

Candidiasis: predisposing factors, prevention, diagnosis and alternative treatment

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SUMMARY

Candidiasis is the most common opportunistic yeast infection. *Candida* species and other microorganisms are involved in this complicated fungal infection, but *Candida albicans* continues to be the most prevalent. In the past two decades, it has been observed an abnormal overgrowth in the gastrointestinal, urinary and respiratory tracts, not only in immunocompromised patients, but also related to nosocomial infections and even in healthy individuals. There is a widely variety of causal factors that contribute to yeast infection which means that candidiasis is a good example of a multifactorial syndrome. Due to rapid increase in the incidence of these infections, this is the subject of numerous studies. Recently, the focus of attention is the treatment and, above all, the prevention of those complications. The diagnosis of candidiasis could become quite complicated. Prevention is the most effective “treatment”, much more than eradication of the yeast with antifungal agents. There are several aspects to consider in the daily routine that can provide a strength protection. However, a therapeutic approach is necessary when the infection is established and, therefore, other alternatives should be explored. This review provides an overview on predisposition factors, prevention and diagnosis of candidiasis, highlighting alternative approaches for candidiasis treatment.

Keywords: Candidiasis; predisposing factors; diagnosis; prevention; alternative treatment; therapeutic approach

1. Introduction

Candida species are involved in the main opportunistic yeast infection in the world, candidiasis, but among the species of the genus, *Candida albicans* continues to be the most common. Although this yeast is responsible for approximately 50-90% of human candidiasis, *C. albicans* is part of the commensal flora of more than half of the healthy population. Colonization by this yeast is beneficial to the host, because not only limits the growth of other opportunistic pathogenic fungi, but also promotes the functioning of the immune system [1–5].

In the last two decades, it has been observed a considerable increase in the incidence of deep fungal infections, not only in immunocompromised patients, but also related to nosocomial infections, and even in healthy population [4,6–15]. Thus, with the increased incidence of deep fungal infections (chronic candidiasis), the primitive idea that they were related to a restrict number of pathogenic fungi and specific geographical area was completely changed. Furthermore, with the rapid increase of candidiasis incidence, other *Candida* species and microorganisms besides *C. albicans*, have been involved in such infections [2,5,6,16–18]. The balance between *C. albicans* and non-*Candida albicans Candida* (NCAC) species determine the profiles associated with virulence. So, the most common species are *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. dubliniensis*, *C. parapsilosis*, *C. orthopsilosis*, *C. metapsilosis*, *C. krusei*, *C. famata*, *C. guilliermondii* and *C. lusitaniae*. Other relevant fact associated with virulence is their capacity to form biofilms with other species, which together with the presence of teleomorph forms (sexual phase of fungi in which the same biologic entity could have two different scientific names), difficult the treatment and alter the susceptibility profiles to traditional antifungals agents [3,9,10,13,19–22].

Although biofilm formation lead to an increase in the persistence and resistance to antifungals, other factors, like adaptation to the pH level, adherence of yeast cells to the host cells, proteolytic enzymes, phenotypic switching, and morphological transition (ability of yeast to change morphologically from blastoconidia to pseudohyphae and hyphae), affect the strategies to prevent and treat this pathogenic infection. Despite *C. albicans* is still the focus of a wide range of studies, some researches have been demonstrated a significant increasing of infections caused by NCAC species. There are some associated factors with the virulence. The presence of hemolytic exoenzymes is very important because it allows an acquisition of iron ions from hemoglobin, by yeasts. Moreover, there is a positive correlation between this metal and the establishment and dissemination of infections. The metabolic activity and the capacity of biofilm formation also appear like important correlating factors of pathogenicity, once they interfere in the level of virulence expression and in the level of resistance to antifungal agents. A high metabolic activity of NCAC species was demonstrated, which could be a cause of the increasing frequency of fungal infections related to these yeasts, including the possibility of systemic infections. According to these facts, it was possible to demonstrate the complexity of the epidemiological chain of colonization – infection processes. Like expression of virulence-associated factors are strain dependent, an accurate identification of yeasts and their virulence-associated factors is essential to detect the emergence of yeasts and to predict the antifungal agents response, considering the increasing tolerance and antifungal resistance mechanisms [1,2,20,22–24].

Due to the increasing evidence of antimicrobials and antifungals resistance, several studies have been developed towards the identification and evaluation of efficient alternative therapeutics. Natural products, in particular, those from plants, have been

explored with that purpose; the therapeutic potential of phytochemicals, the synergistic effects among them and the related mechanisms of action have been extensively studied [25–35]. Nevertheless, many extracts/compounds from plant origin remain unknown and could constitute an alternative or complementary treatment for candidiasis.

Considering all the stated, candidiasis is indeed much more than *C. albicans* overgrowth and, therefore, the most relevant topics involved in this fungal infection are presented and discussed in the present manuscript, namely: description of candidiasis and their main classes, predisposing factors, diagnosis (signals, symptoms and methods), prevention and alternative treatment (diet and nutrition, enhancing immunity system, detoxification, natural anti-yeast agents and therapeutical approach) (**Figure 1**).

2. Description of candidiasis and main classes

Yeasts are part of the commensal fungi flora of the healthy population. However, with the significant and rapid increase in the incidence of opportunistic fungal infections, the focus of attention has been the treatment and, above all, prevention of those complications. Although other fungi species are involved in nosocomial infections, like *Aspergillus* spp., *Zygomycetes* spp., *Fusarium* spp., *Scedosporium* spp., *Cryptococcus* spp., *Trichosporon* spp., *Geotrichum* spp., and *Rhodotorula* spp., *C. albicans* continues to be the most prevalent, counting to 50-90% of the isolates from fungal infections [1,9,10,22,36,37].

