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Review

The Role of *Mortierella spp.* In Mycotic Infections and Using of In Different Fields

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A B S T R A C T

Background/ Aim: *Mortierella* infection there is seen almost exclusively in dairy cows and is typically associated with feeding moldy hay and ensilage. About 90 species of Mortierella are known and they caused to bovine mycotic abortion, hepatitis, meningoencephalitis, pneumonia and systemic mycosis. Also they have been isolated in phycomycoses of man and animals, from tracheal lesions in chickens and from horses with granular dermatitis. The aim of this study is to inform about the role of Mortierella species in mycotic infections.

Conclusion: *Mortierella* colonies are in generally white to light-grey and occurring garlic-like odour on the agar. Species of the genus are usually non-pathogenic for plants and humans. Within the genus Mortierella, the only known antibiotic is fusidic acid (or ramycin), produced by some strains of *M. ramanniana*. EPA (Eicosapentaenoic acid) has been shown to be of major importance in the prevention and treatment of a range of human diseases and disorders.

Key words: Mortierella spp., Mycotis Infections

Mortierella Türlerinin Mikotik Enfeksiyonlardaki Rolü ve Farklı Alanlarda Kullanımı

Ö Z E T

Özbilgi/Amaç: *Mortierella* enfeksiyonu genellikle küflü saman ve silaj ile beslenen süt ineklerinde görülmektedir. Mortierella'nın yaklaşık 90 türü bilinmektedir ve sığır mikotik abort, hepatit, meningoensefalit, pnömoni ve sistemik mantar enfeksiyonlarına neden olmaktadırlar. Ayrıca tavuk ve granül dermatiti olan atların trakeal lezyonlarından, fikomikozis görülen insan ve hayvanlardan da izole edilmiştir. Çalışmanın amacı, Mortierella türlerinin mikotik enfeksiyonlardaki rolü hakkında bilgi vermektir.

Sonuç: *Mortierella* kolonileri genelde beyaz ile açık gri arasındadır ve agarda sarımsak benzeri bir koku meydana getirirler. Mortierella cinsinin türleri genellikle bitkiler ve insanlar için patojenik değildir ve sadece antibiyotik olarak bilinen fusidik asit *M. ramanniana*'nın bazı suşları tarafından üretilmektedir. Tür tarafından üretilen EPA (Eikozapentaenoik asit) insanlarda hastalıkların tedavisi ve önlenmesinde önem taşımaktadır.

Anahtar Sözcükler: Mortierela spp., Mikotik Enfeksiyonlar

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Introduction

Fungi are eukaryotic microorganisms that occur ubiquitously in nature. Number of fungi are an estimated 300,000 all over the world and they caused mycotic infection in domestic animals with economic loss.

In general major groups of pathogenic fungi can be grouped as follows caused by infections;

A. Cutaneous Mycoses

B. The subcutaneous Mycoses

C. The Systemic Mycoses (*Histoplasma capsulatum*, *Coccidioides spp.* and *Blastomyces dermatitidis*)

D. Opportunistic fungi (*Candida spp., Aspergillus spp*. and several genera within the aseptate Phylum *Zygomycota* (notably *Mucor, Rhizopus* and *Mortierella sp*.).

E. Fungal-Like (achorophyllic algae *Prototheca spp., Pneumocystis spp*. and *Pythium insidiosum*).

Fungi can be divided into the subkingdom *Dikarya* and nine basal groups (*Blastocladiomycota, Chytridiomycota, Entomophthoromycotina, Glomeromycota, Kickxellomycotina, Microsporidia, Mucoromycotina, Neocallimastigomycota, Zoopagomycotina.* Zygomycota also appears to be a polyphyletic assemblage (Martin

et al., 2011).

