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Expert Consensus on the Appropriateness of *Saccharomyces cerevisiae* Hydrolysate in Obesity Management Using the RAND/UCLA Appropriateness Method

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Abstract

Nutraceuticals are bioactive compounds with potential roles in disease prevention and treatment. Their accessibility and affordability have driven growing interest in obesity care. Among them, bioactive hydrolysates derived from *Saccharomyces cerevisiae* show promise, yet clinical guidelines seldom address their use. We aimed to develop a guidance statement on their appropriateness using the RAND/UCLA consensus method. A multidisciplinary panel of ten experts rated the appropriateness of a bioactive hydrolysate derived from *Saccharomyces cerevisiae* across clinical scenarios relevant to obesity care, informed by a targeted evidence review and conducted using the two-round RAND/UCLA consensus method, with ratings on a 1–9 scale. The panel deemed the use of the bioactive hydrolysate derived from *Saccharomyces cerevisiae*, in combination with lifestyle modifications, as an appropriate intervention for managing obesity-related outcomes. This included its use in patients with specific comorbidities, as an adjunct to standard pharmacotherapy, and in a set of selected clinical scenarios. Based on evidence and expert consensus, a bioactive hydrolysate derived from *Saccharomyces cerevisiae* is appropriate across a range of clinical scenarios within comprehensive obesity care. Further studies should evaluate long-term effectiveness, broader populations and combination regimens.

Keywords: *Saccharomyces cerevisiae* hydrolysate; obesity; RAND/UCLA appropriateness method; nutraceuticals; weight regain prevention; waist circumference; inflammation; consensus

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1. Introduction

Obesity, defined by excess adiposity, affects nearly every organ system [1,2]. With rising prevalence and substantial health impact, it constitutes a major global threat [3]. Recommended management comprises nutritional counselling, structured exercise, psychological and psychiatric support, pharmacotherapy, and bariatric surgery [2]. Although pharmacotherapy is widely recommended as an integral component of obesity management, significant access barriers limit the use of anti-obesity medications, with only about 2% of eligible patients receiving pharmacological treatment [4]. Additionally, some medications are unavailable in certain regions or are prohibitively costly [3]. Completion of lifestyle modification programmes is uncommon, and many patients decline bariatric surgery because of its perceived invasiveness [5]. Across interventions, weight regain is frequent, with similar recurrence rates reported [6].

Nutraceuticals are bioactive compounds from edible sources that have proved beneficial for disease prevention and management [7,8]. Their affordability and accessibility have attracted growing interest among patients and healthcare professionals [7,8]. Bioactive hydrolysates derived from *Saccharomyces cerevisiae* have shown weight loss efficacy across several clinical trials [9–12].

Several biological mechanisms have been proposed to explain the effects of *Saccharomyces cerevisiae*-derived hydrolysates, including reduced caloric intake, decreased circulating ghrelin levels, modulation of inflammatory pathways characterized by reductions in pro-inflammatory cytokines (IL-6, TNF-α), and increased anti-inflammatory cytokines (IL-10) [10,13–15].

Despite increasing availability, guidance for the routine clinical use of nutraceuticals is limited. Most guidelines do not address these products, leaving uncertainty about their appropriate role in patient care and the validity of manufacturers' claims [16]. Clinical trials also under-represent the complexity of real-world practice, yet clinicians are expected to make evidence-based recommendations [17]. The RAND/UCLA Appropriateness Method is a modified Delphi consensus process that integrates best available evidence with expert clinical judgement to evaluate intervention appropriateness in specific scenarios [17]. Within this framework, an intervention is 'appropriate' when expected benefits clearly outweigh expected risk, irrespective of cost [17].

To address this gap, we convened a clinical expert panel to assess the appropriateness of a bioactive hydrolysate derived from *Saccharomyces cerevisiae* across scenarios commonly encountered in practice using the RAND/UCLA Appropriateness Method. This article presents a guidance statement based on this assessment and intends to support clinicians in making informed decisions about recommending this intervention.

