Chapter 7

Beneficial Microbes: Roles in the Era of Antimicrobial Resistance

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Abstract

The upsurge of resistance in classes of antibiotics in varied bacterial species has increased the search for alternatives to antibiotics in bacterial infections. However, one alternative is the beneficial bacteria in foods, environment and gut. Probiotics is now being embraced as an alternative strategy to combat antibiotic resistant pathogens. A newer application is gut microbiota in its healthy state combating pathogenic and antibiotic resistant microbes. There have been numerous applications of beneficial bacteria against different infectious agents. This article describes the concept of beneficial microbes as antimicrobial agents with current applications as antimicrobial agents, various applications in the human gut with future directions.

Keywords: probiotics, lactic acid bacteria, alternative therapy, pathogens, applications

1. Introduction

Microorganisms exist from where we can imagine to places we least expect e.g. outer space and the dead sea. Much of the global atmospheric oxygen is as a result of microbial activity [1]. They also maintain the gut health by regulating the microflora, stimulating the development of the immune system, production and enhancement of some important nutrients [2] and there seem to be a natural interdependence of life on microorganisms.

At the time of antibiotic discovery, Fleming looked into the future and foresaw that antimicrobial resistance would be a challenge, and he gave a subtle warning about the potential impact of sub-optimal dosage in fostering antimicrobial resistance during his Nobel laureate

acceptance speech. Unfortunately, about 10 years after Penicillin was discovered, Fleming's fears were confirmed when penicillin-resistant pathogens emerged. Since then (and for more than half of a century later), the discovery of a novel antibiotic has always been accompanied by the eventual emergence of antibiotic-resistant strains due to regular and inappropriate usage of antibiotics by humans [3]. Antimicrobial drug resistance is a global threat to public health and human activities contribute significantly to the selection of resistant strains through non prudent use of these antimicrobial agents giving rise to the development of a generation of antimicrobial resistant mutants circulating in the biosphere [3]. Unfortunately, resistance has eventually been seen to nearly all antibiotics that have been developed [4].

2. Probiotics

"Probiotics are live microorganisms which when administered in adequate amount confer a health benefit on the host" [5]. The concept of probiotics evolved from the work of Elie Metchnikoff in the early twentieth century when he observed that certain beneficial microbes particularly lactic acid bacteria in milk consumed by peasant Bulgarians were responsible for their longevity. Lactic acid bacteria and Bifidobacteria are the most commonly used organisms as probiotics, although some other bacteria such as *Escherichia coli* Nissle 1917 [6] and yeast such as *Saccharomyces boulardii* are also used [7]. *Lactobacillus* spp. being an integral part of the intestinal microflora having earned the "Generally Regarded as Safe" status are the most successful probiotic candidates. Lactic acid producing bacteria are known to possess various health benefits such as anti-cancer activity, lowering of serum cholesterol, lactose intolerance alleviation, prevention of antibiotic related diarrhea, stimulation of the immune functions, antimicrobial activity against resistant pathogens [8, 9] prevention and treatment of Inflammatory bowel disease [10], respiratory viral infection [11]. Recently, *Lactobacillus* spp. have also been reported to have beneficial effects in patients suffering psychological disorders, such as depression and anxiety [12–14]. Probiotics have been proposed to exert health benefits through several mechanisms [15], these include enhancement of the epithelial barrier, increased adhesion to intestinal mucosa, and concomitant inhibition of pathogen adhesion, competitive exclusion of pathogenic microorganisms, production of antimicrobial substances and modulation of the immune system. For example, *E. coli* Nissle 1917 has been used as an alternative treatment option of Ulcerative colitis—a chronic intestinal disease [16]. Generally, LAB and probiotics augment the antagonistic activity of the gut commensals against infectious agents, including the opportunistic pathogen *Clostridium difficile* that is implicated in antibiotic-associated diarrhea [17]. Other probiotics have been confirmed to prevent intestinal infections (such as stomach infections caused by *Helicobacter pylori*) and extra-intestinal infections (such as infections of the respiratory tract). This way, the spread of antibiotic resistance diminishes drastically, and the gut microbiota structure and overall health of the host is restored. This bodes well for the future of the human race. The probiotic properties are strain specific and cannot be extrapolated to other strains of the same species, also the organisms are to be administered live hence, they must be safe and produce the desired beneficial effect [18]. There are critical guidelines on the minimum requirement for the selection of probiotic strains as recommended by Food and Agricultural Organization of the World Health Organization [5] and can be summarized as;