Zygomycosis agents are in the genera of *Cunninghamellaceae* and *Mucoraceae* and also all of these fungal genera are in the order of *Mucorales. Mucor, Absidia, Rhizomucor* and *Rhizopus* types are found in *Mucoraceae.*

The phylogenetic position of the *Mortierellales* is controversial discussed and they are either placed within the subphylum *Mucoromycotina* or elevated to an own subphylum, the *Mortierellomycotina.* At present, *Mortierellales* contains one family, *Mortierellaceae,* which comprises six genera, *Aquamortierella, Dissophora, Gamsiella, Lobosporangium, Modicella* and *Mortierella*. The *Mortierellaceae* containing two genera which called *Herpocladium* and *Mortierella*, are saprophytic fungi easily and frequently isolated from soil, overheated silage. They have a widespread distribution in the environment and pathogenic activity of genus seems low (Wagner et al., 2013; Tamas et al., 2011).

The genus of *Mortierella* is presently classified as a member of the family *Mortierellaceae* within the order of the *Mucorales*, class *Zygomycetes.* This order also includes the genera *Rhizopus* and *Mucor*. *Mortierella wolfii* (*M. wolfii)* is a fungus belonging to Phylum *Zygomycota* and known to cause bovine mycotic abortion, hepatitis, meningoencephalitis, pneumonia and systemic mycosis in cattle.

Many of the best-known species, including *M. isabellina, M. ramanniana* and *M. vinacea*, are now placed in other genera such as *Micromucor* or *Umbelopsis*. *Mortierella* spp. have also been isolated in phycomycoses of man and animals, from tracheal lesions in chickens, from the lungs of a buzzard, and from horses with granular dermatitis. *Mortierella* species are usually non-pathogenic for plants and humans. Infection of this fungus in cattle has been reported from New Zealand, Japan, England, and Australia (Cordes et al., 1972; Shinya et al., 2011; Gams, 2004; Wagner et al, 2013).

The first species of the type genus was described by Coemans (1863) as *Mortierella polycephala*, originally isolated from a mushroom. Also mixed mycosis infection has been reported in ruminants and also Fretz and Fischer (1976), isolated *Rhizopus* spp. and *Aspergillus* spp. from the upper airways of horses, in the absence of mycotic lesions (Carrasco et al., 1997; Shinya et al., 2011).

Morphology

Based on morphological similarities and previous classifications, Gams (1977) divided the subgenus *Mortierella* into nine sections based on morphology: *Actinomortierella*, *Alpina*, *Haplosporangium*, *Hygrophila*, *Mortierella*, *Schmuckeri*, *Simplex*, *Spinosa* and *Stylospora* (Gams, 1977). The morphology of filamentous microorganisms usually varies between “pellet” and “filamentous” morphologies, depending on the culture conditions and the genotype of the strains. Fungal cells are most similar to animal cells and they usually shows a fibrillary and multi-layer characteristic in contrast to animal cells. The basic structural units of the molds are tubelike projections known as hyphae and the cell wall is composed of chitin that is seen on the septated hyphae.

Colonies are in general white to light-grey, young mycelium is coenocytic and septate in aged cultures. Morphological identification based solely on asexual features, leading to the aforementioned traditional classification. Overall appearance of the colonies is the typical zonate, rosette-like growth and the often occurring garlic-like odour (Arda M, 2006).

Complete investment of the zygospore by branching hyphae is a feature of *M. rostafinskii* and *M. ericetorum*. The zygospores proper in *Mortierella* are hyaline with thick smooth walls, sometimes showing coarse, undulating folds. *M. stylospora* and *M. zonata* have only sporangiola and sporangia are lacking.

The distinctive feature of this family is that the sporangiophore produces only a rudimentary columella or lacks it altogether. In the most frequently encountered genus, *Mortierella*, zygospores are often heterogametangic and may be naked or enclosed in a weft of mycelium (Webster et al., *2007*; Degawa et al., 1998).

Etiology

Abortions can be due to many factors including malnutrition, temperature, genetics, hormones, stress, and trauma. Mycotic abortion or mycotic placentitis, is caused by different species of fungi and yeasts because of acute fulminant metritis and placentitis, with resultant fetal hypoxia (Cordes et al., 1967).

Mucormycoses is an opportunistic fungal infection which may affect any organ of the body and caused by various species in the genera *Mucor, Absidia* and *Rhizopus*. *Rhizopus* infection described with endophthalmitis and cataracts, in a calf. All of these fungal genera are in the order *Mucorales*. The first record of a fungus isolated from bovine foetal membranes was of *Mucor rhizopodiformis* (*Rhizopus cohnii*) found growing in a gravid uterus by Theobald Smith, 1920 (Sponsler et al., 1992).

