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TREATMENT TRIALS OF EPIZOOTIC LYMPHANGITIS WITH LOCAL MEDICINAL PLANTS: A REVIEW

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REVIEW

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ABSTRACT: The aim of this paper was to review the use of local herbal medicines to treat Epizootic lymphangitis (EZL) and challenges related with safety, efficacy and quality control of herbal medicines. EZL has deleterious effect on both welfare and health of the horses and mules. In addition it has a serious negative impact on mainly the livelihoods of cart-horse owners/drivers. Basically, antifungal drugs for the treatment of EZL are costly and mostly unavailable in such areas especially in developing countries like Ethiopia. Medicinal herbs have a hopeful future since there are about half a million plants around the world, most of them have not yet been studied in medical practice, and current and future studies on medical activities can be effective in treating this disease. Furthermore, there is no gainsaying the fact that the requirements as well as the research protocols, standards and methods needed for the evaluation of the safety and efficacy of herbal medicines are much more complex than those required for conventional pharmaceuticals. These days, there are several trials on local plants like *Xanthium strumarium (X. strumarium)*, *Combretum molle (C. molle)* seed and *Phytolacca dodecandra (P. dodecandra)* extracts inhibited the growth of *Histoplasma capsulatum var farciminosum (H. capsulatum var farciminosum).* Among these, the aqueous and n-butanol extracts of *P. dodecandra* with minimum inhibitory concentration (MIC) of (0.078%-0.156%) and (0.039%–0.078%) respectively have been inhibiting the growth of *H. capsulatum var. farciminosum*. In vivo, over 58.3% horses with the disease responded to treatment then the other two plant extracts. In conclusion, *P. dodecandra* extracts showed a significant effect to inhibit the growth of *H. capsulatum var farciminosum in vitro* and EZL *in vivo*.

Keywords: *Combretum molle*, Epizootic lymphangitis, *Xanthium stramorium*, *Phytolacca dodecandra*, Medicinal herbs.

INTRODUCTION

Epizootic lymphangitis (EZL) is a contagious, chronic disease which mainly affects horses, mules, and camels (Biyashev et al., 2019; Adedokun et al., 2020). It is caused by *Histoplasma capsulatum var. farciminosum* (*H. capsulatum var. farciminosum*). The disease is characterized clinically by a suppurative, ulcerating, and spreading pyogranulomatous, multifocal dermatitis and lymphangitis. It is seen most commonly in the extremities, chest wall and the neck, but it can also be manifested as an ulcerating conjunctivitis of the palpebral conjunctiva, or rarely as a multifocal pneumonia. The organism may also invade open lesions including ruptured strangles abscesses and castration wounds (OIE, 2009).

The source of *the H.capsulatum var. farciminosum* can be the skin lesions, nasal and ocular exudates of infected animals or the soil. This organism can also spread on fomites (common utensil) such as grooming or harnessing equipment. Biting flies in the genera Musca and Stomoxys are thought to spread the conjunctival form. The pulmonary form probably develops when the animal inhales the organism (Public Health Agency of Canada, 2001).

Epizootic lymphangitis is more common in tropical and subtropical regions than in temperate zones (Alsaad et al., 2016). *H.capsulatum var. farciminosum*is endemic in some countries in the Mediterranean region, and in parts of Africa and Asia including India, Pakistan and Japan (OIE, 2009). Many treatment types have been tried, largely without success. Parenteral iodides and amphotericin B have been reported as effective. However, although the disease is highly prevalentand economically important in Ethiopia (Ameni, 2006), the treatment options mentioned have not been employed because of the cost of the drugs and their absence in Ethiopia. This warrants for the need for other approaches including the use of traditional remedies.

Traditional medicine is used throughout the world as it is heavily dependent on locally available plant species and plant-based products and capitalizes on traditional wisdom-repository of knowledge (Awas and Demissew, 2009). The wide spread use of traditional medicine could be attributed to cultural acceptability, economic affordability and efficacy against certain type of diseases as compared to modern medicines. Knowledge of medicinal plants of Ethiopia and of their uses provides vital contribution to human and livestock health care needs throughout the country (Belayneh et al.,

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2012). The plant- based human and livestock health care persists and remains as the main alternative treatment for different ailments in Ethiopia, largely due to shortage of pharmaceutical products, prohibitive distance of the health service stations, unaffordable prices by small holder farmers and pastoralists for conventional drugs, emergence and re-emergence of certain diseases and appearance of drug resistant microbes and/or helminthes (Bekele et al., 2012).

