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REVIEW ON VULVO-VAGINAL CANDIDIASIS AND MEDICINAL PLANTS TARGETING VULVO-VAGINAL CANDIDIASIS

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Abstract
Vulvovaginal candidiasis is an infection of the Candida genus infecting vagina or vulva with a number of clinical symptoms that can occur acutely, chronically or episodically. An approximate 75 % of women have at least one episode of vulvovaginal candidiasis, and 40% to 50% have two or more episodes of vulvovaginal candidiasis, followed by vulvar symptoms such as vaginal discharge, itching, burning, pain and odor. The search for anti-Candida agents with new pharmacological targets is considered as the main therapeutic strategy to prevent and treat these types of infections because they are inherently resistant to antimicrobial drugs such as azole derivatives. Purpose of this study is to review the vulvo-vaginal candidiasis medicinal plants used to treat candidiasis. Different databases such as Google scholar and Science direct etc. were searched for collection of data. Various medicinal plants were found effective in the treatment of candidiasis. This review indicates that medicinal plants possess potential anti-candidal properties and suggests screening the potential of plants possessing broad-spectrum anti-candidal effects against emerging Candida infections.

Key words: Vaginal candidiasis, anti-candida activity, Medicinal plants, Treatment

Introduction
With changes in the medical and surgical management of patients over the past three decades, fungi have emerged as a major cause of human disease. Among dispersed fungi, candidiasis is most frequent, causes by Candida albicans. The C. albicans is more pathogenic and cause more infections compared to other mycoses. The other term used for candidiasis is candidiasis and moniliasis [1].

Candida infections present in numerous ways. The pathogenesis and prognosis of candidial infections depends on host immune condition and also differ to a great extent according to disease presentations [2]. Vaginal candidiasis is a most prevalent reason for gynecological condition seen in primary health care services. Disease is more frequently associated with substantial morbidity, discomfort, healthcare cost and painful intercourse; conversely, it is hardly ever life threatening. This problem must affect 75% of women once in their whole lifetime [3]. C. albicans is frequent colonizer and responsible for Vulvo-vaginal candidiasis. C. albicans exhibits the capability to stay alive and propagate in physiological life-threatening pH, osmolality, accessibility of nutrients and temperature. This adaptability causes the C. albicans to live both as commensal colonizer of vagina and as a pathogen [2].

VVC is classified into complicated and uncomplicated cases. Uncomplicated cases are infrequent episodes of infections caused by C. albicans [4]. Other species of candida may cause the complicated cases. Complicated infections of VVC are serious infection that occurs during pregnancy. They may also be happening in immunosuppression or diabetes. Recurrent VVC (RVVC) is a form of complicated infection. RVVC is defined as four or more than four episodes of VVC per year [5].

Epidemiology of Vulvo-Vaginal Candidiasis

Vulvo-vaginal candidiasis is caused by C. albicans (85%-90%). C. glabrata and C. parapsilosis are responsible for 5%-10% of cases. Vulvovaginal Candidiasis is fungal infection of mucosa of the urinary and genital tract of women. It is caused by Candida albicans [1].

Approximately three-quarters of females throughout their reproductive age suffer in at least one episode of vulvovaginal candidiasis (VVC) and about half suffer in two or more episodes. The most frequent pathogen involve is Candida albicans, which is isolated in, 85 to 90% of all the cases. Asymptomatic colonization is also common. In one of the research studies it is found to be asymptomatic in one-third of women and was identified in 70% of women during a one-year observation period [1]. About, 5-10% of women suffer recurrent VVC, which is defined as three or more incidents of VVC annually [6]. Approximately 5 to 8% of VVC cases are recurrent. C. glabrata and non– C. albicans species are found in 10 to 20% of these cases. However, it is quite difficult to assess the precise incidence of VVC due to infrequent self-treatment with over-the-counter medications. Furthermore, the management and diagnosis are entirely based on signs and symptoms without any tests to confirm the diagnosis [1].