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2.1. Identification of genus, species and strain

Since the probiotic property is a strain specific attribute, it will be important to link specific health benefit to a particular strain and also for epidemiological surveillance purposes, the proposed microorganism must be identified to the strain level, the strains should be correctly identified using both phenotypic and genotypic methods and deposited in an internationally recognized culture collection [19], molecular methods such as DNA/DNA hybridization and 16S rRNA gene sequencing are suggested for strain identification.

2.2. Assessment of safety

Selected strain must be non-pathogenic, non-haemolytic and non-toxic in the intended host. They must be safe and qualify for the qualified presumption of safety (QPS) as stipulated by European Food Safety Authority. The antibiotic resistance susceptibility pattern including the MIC to antibiotics of medical importance should be determined, the intended strain should not possess antimicrobial resistance determinants [18]. Probiotic strains should also be assessed for metabolic activities such as production of D-lactate and bile salt deconjugation. Assessment of toxin production should be done for microbial strains that belong to species that are known to produce mammalian toxins. The demonstration of lack of infectivity of the probiotic strain in animals with deficient immune functions will further substantiate the safety profile of such strain. A post market epidemiological surveillance of adverse effects in the host is also an important safety requirement.

2.3. Functional considerations

2.3.1. Resistance to bile salt and gastric conditions

Probiotic strains intended for oral administration must be able to survive passage through the gastrointestinal tract of the host, where they will encounter an hostile condition characterized with low pH and bile salt and must survive in adequate amount to confer health benefit on the host. Lactic acid bacteria isolated from the guts tends to better survive this route than those isolated from other sources [9].

2.3.2. Ability to adhere and colonize the epithelial cells and tissues

The ability of the probiotic strain to adhere to intestinal mucosa and epithelial cells is an important characteristic for its colonization and survival in the host. Successful colonization of the intestinal mucosa by probiotics is important for immune modulation and inhibition of pathogens by competitive exclusion. Microorganisms that have poor adherence to epithelial cells will easily be washed away and unlikely to colonize the host for a probiotic effect [9].

2.3.3. In vivo validation of health benefits

Probiotics must be able to exert health benefits through their activities in the host, in vitro tests to predict the health benefits to host may not be sufficient. *In vivo* experiments should be carried out to validate *in vitro* health benefit potentials.

2.4. Overview of approved probiotic strains currently used

Health agencies in different countries have specific microorganisms approved as probiotics. For example, Health Canada approves the use of *Lactobacillus johnsonii* La1, Lj1, or NCC 533 strains (to treat *Helicobacter pylori* infections), *Lactobacillus rhamnosus* GG (for prevention/management of antibiotic-associated diarrhea), and *Saccharomyces boulardii/S. cerevisiae* (for prevention/management of antibiotic-associated diarrhea) in doses of $\geq 10^7$ colony forming units (CFU) daily [20]. Other probiotics strains has also been approved by Health Canada [20]. US FDA also have a comprehensive list of approved probiotic metabolites for use as food ingredients or additives after they have been certified as GRAS e.g. *Streptomyces natalensis* and *Streptomyces chattanoogensis* in Natamycin [21]. A probiotic strain is usually identified with internationally approved methods; by the genus, species, subspecies (where applicable), and the specific strain designated with an alphanumeric identity e.g. *Lactobacillus casei* DN-114. Probiotic strain designation is vital, since health benefit(s) to the host must be linked to the particular strain or a combination of strains and these benefits are strain specific. The WHO/FAO guideline stipulates that probiotic strains should be registered in an internationally recognized culture collection [5].

Lactobacillus and Bifidobacteria species are the most commonly used probiotic microorganisms, however, some strains of *Escherichia coli*, Bacillus species and the yeast *Saccharomyces boulardii* are also used. Recently, *Clostridium butyricum* was also approved for probiotic use in European Union [22].

