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Ayurvedic herbs in treatment of vaginal infections: A review

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Abstract
Vaginal infections are so prevalent in women and they represent the main cause to seek medical consultation for adult women. 75-85 % of women in developing countries have ever had a vaginal infection and their symptoms have been associated with anxiety, depression and negative impact on quality of life. Bacterial Vaginosis BV and Vulvovaginal Candidiasis VVC are the two most common forms of vaginal infections in females in developing countries. Ayurvedic herbs have been widely used in treatment of microbial infections and these plant metabolites have been used worldwide for higher therapeutic efficacy and lesser side effects. The extraction and characterization of these metabolites from the natural sources resulted into new drug discovery with better therapeutic effect and acceptability to patients due to lower adverse reactions. This review summarized and focused on those medicinal plants belonging to plant families Alliaceae, Lamiaceae, Myrtaceae, Meliaceae, Poaceae, Ranunculaceae, Geraniaceae, Solanaceae, Apiaceae, Fabeaceae, Berberidaceae, Araliaceae, Cyperaceae, Asteraceae, Grossulariaceae, Melianthaceae, Zygophyllaceae, Ericaceae; used in treatment of bacterial and fungal vaginal infections. The latest researches and their results also summarized here with the description of plant, structures of their active constituents and their related pharmacological effects in inhibiting microbial vaginal infections.

Keywords: Ayurvedic herbs, vaginal infections, bacterial vaginosis, vulvovaginal candidiasis, antibacterial and antifungal medicinal plants.

Introduction
There are 250,000 - 500,000 species of plants on earth [1] out of which some are mainly used as food and for the medicinal purpose in Human beings and as well as in animals. In 400 BC, *Hippocrates* known as 'Father of Modern Medicine' mentioned 300-400 medicinal plants [2]. Later on, in the 1st Century AD, *Dioscorides* discussed in detail the identification, collection, adulteration and therapeutic uses of several thousand plants in *De Materia Medica* which was used as a prototype for modern Pharmacopoeia. The *Charaka Samhita*, an encyclopedia of Indian medicine published in 1000 BC and 100 AD, having the comprehensive record of medicinal plants and their uses. During last few years, medicinal plants have attracted the attention of various Pharmaceutical and Scientific communities due to the decreasing microbial susceptibility towards antimicrobial agents and many evidences are found that has been marked for the potential of antimicrobial activity of plant derivatives [3-7].
Vaginitis, stands for inflammation or infection of vagina and the primary causes of Vaginitis includes; Trichomoniasis, a protozoan infection, Bacterial Vaginosis BV caused by a bacteria and Vulvovaginal Candidiasis VVC, a fungal infection. Out of these causes the most frequent is BV and VVC while Trichomoniasis gets declined worldwide. In developing countries, about 240 million women affected by Vaginitis per year [8], out of which 40 million cases emerged in India alone. A majority of women suffered from vaginal infections faced many complications like pelvic inflammatory disease (PID), cervical cancer, postabortal, infertility, chronic pelvic pain, and ectopic pregnancy. Among many cases, these vaginal infections are found to be asymptomatic, making their detection and diagnosis difficult [9]. Disturbances in the natural vaginal milieu are associated with the presence of vaginal infections or presence of harmful bacteria and fungus. Lactic acid producing bacteria, mainly *Lactobacillus* species is responsible for the normal vaginal flora in reproductive aged women, which consequently maintains the vaginal pH i.e. 3.5-4.5 and it is estimated as a biomarker of healthy condition [10].

Vaginal infections: Etiology of disease
There is a symbiotic relationship exists between *Lactobacillus* and the female vagina. Hormones in women's body modulated this relationship and glycogen is produced by the stimulation of vaginal epithelia. Vaginal *Lactobacilli* metabolized this glycogen and turns into lactic acid which is mainly responsible to maintain the vaginal pH [10]. Vaginal infections caused by different microorganisms alter this healthy status of vagina which results into diseased conditions and this may leads into the physical and mental illness of women, mainly in their reproductive age.

