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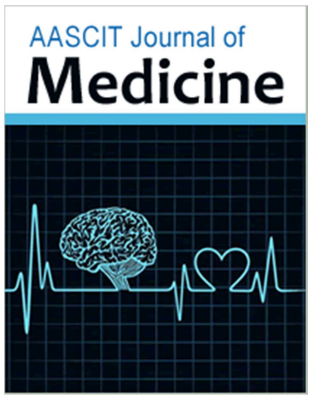

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Probiotics, Paraprobiotics, and Probiotical Cell Fragments (PCFs) as Crisis Management Tools for Important Health Problems

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Abstract
Important current diseases manifest to cover metabolic diseases, respiratory allergies, gastrointestinal (GI) diseases, genital infections, certain neurological disorders, autoimmune disorders, and musculoskeletal pain and fatigue. Patients with these diseases have been known to respond favorably to a treatment method of increasing dosages of composite selective probiotics, (probiotics and paraprobiotics) and probiotical cell fragments (PCFs) supplements. PCFs such as of lactobacilli and bifidobacteria benefit the GI system and have shown substantial local immune enhancing benefits. These treatment methods have demonstrated positive results in 85.5% of cases of chronic tonsillitis and 90% in maxilloethmoidal sinusitis. Consistent amounts of probiotics have been quantified for therapeutic microbial activities on a broad spectrum of pathogenic Candida species in otolaryngology and genital organs, respectively. The combined effects of this article enable selective probiotics and their derivatives as valuable tools for clinical employment in the prevention and adjunctive treatment of significant current diseases.

1. Introduction

Important current diseases further combined with daily discomforts (see Figure 1) momentarily appear to be part of regular patient complaints noticed globally. Up to the middle of the 20th century, incidents of infectious and chronic diseases were the most frequently encountered diseases presenting in the clinics. However, since the 1960's respiratory, metabolic, and certain non-communicable diseases have gradually come to be at the forefront [1]. In particular, cardiovascular and respiratory diseases, diabetes, cancer, and the dietary shift are now part of the process of demographic transition, which favor the spread of all other relevant diseases [1]. Since then, the number of adults with diabetes, for example, have risen to more than double [2]. Recently, the international diabetes federation (IDF) has indicated that there are more than 382 million diabetic people, and this number is expected to rocket to 592 million by 2035 [3]. In addition, diabetes is reported to have caused about 5.1 million deaths in

2013 [3]. In China, diabetes appears to be highly prevalent, especially in the general adult population which may represent a highest diabetes-related burden than any other country in the world [4]. A national survey conducted in 2008 showed that 92.4 million Chinese adults had diabetes while 148.2 million adults had pre-diabetes [4].

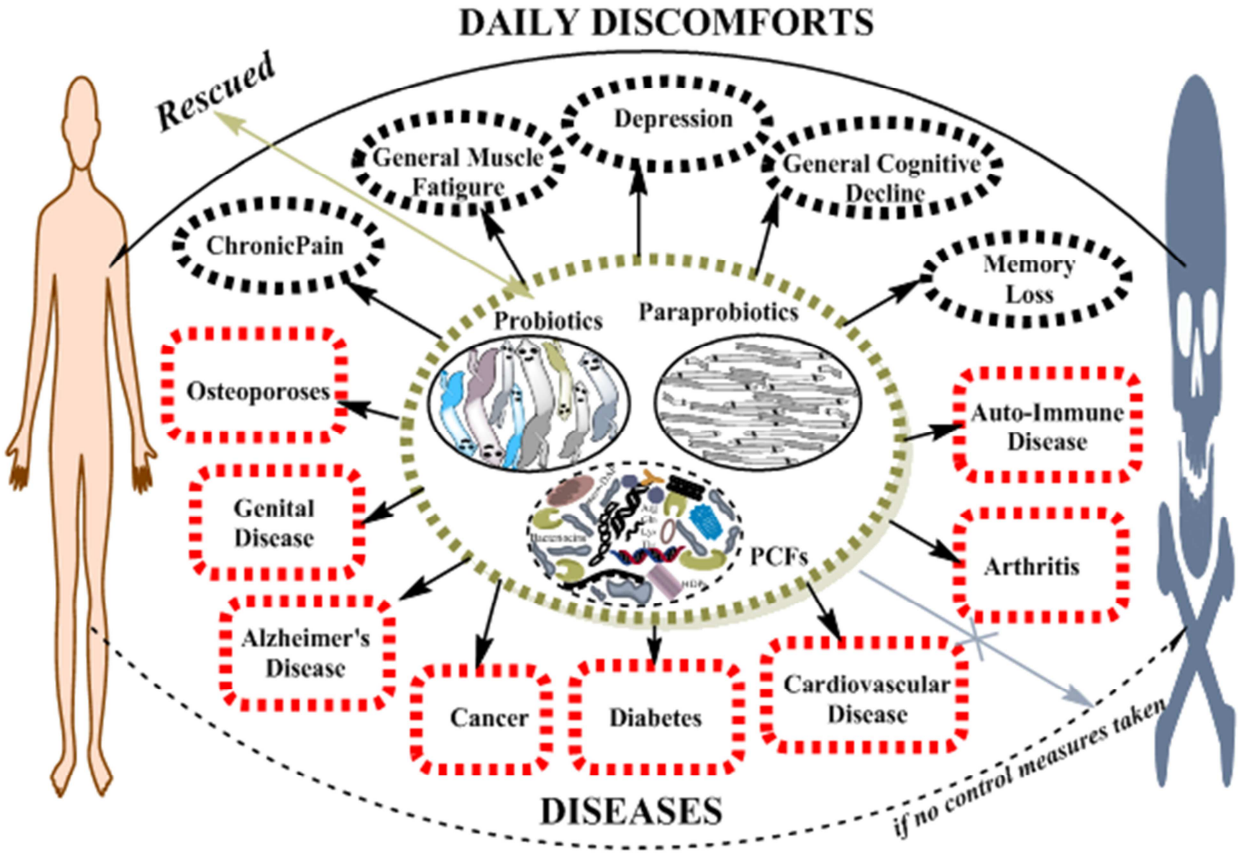

Figure 1. *Probiotics and their derivatives as ideal crisis management tools for health support and protection.*

