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Original Article

EXPLORATION OF ETHNOVETERINARY MEDICINE FOR CATTLE'S LUMPY SKIN DISEASE IN INDONESIA: NARRATIVE REVIEW

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ABSTRACT

Objective: Lumpy Skin Disease (LSD) is a condition characterized by the development of nodules on the skin of affected cattle. Typically, it impacts bovine animals such as cattle and buffalo. Ethnoveterinary medicine focuses on the application of traditional medicine to animals. The efficacy of traditional medicine in addressing the symptoms of lumpy skin condition was established through empirical research. Farmers can utilize medicinal plants from traditional medicine to treat bovine LSD. The primary objective of LSD treatment in cattle is to address the clinical symptoms. The objective of this study was to examine the use of LSD treatment in indigenous medicine in Indonesia.

Methods: A review was conducted primarily targeting traditional medicines that have gained interest as potential treatments for cattle infected with Lumpy Skin Disease Virus (LSDV). Government authorities have specifically advised some precautions, while national mass media has raised awareness about further measures.

Results: The screening result indicates that there are 9 plant species which can be used in the traditional treatment of cattle to cure LSD e. g. *Nicotiana tabacum, Acorus calamus, Allium sativum, Annona muricata, Piper betle, Zingiber officinale, Curcuma xanthorrhiza, Kaempferia galanga,* and *Curcuma domestica*, which have antimicrobial, anti-inflammatory, antioxidant, analgesic, immunostimulant, antidepressant, wound healing, and insect/larvae repellant. This research aims to contribute to the advancement of LSD treatment using conventional herbal remedies.

Conclusion: Evidence from the study revealed the significance of said plants against LSDV, especially in Indonesia.

Keywords: Lumpy skin disease, Ethnoveterinary medicine, Cattle, Indonesia

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INTRODUCTION

Lumpy Skin Disease (LSD) is a significant risk to livestock farming as it can cause both acute and subacute illness in cattle and water buffalo [1, 2]. The World Organization for Animal Health (OIE) has included this transboundary disease on the notifiable disease list because of its substantial economic impact and the high risk of rapid transmission [3]. The recent dissemination of the disease in nations that were previously free from it highlights the significance of its transmission, as well as the need for effective control and eradication measures [4].

The first recorded occurrence of LSD was documented in Zambia in 1929 [5]. In Indonesia, the initial occurrence of LSD outbreak took place in Riau Province February 2022. The discovery occurred in the Indragiri Hulu Regency. Previously, in June 2021, a case pertaining to the detection of LSD took place in Malaysia. The geographical closeness between Riau Province and Malaysia enabled the transmission of LSD in Riau [6]. The outbreak of LSD disease was formally declared in Riau Province in February 2022, with transmission taking place through vectors [7]. LSD has been associated with a reduction in milk production, a drop in body weight, and financial losses for cattle farmers [5]. When animals contract LSDV, it can lead to a sudden illness marked by high body temperature, reduced milk output, excessive tearing, and heightened nasal discharge. In addition, there may be visible physical indications, such as the presence of numerous nodules on the skin [8].

Vaccination is the sole efficacious approach to manage the disease in regions where it is prevalent, in conjunction with limitations on movement and the elimination of infected animals. The expansion of Lumpy Skin Disease Virus (LSDV), *Capripoxviruses'* spread can be attributed to several factors. These include restricted availability of effective vaccines and poverty in farming communities in endemic locations, as well as the growing trade of live animals, both legal and illegal. Additionally, global climatic changes have also played a role in this expansion [9].

The cattle-farming business experiences significant economic loss as a result of LSD, including reduced milk and beef production, fertility issues, and the need to treat or address the health concerns of severely affected animals. The expenses associated with implementing and eliminating control measures, administering vaccinations, and enforcing limitations on cattle movement and trade contribute to the financial losses. Countries that engage in the export of cow skins and hides are adversely affected by the reduced economic worth of the permanently marked skins of the affected animals [10].

Ethnoveterinary medicine focuses on the application of indigenous healing practices to treat animals. This generally pertains to the collective ideas, knowledge, skills, procedures, and practices employed in the field of veterinary care [11]. Medicinal plants have proven to be a valuable reservoir of novel pharmacologically active compounds. For instance, natural products have the ability to serve as an alternative method to eliminate and control the pathogen linked to diseases [12]. In recent times, antibiotics and many other drugs available in the market have exhibited undesirable symptoms and the rise of pathogenic microorganisms that are resistant to these drugs. Additionally, these synthetic drugs have shown toxic effects and withdrawal problems, leading to limitations on their usage in many countries [13]. Consequently, there has been a significant focus on herbal medicines and pharmacologically active compounds derived from various plant species that have been traditionally used in medicine [14]. An investigation was conducted by Chouhan to evaluate the efficacy of traditional medicine in the treatment of LSD in cattle [15]. The research on LSD treatment in conjunction with traditional remedies primarily relies on the practice of ethnomedicine [16, 17]. Indonesia has a plethora of medicinal plants that have utilized for many years. Accessing traditional medicinal plants is a straightforward process, and its adverse effects are minimal. The aim of this study is to conduct a narrative review of traditional preparations from indigenous medicinal plants in the treatment of LSD in Indonesia, focusing on their composition, properties, and possible mechanisms of actions.

MATERIALS AND METHODS

A review was performed focusing on herbal preparations that have gained popularity as potential treatments for LSD. Some of these preparations have been directly recommended by government agencies, whereas others have gained popularity through various other news sources.