2.5. Challenges encountered in formulation and use of probiotics

Due to the well-known benefits of probiotics, food companies incorporate probiotics into foods (termed functional foods) for greater marketability [23]. However, there is always a tendency for these probiotic strains to be lost or greatly reduced in number and viability during food processing and/or storage such that the purported health benefit is eventually lost. Thus, probiotic instability is one challenge faced by food formulators and manufacturers that intend to incorporate probiotic strains into their product. The shelf life is mostly unpredictable, so much that excess of up to 200% viable cells are added in probiotic products to make-up for cells that die before it reaches the consumer, this makes backing up label claims difficult and also increases the production cost. Manufacturers also have to prove that the probiotics will still remain stable and viable within the human body in adequate amounts until they reach the gut where their impact is the greatest [23].

2.6. Antimicrobial activities against pathogens

The ability of the proposed probiotic strain to produce antimicrobial substances against pathogens is an important consideration in the selection of probiotic strains. Lactic acid bacteria produce antimicrobial metabolic compounds during lactic fermentation such as hydrogen peroxides, organic acids such as lactic, acetic and propionic acid. Bacteriocins and other proteinaceous inhibitory substances are also produced by some probiotic organisms [24].

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2.6.1. Organic acids

The end product of fermentation of lactic acid bacteria include organic acids such as lactic acid, acetic acid, propionic acid, butyric acid etc. which reduces the pH of their growth medium and thus makes it unfavorable for the growth of other competing microorganisms. The organic acids exert their antimicrobial activity by interfering with the integrity of the cell membrane, inhibition of various metabolic functions and active transport, lowering of intracellular pH [25].

2.6.2. Hydrogen peroxide

Lactic acid bacteria do not utilize the cytochrome system as a result of lack of the heme group and thus cannot reduce oxygen to water leading to the production of hydrogen peroxide from the action of flavoprotein oxidases or NAD peroxides. The hydrogen peroxide is produced in amount capable of bacterial antagonism particularly against species which lack catalase peroxidase. Free radicals such as hydroxyl radical and superoxides which can damage bacteria DNA may also have hydrogen peroxide as precursor for their production. Lactic acid bacteria had been reported to produce hydrogen peroxide as part of its inhibitory mechanisms [9].

2.6.3. Bacteriocin

Some lactic acid bacteria produce small, heat-stable, ribosomally synthesized inhibitory bioactive peptides produced during their primary phase of growth called bacteriocin. Many bacteriocins exhibit a narrow spectrum of antimicrobial activity, particularly against bacteria strains of species related to the bacteriocin producing species while some display activity across a variety of different bacteria genera. Bacteriocins exhibit a wide diversity as regards their structure, size, mechanism of action, inhibitory spectrum and target cell receptors [26]. Most of the bacteriocins produced by LAB appears to have a narrow spectrum of antimicrobial activity, however nisin and pediocin are known to exhibit a broad antibacterial spectrum [23]. Bacteriocins are easily degraded by proteolytic enzymes particularly by those produced by the guts of mammals which make them safe for human use [27]. Generally, bacteriocins can be sub-divided into three classes according to their structure and mode of antibacterial action. Class I bacteriocins include nisin, which is active against Gram positive bacteria including food spoilage and pathogenic microbes. Nisin has a pentacyclic structure composed of 34 amino acids with one lanthionine residue (Ring A) and four beta-methyllanthionine residues (rings B, C, D, E), heat stable at 121°C but becomes less heat stable on prolong heating, especially between pH 5 and 7 [27]. Bacteriocin has proven to be an efficient natural antimicrobial agent against pathogens and food spoilage bacteria, including *Listeria monocytogenes, Staphylococcus aureus, Bacillus cereus* and *Clostridium botulinum* [28].