Bacterial Vaginosis (BV)
In childbearing age of women, Bacterial vaginosis is the most common form of vaginal infections and it is markedly associated with the loss of healthy bacteria in vaginal flora; decrease in number of colonies of *Lactobacillus* and also associated with the overgrowth of anaerobic polymicrobials within the vaginal lumen. This leads to increase in vaginal pH due to reduction in production of lactic acid. It is correlatively has a interrelation with an increased risk of bringing on the sexually transmitted disease including *Gonorrhea, Chlamydia, Human Immunodeficiency virus*

(HIV) & Herpes simplex virus among women suffered from BV [11]. Anaerobic bacteria which are mainly responsible for Bacterial Vaginosis include *Gardnerella vaginalis, Mycoplasma curtisii, Mycoplasma hominis and Escherichia coli* [12].These anaerobic bacteria lead to several complications in women; like creamy vaginal discharge, rotten fishy smell; especially during menstrual phase or in menopause, stomach pain, chorioamnionitis (inflammation of fetal membranes; amnion and chorion), high risk of acquiring HIV, infertility and abortions [13-15]. BV is mainly characterized by four criteria called Amsel's criteria [16] include the presence of abundant milky homogenous discharge from vagina which can be yellow or grey in color, increased vaginal pH > 4.5, positive amine test and presence of clue cells (exfoliated vaginal cells covered by *Gardnerella vaginalis* clue cells) [17]. Along with Amsel's criteria various diagnostic tests has been developed for the confirmation of this infection. Whiff test, Gram staining, Scoring system on the basis of presence of Gram positive and Gram negative bacteria in vaginal discharge are some diagnostic methods to identify the presence of BV. Apart from these diagnostic methods; analytical methods are also used to detect BV in patient who includes the use of Polymerase Chain reaction and probes of Oligonucleotides. This is an accurate, faster and reliable method to detect BV but this is not available clinically [18-20].

Vulvovaginal Candidiasis (VVC)

Vulvovaginal Candidiasis VVC is the second most commonly acquired vaginal infection in reproductive age of women, after BV. This fungal infection is caused by *Candida* species and largely by *Candida albicans*, pathogenic yeast. In developing countries, it is estimated that 70-80% of women has been suffered from VVC once in their lifetime and this mostly experienced in the age of 25 years [21]. Whether, 8-10 percent has been experienced the recurrence of this disease which is frequently called Recurrent Vulvovaginal Candidiasis (RVVC) and it is predominantly estimated by recurrence more than four times within a year [22].

The pathogenesis of this disease is an acute inflammation of vaginal mucous membrane and vulva, which is marked by the presence of large numbers of *Candida species* organisms that shows commensalism with vagina and remains quiescent [23]. The signs and symptoms associated with VVC are burning sensation of vulva, swelling & pruritis, vaginal irritation, Cottage Cheese like vaginal discharge having ferment and milky odour. In some cases women also experience dysuria, dyspareunia, erythema and excoriations [24-25]. Cervico-vaginal area is well prepared like other body sites to activate adaptive immune response to eliminate the pathogens. Although, Vagina has many humoral and cellular factors which include T helper cells, dendritic cells (DC)as well as cytotoxic and regulatory lymphocytes, B lymphocytes and natural killer cells that produce chemokines and cytokines to activate the defense factors [26-28].

Whether, the symptoms are not pathognomonic in case of VVC infection but the microscopic diagnosis of vaginal fluid demands the mycelia forms of yeast cells. Vaginal samples from symptomatic women must be cultured, when no pseudo hyphae or blastospores are seen in smear examination [29] Mannose binding lectin (MBL) is a protein associated with the defensive mechanism and present in body fluids and blood circulation. It helps in recognition of mannose related carbohydrates on surfaces of microbes. Binding of MBL to microorganisms will cause cell lysis of microbes and opsonization by phagocytic cells. It has been markedly identified that MBL present in vaginal secretions and deficiency of MBL in vaginal secretion is a diagnostic method to identify the presence of fungal infection i.e. *Candida albicans* [30-3]1.

Potential of Ayurvedic Herbs as Antimicrobial Agents

Plants and their secondary metabolites are having limitless ability to cure many diseases and they suggest great potential to treat microbial infections. Large spectrum of antimicrobial activity is supposed by plant's secondary metabolites which include Phenols, Phenolic acids, Quinones, Flavones, Flavonoids, Flavonols, Tannins, Coumarins, Terpenoids, Alkaloids, Essential oils, Resins, Lectins & Polypeptides.

This article is focused on the study about antibacterial and antifungal activities of plants and their metabolites which can be used in treatment of vaginal infections and supposed to discover a new approach in cure of women genital tract infections. These plants are having a wide range of activity according to topography, species and climatic conditions of origin and it may contain various active principles to cure the bacterial and fungal infections.