Article criteria

The study's inclusion criteria consisted of publications that discussed ethnomedicine-based herbal treatment for LSD, as well as documents sourced from official agencies such as government agencies and national mass media that contained news regarding traditional LSD treatment. The exclusion criteria encompassed articles that included both standard therapy and vaccination for LSD.

RESULTS AND DISCUSSION

In response to the LSD outbreak in Indonesia, government organizations and experts have been diligently seeking a remedy for this ailment. In the initial phases of the outbreak, Indonesian government officials advised implementing a treatment approach that integrates traditional medicine with contemporary Synthetics medicine approaches. Subsequently, cattle farmers have increasingly embraced herbal medicine formulations as a potential therapeutic approach for LSD. Table 1 displays the herbal supplements utilized in this therapy approach.

Medicinal plant extracts and their components also have diverse biological properties, such as being able to kill viruses, bacteria, and fungus, as well as reducing inflammation, relieving pain, inducing sedation, relaxing muscle spasms, and acting as local anesthetics, among other activities [22-24].

Table 1: Plant species used in ethnoveterinary medicine, families, traditional uses, parts used preparation and administration forms and citations

Plant name	Mode of preparation/application	Administra-tion dosage	Route of administra-tions	Source
Nicotiana tabacum leaves, *Acorus calamus* rhizomes, *Allium sativum* bulbs, and *Annona muricata L*. leaves.	*Nicotiana tabacum* leaves soaked in hot water overnight. *Acorus calamus* rhizomes, *Allium sativum* bulbs, and *Annona muricata L*. leaves which are boiled using 2L water, are added into tobacco water. After it is warm, add one tablespoon of washing liquid, stirred, left overnight before use.	Every 10 ml of the concoction is mixed with 10 liters of water.	Sprayed on the animal.	[18]
Curcuma domestica rhizomes, *Piper betle* leaves, saline (saltwater).	*Curcuma domestica* rhizomes, *Piper betle* leaves are mixed and pounded until smooth, then put into saltwater and stirred.	-	The concoction is rubbed to the skin lesions of the animal.	[19]
Curcuma domestica rhizomes, *Zingiber officinale* rhizomes, *Kaempferia galangal* rhizomes, *Curcuma domestica* rhizomes, *Allium sativum* bulb, molasses, and water, as well as additional ingredients commercial probiotic mixture which contains lactic acid bacteria (*Lactobacillus Species*), photosynthetic bacteria (*Rhodopseudomonas Species*), *Actinomycetes Species*, *Streptomyces Species*, yeast, and cellulose-decomposing fungi.	Fresh ingredients cut into pieces to ease the pounding. Water is added to the mixture and squeeze. The commercial probiotics mixture and molasses are then mixed with the filtered juice. The mixture is fermented in a close-tightened jar for three days.	One tablespoon/10 ml. Per 200 kg body weight of cattle.	Mixture is given orally to the infected cattle.	[20]
Ten liters clean water, 250 gs salt.	Non-iodized salt is dissolved in clean water.	Ten liters of clean water, 250 gs of salt for one-time use.	Salt solution is poured and rubbed onto the infected animal's body.	[21]

The treatment of LSD is primarily focused on managing symptoms and preventing additional bacterial problems. This is achieved using a combination of antimicrobials, anti-inflammatory drugs, supportive therapy, and antiseptic treatments. Control strategies such as the culling of infected animals, movement limitations, and compulsory and consistent vaccination have been suggested as measures to address the issue [2, 25, 26]. However, eliminating the disease is anticipated to be challenging due to the involvement of arthropod vectors. Therefore, it is important to take into account risk variables when implementing control procedures [9]. The current review reports nine ethnoveterinary plants from different communities around Indonesia that were used to treat LSDV-infected animals.

Tobacco (*Nicotiana tabacum*)

The tobacco leaf extracts were found to contain alkaloids, cardiac glycosides, flavonoids, phenolic compounds, quinones, saponins, steroids, tannins, and terpenoids.

Wound healing properties

Empirical evidence and contemporary studies indicate that tobacco is utilized to accelerate the process of wound healing. Nicotine, a compound present in tobacco, has been demonstrated to speed up the process of angiogenesis. A study involved the application of a saline solution containing nicotine to the wounds of diabetic mice has shown that it significantly sped wound healing based on the histology score and degree of closure. Neovascularization increased in mice that were administered nicotine, as demonstrated by histomorphometry. Nicotine significantly accelerated the growth of capillary-like vascular [27]. LSD skin nodules are consequence of granulomatous reaction that extends into the surrounding tissue from the dermis and hypodermis. Chronic inflammation occurs in cases of infection [28]. Angiogenesis arises in the affected region during granulomatous inflammation [29]. Angiogenesis, the formation of new blood vessels, plays a vital role in the wound-healing process [30]. Administering tobacco can facilitate the enhancement of wound healing in LSD-infected cattle, hence promoting rapid neovascularization.

Insecticidal activities

The presence of the alkaloid nicotine in tobacco leaves caused the death of the insects. Nicotine is a potent insecticide derived from plants, known for its long history of use and its ability to quickly and effectively kill insects by targeting their nervous system. Nicotine

swiftly eradicates insects within one hour, inducing severe tremors, convulsions, and subsequent paralysis [31]. Nicotine not only causes disruption of biological membranes, malfunction of internal organs and metabolism, redox imbalance, and disturbances in the development and reproduction processes in insects, but it can also inhibit food intake. These effects can potentially lead to the death of the insect. The presence of nicotine in tobacco is also beneficial in eliminating vectors of LSDV, hence limiting the spread of the virus from infected cattle to healthy ones.

