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Probiotic Selection: Navigating FAO/WHO Guidelines for Optimal Attributes

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Abstract—*The selection of Probiotics for various applications, whether in the field of medicine, food production, or dietary supplements, has become an increasingly critical process. The Food and Agriculture Organization (FAO) and the World Health Organization (WHO) have established guidelines that offer a framework for evaluating and selecting Probiotic strains. The FAO/WHO guidelines provide clear criteria for probiotic strain selection, encompassing aspects such as safety, efficacy, and the ability to confer health benefits. These guidelines also emphasize the need for rigorous scientific evaluation, ensuring that selected Probiotics meet high standards of quality and effectiveness. One key attribute under scrutiny is the safety profile of probiotic strains. Strains selected must be free from pathogenicity, antibiotic resistance, and other potential risks to human health. This ensures that Probiotics can be used confidently without adverse effects. Furthermore, the efficacy of Probiotics is another critical factor. Selected strains should have demonstrated health benefits supported by scientific research, such as improved gut health, enhanced immunity, or the management of specific medical conditions. Adhering to FAO/WHO guidelines for probiotic selection is not only essential for the well-being of individuals but also for maintaining the credibility and trustworthiness of probiotic products in the market. This article offers insights into the practical application of these guidelines and the challenges associated with selecting Probiotics that meet the recommended attributes. It highlights the importance of rigorous testing and research to ensure that Probiotics not only meet but exceed the standards set by the FAO and WHO.*

Keywords: ***Probiotic, FAO/WHO Guidelines, Strain Characterization, Safety Assessment, Epidemiological Surveillance***

INTRODUCTION:

Probiotics, a term introduced in the early 20th century, have witnessed a remarkable surge in significance in recent years. The mounting body of evidence supporting the multifaceted impact of probiotics on human health has spurred a notable influx of probiotic products into the global market over the past decade. While the popularity of these products has soared, a critical challenge remained: the absence of a systematic and standardized approach for evaluating probiotics in food to ensure their safety and efficacy (Hill et al., 2014). This is where the pivotal role of regulatory authorities comes into play. Regulatory bodies have stepped forward to safeguard consumers and thwart false health claims by formulating comprehensive guidelines for the evaluation of probiotics in food. These guidelines play a crucial role in enhancing the overall safety and quality of probiotic-infused food products, providing a practical and scientific model for their evaluation, and offering a robust foundation for managerial decision-making. Moreover, the significance of these guidelines extends beyond regulatory oversight. They are designed to be adaptable and adoptable by the food industry itself, serving as a means to ensure the safety and efficacy of probiotic products (Parvez et al., 2006; Hao et al 2015).. Furthermore, they establish a rigorous methodology for assessing novel foods containing probiotics, defining clear criteria for their suitability. Notably, these guidelines set specific thresholds for the scientific evidence required to make health claims for probiotic foods, aligning the industry with the best practices for consumer protection and well-informed choices. In this era where probiotics have become a prominent feature in the global food market and their impact on human health continues to be explored, these guidelines provide a critical framework to navigate and standardize this dynamic field. They not only uphold consumer safety but also contribute to the quality and scientific integrity of probiotics in food, promoting responsible industry practices and informed choices (Reid et al 2003; Parvez et al., 2006; Hao et al 2015).

1. GUIDELINES FOR PROBIOTICS IN FOOD :

In light of the increasing popularity of probiotic foods and the absence of a universal consensus regarding the methodology for assessing their efficacy and safety, the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) initiated a collaborative effort to scrutinize the scientific evidence concerning the functional and safety aspects of probiotics in food. Specifically, this endeavor involved an expert consultation on the health and nutritional attributes of powdered milk containing live lactic acid bacteria, held in Cordoba, Argentina in 2001. Subsequently, an expert working group was organized in 2002 to develop comprehensive guidelines for the evaluation of probiotics in food. During the inaugural meeting of this group in 2001, the consultation primarily concentrated on examining the existing scientific evidence related to the properties,

functionality, benefits, safety, and nutritional characteristics of probiotic foods. It brought together 11 experts from 10 different countries to assess the scientific basis for health claims associated with probiotic foods, considering the work conducted by national authorities, FAO, WHO, and other international organizations. The consultation aimed to review the dietary impact of probiotics, evaluate their properties, benefits, safety, nutritional aspects, and potential adverse effects. It also discussed regulatory needs and explored strategies for the safety and nutritional assessment of probiotics, taking into account public concerns and findings related to food safety evaluation (Table1).

