

## NON-*Saccharomyces* YEAST AS AN ALTERNATIVE SOURCE FOR PROBIOTICS AND PREBIOTICS - A REVIEW

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### Abstract

The incorporation of probiotics and prebiotics as food ingredients derived from sustainable microbial sources has gained increasing attention in the food industry. These bioactive compounds play a pivotal role in promoting gut health, improving food quality, and facilitating the development of functional food products tailored to different consumer demands. This study explores the biotechnological potential of probiotic yeasts, including *Kluyveromyces marxianus*, *Kluyveromyces lactis*, *Yarrowia lipolytica*, *Pichia kudriavzevii*, *Pichia kluyveri*, and *Pichia fermentans*, in modulating gut microbiota composition and improving food formulations. In addition, prebiotic compounds from *K. marxianus* and *K. lactis* - particularly fructans (fructo-oligosaccharides, inulin) and galactans (galacto-oligosaccharides) - are recognised for their ability to selectively stimulate the growth of beneficial bacterial populations. The integration of these probiotic and prebiotic ingredients into food systems offers significant opportunities for innovation, sustainability, and nutritional improvement, contributing to the advancement of health-promoting and functional foods.

**Key words:** non-*Saccharomyces* yeast, prebiotics, probiotics, sustainable food ingredients, unconventional sources.

### INTRODUCTION

The global probiotics and prebiotics markets are experiencing significant growth, driven by increasing consumer awareness of gut health and rising demand for functional foods. The probiotics market is forecast to reach USD 105.7 billion by 2029, expanding at a compound annual growth rate (CAGR) of 8.2% from USD 71.2 billion in 2024 (Markets, 2024). Similarly, the prebiotics market, valued at USD 9.21 billion in 2023, is expected to reach approximately USD 31.91 billion by 2032, growing at a CAGR of 14.8% between 2024 and 2032 (Zion, 2024). This significant market expansion underscores the growing importance of probiotics and prebiotics as bioactive food ingredients, supporting advances in food biotechnology, human nutrition, and sustainable product development within the global food industry.

Although yeasts have traditionally been recognised for their role in fermented foods and beverages, the full extent of their diversity across genera and species has only been

elucidated in the last fifteen years (Tamang et al., 2022). In addition to *Saccharomyces* species, due to their technological properties and potential probiotic and prebiotic properties, non-conventional yeasts have attracted considerable scientific interest (Brănescu et al., 2023).

Non-*Saccharomyces* yeasts have emerged as important sources of both probiotics and prebiotics, with significant potential for novel applications in the functional food industry (Rădoi-Encea et al., 2024). In addition to the benefits of live yeast cells, their cell wall components offer considerable potential for valorisation as value-added ingredients in the formulation of functional foods (Shruthi et al., 2022).

Probiotics derived from these yeasts have been associated with antimicrobial and antioxidant activities, as well as gastrointestinal modulation and regulatory functions, contributing to host health (Banik et al., 2019). At the same time, prebiotics, defined as non-digestible food ingredients, selectively stimulate the growth and metabolic activity of beneficial gut

microbiota, thereby improving overall well-being (Fernández-Pacheco et al., 2021). The synergistic effects of probiotics and prebiotics derived from non-*Saccharomyces* yeasts underscore their relevance in advancing functional food formulations, fostering innovation in food biotechnology and promoting human health (Mogmenga et al., 2023).

Non-*Saccharomyces* yeasts with potential for the production of probiotics and prebiotics include *Kluyveromyces marxianus*, *Kluyveromyces lactis*, *Yarrowia lipolytica*, *Pichia kluyveri*, *Pichia kudriavzevii*, and *Pichia fermentans*.

The present work is focusing on a comprehensive analysis of non-*Saccharomyces* yeasts as emerging sources of probiotics and prebiotics, focusing on their biological activity, functional properties, potential health benefits and industrial relevance. Particular emphasis was placed on studies that demonstrated innovative applications of non-*Saccharomyces* yeasts in probiotic and prebiotic development, as well as those that provided insights into future research directions and commercial viability.

## MATERIALS AND METHODS

For this review, we conducted a systematic literature search in several databases, including Web of Science, PubMed, Google Scholar, and ScienceDirect. The search used the key words 'non-*Saccharomyces* yeast', 'probiotics', 'prebiotics', and 'unconventional sources', focusing on publications from 2014 to January 2025 to ensure a comprehensive analysis of recent advances in the field.

