Review Article

Intestinal Side Effects of Improper Antibiotic Use: Cause, Symptoms, and Treatment Through Probiotic Food Sources

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Abstract

When antibiotics emerged, they gained lots of interest on the basis that they could protect and help human beings against a variety of bacterial diseases. These include urinary tract infections, pneumonia, sinus infections, etc. However, they have the potential to cause undeniable side effects including the drastic alter of gut microbiota. Antibiotic-associated diarrhea, nausea, vomiting, and other gastrointestinal side effects could also result from these alterations in gut microbiota. To diminish these side effects, the use of probiotics was proposed. Probiotics are defined as live microorganisms that have health benefits for the host by countervailing the bacteria which were lost in the gut, and they can be gained through different resources such as supplemented capsules and foods (especially dairy products). In this review, we discussed the antibiotic-associated side effects which can be treated or prevented by consuming probiotic foods.

Keywords: *Antibiotics, dairy products, gut dysbiosis, gut microbiota, nutrition therapy, probiotic*

Introduction

Since Sir Alexander Fleming developed the first antibiotic in 1928 (penicillin), hundreds of antibiotic agents have been produced from biological compounds or chemically manufactured.[1] Antibiotics have protected humans against different deadly bacterium attacks during the previous century.[2] An example of a more common disease treated by antibiotics is a urinary tract infection.[3]

One of the major concerns these days is antibiotic abuse or overuse. This is seen in cases in which medicine is being given or bought for non-installed infections and used in methods other than the intended application of the medication. These include signaling antimicrobials as a prophylactic. For example, in cancer therapy and treatment of chronic diseases such as diabetes type 2 and dental procedures, antibiotic abuse can be observed.[4]

Moreover, antibiotics are not completely safe medicines as they may change our gut microbiota.[5] For example, antibiotic resistance genes have recently been identified in the human microbiome, which acts as an amazing reservoir and it was found that resistant bacteria can colonize in the intestine as soon as 3 days after birth,[6] and by choosing resistant bacteria that can behave as opportunistic pathogens, antibiotics can create some alterations in the native microbiota of the host.[7] In addition, a low dosage consumption of sub-therapeutic antibiotic treatment or antibiotics from the environment or food resources can lead to gut dysbiosis. Furthermore, side effects of antibiotics are not limited to gut dysbiosis. For instance, antibiotic use may also lead to allergy, nephritis, hematological problems, disturbance in the nervous system, and problems with electrolytes.[8]

To diminish some antibiotic-associated hazards, several ways have been suggested, and one of the most confident manners is use of probiotics. Probiotics are described as live microorganisms which provide health benefits to the host when applied in appropriate quantities.[9,10] Lactic acid bacteria (notably *Lactococcus* and *Lactobacillus*) are two probiotic strains that have been shown to have a positive impact on human health. All of these strains have been labeled as "generally recognized as safe," and they can be found in some foods which will be discussed in the Probiotic Food Sources section.[11]

Prosperities of Different Types of Probiotics

Probiotics are derived from the Latin word, "pro" means "for" and the Greek word "biotic" means "life."[12] Bacteria-derived products, dead bacteria, metabolites, bacterial growth

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end products, cell wall fragments, enzymes, and neurochemicals have been proposed to have health benefits, but these are not called probiotics because they are not alive when consumed or received.[9,13]

The most common method of receiving a probiotic is orally via a number of different types including foods, pills, sachets, and tablets.[14-16] The selection format of a probiotic can vary due to factors such as product availability, an individual's needs or requirements, and even come down to something as simple as personal preference.[17-19]

In addition to the properties mentioned in Figure 1, there are other properties which should also be considered. For example, a good probiotic must be predominantly of human origin, with empirical proof of positive physiological effects and protection for human usage. It must also be willing to adhere to the target tissue properly.[21]

In food microbiology and human nutrition, *Lactobacillus* species are one of the most important taxa. Several *Lactobacillus* species are utilized as starter cultures or food additives in the fermentation of fermented foods.[22] This particular group of bacteria has probiotic characteristics. Add to the *Lactobacillus* species, *Bifidobacteria* species are also involved in the probiotic group [Table 1]. Bifid or irregular V- or Y-shaped rods resembling branches are the most common morphologies among these bacteria.[23,24] The genus *Bifidobacterium* includes various organisms, some of which have been linked to health benefits such as diarrhea prevention, the establishment of a balanced microflora in premature infants, and even the prevention of gastrointestinal cancers.[25-27] As a result of these benefits, many scholars have proposed *Bifidobacteria* as dietary supplements over the last century.[28]

