. welwitschii is inflorescent with an axillary pyramidal panicle up to 20 cm long, yellowish and hairy with stellate hairs. The bracts are ovate and are 3–8 mm long. Its flowers are also unisexual, regular, 4-merous; pedicel is 2–4 mm long; calyx lobes which are 0.5–1 mm long; free petals which are oblong-elliptical and 2.5–3 mm long and yellow-green in colour. The stamens are eight, free; disk cup-shaped and slightly 8-lobed. Its ovary is superior, 4-celled with styles which is usually 4. It has male flowers with

rudimentary ovary and female flowers with rudimentary stamens [1,14].

The fruits are ellipsoid to nearly globose, slightly compressed drupe which is 6–8 mm long, smooth and blackish purple when ripe. The stone is usually 1-seeded. Seedling has epigeal germination; hypocotyl which is 3.5–5 cm long and epicotyl of length 0.5–1 cm. Cotyledons are linear-lanceolate and 1.5–2 cm long. Its first 2 leaves are opposite, simple, ovate with dimensions 2.5–4 cm × c. 1.5 cm and toothed [1,14].

6. PHYTOCHEMISTRY

Methanol leaf extracts from *L. welwitschii* were found to contain tannins (with varying amounts), steroids, flavonoids, alkaloids, sapogenetic glycosides, and carbohydrates [7].

7. ANALYTICAL TECHNIQUES

Agyare and colleagues established the high performance liquid chromatography (HPLC) fingerprint of *L. welwitschii* (Fig. 2) employing Thermo Finnigan HPLC system using Hypersil Gold C18, reversed phase column (150×4.6 mm) [7]. The concentration of the extract used was 10 mg ml^{-1}. HPLC optimum conditions were injection volume: 10 μl, detection wavelength: 254 nm, mobile phase: 0.1% acetic acid: acetonitrile/60: 40 v/v (isocratic condition), temperature: 22°C, pump pressure: 28 MPa, flow rate: 1 ml min^{-1}, and running time: 10 min.

Groweiss et al. selected the organic extract of *L. welwitschii* for the bioassay-guided fractionation based on its modest potency and preliminary indications of unusual pattern of differential cytotoxicity on NCI 60-cell line [11]. The crude dichloromethane-methanol (1:1) extract was subjected to a solvent-solvent partitioning protocol. Sequential bioassay-guided chromatography on Sephadex LH-20 and silica gel gave two novel metabolites, lanneaquinol (**1**) and 2′(*R*)-hydroxylanneaquinol (**2**), in 1.0% and 0.2% of the crude organic extract, respectively (Fig. 3).

The molecular composition of lanneaquinol, $C_{23}H_{38}O_2$, was determined by High-resolution Electron Ionization Mass Spectrometry (HREIMS) (m/z346.2867), a composition also confirmed by Chemical Ionization Mass Spectrometry (CIMS) and in accord with five degrees of unsaturation. The structure was elucidated mainly by interpretation of the spectral data, especially the ^{1}H- and ^{13}C-NMR and 2D-NMR spectra, and by spectral comparisons with synthetic analogues (Table 3).

The second isolated cytotoxic compound (**2**) was slightly more polar than lanneaquinol; its composition, $C_{23}H_{38}O_3$, was established by HREIMS. Comparing the spectral data of **2** with **1** clearly showed that both compounds were very similar with respect to the aromatic ring and the alkyl moiety with only one exception, the presence of secondary hydroxyl group on the alkyl side chain [11].

