

Influence of the gut microbiome on drug metabolism and efficacy

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ABSTRACT

The human gut microbiome is an ecosystem of trillions of bacteria that has been shown to play an important role in regulating drug efficacy and metabolism. This review article provides a comprehensive overview of the interactions between gut microbes and drugs, revealing the mechanisms by which they influence each other. We investigate the biotransformation of drugs by intestinal bacteria and whether microbial enzymes improve or reduce the bioavailability of the drug. This review provides an overview of the impact of the gut microbiota on drug use and metabolism, highlighting the potential of using the microbiota for personalized medicine and treatment. Understanding the relationship between gut microbiota and drug therapy is important to make drugs more effective and improve health in the era of precision medicine.

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I. INTRODUCTION

The gut microbiome is the collective genome of the whole microbes inhabiting in Mammalian gastrointestinal tract, which contains over 100 species bacteria and about 10¹⁴ times the number of the host body cells(1). Gigantic amount of microorganisms, including bacteria, viruses, fungi, and archaea, are co-residing in the human gastrointestinal (GI) tract, living in a commensal relationship with humans(2). Most of these microorganisms are bacteria, which outnumber eukaryotes (e.g. fungi) and archaea by 2–3 orders of magnitude, and reside primarily in the gastrointestinal (GI) tract. They form a complex and diverse community, called as the gut microbiota (hereafter referred to as gut

microbiota) which includes more than 1000 different bacterial species, with more than 90% of them belonging to two major phyla, the Firmicutes and Bacteroidetes. Less abundant, but still dominant gut phyla are Actinobacteria, Proteobacteria and Verrucomicrobia(3). The human gut was not considered an important part of the human body in the past, other than its well known roles in digestion and absorption of food and drugs. Recently, this 'forgotten' organ has become an uprising star of many studies. These microorganisms create an environment rich in nutrients needed for their own survival. In turn, they make very important contributions to processes, important for human health, such as the normal functioning of the immune system and the metabolism of nutrients, drugs and different neurotransmitters. Many studies have shown that the pharmacokinetic and bioavailability processes of different drugs are often involve complex and dynamic interaction with gut microbiota. This has an important effect on the efficacy of these drugs, as well as on the occurrence of different unwanted toxicological events. Therefore, gut microbiota is recognized as one of the crucial environmental factors influencing the metabolism of drugs and xenobiotics as well as the inter-individual variations of drug effects(4).

The concept that a disturbed intestine microbiome (specifically by antibiotics) impairs responsiveness to immunotherapy suggests that a rich and wealthy microbiome is important for immunotherapy efficacy. In fact, promising data from two small clinical studies (1 study n=15 with clinical benefit in 6 of 15 patients, and the other study n=10) show faecal microbiota transplant (FMT)—a method that enables the composition of the gut microbiome to be changed by transferring the entire gut microbiota from one host (donor) to another (recipient)—can improve immunotherapy efficacy. For example, the efficacy of adoptive cell therapy was shown to be enhanced by selectively targeting and eliminating specific microbes belonging to the Bacteroidetes phylum. Similarly, administration of the commensal microbe, *Bifidobacterium* spp., has been shown to enhance the efficacy of a PD-L1 therapy in a rodent model

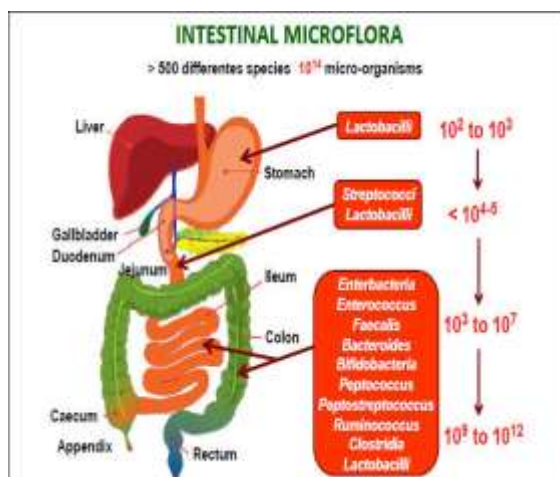
of melanoma, there is a possibility that enhancing efficacy will also increase the risk of toxicity (5)

