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Emerging relevance of cell wall components from non-conventional yeasts as functional ingredients for the food and feed industry

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ABSTRACT

Non-conventional yeast species, or non-*Saccharomyces* yeasts, are increasingly recognized for their involvement in fermented foods. Many of them exhibit probiotic characteristics that are mainly due to direct contacts with other cell types through various molecular components of their cell wall. The biochemical composition and/or the molecular structure of the cell wall components are currently considered the primary determinant of their probiotic properties. Here we first present the techniques that are used to extract and analyze the cell wall components of food industry-related non-*Saccharomyces* yeasts. We then review the current understanding of the cell wall composition and structure of each polysaccharide from these yeasts. Finally, the data exploring the potential beneficial role of their cell wall components, which could be a source of innovative functional ingredients, are discussed. Such research would allow the development of high value-added products and provide the food industry with novel inputs beyond the well-established *S. cerevisiae*.

1. Introduction

Although yeasts have long been recognized for their role in fermented food and beverages, the diversity of genera and species involved has only been deciphered in the last 15 years (Tamang and Lama, 2022). In addition to *Saccharomyces* species, non-conventional yeasts have attracted much interest for their technological properties (in oenology for instance) and their potential probiotic attributes. Thus, the specific functional and biotechnological properties of probiotic *Saccharomyces* and non-*Saccharomyces* species have been explored in many recent works (Fernández-Pacheco et al., 2021). Apart from live yeast cells (Shruthi et al., 2022), their cell wall components can be valorized as value-added products in the production of functional foods such as nutraceuticals. According to the Food and Agriculture Organization of the United Nations and the World Health Organization (FAO/WHO), probiotics are living microorganisms that can be used to improve the health and well-being of the host, while prebiotics are microbial components with beneficial properties to the host. The best-known and best-characterized probiotic yeast is *S. cerevisiae* var. *boulardii* (*S. boulardii*). This yeast species is widely used as a preventive and curative probiotic for the treatment of various gastrointestinal diseases in humans and animals. It has also been shown to be effective in the treatment of inflammatory bowel disease and diarrhea in humans induced by antibiotic treatment (Szajewska and Kołodziej, 2015) or colonization with enterotoxigenic *Escherichia coli* (Gresse et al., 2021). Recently, various screenings of potential probiotic yeasts other than *S. cerevisiae* and *S. boulardii* have been performed (Staniszewski and Kordowska-Wiater, 2021). Yeasts species from oenological and dairy origin were reported to have potential probiotic properties including *Kluyveromyces marxianus* (Smith et al., 2016; Galinari et al., 2018), *Kluyveromyces lactis* (Kumura et al., 2004), *Debaryomyces hansenii* (Ochangco et al., 2016; Angulo et al., 2020), *Torulaspora delbrueckii* (Andrade et al., 2021), *Yarrowia lypolytica, Pichia pastoris* (renamed as *Komagataella* spp.) (Birmann et al., 2021), *Wickerhamomyces anomalus* (Helmy et al., 2019) and *Pichia kudriavzevii* (Saber et al., 2017). Phenotypes ranging from *in vitro* adhesion to enterocytes to immunomodulation, anti-pathogen or anti-oxidative properties (Fortin et al., 2018a; Galinari et al., 2018; Smith et al., 2014) have been explored and open new avenues for future use as food additives. However, despite several reports on their potential functionality, only a few studies explored the molecular basis of these properties. Such studies would be very helpful for the development of prebiotics for the food and feed industry.

Most of these non-*Saccharomyces* yeasts possess a wide range of

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hydrolytic activities on polysaccharides (Escribano et al., 2017) and can survive under extreme conditions (high pH, high temperature or high salt concentration) (Karim et al., 2020; Prista et al., 2016). Their cell wall, whose thickness is thought to be variable depending on the species, allows them to cope with many stresses encountered during biotechnological processes such as temperature and osmotic shock. Also, yeasts are in direct contact with other cell types such as pathogenic bacteria and epithelial cells, mostly through their cell wall components. Since these interactions involve the cell wall at first, its components are very likely the first determinants of the probiotic attributes of these yeasts. Despite the crucial role of the cell wall in the functional properties of these yeasts, only a few works have attempted to find out whether the cell wall composition (mainly β-glucans, mannans and chitin), the degree of connection and branching between these components or their accessibility, are fundamental in determining the probiotic properties of these yeasts. While the cell wall of the model organism *S. cerevisiae* and the pathogenic yeast *Candida albicans* are well-characterized, the current knowledge on the cell wall of other yeast species is more limited. The objective of this review is to present the extraction methods and techniques that are used to study the structure and composition of the cell wall, the key characteristics of the cell wall of non-conventional yeasts and their potential beneficial properties to the host. Thus, we highlight connections between the composition and architecture of the cell wall and the properties as possible functional ingredients of non-conventional yeasts.

2. Investigation methods for the study of the cell wall

2.1. Visualization by transmission electron microscopy

Transmission electron microscopy has revealed that many ascomycetous yeasts such as *S. cerevisiae, K. lactis, W. anomalus, Blastobotrys (Arxula) adeninivorans, Cyberlindnera jadinii* or *K. marxianus* have a cell wall formed by two layers (see Fig. 1; *K. marxianus* and *W. anomalus,* as examples) (Agboola et al., 2021; Backhaus et al., 2011). In these species, the cell wall is composed of a network of chitin, β-glucans and mannoproteins that are all cross-linked to form a complex and flexible structure. Chitin, β-1,3 and β-1,6-glucans form the electron-transparent inner layer and give it its rigidity (Schiavone et al., 2017). The electron-dense outer layer is composed of mannoproteins. This layer is less permeable to macromolecules than the inner layer (Zlotnik et al., 1984). More specifically, the cell wall of the fission yeast *Schizosaccharomyces pombe* has a particular three-layer structure. The inner and outer layer are electron-dense and composed of galactomannans and the electron-transparent middle layer is composed of β-1,3/β-1,6-glucans and α-1,3-glucans (Pérez et al., 2018) (Table 1).

