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Phytochemistry and pharmacology potential of *Lippia javanica*: a bibliometric and systematic review

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Abstract

Lippia javanica (Burm. f.) is an African plant with numerous ethnomedicinal uses, including asthma, tuberculosis, colds, influenza, pneumonia, coughs, and dermatitis treatments. Many of the ethnomedicinal properties and folkloric claims about the plant have since established by numerous scientific studies. In this context, we conducted the bibliometric and systematic analyses of scientific literature on the phytochemistry and pharmacology of *L. javanica* with special focus on the plant's bioactive metabolites. Bibliometric data - using the Web of Science and Scopus databases - revealed that most of the research on *L. javanica* were carried out in Africa, with South Africa accounting for more than 50% of the total outputs. However, the growth in this research domain has been relatively slow in recent years. Furthermore, the critical analysis highlighted the pharmacological activities of various crude extracts of the plant and also identified more than 40 new metabolites as well as their bioactivities. Therapeutic relationships were established between the enumerated bioactives and the potential use of the plant for the treatment of bacterial and viral infections, neurodegenerative conditions, tumours as well as diabetes. In all, it was observed that despite the immense potential of the plant and its metabolites in drug research and development, it remains grossly unexplored in this regard. It is envisaged that the information from this review will facilitate and chart a course for future investigations into the pharmaceutical uses *of L. javanica.*

Introduction

The utilization of native plants as herbal remedies and for nutritional purposes in developing countries - especially by their rural population- continues to rise due to the reliance on these natural products as their primary health support [1]. For instance, more than 80% of the Nigerian citizenry still rely on traditional medicine for their healthcare [2]. Similarly, recent estimates showed that South Africa has between 68,000 to 300,000 traditional healthcare practitioners, with plant-based preparations playing critical roles in addressing various ailments affecting both human and animal health [3]. According to Salmerón-Manzano and Manzano-Agugliaro [4], about 10% (approximately 500,000) of plants are currently used as medicinal plants, thus, signifying a very large landscape that has not been fully utilized. For example, despite the rich biodiversity of the Southern African region, only ~2000 out of the more than 20 000 plant species currently curated are utilized in traditional medicine and are of commercial significance [5]. Hence, it is undeniable that there is huge knowledge gap in this field; a gap further widened by the fact that only a few of the phytochemicals from the plants and their pharmacological importance are currently known. Thus, it is believed that the screening of plants- with medicinal value - for their phytochemicals and their pharmacological activities will help identify new chemical entities with relevance in disease treatment and management [6]. Furthermore, these potent compounds from plants may also serve as potential lead compounds for the development of more effective drug compounds via structural modification.

Lippia javanica (Burm. f.), an endemic Southern African plant, is one of the notable plants that has continually served as an important component of the regions' traditional medicine; it was recently established as a multi-purpose plant with increasing industrial demand [7]. *L. javanica*, sometimes referred to as "fever tea" or "koorsbossie," is an upright, small shrub that can grow up to 4.5m high and found throughout Southern Africa, encompassing nearly the whole country of Swaziland as well as huge areas of South Africa [8]. The plant has also been shown in literature to be found in other parts of Sub-Saharan Africa, in Asia and in the Americas [7]. The applications of the plant range from its use as ordinary tea with fever and pain-relieving benefits to the treatment other ailments including colds, coughs and other bronchial illnesses as well as basic HIV/AIDS symptoms [9]. The plant may also be used topically for disinfection and for the treatment of dermatitis and dry skin; extracts from the plant have also demonstrated significant hepatoprotective effects and radical scavenging activities [10]. It is also combined with *Artemisia afra* for the treatment of malaria and in prevention against dysentery and diarrhoea [11]. Furthermore, its volatile oil contains important phytochemicals, especially terpenoids, such as 3-methyl-6-(1-methylethylidene)-cyclohex-2-en-1-one, which have shown significant antibacterial and antiplasmodial activities [12].

The wide range of biological activities that have been ascribed to *L. javanica* underscores its immense potential as a repository of various pharmaceutically active ingredients and as a basis for future semi-synthetic drugs. As a matter of fact, it is becoming rarer in the wild as a result of its huge demand leading to overharvesting by local consumers and traditional health practitioners [7]. Recently, the increases in the usage of herbal preparations from the plant called zumbani, was hypothesized as one of the key factors that contributed to the remarkable management of the recent COVID-19 pandemic in the Southern African country of Zimbabwe [13]. Against the background, the current appraisal aimed to present a critical and current report on scientific findings on *L. javanica* with respect to its medicinal and pharmaceutical importance. Although many research works have been published on the ethnomedicinal importance, biological activities, and pharmacological potentials of *L. javanica*, no bibliometric study was identified. Generally, bibliometric analyses utilizes mathematical modelling and statistical methods to evaluate a literature information on a specific research field [14]. Thus bibliometric studies are based on the structure, relationship, and variation within curated literature data to facilitate knowledge advances in the target field [15]. Consequently, bibliometric analysis have become instrumental in predicting, identifying and developing hotspots and addressing knowledge gaps in various research endeavours [16,17].

Hence, this paper firstly presents a brief bibliometric assessment of global research outputs on *L. javanica*, with the objective of evaluating the growth (or otherwise) and the distribution of global research output on the plant. Furthermore, using a systematic approach, the paper also critically evaluated the plant's phytochemicals and pharmacological properties while highlighting some of its ethnobotanical and ethnomedicinal importance. It is our expectation that this review will serve as an important guide for all important stakeholders in formulating a solid basis into the medicinal benefits of *L. javanica* as well as its effective utilization in the pharmaceutical industry.

