Review

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An updated review (2015-2022) on the phytochemistry and pharmacological importance of Lippia javanica (Burm. f.) Spreng

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Review

An Updated Review (2015–2022) on the Phytochemistry and Pharmacological Importance of *Lippia javanica* (Burm. f.) Spreng.

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Abstract: *Lippia javanica* (Burm. f.) is a medicinal plant with multiple native uses in the treatment of colds, influenza, pneumonia, coughs, dermatitis, tuberculosis, asthma, and bronchial diseases. However, it remains underutilized in drug development. In this review, existing studies on the pharmacological activities of *L. javanica,* more specifically the antitumor, antiviral, and antibacterial properties as well as recent metabolites identified from the plant were appraised. Background information on the plant's ecological distribution, ethnobotanical importance, toxicity, and cytotoxicity activity was also provided. The information in the review was gathered from major scientific databases (Google scholar, BioMed Central, Scopus, PubMed, Springer, Web of Science, and Science Direct) using journals, conference proceedings, dissertations, books, and/or chapters. The review compiled 66 new metabolites from the plant while establishing the anticancer, antiviral, antibacterial, and other important pharmacological activities of the organic (most especially methanol and acetone) and aqueous extracts of various parts of the plant attributed to several secondary metabolites present in the volatile oil of the plant, which includes carvone, ipsdienone, limonene, linalool, myrcene, ocimenone, caryophyllene, piperitenone, sabinene, p-cymene, sabinene, myrcene, ipsenone, and tagetenone. While some of the metabolites of *L. javanica* have been linked through pharmacological studies to the various traditional uses of the plant, some others remain unexplored, emphasizing how underutilized the plant is in drug research and development. It is envisaged that the reports from this review will help to further encourage future research and guide further investigations into the pharmaceutical and medicinal uses of *L. javanica*.

Keywords: *Lippia javanica***;** Pharmacological; metabolites; ethnobotanical; drug discovery

1.0. Introduction

Many believed that the war against infectious diseases had been won between the mid-twentieth century and 1992, and so the effort in this direction could be reduced. However, much later, new vulnerabilities to epidemics and pandemics became apparent due to population growth, rapid mass movement of people, poverty, unplanned urbanization, societal change, and antimicrobial resistance after experiences with Human Immunodeficiency Virus (HIV), the return of cholera in 1991, the plague outbreak in 1994, the emergence of Ebola in 1995, and more recently, the pandemic with coronavirus disease [1,2]. As it stands today, the leading causes of illness and death in both humans and animals are infectious diseases. Moreover, other chronic diseases such as cancer and diabetes remain a global health concern; hence, the need for the search for potent therapeutics to curb the alarming rate of morbidity and mortality caused by these diseases. Plants and their phytochemicals have been used in the treatment of human diseases since time immemorial, and according to Salmerón-Manzano *et al*. [3], only about 10% (approximately 500 000) of plants, are currently used as medicinal plants, with only a few of their phytochemicals and what pharmacological importance they bring being known. Hence, screening medicinally important plants for their phytochemicals and

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pharmacological activities may help identify potent compounds with relevance in disease treatment and management, especially as plants are readily available [4,5].

Lippia javanica **(**Burm. f.), sometimes known as "fever tea" or "koorsbossie," is an upright, small woody shrub that can grow up to 4.5m long [6]. It is found throughout southern Africa, encompassing nearly the whole country of Swaziland as well as huge areas of South Africa [7]. The uses of the plant ranges from its use as ordinary tea with fever and pain-relieving benefits to the treatment of basic HIV and AIDS symptoms and microbiological diseases such as coughs, colds, and other bronchial illnesses [7,8]. Topical applications include disinfection and treatment of dermatitis and dry skin, as well as lice and scabies treatment [9]. It is also used in conjunction with *Artemisia afra* for malaria treatment and as a prophylactic against dysentery and diarrhea [10]. The volatile oil of *L. javanica* contains a high concentration of carvone, p-cymene, ipsdienone, limonene, linalool, myrcene, ocimenone, caryophyllene, piperitenone, sabinene, myrcenone, ipsenone, and tagetenone [7]. According to Viljoen *et al*. [8], the essential oil profiles of *L. javanica* are differentiated by inter-and intra-species variations due to multiple metabolic pathways leading to their synthesis.