2.2. Extraction of polysaccharides

Many approaches for the extraction of β-glucans and α-mannans from yeast biomass are performed under alkaline conditions (see Table 1). Alkaline extraction can be performed directly on yeast cells or on yeast cell walls obtained after autolysis (Sukumaran et al., 2010; Medina-Córdova et al., 2018; Xing et al., 2018) or cell disruption by bead-milling (Nguyen et al., 1998). Subsequent extractions are then carried out by hot alkali treatment using 3% NaOH or 1M NaOH, which is the condition often preferred to cold alkali to solubilize β-glucans (Table 1). Glucans fractions are therefore defined according to their solubility under alkaline conditions after extraction. Alkali-insoluble glucans have higher molecular weight than alkali-soluble glucans (Fortin et al., 2018a). In non-*Saccharomyces* yeasts, alkali-insoluble glucans range from 6.6 to 20% of the whole cell biomass (Medina-Córdova et al., 2018; Angulo et al., 2018, 2021; Sukumaran et al., 2010; Reyes-Becerril et al., 2020) and from 14.5 to 37.4% of the cell walls (Nguyen et al., 1998). This higher yield can be explained by the fact that cell wall isolation process leads to the removal of intracellular proteins and thus to an increase in the proportion of cell wall's polysaccharides in the starting material. To obtain a mannoproteins-rich fraction (i.e. mannan-protein complexes), the alkali-soluble fraction is further treated with cold organic solvents such as ethanol (Tang et al., 2022; Bzducha-Wróbel et al., 2022; Fortin et al., 2018a) or methanol (Galinari et al., 2017) to precipitate mannoproteins. This yields a low purity mannan fraction (3.2–9.1%) with a molecular weight below 200 kDa (Fortin et al., 2018a; Bzducha-Wróbel et al., 2022). Further purification steps are required to obtain a higher yield and purity of mannoproteins and thus mannans. This could be achieved by taking advantage of the structure of mannoproteins, using an anion exchange chromatography technique with DEAE columns or by ultrafiltration techniques (Galinari et al., 2017; Tang et al., 2022). To summarize, the extraction and quantification of yeast cell wall polysaccharides are highly cumbersome. Notably, there are few information regarding the chitin content, which otherwise is a vital component for *S. cerevisiae* (Shaw et al., 1991). Standard procedures that enable to determine glucans, mannans and chitin contents as well as their isolated monosaccharides remain to be established for non-*Saccharomyces* yeasts. They should enable to compare conditions and strains for changes in cell wall polysaccharides.

2.3. Techniques for the investigation of cell wall architecture from non-conventional yeasts

To quantify the polysaccharides extracted from the cell wall, different common chemical methods are used. The phenol-sulfuric acid method (DuBois et al., 1956) is a well-established method to determine

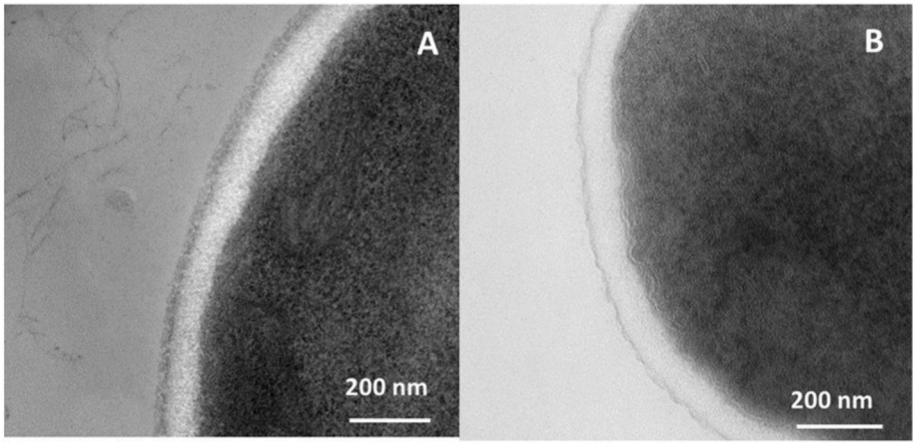

Fig. 1. Transmission electron micrographs (TEM) of *Kluyveromyces marxianus* and *Wickerhamomyces anomalus* (A,B) (unpublished data).

Table 1
Cell wall components extracted from different non-*Saccharomyces* yeasts: methods of extraction, yield, and molecular weight. (Mw, molecular weight; nd, not determined).