Sweet flag (*Acorus calamus*)

Antiviral activity

The ethanol extract of *Acorus calamus* demonstrates inhibitory effects on the replication of Dengue virus (DENV2) when applied to C6/36 cell mosquito larvae. Rat kidney fibroblast cells (BHK-21) served as the host cell. The effectiveness of *Acorus calamus* extract in inhibiting DENV2 infectivity was evaluated using plaque assay and DENV2-induced Cytopathic Effect (CPE). The compound Tatanan A, derived from the ethanol extract of *Acorus calamus*, exhibited the highest anti-DENV efficacy compared to the other 11 compounds [32].

Antiinflammatory, antioxidant, and wound healing properties

Acorus calamus extracts have been traditionally utilized for their analgesic and anti-inflammatory properties, as well as their ability to promote wound healing. *Acorus calamus* extract is utilized in both dried and oily forms for medicinal purposes. Additionally, it is known to possess antioxidant, antimicrobial, and anti-inflammatory properties [33, 34].

Garlic (*Allium sativum*)

Antiviral activity

Garlic extracts have been tested for their antiviral effects on many viruses, including *influenza B, human rhinovirus type 2, human cytomegalovirus (HCMV), parainfluenza virus type 3, herpes simplex type 1 and 2, vaccinia virus,* and *vesicular stomatitis virus* [35]. Allicin functions by inhibiting several thiol enzymes, whereas ajoene's antiviral effect is attributed to its ability to impede the adhesive contact and fusion of leukocytes. In addition, DATS demonstrated efficacy in inhibiting HCMV replication and viral immediate-early gene expression. Its mechanism of action involves boosting the activity of natural killer cells (NK cells), which are responsible for eliminating virus-infected cells [35].

Antibacterial activity

Garlic's antimicrobial properties are attributed to the activity of allicin, which has been observed to be effective against a wide range of microorganisms. These include antibiotic-resistant bacteria, both Gram-positive and Gram-negative, such as *Shigella, Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Streptococcus mutans, Streptococcus faecalis, Streptococcus pyogenes, Salmonella enterica, Klebsiella aerogenes, Vibrio, Mycobacteria, Proteus vulgaris,* and *Enterococcus faecalis.* Several garlic extracts, including aqueous, chloroform, methanolic, and ethanolic extracts, were found to hinder the growth of different pathogenic bacteria to different extents [36].

Antioxidant properties

An antioxidant is a substance that inhibits the oxidation of other molecules, thereby preventing damage to cells and tissues. Garlic may exert its antioxidant properties via regulating Reactive Oxygen Species (ROS), enhancing glutathione levels, and boosting cellular antioxidant enzymes [37]. The study discovered that garlic extract enhanced the functions of certain antioxidant enzymes, such as Superoxide Dismutase (SOD), while reducing the levels of Glutathione Peroxidase (GSH-Px) in the liver tissues of rats [38].

Anti-inflammatory properties

Studies have shown that garlic extracts and the compounds found in garlic have anti-inflammatory properties. Hobauer *et al.* [39] and Gu *et al.* [40] discovered that garlic's anti-inflammatory properties are due to its ability to prevent the movement of neutrophilic granulocytes into epithelial tissues. The chloroform extract of aged black garlic works by inhibiting the activation of Nuclear Factor Kappa B (NF-κB) in human umbilical vein endothelial cells induced by Tumor Necrosis Factor-α (TNF-α). This inhibition prevents the generation of cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) by inactivating NF-κB [41].

Soursop leaves (*Annona muricata* L.)

Annona muricata contains a high concentration of alkaloids, flavonoids, phenolic compounds, acetogenins, and lipophilic chemicals [42]. The traditional use of these advanced metabolites has been well-established for therapeutic purposes. For millennia, all components of A. muricata have been utilized to treat various illnesses and injuries. The manner of preparation varies, including topical treatments, direct intake, decoctions, and juicing [43, 44]. In Indonesia, soursop leaves have traditionally been utilized in bathing rituals to alleviate skin conditions and alleviate discomfort [43, 44].

Antioxidant and antiviral activities

Annona muricata extract's *in vitro* antioxidant ability was evaluated utilizing the 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid (ABTS) and 2,2-diphenyl-1-picrylhydrazyl (DPPH) tests [45]. Rutin was the main component in the phenolic compounds of the soursop leaf ethanol extract. In the DPPH and ABTS tests, this extract demonstrated a high antioxidant activity. Soursop leaf ethanol extract has strong antioxidant activity, which is linked to its antiviral properties. A contact duration of 15–360 min results in virus inhibition ranging from 5–6 log10 plaque forming units/volume (PFU). In human erythrocytes, soursop leaves can reduce oxidative stress and viral infections [46].

It has been discovered that oxidative stress is linked to LSD cases in cattle. According to studies, oxidative stress brought on by LSD infection in cattle might lead to cell damage [47]. Reactive oxygen species provide a threat to cells, which are neutralized by antioxidant chemicals. Derivative compounds that exhibit more reactivity than pure oxygen are known as Reactive Oxygen Species (ROS). Tissue damage is brought on by ROS [48]. After two to three weeks, nodules in LSD cattle will develop into ulceration, which is the loss of the epithelial layer in soft tissue, and necrosis, which is the death of live tissue [49]. Consequently, soursop leaves may assist to prevent necrosis and ulcers.

Antipyretic properties

The antipyretic properties of *Annona muricata* leaves have been studied by Gouemo and colleagues. A separate study demonstrated that administering a solution derived from the leaves, which contained ethanol, resulted in a decrease in both the frequency and death rate associated with seizures [50].