2. Materials and Methods

2.1. RAND/UCLA Appropriateness Method

The RAND/UCLA Appropriateness Method is a formal consensus process that combines the best available evidence with clinical expertise to formulate a group opinion. In situations where available evidence is limited, this methodology supplements this gap with expert opinion. An approach is 'appropriate' when expected benefits clearly outweigh expected risks, irrespective of cost [17]. This method is a validated, systematic approach for evaluating the appropriateness of interventions at a patient-specific level, particularly in cases where clinical trials are not feasible for every scenario. It has been applied across a wide range of interventions [18–23]. Figure 1 outlines the RAND/UCLA process.

Figure 1. Diagram of the RAND/UCLA Appropriateness Method. (**a**) Before the meeting: (1) experts were recruited via professional networks and referrals; (2) clinical scenarios were generated and a PICO-based questionnaire developed; (3) a systematic review was conducted. (**b**) During the meeting: (4) experts independently rated the appropriateness of the intervention across scenarios; (5) ratings were submitted via a custom web form, stored locally, and verified manually; data were processed in Python according to RAND/UCLA guidance, with agreement defined as no more than two ratings falling outside the three-point range containing the median; (6) brief presentations and moderated discussion supported consensus building; (7) experts re-rated the intervention incorporating discussion insights. (**c**) After the meeting: (8) final ratings were analysed to determine agreement levels. Created with BioRender.com.

2.2. Establishment of an Expert Panel

We convened a multidisciplinary panel including clinical endocrinologists, nutritionists, internists, general practitioners, and psychiatrists. Experts were recruited through professional contacts and referrals, with eligibility criteria mandating at least five years of obesity-care experience. Individuals barred from clinical practice were excluded. Panellists received time compensation from the study sponsor; the funder had no role in study design, methods, data analysis, interpretation of results, or panel discussions.

2.3. Generation of Scenarios

We developed a comprehensive list of clinical scenarios to reflect conditions and comorbidities commonly encountered in obesity care. A draft was refined with panellists to ensure clinical relevance, clarity, and alignment with real-world practice. Scenarios informed a structured, PICO-based questionnaire.

Scenario development considered three dimensions: (1) appropriateness of the intervention for obesity-related outcomes in patients with specific comorbidities; (2) appropriateness as an adjunct to conventional pharmacotherapy; and (3) appropriateness in selected special clinical situations. All scenarios were stratified by body mass index (BMI) into four categories: 25–29.9 kg/m^2, 30–34.9 kg/m^2, 35–39.9 kg/m^2, and $\geq$40 kg/m^2.

The intervention under evaluation consisted of a bioactive hydrolysate derived from *Saccharomyces cerevisiae* combined with lifestyle modifications, including medical nutrition therapy, structured exercise, sleep hygiene, and stress management.

2.4. Systematic Review

During the months preceding the two-round consensus, a group of experts and researchers conducted a systematic literature review and meta-analysis to assemble relevant evidence to be considered during the ratings. The methods and results of the systematic review and meta-analysis considered by experts during the ratings are available elsewhere [24]. An updated and peer-reviewed version of these findings is also available [25]. Briefly, a systematic literature review was conducted in March and April 2025, consulting PubMed, SciELO, ClinicalTrials.gov, and Cochrane's CENTRAL databases. To identify relevant studies, we used the following search terms: ("*Saccharomyces cerevisiae*" OR "*S. cerevisiae*" OR "Saccharomyces" OR "Yeast" OR "Bakers yeast") AND ("polysaccharide*" OR "hydrolysate*" OR "*weight*" OR "fat" OR "obes*"). Additionally, a snowballing strategy and expert consultation were employed to identify any additional studies. Interventions containing additional active components (e.g., silymarin, probiotics, minerals), as well as studies involving breastfeeding or pregnant women and children, were excluded. PICOS for inclusion of studies are shown in Table 1. The selected articles, as well as the results of the meta-analysis, were collated in an online repository and shared with panellists one month before the rating rounds.

Table 1. PICOS criteria for inclusion of studies.