Cell wall component	Yeast species	Starting material	Extraction method	Yield (%) (purity)	Mw (kDa)	Reference
β-glucans	*S. boulardii*	Autolyzed cells	1M NaOH – 90 °C	nd (40.5%) [a] nd (24.0%) [b]	1921 0.73–160	(Fortin et al., 2018a)
	D. hansenii	Cells	3% NaOH - 100 °C	6.6–11 (nd)[a]	nd	(Medina-Córdova et al., 2018)
		Cells	3% NaOH - 100 °C	14.8 (63.1%) [a]	nd	(Angulo et al., 2018)
		Cells	3% NaOH - 100 °C Acetic acid 0.5N	19.8 (79.3%) [a]	0.69	(Reyes-Becerril et al., 2020)
		Cells	3% NaOH - 90 °C	12.0–12.4 (98%) [a]	nd	(Sukumaran et al., 2010)
		Cell walls	1M KOH - 4 °C	20.9–48.4 (83–87%) [a] 14.5–37.4 (92–93%) [b]	nd	(Nguyen et al., 1998)
	C. tropicalis	Cells	3% NaOH - 90 °C	8.1 (98%) [a]	nd	(Sukumaran et al., 2010)
	K. marxianus	Autolyzed cells	1M NaOH – 90 °C	nd (49.2%) [a] nd (30.4%) [b]	2086 0.74–165	(Fortin et al., 2018a)
		Cell walls	1M KOH - 4 °C	18.5–40.6 (89–93%) [a] 10.0–48 (95–98%) [b]	nd	(Nguyen et al., 1998)
	P. pastoris	Autolyzed cells	High-pressure hot-water treatment, ultrasonication, isopropanol extraction, and protease treatment	11.7 (85.3%) [a]	nd	(Xing et al., 2018)
	K. apiculata,	Cell walls	1M KOH - 4 °C	(94–97%) [a] (90–92%) [b]	nd	(Nguyen et al., 1998)
	Z. bailii,	Cell walls	1M KOH - 4 °C	20.8–23.8 (96%) [a] 33.9–37.3 (92–94%) [b]	nd	(Nguyen et al., 1998)
	Y. lypolitica	Cells	3% NaOH – 100 °C	9.52 (61.07%) [a]	3.30	(Angulo et al., 2021)
Mannan	*S. boulardii*	Autolyzed cells	1M NaOH - 90 °C, precipitation with ethanol	nd (3.2%)	0.72–87	(Fortin et al., 2018a)
	K. marxianus	Cells	3% NaOH - 80 °C, precipitation with methanol and filtration (cutoff of 100 kDa)	13.3 (90%)	203	(Galinari et al., 2017)
		Autolyzed cells	1M NaOH - 90 °C, precipitation with ethanol	nd (9.1%)	0.48–77	(Fortin et al., 2018a)
		Cells	2% NaOH - 80 °C, precipitation with ethanol, purification with DEAE anion exchange column	71.1–84.7 (91.1–97.1%)	646–698	(Tang et al., 2022)
		Cell walls	1M KOH - 4 °C	25.6–34.1 (93–95%)	nd	(Nguyen et al., 1998)
	W. anomalus	Cells	Autoclave, ethanol precipitation	nd	1.9–84	(Bzducha-Wróbel et al., 2022)
	M. reukaufii	Cells	Autoclave, ethanol precipitation	nd	1.9–150	(Bzducha-Wróbel et al., 2022)

[a] for insoluble glucans.
[b] for soluble glucans.

the total polysaccharide content, while the monosaccharide content is determined after their release by acid hydrolysis using strong acids such as sulfuric acid or trifluoroacetic acid (TFA) (Dallies et al., 1998). Structural features of polysaccharides extracted from yeast cell walls are usually analyzed by Fourier Transformed Infrared (FTIR) or Nuclear Magnetic Resonance (NMR) techniques. The functional chemical groups and hence the purity of the polysaccharides extracted are detected by FTIR (Vaithanomsat et al., 2022; Bacha et al., 2017; Zhao et al., 2022). To unravel the type of linkage and the degree of branching of each polysaccharide, fine chemical analysis can be performed by liquid NMR (Galinari et al., 2017; Vaithanomsat et al., 2022). The structure and molecular weight of polysaccharides extracted from a same yeast species may vary due to divergent yeast strains and culture conditions but also to extraction procedures using different chemical reagents that may alter the native structure of polysaccharides and destroy covalent bonds.

Parietal proteins are studied by proteomic approaches using mass spectrometry. According to the extraction method, cell wall mannoproteins were divided into three groups: non-covalently attached proteins that are extractable by SDS or reducing agents, glycosylphosphatidylinositol (GPI)-anchored proteins extractable by β-1,3-glucanase, and Pir proteins that are extractable with mild alkaline conditions (Lozančić et al., 2021). These proteomic techniques should be applied in the future to investigate the cell wall proteomes of these non-*Saccharomyces* yeasts, which may likely vary under different growth and stress conditions.

In addition to classical extraction methods in which the structure of polysaccharides, other strategies are now being used to study the physical properties of the cell wall at atomic resolution, such as solid-state NMR (ssNMR) and atomic force microscopy (AFM). Recently, ssNMR spectroscopy combined with glycosylated bond analysis has been successfully used to develop a high-resolution model of the cell wall architecture of the filamentous fungus *Aspergillus fumigatus* (Kang et al., 2018). This non-destructive method provides insight into the structure of polysaccharides and the organization of the cell wall (Loquet et al., 2013; Zhao et al., 2020), although it requires $^{13}C/^{15}N$ labelling of the sample. AFM provides access to the mechanical properties of the yeast cell wall through the value of the elasticity modulus or Young's modulus (Francois et al., 2013). Screening of mutants involved in cell wall biosynthesis and assembly has revealed that cross-linking of cell wall components is essential for cell wall strength (Dague et al., 2010). AFM can also be used in single-molecule force spectroscopy mode to map and unfold the polysaccharides at specific sites on the cell wall (Schiavone et al., 2019; Francius et al., 2009). In addition, techniques such as AFM and ss-NMR can evaluate the dynamics of the cell wall, which is a

fundamental property as the structure and composition of the cell wall is constantly changing during the life cycle of yeast and under industrial culture conditions (often stressful and challenging for microorganisms).

