Molecular Biology Reports (2021) 48:951–960
https://doi.org/10.1007/s11033-020-06110-1

MINI REVIEW ARTICLE

Recent advances in the application of probiotic yeasts, particularly *Saccharomyces,* as an adjuvant therapy in the management of cancer with focus on colorectal cancer

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Received: 16 September 2020 / Accepted: 18 December 2020 / Published online: 3 January 2021

Abstract

Today, the increasing rate of cancer-related mortality, has rendered cancer a major global challenge, and the second leading cause of death worldwide. Conventional approaches in the treatment of cancer mainly include chemotherapy, surgery, immunotherapy, and radiotherapy. However, these approaches still come with certain disadvantages, including drug resistance, and different side effects such as gastrointestinal (GI) irritation (e.g., diarrhea, mucositis). This has encouraged scientists to look for alternative therapeutic methods and adjuvant therapies for a more proper treatment of malignancies. Application of probiotics as an adjuvant therapy in the clinical management of cancer appears to be a promising strategy, with several notable advantages, e.g., increased safety, higher tolerance, and negligible GI side effects. Both *in vivo* and *in vitro* analyses have indicated the active role of yeast probiotics in mitigating the rate of cancer cell proliferation, and the induction of apoptosis through regulating the expression of cancer-related genes and cellular pathways. Strain-specific anti-cancer activities of yeast probiotics strongly suggest that their administration along with the current cancer therapies may be an efficient method to reduce the side effects of these approaches. The main purpose of this article is to evaluate the efficacy of yeast probiotics in alleviating the adverse effects associated with cancer therapies.

Keywords Adjuvant therapy · Apoptosis · Bioactive components · Cancer therapy · Probiotic · Yeast

Introduction

The World Health Organization (WHO) defines probiotics as "living microorganisms which confer beneficial health effects to the host when administered in adequate amounts" [1]. The currently recognized probiotics are mainly categorized into the lactic acid bacteria and yeast groups. Along with various strains of bacteria [2], a big number of yeast species, including *Saccharomyces cerevisiae* var. boulardii, *Kluyveromyces*, *Debaryomyces*, *Candida*, *Pichia*, *Hanseniaspora*, and *Metschnikowia* have been shown to possess probiotic properties [3]. The primary salutary effects of yeast probiotics, such as their potential for prevention and treatment of intestinal disorders, along with their immunomodulatory properties, have been reviewed in several studies [4]. Likewise, the anti-cancer properties of yeast probiotics have been extensively investigated by different methods in various studies, including cell-based studies, animal models, and clinical trials. Table 1 summarizes the recent application of probiotics and their strain-specific effects mediated through different mechanisms. In this review, we aim to provide a brief account of the beneficial effects of yeast probiotics, with the emphasis on their anti-cancer properties, particularly in the prevention of Colorectal Cancer (CRC).

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Table 1 List of health benefits of probiotics in the treatment of various diseases

Effect	Probiotic strains	Mechanisms of actions
Immunomodulation	*Lactobacillus*	Induce TNF-α secretion by lipoteichoic acid (LTA) [5]
	Bifidobacterium longum	Modulate TNF-α, IL-6, IL-10 and IL-12 and TH17 responses [6] due to its surface exopolysaccharide
	B. animalislactis Bb-12	Activated intestinal NF-κB [7]
		IgA secretion [8]
Improving the immune system and cytokine production in COVID-19 patients	*Lactobacillus*	As adjuvant nutritional therapies in COVID-19 patients [9–11]
Protective effects against physiological stress	*L. acidophilus* (strain LAP5 and LF33)	Bind to the intestinal epithelial cells and blocked the colonization of Salmonella [12]
	L. acidophilus A4	Antagonize adhesion of the *E. coli* adhesion to epithelial cells by up-regulation of mucin-2, IL-8, IL-1β and TNF-α [13]
	Bifidobacterium spp.	Produce acetate and inhibit Shiga toxin–producing *E. coli* O157:H7 [14]
	Lactobacilus and *Enterococcus*	Produce bacteriocins [15, 16]
	L. salivarius UCC118	Protect infected mice with *L. monocytogenes* [17]
	L. acidophilus La-5 1	Inhibited autoinducer-2 (AI-2) and decreased the virulence factors expression of *E. coli* O157:H7 [18]
	L. acidophilus GP1B	Prevented AI-2 activity of *Clostridioides difficile* [19]
	L. reuteri RC-14	Production of mediators against *Staphylococcus aureus* QS, blocked its virulence, and expression of toxic shock syndrome toxin-1 [20]
Suppression of pathogens	*L. plantarum*	Reduce hydroxy-cis-12-octadecenoic acid via regulation of TNF receptor 2 expression and MEK/ERK pathway [21]
Modulation of gut microbiome and Intestinal Barrier Function	*L. fermentum* and *L. plantarum*	In context to Obesity [22, 23], Produce Short Chain Fatty Acids (SCFAs) and Acetic acid, improve tight junction proteins, regulating the immune response, and stimulating host defense peptides [24]
Other mechanisms	*Lactobacillus* and *Bifidobacterium*	Reduction weight gain, decrease the levels of plasma cholesterol and liver triglycerides [25, 26], bile acids deconjugation [27], impaired glucose tolerance [28]
	L. rhamnosus JB-1	Modified the γ-aminobutyric acid (GABA)-A expression and GABA-B receptors in the brain related to stress and anxiety-related responses [29]
	L. reuteri ATCC PTA 6475	Showed an anti-nociceptive effect via transient receptor potential vanilloid 1 -dependent manner [30]
	L. acidophilus NCFM	Induced expression of μ-opioid and cannabinoid receptors in the gut epithelial cells and presented analgesic impact [31]