Methods

Literature search and selection criteria

Bibliographic data was obtained from the Scopus database using the search term, *Lippia javanica,* within a time frame of 1973 – 2023 (Fig. 1). The Scopus database was also utilized for the evaluation of some bibliometric metrics while further analyses were done using VOSviewer software (version 1.6.19). VOSviewer, which has several visualization functions, is one of the standard tools for bibliometric studies in the sciences including biological sciences [18,19]. Subsequently, the systematic review was done via searches on the ScienceDirect, Scopus, ISI Web of Science and PubMed, using these search strings: (*Lippia javanica* OR *L. javanica*) AND (pharmacology OR pharmaceutical OR medicinal OR therapeutic OR bioactivity) AND (cytotoxicity OR toxicity) [20].

Published works on the bioactivity, pharmacology, medicinal use as well as toxicity of *L. javanica* were included; in addition, only publications in English language were considered. Publications on other species of the genus *Lippia* were excluded, and focus was placed on works between 2003-2023 except for historical purposes. Furthermore, all works from predatory journals, and unpublished literature we also excluded. Separate independent searches were conducted, and the adherence of the selected articles was validated by the stated inclusion/exclusion criteria.

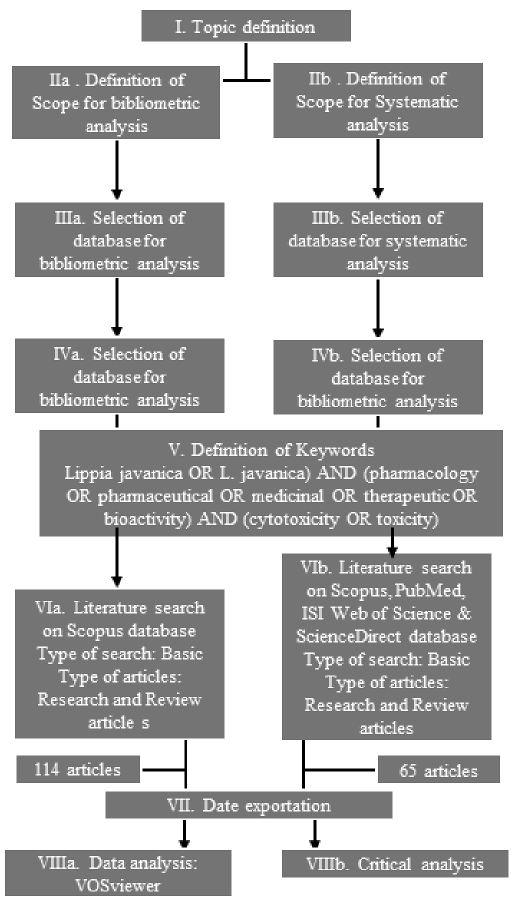

Figure 1: Flowchart for bibliometric and systematic analysis (adapted from Ampese et al. [15]).

Discussion

Bibliometric analysis

A total of 114 articles - published in the last fifty years- were listed from the Scopus database using "*Lippia javanica*" as the keyword. Relative to the bibliometric data of other plants of ethnomedicinal importance, the number of articles retrieved in this study is relatively low pointing out to the shortage of scientific knowledge with respect to the medicinal value of *L. javanica.* For instance, 8192 articles were recorded in the bibliometric analysis of Aloe vera within a period of 20 years [21]; while only 34 articles were listed for *L. javanica* within the same time period. The various papers were mainly distributed across the fields of agricultural sciences, biological sciences, and plant biology. It was observed that following a lack of interest in the plant between 1975 and 1989, scientific enquiry into *L. javanica* experienced a growth from 1990 until 2016, with occasional dips in between (Fig. 2). In the last 5 years, there was a drop in published articles from 2018 to 2021, however, a steep rise was recorded from 2021 until this current year, which might be due to the various claims on the plant's antimicrobial activity, especially with regards to the recent SARS-CoV-2.

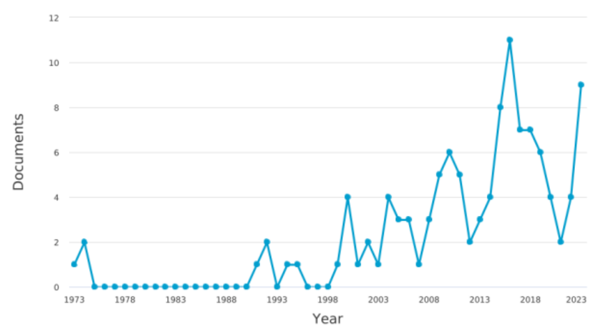

Figure 2: Yearly output of Scopus-indexed articles on *L. javanica* in the last 50 years (blue line) for the keywords "*Lippia javanica*". Accessed February 2024.

Keyword analysis using the VOSviewer software was carried out to evaluate the evolving research themes associated with *L. javanica.* In order to show the interrelationship between these thematic domains, the top keywords identified were further used to generate a keyword network map as illustrated in Fig. 3. In this context, the terms medicinal plants, plant extract, non-human, unclassified drugs and controlled study were identified as the most prominent keywords. These selected keywords signify that the majority of the work carried out on the plant have been at the crude extract level and that the bioactivities were evaluated using *in vitro* and animal models. Based on document analysis, there was no study on the human trial of this plant and its metabolites. It is also noteworthy that the keywords

Africa, African traditional medicine and traditional medicine were also covered in the network, showing the importance of the plant to African ethnomedicine.