Given the traditional medicinal importance of *L. javanica*, it is surprising that the last comprehensive review on its medicinal, phytochemical, pharmacological, toxicological, and economic importance was done six years ago [1], despite recent findings on its phytocompounds and their likely importance in the recent pandemic caused by SARS-CoV-2 and other endemic diseases such as cancer, HIV/AIDS, bacterial infections, and others debilitating diseases. As a result, the current appraisal aimed to provide an up-to-date report on current findings on the plant's phytochemicals and pharmacological properties while providing background information on the ecological distribution, ethnobotanical and ethnomedicinal importance of the plant. It is hoped that this review will encourage future research and guide further investigations into the pharmaceutical and medicinal benefits of *L. javanica*.

2.0. Methodology

The data used in this review was compiled from journal articles, theses, books, book chapters, dissertations, and conference proceedings retrieved from major scientific databases (Google Scholar, Science Direct, Web of Science, PubMed, Springer, Scopus, and BioMed Central) from 2015 to 2022. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) procedure was adopted. Terminologies such as medicinal herbs, ethnomedicinal usage, phytochemical constituents, pharmacological activities, and biochemical properties were searched and cross-reference with each other. Following the removal of duplicates from the 145 research papers obtained from the search of databases, 33 research articles that were not within the scope of the study were excluded. The remaining 81 relevant papers were considered and included as illustrated in Figure 1.

Figure 1. PRISMA flowchart of the literature screened, included, and evaluated for this study.

3.0. Ecological Distribution

L. javanica (Figure 2) is native to the central, southern, and eastern parts of Africa. Specifically, the species is endemic to Ethiopia, Uganda, Botswana, Angola, Malawi, Tanzania, Central African Republic, the Democratic Republic of the Congo, Swaziland, Kenya, South Africa, Zambia, Mozambique, Zanzibar, and Zimbabwe in Sub-Saharan Africa [10]. Conversely, the plant has also been reported in Mexico, Bangladesh, and India. They are typically found on the edges of forests, in grasslands on hillsides, and along the banks of streams [11]. The plant has been discovered in grassy rocky kopjes, riverine vegetation, low to high elevated forests, woody grasslands (as high as about 0-2350m above the sea level), scrub bushland, as well as on dambo and marshy ground borders. It has also been discovered most frequently in footed soil along highways, woodland clearings, plantations, and farmed areas [12–14]. Finally, it has established itself as a weed on derived rangelands [13,14]. The ability of the plant to grow in a wide range of temperature, soil and vegetation conditions suggests that the plant is not likely to die out and can be easily grown in large quantities and is therefore a plus for its medicinal-pharmaceutical uses.

Figure 2. *Lippia javanica* (leaves and flower).

3.1. Ethnobotanical Description

L. javanica (Figure 2) belongs to the Verbenaceae family, which includes about 32 genera and 840 species [15]. Phylogenetic lineages in the Verbenaceae family showed that the genus *Lippia* and other closely related genera such as *Lantana* L. are not monophyletic [15]. Several taxonomy scholars have included species from *Lantana* and other similarly related genera in the genus *Lippia*, indicating that the boundaries separating *Lippia* from other closely related genera are weak [16]. According to de Campos *et al*. [16], the genus *Lippia* has around 200 species of plants, shrubs, and small trees, of which only 15 have been reported in tropical Africa. *L. javanica* is morphologically like *L. scaberrima* (Sond), but it is much taller, and its bracts are shorter than the flowers (Figure 2), while *L. scaberrima* has multiple stems arising from the ground level and is usually less than 0.6 meters high, and its bracts are not longer than the flowers [6,17].

L. javanica is a 4.5 m tall, erect, woody perennial or shrub with strongly fragrant leaves that emit a lemon-like scent when crushed [18]. The stems are brownish, erect or spreading, and branching with inflorescences in virtually all axils. The leaf blades are lanceolate to oblong and densely hairy, rounded and then cuneate at the base and crenate or densely serrate at the margins except at the leaf base [7]. The flowers appear in conical or oblong spikes, are purple or dull reddish in fruit and dry to a dark brownish color [6,17] The flower is sessile or on short peduncles, with oval lower bracts and narrower upper bracts that are hairy, glandular, and densely spreading [17]. The calyx is bilobed, half as long as the corolla, hairy and densely scattered. The petal is yellowish white to greenish (Figure 2), with a yellow neck, a granular-glabrous exterior in the upper half, and a thin spiral tube from a smaller base [15,17].