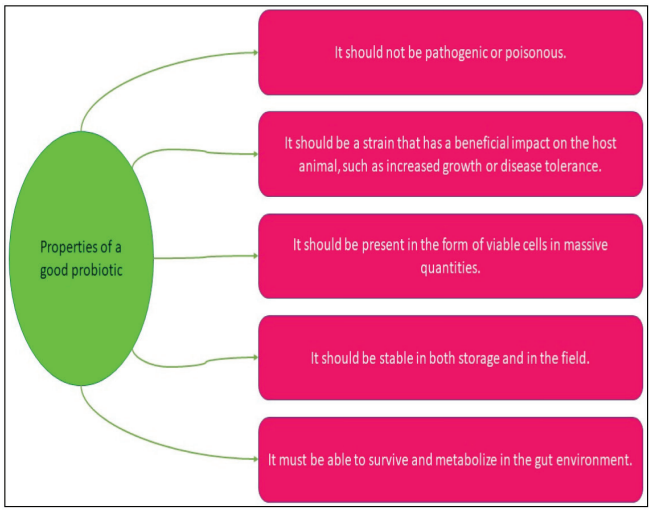

Figure 1: Properties of a good probiotic[20]

Gut Microbiota and Effects of Antibiotics

Recent research has shed light on the possible effects of antibiotic use on the microbiota of the intestine. Antibiotics have been shown to reduce the variability of the gut microbiota in humans, and irritable use of antibiotics can lead to severe and inadvertent problems.[1,34-36] For example, antibiotics raise the amount of host-derived free sialic acid in the intestine, which opportunistic pathogens such as *Clostridium difficile* and *Salmonella typhimurium* may use to boost their development.[37] Furthermore, Jakobsson *et al.*[38] examined the effects of clarithromycin, omeprazole, and metronidazole on fecal taxonomic and pharyngeal composition for 7 days, and they discovered wide taxonomic contrapuntal impact, with quick but only relative recovery; in some cases, the impact lasted for about 4 years. Additionally, Dethlefsen *et al.*[39] used the 16S rRNA sequencing technique and discovered that 5 days of ciprofloxacin reduced taxonomic richness and affected the diversity of around 30% of the bacterial taxa in the intestine within days of early introduction.

Antibiotics can cause dysbiosis in our gut microbiota that can lead to some diseases. For example, immune responses may be dysregulated, antibiotic-associated diarrhea (AAD) may occur, irritable bowel disease may develop, and there may even be neuropsychiatric side effects.[40-44]

Additionally, another field of study about antibiotics effects on the gut microbiota is the resistance effect. For this purpose, several methods have been proposed and the most popular of which is genomic and metagenomic approach, as well as monitoring the phenotypes of specific organisms.[45,46] According to Löfmark *et al.*,[45] up to 2 years after clindamycin application, an enrichment and stabilization of resistant bacteroides strains as well as resistance determinants can be seen. Moreover, a typical *Helicobacter pylori* treatment selects for highly resistant enterococci that can survive without further selection for at least 3 years.[46]

Table 1: A comparison between the *Bifidobacteria* and *Lactobacillus* species

Character	*Bifidobacteria*	*Lactobacillus*	References
Physiology	Anaerobic	Microaerophilic	[29,30]
Phospholipid composition/ teichoic acid	Polyglycerol phospholipids, and Lysol, alanyl phosphatidylglycerol, and di phosphatidylglycerol derived from Lysol	Glycerol	[29,30]
Peptidoglycan type	Ornithine and lysine are variables, essential amino acids in the tetrapeptide, with non-identical shapes of cross-linkage	Lys-D Asp	[29,30]
Lactic acid configuration	L-lactic acid	D-lactic acid	[29,30]
Sugar metabolism	Heterofermentative	Homofermentative	[29,30]
Optimal temperature for growth (°C)	37–41	30–40	[31-33]
Optimal pH for growth	6.5–7	5.5–6.2	[32,33]

Table 2: Effectiveness of probiotics in the treatment of diseases which can be caused by use of antibiotics