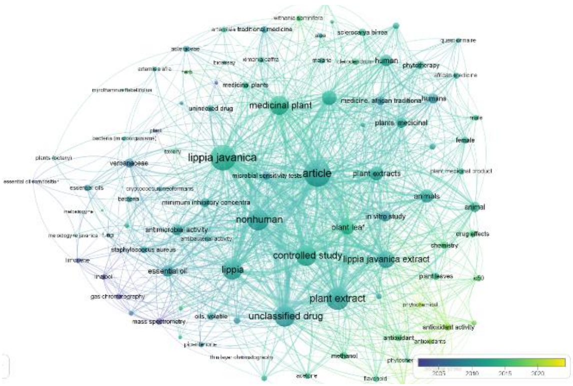

Figure 3: Keyword network map obtained by VOSviewer software version with Scopus- indexed articles (1973- 2023), using "*Lippia javanica*" as a sole keyword, and refined to the relevant research domain. Thicker coloured lines indicate a more significant number of connections while the size of the spheres indicate the relative impact of the keyword.

It was observed that a huge proportion of the investigations on the phytochemistry and pharmacology of *L. javanica* were carried out in ten countries (Fig. 4); thus, indicating the need for more concerted scientific investigations on this plant. Most of the studies were conducted in Sub-Saharan Africa with the exception of Brazil, France, India, the United Kingdom and the United States. The inclusion of countries from the global North in this result is probably as a result of collaborative research between these nations and the African countries. However, the prominence of India amongst this country may be largely because *L. javanica* is also endemic to the Indian sub-continent and it has been the subject of various scientific studies in the region [7,22]. South Africa dominated knowledge production in this research area as it accounted for a large proportion of the studies (more than 50%), followed by Zimbabwe; thus, highlighting the importance of the plant to the traditional medicinal institutions of the Southern African countries.

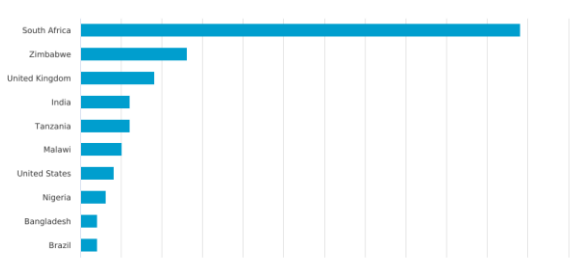

Figure 4: Country distribution of Scopus-indexed articles on *L. javanica* in the last 50 years, for the keyword "*Lippia javanica*". Accessed February 2024.

Systematic analysis

Ethno-medicinal importance of L. javanica

L. javanica (Fig. 3) belongs to the family Verbenaceae, which encompasses approximately 30 genera and 800 species [22]. The genus *Lippia* has around 200 plants species, out of which only 15 have been reported in tropical Africa. Specifically, the specie is endemic to Ethiopia, Uganda, Botswana, Angola, Malawi, Tanzania, Zimbabwe, Central African Republic, Congo (Democratic Republic), Swaziland, Kenya, South Africa, Zambia, and Mozambique, all in Sub-Saharan Africa [11]. Conversely, the plant has also been reported in Mexico, Bangladesh, and India. The plant typically grows on the edges of forests, in grasslands on hillsides, woodland clearings, plantations, farmed areas and along the banks of streams [23]. The plant has also been discovered in grassy rocky kopjes, riverine vegetation, low to high elevated forests, woody grasslands, scrub bushland, as well as on marshy ground borders [24].

The plant's propensity to grow in a broad range of temperature, edaphic and vegetation conditions suggests that the plant is resilient and that it can be easily cultivated in large quantities, which is a plus for its medicinal-pharmaceutical applications. However, there are currently no reports on the production of the plant on a commercial agricultural scale, and this has prompted the attempt at its propagation via tissue culture approach [7]. *L. javanica* is utilized traditionally for a range of therapeutic purposes as summarised in Table 1. Based on the current appraisal, the plant is mostly used traditionally for the management of respiratory tract-related disorders [asthma, nasal congestion, colds, bronchitis, colds, influenza, lung infections, sore throat, tuberculosis, pneumonia, treatment of shortness of breath (dyspnoea), gastrointestinal infections, measles, diarrhoea, scabies, shingles, malaria, abdominal ache, ulcer, headache, kidney problem, fever, antidote, treatment for chicken pox, and inflammation (Table 1). There are also reports on *L.* javanica's potential of the plant in HIV symptoms management [25] as well as claims on its importance in COVID-19 management [13]. Other applications of the plant include food additives, insect repellent, wound treatment, skin treatment, as well as scabies and lice treatment [26].

Pharmacological activities of L. javanica

As earlier stated, *L. javanica* is an important component of the Southern African traditional medicine, and its leaves are usually consumed as tea in different parts of the sub-continent. Thus, *L. javanica* is known to exhibit various biological activities ranging from antimicrobial to antioxidant and to antidiabetic.