3.2. Ethno-medicinal importance

L. javanica is utilized for a range of traditional purposes, the summary of which is presented in Supplementary Table 1 (Table S1). Based on the current appraisal, the plant is mostly used ethnomedicinally for the management of symptoms of HIV, as well as treatment of cancer, respiratory tract-related disorders [asthma, nasal congestion, colds, bronchitis, colds, influenza, lung infections, sore throat, tuberculosis, pneumonia, treatment of shortness of breath (dyspnea)], gastrointestinal infections, measles, diarrhea, scabies, shingles, malaria, abdominal ache, ulcer, headache, kidney problem, fever, antidote, treatment for chicken pox, and inflammation [7,19–24]. Other applications include food additives, insect repellent, wound treatment, skin treatment, as well as scabies and lice treatment [23].

3.3. Phytochemistry of L. javanica

According to the last comprehensive review on *L. javanica* in 2016, about 173 compounds belonging to secondary metabolites, such as derivatives of amino acids, alkaloids, and essential oil were identified [1] indicating the wide diversity in the phytochemical components of *L. javanica*. Of the 173 previously identified metabolites, 21 were phenolics (verbascoside, isoverbascoside, theveside-Na, theveridoside, apigenin, cirsimaritin, 6-methoxyluteolin 4′-methyl ether, luteolin, tricin, isothymusin, eupatorin, 5-dimethyl noboletin, 4-ethylnonacosane, 3-4-7 trimethylether, crassifoliside, chrysoeriol, tricin, diosmetin, genkwanin, salvigenin, and lippialactone); 18 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); 133 essential oil constituents (linalool, α-cedrene, myrcenone, eugenol, icterogenin, 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, myrcene, etc) and only one alkaloid (xanthine) [1]. These compounds were reported to be isolated from the different aerial parts of the plant with the leave mostly implicated. For example, coumarin,

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verbascoside, and isoverbascoside were isolated from the aerial part of the plant [6], while Mujovo *et al*. [45] isolated 4-ethylnonacosane and four flavanones (apigenin, cirsimaritin, 6-methoxyluteolin 4′-methyl ether, and 6-methoxyluteolin 3′,4′,7-trimethyl ether) from ethanolic extracts of *L. javanica* leaves. Ludere *et al*. [46] isolated lippialactone from the ethyl acetate extract of aerial parts of *L. javanica*. Hutchings and van Staden [21] reported the isolated of a toxic triterpenoid saponin, icterogenin, from *L. javanica* leaves. The essential oil constituents of the plant such as those reported by Hutchings and van Staden [21], including triterpenoid, saponin, icterogenin have been implicated to have various pharmacological activities such as anti-inflammatory, hepatoprotective, antimicrobial, and sedative effect [47]. Similarly, flavonoids from the plant have been 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 [48,49]. The amino acid constituents of *L. javanica* are essential to the body and Kamiya [50] demonstrated the health risk of their inadequacy in humans. Other important nutritional components of the plant include minerals such as iron, calcium, zinc, and selenium needed in the body for proper development and functioning [51,52].