After removing duplicate records, we prioritised studies that investigated the potential of non-*Saccharomyces* yeasts as innovative sources of probiotics and prebiotics. In the subsequent screening process, articles were selected based on their alignment with the inclusion criteria, with eligibility assessed through a comprehensive evaluation of titles and abstracts, ensuring a broad yet rigorous approach to literature selection.

The selection criteria for articles were as follows:

- Peer-reviewed journal articles and reviews published in English;
- Studies investigating the potential of non-*Saccharomyces* yeasts as novel sources of probiotics and prebiotics;
- Articles discussing the importance of unconventional sources in the development of probiotics and prebiotics for functional foods.

Exclusion criteria were established to exclude studies that:

- Did not specifically address the role of non-*Saccharomyces* yeasts as sources of probiotics and prebiotics;
- Lacked empirical evidence or did not provide adequate methodological details and results;
- Were published in languages other than English without an accessible English translation.

The selected articles underwent a rigorous evaluation, systematically extracting key information including publication year, authors, study objectives, methodology, key findings, and conclusions.

The synthesised data allowed the identification of emerging trends, areas of agreement, and inconsistencies within the literature, ensuring a critical and systematic review of current knowledge. This methodologically robust approach reflects a commitment to thoroughly analyse and interpret the role of non-*Saccharomyces* yeasts as unconventional sources of probiotics and prebiotics.

## RESULTS AND DISCUSSIONS

### 1. Probiotics and postbiotics

Probiotics are live microorganisms that, when administered in adequate amounts, provide health benefits to the host (Karim et al., 2020). A microorganism to be considered as a potential probiotic candidate has to survive the restrictive conditions of the gastrointestinal tract (GIT), adhere to the intestinal mucosa, and colonise the colon, at least temporarily, and exert potential health benefits on the host (FAO/WHO, 2014).

The dairy industry remains the main source of probiotics, especially lactic acid bacteria (LAB). Most commercialised probiotic strains belong to this group, with *Bifidobacteria* spp. and *Lactobacillus* spp. being the most widely used. However, research has shown that several

non-*Saccharomyces* yeast species can also thrive in an environment rich in proteins, lipids, sugars, and organic acids, demonstrating potential probiotic properties. Despite this, the number of probiotic yeast species available for human consumption remains limited, with only *Saccharomyces cerevisiae* var. *boulardii* and *Kluyveromyces fragilis* (B0399) being commercially available (Chen et al., 2014).

Currently, yoghurt is the most important dietary source of probiotics, which play a crucial role in maintaining the balance of the gut microbiota and promoting overall health (Munteanu-Ichim et al., 2024). As a fermented dairy product, yoghurt contains beneficial strains of bacteria, primarily *Lactobacillus* and *Bifidobacterium*, which contribute to improved digestion, immune modulation, and potential metabolic benefits. Due to its widespread availability, high consumer acceptance, and well-documented health benefits, yoghurt remains the most commonly consumed probiotic-rich food in the modern diet (Nami et al., 2024).

However, recent advances in microbial biotechnology have highlighted the potential of non-conventional yeast species as new probiotic sources, broadening the range of functional ingredients available for food applications (Vrînceanu et al., 2025). Yeast species belonging to the genera *Kluyveromyces* (e.g., *K. marxianus*, *K. lactis*), *Yarrowia* (e.g., *Y. lipolytica*), and *Pichia* (e.g., *P. fermentans*, *P. kudriavzevii*, *P. kluyveri*) have been acknowledged for their notable capacity to produce substantial quantities of probiotic compounds (Diguña et al., 2022). Their incorporation into functional foods represents a promising alternative to traditional probiotic sources such as yoghurt, particularly for those with lactose intolerance or those seeking plant-based options (Shruthi et al., 2022). This shift towards yeast-based probiotics highlights the growing diversification of probiotic sources in the modern diet, paving the way for novel formulations with enhanced nutritional and health benefits. Among these, *Kluyveromyces* and *Pichia* are the most frequently reported genera, highlighting their strong potential for probiotic applications (Vergara et al., 2023).

Non-*Saccharomyces* yeasts exhibit broad-spectrum antimicrobial properties, enhance

digestive health, and contribute to oxidative stress reduction, positioning them as valuable candidates for functional food development and therapeutic applications (Cosoreanu et al., 2024).

A primary advantage of probiotic yeasts is their ability to inhibit pathogenic growth. *P. kudriavzevii* effectively suppresses *E. coli*, *S. Typhimurium*, *S. aureus*, and *B. cereus*, (Vergara et al., 2023), while *P. kluyveri* has demonstrated antagonistic activity against *L. monocytogenes* and *S. enteritidis* through coaggregation (Menezes et al., 2020). Additionally, *K. marxianus* plays a protective role in gut health by safeguarding the epithelial barrier against *Salmonella*-induced damage, suggesting immunomodulatory properties beyond direct pathogen inhibition (Smith et al., 2015) and also produces antibacterial peptides that further enhance its antimicrobial efficacy (Vergara et al., 2023). These findings underscore the role of probiotic yeasts in competitive exclusion, further reinforcing their significance in maintaining a balanced gut microbiome (Andrade et al., 2021).