Epidemiologic figures showed that, at age 25, half of all college females suffer one episode of VVC and an essential risk factor is found to be initiation of sexual activity. Among college females, VVC is more frequent in African America than white women. Several other factors are important in the progression of VVC and RVVC. Common factors are diabetes, estrogen use, antibiotic, immunosuppression, and behavioral factors. Antimycotic therapy is less effective in Diabetic patients, and the disease is prevalent caused by C. glabrata infection. Some females who have RVVC show an impaired tolerance for glucose instead having a similar incidence of conspicuous or preclinical diabetes than controls. Current antibiotic use is also a contributing factor in the development of VVC, because colonization can occur causing episodic events occur. In some women, VVC may be due to systemic immunodeficiency caused by the use of corticosteroids drugs. Candida infection is frequently occurring in HIV-infected females. Immunosuppression rarely causes VVC in female, but its evaluation is considered in the clinical practice. A variety of behavioral factors is proposed as a cause of VVC and RVVC. The factors such as contraceptive use particularly oral contraceptives, diaphragm, spermicide, and use of an intrauterine device contributed in the development of VVC infection. Douching also is a risk factor of RVVC caused by C. glabrata [7].

Prevalence of Vulvo-Vaginal Candidiasis in Pakistan

It is calculated that, yearly, 2,821,440 females of reproductive age suffer from repetitive vulvovaginal candidiasis in Pakistan. Due to intake of self-medication and over- and under-diagnosis with over-

the-counter topical antifungal agents, population-based figure regarding the incidence and prevalence of vulvovaginitis in Pakistan is lacking. Our judgment in the study was determined using data by Foxman et al., who describe vulvovaginitis in ~9% of unselected women based on internet questionnaires. Jabeen et al have used a 6% rate, of 'yeast' infection in women. A study estimates the load of reproductive tract infection in urban females in Pakistan showed vaginal candidiasis as second most frequently occurred genital infection, with a prevalence of 7–12%.

Bushra et al., conducted the prospective, observational study at Al-Sayyed Hospital, Rawalpindi, Pakistan, and found that C. albicans is the foremost species responsible for Candida infections, but non- albican Candida species are also common (Bushra et al., 2017). Parveen et al., determine the rate of vaginal candidiasis in pregnant women attending routine antenatal clinic. Out of total 110 pregnant women the vaginal candidiasis was found to be 38%, in which 27% were symptomatic and 11% were asymptomatic group [9].

Khan et al., conducted the descriptive study to determine the frequency of dyspareunia related with vaginal candida in sexually active women of 16-22. Out of two hundred sexually active females' positive culture of candidiasis was 54% whereas negative culture was only 17%. Dyspareunia was remarkably associated with Candida infection [10].

Vaginal Flora

The vaginal flora consists of bacteria that belong to genus lactobacillus. The lactobacillus is a harmless bacterium and prevents the growth of other harmful microbes. The lactic acid production lower down the pH of vagina that why the harmful pathogens do not grow. The lactobacillus adheres the vaginal epithelium thus preventing the long-term colonization. Due to this the pathogens do not harm the vaginal epithelium [13]. It is found that 96% of Lactobacillus species in vaginal flora produced H_2O_2. L. jensenii and L. vaginalis form more H_2O_2[15]. In summary, hydrogen peroxide is the main antimicrobial component produce by lactobacillus [15] and there seems to be an association between H_2O_2-producing lactobacilli and normal vaginal microflora [14].

Pathogenesis

Candida albicans is commonly isolated fungal pathogen in humans. It mostly causes the infection of oropharyngeal or urogenital tracts [16]. It also causes systemic infection. When it enters the bloodstream, it invades and proliferates in the vital organs such as kidney, brain and heart. Infection of vital organs can be life-threatening. Systemic infections are most frequent in immunocompromised patients, such as in AIDS patients. C. albicans is dimorphic fungus that usually propagates through blastospore phenotype called blastoconidia. Blastospores are oval-shapes, mono-nucleated cells and proliferate via by cellular budding [17]. On environmental stimuli, C. albicans is change into either one of two filamentous forms i.e. psuedohyphae and hyphae. Psuedohyphae are elongated, ellipsoidal cells and attached to one another. Hyphae have cylindrical cellular morphology. These hyphal are separated by septal walls and not have syncytial composition. Psuedohyphal and hyphal forms are filamentous. Recent studies proposed that the filamentous forms of C. albicans are virulence and associated with pathogenicity [17].