General overview of yeast probiotics

To date, several successful attempts have been made at the isolation and characterization of bacterial probiotics (primarily *lactobacillus*) from different sources, including traditional dairy products, plants, and human biological samples [2, 32–35]. Regardless of the bacterial source of most probiotics, the therapeutic potential of non-pathogenic yeasts probiotics warrants prospective clinical trials in this field. An important advantage of yeast probiotics is that they are highly resistant against gastrointestinal enzymes, bile salts, pH variations, organic acids, and variations in temperature. For instance, *Saccharomyces*

is a non-bacterial prototype harboring the same beneficial properties as the bacterial probiotics. In comparison with bacterial probiotics, the size of yeast cells is 10 times larger, with an optimal growth pH and temperature of 4.5–6.5 and 37 °C, respectively. The majority of yeast strains are able to grow at a pH equal to 3.0, however, some species can tolerate an even lower pH (<1.5).

Compared to bacterial probiotics, yeasts possess intrinsic resistance to antibiotics. Non-genetic transferring of antibiotic-resistance genes between bacteria and yeasts may render these probiotics more effective for patients who use antibiotics. Besides, the modification of the immune response is considered an important mechanism to explain the positive effects of yeast probiotics. The structure of yeast cell wall and the secretory bioactive compounds such as β-glucan, mannoproteins, chitin, and nucleic acids are responsible for the immunostimulatory effects of these organisms [36]. The majority of reported investigations on yeast probiotics in clinical and animal studies have been carried out on *Saccharomyces cerevisiae*; however, the probiotic effects of *Candida strains, Hanseniaspora opuntia*, *Hortaea werneckii*, *Meyerozyma guilliermondii*, *Debaryomyces strains* have also been documented [37–39]. *S. cerevisiae* and *S. boulardii* are mostly adopted in probiotic adjuvant therapies to treat antibiotic-associated diarrhea and bacterial infections, improve the intestinal mucosa, modulate mucosal immune responses, and induce the expression of a heterologous protein with several therapeutic properties [40–42].

S. boulardii is most active in the colon, and it can survive the preceding portion of the GI tract until it reaches the colon [43]. Hence, this yeast probiotic would be suitable for human consumption for the treatment of Inflammatory Bowel Disorders (IBD), and any type of gastroenteritis [42, 44, 45]. The optimal growth temperature for *Saccharomyces* strains ranges from 22 °C to 30 °C. However, inside the human body, *S. boulardii* is able to survive at up to 37 °C. Owing to its intrinsic resistance to the gastric acid and intestinal bile, *S. boulardii* is highly likely to survive the effects of antibiotics and proteolysis in the intestinal tract, ultimately improving intestinal inflammations. In an study led by Sougioultzis et al., human HT-29 colonocytes and THP-1 monocytes were immunologically induced with IL-1β, TNF-α or LPS combined with the supernatant of *S. boulardii*. The study reported that *S. boulardii* hindered the production of IL-8 in HT-29 cells by inducing IL-1β or TNF-α. Moreover, *S. boulardii* was also able to inhibit the production of IL-8, prevent the degradation of IB-α, and counteract the upregulation of NF-kB-DNA through binding to NF-kB reporter gene. The anti-inflammatory effects of this yeast were shown to result in deactivation of NF-kB, and down-regulation of IL-8 in intestinal epithelial cells and monocytes. These findings suggest *S. boulardii* as a potential therapeutic candidate to be used either for the treatment of infectious and non-infectious human intestinal diseases [46].