Beyond their antimicrobial properties, non-*Saccharomyces* yeasts contribute significantly to gut microbiota modulation and nutrient bioavailability. *K. marxianus* has been shown to support both gastrointestinal and immune health by increasing gamma-aminobutyric acid (GABA) bioavailability, stimulating *Bifidobacterium* growth, and improving lactose digestion, which is particularly beneficial for lactose-intolerant individuals (Perpetuini et al., 2020). Similarly, *P. kudriavzevii* contributes to digestive health by producing lipases, esterases, proteases, and phytases, while also acting as a natural folate producer, thereby enhancing metabolic function (Greppi et al., 2017). These properties establish non-*Saccharomyces* yeasts as promising candidates for gut health enhancement and metabolic regulation.

Another crucial feature of probiotic yeasts is their capacity to produce antioxidants or enhance the bioavailability of these compounds. Their role in mitigating oxidative stress highlights their potential applications in functional foods and therapeutic interventions aimed at improving overall health (Pantea et al., 2022). As research advances, the exploration of probiotic yeasts in functional

food formulations, encapsulation technologies, and clinical applications continues to expand, offering new opportunities for their integration into health-promoting products.

*P. kudriavzevii*, *P. kluyveri*, and *K. marxianus* exhibit strong antioxidant activity through enzymatic defenses and glutathione production (Vergara et al., 2023). *K. marxianus* demonstrates hydroxyl radical scavenging and metal chelation (Galinari et al., 2018), while *Pichia* species enhance antioxidant capacity in fermented foods via  $\beta$ -glucosidase production. *K. marxianus* CIDCA 8154 has been extensively studied for its antioxidant and anti-inflammatory effects, particularly its ability to modulate the SKN-1 transcription factor via the DAF-2 pathway, making it a promising candidate for gut health and inflammatory bowel disease management (Romanin et al., 2016). Meanwhile, Cho et al. (2018) evaluated four *Kluyveromyces marxianus* strains (*K. marxianus* KU140723-01 (KM1), KU140723-02 (KM2), KU140723-04 (KM4), and KU140723-05 (KM5)) for probiotic properties, including gastric and intestinal resistance, cholesterol reduction, and cell adhesiveness and identified *K. marxianus* KU140723-02 (KM2) as the strain with the highest antioxidant activity among four tested strains, surpassing *Lactobacillus acidophilus* in adhesion properties by 5-25%. The focus of Cho et al. (2018) on adhesion and antioxidant properties contrasts with the approach of Saber et al. (2017), who emphasized the gastrointestinal resistance of *K. marxianus* AS41 isolated from dairy products such as yogurt and cheese, demonstrating its bile salt tolerance (83%) and high survival at acidic pH (71%). These differences highlight the variability within *K. marxianus* strains, with some excelling in oxidative stress mitigation while others display enhanced resilience in the digestive tract.

Further distinctions arise in the mechanisms of bacterial interaction. Díaz-Vergara et al. (2017) observed that *K. marxianus* VM003, VM004, and VM005 exhibited weak auto-aggregation but strong co-aggregation with pathogenic bacteria. This suggests that while these strains may not colonize the gut as effectively as *K. marxianus* KM2, they might play a crucial role in pathogen inhibition by physically

interacting with harmful microorganisms. In contrast, Cho et al. (2018) identified *K. marxianus* KM2 as the most effective strain for intestinal adhesion, reinforcing its potential for direct gut colonization.

The antimicrobial potential of *K. marxianus* has been demonstrated across different studies, though strain origin and isolation conditions influence their effectiveness. Fadda et al. (2017) reported that *K. marxianus* strains derived from artisanal cheese exhibited strong antimicrobial activity, particularly *K. lactis*, which demonstrated substantial pathogen inhibition. In contrast, Díaz-Vergara et al. (2017) found that *K. marxianus* VM003, VM004, and VM005, isolated from whey, displayed high antimicrobial activity against *Salmonella* spp., *Serratia* spp., *E. coli*, and *Salmonella typhimurium*. On the other hand, Smith et al. (2015) showed that *K. marxianus* plays a protective role by safeguarding the epithelial barrier against *Salmonella*-induced damage, suggesting an immunomodulatory effect in addition to its antimicrobial properties. This contrasts with the findings of Fadda et al. and Díaz-Vergara et al. (2017) who primarily focused on the direct antimicrobial properties of *K. marxianus* strains, emphasising their ability to inhibit pathogenic bacteria. In comparison, Smith et al. highlighted a different mechanism, demonstrating the role of the strain in maintaining intestinal epithelial integrity and enhancing host immune defences.