Some of possible pathogens of mycotic abortion include; *Mucor rhizopodiformis, Absidia corymbifera, Absidia ramosa, Aspergillus flavus, Aspergillus nidulans, Aspergillus terreus, Mucor psillus, Rhizopus arrhizus, Aspergillus niger, Rhizopus boyinus, Allescherica boydii, Aspergillus versicolnr, Kontospora lanuginose, Mortierella polycephala, Polystictus versicolor, Mucor disperses, Mortierella zychae and Mortirella* (Ali et al., 2006).

For instance, *Actinomyces*, *Candida, Coccidioides, Hansenula, Monosporium, Nocardia, Paecilomyces*, and *Trichosporon* organisms isolated from the uteri of mares with endometritis.

However, *Mortierella wolfii, Mucor sp*., *Alternaria* sp., *Aspergillus flavus*, *A. fumigatus* and *A. niger* were isolated from cervical, vaginal, or clitoral fossa swabs from mares with chronic infertility problems (Murphy, 2002).

Many species that are found within the *Micromucor* subgenus include *Mortierella ramanniana, M. isabellina,* and *M. vinacea*. Some fungi that belong to the *Mortierella* subgenus include *M. alpina, M. elongata*, and *M. hyalina* (Sponsler et al., 1992).

M. wolfii infection occurs primarily in pregnant animals and in non-pregnant adult cows infection occurs in lung and liver. *Mortierella* fungal encephalitis is rare in cattle, with most cases reported in aborted or neonatal calves. Zygomycosis is also a significant cause of mycotic abortion in cattle and most commonly develops within the lungs or gastrointestinal tract but fungal encephalitis is rare in cattle.

Isolated many species of the genus *Mortierella* from bat dung samples collected in caves. In such locations, *Mortierella alpina, M. indohii, M. polycephala, M. reticulata, M. tuberosa*, etc. were usually abundant. Although no human infections have been recorded (Gams et al., 2004; Gabor LJ, 2003; John et al., 2006; Austwick PKC., 1972).

In humans, endogenous fungal endophthalmitis is usually caused by *Candida spp.*, but this condition is also a terminal complication of rhinocerebral mucormycosis and has been reported in *Rhizopus.* Also ketoacidosis promotes the fungal growth while inhibiting neutrophil function and 80% of patients with rhinocerebral zygomycosis have underlying diabetes mellitus and analysis showed that human central nervous system zygomycoses ocur with 69% rate by spreading fungi from the nose or nasal sinus. (Roden et al., 2005; Sponsler et al., 1992).

Epidemiology

A wide variety of microorganisms have been implicated as causative agent of bovine mastitis including bacteria and fungi. Members of the class *Zygomycetes*, including the genera *Absidia, Mortierella, Mucor, Rhizomucor,* and *Rhizopus,* are responsible for an estimated 21% of mycotic abortions in cattle.

About 90 species of *Mortierella* are known mainly from soil, the rhizosphere, and plant or animal remains in contact with soil. *Mortierella wolfii* is associated with mycotic abortion in cattle and can be isolated from the placenta and foetal stomach contents and from liver. In nature it grows in warm soils, overheated silage and rotten hay and can grow well at 40°C - 42°C.

Many species are psychrophilic and may comprise the bulk of fungal isolates from soil, if the isolation media are incubated near 0°C. However, the other species of *Mortierella*, as noted below, may be isolated in following temperatures. The temperature ranges are;

1) Isolation temperature of 0°C

Mortierella hyalina, Mortierella macrocystis, Mortierella macrocystopsis, Mortierella pseudozygospora, Mortierella sarneyensis, Mortierella verrucosa, Mortierella simplex, Mortierella exigua, Mortierella parvispora, Mortierella humilis, Mortierella zonata, Mortierella alliacea

2) Isolation temperature of 0°C - 25°C

Mortierella elongata, Mortierella pulchella, Mortierella verticillata

3)Isolation temperature of 25°C

Mortierella isabellina, Mortierella ramanniana f. Ramanniana, Mortierella nana, Mortierella jenkini (Austwick, 1976; Domsch et al., 1980; Margaret et al., 1992).