Plant part	Mode of use	Ethnomedicinal importance	Country	Ref
Leaves	Sun dried leaves	Medicinal tea	South Africa, Botswana, and Zimbabwe	[26]
Leaves	*L. javanica* leave and *Cyrtanthus obliquus* decoction are administered orally for several days	HIV/AIDS symptoms management	South Africa, Kenya	[27,28]
Leaves	Decoction made from *L. javanica* leave and *C. obliquus* are administered orally for several days	Cancer	South Africa	[26]
Leaves	Prepared as vegetable	Respiratory problems	Zimbabwe and South Africa	26,29]
Leaves and twigs	Inhalation of smoke of the leave and twigs or concoction from these parts taken orally	Asthma	Botswana, South Africa, and Zimbabwe	[11]
Leaves and twigs	*Camellia sinensis* (L.) cooked alongside the leaves and twigs of *L. javanica* with corn, cassava, groundnuts, and other ingredients	Food additive	Kenya	[30]
Leaves	Taken orally or synergized with other plants	Nasal congestion	Botswana, South, Africa, and Zimbabwe	[31]
Root and Leaves	Root and leave concoction or leave powder	Kidney problem	Swaziland	[32]
Leaves, twigs	*L. javanica* infusion ingested orally, breathed, used topically or as an imbiza, or a mixture of *L. javanica* and *C. obliquus* administered orogastrically.	Cold treatment	Kenya, and Botswana	[11]
Twigs leaves, roots and stems	Decoction from *L. javanica* leaf and root administered orogastrically, or leaf decoction combined with any of the following species' leaves: *Eucalyptus grandis, Tetradenia riparia, Bridelia cathartica, Carallia brachiata,* and *Trichilia emetica* taken oragastrically	Headache, migraine	Zimbabwe, South Africa, and Kenya	[33]
Leaves and roots	The decoction taken orally	Influenza treatment	Mozambique, South Africa	[27,33]
Leaves	Oral infusions	Lung infections	Zimbabwe, South Africa	[34,35]
Leaves	Decoction consumed orally	Sore throat treatment	South Africa	[35,36]
Leaves and stems	Oral consumption of leaf and stem decoction, body washing with an infusion of the leave and stem, or oral consumption of infusion of leaves and stems combined with *Artemisia afra* leaves	Measles	Mexico, Kenya, Zimbabwe and South Africa	[26,37]
Leaves	Leave decoction took orally	Respiratory disorders	India, South Africa	[38]
Leaves	Bathing with the decoction or oral administration	Shortness of breath (dyspnoea)	Zimbabwe	34,39]
Roots and leaves	Decoction taken orally	Diarrhoea	Mozambique and South Africa	[40]
Roots and leaves	Infusion consumed or used topically, also utilized as steam.	Scabies	Zimbabwe, and South Africa	[11]
Leaves	The decoction is taken orally	Malaria treatment	Mozambique, South Africa	[28]
Leaves	Juice consumed after chewing leaves.	Abdominal pains	Zimbabwe	[29]
Roots	Juice consumed after chewing roots as an antidote for food poisoning	Antidote	Botswana	[11]
Leaves and stem	Steaming	Chickenpox	South Africa	[41]
Leaves and stem	Decoction or infusion taken orally	Inflammation	South Africa	[34]
Leaves and stem	Decoction from the leaf and stem eaten orally	Malaria, fever, and use as an insect repellent	Zimbabwe and India	[41]
Leaves and stem	Juice from *L. javanica* and *Allum sativum* taken orally	Ulcers	Bangladesh and India	42,43]

Table 1: Ethnomedicinal applications of *L. javanica* plant parts.

It is quite interesting that the plants, its extract as well as the metabolites have been demonstrated to display significant antiviral activity, both *in silico* and *in vitro*. To this end, this section discusses in detail the major pharmacological activities of *L. javanica* and highlights, for the first time, its therapeutic potential against anti-SARS-CoV-2.

Figure 4: *Lippia javanica* (Burm.f.) Spreng.

Antiviral activities of L. javanica

L. javanica extract is made up of a plethora of active metabolites including saponins, terpenoids, flavonoids, coumarins, polyphenols, alkaloids, as well as proteins, which have been noted previously for their antiviral effects [11,25]. Due to the prevalence of HIV/AIDS on the African continent as well as the recent global COVID-19 scourge, many investigations on the antiviral activities of *L. javanica* have been concentrated on these two diseases. The need for drugs that can selectively inhibit the human immunodeficiency virus (HIV) is critical given that this infection is present on every continent, although more prevalent in Sub-Saharan Africa. Compounds extracted from *L. javanica,* and some other plants were examined by Mujovo et al. (2008) [25] for their suppressive ability on HIV-1 Reverse transcriptase activity in vitro; in the study, three phytocompounds from *L. javanica*, *viz.*, myrcenone, apigenin, and hoslunddiol showed 91, 53, and 52% inhibitory activities respectively against the viral enzyme at 0.1 mg/mL. Even though there are numerous claims about the usefulness of *L. javanica* in treating viral infections in South Africa, the last scientific study on this claim was carried out more than a decade ago, hence, more research on the anti-HIV activities of *L. javanica*'s crude extracts and refined metabolites is required.

SARS-CoV-2, a recently discovered variant of the coronaviruses family, caused a recent respiratory disease pandemic that is now known as COVID-19. Most of the treatment approaches for this pandemic are centred on symptomatic care and supportive therapy. However, a report by Dwarka et al. (2020) [44] found that some metabolites from South African medicinal plants including *L. javanica* may be useful in treating coronavirus infections. In this regard, eight potential druggable inhibitors were identified from *L. javanica* against SARS-CoV-2 protein targets, *viz*., apigenin, carvone, ipsenome linalool, piperitenone, myrcenone, α-terpineol, and α-thujone. Subsequently, it was discovered that seven *L. javanica* phytocompounds (apigenin, aromadendrene oxide, verbascoside, campesterol, T-cadinol, β-phellandrene, and α-thujone) also showed significant activity, in silico, against druggable targets of SARS-human CoV-2's cell proteins (hACE2, Cathepsin L, and TMPRSS2) [6]. Among the *L. javanica* phytocompounds, aromadendrene oxide had the best affinity against hACE2 while verbascoside showed a more promising affinity against TMPRSS2, and Cathepsin. These observations regarding the anti-COVID-19 potential of *L. javanica* indicate the several anti-SARS-CoV-2 phytochemicals contained in *L. javanica*, which require further wet-lab pharmacological studies to ascertain their bioactivities. As no specific anti-COVID-19 drug has yet been identified, pharmacological studies on these promising anti-SARS-CoV-2 plant-derived phytochemicals, could help accelerate and guide the development of new anti-COVID-19 drugs.