3. Cell wall composition and architecture of non-conventional yeasts

3.1. Cell wall composition

Schweigkofler (2002) studied the monosaccharide composition of purified cell walls of 114 ascomycetes fungi. Although the method used did not allow the measurement of the chitin content, this screening allowed determining the sugar content released upon hydrolysis of cell wall polysaccharides by trifluoro acetic acid (TFA). Three types of sugar patterns were found: glucose/mannose, glucose/mannose/galactose and glucose/mannose/galactose/rhamnose. The glucose/mannose pattern was found in 51 out of 114 ascomycetes belonging to the Hemiascomycetes clade with different proportions of glucose (25–75%) and mannose (22–75%). *S. cerevisiae, C. albicans* and *K. lactis* belong to this glucose/mannose group because their cell wall contains glucans, mannans and chitin. The cell wall of *S. cerevisiae* accounts for 20–30% of the dry mass of the cell and it contains 80–90% of polysaccharides (Lesage and Bussey, 2006; Klis, Koster and Brul, 2014). Nguyen et al., 1998 also studied the sugar composition of the cell wall polysaccharides of different non-*Saccharomyces* yeasts, including *D. hansenii, K. marxianus, Zygosaccharomyces bailii* and *Kloeckera apiculate*. These yeasts species belong to the glucose/mannose type and the cell wall represents 26–32% of the dry weight and is composed of 84–89% carbohydrates depending on the species, strain and growth conditions. The cell wall of *K. marxianus* accounts for 33% of the dry mass of the cell (Nguyen et al., 1998) and contains about 90% polysaccharides (Fortin et al., 2018a) (Table 1). Cell walls containing glucose, mannose and galactose were found in 26 species that covered the Hemiascomycetes clade, the Euascomycetes clade and Schizosaccharomycetales fungi from the "Protomyces-clade" that notably included the fission yeast *S. pombe* and *Y. lypolitica*. The percentage of glucose ranged from 28 to 65%, that of mannose from 18 to 56% and the proportion of galactose varied from 2 to 27% (Schweigkofler 2002). The third type of monosaccharide, which contains rhamnose in its cell wall, was found in Euascomycetes clade as well as in *Taphrina* spp. and *Protomyces* spp. of the Promycetes clade.

These global studies provide information on the type of polysaccharides that can be found in the cell wall of different fungi (Table 2). Nevertheless, further studies are needed to determine the nature of the linkages within the parietal polysaccharides of ascomycetes yeast species (β-1,3; β-1,6; β-1,4 or α-1,3). The composition of the cell wall is dynamic and can vary according to growth conditions and carbon sources. Indeed, the cell wall is the direct target of various external physical, osmotic, and mechanical stresses, which requires permanent remodeling such as increasing its polysaccharide or protein content or forming new crosslinks between cell wall components (Aguilar-Uscanga and François, 2003).

3.2. Cell wall architecture

3.2.1. β-glucans

β-glucans represent the common architectural signature of the inner layer of yeast cell walls studied to date (Table 2). In the fission yeast *S. pombe*, the middle layer is composed of β-1,3/β-1,6-glucans (54–60% of the cell wall) and α-1,3-glucans (Pérez et al., 2018). In *S. cerevisiae*, β-glucans (50–60% of the yeast cell wall dry mass) consist of glucose chains that are mainly connected by β-1,3-linkages and include 10–15% of glucose branched by β-1,6-linkages. The β-1,3/β-1,6-glucans vary according to the degree of branching, degree of polymerization and molecular weight. The *S. cerevisiae* β-1,3-glucans have a degree of polymerization of about 1500, while β-1,6-glucans consist of an average of 140 glucose units (Klis et al., 2002). Highly branched β-1,3-glucans are thus found to be alkali-insoluble due to strong hydrogen bonds formed by the hydroxyl groups of their glucans chains and due to their covalent binding with chitin (Hartland et al., 1994). Depending on the strain, alkali-insoluble β-glucans derived from *D. hansenii* can reach up to 12% of the yeast biomass (Medina-Córdova et al., 2018; Sukumaran et al., 2010) (Table 1), but this amount can vary considerably within the same yeast species. NMR analyses showed that the alkali-insoluble fraction of the marine yeast *D. hansenii* consists of low molecular weight β-1,3-glucans with β-1,6 side branches (0.69 kDa) (Reyes-Becerril et al., 2020). In contrast, higher molecular weight alkali-insoluble glucans were extracted from marine strain of *Y. lypolytica* (3.3 10^3 Da) (Angulo et al., 2021), *K. marxianus* and *S. boulardii* (1.9 and 2.10^6 Da, respectively) (Fortin et al., 2018a). In addition, alkali-insoluble particulate β-glucans from *S. uvarum*, *K. marxianus* and *S. boulardii* accounted for 51%, 49% and 41% of the cell wall dry mass, respectively, indicating a difference in cell wall composition (Fortin et al., 2018b; Suphantharika et al., 2003). The cell wall of *K. lactis* is similar to that of *S. cerevisiae,* with 50% of the cell wall dry weight composed of β-1,3-glucans (Backhaus et al., 2010). *W. anomalus* has a higher content of β-glucans than *C. jadinii* (20.4% and 11.1% of the cell dry weight, respectively), resulting in greater stiffness of its cell wall (Agboola et al., 2021). The methylotrophic yeast *Komagataella* spp. has recently been used to produce a β-glucan rich fraction by autolysis and hot water treatment, representing 11.7% of the dry weight of the cell (Xing et al., 2018). As with *S. cerevisiae*, these works support that cell wall composition varies between strains. Finally, these studies showed that the proportion and structure of β-1,3- and β-1,6-glucans can vary depending on the extraction method used. These variations of the cell wall architecture can lead to different *in vivo* properties, with high molecular weight β-glucans and high degree of branching reported to possess important biological activities (see below) (Murphy et al., 2020; Chen et Seviour, 2007).

3.2.2. Mannoproteins

The chemical structure of the mannoproteins from some yeast species has been characterized (Klis 1994). With the exception of the cell wall of *S. pombe*, which contains galactomannans (9–14% of the cell wall) in its inner and outer cell wall, the mannoproteins of most yeasts, including *S. cerevisiae,* present in the outer layer of the cell wall and are highly glycosylated proteins with a carbohydrate fraction (85–90%)

Table 2
Cell wall polysaccharides in different yeasts species.