Antibacterial activity

The leaves, barks, roots, and seeds of *Annona muricata* exhibited significant antibacterial activity against *Staphylococcus aureus, Pseudomonas, Bacillus, Klebsiella,* and *Escherichia coli* [42, 51]. The antibacterial properties of leaf extracts may help explain their usage in the treatment of urinary skin disease.

Insecticidal activities

Annona muricata has also been employed as a biopesticide, particularly in the regulation of mosquito reproduction. According to a study, this occurred because the acetogenins in the plant can be poisonous to mosquito larvae [52].

Immunostimulant properties

Annona muricata, has the potential to enhance the immune system by activating mitogen-activated protein (MAP) kinase signaling pathways [53]. The presence of phenolic components, such as tannins, flavonoids, phenolic acids, and lignin, can enhance the body's ability to counteract oxidative stress by increasing its antioxidant capacity.

Turmeric (*Curcuma domestica*)

Antiviral activity

Curcumin is the primary component found in turmeric. Curcumin has an antiviral activity that may inhibit the reproduction of *Bovine*

Herpes Virus type 1 (BoHV-1). A study was conducted to determine the impact of turmeric's natural phenolic compounds on the replication of BoHV-1 in cell culture. Based on the findings, curcumin had a detrimental effect on BoHV-1 viral particles and caused disruption to the virus. A curcumin derivative may also interfere with the replication of BoHV-1 [54]. Curcumin also exhibits antiviral properties, including the ability to block Long Terminal Repeat (LTR) promoter-directed gene expression without affecting cell survival [55, 56]. Curcumin also exhibits antiviral properties against *Epstein-Barr virus* and HIV [57].

Anti-inflammatory properties

Granulomatosis, a state marked by enduring inflammation in the presence of infection, is seen in the dermis of calves afflicted with LSD [58]. Curcumin, as a very versatile chemical, can interact with a wide range of target molecules that are linked to inflammation. Curcumin regulates the inflammatory response by inhibiting the activity of lipoxygenase, cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (INOS) enzymes. This inhibition results in a decrease in the production of inflammatory substances such INF-α, interleukin (IL)-1,-2,-6,-8, and-12 [59].

Inflammatory indicators such as C-Reactive Protein (CRP), complements, and fibrinogen are produced in response to activation by inflammatory cytokines. Sandur *et al.* [60] found that curcumin, demethoxycurcumin, and bisdemethoxycurcumin are the active chemicals in *Curcuma domestica* that prevent the activation of TNF-induced NF-κB. The presence of methoxy groups on the phenyl ring was found to be the cause of their effects.

Antioxidant activity

An antioxidant is a substance that inhibits the oxidation of other molecules, thereby preventing damage to cells and tissues. The curcumin compound found in turmeric exhibits substantial antioxidant properties comparable to those of both vitamin C and vitamin E, in both water-soluble and fat-soluble extracts. Curcumin has the ability to remove hydroxyl radicals, singlet oxygen, superoxide radicals, nitrogen dioxide, and nitric oxide [61,62]. In a previous study, researchers discovered that the anti-inflammatory and antioxidant properties of curcumin were significantly boosted when combined with quercetin. Additionally, a synergistic protective effect was shown in rats exposed to diazinon-induced toxicity [63].

Antidepressant activity

Chronic moderate stress (CMS) in rats results in elevated levels of IL-6, TNF-α, Corticotropin-Releasing Factor (CRF), and cortisol. It also leads to a smaller medulla oblongata and lower activation of splenic Natural Killer (NK) cells. The ailment induced in the CMS was alleviated with a turmeric extract. The antidepressant activity of *Curcuma domestica* is attributed to its ability to inhibit the buildup of monoamine oxidase in the central nervous system [64].

Antibacterial activity

Curcumin has demonstrated antimicrobial efficacy against many bacterial strains including *Salmonella paratyphi, Trichophytongypseum, Staphylococcus aureus, Streptococci mutans,* and *Mycobacterium tuberculosis* [65-68].

Betelvine leaves (*Piper betle*)

Piper betle is known to contain various kinds of phytoconstituents, including alkaloids, glycosides, tannins, phenolic compounds, flavonoids, terpenes, and oligosaccharides [69]. These phytochemicals have also been documented to be effective against a wide range of human illnesses. The intense and sharp smell emanates from the betel leaves due to the presence of a significant amount of terpenes and phenols in the essential oil [70]. The betel plants were found to contain a diverse array of phytochemicals, including chavicol, chavibetol, hydroxychavicol, eugenol, estragole, methyl eugenol, hydroxy catechol, α-pinene, caryophyllene, β-pinene, 1,8-cineol, and other others [71].

Antiviral activity

The extract derived from *Piper betle* exhibits antiviral activity against the Newcastle disease virus. This investigation was carried out using embryonated chicken eggs that were 9-10 days old. The hemagglutination test (HA) was used to evaluate viral inhibition. The study revealed that the ethanol extract obtained from betel leaves effectively suppressed the growth of the Newcastle disease virus. The ethanol extract of red betel leaves contains particular chemical constituents, such flavonoids, saponins, tannins, and essential oils [72].

Insecticidal activities

The volatile oil dust formulation of *Piper betle*, with a concentration of 30%, demonstrated toxicity against adult insects, resulting in their mortality. Furthermore, it effectively hindered the survival of adult insects and impeded the development of their offspring [73]. Nair and Kavrekar discovered that the methanol extract derived from betel leaves demonstrates potent insecticidal properties against insects, including *Bruchus pisorum, Tribolium castaneum,* and *Sitophilus oryzae* [74].

