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Review Article

Treatment Approaches of Ovine Fungal Diseases using Antibiotics and Ethnoveterinary Medicinal Plants

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ABSTRACT

Sheep and goats are both small ruminants with wide distributions due to their production of milk, wool, and meat. As such the diseases of these animals are of great economic importance to humans. Poor nutrition, poor breeding, poor hygiene and poor management systems are the most responsible factors of these diseases that cause annually significant livestock losses affecting the economy, animal diversity and ecological balance. These diseases are transmitted among animals in different ways and endemic especially in large and common pastures and among the causes of their spreads are contact, vectors, air, water, feeds, wastes, and pollution. Environmental conditions play an important role in increasing the spread of disease, which is often found in humid and warm seasons compared to temperate zones and Saharan zones. So through this review article, we try to show the different ancient and modern methods of treating these diseases and to share them with other societies.

INTRODUCTION

Ovine and caprine animals (sheep and goats) are ruminant herbivores of a genus of mammals belonging to the large Bovidae family. These animals contribute significantly to the economy of farmers worldwide in Mediterranean as well as African, European, and Southeast Asian countries. These small ruminants are valuable assets because of their significant contribution to meat, milk, and wool production, and potential to replicate and grow rapidly.

Several fungal diseases affected sheep and goats may lead to mortality and morbidity losses, and cause great economic losses. Pythiosis, aspergillosis, and ringworm are the common diseases that affect both bovine and ovine, and have similar symptoms and treated in the same ways as described in first part of this study.

Phaeohyphomycosis

Phaeohyphomycosis is caused by the black yeast *Cladosporium cladosporioides*, class Dothideomycetes, order Capnodiales and Davidiellaceae family. This species are ubiquitous and isolated from almost any environmental source as soil, water, plant materials, and air where its spores are important in seasonal allergic disease. Infection occurs mainly through contact or skin puncture, especially through trauma involving wood. While, this species are saprobic dematiaceous fungi, rarely causes invasive disease in animals, only infrequently associated with human and animal opportunistic infections (Seyedmousavi *et al*., 2013; De Graham, 2013).

C. cladosporioides cause pulmonary and cutaneous phaeohyphomycosis. In sheep, pulmonary infection is observed with respiratory distress signs, coughing, fever, anorexia, and death. At necropsy, abnormalities were confined to the lung, abomasums, lymph nodes, kidneys, liver, and heart. Severe hemorrhages were observed in the lungs, and vasculitis with thrombosis was apparent in various organs, which is suggestive of hematogenous dissemination (Haligur *et al*., 2010; Frank *et al*., 2011).

Moreover, subcutaneous phaeohyphomycosis is characterised by papulonodules, verrucous, hyperkeratotic or ulcerated plaques, cysts, abscesses, pyogranuloma, non-healing ulcers or sinuses. However, phaeohyphomycosis is rarely seen in goats and is caused by free-living fungus *Peyronellaea glomerata*. The disease has been recorded in Central Asia but not in the United Kingdom. It forms papules and aural plaques on the ears. It appears to be self-

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limiting. The treatment of choice is aggressive surgical excision of local lesions and antifungal treatment includes fluconazole, itraconazole, ketoconazole, posiconazole, terbinafine and liposomal amphotericin B (Bensch *et al*., 2010; Sang *et al*., 2011, 2012).

Candidosis

Candidosis is a fungal disease affecting the mucous membranes and the skin and may cause infection of any organ or system or systemic infections. The disease is distributed worldwide in a variety of animals and is most commonly caused by yeast species of the genus *Candida* especially *Candida albicans* (Odds, 1988; Refai *et al*., 2017a).