In the current appraisal, the 66 new compounds not reported in the previous review of the plant are presented in Supplementary Table 2 (Table S2) while their two-dimensional structures are presented in Supplementary table S5. The sixty-six new metabolites from *L. javanica* belong to chemical classes such as derivatized amino acids (choline); steroids (sitosterol); cyanide (hydrogen cyanide); phenolic compounds (e.g. ellagic acid, protocatechuic 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); phenol (*cis*-verbenol and 2,4-dimethylpyridin-3,5-diol); monoterpenoids (e.g. 4-isopropenyltoluene, geraniol, p-mentha-1(7),8-diene, and carvyl acetate, etc); Iriloid glycosides (theveridoside); sesquiterpenoids (e.g. epi-bicyclosesquiphellandrene and alloaromadrene, etc); esters (e.g. 3-Tetradecen-5-yne, (E); 9-Borabicyclo (3.3.1) nonane, 9-(3-methoxycyclohexyl) oxy-; 4-Cyclopropylcyclohexane, Cyclohexyldichlorophosphine, 1H-Pyrazole, 1,3,5-trimethyl, etc); ketones (thujone, mesityl oxide, and isophorone) and aldehydes (2-Hexenal (E)) [53–59]. Interestingly, this observation regarding the wide range of compound classes is consistent with a previous report [1] in confirming the diverse range of metabolites in *L. javanica* and could be due to several reasons. According to Viljoen *et al*. [8], variation in phytochemicals could be due to geographical and environmental factors, geographical differences in harvesting times, and differences in the multiple metabolic pathways that generate these compounds. Similarly, studies by Kamanula *et al*. [56], while investigating the chemical variation of the phytochemicals in *L. javanica* also attributed the variations in the leaf extracts to the difference in harvesting times, edaphic conditions, geographic variations concerning sunshine hours, temperature, the maturity stage, and season, as well as the method of extracting the active ingredients which may, in turn, affect its potency. Several of the newly compiled metabolites from *L. javanica* were isolated from the aerial parts of the plant, with the leaf being the most implicated, correlating the assertion of Maroyi [1]. *Cis*-p-coumaric acid, 2,4-dimethylpyridin-3,5-diol, syringic acid, protocatechuic acid, vanillic acid, trans-cinnamic, syringaldehyde, and ferulic acid were isolated by Suleman *et al.* [59], from the leaf extract of *L. javanica* and implicated them to have acetylcholinesterase activity while being effective in reducing Pb-induced brain oxidative stress, inflammation, apoptosis, and neuronal damage. Adeogun *et al*. [57] on the other hand isolated several classes of compounds from the wet and dry leave of *L. javanica* using different oil extraction techniques (Solvent-free microwave extraction and hydrodistillation) and implicated the oil extract to have moderate toxicity toward *Artemia salina,* a pest implicated in spoilage of food. The classes of compounds isolated by Adeogun *et al*. [57] from the dry and wet leave of *L. javanica* include esters, ketones, aldehydes, monoterpenoids, and sesquiterpenoids, many of which have compounds that were reported for the first time from *L. javanica*.

Although Adeogun *et al*. [57] concluded that the extraction techniques they employed had no impact on the yield of the oil extracted but might have however impacted several of the new compounds found in *L. javanica* in this study. Also, drying of the leaves of *L. javanica* had an impact

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on the presence and percentage compositions of the compounds found in the leaves [57] and might have also impacted the wide range of compounds isolated from *L. javanica*. Generally, the 66 new compounds from *L. javanica* reported in this study summing up to approximately 239 phytochemicals (173 compiled by Maroyi [1]) isolated from the plant so far however confirmed that *L. javanica* is phytochemically diverse. This observation lent credence to its native use in the treatment of several diseases and its application in food preservation and as a dietary supplement. Pharmacological activities have been demonstrated for some of the plant's secondary metabolites through pharmacological studies; however, other research has attributed the plant's pharmacological activity to plant extracts, with the actual metabolites involved in the process remaining elusive. Therefore, further pharmacological studies on extracts from the plant and its metabolites are important to exploit the full potential of the plant in drug discovery, especially as new phytochemicals from the plant are discovered.

3.4. Pharmacological Activities of L. javanica

This aspect of the review demonstrated the pharmacological activities of *L. javanica* as an anticancer agent, antibacterial, antiviral, antidiabetic, and antioxidant. Also, for the first time, this study assembled several anti-SARS-CoV-2 phytochemicals endemic to *L. javanica* that required further confirmatory pharmacological studies. Supplementary table (Table S4) highlights the pharmacological effects of extracts of several parts of *L. javanica* and the likely phytochemicals involved in their actions.

3.4.1. Antitumor activities of L. javanica

In all types of cancer, current drugs can only reduce tumor development to a limited extent [66]. Consequently, alternative natural medicines must be identified to overcome the numerous limitations of drugs used to treat breast and prostate cancer. In an earlier study by Fouche *et al.* [67], *L. javanica*'s dichloromethane root extract demonstrated strong anticancer properties against the human breast cancer cell lines MDA-MB-435, MDA-N, and MALME-3M with total growth inhibition of 1.82 μg/mL, 1.86 μg/mL and 2.09 μg/mL respectively [1]. Although studies demonstrating the lead phytocompounds present in the root extract of *L. javanica* are still elusive, however, studies demonstrating phytochemicals implicated in the plant have shown compounds such as linalool to have anticancer activities [66]. An earlier investigation has also demonstrated that limonene has an inhibitory effect on breast and pancreatic cancers [1,67]. Another terpenoid found in *L. javanica* called α-pinene is known to prevent NF-B or p65 protein from entering the nuclei of LPS-stimulated THP-1 cells [1,67]. These results regarding the antitumor pharmacological potentials of *L. javanica* while partially providing scientific support for the usage of the plant as an herbal remedy for cancer treatment in several African countries, further 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 before more confirmatory *in vitro* and *in vivo* pharmacological studies are carried out**.** This is beneficial as computer-aided drug development process is considered to be more cost-effective and timesaving than other traditional cancer method of drug discovery and can therefore further improve productivity and quality in cancer pharmaceutical research.