Enterocin X, plantaricin A and lactococcin G are class 2b bacteriocins commonly produced by *Enterococcus faecium* and lysostaphin, enterolysin A, helveticin J are common class 3 bacteriocins produced by *Lactobacillus helveticus,* they are heat stable with a large molecular weight of more than 30 kDa [29]. Nisin is the only bacteriocin that has been officially approved for

use in the food industry [30], class II bacteriocins are relatively small, heat-stable and contain peptides while Class III bacteriocins are heat stable and also have a relatively large molecular weight [27]. The classes of bacteriocins produced by Gram-positive beneficial bacteria include lantibiotics and non-lantibiotic heat stable proteins [31] while Gram-negative bacteria produce colicin and microcin [32].

2.6.4. Prebiotics

Prebiotics are non-digestible food products that increase the relative abundance of beneficial microorganisms in the gut when ingested. Similar to the influence of complex plant polysaccharides on the gut microbiota composition and beneficial metabolite production, prebiotics enhance the production of short chain fatty acids such as butyrate—a metabolite that serves as an energy source for colonic epithelium. Examples of prebiotics used include inulin, fructooligosaccharides, and galactooligosaccharides, Some of these prebiotics are found naturally in foods (such as barley, wheat), and in garlic and raw onions. These prebiotics have been applied in malnourished Thai children and children from certain countries in Africa [33], South America and Europe in order to improve the adsorption of calcium as well as improvement of growth [34].

3. Synbiotics

Synbiotics is a term used for the combined use of probiotics and prebiotics to achieve a more efficient impact on the gut microbiota [34]. This concept surfaced in order to tackle possible difficulty of the probiotics to establish itself in the gut. In this case, prebiotics and probiotics are co-administered in order to improve the growth/relative abundance and establishment of probiotics in the gastrointestinal tract of its host. The probiotic strains used in conjunction with prebiotics include Lactobacilli and Bifidobacilli, while the prebiotics used along with probiotic strains include inulin, galactooligosaccharide, and fructooligosaccharide. The combination of probiotics and prebiotics in therapy helps to give stability to the gut microbiota, which translates to overall health of the host's gut and the host in general. This combination also helps to enhance antimicrobial activity, and the combined effect includes; competition with the pathogen for adherence sites, production of metabolites that are toxic to the pathogens, production of compounds that degrade toxins produced by the pathogens, obstruction of attachment sites and toxin receptors, and modulation of the immune system to respond effectively to pathogen invasion [35].

4. Antimicrobial potentials of beneficial microbes against antibiotic resistant strains

The antimicrobial activities of beneficial microorganisms particularly lactic acid bacteria isolated from various sources against pathogens have been reported by many authors [7, 36].

Afolayan et al. [37] isolated lactic acid bacteria from different variety of "*Ogi*" a fermented cereal in western part of Nigeria with antimicrobial activities against various gastrointestinal pathogens. *Shigella* spp. are enteric pathogens which cause dysentery and diarrhea and are a leading cause of gastroenteritis- associated deaths in about 3–5 million under 5 years old children in developing countries [38, 39]. Lactic acid bacteria strongly inhibited gastrointestinal *E. coli* in co culture [40]. Cell free supernatant of *Lactobacillus casei* isolated from traditional yoghurt and milk was reported to strongly inhibit multi-drug resistant *Shigella sonnei* and *S. flexneri* [39], and also starter cultures in Nigerian yoghurt and the yoghurt itself has been reported to have strong inhibitory effects on gastrointestinal pathogens [41]. Salmonellosis contributes significantly to global morbidity and mortality. There are about 93.4 million cases of salmonellosis worldwide resulting in 155,000 death annually [42], *Lactobacillus* spp. with antimicrobial activity against *Salmonella typhi* were isolated by Abdel-Daim et al. [43] and *in vivo* anti-salmonella activities of lactobacilli has also been reported by Casey et al. [44] in pigs. Antimicrobial activities of lactic acid bacteria has also been reported against *Pseudomonas aeruginosa, Providencia vermicola, Alcaligenes faecalis* and MRSA in co culture [45].