This yeast is a polymorphic fungus which grows in both yeast and filamentous forms and is the most commonly recorded species in sheep and goats beside others yeasts that are responsible for the mycotic mastitis and abortion diseases including *C. krusei*, *C. guilliermondii*, *C. tropicalis*, *C. lusitaniae*, *C. parapsilosis*, and *C. glabrata* (Khan *et al*., 2010; Hassan *et al*., 2012). Diseases symptoms and treatment is described in (fungal bovine diseases 3.4 and 3.7) (Brilhante *et al*., 2015; Maneenil *et al*., 2015).

Cryptococcosis

Cryptococcosis is a systemic fungal disease that may affect the respiratory tract (especially the nasal cavity), eyes, nervous system (brain) and skin in different domestics. It occurs worldwide and affects immunocompromised animals, goats and sheep causing pneumonia and mastitis but not of meningitis (Stilwell and Pissarra, 2014; Refai *et al*., 2017b).

In addition, signs in animals may include sneezing, snorting, nasal discharge, eye problems, change in behavior, depression, disorientation, seizures, and difficulties with moving around. Moreover, the disease is caused by saprophytic and opportunistic fungal pathogens *Cryptococcus neoformans* or *C. gattii* through the inhalation of basidiospores from environment, ingestion of desiccated yeast cells or more rarely, direct cutaneous inoculation (Woldemeskel *et al*., 2002; Stilwell and Pissarra, 2014; Refai *et al*., 2017b).

Cryptococcosis symptoms vary depending on the organ systems affected by the fungus. Often, symptoms are systemic and nonspecific, such as diminished appetite, weight loss, or lethargy. In sheep, and goats, the lesions are restricted to the respiratory system. Azole drugs including amphotericin B (with or without flucytosine), ketoconazole, fluconazole, itraconazole, and glucocorticoids are the most commonly antifungal used for treatment. In the case of subcutaneous or internal mass, surgery may be performed to remove it, followed by antifungal therapy (Woldemeskel *et al*., 2002; Lacasta *et al*., 2008; Chakraborty *et al*., 2014).

Malasseziosis

Malassezia dermatitis or otitis is a mycotic disease caused by some *Malassezia* species including *M. slooffiae*, *M. globosa*, *M. furfur*, *M. restricta*, and *M. sympodialis* and in particular *M. pachydermatis* that belong to the zoophilic yeast; division *Basidiomycota*. *Malassezia* spp. are lipophilic yeasts belong to normal cutaneous or mucosal microbiota of many warm-blooded vertebrates; it is normally found in low numbers in the external ear canals, in perioral areas, in perianal regions, and in moist skin folds of some animals (Guillot and Bond, 1999; Velegraki *et al*., 2015; Refai *et al*., 2017a).

Malassezia species are recognized as opportunistic pathogens that play a significant role in the development of different human and animal diseases such as otitis externa or seborrheic dermatitis. Malasseziosis occurs most commonly in animals with allergies endocrinopathies (hypothyroidism, Cushing's disease), immunosuppressive diseases and other skin diseases. Infection occurs either when hypersensitivity to the yeast develops or when there is overgrowth of the organism (Uzal *et al*., 2007; Gaitanis *et al*., 2012).

Malassezia dermatitis is uncommon in goats and sheep, where poor nutrition and debilitating underlying disease appear to be predisposing factors. Lesions are nonpruritic to mildly pruritic and nonpainful, and are characterized by erythema, hyperpigmentation, scale, greasiness, yellow waxy crusts, lichenification, follicular orthokeratotic hyperkeratosis, and mild lymphocytic perivascular dermatitis. Lesions are multifocal, often over the back and trunk, and typically become generalized but tend to spare the head and legs (Bond, 2010; Eguchi- Coe *et al*., 2011).

Malassezia otitis externa is common in cattle in South America. There is a ceruminous to suppurative otitis externa caused by predominantly thermotolerant *M. sympodialis* in the summer and a predominantly less thermotolerant species, *M. globosa* in the winter (Duarte *et al*., 1999, 2003). Allows the antifungal used to treat this disease are ketoconazole, itraconazole, fluconazole, and terbinafine (Bond *et al*., 2010; Cafarchia *et al*., 2012; Arendrup *et al*., 2014).