Kluyveromyces lactis is another yeast probiotic with unique features such as resistance to gastrointestinal digestion, β-galactosidase activity, and a high potential for adhesion, prevention of enteric pathogens, and production of Short Chain Fatty Acids (SCFAs) [42, 47]. Several beneficial effects of *K. marxianus* strain B0399 have also been investigated, which includes adhesion, metabolic activity, and immunomodulation of gut microbiota. Accordingly, the adhesion of *K. marxianus* to the Caco-2 cells can ameliorate the inflammatory response by inhibiting pro-inflammatory cytokines, and also improve colonic microbiota by increasing the population of bifidobacteria, and the production of SCFAs (acetate and propionate) [48]. In another investigation, *K. marxianus* S-2-05 and *K. lactis* S-3-05 were isolated from traditional cheese and their activity against Salmonella was evaluated in a GI model. Reportedly, these yeasts were able to survive in the GI environment and form a biofilm on polystyrene surfaces, suggesting their potential for adhesion to Caco-2 cells and probiotic properties [49]. An investigation on the anti-inflammatory effects of *K. marxianus* CIDCA 8154 in IBD concluded that pretreatment of cells with *K. marxianus* might decrease the levels of intracellular reactive oxygen species and IL-6. Moreover, cellular oxidative stress was reported to be modulated by the activation of the SKN-1 transcription factor via the DAF-2 pathway in nematode models [50].

Debaryomyces hansenii is another yeast probiotic strain with immunostimulatory effects on goat leukocytes through β-glucans. *D. hansenii* CBS 8339 can survive in bile salts and the acidic pH of the GI tract, and adhere to the intestinal mucosa. The analysis of immunological and antioxidant properties of this strain confirmed the positive effects of *D. hansenii* on the viability of leukocytes in animal models. On the other hand, a yeast-supplemented diet resulted in the upregulation of TLR receptor genes, modulator genes (such as Raf.1, Syk, and Myd88, AP-1), and cytokine levels (IL-1β and TNF-α). These findings demonstrated that the oral administration of *D. hansenii* CBS 8339 stimulated immune response, antioxidant agents, and immune-associated signaling pathways genes in a short time [51]. Moreover, the effects of *D. hansenii* in combination with Qi-Wei-Bai-Zhu powder were investigated on the gut microbiota of mice with antibiotic-associated diarrhea. The microbial content was evaluated by sequencing the 16S rRNA gene to demonstrate the species-wise diversity. The results indicated a high frequency of *Bacteroidales* S24–7 and *Bifidobacterium*, suppression of *Oscillospira* and *Ruminococcus*, and proliferation of *Erysipelotrichaceae* and *Blautia* in the murine models of diarrhea [52]. The main functions of gut microbiota including digestion, metabolism, and modulation of immune reactions depend on its diversity [53]. As mentioned

earlier, treatment of antibiotic-associated diarrhea with *D. hansenii*, as a part of the intragastric flora, improved the operational taxonomic units of intestinal bacteria and recovered the beneficial bacteria, such as *Bacteroidaceae* [54]. Follow-up analyses confirmed the potential of *D. hansenii* in the maintenance of the normal microbiome ecology, development of lactase-producing bacteria, and inhibition of opportunistic pathogens [55, 56, 39]. The results obtained from animal studies warrant prospective therapeutic clinical applications of yeast probiotics, with an emphasis on management of diarrhea.

The role of yeast probiotics in the management of cancer

According to the WHO reports, cancer is a global health problem with ~9.6 million deaths in 2018 [57]. The most prevalent cancers include lung, breast, colorectal, prostate, skin, and stomach cancer. Yeast probiotics may have important effects on the molecular and cellular pathways, that could be useful in the prevention and treatment of cancers [58]. The basic mechanisms of signal transmission and sensitization underlying the negative regulatory effects of yeasts on cancer cells include modification of microbiota, degradation of carcinogenic substances in the intestinal lumen, production of anti-carcinogenic components like SCFAs, and conjugation of SCFAs to linoleic acid. Modulation of immune responses, improvement of intestinal barriers, inhibition of cell proliferation, and induction of apoptosis are other mechanisms through which yeast probiotics regulate the growth of cancer cells [59].

