

## Review Article

# Phytotherapy: An Alternative Low Cost Therapeutic Management of Endometritis in Dairy Animals: A Review

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## ABSTRACT

Endometritis is inflammation of the endometrial lining of the uterus. In addition to the endometrium, inflammation may involve the myometrium and, occasionally, the parametrium. Antibiotics were commonly used to treat the cases. But due to the side effects and development of cross and multiple resistances in pathogenic microbes as well as their high cost of treatment the use of antibiotics were discouraged. Herbal were an good alternative and have cheap and no resistance or residual effect. Neem, tulsi, garlic, ashwagandha, giloy and many other plants have beneficial effect on gynecological problems like endometritis. These plants were easily available in worldwide as well as some have greater potency than chemotherapy.

### Keywords

Antibiotic,  
Endometritis,  
Ethnoveterinary,  
Drug resistance

## Introduction

India is one of the world's earliest urban civilizations, along with Mesopotamia and Ancient Egypt. Medical science was surprising advances had made in ancient times in India. Particularly, these were in the area of plastic surgery, dental surgery and gynecological field with the knowledge of ethnomedicine. The knowledge of useful plants must have been the first acquired by man to satisfy his hunger, heal his wounds and treat various ailments (Kshirsagar & Singh, 2001, Schultes, 1967). But later allopathic medicines were fully taken over the traditional medicines. The allopathic medicine can cure a wide range of diseases,

but its high prices and occasional side-effects are causing people to return to herbal medicines (Kala, C.P. 2005). Overexploitation use of allopathic antibiotic develops antimicrobial resistance in humans as well as in animals, for using of plants in treatment, which contain phytotherapeutic properties helps to reduce in antimicrobial resistance. The World Health Organization (WHO) has also recognized the importance of traditional medicine and has created strategies, guidelines and standards for botanical medicines. Proven agro-industrial technologies need to be applied to the cultivation and processing of medicinal

plants and the manufacture of herbal medicines. In India nearly 15–20 percent of the Ayurvedic medicine is based on animal derive substance (*Unnikrishnan*). Seventy three percent of the population practices agriculture and animal husbandry as their main occupation (Anonymous, 2011)

Repeat breeding is one of the major causes (40%) of infertility in dairy cow (Bhosrekar, 1973), resulting as considerable economic loss to dairy farmers. Where endometritis is the major cause of endometritis in dairy cattle's and buffaloes. Clinical endometritis is basically referring to a local inflammation of the endometrium, characterized by the presence of purulent or mucopurulent (>50% pus) material in the vagina  $\geq$  21 days postpartum originating from the uterus, not accompanied by systemic illness (Sheldon *et al.*, 2006) The global incidence of endometritis in cattle is highly variable, ranging from 3.4% to 40%, depending on the diagnostic method according to Gilbert, *et al.*, (2005). In postpartum cows, endometritis continues to be a major cause of poor fertility and delayed conceptions (Couto, *et al.*, 2013 and Akshay Sharma *et al.*, 2017). Repeat breeding is one of the important causes of infertility in buffalo that results in delayed conception and increased calving interval, loss of milk production, reduction in calf crop, increased cost of treatment and culling of useful breeding animal leading to heavy economic losses to the dairy producers.

### **Pathogenesis**

Pathologists Jubb *et al.*, (1985) and McEntee, (1990) classified uterine infection into mild, acute and chronic form depending on histopathological changes of uterine tissues. The histopathological changes in mild endometritis are not striking and consist for the most part of a diffuse, light

infiltration of inflammatory cells with slight desquamation of the superficial epithelium and no significant vascular changes. While in acute endometritis, there is a prominent leukocyte infiltration involving all mucosal elements including the glands, and massing at the surface, with suppurative and superficial necrosis. In chronic endometritis, there is a prominent leukocyte infiltration involving all mucosal elements, the uterine wall is thickened with suffused blood and edema, serosa is dull and finely granular with “paint brush” hemorrhages and thin deposition of fibrin or sub serosal vessels may be darkly congested (Dzhuroua and Gulubinov, 1981).

### **Etiology of endometritis**

Endometritis plays a critical role in the modern dairy industry. It is highly prevalent, asymptomatic and has a profound detrimental effect on the reproductive performance. The bovine herpes virus 4 (BoHV-4), a large number of bacteria are responsible for clinical and subclinical endometritis (Williams, *et al.*, 2005 and Prunner, *et al.*, 2014); they are classified according to their pathogenicity and their frequency of isolation (Table 1). *Escherichia coli* and *Trueperella pyogenes* are the most frequently isolated bacteria from the uterine lumen in cows with uterine infections, followed by anaerobic bacteria such as *Provetella* spp., *Fusobacterium necrophorum*, and *Fusobacterium nucleatum* (Sheldon, *et al.*, 2006, Gilbert, *et al.*, 2005, Prunner, *et al.*, (2014) and Prunner, *et al.*, (2014).