Parameters	Inclusion Criteria
Population	Overweight or obese patients
Intervention	Bioactive peptide-rich Saccharomyces cerevisiae hydrolysates + lifestyle modifications (medical nutrition therapy, structured exercise, sleep hygiene, and stress management)
Comparison	Placebo
Outcomes	Changes in body weight, fat composition/mass, BMI, and waist circumference
Study Design	Blinded, randomised, placebo-controlled clinical trials

2.5. Two-Round Consensus

The panel met face-to-face in Mexico City in May 2025. Panellists completed a first round using a structured questionnaire with a 1 to 9 scale, where 1 indicated 'highly inappropriate' and 9 indicated 'highly appropriate'. Ratings were processed on-site in real time. A trained moderator then led a structured discussion to elicit insights and broad participation, followed by two brief presentations summarising evidence on the intervention. A second round was subsequently conducted (Supplementary Dataset S1). Panellists received a revised questionnaire showing their initial ratings alongside peers' summary statistics and could maintain or modify ratings in light of the preceding discussion.

2.6. Statistical Analysis

Panellists' ratings were captured via a custom web form and stored locally on a server running XAMPP (Apache Friends, Version 8.2, 2023). Data were exported to Comma-Separated Values format, visualised in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA; 2010), verified manually, and converted to Tab-Separated Values (TSV) format. Data integrity was independently verified twice by two separate individuals. For analysis, the median score and agreement status for each scenario were calculated using a Python script (Python Language Reference, version 3.12; Python Software Foundation, Wilmington, DE, USA; 2023), following the RAND/UCLA Appropriateness Method guidelines (Santa Monica, CA, USA: RAND, 2001) [14]. Agreement was defined as having no more than two panellists rate outside the three-point range that includes the median [14].

2.7. Ethical Compliance

No ethics committee approval was required due to the nature of this study. However, all participants provided consent for participation and data use.

3. Results

3.1. Summary of Participants and Answers

The expert panel comprised four clinical endocrinologists, one internist, one psychiatrist, one geriatrician, one general practitioner, and two clinical nutritionists (n = 10). Eight primarily worked in private institutions in Mexico, one in a pharmaceutical company and one in a United States academic institution. All panel members fulfilled authorship criteria according to COPE recommendations, with contributor roles specified using the CRediT taxonomy. Experts rated 344 scenarios with a 100% response rate; all achieved agreement and were rated 'appropriate'.

3.2. Appropriateness for Obesity-Related Outcomes in Patients with Specific Comorbidities

Experts evaluated the appropriateness of the bioactive hydrolysate derived from *Saccharomyces cerevisiae* for four outcomes (reduction in excess adiposity, reduction in waist circumference, reduction in weight regain, and reduction in low-grade chronic systemic inflammation and oxidative stress) across thirteen clinical conditions: (1) all patients with excess adiposity; (2) patients aged 65 years or older; (3) those receiving antidepressants; (4) those with anxiety disorder; (5) those with binge-eating disorder; (6) those with a history of pancreatitis; (7) those with a history of cholelithiasis; (8) those with metabolic dysfunction–associated steatotic liver disease; (9) those with arrhythmia; (10) those with heart failure; (11) those with hypertension; (12) those at high risk of cardiovascular disease; and (13) those with chronic kidney disease. Each condition was stratified by BMI into the following categories: 25–29.9 kg/m^2, 30–34.9 kg/m^2, 35–39.9 kg/m^2, and $\geq$40 kg/m^2. In total, 208 scenarios were evaluated; all achieved agreement and were rated 'appropriate'.

Median of ratings of the appropriateness of the intervention for obesity-related outcomes in patients with specific comorbidities are displayed in Table 2.

Table 2. Median ratings of the appropriateness of the intervention (bioactive hydrolysate derived from *Saccharomyces cerevisiae* in addition to lifestyle modifications) for obesity-related outcomes in patients with specific comorbidities, stratified by BMI. Green cells indicate agreement, defined as no more than two panellists rating outside the three-point range containing the median. Shades of green are related to the median rating with the deepest green associated with a median rating of 9. Abbreviations: BMI, body mass index.