Globally, it is also estimated that there are more than 1.1 billion people suffering from obesity, which is a contributor to many chronic diseases including cardiovascular disease. Consequently, many governmental agencies around the world have spent billions of dollars on bariatric research and excess social service healthcare expenses from complications ranging from medications to clinical and hospital visits. Cardiovascular disease is also a leading cause of death in both technologically-advanced and lesser-developed countries in the world [5]. Despite being ranked among the top 5 causes of death in developing countries, the World Health Organization (WHO) projected that by the year 2020, stroke and heart diseases will surpass infectious diseases to become the leading cause of mortality and disability worldwide [5]. Almost all of the current health problems including obesity and colonic cancer are a result of unhealthy eating, nutritional status, alcohol consumption, smoking, and a lack of regular physical activities [1]. Other reasons for the increasing incidence and prevalence of current diseases are influenced by both genetic and environmental components [6]. The combination of environmental offenses, genetic predisposition, disturbed gut microbiota, and the compromised systemic immunity culminates in the mucosal damage on the host. Genetic and environmental factors, specifically, are reported to have given rise to the inflammation that lead to the destruction of the absorptive surface of the intestine [7].

A few studies have recently revealed how poor dietary habits lead to impairment of the intestinal microbiota and contribute to current diseases. It is known that the intestinal microbiota are the bacterial flora which reside in the gut. There are about 100 trillion of these microorganisms in the healthy tract. They include complex genetic information which assists the unique requirements of the host, as well as their myriad functional purposes. Their main objectives are to metabolize bile acids and sterols, synthesize vitamins B and K, and absorb and utilize energy from the fermentation and metabolic processes of short chain fatty acids by various other organ systems. For example, when the food material is digested, the hepatobiliary system metabolizes propionates, butyrates are metabolized by the epithelial tissue of the colon, and skeletal muscle tissue metabolizes acetates. An impaired intestinal microbiota has a causal relationship with the development of many serious diseases such as diabetes [8]; colonic cancer [1]; cardiovascular diseases; brain biochemistry and behavior via immunity; neural and metabolic mechanisms [9]; implication on neurodevelopmental disorders such as autism [9, 10];

schizophrenia [9], and others closely related complications such as Alzheimer's disease. Interestingly, it is reported that patients with celiac disease have a modestly increased mortality risk, with the highest joint cause of mortality being actually cardiovascular disorders [11]. Further, it may be possible that an impaired intestinal microbiota contributes to various other neuropsychological diseases, certain cardiopulmonary disorders, and certain orthopedic disorders. In some cases, life-threatening circumstances resulting in death can occur if left untreated.

In this review, we have summarized the potential use of composite selective probiotics and PCF supplementation (Figure 1) to treat impairment of gut microbiota, and benefit the immune system in the host. Recently, a progression was made by considering the formulation of PCFs as "novel nutraceutical ingredients," of which their mechanisms of action on most of the pathogenesis are described [12, 13].

2. Compositional Changes of Commensal Gut Microbiota in Individuals with Current Health Problems

The commensal microbiota in our body are a dynamic ecosystem such that the composition of the intestinal microbiota at phylum and class levels make changes according to the physical status [14]. Most changes that happen in some of the concerned groups are due to distinct attenuated ratios of both firmicutes and clostridia species [15], a dramatic increase in the numbers of bacteroidetes, and a significant reduction in quantities of firmicutes and actinobacteria [16]. Bacteroidetes and firmicutes are known to dominate most parts of the human gut, and they also affect the human metabolism through several carbohydrate metabolism and transportation systems [17]. Collectively, the disproportionate changes caused especially by the bacteroidetes, firmicutes, actinobacteria, and clostridia sp. in the gut are believed to have an impact on the development of the important disease conditions in humans. Interestingly, composite selective probiotics and PCFs are reported to be able to balance some changes where putrefactive (clostridia and pseudomonads), pathogenic (*Salmonella* sp. and *Listeria* sp.) and toxinogenic bacteria (*Bacillus cereus*, *Staphylococcus aureus*, *Clostridium botulinum*) will be either killed or inhibited [8, 12]. Obese patients may have an imbalance of microbiota which leads to incidences of related diseases and certain cancers. In some cases, the use of composite selective probiotics and PCFs would be an ideal treatment towards reducing obesity and the prevention of certain cancers. Bariatric surgery is currently used as a method of reducing the incidence of cancers and aids in the treatment of obesity by altering gut microflora and decreasing gut firmicutes [18]. Thus far, the scientists are on the edge of being able to manipulate gut microbiota by probiotics and PCFs administration, thus possibly increasing the individual's health.

3. Probiotics-Gut-Brain Axis: A 3-Way Street for Controlling Signals of the Current Health Problems

It is well-known that the human gut hosts complex trillions of microorganisms, including more than 10^{14} bacteria belonging to 1,000 species [19]. Human intestines, for example, contain 9 divisions of bacteria and among those, 6 are not that common [20]. The 3 dominating groups are bacteroidetes, firmicutes, and proteobacteria, which comprised of almost 90% of the bacteria in the intestinal epithelium [21]. The genome size of this microbial structure, collectively termed as microbiome, exceeds the size of the human nuclear genome by 100 times and provides humans with additional biological and metabolic functions for maintaining the homeostasis in the body [22]. Consequently, they (gut microbiota) can have stimulatory effects on the brain. With respect to composite selective probiotics and PCFs engagement on either disease or pain control, they can also be linked to the fact that the human brain could influence the gut microbiota directly or indirectly. The direct connection could be by triggering the lamina propria to release signaling molecules into the GI track. The indirect link could be by changing motility, secretion, and permeability in the intestine, making the gut-brain axis a 2-way street for signals [9]. These findings lead to the conclusion that adequate intake of probiotics and/or PCFs plus the commensal microbiota would facilitate the smooth exchange of metabolites with the host, influence the host nutrients metabolism, influence the immune system, as well as control the host gene functions.