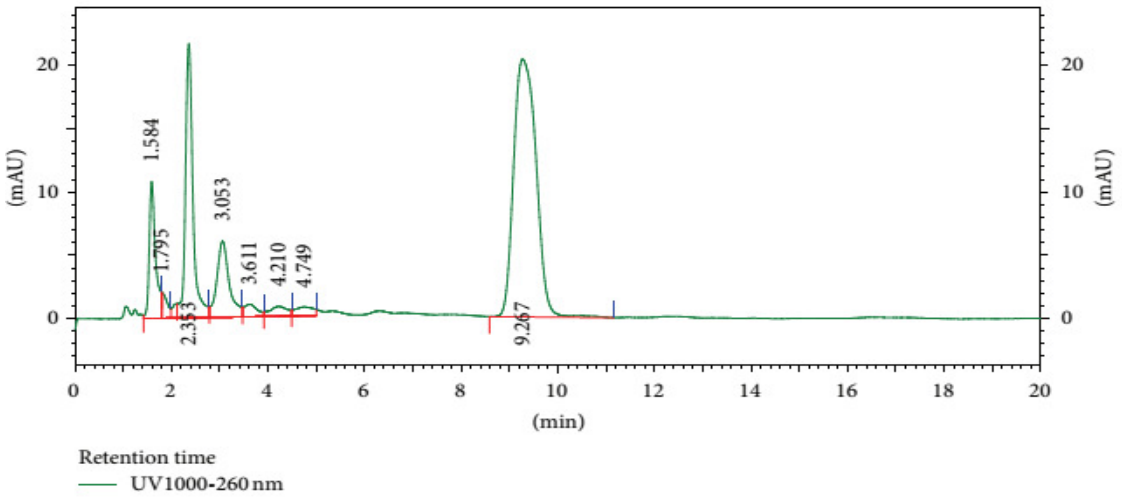

Fig. 2. HPLC chromatogram (finger-printing) of methanol leaf extract of *L. Welwitschii*. λ = 254 nm

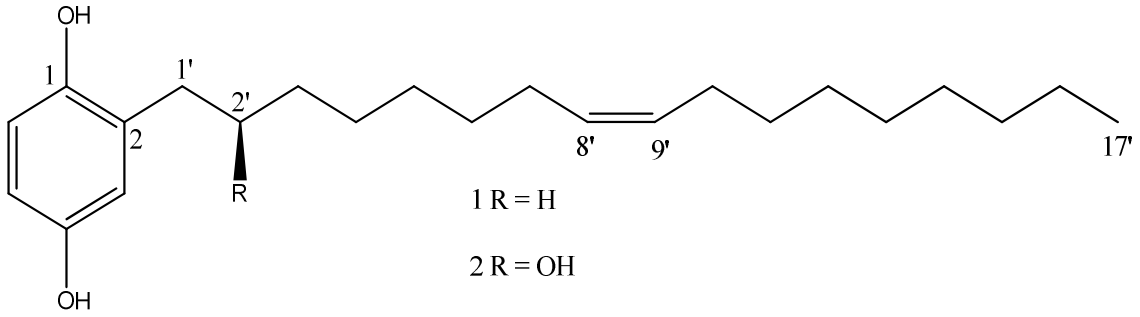

Fig. 3. Cytotoxic metabolites isolated from organic fraction of *Lannea welwitschii*

Table 3. NMR spectra data for compounds 1 and 2*

	^{13}C-NMR Data			^{1}H-NMR Data				
C#	**δ (ppm)**	**mult.**	**HMBC**	**δ (ppm)**	**mult.**	**J (Hz)**	**COSY**	**NOE**
			Lanneaquinol (1)					
4	149.2	C	6.62, 6.60,6.53					
1	147.3	C	6.62, 6.53, 2.52					
2	130.1	C	6.62, 6.60, 2.52					
8' & 9'	129.9, 129.8	CH		5.33	m, 2H		1.99	
3	116.6	CH	6.53, 2.52	6.60	d	2.9	6.53	2.52
6	116.0	CH		6.62	d	8.3	6.53	
5	113.3	CH	6.60	6.53	dd	8.3, 2.9	6.62, 6.60	
1'	30.1	CH_2	6.60	2.52	m, 2H	7.8	1.56	6.60, 1.56
7' & 10'	27.3	2, CH_2	5.33	1.99	m, 4H		5.33, 1.2	
16'	27.7	CH_2		1.25	br s, 22H			
17'	14.2	CH_2		0.86	t, 3H	7.3	1.2	
			2'-Hydroxy-lanneaquinol (2)					
1	149.2	C	6.59, 6.52, 2.75, 2.69					
4	148.9	C	6.75					
8' & 9'	130.2, 129.4	CH		5.33	m, 2H		1.99	
2	126.5	C	6.75, 3.94, 2.75, 2.69					
3	118.0	CH	6.53, 2.52	6.52	d	2.9	6.59	2.75, 2.69
6	117.8	CH	6.59	6.75	d	8.8	6.59	
5	114.7	CH	6.75, 6.52	6.59	dd	8.8, 2.9	6.75, 6.52	6.75
2'	74.5	CH	2.75, 2.69, 1.49	3.94	dddd	10.4, 7.3, 6.5, 2.9	2.75, 2.69, 1.49	
1'	38.9	CH_2	6.52, 3.94	2.75, 2.69	dd dd	14.5, 2.9, 14.5, 7.3	3.94	6.52, 3.94 1.94
3'	36.9	CH_2	2.75, 2.69	1.49	m, 2H		3.94, 1.2	
7' & 10'	27.3, 27.1	2, CH_2	5.33	1.99, 1.2	t, 4H	7.8	5.33, 1.2	
16'	22.7	CH_2	0.86	1.25	br s, 18H			
17'	14.1	CH_3		0.86	t, 3H	7.3	1.2	