Gut microbes play a crucial role in enhancing drug efficacy through various mechanisms, including metabolic activation, drug transformation, and immune modulation. They can convert inactive compounds into active forms, impacting drug absorption and bioavailability. Furthermore, gut bacteria can interact with the immune system, influencing the body's response to medications. Recent studies have highlighted these interactions, shedding light on the potential to optimize drug treatments by considering the gut microbiota.(6)

Composition and Function of the microbiome

The gut microbiota are consists of several types of microorganisms, including bacteria, yeast, and viruses. Taxonomically, bacteria are classified by phylum, classes, orders, families, genera, and species. Only a few phyla are representing more than 160 species(7). The dominant gut microbial phyla are Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia, with the two phyla Firmicutes and Bacteroidetes(8) accounting for 90% of gut microbiota. The Firmicutes phylum is consists of over 200 different genera such as Lactobacillus, Bacillus, Clostridium, Enterococcus, and Ruminococcus. The genus Clostridium makes up 95% of the Firmicutes phylum. Bacteroidetes comprises of predominant genera such as Bacteroides and Prevotella. The phylum Actinobacteria is proportionally less numerous and mainly represented by the Bifidobacterium genus(8)

Examples of taxonomic gut microbiota composition are illustrated in fig:1 (30)



The gut microbiome plays crucial roles in the body's health, including digestion, nutrient absorption, and immune system modulation(9).

Gut bacteria help train the immune system, maintaining a balanced inflammatory response, and protect against pathogens. In addition, the gut microbiome contributes to the breakdown of complex carbohydrates and the synthesis of certain vitamins and short-chain fatty acids(10). It offers insights into the complex relationship between the composition of gut microbiome and its functional roles in maintaining well-being. It discusses how factors such as diet, lifestyle, and medications affect the diversity and balance of gut microbes, emphasizing the importance of understanding this dynamic ecosystem for personalized healthcare approaches. The contributions of the gut microbiome to nutrient metabolism, immune response, and overall homeostasis underscore its key role in human physiology (11).

1) Digestion and Absorption of nutrients:

Gut microbes help breaking down complex carbohydrates, fibers, and other components that are otherwise indigestible by human enzymes. They produce enzymes that contribute to the breakdown of these compounds, allowing for better nutrient absorption.

2) Metabolism:

The gut microbiome influences host metabolism by extracting energy from food components that would otherwise not be digested. It can also affect lipid metabolism and even contribute to obesity by affecting the efficiency of energy acquisition.

3) Regulation of the Immune System:

The gut microbiome plays an important role in training and protecting the immune system. It helps the immune system distinguish between beneficial and harmful microorganisms, contributing to a balanced immune response and reduces the risk of autoimmune diseases.

4) Barrier Function:

The gut microbiome helps maintain the integrity of the gut lining, acting as a barrier against harmful pathogens. It prevents pathogens from adhering to the intestinal wall and colonizing the intestines.

5)Neurological Health:

Recent research suggests a strong connection between the gut and the brain, known as the gut-brain axis. The gut microbiome can influence neurological health, affect mood, stress, and even conditions like depression and anxiety.(12)

Microbiome-Drug Interactions:

Many recent studies suggest that the gut microbiota influenced drug metabolism through direct and indirect mechanisms and alters the efficacy, quality, and toxicity of xenobiotics and drugs(13).Two broad mechanisms by which gut microbiota mediates drug metabolism: the direct

biotransformation mechanism where drug metabolism is carried out by microbial enzymes, while the indirect biotransformation mechanism suggests the effect of microbial metabolites on host receptors and signalling pathways. Intestinal microflora can directly influence a person's response to a particular drug through direct interaction or by producing enzymes and inducing major or minor biochemical transformations in the drug to make it either more or less active/inactive or produce toxic metabolites(14-17).As the gut microenvironment is anaerobic or rarely oxygenated, the metabolism of drug by Intestinal microflora mainly involves hydrolytic and reductive biotransformations(18-19).