	All Patients with Excess Adiposity	Patients with Excess Adiposity and Age 65 or More	Patients with Excess Adiposity Receiving Antidepressants	Patients with Excess Adiposity and Anxiety Disorder	Patients with Excess Adiposity and Binge-Eating Disorder	Patients with Excess Adiposity and History of Pancreatitis	Patients with Excess Adiposity and History of Cholelithiasis	Patients with Excess Adiposity and Metabolic Dysfunction–Associated Steatotic Liver Disease	Patients with Excess Adiposity and Arrhythmia	Patients with Excess Adiposity and Heart Failure	Patients with Excess Adiposity and Hypertension	Patients with Excess Adiposity and High Risk of Cardiovascular Disease	Patients with Excess Adiposity and Chronic Kidney Disease	BMI
Reducing excess adiposity	9	9	9	8.5	8.5	8	8	9	9	9	9	8.5	8	25 to 29.9 kg/m^2
	9	9	9	8.5	8.5	8	8	9	9	9	9	8.5	8	30 to 34.9 kg/m^2
	9	9	9	8.5	8	8	8	9	9	9	9	8.5	8	35 to 39.9 kg/m^2
	9	9	9	8.5	8	8	8	9	9	9	9	8.5	8	≥40 kg/m^2
Reducing waist circumference	9	9	9	9	9	9	9	8	9	9	9	9	9	25 to 29.9 kg/m^2
	9	9	9	9	9	9	9	8	9	9	9	9	9	30 to 34.9 kg/m^2
	9	9	9	9	9	9	9	8	9	9	8.5	9	9	35 to 39.9 kg/m^2
	9	9	9	9	9	9	9	8	9	9	9	9	9	≥40 kg/m^2
Reducing weight regain	9	9	8.5	9	9	8	8	9	9	8	9	9	9	25 to 29.9 kg/m^2
	9	9	8.5	9	9	8	8	9	9	9	9	9	9	30 to 34.9 kg/m^2
	9	9	8.5	9	9	8	8	9	9	9	9	9	9	35 to 39.9 kg/m^2
	9	9	8.5	9	9	8	8	9	9	9	9	9	9	≥40 kg/m^2
Reducing low-grade chronic systemic inflammation and oxidative stress	9	9	9	9	9	9	9	9	9	9	9	9	9	25 to 29.9 kg/m^2
	9	9	9	9	9	9	9	9	9	9	9	9	9	30 to 34.9 kg/m^2
	9	9	9	9	9	9	9	9	9	9	9	9	9	35 to 39.9 kg/m^2
	9	9	9	9	9	9	9	9	9	9	9	9	9	≥40 kg/m^2

3.3. Appropriateness as an Adjunct to Conventional Pharmacotherapy

Experts assessed the appropriateness of prescribing the bioactive hydrolysate derived from *Saccharomyces cerevisiae* as an adjunct to GLP-1 RA, naltrexone/bupropion, orlistat, or phentermine for reducing the impact of clinical obesity across seven clinical domains: (1) cardiovascular (hypertension, heart failure); (2) musculoskeletal (knee and hip pain, rigidity, limited range of motion); (3) reproductive (polycystic ovary syndrome, anovulation); (4) metabolic (hyperglycaemia, dyslipidaemia); (5) hepatic (metabolic dysfunction–associated steatotic liver disease); (6) respiratory (sleep apnoea/hypopnoea, dyspnoea, wheezing); and (7) activities of daily living (ADLs). Each scenario was stratified by BMI (25 to 29.9 kg/m^2, 30 to 34.9 kg/m^2, 35 to 39.9 kg/m^2, and ≥40 kg/m^2). Agreement was reached across all 112 scenarios, supporting the intervention's appropriateness as an adjunct to established pharmacotherapy and lifestyle modifications. Median appropriateness scores shown in Table 3 represent the final ratings obtained after completion of the two-round RAND/UCLA expert evaluation process.