Analgesic and anti-inflammatory properties

The analgesic effects of *Piper betle* were examined by administering hot and cold-water extracts of different concentrations to cross-bred albino mice in tail-flick test, hot plate test, and formalin test models. The cold extract exhibited greater antinociceptive efficacy compared to the hot extract through the opioid-mediated pathway [75]. A study was conducted to investigate the anti-inflammatory effectiveness of the ethanol extract from betel leaf in rats with arthritis produced by full Freund adjuvant. The ethanol extract exhibited dose-dependent anti-inflammatory and anti-arthritic effects by reducing the production of nitric oxide, as compared to the positive control dexamethasone [76]. Another investigation utilized a methanol extract from betel leaves to investigate its anti-inflammatory activity using the carrageenan-induced hind paw edema model. Additionally, the extract's analgesic effectiveness was assessed by the hot plate, formalin test, and writhing test. The extract administration effectively decreased carrageenan-induced paw edema and reduced the number of acetic acid-induced writhing and formalin-induced licks in a dose-dependent manner, with statistical significance ($p<0.05$) [77].

Antioxidant properties

An antioxidant is a substance that inhibits oxidation, which is a chemical reaction that can produce free radicals and damage cells. An *in vitro* study revealed that the extract of *Piper betle* inflorescence effectively scavenged free radicals, including H2O2, superoxide, and hydroxyl radical, with a 50% inhibitory concentration. The DPPH, superoxide, and hydroxyl radical scavenging activity of the aqueous extract of leaves from three varieties of betel (Kauri, Ghanagete, Bagerhati) was determined using a riboflavin/light/9-Nitro Blue Tetrazolium (NBT) system. Additionally, the inhibition of lipid peroxidation induced by FeSO4 was also assessed [78, 79].

Antibacterial activity

Nair and Chanda conducted an experiment to assess the antibacterial properties of betel leaf against various types of bacteria, including *Pseudomonas aeruginosa, Pseudomonas testosteroni, Pseudomonas pseudoalcaligenes, Staphylococcus aureus, S. epidermidis, S. subflava, Proteus mirabilis, Proteus vulgaris, Proteus morganii, Bacillus cereus, Bacillus subtilis, Bacillus megaterium, Citrobacter freundii, Micrococcus flavus, Alcaligenes faecalis, Enterobacter aerogenes, Salmonella typhimurium, Klebsiella pneumoniae, Escherichia coli, Streptococcus faecalis, Streptococcus cremoris,* and *Streptococcus agalactiae*. They discovered that the methanol extract of the betel leaf exhibited greater potency than the aqueous extract when compared to the standard drugs Piperacillin and gentamicin. The essential oil extracted from betel leaves of the Vellaikodi, Bangladeshi, and Deshwari types shown significant antibacterial action against *Staphylococcus aureus, Streptococcus mutans, Lactobacillus acidophilus, Streptococcus epidermidis,* and *Klebsiella pneumoniae* [80].

Larvacidal activities

The efficacy of *Piper betle* in killing mosquito larvae of *Aedes aegypti* was assessed by utilizing methanol extract and essential oil derived from the leaves. The Lethal Dose (LD50) values for the essential oil

were determined to be 86 ppm and 48 ppm after 2 h and 24 h, respectively. Similarly, the LD50 values for the methanol extract were found to be 153 ppm and 125 ppm after 2 h and 24 h, respectively [81,82]. Discovered that the leaves methanol extract had larvicidal action, with Lethal Concentration (LC50) values of 313.58 and 122.99 ppm after 24 and 48 h, respectively. The betel leaf essential oil also has the ability to impede the larval development of *Aedes aegypti* [83].

Ginger (*Zingiber officinale*)

A multitude of bioactive chemicals, including phenolic and terpene compounds, have been discovered in ginger. The primary phenolic compounds found in ginger are gingerols, shogaols, and paradols. These chemicals are responsible for the diverse range of biological activity exhibited by ginger [84]. Ginger has been discovered to exhibit several biological activities, including antioxidant anti-inflammatory, and antibacterial properties [85].

Antiviral activity

The essential oil of ginger has exhibited anti-infective activities against the HSV-1 and-2 *human herpes simplex viruses*. The *caprine alpha herpes virus 1* (CpHV-1) is an animal virus that serves as a model for studying HSV-2 infection due to its similarities with HSV-2. It causes the formation of ulcers in the vagina of its natural host. Live animal trials are particularly advantageous for evaluating the efficacy of antiviral medicines. Ginger essential oil, often known as Ginger EO, demonstrates inhibitory properties against CpHV-1. Ginger essential oil exhibits antiviral activity by impeding the herpes virus envelope and other vital constituents required for the virus to adhere to and infiltrate host cells. Ginger essential oil, due to its lipophilic nature, can permeate the skin/mucosal barrier independently or in conjunction with other molecules [86].

Antioxidant properties

In general, laboratory and animal studies have shown that ginger and its active components, including 6-shogaol, 6-gingerol, and oleoresin, have powerful antioxidant properties. the activation of the Nrf2 signaling pathway seems to plays a vital role in the fundamental mechanisms of action [87].

Anti-inflammatory properties

Multiple studies have demonstrated that ginger and its active components exhibit anti-inflammatory properties, which may provide protection against diseases associated with inflammation. The primary mechanisms responsible for the anti-inflammatory benefits were primarily associated with phoshatidylinositol-3-kinase (PI3K), protein kinase B (Akt), and the nuclear factor kappa light chain-enhancer of activated B cells (NF-κB) [88]

Overall, ginger and its active components have demonstrated efficacy in reducing inflammation. Ginger's anti-inflammatory effects are likely due to its ability to inhibit Akt and NF-κB activation, increase anti-inflammatory cytokines, and decrease proinflammatory cytokines. The utilization of ginger nanoparticles has the capacity to enhance the prevention and treatment of inflammatory bowel disease [89, 90].