3.4.2. Antiviral activities of L. javanica

Infectious viral infections continue to pose a serious public health risk and are a significant problem for humans and animals around the world [68]. Despite improvements in vaccination and antiviral drugs, protective immunizations and effective antiviral drugs are still lacking in both human and veterinary medicine [68]. Therefore, there is a need to search for effective antiviral drugs, including screening of plant secondary metabolites. *L. javanica* extract incorporates a variety of active

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metabolites such as saponins, terpenoids, flavonoids, coumarins, polyphenols, alkaloids, proteins, and many more, which have been demonstrated by earlier researchers to have antiviral effects [1,45].

3.4.2.1. Anti- Human immunodeficiency virus

The need for drugs that can selectively inhibit the human immunodeficiency virus (HIV) is critical given that this infection is present on every continent. Compounds extracted from *L. javanica* and other plants were examined by earlier study of Mujovo *et al.* [45] using a non-radioactive HIV RT colorimetric-based ELISA kit assay to see if they could suppress HIV-1 Reverse transcriptase activity *in vitro* [1]. Three phytocompounds from the *L. javanica*; myrcenone, apigenin, and hoslunddiol showed promising 91, 53, and 52 percent inhibitory activities respectively against the enzymes at 100 g/ml [1,45]. Also, a previous study by Vlietinck *et al.* (1998) has shown luteolin, a flavonoid that is endemic in *L. javanica* to be active against HIV RT [1]. Even though *L. javanica* is used to treat viral infections in South Africa, the last research on its anti-HIV properties was done 13 years ago, so more research on the anti-HIV activities of *L. javanica's* crude extracts and refined metabolites is required. Lack of recent findings on anti-HIV properties of the plant suggests that *L. javanica* is underutilized in the discovery of anti-HIV drugs.

3.4.2.2. Anti-COVID 19 activities of L. javanica

Since the 1960s, the coronavirus family of viruses has been identified in both humans and animals. SARS-CoV-2, a recently discovered variant, has caused a recent respiratory disease pandemic that is now known as COVID-19. Most treatment approaches for this pandemic are centered on symptomatic care and supportive therapy. However, a report by Depika *et al*. [68] found that some metabolites from medicinal plants may be useful in treating coronavirus infections. In their study, which used molecular modeling techniques to identify potential SARS-CoV-2 inhibitors in South African medicinal plant metabolites against the SARS-CoV-2 main protease (3CLpro), the receptor-binding domain (RBD) and the drug target of RNA-dependent RNA polymerase, several phytocompounds implicated in *L. javanica* were observed to have anti- SARS-CoV-2 properties. The molecular docking study was carried out using AutoDock Vina software and among the 25 phytochemicals evaluated, 8 compounds (apigenin, carvone, ipsenome linalool, piperitenone, myrcenone, α-terpineol, and α-thujone) are found in *L. javanica* and their docking scores are presented in Supplementary Table 3 (Table S3). Among the phytochemicals, linalool, apigenin, and piperitenone showed more promising affinity against SARS-CoV-2 main protease, receptor binding domain, and RNA-dependent RNA polymerase druggable target respectively. Following molecular dynamics of these phytocompounds, they were found to be thermodynamically compatible with the three SARS-CoV-2 proteins while interacting with important amino acid residues in the binding pocket of the proteins which necessitate their further *in vitro* and *in vivo* bioactive confirmation. In another study by Uhomoibhi *et al*. [2] using computational methods, they examined the structure-activity relationship inhibitory potential of 99 phytocompounds from African botanicals against druggable targets of SARS-human CoV-2's cell proteins (hACE2, TMPRSS2, and Cathepsin L). The molecular docking study was carried out using AutoDock vina software of Chimera version 1.14 and among the 99 phytochemicals evaluated, 7 phytocompounds (apigenin, aromadendrene oxide, verbascoside, campesterol, T-cadinol, β-phellandrene, and α-thujone) are found in *L. javanica* and their docking scores are presented in Supplementary Table 3 (Table S3). Among the phytocompounds, aromadendrene oxide had the best affinity against hACE2 while verbascoside showed a more promising affinity against TMPRSS2, and Cathepsin L (Table S3).