Cell wall polysaccharide	*S. cerevisiae*	*K. lactis*	*S. pombe*	*D. hansenii*	*K. marxianus*
β-1,3 and β-1,6-glucans	50–65%	50–55%	54–60%	50–60%	50%
α-1,3-glucan	none	none	28–32%	nd	nd
Chitin	1–5%	1–3%	in conidia only	2–7%	1–4%
Mannoproteins	35–40%	30–40%	None	29–35%	20–25%
Galactomannan	None	None	9–14%	None	None

The cell wall components listed were identified from the following sources: *S. cerevisiae* (Klis et al., 2002), *K. lactis* (Backhaus et al., 2010; Bahmed et al., 2002), *S. pombe* (Pérez et al., 2018), *D. hansenii* and *K. marxianus* (Nguyen et al., 1998). Results are the means of each component expressed as % of cell wall dry weight. nd = not determined.

composed of α-linked mannose units (Table 2). Cell wall mannoproteins carry numerous N-linked mannans and clustered O-linked mannans. N-linked glycans have a hypermannosylated outer chain composed of a long backbone of about 50 α-1,6 mannose residues with short side chains of mannose units linked to the backbone by α-1,2 and α-1,3-linkages, whereas O-linked mannans have a smaller core structure of α-1,6-linked mannose (Munro 2001). Golgi glycosyltransferases involved in N-glycan modifications were first identified by genetic analysis of mannans synthesis mutants (*mnn*) in *S. cerevisiae* (Rayner and Munro, 1998). Other screens affecting Golgi N-glycosylation (*och1*, mnn9) have been performed in other yeasts species such as *Y. lypolitica* (Barnay-Verdier et al., 2008), confirming that the mechanisms of mannosylation synthesis are conserved. Different amounts of phosphate can be esterified to N- and O-linked mannans in *S. cerevisiae*, with phosphate being esterified to the hydroxyl groups of α-1,2 linked mannans chains (Jigami and Odani, 1999). Kocourek and Ballou observed a proportion of phosphates in the mannan fraction ranging from 0.04% (*K. lactis*) to 4.4% (*Candida atmospherica*), testifying to a difference in the structure of the side branches decorating the α-1,6-mannans chain backbone (Kocourek and Ballou, 1969). The mannans of *K. marxianus* appear to be similar to those of *S. cerevisiae*, with a structure consisting of an α-1,6-mannan backbone substituted with α-1,3 and α-1,2 branches (Galinari et al., 2017). Tang et al. reported the isolation of α-1,6-mannans from two different *K. marxianus* strains LZ-JM1 and GY3 with molecular weights ranging from 650 to 700 kDa (Tang et al., 2022), while others have isolated water soluble α-mannans with low molecular weights ranging from 0.5 to 77 kDa from the same yeast species (Galinari et al., 2018; Fortin et al., 2018a). These variations in molecular weight could be related to the yeast strain, the composition of the culture medium and/or the extraction method used (Table 1). Nevertheless, the α-mannans extracted from *K. marxianus* seem to have a higher structure than those of *S. boulardii*, for which an isolation of mannans from *S. cerevisiae* var. *boulardii* ATCC MYA-796 with molecular weights ranging from 0.1 to 10 kDa has been reported (Fortin et al., 2018a).

Cell wall proteins are mainly divided into two main classes: cell wall proteins that can be retained covalently through a glycosylphosphatidylinositol (GPI) anchor to β-1,6-glucan (GPI-CWPs) and Pir family cell wall proteins covalently bound by an alkali-sensitive linkage to β-1,3 glucans (Pir-CWPs). In the *S. cerevisiae* genome, 60 putative GPI-CWPs have been identified (Caro et al., 1997). These GPI-glycosylated proteins have many roles, some serving as enzymes for cell wall biosynthesis and maintenance or as structural components, while others are adhesive proteins involved in flocculation, biofilm formation or invasive growth (Pittet and Conzelmann, 2007). Like the polysaccharide content, the cell wall proteome can vary according to the growth conditions (Groot et al., 2005). Recently, an *in silico* analysis of cell wall proteins from 92 yeast species showed that they are largely conserved, but some are highly species-specific (Lozančić et al., 2021). Yeasts that are taxonomically close to *S. cerevisiae* show a similar protein profile. For example, *S. boulardii* and *S. cerevisiae* have the same GPI-bound proteins, non-covalently attached proteins and alkaline-extractable proteins. In contrast, the genera *Kluyveromyces, Lachancea, Wickerhamii* show different profiles (Lozančić et al., 2021). Pir proteins are present in many budding yeasts and *S. cerevisiae* PIR homologous genes have been found in several yeasts including *K. lactis* (Backhaus et al., 2010) and *Y. lypolytica* (Jaafar et al., 2003) but not in *S. pombe* (Sharifmoghadam et al., 2006). This suggests a unique role for these genes in the budding yeast. In *K. lactis*, two Pir proteins have been identified so far by proteomics (KlPir1a, KlPir1b) (Backhaus et al., 2010), which is in contradiction with a recent work (Lozančić et al., 2021) that did not detect any Pir protein in *K. lactis* and other *Kluyveromyces* species using specific antibodies to streptavidin/biotin. Also, Pir proteins were not found in *D. hansenii, B. adenivorans* and *S. pombe* neither *in silico* nor by streptavidin/biotin blot (Lozančić et al., 2021). In *Y. lypolitica* only YlPir1 has been identified so far (Jaafar et al., 2003). Further studies are therefore needed to confirm these findings and to determine whether their potential absence could have a physiological role in cell wall architecture. The cell wall proteome of *K. lactis* has similar characteristics to that of *S. cerevisiae* and mass spectrometry analyses revealed that many *K. lactis* cell wall proteins were homologous to those of *S. cerevisiae*. However some species-specific proteins still have unknown functions (Backhaus et al., 2010). Among the non-conventional yeasts, *Komagataella* spp. and *Y. lypolitica* are two well-established yeasts used in biotechnology for the production and secretion of heterologous proteins. However, little is known about their cell wall structure. In *Y. lypolitica,* only Ylcwp1, a GPI-CWP (Jaafar and Zueco, 2004), and Ylywp1, a cell wall protein bound covalently bound to mycelial-specific β-1,3-glucans (Ramon et al., 1999), have been identified, but the total number of cell wall proteins is not known. Analysis of the secretome of *Komagataaella* spp grown on methanol, glycerol or glucose in fed-batch bioreactor identified a core of cell wall proteins (Pir1, Scw10) or cell wall-associated proteins (flocculins, chitinase and glucanase) that are present independently of the carbon sources used, but whose abundance changes during fermentation (Burgard et al., 2020). Despite minor differences, a high degree of similarity in the secretome was observed for all carbon sources in *Komagataella* spp, which contrasts with the effects of carbon sources on the secretome of *S. cerevisiae*, *K. lactis* and *C. utilis* (Madinger et al., 2009; Giardina et al., 2014; Buerth et al., 2011). These differences could be explained by a difference in the regulatory mechanisms underlying cell wall biogenesis between these different yeasts, which have been investigated so far only in the yeast *S. cerevisiae* (Levin 2011).