[a] *Recorded in $CDCl_3$*

8. PHARMACOLOGICAL ACTIVITY

8.1 Anti-diarrhoeal Activity

With the attempt to provide scientific data to support the folkloric use of *L. welwitschii* in the management of diarrhoea, Amole et al. investigated the anti-diarrhoeal activity of the aqueous bark extract in mice using pharmacological models [10]. The normal intestinal transit, intestinal fluid accumulation, castor oil-induced transit and diarrhoea as well as gastric emptying protocols were employed in their study.

In the normal intestinal transit study, *L. welwitschii* (50 – 400 mg kg^{-1}) produced significant ($p < 0.05$) dose-dependent reduction in normal intestinal transit. Peak effect was produced at 400 mg kg^{-1}, giving a peristaltic index of 65.04 ± 2.69 corresponding to 33.09% inhibition. It must however be stated that the peristaltic index obtained for *L. welwitschii* was lower than that of morphine (10 mg kg^{-1}). In the intestinal fluid accumulation study in mice, oral administration of castor oil produced intestinal fluid volume of 2.33 ± 0.17 ml, the aqueous bark extract of *L. welwitschii* at 400 mg kg^{-1} significantly ($p < 0.05$) reduced the volume of intestinal fluid to 1.40 ± 0.25 ml. The aqueous extract caused a significant ($p < 0.05$) dose-dependent reduction in transit time with a maximal inhibition of 58.55% at 200 mg kg^{-1}. This effect of the extract was not antagonized by yohimbine but by isosorbide dinitrate (IDN). Again, pre-treatment of mice with the extract produced a significant ($p < 0.05$) dose-dependent delay in the onset of copious diarrhoea as well as the frequency of purging in the castor oil-induced diarrhoea model. The extract expectedly did not produce any significant effect on gastric emptying [10].

It was realized from the study that the extract is more effective as an anti-diarrhoeal in diseased state than in a normal state. The absence of inhibitory effect upon yohimbine administration signifies that the extract lacks α_2-adrenoceptor stimulant activity. The extract however could be realized to prevent diarrhoea as well as suppress existing diarrhoea [10]. This study provides data to affirm the folkloric use of *L. welwitschii* in the management of diarrhoea.

8.2 Antimicrobial, Antioxidant and Wound Healing Activity

Microbial infections of wounds lead to complications such as wound dehiscence, gas gangrene and prolonged hospitalization. All these result in delay in wound healing and reduced quality of life. Among plants traditionally employed in the management of microbial infections and wounds is *L. welwitschii.* A number of reported studies give scientific credence to this traditional use of the plant. *In vitro* experimental studies have been explored to establish the antimicrobial activity and antioxidant activity of the plant as well as *in vivo* models to affirm the wound healing potential of *L. welwitsschii*.