The increasing emergence of antibiotic resistant uropathogens, yeast infection and recurrent infection has necessitated special interest in the antibacterial activity of lactic acid bacteria against uropathogens [46]. There are increasing scientific evidences that LAB can prevent the growth and attachment of pathogens to epithelial cells [47]. It was reported by Adeniyi et al. [48] that lactic acid bacteria isolated from various Nigerian based fermented foods exhibited varying antimicrobial activity against organisms implicated in urinary tract infections. *Weissella* spp. isolated from African fermented food and cow intestine demonstrated significant inhibitory activity against multi drug resistant uropathogens [7]. Lactic acid bacteria isolated from a menstruating Nigerian woman was shown to have antimicrobial activity against an array of uropathogens; *Escherichia coli, Proteus mirabilis* 42P, *Pseudomonas aeruginosa*, *Citrobacter freundii* and *Enterobacter cloacae* [49]. The organic acid produced by lactic acid bacteria has been proven to be inhibitory to *Neisseria gonorrhoeae* [50]. The antibacterial activity of lactic acid bacteria isolated from selected Nigerian vegetables against *Pseudomonas aeruginosa, Escherichia coli, Proteus penneri,* and *Enterococcus faecalis* was published by Bamidele et al. [51]. *Lactobacillus* spp. have been reported to inhibit the growth of *Candida albicans* and prevent the relapse of yeast infection [52]. The metabolite of *Lactobacillus plantarum* strain N4 was discovered to possess antiviral activities against coronavirus causing gastroenteritis [53], certain lactic acid bacteria have been suggested to be effective in reducing the severity and duration of acute rotavirus gastroenteritis [54].

5. Beneficial microbes in the gut; effects on antibiotic resistant strains

In the gut lies a community of beneficial microorganisms that have carved a niche and have evolved with humans over several generations—collectively known as the gut microbiota. Microorganisms that make up the gut microbiota include members of bacteria, fungi, viruses, archaea, and protists. Before the advent of next-generation sequencing technologies, very

little was known about the composition and functions of this microbial community, and as such were not thought as agents to be considered in health and disease. Now, we are just beginning to scratch the surface of the potentials of this novel 'organ', and its implication in the overall health of humans. It is referred to as an 'organ' because the gut microbiome (the gut microbiota, gut microbial genomes, and the living environment) is made of millions of bacterial cells that collectively weigh about 1.5 kg, possesses about 150 times more genes than human genes, and contribute significantly to human health. As a result of advances in research, scientists are beginning to appreciate the beneficial roles of gut microbes, and their symbiotic relationship with us, their host. Although previously thought to be responsible for the production of essential vitamins B and K alone, the gut microbiota has been discovered to be implicated in various aspect of human health, and its effects extend beyond the gastrointestinal tract through the release of biosynthesized metabolites (by the gut microbes) from the gut into the systemic circulation. For example, the response of immune cells to inflammation is modulated by the gut microbiota [55]. The effect of these metabolites extends even to the central nervous system where they influence behavior, mood, and emotions.

In the gastrointestinal tract, the gut microbiota protects the gut against invading pathogens by competing with them for nutrients and attachment site. Most of the antibiotic-resistant disease-causing infectious agents that invade the gastrointestinal tract are food-borne or water-borne, and they include *Salmonella*, *Shigella*, *Campylobacter*, and *Listeria monocytogenes*. On the other hand, the gut microbiota is dominated by members of the Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria. Other less dominant bacterial phyla include the Fusobacteria, Tenericutes, Spirochaetes (differentially abundant in the gut of hunter-gatherers and rural individuals who consume plant-based foods), Elusimicrobia, and Verrucomicrobia. *Prevotella*—a member of the phylum Bacteroidetes—has also been found to be more abundant in individuals whose lifestyle resembles those of the Paleolithic (such as the hunter-gatherers) and Neolithic (such as the subsistence agriculturalists) era. Conversely, *Bacteroides*—another member of Bacteroidetes—is more abundant in populations that practice a westernized lifestyle, characterized by high-fat, low-fiber diet. Many of the gut commensals such as *Eubacterium*, *Ruminococcus*, *Roseburia*, and *Faecalibacterium* are members of the Firmicutes that produce short-chain fatty acids (such as butyrate, acetate, and propionate) as a product of microbial fermentation (the breakdown of complex polysaccharides), and these acids diminish diarrhea and gastrointestinal inflammation. These short chain fatty acids (SCFA) also create a harsh environment for the colonization of invading gastrointestinal pathogens by the reduction of intestinal pH. Other pathogen-inhibiting metabolites produced by gut commensals include phenols, ammonia, bacteriocins, and ammonia [56].