Cancer (CRC) is the second cause of cancer-related mortality with an annual number of 862,000 deaths. Today, there is a rising debate regarding the efficacy of conventional cancer treatment methods. CRC is a multistage malignancy with various risk factors including genetic factors, familial background, age, gender, nutrition, smoking, and limited physical activity. In search of novel therapeutics, the clinical application of safe yeast probiotics is speculated to yield promising results [60, 61]. Probiotics could provide a non-expensive and non-invasive adjuvant therapy for the treatment of CRC by modulating the genes and signaling pathways involved in the pathogenesis of CRC. In addition, using probiotic yeasts in the treatment of CRC could reduce the side effects of current cancer therapies. The administration of probiotics to CRC patients could enhance the gut flora, produce antimicrobials materials and anti-carcinogenic agents, remove 32–3 carcinogens, provide intestinal permeability, and improve the function of tight junctions and enzyme activity in CRC patients. However, not all of the probiotic strains possess anti-CRC properties. Hence, further studies are required to identify potent probiotics, as probiotic-based therapeutic agents, to prevent and treat CRC [62].

Shamekhi et al. reviewed the promising biotherapeutic effects of yeast probiotics in the prevention and treatment of CRC [63]. In terms of cancer therapy, *S. boulardii* and *S. cerevisiae* improve enterocyte tight junctions, modulate host cell signaling, inhibit the activity of ERK1/2 and EGFR signaling, and inactivate tyrosine kinase receptors [64, 65] (Table 2). The β-Glucan of *S. cerevisiae* was reported to stimulate the mammalian immune system, suggesting potential therapeutic implications in the treatment of infectious diseases and cancer [66]. The immunomodulatory effects associated with yeast probiotics mostly involve receptors like Dectin-1, Complement Receptor 3 (CR3) and TLR-2/6. In addition, the immune systems can be modulated by triggering immune cells including macrophages, neutrophils, monocytes, Natural Killer Cells (NKCs), Dendritic cells (DCs), and increasing the opsonic and non-opsonic phagocytosis.

An investigation revealed that upon oral administration, animals were not able to digest a specific chain of β-glucans (backbone 1 → 3 linear β-glycosidic). As a result, the excessive β-glucans are transferred to the proximal small intestine, where a small amount of these molecules are captured by macrophages. After internalization and fragmentation of β-glucans within these cells, macrophages migrate to the bone marrow and endothelial reticular system. Different immune responses are activated when small fragments of β-glucans released by macrophages are taken up by other immune cells. It has been confirmed that different sizes of β-glucans and branching patterns have variable immunogenicity. In this regard, to investigate the effect of β-glucans in clinical studies, a careful selection of probiotics is essential [67]. Further studies have indicated that β-glucans of yeasts can induce secretion of cytokines, and lead to production of IL-12 in DCs. In one study, the production of cytokines was noticeably reduced in Myeloid Differentiation factor 88 (MyD88)-deficient macrophages and DCs. These findings indicated that β-glucans could be used in adjuvant therapy of cancer due mostly to their bioavailable moiety, and their modulatory effects on the cytokine secretion through DCs, and phagocytosis of iC3b-opsonised tumor cells by macrophages [68]. Another study conducted on animal cancer models confirmed that a combination of yeast β-glucans with anti-cancer monoclonal antibodies would improve the clinical therapeutic efficacy in tumor regression and long-term survival during cancer treatment [69]. It has been revealed that *S. cerevisiae* is considerably suppressed in CRC. The beneficial effects of yeasts on Colorectal Adenoma (CRA) were validated by *in vivo* (C57BL/6 and APCMin/+ mouse models) and *in vitro* cells assays. Murine models of CRA/CRC were divided into test and control groups, with the former receiving *S. cerevisiae*,

Table 2 Anti-cancer activity and biotherapeutics effects of different yeast probiotics on CRC

