INTRODUCTION

Probiotics are live microorganisms which when administered in adequate amounts confer a health benefit on the host. This definition used at present was given by the Food and Agriculture Organization of the United Nations World Health Organization ***(FAO/WHO, 2001)***. Most probiotics are bacteria similar to those naturally found in people's guts, especially in those of breastfed infants (who have natural protection against many diseases). Most often, the probiotic bacteria come from two groups, *Lactobacillus* or *Bifidobacterium*. Within each group, there are different species (for example, *Lactobacillus acidophilus* and *Bifidobacterium bifidus*), and within each species, different strains (or varieties). A few common probiotics, such as *Saccharomyces boulardii*, are yeasts, which are different from bacteria ***(Alvarez-Olmos and Oberhelman, 2001)*.**

Specific strains of probiotic lactic acid bacteria have been shown to beneficially influence the composition and/or metabolic activity of the endogenous microbiota and some of these strains have been shown to inhibit the growth of a wide range of enteropathogens. Competition for essential nutrients, aggregation with pathogenic micro-organisms, competition for receptor sites, and production of anti-microbial metabolites were reported as probiotics properties ***(Guéniche et al., 2009***).

In skin diseases with some imbalance in microorganisms, such as impure skin/mild acne or dry skin/mild atopic dermatitis,

pre- and probiotic concepts represent an effective alternative to strictly antibacterial products. Prebiotics rebalance the skin microflora, while probiotic approaches predominantly consist of applying an inactivated microbial biomass of beneficial bacteria ***(Simmering and Breves, 2009).***

Because of their immunomodulating properties, probiotics and prebiotics may constitute valuable tools to treat and prevent immune disorders such as allergy, yet their mechanisms of action are not fully understood ***(Gourbeyre, 2011***). Thus, these can be a promising tool to control some diseases caused by dysregulated immune responses. ***(Shida and Nomoto, 2013).*** Probiotics have been suggested to be useful in children with atopic dermatitis (AD) with a substantial clinical improvement and a significant decrease in chemokine levels, reflecting the severity of the disease ***(Woo et al., 2010).*** Topical application of probiotics led to a reduction of the AD-associated signs and symptoms such as erythema, scaling, and pruritus in all patients ***(Di Marzio et al., 2008).*** This could be partially due to increasing ceramide levels in stratum corneum ***(Cinque et al., 2010).*** Their role in acne, wound healing, and photoprotection is promising, but larger trials are needed before a final recommendation can be made***. (Baquerizo and Yim, 2014)***

Modern analytical methods in molecular biology revealed new insights into the complex diversity of partially unculturable microbial organisms. Most of the resident microbes on healthy

skin can be regarded as being harmless or even beneficial to skin. Several examples of successful in vivo studies illustrate this new principle for gentle cosmetics derived from the food sector ***(Simmering and Breves, 2009).***

All of the above-mentioned observations opened new potential probiotic-based strategies against pathophysiological skin alterations, including aging associated with a reduced amount of the ceramide; the major water holding molecule in the extracellular space of the horny layer ***(Cinque et al., 2010)***. Understanding microbe-host interactions and discovering the factors that drive microbial colonization will help to understand the pathogenesis of skin diseases and develop new promicrobial and antimicrobial therapeutics. ***(Chen and Tsao, 2013).***

AIM OF THE ESSAY

The aim of this essay is to present a comprehensive review of the role of probiotics in dermatology with special emphasis on their definition, origin, mechanism of action, implications in dermatology, side effects, drug interactions, contraindications and precautions.

Chapter 1

PROBIOTICS

The term '**probiotics**' was derived from the Greek word, meaning "for life"***(Reid et al., 2003***). An expert panel commissioned by ***FAO (Food and Agriculture Organization) and World Health Organization (WHO) in 2001*** defined probiotic as "live micro-organisms," which, when administered in adequate amounts confers a health benefit on the host". They are – like normal microflora of the human gastro-intestinal tract (GIT) and skin - non-pathogenic microbes, which do not induce inflammatory responses ***(FAO/WHO, 2001***).