Antibacterial activity

Antimicrobial resistance has posed a significant public danger by facilitating the transmission of bacterial, fungal, and viral infectious illnesses. A number of herbs and spices have been transformed into natural antibacterial agents that are highly efficient against various pathogenic microbes [91]. Ginger has demonstrated antibacterial and antifungal properties in recent studies [92].

Javanese turmeric (*Curcuma xanthorrhiza Roxb.*)

Curcuma xanthorrhiza Roxb., a member of the Zingiberaceae family, is an indigenous Indonesian plant commonly known as "Temulawak" or Java turmeric, which holds significant value locally. The C. xanthorrhiza rhizome was shown to contain a high concentration of terpenoids and curcuminoids, according to scientific research [93]. Thus, the therapeutic effects of *Curcuma xanthorrhiza* are mostly attributed to these two prominent categories of chemicals. The rhizome of *Curcuma xanthorrhiza* is the primary therapeutic component, containing many sesquiterpenoids and curcuminoids [94].

Immunomodulatory (Immuno-stimulant) activities

Curcuma xanthorrhiza is rich in curcuminoid chemicals. Using it can significantly improve stamina. Curcuma powder exhibits an immunomodulatory effect on antibody titers. The reason for this is because curcumin stimulates the proliferation of T cells, which in turn modulates the functioning of the immune system. T lymphocytes play a crucial part in the inflammatory process, the stimulation and proliferation of B lymphocytes to produce antibodies, and the facilitation of macrophages in engulfing foreign substances. T lymphocytes also play a function in identifying and eliminating cells that have been infected by a virus. T cells comprise T helper cells, which stimulate macrophages to resist pathogens, and Cytotoxic T Lymphocyte (CTL)/Tc cells, which eradicate cells that are infected with bacteria or viruses and eliminate the source of the infection [95].

Anti-inflammatory properties

The anti-inflammatory properties of the methanol rhizome extract of *Curcuma xanthorrhiza* have been extensively studied in relation to carrageenan-induced edema, vascular permeability generated by acetic acid, and the writhing phenomena in rats [96]. The extract demonstrated significant anti-inflammatory properties, primarily due to the presence of germacrone. The anti-inflammatory capacity of *Curcuma xanthorrhiza* is likely associated with its curcuminoid concentration, particularly curcumin. Curcumin exhibits greater anti-inflammatory efficacy compared to other curcuminoid derivatives, such as demethoxy-or bisdesmethoxy-form [97]. Moreover, the anti-inflammatory capacity of *Curcuma xanthorrhiza* is undoubtedly attributed to xanthorrhizol, which serves as its marker compound.

Antioxidant properties

Traditionally, it has been claimed that *Curcuma xanthorrhiza* possesses antioxidant properties that can effectively scavenge free radicals, perhaps providing treatment for an inflammatory joint disease. Moreover, the conventional effectiveness of *Curcuma xanthorrhiza* for skin therapy is closely linked to its antioxidant capability [98].

Antimicrobial activities

The rhizome extract of *Curcuma xanthorrhiza*, as well as pure xanthorrhizol and its essential oils, have been demonstrated to have the capability to inhibit or kill pathogenic bacteria. These substances exhibit a range of action, from moderate to strong killing ability [99]. The antibacterial efficacy of *Curcuma xanthorrhiza* is likely attributed to its phenolic component composition, specifically xanthorrhizol and curcuminoids, which serve as the primary active ingredients. According to reports, the phenolic chemical has the potential to block the cell walls or membranes of microorganisms by changing their permeability. This leads to the loss of important components, including ATP, RNA, protein, and DNA [100]. The exact mechanism by which xanthorrhizol acts as an antibiotic is not fully understood. However, it is believed that xanthorrhizol may have the ability to decrease NF-κB and Mitogen-Activated Protein Kinase (MAPK), which are activated in response to microbial infection [101]. Regarding curcumin, its antimicrobial effects are attributed to its ability to inhibit cytokinesis and bacterial cell multiplication, as well as disrupt bacterial cell wall and membrane, leading to cell lysis [102]. According to a paper, curcumin can interact with the cell membrane and wall of fungi through electrostatic and/or hydrophobic forces, causing a disruption of the membrane structure. Although the antibacterial property of *Curcuma xanthorrhiza* appears to be effective against both Gram-positive and some Gram-negative bacteria, it exhibits greater potency against Gram-positive bacteria due to the nature of their cell walls [103].

Galangal (*Kaempferia galanga*)

Kaempferia galanga, a member of the *Zingiberaceae* family, is a fragrant perennial herb that possesses tuberous rootstocks. It is grown extensively in Southeast Asia and has also been imported to Northern

Australia [104]. The rhizome of the plant holds significant value in traditional medicine. In China, this herb is utilized for its analgesic and anti-inflammatory properties [105]. Additionally, it has a lengthy historical background in the utilization of fragrances to alleviate restlessness, stress, anxiety, and sadness. In Japan, *Kaempferia galanga* has been utilized for enhancing sleep quality and reducing stress levels [106]. Various pharmacological activities have been documented, including anti-inflammatory and analgesic effects [107], mosquito repellent and larvicidal qualities [108], vasorelaxant effects [109], sedative effects [106], antibacterial effects [110], and antioxidant activity [111]. The plant's rhizomes contain volatile oil and other significant substances with immense medicinal properties, making them highly sought after by traditional healthcare practitioners. The plant has already been found to contain the important compounds ethyl-cinnamate and ethyl–para-methoxycinnamate, which have been identified in previous studies [112].