The composition of the gut microbiota can be positively or negatively affected by dietary habits and other lifestyle factors, the use of antibiotics, age, the state of health, and surgery amongst other factors [57]. The regular consumption of a fiber-rich, plant-based diet improves the compositional profile of the gut microbiota in terms of richness and diversity, and also improves the functional capabilities of the members of the gut microbiota. Good lifestyle practices such as the consumption of fiber-rich foods and fruits increases the relative abundance of beneficial gut microbes which produce metabolites that are responsible for overall gut epithelial health [58]. The impact of diet on the stability of the gut microbiota cannot be overemphasized. This is

because an imbalance in the structure of the gut microbiota is a risky phenomenon in the development of gastrointestinal and extra-gastrointestinal diseases. Antibiotics do not differentiate between beneficial bacteria and pathogenic bacteria, and as such, there is a significant decrease in the richness and diversity of the gut microbiota after antibiotic administration. This places a fatal dent on gut microbiota stability and creates an environment for opportunistic pathogens such as antibiotic-associated *Clostridium difficile* to thrive resulting in diarrhea. Dysbiosis (impairment in the natural balance) of the gut microbiota has been associated not only with the risk of antibiotic-associated diarrhea, but a plethora of other diseases such as type 2 diabetes, cancer, obesity, inflammatory bowel diseases and irritable bowel syndrome [59]. Adulthood is generally characterized by a stable gut microbiota, with occasional shifts in gut microbial diversity due to change in dietary habits, medication, illness or travel. On the other hand, the gut microbiota of infants is quite volatile and changes rapidly depending on the mode of birth, whether they are breast-fed or formula-fed, and whether they have been weaned or not. By the age of 2–5 years, their gut microbiota begins to resemble that of a typical adult. At the tail end of life, age-related changes in physiology of the body and changes in dietary habits due to loss of dentition could have a negative impact on the gut microbiota thereby making it less stable [60]. At this age also, the use of medication is high because they are more prone to diseases and impairments, which could influence gut microbial profiles. All of these factors mentioned above have to be considered when designing strategies aimed at restoring or contributing to the natural balance of the gut microbiota.

6. Current applications

The beneficial role played by bacteria in ingested fermented foods was linked to increased longevity in Balkans [61]. The administration of probiotics has also reduced the shedding of a pathogenic serotype of *E. coli* (*E. coli* O157: H7) by farm animals, thereby reducing the spread of these resistant strains from animals to humans who handle them regularly [62]. Also, there is hope that probiotics wills soon replace antibiotics in the veterinary field to treat diseases of farm animals while enhancing the growth of these farm animals. This way, antibiotic-resistant zoonotic pathogens do not re-emerge and enter the food chain. Also, the cost of production and maintenance of livestock will drop significantly if probiotics are being utilized rather than antibiotics.

Researchers and clinicians are getting conscious of the fact that probiotics isolated from the host have a higher tendency to remain endogenous when administered than probiotics gotten from other sources. This fact informs their decision on the choice of probiotics to be administered. Capsules of probiotics are sometimes used in concert with antibiotics to treat particular diseases with greater effect than if either of them (probiotics or antibiotics) was used alone [17]. This co-administration is done with the hope that this action will reduce antibiotic selective pressure, and decrease the emergence of drug-resistant pathogens. Currently, research is ongoing on the packaging of lyophilized lactic acid bacteria into capsules so that they can be used in the veterinary field (as probiotics) to inhibit the proliferation of zoonotic pathogens [36]. This method will limit the spread of diseases from animals to humans through

