



Probiotics: A Review

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Abstract:

According to the definition given by FAO/WHO (World Health Organization), probiotics must be alive and abundant once they're ingested. However, within the last few years, new definitions are added to the probiotic terminology namely, 'paraprobiotics' (dead/inactive cells of probiotics) and 'postbiotics' (healthful metabolites of probiotics), because findings have shown that dead cells (either intact or ruptured) can even show significant health benefits after their ingestion in the body. However, mentioned terms aren't accurate and impressive enough to reflect the intended meanings regarding all states of probiotic benefits and it seems that a disturbance and confusion in probiotic glossary has been occurred. As a result, a replacement terminology supported a replacement efficient approach and conceptualization is required for a worldwide agreement and usage. In the present review article, we have briefly described different terms that are closely associated with probiotics.

Keywords: Beneficial Microbes, Gut Microbiota, Functional Foods, Human Health, Nutritional Supplements, Food Processing.

Introduction:

According to the Greek language, the term probiotic means 'for life'. For life, meaning each substance or organism that promote health quality to the host. In 2002, the WHO and FAO considered probiotics as 'live microorganisms and after they are administered in adequate amounts to the host confers health benefits. Probiotic microbes provides several health benefits and a few of them are listed below.

- a) Enhancing nutritional value of food products.
- b) Controlling and reducing the serum cholesterol.

c) Preventing gut infections and suppressing antibiotic-associated diarrhoea.

d) Reducing hereditary condition symptoms.

e) Reduction of carcinoma risk.

f) Improving the digestion of gliadin against celiac in gluten having foods which are smitten by the kind of probiotic strain [1, 2].

Regarding these functionalities, people have an interest in consuming those products which contains probiotics. Among the products whose allegations of health benefits are developed and advertised by media during the last couple

of years [3]. Differing types of delivery systems of probiotics are commercialized and are considered as a source of probiotics including, food products (e.g., dairy products, processed meat, vegetable products, juices and three cereal-based products), nutritional supplements (liquid, tablet, capsule, and powder) and medicines [4]. The definition of the term probiotic has been changed and broadened with the passage of time. Although, the definition developed by WHO and FAO is accepted by almost all researchers, but during the recent years, new definitions are added to the probiotic terminology like ‘paraprobiotics’

(dead/inactivated cells of probiotics) and ‘postbiotics’ (healthful metabolites of probiotics). Accordingly, findings have shown that dead cells (intact cells or ruptured cells/cell extracts) and also cell metabolites can provide significant health benefit to human beings [5]. Therefore, mentioned terms aren't accurate and comprehensive enough to reflect the intended meanings of all beneficial aspects of probiotics and it seems that a disturbance in glossary has been occurred. As a result, a replacement approach and conceptualization in probiotic terminology is required to be developed for global usage. This review is aimed to fulfil mentioned necessary idea.

Terms Associated With Probiotics:

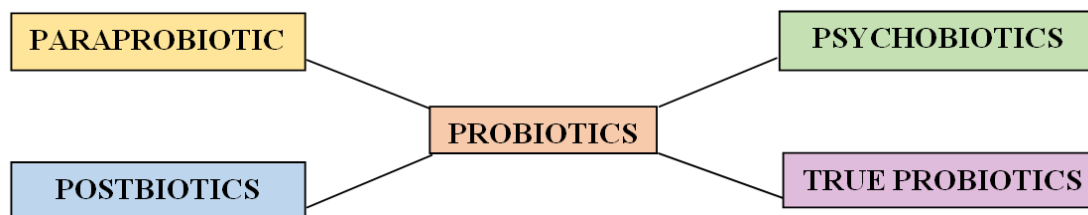


Fig. 1: Probiotic and terms closely associated with it.

1. Probiotic:

The first probiotic definition was given during the year 1908 by Metchnikoff, who proposed that consumption of fermented milk products prolongs the lifetime of humans (longevity effect) [6].

In 1956, Lilly and Stillwell proved that a microorganism secretes some growth stimulators for other microorganisms [7]. This positive effect may cause the applying of the term probiotic for these types of microorganisms.

The term "**probiotic**" was first used by **Parker in 1974** to describe **substances and organisms** that help maintain the

microbial balance in the digestive system of humans and animals [8]. However, including the word "**substances**" made the definition too broad, as it could also include things like **antibiotics**.

Fuller [9] improved Parker's definition and defined probiotic as a live microorganism that possess positive affects when ingested by the warm-blooded animal by restoring the natural gut microflora. Fuller's definition emphasized on the importance of probiotic that confers positive effect on animals.

In 1992, **Haveenar and In't Veld** defined **probiotics** as **live microorganisms**,

used alone or in mixtures, that are given to **humans or animals to improve gut microflora and provide health benefits** [10].

