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Exploring biotechnological and functional characteristics of probiotic yeasts: A review

B. Shruthi, N. Deepa, Rakesh Somashekaraiah, G. Adithi, S. Divyashree, M Y Sreenivasa *

Applied Mycology laboratory, Department of Studies in Microbiology, Manasagangotri, University of Mysore, Mysuru 570006, India

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ABSTRACT

Probiotics are vital and beneficial organisms which offers the health benefits to the host organisms. The fungal probiotic field is one of the developing fields nowadays. Yeast has an enormous and diverse group of microorganisms that is attracting and expanding the attention from researchers and industries. *Saccharomyces boulardii*, the only patented strain belonging to yeast genera for the human use, has been broadly evaluated for its probiotic effect. Yeasts belonging to the genera *Debaryomyces, Pichia, Yarrowia, Meyerozyma, Kluyveromyces* etc.., have attained more interest because of their beneficial and probable probiotic features. These yeast probiotics produce VOCs (Volatile organic compounds), mycocins and antimicrobials which shows the antagonistic effect against pathogenic fungi and bacteria. Additionally, those yeasts have been recorded as good plant growth promoting microorganisms. Yeast has an important role in environmental applications such as bioremediation and removal of metals like chromium, mercury, lead etc., from waste water. Probiotic yeasts with their promising antimicrobial, antioxidant, anticancer properties, cholesterol assimilation and immunomodulatory effects can also be utilized as biotherapeutics. In this review article we have made an attempt to address important yeast probiotic attributes.

1. Introduction

Probiotics are vital microorganisms which when ingested in suitable quantity offer a health benefit to the host [1]. Much research has been conducted with the bacterial probiotics but not with the yeast [2]. Even though many species belonging to *Lactobacillus* species are well known probiotic organisms, in existence an uprising interest is appearing for yeast as probiotics. Yeasts are broadly used in biotechnological and industrial applications for the production of fermented food products, including enzymes, acids and vitamins in large scale. Yeasts are unicellular eukaryotic fungi and they belong to the phyla Ascomycota (e.g., *Saccharomyces, Debaryomyces, Candida* etc.,) and Basidiomycota (e.g., *Cryptococcus, Rhodotorula*) and can reproduce both asexually and sexually [3]. To act constrictively, probiotics should be in the living condition to create a symbiotic stability in the host alimentary tract. As yeasts are not affected by the antibacterial agents, they are specifically favorable. Being resistant to antibiotic proves to be a beneficial characteristic of a probiotic organism. As yeast is naturally resistant to antibacterial antibiotics which is one of the features of fungi, it seems to be an important attribute for the use as probiotic. The major threat related with the antibiotic resistant *Lactobacillus* strains is the capability of transfer of resistant gene to the pathogenic bacteria. As transfer of gene among yeast and bacteria is rare, their application as probiotics is secure and advisable [4]. *Saccharomyces cerevesiae var boulardii* is the utmost common human yeast probiotic which is accessible in market presently. Yeasts promotes both the human and animal health, also they intensify the bioavailability of minerals through hydrolysis of phytate, folate biofortification, detoxification of fungal toxins and xenobiotics. Some yeasts other than *Saccharomyces* yeasts shown survivability in the digestive conditions, resistance to antibiotic which has made them the probable candidates as novel probiotics. Microbe-based systems are important and versatile biotechnological processes for the production of various chemical substrates because of the limited space essential for their quick growth and cultivation, along with diverse physiological and biochemical properties [5]. Potential probiotic yeast having the potentiality to produce the commercially important compounds are used as cell factories in industrial applications. Phagocytic cells yield high concentrations of microbicidal ROS (reactive oxygen species) like hydrogen peroxide and superoxide anion during phagocytosis to attack invading foreign pathogens. Though, excessive relative oxygen species

* Corresponding author.
E-mail addresses: mys@microbiology.uni-mysore.ac.in, sreenivasamy@gmail.com (M.Y. Sreenivasa).

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are generated, it can cause, mutations in DNA, damage to proteins and oxidation of membrane phospholipids. In this content, catalase and super oxide dismutase are the crucial enzymes that convert ROS into less detrimental oxygen species in the host [6]. Volatile organic compounds (VOCs) are metabolites with less molecular weight and high vapor pressure and low polarity. Some yeast produce mycocin which is also called as killer toxins. Yeast's genera that produce mycocin or killer toxin include *Saccharomyces, Candida, Cryptococcus, Debaryomyces, Kluyveromyces, Pichia, Torulopsis and Zygosaccharomyces*. The well-known mechanisms of the killer toxins are they block the synthesis of DNA and interrupt the cell division, killer toxin also inhibits component called β 1,3-glucan which is required for synthesis of cell wall [7] . These VOCs and killer toxins have the antagonistic effects against the pathogens. Probiotic yeast cells and the yeast metabolites show virtuous antioxidant properties. The free radicles produced are neutralized by the chemical compounds called as antioxidants, but oxidative stress arises when endogenic antioxidants are deficient. Probiotics modify the hosts defences against oxidative stress by the means of antimicrobial metabolite production, metal ion chelating and the antioxidant capability of probiotic helps in decreasing the gut microbiota [8] .

In this review we summarize the probiotic attributes of yeasts other than *Saccharomyces boulardii* and address the various applications of these probiotic yeasts in biotechnology. This review comprises of the probiotic attributes, antagonistic activity of probiotic yeasts against pathogenic fungi and bacteria, plant growth promoting attributes of yeast and biotherapeutic potentials of probiotic yeasts.