Whole plant of *Xanthium strumanrium* (*X. strumanrium*) as well as all parts separately is used in medicine (Bhogaonkar and Ahmad, 2012; Fan et al., 2019). The genus xanthium also possess antibacterial, antiviral, antimalarial, fungicidal, insecticidal and cytotoxic activities against cancer cell lines (Sravani et al., 2010; Passos et al., 2019). *Phytolacca dodecandra* (*P. dodecandra*) is one of the many plants claimed to have antifungal secondary metabolites. The antifungal effect of the crude aqueous extract of *P. dodecandra* was demonstrated *in- vitro* against different genera of dermatophytes of human pathogen and four clinical isolates of *Candida albicans* (Woldeamanuel et al., 2005; Tura et al., 2017).

Combretum molle was used as a medicinal plant since ancient times (Grønhaug et al., 2008). The test of *C. molle* seed extract as antifungal property has been demonstrated in various studies (Masoko et al., 2007; Anato and Ketema, 2018). Medicinal herbs have a hopeful future since there are about half a million plants around the world, most of them have not yet been studied in medical practice, and current and future studies on medical activities can be effective in treating diseases (Singh, 2015).

In terms of population exposure alone, it is essential to identify the risks associated with the use of herbal medicines, and in this regard, the safety of these products has become an issue of great public health importance (WHO, 2004; WHO, 2005). There is no gainsaying the fact that the requirements as well as the research protocols, standards and methods needed for the evaluation of the safety and efficacy of herbal medicines are much more complex than those required for conventional or orthodox pharmaceuticals (WHO,2005; Zhou et al., 2013). Thus, the general requirements and methods for quality control of finished herbal products remain far more complex than for other pharmaceuticals (WHO, 2003; WHO, 2004; WHO, 2005). Therefore the main objectives of this paper is to review the commonly used local herbal medicine to treat EZL and challenges related with safety, efficacy and quality control of local herbal medicines.

TREATMENT TRIALS FOR EZL USING HERBAL MEDICINE

The Xanthium strumarium leaf extract

The *X. strumarium,* a rough cocklebur is broad leaved, tap rooted herbaceous annual plant. This is in a family of asteraceae, sub family asteroideae, tribe heliantheae, and genus Xanthium and species *X. strumarium*. It grows as weed throughout on waste lands. Cockleburs are short day plants and they can also flower in the tropics where the day length is constant. The herb is reputed as medicine in Europe, China, Indo-china, Malaysia and America also (Bhogaonkar and Ahmad, 2012). Stem is erect, ridged, rough and hairy and frequently branched which results somewhat bushy plants from 30-120 cm tall. It has small greed unisexual flower occurring in separate cluster at the end of the brunches and main stems. The fruit is brown, hard, woody, bur from 0.4-0.8 inch long and coved with stout, hooked bristle. Its seed are produced in hard, spiny, globes or oval double chambered single seeded bur (Agharkar, 1991).

Beside its medicinal values if a small quantity of parts of the mature plants is consumed, the seeds and seedlings will cause intoxication because extremely toxic chemical carboxyatratyloside is contained in them (Madalln and Sing, 2001). Whole plant of *X. strumanrium* as well as all parts separately is used in medicine (Bhogaonkar and Ahmad, 2012). The genus *xanthium* also possess antibacterial, antiviral, antimalarial, fungicidal, insecticidal and cytotoxic activities against cancer cell lines (Sravani et al., 2010).