Candida albicans is a common species in genitourinary and gastrointestinal tracts of healthy people, but it is also able to cause problems, mainly vaginal infections in woman. This microorganism is responsible for mouth and mucocutaneous infections. However, it has been frequently observed an evolution to chronic forms, generating complicated infections, such as septicemia, endocarditis, meningitis, and peritonitis,

especially in patients with reduced immune function or taking antibiotic therapies. Some reports described that oral candidiasis appeared as early as the 2nd century A.D. by Galen, who described it as *aphthas albus*. Other reviews reported that it was not until the mid-19th century that clinical nature of oral candidiasis was defined and the etiologic agent identified. Notwithstanding, and despite the other types of mucocutaneous candidiasis, oral candidiasis is still the most frequent. There has been a wide variety of synonyms used for the members of genus *Candida*, 166 synonyms being recognized for *C. albicans* worldwide. Actually, there are between 150 and 200 species recognized in the genus, but only seven *Candida* species are classified as having major medical importance, being *C. albicans* the most important one. Other *Candida* species like *C. tropicalis*, *C. glabrata*, *C. parapsilosis*, *C. stellatoidea*, *C. krusei* and *C. kyfer* are encountered in human infections [2,5,15,38,39].

The increase in the number of organ transplantations, the rise of immunocompromised individuals and the use of invasive devices (catheters, artificial joints and valves) are a major factor that contributes to higher patient's susceptibility to nosocomial infections. Despite being *Candida* species the fourth leading cause of hematogenous infections, these species are not exclusively related to nosocomial infections (candidemia), because the same infections can also occur in healthy population. There are several classes of candidiasis, which have become more common in recent years [4,6,13,17,40,41]. Depending on body location, the mucocutaneous candidiasis can be classified as: genital candidiasis, intrauterine candidiasis, anal candidiasis, nails candidiasis and oral candidiasis (**Figure 1**).

2.1. Genital candidiasis

Vulvovaginal candidiasis (VVC) is the most frequent type of genital yeast infection. Approximately 75% of women experience, at least once in their lifetime, an episode of VVC, 40-50% experience at least one additional episode of infection, 20-50% remain without any clinical manifestation, and lastly, 5% experience recurrent VVC episodes [9,10,42,43]. Although, not being a threat to life, it is unpleasant and problematic, causing a variable degree of itching and whitish discharge, abundant and flocculent. This infection is very common in pregnant women, especially in the last trimester of pregnancy, when a variation of progesterone, estradiol and glycogen, associated with an increase in vaginal pH, favors the emergence of these infections. In this case, special attention should be given due to the potential occurrence of contamination of the fetus in the uterus, or even the child during childbirth. On the other hand, it has been observed that, in individuals with diabetes, the incidence of vaginal candidiasis is higher. Similarly, patients submitted to broad-spectrum of antibiotic therapy, used to treat bacterial infections, and even the use of oral contraceptives, are also important factors associated with higher rates of incidence of VVC [42,44–47].

In men, balanitis, which usually appear after sexual contact, is characterized by the appearance of a rash, more or less prickly, followed by small pustules on rocking groove-preputial discharge, more or less abundant. Although this kind of injury is well defined, in particular cases it can extend to the groin and perianal region. The major factors associated with this type of infections are antibiotic therapies, diabetes and vaginal secretions of the sexual partner [1,17,48].

2.2. Intrauterine candidiasis

This type of infection is frequent during pregnancy. It is important to avoid the occurrence of this type of intense vaginitis in the last few weeks of pregnancy, because

it can complicate and extend to the uterus, infecting the child before birth. At childbirth, or in the first hours of life, it can be observed a widespread rash, maculopapular or pustular-vesicular. During the following weeks after birth, the clinical status may be complicated, extending to other body locations, which usually are treated with local antibiotics [5,42,43,49].

2.3. Anal candidiasis

This type of infection is characterized by intense itching/pruritus, accompanied by burning sensation, and localized erythema around the anus. Skin may appear macerated with circumscribed lesions, which may eventually invade the intergluteal groove [49–51]. This type of infection is most common in children; despite the frequency in women due to the use of hormonal contraceptives, intimate hygiene products, clothing and their practice of oral and anal intercourse, functioning as transient colonization of local organisms shed from the intestinal tract. As candidiasis can be sexually acquired, males can be affected, because they may acquire infection from the gastrointestinal tract of their partners. However, in some cases, the factors causing that condition are still unknown, but seems that the main problem of this pathogenesis are secondary infections caused by aerobic and facultative anaerobes microorganisms, such as *Staphylococcus* spp., *Streptococcus* spp. and *Escherichia coli* [48,50–52].

2.4. Nails candidiasis

Candida species are not considered normal yeasts on nails flora. Therefore, this type of infection is a sign of colonization (secondary growth) despite primary infections of nail fold and nail bed with *Candida* species may also occur, which are related to a disease of the nails. Onyxisdystrophy or periungual tissue is related to nail disease. This type of

infection may appear, like paronychia and onychia. The paronychia is characterized by an inflammation, more or less painful, in peripheral skin nail, which appears red and brilliant. The predisposing factors are essentially, sex, different traumas (*e.g.*, in manicure), professional activity and hormonal variations. Although infrequent in males, this infection can appear in cooks, confectioners and employees of canning factories [1,17,49].

Usually, the nail injury itself, or onyxia (ingrown nail), is secondary to paronychia. It is characterized by a progressive striation, dyschromias (discoloration) and opacity of the nail plate, which ultimately becomes crumbly. This infection appears abruptly and painfully, leading to detachment of the nail and can spread to other nails. Still, it can be observed fungal colonization in interdigital areas, by *Candida* species, commonly known as digital intertriginous. Preferentially, it is located in the hands and between the ring and middle fingers, although it can also appear in the corners of the fingers. It is commonly associated with professions or occupations in which there is a frequent contact with water. The injury erythema-scaly, itchy and exudative generally is well delimited peripherally and the epidermis appears detached. It is less frequent in feet, but can reach one or more commissures of fingers [1,17,49,50].

Intertriginous can still be located at the level of the submammary, mainly in obese women, suprapubic fold, groin and intergluteal cleft. It is characterized by the appearance of small vesicles and pustules which, by breakage, give rise to exudative red spots [1].

