Biotechnology Reports 38 (2023) e00800

Contents lists available at ScienceDirect

Biotechnology Reports

journal homepage: www.elsevier.com/locate/btre

Review

Probiotics and their postbiotics for the control of opportunistic fungal pathogens: A review

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ARTICLE INFO

Keywords:
Antifungal agents
Aspergillus. Candida
Mucor
Opportunistic fungal infections
Postbiotics
Probiotics

ABSTRACT

During past twenty years the opportunistic fungal infections have been emerging, causing morbidity and mortality. The fungi belonging to *Aspergillus, Mucor, Rhizopus, Candida, Fusarium, Penicillium, Dermatophytes* and others cause severe opportunistic fungal infections. Among these *Aspergillus* and *Candida spp* cause majority of the diseases. The continuum of fungal infections will prolong to progress in the surroundings of the growing inhabitants of immunocompromised individuals. Presently many chemical-based drugs were used as prophylactic and therapeutic agents. Prolonged usage of antibiotics may lead to some severe effect on the human health. Also, one of the major threats is that the fungal pathogens are becoming the drug resistant. There are many physical, chemical, and mechanical methods to prevent the contamination or to control the disease. Owing to the limitations that are observed in such methods, biological methods are gaining more interest because of the use of natural products which have comparatively less side effects and environment friendly. In recent years, research on the possible use of natural products such as probiotics for clinical use is gaining importance. Probiotics, one of the well studied biological products, are safe upon consumption and are explored to treat various fungal infections. The antifungal potency of major groups of probiotic cultures such as *Lactobacillus spp, Leuconostoc spp, Saccharomyces* etc. and their metabolic byproducts which act as postbiotics like organic acids, short chain fatty acids, bacteriocin like metabolites, Hydrogen peroxide, cyclic dipeptides etc. to inhibit these opportunistic fungal pathogens have been discussed here.

1. Introduction

The emergence of opportunistic fungi which infect immunosuppressed individuals is a growing health concern [1], presenting a massive problem and confront for treatment and diagnosis to health care professionals causing significant mortality and morbidity. These evolving fungal infections are increasingly affecting patients with predisposing circumstances such as complex HIV infection, cancer, granulocytopenia, organ transplantation, severe burn, diabetes, trauma, malnutrition and other issues leading to low immunity [2].

The appearance and re-appearance of opportunistic fungal infections like Candidiasis, Cryptococcosis, Zygomycosis, Mucormycosis and Pneumocytosis are fairly common. In a nationwide surveillance study done in US hospitals, one of the most common nosocomial pathogens causing bloodstream infections was *Candida spp*. Of the different species isolated from 1890 cases in this study, *C albicans* tops the list responsible for 54% of cases, followed by *Candida glabrata* (19%), *Candida parapsilosis* (11%), *Candida tropicalis* (11%), and *Candida krusei* (5%) [3]. Several studies have stated that, candidiasis, specifically candidemia, was the most common mycotic infection of hospitalized patients and is associated with significant mortality and prolonged hospital stay [4]. Similarly, *Aspergillus* spp such as *Aspergillus fumigatus, Aspergillus terreus, Aspergillus flavus, Aspergillus nidulans* and *Aspergillus niger* are opportunistic moulds which cause invasive and allergic infections such as aspergillosis can affect about more than 45% of immunocompromised patients. It is alarming to observe that among the patients hospitalized in ICU due to invasive fungal infections there is a mortality rate of 67% [5]. Like *Aspergillus* species, Zygomycetes are common nosocomial pathogens causing systemic Zygomycosis, and they are widespread among people with uncontrolled diabetes mellitus, burns, metabolic acidosis and malignant hematological disorders all around the globe [6] (Fig.1).

For a few decades local and systemic antifungal agents like nystatin, amphotericin B and fluconazole have been effectively used as prophylactic and therapeutic agents to preclude colonization of invasive opportunistic infections of fungi [7]. Though, their effectiveness is compromised because for thier frightening raise in the appearance of

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https://doi.org/10.1016/j.btre.2023.e00800
Received 11 January 2023; Received in revised form 11 April 2023; Accepted 3 May 2023
Available online 4 May 2023

antibiotic resistant fungal strains globally [8]. Therefore, alternative therapies have been implicated for opportunistic fungal diseases/infections together with the usage of natural products like oils, phytochemicals and peptides [9]. Although promising, their bio-tolerance and toxicities of these compounds are of apprehension. Hence, they are until now in the investigational period of improvement [10]. Hence, for these concerns, the need of biocontrol agent such as probiotic bacteria and its postbiotics has been anticipated as an substitute approach of treatment against opportunistic human fungal infections [11].

According to Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO), Probiotics and beneficial microorganisms, that when administered in sufficient quantity provide health advantage on host [12]. The mainly common probiotic microorganisms are strains from the genera *Lactobacillus* (i.e., *Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactiplantibacillus plantarum, L actobacillus delbrueckii* subsp. *bulgaricus, Lactobacillus casei,* etc.) and *Bifidobacterium* (i.e., *Bifidobacterium animalis* subsp. *lactis, Bifidobacterium infantis, Bifidobacterium longum,* etc.). Other probiotic bacteria include *Lactococcus lactis* subsp. *lactis, Pediococcus acidilactici, Bacillus subtilis, Leuconostoc mesenteroides, Enterococcus faecium, Escherichia coli* and *Streptococcus thermophilus* etc. [13]. Certain yeasts like *Saccharomyces boulardii* as well proved to be probiotics [14,15]. These organisms have been proposed to control many human pathogens including fungi.

Antagonism is most significant probiotic management method caused by immune modulation through stimulating the host defense systems and competitive exclusion involves the production of secondary metabolites (antimicrobial compounds), prevention of pathogen adhesion to epithelial cells and toxin bioavailability reduction. In addition, signaling molecules also triggers gene expression changes. Major antimicrobial compound produced by probiotic microorganisms include formic acid, lactic acid, phenyllactic acid, benzoic acid, acetic acid and also organic acids that lower pH, hydrogen peroxide, short chain fatty acids, diacetyl, acetoin, carbon dioxide, acetaldehyde, bacteriocins and bacteriocin like protienaceous compounds [13] (Fig. 2).

2. Challenges

Challenges in the management of opportunistic fungal diseases are major and multiple. Firstly, it is difficult in making an early diagnosis of most of the opportunistic fungal infections. Second, the antifungal agents are effective *invitro* often for the management of the fungal diseases is not as effective *in vivo* conditions. Third, problems related to appropriate and sufficient amount of drug doses for the treatment, and uncertainty in making the decision of when to stop antifungal therapy [15]. These problems are most apparent in the management of opportunistic fungal diseases with chemical drugs. Therefore, the extensive use of antifungal agents may also lead to several health issues [16] with patients undertaking solid-organ transplantation, neoplastic disease, blood and bone marrow transplantation as well as major surgery, immunosuppressive therapy and those with AIDS, advanced age, or premature birth [17].

The exploitation of antifungal drugs and antibiotics can effortlessly escort to the progress of drug resistance. This not only contradicts the outcome of the existing antifungal drugs but also guide to the variation in microbe flora of human. Moreover, a reduction in the immunity of body, creating invasive opportunistic fungal diseases more difficult to control [18]. Every year, exact analysis and the successful practice of suitable antimycotic remedy are tough, which conduct a high death rate in immunosuppressed patients with invasive fungal infections (IFI) [31]. The epidemiology of opportunistic pathogens has altered accompanying with the extensive use of antifungal prophylaxis [32]. Non-fumigatus *Aspergillus*, Non-albicans *Candida*, and other molds have turned out to be more frequent opportunistic pathogens instigating invasive infections, and the majority of these incipient invasive fungi are less susceptible or resistant to standard antifungals [17]. Therefore, opportunistic fungal infections owing to this formerly erratic fungus are further difficult to treat and prevent. Advances in additional compelling and fewer noxious antifungal agents like fluconazole, amphotericin B,