Table 1 : Impact of gut microbes on drug pharmacokinetics

Drug	Pharmacotherapeutic classification	Effect of the gut microbiota on drug pharmacokinetics	Implicated microbe
Digoxin	Cardiac glycoside	Increase in metabolism	Eggerthellalenta(32,33,20)
Levodopa	Anti-parkinson	Decrease the absorption	Helicobacter pylori(34,35,36,37,27)
Amiodorone	Class 3 antiarrhythmic	Increase the absorption	Escherichia coli Nissle(38)
Irinotecan	Topoisomerase 1 inhibitor	Increase the metabolism and delayed excretion	β -glucuronidase enzymes produce by Bacteroides vulgatus(39)
Paracetamol	Analgesic and antipyretic	Decrease the metabolism	Clostridium difficile(40)

1) Digoxin

The knowledge of how the microbiome influences drug response is still in its infancy and interaction of the gut microbiome with cardiovascular drugs is only now being uncovered(21).A classic example where the gut microbiome can interfere with the bioavailability of a drug is digoxin, a drug used for the treatment of heart failure. In 10% of patients, digoxin is converted to the inactive microbial metabolite

dihydrodigoxin by, Eggerthellalenta, which limits the amount of active drug that is absorbed into the systemic circulation(20)Eggerthellalenta which possess the cardiac glycoside reductase (cgr) operon show a high rate of digoxin inactivation. since the mechanism of inactivation and bacteria responsible are known, successful dietary and antibiotic interventions are possible to prevent digoxin inactivation(22).

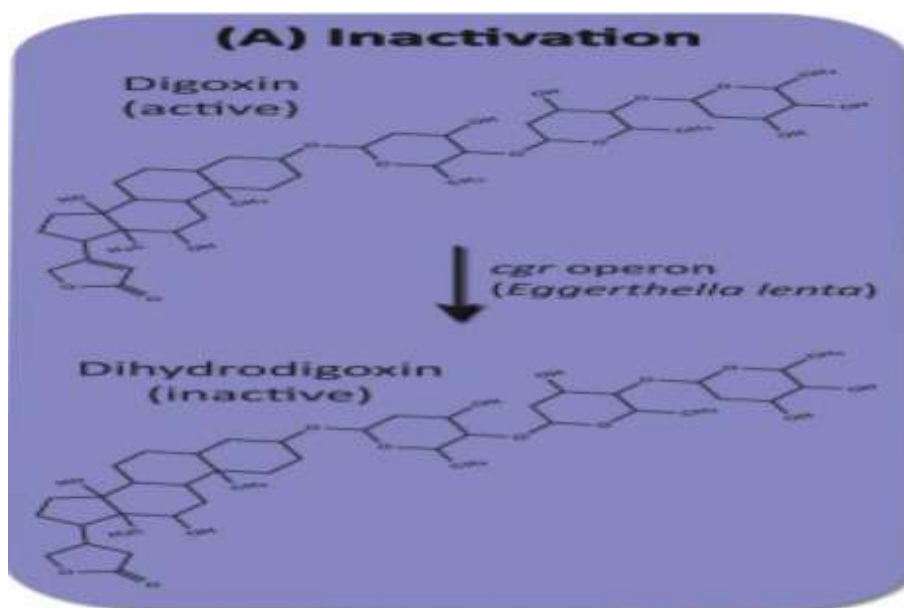


Fig. 2 Inactivation of Digoxin by Eggerthella lenta(31)