Deji-Agboola and Olajubu have reported that the aqueous and ethanol stem bark extract of *L. welwitschii* showed activity against *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and some pefloxacin resistant strains of *Escherichia coli* [6]. It however showed its highest antibacterial activity against *S. aureus* with a 2log unit reduction in the number of viable *S. aureus* cells in 2 h and a total kill after 4 h incubation period. The extract was however bacteriostatic at 1.57 mg ml^{-1} and bactericidal at 3.13 mg ml^{-1} concentrations. Agyare et al. also further confirmed the antimicrobial activity of *L. welwitschii* using agar well diffusion and microdilution assay methods [7]. The MICs of the methanol leaf extract of *L welwitschii* against *E. coli*, *P. aeruginosa*, *S. aureus* and *B. subtilis* were 5, 10, 5, 2.5 and 2.5 mg ml^{-1} respectively with that of ciprofloxacin obtained to be 0.025, 0.055, 0.025, 0.02 mg ml^{-1} against the respective organisms. The MICs of the methanol leaf extract and clotrimazole against *C. albicans* were 2.5 and 0.025 mg ml^{-1} respectively. The MBC/MFC of the extract was between 10 and 50 mg ml^{-1}.

The *in vitro* antioxidant study investigated the free radical scavenging activity of the methanol leaf extracts which was performed using 2,2-Diphenyl-1-Picrylhydrazyl (DPPH). The extract had an IC_{50} of 81.8 μg ml^{-1} with that of α-tocopherol obtained to be 1.5 μg ml^{-1} [7].

The methanol leaf extracts of *L. welwitschii* gave a significant reduction in wound size as compared to the untreated wounds. The rates of wound closure after the application of the extract (7.5% w/w) were compared to the untreated wounds. On the 13th day, *L. welwitschii* extract had a percentage wound closure of 95% ($p < 0.05$) when compared to the untreated wounds. The recorded wound closure (measured as the area) on the 13th day for the *L. welwitschii*-treated wound was 26.15 ± 12.00 mm^2; with that for untreated wound, cream only-treated wound and silver sulphadiazine (1% w/w)-treated wound recorded as 73.00 ± 26.54, 33.58 ± 18.89 and 13.51 ± 8.70 mm^2 respectively. This showed statistically significant and comparable wound closure by the extract and silver sulphadiazine when compared with the untreated wound. The extract significantly ($p < 0.01$) increased the tensile strength of wounds compared to the untreated wounds. The extracts treated wound tissues showed improved angiogenesis,

collagenation, and re-epithelialization compared to the untreated wound tissues [7].

The observed attributes of *L. welwitschii* can be due to the presence of saponins, flavonoids, anthraquinones and tannins in the extracts [6] [7]. The above results give scientific credence to the traditional use of *L. welwitschii* as an antimicrobial and wound healing agent.

8.3 Analgesic Activity

Obiri et al. have reported on the analgesic potential of *L. welwitschii* in mice. This study was informed by the ethnopharmacological use of the plant in pain management [8]. This investigation was made by employing the tail immersion test protocol which predicts centrally mediated pain as described by Janssen et al. [21] and modified by Savegnago et al. [22].

L. welwitschii, at doses of 50, 200, 400 mg kg^{-1}, caused a significant ($p < 0.0001$) and dose-dependent increase in the mean reaction time of treated mice to 49.67 ± 2.18%, 63.20 ± 2.54% and 59.42 ± 0.84% respectively compared to vehicle control group while the total analgesic effect (AUC) was significantly ($p < 0.0001$) and dose-dependently increased to 159.20 ± 19.65, 202.30 ± 12.44 and 228.8 ± 11.29, respectively and were not statistically different from analgesia produced with 100 mg kg^{-1} aspirin.

L. welwitschii showed significant analgesic activity in the entire experimental model which may be due to its high flavonoid content. The role of flavonoid in analgesic activity is primarily to target prostaglandins [23,24] through inhibition of eicosanoid biosynthesis.

8.4 Anti-inflammatory Activity

Various parts of *L. welwitschii* find use in traditional medicine in the treatment of pain and oedema. Obiri et al. evaluated the anti-inflammatory effect of a 70% (v/v) aqueous ethanol extract of the stem bark of *L. welwitschii* in mice using the carrageenan-induced paw oedema model [8].