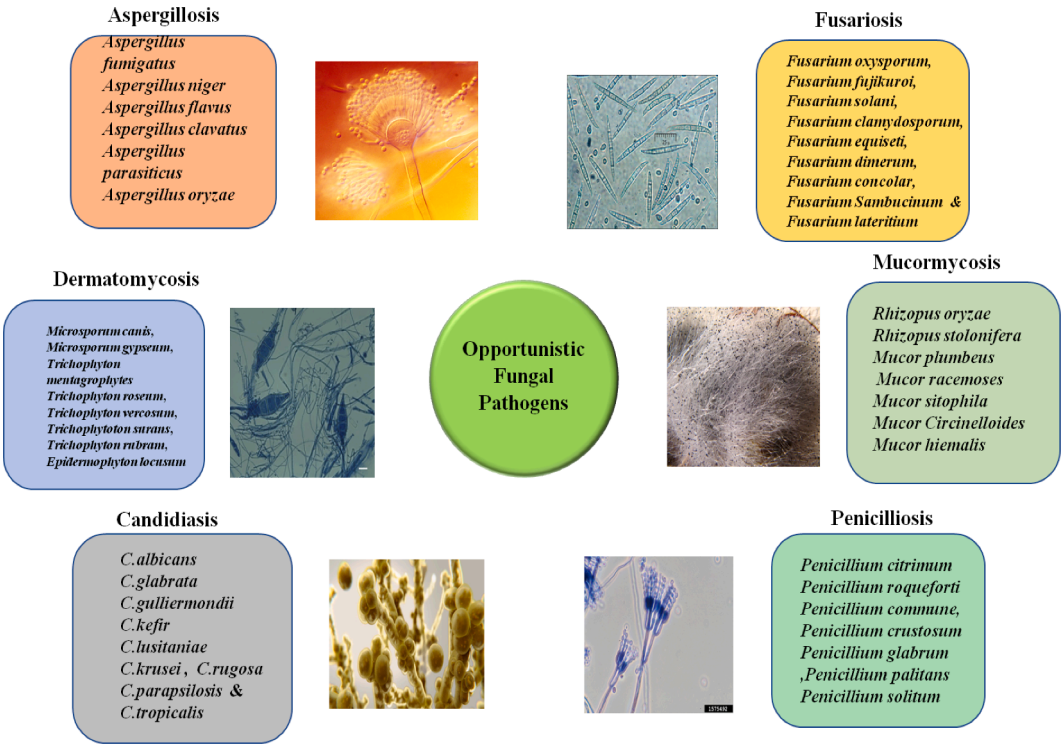

Fig 1. Different species of fungi which cause opportunistic fungal infections such as Aspergillosis, Fusariosis, Mucormycosis, Penicilliosis, Candidiasis and Dermatomycosis.

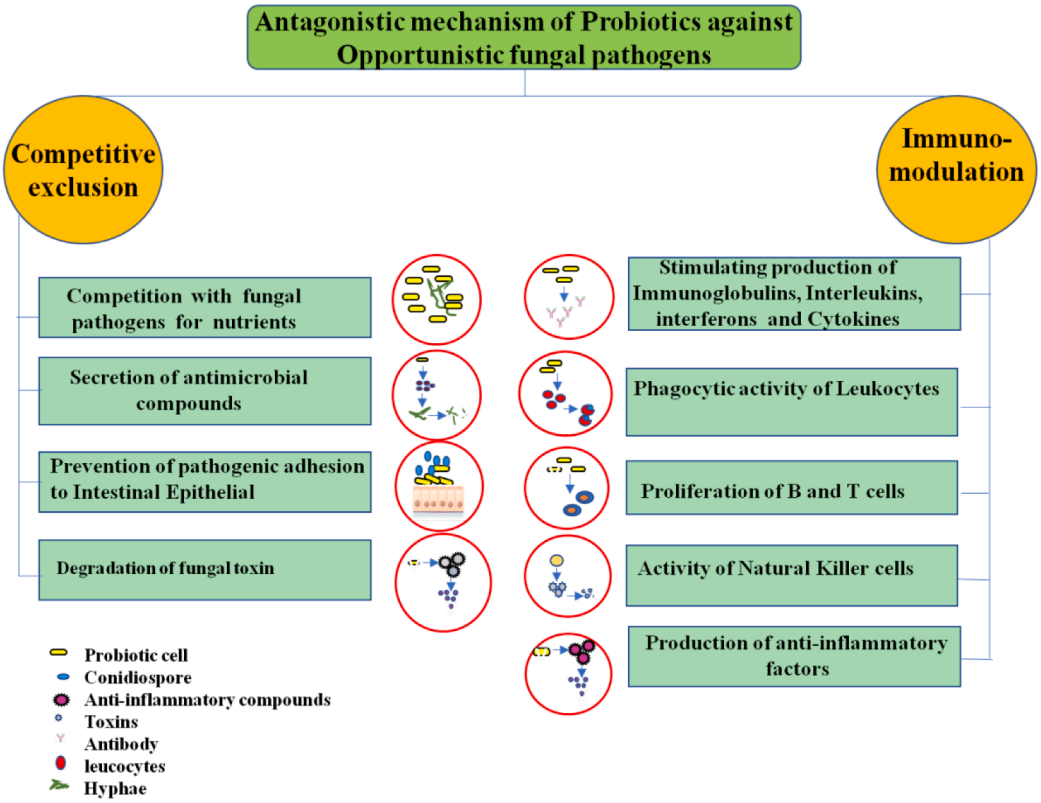

Fig 2. Antagonistic mechanism of probiotics for the prevention of opportunistic fungal pathogens in humans.

flucytosine, itraconazole, echinocandins and triazoles, may potentially progress the outcomes of these invasive fungal infections [16]. Hence, it is indispensable to develop more effective and also safe chemical drug alternatives to treat opportunistic fungal infections. Therefore, use of biocontrol agents from probiotics as alternative therapeutic mode of treatment against opportunistic fungal pathogens has been explored.

Worldwide, probiotics are currently available in a variety of food supplements. With the GRAS status, they tend to supply as enhancement/supplement to the microflora of host and are not as obvious considered pathogenic. Probiotics are well-known for promising results like enhanced gut barrier function; adding up to their sole ability to battle with pathogenic microorganisms for adhesion to the gut epithelial cells and develop their colonization [19–21]. Consumption of potential probiotics/postbiotics is connected with a series of health benefits including protection against diarrheal diseases, lowering of cholesterol, stimulation/modulation of the immune system (Fig. 3), nosocomial and respiratory tract infections, reduction of immune inflammatory disorders [22]. Therefore the use of probiotics to prevent and treat a variety

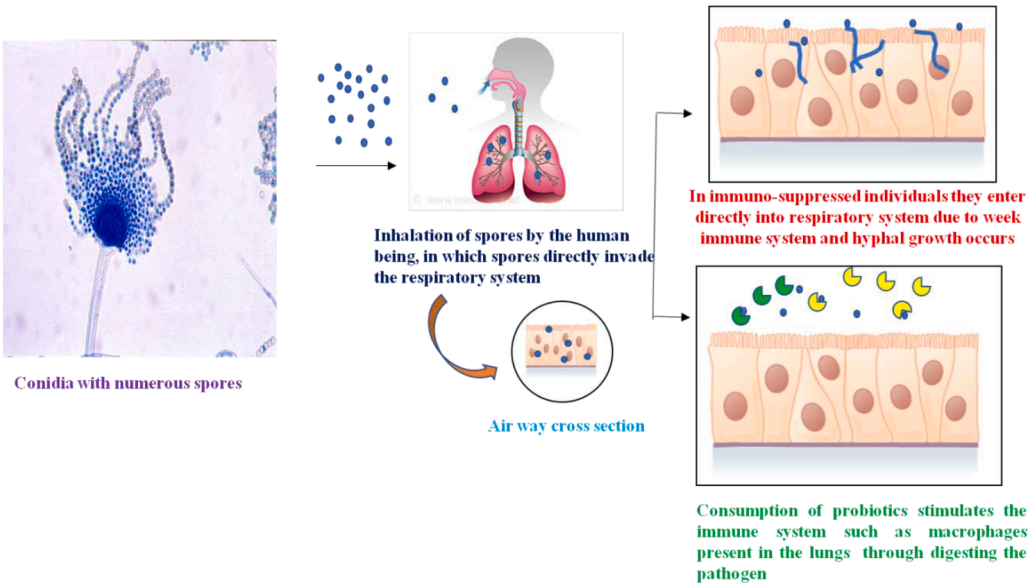

Fig 3. Fungal agents enter the respiratory tract and cause invasive fungal infections in immunosuppressed patients, whereas consumption of probiotics stimulates the immune system to fight against fungal agents.

of disease conditions has procured approve in the past ten years. This is relatively, due to a requirement to find alternative to conventional therapies such as antifungal agents/antibiotics for opportunistic fungal infections and disease.