Allium sativum

Garlic extract from *Allium sativum* of family Alliaceae containing allicin has the remarkable antimicrobial activity and found as components of OTC products which are used for vaginosis treatment. Fresh garlic cloves contain the sulfur-containing compounds allicin, ajoene, diallyl polysulfides, vinyldithiins, S-allylcysteine, enzymes, saponins and flavonoids. Allicin is known as the main component of garlic and due to presence of allicin garlic possess a broad spectrum activity including fungicidal and bactericidal activity. Studies has demonstrated its bacteriostatic and bactericidal effect, which may cause disruption of cell metabolism in bacteria by-

1. Causing inactivation of proteins by thiols to disulphide oxidation.
2. Combining with cysteine and glutathione and inhibit their activity competitively
3. Causing inhibition of enzyme activity by binding to –SH group noncompetitively at allosteric sites and cause oxidation.

Garlic & Thyme extract have been formulated as a vaginal cream; having similar efficacy to Clotrimazole vaginal cream with lesser adverse effects when tested clinically. Garlic tablets inserted in vagina or chewed; have been reported the decreased Amsel's criteria with lesser adverse effects and similar efficacy to Metronidazole tablets in bacterial vaginosis treatment [32-34].

Thymus vulgaris

Thyme, *Thymus vulgaris* of family Lamiaceae has been examined for the microbial infections of women genital tract and it has remarkable anti-microbial effect in vaginal infections treatment. Major components of this plant include terpinen-4-ol (11.3%), Linalool (35.2%), myrcene (7.8%) and thymol (35-45%) extracted as the essential oil of thymus leaves. Monoterpenes units which are derived from hydrocarbons of isoprene molecules or their attachment are

the essential component of thymol and these are widely used as antifungal or antimicrobial agents in vaginitis. Thymol is hydrophobic or amphipatic in nature; this may cause the asymmetry in microbial membrane tensions due to interrupted cell membranes and their surface electrostatics caused by thymol. Product evaluation of thymol containing formulations revealed MIC and fungicidal properties when compared with non thymol containing products indicates its antifungal activity. Thymol is also considered for its antioxidant activity and its inhibitory concentration can interrupt the fungal and bacterial adhesion to vaginal epithelial cell and can cause the killing of microbes [35-37].

Melaleuca alternifolia

TTO, tea tree oil is an essential oil extracted from the *Melaleuca alternifolia* leaves belongs to family Myrtaceae. TTO has been identified and proved its efficacy in treatment of vaginitis due to the presence of its components such as linalool, terpinen-4-ol, α-pinene, β-pinene; which are mainly responsible for its antifungal activity [38]. It shows remarkable effectiveness against *Candida* species, *Gardnerella* species and *Trichomonas* species. Studies revealed that anaerobic and aerobic bacteria causing BV are susceptible to tea tree oil and *Lactobacillus* shows resistance to TTO. Further studies explained that TTO containing terpinen-4-ol were more potent than 5-Fluorocytosine and Amphotericin B in treatment of fungal vaginal infections [39]. Vaginal pessaries containing TTO was reported to treat vaginosis in a patient, after five days treatment with pessaries containing 200 mg tea tree oil with vegetable oil base. Recently, a combined formulation was developed containing TTO & Itraconazole as nanoemulsion thermosensitive bioadhesive gel. When tested on rat model it was verified that they shows synergistic antifungal potential with faster clearance than single drugs. It was demonstrated that TTO was also responsible to enhance the drug permeability across vaginal epithelium cell membrane. It was proved in many studies that TTO and many essential oils are act as permeation enhancers and this is because of causing modifications in partition coefficient of drugs or changes in epithelium structure [40-42].

Azadiracta indica

Recent studies explained the antibacterial and antifungal effect of *Azadiracta indica* or Neem, an evergreen tree belongs to family Meliaceae and it was concluded that it has better potential to treat vaginal infections mainly against *Candida* species and in Bacterial vaginosis [43]. Tetranortriterpenes are the major antimicrobial constituents of Neem and it includes Azadirachtin A, Azadirone, Epoxyazadiradione, Azadiriadione, Nimbidin, Nimbin, Salannin, 17-hydroxydiradione and its derivatives. Neem oil extract contained Azadirachtin A was tested on mice to protect it from systemic candidiasis, in which it was administered IV of 60 mg/kg body weight, twice a day for seven days and resulted into reduction of colonies of *Candida* in vaginal smear [44]. In recent studies, a placebo controlled clinical trial was performed in which fifty five women having bacterial vaginosis, were inserted 5ml oil in vagina daily for two weeks. It was reported in that it can cure the infection and having bactericidal efficacy with lesser adverse effects [45].