These observations regarding the anti-COVID-19 potential of *L. javanica* indicate the several anti-SARS-CoV-2 phytochemicals endemic to *L. javanica*, which required further *in vitro* and *in vivo* pharmacological studies on their pharmacological activities. As no specific anti-COVID-19 drug has yet been identified, pharmacological studies on promising anti-SARS-CoV-2 plant-derived phytochemicals, such as those identified from *L. javanica* in this review, could help accelerate and guide the development of new anti-COVID-19 drugs.

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3.4.2.3. Antimicrobial activities of L. javanica

L. javanica is a well-known ethnomedicinal plant that is commonly used to cure a number of bacterial infectious illnesses. The antibacterial potential of the essential oil from the aerial parts of *L. javanica* and *Lantana camara* on five bacteria was studied by Marsi et al. [69], who discovered that L. javanica essential oil had a moderate inhibitory activity on *Klebsiella pneumoniae* and *Streptococcus pneumoniae* with a MIC value of 0.76 mg/mL, and with a MIC value of 1.50 mg/mL against *Escherichia coli*, *Staphylococcus aureus*, and *P. aeruginosa* Relative to *Lantana camara*, *L. javanica* displayed higher antibacterial activities. In the same study, Marsi *et al*. [69], determined the antifungal activities of the essential oil of *L. javanica* on *Candida albicans* and their finding shows that the essential oil of *Lantana camara* and Germicide were inactive against *C. albicans* when tested by the disk method, whereas, essential oil from the aerial parts of *L. javanica* had a MIC value of 3.28 mg/mL. Nkala *et al*. [70], demonstrated the antibacterial activities of the methanolic extract of *L. javanica* using the microplate dilution method, their findings show that the extract had inhibition and bactericidal effects against *E. coli, S. aureus, and E. faecalis* with MIC values ranging from 0.25 to 1.13 mg/mL. *Lippia javanica* demonstrated the greatest antibacterial activity against *E. coli, S. aureus,* and *E. faecalis* when compared to other investigated plants, such as *Ziziphus mucronata* (0.44 0.00 to 1.00 0.00 mg/ml); *Erythrina lysistemon* (0.44 0.00 to 1.08 0.00 mg/ml); and *Schkuhria pinnata* (0.5 ± 0.00 to 1.34 ± 0.00 mg/mL) [70]. Makhafola *et al*. [71], discovered that the acetonic extract of *L. javanica* had significant antibacterial activity, with MIC values of 0.04 mg/mL against *P. aeruginosa* and 0.28 mg/mL against *S. aureus*. Endris *et al*. [55], used the disc diffusion method to test the antibacterial properties of *L. javanica* essential oil against two bacterial strains (*Bacillus cereus* and *K. pneumoniae*) and one fungal pathogen (*Cryptococcus neoformans*). Findings from the study show [*B. cereus* (50 μg/mL); *K. pneumoniae* (>5 μg/mL), and *Cryptococcus neoformans* (10 μg/mL)] that *K. pneumoniae* was the most susceptible bacteria to the essential oil of *L. javanica* with a MIC value of < 5 μg/mL while implicating phytochemicals such as *cis*-Sabinene hydrate, limonene, germacrene D, linalool, 1,8-cineol (3.9%), borneol, β-caryophyllene, terpinen-4-ol, myrcene and camphene in such activities. Earlier studies have also demonstrated that phytochemicals such as lippialactone have antibacterial activities against *E. coli* and *S. aureus* at a concentration of 10 mg/mL [46]; piperitenone has antibacterial activities against *Acinetobacter calcoaceticus, B. subtilis, E. coli, Salmonella typhi, Micrococcus kristinae,* and *S. aureus* at a MIC ranging from 12 to 50 *μ*g/mL [72,73] as well as apigenin against *Vibrio cholera, E. faecalis, S. typhi, P. mirabilis,* and *P. aeruginosa* [74]. The findings from the antibacterial evaluation of *L. javanica* in this study lent credence to the use of the plant in traditional medicine for the treatment of several bacterial and fungal infections. Hence, more pharmacological studies on promising metabolites from *L. javanica*, could help accelerate and guide the development of novel antibacterial drugs that could help in the fight against antibiotic resistance.

3.4.2.4. Other pharmacological activities

a. Antidiabetic Activity.