In this review the opportunistic fungal diseases and their negative impacts caused to human health are underscored. To overcome this impact the role of Probiotics/Postbiotics to control the growth of such fungi is discussed in this review.

3. Probiotics used against Candida species

Candida species are implicated as the major opportunistic yeast infections in the globe. however among the species of this genus, *C. albicans* endures to be the mainly widespread which is accountable for almost 50–90% of candidiasis in human [23]. Furthermore, with the hasty rise in candidiasis prevalence, species of Candida other than *Candida albicans* have been concerned in such infections [24–26]. The most general species are *Candida glabrata, Candida metapsilosis, Candida dubliniensis, Candida tropicalis, Candida parapsilosis, Candida famata, Candida orthopsilosis, Candida kruseri, Candida guillermondii* and *Candida lusitaniae* [27–30]. Depending on the locality on the body, candidiasis classified as intrauterine candidiasis, Genital candidiasis, nail candidiasis, anal and oral candidiasis. In addition, the giantism of *Candida albicans* is an imperative source of an extensive range of indications that influence straightly to the welfare of individuals, consequently there is a crucial necessity to diagnose candidiasis as a multifaceted medical syndrome and appraise the degree of related problem concerning prevention and treatment, which passes throughout the prevention of the risk factor.

Applying probiotics to treat and prevent candida fungal infections is derived from the evidence that assured probiotic strains employ a defensive outcome *in vivo* by hindering the epithelial cells adhesion and colonization by the infectious fungus to the mucosa, secretion of metabolites and also increasing epithelial cell immune defense mechanisms [33]. The different *Lactobacillus* spp which have demonstrated potential antifungal activity against *C. albicans* include *L. plantarum, L. fermentum* [34,35], *L. reuteri, L. rhamnosus, L. johnsonii* [36], *L. acidophilus* [37], *Lactobacillus* paracasei [38], *Lactobacillus* pentosus [39], *L. crispatus, L. gasseri* and *L. vaginalis* [40]. In addition, many of these species have also shown activity against non-albicans *Candida* species like *Candida crusie, Candida glabrata, Candida lusitaniae, Candida tropicalis, C. paropsilosis* etc., [39–42]. The two standard probiotic ATCC cultures *L. reuteri* RC-14 and *L. rhamnosus* GR-1 have been repeatedly used to demonstrate their antifungal activity against different *Candida* species. One such study with these two cultures has been tested against *C. albicans* causing vulvovaginal candidiasis (VVC). Transcriptome analysis of *C. albicans* chromosome revealed increased gene expression related to stress and under expression of fluconazole resistance related genes which asserted the effect of probiotic cultures on *C albicans* survival [36]. Various probiotic *lactobacillus* demonstrating potential anticandidal activity against different pathogenic strains has been shown in Table 1. Apart from different *Lactobacillus* species, other probiotic cultures that have exhibited anticandidal activity include lactic acid bacteria like *Pediococcus pentosaceous, Weisella confusa* [34], *Pediococcus acidilactici* [43], *Bifidobacterium bifidum* [44], *Bifidobacterium breve* and yeasts like *Saccharomyces boulardii* [45], *S cerevisiae* [46] etc.,

Biofilm formation among *Candida* spp is one of the most important factors that contributes towards virulence [47]. Numerous studies with probiotic isolates and their culture filtrates (CFS) have shown efficient antibiofilm activity towards *Candida* spp. A study conducted using *Lactobacillus pentosus* (LAP1 strain) manifested significant antibiofilm property against *Candida tropicalis, Candida albicans* and *Candida krusei*. Additionally, In the time killing assay, these three *Candida* spp were completely killed at 8 hrs with the culture filtrate [39]. In another study, mature biofilm formed by single species as well as consortium with *Candida* non-albicans along with *Candida tropicalis, Candida krusie* and *C*

Table 1
Antifungal activity of probiotic isolates against *Candida* species.

Sl No	Probiotic isolate	Pathogen	Results	References
1	*L. acidophilus* ATCC 4356	*C. albicans* ATCC 18,804	*L. acidophilus* cell free supernatant efficiently reduced growth of *C. albicans* cells by 45.1%	Vilela et al. [37]
2	*L. rhamnosus GR-1*ATCC 55,826 *and L. reuteri RC-14*ATCC 55,845	*C. glabrata* ATCC 2001 *C.glabrata* (vaginal isolates) namely *C. glabrata* 95,670, 91,152, 94,885, 98,328	*Lactobacilluscells and their culture filtrate increased the* candidicidal activity against *C. glabrata.* - in addition, Both *Lactobacillus* exhibited strong coaggregation and autoaggregation in the presence of *Candida*	Chew et al. [50]
3	*L. rhamnosus* GR-1 and *L. reuteri RC*-14 *Lactobacillus johnsonii* PV016	*C. albicans SC5314*	*Lactobacillus* showed visible zones of candida growth inhibition in agar plates and suppressed the biofilm formation in broth culture.	Köhler et al. [36]
4	*L. rhamnosus* IMC 501 - *L. paracasei* IMC 502 Combination of both SYNBIO(1:1 combination)	*C. albicans* ATCC 10,261, ISS2,ISS7,*C. albicans* resistant ISS1, *Candida Glabrata* ISS3, *Candida kruseiI*SS4, *Candida parapsilosis* ISS5, and *Candida tropicalis* ISS6	*L. rhamnosus* - Inhibitory activity against two *C. albicans* strains (ATCC 10,261 and ISS7). All Candida spp were inhibited except *C. glabrata* and *C. tropicalis*. SYNBIO- Inhibitory activity especially *C. albicans* and *C. krusei.* SYNBIO gave a high antagonistic activity against all pathogens with a percentage of antagonistic effectiveness between 75% and 100%.	Coman et al. [123]
5	*L. paracasei subsp paracasei* 303, *L. plantarum* 319, *L. fermentum* 404, *L. rhamnosus* IMC 501, and *L. paracasei* IMC 502	*C. albicans* ISS2, *C. glabrata* ISS1, *C. krusei* ISS4, *C. parapsilosis* ISS5, *C.tropicalis* ISS6 (clinical isolates)	All *lactobacillus* had the potential to inhibit the candida and able to produce antimicrobial compounds such as hydrogen peroxide. All lactobacillus able to coaggregate well with candida species in different degree followed by SYNBIO.	Verdenelli et al. [41]
6	*L. plantarum* (ATCC 8014) and *L. johnsonii* (clinical isolate)	*C. albicans* (ATCC 14,053)	Conventional hole-plate diffusion: *lactobacillus* cell free supernatant	Kheradmand et al. [124]

(*continued on next page*)

Table 1 (*continued*)

Sl No	Probiotic isolate	Pathogen	Results	References
			combination with selenium dioxide showed anti-candida activity; whereas supernatant without selenium did not showed antifungal activity.	
7	CFS of Lactic acid bacteria	*C. albicans*	Eight of the 41 fractions excibited antifungal effects against *C.albicans*. among these eight fractions (A8, A10, B8 and B9 exhibited a complete growth inhibitory effect (100%) in the broth microdilution assay when incubated with *C. albicans* for 48 h or more.	Seneviratne et al. [125]
8	*L. paracasei* 28.4, *L. rhamnosus*5.2 and *L. fermentum* 20.4	*C. albicans* ATCC 18,804,60 (CA60) and CA230S	The most significant reduction in the number of recovered fungal CFUs was attributed to *L. paracasei* 28.4 that reduced fungal cells by 0.72 Log ($p = 0.0001$). *Lactobacillus* supernatant decreased the *C. albicans* growth by 0.4 Logfor *L. rhamnosus* 5.2 ($p = 0.0001$), 0.6 Log for *L. fermentum* 20.4 ($p = 0.0001$) and 0.6 Log for *L. paracasei* 28.4 ($p = 0.0001$).	Rossoni et al. [38]
9	*Lactobacillus rhamnosus* GG	*C.albicans* SC5314	LGG had a significant impact on major virulence attributes, including adhesion, invasion, and hyphal extention, whose reduction consequently prevented epithelial damage.	Mailänder-Sánchez et al. [51]
10	*S. cerevisiae* CNCM I −3856	*C.albicans* (CA-6)	Affected the expression of virulence traits of *C . albicans* such as aspartyl proteinases as well as hyphae-asso3ciated proties Hwp 1 and Ece 1 in the vaginal cavity.	Gabrielli et al. [46]