Disease	Study population	Duration of treatment	Medication used	Outcomes and results	References
Crohn's disease (CD)	18–65 years old who were suffering from ileocecal resection for CD	12 weeks	*Lactobacillus johnsonii* LA1 or placebo	No significant difference was observed between endoscopic recurrence or severe endoscopic recurrence (P= 0.33)	[49]
Ulcerative colitis (UC)	18–70 years old	4 weeks	Symprove (four strains of naturally occurring bacteria: *Lactobacillus rhamnosus* NCIMB *Lactobacillus acidophilus* NCIMB 30175 30174, *Enterococcus faecium* NCIMB 30176 and *Lactobacillus plantarum* NCIMB 30173) in a water-based suspension	In patients with UC, Symprove may be linked to less intestinal inflammation	[50]
UC and CD	19–68 years old among UC 24–65 years old among CD	4 weeks	*Lactic acid bacteria* in kefir	Significant difference was observed in first and last measurements of *Lactobacillus* bacterial load of feces P=0.001 in UC and P=0.005 in CD	[51]
Irritable bowel syndrome (IBS)	Age mean among the placebo group: 39.9 and active 40.6 Rome III criteria	12 weeks	*Lactobacillus casei* LBC80R, *L. rhamnosus* CLR2, and *L. acidophilus* CL1285	For IBS symptoms, the active drug has a therapeutic advantage over placebo	[52]
IBS	Above 18 years old	12 weeks	*Bifidobacterium longum* or *Lactobacillus paracasei*	When compared with baseline, both *L. paracasei* and *B. longum* supplementation enhanced mental well-being and social functioning (all P<0.05)	[53]
AAD	Children (3 months to 14 years old) who used antibiotics in the hospitals for common infections	3–30 days (antibiotic treatment)	*L. rhamnosus* or placebo	In the probiotic-treated group, there was a significantly decreased frequency of any diarrhea	[54]
AAD	11–36 months children who underwent hypospadias repair	Variable between 4 and 16 days	*L. rhamnosus* GG	Significant lower incidence of AAD in the probiotic-received group (P=0.002)	[55]
Depression and brain activity	Patients 26–58 years old who suffered from IBS	10 weeks	*B. longum* NCC3001	Probiotics can decrease depression and limbic activity. Also, quality of life increased among the probiotic-received group; however, the level of anxiety does not change significantly (P=0.04)	[56]
Depression and anxiety	The average was 33.6 years old who were pregnant women	From 14 to 16 weeks' gestation until the offspring became 6 and 12 months	*L. rhamnosus* HN001	Mothers who used probiotic had significantly lower depression (P=0·037) and anxiety (P=0·014)	[57]
Major depressive disorder (MDD)	The average was 39 years old who suffered from MDD and used selective serotonin reuptake inhibitors	8 weeks	*L. plantarum* or placebo	Among the probiotic group, the cognitive function improved and the kynurenine concentration in the brain decreased	[58]

Probiotics Effects on Lowering Antibiotics-related Disease

It has been proposed that modulating the gut microbiome may be a useful therapeutic method for reducing the harmful side effects of drugs that have a negative impact on the gut microbiota [Table 2].[47] For example, Koning *et al.*[48] could modulate the side effects of amoxicillin by probiotic intake.

In the human body, the specific mechanism of probiotics is poorly understood and is thought to work by limiting pathogenic bacteria proliferation and avoiding pathogenic penetration of the host, increasing the function of the gut wall and receptor connections, and generating or secreting substances including short-chain fatty acids and neurotransmitters.[59]

Probiotic Food Sources

Diet has a key role on the gut microbiota and can significantly impact gut microbial richness and diversity. Dairy products including yogurts, kefirs, and cultured drinks are the main food sources for probiotic applications,[60] and the application of probiotic bacteria in dairy products has been widely increased in the dairy industry.[61] Furthermore, ice cream and frozen dairy treats have shown to be excellent transporters for probiotic microorganisms, because they benefit from useful features during the storage period and this leads to higher probiotic survivability at the time of consumption.[62]

Fermented foods and beverages such as fermented milk, meat (e.g., fermented sausages), and plant-based foods (e.g., sauerkraut) have long been consumed as an important part of the human diet in almost every culture on every continent. Regarding curing salts, spices, and other ingredients used in the formulation of the fermented sausages, selected microorganisms for these products are resistant to these ingredients as well as fermentation process.[63] Due to the growing trend of vegetarians and the high incidence of lactose intolerance in many regions around the world, plant-based cuisines have also been introduced. Lactose intolerance, cholesterol levels, and allergic milk proteins are all important downsides of dairy consumption, necessitating the creation of new non-dairy probiotic meals.[60]

Fruit juices are being examined as a substitute substrate for non-dairy probiotic beverages. Fruit juices provide additional benefits for the survival and growth of probiotic microbes. They are particularly high in minerals and carbohydrates, both of which are necessary for probiotic development.[60,61]

Conclusion

Antibiotics are exceptionally useful in the treatment or prevention of bacterial diseases in different creatures. However, improper use of antibiotics may lead to a wide range of inevitable hazards such as dysbiosis which is modification of gut microbiota balance. This change can lead to some further problems such as psychological disorders, IBS, diarrhea, etc. Several methods are proposed to reduce these side effects, and one of them is food-probiotic-resources consumption (such as fruit juices and dairy products), because probiotics are good substitute for lost bacteria. Additionally, their efficacy in the treatment of different antibiotic-associated side effects has been proved in several studies. For example, the incidence of AAD among patients who received probiotics for 4–16 days was absolutely lower than that of the placebo group.

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Conflicts of interest

There are no conflicts of interest.

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