### **Ethnoveterinary medicines (phytotherapy) for treatment of endometritis**

Modern medicine recognizes herbalism as a form of alternative medicine and

pseudoscience, as the practice of herbalism is not strictly based on evidence gathered using the scientific method. Modern medicine makes use of many plant-derived compounds as the basis for evidence-based pharmaceutical drugs. Although phytotherapy may apply modern standards of effectiveness testing to herbs and medicines derived from natural sources, few high-quality clinical trials and standards for purity or dosage exist. The plants which is used for treating of endometritis in dairy animal's are-*Tinospora cordifolia* (Giloy)

*Tinospora cordifolia*, which is known by the common names heart-leaved moonseed, guduchi and giloy, is an herbaceous vine of the family Menispermaceae indigenous to the tropical areas of India, Myanmar and Sri Lanka. In Ayurvedic medicine, *T. cordifolia* is considered to be one of the most divine herbs. The plant extract have shown to have many medicinal activity. A variety of active components derived from the plant like alkaloids, steroids, diterpenoid lactones, aliphatics, and glycosides have been isolated from the different parts of the plant body, including root, stem, and whole plant.

Recently, the plant is of great interest to researchers across the globe because of its reported medicinal properties like anti-diabetic, anti-periodic, anti-spasmodic, anti-inflammatory, anti-arthritis, anti-oxidant, anti-allergic, anti-stress, anti-leprotic, anti-malarial, hepatoprotective, immunomodulatory and anti-neoplastic activities (Saha and Ghosh, 2012). *Tinospora cordifolia* has been suggested to have direct antibacterial effect, besides causing nonspecific stimulation of immune response and it induces leukocytosis (Rege *et al.*, 1999 and Thatte *et al.*, 1989). *Tinospora cordifolia* was used extensively for the treatment of endometritis. Kumar *et*

*al.*, (2004) administered 50ml (3000 mg total dose) of aqueous extracts of *Tinospora cordifolia* to the endometritic cows for 3 consecutive days and he obtained recovery rate and conception rate of 66.67% and 27.27%, respectively. Giloy have an immunomodulator, antibacterial, anti-inflammatory & anti-infective properties which can be utilize as alternative low-cost medicine for treatment of endometritis in repeat breeder cows.

### ***Withania somnifera* (Ashwagandha)**

*Withania somnifera*, known commonly as ashwagandha, Indian ginseng, poison gooseberry, or winter cherry, is a plant in the Solanaceae or nightshade family. Several other species in the genus *Withania* are morphologically similar. Although commonly used as a medicinal herb in Ayurvedic medicine. The species name *somnifera* means "sleep-inducing" in Latin.

The name, *ashwagandha*, is a combination of the word *ashva*, meaning horse, and *gandha*, meaning smell, reflecting that the root has a strong horse-like odor. The main chemical constituents are alkaloids and steroidal lactones. These include tropine and cuscohygrine and the leaves contain the steroidal lactones, with anolides. Owis *et al.*, (2005) found the antibacterial activity of alcoholic extract made by ashwagandha roots against *Salmonella typhimurium*. Moreover, the extract did not induce lysis on incubation with human erythrocytes advocating their safety to the living cells.

Kumar, (2016) and Rahi *et al.*, (2013) resulted that hydro alcoholic extract of ashwagandha with garlic may be recommended as alternative treatment for endometritis repeat breeding cross bred cows over conventional antibiotic therapy.

### ***Zingiber officinale* (Ginger)**

Ginger is in the family Zingiberaceae, to which also belong turmeric (*Curcuma longa*), cardamom (*Elettaria cardamomum*), and galangal. The characteristic fragrance and flavor of ginger result from volatile oils that compose 1-3% of the weight of fresh ginger, primarily consisting of zingerone, shogaols and gingerols with (Caldwell, 1998), gingerol (1-[4'-hydroxy-3'-methoxyphenyl]-5-hydroxy-3-decanone) as the major pungent compound (An *et al.*, 2016). Zingerone is produced from gingerols during drying, having lower pungency and a spicy-sweet aroma. Ginger has a sialagogue action, stimulating the production of saliva, which makes swallowing easier. The evidence that ginger helps alleviate chemotherapy-induced nausea and vomiting is inconclusive and it is not recommended for clinical use for this or for any type of nausea (Marx *et al.*, 2013). Studies have found no clear evidence of harm from taking ginger during pregnancy, though its safety has not been established and it is a suspected risk for mutagenicity. Labania, (2005) and Abu Baker (2013) conformed that the ability of ginger to improve the functional efficiency of the uterus and ovary. Ghusoon and AL-Neamah, (2016) investigated that cadmium chloride induce toxicopathological changes in uterus and ovaries of rats and these changes were improved after giving ginger extract, which provide a strong evidence for the beneficial role of antioxidants plants in improving the effect of cadmium chloride toxicity in rat's female.

