Journal of Pharmacognosy and Phytochemistry

Available online at www.phytojournal.com

J P P Journal of Pharmacognosy and Phytochemistry

E-ISSN: 2278-4136
P-ISSN: 2349-8234
JPP 2015; 3(6): 74-82
Received: 27-01-2015
Accepted: 01-03-2015

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Leonotis leonurus: A herbal medicine review

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Abstract
Leonotis leonurus (L.) R. Br. is a shrub widely known as wild dagga found in most parts of the world and belongs to the Lamiaceae family. Some of the many traditional applications of *L. Leonurus* include the leaf decoction being a strong purgative and used for wound healing and asthma. The leaves and stem are topically applied to sores and skin infections, or taken for high blood pressure and diabetes. The isolated 37 phytochemicals are largely constituted by flavanoids, labdane type diterpenoids and other phenolics detected in the acetone and methanol extracts. The plant contains significant amounts of nutrients and minerals. The essential oils have high content of monoterpenoids and sesquiterpenoids showing significant antimicrobial activities. The plant extracts has good antioxidant and antibacterial properties. A few metabolites responsible for the extract activities have been identified, such as luteolin-7-O-glucoside, leoleorin L, Leoleorin C and Marrubin. An array of pharmacological studies based on traditional claims reported anticonvulsant, antinociceptive, anti-inflammatory, antidiabetic, anthelmintic activities and hypoglycemic properties of *L. leonurus*. The therapeutic value and clinical trial data for the plant should be established to guide its safe use as a herbal product.

Keywords: *Leonotis leonurus,* Traditional use, Pharmacology; Phytochemicals, Diterpenes; Flavanoids

1. Introduction
Leonotis leonurus (L.) R. Br. is a shrub belonging to the Lamiaceae (mint) family, which comprises of about 3,200 species in 200 genera. *L. leonurus* is commonly called 'wild dagga' or 'lion ear' and is found on the rocky hillsides, river banks and tall grassland of tropical Asia, Africa and southern India [1, 2]. The plant stems emanates from a thick wood base. The green leaves are opposite each other on the stems and have abundant glandular trichomes on the leaf lamina [1, 3]. The plant produce orange, apricot or white flowers in clusters and the hairy flowers a resemble lion's ears, hence the name *"leonurus* (lion coloured*)"* [1, 3, 4]. The flowers produce nectar which attracts birds, bees and butterflies. The fruits are 2 mm nutlets. All the plant parts have a strong mint smell similar to other Lamiaceae species [5]. The Lamiaceae family is characterised by short-stalked epidermal glands bearing ethereal oils, populated by monoterpenoid, sesquiterpenoid or diterpenoid [6]. Many of the species of the Lamiaceae family have been used in folk medicine [7].
The Literature surveyed shows that *Leonotis leonurus* is an important plant with traditional medicinal uses such as a remedy for hypertension, coughs and headaches. Many pharmacological and phytochemistry studies have been reported as an attempt to show the pharmacological credence to traditional usage of the plant as a herbal medicine. This review harmonises the traditional, pharmacological and phytochemical studies from 1962-2014 to support future scientific investigations on this plant.

2. Traditional uses
L. leonurus has many reputed traditional medicinal applications and is mainly taken orally or per rectum and as a topical application [8, 9]. Hottentots were particularly fond of smoking it instead of tobacco and used a decoction of the leaf as a strong purgative and as an emmenagogue [4, 9, 10]. Early colonialists employed it in the treatment of leprosy. The leaf tea has a hypnotic effect, is diuretic and relieves headache. The leaf and stem decoction or inhalations have been used internally for cough, common cold, influenza, bronchitis, wound healing and asthma [1, 11-14]. The fresh stem juice is an infusion drunk for 'blood impurity' [4]. The infusions made from flowers and seeds, leaves or stems are widely used as tonics for tuberculosis, jaundice, muscular cramps, high blood pressure, diabetes, viral hepatitis, dysentery, and diarrhoea [1, 6, 15, 16]. Tea made from the whole plant is used for arthritis, piles, bladder and kidney disorder, obesity, cancer and rheumatism [17]. The leaves and stems