Table 3. Median of ratings of the appropriateness of the intervention (bioactive hydrolysate derived from *Saccharomyces cerevisiae* in addition to lifestyle modifications) as an adjunct to conventional pharmacotherapy for reducing the impact of clinical obesity across seven clinical domains, stratified by BMI. Green cells indicate agreement, defined as no more than two panellists rating outside the three-point range containing the median. Shades of green are related to the median rating with the deepest green associated with a median rating of 9. Abbreviations: BMI, body mass index; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

	Cardiovascular	Musculoskeletal	Reproductive	Metabolic	Activities of Daily Living	Hepatic	Respiratory	BMI
GLP-1 RA	8	8	8.5	8	8	8.5	8	25 to 29.9 kg/m^2
	8	8	8.5	8	8	8.5	8	30 to 34.9 kg/m^2
	8	8	8.5	8	8	8.5	8	35 to 39.9 kg/m^2
	8	8	8.5	8	8	8.5	8	≥40 kg/m^2
Naltrexone/Bupropion	8	8	8	8	8	8	8	25 to 29.9 kg/m^2
	8	8	8	8	8	8	8	30 to 34.9 kg/m^2
	8	8	8	8	8	8	8	35 to 39.9 kg/m^2
	8	8	8	8	8	8	8	≥40 kg/m^2
Orlistat	8	8	8	8	8	8	8	25 to 29.9 kg/m^2
	8	8	8	8	8	8	8	30 to 34.9 kg/m^2
	8	8	8	8	8	8	8	35 to 39.9 kg/m^2
	8	8	8	8	8	8	8	≥40 kg/m^2
Phentermine	8	8	8	8	8	8	8	25 to 29.9 kg/m^2
	8	8	8	8	8	8	8	30 to 34.9 kg/m^2
	8	8	8	8	8	8	8	35 to 39.9 kg/m^2
	8	8	8	8	8	8	8	≥40 kg/m^2

3.4. Appropriateness in Special Situations

Experts evaluated the appropriateness of a bioactive hydrolysate derived from *Saccharomyces cerevisiae* in six special scenarios: (1) prevention of progression to clinical obesity; (2) Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA) dose reduction; (3) maintenance of low-dose GLP-1 RA therapy; (4) use before initiating pharmacological treatment or bariatric surgery; (5) prevention of weight regain; and (6) transition to a medication-free period. Each scenario was stratified by BMI (25 to 29.9 kg/m^2, 30 to 34.9 kg/m^2, 35 to 39.9 kg/m^2, and ≥40 kg/m^2). Agreement was reached in all 24 scenarios, supporting its appropriateness within comprehensive obesity care. Median of ratings of the appropriateness of the intervention in special clinical situations are displayed in Table 4.

Table 4. Median of ratings of the appropriateness of the intervention (bioactive hydrolysate derived from *Saccharomyces cerevisiae* in addition to lifestyle modifications) in special clinical situations, stratified by BMI. Green cells indicate agreement, defined as no more than two panellists rating outside the three-point range containing the median. Shades of green are related to the median rating with the deepest green associated with a median rating of 9. Abbreviations: BMI, body mass index; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonists.

		BMI
Prevention of progression to clinical obesity	8	25 to 29.9 kg/m^2
	8	30 to 34.9 kg/m^2
	8	35 to 39.9 kg/m^2
	8	≥40 kg/m^2
GLP-1 RA dose reduction	9	25 to 29.9 kg/m^2
	9	30 to 34.9 kg/m^2
	9	35 to 39.9 kg/m^2
	9	≥40 kg/m^2
Maintenance of low-dose GLP-1 RA therapy	9	25 to 29.9 kg/m^2
	9	30 to 34.9 kg/m^2
	9	35 to 39.9 kg/m^2
	9	≥40 kg/m^2
Prior to initiating pharmacological treatment or bariatric surgery	8.5	25 to 29.9 kg/m^2
	8.5	30 to 34.9 kg/m^2
	8.5	35 to 39.9 kg/m^2
	8.5	≥40 kg/m^2
Prevention of weight regain	9	25 to 29.9 kg/m^2
	9	30 to 34.9 kg/m^2
	9	35 to 39.9 kg/m^2
	9	≥40 kg/m^2
Transition to a medication-free period	9	25 to 29.9 kg/m^2
	9	30 to 34.9 kg/m^2
	9	35 to 39.9 kg/m^2
	9	≥40 kg/m^2

4. Discussion

We conducted a formal consensus process using the RAND/UCLA Appropriateness Method to generate expert guidance on the clinical use of a bioactive hydrolysate derived from *Saccharomyces cerevisiae* across three dimensions: the appropriateness for obesity-related outcomes in patients with specific comorbidities, use as an adjunct to conventional pharmacotherapy, and use in special clinical situations.