Rhodotorulosis

The disease results from infection with the genus *Rhodotorula*. Although the yeast is recovered word-wide from a variety of sources, infection is generally only seen in the immunocompromised host. The fungi from the genus *Rhodotorula* are imperfect basidomycetous yeast belonging to the family Cryptococcaceae (Tuon and Costa, 2008; Vazquez, 2011).

Table I. Drug for treatment of some infectious fungal diseases in sheep and goats.

Disease	Causative organism	Transmission	Geographic distribution	Pathogenesis	Drug for treatment	References
Pneumocystosis	Opportunistic fungal pathogen *Pneumocystis carinii* Class Fungus (*Ascomycota*) Family *Pneumocystidaceae* Order Pneumocystidales	Direct contact Airborne routes (aerosol)	World-wide	Fatal pneumonia in immunosuppressed hosts Abomasal and intestinal hemorrhage coupled with immune dysfunction	Pentamidine isethionate Trimethoprim sulfamethoxazole Atovaquone Trimetrevate	de Souza and Benchimol 2005 Sakakibara *et al*. 2013 Kondo *et al*. 2014
Microsporidiosis	Emerging opportunistic fungal pathogens *Enterocytozoon bieneusi* and *E. intestinalis* Class *Enterocytozoon* Family *Enterocytozoonidae* Order Chytridiopsida	Water sources	World-wide	Infects the intestinal epithelial cells Lesions in kidneys Diarrhea	Fenbendazole	Wenker *et al*. 2002 Malčeková *et al*. 2010 Zhao *et al*. 2015
Scopulariopsis	Dematiaceous fungi *Scopulariopsis brevicaulis* and *S. brumptii* Class Sordariomycetes Family *Microascaceae* Order Microascales	Soil, air, in plant litter, paper, wood, dung, and animal remains	World-wide	Hair loss and skin changes	Itraconazole D-biotin	Ozturk *et al*. 2009 Sallam and ALKolaibe 2010 Awad 2017
Keratinophilic fungi	*Trichophyton mentagrophytes*, *T. verrucosum*, *Microsporum nanum*, *Arthroderma cuniculi*, *Ar. curreyi*, *Acremonium kiliense*, *Alternaria alternata*, *Aspergillus flavus*, *A. versicolor*, *Cladosporium carionii*, *Chrysosporium tropicum*, *Ch. Anamorph*, *Acremonium kiliense*, *Aphanoascus fulvuscens*, *Paecilomyces lilacinus*, *Scopulariopsis brevicaulis*, and others	Hair, wool, cloven-hooves, and horns of goats and sheep Contaminating working areas and dwelling places Wet and dirty surfaces	World-wide	Infections of the skin like club fungus, athletes foot, tinea infection of some keratinized surfaces and ringworm of the hair and nails	Fluconazole, Ketoconazole Miconazole	El-Said *et al*. 2009 Eljack *et al*. 2011 Emenuga and Oyeka 2013 Kalaiselvi *et al*. 2014 Biswas *et al*. 2015
Facial eczema (pithomycotoxicosis, photodermatitis)	*Pithomyces chartarum* Class Dothideomycetes Family *Pleosporaceae* Oreder Pleosporales	Presence of the mycotoxin sporidesmin in forage grasses	subtropical countries and other localities with warmer climates such as New Zealand United Kingdom, Europe and Netherlands	Facial eczema Drooping ears and swollen eyes Skin lesions	Feeding cattle zinc or by using benzimidazole fungicides on pastures	Smith and Embling 1991 Ozmen *et al*. 2008 Di Menna *et al*. 2009 Refai *et al*. 2017a

Rhodotorula rubra (*R. mucilaginosa*) is the species most frequently associated with mammal infection. *Rhodotorula* species are commonly recovered from sea water, lakes, ocean water, plants, soil, air, food, and occasionally from humans. The genus *Rhodotorula* includes eight species, of which *R. mucilaginosa*, *R. glutinis*, and *R. minuta* were reported to cause mastitis in ruminants (Vazquez, 2011; Wirth and Goldani, 2012).