2.5. Oral candidiasis

Oral and perioral candidiasis is the more common type of acute mucocutaneous candidiasis. It is characterized by the appearance of small spots or whitish papules on

the tongue, inside the cheeks and in the palate, forming a creamy and very adherent layer mucosa. In some cases, it may extend up and cover the tongue, palate and pharynx, but also corners of the mouth could be reached. When this happens, it is labeled as angular cheilitis, being evidently a mucosal thickening and cracking. This type of candidiasis particularly affects people with immune system disorders and people with dental prostheses. It can be also found in patients receiving chemotherapy for cancer treatment, or taking immunosuppressive drugs to protect transplanted organs or in patients infected by HIV. In children and young people, it may be involved with oral ("thrush") and lingual disease. In addition, and despite being very rare, esophageal candidiasis can occur in patients infected by HIV and cancer [2,5,40,53–55].

3. Predisposing factors

Although *Candida* species is commensal to human organism and virtually present in healthy people, in the past two decades, an abnormal overgrowth in the gastrointestinal (GI), urinary and respiratory tracts has been observed [2,3,6,10,56]. During some days after childbirth, that species colonize the mucosa of GI tract (40-50%) and upper respiratory passages, as well as the mouth, pharynx and larynx. Normally, *C. albicans* lives smoothly in the inner warm creases and crevices of the GI tract (and vaginal tract in women). During pregnancy, *Candida* species colonization increases 30-40%, depending upon altered immune response, bacterial flora, positive variations of glycogen and pH levels; however, mostly during the normal life cycle, other factors can affect, such as hygiene and oral contraceptive use, which contributes to 5-30% of the infections. In men, up to 10% of these species are found on the genitalia, in the transitional zone, between the mucous membrane and the skin [1,13,18,40,44,46]. The overgrowth of *C. albicans* is an important cause of a wide variety of symptoms that

affect directly the wellbeing of individuals, therefore there is an urgent need to recognize candidiasis as a complex medical syndrome and evaluate the magnitude of the problem regarding prevention, which passes through the control of risk factors.

There are several factors that contribute to yeast infection, which means that candidiasis, and more especially chronic candidiasis, is a good example of a multifactorial syndrome. In the next steps the major and most important factors are explained namely, decreased digestive secretions, dietary factors, nutrients deficiency, impaired immune system and underlying disease states, impaired liver function, drugs and prolonged use of antibiotics, and altered bowel flora (**Figure 1**).

3.1. Decreased digestive secretions

In a normal organism the digestive secretions, such as hydrochloric acid, bile and pancreatic enzymes have an important role not only for a correct digestion, but also to prevent *Candida* overgrowth and its penetration into absorptive surfaces in the GI tract. Therefore, an improvement of digestive secretions is pivotal and, in some cases, is an important step to treat chronic candidiasis.

Pancreatic enzymes perform an important role as therapeutic agents enabling an efficient and complete digestion of proteins and other dietary compounds. Any dysfunction on this process leads to several problems, such as food allergies and formation of toxic substances. Furthermore, those enzymes are responsible for the preservation of the integrity of small intestine without parasites and other opportunist microorganisms (bacteria, yeasts, worms, protozoa), helping in the degradation of immunocomplexes [57,58].

The intake of antacids and antiulcer drugs has a high risk of GI infections, showing a *Candida* species overgrowth in the stomach. Therefore, to restore the normal digestive

secretions to proper levels, through the use of supplementary hydrochloric acid, pancreatic enzymes and substances that promote the normal bile flow, is highly important in the treatment of chronic candidiasis [57,58].

3.2. Dietary factors and nutrients deficiency

A balanced organism needs all the macro and micronutrients in right proportions and, therefore, any unbalanced diet affects the wellbeing of the body and potentiates growing and colonization of certain invaders. Some foods, like refined sugars, sucrose, fruit juice, honey and maple syrup have an important interference, functioning like growth enhancers. Moreover, foods with high content of yeast and fungi favor the growth of *Candida*; some examples are cheeses, alcoholic beverages and dried fruits. Another food group that stimulates growth is milk and dairy products, not only because of the high content of lactose but also, in some cases, due to the presence of antibiotics. Another important situation observed in most individuals with chronic candidiasis, is the presence of food allergies, therefore all known allergens should be eliminated [40,42,55,57,59–61]. Thus, dietary factors should be monitored according to the needs of each individual.

Some essential nutrients usually in deficit on chronic candidiasis are zinc, magnesium, selenium, essential fatty acids, folic acid and vitamins B6 and A [57,59,60,62]. Furthermore, iron has been considered as an essential micronutrient rather than a supplement, and there are several recent studies that indicate its important role in fostering and colonization by microorganisms, including *Candida* and other yeasts [9,42,63–66].

3.3. Impaired immune system and underlying disease states

Dysfunctions of the immune system turn the human body more vulnerable to various kinds of infections. Thus, it is of extreme importance to maintain the good conditions of the immune system in order to prevent overgrowth of certain microorganisms and opportunistic infections. By itself, a weak immune system is already sufficient to constrain the health and resistance of individuals, although with the current and prolonged/frequent consumption of antibiotics, chemotherapy, steroids, radiation, stress, as well as some environmental contaminants, the body is still more susceptible. Furthermore, any disease that, directly or indirectly, affects the immune system increases the body's susceptibility to the growth and development of pathogenic and opportunistic microorganisms. This is the case of some increasing prevalence diseases, such as cancer, diabetes, and hypothyroidism, that in addition to debilitate immune system of individuals, has led to a continuous and exacerbated prescription of immunosuppressant drugs [1,11,17,18,24,37,40,41,67–69].

In fact, the most common diseases that predispose to an increased sensitivity to *C. albicans* overgrowth are diabetes mellitus, cancer, leukemia, AIDS, thyroid dysfunction and other diseases, in which host defense mechanisms are suppressed or adrenal cortex steroids/antibiotics/other similar drugs are used (immunosuppressed patients) [6,10,12,24,25,37,40,53,56,70–72].