Antifungal activity can be determined by the agar diffusion method. Test samples are diluted in Sabouraud dextrose agar followed by solidification in slanting positions. Test fungal cultures are inoculated on the slant and are incubated at 29°C for 3-7 days (Paxton, 1991; Nisaret al., 2010). The principal compounds isolated from *X. strumanrium*leaves are found to contain, isoxanthanol, hydroquinone, caffeyolquinic acids, xanthanol, anthraquinone, cardenolide, leucoanthocyanin, simple phenolic striterpenoids and thiazinedione (Bhogaonkar and Ahmad, 2012). *X. strumanrium* produces secondary metabolites such as alkaloids, tannins, terpenoids, flavonoids, chloroform and n-hexane fractions whose activity has been demonstrated to be antifungal (Gujar and Talwankar, 2012). Antifungal activity of these molecules from *X. strumarium* exhibited 60% and 50% inhibition activity against the major dermatophyte fungi, *Microsporum canis* (Bharathi et al., 2010).

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Figure 1 - Lesions of Epizootic lymphangitis (Wondmnew and Teshome, 2016).

The Phytolacca dodecandra extracts

Antifungal effect is one of the effects of secondary metabolites produced by plants. It is one of the many plants claimed to have antifungal secondary metabolites. Many studies indicated that, saponins are responsible for its antifungal effect. The antifungal effect of the crude aqueous extract of *P. dodecandra*is demonstrated *in vitro* against different genera of dermatophytes of human pathogen and four clinical isolates of *Candida albicans* (Woldeamanuel et al., 2005). The crude aqueous extract is also found to have effect against *H. capsulatum var farciminosum* both *in- vitro* and *in- vivo* (Ameni and Tilahun, 2003; Hadush et al., 2008). The n-butanol and aqueous extracts of *P. dodecandra* are evaluated for their effects on the isolates of *H. capsulatum var. farciminosum* and for the treatment of cases of epizootic lymphangitis. The phytochemical analysis of *P. dodecandra* shows the presence of saponins, alkaloids, and phenolic compounds in the berries of *P. dodecandra*. Thus, the secondary metabolites identified in the berries are all active antifungal compounds (Arif et al., 2009), which could imply that these secondary metabolites could be responsible for the antifungal activity of the berries observe in the n-butanol extract of the berries.

The antifungal effect of n-butanol extract is observed to be much greater than that of the aqueous extract. The minimum inhibitory concentration (MIC) of n-butanol extracts range from (0.039%–0.078%); whereas that of the aqueous extract is in the range of (0.625%–1.250%). Similar finding for the aqueous extract is reported in which the MIC of *P. dodecandra* against the yeast forms of different *Candida* species is higher than 0.5% (Woldeamanuel et al., 2005). Another study shows that the MIC of the aqueous extract of *P.dodecandra* is 1% (Ameni and Tilahun, 2003). The MIC for novel pharmacological compounds should be <0.1% (Kuete, 2010).

The minimum fungicidal concentration (MFCs) of aqueous and n-butanol extracts of *P. dodecandra* ranges from (1.250%–2.500%) and (0.078%–0.156%), respectively. The prepare ointment is topically applied and the result shows that, 58.3% are completely healed, while 41.7% did not cure. Comparable results are reported with the aqueous extracts (Ameni and Tilahun, 2003; Hadush et al., 2008). The n-butanol extract of *P. dodecandra*is effective against *H. capsulatum*

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var. farciminosum. Previous toxicity studies on *P. dodecandra* indicated that human and guinea pigs can tolerate skin irritation of *P. dodecandra*. Moreover, oral LD50 are found to be 2.6 and 2.2 g/kg in mice and rats, respectively (Ameni and Tilahun, 2003; Hadush et al., 2008).

Combretum molle extracts

Combretum molle (*C. molle*) is used as a medicinal plant since ancient times (Grønhaug et al., 2008). The test of *C.molle* seed extract as antifungal property has been demonstrated in various studies (Masoko *et al*., 2007). Phytochemical studies carried out in the genus *Combretum* have shown the occurrence of many classes of constituents, including triterpenes, flvonlds, lignans, non-protein amino acid and tannins from different parts of the plant (Pietrovsk *et al*., 2006). *C. molle* has been widely used as a medicinal plant to treat various diseases such as parasitic, protozoan, and fungal infectious diseases in East and West Africa (Grønhaug et al., 2008). Antifungal activity is reported in numerous fungal models that used *Candida albicans*, *Candida neoformans, Epidermophyton flccosum, Microsporum gypseum, Trichophyton mentagrophytes, Aspergillus fumigatus, Sporothrix schenckii and Microsporum canis* (Masoko et al., 2007).