2. *Saccharomyces boulardii* as probiotic

Saccharomyces boulardii is a probiotic yeast habitually used for the treatment of gastrointestinal tract disorders [9]. It is genetically close and share similar karyotype to the model yeast *Saccharomyces cerevesiae* [10]. *Saccharomyces boulardii* optimal growth temperature parallels to the human host temperature (37°C) and this yeast is also resistant to very high temperature keeping 65% viability after one hour at 52°C [11]. The main stressors in the intestine include the high concentration of bile salts, pancreatic enzymes, hydrolytic enzymes, pancreatin, organic acids and bile salts [12]. Bile salts are detergents formed by liver and secreted to the intestine to progress nutrient absorption. As bile salts are detergent like molecules, can be fatal to gastrointestinal tract microorganisms by disrupting their cell membrane [11]. *Saccharomyces boulardii* remain viable after exposure to simulated gastric juice containing HCl, pepsin and bile salts [13]. Probiotics are thought to exhibit a various mechanism such as cellular adhesion, interactions with brain-gut axis, mucin production, cellular antagonism, antitoxin effects, modulation of normal microbiome, immune regulations, metabolic regulations and signal pathway modification, physiological protection and pathogen competition [14, 15,16]. *Saccharomyces boulardii* take part in a number of these effects as part of its probiotic properties [9]. *Saccharomyces boulardii* is a good antimicrobial agent and kills the pathogens. Hence it is used in the treatment of *Clostridium difficle* infections, inflammatory bowel diseases, candiasis, diarrhea, small intestine bacterial overgrowth in patients with multiple sclerosis [17]. Metabolites produced by the gut microbiome can perform immunomodulatory and anti-inflammatory functions that arouse immune cells, this aptitude arises from the interaction between the probiotics and the epithelial cells, dendritic cell monocytes, macrophages and lymphocytes [14,15]. Probiotics also promote phagocytic activity, cell proliferation and production of secretary immunoglobulins IgA and IgM [18]. *Saccharomyces boulardii* can modulate immunological function by acting as a stimulant or a proinflammatory inhibitor. It is capable of modulating inflammatory process by lessening the levels of proinflammatory molecules such as cytokine interleukin-8, mitogen activated protein (MAP) kinases and the (nuclear factor kappa B) NF-kB signaling pathway in the infection by S. *typhimurium, E coli, C. difficle, C. albicans* [19,20,21]. *Saccharomyces boulardii* is a modulator of enzyme activity required to uphold a healthy gastrointestinal tract. It employs trophic effects such as stimulation of digestive enzymes and nutrient transporter activity [22]**.** Clinical trials have examined the efficiency of *Saccharomyces boulardii* in upgrading several gastrointestinal conditions outcome. This yeast was seen to progress the outcome of several diarrhea, antibiotic associated diarrhea, acute diarrhea, traveller's diarrhea caused by bacterial, viral or parasites and enteral nutrition related diarrhea [9].

3. Probiotic attributes of yeasts

A new scope in the probiotic market is now exhibiting by the diversified category of beneficial and useful fungal community. To select the probable probiotic microbes, the selection criteria include the capability of the microorganisms to tolerate the digestive tract conditions, ability to adhere abdominal epithelial cells and also immunomodulating effects [23]. However, some authors reported many other attributes like hydrophobicity, antibiotic resistance, antagonistic activity against pathogens, good antioxidant properties are the selection criteria to select a potential probiotic [24, 25].

The gastric juices existing in the stomach has the low pH, also has the prohibitory action against pathogens and hence it is the chief barrier to microorganisms [26]. The yeast strains were exposed to endure in digestive tract conditions under unchanged conditions, three strains of *Saccharomyces cerevesiae* were more tolerant to these conditions. *Hanseniaspora osmopholia* 1056, *Saccharomyces cerevesiae* 146, *Hanseniaspora osmopholia* 1092 and *Kluyveromyces thermotolerance* were also unaffected to gastro intestinal tract conditions [27]. The two strains of *Kluyveromyces marxianus* FS14KM1 and 6688KM exhibited 100% survival rate in the gastric juice conditions after 3 h of incubation and these strains are not been affected by the high bile salt concentration which is higher than 1% used in the assay [28] . In another study, 18 yeast cultures were isolated from table olives, namely *Candida orthopsilosis, Candida tropicalis, Debaryomyces hansenii, Pichia guillermondii, Meyerozyma caribacca* and 15 out of 18 isolates survived in gastrointestinal conditions with low pH and bile salt concentrations showing the final count of 7 log CFU/ml [24]. Research revealed that *Debaryomyces hansenii, Saccharomyces cerevesiae and Debaryomyces occidentalis* have the capability to survive at pH 2 in 0.5 sodium chloride solution which contains 1 M Hcl for 3 h [29]. The *Cryptococcus* species, a recently isolated marine yeast has numerous beneficial characteristics to be claimed as a probiotic microorganism and also they could be convenient in the progressive development of functional food or exotic food additives [30] .The yeast species *Debaryomyces hansenii*, which have the capacity to tolerate high salt concentration, isolated from several natural environments and foods, found to obtain advantageous and useful effect for applications as probiotics in *Pisces* [2] .

In another work, two strains of *Kluyveromyces marxianus*, 15 strains of *Saccharomyces cerevesiae*, one strain of *Pichia membranifaciens*, one strain of *Pichia guillermondii*, two strains of *Candida orthopsilosis*, two strains of *Pichia kudriavzevii* and three strains of *Hanseniaspora osmopholia*, one strain of *Candida quercitresa* survived in alimentary tract by tolerating the gastric conditions with acidic pH and bile salts [31]. The non-*Saccharomyces* yeasts *Meyerozyma guillermondii* was isolated from raw honey bee samples found to be thermotolerant which mean survived in the temperature of 27°C, 37°C, 42°C and also tolerated the conditions of low pH and bile salts [32] .

Auto aggregation is normally interposed by surface structures which were self-recognizing that included proteins and exopolysaccharides, altogether entitled as auto agglutinins. Some evidences exhibit that aggregating bacterium conversely yeast cells are protected and safeguarded from environmental stress which represents one of the important properties of probiotic strain [32]. Yeast cells are larger and denser than bacteria and hence it facilitates the yeast cells to participate faster in larger proportion. Consequently, the auto aggregation capability of

Table 1
Yeasts with their potential probiotic properties.