decoction are applied topically as a treatment for eczema, skin infections and itchiness [9, 18, 19]. The leaves, roots and bark are widely used as an emetic for snakebites, bee and scorpion stings [1, 6, 20]. The *L. Leonurus* smoke has marijuana-like effects.[21] -pungent odour and is occasionally mixed with flowers and fruits [22]. In ethnoveterinary the roots and leaves water drink is used in poultry, against cattle gall sickness and eye inflammation [23, 24]. Generally the plant is a general tonic, having reputed dermatological, hypertension, anti-inflammatory, pain and wound healing properties.

3. Phytochemistry

L. leonurus aqueous leaf extract phytochemical analysis reports shows the presence of sterols, diterpenes, triterpenoids, tannins, flavonoids, alkaloids, quinines and saponins [25-27].

3.1. L. leonurus essential oil

The oil yield is 0.03% from the leaves and 0.05% from the flowers and sepals [28, 29]. The essential oil profile indicates chemotypic differences based on the origin of the species. The North Africa and European types have sesquiterpenoids, the southern African specie has both monoterpenoids and sesquiterpenoids, while the Indian species have phenols and monoterpenoids [28, 30-32]. Table 1 shows the compositional variations of the leaf, flowers and sepals oil, only the key components are shown.

Table 1: % Composition of the leaf, flowers and sepals oil

Compound	Leaf	Flowers	Sepals
p-Cymene	3.5	1.2	4.4
Limonene	15.6	7.2	5.6
(*Z*)-*β*-Ocimene	7.5	10.8	4.8
(*E*)-*β*-Ocimene	3.0	2.5	0.6
γ-Terpinene	4.7	4.0	nr
Terpinolene	3.6	2.4	0.4
β-Bourbonene	2.1	2.0	0.7
β-Cubebene	2.2	2.4	1.2
β-Caryophyllene	15.2	19.6	30.8
α-Humulene	4.6	6.5	7.8
Germacrene D	18.9	20.0	3.6
Bicyclogermacrene	3.0	3.6	nr
Caryophyllene oxide	2.5	2.9	8.4
Spathulenol	0.9	0.8	2.1

nr-not reported

3.2. L. leonurus phytochemicals

The phytochemical studies on *L. leonurus* have reported the isolation and characterization of labdane diterpenes, acyclic diterpenes, iridoid glycosides, alkaloids, dicarboxylic acid and flavanoids. In all, 37 metabolites have been identified, which includes 21 labdane diterpenes. The occurrence of lactones between C-18 and C-20, C-19 and C-6, and unsaturated ketone at C-7 are the key features of Leonotis labdane diterpenes. The labdane diterpenes presence in *Leonotis leonurus* and other species are a chemotaxonomic marker for the genus and the mint family, Lamiaceae.[33,34] Compounds **4**, **18**-**20** were not given names and because of their structural similarities to the other labdane diterpenoids, they are here named Leoleorin K (**4**), Leoleorin L (**18**), Leoleorin M (**19**) and Leoleorin N (**20**) [33]. Compounds **14**-**16** were also identified as Leonurenones A-C from the leaves water extract [35]. The secondary metabolites identified from *L. leonurus* are shown in Table 2.

Table 2: *L. leonurus* secondary metabolites

Part and Extract	Compound	Reference
Leaves	13R-premarrubin **1**	25
Acetone	13S-premarrubin **2**	
	Leonurun **3**	36
	Compound X **4**	37, 38
	Compound Y/Leoleorin A **5**	37, 40, 41
	Marrubin **6**	
	Hispanolone **7**	42

