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Multidrug Resistant Probiotics as an Alternative to Antibiotic Probiotic therapy

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Abstract

Drug-resistance is a major problem globally, the number of drug-resistant bacteria has increased substantially through horizontal gene transfer. Even *Mycobacterium tuberculosis* are reported to have acquired antitubercular drug-resistance and named as MDR *Mtb*. The acquisition of immunity has not given up, here; it is needed to be a continuous procedure. Further causing the microbial adapting to a very high and larger number of drugs recognized as extreme drug and total drug-resistance. The mechanistic aspects of MDR *Mtb* are well understood. Nevertheless, this is not the case with Probiotic microbes such as *Bifidobacterium adolescentis*. Herein, we report the mechanistic aspects of antitubercular drug-resistance in this organism for the first time. This review discusses the report by a mutation that confers multi drug-resistance in Bifidobacteria.

Introduction

Penicillin was introduced for the first time in 1928[1]. Afterward, in the 1940s, bacterial resistance against penicillin developed, which made headlines. Later, to overcome this resistance various antibiotics came into the market[2]. At late times, the world is facing a crisis in terms of antibiotic resistance[3]. Bacterial resistance is inevitable and its evolution is uncertain[4]. Pharmaceutical companies initially gave up investing in designing new antibiotics; this was accompanied by a decrease in the use of antibiotics, and finally the minimization of new drug introduction a continuous process[5]. The best means to circumvent antimicrobial resistance, the widespread and indiscriminate use of antibiotics is to use an alternative in the form of probiotics. One of the most important characteristics of probiotics is the synthesis and secretion of antimicrobial proteins/peptides. Probiotics are simply not very effective in providing good health effects exhibiting health benefits, but likewise do not introduce antimicrobial resistance in the target organism, as antibiotics do. Hence, to address the pressing need, the only effect is the economic consumption of probiotics as an alternative to antibiotics to treat few diseases caused by pathogens[6]. Probiotics, defined as live microbial consortia, have the power to offer secure health and also replenish gut flora[7].

Globally, many laws and ordinances have been implemented for the ethical use of microbes for therapy and good health. The most important and efficacious of these are the European laws. According to European standards, microbes should undergo Qualified Presumption of Safety (QPS) tests before human use can be considered[8]. *Lactobacillus* and Bifidobacteria are two major

inhabitants of the host and a few species are used as starter cultures in many food industries[9]. In that respect are various commercially available probiotics with Generally Recognized As Safe (GRAS) status recommended for human consumption that are described to cause antibiotic-resistant genes[10]. These are believed safe for human consumption as they do not cause any disease, and more significantly, on that point is a low risk/negligible risk of shifting the resistance gene present in genomic DNA[11]. To date, there are no reports of horizontal transfer of antibiotic resistance genes between probiotics and pathogenic microbes or vice versa.

Globally, the most common and infective/pathogenic microbes are *Salmonella*, *Listeria*, *Vibrio* spp, and so on. The other most dreaded microbes that cause chronic disease is *Mycobacterium tuberculosis*. Until lately, this was seen as a disease of the impoverished as it was mentioned frequently in epidemics only in developing nations. However, the causative agent of tuberculosis recognized and found in developed and advanced countries is more virulent. The World Health Organization (WHO) reports suggest that one-third of the population gets infected every year by *Mycobacterium tuberculosis*[12], and most recover due to effective resistance. Only about 5–10% develop active tuberculosis[13]. Antimicrobial resistance to *Mycobacterium tuberculosis* has led to the creation of multidrug resistant (MDR), extensive drug resistant (XDR), and total drug resistant (TDR) forms of tuberculosis. According to WHO guidelines, drug-sensitive tuberculosis can be treated by administering a combination of four first-line antibiotics, namely Rifampicin, Isoniazid, Ethambutol, and Pyrazinamide for two months and subsequently, rifampicin and isoniazid for at least four months on a daily basis[14,15,16]. Out of the four, rifampicin alone shows broad-spectrum activity[17], whereas the other three specifically target the Mycobacterial spp[18–20].