SL No	Probiotic isolate	Source	Methods	Results	References
1	*S. cerevesiae* *P. guillermondii* *C. orthopsilosis* *C. tropicalis* *M. caribacca* *D. hansenii*	Naturally fermented table olives	Isolated isolates are tested for safety, acid and bile tolerance, adhesion assay and auto aggregation, co aggregation and hydrophobicity assay, antimicrobial assay were performed	All were resistant to GI conditions, good percentage of hydrophobicity (42.5–92.2%) Adhesion to caco 2 cell (62–82%)	[24]
2	*K. marxianus JYC2614*	Fermented food products and beverages	Evaluated for survivability in gastric conditions, cell surface hydrophobicity, auto aggregation assay, antioxidant assay and β galactosidase activity.	Survived in acid and bile conditions, showed significant results for aggregation and hydrophobicity assays	[33]
3	*K. lactis* *S. unisporus*	Kefir	Survival in GI tract, aggregation assay hydrophobicity assay, hydrolytic enzyme production assay was performed	Both survived in GI conditions, *K. lactis* showed good Hydrophobicity with 88.75% None of them produced hydrolytic enzymes.	[88]
4.	*K. lactis* *P. fermentans*	Cheese samples	Evaluated for Survival at acidic pH and in bile salts, auto aggregation and hydrophobicity and also antioxidant properties	*P. fermentans* showed better antioxidant property than *K. lactis*.	[89]
5	*M. caribacca 9D* *C. lusitaniae 4I*	Pineapple peel and juice	Isolates are examined to tolerate pH 2,30.0 g/l pepsin, 0.1% bile. Assay include Auto aggregation and cell surface hydrophobicity and antimicrobial activity were done.	Both survived gastric conditions. *M. caribacca* showed good auto aggregation capability with 98.52%	[34]
6	*S. cerevesiae* *M. guillermondii*	Raw honey bee samples	Examined for GI conditions survivability, auto aggregation assay, organic acid production.	All the isolates survived GI conditions and showed good aggregation capacity with 80- 100%	[32]
7	*S. cerevesiae* *P. kluvyeri*	Fermented beverage, kefir and cocoa fermentation	Assessed to endure in pH 2,0.3% bile, auto aggregation and hydrophobicity assay with antioxidant and phytate hydrolyzing assay, adhesion to caco2 cells	All isolates showed high% of adhesion >63% and antioxidant activity 18–62%	[31]
8	L.*thermotolerans* *T. delbruekii* *M.ziziphicola*	Spontaneous processed food, sour dough, cheese, wine, barks, sugarcane juices, soil	Isolates are assessed to grow in 37°C, acidic pH and bile. Antimicrobial and antioxidant assay were also performed	Showed better results compared to control codex	[90]
9	*A. Pullulans* *D.rogusa* *A. proteae* *P. fermentans* *H. guillermondii* *E. coryli*	Pistachio fruits	Preliminary probiotic screening under gastral conditions, examined for auto aggregation, antioxidant, hydrophobicity, properties fungicidal activity and biofilm formation assay	*D.rogusa 8,* *H. guillermondii 6,* *A. proteae 5* showed good antioxidant properties than control	[25]
10	*Kluyveromyces* strains	Fiore Sardo cheese	Evaluated for tolerance for GI tract conditions, adhesion assay, auto aggregation assays and hydrophobicity assay were performed	*K. marxianus* strains showed significant adhesion up to 68%with hydrophobicity > 50%.	[28]
11.	*D. hansenii*	Fish gut and food	Screened for probiotic attributes, adhesion assay and immunomodulatory assay	Survived GI tract. Induce high IL10/ IL12 ratio	[38]
12	*S. cerevesiae* *P. kudriavzevii*	Toddy nectar	Cytotoxic and antioxidant assay adhesion assay with tolerance in GI conditions	*S cerevesiae* has good cytotoxity, antioxidant activity	[91]

yeast strains is one step ahead than that of probiotic bacteria [33]. The strains of *Diutina rugosa* 7 and 9 and *Pichia fermentans* 19 expressed virtuous aggregation abilities with 71% and 77.5% respectively, whereas the auto aggregation capability of *Saccharomyces boulardii* was 37.15% which is used as control [25] . But in other studies, it is reported that the auto aggregation capacity of the control *Saccharomyces boulardii* is > 90%.

Meyerozyma caribacca 9C and 9D yeast strains expressed favorable properties of probiotics with 99.36% and 98.52% of auto aggregation respectively after 24 h of incubation time and these outcomes are near or higher than the reference strain [34] . *Lipomyces starkeyi* VIT-MNO3 revealed good probiotic assets with 95% of self-adhesion [35]. The auto aggregation capacity of *Candida quercitresa* CCMA 0560 isolated from indigenous fermented foods exhibited 95%±3.6% which was similar to reference strain *Saccharomyces boulardii* with 95.5%±0.1%. The auto aggregation capacity of probiotic yeast *Sporidiobocus ruineniae* A45.2 was up to 88.2 ± 1.2% [36]. Two strains of *Meyerozyma guillermondii* reported the aggregation capacity of 91% and 95% which was similar nearer to the positive control isolate *Saccharomyces boulardii* with 96% [32] .

Cell surface hydrophobicity and auto aggregation assay are considered as direct screening tools to assess and select the adhesion capability of the probiotic isolate. The cell surfaces of yeast with high hydrophobicity afford both the greater aggregation capacity and also the adhesion capacity *Debaryomyces hansenii* in the cell surface hydrophobicity assay with 92.23±1.2% of hydrophobicity showed noticeable results when compared to control strain [24]. *Lipomyces starkeyi* VIT-MNO3 revealed good probiotic assets with 85% hydrophobicity [35]. About 68.53% ±11.37% of cell surface hydrophobicity was reported by *Kazachstenia turicansis* whereas percentage of *Saccharomyces cerevesiae* JYC2619 was 6.10±1.5% [33]. *Kluyveromyces marxianus* exhibited 100% of hydrophobicity where as other isolates *Pichia membranifaciens* (CCMA 0016) showed 99.7%±0.1%, *Candida orthopsilosis* (CCMA 0566) showed 100% and *Pichia kluvyeri* (CCMA 0615) showed 99.3%±0.9% of hydrophobicity. The outcomes were similar and significant with reference strain *Saccharomyces boulardii* exhibiting 99.4%±0.2% [31].

The capacity of yeast cells to adhere the surface of intestinal cells were assayed in vitro with Caco-2/TC4 intestine derived cell line. Non-*Saccharomyces* strains isolated from the wine *Lachancea thermotolerans* (1039) and *Candida vini* (1063) and *Saccharomyces cerevesiae* (3) adhered to the cells with percentage of 78.30±0.49%, 75.52±2.96% and 76.37±2.10% respectively [37]. The adhesion capacity of yeasts *Meyerozyma caribacca, Debaryomyces hansenii, Pichia guillermondii, Candida orthopsilosis* are 82±6.82%, 76±1.88%, 72±3.01%, 71±1.30% whereas the adhesion percentage of *Saccharomyces boulardii* was 57 ±3.16% [24]. The two strains of *Debaryomyces hansenii* DIO2 and DIO9 has the strongest adherence to the surfaces of mucins and Caco-2 cells [38]. Furthermore, two strains of *Kluyveromyces lactis* showed notable higher adhesion to Caco-2 cells than *Saccharomyces boulardii* codex which is used as positive control [28]. Adhesion ability efficiency of

Table 2
Effect of VOCs on Fungal pathogens.