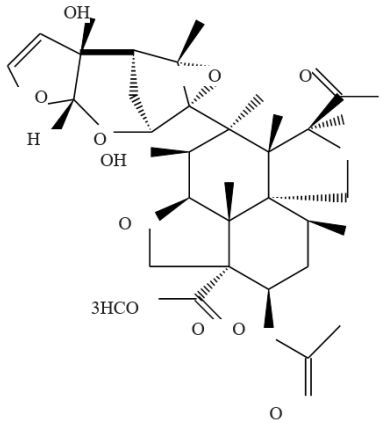

Fig 1: Chemical Structure of Azadirachtin A

Zataria multiflora

Antifungal and antibacterial property of combinations of plants extracted essential oils, including *Zataria multiflora* extracted oil is due to the presence of phenolic monoterpenes, thymol and carvacrol [46]. *Zataria multiflora* is thyme like plant belongs to family Lamiaceae and the main components of plant extracted essential oil are oxygenated monotrpenes, monoterpene hydrocarbons and oxygenated sesquiterpenes. Indian ecotype of this plant contains phenols (69%), mainly carvacrol and non-phenolic component p-cymene. Further studies revealed that its fresh plant contains thymol (73.21%) and dried plant contains carvacrol (62.87%), which are well known antifungals and antimicrobial agents [47]. It has been reported that these components are having lipophilic nature, act on the cell membrane of microbes and cause morphological dysfunctioning and results into permeability changes [48]. Carvacrol and p-cymene gives synergistic antimicrobial effects which results in destabilization of microbial membrane. According to various random clinical studies, essential oil of *Zataria multiflora* has been used against *G.vaginalis* and it has in vitro bactericidal effects [49-50]. In recent studies, *Zataria multiflora* essential oil and Metronidazole 1% gel was used for the treatment of two groups of 87 women (age of 18-40 years) suffered from Bacterial vaginosis. After 5 days, it has been observed that clinical signs and symptoms was suppressed by both treatments but *Zataria multiflora* essential oil containing vaginal cream was more potent in case of vaginal edema and arrhythmia with lesser side effects [51]. Further studies revealed that the antifungal activity of *Zataria multiflora* was higher than nystatin, ketoconazole and fluconazole against *Candida species* [52].

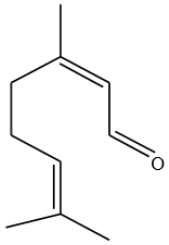

Fig 2: Chemical Structure of Citral

Cymbopogon citratus

Lemongrass oil from the plant *Cymbopogon citrates* of family Poaceae has remarkable antibacterial and antifungal activity and it is beneficial against *Candida albicans* and

other species which are mainly responsible for vaginitis [53-54]. Major components of lemongrass oil are monoterpenes, Citral (65-85%), myrcene, geranylacetate and geraniol [55]. The antifungal activity of lemongrass oil was estimated by disk diffusion method in which lemongrass oil was used against eight strains of *Candida* species and nystatin was used as antifungal reference substance. In results lemongrass oil has been proven its better potential as an antifungal agent. Antibacterial activity of lemongrass oil was estimated in various studies in which Broth dilution method was used. Gram positive bacteria are more sensitive for lemongrass oil than gram negative bacteria. Results revealed that MIC of lemongrass oil for various strains of bacteria was observed at 0.03% [56-57].

Allium hirtifolium

Persian Shallot or *Allium hirtifolium* is of family Alliaceae has been proved for having antifungal & bacteriostatic properties in gram positive bacteria responsible for vaginal infections and this is due to the presence of chemical components such as, 5-chloroorcylaldehyde, pentylthiophene, methylthiomethyl disulfide, triclosan, dimethyl trisulfide, 9-hexadecenoic acid, n-hexadecanoic acid, [11,14] eicosadienoic acid, linoleic acid and linolenic acid [58]. Its antibacterial, antifungal and antiprotozoal activity has been reported in many recent researches and in vitro studies. The plant extract was reported to decrease the growth and oxygen uptake of microorganisms. It also inhibits proteins, lipids and synthesis of nucleic acid in microorganisms, which may cause the damage of microbial membranes [59]. Its anti-candida activity was tested against 33 *Candida* species and it was compared with metronidazole. Results estimated that it has better anti-candidal activity, can be used in treatment of chronic vaginal candidiasis. It exhibits antibacterial activity against bacteria like *E. coli, S. aureus, Proteus mirabilis,* and many more [60-62].

Hydrastis canadensis

Goldenseal, *Hydrastis Canadensis* belongs to family Ranunculaceae contains isoquinoline alkaloids including berberine, hydrastine, hydrastinine, berberastine, canadine and canalidine which are mainly responsible for its antifungal and antibacterial properties. Rhizomes extracted constituents i.e. hydrastine and berberine from this plant has been proved its antimicrobial activity for a wide range of bacteria [63]. Clinical studies proved that it can inhibit the bacterial growth and morphological changes in cell wall of bacteria causing positive effect in treatment of BV. Anticandida activity of Goldenseal was demonstrated in vitro studies in which it caused the removal of 64-89% of *Candida* cells [64].