3.4. Impaired liver function

The modifications of the liver functions, as a result of injury or chemical causes, can change detoxification mechanisms. In this situation, as the liver is not able to perform its functions properly, toxins are absorbed by the intestine being accumulated, which affects more the liver and other organs function, and increase the body's sensitivity to chemicals. The accumulation of toxins in the body, as a result of liver damage,

associated with changes in the mechanisms of detoxification, also stimulates *C. albicans* overgrowth. One way to diagnose if liver function is affected or if the mechanism of filtration of the blood is not properly being done, is through the manifestation of symptoms (*e.g.*, psoriasis, premenstrual syndrome, among others) of chronic candidiasis outside of digestive tract [57,60,73,74].

3.5. Drugs and prolonged use of antibiotics

Antibiotics have been identified as a major responsible factor for the development of chronic candidiasis. Since its mode of action is based on the elimination of intestinal bacteria, responsible for preventing the growth of yeasts and other pathogenic organisms, as well as suppressing the immune system, antibiotics action result in a *C. albicans* overgrowth. This situation becomes shortly a vicious cycle: a person with an alteration of the immune system is more susceptible to infections and, consequently, more infections will appear – increasing the doses and frequency in the consumption of antibiotics. This fact not only favors the overgrowth of *C. albicans* and other yeasts, but particularly bacteria, which increasingly develop mechanisms of resistance against antibiotics [6,17,42,57,69].

An established fact is that, the indiscriminate use of antibiotics substantially increases the risk of developing complications caused by *C. albicans* and other resistant pathogens. This is particularly important in hospitals because nosocomial infections by resistant microorganisms often lead to lethal complications. Therefore, the reduction of the prescription and use of antibiotics can be considered an effective alternative to control and/or minimize the resistance problem. Another alarming factor is the widespread use of antibiotics in animals, which not only contribute to microbial

resistance in animals themselves, but also indirectly affect humans: antibiotic resistance and consumption of food contaminated by antibiotics [1,6,17,23,40,42,43,46,70,75,76].

The increasing incidence of Crohn's disease and other inflammatory bowel diseases, which previously were only prevalent in populations with a strong genetic component, is also an important factor [77–86].

Other drugs that could favor *C. albicans* overgrowth are corticosteroids, oral contraceptives and anti-ulcer drugs. It should be emphasized that individuals who take anti-ulcer drugs, like ranitidine and cimetidine, may develop *C. albicans* in the stomach [6,7,40,42,43,46].

3.6. Altered bowel flora

As described, drugs and other chemical compounds greatly affect the wellbeing of the body. If the liver does not work properly, products and metabolites resulting from poor digestion are accumulated in the body causing toxicity and, at the same time, favoring pathogenic strains, and also *C. albicans* overgrowth. Therefore, intestinal flora is of utmost importance in maintaining proper intestinal health and balance, being involved in the maintenance of nutritional status, immune system function, cholesterol metabolism, carcinogenic agents and aging. It is imperative to promote healthy and growth of beneficial intestinal flora, not only after taking antibiotics, but also in other situations. It should also be noted that chronic stress greatly affects the balance of intestinal flora and suppresses the immune system function. In other hand, especially in women, the hormonal balance is very important and the oral routine of contraceptive use is itself a predisposing factor to *C. albicans* overgrowth once it is a causative agent of variation in the balance of the intestinal microflora [1,6,9,23,40,42,46,87,88].

4. Diagnosis

In some cases, the diagnosis of candidiasis becomes quite complicated and difficult to establish, since the patients present different signals and symptoms according to age, gender, host resistance and exposure to environmental factors. Nevertheless, some tools could be used to screen and determine the presence of yeast infections (diagnosis) namely, questionnaire, comprehensive digestive stool analysis (CDSA) and laboratorial techniques (**Figure 1**).

4.1. Signals and symptoms

Despite fungi and other microbials being widespread in the environment, the systemic infections thrive very slowly. Most of the times, the individual infected does not have symptoms or visible signals. According to some authors, namely, oral candidiasis is classified considering the following aspects: duration (acute or chronic), clinical features, like color (erythematous/atrophic), location (median rhomboid glossitis, denture stomatitis, multifocal candidiasis, angular cheilitis), presence of skin lesions, as well as oral lesions (mucocutaneous), and association with an immunocompromised host (HIV associated). Other clinical aspects included hyperplastic or hypertrophic appearance, characterized by papillary hyperplasia of the palate, candida leukoplakia and hyperplastic median rhomboid glossitis [1,5,17,48,49,57,59,60].

In a more developed stage of infection, a simple sensation of flu or constipation could occur, like cough or fever, chest pain, chills, weight loss or breathing difficulties. However, the type and the intensity of signals and symptoms depend on the type and location of the infection. One of the major explanations for yeasts overgrowth is that the immune system mechanisms are depleted, or the normal lining of the intestinal tract is damaged. When this happens, the body can absorb yeast cells, particles of yeast cells, a

wide of toxins and other substances, resulting in the development of yeast syndrome [5,49,62].

The major symptoms of patients with yeast infection are divided in different categories, which are described below. General symptoms include chronic fatigue, loss of energy, general malaise, and decreased libido. Other category includes gastrointestinal symptoms, like thrush, bloating, gas, intestinal cramps, rectal itching, and altered bowel function. In genitourinary system, the major complaints are vaginal yeast infection and frequent bladder infections. Depression, irritability and inability to concentrate are the general complaints of nervous system. The occurrence of allergies, chemical sensitivities and low immune function are also very frequent. A great majority of patients has shown, in the past history, one or more of these conditions: chronic vaginal yeast infections; chronic antibiotic use for infections or acne; oral birth control and oral steroid hormone usage, as well as premenstrual syndrome; sensibility to foods, chemicals and other allergens; endocrine disturbances; eczema; psoriasis; irritable bowel syndrome. One of the most important aspects is that most patients have craving for foods rich in carbohydrates or yeast [1,5,49,62].

Occasionally, patients saying that “feel sick all over” characterize the syndrome. It is important to consider that women patients have eight times more yeast infections compared to men, due to the effects of estrogen, birth control pills and the large number of antibiotics prescriptions [1,5,49,62].