Sl No	Probiotic yeast	VOCs	Fungal pathogen	Targeted site	% Inhibition	References
1	*D. neipalensis*	β phenyl ethyl alcohol	*C. gloeosporioides*	Slowdowns the fungal growth, inhibit the spore germination	39.98–41.63%	[92]
2	*Pichia species*	2- phenyl ethanol	*M. purpures*	Inhibit mycelial growth and conidial germination	39.22%	[93]
3	*P. kudriavzevii* *P. occidentalis* *M. guillermondii* *M. caribacca*	Ethyl esters of medium chain fatty acids, phenyl ethyl alcohol, acetate esters	*Mucor,* *P. crysogenum,* *P. expansum* *A. falvus* *F. poea* *B. cineria* *F. cereals*	Reduce colony size and fungal growth	Greater than 50%	[94]
4	*P. galeiformis*	Ethanol, 3 methyl 1- butanol, phenyl ethyl alcohol Benzaldehyde Benzene acetaldehyde Acetic acid esters	*P. digitatum*	Affects the mycelial growth and spore germination	60%	[95]
5.	*H. uvarum*	Acetic acid, Octanoic acid, Ethyl propionate, *n*- propyl acetate, 2-methyl butyl acetate, Furfuryl acetate, Phenylmethyl acetate, 2- phenylethyl acetate	*B. cineria*	Decrease in the mycelial growth	45.6%−72%	[96]

Table 3
Biotherapeutic applications of probiotic yeasts.

Sl no	Probiotic isolate	Therapeutic property	References
1	Pichia kudriavzevii	Antibacterial property: *Pichia kudriavzevii* RY55 produced mycocins and inhibited the growth of potential bacterial pathogens like *E. coli, Enterococcus faecalis, Klebsiella* spp., *Staphylococcus aureus, Pseudomonas aeruginosa* and *Pseudomonas alcaligenes.*	[97]
2	*Saccharomyces boulardii* CNCM I-745	Immunomodulatory effect: stimulates the release of immunoglobulin molecules and numerous cytokines and also has an effect on the development of immune cells.	[4]
3	*K. marxianus* CIDCA 8154	Antioxidant property: The capacity to modulate oxidative stress in vivo was assessed using a *Caenorhabditis elegans* model. The yeast was able to protect the nematodes from oxidative stress by modulating the SKN-1 transcription factor trough the DAF-2 pathway. These results indicate *that K. marxianus* CIDCA 8154 could control the intestinal inflammation and cellular oxidative stress.	[98]
4	*Kluyveromyces marxianus* AS41	Anticancer property: The CFS was used for the assay. Significant downregulation on expression level of Bcl-2 and upregulation in BAD and CASP 9 in AGS (adenocarcinoma gastric cell lines)	[99]

yeast *Lipomyces starkeyi* VIT-MNO3 inoculum containing 5.5 × 10^7 CFU/mL per 9.2 cm2 of Caco-2 cells was noted [35].

Prebiotics are the source of food for the good bacteria which is present in gut. It is very much important to understand which nutrient is much appropriate for the better growth of these strains. Comparing to *Saccharomyces* yeasts, *Hanseniaspora osmopholia* (1094) assimilated all the prebiotics within 24 h of incubation time, excellent results were also reported by *Pichia* species (1003 and 1090) and *Candida Vini* (1063) [37].

High level concentrations of cholesterol in the blood serum are well-thought-out as the main threatening aspect for the cardio vascular diseases. Excessive amount of cholesterol in the serum leads to the various heart diseases and also give rise to colon cancer. It is found that yeast strains eliminate cholesterol. *Lipomyces starkeyi* VIT-MNO3 displayed a cholesterol removal percentage with 90% [35]. Some of yeast probiotics isolated from different sources with their probiotic attributes are listed in the Table 1.

4. Antibacterial activity

Probiotic bacteria have been very well documented for their antibacterial activity by many authors [39,40]. Most yeast scavenge pathogenic bacteria by the means of indirect mode of action such as auto aggregation, co aggregation and adhesion ability [41]. Immunomodulation is one of the mode of actions performed by the probiotic yeasts to kill pathogen. β-Glucans are naturally occurring (1→3)-β-D-linked polymers of glucose, which are seen in the cell walls of certain yeast. Several studies have confirmed that β-glucans, either in particulate or soluble forms, have stimulating assets on innate immune cells [macrophages, neutrophils (PMN), and natural killer (NK) cells], on antibacterial and anti-tumor activities, and on the production of cytokines [42]. One of the significant features of the potential probiotic is its antimicrobial property and because of this feature of killing the pathogen it can also be used as starter cultures. The antimicrobial property of an organism inhibits the pathogenic bacterial growth, avoid the formation of microbial colonies and may destroy microorganisms. So, these probiotic organisms can be used to treat the infections of gastro-intestinal tract. The yeast produces several molecules like organic acids, polyamines, proteases, mycocins or killer toxins and these acts as antimicrobial compounds which destroy the pathogenic bacteria [24].Fig.1

Saccharomyces boulardii CNCMI-745 showed significant and beneficial antimicrobic effect against infectious and bacterial pathogens like *Vibrio cholerae, Salmonella, C. difficle, E. coli, Shigella, Retrovirus* and *Candida albicans* using cellular and animal models [43]. The antimicrobial peptides which are formed by the yeast cells are very effective in their antagonistic activity because of the electrostatic reaction that occurs inside the cell membranes [44]. Antimicrobial peptides produced by *Saccharomyces cerevesiae* decreased the survivability of *B. subtilis, E. coli, K. aeruginosa, S. aureus* when equated to control strain. The

