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Abstract

Background: Nutraceuticals are bioactive compounds that have shown promise in disease prevention and management. Due to their accessibility and affordability, they have gained increasing interest in obesity management. Some such nutraceuticals are *Saccharomyces cerevisiae* hydrolysates. Despite this growing interest, clinical practice guidelines rarely address their use, leaving clinicians with limited direction of their usage in routine care. This study aimed to develop a general guidance statement on the appropriateness of a *Saccharomyces cerevisiae* hydrolysate using a RAND/UCLA consensus process. Methods: A multidisciplinary panel of nine experts was convened to evaluate the appropriateness of a *Saccharomyces cerevisiae* hydrolysate in various clinical scenarios related to obesity management. Results: The panel deemed the use a *Saccharomyces cerevisiae* hydrolysate, 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. Conclusions: Combining practitioners' insights with available data, the panel reached consensus that a *Saccharomyces cerevisiae* hydrolysate represents an appropriate intervention in a range of clinical scenarios for obesity management.

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

Background

Obesity is a condition in which there is an excess accumulation of adipose tissue and affects nearly all systems in the body.[1,2] Due to its increasing prevalence and implications in well-being, it is considered a major health crisis and a significant threat to global health.[3] Current recommended management strategies include nutritional counseling, 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, certain medications are not readily available in some regions, or their cost may be prohibitive.[3] Few individuals complete lifestyle modification programs, and many are hesitant to undergo bariatric surgery due to the perception of it being a major invasive procedure.[5] Moreover, even among those who undergo treatment, a substantial proportion eventually regain weight, with similar recurrence rates observed across all intervention types.[6]

Nutraceuticals are bioactive compounds derived from edible sources that have proven beneficial in the prevention and management of disease.[7,8] Owing to their affordability and accessibility, they have attracted growing interest from both patients and healthcare providers.[7,8] Bioactive peptide-rich hydrolysates derived from *Saccharomyces cerevisiae* have demonstrated efficacy as weight loss-promoting agents across several clinical trials.[9–12]

Despite the growing availability of nutraceuticals, there remains a significant lack of guidance on their use in routine clinical practice. These products are generally excluded from clinical practice guidelines, leaving clinicians uncertain about their appropriate role in patient care and the validity of manufacturers' claims.[13] Moreover, clinical trials often fail to capture the complexity and variability of real-world settings. Nevertheless, clinicians are expected to make evidence-based decisions about whether to recommend any given product.[14] The RAND/UCLA Appropriateness Method is a modified Delphi consensus process that combines the best available evidence with expert clinical judgement to evaluate the appropriateness of an intervention for specific scenarios.[14] Within this framework, an intervention is considered "appropriate" when the expected benefits substantially outweigh any potential expected risk, regardless of cost considerations.[14]

To address the current lack of clinical guidance, we convened a panel of clinical experts to assess the appropriateness of this intervention across a range of scenarios commonly encountered in clinical 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.

Methods.

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. The appropriateness of an approach is determined as whether the expected health benefits outweigh the potential negative consequences by a significant margin to justify a procedure, regardless of cost.[14] 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.

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It has been used to a wide range of interventions.[15–20] A diagram of the RAND/UCLA Appropriateness Method is depicted in Figure 1.

Establishment of an Expert Panel

We assembled an expert multidisciplinary panel comprising clinical endocrinologists, nutritionists, internists, general practitioners, and psychiatrists. The experts were recruited through professional contacts and referrals, with eligibility criteria mandating a minimum of five years of experience in managing patients with obesity; those barred from clinical practice were excluded. Panelists received compensation for their time from the study sponsor. However, the funder was not involved in the study's design, methodology, data analysis, interpretation of results, or panel discussions.

Generation of Scenarios

A comprehensive list of clinical scenarios was developed to reflect the range of conditions and comorbidities commonly encountered in obesity management. An initial draft was refined in collaboration with members of the expert panel to ensure clinical relevance, clarity, and alignment with real-world practice. These scenarios formed the basis of a structured questionnaire, with each item framed according to the Population, Intervention, Comparison, Outcome (PICO) format.