Research has also identified *K. marxianus* AS41 as a potential anticancer agent. Saber et al. (2017a) demonstrated that this strain induced 53.8% mortality in AGS gastric cancer cells, exhibiting cytotoxicity comparable to 5-Fluorouracil while sparing normal cells. Interestingly, the same author also reported that *P. kudriavzevii* AS-12 was highly effective in inhibiting the growth of colon cancer cells (HT-29 and Caco-2), suggesting that while *K. marxianus* strains may be more suited for gastric cancer prevention, *Pichia* strains might be particularly relevant for colon cancer therapies (Saber et al., 2017b).

From an industrial perspective, *K. marxianus* B0399 remains the only non-*Saccharomyces* yeast currently commercialized as a probiotic, underscoring its recognized viability in functional foods (Tabanelli et al., 2016;

Vergara et al., 2023). This strain has been shown to enhance bifidobacterial concentration, modulate colonic microbiota, and promote the production of short-chain fatty acids, reinforcing its benefits for gut health. However, Merchán et al. (2020) analyzed the probiotic potential of 54 yeast strains from traditional cheese and identified *P. fermentans* as a strong probiotic candidate in functional cheese applications, demonstrating superior antioxidant activity, auto-aggregation, and antimicrobial properties. These findings suggest that while *K. marxianus* is more commercially viable, *P. fermentans* may hold potential for niche food applications.

Compared to *Kluyveromyces*, *Pichia* species have received less attention regarding direct probiotic applications, yet their potential remains significant. Galinari et al. (2018) highlighted the role of *Pichia* species in enhancing antioxidant activity in fermented foods via  $\beta$ -glucosidase production, though their direct impact on gut health is less studied. While Merchán et al. (2020) provided further evidence of *P. fermentans* from traditional cheese as a robust probiotic, highlighting its superior tolerance to gastric conditions and bile salts, Ogunremi et al. (2015) focused on *Pichia kudriavzevi* OG32, isolated from Nigerian fermented cereal-based foods, demonstrating its significant role in cardiovascular health. Merchán et al. (2020) emphasized *P. fermentans*'s resilience in dairy-based environments, whereas Ogunremi et al. (2015) highlighted *P. kudriavzevi* OG32's metabolic benefits, particularly its ability to enhance lipid metabolism and antioxidant status. Supplementation with its fermented cereal mix significantly increased plasma antioxidant activity while reducing serum total cholesterol, triacylglycerol, and LDL-cholesterol levels. The atherogenic index decreased from  $1.94 \pm 0.05$  to  $0.66 \pm 0.01$ , and hepatic cholesterol and triacylglycerol levels were also reduced, reinforcing its potential for lipid regulation and cardiovascular benefits. This comparison underscores the influence of isolation sources on probiotic functionality, with *P. fermentans* excelling in gastric survival and *P. kudriavzevi* OG32 demonstrating systemic health benefits. On the other hand, Menezes et al. (2020) analyzed 116 yeast isolates to assess their

probiotic potential, identifying *Pichia kluyveri* from cocoa fermentation as a promising probiotic candidate. This strain exhibited remarkable tolerance to low pH, bile salts, and  $37^\circ\text{C}$ , crucial factors for gastrointestinal survival, and notable antioxidant activity.

Regarding antimicrobial potential, *P. fermentans* has demonstrated the highest pathogen inhibition among *Pichia* strains, exhibiting strong auto-aggregation and hydrophobicity (Merchán et al., 2020). This aligns with the findings of Lara-Hidalgo et al. (2019), who isolated a *Pichia kudriavzevii* strain from the spontaneous fermentation of Guajillo pepper and reported that it displayed significant co-aggregation with pathogens, reinforcing its antimicrobial capacity. Additionally, *P. kluyveri* demonstrated autoaggregation, coaggregation with *Escherichia coli*, and adhesion to Caco-2 cells, as reported by Menezes et al. The antimicrobial mechanisms of *Pichia* appear to be strain-specific, with *P. kudriavzevii* excelling in pathogen inhibition through competitive exclusion, while *P. fermentans* and *P. kluyveri* exhibit a combination of antimicrobial properties, including auto-aggregation and strong adhesion capabilities.