4.2. Diagnosis methods

4.2.1. Questionnaire

C. albicans questionnaire is one of the most useful screening methods to determine and understand the likelihood of yeast-related illness. It is composed by three sections:

anamnesis, main symptoms and other symptoms. The complete evaluation is made by the sum of those sections, directing the treatment and establishing hierarchy of intervention. Although *Candida* questionnaire can be profitable, clinical evaluation is one of the most important and credible methods of diagnosis, including patient's history and clinical picture. Promptly, and according to the necessity, laboratory examinations, like stool cultures for *C. albicans* and measurement of antibody levels or antigens in the body, are very useful and accurate [5,43,57].

4.2.2. *Comprehensive digestive stool analysis (CDSA)*

The stool sample culture exam is very common, but it is inconclusive and provides little information in the case of active infection. CDSA is an extremely useful and effective method to determine the existence of some digestive disturbances, functional and clinical status of the GI tract, which can be one of the major responsible factors of *Candida* overgrowth. It also allows determination of the symptoms that are not related with *Candida* overgrowth, but associated with the intestinal bacteria overgrowth or presence of inflammatory bowel disease [57,59,60,62,89].

CDSA is also considered very important to maintain the optimal functioning and ecology of the GI tract to improve human health and wellness. This noninvasive method of diagnosis can be considered as an integrated tool. It provides advanced clinical insight and allows, carefully, an evaluation and examination not only of digestion, absorption and intestinal capacity or function, but also of intestinal environment, gut immunology and metabolism, microflora balance and colon risk cancer. Therefore, in the last instance, it is helpful in the diagnosis and monitorization of disease-specific infections or conditions, but also determines the etiology of diseases [57,59,60,62,89].

4.2.3. Laboratorial techniques of diagnostic

Laboratory techniques only confirm the patient's history, physical examination and CDSA, only few additional data is provided and it is rarely used. However, there are situations in which the physician or the patients intend to objectify which *Candida* species is the main etiogenic agent. In this case, microbiologic, molecular and biochemical assays could be used. For example, the blood analysis can be useful, not only as a method of determination/confirmation, as well as to monitoring therapy. This test is based on measuring the level of antibodies to *Candida* antigens. Other techniques, like urine test, used to measure yeast metabolites and intestinal permeability, help to assess metabolic reasons for candidiasis [57,59,60,62].

5. Prevention

Considering the facts described above, and being *C. albicans* a commensal microorganism and that is present in all people, it is important to control the number and magnitude of its population. As prevention is the most effective treatment, much more than the eradication of the yeast with antifungal agents – synthetic or naturals, it is fundamental to address and amend the predisposing factors. Therefore, maintaining a good personal hygiene is essential. Moreover, being woman more prone to this kind of infection, a good vaginal and oral hygiene is essential, in order to reduce the probability of candidiasis occurrence [5,17,42,46,49,59,60]. Some general guidelines for personal hygiene are listed in **Table 1**.

Since deep infections have been increasing, mainly in hospitals, the following aspects should be considered: probes and catheters should be regularly monitored and removed,

as soon as possible; and the frequency, duration and amplitude of the quantities of antibiotics should be kept to a minimum [3,6,9,14,49,72,90].

Not less important, is to avoid certain risk factors, such as diets rich in sugar and poor in vitamins and minerals, or the use of antibiotics.

6. Alternative treatment

C. albicans is an opportunistic yeast that cause infectious but, in some levels, lives and grows inside most human bodies. In normal situations, *Candida* is not harmful because our bodies are able to keep it under control, mainly by immune cells and probiotic bacteria. However, some factors previously discussed, like allergies, high-sugar diets, medications/drugs, and other factors that directly affect the normal balance of intestinal environment, can kill the friendly bacteria and stimulate the overgrowth of pathogenic microorganisms [1,68,69,84,87,88]. Therefore, the best complementary treatment is to reduce and control *Candida* levels. Several recommendations/interventions are necessary according to each person. In most of the cases, direct therapy for *Candida* species destruction is advantageous, because it assists the body on lowering *Candida* species to controllable levels [49,57,59,60]. However, depending on the profile of the patient, other procedures (diet and nutrition, enhancing immunity system, detoxification and natural anti-yeast agents; **Figure 1**) are required and will be discussed.

6.1. Therapeutic considerations

6.1.1. Diet and nutrition

As previously discussed, some dietary factors affect and promote the overgrowth of *C. albicans*; therefore, following a special diet for the treatment of candidiasis is crucial. The most important elements are refined sugars, such as sucrose, fruit juice, honey and

other sweet foods, because *C. albicans* grows in sugar environments. Foods with high content of fungi or yeasts, like alcoholic beverages, cheeses, dried fruits, bread and fermented products should be avoided, as also milk and dairy products due to the high content of lactose and, in some cases, trace levels of antibiotics. Likewise, all the allergens present in food should be eliminated, since allergies weaken the immune system, promoting the growth of pathogens. There are several reasons to restrict or eliminate milk and other dairy products, not only for the high levels of lactose, that promote *Candida* overgrowth, but also because it is one of the most frequent food allergens, and the presence of trace levels of antibiotics disrupt the GI bacterial flora [42,55,57,59,60,70,87].

Food allergies could be assessed by some immunoanalytical methods, such as ELISA tests, which determine both IgE- and IgG-mediated food allergies and often help in the identification of allergies [91–95].

Foods that can be eaten without problems and/or constraints are vegetables, sources of proteins, such as fish, meat and organic poultry, legumes and whole grains. The latter consumption is dependent of each individual tolerance. For fruits, although being the majority alkaline, the recommendation is to eliminate the consumption for a month of citrus and acidic fruits (*e.g.*, oranges, grapefruit, lemons, tomatoes, pineapple, and limes); afterwards the consumption can be made twice a week. Apples, cranberries, cherries, pears and other soft fruits can be daily consumed. Although the existence of conflicting opinions, the consumption of yogurt containing live probiotic cultures is recommended in order to replace friendly bacteria. In some cases, for vaginal candidiasis, a natural unprocessed and unsweetened yogurt can be applied directly into the vagina or a mixture of one small container of plain yogurt with an equal amount of water can be used as a douche, once or twice a day, until improvement is observed.