Scenario development followed three key dimensions: (1) the appropriateness of the intervention for managing obesity-related outcomes in patients with specific comorbidities; (2) its appropriateness as an adjunct to conventional pharmacotherapy; and (3) its appropriateness in a set of special clinical situations. All scenarios were stratified by body mass index (BMI) into four categories: 25–29.9 kg/m², 30–34.9 kg/m², 35–39.9 kg/m², and ≥40 kg/m².

The intervention under evaluation consisted in a bioactive peptide-rich *Saccharomyces cerevisiae*-derived hydrolysate in combination with lifestyle modifications, including medical nutrition therapy, structured exercise, sleep hygiene, and stress management. Interventions which included additional components (such as silymarin, probiotics, minerals, etc.) where excluded from the study.

Systematic Review

We conducted a systematic literature review to gather relevant evidence. Scientific articles were compiled in an online repository and disseminated among the expert panel members prior to the rating rounds. The literature review was conducted in March and April 2025 consulting Pubmed, SciELO, ClinicalTrials.gov, and Cochrane's CENTRAL. 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 "neuropeptide Y" OR "*weight*" OR "fat" OR "obes*"). Additionally, a snowballing strategy and expert consultation were employed to identify any additional studies. PICOS for inclusion of studies is displayed in Table 1.

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 abdominal perimeter

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Study Design	Blinded, randomized, placebo-controlled clinical trials

Two-Round Consensus

The expert panel convened for a face-to-face meeting in Mexico City in May 2025. During this session, panelists completed the first round of ratings using a structured questionnaire, in which each scenario was evaluated on a 9-point scale, where "1" indicated "highly inappropriate" and "9" indicated "highly appropriate." Ratings were processed on-site in real time. Following the initial round, a trained moderator facilitated a structured discussion to elicit expert insights, promote broad participation, and encourage the expression of diverse perspectives. The discussion was followed by two brief presentations summarizing relevant literature and evidence pertaining to the intervention under evaluation. Subsequently, a second round of ratings was conducted **(Supplementary Dataset S1).** In this round, panelists received a revised version of the questionnaire that included their initial ratings alongside summary statistics of their peers ratings. Panel members were invited to either maintain or modify their ratings based on the information and viewpoints presented during the discussion and presentations.

Statistical Analysis

Panelists' ratings were collected via a custom-designed web form and stored locally on a server running XAMPP (Apache Friends, 2023). The collected data was exported into a Comma-Separated Values format and visualized with Microsoft Excel (Microsoft Corporation, Redmond, WA; 2010), manually verified for accuracy, and then 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; 2023), following the RAND/UCLA Appropriateness Method guidelines (Santa Monica, California: RAND, 2001).[14] Agreement was defined as having no more than two panelists rate outside the three-point range that includes the median. [14]