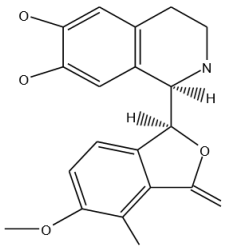

Fig 3: Chemical Structure of Hydrastine

Rosemarinus officinalis

Rosemary, *Rosemarinus officinalis* an aromatic plant of family Lamiaceae contains antibacterial components eucalyptol, α-pinene and borneol; has been proved for antibacterial effect against wide range of Gram positive and Gram negative bacteria in many recent studies. Main constituents present in rosemary oil are oxygenated monoterpenes, sesquiterpenes and monoterpinic hydrocarbons. It consisted of p-cymene, thymol, linalool, eucalyptol, α-pinene, β-pinene, γ-terpinene and camphor [65-66]. In a clinical study it was estimated that MIC/MBC value of rosemary oil was proved its antibacterial efficacy against bacteria causing BV in a patient, while that species were resistant for various commercial antibiotics used [67]. Extracted oil of Rosemary showed an anti-candidal activity against two strains of *Candida* species resulted in to antifungal activity at 1 mg/ml. In vitro studies showed MIC/MFC ratio was at 1.2-5 mg/ml which proved it, an efficient antifungal agent [68].

Pelargonium graveolens

Geraniol is major component of *Pelargonium graveolens* or Geranium belongs to family Geraniaceae and it has been proved for its antifungal activity in a very low concentration. Geranium oil contains main components i.e. geraniol, citronellol, linalool, citronellyl formate, geranyl acetate, α-pinene, terpineol and myrcene etc [69].Clinical studies demonstrated that Geranium oil when used in form of vaginal washing it results in significant lowering of *Candida albicans* cells growth in a patient suffered from VVC. In-vivo activity of Geraniol was estimated in a study on six week old mice having vaginal Candidiasis, results in to anti candida activity in concentration range of 25-50µg/ml [70]. In a combination therapy against BV treatment; Geranium oil showed better susceptibility for causative agents and lowers the microbial growth and the inhibition zone was therapeutically identified with MIC/MBC ratio according to broth dilution method [71]. *Bacteroides vulgates & Gardnerella vaginalis* were highly susceptible for Geranium oil with other combinations.

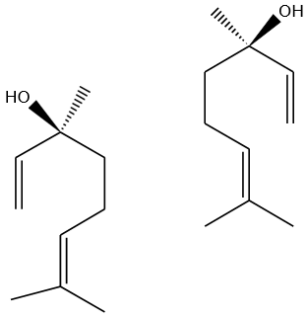

Fig 4: Chemical Structure of Linalool

Calendula officinalis

The extract of leaves, flowers and roots of Marigold, *Calendula officinalis*, family Asteraceae were used as antibacterial agent against *Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae, Salmonella,* and *Agrobacterium tumefaciens.* Chemically it contains carotenoids, flavoxanthin, auroxanthin and triterpenoid esters. Other carotenoids present are lutein, zeaxanthin and β-carotene. Flowers contain mainly saponins, sesquiterpene glucosides, flavonol glycosides and oleanane. In a study, it was estimated that *Calendula*

officianlis methanol extract containing vaginal cream showed better therapeutic efficacy in treatment of BV patient in comparison to Metronidazole without any side effect [72-73]. Additionally, it shows the antifungal activity with same effectiveness as clotrimazole in a group of females infected from VVC. It helps to enhance defensive mechanism of vagina and it seems to be very effective against vaginal candidiasis. Its flower extracted volatile oil possessed antifungal activity against many strains of *Candida* species [74].

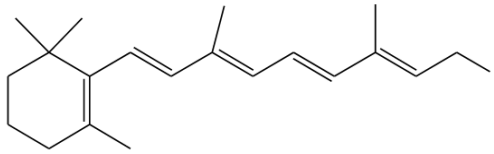

Fig 5: Chemical Structure of Beta- Carotene

Withania somnifera

Withania somnifera or Ashwagandha belongs to family Solanaceae contains phytochemicals include withanolides such as triterpene lactones, Withaferin A, steroidal lactones, alkaloids and cuscohygrine. Withanolides a & D exhibit antibacterial and antifungal effects in many in vitro studies [75]. Aqueous extract of leaves has been proved its antifungal activity against *Candida albicans* in an in-vitro study with MIC 10mg/ml. It shows fungicidal and bactericidal effect by causing cytotoxicity, immune potentiation and gene silencing in microbes and it proved its antimicrobial potency at the concentration of 1.56 mg/ml aerial extract [76-77]. Ethanolic extract of roots has been estimated for its antibacterial activity with greater inhibition zone at 40mg/ml concentration. Methanolic extract of roots of Withania somnifera containing bound flavonoids possess antifungal activity against *Candida* species with greater inhibition zone and activity index [78].