Consistent with the Salminen definition, a probiotic could be a viable microorganism when inoculated in dairy products improves the health and nutrition of the host [11]. Similarly, Schaafsma [12] broadened the definition by proposing that the probiotics are viable microorganisms that have health effects on the host, if ingested in sufficient numbers and when consumed over inherent basic nutrition.

In 2001, Schrezenmeir and de Vrese [13] considered probiotics as viable microorganisms that confers health effects independent of the location of action. In the same year WHO and FAO considered probiotics as 'live microorganisms which when administered in required amounts provides health benefit on the host'.

In 2014, the **International Scientific Association for Probiotics and Prebiotics (ISAPP)** slightly updated the definition of probiotics. They defined them as "**Live microorganisms that, when taken in the right amounts, provide a health benefit to the host.**" This definition has been widely accepted by the scientific community and is now used by many **Government agencies** to decide whether a **drug, food, or supplement** can be called a **probiotic**.

Recent studies have shown that even **dead or inactivated probiotic cells** (whether whole, broken, or as cell extracts), as well as their **metabolites**, can provide important **health benefits** to warm-blooded animals. So, the strict requirement for "**live**"

cells in all probiotic definitions should be **reconsidered and updated** [5].

On the other hand, it is worth to say that using living cells in some especial cases may need an adverse effect on the health. For instance, it's been determined that probiotics can modulate the immune system; however, when live probiotic cells are administered to the host with weak system increases inflammatory responses [14]. In such cases, use of dead/inactivated cells might be a decent substitute. Therefore, the administration of killed or inactivated probiotics developed a replacement area in probiotic field and thus, different scientists tried to propose new terms to hide mentioned usages. However, the recommended terms don't seem to be precise and comprehensive from scientific meaning point of view. Also, they're somehow confusing.

2. Paraprobiotic:

After 2004, many researchers began to report functional properties of dead/killed probiotics. Zhang *et al.*, [15] showed the beneficial effect of heat-killed *Lactobacillus rhamnosus* GG (LGG) cells and stated that killed probiotic cells were more practical than viable probiotic cells on down-regulation of an inflammatory response because of their high ability to decrease the assembly of interleukin-8 (IL-8).

In 2008, Lopez *et al.*, [16] proved that the UV-inactivated *Lactobacillus rhamnosus* GG (LGG) cells were very effective in decreasing the assembly of IL-8 within the intestinal epithelium [16].

In 2009, Ostad *et al.*, [17] determined the power of heat-killed *Lactobacillus* species (*Lactobacillus acidophilus*, *Lactobacillus agilis* and *Lactobacillus casei*) in preventing the adhesion property of *Salmonella typhosa* and *Escherichia coli* to Caco-2 cells. They proposed that heat-killed cells are the same as viable cells which were ready to inhibit pathogenic bacteria adhesion property. Similarly, a study of Rampengan *et al.*, [18] on children with lactose malabsorption indicated that using probiotics (viable or killed cells) had a good effect on decreasing milk intolerance symptoms in children.

In 2011, Taverniti and Guglielmetti [19] introduced the term ‘paraprobiotic’ to point inactivated/killed microbial cells or cell fractions to confer health benefits to the host. Taverniti and Guglielmetti [19] proposed the term paraprobiotic for inactivated microbial cell fractions which are capable of conferring health benefits to the host. Consistent with Taverniti and Guglielmetti [19], the term paraprobiotic refers to ‘non-viable cells (intact or tact) or cellular extract which confer health benefits to the host when administered in adequate/required amounts’. Supported this definition, both tact and intact cells considered as paraprobiotics which is one amongst the confusing points of this definition. Additionally, entering the cellular extracts of probiotics into the definition of paraprobiotics as a beneficial factor is another confusing point. Inherently, while the basis of term ‘probiotic’ (for life) comprises any health benefits to the host by microbial cells or any cell-associated

derivatives, the term ‘paraprobiotic’ doesn't literally reflect an informative impression. In other words, this paraprobiotic isn't self-expressive to the intended meanings.

The prefix "**para**" means "**in front of**" in Latin (commonly used in chemistry along with "ortho" and "meta"). The word "**probiotic**" generally means "**for life**" or **health-promoting**, while it's opposite is "**antibiotic**", which means **against life or not healthful**.

So, using the term "**paraprobiotic**" together with "probiotic" doesn't really make sense. In some scientific papers, "paraprobiotic" is explained as "**beside-for life**", but this meaning is unclear and **not convincing**.