In an investigation of the *in vivo* anti-diabetic effects of *L. javanica* aqueous leaf extracts in white male alloxan-induced albino mice, Arika *et al.* [75], discovered that both oral and intraperitoneal administration of *L. javanica* aqueous leaf extracts significantly lowered blood glucose levels at all dose levels. In another study by Nkala [76], while demonstrating the antidiabetic activities of the methanolic extract of *L. javanica* using the alpha-amylase (α-amylase) inhibition assay, their findings show that *L. javanica* exhibited an alpha-amylase inhibitory effect of 80% with an IC_{50} value lesser than 1000 μg/mL. Their findings implicated functional groups such as alkaloids, cardiac glycosides, flavonoids, phenols, saponins, steroids, tannins, anthocyanins, betacyanin, coumarins, and terpenoids present in *L. javanica* in the antidiabetic activities observed. Specifically, earlier studies by Mahlangeni *et al*. [25] have demonstrated the ability of flavonoids to help regulate blood sugar levels, through their ability to modulate the insulin-mimetic properties while stimulating lipogenesis and glucose uptake in the adipocytes. Hence, the findings from the antidiabetic evaluation of *L. javanica* in this study to some extent, support the traditional use of the plant for the treatment of diabetics and improved antidiabetic studies on promising metabolites from *L. javanica*, could therefore help hasten and direct the development of novel antidiabetic drugs that could help in the fight against the disease.

b. Neuroprotective activity

Oxidative stress is brought on by the body's inability to maintain homeostasis as a result of high ROS levels, and it is characterized by oxidative damage to proteins, nucleic acids, and membrane lipids (lipid peroxidation) [1]. Cellular consequences of oxidative damage also encourage inflammation and cell death. Antioxidants have been used in research to treat Pb-induced neurotoxicity and oxidative stress, and some of these studies have shown promise. In contrast to Pb-exposed rats, Suleman *et al*. [59], discovered that treatment with *L. javanica* improved (p 0.05) total brain antioxidant status (glutathione and superoxide dismutase activities) and reduced (p 0.05) lipid peroxidation. TNF-alpha, a pro-apoptosis protein, and anticholinesterase activity were also decreased (p 0.05) in Pb-*L. javanica*-treated rats compared to those that had been exposed to Pb. Their histological study verified the neuroprotective benefits of *L. javanica*, as demonstrated by decreased apoptosis/necrosis and inflammation-induced vacuolization 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, while investigating the effects of a 5 percent *L. javanica* infusion on Pb-induced brain damage in adolescent rats, Sewani-Rusike [77] discovered that *L. javanica* was beneficial in lowering brain oxidative stress, lipid peroxidation, and neuronal damage and that it may be useful in avoiding the onset of oxidative stress-induced neurodegenerative disorders. As a result, the results of the neuroprotective assessment of *L. javanica* in this study provide some support for the traditional use of the plant in the treatment of headaches and migraines, and an improved pharmacological study of the plant's lead metabolite may help identify new drugs for neurological disorders.

c. Antioxidant Activity.

Suleman *et al*. [59], employed the leaf extract of *L. javanica* to assess the effects of *L. javanica* infusion on brain antioxidant status. Their findings demonstrate that *L. javanica* leaf infusions showed antioxidant activity, which was connected to the plant's phenolic composition. According to their study, *L. javanica* treatment with or without Pb increased GSH compared to the Pb group, but Pb exposure caused GSH to be depleted (p 0.05) compared to the control. All groups had greater SOD activity (p 0.05) in comparison to the control, which is consistent with the enzymatic antioxidant SOD. Higher MDA concentrations in the Pb exposed group indicated more lipid peroxidation, while lower MDA levels were seen in the Pb + *L. javanica* and *L. javanica* treated groups (p 0.05). In different research, Nkala, [76], found that the methanolic leaf extract of *L. javanica* has antioxidant properties that showed scavenging activity of more than 80%, and they linked this finding to the presence of phenolic and flavonoids. Bhebhe *et al*. [29] investigated the antioxidant capabilities of *L. javanica* using the DPPH, reducing power, and phospholipid peroxidation inhibition tests. *L. javanica's* free radical scavenging action is linked to phenolic chemicals, which have suitable structural chemistry for such activity [78]. The DPPH test was used by Bhebhe *et al*. [29] to investigate how different solvents influenced *L. javanica's* ability to scavenge free radicals. The IC50 for free radical scavenging activity varied from 0.022 ± 0.001 g/mL to 0.066 ± 0.001 g/mL. 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 and further utilization in the food industry following more identification of potent lead antioxidant from *L. javanica* will have greater economic importance to the plant.