The minimum inhibitory concentration (MIC) of *C.molle* seed extracts obtain in the study is 0.0156 %. However, the difference between the MIC (0.0156%) and the maximum none inhibitory concentration (0.0078%) suggests that the MIC could be lower. As Kuete (2010) stated, the MIC for novel pharmacological compounds should be <0.1%. So, the MIC (0.0156 %) is below 0.1% and hence this extract can be considered active. The positive control Ketaconazole is found to be more potent than *C.molle* seed extracts in inhibiting the growth of the mycelia form of *H. capsulatum var. farciminosum* (Asres et al., 2006). The *C.molle* seed extracts has inhibitory effect on *H. capsulatum var. farciminosum*. The Minimum inhibitory effect of *C.molle* seed extracts obtained from the study by Wondmnew and Teshome (2016) is also in harmony with previous studies made on fresh garlic extract (0.5 mg/ml, 0.05%) by Mesfi (2012), *P. dodecandra* (0.03%) by Mekonnen et al. (2012). According to a study by Mekonnen et al. (2012), the MICs of n-butanol and aqueous extracts of *P. dodecandra* are (0.039%-0.078%) and (0.625%-1.250%), respectively. The difference in MIC of the two extracts of *P. dodecandra*can be ascribing by the difference in the polarity of the solvent used in the extraction process. This is supported by Masoko et al. (2007); Eloff et al. (2005); and Cowan, (1999), as the polarity of the solvent has great effect on the quantity and types of bio-molecules extract.

The main antifungal molecule in *C.molle* seed extract is tannin (Mishra et al., 2009). The presence of phenolic hydroxyl groups on the surface of tannin molecules participate strongly in the biological activities of tannins. It combines with protein and other polymers to form stable complexes through nonspecific forces such as hydrogen bonding, hydrophobic effects and covalent binding (Stern et al., 1996). This is done by hydrolysis of ester linkage between gallic acid which eventually affects the biosynthesis of cell wall and cell membrane. Impairment of biosynthesis of cell wall and cell membrane cause to increase the permeability of cell membrane and alterations of cell wall .This leads to decrease cell volume and disjunction of cell membrane from the cell wall (Suraya and Darah, 2002). Moreover, this leads to leakage of internal contents and no more exchange of molecule between cell wall and cell membrane.

As Haslam (1996) tannins have two forms, and these are hydrolysable and condensed tannins which affect fungal growth. In the same study make by Ndip et al. (2007) both hydrolysable and condensed tannins have been found to possess antifungal effect. However, the hydrolysable tannins are found to be more effective against fungi. This is because hydrolysable tannins (gallic acid and ellagic acid) are linked to esters of core molecules which will be hydrolyzed easily while condensed tannins are not susceptible to hydrolysis (Haslam, 1996). In other research done by indicated that the fungicidal effect of the extract is due to the presence of high amount of hydrolysable tannins. In addition to its fungicidal effect, when *C.molle* seed extract is used topically, it will promote tissue healing, stop bleeding, stop further infection and heal the wound internally. As mentioned by Stephane et al. (2004), the ability of tannins to form a protective layer over the exposed tissue keeps the wound from being infected even more.

Challenges associated with monitoring safety of local Herbal Medicine for EZL

In terms of equine exposure alone, it is essential to identify the risks associated with the use of local herbal medicines, and in this regard, the safety of these products has become an issue of great animal health importance (WHO, 2004; WHO, 2005). There is no doubt that the increasing cases of poisoning associated with the use of local herbal medicines in many parts of the world in recent times, is necessitating the need to ensure thorough toxicity assessment alongside active pharmacovigilance on these products in order to promote their safe use and protect animal health (Zhou et al., 2013).