Antibacterial activities of L. javanica

L. javanica has been demonstrated to have immense potential to treat several bacterial infections[45]. Essential oil from *L. javanica* aerial parts were demonstrated to possess significant bioactivities against five bacteria species; exhibiting inhibitory activity on *Klebsiella pneumoniae* and *Streptococcus pneumoniae* at a minimum inhibitory concentration (MIC) of 0.76 mg/mL, some remarkable bioactivities were also recorded against *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. *L. javanica* essential oil were found to be active against *Bacillus cereus* and *Klebsiella pneumoniae* as well as against *Cryptococcus neoformans*, a fungal pathogen [46]. The bioactivity against *K. pneumoniae* was quite remarkable as the essential oil was active even at a MIC value of < 5 µg/mL, while implicating phytochemicals such as cis-Sabinene hydrate, camphene, borneol, limonene, germacrene D, myrcene, linalool, 1,8-cineol, and terpinen-4-ol in such activities [46]. The inhibitory and bactericidal activities of its crude extract against *E. coli*, *S. aureus*, and *Enterococcus faecalis* were also shown with MIC values 0.25 - 1.13 mg/mL [45]. Makhafola et al. (2019) [47] demonstrated the significant antibacterial activity of the plant's acetone extract recording MIC values of 0.04 mg/mL and 0.28 mg/mL against *P. aeruginosa* and *S. aureus*. Earlier studies have also demonstrated that *L. javanica* phytochemicals such as lippialactone have antibacterial activities against *E. coli* and *S. aureus* [48]; piperitenone against *Acinetobacter calcoaceticus*, *Bacillus subtilis*, *E. coli*, *Salmonella typhi*, *Micrococcus kristinae*, and *S. aureus* [12,49] and apigenin against *Vibrio cholera, E. faecalis, S. typhi, Proteus mirabilis*, and *P. aeruginosa* [50]. The findings from the antibacterial evaluation of *L. javanica* in these studies gives some validation to the use of the plant in traditional medicine for the amelioration of several bacterial and fungal infections. Hence, more pharmacological studies on promising metabolites from *L. javanica* could help accelerate the development of novel antibacterial drugs that could help in the fight against antibiotic resistance.

Antitumor activities of L. javanica

In an earlier study by Fouché et al. (2008) [51], *L. javanica* dichloromethane root extract demonstrated strong antiproliferative properties against the breast cancer cell lines MDA-MB-435, MDA-N, and MALME-3M with total growth inhibition of 1.82, 1.86 and 2.09 µg/mL respectively [11]. Although studies demonstrating the lead phytocompounds present in *L. javanica* root extracts are still elusive, however, studies have shown that linalool, a phytochemical found in the plant, exhibits significant antitumour activities [52]. An earlier investigation has also demonstrated that limonene (another *L. javanica* metabolite) has inhibitory effects on breast and pancreatic cancers [51]. Another terpenoid found in *L. javanica* called α-pinene has been noted to prevent p65 protein from entering LPS-stimulated THP-1 cells [51]. These results point to the need for more scientific research in lead identification and isolation from *L. javanica* for anticancer pharmacological studies. This can be accelerated via computational drug design method against some of the stem cell metabolic pathways, proteins and genes implicated in breast and prostate cancer for lead identification followed by both *in vitro* and *in vivo* pharmacological studies.