Methanol Methanol/ Dichloromethane	Leoleorin B **8**/Anhydro **5** Leoleorin C **9** Leoleorin D **10** Leoleorin E **11** Leoleorin F **12** 16-*epi*-Leoleorin F **13** Leoleorin G **14** Leoleorin H **15** Leoleorin I **16** Leoleorin J **17** Leoleorin L **18** Leoleorin M **19** Leoleorin N **20** Nepetaefolin **21**	43, 33, 43 43, 35 43, 34 33, 35
Flowering tops Ethanol (95 %) Leaves and Flowering parts Water and 70% methanol Flowering aerial parts 70% Methanol	Dihydroxyphytyl palmitate **22** Succinic acid **23** Uracil **24** Acteoside **25** Geniposidic acid **26** Luteolin **27** Luteolin 7-O-β-glucoside **28** Apigenin **29** Apigenin-8-C-β-glucoside **30** Apigenin-7-O-β-glucoside **31** 4′, 6-Dimethoxyluteolin **32** 3′-Methoxyluteolin 7-O-β-glucoside **33** 3′-Methoxyluteolin **34** Apigenin-7-O-(6″-O-*p*-coumaryl)-β-glucoside **35** Apigenin-6-C-α-arabinoside-8-C-β-glucoside **36**	45 35, 46 46 46
Leaves Water and methanol	Leonurine **37**	1, 47

4. L. Leonurus Pharmacology

4.1. Effects of plant material storage

The TLC profiling of the chemical and biological activity indicated changes due to the ageing of plant material or extract. The fresh plant antibacterial activities increased from 90 days and are consistent for up to 5 years at 20 ºC, while the extracts activity increased from 5 days, but deteriorated after 15 days at 55 ºC and 100% humidity [48]. The polar spots that develops during ageing of both hexane and ethanol extracts could be attributed to the opening of the labdane diterpenes lactone ring to form free hydroxyl groups. The storage of plant materials affects their chemical and biological activity profiles and this is influenced by temperature, light, pH, microbes and enzymes [49]. The room temperature ageing offers time for slow cell membrane degradation that allows greater extraction of active components. An HPLC finger printing of the ageing process coupled with metabolites isolation would provide insights into the chemical changes.

4.2. Total polyphenol content

The leaves total phenolic contents of the acetone, methanol and water extracts is 15.48, 14.42 and 8.02 mg tannic acid/g of dry material respectively [50]. Acetone and methanol extracts are good solvents to extract the plant polyphenols.

4.3. Nutritional analysis

L. leonurus leaves proximate analysis, composition was moisture content (58.9%), ash content (12.0%), crude protein (19.0%), crude lipid (6.0%), carbohydrate (51.0%), alkaloids (0.35%), saponins (4.0%), phytate (7.31%), crude fibre (12.02%) and had a calorific value of 334 kcal/100 g. The elements that constitute the leaves are Mg, Ca, K, P, Na, Fe, Zn, Cu and Mg [50].