Challenges related to the assessment of safety and efficacy of local Herbal Medicine

There is no gainsaying the fact that the requirements as well as the research protocols, standards and methods needed for the evaluation of the safety and efficacy of local herbal medicines are much more complex than those required for conventional or orthodox pharmaceuticals (WHO, 2005; Zhou et al., 2013). A single local herbal medicine or medicinal plant may contain hundreds of natural constituents, and a mixed local herbal medicinal product may contain several times that number. Suppose every active ingredient is to be isolated from individual herb from which the local herbal medicine is formulated or produced, the time and resources required would be tremendous. Such an analysis may practically be impossible especially where local herbal product is a mixture of two or more herbs (WHO, 2005).

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Medicinal herbs in the future perspectives

Medicinal herbs have a hopeful future since there are about half a million plants around the world, most of them have not yet been studied in medical practice, and current and future studies on medical activities can be effective in treating such diseases (Singh, 2015). The use of medicinal plants has a long history; however, the use of the whole plant or raw materials for treatment or experimentation has many drawbacks, including changes in the plant's compounds in different climates, simultaneous development of synergistic compounds that lead to adverse effects of antagonists, or other unexpected changes in bioactivity, and changes or loss of bioactivity due to the variability and accumulation, storage and preparation of raw materials; therefore, advancing towards the isolation of compounds and the use of pure substances with bioactivity, instead of the plant benefits, has certain benefits including convenient examination of therapeutic effects and determination of toxic doses to control the quality of the therapeutic formulation (Zhang, 2011). The beginning of the development of herbal medicines is concurrent with the development of chemistry and isolation, purification, and determination of plant compounds (Shakya et al., 2012).

In the past, the drug discovery of the biological compounds from plant materials and the process of identifying the structures of active compounds from the extracts are problematic depending on the complexity of the compounds and might take weeks, months or even years. Nowadays, the rate of bioassay-guided fractionation has been significantly enhanced by the development of precision instruments such as high-performance liquid chromatography (HPLC), liquid chromatography mass spectrometry (LCMS), magnetic field and nuclear magnetic resonance (NMR) is a recent major breakthrough for the categorization (NMR) is a recent major breakthrough for the categorization of compounds that are extremely limited in quantity in their organisms of origin (Schroeder and Gronquist, 2006). Despite the success of research to produce medicinal plants over the past few decades, future efforts face many challenges. The quality of the herbal product has been studied. Standardization of raw materials is an important issue for the plant industry (Yadav et al., 2014).

Herbaceous plants can be easily infected during growth, processing and collection. Contamination and pollution with heavy metals are two main problems with herbal drugs. It is therefore necessary to improve the quality and quantity of bioactive compounds for the production of herbal drugs while making effort to discover more new herbal drugs (Clark, 1996). Due to expanding the use of natural substances around the world, the quality and safety ofplant-derived medicines should be comprehensively and accurately studied issues and the traditional and the millennial beliefs about these issues cannot be surely trusted; therefore, scientific and enlightening studies are essential to obtain reliable information for the use of medicinal plants in health care (Firenzuoli and Gori, 2007).

Table 1 - Results of the *in vitro* evaluation of methanol extracts of *P. Dodecandra*, *C. longa*, and *D. stramonium* on *H. capsulatum var. farciminosum*

C. longa		*P. dodecandra*		*D. stramonium*		Ketoconazole	
Conc.	Growth	Conc.	Growth	Conc.	Growth	Conc.	Growth
5mg/mL	X	5mg/mL	X	5mg/mL	+	0.8µg/mL	X
2.5mg/mL	X	2.5mg/mL	X	2.5mg/mL	+	0.4µg/mL	X
1.25mg/mL	X	1.25mg/mL	X	1.25mg/mL	+	0.2µg/mL	X
0.625mg/mL	X	0.625mg/mL	X	0.625mg/m	+	0.1µg/mL	X
0.312mg/mL	X	0.312mg/mL	X	0.312mg/m	+	0.05µg/mL	X
0.156mg/mL	X	0.156mg/mL**	X	0.156mg/m	+	0.025µg/mL**	X
0.07mg/mL**	X	0.07mg/mL	+	0.07mg/mL	+	0.0125µg/mL	+
0.03mg/mL	+	-	-	-	-	-	-