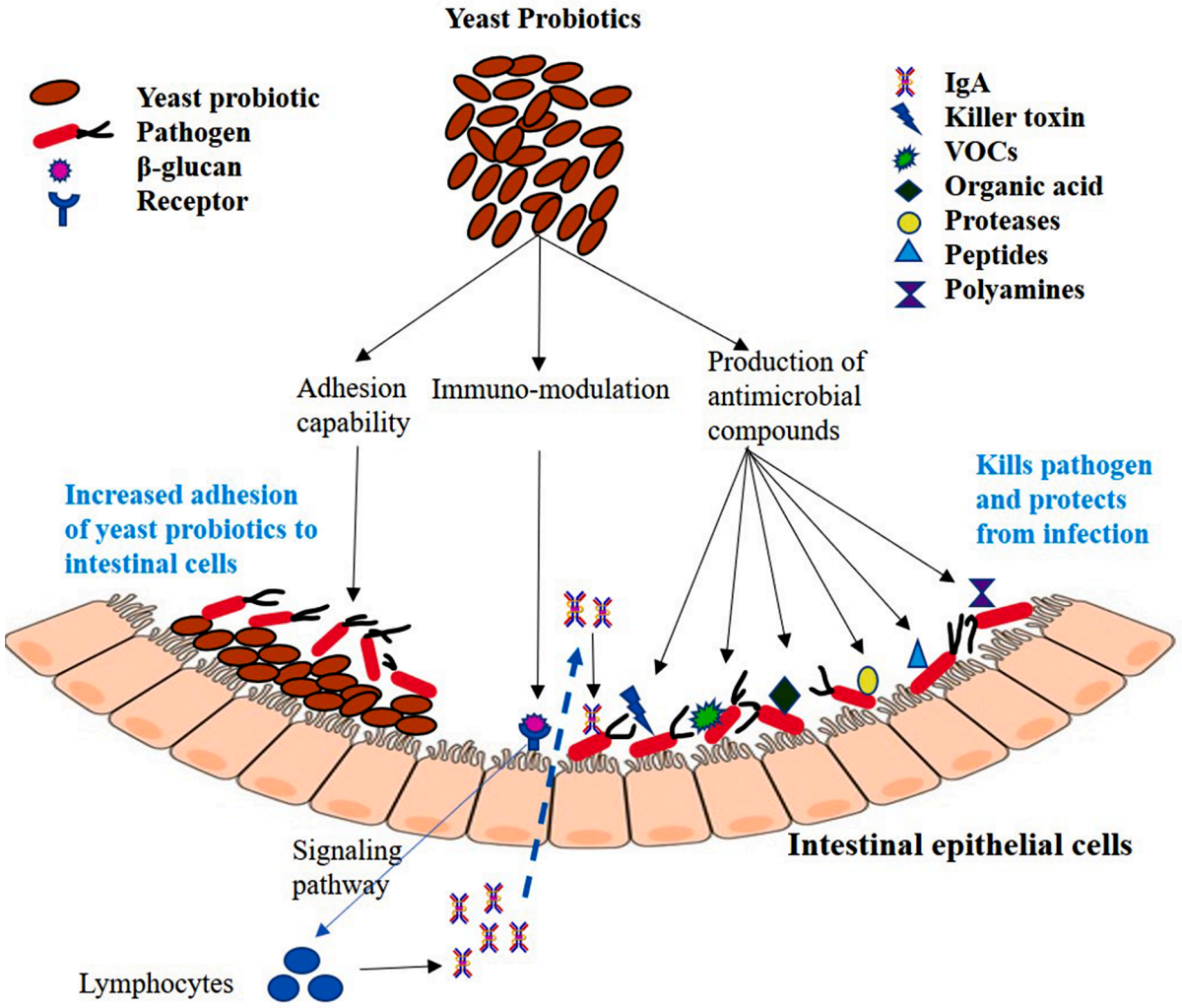

Fig. 1. Antagonistic activity of probiotic yeasts against pathogens with their mode of actions.

antimicrobial peptide's mechanism of action basically relays on the response of bioactive peptides with the cell membrane of bacteria and cells intestinal composition [45].

Selected wine yeast with killer activity were selected from 103 yeasts isolates and the antimicrobial activity was performed with both the supernatant and yeast cells against the bacterial pathogens *E. coli* ATCC 25922, *Lanchancea monocytogens* (ATCC13932), *S. thyphimurium* (ATCC14028), inhibition was not found when supernatant was used, and results were not observed even with 10X and 33X lyophilized concentrated supernatant and also reported that the incidence of live and metabolically active cells of yeasts are requisite to notice the antimicrobial activity [46]. In another study, *Candida kefir* (five isolates), *Saccharomyces cerevesiae* (four isolates), *Candida intermediate* (three isolates), *Candida tropicalis* (two isolates) were isolated from 160 milk and meat products and were assessed for their antagonistic activity against the pathogens *E. coli, P. aerogenosa, S. aureus. Candida kefir* showed highest activity for *E. coli* with 20 mm inhibition zone. *Saccharomyces cerevesiae* for *E. coli* with 12 mm, *Candida intermediate* for *E. coli* with 20 mm and for S. *aureous* with 24 mm, *Candida tropicalis* for *E. coli* with 14 mm, *Candida luciteniae* for *S. aureus* with 22 mm [47]. The carotenoid producing yeast *Sporidiobocus ruineniae* A45.2, which is a latent and capable probiotic yeast was able to produce cell associated tannase (CAT), gallic acid and live cells with antioxidant activity after they are grown in the substrate tannic acid and also expressed a significant co-aggregation ability with *S. agalactrae* (51.5 ± 2.6%), *S. typhimurium* (45.8 ± 0.1%) and *S. aureus* (44.0 ± 0.8%) [36]. *Hanseniaspora opuntiae* IPNFG2 which is isolated from *Guajillo pepper* showed antimicrobial activity against *S. typhimurium* and *Candida albicans* with 7.5-fold supernatant, and also 7.5-fold supernatant showed bacteriostatic effect against these two pathogens. The results revealed that there was the reduction in the adhesion of pathogens *E. coli,* L. *monocytogens, S. aureus* to Caco-2 cells [48]. The inhibition rate was similar or higher than that of *Saccharomyces boulardii* which was the commercial probiotic, 50% of decrease in the infection was seen by the yeast cells. In general, the assays demonstrated that when yeast and pathogens were co-incubated, the adhesion capacity of pathogenic microorganisms to Caco-2 cells decreases, showing the antagonistic effect of yeasts on bacteria in the adhesion to intestinal cells**.** *Yarrowia lipolytica* exhibited strong repressive activity against *P. damselae* (60%), *V. parahaemolyticus (*35%), *V. vulfinicus* (30%), *A. hydrophila* (20%) [49]. The highest coaggregation ability of probiotic yeast *Lipomyces starkeyi* associated with *Salmonella* species was 93%, *E coli* was 85%, *Klebsiella* species was 72%, *Staphylococcus aureus* was 69% and also reported 86% of biosurfactant activity [35]. Probiotic yeast and their metabolites, with their potential antimicrobial features could be used as therapeutic agents to treat diseases related to gastrointestinal tract and urinary tract.