Alternatively, or complementary, it is also possible to take supplemental acidophilus or bifidus, or to open two capsules of acidophilus and add the contents to a douche. It is also recommended to consume daily oat bran and/or flaxseed, not only as a source of fiber, being the latter also very effective due to antifungal properties [49,57,59,60].

Table 2 summarizes the most important dietary aspects in fungal infections.

6.1.2. Enhancing immune system

In most cases of chronic candidiasis, the immune system is altered (mostly depressed) allowing a quick growth of *C. albicans*. This explains why the patients have repetitive cycles of infection that lead to increase damages, and further resistance weakening. Thereby, it is very important to potentiate the immune function, in order to protect the organism against foreign/opportunist agents. Additionally, in patients suffering from AIDS or taking immunosuppressive drugs, the immune system is affected, which favors the *C. albicans* overgrowth. In both cases, the prevalence of candidiasis is considerable, being the strength of the immune function very important. In some cases, the debility of the immune system is related to a decrease in thymus function, represented by an impairment of cell-mediated immunity [57,59]. There are some points that help to strength the immune function and that eliminate, suppress or amend the causes of depressed immune function. The major triggers of impaired immunity and that lead to *C. albicans* overgrowth are antibiotics, corticosteroids and other drugs that suppress immune system, as also nutrients deficiency, food allergies and stress [1,37,40,53,69,75,80,84].

Accordingly, restoring proper immune function is one of the major objectives in the treatment of chronic candidiasis; to reach this goal, some strategies could be followed: stress management, diet restriction, nutritional supplementation, glandular therapy,

exercise and the use of plant-based medicines. However, as the clinical remission of candidiasis is directly dependent on T-cells function, it is also crucial to improve thymus gland function. To achieve this, it is necessary to guarantee an adequate intake of antioxidants, through nutritional supplementation, such as carotenes, vitamins A, C and E, zinc and selenium. Some plants could be used to complement this intervention namely, *Echinacea angustifolia*, *Hydrastis canadensis* and *Glycyrrhiza glabra* [49,57,59,62,96].

6.1.3. Detoxification

The human body is continuously exposed to substances and toxic agents, which accumulates in the body. Therefore, the body detoxification process is continuous, being widely recognized that different substances (*e.g.*, heavy metals, pesticides, microbial toxins, solvents) have considerable interferences in the health and well-being of individuals. The liver is an extremely important organ in the body, responsible for vascular, metabolic and secretory functions. In addition, it is also responsible for the detoxification of all the chemical substances at which we are constantly exposed (not only those ingested through diet and as a result of the environment interaction, but also those resulting from endogenous metabolic processes, such as drugs and other cellular metabolisms). It has been observed that the majority of subjects with *C. albicans* overgrowth, present some problems in liver detoxification mechanisms. Moreover, the presence of multiple chemical sensibilities and allergies is frequent in patients with chronic candidiasis, which is a direct indicator of problems in detoxification reactions. The damage of liver is an underlying factor in chronic candidiasis, as well as in chronic fatigue, because when the liver is damaged by chemical toxins and others, the immune function is severely compromised. Thus, enhanced liver function is vital, not only

before, but also during and even after procedures that destroy yeasts, in order to increase the likelihood of success in candidiasis treatment [49,57,59,60,62].

Some procedures could help in the improvement of detoxification process by liver (**Table 3**).

6.1.4. Natural anti-yeast agents

Natural anti-yeast agents with proven activity against *C. albicans* can be used to treat the infection concomitantly to other procedures. Nevertheless, to be effective as primary therapy, predisposing factors to chronic candidiasis, diet and lifestyle should also be taken into account. The most studied compounds that act as natural agents against *C. albicans* are caprylic acid; berberine-containing plants; probiotics; grapefruit seed extract; garlic; tea tree oil; and enteric-coated volatile oil preparations containing oregano, thyme, peppermint, and rosemary; propolis; ginger and cinnamon. However, the occurrence of Herxheimer reaction is very frequent when an effective anti-yeast therapy is used, due to the rapid elimination of the microorganisms, and subsequent absorption of large amounts of yeast toxins, cell particles and antigens. The mentioned reaction can be eliminated through supporting liver function, following dietary recommendations and starting anti-yeast medications in low and gradually increasing doses [49,57,59,60,97].

6.2. Therapeutic approach

In order to successively control the growth of *C. albicans* and related infections (candidiasis), a therapeutic intervention is required.

After identification of the predisposing factors, it is essential to develop a diet to control *C. albicans* growing. The most commonly used substances and phytotherapies in the complementary treatment of candidiasis are presented in **Table 4**.

Besides the mentioned phytotherapies there are other plants with documented antifungal activity, particularly against *C. albicans*, such as essential oils from ginger (*Zingiber officinale*) [98–100], cassia (*Cinnamomum cassia*) [98,101] and others *Cinnamomum* species [32,102], chamomile (*Matricaria chamomilla*) [57,103,104], lemon balm (*Melissa officinalis*) [32,101,105], thymus (*Thymus vulgaris*) and rosemary (*Rosmarinus officinalis*) [101,106–109].

Nevertheless, there are still several unknown compounds from plants, that could act synergistically, among themselves and with other natural compounds, against yeast infections [57,59,60,97,110].

Other aspects should also be considered namely, rest and liquids intake mainly vegetable diluted juices, soups and plant infusions. Moreover, it is necessary to promote a positive mind and help patients to cope stress. Alcohol, simple sugars, tobacco and cholesterol should be avoided due to their capacity of stimulating *C. albicans* overgrowth, and impair the immune function. The support to thymus gland function is also provided by 500 mg of crude polypeptide fractions, twice daily [57,59,60,62,96,111].