C. albicans is commensal organism and routinely present in healthy mucosal micro flora. It became pathogen in certain circumstances. There are several environmental circumstances that involve in hypha formation and thus involve in initiating infections. The filamentous form allows the pathogen to adhere and invading vaginal epithelial cells thereby producing virulence factors [18]. Virulence factors of Candida albicans depends on the type of infection, the site and stage of infection, and nature of host response [18].

Host Defense against Vaginal Candidiasis

Candida albicans infection results, the majority of healthy adults develop adaptive immunity that is specific to candida. The adaptive immunity is identified by the presence of mucosal antibodies or

serum antibodies, delayed skin test reactivity and in vitro T-cell responses [19]. The cause of the development of adaptive protected responses in the anticipation of Candida infections is not completely understood, but the current research demonstrates that this seem to be insignificant (Calderone). Since the last twenty years, number of studies has been conducted to determine host-pathogen interactions and mechanism of urogenital infection by C. albicans. Regardless the numeral researches remain idiopathic studies conducted to recognize the defensive host mechanisms contrary to vaginal inflammation still the cause is unknown that in what way our defense system deals with strong pathogenic commensals of urinary and genital tract. Gastrointestinal, Oropharyngeal, esophageal and genital infections are known as mucosal candidiasis [19]. However, prior to epidemic of AIDS, researchers believed mucosa of all body part equally vulnerable to Candida infection via same phenomena [19]. Large number of AIDS patients suffer in T-cell immuno-suppression have candidiasis of mucosa; therefore, experimental models showed T-cells suppression having strong association in developing Candida infection.

Clinical and animal studies about recurrent VVC showed that there has been no part for local cell-mediated immunity (CMI) at vaginal mucosa. Fidel et al. conducted the study to search mechanism or factors that prevent CMI protect the vaginal candidiasis. A research study exposed a robust down regulatory cytokine, TGF-β, occurs in mucosa of vagina. Its secretion was increased by vaginal epithelial cells in reply to infection.

Further cytokines affecting Th1/Th2 cells were tremendously low at the time of infection. Fidel et al. study explained somehow the obvious lack of cell mediated immunity that protects the vaginal infection. Fidel has recommended that meanwhile C. albicans normally live in vagina, the progression of immunoregulation to evade long-lasting inflammation in reproductive host tissue, would make stronger symbiotic relationship [20]. Research revealed that there has been no role of innate immunity in the protection of vaginal mucosa and no association of natural killer cells and polymorphonuclear neutrophils in infection [19]. Fidel et al. during his studies showed that epithelial cells of vagina from humans and mice possess capability to hinder C. albicans growth [19]. This inhibitory activity is due to the acid-labile protein attach to epithelial cell of vaginal wall causing initiation of unknown intracellular events after becoming in contact with C. albicans resulting in the inhibition of its growth [21].

Predisposing Factors

Broad-spectrum antibiotic normally destroys vagina flora, such as Lactobacillus. These bacteria usually assist to limit yeast colonization [6]. Estrogen hormone produced in high amount during pregnancy which makes women more likely to develop yeast infection. Uncontrolled diabetic has increased rates of infection. The hazard of VVC is too increased in patients having poor defense functions for instance, AIDS or HIV, or on chemotherapy. In which the body's defense system, is not capable to efficiently control the spread of Candida fungus [6].

Clinical Presentation and Diagnosis of Vulvo-Vaginal Candidiasis

The clinical presentation includes white curdy discharge, itching, soreness, erythema, edema, burning during micturition and dyspareunia.

Yeast infections may cause uneasiness but hardly ever cause serious health problems. Sometimes vaginal yeast infections often resolve without taking medications, usually when menstruation starts. Recurrent infections might be difficult to prevent or treat [21].

Diagnosis of VVC usually is done by pelvic examination. Thick white curdy discharge, vulvar pruritis, redness and swelling of vulvar and vaginal tissues are the diagnosis of VVC. Vaginal secretions of pH < 4.5, yeast budding and pseudo hyphae may be observed on wet mount. Gram stain show the presence of polymorphonuclear cells, yeast budding and pseudo hyphae [22]. Importantly,

genital itching is the important sign of disease; about 50% women with vulvar itching has VVC. Cultures are therefore helpful in women with consistent presentations of vulvar pruritus as many females may be infected with non-albicans Candida species.

