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GIT Microbiome and Pharmacology: Implications for drug Metabolism and Therapeutic Outcomes

Ahmed M. Al-Yassen[*,1], **Ibrahim Amer Alobaidi**[1]

[1] College of pharmacy, Al-Farabi University, Baghdad, Iraq

***Corresponding author**

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ABSTRACT

Introduction and analysis: A comprehensive literature search was performed using PubMed and Google Scholar databases. The paper analyses works published within 2013 and 2025 were highlighted to ensure up-to-date judgements. Microorganism settle with all human body surfaces like gastrointestinal tract. Affecting broad of aspects regarding body physiological activities as a mediator, homeostasis, metabolism, inflammatory responses and most important is the interaction between gut microbiota enzymes and orally administered drugs. The review discuss many interventions regards microbiota within drugs that leads to hinder and fluctuates the bioavailability and effectiveness. Some interactions lead to reduce the efficacy of intake drugs while other may boost the therapy, by its effect on absorption, metabolism and reconditioning. A list of examples easy to access within database reveals the dug microbiota interaction by different mechanism, this review shows few examples upon different way of interaction to present a clear understands to such interventions.

Conclusion: It is worthy to aim targeting the gut microbiota in different diseases, to assist in slow progression and improve the treatment. Therefore, by concentrating on all of these gaps and offering a genuine answer through creative methods, new trustworthy diagnostic tools, and microbiome targeted therapy, it is hoped to reduce response fluctuation and improve quality of life.

Key words: Gut Microbiota, Drug–Microbiome Interaction, Drug Bioavailability, Microbial Enzymes, Microbiome-Targeted Therapy

INTRODUCTION

Gut Microbiome is a set of microorganisms in well-regulated ecosystem and take a wide concern in recent literatures and targeted therapy [(1)]. Microbes settle with all human body surfaces. Also, it is good to note that a remarkable number of microbes exist in the Gastrointestinal tract (GIT). The human body gut retains nearly more than 1000 microbial species that are presented as a unique ecological community named by gut microbiota [(2)]. It is considered as one of main mediators of human body homeostasis, affecting pharmacokinetics, such as metabolism, inflammation and barrier homeostasis, through both gut and extra-GIT processing. Since its act in multiple ways and act as bridge with many organs through, endocrine, neural, and immunological, pathways, it lately classified as a "vital organ". Dysbiosis (change in microbial community) usually results in gut beside other organs issues, still the mechanism of such association is not fully comprehended [(3)].

According to Enright et al, gut microbiota density and diversity increase distally [4]. The diversity of gut microbial mostly affected by many factors like, lifestyle, dietary habits, environment and age. As well as, the antibiotics cause significant change on microbiota composition [5]. On the other hand, pharmacokinetics (absorption, metabolism and bioavailability) and toxicity affected vigorously by microbial changes. Biochemical changes occur when oral drugs pass and get direct contact with microbial enzyme in both small and large intestine results in marked manipulation in drugs and its metabolites [6].

Imagine that the beneficial effects of gut microbiota extend beyond vitamin production, bile acid metabolism, and vitality. In addition, it maintains the integrity of the intestinal barrier and supports immunity by ensnaring pathogens and enhancing immunity. [7]. Metabolism by gut microbiome may occur before and after absorption within epithelia or after liver biliary excretion, that mostly result in recycling of medications through enterohepatic system [8]. This review gathers the impact of pharmacology modifications of drugs mainly the metabolism with gut microbiome and its consequences.

Gut Microbiota as a Hidden Pharmacological Organ

The concept of gut flora is more than just a layer of microorganism on the surface of the monolayer gut epithelium but extends to scavenge the undigested food within the GIT, and this surely supported by a number of verifications [9]. One hundred tons' gut microorganisms' cells are well known to play vital role in nutrition and human body functioning [10]. The gastrointestinal system contains different numbers of flora that is around 10^1 per gram in stomach (low level due to acidity) to 10^{12} within intestine [11]. More studies have attached that re-support gut microflora in animal models cause refunction of mucosal immunity [12].

Gut microbiota by direct and indirect methods markedly alter mucosal barriers, the latter consider the major site of absorption and significant barrier to metabolize different molecules (foreign bodies and medications) [13]. Normal flora seems to help in smooth uptake of glucose even with low calories level, although, to maintain normal body weight, more calories consumption should be taken in the deficiency of gut microbiota [14].