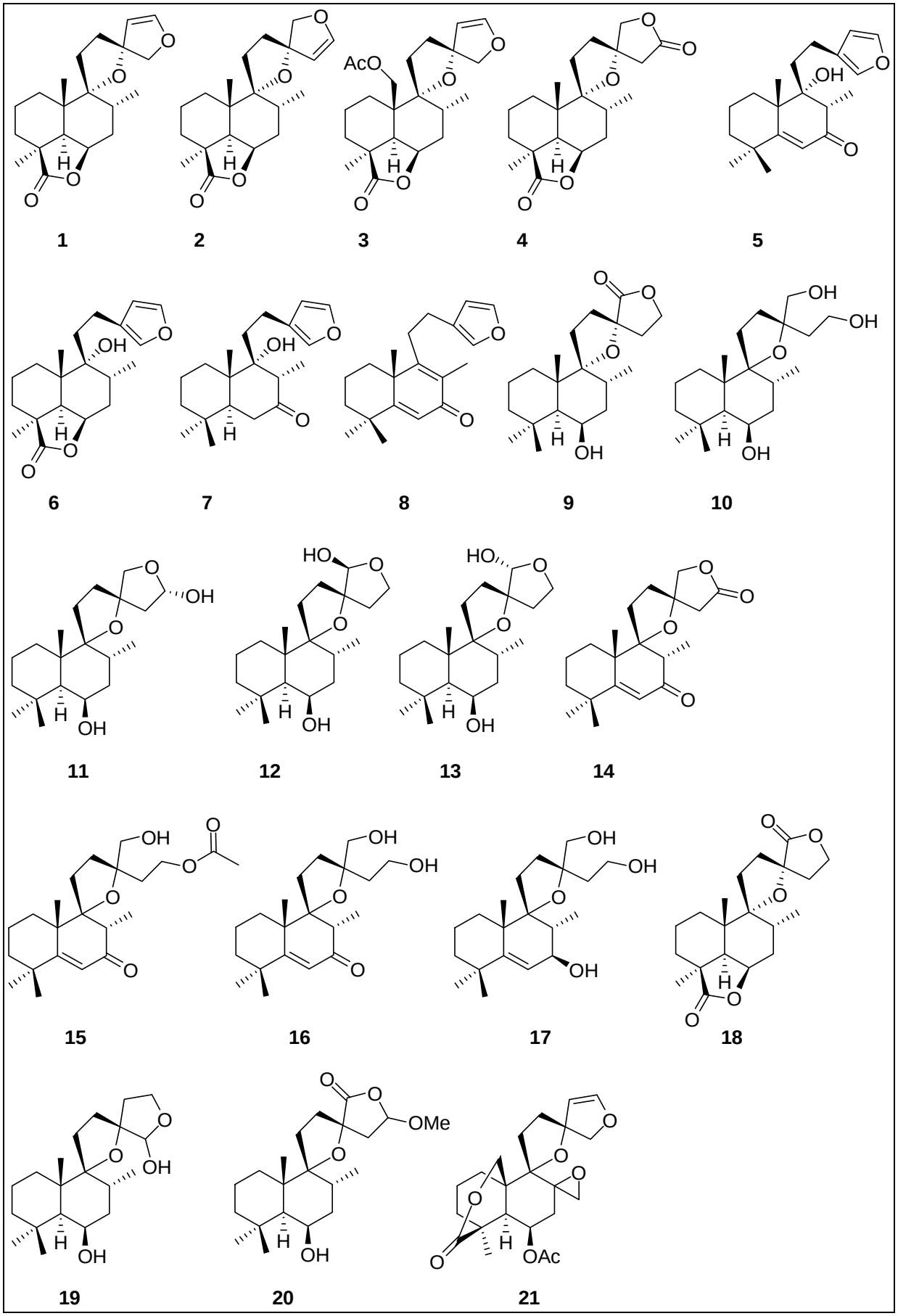

Fig 1: Diterpenes reported from *L. leonurus*

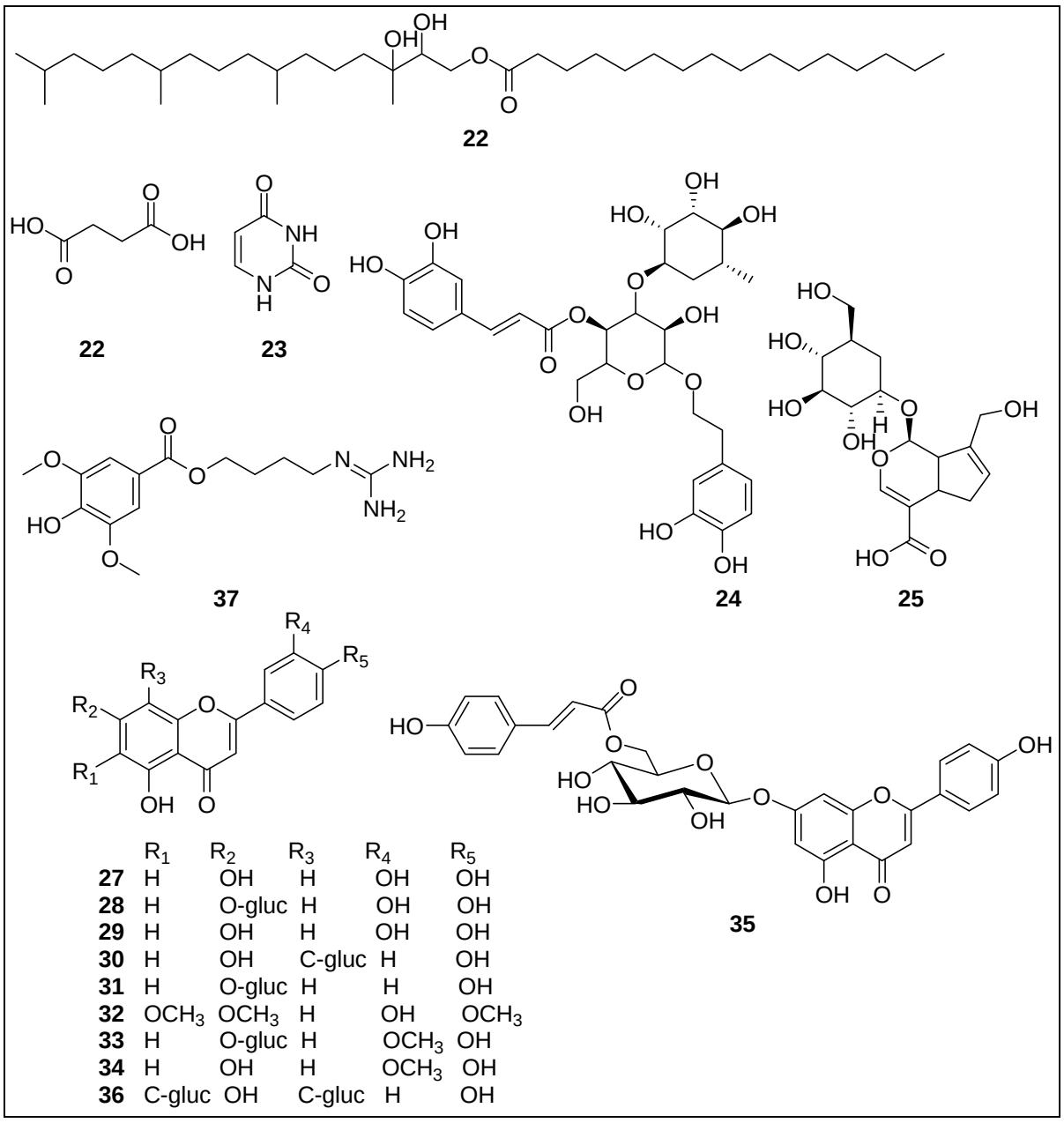

Fig 2: Polyphenols from *L. leonurus*

4.4. Radical scavenging

The ferrous reducing antioxidant power (FRAP) values of leaf acetone, methanol and water extracts are lower than those of catechin, ascorbic acid and quercetin, but these extracts at 1 mg/mL mopped up 91-99% of DPPH radical [50]. Frum and Viljoen reported the aqueous leaf extract DPPH IC_{50} value of 34.2 ppm [51]. Good antioxidant properties are necessary for plants used in wound healing as they accelerate the wound healing process [52, 53] and in the prevention, and management of obesity, diabetes mellitus and retinopathy [54-56].

4.5. Antibacterial

The leaves acetone and methanol extracts showed antibacterial activities (MIC = 1-5 mg/mL), while the water extracts were inactive using agar diffusion or dilution method against standard strains *Bacillus cereus, Staphylococcus epidermidis, Micrococcus kristinae, Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, Salmonella pooni, Serratia marcescens* and *Pseudomonas aeruginosa*. *Klebsiella pneumonia,* which is commonly implicated in hospital infection was not responsive to leave extracts [50, 57]. The ethanol extract has activity against *K. pneumonia* with MIC values of 1.56 mg/mL for fresh leaves and 0.78 mg/mL for 90 days and one year aged leaves [48]. The plant flower and leaves essential oils shows activities against the clinical isolates of the above strains and *Shigella sonnel* (MIC =0.04-1.3 mg/mL).[28] The ethanolic and ethyl acetate extracts exhibited antifungal activities against the clinical (MIC = 1.01 mg/mL) and standard strains (MIC = 2.09 mg/mL) of *Candida albicans*, while the hexane and aqueous extracts were inactive. The compounds (**22**-**26** and **29**) isolated from the chloroform fraction of the ethanol extract show no antimicrobial activities