4. Strength of Probiotics and PCFs in Persons with Current Health Problems

4.1. Inflammations Combined with Metabolic Disorders and Diseases

The current understanding about low-grade chronic systemic inflammations are that they initiate cardiovascular disease developments and also contribute to the development of diabetes, insulin resistance, and obesity [23, 24]. The lipopolysaccharide (LPS) from the Gram (–) commensal microbiota (Figure 2) has been considered as a triggering factor of inflammation and maintains a low-tone continuous inflammatory state when feeding on a high-fat diet [25, 26]. The increased concentration of the LPS in the plasma leads to metabolic endotoxemia, which markedly increases the expression of genes coding for the cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1, IL-6, and plasminogen activator inhibitor-1 (PAI-1) in the adipose tissue, muscle, and liver [25]. Although antibiotic treatments (neomycin and ampicillin) have been found to reduce both metabolic endotoxemia and Gram (–) LPS dramatically in caecal content of the experimental animals [25], probiotic

treatments with lactobacilli and bifidobacteria showed a significant reduction in the pathogenic species of *Bacteroides-Prevotella* and could normalize the gut microbiota [26]. Interestingly, the main components of the cell wall fragment in Gram (–) bacteria include LPS and flagellins [27]. It is observed that both LPS and flagellins are not part of the structural fragments of the Gram (+) bacteria [12, 27].

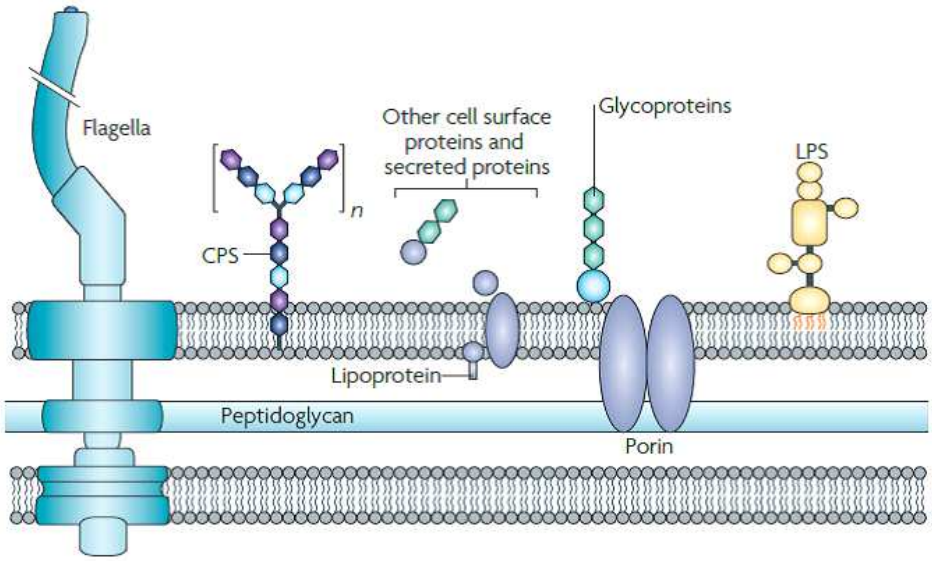

Figure 2. *The core constituents of the cell wall macromolecules in the commensal Gram (–) bacteria; LPS is lipopolysaccharides; CPS is capsular polysaccharides; n represents that the CPS molecules can be homo- or hetero-polysaccharides with an exceedingly variable sugar structure (Modified from reference [27]).*

In addition, research has shown that the inflammatory responses initiated by Gram (–) LPS in the host are recognized through the toll-like receptor (TLR)-2 and TLR-4 pathways [28, 29]. TLRs are germline-encoded pattern recognition receptors (PRRs) and heavily involved in host cell recognition of bacterial modulins, having either pathogen-associated molecular patterns (PAMPs) or microbe-associated molecular patterns (MAMPs) (see Figure 3), and subsequently leading to the initiation of innate immune responses [12, 30]. Fascinatingly, the PRRs recognize the PCFs as MAMPs [12] and perhaps know the LPS as PAMPs. Typically, the PRRs brilliantly fine tune signals that explicitly recognize the quality and quantity of the bacterial moieties related to either MAMPs or PAMPs. Following binding of the bacterial moieties to the PRRs, activation of macrophages and dendritic leads to diverse cellular responses that discriminate between MAMPs and PAMPs by interferon (IFN)-mediated TLRs gene regulation [31]. In Figure 4, the evidence is being established that the recruitment of PCFs in the gut or the upper air passage would indeed serve as MAMPs that would finally activate the appropriate PRRs of both innate and adaptive immunities [12]. It is however essential to indicate here that, the combined effects of both Gram (+) probiotics and PCFs would lower down the concentration of LPS in the plasma and altogether, this would be an effective strategy for controlling the metabolic disorders and inflammatory diseases.

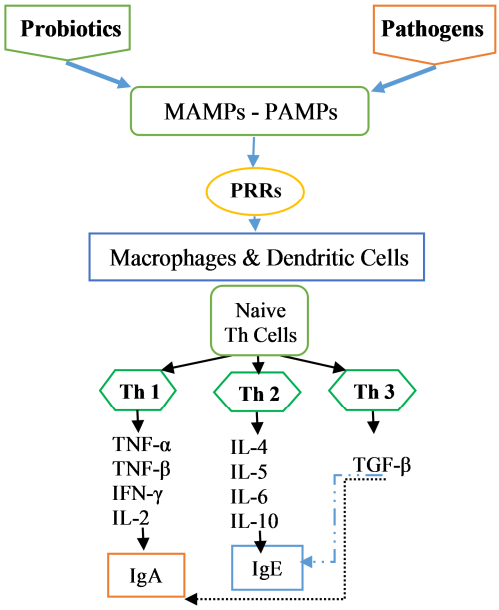

Figure 3. *Characterization of the PRRs as host receptors of both MAMPs and PAMPs. MAMP is microbe-associated molecular pattern; PAMP is pathogen-associated molecular pattern; PRR is pattern recognition receptor; Th is T helper cells; TNF is tumor necrosis factor; α denotes alpha; β means beta; γ denotes gamma; IFN is interferon; IL is interleukin; IgA is immunoglobulin A; IgE is immunoglobulin E; TGF is transforming growth factor.*