2) Levodopa

Parkinson's disease (PD) is a neurological movement disorder. This leads to tremors and difficulty in walking and balance. It affects >1% of the population aged >60 years (23). The most effective drug for PD is levodopa (L-dopa), which is prescribed to alleviate motor symptoms (24). L-dopa is absorbed in the gut and must enter the brain so as to be converted by the aromatic amino acid decarboxylase to the neurotransmitter dopamine to be functional in co-ordinating brain to muscle signalling (25). Gut microbes metabolize the Parkinson's drug L-dopa. Decarboxylation of L-dopa by *E. faecalis* TyrDC and human AADC likely limits drug availability and contributes to side effects. *E. lentae* hydroxylates dopamine produced from L-dopa using a molybdenum-dependent enzyme. (26) The bioavailability of L-dopa to the

brain at the site of active intestinal microbial metabolism is therefore one key factor determining drug effectiveness. Eradication of specific bacterial population with antibiotics has been found to improve the L-Dopa treatment in humans, suggesting that drug effectiveness is suppressed by some gut bacteria (27,28). To make L-dopa more effective in PD patients L-dopa-utilizing bacteria, is simultaneously administration of inhibitors of intestinal bacterial L-dopa decarboxylation are proposed to be coadministered. Since tyrosine is the substrate of preference for TyrDCs, the mimic (S)-α-fluoromethyltyrosine (AFMT) was considered and used to reduce L-dopa decarboxylation, by improving the therapeutic effect (29).

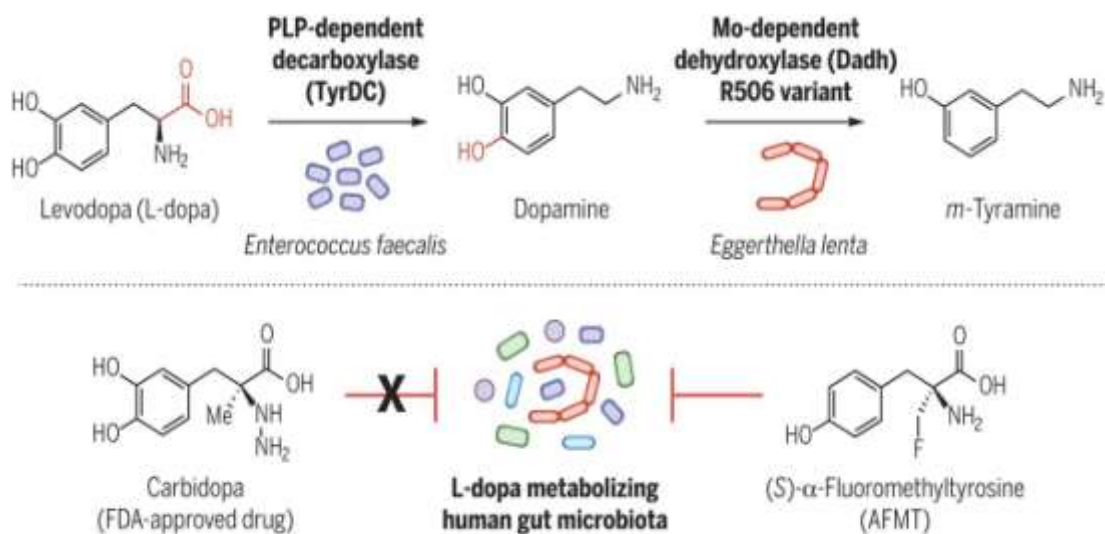


Fig 3: Gut microbes interferes with metabolism of levodopa (41)

3) Amiodarone

Amiodarone is a member of a new class of antiarrhythmic drugs with mostly Class III (Vaughan Williams classification) classification and indicated for treatment of life-threatening supraventricular and ventricular arrhythmias, such as ventricular fibrillation or haemodynamically unstable ventricular tachycardia(42). While the United States FDA has labelled amiodarone for the treatment of life-threatening ventricular arrhythmias, the drug is commonly used off-label to treat supraventricular tachyarrhythmias such as atrial fibrillation as well as for the prevention of ventricular tachyarrhythmias (VTs) in high-risk patients(43,44,45).

