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PHYTOTHERAPY OF BOVINE ENDOMETRITIS LIKE RELIABLE, SAFE, EFFECTIVE AND CHEAP EVIDENCE-BASED CONCEPT

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Abstract: In dairy cattle, reproductive diseases are a huge challenge that is most often solved by treating affected cows with antibiotics and hormones, often with reduced fertility and very high direct and indirect costs. Uncontrolled use of antibiotics, often without adequate sampling and sensitivity testing, can lead to multi-drug resistance as well as residues of antibiotics, disinfectants or hormones in milk and meat, endangering human health. From various studies that have been intensified in the last two decades, it seems that phytotherapy is a possible alternative treatment for dairy cows suffering from endometritis (EM).

Keywords: endometritis, milking cows, reproduction, phytotherapy, synergy

Introduction

In dairy cattle breeding, postpartum reproductive disorders lead to enormous economic losses through disruptions in reproduction, reduced milk production, and herd survival (Mandhwani et al., 2017). Sheldon et al. (2006) define postpartum endometritis (EM) as inflammation of the endometrium of dairy cows that occurs 21 days or more after parturition without systemic signs of disease. Metritis is an inflammation of the uterine wall (the layers are the endometrium, myometrium, and serosa), primarily within 7-10 days up to 21 days after calving, affecting up to 40% of dairy cows in the herd (Várhidi et al., 2024). Based on the accompanying systemic symptoms, EM is classified into 3 grades. In grade 1 EM, there are no systemic signs of illness or fever. Symptoms of acute puerperal metritis (grade 2 EM) include inappetence, fever (>39.5 ◦C), decreased milk production, and lethargy. Grade 3 EM involves toxic metritis, with the cows lying down, with noticeable signs of toxemia. The median cost of a metritis case was $513 (95% of scenarios ranged from $240 to $884). Milk price, treatment costs, replacement costs, and feed

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costs accounted for 59%, 19%, 12%, and 7%, respectively, of the total variation in cash flow differences, as revealed by stochastic analysis (Pérez-Báez et al., 2021).

The success of treating EM with antimicrobial drugs is variable, recovery rates have not been consistent, milk storage, the emergence of microbial resistance and reduced phagocytic activity of polymorphonuclear leukocytes (PMN cells). The most common approaches to EM therapy are the use of prostaglandin analogues and antimicrobial agents (singly or in combination). The massive, uncontrolled and prolonged use of antimicrobial agents has contributed to the emergence of resistant strains of bacteria.

The 2016 United Nation's meeting (Sun et al., 2021) clearly demonstrated that antimicrobial resistance (AMR) has become among the biggest public health and socio-economic threats around the world. In many societies and countries, developed and developing alike, the appearance of antimicrobial-resistant bacterial strains endangers their physical and social wellbeing through longer illnesses and more deaths (Darwish et al., 2023; San Martin et al., 2023).

The issue of increasing AMR is attributed to the fact that not enough new antibiotics are being developed as a result of the high costs involved in a lengthy approval process coupled with low economical returns for the responsible pharmaceutical companies (Manzoor et al., 2023). These two factors have contributed to a less-than-optimum replacement of older or ineffective antibiotics with phytotherapy (Kurćubić et al., 2024a). The use of herbal medicine is becoming popular due to the low toxicity of natural herbal remedies and there is no risk of residue in milk; clinicians want to find an alternative therapy for the treatment of uterine infections as soon as possible by applying immunomodulators and phytotherapeutic measures to activate the natural defense mechanism in the uterus.

Due to all of the above, it is imperative to conduct comparative studies of treatment options with antibiotics, non-antibiotics, or different combinations.

Phytotherapy of EM in milking cows

Puerperal metritis can lead to pneumonia, fever, acidosis, indigestion, acute pericarditis and mastitis, and often to hypocalcemia. Treatment of puerperal metris and EM is necessary to return breeding milk cows to reproduction. The modern approach to drug therapy requires the additional application of physical therapy, phytotherapy, the use of phytopharmaceutical preparations such as St. John's wort oil (*Hypericum perforatum* L.) and extracts of various plants, with uterine massage, all in order to avoid the use of antibiotics and disinfectants (Petrujkić et al., 2003). A mentioned study that lasted two years and included 212 dairy cows with various

degrees and durations of endometritis, peri and parametritis that were treated with St. John's wort oil once, twice or more during the puerperium shows that 128 cows were cured and remained pregnant after artificial insemination (59.14%). St. John's wort oil with extracts of other plants, wax, pollen and propolis and sunflower and olive oils are an economically profitable therapy (three therapies for 30 euros), so when viewed per 100 cows, the costs of EM treatment are minimal compared to the previous classical therapies because for treating the same number of cows with classical therapy would cost £833 (Esselmont and Kossaibati, 1997).