3.2.3. Chitin

Chitin is a polymer of β-1,4-linked N-acetylglucosamine units, which accounts for 1–5% of the cell wall of *S. cerevisiae.* As shown in Table 2, the chitin content can vary from 1 to 7% in non-*Saccharomyces* species *D. hansenii*, *K. lactis, K. marxianus* and *Z. baili* (Nguyen et al., 1998). Although a minor component of the yeast cell wall, chitin is essential for yeast survival since simultaneous deletion of the three genes encoding chitin synthases (*CHS1* to *-3*) is lethal in *S. cerevisiae* (Shaw et al., 1991). This property is probably shared by other yeast species, but this has not yet been directly demonstrated. Indeed, yeast species such as *C. albicans* or filamentous fungi such as *A. fumigatus* have several genes encoding chitin synthases (see review (Rogg et al., 2012)), which may reflect a functional redundancy representing a survival mechanism. The exception is *S. pombe*, which contains only two chitin synthases, one of which is apparently inactive (Martín-García et al., 2003). In *K. lactis*, there are three chitin synthases and KlChs2 has an essential role in cytokinesis. The deletion of this gene results in a defect in spore germination (Rippert and Heinisch, 2016). In conclusion, chitin synthases are conserved among yeast species, but it remains to be investigated whether the synthesis and distribution of chitin in these non-*Saccharomyces* yeast species is comparable or different from what has been described in *S. cerevisiae* (Orlean and Funai, 2019; Sánchez and Roncero, 2022) and whether the lack of chitin is lethal in these non-*Saccharomyces* species as in the case of *S. cerevisiae.*

4. Relationship between cell wall biochemical composition and structure and probiotic properties

Live yeasts and their derivatives in the form of inactive cells, total extracts and cell wall extracts have various applications with health-promoting properties in the food industry. A recent review summarized the probiotic attributes of yeasts other than *S. boulardii* and showed that these other probiotic yeasts could have various applications in food biotechnology (Shruthi et al., 2022). Here we report data exploring the role of cell wall components in the probiotic effects of live yeasts or the use of cell wall components as prebiotics.

4.1. β-glucans

The cell wall of *S. cerevisiae* is rich in β-glucans, which have been shown to have numerous nutritional and functional properties in human and animal health. Indeed, fungal β-glucans composed of a mix of β-1,3 and β-1,6-linkages have various biological activities, including immunostimulation (Batbayar et al., 2012). For example, *S. cerevisiae* β-glucans are able to stimulate TNF-α production and induce IL-6 production when lipopolysaccharides are used as co-stimulators (Seong and Kim, 2010). A more detailed study then showed that yeast cell wall extracts containing β-glucans, from *S. boulardii* and *K. marxianus*, are potent inducers of IL-1β, IL-6, and IL-10, but not IL-12, in dendritic cells (Smith et al., 2016). Interestingly, stronger stimulatory effects on mouse macrophages were detected with β-1,3-glucans with a higher molecular weight or a greater degree of β-1,6-branching (Cleary et al., 1999). Anti-inflammatory and antioxidant effects conferred by *S. cerevisiae* β-glucans have also been observed (Bacha et al., 2017). In a mouse model, *S. cerevisiae* β-1,3-glucans significantly increased the expression levels of IL-2, IL-6, and TNF-α (Mo et al., 2017). This stimulation of host immune function by β-1,3-glucans was associated with anti-tumor effects without toxicity to normal mouse cells. Thus, β-1,3-glucans are known potentiators of innate immunity.

The action of β-glucans on the immune system has been studied for antitumor targeting (Qi et al., 2011; Geller et al., 2019). In addition, insoluble extracts of β-glucans and mannoproteins from *S. boulardii* showed chemopreventive properties in a rat model of colorectal cancer *in vivo* (Fortin et al., 2018b). Numerous other studies have also demonstrated anticancer effects of *S. cerevisiae* β-glucan (Sambrani et al., 2021) including prevention of DNA damage in CHO cells (Oliveira et al., 2007), induced proliferation and activation of peripheral blood monocytes in patients with advanced breast cancer (Demir et al., 2007) and a variety of other immunostimulatory effects on various cell lines (Yoon et al., 2008) and *in vivo* (Mo et al., 2017). *S. cerevisiae* β-glucans have also been reported as antidiabetic agents through their effects on blood glucose levels and insulin resistance (Cao et al., 2017), as potential prebiotic compounds by altering gut microbiome and metabolite profiles (Zhen et al., 2021; Wang et al., 2020), and finally as capable of reducing blood cholesterol levels and promoting wound healing (Borchani et al., 2016).