Ethical Compliance

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

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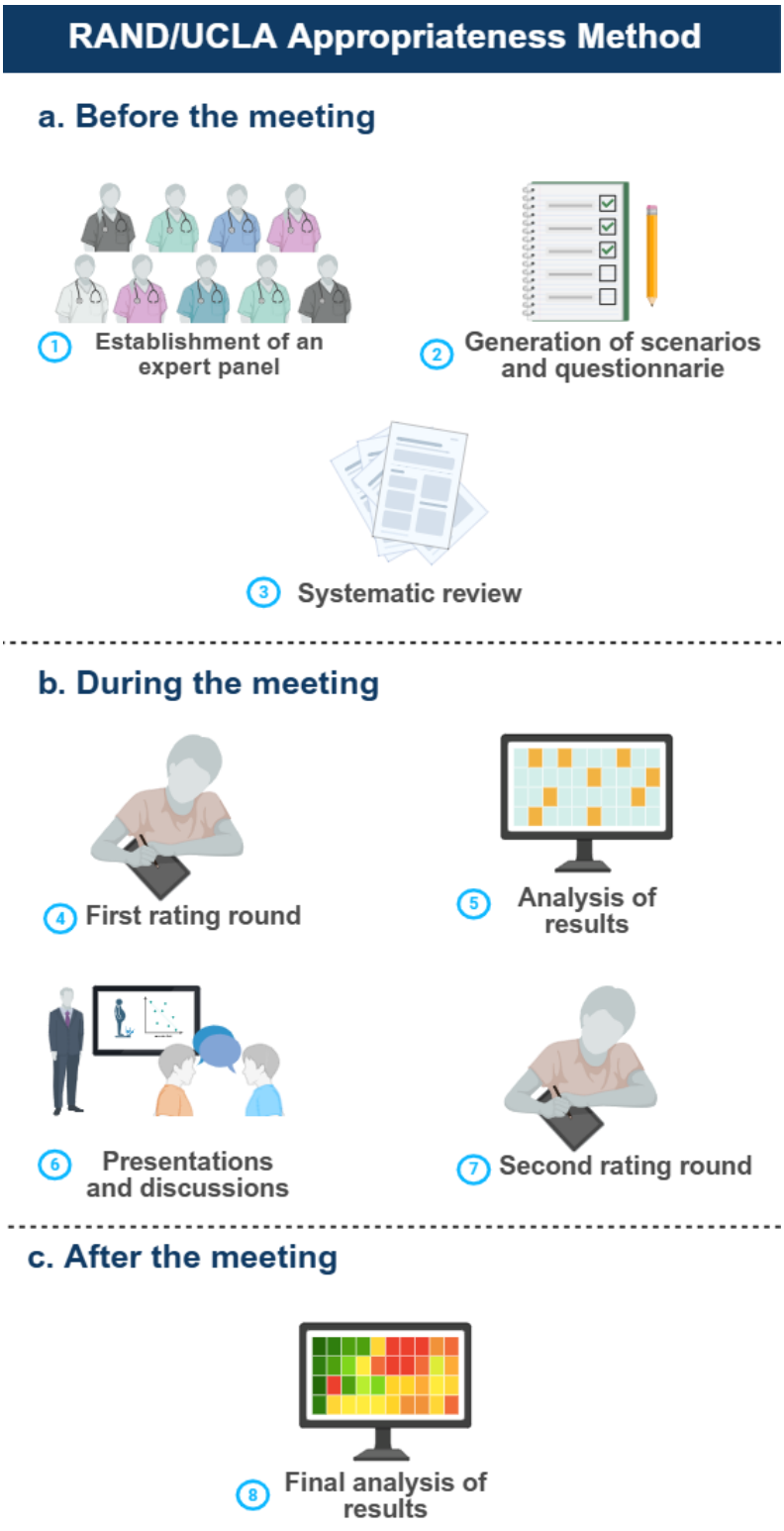

Figure 1. Diagram of the RAND/UCLA Appropriateness Method. a. Before the meeting: (1) Experts were recruited via professional networks and referrals. (2) Clinical scenarios were generated through preliminary discussions with the panel, and a PICO-based questionnaire was developed. (3) A systematic review was conducted. b. During the meeting: (4) Experts independently rated the appropriateness of each intervention across scenarios. (5) Ratings were submitted via a custom web form, stored locally, and manually verified. Data were processed in Python following RAND/UCLA guidelines. Agreement was defined as no more than two ratings falling outside the 3-point range containing the median. (6) Brief presentations and moderated discussion supported consensus-building. (7) Experts re-rated each intervention, incorporating insights from the

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discussion. c. After the meeting: (8) Final ratings were analyzed to determine agreement levels. Created with BioRender.com. .

Results

Summary of Participants and Answers

The expert panel was comprised of 4 clinical endocrinologists, 1 specialist in internal medicine, 1 psychiatrist, 1 general practitioner, and 2 clinical nutritionists. Eight of them had a primary role in private institutions in México and one of them in an academic institution in the United States. Collectively, experts rated 344 scenarios with a 100% answer rate. Agreement was reached in all 344 scenarios (100%) with all 344 of them (100%) rated as "Appropriate".

Appropriateness of the Intervention for Managing Obesity-Related Outcomes in Patients with Specific Comorbidities

Experts rated four outcomes (reduction of excess adiposity, reduction of waist circumference, reduction of weight regain, and reduction of 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) with binge-eating disorder; (6) with a history of pancreatitis; (7) with a history of cholelithiasis; (8) with metabolic dysfunction–associated steatotic liver disease; (9) with arrhythmia; (10) with heart failure; (11) with hypertension; (12) at high risk of cardiovascular disease; and (13) with chronic kidney disease. Each condition was further stratified by BMI into the following categories: 25–29.9 kg/m², 30–34.9 kg/m², 35–39.9 kg/m², and ≥40 kg/m². A total of 208 scenarios were evaluated, and an "Appropriate" agreement was reached for all these scenarios.