Yeast probiotic/components	Model of study	Anti-cancer effects	Ref
Heat-killed *S. cerevisiae*	Breast cancer cells (MCF-7 and ZR-75-1) and non-metastatic breast cancer cells (HCC70)	Induction of apoptosis Mitochondrial membrane Disruption Activation of caspases (8, 9 and 3)	[70]
	Squamous cell carcinomas of the tongue (SCC-4 and SCC-9) and adenocarcinomas of the colon (Caco-2 and DLD-1)	Induction of apoptosis	[71]
	SW480	Lower the of expression of p-Akt1, Rel A, Bcl-XL, pro-caspase 3, and pro-9, and could rise the BAX, cleaved caspase-3, and cleaved caspase-9 expression	[72]
	HeLa	Induction of apoptosis: cell enlargement, membrane bleb, and chromatin condensation	[73]
	Mice model of Solid Ehrlich Carcinoma tumor (SEC)	Cause tumor degeneration, apoptosis, and ischemic (coagulative) and liquefactive necrosis Recruitment the leukocytes, macrophages into the tumors Higher the TNF-α and IFN-gamma plasma and lowered the IL-10 levels	[74]
	Metastatic breast cancer (MBC) cells	Cells phagocytized yeast and underwent apoptosis due to elevation of intracellular $Ca^{2+,}$ decreasedBcl-2 expression and increase in Bax expression	[75]
Supernatant of *S. cerevisiae*	HT-29 colon cancer cell line	Higher the PTEN and Caspas3 expression Lower the Bclxl and RelA genes expression Induce apoptosis and reduce the metastasis	[76]
Ergosterol	MCF-7 cells	Produce the oxidation form of ergosterol and inhibit the cancer cells growing	[77]
β-glucan of *S. cerevisiae*	CHO-k1 and CHO-xrs5 cell lines	Prevent DNA damage	[78]
	Patients with advanced breast cancer	Induced the proliferation and activation of peripheral blood monocytes	[79]
	Lung metastasis of colon 26-M3.1 carcinoma or B16-BL6 melanoma cells	Macrophages were induced by IS-2 and produced cytokines (IL-1β, IFN-γ, and IL-12).	[80]
	Mice feeding with the insoluble β-glucan (1 week), murine hepatoma MH-22a cells	Increase the count of neutrophil blood and reduce the lymphocyte count	[81]
	S180 tumor-bearing mice	Decrease the weight and tumor volume Decrease the CD4–CD8 ratio Increase the IL-2, IL-6, and TNF-α levels Up-regulate the Bax expression Down-regulate the Bcl-2 expression	[82]
Saccharomyces boulardii	Apc^{Min} mice orally received the yeast	Inhibits EGFR and other receptor tyrosine kinase signaling	[83]
Carboxymethyl-glucan: soluble derivative of β-glucan	Advanced prostate cancer patients	Higher the total leukocyte count, red blood cell, hematocrit, hemoglobin and platelet counts. Could be an adjuvant to cancer treatment	[84]
Cytoplasmic extract and cell wall of *S. cerevisiae* and *S. boulardi*	Cell line K562	Cell apoptosis and necrosis	[85]

Table 2 (continued)

Yeast probiotic/components	Model of study	Anti-cancer effects	Ref
Selenium-enriched *S. cerevisiae*	Rats model of CRC	Reduce CRC progression by decrease the number / size of aberrant crypt foci (ACF) and alteration the function of P53, BCL2, and CD31	[86]
	Mucositis mice induced by 5FU	Selenium-enriched yeast reduced eosinophil peroxidase activity	[87]
S. boulardii: Insoluble glucan, cell wall polysaccharides	Male F344 rat CRC model	↓ACF: prevention biomarkers Reduction of quinone reductase activity	[60]
	HT-29 cell lines	antiradical and anti-proliferative effect	[60]
Herbal medicine and *S. cerevisiae*	Hepatocellular carcinoma HepG2 cells HepG2 cells- bearing nude mice model	Anti-proliferation effect Inhibit tumor growth	[88]
Paclitaxel in the presence or absence of *S. cerevisiae*	Metastatic murine 4 T1 line	Decreased 4 T1 cell viability, triggered DNA damage, induced the apoptosis, and inhibit cell proliferation	[89]
	Murine Ehrlich ascites carcinoma (EAC) line Human breast cancer MCF-7 line	Chemosensitizing effect of yeast along with paclitaxel increased Be as novel adjuvant for chemotherapy treatment	

along with antibiotics, for 8 weeks. According to the results, the density of *S. cerevisiae* in CRA and CRC patients were 2.68-fold and 3.94-fold lower in comparison to the control groups, respectively. In addition, the outcomes of *in vivo* analysis displayed the potential of *S. cerevisiae* in mitigating the progression of CRC by inducing apoptosis, modulation of gut microbial profiles, and intestinal immunity. Moreover, *S. cerevisiae* downregulated NF-κB and rapamycin-mediated signaling pathways (mTOR). The apoptotic effects of yeast probiotics and their ability in modulating the mucosal microbial profile in CRC confirmed the important role of probiotic *S. cerevisiae* in the treatment of CRC, warranting further investigations [9].