Historical overview

Havenaar and Huis In't Veld (1992) defined probiotics as: "A preparation of or a product containing viable, defined microorganisms in sufficient numbers, which alter the microflora (by implantation or colonization) in a compartment of the host and by that exert beneficial health effects in this host". Reasons for the revision of **Havenaar and Huis In't VelD (1992)** definition were as follows:

1) The need to include products in addition to microorganisms, or preparations of microorganisms;

2) The requirement of sufficient microbial numbers to exert health effects;

3) Preference for the phrase "alteration of the microflora" over "improving the properties of the…microflora," because the optimal properties of the indigenous microflora were not defined and the evidence of benefit could be shown only by health effects; and

4) Definition of the term "indigenous microflora" refers to "the usually complex mixture of bacterial population that colonizes a given area in the host that has not been affected by medical or experimental intervention, or by disease", and use of "to colonize" to describe a bacterial population that establishes in size over time without the need for periodic reintroduction of the bacteria by repeated oral doses or other means ***(Freter, 1992)***.

"Transplantation" is considered to have occurred when the administration of microorganisms results in colonization. "Transient invasion" is defined as the administration of microorganisms in large numbers such that the microorganisms can be cultured regularly from various regions. If these definitions were used, "improving the properties of the indigenous microflora" would unnecessarily confine the definition of probiotics. The positive effect of *Lactobacilli* on the infection outcome by pathogenic bacteria could be called probiotic only if the effect is achieved beyond implantation of the administrated bacteria or due to a change in the colonizing indigenous microflora ***(Sepp et al., 1995)***. A direct inhibitory

effect exerted by bacteria transiently passing through the GIT would fail to meet the definition. Because the transient state is the most common condition under which probiotics are used, the expression "microflora in a compartment of the host" was preferred to "indigenous microflora" ***(Salminen and Isolauri, 1996).***

The above definition confines the probiotic concept of effects produced by viable microorganisms but is applicable independent of the probiotic site of action and the route of administration. Therefore, this definition may include such sites as the oral cavity, the intestine, the vagina, and the skin ***(Schrezenmeir and De Vrese, 2001).***

The term prebiotic:

The term **prebiotic** was introduced by **Gibson and Roberfroid (1995)** who exchanged "pro" for "pre," which means "before" or "for." They defined prebiotics as "a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon." This definition more or less overlaps with the definition of dietary fiber; many dietary fibers, especially soluble fibers, exhibit some prebiotic activity; however, **Roberfroid** only identified two groupings of nutritional compounds that meet his definition. These two groupings or sub-categories can be described as inulin-type

prebiotics and galacto-oligosaccharides (GOS), with selectivity for certain species. This selectivity was shown for *Bifidobacteria*, which may be promoted by the ingestion of substances such as fructo-oligosaccharides and inulin ***(Gibson and Roberfroid, 1995)***, trans-galactosylated oligosaccharides ***(Tanaka et al., 1983)***, and soybean oligosaccharides ***(Hayakawa et al., 1990).***

Classification of some naturally occurring and synthetic prebiotics and their sources are given below in **table 1** ***(Ramanamma, 2012).*** The prebiotics with their monomers and defined degrees of polymerization are demonstrated in **table 2** ***(Farage et al., 2010).***

Both **probiotics** and **prebiotics** are together, **synbiotics**; improve the survival of the bacteria in the GIT, so that their effect is more ***(Gupta, 2009).*** Because the word alludes to synergism, this term should be reserved for products in which the prebiotic compound selectively favours the probiotic compound. In this strict sense, a product containing oligo-fructose and probiotic *Bifidobacteria* would fulfil the definition, whereas a product containing oligo-fructose and a probiotic *Lactobacillus casei (L. casei)* strain would not. However, one might argue that synergism is attained in vivo by ingestion of *Lactobacilli* and promotion of indigenous *Bifidobacteria* ***(Schrezenmeir and De Vrese, 2001).***

Table (1): Classification of some naturally occurring and synthetic prebiotics and their sources ***(Ramanamma, 2012).***

Sl. No.	Classification	Origin / Manufacturing Procedure
I	**Disaccharides**	
1	Lactulose	Lactose synthetic
2	Lactitol	Lactose synthetic
II	**Oligosaccharides**	
	Fructo- oligosaccharides	Legumes, vegetables, extracts / hydrolysis of cereals.
	Soybean oligosaccharides	Extraction / hydrolysis of soy bean
	Xylo-oligosaccharides	Plant sources
	Trans Galacto-oligosaccharides	Lactose synthetic
III	**Polysaccharides**	
	Inulin	Extracts obtained from legumes, vegetables and cereals.
	Resistant starches	Extracts obtained from legumes, vegetables and cereals.