Recently, BMI-based definitions of overweight and obesity have been increasingly questioned because they do not adequately capture the heterogeneity of adiposity-related health risk [1]. Consequently, the terms preclinical obesity and clinical obesity have been proposed to distinguish stages of disease according to the absence or presence of obesity-related organ dysfunction, independent of BMI alone [1]. In this framework, clinical obesity is defined as excess adiposity associated with established organ dysfunction or obesity-related complications, whereas preclinical obesity refers to excess adiposity without overt clinical manifestations but with increased risk of disease progression [1]. Accordingly, therapeutic interventions should aim not only at weight reduction but also at decreasing adiposity, improving obesity-related manifestations, and preventing end-organ damage [1]. In individuals with preclinical obesity, early interventions should focus on preventing progression to clinical obesity and reducing future cardiometabolic risk [1].

Personalising pharmacotherapy to patient characteristics is central to effective obesity care [4]. Several drug classes deliver clinically meaningful weight-loss, metabolic improvement, and reduced obesity-related complications when combined with lifestyle modifications [26]. In practice, impact is constrained by variable response, treatment discontinuation, adverse effects, and access barriers, particularly cost [2,4,26]. A recent Congressional Budget Office projection estimated that extending Medicare coverage for anti-obesity medicines—such as GLP-1 receptor agonists, GIP/GLP-1 dual agonists, and legacy agents like orlistat, bupropion/naltrexone, and phentermine/topiramate— from 2026 could increase federal spending by 35 billion USD over nine years, with healthcare savings only partly offsetting per-user costs [27].

Clinical decision-making must also weigh patient-specific risks and contraindications. For example, GLP-1 RA warrants caution in older patients, and in patients with depression, cholelithiasis, or arrhythmias, and is contraindicated in individuals with a history of pancreatitis [4]. Naltrexone/bupropion requires caution in older adults and in chronic kidney disease, heart failure, or metabolic dysfunction–associated steatotic liver disease (MASLD); and is contraindicated in uncontrolled hypertension [4]. Orlistat also requires caution in older adults and in binge-eating disorder, depression, pancreatitis, cholelithiasis, or heart failure [4]. Phentermine may be used in selected patients; however, prolonged treatment should be approached cautiously, particularly in individuals with anxiety or depressive disorders or elevated cardiovascular risk [4]. In scenarios involving such risks or contraindications, the panel judged the bioactive hydrolysate derived from *Saccharomyces cerevisiae* appropriate, given its safety profile.

Saccharomyces cerevisiae hydrolysates have demonstrated a favourable safety profile across clinical trials. In Valero-Pérez et al., the only adverse effect significantly more frequent than placebo was bloating, reported in 24% of participants [11], while in Santas et al., one participant reported flatulence [12]. Across three studies totalling 217 patients, only one discontinued participation due to adverse effects [10–12]. In addition to its safety, the intervention has shown clinically meaningful efficacy. In the study by Valero-Pérez et al., participants with obesity experienced an average weight loss of 5.27 kg over 12 weeks, of which 3.44 kg corresponded to fat mass, along with a 1.99 kg/m^2 reduction in BMI [11]. Similarly, Santas et al. (2017) reported a 1.5 cm reduction in waist circumference after

12 weeks of treatment [12]. These outcomes may be partly mediated by ghrelin-related appetite suppression, as observed in both animal models and human studies [10,13].