Key: x= No growth observed
+= Growth observed

Source: Hawi (2019)

Table 2 - Growth of HCF in different concentrations of *C.molle* seed extract and ketoconazole

Concentration %	Growth	Concentration %	Growth
2%	-	2 × 10⁻¹%	-
1%	-	1 × 10⁻¹%	-
0. 5%	-	5 × 10⁻²%	-
0.25%	-	2.5 × 10⁻²%	-
0.125%	-	1.25 × 10⁻²%	+
0.0625%	-	6.25 × 10⁻³%	+
0.0312%	-	3.12 × 10⁻³%	+
0.0156%	-	1.56 × 10⁻³%	+
0.0078%	+	7.8 × 10⁻⁴%	+
0.0039%	+	3.9 × 10⁻⁴%	+
0.0019%	+	1.95 × 10⁻⁴%	+
0.0009%	+	9.75 × 10⁻⁵%	+
0.0004%	+	4.88 × 10⁻⁵%	+
0.0002%	+	2.44 × 10⁻⁵%	+
0%	+	0%	+

*MIC=no visible growth **visible growth

Source: Wondmnew and Teshome (2016)

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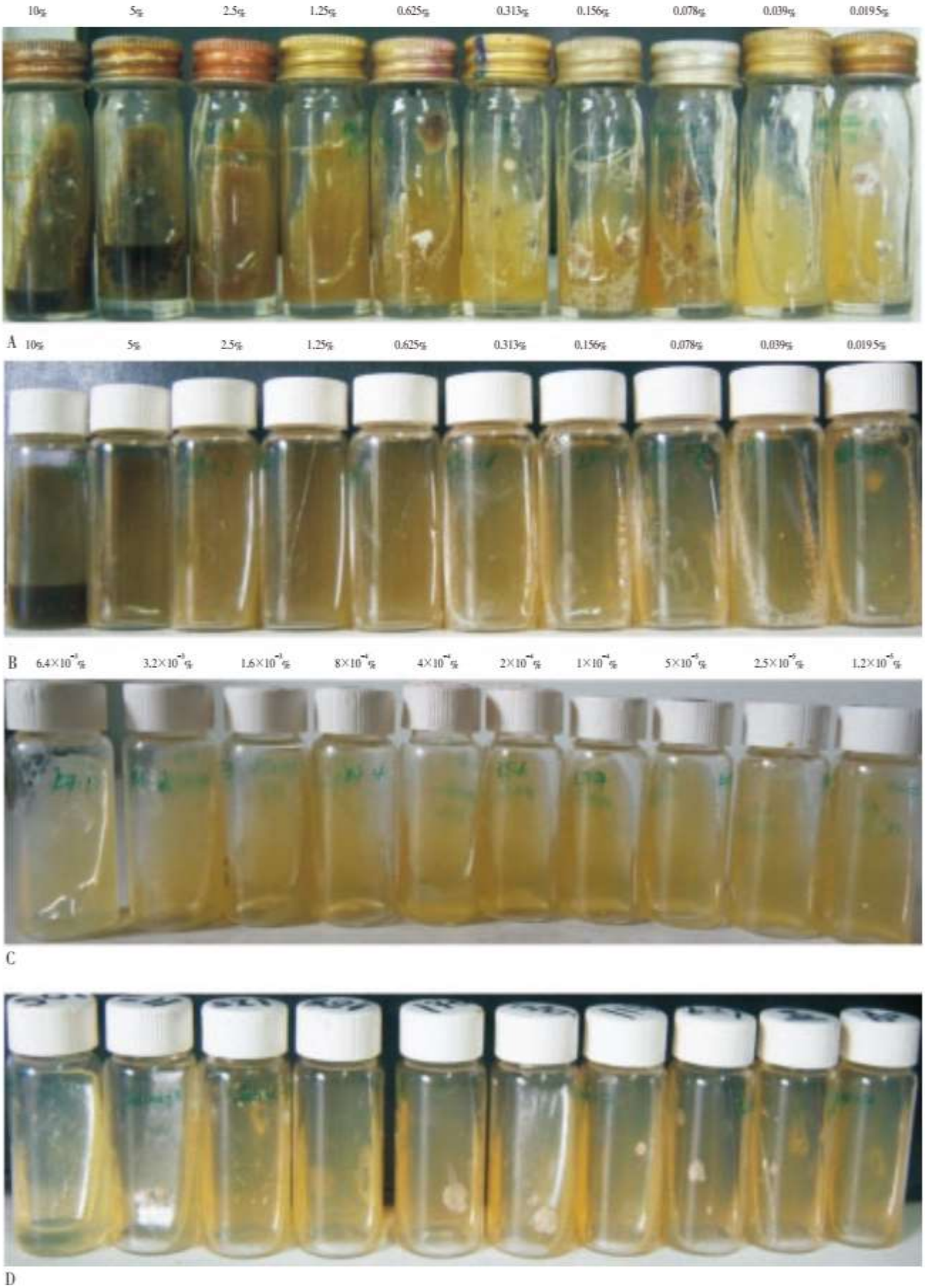