Foeniculum vulgare

Antimicrobial activity of fennel oil, extracted from *Foeniculum vulgare*, family Apiaceae is due to the presence of its active components anethole, camphene, estragole, limonene, α-pinene, β-pinene, β-myrcene, p-cymene, fenchone and safrole. In a clinical study on 127 women affected from BV, *Foeniculum vulgare* showed characteristic therapeutic effect after 14 days of administration as suppositories compared to Metronidazole without any adverse effect [79]. In seed extract of fennel plant, Phytoestrogens has been proved their efficacy in treatment of vaginosis. In vitro antifungal activity of *Foeniculum vulgare* was demonstrated by microdilution method in comparision of Fluconazole for *Candida albicans* biofilms formation resulted in to higher antifungal activity with MIC90 of 12.5%. This study proved the higher antifungal activity of fennel for biofilm eradication and has a significant impact in treatment of vaginal fungal infection caused by *Candida albicans* [80-82].

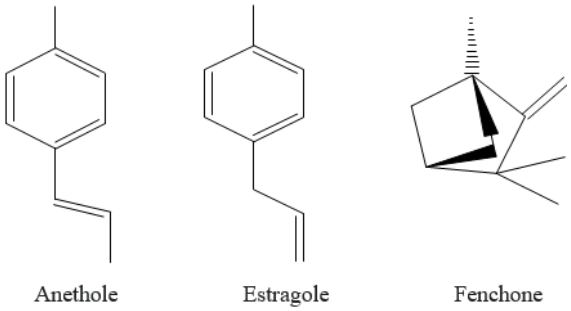

Fig 6: Chemical Structure of Anethole, Estragole and Fenchone

Cassia alata

Senna, *Cassia alata* of Leguminosae family having active compounds such as kaempferol, kaempferol-3-O-beta-D-glucopyranoside, flavanones, quercetin, palmitic acid ceryl ester, palmitic acid and stearic acid which is mainly responsible for its remarkable antimicrobial activity. Methanolic extract of stem, leaves and barks of Senna plant has demonstrated for its antibacterial and antifungal activity against a wide range of microbes [83]. In vitro study of ethanolic and water extract of barks and leaves of *Cassia alata* has been proven its antimicrobial activity against *Candida albicans* and bacteria species. Results were compared with antibiotic Chloramphenicol and antifungal agent Amphotericin B and it has been proved in the study that it is a potent antibacterial and antifungal agent [84]. In another study, the hexane extract of Cassia alata leaves containing steroids has been identified for possessed 10% MIC and MFC against *Candida albicans* species; mainly targets on the hyphae formation and biofilm formation in fungi and demonstrated by two fold method. In vitro study revealed that *Cassia alata* leaf extract is beneficial in case of dermatophytic fungi rather than non-dermatophytic fungi and this antifungal activity is due to the presence of chrysophanol in the leaf extract and it has been used for a wide range of bacteria, fungus and yeast [85].

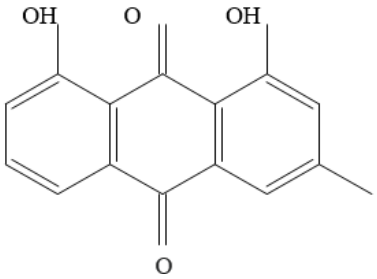

Fig 7: Chemical Structure of Chyrsophanol

Panax ginseng

Saponins are the majorly active compound of *Panax Ginseng*, family Araliaceae and two major groups of saponins called ginsenosides are responsible for its antimicrobial activity; protopanaxotriols and protopanaxodiols. Two polyacetylenes were identified in ginseng root culture which showed high antimicrobial

activity against a wide range of microorganisms [86]. In a study, ginsenosides were evaluated for the antibacterial and antifungal efficacy against 5 Gram positive, 7 Gram negative bacteria and 4 fungi strains, resulted in to higher efficacy of Rb2 & Re (ginsenoside) as antimicrobial agent against *Candida albicans & E. coli* and other microbes obtained from vaginal swab [87]. In another in vitro study, Ginseng stem leaves saponins (GSLS) tested against 31 species of *Candida albicans* of genital candidiasis with antifungal drug Fluconazole, and it was considered that Ginseng stem leaves saponins has antifungal activity against Candida and non-Candida species with MIC range < 0.49 µg/ml for 24 hours [88].