d. Toxicity and cytotoxicity activity of *L. javanica*

Triterpenoids derived from the genus Lippia are icterogenic and may result in jaundice due to liver injury, according to previous research by Maroyi [1]. Reports have also shown that xanthine (a phytocompound endemic in *L. javanica*) ingestion has harmful effects on mammals [1,79] as they have pharmacological effects on the central nervous system (CNS), smooth muscle (particularly bronchial muscle), myocardium, peripheral vasoconstriction, and diuresis. Hence, continuous usage of *L. javanica* at high dosages for an extended period of time could be dangerous. However, many other

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functional groups such as phenolic glycosides, flavonoids, and essential oils have been demonstrated to be safe and do not cause acute toxicity [1,80]. A study by Makhafola et al. [71], studied the cytotoxicity of five plants on liver cells, including *Hilliardiella elaeagnoides, Lantana rugosa, L. javanica, Withania somnifera* and *L. wilmsii*. The least cytotoxic extracts were the aqueous and acetonic extracts of *L. wilmsii* (LC_{50} > 1000 µg/mL) and the hexane extract of *L. javanica* (LC_{50} > 1000 µg/mL) while the *L. javanica* acetonic extract (0.01 g/mL) and *L. wilmsii* hexane extract (0.03 g/mL) were the most cytotoxic. The study concluded that the cytotoxicity of these plants should be properly understood and carefully considered before using them in conventional medicine, since only the aqueous and acetonic extracts of *L. wilmsii* and the hexane extract of *L. javanica* were found to be toxic. This observation regarding the toxicity and cytotoxicity activity of *L. javanica*, highlights the significance of solvent selection for extraction in the toxicity and cytotoxicity of *L. javanica*. 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.

e. Pesticidal activities of *L. javanica*

Adeogun *et al*. [57] investigated the effectiveness of oils made from fresh and dried leaves of *L. javanica* against *Artemia salina* and observed as moderate to mild pesticidal properties of *L. javanica* against *A. salina*. The study found that the median lethal concentration (LC_{50}) of fresh and dried leaves oils extracted using hydrodistillation were 90.11 and 128.49 g/mL, respectively, whereas the solvent-free microwave extraction technique yielded LC_{50} values of 96.52 and 101.13 g/mL, respectively. Majoro [81], evaluated the efficacy rates for *L. javanica* leaf powder at dosage levels (0. 5g, 10g, and 15g). Findings showed the positive control and the highest dosage treatment (15g) had no statistically significant difference, while the leaf extract treatment at 0.5g and 10g had a significant difference. The 15g had the greatest mortality rate of 85.25 percent. When compared to the negative control, maize grain treated with 10g and 15g dosage levels of the leaf extract showed significant reductions in the number of damaged grains by the maize weevil, maize weevil reproduction, and weight loss in stored maize. The results of the pesticide evaluation of *L. javanica* demonstrated the pesticidal activities of the plant and further exploitation of *L. javanica* through pharmacological studies could help identify potent lead metabolites that could be further developed for pest control.

4. Conclusion

Significant advances in the phytochemistry and pharmacology of *L. javanica* have been made in recent years. This review revealed that *L. javanica* has diverse metabolites and potentiate biological activities, some of which support its ethnomedicinal importance. Given that *L. javanica* is combined with other plant species in traditional medicine, it is beneficial to explore the possibility of synergistic effects of the different plant species. This is the first report on the phytochemicals discovered in this plant since 2016. The 66 new metabolites compiled in this report belonging to 12 chemical classes which are different from the 173 compounds earlier reported from the plant confirmed diverse and varied nature of metabolites and hence, justifies the wide range of indigenous application and pharmacological activities reported on the plant. However, in very limited studies, specific phytochemicals from the plant have been demonstrated through pharmacological studies on their activities, whereas in several other studies, the pharmacological activity of the plant has been attributed to plant extracts, with the actual metabolite(s) implicated remaining 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.

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Legends for Figures

Figure 1. PRISMA flowchart of the literature screened, included, and evaluated for this study.

Figure 2. Pictorial representation of *L. javanica* leaves and flowers.

Figure 3. Structural representation of new phytochemicals isolated from *L. javanica* between 2015 to 2022 (number corresponding with serial number in Supplementary Table S2)**.**

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