Table 1: Nutshell of FAO/WHO Guidelines for Evaluation of Probiotics for Food Use

Aspects	Description
Definition	Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.
Strain Characterization	Probiotic strains should be precisely characterized, including their genus, species, and strain designation. Strain designation should not be misleading about functionality.
Safety Assessment	Comprehensive safety assessments are required, considering antibiotic resistance patterns, metabolic activities, and potential side-effects in human studies.
Epidemiological Surveillance	Post-market epidemiological surveillance should be conducted to monitor adverse incidents related to probiotic consumption.
Toxin and Hemolysis Testing	If a probiotic strain belongs to a species known for producing toxins or having hemolytic potential, testing for toxin production and hemolytic activity is required, respectively.
Validation of Health Claims	Specific health claims related to probiotics, supported by scientific evidence, should be allowed on product labels and promotional material. Third-party scientific expert review should ensure claims are truthful and non-misleading.
Label Information	Product labels should include the genus, species, and strain designation of probiotics, minimum viable numbers at the end of shelf-life, serving size delivering the effective probiotic dose, health claims, storage conditions, and corporate contact details for consumer information.
International Promotion	Guidelines should be promoted at an international level to encourage consistent probiotic standards.
Good Manufacturing Practices (GMP)	GMP should be applied in the manufacture of probiotic foods, ensuring quality assurance and established shelf-life conditions.

2. GUIDELINES FOR PROBIOTICS USE:

1. Genus/species/strain Identification:

Recognizing the critical need for precise identification of probiotic strains, it is imperative to determine both the genus and species of each probiotic strain. The current body of scientific evidence underscores the strain-specific nature of probiotic effects, underlining the importance of linking a particular strain to specific health effects and facilitating accurate surveillance and epidemiological studies (FAO/WHO, 2002).

To establish the speciation of probiotic bacteria, it is recommended to employ the most current and valid methodologies. While DNA-DNA hybridization is considered the reference method for specifying strain-to-species relationships, it is often resource-intensive, necessitating a large reference strain collection (FAO/WHO, 2002). As a more practical alternative, utilizing DNA sequences encoding the 16S rRNA gene is suggested, provided that this genotypic technique is complemented with phenotypic tests for verification (FAO/WHO, 2002). These phenotypic tests should include the analysis of fermentation patterns resulting from a range of sugars and the final fermentation products obtained from glucose utilization (FAO/WHO, 2002).

In addition, it is crucial that the nomenclature used for probiotic bacteria conforms to the current, scientifically recognized names. Prolonged use of outdated or misleading nomenclature on product labels is considered unacceptable, as it hinders the proper identification of the probiotic bacterium in the product, compelling consumers and regulatory agencies to make assumptions about the true identity of the microorganism being marketed (FAO/WHO, 2002).

Furthermore, strain typing must be conducted using a reproducible genetic method or by investigating a unique phenotypic trait. Pulsed Field Gel Electrophoresis (PFGE) is widely regarded as the gold standard for this purpose, ensuring robust and reliable results (FAO/WHO, 2002). Although Randomly Amplified Polymorphic DNA (RAPD) can also be employed, it is considered less reproducible (FAO/WHO, 2002). The determination of the presence of extra chromosomal genetic elements, such as plasmids, can contribute significantly to strain typing and characterization (FAO/WHO, 2002).

2. In vitro tests to screen potential probiotics.

In the assessment of probiotic microbes, in vitro tests play a pivotal role in evaluating their safety and shedding light on the mechanisms underlying their probiotic effects. These tests offer valuable insights into the characteristics of probiotic strains and their potential benefits. However, it's important to note that the currently available in vitro tests have limitations in accurately predicting the functionality of probiotic microorganisms within the human body.