Bereberis aristata

Blueberry, *Berberis aristata* family Berberidaceae contains alkaloids such as Berberine, Berbamine, Oxyberberine, Protoberberine alkaloid Karachine, taxilamine, palmitine and tannins. Berberine has been identified as potent antimicrobial agent in many studies [89]. In a gene expression study Berberine was used against *Candida albicans* species and it's identified genes which are susceptible and resistant for Fluconazole and it was resulted in demonstrating the potent activity of Berberine for those specified genes. In another study aqueous & alcoholic extract of berberis roots, containing Berberine as main constituent identified to inhibit the Candida growth by intercalating with DNA and inhibiting protein biosynthesis which cause cell death [90]. In a clinical study on 120 women affected by BV; *Berberis vulgaris* and *Myrtus communis* combination vaginal gel was used for 5 days in comparison of Metronidazole vaginal gel and it was estimated that Berberine containing vaginal gel was more potent than Metronidazole containing gel [91].

Cyperus articulatus

Essential oil of *Cyperus articulatus* has been used as antifungal agent and antimicrobial agent from ancient time. *Cyperus articulatus* is an aromatic plant of family Cyperaceae, constitutes antimicrobial properties due to presence of α-pinene, β-pinene, muskatone, caryophyllene oxide, myrtenal, ledol, trans-pinocarveol and α-cyperone. A strong antifungal activity of ethanolic extract 48.5% was discussed in a study and demonstrated its MIC 1.6 mg/ml [92-93]. In an in-vitro study, red and black type of *Cyperus* rhizomes were used against Gram positive & Gram negative bacteria resulted in to higher antibacterial properties in extracted essential oil of this plant and it was concluded that Gram negative bacteria were more sensitive for the oil. In an antifungal assay performed by Disc Agar Diffusion method rhizomes of this plant were used in combination of other antimicrobial plants resulted that it is fungistatic against *Candida albicans* species [94].

Anthemis nobilis

Chamomile, *Anthemis nobilis* belongs to family Asteraceae, is a medicinal containing flavonoids, sesquiterpenes, coumarins and polyacetylenes as major constituents. Active components of Chamomile plant are Terpenoids- α-bisabolol oxide A & B, α-bisabolol, chamazulene, coumarins-umbelliferone, sesquiterpenes, flavanoids-apigenin, luteolin, quercetin and others are polysaccharides, phytoestrogens, choline, tannins and anthemic acid. The plant essential oil containing α-bisabolol was tested by disc diffusion method for having antimicrobial capacity and it was resulted into strong antibacterial agent against wide spectrum of bacteria and antifungal agent against *Candida* albicans [95]. In a comparative study of two species of Chamomile plant it was concluded that essential oil of these plants possess strong antibacterial property [96].

Ribes nigrum

Ribes nigrum, of family Grossulariaceae berries contain anthocyanin, anthocyanoside, astragalin, α-linolenic acid, γ-linolenic acid, omega-3 fatty acids, phenolic compounds, quercetin and polyphenolic antioxidants. In vitro study of four species of Ribes nigrum revealed the antimicrobial activity of methanolic extract or juices and the data resulted that it has antifungal and antibacterial potency [97]. In another study essential oil extracted from the leaves of Ribes nigrum was evaluated for antimicrobial potency against 14 microbial strains by broth dilution method and it was concluded that it is a potent antimicrobial agent [98].

Trillium grandiflorum

Trillium grandiflorum belongs to family Asteraceae, contain saponins, sapogenins, flavonoids, starch, fixed oil, tannins and an acid. The antifungal property of this plant is due to the presence of spirostanol saponins. In a study the anticandida (*Candida albicans)* activity of this plant was demonstrated because of (3β,25*R*)-spirost-5-en-3-yl *O*-6-deoxy-α-l-mannopyranosyl-(1→2)-*O*-[6-deoxy-α-l-mannopyranosyl (1→4)]-β-d-glucopyranoside with MIC 1.56 µg/ml [153]. In an investigation it was concluded that *Trillium* has a potent activity in treatment of BV and ethanolic extract of rhizome possessed antifungal activity against *Candida albicans* [99].