Table (2): Examples of substances commonly used for their prebiotic properties (***Farage et al., 2010).***

Prebiotic	Abbreviation	Main monomer (s)	Degree of Poly-merization	Linkage
Fructo-oligosaccharide(Oligofructose)	FOS	Fructose	1-7	B-(1,2)*
Galacto-oligosaccharide (Trans galacto-oligosaccharide	GOS (TOS)	Galactose	1–6	B- (1,4)*
Inulin	-	Fructose	10-60	B-(1,2)
Lactitol	-	Galactose, Glucitol,	2	α-(1,4)
Lactulose	-	Galactose, Fructose	2	B-(1,4)
Partially hydrolysed guar gum	PHGG	Mannose, Galactose	10-300	B-(1,4) α-(1,6)
Polydextrose	PDX	Glucose	12-30	(1,6)
Xylo-oligosaccharide	XOS	Xylose	2-7	B-(1,4)
Resistant starch	RS	Glucose	10-100	α-(1,4) α-(1,6)

Microbiota of normal human body:

Gastrointestinal Microflora

The human intestine harbors an enormously complex, diverse, and vast microbial community, referred to as gut microflora or microbiota ***(Hooper and Gordon, 2001)***. The human gut microbiota is estimated to consist of at least 10^{14} bacteria and archaea (microorganisms which are similar to bacteria in size and simplicity of structure but radically different in molecular organization. They are now believed to constitute

an ancient group which is intermediate between the bacteria and eukaryotes), composed of approximately 1,100 prevalent species, with approximately 160 such species per individual. In its entirety, the microflora is estimated to contain 150-fold more genes than our own host genomes ***(Qin et al., 2010).***

New molecular, culture-independent techniques that are based on microbial DNA sequencing have profoundly transformed our ability to study microbial communities ***(Andersson, 2008).*** These techniques have demonstrated that the mammalian gut microbiota belongs predominantly to four bacterial phyla: the Gram-negative *Bacteroidetes* and *Proteobacteria* and the Gram-positive *Actinobacteria* and *Firmicutes* ***(Ley et al., 2005).***

Any impairment of the GI microbiome, for example, by administration of oral antibiotics ***(Jeong et al., 2009)***, or by an unbalanced diet such as a carbohydrate-rich diet ***(Sonnenburg et al., 2010)*** will affect the functionality of the host's local defense systems. On the other hand, any malfunction of the epithelium, the immune cells or the enteric nervous system will affect microbiota diversity and functionality. In particular; the GI barrier and, consequently, gut health, will be directly altered, not only by local disturbances (such as increased epithelial permeability due to infection or any loss of function of particular immune cells and their mediators), but also by any systemic burden (such as reduced oxygenation in intensive care unit

patients, malnutrition in cancer patients and the elderly, or altered nerve input because of ongoing stress or depression) ***(Rhee et al., 2009)***. Thus, a normal GI microbiota of rich diversity, as well as an intact GI barrier that counteracts the bacteria and cooperates with the commensal flora, is, needed, important to maintain gut health. ***(Bischoff S, 2011)***

Skin Microbiota:

Human skin is covered with a continuous layer of microbes, which reside within epidermis, dermis, and the skin-associated glands and follicles, forming a diverse multi-cellular community known as the normal skin microbiota. The skin microbiota constitutes mainly of different bacteria but also of fungal species. The total number of microbes on the skin surface is typically within the range of 10^4–10^6 cells/cm^2 ***(Gao et al., 2007)***.