Table 2. Median of ratings of the appropriateness of the intervention with a bioactive polypeptide-rich *Saccharomyces cerevisiae* hydrolysate in addition to lifestyle modifications for managing obesity-related outcomes in patients with specific comorbidities and stratified by BMI. The boxes in green indicate that an agreement was reached, defined as having no more than two panelists rating outside the three-point range that includes the median. BMI = Body Mass Index.

	All patients with excess adiposity	Patients with excess adiposity and age 65	Patients with excess adiposity receiving	Patients with excess adiposity and anxiety	Patients with excess adiposity and binge-	Patients with excess adiposity and history	Patients with excess adiposity and history	Patients with excess adiposity and	Patients with excess adiposity and	Patients with excess adiposity and heart	Patients with excess adiposity and	Patients with excess adiposity and high	Patients with excess adiposity and chronic	BMI
Reducing excess adiposity	9	9	9	8.5	8.5	8	8	9	9	9	9	8.5	8	25–29.9 kg/m²
	9	9	9	8.5	8.5	8	8	9	9	9	9	8.5	8	30–34.9 kg/m²
	9	9	9	8.5	8	8	8	9	9	9	9	8.5	8	35–39.9 kg/m²
	9	9	9	8.5	8	8	8	9	9	9	9	8.5	8	>40 kg/m²
Reducing waist	9	9	9	9	9	9	9	8	9	9	9	9	9	25–29.9 kg/m²

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circumference	9	9	9	9	9	9	9	8	9	9	9	9	9	30–34.9 kg/m²
	9	9	9	9	9	9	9	8	9	9	8.5	9	9	35–39.9 kg/m²
	9	9	9	9	9	9	9	8	9	9	9	9	9	>40 kg/m²
Reducing weight regain	9	9	8.5	9	9	8	8	9	9	8	9	9	9	25–29.9 kg/m²
	9	9	8.5	9	9	8	8	9	9	9	9	9	9	30–34.9 kg/m²
	9	9	8.5	9	9	8	8	9	9	9	9	9	9	35–39.9 kg/m²
	9	9	8.5	9	9	8	8	9	9	9	9	9	9	>40 kg/m²
Reducing low-grade chronic systemic inflammation and oxidative stress	9	9	9	9	9	9	9	9	9	9	9	9	9	25–29.9 kg/m²
	9	9	9	9	9	9	9	9	9	9	9	9	9	30–34.9 kg/m²
	9	9	9	9	9	9	9	9	9	9	9	9	9	35–39.9 kg/m²
	9	9	9	9	9	9	9	9	9	9	9	9	9	>40 kg/m²

Appropriateness of the Intervention as an Adjunct to Conventional Pharmacotherapy

Experts assessed the appropriateness of prescribing a bioactive polypeptide-rich *Saccharomyces cerevisiae* hydrolysate as an adjunct to GLP-1 receptor agonists, naltrexone/bupropion, orlistat, or phentermine for reducing the impact of clinical obesity across seven physiological domains: (1) cardiovascular (hypertension, heart failure); (2) musculoskeletal (knee and hip pain, rigidity, limitations in range of motion); (3) reproductive (polycystic ovary syndrome, anovulation); (4) metabolic (hyperglycemia, dyslipidemia); (5) hepatic (metabolic dysfunction–associated steatotic liver disease); (6) respiratory (sleep apnea/hypopnea, dyspnea, wheezing); and (7) daily life activities. Each scenario was stratified by BMI into four categories: 25–29.9 kg/m², 30–34.9 kg/m², 35–39.9 kg/m², and ≥40 kg/m². Agreement was reached across all 112 evaluated scenarios, supporting the appropriateness of this intervention as a complementary therapy to established pharmacological treatments and lifestyle modifications.

Table 3. Median of ratings of the appropriateness of the intervention with a bioactive polypeptide-rich *Saccharomyces cerevisiae* hydrolysate in addition to lifestyle modifications as an adjunct to conventional pharmacotherapy and stratified by BMI. The boxes in green indicate that an agreement was reached, defined as having no more than two panelists rating outside the three-point range that includes the median. BMI = Body Mass Index. GLP-1 RA = glucagon-like peptide-1 receptor agonist.

