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Drug Interactions, Safety and Efficacy of Probiotics

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Authors' contributions

This work was carried out in collaboration between all authors. Author KM designed the contents of the study and interpreted the data. Author SK revised the content of the manuscript while author KB produced the initial draft. All authors read and approved the final manuscript.

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ABSTRACT

The term "probiotic" etymologically appears to be composed of the Latin preposition *pro,* meaning "for" or "in support", and the Greek adjective "biotic" from the noun *bios* meaning "life", together these two words gave the meaning 'for life' or 'in support of life'. Commercially available probiotics are formulations of live microbial cells such as *Bacillus clausii, Lactobacillus* and *Bifidobacterium* that contribute to intestinal microbial balance. Prebiotics are selectively fermented ingredients that allow specific changes, both in the composition and/ or activity in the gastrointestinal microbiota that confers benefits upon host well-being and health. The term synbiotic is used when a product contains both probiotics and prebiotics. Probiotics are most commonly used for gastro-intestinal problems, such as inflammatory diseases and diarrhea, and for yeast and urinary tract infections. Probiotics are generally considered as safe, but there are reports of their unwanted outcomes and side effects, which could be associated with unregulated use, interactions with other drugs, and efficacy and storage conditions of these microbial formulations. Thus, this paper emphasizes on the issues related to such unwanted sequels due to administration of probiotics, so as to understand and cautiously use, and develop appropriate administrative regimes for this important dietary supplement.

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1. INTRODUCTION

Bacteria that can cause positive influence on digestion and immune system, and other beneficial outcomes to human health are collectively called as probiotics [1]. Probiotics are defined by the World Health Organization (WHO) as ‘‘live microorganisms, which when administered in adequate amounts, confer health benefits upon the host’’ [2]. The most commonly used probiotics are *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces boulardii*. *Lactobacillus* and *Bifidobacterium* are Gram-positive bacteria, whereas *S boulardii* is a yeast. [3]. The use of probiotics has been reported since olden times, as observed in some products used by the Pharaonic civilization [4]. The mechanisms of action of probiotics are not clear. However, it is proposed that they brought about beneficial outcomes due to their immunomodulating effects, as well as their ability to modify the activity of other bacteria, thereby affecting the ‘‘ecosystem’’ of the gut [5,6]. The first commercialized probiotic product containing *Lactobacillus casei* was developed by Minoru Shirota in 1930, and was named as Yakult [7]. Another well known probiotic containing *Lactobacillus rhamnosus* strain *Lactobacillus rhamnosus* GG (LGG) was launched in Finland in 1990 under the brand Gefilus®, which has since developed various *Lactobacillus rhamnosus* GG products including buttermilks, yoghurts, milk, fruit drinks, "daily dose" drinks and fermented whey-based drinks [8]. At present, the most common genera in probiotics are lactic acid bacteria (LAB) such as *Lactobacillus* and *Bifidobacterium*, as they are considered as Generally Recognized as Safe GRAS [9–11]. However, bacterial species belonging to the genera *Lactococcus*, *Enterococcus* and *Propionibacterium*, yeasts (e.g. *Saccharomyces cerevisiae* and *Saccharomyces boulardii*) and filamentous fungi (e.g. *Aspergillus oryzae*) are also used in probiotics due to their health-promoting effects [12-14]. A survey reported that the global nutraceutical market has been estimated at 749.6 billion USD [15], and the demand of probiotic food alone in global market was estimated at 27.9 billion USD in 2011 and is expected to increase at a 6.8% compound annual growth rate (CAGR) in 2016 [16]. With growing reports on health benefits of probiotics and the resulting widespread use of these products, it is important to understand the side effects and safety issues. Some probiotics have been used for thousands of years without being associated to undesirable effects. However, the health effects of probiotics are strain-dependent and should not be generalized without prior confirmation. Studies concerning safety of these products are still very limited and there are no established guidelines for evaluation. Probiotics contain live organisms, and although very rare associated with undesirable effects, they may cause infections and other complications if their use is not properly regulated.