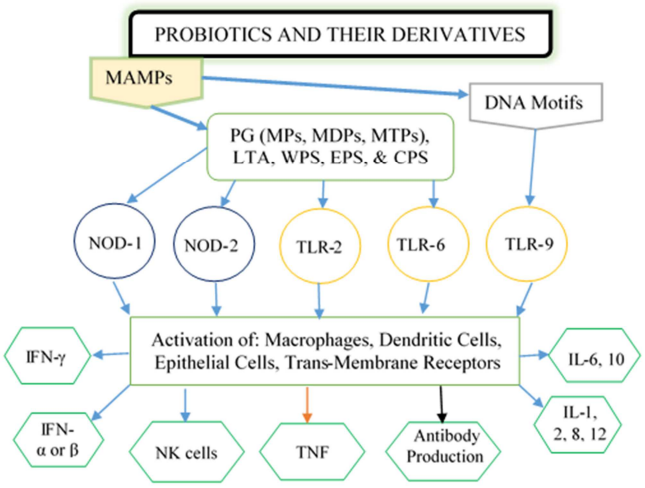

Figure 4. *Immunoactivation mechanisms of the probiotics and probiotical lysate derivatives. MAMP is microbe-associated molecular pattern; PG is peptidoglycan; MTPs are muramyl tripeptides; MDPs are muramyl dipeptides; MPs are muramyl peptides; LTA is lipoteichoic acid; CSP is cellular surface proteins; WPS is wall polysaccharides; CPS is capsular polysaccharides; EPS is exopolysaccharides; NOD is nucleotide-binding oligomerization domain containing protein; TLR is toll-like receptor; IFN is interferon; α means alpha; β denotes beta; γ denotes gamma; TNF is tumor necrosis factor; IL is interleukin; NK is natural killer cells (Modified from reference [12]).*

4.2. Probiotics and a Leaky-Gut Permeability: An Insight to Current Health Problems

Recently, it has become known that an altered bowel function of the intestinal wall contributes to the pathogenesis of current health problems, particularly diabetes [32]. Poor diet, pathogenic bacteria, sulfites in foods, inflammations, stress, alcohol, smoking, and GI infections can cause damage to the gut lining [13]. The significant progress in the treatment of increased intestinal permeability or as known as "leaky gut syndrome" has been pragmatic when probiotics or PCFs are adequately taken along with a carefully chosen diet [13]. In addition to the appropriate amount of bifidobacteria in the gut, the reduction phenomenon in the bifidobacteria has been linked to the reducing expression of several epithelial tight junctions {zonula occludens-1 (ZO-1), occludin, and glucagon-like peptide-2 (GLP-2), respectively} [33]. GLP-2 is an intestinal diet-stimulated hormone that mediates the cleavage of proglucagon in the intestinal endocrine L cells [34]. The literature confirms that GLP-2 can contribute to the improvement of the mucosal barrier functions and, therefore, can be associated with diabetes and obesity through insulin-like growth factors-1 (IGF-1) and β-catenin pathways [35, 36]. However, the mechanisms linking GLP-2 to IGF-1expression or the bifidobacteria promoting GLP-2 production are still to be determined.

4.3. Probiotics as Ideal Tools in Sinus Infections

Sinusitis refers to inflammation of the lining of the sinuses, called the mucosa, and is categorized as one of the global chronic health problems. Stuffs that can trigger or initiate inflammation of the mucosa include allergies, cold, a deviated septum, nasal polyps, reflux diseases, and certain chronic illnesses. Sinusitis inflammation can block the narrow passage in the sinuses and prevent mucus from draining properly, leading to infections. The nose being a bacterial reservoir, it may harbor potentially pathogenic bacteria such as *Streptococcus pneuromoniae, Haemophilus influenza, Staphylococcus aureus, Moraxella catarrhalis*, β-hemolytic streptococci, and many others including fungal pathogens [37]. In our previous experimental work, the use of different probiotic formulas based on *Lactobacillus rhamnosus* (*L. rhamnosus*) LB3 resulted in the statistically reliable increase in the number of tonsillar cells producing Immunoglobulin A (IgA) while *Lactobacillus delbrueckii* (*L. delbrueckii*) LE increased the activity of the natural cytotoxic tonsillar cells against xeno-erythrocytes [37]. Most of the researched probiotic formulations also induced formation of healthy immune responses by Th1 type, inhibited fatty cellular infiltration of the tonsil's tissue, reduced the risk of the inflammatory edema, and encouraged progression of B-cell lymphocytes plus high glycogen macrophages [37–42].

We also observed that probiotic formulations (*L. rhamnosus* LB3 and *L. delbrueckii* LE) stimulated IFNs up to 4.5 folds, influenced the production of the IL-4, increased the production of IgGs and IgAs up to 2.5 folds, and intensified glycogen synthesis in phagocytes [37]. In a comparison made between those 2 lactobacilli, the strain of *L. rhamnosus* LB3 has shown more efficient activation of humoral immune response; whereas, *L. delbrueckii* LE showed mostly cell-mediated immune response. In clinical conditions, a combination of *L. rhamnosus* LB3 and *L. delbrueckii* LE (see Table 1) proved positive results in 85.5% cases of the chronic tonsillitis and 90% in maxilloethmoidal sinusitis as compared to positive results in 72.8% cases in the control patient group using antibiotics and antifungal substances. Performance capability was increased to 100% cases; the physiological flora was restored; the amount of pathogenic and opportunistic flora was reduced to about 4–6times; enzymatic activity was restored to a normal level, and the immune parameters were normalized. Probiotics were well-tolerated by patients, demonstrated high clinical results, and had a positive effect on the microflora of the upper air passage [37]. Interestingly, other research revealed that oral intake of heat-lysates of *L. pentosus* b240 could not prolong the survival stage of pneumococcal infected mice, however, led to reduced bronchitis plus significant reduction in the body weight loss [43].