Furthermore, supported its literal meaning of ‘para’ (beside) in conjunction with ‘probiotic’, it could be perceived that paraprobiotics would have their activity and efficiency only administered beside probiotics and their activities are addicted to the presence of probiotics. Given above, the term paraprobiotic is somehow confusing. It should be mentioned that the words ‘inactivated probiotic’, ‘dead probiotic’, ‘nonviable probiotic’, and ‘ghost probiotic’ are also used as synonyms for paraprobiotic. It is worth to say that inactivation of probiotic cells doesn't necessarily guarantee their death (being inviable or nonviable). The cells could be viable, but not active. Also, some cells are active in a very matrix, but inactive in another one. In other words, the microbial cell could be ‘viable- but-not-culturable’ (VBNC or vbnc). This narrow point is another unclarity of paraprobiotic term.

3. Postbiotic:

The term "**paraprobiotic**" mainly refers to whole inactivated (dead) probiotic cells or parts of their cell membranes. In contrast, "**postbiotic**" refers to the soluble extracts from non-living probiotics, usually with a molecular weight between 50-100 kDa. Overall, probiotics present in a very viable state, can produce postbiotics. Postbiotics additionally defined as cell-free supernatants, biogenics, metabolites, and metabolic waste of activity of probiotic. In 2013, Tsilingiri *et al.*, [20] defined postbiotic as any affects obtaining from metabolites of probiotics or any extracted or secreted from probiotics molecule that gives health benefits to the host directly or indirectly. These soluble compounds include enzymes, exo and endo polysaccharides, surface proteins, vitamins, organic acids, fatty acids and peptides [20-22].

Aguilar-Toala *et al.*, [21] defined postbiotics as soluble factors (products or metabolic by-products), secreted by live bacteria or released after bacterial lysis. Most of literatures discussed the character of postbiotics and their beneficial effects instead of its terminology that can't cover the entire meaning of nature and effects. The prefix 'post' literally means 'after' and also the 'postbiotic' means 'after life'. Therefore, if it absolutely was meant after the viability of microbial cells (nonviable cells), the meaning is mixed with paraprobiotic, because both states are beyond the viability. Moreover, it must underline that the functions mentioned for postbiotic aren't just associated with the dead cells and people health promoting components is obtained also from viable

cells. As appeared, postbiotic in meaning is confusing and ambiguous yet as paraprobiotic.

Tsilingiri and Rescigno [20] have proposed postbiotic for any substance (bacteria metabolites, cell extraction, or molecule/s secreted by probiotic organism) that affect beneficially on the host directly or indirectly.

4. Psychobiotic:

In 2013, **Dinan and colleagues** introduced the term "**psychobiotic**" to describe certain **probiotics** that, when taken in the right amount, can improve **mental health** by interacting with the **gut microbiota** [23]. Later, **Nishida et al.**, suggested the term "**parapsychobiotic**" for **inactivated probiotics** (paraprobiotics) that also have positive effects on mental health [24].

Some **microbial metabolites** (substances made by microbes) can also affect the brain and mental processes [25]. Research has shown that **psychobiotics** may help with mood, memory and learning [26], cognitive function, production of important brain chemicals (like GABA, serotonin, dopamine, acetylcholine), managing stress by affecting the **HPA axis** (a key stress-response system) and reducing inflammation [27].

On the other hand, many studies showed that the **gut microbiota** plays a major role in **brain function and behavior**. So, changing the makeup of gut microbes can help improve brain-related disorders [27]. This means that **live probiotics, inactivated probiotics** and their **metabolites** can all influence the gut microbiota and through that, affect the brain.