2. DRUG INTERACTIONS

The use of probiotics has considerably increased and their potential domain of application has extended into bowel inflammatory diseases or infectious diseases, protection against diarrhea, *Helicobacter pylori* infection, lactose intolerance, hypercholesterolemia, systemic diseases. The clinical utility of probiotics may even further extend to fields such as allergic disease and cancer [17-20]. Due to its wide applications, it is therefore important to understand the interaction of probiotic with other drugs. Studies have recommended that administration of antibiotics and bacteria-derived probiotics be at least separated by two hours [21,22]. *Saccharomyces boulardii* present in probiotics might interact with antifungals, reducing the efficacy of this probiotic [23]. According to the manufacturer of Florastor, a probiotic which contains *S. boulardii*, it is instructed not be taken with any antibiotics and antifungals like clotrimazole (Mycelex Troche), ketoconazole (Nizoral), griseofulvin (Gris-PEG), and nystatin (Mycostatin). Probiotics should also be used cautiously in patients taking immunosuppressants, such as cyclosporine, tacrolimus, azathioprine, and chemotherapeutic agents, since probiotics could cause an infection or pathogenic colonization in immuno-compromised patients [21-23]. Histamine has been reported to cause histamine intoxication, while tyramine has been reported to affect hypertensive problems in individuals who are administered with monoamine oxidase inhibitors [24-26]. Considering these outcomes, it is important to note that only amine-negative isolates are selected as probiotics, dietary adjuncts, and starter cultures [27].

3. SAFETY ISSUES

Safety of probiotics has not been thoroughly studied scientifically in many of the probiotic formulations. Some studies reported mild side

effects such as gas or bloating [28-30], but new researches indicated that many probiotics are ineffective and some may even cause harm. *Lactobacillus rhamnosus* have been suggested to be the cause of infections such as liver abscess, bacteremia and endocarditis [31-35]. These reports are highly suggestive of probiotic supplements related sepsis, but it should be noted that LGG and other strains of *L. rhamnosus* can sometimes be found in the intestinal microbiota of healthy humans, so the source of infection in these cases cannot be conclusively proven. For instance, an initial report of an adult with endocarditis was thought to be due to *L. rhamnosus* based on bacterial species identification with the use of API 50CH, but molecular typing with the use of randomly amplified polymorphic DNA (RAPD) showed it to be due to a different unknown strain [36]. The role of *Bacillus subtilis* has also been suggested in causing bacteremia [37-39]. Similarly, *Saccharomyces boulardii* have also been suggested as the cause of fungemia, septic shock, fungemic shock, septicemia and fatal fungemia in various studies [40-51]. Reports on *Bifidobacterium* sepsis related to use of probiotic is not yet available [52], which could be due to more common use of other genera such as Lactobacilli in currently available probiotic formulations. All cases of probiotic bacteremia or fungemia have been reported from patients with immune compromised conditions, chronic disease, or debilitation, and no such complications and illness have been reported in otherwise healthy persons [53]. In some other cases the outcomes of probiotic use have been fatal, but these fatalities were usually related to underlying diseases [38,42,51], such as preexisting intestinal pathology, including diarrhea and short intestine. Premature infants, debilitated or immune-compromised individuals are reported to be most susceptible to such outcomes. The increased susceptibility of premature infants and immune-compromised individuals to probiotic sepsis is further supported by animal studies [52]. Based on various studies Boyle et al proposed risk factors for probiotic sepsis, namely major risk factors and minor risk factors. Included in the major risk factors are immuno-compromised individuals including a debilitated state or malignancy, and premature infants, whereas included in minor risk factors are those individuals who are under central venous catheter (CVC), impaired intestinal epithelial barrier (e.g, diarrheal illness, intestinal inflammation), administration of probiotic by jejunostomy, concomitant administration of broad spectrum antibiotics to which probiotic is resistant, probiotics with properties of high mucosal adhesion or known pathogenicity, and cardiac valvular disease. It was suggest that the presence of a single major risk factor or more than one minor risk factors in individuals merits caution in using probiotics [29]. Thus, it can be suggested that, although probiotics are beneficial to healthy persons, individuals with already underlying health problems, premature infants and immune-compromised person should take caution in using probiotics containing *Saccharomyces boulardii, Lactobacillus rhamnosus* and *Bacillus subtilis.* Probiotics have also been shown to adhere strongly to intestinal epithelium in both *In vitro* and *In vivo* studies [53]. Adherence to the intestinal mucosa may also increase bacterial translocation and virulence. The relation between mucosal adhesion and pathogenicity in *Lactobacillus spp*. is supported by the finding that blood culture isolates of *Lactobacillus spp*. can adhere to intestinal mucus in greater numbers as compared to isolates obtain from human feces or dairy products [54]. Another risk in use of multi-drug resistant probiotics, is the high probability of transfer of antibiotic resistance genes to pathogenic bacteria. Lactic acid bacteria, like all other bacteria, exchange antibiotic resistance genes to enhance their own resistance [55]. Systemic infections, deleterious metabolic activity, excessive immune stimulation and risk of gene transfer are four examples of adverse side-effects [56]. The production of antimicrobial compounds is also considered as an important probiotic feature that help in providing protection against pathogens. However, extremely potent antimicrobial activity of probiotics could be detrimental as it could lead to disrupting of normal intestinal biota [57]. Therefore, evaluating the capacity of probiotics that produce strong antimicrobial activities is an important part of characterizing its safety for human use [58]. The production of H_2O_2 is taken as a predictor of long term colonization by probiotics [59], and is considered to impart potent antimicrobial activities [60]. Thus, probiotic strains to be explored for functional food development should not be among high H_2O_2 producers. Another study reported that biogenic amine formation is strain dependent and not related to the species [61]. Therefore, careful screening for amino acid decarboxylase activity is recommended while selecting LABs as appropriate starter or probiotic strains in food and dairy products. A thorough study on 6 genera viz. *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus,*