Table 1. *Live probiotical doses with fungicidal and fungistatic activities against Candida pathogenic strains ($p < 0.05$).*

Activity	LE	LB3	LB3+LE
Fungicidal (CFU/mL)	5.0×10^9	1.5×10^9	0.5×10^8
Fungistatic (CFU/mL)	2.5×10^9	6.25×10^8	2.5×10^7

4.4. Probiotics in Prevention and Treatment of Candidiasis, Chronic Candidomicosis, and Recurrent Chlamydial Infections in Otolaryngological and Genital Organs

Candidiasis refers to a variety of infections triggered by fungi of the genus Candida, occurring most regularly in the mouth, respiratory tract (bronchocandidiasis) or vagina. Candidiasis treatment today has become a critical problem with regards to the increase of mycoses and the spreading of Candida strains being resistance to antifungal drugs. The nasopharynx, for example, is the initial part of the upper respiratory tract, where the colonization of anaerobic and micro-aerobic microflora constantly persists. It has been demonstrated that probiotic strains of *L. rhamnosus* LB3, *L. delbreuckii* LE, and a blend of these 2 lactobacilli had a positive fungicidal impact on *Candida albicans* (*C. albicans*), *C. tropicalis*, and *C. krusei*, isolated from the patients [44]. In the same study, different supernatant levels of the latter probiotics were quantified for therapeutic fungicidal and fungistatic activities on a broad spectrum of those pathogenic Candida sp. The synergistic fungicidal properties of the metabolic products of *L. rhamnosus* LB3 and *L. delbreuckii* LE were conducted in the presence of various anti-fungal drugs including nystatin, itraconazole, fluconazole, amphotericin, and clotrimazole. As a consequence, the preponderance of the data indicated significant synergistic activities when probiotic supernatants were presented in combination with anti-fungal agents. In fact, there have been selective and varying degrees of synergistic activities illustrated [44]. The impact on the fungi microflora could be directly attributed to the effect of the metabolic products of both *L. rhamnosus* LB3 and *L. delbreuckii* LE. Therefore, joint use of specific antifungal agents with probiotic medications based on selected probiotic cultures such as those of *L. rhamnosus* LB3 and *L. delbreuckii* LE appear to be recommendable for the treatment of different types of fungal infections, notably the Candida species of otolaryngology organs.

In our earlier clinical experiment, the efficiency of the *L. delbrueckii* LE on treatment of 4 couples with chronic candidomicosis and 2 other couples with chlamydial infection with a history of unsuccessful antibacterial treatment was assessed. For all subjects, doses of *L. delbrueckii* LE (5×10^8 CFU/mL) were administered orally. For the women subjects, the same dose was additionally administered intravaginally one dose per day. The results showed that all patients had no complaints and no clinical manifestations of the infections or dysbiosis after that therapy. Even after 6 months later, the patients had no symptoms or grievances of chronic candidomicosis or recurrent chlamydial infections. Those results further demonstrated that probiotics can be excellent and efficient therapeutical prescription for current health problems.

In numerous studies, aggressive probiotic treatments in combination with antibiotics provided long lasting cure in patients with bacterial vaginosis (BV) [45–47], Gardnerella vaginalis [46], and Atopobium vaginae [48]. BV has been perceived as a risk factor for acquisition of sexually transmitted infections covering human immunodeficiency virus (HIV), post-abortion endometritis, and adverse pregnancy outcomes such as late miscarriage and preterm birth [48].

4.5. Influence and Immunobiological Properties of Probiotics and their Lysates on the Microbial Diseases Affecting Lungs

The data presented in Figure 4 confirm high levels of stimulation of macrophage activity, which is an integral indicator of the activation of immunologic reactivity of the body. Apart from this, immunomodulatory properties of probiotic cultures may also be amplified by a number of factors, including growth stimulators, interferon generation, TNF production, and more. When probiotics had been orally administered to mice, a number of IgA cells were observed to have increased not only in the intestinal mucosa, but also in the lungs [49, 50] and mammary glands [49]. Additionally, as the TLRs activate the macrophages and dendritic cells, they were also reported to have caused a downregulation of the $\alpha_v\beta_6$ integrin which tethers TGF-β to the epithelial surface of the lung [51] (see also Figure 3 for comparison).

Probiotics and their derivatives are known to induce the production of the IFNs, TNFs, ILs, and NK cells (Figure 4). In addition to epithelial cells, NK cells have been found to be widely distributed throughout the body and in both lymphoid and non-lymphoid tissues. They are critical effector cells of innate immunity for protecting against various infections caused by viruses [51]. NK cells constitute 10% of resident lymphocytes in the lung, and their survival may be supported by bronchial epithelial cells which instinctively produce IL-15 [51]. It is reported that within hours of inflammatory stimulation or days of infection, a large numbers of NK cells are recruited to the lungs from the blood and become activated to secrete cytokines, particularly IFN-γ [52]. In addition, NK cells can directly lyse virus-infected lung cells and release IFN-γ, which can limit viral growth, activate macrophages to become more efficient phagocytes, and trigger dendritic cells maturation [53]. At the proper dosages, other researchers demonstrated also that orally administered probiotics increased the rates of *Streptococcus pneumoniae* clearance in the lungs, prevented pneumococcal dissemination into the blood, improved survival of infected mice, and reduced lung injuries [51, 54]. Consequently, the ability of the probiotics or probiotic derivatives to increase resistance against pneumococcal diseases could be established.

4.6. Advantages of Probiotic Cell Fragments Technology (CFT™)

The benefits of probiotic CFT™ include the isolation and purification of the structural fragments from the renowned live probiotic cells. It has been found that probiotic lysates

contain MPs, MDPs, MTPs, muramyl polypeptides (MPPs), LTA, DNA motifs, WPS, EPS, CPS, and CSP (see Figure 4). These PCFs have shown high immune balancing activities, anti-tumor, anti-inflammation, anti-mutagenic, detoxification strengths, and physicochemical- or radio-protective strength [12, 55]. Orally administration of a distinctive product with PCFs (known as Del-Immune V®) leaded to immune responses that manifested a high level of the TNFs within 8 h and the IFNs production levels were also raised 2.5–3times [12, 56]. Del-Immune V® also showed the ability to induce the production of NK cells and to regulate the production of neutrophils, IL-4, IL-10, and IL-12 [56]. Overall, the distinguished advantages of PCFs include immune system modulation, the anti-colon cancer strength, anti-allergy, anti-encephalopathy, hepatic, anti-bacterial, and anti-viral properties [13, 56]. Remarkably, PCFs can work directly via immune cell's receptors as shown in Figure 4. The products of probiotic CFT™ have demonstrated a marketed potential for clinical application when used alone or as an adjunctive therapy. A purified fraction of peptidoglycan as *N*-acetylglucosaminyl-β (1-4) *N*-acetylmuramyl pentapeptide was found to accelerate normalization of humoral immunity, to increase the activities of NK cells and phagocytosis, to raise production of TNFs, IL-1, and IL-2 by peripheral blood mononuclear cells [56], to significantly increase the activities of T-lymphocytes, to normalize the content of IgA and IgG, to induce cytosuppression, to prevent side effects after antibiotics or cyclophosphamide administration, and to increase resistance to bacterial and viral infections [12, 56]. Paraprobiotics and PCFs may, therefore, qualify to be used in creams, liquids, gels, gummies, and powders for functional foods, supplements, drugs, cosmetics, pets and more [12].