5. Antifungal activity

Yeasts isolated from fruits has become an interesting source of strains

Fig. 2. Advantages of yeasts as probiotics.

with biocontrol capability against molds, which is valuable and useful in food and feed industry [50]. Yeast based products and yeasts, *Lactobacillus species* are now projected as safer biocontrols against mycotoxins are gaining demand in food manufacturing industries [32,51,52,53,54]. Essential oils were also been used for the control of pathogenic fungi [55] . Nine yeast isolates were carefully chosen, among those *Pichia anomola* as a biocontrol agent significantly reduced the progressive growth of *Colletotrichum gloeosporioides* with inhibition percentage of 79.63% and combination treatment of *T. harianum* and *Pichia anomola*, found to inhibit 93.22% of disease [56]. *Fusarium* species are one of the major contaminants found in the cereals [57,58,59].The biocontrol yeast *Kluyveromyces marxianus* QKM-4 showed the significant drop in the growth of fungal species of *Aspergillus, Penicillium* and *Fusarium* genera by the VOC production and percentage of reduction of OTA biosynthesis is 99.6% for *Penicillium verecosum* and 98.7% for *A. carbonarious* [60]. The strains of *Debaryomyces hansenii*, which produce the killer toxins significantly inhibited the fungal pathogen growth of *Alternaria brassicola, Alternaria citri, Aspergillus niger* and *Rhizopus stolonifera* as these fungal pathogens are most common causes of post-harvest decays on fruits like apple lemon and tomato [61]. About 57.7% and 56.6% of inhibition of *Macrophomina phaseolina* growth was reported by *Saccharomyces cerevesiae* and *Saccharomyces boulardii* respectively [62]. *Hanseniaspora guillermondii* 6 and 15 controlled *F. gramenarium* with 34.79±2.26% and 32.8 ± 0.5% respectively. About 22.5 ± 1.13% of inhibition of *A. paraciticus* growth was seen by *Diutina rogusa* 11 and *Diutina rogusa* 10 showed 31.2 ± 1.3% inhibition for *P. crustrotum. Eremothecium coryli* decreased the growth of *P. crustrotum* by 34.4 ± 2.19% [25]. *Hanseniaspora opuntiae,* one of the biocontrol yeasts produced the compounds and those compounds can avert the host plants *Arabidopsis thaliana* and *Glycine* max against the fungal pathogen *B. cinerea* and *C. cassiicola* [63]. The *Saccharomyces, Pichia, Metshinkowia, Dekkara and Rhodotorula* which belongs to yeast genera are most competitive strains showed substantial decrease in the growth of fungal mycelium, colony size and also reduced the production of fungal toxin produced by *Aspergillus carbonarious* in both solid and liquid media [64]. Some endophytic and epiphytic yeasts were isolated from sugarcane, leaves of rice and corn, among these *Candida nivariensis* DMKU-CE18 was most effective in controlling the development of mycelium by 64.9 ± 7.0% and they inhibit the conidial germination with 49.3 ± 3.3% of inhibition and condensed the aflatoxin production with 74.8 ± 6.5% of *A. flavus* in corn grains [65]. The decrease in the fungal colony by *Saccharomyces cerevesiae* Y33 is of > 90% and 93%