The body ability to detoxify and eliminate some substances is mostly dependent of healthy diet and lifestyle. As previously mentioned, liver is the responsible for the detoxification of all chemical substances. Therefore, the optimization of liver function, promoting their protection and using lipotropics factors, accelerates the elimination and fat deposition in liver, and could offer significant benefits [57,59,60,97]. In some cases,

the use of formulas containing natural plant fibers derived from psyllium seed, kelp, agar, pectin and plant gums, is necessary to help elimination of toxic substances and protect the bowel wall from irritation. Moreover, these fiber formulas promote natural bowel movements and, if anti-yeast therapies are employed, they guarantee that dead yeast cells are excreted and not absorbed; 3-5 g of soluble fiber at bedtime are required for the treatment of candidiasis [57,59,60,87,88,112,113].

The repair of intestinal flora is another crucial factor. Particularly, *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Lactobacillus bulgaricus* and *Streptococcus thermophilus* are very important, not only as antifungals, antibacterials and antivirals, but also in digestion and in production of vitamins and other substances important to maintain gut and the all body healthy. The recommendation is a product containing 4-10 billion viable active organisms, 30 minutes after a meal. However, some foods, like yogurt and kefir, could also be a good source of probiotics, but is necessary to take care, mainly due to fact that the yogurt itself does not have the necessary amount of bacteria and, in other hand, the presence of sugar promotes the overgrowth of *C. albicans* and other microorganisms. Therefore, the yogurt should have the proper bacteria and should not be sweetened [57,59,60,87,88,112,113].

Lastly, the use of nutritional supplements or herbs seems to be the best option to help and control *C. albicans* overgrowth, and to promote a healthy bacterial flora. Antifungal drugs should be prescribed only if necessary. In most cases, these therapeutic interventions are effective to threat candidiasis, including chronic candidiasis. However, if the patient cannot achieve a significant improvement and/or eradicate the infection, it is necessary to perform a deeper evaluation [57,59,60,62]. If the organism is still present, after repeat stool cultures and measure antigen levels, antibiotics could be prescribed, combined with other recommendations [57,59,60]. Despite until now the

majority of studies focused essentially in the role of oils of plants, currently other natural matrices preparations have been studied, namely, aqueous and alcoholic extracts. It is very important to underline that the use of plants and other botanical preparations are used, since ancient times, by primitive societies, due to healing properties and therapeutic and psychotherapeutic benefits. It is important to address the fact that plants are widely used to obtain a large variety of drugs, being used in folk medicine for a long time [26–29,32–35]. Concerning that plants represent an economic, easily and which are accessible for all of people, they can be used into a variety of diseases, constituting an excellent source of biomolecules able to act like natural antifungal agents and, at the same time, to encourage the search for other alternative treatments. They can be used, both to complement a conventional treatment with antifungal agents, and singly like a natural alternative treatment. In both situations, the counseling and following of a growing control diet are crucial to ensure successful of therapy.

Moreover, despite the increasing interest of several studies towards the identification of several compounds with therapeutic potential and their synergistic effect, in combination with other compounds, many properties of plants remain unknown, as well as their main compounds. Thus, not only it is necessary to deepen the study of other preparations of known plants but also investigate other therapeutic effects provided by plants and the major responsible compounds.

7. Concluding remarks

All people are exposed to a variety of candidiasis predisposing factors, and some of them are impossible to avoid. Candidiasis can affect different parts of the body (nails, GI tract, and vagina, among others) being characterized by several symptoms, which

often-difficult diagnosis; additionally, the individual characteristics alter the manifestation of signals and symptoms. As this infection is very uncomfortable and, in some cases, offers a considerable health risk, the major and most important aspect is prevention. Therefore, there are several aspects to consider and include in the daily routine, which at first might seem insignificant, but that could provide a strength protection.

To combat the infection different procedures are necessary according to the pathologic conditions of the patient; if all daily care is considered, the probability of the infection occurrence will be considerably reduced. However, in face of an infection, a rapid intervention is necessary and, for this, other alternatives to antifungals and antimicrobials are necessary.

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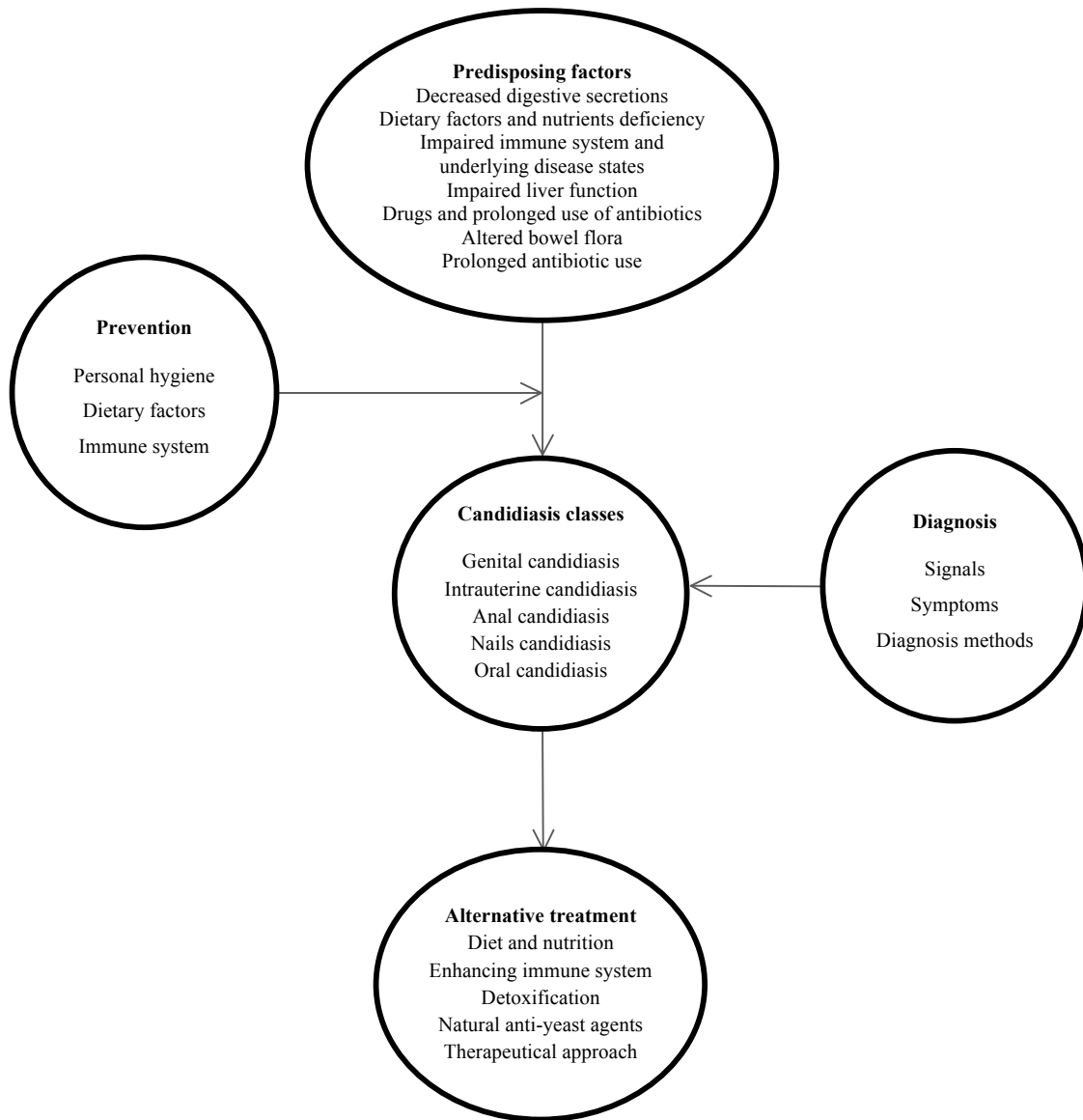