Compound name	Common name	Pharmacological potential	Ref
Hydroxyethyl(trimethyl) azanium	Choline	Gallbladder regulation, liver function, and lecithin (a key lipid) formation.	[60]
(3S,8S,9S,10R,13R,14S,17R)-17-[(2R,5R)-5-ethyl-6-methylheptan-2-yl]-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol	Sitosterol	Methyltransferase inhibitor,anticholesteremic and antioxidant activities	[61]
Formonitrile	Hydrogen cyanide	ND	62]
methyl (15R,16S,20)-16-methyl-17-oxa-3,13-diazapentacyclo[11.8.0.02,10.04,9.015,20]henicosa-1,3,5,7,9,11,18-heptaene-19-carboxylate	Serpentine	Hypertension, mild high blood pressure, nervousness, and(insomnia)	[46]
(2,3,4,5,6-pentaphosphonooxycyclohexyl) dihydrogen phosphate	Phytic acid	Antioxidant	62]
Oxalate	Oxalic acid	Antimicrobial	62]
Methyl(1S,4aR,7aR)-4a-hydroxy-7-(hydroxymethyl)-1-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl]oxy-5,7a-dihydro-1H-cyclopenta[c]pyran-4-carboxylate	Theviridoside	ND	61]
(1R,2R,5R)-4,6,6-trimethylbicyclo [3.1.1]hept-3-en-2-ol	cis-Verbenol	Antioxidant	61]
2,4-dimethylpyridin-3,5-diol	NA	ND	53]
Thujone	Thujone	ND	55]
Mesityl oxide	Mesityl oxide	ND	55]
Isophorone	Isophorone	ND	
3,4-dihydroxybenzoic acid	Protocatechuic acid	Antibacterial, antiulcer, antidiabetic, anticancer, anti-inflammatory, and antiviral..	
4-hydroxy-3,5-dimethoxybenzoic acid	Syringic acid	Anti-inflammatory, antibacterial, and antiendotoxic properties.	[53]
(Z)-3-(4-hydroxyphenyl) prop-2-enoic acid	*cis*-p-Coumaric acid	Antioxidant, antidiabetic, anti-inflammatory, antiplatelet, anti-cancer and anti-ulcer	[63]
4-hydroxy-3-methoxy benzoic acid	vanillic acid	Anti-nflammation	
(E)-2,3-dideuterio-3-(2,3,4,5,6-pentadeuteriophenyl) prop-2-enoic acid	*Trans*-cinnamic acid	Antimicrobial	
4-hydroxy-3,5-dimethoxybenzaldehyde	Syringaldehyde	Food additive	
(E)-3-(4-hydroxy-3-methoxyphenyl) prop-2-enoic acid	Ferulic acid	Anti- thrombosis, anti-, and mutagenic	
2-(3,4-dimethoxyphenyl)-5-hydroxy-6,7,8-trimethoxychromen-4-one	5-Demethylnobiletin	Anti-inflammation	
5-hydroxyl-6,7,40-trimethoxylflavone	5-hydroxyl-6,7,4-trimethoxylflavone	ND	[63]
6,7,13,14-tetrahydroxy-2,9-dioxatetracyclo[6.6.2.04,16.011,15]hexadeca-1(15),4,6,8(16),11,13-hexaene-3,10-dione	Ellagic acid	Antioxidant, anti-inflammatory, , and antiproliferative.	[60]
2-Butanone, 4-phenyl	Benzylacetone	ND	[55]
Benzene, 1-ethoxy-4-ethyl-	4-Ethylphenetole	ND	[55]
3,9- Epoxy-p-mentha-1,8 (10)-diene	Menthofuran	ND	[64]
naphthalene,1,2,3,4, 4a, 5, 6, 7-octahydro-4a-methyl 15.94 10.90 1062 Benzene, 1-ethoxy-4-ethyl	naphthalene	ND	
3,4-dimethylbenzyl alcohol	Benzenemethanol	ND	
6-epi-shyobunol	6-epi-shyobunol	ND	
Allylguaiacol	Allylguaiacol	ND	
Isoborneol	Isoborneol	ND	
(2E)-3,7-dimethylocta-2,6-dien-1-ol	Geraniol	ND	
2-hydroperoxy-1-methylidene-4-prop-1-en-2-ylcyclohexane	*ρ*-Mentha-1(7),8-diene	ND	[65]
(2-methyl-5-prop-1-en-2-ylcyclohex-2-en-1-yl) acetate	Carvyl acetate	ND	[46]
1-methyl-4-propan-2-ylbenzene	4-Isopropenyltoluene	Implicated in the prevention of coughs and eliminating anti-phlegmatic	[55]
1,1,4,8-Tetramethyl-cycloundeca-4Z,7Z,10Z-triene (1z,4z,7z)-1,5,9,9-tetramethyl cycloundeca triene	Cycloundecatriene	ND	[55]
Panasinsene	Panasinsene	ND	
α- Cadinol	α- Cadinol	ND	
β- Maaliene	β- Maaliene	ND	
Gemacrene D	Gemacrene D	ND	
Neryl (S)-2-Methylbutanoate	Neryl (S)-2-Methylbutanoate	ND	
Cycloheptane, 4-methylene-1-methyl-2-(2-methyl-1-propen-1-yl)-1-vinyl	Cycloheptane	ND	
Chamigran-7-en-9-ol, 2, 10-dibromo-3-chloro	Chamigran-7-en-9-ol	ND	
Binapacryl	Binapacryl	ND	
Chamigran-9-one, 2, 10-dibromo-3-chloro	Chamigran-9-one	ND	
Isobornyl acetate	Isobornyl acetate	ND	
Sorbic acid vinyl ester	Sorbic acid vinyl ester	ND	
3-Methylbut-2-enoic acid, 2,3,4,6-tetrachlorophenyl ester	NA	ND	
(E) -2-Isopropyl-5-methylphenyl 2-methylbut-2-enoate	NA	ND	[55]
1,4-Cyclooctadiene	1,4-Cyclooctadiene	ND	
Cyclopentane, (3-methylbutylidene)	Cyclopentane, (3-methylbutylidene)	ND	
2,4-Hexadiene, 2,5-dimethyl	Biisocrotyl	ND	
1,4-Cyclohexadiene, 1-ethyl	1-Ethyl-1,4-cyclohexadiene	ND	
Epi-bicyclosesquiphellandrene	Epi-bicyclosesquiphellandrene	ND	
1,1,7-trimethyl-4-methylidene-2,3,4a,5,6,7,7a,7b-octahydro-1aH-cyclopropa[e]azulene	Alloaromadrene	Anti-HIV and antibacterial	
3-Tetradecen-5-yne, (E)	3-Tetradecen-5-yne, (E)	ND	
Furazan,3-(dimethylaminomethylenamino-4-(1,2,4-triazol-3-yl)	NA	ND	[36]
1H-Pyrazole, 1,3,5-trimethyl	1,3,5-Trimethylpyrazole	ND	[55]
9-Borabicyclo [3.3.1] nonane, 9-(3-methoxycyclohexyl) oxy-	NA	ND	[55]
Cyclohexyldichlorophosphine	Cyclohexyldichlorophosphine	ND	
4-Cyclopropylcyclohexane	4-Cyclopropylcyclohexane	ND	

***NA: Not applicable; ND: Not determined.**

Table 2: Profile of the newly identified *L. javanica* phytochemicals

Neuroprotective activity of L. javanica

Suleman et al. (2022) [53], showed that treatment with *L. javanica* extract improved glutathione and superoxide dismutase activities, which served as markers for brain antioxidant status and decreased lipid peroxidation in animals exposed to lead poisoning. In addition, TNF-alpha, a pro-apoptotic protein, and anticholinesterase activity were also decreased in rats treated with *L. javanica* relative to those that had been exposed to Pb without any treatment [53]. Their histological study verified the neuroprotective benefits of the plant, as demonstrated by decreased vacuolization, apoptosis and oedema in the hippocampus, and they linked the observed activities to the phenolic-rich content (cis-p-coumaric acid, 2,4-dimethylpyridin-3,5-diol, syringic acid, protocatechuic acid, vanillic acid, trans-cinnamic, syringaldehyde, and ferulic acid) of *L. javanica*. Similarly, 5% percent *L. javanica* infusion was found to be beneficial in lowering brain oxidative stress, lipid peroxidation, and neuronal damage in Pb-induced brain damage using rat models, suggesting that the plant may be useful in mitigating the onset of oxidative stress-induced neurodegenerative disorders [53]. These significant results of the neuroprotective assessment of *L. javanica* provide some support for the traditional use of the plant in headache and migraine treatments.