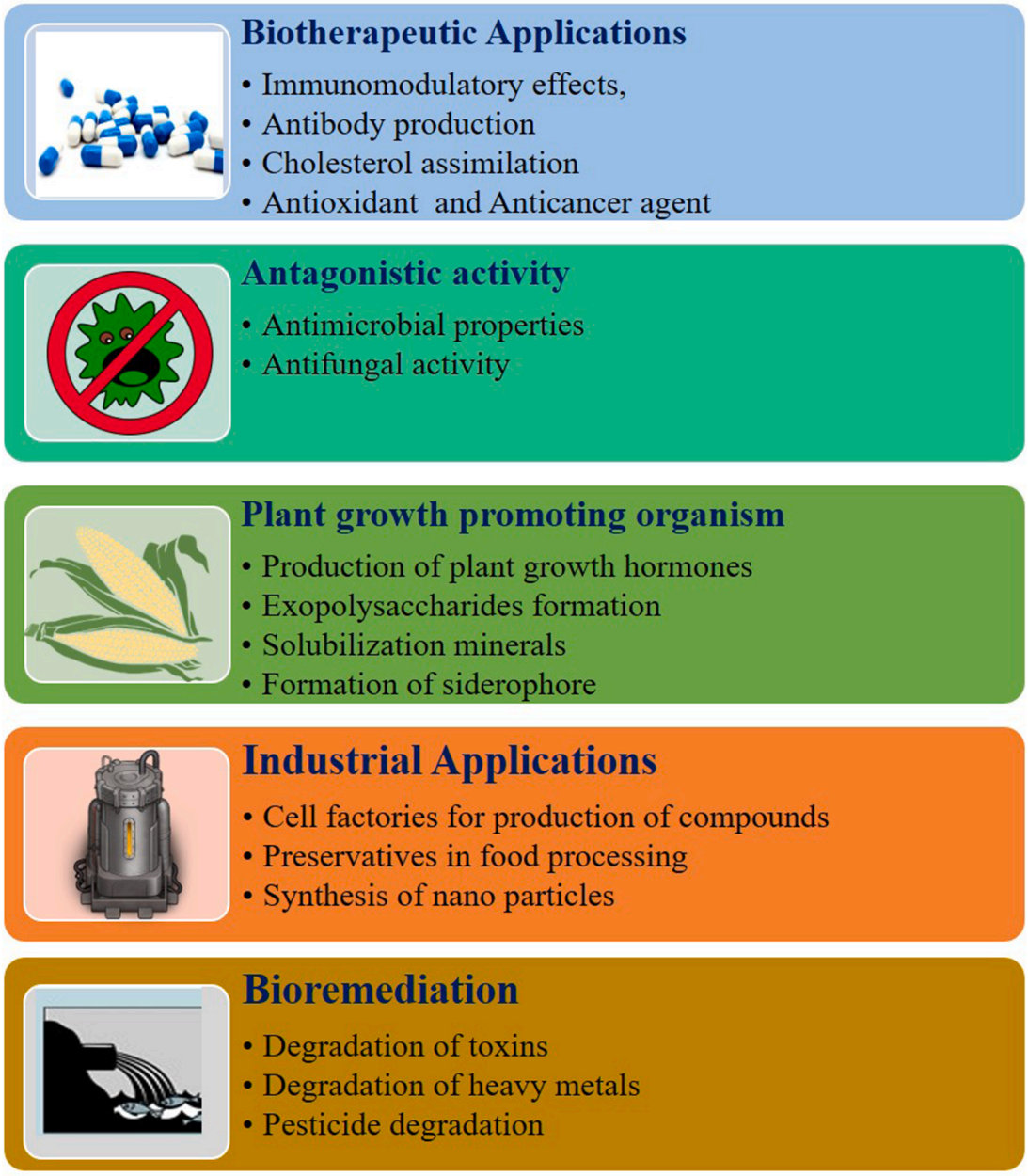

Fig. 3. Biotechnological applications of probiotic yeasts.

subsequently in the coculture of three and four days respectively [64]. *Aureobasidium pullulans* (YA05) and *Rhodoturala mucilaginosa* (YA07) are the yeast isolates isolated from dark chest nut soil which was collected from rhizosphere of the legume plant showed the maximum inhibition zone against the pathogen *Fusarium gramenarium* and *Phytophthora infestans* by the large zone of inhibition from 21.6 ± 0.3 to 30.6 ± 0.5 mm [66].

The quantity of toxins formed by pathogenic fungi was decreased from 14,983 to 5 ng/mL and 31,565 ng/mL to 1 ng/mL which was below the limit of degradation, when cultured along with *Saccharomyces cerevesiae* Y33 for 8 and 15 days respectively [64]. Probiotic yeasts with their effective antifungal activity against fungal pathogens could be, used as biofertilizers which replaces the fungicides and reduces the fungicidal contamination in the ecosystem. As these yeasts has significant role in degradation of mycotoxins, they can be used to improve food or feed product preservation in food and feed industries.

6. Production of VOCs by yeast probiotics

Various mechanisms are involved in the antagonistic functions of yeasts such as toxin production, induction of resistance in plants, competition for nutrients and space, release of organic compounds (VOCs), secretion of enzymes. VOCs are usually small molecules <300 Da, with high vapor pressure and these are least soluble in water [67]. VOCs represent one of the many biological controls of antagonism interactions which are very effective and significant against pathogens. VOCs include many molecules like alcohols, thioesters, thioalcohols, cyclohexanes, hydrocarbons, aldehydes, heterocyclic compounds, phenols, ketones and benzene derivatives [68]. The chemical composition of volatile organic compounds produced by the yeast changes depending upon the producing yeast, ecological niche and the pathogen [69]. Recently many researches revealed that yeast volatiles play a key role in yeast pathogen interactions. VOCs can cause alterations in the biosynthesis of amino acids and proteins in the mitochondria and the nuclei of fungi and bacteria and inhibits the growth of pathogen. Some examples

of VOCs produced by probiotic yeast isolates against fungal pathogens are listed in Table 2.

7. Probiotic yeast as plant growth promoting microorganism

The plant growth promoting microorganisms promote the growth of plants by providing some beneficial results like fixing the atmospheric nitrogen, production of plant growth promoting hormones like auxin, cytokine and gibberellins, production of antibiotics, antifungals, vitamins and organic acids, by solubilizing the minerals and nutrients, having capability to reduce the several substances and toxins [70, 71]. Exopolysaccharides also called as extra polymeric substances are the polymers with high molecular weight which are secreted by some microorganisms into the surrounding environment [72]. These helps the microorganisms to live and tolerate the stressful environmental conditions. *Rhodotorula species* strain CAH2 which is secluded from the rhizosphere soil of *Beta vulgaris* tolerate the large quantities of polyethylene glycol 600 (15% w/v), sodium chloride (150 mm) and Al (6 mm) and also the synthesis of exopolysaccharides by these organisms is 7.5 g/L of medium [73]. *Aureobasidium pullalans* YA05 and *Rhodotorula mucileginosa* YR07 showed good zone of 21.6 ± 0.3 to 30.6 ± 0.5 mm against fungal pathogens and produced about 51.7 ± 2.1 μg/mL of indole acetic acid [66]. 796 strains belonged to yeasts were isolated from peel of citrus, citrus leaves, citrus pulp and soil of *Nanjing mandarin* sample and IAA production was analyzed. Total yeast species belonging to *Hanseniaspora, Pichia, Candida, Sporidiobocus, Meyerozyma, Symmetrospora, Rhodotorula* produced IAA. But *Rhodotorula species* produced the highest IAA concentration of 76.23 mg/ml [74]. Effective microbes are the useful microorganisms which coexists naturally, when applied as inoculant they increase the useful and beneficial microflora in the soil ecosystem which facilitates the production of agricultural products [75]. Effective microbes' formulation of yeasts degrades dead plant tissues and they stimulate the growth of the roots [76]. The highest inorganic phosphate solubilization was shown by *Trichosporum ovoides* IFM 63,839 (2.98 mg/ml) and *Saccharomyces cerevesiae* F125-IF (2.54 mg/ml) also, two strains namely *Trichosporum ovoides* YEAST 6 and *Yarrowwia lipolytica* YEAST 16 showed high percentage of siderophore production with 67.40±0.33% and 74.85±0.78% respectively [77]. Siderophore producing microorganisms have been also considered as important features of plant growth promoting microorganisms which enhances the tolerance to heavy metal in plants. *Debaryomyces hansenii* Dh-67, *Saccharomyces cerevesiae Sc*-6 and *Lanchancea thermotolerance* Lt 69 promoted the seedling development with 10% increase in dry weight [78]. These evidences conclude the potential probiotic yeast could be used as plant biofertilizers for effective growth and development of plant under controlled and field environmental conditions.