A direct comparison between *Kluyveromyces* and *Pichia* species reveals distinct probiotic functionalities. *K. marxianus* CIDCA 8154 and KM2 demonstrated the highest antioxidant activity (Romanin et al., 2016; Cho et al., 2018), whereas *P. fermentans* also exhibited strong antioxidant properties (Merchán et al., 2020). For gastrointestinal resistance, *K. marxianus* AS41 showed the highest survival rates, followed by *P. fermentans* (Saber et al., 2017; Merchán et al., 2020). While *K. marxianus* KM2 excelled in adhesion to intestinal cells, *Pichia* species have not been extensively studied in this regard (Cho et al., 2018). In terms of antimicrobial effectiveness, *P. fermentans* exhibited the strongest pathogen inhibition, followed by *K. lactis* and *K. marxianus* VM strains (Fadda et al., 2017; Díaz-Vergara et al., 2017; Merchán et al., 2020). Regarding anticancer potential, *K. marxianus* AS41 has been linked to gastric cancer inhibition, while *P. kudriavzevii* AS-12 has shown strong activity against colon cancer cells (Saber et al., 2017). Finally, the industrial

potential of *K. marxianus* remains more developed, with B0399 being the only commercialized non-*Saccharomyces* probiotic (Tabanelli et al., 2016; Vergara et al., 2023), whereas *Pichia* species, despite their strong probiotic properties, have not yet achieved widespread commercial availability.

In addition to the probiotic activity of non-*Saccharomyces* yeasts, their postbiotic potential is increasingly recognized due to the presence of  $\beta$ -glucans and mannans in their cell wall structure. These bioactive components contribute to a range of physiological effects, particularly in immune modulation, antioxidant defense, and metabolic regulation, as demonstrated by multiple studies, positioning them as promising functional ingredients in postbiotic applications.

According to Smith et al. (2016),  $\beta$ -glucans from *K. marxianus* stimulate the production of key cytokines, including IL-1 $\beta$ , IL-6, and IL-10, in human monocyte-derived dendritic cells, highlighting their immunomodulatory potential. Similarly, Fortin (2018) reported that these  $\beta$ -glucans enhance superoxide anion scavenging capacity, induce NAD(P)H: quinone reductase, and exert antiproliferative effects in human HT-29 cells, further demonstrating their antioxidant and protective properties.

In comparison,  $\beta$ -glucans from *Y. lipolytica* have been shown to enhance immune function in goat leukocytes by increasing cell viability, improving phagocytic activity, stimulating nitric oxide production, and activating immune-related signaling pathways (Angulo et al., 2021). These findings suggest that *Y. lipolytica*  $\beta$ -glucans may exert a broader immunostimulatory capacity across different biological systems.

Beyond  $\beta$ -glucans, mannans from *K. marxianus* also exhibit notable biological activity. Galinari et al. (2018) observed that these mannans induce mitogenic activity and nitric oxide production in murine macrophages (RAW 264.7), reinforcing their immunostimulatory effects. Moreover, in human Hep-G2 tumor cells, *K. marxianus* mannans have demonstrated antiproliferative and hypocholesterolemic activities, as well as the ability to modulate gut microbiota composition (Tang et al., 2022). Notably, Zhao et al. (2022) reported that certain *K. marxianus* strains

exhibit greater hypocholesterolemic activity than *S. cerevisiae*, with this effect being dependent on the mannans' side chain length and phosphate content.

While both *Kluyveromyces* and *Pichia* species possess strong probiotic potential, their applications differ. *K. marxianus* strains, particularly KM2 and AS41, excel in adhesion, gastrointestinal survival, and industrial applications, making them ideal for direct gut health benefits. Similarly, *P. fermentans* and *P. kudriavzevii* demonstrate superior antimicrobial activity, while *P. kudriavzevii* OG32 has shown promising cardiovascular benefits.

While their probiotic potential is well established, their postbiotic activity is also gaining recognition, primarily due to their production of  $\beta$ -glucans, mannans, and other bioactive metabolites that exert immunomodulatory, antioxidant, and metabolic effects. Future research should aim to optimize these strains for both probiotic and postbiotic formulations, expanding their use in dairy and non-dairy functional foods.