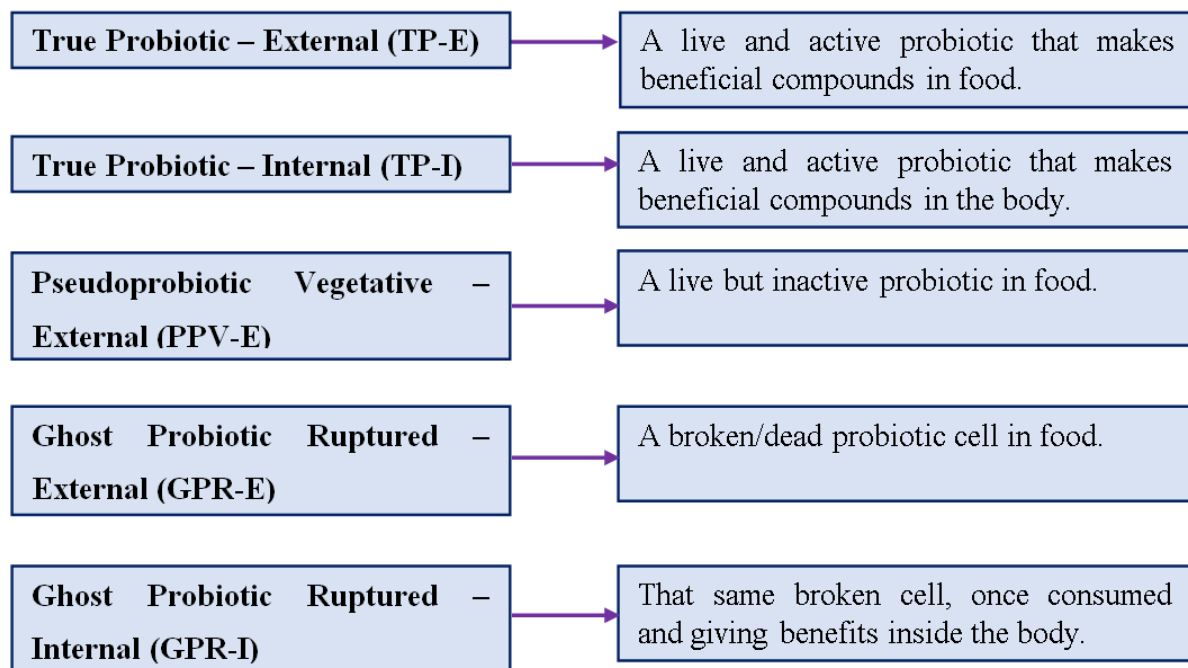
Finally, the term "**psychobiotic**" focuses on mental health. It **doesn't introduce a completely new class** of probiotics. Its actions are still based on known mechanisms of **probiotics, paraprobiotics, and postbiotics**. So, calling it a new category isn't really accurate. It's similar to inventing names like "**gutbiotic**" or "**gastroprobiotic**" for gut health, which don't add new scientific meaning.

New Conceptualization On Meaning Of Probiotic:

The idea behind creating clearer probiotic terms comes from the Greek word "probiotic," which means "for life." Based on this, we define probiotics as 'Live or

dead microbial cells (vegetative or spore form; whole or broken) that can give health benefits to the host'.

In order to make things clearer, we suggest dividing probiotics into three main categories namely, True Probiotic (TP) Alive and active, Pseudoprobiotic (PP): Alive but inactive (can be in vegetative or spore form → PPV or PPS) and Ghost Probiotic (GP): Dead (non-viable), either whole or broken (→ GPI or GPR). Each of these can also be grouped based on where they perform their action like, External (E): Outside the body, like in food or supplements and Internal (I): Inside the body, after being consumed. An explanatory diagram is shown below.



1. True Probiotic:

According to the FAO/WHO, one important rule for something to be called a **probiotic** is that it must contain **live (viable) microbes**. If a microbe can **grow** (multiply) and **produce useful substances** (like

vitamins or enzymes), it is considered **alive and active** [28, 29].

However, the FAO/WHO definition doesn't clearly say whether a probiotic must be active, only that it must be alive. That's

why we suggest using a new term, "**true probiotic**," to make things clearer.

A **true probiotic** should be **alive and active**, not just alive. Being active means the microbe is doing useful things in the body such as, lowering gut pH, making vitamins and enzymes, producing natural antimicrobials, balancing gut bacteria, helping to recover from diarrhoea, lowering cholesterol, supporting the immune system, reducing allergies and lactose problems, helping with calcium absorption and supporting recovery during antibiotic use [30].

When probiotics enter the body through the digestive system, they should first be **alive and active** outside the body (like in food or supplements), and then **remain alive and active** inside the body too. In order to remain alive and active inside the body they must survive tough conditions like, saliva in the mouth, stomach acid and enzymes, bile salts in the intestines and competition from other gut microbes.

So, the most important feature of a **true probiotic** is that it must work where it is needed in the body and give real health benefits.

Conclusion:

Current definitions of probiotics usually stress that the microbes must be alive and preferably active to be effective. However, recent studies have shown that even when probiotic cells are inactivated, dead, or broken, they can still provide health benefits to the host. At the same time, there are some safety concerns about using live microbes. These findings have led to the introduction of new terms like

paraprobiotics and **postbiotics**, which refer to the beneficial effects of inactive or non-viable probiotics. However, these terms can be confusing and unclear for several reasons.

To bring more clarity, we propose a new, more structured terminology to cover all forms of probiotics and their effects:

- **True Probiotic (TP):** Live and active microbial cells.
- **Pseudoprobiotic (PP):** Live but inactive cells, either in vegetative form or as spores.
- **Ghost Probiotic (GP):** Dead cells, which may be whole or broken.

Based on this approach, we suggest updating the definition of **probiotics** to: "**A viable or non-viable microbial cell (vegetative, spore, intact, or ruptured) that provides potential health benefits to the host when given in the right amount.**"

We believe this new framework will help scientists and researchers around the world agree on a clearer and more consistent way to describe all types of probiotics and their effects, reducing confusion and improving communication in the field.

Conflict Of Interest:

The authors declare no conflict of interest.

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