Kaempferia galanga's rhizome contains essential oils with antioxidant effects. Ethyl p-methoxy cinnamonate, a crucial constituent included in essential oils, functions as an antioxidant. Uncontrolled reactive oxygen species (ROS) and other chemically active metabolic byproducts have the potential to cause harm, but they can be counteracted by antioxidant molecules. ROS species have the ability to trigger degenerative processes in cells. The ROS consist of hydroxyl radicals, hydrogen peroxide, nitric oxide, superoxide anion, peroxy nitrite, and other by-products of metabolism. Chemical compounds like flavonoids, polyphenols, and phenolic acids are classified as antioxidants due to their ability to capture reactive oxygen species (ROS) radicals. Essential oils can be used as a suitable replacement for synthetic antioxidants, providing effectiveness without any negative side effects [113].

Salt/sodium chloride

Sodium chloride, commonly referred to as table salt, has efficacy in the process of wound healing. Based on research, immersing wounds in a 7% salt solution can significantly accelerate wound healing, leading to a decrease in wound size by the third day and complete healing by the seventh day. Mesalt is a kind of dressing made of sodium chloride that promotes the removal of excess fluid from wounds during the inflammatory phase, therefore aiding in the healing process of the wound. Curity sodium chloride dressings are specifically formulated to improve biological cleaning and facilitate the autolytic debridement process [114]. Administering a saline solution can enhance the healing process of wounds in cattle affected by LSD by promoting wound cleaning during the inflammatory phase.

DISCUSSION

The incubation period for LSD virus infections typically spans from 4 to 7 d following infection, while naturally occurring infections may have an incubation period of up to 5 w. This condition can manifest in three separate ways: acute, subacute, and chronic. LSDV proliferates within pericytes, fibroblasts, endothelial cells, and macrophages and then spreads throughout the circulatory system, resulting in inflammation of blood vessels (vasculitis) and lymphatic vessels (lymphangitis) in the affected organs. The duration of the presence of the LSD virus in the bloodstream ranges from 1 to 10 d [49].

Following the period of incubation, there are four clearly defined stages during which clinical symptoms become apparent. During the early phase of LSD infection, the animal displays symptoms of a severe fever, reaching a temperature of 41 °C, which persists for a duration of 7-10 d. Other symptoms include loss of appetite, excessive tearing, feelings of sadness, increased mucus from the nose, reduced production of breast milk, heightened secretion of saliva, and the existence of sores on the skin and mucous membranes. In the second phase, there is an enlargement of the subscapular and precrural lymph nodes, along with an increase in multiple nodules with diameters ranging from 0.5 to 5 cm. These nodules are primarily located in multiple areas, including the head, neck, torso, genitals, udder, mucous membranes, nasal cavity, mouth, and plaque regions. After 1-2 d, the nodule bursts, causing the infection to spread to the surrounding environment. Following a duration of 2-3 w, the nodules in the third stage will experience ulceration and necrosis. Severe cases of this ailment are characterized by the presence of ulcerated sores on the mucous membranes of the eyes and nasal cavities, as well as excessive salivation, lacrimation, and nasal discharge. The animal's feces may contain the LSD virus, which has the capability to infect other animals. In the fourth phase, which lasts at least one month, the ulcer heals, causing the skin to thicken and the development of darkening of the skin around the damaged area [49].

Secondary bacterial infection in skin lesions can exacerbate severity and prolong the duration of the disease. The bacterial community of the lesion was identified to consist of 98 species, with the majority belonging to the phyla *Proteobacteria, Firmicutes, Actinobacteria,* and *Bacteroidetes*. All bacterial species discovered are known as opportunistic pathogens yet resistant to inflammatory reactions [115].

The management of LSD involves addressing symptoms and preventing additional bacterial problems with the use of a combination of antimicrobials, anti-inflammatory drugs, pain relievers/fever reducers, and antiseptic treatments [116].

The LSDV is transmitted via arthropods, specifically hematophagous insects. Nevertheless, the extended connection to the host does not account for the swift emergence of widespread epidemics. Thus, it appears that ticks may serve as reservoirs for the virus. *Aedes aegypti* is the only type of fly that can completely transmit the virus to cattle who are vulnerable to it. The virus was found to be non-transmissible by mosquitoes such as *Culicoides nubeculosus, Culex quinquefasciatus Say,* and *Anopheles stephensi Liston* [8]. According to Gubbins *et al.* (2008) there is a positive correlation between the ratio of biting insects to host population and the likelihood of transmission [117].

The pharmacological effects of medicinal plants are mainly due to a range of bioactive phytochemicals that have biological and pharmaceutical importance. The treatment aims to reduce clinical symptoms and improve the overall health of diseased cattle while also addressing skin nodules. This is accomplished by the administration of certain herbal medicines.

An assessment was conducted on several plants to determine their efficacy in preventing or eliminating LSDV. The plants that demonstrate the most effectiveness in enhancing the well-being of cattle are those that possess antimicrobial capabilities. All plants reviewed in this study, except *Kaempferia galanga* and *Nicotiana tabacum* have antiviral activities. Antiviral therapies for LSD effectively mitigate vasculitis and lymphangitis in infected tissue by inhibiting viral replication [49]. Eventhough each antiviral agent target specific virus, some broad-spectrum antivirals can works against multiple viruses. All plants recommended for treating LSD by goverment agencies in Indonesia except *Nicotiana tabacum* and *Acorus calamus* possessing antibacterial characteristics, which can prevent animals from subsequent bacterial infections caused by skin lesions (nodules).