The bacterial agents commonly isolated from the uterus of postpartum cows are *E. coli*, *Streptococci* spp., *Trueperella pyogenes*, *Bacillus licheniformis*, *Prevotella* spp., and *Fusobacterium necrophorum* (Williams et al., 2005).

The study by Paiano et al. (2020) was conducted to investigate the chemical composition and antibacterial (AB) activity of essential oils of rosemary, cinnamon, clove, eucalyptus, lemon, oregano and thyme on the reference strain *Escherichia coli* (ATCC 25922), *Fusobacterium necrophorum* (ATCC 25286), *Trueperella pyogenes* (ATCC 19411) and *Staphylococcus aureus* (ATCC 29213). The AB effects on the mentioned bacteria are investigated because they are recognized as the most common causes of EM. The chemical composition of 7 essential oils was analyzed by GC-MS and the AB effects were estimated by the disk diffusion method. A total of 36 components were identified, the most abundant of which were cinnamaldehyde (86.5% for cinnamon essential oil), eugenol (85.7% for clove essential oil), 1,8-cineole (80% for eucalyptus essential oil and 47.8% for rosemary essential oil), limonene (65.5% for lemon essential oil), carvacrol (72.1% for oregano essential oil) and thymol (48.8% for thyme essential oil). The best results were found for cinnamon, clove, oregano and thyme essential oils compared to other essential oils, so they can be considered as potential agents for use as an alternative in the treatment of bovine EM.

Sarkar et al. (2006) evaluated the efficacy of garlic extract and prostaglandin F2 α in the treatment of EM in cows. After treatment, there was a significant reduction in bacterial load whereas it was increased in control group. The estrual cervicovaginal mucus turned clear in 70% animals treated with garlic extract. The overall conception rate was 50% in treated groups as compared to nil pregnancy in the control group. One of the active principles of freshly cut garlic homogenates is allicin, which has a variety of antimicrobial activities, and the antibiotic activity of 1 mg of allicin is equated to that of 15 IU of penicillin (Sadanandan et al., 2014; Gopikrishnan et al., 2022).

Aqueous garlic extract in EM therapy has been shown to increase the conception rate to 50% and the recovery rate to 75% (Rahi, 2011).

Esparza-Borges and Ortiz-Márquez (1996) applied extracts of garlic (*Allium sativum* L.), eucalyptus (*Eucalyptus globulus*, Labill.) and Gordolobo (*Gnaphalium conoideum*, H.B.K.) as intrauterine infusions to 3 experimental groups of Holstein cows (n=45) and repeated the treatment every 48 hours until a clinical response was noted. The following were evaluated: the number of treatments required, days to the first visible estrus after parturition, open days and conception rate. When assessing the therapeutic efficacy of plant extracts in the treatment of acute EM and uterine involution in this study, statistical analysis of the results revealed that garlic extract was the most effective. Eucalyptus extract was effective if a larger number of treatments were performed. No significant differences in conception rates were found among the three experimental groups. The effect of garlic was superior to the effects of Gordolob administration in terms of first visible estrus and open days, with high statistical significance ($p<001$).

Tomar et al. (2017) divided an equal number of twenty-four endometrial crossbred cows into four experimental groups, which received intrauterine treatment once daily during estrus with 1) 15 mL of normal saline 2) ciprofloxacin 3) neem or 4) garlic. Most cows treated with antibiotics or herbal extracts during the next estrus after treatment had a similar recovery ($p>0.05$). Evidence for this conclusion was the secretion of clear mucus, a negative white side test and the pH value of cervical mucus.

The study of Yildiz (2016) examined the therapeutic efficacy of infusion of *Allium sativum* (garlic) extract on recovery and conception rate in 42 cows with subclinical EM, randomly divided into 2 equal groups. In the treated group (group T), cows received a single intrauterine dose of 10 mL of garlic extract mixed with 40 mL of saline; in the control group (group C) cows, no intrauterine treatment was administered. Samples were collected again from all animals in both groups on the 14th day after treatment and the same laboratory tests were repeated. Artificial insemination was performed in the following estrus. 10 (23.8%) of the 42 cows had subclinical EM without bacteria in the uterus; The majority of cows with subclinical EM were positive for bacterial infection (76.2%). The bacterial load in group T was significantly lower compared to pre-treatment and group C. The cure rates for groups T and C were 100.0 and 19.0%, and the conception rates in groups T and C were 52.4 and 14.3%, respectively. Intrauterine use of garlic extract can reduce endometrial inflammation and bacterial load, thereby increasing conception rates.