Table 1 (*continued*)

Sl No	Probiotic isolate	Pathogen	Results	References
11	LAB 1 CFS (*Lactobacillus pentosus* strain LAP 1)	*C.albicans, C. tropicalis and C. krusei*	- The viability of *C. albicans* was found to be slightly reduced at 0.5 × MIC of CFNS *C. albicans* was killed after 8 h and 4 h at MIC and 2 × MIC values, - the killing of *C. tropicalis* was observed within 8 h and 4 h at MIC and 2 × MIC values *C. krusei* was killed after 8 h and 6 h at MIC and 2 × MIC values of CFNS.	Aarti et al. [39]
12	*Lactobacillus fermentum* MG901 and *L. plantarum* MG 989	*C.albicans*	*C.albicans* cells lost metabolic activity and eventually killed . -high surface hydrophobicity that enhanced its adhesion ability to epithelial cell and showed coaggregation with *C.albicans* to affect their adhesion and colonization,	Kang et al. [35]
13	*L. gasseri* and *L. rhamnosus*	*C.tropicalis* BF, *C.krusei* BF and *C. parapsilosis* BF	64.66%, 67.83% and 33.03% reduction were observed when the biofilms treated with *L. gasseri.* (CFS) 66.84%,70.56% and 41.33% reduction were observed when the biofilms treated with *L. rhamnoses* (CFS)	Tan et al. [42]
14	*L.crispatus* B1-BC8, *L.gasseri* BC9-BC14 and *L. vaginalis* BC15-BC17	*C.albicans, C. glabrata, C.krusei, C. tropicalis, C. lusitaniae*	Braod spectrum activity was observed for *L. crispatus* BC1, BC4, BC5 and *L.vaginalis* BC 15, demonstrating fungicidal activity against all isolates of *C.albicans* and *C.lusitaniae* and reduced pathogen adhesion.	Parolin et al. [40]
15	*L.fermentum,L. rhamnosus, L. plantarum, L.acidophilus*	*C. albicans* and *C. pseudotropicalis*	A small proportion of the *lactobacilli* tested adhered strongly to cultured Vaginal epithelial cells and Inhibited the growth of *C. albicans* but not of *C. pseudotropicalis*	Strus et al. [126]

parapsilosis was also disrupted by cell free supernatants of *lactobacilli* in 24 hrs. This has been examined and certified by scanning electron microscopy (SEM) and confocal laser scanning microscopy (CLSM) [48]. One more study by Hager et al. [45] proved that culture filtrates of probiotic strains *L. acidophilus, Lactobacillus rhamnosus, Saccharomyces boulardii,* and *Bifidobacterium breve* prevented polymicrobial biofilm formation by *Candida tropicalis* along with the combination of *Serratia marcescens* and *E. coli*.

With the intention of better understanding the anticandidal activity of potential probiotic cultures, vaginal epithelial cell line of human such as VK2/E6E7 has been used as an experiment model [49]. This study has shown that *Lactobacillus reuteri* RC-14 alone and in conjunction with *Lactobacillus rhamnosus* GR-1 have the ability to hinder *Candidal* growth and their cell free supernatant may upregulate interleukin secretion by epithelial cell line which could play a role in clearing the yeast growth *in vivo*. The same group has done a clinical trial in 2009 demonstrating the efficacy of these two strains as a therapeutic and prophylactic adjuvant in the prevention or treatment of vulvovaginal candidiasis (VVC) [49]. Further, the antifungal outcome of these two strains was experimented against *Candida glabrata* by plate based microtitre method, spot agar overlay method and live/dead yeast viability method using CLSM. The metabolic actions of all the 4 strains of *C. glabrata* clinical isolates were found to be hindered by the probiotics exhibiting strong coaggregation and autoaggregation traits [50].

An interesting study establishing the protective cause of probiotic strain *Lactobacillus rhamnosus* GG (LGG) on the epithelial tissue of oral cavity from the damage caused by *Candida albicans* was published in 2017 [51] in which an in vitro representation of reconstructed human oral epithelial multilayers (RHOEs) and human keratinocytes (TR146 monolayers) were used. This study not only proved the protective action of probiotic by inhibiting fungal adhesion, invasion and hyphal extension, but also indicated the metabolic reprogramming in *Candida* due to nutrient depletion. Many *Lactobacillus* species are robust at inhibiting *Candida* infection. The anticandidal activity of potential probiotics is represented in the Fig. 4.

4. Probiotic bacteria against *Mucor* and *Rhizopus* species

The second most recurrent mold infection seen in immunosuppressed patients is Mucormycosis. This infection can progress expeditiously in

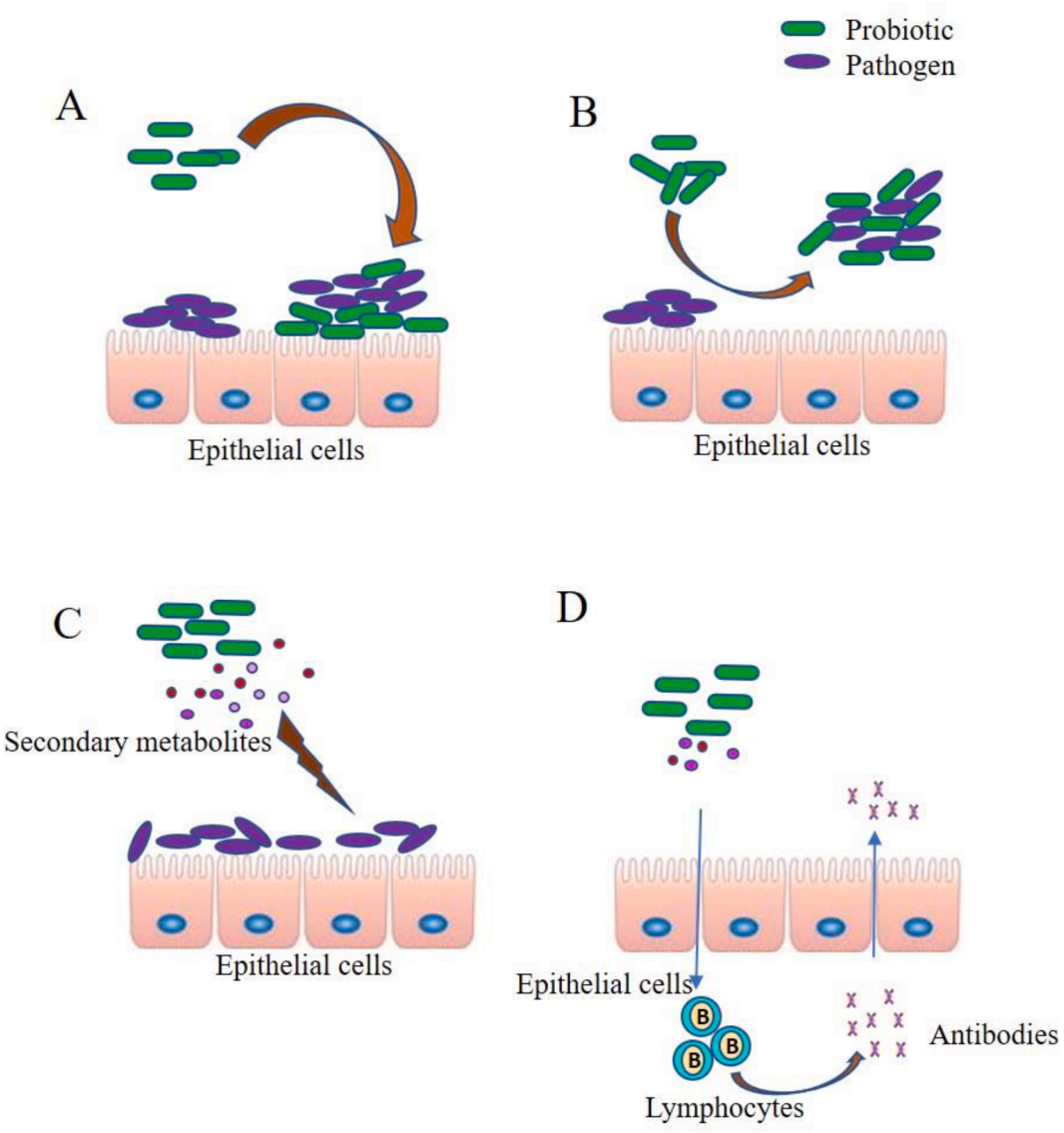

Fig 4. Anticandidal activity of probiotic isolates by different mode of actions. A) Anticandidal activity competition adhesion by the probiotics to the epithelial cells, B) Anticandidal activity by Coaggregation of pathogens and probiotics, C) Anticandidal activity by the production of secondary metabolites that kills the pathogen, D) Anticandidal activity by immunomodulation.