animal-derived products. Probiotics have been introduced into milk, formula, and other infant foods as a supplement, in order to improve the human gut microbiota stability and tap into the purported benefits of probiotics. The viability of probiotics is enhanced in its lyophilized state within low-fat milk or fruit juice by food formulators and manufacturers [22]. The improvement of the viability of probiotic strains can also be achieved by microcapsulation—a formulation approach that employs the use of microcapsules to package solids, liquids, or gases where these contents could be released in a controlled manner under specific conditions [22]. With this technique, the formulation, storage, and successful transport of probiotic strains to their destination in the gut is assured. Although probiotics are generally regarded as safe, there is a conscious effort to confirm that they do not carry and transfer genes conferring antimicrobial resistance, as this will defeat the purpose of probiotics usage [63]. By and large, the ultimate aim of the use of probiotics is to ensure the stability of the human and animal gut microbiota so as to take advantage of the symbiotic activity of the probiotic and the gut microbial community in the fight against multi-drug resistant gastrointestinal pathogens [8].

Probiotics are most commonly sold as foods or food supplements, powders, lozenges, tablets (could be chewable, enterocoated or not), sticks, capsules, bottle caps, sachets, stick packs, and oil suspensions (usually for babies) probiotic nasal spray and ointments have also been developed. Most probiotic products available in the market are dairy based foods, including fermented milks, yogurts, cheese etc. The health claims on most probiotics labels tend to be general and such products are intended for the general healthy population. However, manufacturers, food companies, and the media have dispersed unproven information about the purported health benefits of probiotics even before a comprehensive clinical trial has been conducted to validate the efficacy, and the risk–benefit association In terms of probiotics acceptability, although probiotics have been used in the food industries for decades, the discovery of novel strains and genetic manipulation of known strains (some of which are pathogenic) is usually accompanied with a mirror image of the consumer skepticism associated with the marketing of genetically modified foods.

Another current application of beneficial gut microbes is the method of fecal microbiota transplantation (FMT). Fecal microbiota transplantation is a technique that involves the reconstitution of the deliberately-emptied gut of gastrointestinal-diseased patients with the gut microbiota of healthy donor as a therapeutic alternative measure to antibiotic administration for the restoration of the healthy gut microbiota [64]. This method has enabled the majority of those who have been suffering from antibiotic-associated diarrhea and inflammatory bowel diseases to lead a normal life after treatment. Although the filtered donor stool suspension can be passed into the gut of the recipient through rectal enema, nasoduodenal tube, or the nasogastric tube, colonoscopy is the most preferred method of stool suspension transfer. These donor stools could also be lyophilized and packaged into capsules, to be used in treating gastrointestinal infections. Stool banks are currently available in Europe and North America for the storage of tested, pathogen-free donor stools until they are needed by the medical practitioners [65]. Knowledge about the microbial composition of each donor stool and other components of the stool will also inform the medical practitioner and the patient on what to expect after transplantation. Due to the fact that the mental receptiveness of the fecal microbiota transplantation by the patient could have an effect on the effectiveness of this

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procedure, and the fact that there is a risk of undetected pathogens/diseases transfer from the donor to the recipient, some scientists advocate for an alternative to FMT. They believe that isolation and identification of the key players in the restoration of gut microbiota balance will help in the design of a consortium of these microbial players. An artificial stool could be prepared using this donor-sourced purified consortium of gut bacteria which would then replace the use of the donor stools in a less risky, more efficient and more mentally-acceptable manner [66]. This burgeoning field is known as Microbial Ecosystem Therapeutics.