Cardiovascular	Musculoskeletal	Reproductive	Metabolic	Daily-life limitations	Hepatic	Respiratory	BMI

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GLP-1 RA	8	8	8.5	8	8	8.5	8	25–29.9 kg/m²
	8	8	8.5	8	8	8.5	8	30–34.9 kg/m²
	8	8	8.5	8	8	8.5	8	35–39.9 kg/m²
	8	8	8.5	8	8	8.5	8	>40 kg/m²
Naltrexone/Bupropion	8	8	8	8	8	8	8	25–29.9 kg/m²
	8	8	8	8	8	8	8	30–34.9 kg/m²
	8	8	8	8	8	8	8	35–39.9 kg/m²
	8	8	8	8	8	8	8	>40 kg/m²
Orlistat	8	8	8	8	8	8	8	25–29.9 kg/m²
	8	8	8	8	8	8	8	30–34.9 kg/m²
	8	8	8	8	8	8	8	35–39.9 kg/m²
	8	8	8	8	8	8	8	>40 kg/m²
Phentermine	8	8	8	8	8	8	8	25–29.9 kg/m²
	8	8	8	8	8	8	8	30–34.9 kg/m²
	8	8	8	8	8	8	8	35–39.9 kg/m²
	8	8	8	8	8	8	8	>40 kg/m²

Appropriateness of the Intervention in a Set of Special Clinical Situations

Experts evaluated the appropriateness of a bioactive polypeptide-rich *Saccharomyces cerevisiae* hydrolysate in six special clinical scenarios: (1) prevention of progression to clinical obesity; (2) GLP-1 receptor agonist dose reduction; (3) maintenance of low-dose GLP-1 receptor agonist therapy; (4) use prior to initiating pharmacological treatment or bariatric surgery; (5) prevention of weight regain; and (6) transition to a medication-free period. All scenarios were stratified by BMI into the following categories: 25–29.9 kg/m², 30–34.9 kg/m², 35–39.9 kg/m², and ≥40 kg/m². Agreement was reached across all 24 scenarios, supporting the appropriateness of the intervention as part of a comprehensive obesity management strategy.

Table 4. Median of ratings of the appropriateness of the intervention with a bioactive polypeptide-rich *Saccharomyces cerevisiae* hydrolysate in addition to lifestyle modifications in a set of special clinical situations and stratified by BMI. The boxes in green indicate that an agreement was reached, defined as having no more than two panelists rating outside the three-point range that includes the median. BMI = Body Mass Index; GLP-1 RA = Glucagon-Like Peptide-1 Receptor Agonists.

		BMI
Prevention of progression to clinical obesity	8	25–29.9 kg/m²
	8	30–34.9 kg/m²
	8	35–39.9 kg/m²
	8	>40 kg/m²
GLP-1 RA dose reduction	9	25–29.9 kg/m²
	9	30–34.9 kg/m²
	9	35–39.9 kg/m²
	9	>40 kg/m²
Maintenance of low-dose GLP-1 RA receptor agonist therapy	9	25–29.9 kg/m²
	9	30–34.9 kg/m²
	9	35–39.9 kg/m²
	9	>40 kg/m²

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Prior to initiating pharmacological treatment or bariatric surgery	8.5	25–29.9 kg/m²
	8.5	30–34.9 kg/m²
	8.5	35–39.9 kg/m²
	8.5	>40 kg/m²
Prevention of weight regain	9	25–29.9 kg/m²
	9	30–34.9 kg/m²
	9	35–39.9 kg/m²
	9	>40 kg/m²
Transition to a medication-free period	9	25–29.9 kg/m²
	9	30–34.9 kg/m²
	9	35–39.9 kg/m²
	9	>40 kg/m²

Discussion

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

Excess adiposity is now recognized as a defining feature of obesity, with independence of BMI.[1] Accordingly, interventions should not focus solely on weight reduction, but also on decreasing adiposity, improving obesity-related manifestations, and preventing end-organ damage.[1] Even in patients with preclinical obesity, early interventions should aim to prevent progression to clinical obesity and reduce the risk of associated comorbidities.[1]