Streekstra (1997) , indicated the other suspected pathogenity of *Mortierella* species such as; *M. alpina* (liver lesions in calves), *M. hyalina* (lung mycosis in birds), *M. mycetomi* (subcutaneous lesion in man), , *M. niveo-velutina* (ulcer of the leg in man), *M. polycephala* (lung mycosis in cow), *M. zychae* (abortion and pneumonia in cow) , *M. niveo-luteum* than *M. wolfii* (abortion and pneumonia in cow, histological sections of cow (Streekstra H,1997).

Mortierella wolfii is a fungus belonging to phylum *Zygomycot*a and known to cause abortion, pneumonia, hepatitis, and meningoencephalitis in cattle. This organism is reported to have a widespread distribution in the environment, to be frequently isolated from silage and to cause systemic infection. Ophthalmic signs including hypopyon are also described in a neonatal calf with disseminated infection of *M. wolfii* (Shinya et al., 2011).

Mortierella was furthermore divided into nine sections based on morphology: *Actinomortierella*, *Alpina*, *Haplosporangium*, *Hygrophila*, *Mortierella*, *Schmuckeri*, *Simplex*, *Spinosa* and *Stylospora* (Gams, 1977).

The genera *Dissophora*, *Gamsiella* and *Lobosporangium* are placed within the genus *Mortierella* (Wagner et al., 2013). *Mortierella wolfii* infection there is seen almost exclusively in dairy cows, and is typically associated with feeding moldy hay and ensilage. In practice, only a fraction of bovine abortions are actually observed by dairy producers, and embryonic deaths are only occasionally observed (Georges et al., 1993). Experimental infection of *M. wolfii* is described in cattle and other species. When given intravenously, it causes abortion and pneumonia in cattle and acute death in rabbits. In sheep, intravenously inoculated *M. wolfii* was isolated from the lung (Cordes et al., 1972).

The first species of the type genus was described by Coemans (1863) as *Mortierella polycephala*, originally isolated from a mushroom. *Mortierella umbellata* was described in 1972 from soil from a broad-leaf forest in Athens, Georgia, U.S.A. Later, C. Y. Chien established a pair of mating isolates with similar morphology from soil in Taiwan and registered them in ATCC as ` *Mortierella formosensis* '. Zygospore formation was not described (Degawa et al., 1998).

Many species of the genus *Mortierella spp.* have isolated from bat dungs. In such locations, *Mortierella alpina, M. indohii, M. polycephala, M. reticulata, M. tuberosa*, etc. were usually abundant. *Mortierella hypsicladia* shows an extreme acrotonous sporangiophore branching and may thus be related to *M. wolfii.* While maternal disease is not observed in most cases of fungal abortion, approximately 20% of cows that abort from *M. wolfii* infection develop acute fatal pneumonia as a sequel to placentitis (Jennifer et al., 2010; Gams et al., 2004).

Since 1967, however, *M. wolfii* has been isolated in many spontaneous cases of mycotic abortion and pneumonia. Fungal infection causes around 6% of bovine abortions in North America and *M. wolfii* is the most important cause of fungal abortion in cattle and is the etiologic agent in up to 46% of cases of mycotic placentitis in New Zealand (Pachauri et al., 2013; Jennifer et al., 2010; Knudtson et al., 1992).

Compare and contrast of the prevalence of fungal infections

such as *Candida albicans*, in clinical and subclinical cases was all found to be 30% and 25%. The overall infectivity of *Candida albicans* was 26% and this higher rate of infectivity may be due to the summer.

Prevalence of *Aspergillus spp*. in clinical and subclinical cases was found to be 40% and 37.5% *Mortierella wolfii* was identified in 0,4- 0,5% of cases of mycotic abortion in cattle in 1 survey in the United States. *Aspergillus* species are responsible for 71% of these (John et al., 2006; Cordes et al., 1972).

Mortierella wolfii has been infrequently reported from Australian herds with combination of mycotic abortion and pneumonia which has commonly been associated with the fungus. Also, stated in a research the mycotic endometritis suggest the cows to aborted before developing encephalitis (Knudtson et al., 1992).