Probiotic yeasts, particularly *Pichia* and *Kluyveromyces*, have demonstrated significant potential in food fermentation and functional food development. *K. marxianus* has been successfully applied in dairy fermentation, enhancing texture, aroma, and nutritional value, with its postbiotic components additionally contributing to gut health and immune support. In contrast, *P. kudriavzevii* has shown benefits in non-dairy products by improving stability, gut microbiota modulation, and sensory properties (Tabanelli et al., 2016; Di Cagno et al., 2020). Furthermore, their role in producing bioactive compounds such as GABA, exopolysaccharides, and  $\beta$ -glucans reinforces their value in health-promoting foods (Li et al., 2022). Although their probiotic effects support gut microbiota balance, their postbiotic components - such as cell wall fractions, peptides, and metabolic byproducts - provide additional benefits by enhancing immune modulation and metabolic homeostasis.

Advancements in probiotic encapsulation and strain optimization continue to improve yeast viability and functionality, expanding their applications in next-generation functional foods and beverages (Chu et al., 2023). Additionally,

their ability to produce neuroactive compounds like melatonin and serotonin highlights their potential in promoting mental health (Hornedo-Ortega et al., 2016). While probiotic yeasts play a direct role in maintaining microbial balance, their postbiotic derivatives further enhance their impact by delivering bioactive compounds that contribute to gut health and metabolic regulation. Given their diverse benefits, *Pichia* and *Kluyveromyces* have emerged as promising alternatives to traditional probiotics, significantly influencing food

fermentation, nutritional enhancement, and microbiota modulation.

Their expanding applications in bioactive compound production, product stability improvement, and functional food development position these yeasts as valuable candidates for innovation in the functional food industry.

To provide a comprehensive perspective, Table 1 presents key findings on probiotic yeasts, highlighting their potential contributions to functional foods and health applications.

Table 1. Overview of potential probiotic non-conventional yeast strains and their postbiotic contributions

| Probiotic yeast strains                       | Isolation source                      | Postbiotic compound  | Reference                  |
|---|---------------------------------------|--|----------------------------|
| <i>K. marxianus</i>                           | Artisanal cheese                      | Bioactive metabolites with antimicrobial, adhesion-promoting, and protective properties                                  | Fadda et al., 2017         |
| <i>K. marxianus</i> CIDCA 8154                | -                                     | Antioxidant and anti-inflammatory metabolites  | Romanin et al., 2016       |
| <i>K. marxianus</i> (KM1, KM2, KM4, KM5)      | Kefir                                 | Antioxidants, Cholesterol-lowering compounds, Adhesion-enhancing proteins  | Cho et al., 2018           |
| <i>K. marxianus</i> (VM003, VM004, and VM005) | Whey                                  | Bioactive metabolites with antimicrobial properties and compounds involved in microbial interactions                     | Díaz-Vergara et al., 2017  |
| <i>K. marxianus</i> B0399                     | Milk                                  | Short-chain fatty acid and bioactive metabolites involved in gut microbiota modulation                                   | Tabanelli et al., 2016     |
| <i>K. marxianus</i> AS41                      | Yogurt and cheese                     | Antimicrobial peptides, metabolites with anticancer properties   | Saber et al., 2017a        |
| <i>P. fermentans</i>                          | Traditional cheese                    | Antioxidant and antimicrobial metabolites, Surface proteins involved in auto-aggregation and hydrophobicity,             | Merchán et al., 2020       |
| <i>P. kudriavzevii</i> AS-12                  | -                                     | Bioactive probiotic metabolites with anticancer properties   | Saber et al., 2017b        |
| <i>P. kudriavzevii</i> OG32                   | Nigerian fermented cereal-based foods | Antioxidant metabolites, lipid-regulating compounds and metabolites involved in cardiovascular health                    | Ogunremi et al., 2015      |
| <i>P. kudriavzevii</i>                        | Fermented vegetables                  | Antimicrobial inhibitors   | Vergara et al., 2023       |
| <i>P. kudriavzevii</i>                        | Guajillo pepper                       | Antioxidant metabolites, adhesion-promoting molecules, Cholesterol-lowering compounds, protective bioactive metabolites. | Lara-Hidalgo et al., 2019  |
| <i>P. kluyveri</i>                            | Cocoa fermentation                    | Adhesion-promoting compounds, antioxidant metabolites  | Menezes A. G. et al., 2020 |

## 2. Prebiotics

A prebiotic is defined as a substrate that is selectively utilized by host microorganisms, resulting in a health benefit (Yoo et al., 2024). For a compound to be classified as a prebiotic,

it must meet three key criteria: resistance to digestion, fermentation by the gut microbiota, and selective stimulation of beneficial bacteria. Currently, fructans, including fructooligosaccharides, inulin, and galactans, such as

galacto-oligosaccharides (GOS), are considered the predominant prebiotics, as evidenced by extensive research demonstrating their prebiotic effects.