both immunocompetent and immunocompromised patients [52]. *Rhizopus* species (34%), *Mucor* species (12%), *Leichteimia* species (19%) and *Rhizomucor* (23%) are the most common agents that cause mucormycosis [53]. These moulds enter the body of the human through skin or respiratory tract and less usually by the means of gastrointestinal tract, evoking an response of acute inflammatory [54] (Fig.2). Under suitable circumstances like in immunocompromised individuals, these moulds plague the blood vessels and causing substantial thrombosis of vessels as well as ischemic tissue necrosis [6]. Even after active management of these infections, they are quickly/rapidly increasing and resulting in high rate of death [55]. The antifungals, Amphotericin B (AMB) and their lipid formulations, and newly introduced antifungal agent isavuconazole have been considered as initial treatment for mucormycosis [56]. The pro-drug isavuconazonium sulfate derive from the biologically active antifungal agent such as new broad spectrum triazole and isavuconazole [57]. Some other antifungal agents such as caspofungin, micafungin or anidulafungin, deferasirox and echinocandins also been used for the treatment of mucormycosis. However, these antifungal treatments are nephrotoxic, dose dependent and do not seem to propose an increased chance of survival [58]. Moreover, Rhino orbital mucormycosis reports have been increased in populace among coronavirus disease 2019 particularly in India. In addition, Diabetes mellitus (DM) is one more an autonomous threat factor for both mucormycosis and severe COVID-19 [59]. Incidence of Mucormycosis is apparent typical in the context of immunosuppression like, Solid organ transplantation, diabetes mellitus, hematopoietic stem cell transplantation and hematologic malignancy [60]. Subsequent angioinvasion by hyphae onsets with an accurate interaction with endothelial cells and can bring about systemic proliferation of the disease [58]. Diverse clinical syndromes can emerge in liable hosts such as rhino orbito-cerebral, gastrointestinal, pulmonary cutaneous, disseminated and uncommon appearances [61].

Numerous evidence of the probiotics antifungal effects in vitro against *Mucor* and *Rhizopous* species has proved probiotics and their postbiotics as potential biocontrol strategies. *Lactobacillus lactis, Pedicoccus pentosaceus, Lactobacillus plantarum* and *LactoBacillus brevis* expressed significant antifungal activity against *Rhizopus stolonifer* [62]. Sodium caseinate fermentate from *Lactobacillus fermentum* NCDC141 depicted the inhibitory effect against mold culture *Rhizopous oryzae* NCDC52 [63]. In another report *Rhizopus stolonifer* populaces were totally repressed by the use of *Lactobacillus plantarum* A6 coating. This outcome validates the *Lactobacillus platarum* A6 strains antagonistic activity and confirms the constructive effects of edible coating applications [64]. Mucor plumbeus was inhibited by *Lactobacillus* species like *L. casei, L. reuteri, L. plantarum* and *L. bucheneri* in the invitro antifungal assays [65]. In another study, *Lactobacillus rhamnosus* strain 2002 showed significant antifungal activity against *Mucor plumbeus* [66]. *Lactobacillus harbinansis* L172, *Lactobacillus plantarum* L244, *Lactobacillus plantarum* CIRM-BIA1108, *Lactobacillus casei* L142, *LactoB. brevis* L128, *Lactobacillus mesenteroides* L126 and *Lactobacillus citreum* CIRM-BIA1456 exhibited good antagonistic activity against *Mucor racemoses* with strong zone of inhibition [67]. *Lactobacillus plantarum* TF10 and *Lactobacillus plantarum* IT10 showed good antifungal activity against *Mucor sitophila* MD6 with 57.33±4.50 mm and 44.66±4.50 mm of zone of inhibition respectively. CFS characterization of these LAB proved the role of low molecular weight peptides as antifungal compounds [68]. Another report reveals that *Mucor circinelloides* 01,180,023 and 3 strains of *Mucor plumbeus* 01,180,036, 01,180,037, 0,110,010 were strongly inhibited by probiotic bacteria such as *Lactobacillus rhamnosus* LRH01, LRH05, LRH14, LRH16, LRH43, *Lactobaillus plantarum* LP01, LP37, LP48, *Lactobacillus paracasei* LPC44, LPC46, *Lactobacillus parabuchneri* LPB02, LPB04 [69].The antimicrobial peptides produced by *Lactobacillus plantarum* LR/14 has been shown to have potential activity against *Rhizopus stolonifer*, and *Mucor racemosus* [70].

5. Use of probiotic bacteria for the control of dermatomycosis causing fungi

Dermatophytes are most filamentous keratinophylic fungi usually from the genera *Trichophyton, Epidermophyton, Microsporum*, and *Nannizzia,* which have an effect on skin, nails and hair. The main significant is dermatophytic fungi are slow in growing and as well the time, probably to get the ultimate result of culture is commonly 2–3 weeks. Therefore, initially the infections are commonly treated by practical administration of potential antifungal agents. Moreover, the only antifungal drugs that the Food and Drug Administration (FDA) of the United States(US) has permitted for the better treatment and prevention of superficial mycoses is terbinafine, griseofulvin, itraconazole and ciclopirox [71]. Though many such antifungal drugs have been developed in current years for dermatomycoses, they are restricted to a small number of chemical groups. Additionally, the incidence of resistance to these drugs has been observed in clinical strains results in failure in the treatment [72–74]. Apart from this various side effects such as affecting estrogen levels, liver-damage and allergic reactions are also found inpatients. For example, the azole group of drugs causes anaphylaxis [75]. The azole antifungals like ketoconazole and itraconazole able to act as both inhibitors and substrates of glycoprotein, that which eliminates toxins into the intestines [76]. These azole drugs also block steroid synthesis in humans [77].

Probiotics are well-known to hinder the development of dermatophytes and some reports indicate that they can used to prevent and treat the dermatophytic fungal infections as they are effective antifungal agents as well as safe upon consumption. A significant study was carried out by Guo et al., [78] in which among the 5 strains that showed strong antidermatophytic activity, the strain *Lactobacillus reuteri* R2 has effective inhibitory activity against *T tonsurans* and when the freeze dried supernatant of the LAB culture was incorporated at >1% concentration the mycelial growth and the conidial germination were inhibited completely. characterization of the CFS demonstrated the non proteinaceous nature of the antifungal compound found in it. Further the research from the same laboratory has shown that the antidermatophyte strain *L reuteri* ee1p exhibited activity against *Microsporum gypseum, M canis* and *E floccosum*. LCMS analysis of the CFS resulted in the detection of atleast 10 antifungal compounds including Hydroxyisocapric acid, hydrocinnamic acid, phenyllactic acid, azelaic acid, vanillic acid, p coumaric acid, 4-hydroxybenzoic acid, hydroxyphenyl lactic acid and also 3-hydroxydecanoic acid [78]. *Lactobacillus plantarum* KCC-10 inhibited *Epidermophyton floccosum* (KACC 44,918), *Trichophyton roseum* (KACC 40,956) and *Trichophyton mentagrophytes* (KACC 45,479) and 3-phenyl lactic acid was the antifungal agent produced by the isolate [79]. *L. acidophilus* and *Saccharomyces cerivisiae* expressed good antifungal potential against *Candida albicans*, and *Trichophyton mentagrophytes.* The in vitro study with the potential probiotics with 0.25, 0.5, 0.75, 1 and 1.5% (w/v) concentrations inhibited the *Trichophyton mentagrophtyes* growth with inhibition percentage 76%, 79%, 82.8%, 86% and 87% [80]. *Lactobacillus casei* (PTCC 1608), the microorganisms which is freeze dried and sealed glass ampoules that are used to inhibit the growth of *Tricophyton rubrum* (PTCC 5143), *Tricophyton verocosum* (PTCC 5056), *Microsporum canis* (PTCC 5069) and *Microsporum gypseum* (PTCC 5070). The utmost average inhibition zone was measured as 34 mm against *Tricophyton rubrum*. The Minimum Inhibitory Concentration assay showed that stabilized extract of probiotic had additional antidermatophyte activities compared to cell free supernatant [81]. There are several cases nearly 101 in which the potential probiotics are administered in combination with conventional drugs clinically for more than 102 fungal infections like vulvovaginal candidiasis. Moreover, 103 patents have been obtained for these probiotic formulations for topical applications [143] . The selective probiotic isolates with their specific antidermatophytic activity has been given in Table 2.