L. welwitschii (50, 200, 400 mg kg^{-1}) when administered prophylactically caused the mean maximal swelling, at a dose of 200 mg kg^{-1}, to be significantly suppressed to 17.26 ± 3.70% of the inflamed control response while the total paw swellings induced over the 6 h (measured as the area under the time course curve, AUC) was also significantly suppressed to 44.09 ± 4.91% of the inflamed control response and were comparable to that of aspirin (100 mg kg^{-1}). Administered in the same doses after the induction of the carrageenan paw oedema (curative), *L. welwitschii* caused a suppression of the mean maximal swelling, at the 200 mg kg^{-1} administered dose, to 14.49 ± 2.43% of the inflamed control response. The total paw swellings induced over the 6 h were also significantly suppressed to 37.19 ± 4.38% of the inflamed control response. In both protocols the maximal inhibitory effects were realized at the submaximal dose of 200 mg kg^{-1} [8].

This possibly could be due to an increase in concentration of some pro-inflammatory constituents of the crude extract with increasing dose albeit both doses causing significant suppression. Nevertheless, it is evident from this study that *L. welwitschii* possesses anti-inflammatory activity.

8.5 Anti-allergic Activity

Allergy, a component of the inflammatory response is a consequence of the action of released chemicals such as histamine, lipid derivatives and cytokines from allergen–specific IgE-activated mast cells. The inhibitory effect of *L. welwitschii* in allergic response was investigated by Obiri et al. [8]. To investigate this, passive cutaneous anaphylactic model, lipopolysaccharide (LPS)-induced septic shock model, clonidine- and haloperidol-induced catalepsy models in murine were employed.

From the passive cutaneous anaphylaxis study, it was realized that, antigen-induced pinnal inflammation in bovine serum albumin sensitized mice was significantly ($p \leq 0.005$) and dose-dependently inhibited by the ethanol leaf extract of *L. welwitschii* by as high as 84.22% while dexamethasone (10 mg kg^{-1}) and aspirin (100 mg kg^{-1}) suppressed same by 89.53 % and 91.38 % respectively. In the LPS-induced anaphylactic shock study, *L. welwitschii* offered up to 75% protection against endotoxic shock. The dexamethasone (10 mg kg-1)-treated group exhibited maximum protection against endotoxic shock induced with the LPS presenting a survival proportion of 100%. *L. welwitschii* at doses of 50, 200, 400 mg kg^{-1} and chlorpheniramine (10 mg kg^{-1}) showed significant inhibition of clonidine-induced catalepsy in both prophylactic and therapeutic protocols. Haloperidol-induced catalepsy, however, was not inhibited by the extract [8].

From this work, it is realized that *L. welwitschii* inhibits the initial phase of immediate type allergic reactions, probably through interference with the degranulation mechanism. Again, *L. welwitschii* showed a dose-dependent protection against LPS-induced endotoxic shock probably due to reduction or inhibition of release of some mediators of the allergic response [8]. *L. welwitschii* inhibited clonidine-induced catalepsy in mice and this finding is consistent with earlier reports that extracts having anti-histaminic or mast cell stabilizing effect inhibit clonidine-induced catalepsy [25]. From the haloperidol-induced catalepsy, it is evident the extract may not have effect on the dopaminergic system.

These findings suggest that *L. welwitschii* might be useful in the treatment of allergy.

8.6 Antidiabetic Activity

Diabetes and diabetic complications are on the rise worldwide. This has made it necessary that research into antidiabetic medications continue and be given the needed attention. Plants do serve as potential for research into suitable antidiabetic agents. One such plant which is believed to be traditionally employed as a hypoglycaemic agent is *L. welwitschii*, an integral component of the herbal preparation ADD-199. ADD-199 is prepared from *Maytenus senegalensis*, *Annona senegalensis*, *Kigelia africana* and *Lannea welwitschii* and is believed to be an effective antidiabetic preparation. Okine et al. investigated the hypoglycaemic activity of ADD-199 in mice by employing the streptozotocin (STZ)-induced diabetic model [9]. Plasma glucose, insulin and lipids as well as liver glycogen, lipids and lipid peroxidation were measured following treatment for 8 weeks.