Galacto-oligosaccharides (GOS) and fructo-oligosaccharides (FOS) are among the most important prebiotic sources and both play a key role in the regulation of the gut microbiota, metabolic health and digestive function. While GOS are lactose-derived oligosaccharides that primarily support *Bifidobacteria*, *Lactobacilli* and *Anaerostipes* (Bothe et al., 2017), FOS are fructose-based fructans classified into short-chain (DP3-DP12) and high polymerisation degree (DP > 12) forms that contribute to SCFA production and gut homeostasis (Belmonte-Izquierdo et al., 2023).

Despite their bifidogenic effects, GOS are particularly beneficial in infant nutrition and immune support, whereas FOS are more commonly associated with gut motility and metabolic regulation. In addition, GOS contains specific non-lactose disaccharides such as allolactose and lactulose, whereas FOS acts primarily as fermentable fibres. Their different structural characteristics and fermentation patterns make them complementary prebiotic ingredients in functional foods and dietary formulations (Bothe et al., 2017; Belmonte-Izquierdo et al., 2023).

Yeast species such as *K. marxianus* and *K. lactis* are recognized for their ability to synthesize bioactive compounds with high added value, particularly oligosaccharides with prebiotic properties (Binati et al., 2021).

The prebiotic potential of *Kluyveromyces* species has been extensively investigated, particularly in the biosynthesis of GOS from lactose. *K. lactis* CECT1931 has been reported to facilitate GOS production, highlighting its applicability in functional food and dairy formulations (Rodriguez-Colinas et al., 2011). In contrast, Padilla et al. (2015) demonstrated a broader prebiotic potential by utilizing *K. marxianus* and *K. lactis* in the isomerization of transgalactosylated cheese whey permeate, leading to the formation of a diverse range of prebiotic carbohydrates, including lactulose, lactulose-derived oligosaccharides (OsLu), tagatose, and GOS. This suggests that while Rodriguez-Colinas et al. (2011) focused on

direct GOS production from lactose, Padilla et al. (2015) explored a more complex bioconversion process that yielded multiple bioactive compounds.

Additionally, Sun et al. (2016) expanded upon previous findings by demonstrating that *K. lactis* could be employed not only for GOS synthesis but also for its purification, achieving high-purity GOS (>95%). Compared to Rodriguez-Colinas et al. (2011) and Padilla et al. (2015), who primarily examined prebiotic formation, Sun et al. (2016) highlighted the potential of *K. lactis* in enhancing the quality and purity of prebiotic compounds.

Species such as *Candida* spp. LEB-I3, *Rhodotorula* spp., and *Xanthophyllomyces dendrophorus* have also been investigated for their prebiotic synthesis potential, with studies reporting their ability to produce fructo-oligosaccharides (FOS) from sucrose and isomalto-oligosaccharides (IMO) from maltose (Rai et al., 2019). While *Kluyveromyces* species have been extensively studied for their role in GOS production, these non-*Saccharomyces* yeasts offer an alternative approach by utilising different carbohydrate substrates.

The biochemical composition and structure of the cell wall are key determinants of its prebiotic properties, as the specific components within the cell wall can be used as prebiotics to selectively modulate the gut microbiota and promote host health (Schiavone et al., 2023).

The cell wall composition of *K. lactis* and *K. marxianus* places them in the glucose/mannose group, as their cell walls are mainly composed of glucans, mannans, and chitin, whereas the cell wall of *Y. lipolytica* contains glucose, mannose, and galactose, highlighting its distinct carbohydrate composition compared to other yeast species (Lozančić et al., 2021). In *K. marxianus*, the cell wall represents approximately 33% of the dry mass of the cell, with polysaccharides accounting for almost 90% of its composition (Fortin et al., 2018).

$\beta$ -glucans are naturally occurring polysaccharides found in the cell walls of yeast, and are recognised for their diverse biological activities and health benefits (Bacha et al., 2017). They serve as a structural component of the yeast cell wall and have been extensively

studied for their immunomodulatory, cholesterol-lowering, and anti-inflammatory properties (Vieira et al., 2016).

Mannans are key structural polysaccharides in yeast cell walls, playing a crucial role in cell integrity and immune interactions (Rai et al., 2019). The mannans of *K. marxianus* closely resemble those of *S. cerevisiae*, featuring an  $\alpha$ -1,6-mannan backbone with  $\alpha$ -1,3 and  $\alpha$ -1,2 branches, a composition that may influence their functional and biological properties (Galinari et al., 2017). Previous studies have shown that *K. marxianus* mannans exhibit structural variability. For example, Tang et al. (2022) reported isolating high-molecular-weight  $\alpha$ -1,6-mannans, ranging from 650 to 700 kDa, from strains LZ-JM1 and GY3. In contrast, other researchers have isolated water-soluble  $\alpha$ -mannans from the same species with significantly lower molecular weights ranging from 0.5 to 77 kDa, highlighting the diversity of yeast-derived mannans (Fortin et al., 2018). The structural composition of mannans plays a pivotal role in shaping their functional

properties, with variations in backbone architecture and molecular weight influencing their biological activity, including immunomodulation, cell adhesion, and prebiotic potential.