Polymerase chain reactions (PCR) have greater compassion and specificity, but are expensive showing no advantage in symptomatic women. Yeast bodies can be showed in 25% of cytology samples from patients with culture positive, characteristics VVC [23].

Quality of Life

Frequent candidiasis infections can disturb life quality. Fashion-sensible women may wear tightfitting cloth, legging, under wears; these tight-fitting cloths may adverse the symptoms of VVV. Research suggests that women with recurrent vulvovaginal candidiasis and its manifestations have considerable negative influence on work and social life [24].

Chapple (2001), conducted the study on South Asian women to determine the effect of vaginal candidiasis on the quality of women life. The study concluded that women suffering from vaginal candidiasis have continuous need to scrape, and this usually becomes difficult to disguise their complaints in public places; the symptoms make females feel irritable, discomfort irritated and humiliate, and express unwillingness to have intercourse with partners. They narrate their problems and hide the complications and uneasiness [25]. Females usually gets shy and do not discuss the issues, especially with a male physician, and usually take self-medications [25].

Vulvo-Vaginal Candidiasis Classification

The severity of complications, such as pruritis, soreness, vaginal discharge, and redness, was allocated the score based on the following scale: absent= 0; mild=1; moderate=2; severe=2. Patients with score 7 or above were selected as having SVVC. Uncomplicated VVC have mild to moderate symptoms and caused by C. albican normally, in no pregnant women [26].

Treatment

Topical and oral formulations are available for the treatment of VVC which includes imidazole's and triazoles formulations. Azoles formulations have better results than nystatin vaginal sponge or creams. Topical drugs prescribed for 7 to 14 days. Single dose drugs are also available.

Topical azoles have no systemic adverse effects and toxic effects in pregnant females. The oral azoles available are fluconazole, itraconazole and ketoconazole. Fluconazole is (150 mg prescribed as a single dose) only permitted by the FDA for VVC in the US. Oral azoles are also effective like topical agents and no side effects. Uncomplicated (90%) vaginal disease can be efficaciously treated with any available topical or oral antifungal drug, including short duration course and single dose [2].

Side Effects

The side-effects of oral treatment for yeast infection include; Abdominal pain, Headache, Diarrhea, Dyspepsia, Nausea, Rash. An oral treatment is contraindicated in pregnancy, breast feeding or in suspected pregnancy.50% of women will experience irritation or burning on application of cream. Pessary should be taken carefully in pregnant females in order to prevent cervix from damage.

Anticandidal Activity of Medicinal Plants

The prevalence of life-threatening infections cause by pathogenic microbes has increasing worldwide. This life-threatening agent causes considerable morbidity and mortality in immuno compromised patients in especially develops countries [27]. Even though varieties of antimicrobial agents have been available, but pathogenic microbes develop a strong resistance to these antimicrobial agents [28]. In addition, several antifungal agents have undesirable side effects [29].

It is essential to or more efficacious and less toxic antifungal compound that would overcome the problems. The pathogens causing skin problems are mostly dermatophytes and candida species [29], [30]. Under certain conditions, C. albicans causes oral, vaginal, and systemic candidiasis in immune compromised patients [31]. Approximately, 75% of women suffer once in vulvovaginal candidiasis (VVC) during their whole life time. C. albicans also affect the esophagus and a very serious condition, a fungemia called candidemia [22]. It is also involved in causing infections like mucosal candidiasis, vaginal infections, skin infection and diaper rash [32], [33].

There are limited numbers of antifungal agents available for C. albicans infections. The available agents result in adverse effects, relapse of Candida infections and are expensive [34]. With the intention to overcome the problem of limited availability of drugs required to treat candidiasis, folk medicine derived from plants are still being used [35].