5. Concluding Remarks

Composite selective probiotics, PCFs, and the commensal gut microbiota play a significant role in GI health and pathology as the various mechanisms in inflammation and metabolic disorders. They are all involved in managing the current health problems including respiratory allergies, gut disorders, and others. Sufficient evidence supports that the engagement of probiotics and PCFs may be used as a new therapy approach depending on the particular health problem, dosages of probiotic strains and the host response. Although the complexity of the microbial community in different individuals varies considerably, the current health concerns are also influenced by inheritance, difference in diet selection, body constitution, aging, and environmental factors. As probiotics, paraprobiotics, and PCFs are all MAMPs suppliers and work as biological response modifiers (responsible for body health and homeostasis), they play a significant role in the reduction of daily discomforts found in immune disorders such as in low-grade inflammations; neuropsychiatric disorders such as in Alzheimer's disease, chronic depression, mild memory loss and general cognitive decline; orthopedic disorders such as in general muscle fatigue syndromes and chronic pain; respiratory disorders such as in bronchitis, sinusitis; metabolic disorders such as in diabetes; certain cardiovascular disorders; gut diseases such as in celiac disease, and colonic cancer; and genital infections such as bacterial vaginosis. Hence, probiotics and their derivatives would be an excellent alternative treatment tools, either on their own or as supplementation to antibiotic treatment for current health problems.

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References

[1] K. Sivieri, R. Bedani, D. C. U. Cavallini, and E. A. Rossi, "Probiotics and Intestinal Microbiota: Implications in Colon Cancer Prevention," In: *Lactic Acid Bacteria—R & D for Food, Health and Livestock Purposes*, M. Kongo, editor, InTech, Croatia, pp. 217–262, 2013.

[2] G. Danaei, M. M. Finucane, Y. Lu, G. M. Singh, M. J. Cowan, C. J. Paciorek, J. K. Lin, F. Farzadfar, Y. H. Khang, G. A. Stevens, M. Rao, M. K. Ali, L. M. Riley, C. A. Robinson, and M. Ezzati,"National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants," *The Lancet*, vol. 378, no. 9785, pp. 31–40, 2011.

[3] M. Hirst, "Diabetes in 2013. The new figures," *Diabetes Research and Clinical Practice*, vol. 102, no. 3, pp. 265, 2013.

[4] W. Yang, J. Lu, J. Weng, W. Jia, L. Ji, J. Xiao, Z. Shan, J. Liu, H. Tian, Q. Ji, D. Zhu, J. Ge, L. Lin, L. Chen, X. Guo, Z. Zhao, Q. Li, Z. Zhou, G. Shan, and J. He, "Prevalence of diabetes among men and women in China", *The New England Journal of Medicine*, vol. 362, no. 12, pp. 1090–1101, 2010.

[5] A. Pihlanto, "Lactic Fermentation and Bioactive Peptides" In: *Lactic Acid Bacteria—R & D for Food, Health and Livestock Purposes*, M. Kongo, editor, InTech, Croatia, pp. 309–332, 2013.

[6] U. Risérus, W. C. Willett, and F. B. Hu, "Dietary fats and prevention of type 2 diabetes," *Progress in Lipid Research*, vol. 48, no. 1, pp. 44–51, 2009.

[7] A. Rubio-Tapia and J. A. Murray, "Gluten-Sensitive Enteropathy," In: *Food allergy: adverse reactions to foods and food additives*, D. D. Metcalfe, H. A. Sampson, R. A. Simon, and G. Lack, editors, Wiley-Blackwell Publishing Ltd., Oxford, UK, pp. 217–229, 2013.

[8] R. Burcelin, M. Serino, C. Chabo, V. Blasco-Baque, and J. Amar, "Gut microbiota and diabetes: from pathogenesis to therapeutic perspective," *Acta Diabetologica*, vol. 48, no. 4, pp. 257–273, 2011.

[9] Ö. C. O. Umu, M. Oostindjer, P. B. Pope, B. Svihus, B. Egelandsdal, I. F. Nes, and D. B. Diep, "Potential applications of gut microbiota to control human physiology". *Antonie van Leeuwenhoek*, vol. 104, no. 5, pp. 609–618, 2013.

[10] R. D. West, E. Roberts, L. S. Sichel, and J Sichel, "Improvements in gastrointestinal symptoms among children with autism spectrum disorder receiving the Delpro® probiotic and immunomodulator formulation," *Journal of Probiotics and Health*, vol. 1, no. 1, e1000102, 2013.

[11] J. F. Ludvigsson, S. M. Montgomery, A. Ekbom, L. Brandt, and F. Granath, "Small intestinal histopathology and mortality risk in celiac disease," *The Journal of the American Medical Association*, vol. 302, no. 11, pp. 1171–1178, 2009.

[12] N. Shigwedha, L. Sichel, L. Jia, and L. Zhang, "Probiotical Cell Fragments (PCFs) as "novel nutraceutical ingredients"," *Journal of Biosciences and Medicines*, vol. 2, no. 3, pp. 43–55, 2014.

[13] N. Shigwedha, L. Zhang, L. Sichel, L. Jia, P. Gong, W. Liu, S. Wang, S. Zhang, X. Han, and W. Gao, "More than a few LAB alleviate common allergies: Impact of paraprobiotics in comparison to probiotical live cells," *Journal of Biosciences and Medicines*, vol. 2, no. 3, pp. 56–64, 2014.

[14] R. E. Ley, M. Hamady, C. Lozupone, P. Turnbaugh, R. R. Ramey, J. S. Bircher, M. L. Schlegel, T. A. Tucker, M. D. Schrenzel, R. Knight, and J. I. Gordon, "Evolution of mammals and their gut microbes," *Science*, vol. 320, no. 5883, pp. 1647–1651, 2008.