The composition of the normal microbiota of the human skin is diverse and differences between the skin microbiota of different individuals are high, although some studies suggest a relatively low interpersonal variation. Notably, the composition of skin microbiota also varies between different anatomical sites, which provide different environmental conditions (e.g., moisture, temperature, pH, presence of hairs, follicles and other microbes, sweat, nutrients, exposure to light and oxygen) for microbes to proliferate ***(Grice et al., 2008)***. Normal skin bacterial microbiota is dynamic over time ***(Gao et al., 2008)***;

while the fungal skin microbiota is thought to be more stable ***(Paulino et al., 2006).***

The composition of normal skin microbiota is not fully characterized to date. Most of the conventional knowledge on the microbes associated with the skin originates from traditional cultivation studies, in which samples taken from skin (e.g., swabs) are cultured in laboratory conditions and the colony-forming microbes are identified based on growth requirements and phenotypic characteristics. Based on cultivation studies, the healthy human microbiota has been proposed to constitute mainly of *Propionibacterium* (e.g., *P. acnes*), *Staphylococcus* (e.g., *S. epidermis* and *S. hominis*), *Corynebacterium*, *Streptococcus*, *Pseudomonas*, *Micrococcus*, *Acinetobacter*, *Brevibacterium*, and *Dermabacter hominis*, and the yeast *Malassezia* ***(Paulino et al., 2006)***. The obvious limitation of traditional cultivation studies is that the characterization of skin microbes is biased towards microbes which are readily cultivable using standard laboratory methods, while ‘‘yet-to-be cultivated’’ microbes for which the suitable laboratory growth conditions have not been established remain undetected (***Farage et al., 2010***).

The healthy skin microbiota contributes to skin homeostasis and plays a role in both health and disease ***(Farage et al., 2010).***

Probiotic microorganisms:

Probiotic microorganisms are those which confer a benefit when grow in a particular environment, often by

inhibiting the growth of other biological organisms in the same environment. Examples of probiotic organisms include bacteria and bacteriophages, which possess the ability to grow within the GIT, at least temporarily, to displace or destroy pathogenic organisms, as well as providing other benefits to the host ***(Elmer et al., 1996).***

Some probiotics are members of the normal colonic microflora and are not viewed as being overtly pathogenic. However, All cases of probiotic bacteremia or fungemia have occurred in patients with underlying immune compromise, chronic disease, or debilitation, and no reports have described sepsis related to probiotic use in otherwise healthy persons ***(Boyle et al., 2006).***

The best known probiotics are the lactic acid-producing bacteria (i.e., *Lactobacilli*) and *Bifidobacteria*, which are widely utilized in yogurts and other dairy products. These probiotic organisms are non-pathogenic and non-toxigenic, retain viability during storage, and possess the ability to survive passage through the stomach and small intestine. Since probiotics do not permanently colonize the host, they need to be ingested or applied regularly for any health-promoting properties to persist ***(Gibson et al., 1995).***

Classification and identification of individual strains

Classification is the arranging of organisms into taxonomic groups (taxa) based on similarities or relationships.

Nomenclature is the assignment of names to the taxonomic groups according to rules. Nomenclature of the bacteria must confirm to the current, scientific recognized name. Protracted use of older or misleading nomenclature is not acceptable on product label. Identification is the process of determining that a new isolate belongs to one of the established, named taxa. **FAO/WHO** Expert Consultation recommended that probiotics be named according to the International Code of Nomenclature to ensure understanding on an international basis. The Consultation strongly urged that for the sake of full disclosure, probiotic strains be deposited in an internationally recognized culture collection ***(FAO/WHO, 2001).***

It is necessary to know the genus and species of the probiotic strain. It is well-recognized that probiotic effects are strain, condition and dose specific. Strain identification is done by phenotype and genotype methods ***(Dash, 2009).***

Since probiotic properties are strain related, it is suggested that strain identification (genetic typing) be performed, with methodology such as pulse field gel electrophoresis (PFGE). It is recommended that phenotypic tests be done first, followed by genetic identification, using such methods as DNA/DNA hybridization, 16S RNA sequencing or other internationally recognized methods. For the latter, the RDP (ribosomal data base project) should be used to confirm identity ***(FAO/WHO, 2001)***.