Gabor (2003), is reported that from 1990 to 2002, 45 bovine cases of mycotic pneumonia were recorded in Tasmania **(**Gabor LJ, 2003).

Pathogenesis

Abortions caused by fungal infections occur because of acute fulminant metritis and placentitis, with resultant fetal hypoxia and fungal pathogens are enter the body by using a path of respiratory or gastrointestinal tract. Subacute to chronic fungal metritis and placentitis allow fetal infection. In calves born to dams with experimental *Mortierella wolfii* placentitis, the liver was involved in 4/5, brain in 3/5, and spleen in 1/5 (Cordes DO, 1967).

Mixed fungal infections are relatively common, in which case both septate and none septate hypae may be observed in placenta. Abortions occurs late in gestation between the sixth and eight month and the placenta is often firmly retained. Mycotic lesions are rarely found in organs other than the lungs or uterus. Since that fungus has a high oxygen requirement, oxygen tension in the uterus may be a factor in the pathogenesis of the disease.

İnfection begins in enlarged, necrotic and hemorrhagic placentomes then spread to the interplacental space where a rich growth of hyphae. However, suppurative placentitis, vasculitis seen widespread and secondary infections may follow retention of the placenta (Cordes DO, 1972).

Clinical Aspect

Mycotic abortions usually occur in the third trimester of pregnancy and clinical signs in the dam are infrequently observed apart from retention of the placenta. Ophthalmic signs including hypopyon are also described in a neonatal calf with disseminated infection of *M. wolfii*. *Mortierella wolfii* has not been detected in either the normal or diseased equine eye.

The fetus may appear normal, but often there are characteristic cutaneous lesions and these lesions are seen most commonly periorbit, occiput, shoulders, back and sides.

Cordes et al, have been inoculated intravenously five million spores of a pathogenic isolate of *Mortierella wolfii* into pregnant and nonpregnant cows and after inoculation caused an acute mycotic pneumonia that resulted in death in less than 4 days in cows. Also, intratracheal, subcutaneous, and oral administration of *M. wolfii* spores were not produced lesions in cattle and intravenous administration of large numbers of spores of *M. wolfii* to pregnant sheep were not caused lesions.

Inoculated five large doses of spores of a pathogenic strain of *M. wolfii* to adult cows and these strains developed acute mycotic pneumonia and after receiving an intravenous dose of $5 \times l0^5$ *M. wolfii* spores cows have died within 100 h.

Also, pneumonia, placentitis splenitis, emphysematous diaphragma and abortion has been induced experimentally by their intravenous inoculation of *Mortierella wolfii* spores. Smaller doses caused acute pneumonia in five 6-month-old calves.

In early stages of mycotic placentitis seen in cows, before abortion red infarcts which were present in the caruncle and after abortion, most caruncles were uniformly dark red and be full of hyphae. Lesions in other tissues, such as vasculitis, arteritis which were thrombosed with their necrotic and invaded walls by hyphae and thrombosis were characteristic features. However, encephalitis was characterised by vasculitis and malacia, an abundance of neutrophils, and phycomycotic hyphae (Cordes DO, 1972).

Diagnosis

In identification of *Mortierella wolfii* the samples are subcultured on Sabouraud dextrose agar and incubated at room temperature for 3 days. After staining with lactophenol cotton blue dye with using a sticky tape preparation mycelium can be seen under a light microscope. In addition, *Mortierella spp.* can grow on yeast extract, fish meal, potato dextrose agar or corn meal agar at 20 °C and pH 6.5. Malt extract agar, which contains high concentrations of soluble sugars, has been used for many years as a standard medium for the cultivation of *Mortierella spp.* Also isolation of *Mortierella spp.* was successful from compost particles placed on tap-water agar and incubated at 18 °C or 4 °C.

Fungus can be isolated from the contents of stomach and can be seen in smear which prepared with it. Species of *Mortierella* are common isolates from soils and direct identification of the fungi by using a potassium hydroxide may facilitate the diagnosis at field (Roland et al., 2003).

Hyphae were usually Periodic Acid-Schiff positive and PAS is a staining and one of the most widely used histochemical method used to detect polysaccharides (glycogen) and (glycoproteins, glycolipids) in tissues.