During the histological analysis of skin nodules, specific eosinophilic intracytoplasmic inclusion bodies can be observed in the keratinocytes, macrophages, endothelial cells, and pericytes. There is infiltration of inflammatory cells, including macrophages, lymphocytes, and eosinophils, into the superficial dermal tissue of the affected sites. Furthermore, certain patients may exhibit a prevalence of vasculitis and a significant occurrence of coagulative necrosis in the subcutaneous muscles [118, 119]. The virus replicates within fibroblasts, macrophages, pericytes, and endothelial cells, resulting in inflammation of blood vessels (vasculitis) and lymphatic vessels (lymphangitis) in the affected tissues [120]. Thus, the 9 recommended plants with anti-inflammatory qualities can help alleviate inflammation. Some selected herbs also possess supplementary analgesic and antipyretic pharmacological properties, which aid in pain relief and fever reduction.

The skin nodules in infected cattle have the ability to spread to the mucosal membranes and internal organs [121]. Lesions in internal organs lead to gastrointestinal and respiratory problems, including ruminal atony, dyspnea, and pneumonia [122]. The infection

modifies hematological and biochemical parameters while inducing oxidative stress [123]. Oxidative damage is a primary factor in the development of numerous acute and chronic illnesses. This damage occurs due to an excessive production of free radicals and a decrease in the body's ability to counteract their harmful effects through antioxidants. Infected animals have shown increased levels of oxidative stress and indicators of lipid peroxidation [124].

Ikrima, Amalia, and Levita (2020) assert that ROS is causally linked to tissue injury. Catlle's skin, which is damaged by LSD will develop lesions that will advance to ulceration, resulting in the loss of the outer layer of soft tissue and necrosis, which is the death of tissue [48]. The described sequence of events usually takes place over a period of 2-3 w [49]. Antioxidant molecules protect cells from the dangers posed by reactive oxygen compounds.

All plants, but not the *Nicotiana tabacum*, demonstrate antioxidant activities. Most of the recommended plants also demonstrates anti-inflammatory characteristics. Some plants (*Curcuma domestica* and *Kaempferia galanga*) possesses the capacity to relax the body's as an antidepressan, sedative, vasorelaxant. In addition, the use of *Nicotiana tabacum*, *Acorus calamus*, and salt/sodium helps in the healing process of wounds in cattle.

The role of the livestock immune system is crucial in aiding the process of healing. If the infected livestock does not possess sufficient innate immunity, it will be susceptible to secondary infection with other bacterial/viral diseases, leading to an increase in mortality rate [125].

During the early phase of LSD infection, the animal experiences signs of a high fever, reaching a temperature of 41 °C, which persists for a duration of 7 to 10 d. Other symptoms include loss of appetite, excessive tearing, depression, increased mucus from the nose, decreased production of breast milk, heightened saliva production, and sores on the skin and mucous membranes [49]. T cells are crucial in the immune system as they trigger protective responses to LSD. A study on dairy cattle examined the extended immune responses to recombinant LSD virus and highlighted the importance of T cell proliferation in protecting against the disease [126]. Plants with immunomodulatory qualities, particularly those that act as immunological stimulants, such as *Curcuma xanthorrhiza* and *Annona muricata* leaves, are highly advantageous for enhancing the overall health of animals. Additional effect of analgesic and antipyretic from soursop leaves and galangal would reduce symptoms in infected animals.

LSDV can be transmitted through vectors, and it is important to maintain protection against this virus. The presence of arthropod vectors complicates the eradication of the disease, and any delays in removing affected animals increase the chances of LSD transmission [2]. The utilization of herbal medications with insecticidal properties such as *Nicotiana tabacum*, *Annona muricata* leaves, *Piper betle*, and *Kaempferia galanga* can be quite advantageous.

Certain plants has the capacity to treat LSD, herbal agents that significantly make positive contribution on the wellbeing of farm animals. This review has identified the beneficial effects of locally accessible plants that have pronounced medicinal properties, in combination with veterinary-prescribed treatments, on the breakout LSDV infections.

CONCLUSION

Currently, there is no targeted treatment for the LSD virus. Researchers are shifting their attention towards natural sources, like plant extracts, which have the potential to exhibit antiviral properties. This is due to the limits and drawbacks associated with vaccinations. The literature has multiple research studies that have proved the antiviral, antibacterial, antioxidant, anti-inflammatory, analgesic, antipyretic, immunostimulant, wound healing, and antidepressive efficacies of different plant extracts. The indigenous knowledge of botanical remedies for the treatment of LSD has been substantiated and has contributed to expedited recovery from the sickness. Therefore, utilizing these herbs for the treatment of LSD will yield positive results. The results suggest that the use of *Nicotiana tabacum* leaves, *Acorus calamus* rhizomes, *Allium sativum* bulbs, *Annona muricata* leaves, *Curcuma domestica* rhizomes, *Piper betle* leaves, *Zingiber officinale* rhizomes, *Curcuma xanthorrhiza* rhizomes, and *Kaempferia galanga* rhizomes are indicated for treating LSD, following the recommendations of the official veterinary department of Indonesia. These plants are inexpensive, readily accessible, and simple to apply.

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AUTHORS CONTRIBUTIONS

Zakky Cholisoh: supervising, conceptualizing, literature review, writing original draft, and critical evaluation,; Ahda M. U. Nurinnafi'a: data curation, literature review, writing original draft; Suranto: critical evaluation, editing, and proofreading; Erindyah R. Wikantyasning: critical evaluation, editing, and proofreading.

CONFLICTS OF INTERESTS

The authors declare no conflict of interest.

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