Tribulus terrestris

Tribulus terrestris of family Zygophyllaceae, chemically contains mainly saponins, steroids, alkaloids, sterols, flavonoids, lignin amides, minerals and cinnamic acid. Main active components of this plant are saponins: dioscin, prototribestin, protodioscin, diosgenin, flavonoids: Kaempferol, astragalin, quercetin. The antimicrobial activity of *Tribulus terresteris* was evaluated and demonstrated in many studies. It was reported that methanolic extract of this plant parts have antibacterial properties and can be used against a wide range of bacteria including *Escherichia coli & Enterococcus faecalis* at concentration of 2-4 mg/ml [100]. In a study seven saponins isolated from this plant were evaluated for antifungal activity against *Candida albicans* & other species, resulted into proving it a potent antifungal agent. Eight isolated saponins isolated from Tribulus plant were used in a vaginal infection animal model tested on 40 rats infected from BV & VVC, resulted that the active components interfere with the hyphae formation in *Candida albicans* and other *Candida* species. Antibacterial property of this plant was resulted by the presence of saponins which cause damage to the cell membrane and leads into leakage of cellular structures and cell death [101-102].

Calluna vulgaris

Calluna vulgaris, family Ericaceae has phenolic compounds: chlorogenic acid, linolenic acid, linoleic and palmitic acid, eicosapentarenoic acid, triterpenoids: oleanolic and ursolic acid. Its organic and aqueous extract was used for evaluating antimicrobial activity in vaginal microbiota against Gram negative microbes *Gardnerella*

vaginalis & E. coli and many other microbial strains and resulted in strong potency of extract as antibacterial agent [103].In a bioassay phenolic compounds myricetin-O-rhamnoside & myricetin-3-O-glucoside extracted from *Calluna vulgaris* were identified for having antibacterial property. In vitro antifungal activity of *Calluna vulgaris* ehanolic, aqueous and ethyl acetate extract was evaluated in vaginal microbiota and it was concluded that it has antifungal activity against *Candida albicans* species [104].

Saturella hortensis

Saturella hortensis belongs to family Lamiaceae and main antimicrobial components of this plant are thymol, carvacrol, cuminal, carvone, p-cymene and γ-terpinene which are responsible for its bactericidal and fungicidal properties. In vitro study was performed in which Saturella essence were used against *Gardnerella vaginalis & Candida albicans* isolated from vaginal swab of a patient. It was demonstrated in the study that it has strong potency against these two microbes in a systemic way [105]. Plant essential oil was analyzed by broth micro well dilution method against ten species of bacteria in a study, resulted that it shows antibacterial activity against all microbes with high microbicidal efficacy and MIC/MBC ratio was identified 0.78-25 µl/ml [106].

Eucalyptus globulues

Major antimicrobial components of *Eucalyptus globules* belongs to family Myrtaceae included [1, 8]-cineole or eucalyptol, aromadendrene, α-pinene, α-terpineol or o-cymene. Eucalyptol isolated from leaves of eucalyptus plant is mainly responsible for its antibacterial properties and identified as a potent agent against a wide range of bacteria in a study [107]. The antimicrobial potential of eucalyptus essential oil was evaluated for six vaginal bacteria isolates and two vaginal fungal isolates in antimicrobial assay study and it was concluded that eucalyptus oil was performed as a potent antifungal and antibacterial agent against all isolated microorganisms and its activity was compared with various commercial antibiotics which demonstrated its potency as a strong antifungal and antibacterial agent in vaginal infections [108].

Carum carvi

Caraway, *Carum carvi*, of family Apiaceae contains oxygenated sesquiterpenes, oxygenated monoterpenes, monoterpene hydrocarbons, saturated and unsaturated fatty acids, ketones, aldehydes and esters as antimicrobial agents. Essential oil of caraway seeds was evaluated for antimicrobial potency against ten pathogenic bacteria and six fungi. The antifungal and antibacterial screening of essential oil of seeds showed inhibition of mycelia growth at 100 ppm for all tested fungi and it showed promising activity against all the tested bacteria species with MIC 100-300 ppm and MBC 200-400 ppm [109]. Pharmacokinetic study was evaluated in a comparative study with various commercial antibiotics and it was concluded that Caraway act as potent agent and having potent antimicrobial properties [110].

Conclusion

Ayurvedic herbs have been used for centuries to treat various diseases and these are considered to be more effective and safe I treating chronic diseases and infections. Vaginitis is the main problem and it has huge impact in quality of women's life. Recent advancement and investigations of herbs have been identified for their promising effectiveness in treatment of vaginitis and development of formulations by using antimicrobial ayurvedic herbs is of major concern to improve the distribution and controlled release of the drug to enhance the retention of drug in vaginal tract, particularly for the treatment of BV and VVC. These plants contain those antimicrobial properties which can lead to development of such formulations which can be useful therapeutically and with lower risk of adverse effects. These antimicrobial plants may have significant clinical effects in treatment of resistance showing microorganisms. It is concluded that ayurvedic plants can be used as antibacterial and antifungal agents in development of formulations for the treatment of vaginal infections.

Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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