[15] N. Larsen, F. K. Vogensen, F. W. J. Van den Berg, D. S. Nielsen, A. S. Andreasen, B. K. Pedersen, W. A. Al-Soud, S. J. Sørensen, L. H. Hansen, and M. Jakobsen, "Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults," *PloS One*, vol. 5, no. 2, e9085, 2010.

[16] M. Murri, I. Leiva, J. M. Gomez-Zumaquero, F. J. Tinahones, F. Cardona, F. Soriguer, and M. I. Queipo-Ortuño, "Gut microbiota in children with type 1 diabetes differs from that in healthy children: a case-control study,"*BioMed Central Medicine*, vol. 11, no. 1, pp. e46,2013.

[17] P. J. Turnbaugh, M. Hamady, T. Yatsunenko, B. L. Cantarel, A. Duncan, R. E. Ley, M. L. Sogin, W. J. Jones, B. A. Roe, J. P. Affourtit, M. Egholm, B. Henrissat, A. C. Heath, R. Knight, and J. I. Gordon, "A core gut microbiome in obese and lean twins," *Nature*, vol. 457, no. 7228, pp. 480–484, 2009.

[18] N. A. Berger, "Obesity and cancer pathogenesis," *Annals of the New York Academy of Sciences*, vol. 1311, pp. 57–76, 2014.

[19] A. S. Neish, "Microbes in gastrointestinal health and disease," *Gastroenterology*, vol. 136, no. 1, pp. 65–80, 2009.

[20] R. E. Ley, D. A. Peterson, and J. I. Gordon, "Ecological and evolutionary forces shaping microbial diversity in the human intestine," *Cell*, vol. 124, no. 4, pp. 837–848, 2006.

[21] F. Bäckhed, R. E. Ley, J. L. Sonnenburg, D. A. Peterson, and J. I. Gordon, "Host-bacterial mutualism in the human intestine," *Science*, vol. 307, no. 1 5717, pp. 1915–1920, 2005.

[22] G. Musso, R. Gambino, and M. Cassader, "Obesity, diabetes, and gut microbiota: the hygiene hypothesis expanded?," *Diabetes Care*, vol. 33, no. 10, pp. 2277–2284, 2010.

[23] K. E. Wellen and G. S. Hotamisligil, "Inflammation, stress, and diabetes," *The Journal of Clinical Investigation*, vol. 115, no. 5, pp. 1111–1119, 2005.

[24] S. Ding, M. M. Chi, B. P. Scull, R. Rigby, N. M. J. Schwerbrock, S. Magness, C. Jobin, and P. K. Lund, "High-fat diet: bacteria interactions promote intestinal inflammation which precedes and correlates with obesity and insulin resistance in mouse," *PloS One*, vol. 5, no. 8, e12191, 2010.

[25] P. D. Cani, J. Amar, M. A. Iglesias, M. Poggi, C. Knauf, D. Bastelica, A. M. Neyrinck, F. Fava, K. M. Tuohy, C. Chabo, A. Waget, E. Delmée, B. Cousin, T. Sulpice, B. Chamontin, J. Ferrières, J. F. Tanti, G. R. Gibson, L. Casteilla, N. M. Delzenne, M. C. Alessi, and R. Burcelin, "Metabolic endotoxemia initiates obesity and insulin resistance,"*Diabetes*, vol. 56, no. 7, pp. 1761–1772, 2007.

[26] P. D. Cani, R. Bibiloni, C. Knauf, A. Waget, A. M. Neyrinck, N. M. Delzenne, and R. Burcelin, "Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice," *Diabetes*, vol. 57, no. 6, pp. 1470–1481, 2008.

[27] S. Lebeer, J. Vanderleyden, and C. J. de Keersmaecker, "Host Interactions of probiotic bacterial surface molecules: Comparison with commensals and pathogens," *Nature Reviews Microbiology*, vol. 8, pp. 171–184, 2010.

[28] H. Liang, S. E. Hussey, A. Sanchez-Avila, P. Tantiwong, and N. Musi, "Effect of lipopolysaccharide on inflammation and insulin action in human muscle," *PloS One*, vol. 8, no. 5, e63983, 2013.

[29] A. M. Caricilli, P. K. Picardi, L. L. de Abreu, M. Ueno, P. O. Prada, E. R. Ropelle, S. M. Hirabara, A. Castoldi, P. Vieira, N. O. S. Camara, R. Curi, J. B. Carvalheira, and M. J. A. Saad,"Gut microbiota is a key modulator of insulin resistance in TLR 2 knockout mice" *PLoS Biology*, vol. 9, no. 12, e1001212, 2011.

[30] T. Kawai, and S. Akira, "Toll-like receptors and their crosstalk with other innate receptors in infection and immunity," *Immunity*, vol. 34, no. 5, pp. 637–650, 2011.

[31] M. Miettinen, V. Veckman, S. Latvala, T. Sareneva, S Matikainen, and I. Julkunen, "Live *Lactobacillus rhamnosus* and *Streptococcus pyogenes* differentially regulate toll-like receptor (TLR) gene expression in human primary macrophages," *Journal of Leukocyte Biology*, vol. 84, no. 4, pp. 1092–1100, 2008.

[32] S. de Kort, D. Keszthelyi, and A. A.Masclee, "Leaky gut and diabetes mellitus: what is the link?," *Obesity Reviews*, vol. 12, no. 6, pp. 449–458, 2011.

[33] P. D. Cani, S. Possemiers, T. van de Wiele, Y. Guiot, A. Everard, O. Rottier, L. Geurts, D. Naslain, A. Neyrinck, D. M. Lambert, G. G. Muccioli, and N. M. Delzenne, "Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability," *Gut*, vol. 58, no. 8, pp. 1091–1103, 2009.

[34] P. E. Dube and P. L. Brubaker, "Nutrient, neural and endocrine control of glucagon-like peptide secretion,"*Hormone and Metabolic Research*, vol. 36, no. 11/12, pp. 755–760, 2004.

[35] P. E. Dube, K. J. Rowland, and P. L. Brubaker, "Glucagon-like peptide-2 activates beta-catenin signaling in the mouse intestinal crypt: role of insulin-like growth factor-I," *Endocrinology*, vol. 149, no. 1, pp. 291–301, 2008.