Tailoring pharmacological treatment to individual patient characteristics is a fundamental aspect of effective obesity management.[4] Various drug classes have shown meaningful weight-loss benefits, improved metabolic profiles, and reduced obesity-related complications, especially when used alongside lifestyle modifications. [21] Nonetheless, their real-world impact is often constrained by inconsistent individual responses, treatment discontinuation, side effects, and limited accessibility; most notably due to high costs. [2,4,21] A recent projection from the Congressional Budget Office suggested that expanding Medicare coverage to include anti-obesity medications—such as GLP-1 receptor agonists, GIP/GLP-1 dual agonists, and legacy agents like orlistat, bupropion/naltrexone, and phentermine/topiramate—starting in 2026 could raise federal expenditures by $35 billion over a nine-year span. [22] In contrast, anticipated healthcare savings from better health outcomes would be relatively modest, with per-user annual costs significantly surpassing estimated offsets. [22]

Beyond economic implications, clinical decision-making must also consider patient-specific risk factors and contraindications associated with anti-obesity pharmacotherapies. For example, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) should be used with caution in elderly patients, and those with depression, cholelithiasis, or arrhythmias, and are contraindicated in individuals with a history of pancreatitis.[4] Similarly, naltrexone/bupropion should also be used cautiously in elderly patients and those with chronic kidney disease, heart failure, or metabolic dysfunction–associated steatotic liver disease (MASLD); it is contraindicated in patients with uncontrolled hypertension.[4] Orlistat also requires caution in the elderly and in individuals with binge-eating disorder, depression, pancreatitis, cholelithiasis, or heart failure.[4] Phentermine while effective in the short term, is not recommended for long-term use and should be avoided or used cautiously in patients with anxiety or depressive disorders, as well as those with elevated

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cardiovascular risk.[4] When considering a clinical scenario with a patient with any of these risk factors or contraindications, the expert panel convened that an intervention with a bioactive polypeptide-rich *Saccharomyces cerevisiae* hydrolysate is appropriate due to its safety profile.

Saccharomyces cerevisiae hydrolysates have demonstrated a favorable safety profile across several clinical trials. For example, in a study by Valero-Pérez et al., the only adverse effect significantly more frequent than placebo was bloating, reported in 24% of participants.[11] Similarly, in a trial by Santas et al., only one participant reported flatulence as an adverse event. [12] Across three studies involving a total of 217 patients, only one individual discontinued participation due to side 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/m² 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.[10,23]

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 ($p<0.05$), despite changes in physical activity.[10] In a separate study 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 3.2kg in fat mass ($p<0.001$) relative to placebo.[24] Similarly, Mosikanon et al. reported a significant reduction of waist circumference of 8.19cm after 6 weeks of treatment compared to placebo ($p<0.05$).[25]

Weight regain following successful 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 behavioral 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.[25] [6,26]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] Based on this body of evidence, our expert panel concluded that administration of a bioactive polypeptide-rich *Saccharomyces cerevisiae* hydrolysate is appropriate for preventing weight regain and mitigating low-grade systemic inflammation and oxidative stress.

The combination of pharmacological agents is a common strategy in therapeutic development, particularly when monotherapy fails to achieve the desired clinical outcomes.[27] Agents with complementary mechanisms of action can enhance efficacy while allowing for lower doses of each component, thereby reducing the risk of dose-dependent side effects and toxicities.[27] For instance, the phentermine/topiramate combination capitalizes 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.[27,28]

Although no clinical trials have evaluated *Saccharomyces cerevisiae* hydrolysates in combination with other pharmacological agents, 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,

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musculoskeletal, reproductive, metabolic, hepatic, respiratory, and daily functioning outcomes). 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 of GLP-1 receptor agonists (GLP-1 RAs); (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 its appropriateness in delaying the onset of clinical obesity.[10–12] When used alongside GLP-1 RAs, this intervention may enhance efficacy through complementary mechanisms of action while enabling dose reduction or maintenance of lower doses. Likewise, initiating treatment with a bioactive polypeptide-rich *Saccharomyces cerevisiae* hydrolysate before starting pharmacological or surgical therapies may prime patients with excess adiposity for improved outcomes. Furthermore, its immunomodulatory capacity could help prevent weight regain and facilitate the transition to a medication-free period.[6,25,26] Based on this collective evidence, the expert panel reached consensus that a bioactive polypeptide-rich *Saccharomyces cerevisiae* hydrolysate is appropriate for all six clinical scenarios.