Drug-resistant strains of *Mycobacterium tuberculosis* have originated mainly due to intermittent and discontinuous use of prescribed drugs during therapy. At the molecular level, anti-tubercular drug resistance is primarily due to modification of the *rpo β* gene. The modified RNA polymerase β subunit (*rpo β*) (a housekeeping gene) loses its shape so that it no longer has the capacity to bind to make a complete protein in order to function. Thus, in one case the change is negatively affected, subsequently it stops participating in protein translation/transcription, ultimately creating drug resistant *Mycobacterium tuberculosis*. Studies show that mutations in the *rpo β* gene lead to rifampicin resistance and also affect the glutamine metabolism[21].

In present day circumstances, many organisms similar to *Mycobacterium tuberculosis* are acquiring resistance to first-line anti-tubercular drugs in a similar fashion. To mention a few, organisms, *Escherichia coli*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Neisseria meningitides*, *Streptococcus pneumoniae*, *Rhodococcus equi*, and Bifidobacteria are intrinsically resistant to rifampicin[22,23]. A few others, including *Pseudomonas fluorescence*, Enterobacteriaceae, Treponema spp, Borrelia, Leptospira, Mycoplasma, Urea-plasma, and Spiroplasma species shown resistance due to membrane impermeability, plasmid-mediated efflux systems, influx/efflux prophylaxis, and refractory ribonucleic acid polymerase (RNAP)[24–27]. Nocardia spp. Show resistance to rifampicin by inactivating the drug by glycosylation, ribosylation, phosphorylation, and de-colorization[28–30]. What is alarming is that recently a few of the GRAS organisms, such as *Bifidobacterium adolescentis* have also been observed to be multidrug resistant.

A study on controlling tuberculosis pathogenicity using gut microbiota revealed that altered gut flora due to antibiotic perturbation increases the mycobacterial burden in the lungs and also leads to dissemination to other organs, such as spleen and liver[31]. Antibiotics are the cornerstone of innovative health measures; intake of different classes of antibiotics, which are explicitly or broadly designed to kill bacteria leads to depletion of commensals, including gut bacteria[32]. In such cases, development of multidrug-resistant gut microbes becomes a critical issue[33]. Therefore, it is very essential to understand the mechanistic aspects of resistance to first-line anti-tubercular drugs in probiotic microbes, specifically concerning *Bifidobacterium adolescentis* as a model organism. This review focuses on the studies carried out with anti-tubercular drug resistance in Bifidobacteria.

In our previous work published in Scientific Reports in 2018, we reported that probiotic organisms, such as *B. adolescentis, B. animalis, and B. longum* show resistance and also adapt to a higher concentration of rifampicin and grow luxuriantly in the presence of the other three first-line antitubercular drugs. Apart from these, there are many commercially available probiotics reported to be multidrug resistant and capable of horizontal gene transfer of pathogens, as well as other commensal present in the human gut[34]. Inherited resistance in probiotics can be genetic-, plasmid-, or transposon-mediated. Getting rid of the plasmid responsible for immunity from the probiotic strains before using them as a food supplement is one of the best ways to avoid horizontal gene transfer[35]. Acquired resistance occurs because of cell wall modifications, active efflux systems, enzymatic intoxication, target modification, or metabolic re-arrangement[36,37]. For developing new treatment strategies, it is necessary to counteract the adverse effects of antibiotics on the host microbiome[38].

Concluding remarks

The study concludes that even Bifidobacteria show anti-tubercular resistance. Being a GRAS organism, this is not

only very alarming and dangerous, but also throws doubt over their use as probiotic microbes. There are two different ways to use these microbes for human betterment despite their anti-tubercular resistance. The most significant way may be to take out the plasmid from the organism that causes the impedance. All the same, the problem rises if it is genomic in origin.

The other strategy could be supplementing antibiotic-resistant probiotics for antibiotic probiotic therapy. Prior to adopting new drugs in probiotics, it is necessary to determine and record inherited, as well as spontaneous mutations. If there is a resistance gene, which is likely to be transferred, it should be removed before therapy. A combination of two or three inherently resistant probiotics for different antibiotics is also one of the best choices for treatment. Creating a database with a GRAS organism screened for antibiotic-resistance gene profiles in a single platform will be advantageous for future use.

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