Table 2
Antifungal activity of probiotic isolates against dermatomycosis.

Sl No	Probiotic isolate	Pathogen	Results	References
1.	*L. acidophilus* (10^8 cfu /g) *Bacillus subtilis* (10^9 cfu/g; *Lactobacillus* spp. (10^8 cfu /g) and *Saccharomyces cerevisiae* (10^9 cfu/g)-Iraqi probiotic	*Trichophyton mentagrophyte*	Mean inhibition percentage of *T. mentagrophytes* in 0.25%, 0.5%, 0.75%, 1% and 1.5% concentration of probiotic is 76%, 79%, 82.8, 86% and 87% compared with control.	Ajah et al. [80]
2.	165 LAB isolates from sourdough, cereals, cheese, intestines of human, pig and cow.	*T. tonsurans DSMZ12285*	Five strains showed anti dermatophytic activity.*L reuteri* R2 and its CFS at >1% conc had strong inhibitory effect. Antifungal compound was of non proteinaceous in nature.	Guo et al. [78]
3.	220 LAB isolates from sourdough, cheese, cereals, intestines of human infants, cow, pig, mice	*M. canis DSM10708, M. gypseum DSM3824 and E. floccosum DSM10709*	4 strains showed strong inhibitory activity.*L.* reuteri ee1p and its CFS at >2% conc exhibited maximuminhibition. 10 antifungal metabolites were detected.	Guo et al. [78]
4.	*Lactobacillus casei* PTCC 1608	*Microsporum canis PTCC 5069, Microsporum gypseum PTCC 5070, Trichophyton rubrum PTCC 5143, Tricophyton verrucosum PTCC5056.*	Greatest zone of inhibition was seen against *T.rubrum.* Stabilized probiotic extract had more antidermatophyte effect compared to supernatant ($P <$ 0.01).	Alamderloo *et al.* [81]
5.	Fermentation product of herb by LAB (FHL), *Enterococcus faecalis*	*T rubrum T mentagrophytes*	The antifungal activity of FHL at a concentration of 34.6 mg/ml was as high as that of the synthetic fungicide. FHL had a higher level of antifungal activity under the low-pH conditions.	Kuwaki et al. [127]

6. Probiotic bacteria for the control of *Aspergillus* species

Aspergillosis is the utmost habitual mold infection in human beings, accounting for >85% of invading mold disease [82]. In immuno suppressed patients, *Aspergillus* species proceed to be a major source of life intimidating infection [83]. Morbidity and mortality are caused significantly due to the infections occurred by the *Aspergillus* species. Among 250 species of *Aspergillus*, only about 40 are revised as clinically important but the index is now growing [84]. The majority of species causing aspergillosis in humans are the *Aspergillus fumigates, Aspergillus flavus* and *Aspergillus terreus.* Some of the most commonly used drugs for the treatment are prednisone, prednisolone, caspofungin, voricanazole, methylprednisolone and itraconazole. Though these antifungal medications are generally used to treat infection, their efficacy is compromised due to the serious side effects including nephrotoxicity, hypersensitivity, electrolyte disturbances, kidney and liver damage, visual disturbances, described as photophobia, blurred vision, and altered color perception[85]. Hence there is a necessity for an alternative drug. Use of probiotics and postbiotics has opened a new avenue for the prevention and treatment of opportunistic infections such as aspergillosis which can be supplemented in the diet or added to medical formulations.

Numerous studies have reported on probiotics isolates for the control of *Aspergillus* growth. Probiotics strains isolated from cereal gruels [86], vegetables [87], kimchi- a soy based fermented food [88] and thai food [89] showed complete inhibition of growth of *A. flavus*. In addition, the reduction in fungal mat by *Lactobacillus* species also reported by numerous studies. Coculture of the probiotic isolates from Egyptian fermented food such as *Lactobacillus rhamnosus, Lactobacillus paracasei, L. plantarum* and *L. acidophilus* demonstrated efficient antifungal effect against different *Aspergillus* species i.e. *A. niger, A. flavus* and *A. fumigatus*. Among these, *L. rhamnosus* exhibited strong inhibition of all the fungi used for the study. Whereas *L. paracasei* partially inhibited *A. fumigatus* and minimal inhibition was obtained with *A. flavus* and *A. niger*. *L. plantarum* and *L. acidophilus* had shown minimal to partial inhibition with all the fungal pathogens [90]. A study done by Pundir et al. [91] out of the 26 Lactic Acid Bacteria isolates from different fresh foods, eight isolates showed potential antifungal activity against human pathogenic strains *A. fumigatus* and *C. albicans*.

Additionally, the concentrated Cell Free Supernatant (cCFS) of the strain *Lactiplantibacillus plantarum* 16 strain isolated from steep water during malt production completely controlled the spore germination and hyphal development in *A. fumigatus* and *R. stolonifer* [92]. Trancriptomic analysis of the above pathogen revealed many genes with altered transcription suggesting total metabolic shutdown resulting in cell death. The *Lactobacillus delbrueckii* and *Lactobacillus. brevis* exhibited significant effects on A*spergillus* biomass growth as reported by Bayankaram et al. [93] with 67.43% and 69.38% reduction in biomass of *Aspergillus parasiticus* and *Aspergillus flavus* respectively. The antagonistic activity of *Lactobacillus* species isolated from a diversity of sources is due to the production of antifungal postbiotics [94,95]. These secondary metabolites have been recognized as diverse phenyl lactic acids, organic acids, phenolic acid, hydrogen peroxide, hydroxyl fatty acids, cyclic dipeptides and proteinaceous secondary metabolites [96].

The work done by Ström et al. [97] demonstrated the antifungal effect of *Lactobacillus plantarum* strain (MiLAB 393) isolated from source grass silage against *A. fumigatus*. The antifungal cyclic dipeptides, cyclo (L-Phe-trans-4-OH-L-Pro) and cyclo(L-Phe-L-Pro) production by the LAB has been reported in this study for the first time. Another antifungal compound that was identified in this study was 3 - phenyllactic acid. According to Arasu et al. [79] in their work have demonstrated the antifungal efficiency of a novel isolate *L. plantarum* K46 and *L. plantarum* KCC-10 against 24 fungal strains including *Aspergillus clavatus* (KACC 40,071), *Aspergillus fumigatus* (KACC 40,080), *Aspergillus niger* (KACC 40, 280) and *Aspergillus pullulans* (KACC 41,291).The NMR spectral analysis of the purified antifungal compound was identified as 3-phenyllactic acid. The Minimum Inhibitory Concentration of the antimicrobial compound against *Aspergillus oryzae* and *Aspergillus clavatus* was 2.5 mg/ml and with respect to *Aspergillus fumigatus* and *Aspergillus niger* were 5.0 mg/ml.

Antifungal metabolites from two *Lactobacillus* species *Lactiplantibacillus plantarum* BCH-1 and *L* coryniformis BCH-4 which showed remarkable inhibition of *A. fumigatus* and *A. flavus* were identified by HPLC and GC–MS analysis. Citric acid and Lactic acid are seen as foremost organic acids produced from L coryniformis and *Lactiplantibacillus plantarum* respectively. In addition, these two species also produced hexadecanoic acid and 9, 12-otadecadienoic acid (Z, Z)-methyl ester as main fatty acids and also found as potential secondary metabolite against these filamentous fungi from these two species [98]. The study directed by Yang et al. [88] discovered the presence of another low molecular weight antifungal compound such as δ-dodecalactone from

L. plantarum AF1isolated from Kimchi showing strong antifungal activity against *A. fumigatus, A. flavus, A. ochraceus, A. petrakii, and A. nidulans.* Therefore, some of the *Lactobacillus* species used to control the growth of *Aspergillus* mold is listed in the Table 3.