against *Candida albicans, Escherichia coli, Pseudomonas aeruginosa, Candida neoformans, Mycobacterium intracellulare and Aspergillus fumigates*.[45]
Compound **9**, **11** and **20** do not show activity against *M. tuberculosis* [33]. Therefore the compounds responsible for the extract antimicrobial activity are unknown. The antibacterial, antifungal and antioxidant activities lend credit to the use of the plant for the treatment of microbial infections, wounds healing [51, 58]. Skin disease and anti-inflammatory, while its leaves could be a supplementary nutrient for the major sources. The stem and leaves aqueous and methanol extracts do not stimulate fibroblast growth [57]. The aqueous leaf and stem extracts have no *in vitro* antiphage activity against bacteriophages [59].

4.6. Anti-malaria
The twigs and leaves dichloromethane/methanol (1:1) extract has antimalarial activity against the chloroquine-sensitive strain (D10) of *Plasmodium falciparum*, IC_{50} = 5.4 ug/mL. The roots, twigs and leaf aqueous extracts were inactive [60, 61]. Compound **28** from EtOAc extract have antimalarial activity against the D6 clone (2.2 mg/mL) and the chloroquine-resistant (W2) strain (1.8 mg/mL) [45, 62].

4.7. Anti-inflammatory
Cyclooxygenase (COX-1) inhibition was consistent for up to 1 year (92% inhibition) of plant material storage, while the inhibition deteriorated rapidly when the plant ageing process was accelerated [48]. The flowering parts ethanol and chloroform extracts show strong hepatoprotective and anti-inflammatory activities in rats [46]. The leaf and stems extracts (methanol and water) and essential oils also indicated anti-inflammation activity using the 5-lipoxygenase assay [56]. The inflammatory cascade is complex and diverse, hence the need to do bioactivity guided fractionation to establish simpler fractions that exert COX-1, 5-lipoxygenase and antioxidant activity rather than isolating molecules that show a singular property. It is also common phenomena to find extracts that exert better activities than their purified components [63]. Therefore, simple fractions would enable other pharmacological effects on a number of targets involved in effective *trans*-membrane drug delivery and place high concentrations of the active agent at the pathophysiologically relevant site [64]. The dose ranges for the anti-inflammatory and analgesic properties are 25-75 mg/ml [65].

4.8. Cardiovascular activity
The leaves methanol extract exhibited cyclooxygenase enzyme inhibitory activity and antihypertensive effect. The positive chronotropic and inotropic effect both *in vivo* and *in vitro* were attributed to the β1 agonist effect and direct vasoconstrictive effect [27, 66]. The aqueous extract shows hypotensive effect in hypertensive and normotensive male Wistar rats, [67, 68] while it decreased the blood pressure (BP) and heart rate (HR) in hypertensive rats [67] and had no effect in normotensive rats.[69] The leaf methanol fraction increased both BP and HR, which contrasts the effects shown by the water extracts [66]. The aqueous extract has positive inotropic and negative chronotropic activity at low concentrations, while at higher doses (> 2 mg/mL) it has toxic effects on isolated perfused rat heart [70]. This indicate that the aqueous and alcoholic extract contains different cardioactive compounds. There is a lack of clinical trial data about the leaf cardiovascular activity of *L. leonurus* and this need to be explored to validate the traditional healer's claims. The leaf aqueous extract has shown an antiepileptic effect and anticonvulsant activity in mice, while the leaf ethanol extract *in vitro* inhibited cyclooxygenase enzyme [26, 71]. Compound **18** is the diterpenoid with cardiovascular activity and negative chronotopic effect [44]. Marrubin which constitute 5% of the leaves acetone extract has shown cardioprotective and vasorelaxant properties [72]. Therefore the isolation of cardiovascular active compounds on the intact and isolated rat heart would be valuable data.

4.9. Diabetes
Traditionally the plant leaf and flowers are used to treat diabetes and hypertension [1, 17, 73, 74]. The leaves aqueous extract show hypoglycaemic effects in streptozotocin (STZ)-induced diabetes mellitus, by reducing the blood glucose and low density lipoprotein while increasing high density lipoprotein levels [75]. The diabetic activity were pertinently attributed to the different flavonoids, diterpenoids, polyphenolics, [76] but recently Marrubin was identified as the antidiabetic active constituent of the organic extracts [40,41]. Marrubin also has anticoagulant, antiplatelet and anti-inflammatory properties [40].