The diagnosis of fungal abortion is associated with the presence of fungi which include placental lesions diffusely thickened intercotyledonary placenta with necrotic, haemorrhagic infarcts in the cotyledons. Occasionally, locally extensive circular skin lesions may be present on the fetus.

As mentioned before following abortion in a cow *Mortierella wolfii* caused systemic infection. Davies et al (2010), observation of the endometrium at necropsy was diffusely thickened, reddened and covered by necrotic debris and fungal elements in the kidney were surrounded by radiating, club-shaped, aggregations of brightly eosinophilic material consistent with Splendore - Hoeppli reaction (asteroid bodies) which is the in vivo formation of intensely eosinophilic material (radiate, asteroid or club-shaped configurations) around microorganisms (fungi, bacteria) or biologically inert substances. Also leptomeninges were thickened, red, opaque and purulent material was present and fungal hyphae were seen within the thrombi, in the vessel walls (Jennifer et al., 2010; Hussein, 2008).

Treatment

Within the genus *Mortierella*, the only known antibiotic is fusidic acid (or ramycin), produced by some strains of *M. ramanniana.* EPA (Eicosapentaenoic acid) has been shown to be of major importance in the prevention and treatment of a range of human diseases and disorders (Bajpai et al., 1991; Streekstra H., 1997).

Biotechnology

Species of the genus *Mortierella* have not been used extensively for food production, but a number of examples exist. It has been mentioned that various *Mortierella* species are good producers of fats, oils and fatty acids that may be used as food and feed ingredients. The highest arachidonic acid (ARA) productivity was obtained at *M. alpina* indicated a consumed C/N ratio of 20. *Mortierella elongata can* also produce C 24:1 fatty acid in small amounts. Cultivation and growth of *Mortierella spp.* are affected by the carbon source and amount of them in the medium was correlated with increased yield of mycelium (Higashiyama et al., 2002; Peberdy, J.F., 1965).

In animals, ARA content is about 10% in vital organs such as blood and liver. Various physiological functions of ARA have been reported, such as protection of gastric mucosa, treatment of skin psoriasis, reduction of fatty liver, killing of tumor cells, and improvement of lipid metabolism of cirrhotic patients Arachidonic acid (ARA) is a major constituent and plays the role of maintaining membrane fluidity in biological cells. ARA has also attracted attention as a precursor of prostaglandins, thromboxane, prostacyclin, and leucotrienes, which have potent and various physiological actions including uterine muscle contraction, relaxation, vasodilatation, and antihypertensive action. Longer-chain polyunsaturated fatty acids, particularly arachidonic (AA) and docosahexanoic (DHA) acid should be considered as essential nutrients for the preterm infant because of their presence in structural lipids in brain and nervous tissue. DHA was derived from egg yolk and tuna oil that was low in eicosapentaenoic acid, and the source of AA was egg yolk and a single-cell oil produced by a common soil fungus, *Mortierella alpina*. (Lanting et al., 2003; Park et al., 2001; Higashiyama et al., 2002).

Nervonic acid (C 24:1) is a major very-long-chain monounsaturated fatty acid contained in sphingolipid, comprising the white matter and myelin sheath of the human brain. In demyelinating diseases which cause adrenoleukodystrophy and multiple sclerosis, the levels of nervonic acid in cerebral sphingolipid decrease. Dietary therapy involving the ingestion of oil containing nervonic acid has been shown to be useful for treatment of these diseases (Umemoto et al., 2014).

Toxigenicity has been described for some species of the genera *Rhizopus* and *Mucor*, and *Mortierella wolfii* (Reiss, J., 1993).

Most of the toxic activity with the fungal hyphae and this toxin could also be demonstrated in culture fluids after spontaneous autolysis of the fungal. Furthermore, they has been extracted a toxic substance for mice from the washed mycelia of *Mortierella wolfii.*

Aspergillus fumigatus and *Aspergillus flavus* have a similar toxin which has been isolated from *M. wolfii* in the properties of heat lability, trypsin sensitivity, activity over a wide pH range, and renal involvement in experimental animals (Davey et al., 1973).

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