Although not formally addressed in the questionnaire, discussions among the experts during the meeting yielded several notable clinical considerations. Clinical nutritionists highlighted the advantage of recommending this intervention to patients, given that it is a non-pharmacological agent and available without a prescription. 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. Another point raised was its potential use in patients who are hesitant to initiate pharmacological treatment for weight management. A relevant perioperative application was also identified: given that GLP-1 receptor agonists must be discontinued at least one week prior to surgery due to their effects on gastrointestinal motility, a bioactive polypeptide-rich *Saccharomyces cerevisiae* hydrolysate 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 RAs. Clinicians noted that weight regain remains a major concern in this context and recognized the potential of a bioactive polypeptide-rich *Saccharomyces cerevisiae* hydrolysate 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 the inclusion of an expert panel comprising professionals from diverse disciplines. Nonetheless, certain limitations should be acknowledged. First, although the number of panel members is sufficient to obtain reliable results, a larger panel may have enhanced the breadth of perspectives and introduced greater variability in opinion, potentially enriching the consensus process. Second, the panel was composed by professionals of Mexican origin, who considered the conditions of patients in Mexico and Latin America, which limits the extrapolation of their opinion to worldwide scenarios. In a similar way, certain populations were excluded from the beginning, such as children and pregnant women. Third, although the RAND/UCLA Appropriateness Method is well-suited for scenarios lacking high-quality evidence, it inherently relies on expert judgment and cannot substitute for clinical trial data or real-world effectiveness studies. Therefore, specific clinical trials and post-marketing surveillance are warranted to better address these gaps in knowledge. Fourth, although the sponsor had no role in study design or data interpretation, industry funding may introduce perceived bias. This was limited by the introduction of a methodological panel which functioned as an impartial observer and collected and analyzed data independently to reduce the perception of bias. Finally, the limited number of high-quality clinical trials on *Saccharomyces cerevisiae* hydrolysates constrains the

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extrapolation of findings beyond short-term use. This limitation, however, underscores the need for future research to validate the intervention's effectiveness and broaden its clinical applicability.

Conclusions

This RAND/UCLA consensus process evaluated the appropriateness of a bioactive polypeptide-rich *Saccharomyces cerevisiae* hydrolysate as part of obesity management. Across 344 clinical scenarios, the intervention was rated as "appropriate" by a multidisciplinary panel of experts, with full agreement achieved in all cases. The panel supported its use for managing obesity-related outcomes in patients with diverse comorbidities, as an adjunct to conventional pharmacotherapy, and in a variety of special clinical situations.

The panel also identified several clinically relevant considerations beyond the formal questionnaire, including its utility in patients reluctant to initiate pharmacological therapy, in the perioperative setting, and during transitions to a medication-free period. Given its favorable safety profile, immunomodulatory properties, and accessibility without prescription, this intervention represents a promising adjunct in comprehensive obesity care. While current evidence supports its short-term efficacy, further research is warranted to validate its long-term effectiveness, assess outcomes in broader populations, and explore its role in combination therapies. These findings may inform clinical practice and guide future updates to obesity management recommendations.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

Author Contributions: J.Y.: Conceptualization, Investigation, Writing – review & editing; C.A.R.: Investigation, Writing – review & editing; R.A.C.: Investigation, Writing – review & editing; C.O.M.: Investigation, Writing – review & editing; A.M.: Investigation, Writing – review & editing; H.S.M.: Investigation, Writing – review & editing; J.V.G.: Investigation, Writing – review & editing; R.V.O.: Investigation, Writing – review & editing; P.Z.: Investigation, Writing – review & editing; B.C.T.: Conceptualization, Data curation, Formal analysis, Methodology, Software, Writing – original draft, Writing – review & editing; E.R.R.: Conceptualization, Data curation, Formal analysis, Methodology, Software, Writing – original draft, Writing – review & editing; A.A.P.G.: Conceptualization, Funding acquisition, Project administration, Writing – review & editing.

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Abbreviations

The following abbreviations are used in this manuscript:

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

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