Figure 2 - The MICs of aqueous and n-butanol extracts of *P. dodecandra* against *H. capsulatum var. farciminosum*. A: MIC of aqueous extract: growth was observed starting at 0.625%; B: MIC of n-butanol extract: growth was observed starting from 0.039%; C: MIC of ketoconazole (standard): growth was observed at a concentration of 1.2×10^{-5}%; D: Saline diluted Sabourauds dextrose agar (negative control): growth was observed in all agar plates (Mekonen et al., 2012).

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CONCLUSION and RECOMMENDATION

The *X. strumarium* leaf extract has strong inhibitory effect on the growth of the mycelial form of *H. capsulatum var. farciminosum*. The *X. strumarium* leaf extract can be included in the treatment of epizootic lymphangitis provided that convenient methods of preparation, dose and route of administration should be established through rigorous *in -vitro* and *in -vivo* trials. The n-butanol extract of *P. dodecandra* demonstrated minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC) values that are considered to have antifungal properties. Therefore, since antifungals are not available for veterinary use in Ethiopia and also as they are expensive; searching for available and affordable antifungals such as n-butanol extract of *P. dodecandra* is recommended for the treatment of epizootic lymphangitis. The investigation of chemical compounds from natural products is fundamentally important for the development of new drugs. Ethanol macerated *C. molle* seed extract have a promising anti-fungal effect on mycelial form of *H. capsulatum var. farciminosum*. The main anti-fungal molecule in *C. molle* seed extract is hydrolysable tannins. The main action of tannin on *H. capsulatum var. farciminosum* is inhibition of cell wall and cell membrane biosynthesis. In topical application tannin has haemostatic and wound closure effect. The *C. molle* seed can be used for the treatment of epizootic lymphangitis if convenient methods of preparation, dose, and route of administration are established through meticulous *in vitro* and *in-vivo* trials. Medicinal herbs have a hopeful future since there are about half a million plants around the world, most of them have not yet been studied in medical practice, and current and future studies on medical activities can be effective in treating diseases. Those all parts of the plant have the chemicals upon extraction, the seed of the plants primarily and leaves secondly are preferable than the other parts of the particular plant because the seeds have higher concentration of the ingredients or chemicals required to use. The combination of the results got from both in vivo and in vitro trials are mandatory to witness the effectiveness of the particular plant's medicinal value.

Based on the above conclusions the following recommendations are forwarded: The appropriate treatment decision should be achieved to avoid suffering of equine from EZL. Challenges related with safety, efficacy and quality control of local herbal medicines for EL should be avoided. Any other local herbal medicines should be tried on EZL like ''embuay and ambacho''. *In-vivo* studies must be conducted so that the safety margin, toxicity and cure rates will be known in order to use them commercially. Study on the mechanism action of the local herbal medicine extracts and their toxic effect on lab animals should be reported .Antifungal drug should be produced by using herbal medicines that serve to cure the disease and shall be scale up later at industry level.

DECLARATIONS

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Authors' contribution
All the three authors reviewed the paper and contributed in developing the content.

Conflict of Interest
The authors declare they have no competing of interests.

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