8. Probiotic yeasts as biotherapeutics

As yeast probiotics are highly tolerant to gastro intestinal enzymes they also tolerate the pH variations and bile salt environments as well as organic acids. Also, they can endure in the different temperatures, they have numerous advantages [79]. The first strain that has been studied and surveyed for the usage as probiotics in the human medicine is *Saccharomyces boulardii* CNCM 1–745 and this strain is used to prevent and treat the diarrhea related with *Clostridium difficle* and antibiotic related diarrhea [43]. Two non-saccharomyces yeasts *Kluyveromyces marxianus* and *Meyerozyma gruessi* have the capability to guard the human epithelial cells from the pathogenic bacterial invasions. *Kluyveromyces marxianus* significantly expressed the stronger characteristic feature of (TER) transepithelial electrical resistance by 50% increase [80]. *Saccharomyces boulardii* CNCMI-745 modulate the response to infections by acting either on pathogen or directly on the toxins produced by bacteria and also, they act directly on the colonic membrane of the intestine of the host individual [43]. *Kluyveromyces lactis* M3 isolated from hypersaline sediment supplemented at 0.5 or 1.1% of the basal food improved bactericidal action against *Vibrio species* compared to fish fed commercial food *in-vivo* experiment inside gilthead seabream. It also had high antioxidant capability and immune stimulant activity [81]. Supplementation of *Saccharomyces boulardii* reduces the remanent lipoprotein, as this lipoprotein is the predictable biomarker and potential therapeutic target for the synthesis and also the production of coronary artery diseases. This probiotic yeast reduced 15.5% of lipoprotein in 8 weeks [82]. The yeast isolates *Pichia kudriavzevii* minimized the cholesterol by 20.29% from the media where as standard *Saccharomyces boulardii* used as control reduced cholesterol with 11.8%. Considering the attributes of *Pichia*, it can be concluded that it can control the cholesterol in blood serum [83].The strong antioxidant ability to scavenge DPPH and hydroxyl radicle by 71% and 58% respectively was reported by the extra polysaccharides produced by probiotic yeast *Lipomyces starkeyi* [35]. *Saccharomyces cerevisiae* IFST062013 amplified IFN-γ levels by 248 pg/mL at higher dose 5×10^{9} CFU / mouse compared with control group (189 pg / mL) on day 20 ($P<0.05$). Interleukin-10 concentration levels were predominantly increased by *Saccharomyces cerevisiae*(711pg/mL) at the higher dose on day 10, when compared with the control group (635 pg/mL) ($P<0.05$). Increase in the gene expressions of cytokines TLR-2, IFN-γ was seen in treated mice in a dose dependent manner [84]. *Saccharomyces cerevesiae* (HII3I) cell's Beta glucans were extracted and assessed for immune modulatory effect with mice. It was found that low dose of HII3I-BG encourages the expression of selected proinflammatory (IL-17, IFN-Y) and anti-inflammatory cytokine (IL-10), while high dose was essential to alter the gene expressions of TGF-β and IL-6 [85]. *Yarowwia lipolytica*D-1 and N-6 using fish, were analyzed for their immunological parameter in skin mucus and serum. IgM level in the serum increased after second and fourth weeks in fish fed with both probiotic yeasts compared with control [8]. Evaluation of cell viability, inducing apoptosis and change in surviving gene expression of EPG85–257P (EPG) and EPG85–257RBD (resistant to Daunorubicin, RDB) cell lines under exposure of *Saccharomyces boulardii* supernatant (SBS) after 24, 48, 72 hrs was done, SBS induced apoptosis, decreased cell viability and abridged surviving gene expression in treated EPG and RDB cells with extensive IC 50 values of 387 and 575 μg/mL after 72 and 48 hr for EPG and RDB respectively [86]. Exopolysaccharides formed by two probiotic yeast *Kluyveromyces marxianus* and *Pichia kudriavzevii* induced apoptosis which was confirmed by Annexin V/PI assays and DAPI, they could delay the AKT-1, mTOR and JAK-1 pathways and induce apoptosis of colorectal cancer cells [87].Table 3

With these reports and references, the probiotic yeasts present a beneficial effect on host as a therapeutic agent. But before therapeutic application, further research should be done to ensure safety and efficacy of the potential probiotic yeast.

Saccharomyces boulardii is the most well studied probiotic fungus and basically a model yeast, some studies specify that other yeasts may have potential as probiotics. A yeast probiotic has been used efficiently in the management of different types of gastrointestinal disorders and also in numerous adverse health situations. Some other strains of yeast also fulfilled the required probiotic properties, while some potentials make them a striking probiotic. Their efficacy could be theoretically be improved by recombinant DNA technology to intensify inherent benefits or enhance new probiotic characteristics. These probiotics can be used for heterologous expression of several proteins that can used as therapeutic agents. These probiotic yeasts can also be used in industrial and agricultural applications. Fig.2 & 3

9. Conclusion

Saccharomyces and non-*Saccharomyces* yeasts other than the commercially available *Saccharomyces boulardii* have favorable, beneficial and significant probiotic properties. Yeasts have numerous advantages in food, feed, fermentation, medicinal, agricultural, biofuel in ecological protection and also in chemical industries. The selected

potential, probable probiotic strain could be used as supplement for industrial fermentations, and in the manufacture of functional food products. Probiotic yeasts with their hostile activity against pathogens and also as a virtuous plant growth promoting organism reduce the reliance on chemical fertilizers and fungicides. Yeasts can also be used for the removal of noxious and other chemical contaminants and pollutants existing in the ecosystem. Advanced and additional studies on these non-*Saccharomyces* yeasts are necessary prior to administer these yeasts as potential probiotics for health and wellbeing. Further research and extensive studies are essential to exhibit their therapeutic properties.

CRediT authorship contribution statement

B. Shruthi: Conceptualization, Writing – original draft. **N. Deepa:** Formal analysis, Writing – review & editing. **Rakesh Somashekaraiah:** Formal analysis, Writing – review & editing. **G. Adithi:** Formal analysis, Writing – review & editing. **S. Divyashree:** Formal analysis, Writing – review & editing. **M Y Sreenivasa:** Conceptualization, Supervision, Writing – review & editing.

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'**.

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