### ***Gunnera perpensa***

*Gunnera perpensa* is the only species of the genus *Gunnera* that has been recorded in Africa. Its leaves, rhizomes, roots, and stems are reported to possess diverse medicinal properties and used to treat or manage

various human and animal diseases and ailments. *Gunnera perpensa* is an ingredient in many herbal concoctions and prescriptions which have been used to induce or augment labour, postnatal medication, to treat parasitic diseases, urinary complaints, kidney problems, general body pains, sexually transmitted infections, and many other diseases. Several classes of phytochemicals including alkaloids, benzoquinones, ellagic acids, flavonoids, phenols, proanthocyanidins, tannins, and minerals have been isolated from *G. perpensa*.

Scientific studies on *G. perpensa* indicate that it has a wide range of pharmacological activities including acetylcholinesterase, anthelmintic, antibacterial, antifungal, antinociceptive, anti-inflammatory, antioxidant, antitumour, lactogenic, and uterotonic. *Gunnera perpensa* has a lot of potential as a possible source of pharmaceutical products for the treatment of a wide range of both human and animal diseases and ailments. The application of *Gunnera perpensa* in treating endometritis and related ailments may therefore largely be due uterotonic activity (Kaido *et al.*, 1997). Mc Gaw, *et al.*, (2005) resulted that *G. perpensa* extracts have antimicrobial activity and indicate that although the extracts demonstrated a level of pharmacological activity, the relatively weak antibacterial activity is unlikely to justify the use of *G. perpensa* rhizomes in the traditional treatment of endometritis.

Rather, the slightly antibacterial nature of the rhizomes may contribute to an additive effect, along with their known uterotonic activity, to the overall efficacy of the preparation. Kaido *et al.*, (1997) investigated the uterotonic activity of the crude decoction of *G. perpensa* on the isolated rat uterus and ileum preparation.

**Table.1** Classification of bacteria isolated from the uterine lumen according to their potential pathogenicity (Williams, *et al.*, 2005 & Mounir, *et al.*, 2017)

Uterine pathogens	Potential pathogens	Opportunist contaminants
<i>Prevotella melaninogenicus</i>	Streptococci, nonhemolytic	<i>Streptococcus acidominimus</i>
<i>Escherichia coli</i>	<i>Peptostreptococcus</i> sp.	<i>Staphylococcus</i> sp., coagulase-negative
<i>Fusobacterium necrophorum</i>	<i>Mannheimia haemolytica</i>	<i>Proteus</i> sp.
<i>Trueperella pyogenes</i>	<i>Pasteurella multocida</i>	<i>Aspergillus</i> sp.
<i>Bacteroides</i> sp.	<i>Enterococcus faecalis</i>	<i>Klebsiella pneumoniae</i>
	<i>Staphylococcus aureus</i>	<i>Clostridium perfringens</i>
	<i>Bacillus licheniformis</i>	$\alpha$ -Hemolytic streptococci
		<i>Micrococcus</i> sp.

Aqueous extract of *G. perpensa* initiated contractions in the isolated rat uterus, showed direct smooth muscle activity on the uterus, and potentiated the initial response of the uterus to oxytocin. Khan *et al.*, (2004) evaluated the effect of aqueous *G. perpensa* extract, ethyl acetate, ethyl acetate-methanol extract, and pure Z-venusol 5 on rat uterine and ileal muscles. *Gunnera perpensa* extract stimulated direct contractile response on isolated uterine smooth muscle and induced a state of continuous contractility of the uterus once all physiological buffer had been removed from the organ bath. By contrast, Z-venusol 5 did not trigger the direct contractile response but induced the state of continuous contractility once the organ bath was flushed (Khan *et al.*, 2004). These uterotonic properties of *G. perpensa* which promote uterine contractions were identified by traditional healers in southern Africa several years ago, and the species is now widely used to induce or augment labour, as an antenatal medication to tone the uterus and to assist in the expulsion of the placenta.