In addition to β-glucans from *S. cerevisiae* and *S. boulardii*, β-glucans extracted from different non-*Saccharomyces* yeasts also showed prebiotic effects on animals or cell lines (Table 3). Cancer chemopreventive activities as well as antiproliferative and antioxidant effects of the polysaccharides (glucan, chitin, and mannan) from the *K. marxianus* cell wall were observed on HT-29 cells *in vitro* (Fortin et al., 2018a). Few other studies have analyzed the effects of non-*Saccharomyces* β-glucans together with their molecular architecture. For example, proton NMR studies revealed structures containing β-1,3-glucans branched with β-1,6 in different strains of *D. hansenii* of marine origin, which are probiotic and immunostimulatory in fish. These β-glucans increase cellular immune parameters (phagocytic capacity, reactive oxygen species production (respiratory burst), peroxidase activity and nitric oxide production) in goat peripheral blood leukocytes (Medina-Córdova et al., 2018). Similarly, Reyes-Becerril et al. (2020) observed by NMR that one of these marine strains of *D. hansenii* (BCS004) contains β-1,3-glucans branched with β-1,6 of low molecular weight (Reyes-Becerril et al., 2020). These β-glucans can upregulate macrophage receptor genes in the gut of the Pacific red snapper *Lutjanus peru*, and exhibit significant free radical scavenging capacity. Another study also showed that, upon challenge with *E. coli*, β-glucans from a strain of *D. hansenii* isolated from the rainbow trout gut increased leukocyte viability, phagocytic capacity and nitric oxide production (Angulo et al., 2018). Thus, yeast β-glucans are immunomodulators for fish (see for review Machuca et al., 2022). In addition, β-glucans from *K. marxianus* also induce cytokine secretion by dendritic cells that is dependent on the Dectin-1 receptor (Smith et al., 2016). The β-glucans recovered from *K. marxianus* have recently been analyzed by NMR for their purity, functional groups, linkages and tested for their functional properties such as glucose adsorption capacity among others (Vaithanomsat et al., 2022). Finally, *Y. lipolytica*–derived glucans have also been tested on goat leucocytes which showed increased phagocytic ability and nitric oxide production (Angulo et al., 2021). Several immune-related signaling pathways were also stimulated by these *Y. lipolytica* β-glucans, leading to the conclusion that they are immunostimulants in animals.

4.2. Mannans

Mannans from *S. cerevisiae* have potential beneficial effects on human and animal health (Faustino et al., 2021), including anti-inflammatory (Lew et al., 2017) and immunomodulatory effects (Jin et al., 2019), and wound repair (Michael et al., 2017). Mannans also have various other beneficial effects, for example as a feed supplement in aquaculture. Dietary supplementation with mannans can improve the resistance of fish to bacterial infections (Torrecillas et al., 2007; Liu et al., 2013) and it has recently been shown that mannans also have beneficial effects on the antiviral immune response of fish (Liang et al., 2023). A multi-strain yeast fraction combining selected fractions of *S. cerevisiae* and *C. jadinii* and having a high level of long chains of

Table 3
Prebiotic effects on animals or cell lines of cell wall components extracted from different non-*Saccharomyces* yeasts.

Cell wall component	Yeast species	Animal or cell line	Beneficial properties	Reference
Beta-glucans	*K. marxianus*	Human monocyte-derived dendritic cells	Induction of IL-1β, IL-6, and IL-10	(Smith et al., 2016)
	K. marxianus	Human HT-29 cells	Improved superoxide anion scavenging (antiradical capacity), NAD(P)H: quinone reductase induction and antiproliferative properties	(Fortin et al., 2018a)
	D. hansenii	Goat peripheral blood leukocytes	Increased phagocytic capacity, reactive oxygen species production, peroxidase activity and nitric oxide production	(Medina-Córdova et al., 2018)
	D. hansenii	Pacific red snapper (*Lutjanus peru*)	Upregulated macrophage receptor genes in the gut, improved free radical scavenging capacity	(Reyes-Becerril et al., 2020)
	Y. lipolytica	Goat leukocytes	Increased leukocyte viability, phagocytic ability, nitric oxide production and immune-related signalling pathways	(Angulo et al., 2021)
	D. hansenii	Goat peripheral blood leukocytes	Increased leukocyte viability, phagocytic capacity and nitric oxide production upon challenge with *E. coli*	(Angulo et al., 2018)
Mannans	Combined fractions of *S. cerevisiae* and *C. jadinii*	Atlantic salmon (*Salmo salar*)	Enhanced gut and skin mucosal barriers	(Rawling et al., 2019)
	K. marxianus	Murine macrophages (RAW 264.7)	Mitogenic activity and induction of nitric oxide production	(Galinari et al., 2018)
	K. marxianus	Human Hep-G2 tumor cells	Antiproliferative activity	(Galinari et al., 2018)
	K. marxianus	Wistar rats	Hypocholesterolemic activity	(Yoshida et al., 2009)

α-mannans (Rawling et al., 2019) produce positive effects on the immune balance and gut health of different aquatic species (Leclercq et al., 2020; Xie et al., 2022). This indicates that the use of non-conventional yeast components alone or in combination with *S. cerevisiae* components could be of interest for the improvement of host health.

S. cerevisiae mannans also possess *in vitro* antioxidant activities against several types of free radicals depending on their concentration and molecular weight (Zhao et al., 2022). This property depends on the composition of the mannans and suggests interesting applications in the food and medical industries. In addition, yeast mannans can be utilized by intestinal bacteria, in particular *Bacteroides thetaiotaomicron* (Cuskin et al., 2015), and may have an impact on the gut microbiota ecosystem as they increase the abundance of *B. thetaiotaomicron* in *in vitro* fermentation of rat feces (Oba et al., 2020a,b) and of *B. thetaiotaomicron* and *Bacteroides ovatus* in a human colonic microbiota model (Tanihiro et al., 2020; Oba et al. 2020a). Thus, there is increasing evidence for the bioactivity of *S. cerevisiae* mannans, suggesting that they represent a sustainable source of functional ingredients and paving the way for their use in food, feed and pharmaceutical industries (Faustino et al., 2021). The cell wall of *S. boulardii* has a different oligosaccharide composition from that of *S. cerevisiae*, including a higher mannan content (Bzducha-Wróbel et al., 2013). Recent metabolic engineering strategies have attempted to modify the mannan content of the *S. boulardii* cell wall with success and increasing the mannan content of the *S. boulardii* cell wall improves its ability to adhere to *Salmonella enterica Typhimurium* (Kwak et al., 2022).