7. Future directions

As previously mentioned, MET is one proposed alternative to FMT. Apart from the fact that this procedure is less disgusting and less risky than FMT, it has the potential to be regulated and standardized more efficiently than FMT [67]. MET procedure involves the isolation, characterization, and screening of gut microbes (for antibiotic resistance, presence of virulence determinants, etc.) from a healthy donor. Gut microbes that pass the screening test will then be recombined into a microbial ecosystem where their combined efforts and synergistic relationships will be more effective in tackling invasive enteropathogens and opportunistic pathogens such as *Clostridium difficile* [68]. In the future, this consortium of synergistic gut microorganisms will be packaged and lyophilized in their live form into capsules and prescribed as a drug. MET is still in its infancy, and it also has to go through regulatory procedures just like a drug, and standardized before it is globally accepted for use in treating gastrointestinal diseases such as antibiotic-induced diarrhea as a therapeutic alternative measure to antibiotic administration. Nevertheless, it offers a promising and a more effective alternative to the use of FMT. Furthermore, since the exact composition of the consortium is defined, it will be easy to track the long-term effect of this potential drug on human health. Also, questions about the interaction between the consortium and the resident gut microbiota and their combined effect on the health of the human host will be answered in detail when this emerging procedure is studied in detail (which can be aided by adequate funding and government support) [67]. In the future, these studies will also open our eyes to the benefits MET has over FMT, and whether there are risks associated with the MET procedure. This information will give the medical community a holistic idea about the merits and demerits of the MET procedure, and will allow the medical practitioners (and patients) to make an informed decision on whether to use MET or stick to FMT or antibiotic administration (or a combination of either two of the three options, or combination of the three options). It will also be interesting to find out whether the MET procedure will be effective in the treatment of extra-intestinal diseases in the nearest future [67].

For the advancement of personalized medicine, another prospect is the use of antimicrobial peptides and/or nucleic acid-based methods to selectively kill pathogenic microorganisms in the gut without compromising the structure or function of the gut microbiota (a prominent demerit of antibiotics usage) [69]. Probiotic strains and the gut microbiota have also been thought of as reliable sources of new antimicrobial peptides and antimicrobials, such as bacteriocins [70]. This is because of the complex interaction between the microbial community and

its host, especially in the production of metabolites that are active against a narrow spectrum and a broad spectrum of invasive pathogens. Nanotechnological and genetic engineering approaches could widen the precision and spectrum of activity of bacteriocins in future, making them the next generation of antimicrobials [71]. If these products can be utilized, they can effectively guard against antimicrobial resistance (in addition to the maintenance of gut microbial homeostasis) and can serve as therapeutic alternatives in the treatment of inflammatory bowel diseases, irritable bowel syndrome, colorectal cancer, and extra-intestinal diseases such as diabetes. Scientists believe that probiotics will replace antibiotics as drugs vetted by the FDA and European regulatory bodies in the nearest future. This laudable goal is dependent on the correct identification of probiotic strains (with the aid of next-generation sequencing technologies), the palatability of these strains to the sensory organ, validated storage and transport of intact cells to the gut (via microencapsulation approaches, or functional foods, and the fulfillment of all requirements and validation of all necessary stages for its approval as a new drug [72].

There is also a proposal that gut microbes can be genetically engineered so that they possess characteristics that detect what food is present in the gut, monitor inflammation, detect and fight against gastrointestinal pathogens thereby reducing reliance on antibiotics, and exert extra-intestinal effects such as the regulation of behavior and mood and treatment of cancer [73]. Genetically engineered microbes have been reported to be effective against *Vibrio cholerae* in mice especially when this pathogen was ingested 8 hours after the administration of the genetically engineered microbe [74]. There are still many ongoing trials seeking to manipulate and monitor the activities of genetically-engineered microbes in the gut, albeit in animal models. These microbes have to be tested for their safety and their ability to be fit enough to endure gastrointestinal conditions (stomach acid and bile) and successfully colonize the host's gut [75]. There is also the fear about the effect of horizontal recombinant gene transfer on the natural gut commensals. Although microbiome engineering is challenging, it is expected that this strategy will be less expensive and more effective than the traditional methods of gastrointestinal and other extra-intestinal disease control if achieved [76]. The major goal of genetic manipulation of gut microbes is to improve the health of humans.

8. Conclusions

One of the most effective ways to reduce the abundance of multi-drug resistant pathogens is with the use of beneficial microorganisms and/or their metabolites, analogous to the effective environmentally-friendly biological method of eliminating stubborn pests in farmlands by agriculturalists. The benefits of the gut microbiota are being constantly unraveled as advanced next-generation sequencing techniques arise. The field of microbio-therapeutics is steadily growing. Harnessing the potentials of these microbes is paramount to making the world a healthier and better place to live.

Conflict of interest

The authors declare that there is no conflict of interest.

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