Saccharomyces cerevisiae hydrolysates have consistently demonstrated efficacy in promoting weight loss and reducing fat mass. For instance, Jung et al. reported significant reductions in weight, BMI, and fat mass after 8 weeks of treatment compared to placebo [10]. Notably, participants receiving the intervention also demonstrated a significant decrease in calorie intake and a reduced preference for sweet flavors compared to placebo ($p < 0.05$), independent of changes in physical activity [10]. In a separate study by the same group, daily caloric intake was decreased by an average of 264.38 Kcal after 10 weeks of treatment ($p < 0.01$), resulting in a mean reduction of 3.43 kg in body weight ($p < 0.001$), 1.19 in BMI ($p < 0.001$), and 3.2 kg in fat mass ($p < 0.001$) relative to placebo [14]. Similarly, Mosikanon et al. reported a significant reduction in waist circumference of 8.19 cm after 6 weeks of treatment compared to placebo ($p < 0.05$) [15].

Weight regain after weight loss remains a major challenge in long-term obesity management [6]. This phenomenon occurs regardless of the intervention used to induce weight loss, whether behavioural therapy, pharmacotherapy, or bariatric surgery, and the rate of regain appears consistent across different treatment modalities [6]. While the underlying pathophysiological mechanisms are only partially understood, current evidence implicates low-grade inflammation in adipose tissue and circulating immune cell activation in post-weight-loss regain [6]. *Saccharomyces cerevisiae* hydrolysates have demonstrated immunomodulatory effects, including reductions in pro-inflammatory cytokines (IL-6, TNF-α) and elevations in anti-inflammatory IL-10, as shown in a clinical study by Mosikanon et al. [6,15,26]. In line with these mechanisms, Valero-Pérez et al. reported 2 kg less weight regain at 9 months in patients receiving this intervention compared to placebo [11]. On this basis, the panel considered the bioactive hydrolysate derived from *Saccharomyces cerevisiae* appropriate for preventing weight regain and mitigating low-grade systemic inflammation and oxidative stress.

Combination therapy is common when monotherapy is insufficient, since complementary mechanisms can enhance efficacy while permitting lower doses and potentially fewer dose-related adverse events [28]. For instance, the phentermine/topiramate combination capitalises on the appetite-suppressing properties of phentermine and the satiety-enhancing effects of topiramate, while naltrexone/bupropion acts through bupropion-mediated stimulation of pro-opiomelanocortin (POMC) neurons and naltrexone's blockade of inhibitory feedback on these same neurons, ultimately reducing caloric intake [28,29].

Although no clinical trials have evaluated *Saccharomyces cerevisiae* hydrolysates in combination with anti-obesity medicines, the expert panel agreed, based on the principle of complementary mechanisms of action, that such combinations may offer enhanced efficacy with acceptable safety. This consensus was consistent across all proposed co-interventions (including GLP-1 receptor agonists, naltrexone/bupropion, orlistat, and phentermine) and clinical domains (cardiovascular, musculoskeletal, reproductive, metabolic, hepatic, respiratory, and activities of daily living). Nevertheless, clinical trials are needed to confirm the safety and effectiveness of these proposed combinations.

These rationales led to the evaluation of six special clinical scenarios: (1) prevention of progression to clinical obesity; (2) dose reduction in GLP-1 RA; (3) maintenance of low-dose GLP-1 RA therapy; (4) pre-treatment prior to initiating pharmacotherapy or bariatric surgery; (5) prevention of weight regain; and (6) transition to a medication-free period.

Saccharomyces cerevisiae hydrolysates have consistently demonstrated reductions in adiposity across diverse clinical contexts, supporting the appropriateness of this intervention in delaying the onset of clinical obesity [10–12]. When used alongside GLP-1 RA, this intervention may enhance efficacy through complementary mechanisms of action

while enabling dose reduction or maintenance of lower doses. Initiating treatment with a bioactive hydrolysate derived from *Saccharomyces cerevisiae* before pharmacological or surgical therapy may prime patients with excess adiposity for better outcomes. Furthermore, its immunomodulatory capacity could help prevent weight regain and facilitate the transition to a medication-free period [6,15,30]. On this collective evidence, the panel reached consensus that a bioactive hydrolysate derived from *Saccharomyces cerevisiae* is appropriate across all six scenarios.