Among the few references about the pathogenicity of *Rhodotorula* spp. in animals, there are several reports of an outbreak of skin infections in chickens and a report of a lung infection in sheep, both caused by *R. mucilaginosa*. Amphotericin B, fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole, and flucytosine are the main antifungal drugs for treatment animals (Wirth and Goldani, 2012; Dhama *et al*., 2013).

Conidiobolomycosis

Conidiobolomycosis is a zygomycosis caused by fungi of the class Zygomycetes, order Entomophthorales, affecting humans and animals. The main *Conidiobolus* species involved are *C. coronatus*, *C. incongruus*, and *C. lamprauges*. *Conidiobolus* spp. are found mainly in soil, decaying vegetation, and insects of tropical and subtropical regions, in areas of high humidity, particularly in Central America, equatorial Africa, and India; however, cases have been reported worldwide including Brazil (Silva, 2007; Aguiar *et al*., 2014; Weiblen *et al*., 2016).

In animals, conidiobolomycosis caused by *C. coronatus*, *C. lamprauges*, and *C. incongruus* are reported mainly as subcutaneous infections (granulomatous and necrotic) or rhinofacial, nasopharyngeal, or oral infections. These fungal infections are very important, since they compromise the health status of the sheep flock and cause serious economic losses to the sheep industry (Ubiali *et al*., 2013; El-Shabrawi *et al*., 2014). However, there was no effective treatment for the disease, but in 2013 a group of antifungal drugs was described from sheep including amphotericin B, azoles, echinocandins, and terbinafine; but only the terbinafine was active against this fungus and the microorganism demonstrated resistance or reduced susceptibility to the other antifungal drugs evaluated (Tondolo *et al*., 2013; El-Shabrawi *et al*., 2014).

ETHNOVETERINARYMEDICINALPLANTS

The historical utilization of plants as health remedies both for human and animal are centuries old. It has been recognized that plants have the capacity to combat several types of diseases ethnoveterinary medicines, a term generally used for folk skills, beliefs, knowledge, practices, methods related to animals' health, and cure of various ailments in the rural areas.

Ethnoveterinary practices have achieved immense significance for the last decade owing to the discovery of some effective ethnoveterinary products. The utilization of traditional remedies poses a cheaper, easier, and sustainable alternative to synthetic drugs and pharmaceuticals (Dzoyem *et al*., 2020; Eiki *et al*., 2021).

Mobile grazing, also called bedouin grazing, is an ancient approach to raising livestock that dates back thousands of years, and involves the regular movement of people with their livestock in search of good grazing conditions such as water, food and a suitable climate.

The majority of shepherds move with livestock to many mountainous, steppe and valley areas where various medicinal herbs grow, especially in the spring, so that livestock benefit from them as food and treatment at the same time. In addition, these herbs give a distinctive flavor and a special taste to the meat. The most important of these plants are presented in the Table II.

OTHER TREATMENTS AND PREVENTIVE METHODS

Apple cider vinegar, honey and salt

Shepherds have used apple cider vinegar, honey and salt since ancient times for their great benefit in treating wounds, ulcers, fungal and bacterial infections. In addition to its effective role to (1) improves the quality and yield of wool, (2) reduces the incidence of urinary calculi and kidney stones, (3) has powerful healing, (4) cleansing, natural antibiotic and antiseptic qualities. helps with the internal and external prevention and management of itch, fleas, ticks and bot flies, (5) skin conditions, arthritis, mastitis and cystitis. For treatment, apple cider vinegar is diluted and added to ovines drinking water or used topicaly on sores, wounds and pimples areas; and the same method applies to honey and salt (topical) (Schmida *et al*., 2012; Koushlesh *et al*., 2020).