Other biological activities of L. javanica

The anti-diabetic effect of extracts from *L. javanica* was demonstrated in male alloxan-challenged mice, as both intraperitoneal and oral administration significantly lowered blood glucose levels at all dose levels [54]. The antidiabetic activities of the methanolic extract of *L. javanica* was shown as it exhibited alpha-amylase inhibitory effect with IC_{50} value lower than 1000 µg/mL. AdeogunMaroyi and Afolayan (2018) [55] investigated the effectiveness of oils made from *L. javanica* leaves against *Artemia salina* and observed its moderate to mild pesticidal properties against the organism. The study found that the median lethal concentrations of fresh and dried leaves oils were 90.11 and 128.49 g/mL, respectively, whereas the solvent-free microwave extract yielded LC_{50} values of 96.52 and 101.13 g/mL, respectively. Like other plants, the various bioactivities of the plant under study can be attributed to the radical scavenging ability of its various metabolites [45,53]. Suleman et al. (2022) demonstrated that *L. javanica* leaf infusions showed remarkable antioxidant activity, which was connected to the plant's phenolic composition. In a different research, the methanolic extract of *L. javanica* leaves, which had significant phenolic and flavonoids, displayed high scavenging activity of more than 80% [45]. The results of the antioxidant evaluation of *L. javanica* in this study have demonstrated the antioxidant ability of the plant, which could justify its various health properties, and its application in food as a dietary supplement. Consequently, further utilization in the food industry following identification of potent lead antioxidants from *L. javanica* will confer greater economic importance to the plant.

Phytochemistry of L. javanica

A previous study had earlier enumerated 173 different metabolites from *L. javanica*, including alkaloids, phenolics, and essential oils components, thus indicating wide diversity in the phytochemical components of the plant [11]. It was observed that more than 75% of the identified phytochemicals were essential oil constituents including linalool, α-cedrene, myrcenone, icterogenin , eugenol, nonanal, perilline, ipsenone, camphor, cis-tagetone, verbenone, germacrene, carvone, nerolidol, linalool oxide, geraniol, geranial, ipsdienone, eucalyptol, 3-carene, terpinen-4-ol, ß-alaskene, nerolidol, α-terpineol, α-thujene, γ-terpinene, linalool acetate, and myrcene [11]. Furthermore, 21 of the 173 previously identified metabolites were phenolics (verbascoside, isoverbascoside, theveside-Na, theveridoside, cirsimaritin, eupatorine, 6-methoxyluteolin 4'-methyl ether, luteolin, apigenin , tricin, isothymusin, 5-dimethyl noboletin, 4-ethylnonacosane, 3-4-7 trimethylether, crassifoliside, chrysoeriol, tricin, diosmetin, genkwanin, salvigenin, and lippialactone). Eighteen amino acids (valine, isoleucine, aspargine, phenylalanine, lysine, histidine, tyrosine, tryptophan, alanine, glycine, tryptophan, alanine, proline, serine, glutamic acid, glutamine, ß-alanine, ß-amino isobutyric acid, 4-hydroxyproline and α-aminoadipic acid) and one alkaloid, xanthine were also identified [11]. These compounds were noted to be isolated from the different parts of the plant with the leave mostly implicated. For example, coumarin, verbascoside, and isoverbascoside were isolated from the aerial part of the plant [8]. The essential oil constituents of the plant such as those reported by Hutchings and van Staden (1994) [56], including triterpenoid, saponin, icterogenin have been implicated to have various pharmacological activities such as anti-inflammatory, hepatoprotective, antimicrobial, and sedative effect [57]. Similarly, some flavonoids from the plants have been shown in other studies to be associated with anticancer, antibacterial, antioxidant, antiviral, and hepatoprotective properties. For example, apigenin and luteolin have been linked to antibacterial, antiviral (anti-HIV, herpes simplex virus), analgesic, and anti-inflammatory activities [58]. In the current review, we highlight more than 40 new compounds that are entirely different from the previously reported compounds (Table 2). Some of the newly identified metabolites belong to chemical classes such as derivatized amino acids (choline); steroids (sitosterol); cyanide (hydrogen cyanide); phenolic compounds (ellagic acid, cis-p-coumaric acid, vanillic acid, trans-cinnamic, syringaldehyde, syringic acid, ferulic acid, 5-demethylnobiletin, and 5-hydroxyl-6,7,4-trimethoxylflavone); alkaloids (serpentine); phytate (phytic acid); oxalate (oxalic acid); and phenol (cis-verbenol and 2,4-dimethylpyridin-3,5-diol). The remaining metabolites were observed to belong to other classes including; monoterpenoids (4-isopropenyltoluene, geraniol, p-mentha-1(7),8-diene, carvyl acetate, etc); iriloid glycosides (theveridoside); sesquiterpenoids (epi-bicyclosesquiphellandrene, alloaromadrene, etc); esters (3-tetradecen-5-yne, (E); 1H-pyrazole, 9-(3-methoxycyclohexyl) oxy-; 4-cyclopropylcyclohexane, cyclohexyldichlorophosphine, 1,3,5-trimethyl, etc); ketones (thujone, mesityl oxide, and isophorone) and aldehydes (2-Hexenal (E)). The variation in the phytochemicals constituents of *L. javanica* could be due to geographical and environmental factors, geographical differences, harvesting times, and differences in the multiple metabolic pathways [9]. According to Kamanula et al. (2017) [59], variation in *L. javanica* phytochemicals profile was due to differences in harvesting times, edaphic conditions, climatic variations, the maturity stage, season, as well as the method of extraction . Similar to earlier observations, majority of the newly compiled *L. javanica* metabolites were isolated from the plant aerial parts, with the leaf being the most implicated. Cis-p-coumaric acid, 2,4-dimethylpyridin-3,5-diol, syringic acid, protocatechuic acid, vanillic acid, trans-cinnamic, syringaldehyde, and ferulic acid were isolated from the leaf extract of *L. javanica* and were shown to possess acetylcholinesterase activity while being effective in reducing Pb-induced brain oxidative stress, and neuronal damage [53]. Adeogun, Maroyi and Afolayan (2018) [55], on the other hand isolated various compounds from *L. javanica* leaves using different oil extraction techniques (solvent-free microwave extraction and hydrodistillation) and demonstrated their pesticidal activity against *Artemia salina*. These compounds were noted to belong to the esters, ketones, aldehydes, monoterpenoids, or sesquiterpenoids classes [55]. Thus, the phytochemical diversity of *L. javanica* lends credence to its native use in the treatment of several diseases and its application in food preservation and as a dietary supplement. However, further pharmacological studies on extracts from the plant and the constituent metabolites are important to exploit the full potential of the plant in drug discovery, especially as new phytochemicals from the plant are discovered.