7. Probiotic bacteria against *Fusarium* and *Penicillium* species

Fusariosis is a contagion that affects animals, plants as well as humans and are brought about by several fungi of the genera *Fusarium* [99]. In therapeutic arena, various *Fusarium* species have been correlated to systemic or local invasive infections in both immune competent personalities and immune depressed individuals [100]. Furthermore, it is probable that ecological isolates from the *Fusarium* species attain resistance owed to earlier contact to antifungals that are used in agronomic practices and these *Fusarium* species may spread and therefore, infect human biengs [101,102]. *Fusarium* species reveal worldwide distribution and it is assumed that nearly 10 species were associated to human pathogens including, *Fusarium oxysporum, Fusarium fujikuroi, Fusarium solani, Fusarium clamydosporum, Fusarium incarnateum-equiseti, Fusarium dimerum, Fusarium concolar, Fusarium Sambucinum* and *Fusarium lateritium.* Among these species, members of *Fusarium solani* are quite common and infectious, afterward *Fusarium oxysporum, Fusarium fujikori* and *Fusarium moniliforms* [103]. *Fusarium* species are source for a diverse range of human infections, extending from superficial, localised to disseminate with the most predominant being onychomycosis, keratitis and skin infections [104,105].

The most used antifungal agents comprise voriconazole, natamycin, parconazole and amphotericin B. *Fusarium* species exhibit inherent resistance to antibiotics echinocandins and some species show resistance to antibiotic azoles [106]. Moreover, minimum inhibitory concentration (MIC) and minimum fungicidal concentrations (MFC) have also not been well-known for *Fusarium* spp [107]. Aspects that subsidize to the fusariosis severity include amplified occurrence of multidrug resistance to species and the dearth of the research concerning to expansion of novel therapeutic options for prevention and treatment [104]. Therefore, biological control strategies are being increasingly explored. Several invitro studies have proved *Fusarium* species are sensitive to different strains of lactic acid bacteria. Two LAB isolates *L. plantarum* LPLUV10 and *L. paracasei* LPAUV12 are shown to have growth inhibitory effect on *Fusarium oxysporum* by 76% and 55% respectively [108]. In another study, 14 probiotic strains of *Lactobacillus* (*Lactobacillus pentosus, Lactobacillus plantarum, Lactobacillus. brevis*) and their CFS showed good antifungal activity against *Fusarium oxysporum* including biomass inhibition and mycelial growth inhibition. The antifungal nature of the compound found in the CFS was investigated and some of them were found to be proteinaceous in nature suggesting the presence of bacteriocin like compounds or peptides [109]. The antifungal effect of another strain *L. salivarius* and its culture filtrate was determined with *F solani* and it was found that mycelial growth and conidial germination of the pathogenic fungi was significantly inhibited by the culture filtrate. Characterization of CFS showed a synergistic effect of pH and proteinaceous substance for their antifungal activity [110]. The work of Zeboudj et al. [111] revealed the antifusarial effect of *Lactococcus lactis* subsp.*lactis* biovar *diacetylactis* and *Leoconostoc mesenteroides* subsp *mesenteroides* biovar *dextranicum against* 12 strains *F. oxysporum* showing inhibitory percentage ranging from 13.5% to 100%.The CFS of the selected strains showed 49.41% inhibition. The antagonistic compounds identified include organic acids [112], bacteriocins, hydrogen peroxide, compounds with low molecular weight (cyclic dipeptides, reuterin, phenyllactic acid, methylhydantoin, benzoic acid, mevalonolactone and hydroxylated fatty acids) [113]. Evidence of the probiotics antifungal effects in vitro against *Fusarium* species are listed in the Table 4.

Penicilliosis is a fungal infection instigated by *Penicillium marnaffei*, a dimorphic fungus thermally. In humans, *Penicillium marneffei* is an opportunistic mold that infects immunocompromised patients and also HIV positive patients. Incorporation of fungus conidia might be the

Table 3
Antifungal activity of *Lactobacillus* against *Aspergillus* species.

Sl no	Probiotic isolate	Fungal pathogen	Results	References
1	*Lactobacillus plantarum 62* *L. plantarum 16*	*A. fumigatus*	Inhibited the growth of pathogen by the production of Antifungals and organic acids	Crowley et al. [92]
2.	*L. plantarum LB-1* *L.plantarum F-3* *L. plantarum F-50*	*A. ochraceous*	Exhibited stronger antifungal activity with 20 mm diameter of inhibition zone	Sun et al. [128]
3	*L. plantarum Lp MYS44*	*A. parasiticus*	Suppressed the germination and growth of the spores and reduced the toxin by 34.2%	Poornachandra Rao et al. [129]
4.	*L. cellobiosus* *L. rhamnosus* *P. pentosaceus*	*A. flavus* *A. repens*	Bacteriocins produced by the *Lactobacillus* expressed good antifungal activity against the aspergillus species	Adesina et al. [130]
5	*L. plantarum CH1* *L. paracasei* *L. mesenteroides*	*A. tubingensis*	Complete inhibition of the pathogen was observed	Ouiddir et al. [131]
6	*L. plantarum* *L. rhamnosus* *L. paracasei and acidophillus*	*A. niger* *A. flavus* *A. fumigatus*	*L. rhamnosus* inhibited all the pathogens *L. plantarum* inhibited *A. flavus*, strong inhibition was seen by *Lactibacillus acidophillus* against *A. niger, Aspergillus fumigatus* was inhibited by *L paracasei.* The inhibition is due to the bacteriocins produced	Ali et al. [132]
7	*L. plantarum* UT9121	*A. flavus*	Probiotic modulate the mold growth and inhibited the fungal growth	Russo et al. [133]
8.	*L. plantarum*	*A. flavus*	Peptide mixture as the biocontrol agent reduce the spore formation	Muhialdin et al. [134]
9	*L. mesenteroides* DU15 *L.* plantarum TE10 *L. plantarum* IT10 *L. plantarum* IS10	*A. niger*	The CFS with low molecular peptides inhibited the pathogen by 94%, 93%, 94% respectively	Muhialdin et al. [68]
10	*L. kefir* FR7	*A. flavus* *A. carboneras*	Inhibited A flavus by 51.67% and A carbonarius by 45.56%.	Ben Taheur et al. [135]

(*continued on next page*)

Table 3 (*continued*)

Sl no	Probiotic isolate	Fungal pathogen	Results	References
			Reduced the% of AFB1,AFB2, OTA by 97.22%, 76.26%, 75.2% respectively	
11	*L. pentosaceus* *L. planatrum*	*A. niger* *A. carneus*	84% 0f OTA was reduced by P pentosaceus 94% of OTA by L plantarum	Taroub et al. [136]
12	*Bifidobacterium bifidum* (DSM 20,082), *L. acidophilus* (DSM 20,079) and *Lactobacillus plantarum* (DSM 20,174)	*Aspergillus flavus* strain (EMCC 274) and *Aspergillus parasiticus* (EMCC 886T)	Probiotic culture supernatant (PCS) at 1% concentration achieved high inhibition of AFB1 production by *Aspergillus flavus* by percentage reached to 76%. But this percentage was increased up to 77% in case of *Aspergillus parasiticus*.	Hamad et al. [137]
13.	*Lactobacillus plantarum* KCC-10	*Aspergillus clavatus* (KACC 40,071), *A. fumigates* (KACC 40,080), *A. niger* (KACC 40,280), *A. oryzae* (KACC 44,823), *A. pullulans* (KACC 41,291),	3-phenyl lactic acid was found as antifungal agent. The minimum inhibitory concentration of the compound against *Aspergillus clavatus, A. oryzae* was 25 mg/ ml and against A. *fumigatus, A. niger* was 50 mg/ ml, respectively.	Arasu et al. [79]

approach of transmission to human host. Even though the most frequent forms of disease appearance are non-specific as well as constitutes of anemia, low-grade fever and weight loss and the distinctive lesion in skin (central umbilicated papule) and even respiratory infections may also occur [114].