The results indicated that plasma insulin levels in normal controls at termination were about 76 μmol l^{-1} compared to trace levels in untreated diabetic mice. ADD-199 increased insulin levels in diabetic mice up to 70% of levels in untreated non-diabetic mice. Basal plasma glucose levels in diabetic controls (18.8 mM) were reduced to 14.0 mM by 100 mg kg^{-1} ADD-199 in less than 2 weeks of administration compared to 4 and 6 weeks for glibenclamide and metformin, respectively. This hypoglycaemic effect of ADD-199 appeared to be associated with the alkaloidal content of the extract. Treatment with ADD-199 reversed the observed elevation in plasma lipids but increased hepatic glycogen, triacylglycerol and cholesterol levels. Again, treatment increased glucose uptake by isolated diaphragms and attenuated hepatic lipid peroxidation. These anti-hyperglycaemic and antioxidant actions of ADD-199 at a dose of 100 mg kg^{-1} day^{-1} are comparable to those of the maximum daily therapeutic doses of glibenclamide (0.25 mg kg^{-1}) and metformin (50 mg kg^{-1}) [9]. These could explain the basis for use of ADD-199, of which *L. welwitschii* is a principal constituent, in the management of diabetes mellitus (DM).

8.7 Cytotoxicity

The search for effective antiproliferative agents continues unabated. This has been made necessary by the side effects and efficacy of most of the existing antiproliferative and cytotoxic agents. Groweiss et al. investigated the cytotoxicity or otherwise of the two novel metabolites isolated from the organic extract of *L. welwitschii* [11].

Lanneaquinol and 2'(*R*)-hydroxylanneaquinol exhibited modest cytotoxicity against the NCI panel of 60 human tumor cell lines. These compounds could therefore be possible leads for the synthesis of newer anti-cancer agents [11].

8.8 Toxicological Assessment

8.8.1 Subchronic toxicity

The subchronic toxicity of the aqueous antidiabetic herbal extract ADD-199, which contains *L. welwitschii*, and administered at a daily dose of 100 or 500 mg kg^{-1} body weight over 30 days, was investigated in male Wistar albino rats. Certain haematological, urine and plasma biochemical parameters, and modulation of some hepatic cytochrome P450 isozymes were measured as indices of organ specific toxicity or potential for drug interactions.

ADD-199 did not affect plasma aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and albumin or creatinine kinase levels. It also did not affect plasma creatinine and urea levels. Furthermore, ADD-199 neither affected pack cell volume (haematocrit) nor blood haemoglobin, red blood cells, reticulocytes, platelets, lymphocytes and granulocyte levels. It, however, caused significant dose-dependent reduction in white blood cells counts at day 15 with varying degrees of recovery by day 30. It also reduced the rate of body weight increase after week 3. However, no changes were observed in organ weights at

termination. ADD-199 did not significantly affect zoxazolamine-induced paralysis and pentobarbital-induced sleeping times as well as certain cytochrome P450 isozyme activities in rats [26].

A conclusion was drawn from this study that, ADD-199 had no overt organ specific toxicity and did not demonstrate a potential for drug interactions via cytochrome P450-mediated metabolism in the rat on subchronic administration.

9. CONCLUSION

Further scientific research into the medicinal bases of *Lannea welwitshcii* is of great importance. This is due to the wide application of the various parts of this plant in the management of afflictions of man. We believe this has become a necessity due to the growing demand for medicines with improved efficacy and much tolerable side effect profile which are also cost effective.

This comprehensive review on the phytochemical, pharmacological as well as the toxicological studies conducted on *Lannea welwitschii* has given a strong indication of the vast importance this plant may contribute to health care delivery. With further studies on product development and clinical trials, on the crude preparations of this plant, we could be looking at very efficacious product of natural origin.

Lastly we are of the belief that further studies conducted on the isolated and characterized metabolites from *Lannea welwitschii* could help arrive at new lead compounds for research into pharmacologically active agents. We henceforth conclude on a note that *Lannea welwitschii* holds promise in new drug discovery and treatment protocol.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/17554