Amiodarone blocks the potassium current that causes myocardial repolarization in the third phase of cardiac potential. As a result, amiodarone increases the action potential duration as well as the effective refractory period for cardiac cells (myocytes). Therefore, cardiac muscle cell excitability is reduced, preventing and treating abnormal heart rhythms(46,47). Amiodarone also interferes with the activity of beta-adrenergic receptors, sodium channels, and calcium channels. These actions, at times, can lead to undesirable effects, such as hypotension, and bradycardia(48).

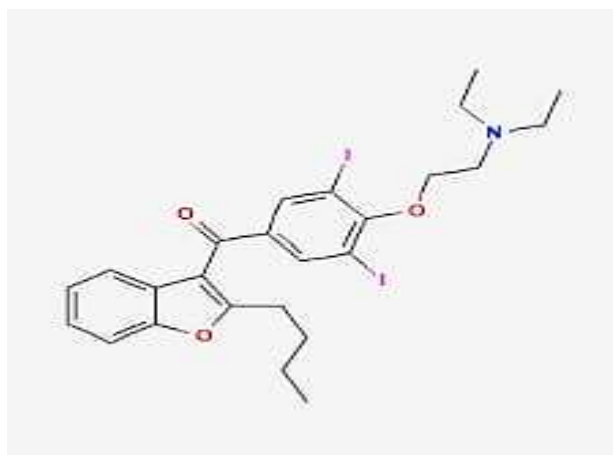


Fig 4: Structure of amiodarone (51)

In 1917, Escherichia coli Nissle GM was identified to increase the bioavailability of amiodarone,

thereby lowering the pH in the stomach and therefore improving the ionization and absorption of the

e drug. It is also theorized that the increased bioavailability of amiodarone is due to the upregulation of the OATP2B1 transported gene by the GM. Additionally, the concentration of amiodarone metabolite Additionally, the concentration of amiodarone metabolite N – desethylamiodarane increase 1.5 fold after probiotic E.coli Nissle 1917(49). Owing to its narrow therapeutic range, certain gut microbes, in certain conditions can precipitate amiodarone mediated toxicity(50)

II. CONCLUSION

This review article has shed light on the fascinating and complex interplay between gut microbes and drug metabolism, with a specific focus on the drugs digoxin, levodopa, and amiodarone. Through a comprehensive analysis of existing research, it is evident that the gut microbiota plays a pivotal role in influencing the pharmacokinetics and therapeutic outcomes of these medications.

The microbial communities residing in our gastrointestinal tract have the capacity to biotransform, modify, or even inactivate drugs, thus directly impacting their efficacy and safety. The case of digoxin exemplifies how gut bacteria can metabolize a drug, potentially altering its bioavailability and therapeutic window. Similarly, levodopa, a cornerstone treatment for Parkinson's disease, faces the intricate challenge of gut microbes converting it into dopamine, potentially affecting both efficacy and side effects. Additionally, the proarrhythmic potential of amiodarone may be modulated by the gut microbiota, emphasizing the importance of understanding these interactions for personalized medicine.

As we delve deeper into this burgeoning field of research, it becomes increasingly evident that harnessing the influence of gut microbes on drug metabolism could lead to revolutionary advancements in drug development and optimization. However, the complexity of these interactions also calls for cautious consideration in clinical practice, as individual variations in gut microbiota composition can lead to unpredictable responses to medication.

In light of these findings, future research should continue to unravel the specific mechanisms by which gut microbes impact drug metabolism and explore strategies to modulate the microbiota to enhance drug efficacy while minimizing adverse effects. Ultimately, the integration of microbiome

analysis into clinical decision-making could usher in a new era of personalized medicine, where drug therapy is tailored to an individual's unique gut microbial profile, thereby maximizing therapeutic benefits and minimizing risks

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