Although not formally captured in the questionnaire, meeting discussions yielded several practice-oriented considerations. Clinical nutritionists noted the advantage of recommending this intervention to patients, given that it is a non-pharmacological, over-the-counter option. For example, Stetikal® (a bioactive hydrolysate derived from *Saccharomyces cerevisiae*) is commercially available in Mexico. Reproductive outcomes also emerged as an area of interest; since the intervention reduces both adiposity and low-grade systemic inflammation, it may offer additional benefits for women with reproductive disorders such as infertility or polycystic ovary syndrome. The intervention may also suit patients reluctant to initiate pharmacotherapy for weight management. A relevant perioperative application was also identified: given that GLP-1 RA must be discontinued at least one week prior to surgery due to its effects on gastrointestinal motility, a bioactive hydrolysate derived from *Saccharomyces cerevisiae* could serve as a temporary substitute during that interval. Finally, particular interest was expressed in its use to support the transition to a medication-free period, especially in patients previously treated with GLP-1 RA. Clinicians noted that weight regain remains a major concern in this context and recognised the potential of a bioactive hydrolysate derived from *Saccharomyces cerevisiae* to mitigate this risk while promoting sustained lifestyle changes. These insights reflect the intervention's perceived value in diverse real-world scenarios and warrant further investigation in future studies.

This study is strengthened by the use of a formal consensus methodology and a multidisciplinary expert panel. Nonetheless, certain limitations merit consideration. First, although panel size was sufficient for reliable results, a larger panel may have broadened perspectives and increased opinion variability. Second, the panel comprised Mexican professionals considering patients in Mexico and Latin America, which may limit generalizability; specific populations such as children and pregnant women were excluded. Third, although the RAND/UCLA Appropriateness Method is well suited for clinical scenarios lacking high-quality evidence, it inherently relies on structured expert judgement and does not replace evidence derived from randomized clinical trials or real-world effectiveness studies. Expert consensus represents a lower tier within the hierarchy of evidence-based medicine; therefore, prospective clinical trials and post-marketing studies are necessary to further evaluate the efficacy and safety of this intervention and to address existing knowledge gaps. Fourth, although the sponsor had no role in study design or data interpretation, industry funding may introduce perceived bias. This was mitigated by the introduction of a methodological panel, which functioned as an impartial observer and collected and analysed data independently to reduce the perception of bias. Finally, the limited number of high-quality clinical trials on *Saccharomyces cerevisiae* hydrolysates constrains inferences beyond short-term use, underscoring the need for further research to validate effectiveness and expand clinical applicability.

5. Conclusions

This RAND/UCLA consensus process evaluated the appropriateness of a bioactive hydrolysate derived from *Saccharomyces cerevisiae* within obesity care. Across 344 clinical scenarios, a multidisciplinary panel rated the intervention as 'appropriate' with full agreement. The panel supported its use to address obesity-related outcomes across di-

verse comorbidities, as an adjunct to conventional pharmacotherapy, and in six special clinical situations.

Practice-oriented considerations beyond the questionnaire included suitability for patients reluctant to initiate pharmacotherapy, potential peri-operative use when GLP-1 RA is paused, and support during transitions to a medication-free period. Given its favourable safety profile, immunomodulatory properties, and over-the-counter availability, the intervention represents a promising adjunct to comprehensive obesity care. Evidence supports short-term efficacy; further research should assess long-term effectiveness, broader populations, and combination regimens. These findings may inform clinical practice and future iterations for obesity-management guidance.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/obesities6020018/s1, Table S1: Supplementary Dataset S1—Questionnaire.

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Abbreviations

The following abbreviations are used in this manuscript:

BMI	Body Mass Index
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
IL-10	Interleukin-10
IL-6	Interleukin-6
MASLD	Metabolic dysfunction-associated steatotic liver disease
PICO	Population, Intervention, Comparison, Outcome
PICOS	Population, Intervention, Comparison, Outcome, Study design
POMC	Pro-opiomelanocortin
RAND/UCLA	RAND/University of California, Los Angeles (Appropriateness Method)
TNF-α	Tumor necrosis factor-alpha

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