Along with the anti-cancer effects of *S. cerevisiae* and *S. boulardii*, the inhibitory role of the exopolysaccharide (EPSs) of *K. marxianus* and *P. kudriavzevii* on SW-480 (non-metastatic), HT-29 (low-metastatic), and HCT-116 (highly-metastatic), and human embryonic kidney normal cell line (KDR/293) were investigated. According to the results, EPSs considerably induced apoptosis by up-regulation of pro-apoptotic genes (BAX, Caspase-3, and Caspase-8) and down-regulation of anti-apoptotic genes (Bcl-2). Furthermore, a depressed expression of inflammation pathway genes (AKT-1, JAK-1, and mTOR) in cancer cells treated with both extracted EPSs was detected with insignificant changes when compared to the normal cell lines.

The ferroptosis signaling pathway was assessed by evaluating the Nrf-2 and CoQ10 genes. The Nrf-2 mRNA levels increased, while the CoQ10 mRNA levels were not significantly upregulated. Therefore, it was assumed that these EPSs of probiotic yeast could be applied as therapeutic agents against CRC-targeted molecules [90]. Kourelis et al. evaluated the *in vitro* ability of probiotic yeasts isolated from different sources (feta cheese or infantile gastrointestinal tract). All strains displayed *in vitro* probiotic properties including resistance to acid and bile, adhesion to Caco-2 cells, removal of cholesterol, and immunostimulatory activity. Moreover, it was found that beside the *Saccharomyces* strains, other yeast species such as *K. lactis* could also be considered as probiotics. Despite these valuable results, further studies are necessary to elucidate the beneficial effects of yeasts on the GI system after oral administration [91]. Shamloo et al. investigated the role of *P. fermentans* metabolites on the induction of apoptosis in Squamous Cell Carcinoma (SCC). Similar to cisplatin, the metabolites of this yeast imposed a cytotoxicity of 85% to the tumor cells, while in the normal cells only a cytotoxicity of 21% was recorded. In addition, the effects of *S. cerevisiae* was not the same as *P. fermentans* results, which actually pointed to strain-dependent bioactivity of yeasts. The cytotoxicity mentioned here was shown to be due to the effects of the yeast on the mechanisms involved in apoptosis, mediated mostly through the regulation of BAX and CASP genes [92].

Conclusion

According to the recent studies, *S. cerevisiae* is a safe microorganism that can be used as a promising therapeutic approach for effective inhibition of tumor cell proliferation. More robust and coherent studies on the effects of probiotics on cancer cell types are required to achieve more reliable results. This can be an important step in the treatment and prevention of cancer. Until now, efficient therapies using yeast probiotics have been confirmed for the treatment of different diseases. However, finding the exact dosage and viability potential of yeast probiotics still remains a significant challenge. This requires further well-designed clinical studies to elucidate the exact benefits of probiotics, identify and demonstrate their criteria and strain-specific properties, and assess their biosafety. Furthermore, increasing the half-life of probiotic products, preservation against the GI secretions, and raising the adherence potential of these microorganisms to the GI epithelium are all essential in this context. Gene technology can help discover novel potential yeast strains. Application of a combination of probiotics may leave a greater positive impact on the efficacy of cancer treatment regimens when compared to a single probiotic. Given the confirmed anti-cancer potentials of probiotics, a wide range of these microorganisms has recently been considered for their immunomodulatory effects and antiviral activity, especially against Coronavirus Disease-2019 (COVID-19). However, since COVID-19 is a newly spreading viral infection with a high rate of mortality, more researches are necessary to affirm probiotics as a safe and effective therapy against COVID-19.

Author contributions All authors equally contributed in the wiring of the manuscript.

Funding Funding was provided by Drug Applied Research Center, Tabriz University of Medical Sciences.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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