Toxicity and cytotoxicity activity of L. javanica

Although preparations from plants are considered safe or possess minimal toxicity, there are instances when some of these phytoconstituents might be toxic, especially when consumed at higher concentrations [66]. Hence, to ensure the safety of *L. javanica* for human consumption as well as for the purpose of standardization of preparations and formulations from the plant, it is considered imperative to review the toxicity of *L. javanica*. However, compared to other plants of equal ethnomedicinal importance, only a few studies have been carried to evaluate the toxicity of *L. javanica.* It was previously noted that triterpenoids derived from the genus *Lippia* are icterogenic and their consumption may result in jaundice due to liver injury [11]. Reports have also shown that the ingestion of xanthine (a phytocompound endemic in *L. javanica*) has harmful effects on mammals as they have pharmacological effects on the central nervous system, peripheral vasoconstriction, bronchial muscles, myocardium, and diuresis [11]. In this regard, continuous usage of *L. javanica* at high dosages for extended period of time could be lethal. However, many other *L. javanica* secondary metabolites - such as flavonoids, phenolic glycosides, and essential oil- have been demonstrated to be safe and do not cause acute toxicity. The study by Makhafola et al. (2019) [47], showed that *L. javanica* hexane extract was significantly less toxic than the acetonic extract. The study concluded that the cytotoxicity of these plants should be properly understood and carefully considered before using them in conventional medicine. The observation regarding the toxicity and cytotoxic activities of *L. javanica*, highlights the significance of solvent selection for extraction in the toxicity and cytotoxicity of *L. javanica* [47]. Hence, dose to time response must be appropriately researched and calculated prior to administration, however, adverse effects of some of the metabolites that have been implicated in toxicity may be ameliorated with the development of micro- and nano-based therapeutic formulations.

Conclusion

This review has brought to the forefront the notable progress that have been made with regards to the phytochemistry and pharmacology of *L. javanica* in recent years, especially in Southern African countries due to the importance of the plant to the region's traditional medicine. The bibliometric survey in this study showed that the generation of scientific knowledge on the plant is relatively low when compared to other medicinal plants and has also tuned down in the last five years. However, this review further established that *L. javanica* has diverse metabolites with potential biological activities, some of which support its ethnomedicinal importance. Given that *L. javanica* is combined with other plants in ethnomedicine, it is beneficial to explore the possibility of its synergy with the different plant species. The new metabolites compiled in this report were classified into 12 chemical classes which are different from those of the 173 compounds earlier reported from the plant. This further establishes the diverse nature of *L. javanica* metabolites, hence, justifying the wide range of indigenous applications and pharmacological activities reported on the plant. It was observed that most of the studies on the pharmacological activity of the plant have been evaluated at the crude extract level, while the actual metabolite(s) specifically responsible for these bioactivities remain elusive. As a result, more pharmacological activities of the plant phytochemicals are required to fully realize the high potential of the plant in drug discovery, particularly as new phytochemicals keep emerging from the plant. Furthermore, the review has shown that the pharmacological studies on *L. javanica* as well as its metabolites were all preclinical studies, specifically in vitro, in vivo and recently in silico investigations. Hence, it is suggested that clinical studies should be carried out to establish the efficacy of the plant and its various metabolites in different human conditions and pathologies as well as their toxicity. In summary, an increase in the knowledge of *L. javanica* phytochemistry and pharmacology will also enhance its efficient utilization in various fortified nutraceutical as well as health booster products.

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Author Contributions

Francis O Shode: Conceptualization, Funding acquisition, Writing - original draft, Writing - review & editing; Ayodeji Amobonye: Formal analysis, Writing - original draft, Writing - review & editing ; Jamiu O Aribisala: Formal analysis, Writing - original draft; Saheed Sabiu: Writing - original draft, Writing - review & editing; Krishna Govender: Writing - original draft, Writing - review & editing. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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