In recent years, among non-*Saccharomyces* species (Table 3), several α-mannans from *K. marxianus* have attracted interest because of their copper and iron chelating abilities (Galinari et al. 2017, 2018), their mitogenic activity in macrophages, their antiproliferative activity on Hep-G2 tumor cells (Galinari et al., 2018) or their ability to regulate the composition of the gut microbiota (Tang et al., 2022). Interestingly, some *K. marxianus* also show a more potent hypocholesterolemic activity than *S. cerevisiae* and this functional activity depends on the side chain length and phosphate content of the mannans (Yoshida et al., 2009). Another recent study also tested the effects of mannoproteins or oligosaccharide fractions from *S. cerevisiae* and two non-*Saccharomyces* yeasts, *Metschnikowia reukaufii* and *Wickerhamomyces anomalus,* on the growth of a variety of bacteria and showed a positive effect on the growth of beneficial lactic acid bacteria while decreasing the abundance of pathogenic bacteria (Bzducha-Wróbel et al., 2022). Interestingly, the degree of stimulation or inhibition of bacterial growth is dependent on the composition and dose of mannoproteins and the bacterial strain, but it remains to be determined how the structure and/or composition of mannoproteins can impact bacterial growth.

4.3. Chitin

Chitin can be obtained from non-plant sources, including fungi, and has a particular impact on the human gut microbiota (Lopez-Santamarina et al., 2020). Although their chitin content is lower than that of crustaceans, fungi are an alternative source of chitin that is of increasing interest to scientists and the food industry. However, very few studies have examined the health and/or nutritional benefits of yeast chitin. Chitin is known to stimulate immunogenic activity during fungal infection (Bueter et al., 2013) and is a conserved Microbe-Associated Molecular Pattern (Lee et al., 2008). As such, it can induce immunity in monocytes and it is interesting to note that the different chitin contents of different *S. cerevisiae* strains could explain the differences between strains in terms of induced-driven immunity (differences in cytokine production) and antimicrobial activity *in vitro* and *in vivo* (Rizzetto et al., 2016). Thus, although studies on the effects of yeast chitin on immunity are still in their infancy, these results suggest that chitin content may be an important factor in the immunomodulatory properties of various *Saccharomyces* and non-*Saccharomyces* species.

5. Conclusion

For decades, yeast have played a vital role in the production of fermented food and beverage. Recently, however, the potential health benefits of non-*Saccharomyces* yeast species have come to light, sparking growing interest in their use that may be promising in many applications, including health and welfare. For now, *S. boulardii* is the only probiotic yeast that shows well-characterized effects on the prevention and treatment of intestinal disorders, but there are increasing evidence that some non-conventional yeasts such as *Debaryomyces, Kluyveromyces, Komagataella* have such probiotic potential. Beneficial effects on the health of the host with these new yeasts are strain-specific and mediated through the recognition of their cell wall. For instance, their mannans and β-glucans have important biological activities including antioxidant properties, promotion of the host immunity by modulation of cytokines secretion and enhancement of the phagocytic efficiency as well as limitation of the bacterial invasion. Therefore, their unique cell wall components have been identified as a promising source of functional ingredients, particularly as prebiotics.

However, to harness their full potential, the composition, structure, and 3D architecture of these components need to be investigated. While research on the cell wall components of *S. cerevisiae* and *C. albicans* (Orlean 2012; Gow and Lenardon, 2023; Klis et al., 2002) has been extensive, integrated molecular, biochemical, and biophysical approaches need to be applied to study the cell wall of non-conventional yeasts. In addition to these studies on the cell wall, more mechanistic and systemic approaches are required to fully understand how these compounds exert their beneficial properties. The rapid development of new *in vitro* and *in vivo* models such as the Zebrafish (*Danio rerio*) could serve as interesting platforms for the study of the relationships between cell wall structure and beneficial effects on health. The evaluation of the safety of use of these new yeasts cell wall as prebiotics must be also further evaluated.

Ultimately, these new microbial products may require a pre-market approval by the authorities in some jurisdictions for their use as food/feed ingredients. In Europe, the European Food Safety Agency (EFSA) developed in 2007 a Qualified Presumption Safety (QPS) procedure. When sufficient scientific studies on a species are available to assess its safety, it can be included in the QPS list. In 2023, the re-evaluated QPS list included 17 yeast species (Koutsoumanis et al., 2023). This list is not exhaustive and does not preclude a non-QPS microorganism for a pre-market assessment for EFSA. In US, there are three possibilities to approve a new ingredient in the food and feed industry: the certification of the ingredient as Generally Recognized As Safe (GRAS) by the Food and Drug Administration (FDA), the recognition of the ingredient by the Association of American Feed Control Officials (AAFCO) or by the FDA through the food additive petition (FAP). The annual official publication of the AAFCO lists all the legal ingredients and is recognized by all states but only few non-*Saccharomyces* species are included. As already reviewed for the beer industry, these regulatory processes for non-*Saccharomyces* are limited (Miguel et al., 2022) and may represent a limitation for the rapid development of new products from yeast species that would not yet be on these lists.

Despite the vast potential of non-*Saccharomyces* yeasts in promoting health and well-being, only few studies have investigated the functional properties conferred by their cell wall components. With numerous non-*Saccharomyces* yeast species of interest for such applications, this research field is poised to advance rapidly in the coming years. This will pave the way for the future use of non-*Saccharomyces* cell walls as additives in the food and feed industry.

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CRediT authorship contribution statement

Marion Schiavone: compiled the data, wrote the manuscript and created tables and figures. **Jean M. François:** reviewed and edited the original draft. **Didier Zerbib:** reviewed and edited the original draft. **Jean-Pascal Capp:** compiled the data, wrote the manuscript and created tables and figures.

Declaration of competing interest

MS is an employee of Lallemand SAS.

Data availability

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