### ***Curcuma longa* (Turmeric)**

Turmeric is a rhizome and plant of the ginger family, Zingiberaceae. It is native to the Indian Subcontinent and Southeast Asia,

and requires temperatures between 20 and 30 °C (68–86 °F) and a considerable amount of annual rainfall to thrive. Turmeric (Haridra) is explained extensively and well documented for its therapeutic efficacy in Indian material medica. The genus of this plant is *Curcuma*. Acharya Charaka has explained Haridradi dhumvarti (fumes wick) in the condition like asthma and congestion. Curcumin is observed as a best anti-inflammatory agent in many of the research works. Curcumin has been shown to inhibit a number of different molecules involved in inflammation including phospholipase, lipooxygenase, COX-2, leukotrienes, thromboxane, prostaglandins, nitric oxide, collagenase, elastase, hyaluronidase, MCP-1, interferon-inducible protein, tumor necrosis factor, and interleukin-12 (Chainani, 2003). Studies has proven bisdemethylcurcumin (BDC) is more potent as an anti-inflammatory agent as indicated by suppression of TNF induced NF- $\kappa$ B activation, more potent as an anti-proliferative agent, and more potent in inducing reactive oxygen species (ROS). A Hispolon analogue, which lacks one aromatic unit in relation to curcumin, also exhibited enhanced anti-inflammatory and anti-proliferative activities (Ravindran, 2010). It is also ought to be one of the best anti-oxidant. Khanna, (1999) reported that

Curcumin and other curcuminoids present in turmeric inhibit the growth of *Salmonella paratyphi*, *Staphylococcus aureus*, *Trichophyton gypseum* and *Mycobacterium tuberculosis*. Kumar, (2016) founded in their comparative study that hydroalcoholic extract of turmeric was found broad spectrum antibacterial is nature as it shows maximum zone of inhibition among ashwagandha and garlic herbal extracts.

### ***Viburnum opulus* (Guelder-rose)**

It is the species of flowering plant, family Adoxaceae (formerly Caprifoliaceae) native to Europe, northern Africa and central Asia. The bark, known as cramp bark, is employed in herbal medicine. It used formerly to be included in the United States Pharmacopoeia, but is now omitted though it has been introduced into the National Formulary in the form of a fluid extract, compound tincture and compound elixir, for use as a nerve sedative and anti-spasmodic in asthma and hysteria. *V. opulus* is a powerful antispasmodic and is much used in the treatment of asthma, cramps and other conditions such as colic or painful menstruation. It is also used as a sedative remedy for nervous conditions. The bark is antispasmodic, astringent and sedative.

The bark contains "scopoletin", a coumarin that has a sedative affect on the uterus. A tea is used internally to relieve all types of spasms, including menstrual cramps, spasms after childbirth and threatened miscarriage. An endometritic study was conducted as induced by suturing 15mm piece of endometrium into abdominal wall of Sprague Dawley rats and studied that the effectiveness of the fruit extract of *V. opulus* could be partially attributed chlorogenic acid. Other phenolic compounds could potentiate the activity due to their amount (Saltan *et al.*, 2016).

### ***Azadirachta indica* (Neem)**

Neem has been called "the wonder tree" and "nature's drug store." All parts of this tree, particularly the leaves, bark, seed-oil and their purified products are widely used for treatment of different diseases. It is also called 'Sarvaroganivarini' meaning 'the curer of all ailments'. Neem has attracted worldwide prominence due to its vast range of medicinal properties like antibacterial, antiviral, antifungal, antiprotozoal, hepatoprotective and various other properties without showing any adverse effects (Talwar *et al.*, 1997). Although a large number of compounds have been isolated from various parts, a few have been studied for biological activity. Nimbidin, a major crude bitter principle extracted from the oil of seed kernels of *A. indica* demonstrated several biological activities. From this crude principle some tetranortriterpenes, including nimbin, nimbinin, nimbidinin, nimbolide and nimbidic acid have been isolated (Chhibber and Sharma, 2014). Nimbidin and sodium nimbidate possess significant dosedependent anti-inflammatory activity. According to Brindrawan, (2001), Neem was used in treating endometritic cows with satisfactory results. Singh, (2005) studied the therapeutic efficacy of neem oil and reported heavy reduction of uterine pathogens and increased conception rate in endometritic cows. Kumar *et al.*, (2013) also reported that all the cows received treatment with neem oil extract were recovered from endometritis, caused decline in bacterial load (96.02 + 2.02 %) and increased conception rate (71.4%).