Some of the probiotic bacteria showed antifungal activity against various *Penicillium* species. *Lactobacillus lactis, Pediococcus pentosaceus, LactoB. brevis* and *Lactiplantibacillus plantarum* inhibited the growth of *penicillium citrimum* with 26.50±1.50 mm, 2.50±3.50 mm, 29.00±1.00 mm,20.00±0.00 mm of inhibition zone [62]. In another study, *Penicillium roqueforti* was inhibited by the *Lactobacillus plantarum* TE10 and IT5 with 72.33±1.52 mm and 71.00±2.64 mm diameter of inhibition zone respectively [68]. *Lactobacillus Rhamnosus* R-2002 endowed significant antifungal activity against *Penicillium aurantioviolaceum* [66]. Probiotic bacteria such as *Lactobacillus Rhamnosus* LRH01, LRH05, LRH14, LRH16, LRH43, *Lactobaillus plantarum* LP01, LP37, LP48, *Lactobacillus paracasei* LPC44, LPC46, *Lactobacillus parabuchneri* LPB02, LPB04 strongly inhibited *Penicillium commune* 01,180,002, 01,180,014, 01,180, 015, *Penicillium crustosum* 01,180,001, *Penicilium glabrum* IS13, *Penicillium palitans* PPao1, *Penicilium solitum* IS15 [69].

Table 4
Antifungal activity of *Lactobacillus* species against Fusarium species.

Sl No	Probiotic isolate	Fungal pathogen	Results	References
1	*Lactbacillus sakei* KTUO5–7	*F. culmorum* ʟ-2 *F. avenaceum* *F poe* *F. solani*	Probiotic inhibited fusarium species with 13.5 ± 1.4 mm zone of inbition for *F. culmorum* ʟ-2, 11.8 ± 0.5 mm for *F. avenaceum,* 9.3 ± 1.0 mm for *F. poe*, 13.8 ± 0.5 mm for *F. solani.*	Juodeikiene et al. [138]
2	*L. plantarum* LPLUV10 *L. paracasei* LPAUV7	*F. oxysporum f.* ssp.*lycoperici*	*L. plantarum* LPLUV10inhibited fusarium by 55% and about 76% of inhibition was observed by *L. paracasei* LPAUV7	López-Seijas et al. [108]
3.	Four strains of *Lactobacillus* strains of *L. plantarum, L Leuconostoc and L brevis*	*Fusarium oxysporum*	All the isolated inhibited the growth of pathogen with 20.15–22.8 mm of inhibition zone	Abouloifa et al. [109]
4	*L. salivarius* ssp. *Salivarius* JCM1231	*F. solani*	Conidial germination and mycelia growth of *F. solani* was significantly inhibited by the *Lactobacillus salivarius* culture filterate	Hu et al. [110]
5	*L. paracasei* ssp. *Tolerans*	*F. proliferatum* M5689,M5991 *F. graminearum* R4053	The probiotic isolated completely inhibited the mycelial growth of the fusarium species	Hassan and Bullerman, [139]
6.	*L. planatrum* 108 and 121	*F. culmorum*	CFs of the probiotic isolate inhibited the pathogen by 62% and 60% respectively	Russo et al. [140]
7	*L. plantarum* KCC 37 *L. plantarum* KCC-38	*F. oxysporum*	Showed intense antifungal activity with inhibition zone of 35.03±0.33 mm and 30.72±1.28 mm respectively	Muthusamy et al. [141]
8	*Leuconostoc mesenteroides ssp dextranicium*	*F. oxysporum* *F. redulene* *F. solani*	All the fusarium species are inhibited by the LAB isolate between 4.3 and 19.7% after 72 hour incubation on PDA plates	Zebboudj et al. [111]
9	*L. plantarum* TR71	*F. verticilloides*	Yellow mustard fermented extract with *L. plantarum* TR71 reduced the Fuminosin B1 by 92.6% and the antifungal metabolites produced are lactic acid, #- phenyl acetic acid, benzoic acid.	Torrijos et al. [142]

8. Use of postbiotics from probiotics

Commensal bacteria produce byproducts of metabolites to maintain their perseverance in the host and award a survival benefit over invading fungal pathogens [115]. Lactic Acid Bacteria generate various short chain

aliphatic organic acids like acetic acid and lactic acid, H_2O_2 and other compounds. Production and release of H_2O_2 is an important probiotic attribute of *Lactobacillus* species to fight against fungal diseases [116]. Other antifungal products formed by bacteria are minute molecules like biosurfactants and bacteriocins [117]. Bacteriocins are proteinaceous substances produced by bacteria, mainly by lactic acid bacteria, that show antimicrobial activity against closely related species. However when they are not fully characterised, they can be called bacteriocin like inhibitory subtsances and often hinder a broader range of species such as gram positive, gram negative bacteria and infection causing fungi [118]. *Lactobacillus plantarum* BCH-1 produced tartaric acid, pyruvic acid, lactic acid, citric acid, malic acid, formic and succinic acid. Among these acids the concentration of Citric acid and Lactic acid is more than other acids. *Lactobacillus coryniformis* BCH-4 secreted pyruvic acid, tartaric acid, citric acid, malonic acid, malic acid, lactic acid and succinic acid. Furthermore, among them, tartaric and lactic acid were found more in concentration [98]. *Lactobacillus plantarum* produced tetra deconoic acid, 1-methyl ethyl ester, pentadeconoic acid, hexadeconoic acid, 12-hydroxydeconoic acids and are found to have antifungal properties. In addition, *Lactobacillus casei* AST18 expressed good antifungal activity due to the assembly of some antifungal agents such as lactic acid (93.70 mg/ml) acetic acid (2.42 mg/ml), citric acid (1.29 mg/ml), tartaric acid (9.59 mg/ml) and reported as lactic acid is the major antifungal compound. Also cyclo(Leu-pro):5, 10diethoxy-2,3,7,8-tetrahydro-1H-dipyrrolo[1,2-a:1′,2′-d] pyrazine:2, 6-diphenyl-piperidine was found as a good antifungal compound by GCMS [119]. *Lactobacillus plantarum* produced bioactive compounds from which 3 purified peptides were presented with amino acid sequences LVGKKVQTF, SGADTTFLTK, and GTLIGQDYK as identified from bioinformatics program. Among these SGADTTFLTK inhibited *Penicillium expansum* by 58% and *Aspergillus parasiticus* by 73% [120]. The most copious antifungal compounds found in *Lactobacillus rhamnosus* derived fermentatives corresponded to lactic acid and acetic acid. Other organic acids, volatile organic compounds, free fatty acids were also found at lower levels. In addition, 9-amino acid peptides resulting from άs2-casein from the *Lactobacillus rhamnosus* resultant fermentate inhibited *Mucor racemoses* and *Rhizopus mucilaginosa* [121]. Similarly twelve organic compounds have been reported from liquid-liquid extraction of CFS-*Lactobacillus plantarum* MYS6 [112]. The purified active antifungal compounds of Lactobacillus plantarum EM were identified as 3-hydroxy-5-dodecenoic acid, lactic acid and acetic acid. Combine usage of these 3 acids cause severe damage to *Aspergillus* mycelial conidia cells in conjunction with aggregation of cells that are damaged, consequently, in fungicidal activity against *Aspergillus fumigatus* [122].

9. Conclusion and future perspectives

Opportunistic fungal pathogens together with the antifungal drugs resistance symbolize serious human health problem. The treatment and prevention with probiotics restores the natural microbiota with reward over conventional antifungals because they are non toxic and do not persuade microbial resistance that when administered in sufficient quantity, and as a result probiotics do not create adverse side effects, and further modulate the immune system. Therefore, the properties of probiotics have made it a subject of interest for various fields. Hence, there is a requirement for further elaborate assays, especially *in vivo* assays which would better characterize the complex interactions among the probiotics/postbiotics and the pathogenic fungi to realize the consequences of the antimicrobials production of the microorganisms. Even though all these specifics make research on antagonistic activity of potential probiotics organisms even more complex, nonetheless it presents an enormous opportunity for research in future.

CRediT authorship contribution statement

The author contributions are as follows: **S. Divyashree:** Conceptualization, Writing- original draft, Data curation, Software, Validation, Vizualization, Investigation, Methodology **B. Shruthi and P R. Vanitha:** Formal analysis, Resources, Coordinating, Editing, Correcting. **M. Y. Sreenivasa:** Conceptualization, Supervision, Funding acquisition, Project administration, Validation, Visualization, Review, and Editing. All authors contributed to the study conception and design. All authors have read and agreed to the published version of the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have **no conflict of interest** for the possible consideration for publication in the reputed journal **"Biotechnology Reports"**.

Data availability

No data was used for the research described in the article.

Acknowledgements

DS (FBO/Fell/1/2022-ECD-II) and SB (Myco/Fell/8/2022-ECD-II) are grateful to the Indian Council for Medical Research (ICMR; New Delhi) for a SRF fellowship.

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