Enterococcus, and Bacillus concluded that "the current literature is not well equipped to answer questions on the safety of probiotics in intervention studies with confidence" [62]. Another concern on the use of Probiotics include their effects on the production of D-lactate and deconjugation of bile salts [63]. Therefore, to prevent such undesirable consequences, probiotic strains should be assessed for safety by conducting studies on their intrinsic properties and pharmacokinetics and interactions with the host [56,64], along with properly regulated used in immuno-compromised individuals and individuals with other underlying health problems.

4. EFFICACY

Probiotics/ synbiotic supplements are a group of functional foods with growing market shares and increasing commercial interest due to various health benefits. Presently, various kinds of probiotic formulations have been developed which includes fermented milk, chewing gum, sachets and capsules [65-68]. Most probiotic formulations are developed for oral administration, as site of action for these probiotics is at gastrointestinal (GI) tract. Oral delivery has been considered as best way to deliver live cells to humans for therapy. Colon, which is a part of the gastrointestinal (GI) tract, is the oral targeted site [69,70]. Probiotics exert their beneficial effects after colonization in the gut environment. Hence, it is the primary requirement that probiotics should reach (GI) tract in viable condition. For effective results the level of viable probiotics needed to obtain a clinical effect is often quoted as ≥ 10^6 cfu/ml in the small bowel and ≥ 10^8 cfu/ml in the colon [71]. Therefore, orally administered probiotics should able to efficiently implant in the intestine, and adhere to the intestinal mucosa where they should proliferate and provide beneficial health effects. The physiological stress of probiotics begins in the stomach, where the pH may reach 1.5 [72]. In addition, bile secreted in the small intestine reduces the survival of bacteria by changing the composition of lipids and fatty acids in their cell membranes [73]. Acid and bile tolerance are therefore considered key criteria in the selection of probiotics [72]. Del Piano et al. studied seven *Lactobacillus plantarum* probiotic strains for their ability to survive in simulated gastric juice and human gastric juice. It was found that less than 20% of the bacteria survived after an hour of exposure to simulated gastric juice, while human gastric juice allowed a survival rate between 15% and 45% [74]. Viability of probiotics is strain dependant, and is influenced by pH and exposure time, but on average 10 to 25% of the ingested cells are able to survive and reach the gut, thus exerting their probiotic benefits [75].