4.10. CNS effects
L. leonurus is known as "wild dagga" that is a mild narcotic, a habit forming drug and its leaves are smoked for partial paralysis and epilepsy [4, 21]. The leaves aqueous extract shows 81% inhibition (at 1g/mL) in a binding assay at the $GABA_A$ site. Compounds **14** and **16** were not the active metabolites as they had no activity in the assay [35] and the aqueous extract $GABA_A$ active metabolites are unknown. In a CNS receptor binding assay, compound **5**, **10**, **15** and **16** inhibited binding at the serotonin 5-HT_{1A} receptor, compounds **10**, **11**, **14** and **15** were active at the D1- dopamine receptor. Compound **9** activities were at the H1-histamine and Sigma-1 receptors, where it also showed moderate affinity for Sigma-1 receptors [43]. The modulation of dopaminergic system [21] was proposed to be the reason for the calming effect of dry leaves smoke. The leaves ethanol extract displaced 66% transport protein bound [3H] citalopram at the serotonin reuptake protein SSRI binding site, which was a non conclusive anti-depressive effect as the plant might have other mode of action which needs further probing [77]. The leaf ethanol extract exhibited moderate monoamine oxidase (MAO) inhibitory activity (IC_{50} = 63 µg/ml) and aqueous extract has poor non-selective and specific MAO inhibition [48].

4.11. Anthelmintic activity
The leaves ethanol and water extracts were inactive in the anti-amoebic activity against *Entamoeba histolytica* but showed anthelmintic activity against *Caenorhabditis elegans*, [16] the aqueous extract inhibited the egg hatching and larval development of nematode parasites in small stock [78, 79]. The plant is safe to use at levels of 100 mg/ml [65]. The anthelmintic metabolites are not identified, but the reports support the careful use of the plant against nematodes parasites.

4.12. Toxicity
The leaves toxicity profile in female rats was acute toxicity at 3200 mg/kg dose, sub-acute toxicity at 1600 mg/kg and chronic toxicity at 200 mg/kg doses. The male rats acute toxicity was higher than 5000 mg/100g body weight for the aerial parts methanol and chloroform extracts [46]. The herb produces alterations to hematological, biochemical and

histopathological changes in rats, which may have expedient effects on the normal functioning of the blood system, kidney and liver of the animals [80, 81]. The ethyl acetate and chloroform flowering tops extracts and compounds **22**, **25**, **26** and **28** were not cytotoxic to kidney fibroblasts and Vero cells (4.76 µg/mL) [45]. The plant extracts had no effects on brine shrimps [59]. The tea made from stems, leaves and flowers were not recommended during pregnancy [17] and should be taken fresh. The plant should be carefully used for medicinal purposes. The value of herbal medicines lies in their "therapeutic" value and its healthful benefits to society, hence the therapeutic value for the purported uses of *L. leonurus* should be evaluated.

5. Conclusions

This literature survey of the phytochemistry, pharmacological and traditional applications of *Leonotis leonurus* L. R. has shown that the plant has diverse activities such as anticonvulsant, antinociceptive, anti-inflammatory, antidiabetic, antibacterial, anti-oxidant, anthelmintic activities and hypoglycemic properties, which justifies the herb use in the management and control of pain, arthritic, diabetes, dermatological, hypertension, anti-inflammatory and wound healing properties. Thirty seven secondary metabolites were reported, which includes 21 labdane diterpenes which are chemotaxonomic markers for the *Leonotis* genus and the mint family, Lamiaceae. The leaf, flowers and sepals essential oils are mostly constituted by monoterpenoids and sesquiterpenoids. The isolation of metabolites responsible for extracts activities is recommended and the data on clinical trials about the *Leonotis leonurus* herb and its extracts is of fundamental importance.

6. Acknowledgement

The Author thanks the University of Botswana Library's Inter Library Loan in assistance with the Literature search.

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