[36] P. E. Dube, C. L. Forse, J. Bahrami, and P. L. Brubaker, "The essential role of insulin-like growth factor-1 in the intestinal tropic effects of glucagon-like peptide-2 in mice," *Gastroenterology*, vol. 131, no. 2, pp. 589–605, 2006.

[37] L. Sichel, D. Zabolotna, and D. Zabolotny, "Perspectives of probiotic therapy in sinus infection", Available at http://www.lyoferm.com/research, Accessed March 21, 2015.

[38] S. Alvarez, J. Villena, M. Tohno, S. Salva, and H. Kitazawa, "Modulation of innate immunity by lactic acid bacteria: impact on host response to infections," *Current Resources in Immunology,* vol. 3, pp. 87–126, 2009.

[39] S. Racedo, J. Villena, M. Medina, G. Agüero, V. Rodríguez, and S. Alvarez, "*Lactobacillus casei* administration reduces lung injuries in a *Streptococcus pneumoniae* infection in mice," *Microbes and Infections*,vol.8, no. 9-10, pp. 2359–2366, 2006.

[40] S. Racedo, J. Villena, S. Salva, and S. Alvarez. "Influence of yogurt consumption on the respiratory immune response,"*Food and Agricultural Immunology*, vol. 20, no.3, pp. 231–244, 2009.

[41] J. Villena, M. Medina, E. Vintiñi, and S. Alvarez, "Stimulation of respiratory immunity by oral administration of *Lactococcus lactis*,"*Canadian Journal of Microbiology*, vol. 54, no. 8, pp. 630–638, 2008.

[42] S. Salva, J. Villena, and S. Alvarez, "Differential immunomodulatory activity of *Lactobacillus rhamnosus* strains isolated from goat milk: impact on intestinal and respiratory infections,"*International Journal of Food Microbiology*, vol. 141, no. 1-2, pp. 82–89, 2010.

[43] A. Tanaka, M. Seki, S. Yamahira, H. Noguchi, K. Kosai, M. Toba, Y. Morinaga, T. Miyazaki, K. Izumikawa, H. Kakeya, Y. Yamamoto, K. Yanagihara, T. Tashiro, N. Kohda, and S. Kohno, "*Lactobacillus pentosus* strain b240 suppresses pneumonia induced by *Streptococcus pneumoniae* in mice," *Letters in Applied Microbiology*, vol. 53, no. 1, pp. 35–43, 2011.

[44] O. G. Volska, L. M. Shynkarenko, I. S. Zarytska, and D. D. Zabolotna, "Study of the possibility of using lactobacilli in prevention and treatment of candidosis in otolaryngological organs," *Odessa Medical Journal*, vol. 4, no. 96, pp. 32–36, 2006. (Ukrainian)

[45] P. G. Larsson, E. Brandsborg, U. Forsum, S. Pendharkar, K. K. Andersen, S. Nasic, L. Hammarström, and H. Marcotte, "Extended antimicrobial treatment of bacterial vaginosis combined with human lactobacilli to find the best treatment and minimize the risk of relapses," *BioMed Central Infectious Diseases*, vol. 11, no. 1, pp. 223, 2011.

[46] W. Ya, C. Reifer, and L. E. Miller, "Efficacy of vaginal probiotic capsules for recurrent bacterial vaginosis: a double-blind, randomized, placebo-controlled study," *American Journal of Obstetrics and Gynecology*, vol. 203, no. 2, pp. 120-e1, 2010.

[47] A. Homayouni, P. Bastani, S. Ziyadi, S. Mohammad-Alizadeh-Charandabi, M. Ghalibaf, A. M. Mortazavian, and E. V. Mehrabany, "Effects of probiotics on the recurrence of bacterial vaginosis: A review," *Journal of Lower Genital Tract Disease*, vol. 18, no. 1, pp. 79–86, 2014.

[48] P. Hay, "Bacterial vaginosis," *Medicine*, vol. 42, no. 7, pp. 359–363, 2014.

[49] C. M. Galdeano, A. C. Dogi, and G. Perdigón, "Difference in the signals induced by commensal or probiotic bacteria to the gut epithelial and immune cells," In: *Probiotics: Immunobiotics and Immunogenics*, H. Kitazawa, J. Villena, and S. Alvarez, editors, *CRC Press*, Boca Raton, pp. 36–53, 2013.

[50] H. N. Youn, D. H. Lee, Y. N. Lee, J. K. Park, S. S. Yuk, S. Y. Yang, H. J. Lee, S. H. Woo, H. M. Kim, J. B. Lee, S. Y. Park, I. S. Choi, and C. S. Song, "Intranasal administration of live *Lactobacillus* species facilitates protection against influenza virus infection in mice," *Antiviral Research*, vol. 93, no. 1, pp. 138–143, 2012.

[51] J. Villena, S. Salva, N. Barbieri, and S. Alvarez, "Immunobiotics for the prevention of bacterial and viral respiratory infections," In: *Probiotics: Immunobiotics and Immunogenics*, H. Kitazawa, J. Villena, and S. Alvarez, editors, *CRC Press*, Boca Raton, pp. 128–168, 2013.

[52] F. J. Culley, "Natural killer cells in infection and inflammation of the lung," *Immunology*, vol. 128, no. 2, pp. 151–163, 2009.

[53] T. Strowig, F. Brilot, and C. Münz, "Noncytotoxic functions of NK cells: direct pathogen restriction and assistance to adaptive immunity," *The Journal of Immunology*, vol. 180, no. 12, pp. 7785–7791, 2008.

[54] M. H. Zelaya, and M. G. Agüero, "Immunobiotics and Inflammation-Coagulation," In: *Probiotics: Immunobiotics and Immunogenics*, H. Kitazawa, J. Villena, and S. Alvarez, editors, *CRC Press*, Boca Raton, pp. 248–279, 2013.

[55] J. L. Strominger, "Bacterial cell walls, innate immunity and immunoadjuvants,"*Nature Immunology*, vol. 8, pp. 1269–1271, 2007.

[56] Del-Immune V®. http://www.delimmune.com/research, Accessed March 24, 2015.