Furthermore, it was observed that the in vitro data available for specific strains are insufficient on their own to categorize

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them as probiotics. To establish probiotics for human use, it is imperative to substantiate their efficacy through human trials. To bridge the gap between in vitro and in vivo assessments, it is recommended to develop and employ target-specific in vitro tests that can reliably correlate with in vivo results. A comprehensive list of the primary in vitro tests currently used for the study of probiotic strains are:

i. **Survival in Gastric Acid:** Assessing the ability of probiotic strains to survive exposure to the acidic conditions of the stomach, which is crucial for their efficacy.
ii. **Bile Tolerance:** Measuring the ability of probiotics to withstand the bile salts present in the gastrointestinal tract, as this impacts their survival and functionality.
iii. **Adhesion to Intestinal Epithelial Cells:** Evaluating the capacity of probiotics to adhere to the intestinal lining, which is linked to their ability to colonize the gut.
iv. **Antimicrobial Activity:** Examining the potential of probiotics to inhibit the growth of harmful pathogens, contributing to a healthier gut environment.
v. **Fermentation and Acid Production:** Assessing the ability of probiotics to ferment carbohydrates and produce beneficial compounds such as short-chain fatty acids.
vi. **Resistance to Antibiotics:** Evaluating the resistance of probiotics to common antibiotics to ensure their safe use.
vii. **Viability and Shelf-Life:** Checking the stability and viability of probiotic strains during storage, which impacts product quality.
viii. **Immune Modulation:** Studying the influence of probiotics on the immune system to understand their potential immunomodulatory effects.

While these tests are valuable tools, it's essential to emphasize the importance of validation through in vivo performance to ensure their reliability and relevance in assessing probiotic functionality and safety.

3. Safety considerations:

Requirements for proof that a probiotic strain is safe and without contamination in its delivery form. Throughout history, lactobacilli and bifidobacteria associated with food have consideration for safety (Adams & Marteau, 1995). Their status as normal commensals in the mammalian flora, coupled with their extensive and safe use in various foods and supplements worldwide, supports this longstanding perception. Nevertheless, it's important to acknowledge that probiotics, in theory, could potentially give rise to four types of side-effects, as outlined by Marteau (2002):

i. **Systemic Infections:** While documented cases of systemic infections linked to probiotic consumption are scarce, those that have been reported primarily occurred in individuals with underlying medical conditions.
ii. **Deleterious Metabolic Activities:** Probiotics might exhibit metabolic activities that could have adverse effects.
iii. **Excessive Immune Stimulation in Susceptible Individuals:** In some cases, probiotics could trigger excessive immune responses, especially in individuals with heightened sensitivity.
iv. **Gene Transfer:** There's the theoretical possibility of probiotics being involved in gene transfer events.

Recognizing the paramount importance of ensuring safety, even among bacteria classified as Generally Recognized as Safe (GRAS), the Working Group recommends a minimum set of tests for the characterization of probiotic strains. These tests include:

i. **Determination of Antibiotic Resistance Patterns:** Assessing the strain's antibiotic resistance is crucial to understand potential risks.
ii. **Assessment of Certain Metabolic Activities:** Evaluating metabolic activities such as D-lactate production and bile salt deconjugation can reveal important insights into safety.
iii. **Assessment of Side-Effects During Human Studies:** This step involves monitoring and assessing any side-effects that may arise during human studies.
iv. **Epidemiological Surveillance of Adverse Incidents in Consumers (Post-Market):** This post-market surveillance is vital for tracking any adverse incidents related to probiotic consumption.
v. **Testing for Toxin Production:** If the strain belongs to a species known for producing toxins, it must be tested for toxin production.
vi. **Hemolytic Activity Testing:** If the strain belongs to a species with known hemolytic potential, determining hemolytic activity is required.

4. In vivo studies using animals and humans

In certain instances, animal models can serve as valuable tools to corroborate in vitro effects and elucidate probiotic mechanisms. Where relevant, the Working Group strongly encourages the utilization of these models prior to embarking on human trials. However, the primary focus in evaluating probiotic efficacy should be on human trials, with the principal outcomes being well-substantiated benefits in clinical settings.