In the current article, gut microbiota is emphasized a lot. as invisible organ that its pharmacological effect unavoidable and should be taken in consideration and plan to deal with it.

Gut microbiota and Pharmacokinetics

Absorption

The effectiveness of many oral medications is diminished because of GIT's poor level of bioavailability. This effect and continuous changes upon molecules may come from the concept of cooperative and mutualistic nature of gut microbiome that obligate the balance to be changed at specific manner and also encompass a change to GIT properties [15].

The characteristics of the medication, such as its solubility and permeability, determine how effectively this process occurs. [16,17] specific biochemical characteristics such as the pH and GIT transit time, transport systems, and other elements like nutrition [18]. According to certain studies, gut microbes can alter intestinal characteristics and have direct impact on the bioavailability of oral medications. By altering the first pass effect and metabolism of oral medications, gut microbial enzyme activity can have a direct impact on their bioavailability and net outcomes [19] or enterohepatic recirculation [20].

By fermenting dietary fibers and break down complex carbohydrates, the gut microbiota promotes digestion, metabolism and produces short chain fatty acids, which are essential for colon health [21]. As reviewed previously, it is vital for development and control of the immune system, which guards against autoimmune diseases and infections. Essential vitamins, such as vitamin K and some B vitamins, are synthesized by specific gut flora, which further supports common condition [22].

Metabolism and recycling

It is certain and inevitable that the GI microorganism will lead to direct and indirect modulation on xenobiotic drug and metabolism and that lead to consequences for its efficacy and toxicity. Still, greater understanding is crucial since the gut microbiome is a source of physiological heterogeneity in both people and populations, in addition to the fact that the microbiota carry out a variety of significant metabolic processes. The toxicity along with disposition of medications and their metabolites may be impacted by such disparity [23].

The gut microbiota expresses the GIT microbial β-glucuronidase (gmGUS) enzymes, which are vital for the host's health since they eliminate medications, food, and vital endogenous substances like bile acids, bilirubin, neurotransmitters (like dopamine), and steroid hormones [24]. Numerous high-impact studies performed over the last 20 years have demonstrated how gmGUS inhibitors might improve chemotherapeutic medication efficacy and reduce drugs-induced toxicity in the lower digestive tract. As a reverse reaction of glucuronidation, gmGUS stimulates the hydrolysis of glucuronides in the gut to liberate the aglycones. This process de-glucuronidation regenerates parent chemicals, encourages cycling, and suspends the removal of various substances (Figure 1) [25].