### ***Ocimum sanctum* (Tulsi)**

World health organization (WHO) has advocated the evaluation of therapeutic potential of *Ocimum sanctum* for diseases

where we lack safe allopathic drugs. *Ocimum sanctum* described as sacred and medicinal plant in ancient literature, commonly known as *Tulsi* is derived from 'Sanskrit', which means "the incomparable one". This plant belongs to the family Lamiaceae which is native throughout the Old World tropics and cultivated for religious and medicinal purposes. According to Gupta *et al.*, (2002) different parts of tulsi plant, like leaves, flowers, stem, root, and seeds, are known to possess therapeutic potentials and have been used by traditional medical practitioners as expectorant, analgesic, anticancer, antiasthmatic, antiemetic, diaphoretic, antidiabetic, antifertility, hepatoprotective, hypotensive, hypolipidemic, antimicrobial, and antifungal activity. The chemical constituents isolated from various parts of the plant include eugenol, cardinene, cubenol, borneol, linoleic acid, linolenic acid, oleic acid, palmitric acid, steric acid, vallinin, vicenin, vitexin, vallinin acid, orientin, circineol, gallic Acid, vitamin A, vitamin C, phosphorous and iron. Eugenol is a phenolic compound and major constituent of essential oil extracted from different parts of tulsi plant, which may be responsible for antimicrobial activity resulted by Bhatt *et al.*, (2012). Singh, (2016) found that the cows exhibited clear discharge with ciprofloxacin (93%) followed by garlic (88.33%) and neem (86.67%) after treatment and found a significant difference in PMN%, TLC, and lymphocyte and monocyte counts.

### ***Allium sativum* (Garlic)**

Garlic, *Allium sativum* is a member of the Alliaceae family, has been widely recognized as a valuable spice and a popular remedy for various ailments and physiological disorders. The name garlic may have originated from the Celtic word

'all' meaning pungent. Garlic contains at least 33 sulfur compounds, several enzymes, 17 amino acids, and minerals such as selenium. It contains a higher concentration of sulfur compounds than any other *Allium* species. The sulfur compounds are responsible both for garlic's pungent odor and many of its medicinal effects. Dried, powdered garlic contains approximately 1% alliin (S-allyl cysteine sulfoxide). One of the most biologically active compounds, allicin (diallyl thiosulfinate or diallyl disulfide) does not exist in garlic until it is crushed or cut; injury to the garlic bulb activates the enzyme allinase, which metabolizes alliin to allicin. Allicin is further metabolized to vinylthiines. Allicin has antimicrobial effects against many viruses, bacteria, fungi and parasites. Garlic oil, aged garlic and steam-distilled garlic do not contain significant amounts of alliin or allicin, but instead contain various products of allicin transformation (Kemper, *et al.*, 2000). Allicin has a variety of antimicrobial activities, and the antibiotic activity of 1mg of allicin is equated to that of 15 IU of penicillin (Sadanandan *et al.*, 2014). Sarkar *et al.*, (2006) evaluated the efficacy of garlic extract and prostaglandin F<sub>2</sub> α in the treatment of endometritis in cows. After treatment, there was a significant reduction in bacterial load whereas it was increased in control group. The estrual CVM 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. Rahi, (2011) found 50% conception rate and 75% recovery rate of endometritis when treated with aqueous extract of garlic.

### **Other phytotherapeutic agents**

Hanafi *et al.*, (2010) explained about new antifungal compounds i.e. *Thymus vulgaris* and *Rosemarinus officinalis* against micotic

endometritis induced by candida albicans and have observed that they have good curative effect, radical scavenger properties and immuno-stimulant free. Herbal extracts provide safe as well as cheap treating any diseases. Borowieck (1989) observed and Sarkar, P (2016) reviewed about 84% conception rate in cows treated with alcoholic extracts of 5 plants (chamomile, marigold, comfrey, salvia and yarrow) for endometritis.

Gynecological dysfunction is a major problem of dairy industry and responsible for biggest loss in the sector. Amongst the dysfunctions endometritis is the common most outcomes. Antibiotics that were routinely used to treat the endometritis were discourage by various researches because of their high cost of treatment, side effects and their residual effects in milk and milk products that leads to development of drug resistance in human as well as pathogenic microbes in animals. Because of these problems veterinarians and researchers moves toward ethno veterinary medicine. The above mentioned herbal medicinal plants were proved for their curative impacts on gynecological dysfunctions like endometritis. There are a lot of other medicinal herbs all the around world which impact on gynecological dysfunction were remained to study.

### Competing Interests

The authors declared that they have no competing interests.

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