These benefits should include statistically and biologically significant improvements in various aspects, such as the condition, symptoms, signs, well-being, or quality of life of individuals. Other benefits can encompass reduced disease risk, longer intervals between disease occurrences, or faster recovery from illnesses. Importantly, these benefits should be demonstrably linked to the specific probiotic tested. Probiotics have been extensively examined for their impact on a range of clinical conditions. Standard methods for clinical evaluations generally comprise:

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i. **Phase 1 studies:** These studies primarily focus on assessing the safety of probiotics.
ii. **Phase 2 studies:** Typically designed as randomized, double-blind, placebo-controlled (DBPC) trials, these investigations measure the efficacy of probiotics compared to a placebo. Phase 2 studies also evaluate any adverse effects. It is recommended that, for probiotic foods, the placebo should consist of the food carrier devoid of the test probiotic. Sample sizes must be calculated for specific endpoints, and statistically significant differences should be relevant from a biological perspective.
iii. **Phase 3 studies:** Probiotics delivered in food are generally not subjected to Phase 3 studies, which involve comparisons with standard therapies.

In cases where probiotics are claimed to influence a disease state, these claims should be grounded in robust scientific evidence derived from human subjects. In Phase 2 and 3 studies, the Working Group acknowledges the value of employing validated quality of life assessment tools. Moreover, it is advisable that human trials be replicated by multiple research centers to validate the results. In the context of probiotic consumption through food, no adverse effects should be experienced. Any adverse effects should be meticulously monitored, and incidents should be reported. The Working Group recommends the publication of accumulated information, including clinical trial evidence, in peer-reviewed scientific or medical journals. Furthermore, the publication of negative results is encouraged, as these findings contribute to the overall body of evidence supporting probiotic efficacy. For further details on generating and using clinical information to substantiate health effects, additional information can be accessed at www.ftc.gov/bcp/conline/pubs/buspubs/dietsupp.htm#IIb.

5. Health claims and labeling

In most countries, the current regulations typically permit only general health claims on foods containing probiotics. However, the Working Group strongly recommends allowing specific health claims related to the use of probiotics on food products, provided there is sufficient scientific evidence to support these claims, in accordance with the guidelines outlined in this report. These specific health claims should be prominently displayed on product labels and in promotional materials. For instance, a specific claim stating that a probiotic "reduces the incidence and severity of rotavirus diarrhea in infants" would provide more informative guidance to consumers compared to a general claim like "improves gut health." To ensure the accuracy and integrity of these health claims, it is advisable that product manufacturers engage in an independent third-party review by scientific experts in the field. This review process should establish that the health claims are truthful and do not mislead consumers. Furthermore, the Working Group recommends that the following information be clearly described on product labels:

i. Genus, species, and strain designation of the probiotics.
ii. The strain designation should not convey misleading information about the strain's functionality. Minimum viable numbers of each probiotic strain at the end of the product's shelf-life.
iii. The suggested serving size must be adequate to deliver the effective dose of probiotics associated with the health claim.
iv. Health claim(s) should be prominently displayed.
v. Proper storage conditions to maintain probiotic viability.
vi. Corporate contact details for consumer inquiries and information.

6. Key Recommendations:

i. Endorsement of the definition of probiotics as "Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host."
ii. Adoption of the guidelines outlined in this report as a prerequisite for designating a bacterial strain as "probiotic."
iii. Establishment of a regulatory framework permitting specific health claims on probiotic food labels where there is scientific evidence supporting such claims, following the guidelines presented in this report.
iv. Promotion of these guidelines at an international level to ensure consistent probiotic standards.
v. Implementation of Good Manufacturing Practices (GMP) for the production of probiotic foods, ensuring quality assurance and defining shelf-life conditions.
vi. Ongoing development of methods, both in vitro and in vivo, for the evaluation of probiotic functionality and safety, aligning with evolving scientific understanding.

CONCLUSION:

The FAO/WHO guidelines provide an essential framework for evaluating and selecting probiotics, contributing to consumer well-being and product credibility. By adhering to these guidelines, the probiotic industry upholds the highest standards of quality, safety, and efficacy, ensuring responsible practices and informed choices for consumers.

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