Figure 1. Representative scheme of interactions between the main variables related to candidiasis.

Table 1. Main general guidelines for personal hygiene [49,59,60,62]

	Procedures
Superficial infections	Avoid contact with other body parts, as well as with other persons Maintain the skin clean and dry During menstruation, compresses without cosmetic products should be used
Vaginal candidiasis	Avoid frequent use of vaginal douches and intimate hygiene products (they alter the normal vaginal pH, causing unbalance and favoring the onset of infection) Maintain external vaginal area completely dry Avoid prolonged use of bathing suit or damp or wet underwear The act of cleaning up should always be done backward Avoid sexual relations during antifungal therapy
Personal belongings	Bed linen, bathroom and personal clothing should be washed with very hot water, separated from the others at home and disinfected after use Avoid tight clothing and use cotton underwear

Table 2. Dietary considerations in the treatment of candidiasis [57,59,60,62,97]

	Food characteristics	Food products
To avoid	Refined carbohydrate sources	Refined sugars (sucrose, fructose, corn syrup), fruit juice, honey, maple syrup
	Fungi and/or yeast sources	Alcoholic beverages, dried fruits, cheeses, peanut
	Lactose and antibiotic sources	Dairy products
	Allergenic foods	Dairy products, eggs, chocolate, fried and processed foods, wheat, peanuts
To limit	Carbohydrate sources	Corn and potatoes
To consume	Vitamin sources	Vegetables, fruits (apples, pears, cranberries, cherries, blueberries and other soft fruit)
	Protein sources	Fish, meat and biological poultry
	Fiber sources	Whole grains, ground flaxseeds

Table 3. Procedures to improve liver function and detoxification [49,57,59,60,97]

	Procedures
Improve liver function	Consuming garlic, onions, chlorella, spirulina, wheatgrass; Diet based on fresh fruits and vegetables, whole grains, legumes, nuts and seeds; Avoiding alcohol and adopt others healthy lifestyles; Supplementation with a high-potency multiple vitamin and minerals; Regular exercise
Improve detoxification	Diet based on high-fiber plant foods to supplying a high amount of dietary fiber; If necessary, prescribed additional fiber formulas- 3 to 5 g of soluble fiber at the bedtime- composed by natural plant fibers, derived from psyllium seed, kelp, agar, pectin, guar, and others that promote a natural mechanism of bowel movement; Using lipotropic formulas* such as choline, betaine and methionine or cysteine, silimarin to protect the liver

*The importance of lipotropic factors is related to increased levels of two important liver substances: SAMs (S-adenosylmethionine) and glutathione, that are the major lipotropic and detoxifying compounds in the liver, respectively.

Table 4. Substances and phytochemicals commonly used in alternative treatment of candidiasis

Substance	Dosage/Description
High-potency complex of multivitamins and minerals formula	Hypoallergenic formulas, free of yeasts
Zinc picolinate	45 mg/day
Selenium	200 µg/day
Caprylic acid	Formula of slow liberation (1 g with meals)
Probiotics (intestinal flora)	Products containing <i>Lactobacillus</i>
Fiber supplement	Guar gum, pectin or psyllium seeds (1 teaspoon before bedtime)
Phytotherapies	Dosage/Description
<i>Tabebuia impetiginosa</i> (lapacho)	15-20 g of bark in 0.5 L boiling water for 5-15 minutes, 3-4 times/day;
<i>Berberis vulgaris</i> (barberry)	The following doses, 3 times/day: Dried bark of the root (as tea): 1-2 g Tincture (1:5): 4-6 mL (1-1 and ½ teaspoon) Liquid extract (1:1): 0.5-2 mL (¼-½ teaspoon)
<i>Hydrastis Canadensis</i> (goldenseal)	Powdered solid extract (4:1): 250-500 mg The following doses, 3 times/day: Dried root (as tea): 1-2 g Tincture (1:5): 4-6 mL (1-1 and ½ teaspoon) Liquid extract (1:1): 0.5-2 mL (¼-½ teaspoon)
<i>Origanum vulgare</i> (oregano) oil	Powdered solid extract (4:1): 250-500 mg 300-500 mg by capsule or liquid form, 3 times/day, with meals to avoid digestive unease
<i>Allium sativum</i> (garlic)	Actual guidelines based on allin (10 mg) and allicin (4000 µg), which is equivalent to 4000 mg of fresh garlic or 500-1000 mg of aged garlic
<i>Citrus paradise</i> (grapefruit) seed extract	200 mg, 2-3 times/day