Introduction
Past two decades have witnessed a steady increase in the incidence of fungal infections accounting to about 8.4% of nosocomial bloodstream infections [1], of which Candida spp. constitute 80% [2]. Yeasts of the genus Candida, especially of Candida albicans are known to be pathogenic in humans. They are of endogenous origin and survive in harmony with other microorganisms on mucosal surfaces and other body parts as commensal. Multiplication of these organisms is normally kept in check through physical barriers such as the skin, by competition with endogenous microflora, low pH at vaginal mucosa, and through host defense mechanisms. Under certain predisposing conditions it causes infections ranging from superficial mycosis to deep-seated chronic infection from where the organism reaches bloodstream and causes hematogenously disseminated life threatening systemic disease [3, 4]. These infections are more common in early childhood and in adults with conditions such as diabetes, cancer, and treatment with immunosuppressive agents after organ transplantation or severe burns, and in patients undergoing long-term antibiotic treatment. In patients with implanted devices such as catheters or prosthetic heart valves, the composite material provides a surface for the Candida-biofilm formation. Biofilms consist of matrix-enclosed microcolonies of yeast and hyphae arranged in bilayer structure and are resistant to a range of antifungal agents currently in clinical use [5]. Another susceptible class of population consists of otherwise healthy women, 75% of whom suffer from at least one episode of vulvovaginal candidiasis during their reproductive years, and some 5% of them develop recurrent vulvovaginal candidiasis [6].

The clinical manifestations of Candida infections may be acute, subacute or chronic to episodic. Involvement may be localized to the mouth, throat, skin, scalp, vagina, fingers, nails, bronchi, lungs, or the gastrointestinal tract, or become systemic as in septicemia, endocarditis and meningitis. Intertriginous infections, the most common type, appear as well demarcated, erythematous, sometimes itchy, exudative patches of varying size and shape. The lesions are usually rimmed with small red-based papules and pustules that produce white macerated pruritus ani. In women, vulvovaginal candidiasis often associated with
the use of broad-spectrum antibiotics, causes intense vulval pruritus, burning, erythema and dyspareunia associated with a creamy white, curd-like often-smelly discharge. *Candida* is now the fourth most prevalent organism found in bloodstream infections [4]. Such hematogenous infections usually present with antibiotic resistant fever, which sometimes resemble with bacterial sepsis, with a fulminating course that may include shock, oliguria, renal shutdown, and disseminated intravascular coagulation. Relatively few antifungals are available to treat these infections; amphotericin B, flucytosine, miconazole, ketoconazole, fluconazole and itraconazole are currently in clinical use. However, these compounds show some limitation due to either their toxicity (amphotericin B), or emergence of resistance and limited spectrum (azoles). In addition, most azoles are fungistatic giving rise to the possibility that the fungi are not cleared from patients, particularly in immunocompromised individuals. Thus, there is an urgent need for newer molecules with completely different mode of action. This is otherwise important because fungi are eukaryotic organisms and drugs that interfere with DNA or protein synthesis may be potentially toxic in humans.

Fungi are protected from various environmental stress including antifungal agents and macromolecules like proteases by their cell wall. This cell wall consists of macromolecules like mannan, chitin, and cellulose that are unique to fungi and are not present in humans or animals. A number of drugs, such as echinocandins [7] (caspofungin, anidulafungin and mycofungin), pneumocandins and nikkomycin that are in development or under clinical trials are targeted towards de-stabilizing cell wall. Other molecules that are under different stages of development are variations on triazole theme (such as voriconazole, posaconazole, and ravuconazole), sordarin derivatives, and cispentacin derivatives [8]. All these molecules are chemically derived ones and may possess some level of toxicity when used for longer duration in patients with debilitated immunity. Thus, other modes of treatments were sought after, that increase the patients immuno-competence to fight against fungal infections like vaccination and INF-γ [9] or complement immunity by administration of antibodies directed against specific epitopes of fungi.
Antibodies offer protection by a variety of mechanisms like opsonization-mediated phagocytosis, inhibition of germ tube formation [10, 11], inhibition of attachment with host tissue [12-15], neutralization of secreted aspartyl proteases [16] and direct candidacidal activity. Two antibodies viz. anti-idiotypic yeast-killer toxin like antibody [17] that binds with β-glucans [18], and C7 raised against the main target (>200kDa mannoprotein) of salivary sIgA were shown to be directly candidacidal [19]. It is interesting to note that all of these antibodies have their target in the cell wall of Candida. The cell wall on its outer surface carries mannan that consists of a large number of various hyper mannosylated proteins. This mannan keeps on dissolving from the site of infection and can be detected in serum of patients suffering from disseminated candidiasis [20]. Body responds vigorously to these foreign molecules by producing antibodies, especially directed against the mannosyl moieties [21]. Clinical investigations suggest that patients who have high titers of anti-Candida-antibodies may still develop hematogenously disseminated candidiasis suggesting little or no role of antibodies in protection against candidiasis [22]. Although evidences have accumulated that antibodies directed against certain cell surface epitopes may be protective [23], anti-mannan sera developed using mannan as vaccine [24] or anti-mannan antibodies from infected animals were found to protect animals in infection models [16]. Fine structure of mannosyl moieties is very complex. Han et al. described two antibodies, B6.1 and G3, which bind with the acid-labile region of mannan and protect animals against candidiasis [25, 26]. Whereas another monoclonal antibody (B6) that binds with the acid stable region failed to protect animals [27]. This gave rise to the notion that there exist two kinds of antibodies, the protective, and the non-protective antibody, and it is quite possible that either the concentration of protective antibody is too low, or the protective epitope is masked by non-protective antibody that results in candidiasis.

Recently a humanized monoclonal antibody directed against heat shock protein (HSP90) has entered clinical trials for the treatment of candidiasis. This antibody also has its target in the cell wall of C. albicans. Thus, though not all
antibodies that are produced in response to infection may be protective, selective antibodies directed against specific epitopes are protective against local and systemic infection and may form the basis for immunotherapy. These antibodies can be used singly or in combination with other antifungal agents [28]. The question remains as to what proteins against which the monoclonal antibodies should be directed. Proteomic analysis revealed that the cell wall contains hundreds of proteins but the body produces antibodies against selective antigens in response to infection. One strategy may be to produce monoclonal antibodies against these selective antigens, and verify their efficacy in animal models of infection. This, in a way will be a method to support body's own immune system to fight against infections. Cell wall of *Candida* is rich in proteins and harbor molecules that help it in recognition and attachment with host tissue, proteins responsible for cell growth and yeast-hyphal-morphogenetic transformation, and other quorum sensing proteins that respond to changes in pH, nutrition and etc. Another strategy would be selectively blocking these proteins using monoclonal antibodies.

In this piece of work resolving power of 2-D gel electrophoresis was employed to elaborate different proteins of cell wall of *C. albicans* and immunogenic proteins were identified on 2-D immunoblots using sera from patients suffering from candidiasis. These proteins were characterized by peptide mass fingerprinting using MALDI-MS technique. Monoclonal antibodies were developed against these immunogenic and various other proteins of cell wall of *C. albicans* and screened *in vitro* for candidacidal activity and *in vivo* for their efficacy against experimental candidiasis in mice.