Probiotic products contain live delicate organisms that require appropriate handling to maintain maximum activity during storage. The potency of probiotics can be adversely affected by prolonged exposure to high temperature and humidity. Thus, refrigeration is recommended during storage of probiotics. Although probiotic strains vary in their sensitivity to heat, most studies showed that bacterial organisms lose viability over time at room temperatures. This can create significant product quality issues, especially in retail settings where probiotic products are often sold unrefrigerated. An industry study undertaken in the 1990s found that up to half of probiotic products purchased from retail stores contained significantly fewer live organisms than what is claimed on the label. For example, *L. acidophilus* showed a rapid decline in viability at pH 2.0 (the stomach's pH is typically even lower, 1.5). Additionally, *Bifidobacterium adolescentis* and *B. breve* could survive poorly at all pH levels (1.5, 2.0, 2.5 and 3.0) tested [76]. It is agreed that there is no perfect probiotic. However, probiotics should be comprised of microbial organisms with most desirable properties and least undesirable properties. Liquid preparations like yogurt have some major disadvantages such as i) short shelf-life, ii) bacteria damaged by pasteurization and/or centrifugation, iii) use of additives and preservatives, iv) difficult transport and storage because of its bulky nature, v) use of normally only one or more strains of bacteria (multiple strains probiotics are more potent.), vi) damage by stomach acidity, vii) refrigeration requirement. The disadvantages of freeze dried powder probiotics are i) bacteria damage by freeze drying, ii) short powder shelf life, iii) upon absorption of water by powder, bacteria become activated and die, iv) poor adherence, colonization and survival in the gut due to damage caused by freeze drying, v) probiotics may become weakened due to addition of stabilizers and preservatives [77]. Another area of concern is that probiotics are commonly commercialized as food or dietary supplements and, therefore, there is no requirement to demonstrate the purity of these products [29]. However, reports related to mislabeled number of live organisms and identification of strains indicate a need for recognized regulations

concerning labeling issues, claims, and efficacy of these products [78,79]. Therefore, production of probiotics that can withstand harsh conditions in the stomach, intestine, storage temperatures and manufacturing processes, along with stringent microbial strain verification is the approach currently receiving considerable interest [80].

5. CONCLUSIONS

Although many studies have shown the health benefits of probiotics such as improving the immunity and GI tract environment, prevention or suppression of colon cancer, and cholesterol reduction etc., the therapeutic potential of probiotics in humans requires deeper elucidation and understanding. It is important to mention that technical challenges aren't the only barrier to the development of the probiotic, as consumer understanding presents an equally immense obstacle, wherein in most cases, probiotics are sold as health supplements. The physiological effects of probiotics in the gastrointestinal, nervous, and immune systems, with an aim to advance probiotics research and its contributions to public health enquire regulation to prevent development of fatal and undesirable outcomes. Thus, careful assessments of the risks versus benefits must be made before probiotic products are given out to markets. With respect to probiotic bacteria as source of development of multidrug resistant in other pathogenic bacteria, careful scientific assessments and evaluations should be taken up in order to reduce and minimize chances of gene transfer. Probiotics function by residing in the GI tract and interact with the commensal flora present in it. Therefore, during these interactions, the presence of transferable antibiotic resistant genes in probiotic strain could even lead to cause serious transfer of resistance genes to the pathogenic microbes present in the GI tract. Thus, it is very important to assess the transferability of antibiotic resistance genes from probiotic strains. The presence of such genes can be analyzed by following standard PCR protocols such as RTqPCR and genome sequencing approaches. Also, to prevent any other unwanted complications due to unregulated use of probiotics, it is advisable to remove them from the category of food supplements, and rather be included in prescription drugs.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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