The distinctive cell wall components of non-*Saccharomyces* yeasts position them as a promising source of functional ingredients, particularly as prebiotics – non-digestible substances that serve as a substrate for the gut microbiota. These components have the potential to selectively promote the growth and activity of beneficial bacteria, thereby contributing to gut health and overall well-being. As research in this field continues to advance, non-*Saccharomyces* yeasts may play an increasingly significant role in developing innovative prebiotic solutions to enhance human health.

A summary of the prebiotic components produced by various non-conventional yeast species is given in Table 2.

Table 2. Overview of potential prebiotic non-conventional yeast strains

| Prebiotic yeast strains                             | Prebiotic compounds                               | References                     |
|---|---|--------------------------------|
| <i>K. lactis</i> CECT1931                           | galacto-oligosaccharides (GOS)                    | Rodriguez-Colinas et al., 2011 |
| <i>K. marxianus</i>                                 | lactulose, lactulose-derived oligosaccharides     |                                |
| <i>K. lactis</i>                                    | (OsLu), tagatose, and GOS                         | Padilla et al., 2015           |
| <i>K. lactis</i>                                    | high-purity galacto-oligosaccharides (GOS) (>95%) | Sun et al., 2016               |
| <i>Candida</i> spp. LEB-I3, <i>Rhodotorula</i> spp. | fructo-oligosaccharides (FOS)                     | Rai et al., 2019               |
| <i>Xanthophyllomyces dendrorhous</i>                | isomalto-oligosaccharides (IMO)                   | Rai et al., 2019               |

## CONCLUSIONS

For many decades, yeasts have played a fundamental role in the production of fermented foods and beverages. More recently, however, the potential health benefits of non-*Saccharomyces* yeast species have attracted increasing scientific interest, highlighting their promising applications in health and well-being. At present, *S. boulardii* and *K. fragilis* B0399 are the only probiotic yeasts for which the mechanisms by which they prevent and treat intestinal disorders have been well characterised. However, emerging evidence suggests that certain non-conventional yeast species, including *Kluyveromyces*, *Pichia*,

*Candida*, and *Yarrowia*, also possess probiotic potential, thereby expanding the spectrum of beneficial microbes beyond traditional bacterial probiotics. It has been demonstrated that these yeasts possess several key probiotic properties, including high survival rates under gastrointestinal conditions, adherence to intestinal epithelial cells, and antimicrobial activity against pathogens. In addition, some strains produce bioactive metabolites with immunomodulatory effects, known as postbiotics, such as short chain fatty acids (SCFAs), organic acids, antimicrobial compounds, and extracellular vesicles, which contribute to host protection against infection and intestinal homeostasis. Furthermore, their

resistance to gastric acidity and bile salts renders them suitable for probiotic applications, particularly in functional foods and dietary supplements.

Of particular interest are yeast cell wall components, such as mannans and  $\beta$ -glucans, which have been shown to possess significant prebiotic properties. These components have been observed to modulate gut microbiota while concurrently exerting antioxidant, immune-modulating, and antimicrobial effects. Experimental studies have demonstrated that certain non-*Saccharomyces* yeast species, such as *Kluyveromyces marxianus* and *Kluyveromyces lactis* exhibit prebiotic potential, primarily due to their cell wall polysaccharides that serve as fermentable substrates for beneficial gut microbiota. These structural components play a pivotal role in enhancing host immunity through cytokine modulation, improving phagocytic efficiency, and limiting bacterial invasion, further reinforcing the role of non-*Saccharomyces* yeasts as valuable probiotic and prebiotic sources.

The incorporation of non-conventional probiotic yeasts and alternative prebiotic substrates has been demonstrated to enhance product integrity and reduce reliance on heavily commercialised, fraud-prone sources. This approach facilitates the development of more sustainable and scientifically validated functional foods, thereby ensuring consumer trust and confidence.

As research continues to advance, the integration of non-*Saccharomyces* yeasts into probiotic and prebiotic applications shows great potential for the development of next-generation functional foods with enhanced health benefits, scientific credibility, and consumer confidence.

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