This motivates the search for new and active anti-C. albicans agents from the plant sources. Medicinal plants contain valuable therapeutic agents that have beneficial effects on the human body [36]. Owing to all these benefits, medicinal plants continue to be a most important resource of novel compounds. Currently, the non-as systematic use of available antimicrobial drugs has caused serious drug resistance in human pathogenic microorganisms [37]. These circumstances lead scientists to seek out new and valuable antimicrobial compound to replace the present regimens [38].

Euphorbia hirtaL.

Methanol extract of E. hirta leaves were evaluated for its anticandidal activity. A transmission electron microscopy (TEM) study of the C. albicans cells showed the major microstructural changes in the microstructure of C. albicans. The changes include in the morphology, cell lysis and collapse of yeast cells. While control group showed no change in morphology of Candida cellsand no yeast cell collapse happen [39]. In another study the methanol extract of E. hirta showed inhibitory effects against C. albicans [40]. Extract of seed of E. hirta exhibited anticandidal activity against C. albicans in the electron microscopy examination [39].

Peganum harmala L.

In one of the research steady antifungal effect of P. harmala alone and in combination with six honeys from different regions of the Algeria against C. albicans strain was assessed showing that the powder of P. harmala and honey possess significant activity against the tested albican. The combination of P. harmala with 6 honeys samples exhibit significant potential against organism [41, 42]. It is observed that synergistic action is happen between honey and tested medicinal plants [43].

Allium sativum Linn., Zingiber officinale Roscoe.

Lozenges extract of garlic and ginger exhibited inhibitory activity against albicans strains of C. [44].

Hybanthus enneaspermus F Muell.

The methanol, petroleum ether and chloroform extracts of plant H. enneaspermus, were evaluated against C. albicans and C. tropicalis by using well diffusion method. Methanol extract showed significant antifungal potential on both tested pathogens C.albicans and C. tropicalis [45].

Cinnamomum cassia (Nees) Nees ex. Blume.

The methanol extract of C. cassia bark exhibited significant antifungal effect against C.glabrata, parapsilosis and Candida guilliermondii [46].

Withania somniferaL. Dunal

The toluene, ethanol, Iso propyl alcohol, acetone and hexane extract of W. somnifera flower and leaf was evaluated against two fungi C. albicans and A. flavus. The effect of the extract was comparable to that of ketoconazole, the standard antifungal [47].

Areca catechu
Pahadia et al., investigated hydro alcoholic extract of Areca Catechu for antimicrobial activity against two bacteria species E. Coli and S. aureus and two fungi species (Candida albicans and Bacillus subtilis) and found that hydro alcoholic extract showed the largest zone of inhibition against Candida albicans [48].

Punica granatum
Anibal et al., found that the ethanolic crude extracts of the different parts and whole fruit of Punica granatum, possess anti-candidal activity. Their study revealed the potential antifungal effects against cells of Candida genus, and phyto-constituents might be responsible for the changes in the cell morphology and as well as in structure [49].

Quercus infectoria
Jamil (2014) tested antifungal activity of some plant extracts and found that all studied plant including Q.infectoria exhibited significant activity against Candida albicans[50].Baharuddin et al., evaluated Q. infectoria galls extract for anti-candidal activity. He prepared extract in methanol and ethanol. Candida species selected were Candida albicans, Candida krusei, Candida glabrata, and Candida tropicalis. Both the extracts showed significant anti-Candida activity and theysuggested that Q. infectoria gall extracts are good source to find new anti-candidiasis agent [51].

Elettaria cardamomum, Amomum sublatum
Aneja et al., studied the antimicrobial activity of methanol, ethanol and acetone extract of Amomum subulatumand Elettaria cardamomum fruit extracts against Staphylococcus aureus, Streptococcus mutans, Lactobacillus acidophilus, Candida albicans and Saccharomyces cerevisiae. Both the extract showed significant activity against microorganism [52].

Conclusion
Multiple drug resistance in human pathogenic microbs has now been caused by the indiscriminate use of industrial antimicrobial drugs. The strains of resistance of C. Albicans have become a source of serious health problems and need new antifungal agents to resolve this problem. This has prompted scientists to look for new and efficient antimicrobial agents in order to replace existing regimens. This review indicates that medicinal plants possess potential anti-candidal properties and suggests screening the potential of plants possessing broad-spectrum anti-candidal effects against emerging Candida infections.

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