Garlic and onion

They are used as a treatment to expel worms from the stomach and intestines. Protecting livestock from blood poisoning, intestinal poisoning, and various fungal and bacterial infections. Both onions and garlic work as (1) a powerful antibiotic to treat respiratory diseases such as: lung infections and severe coughing. Sheep get rid of harmful bacteria and germs; (2) a strong antiseptic for the digestive system, to get rid of worms in the stomach, and a stomach cleaner; (3) boost immunity; (4) it prevents the shedding of the sheep's fur and increases its durability and finaly (5) treatment of smallpox, plague and pomegranate peel. The mashed garlic or onion were added to livestock

water or feeds for treatment diseases or applied directely on sores, wounds and pimples areas (Schmida *et al*., 2012; Koushlesh *et al*., 2020).

Pomegranate peel

Adding pomegranate peel to ovines's feed improves the quality and quantity of milk produced by them and accelerates the healing of wounds, but also cleans them of pathogens by applied the mashed peels topicaly on infected skin. In addition, it strengthens the immune system and helps fight diseases that affect the digestive system by adding it to the livestock feeds and water. Pomegranate peel prevents hardening of the arteries of ovines, as the peel of the pomegranate contains many antioxidants that are beneficial for their health (Schmida *et al*., 2012; Koushlesh *et al*., 2020).

Table II. Health benefits of some medicinal plants to treat diseases in sheep and goats (Halimi *et al*., 1997).

Plant botanical name	Family	Parts used	Method of use (administration)	Indications
Origanum vulgare L.	Lamiaceae	Whole plant	Topical Oral with feeds and water or added to treatment bath	Sores and pimples Stomach wounds Scabies disease Mycoses
Juniperus phoenicea	Cupressaceae	Whole plant	Oral	Wounds and sores Pneumocystosis Digestive disorders, Urinary tract infection
Artemisia herba – alba (L)	Asteraceae	Whole plant	Oral Topical (the leaves were burned and the ashes mixed with olive oil and applied to wounds and sores)	Digestive disorders Urinary tract infection Antipyretic Kill and expel intestinal worms Pneumocystosis Mycoses
Lavandula stoechas (L)	Lamiaceae	Leaves and flowers	Oral	Pneumocystosis Digestive disorders Urinary tract infection Mycoses Candidiasis Wounds, ulcers and infections
Peganum Harmala (L)	Zygophyllacées	Seeds, twigs and leaves	Oral or It is placed in the form of tied bundles and then soaked in water and presented to the animal	Kill and expel worms from stomach Mycoses Eliminate lice, parasites and insects from animal hair, wool and leather Reduce the temperature at infection
Ruta graveolens (L)	Rutaceae	Whole plant	Oral or it is placed in the form of tied bundles and then soaked in water and presented to the animal	Kill and expel worms from stomach Digestive disorders Urinary tract infection Mycoses Candidiasis Wounds, ulcers and infections
Urtica dioica (L)	Urticaceae	Leaves, seeds, veins	Oral	Pneumocystosis Digestive disorders Urinary tract infection Mycoses Candidiasis Wounds, ulcers and infections
Malva parviflora L.	Malvaceae	Whole plant	Oral Topical	Wounds Mycoses Bites and bruises Swellings and infections Pneumocystosis Digestive disorders Urinary tract

CONCLUSIONS

Biosecurity and hygiene, veterinary surveillance, health and welfare programmes, buying, registering and moving sheep and goats, appropriate grazing systems and animal selection to improve resistance are the alternative management strategies to prevent and control disease in small ruminants. Also, the knowledge of medicinal herbs and their therapeutic benefit sings us away from the use of expensive antibiotics and their side effects on animal health and nature.

Statement of conflict of interest

The authors have declared no conflict of interest.

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