In the study by Hajibemani et al. (2016), the effect of intrauterine infusion of *Zataria multiflora* extract on cows diagnosed with clinical EM was investigated. Cows were randomly divided into three groups: *Z. multiflora* extract (n = 56), penicillin + streptomycin (pen + strep, n = 55) and placebo (n = 20). The clinical cure

rate of experimental cows with EM 1 was 45.5, 34.5 and 53.6% in placebo, pen + strep and *Z. multiflora*, respectively. The clinical cure rate of cows with EM 2, 3 was 66.7, 84.6 and 56.0% in placebo, pen + strep and *Z. multiflora*, respectively. Overall, the proportions of successfully treated cows were 55.0, 58.2 and 54.7% in placebo, pen + strep and *Z. multiflora*, respectively ($p > 0.05$). In placebo, none of the parameters differed significantly between the first and second examinations, while in the other groups we found significant differences in the percentage of neutrophils and leukocyte esterase activity ($p < 0.05$). Pen + strep and *Z. multiflora* extract may be effective in clinical EM and may improve reproductive performance. *Z. multiflora* extract may be useful as an alternative therapy for the treatment of clinical EM in lactating dairy cows.

Kadivar et al. (2022) set as the aim of their study the evaluation of the effects of mixed essential oils of *Satureja bachtiarica* Bunge, *Artemisia Aucheri* Boiss and *Syzygium aromaticum* (L.) Merr. & L.M. Perry in the treatment of clinical EM in 120 dairy cattle randomly assigned to three groups. Cows in the HM group received intrauterine injections of mixed herbal essential oils; the OX group received 2.5 g oxytetracycline HCl; the EX group received 1 g ceftiofur sodium. The rate of cleaning and first service conception was significantly higher in the HM group than in the EX group, while the mean open days were lower in the HM group than in the EX group. The number of services per conception was also significantly lower in the HM group than in the OX and EX groups. Overall, reproductive performance after herbal treatment was quite comparable to chemical antibiotic therapy, and even better in some other reproductive indices, and represents an effective alternative to postpartum therapy for cows with clinical EM.

Kumar et al. (2013) found that hydroalcoholic and hydroacetone extracts of neem (*Azadirachta indica*, fam. Meliaceae) have potent immunomodulatory and therapeutic efficacy on EM in crossbred cows in repeated breeding, as reflected in a significant increase in total leukocyte count (TLC), PMN and immunoglobulin concentration in both treated groups. Neem is rich in numerous compounds with pharmacological potential, of which triterpenes (Nimbin) are prominent, with pronounced antipyretic, fungicidal, antihistamine, antiseptic, anti-inflammatory and antioxidant activities (Islas et al., 2020).

Also, Kumar et al. (2013) found that phytocomplex cocktails prepared from garlic and neem or garlic + turmeric + neem have stronger therapeutic (synergistic) effects than when the plants are used individually in EM therapy; synergistic effects were observed as a significant increase in TLC and PMN% in uterine lavage after treatment with the plant material.

In the study by Rahi et al. (2013), a phytocomplex cocktail prepared from garlic and ashwagandha extracts was confirmed to be the most effective treatment among all treatment groups, with the potential to replace conventional antibiotics in the future in the treatment of EM of bacterial origin that leads to recurrent reproductive failure in crossbred cows.

Singh (2016) revealed that after treatment with ciprofloxacin (93%), garlic (88.33%), and neem (86.67%), cows showed clear uterine discharge, with a significant difference in PMN%, TLC, and lymphocyte and monocyte counts.

Postulates that must be met in order to be able to apply an antimicrobial or antiseptic agent are that 1) it works effectively against aerobic and anaerobic, gram positive and gram negative bacteria, especially against the growth of anaerobic bacteria in the uterus; 2) AM agent must be applied in a solution concentration that allows the substance to be quickly resorbed and distributed in the uterine lumen and penetrate well into the superficial layers of the endometrium, without "braking" the uterine contraction and secretion mechanisms in the cellular components, as if it does not damage the endometrium (that it certainly does not cause necrotic endometritis and does not create irreversible changes in the genital tract); 3) that the distribution and kinetics of the drug from the uterus and excretion in milk are known; 4) the treatment should be cheap and profitable.

Conclusion

Based on the results of a series of studies, it can be concluded that treating EM without antibiotics or other pharmaceutical agents is possible, because phytotherapy and certain non-antibiotic therapies offer the possibility of using milk and meat without a withdrawal period during the treatment of warts. Phytotherapy can be very economically profitable and sustainable since it is eco-friendly ("green" agent that does not pollute and does not endanger the health of humans, animals and the environment), which is a requirement that every therapy will have to fulfill in the future. It is especially important that subclinical EM is treated more with phytotherapy compared to classical therapies, because there are no harmful residues in the milk and meat of cows, thus improving public health. It is expected that future research will test the use of synergistic phytocomplex mixtures as intrauterine drugs for EM therapy in a larger number of cattle.

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