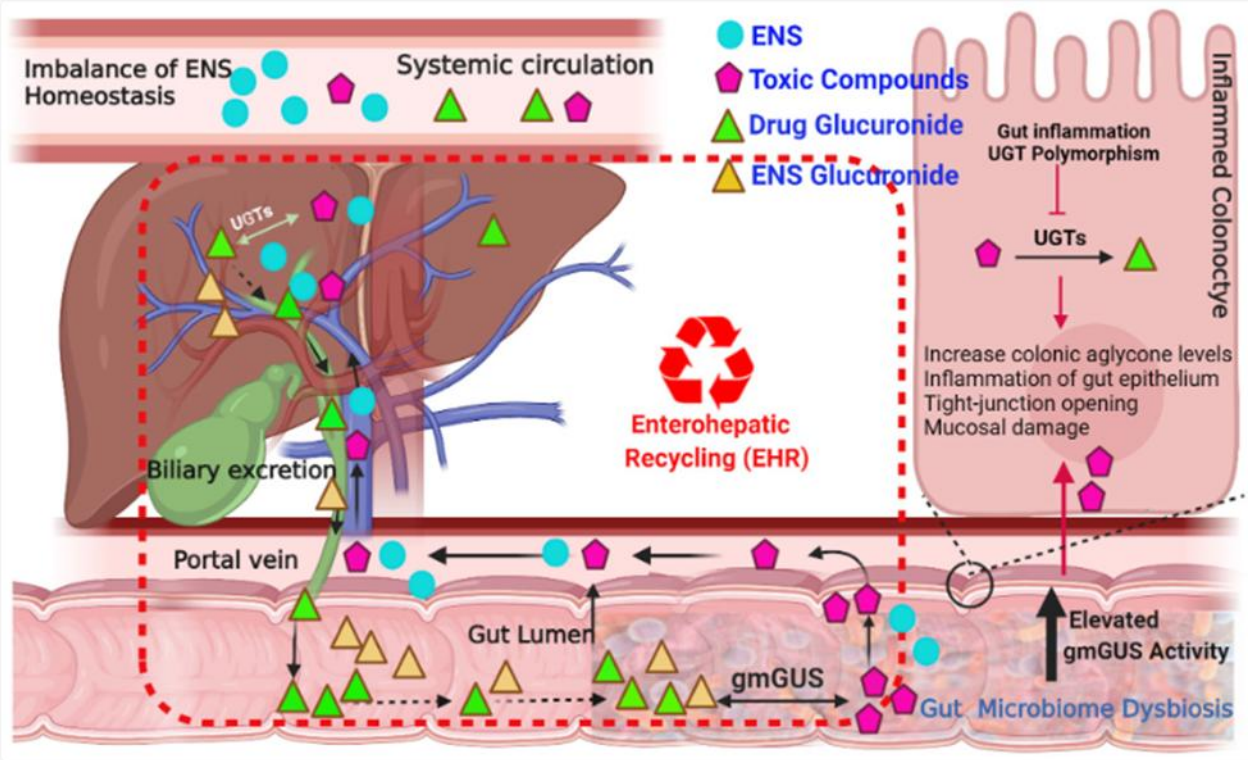

Figure 1: Graphic illustration of microbial β-glucuronidases pathophysiology. It seems to play critical role in the enterohepatic recycling of toxic substances and endogenous substrates [26].

Numerous instances demonstrate the GI microbiota's reducing effect, such as the activation of azo bond prodrugs (like sulfasalazine), hydrazone linkages (like eltrombopag), which render the drug inactive, and the conversion of loperamideoxide (a prodrug) to loperamid by gut bacteria, which is essential for the drug's activity [27]. This metabolic variance can be changed since dietary components like arginine can inhibit the development of bacterial reductases, providing a possible remedy [28]. Maintaining a healthy level of normal flora is crucial for a healthy profile of drug intake since CYP3A4 is known to be susceptible to changes based on gut microbiota activity [29].

Examples of Drug–Microbiome Interactions:

Direct and indirect interaction (Table 1) occur between drugs and microbiome enzymes as a complex bidirectional interaction led to marked change in the outcomes of the medication bioavailability [30].

Table 1: The table show both direct and indirect interactions examples

No.	Drug	*In Vivo /In Vitro*	Organism\Enzyme	Notes
1	Digoxin	Both	*Eggerthella lenta*	E. lenta reduces cardiac glycoside reductase 2 → less reduction of digoxin [30].
2	acetylsalicylic acid	Both	*Lysinibacillus sphaericus*	Reduced gut microbial ASA-metabolizing activity by 67% in rats [31].
3	Irinotecan	Both	*Bacteroides uniformis and E. coli*	Gut microbial enzymes promote drug toxicity by hydrolyzing the inactive drug → active drug [32].
4	Levodopa	*In vivo*	*Enterococcus faecalis and E. lenta*	Microbes cause less levodopa to be available to cross the blood–brain-barrier [33].
5	Acetaminophen	*In vivo*	SULT1A1	P-cresol competes with acetaminophen binding to SULT1A1 → prevents host from detoxifying acetaminophen [34].
6	Metformin	*In vivo*	Oct1	Pharmacokinetic changes likely owing to ↓ Oct1 expression in the liver → altered hepatic uptake of metformin in vivo [35].
7	Omeprazole	*In vivo*	CYP2C19	Decreased CYP activity when treated with cefprozil. [36].
8	Progestogens	*In vivo*	CYP450	Hydroxylation of progestins are likely CYP450 mediated [37].
9	Caffeine	*In vivo*	CYP1A2	Decreased CYP activity when treated with cefprozil [38,39].
10	Midazolam	*In vivo In vitro*	CYP3A; UGT	*Low levels of CYP3A activity in GF mice decrease drug metabolism in vivo *Decreased CYP activity when treated with cefprozil [40].

Short-term and long-term complications are noted to develop as direct consequences of dysbiosis and Table 2 shows few examples [41].

Table 2: show complications associated with Dysbiosis related drugs

No.	Drugs associated with Dysbiosis	Consequences	References
1	Antibiotics	decreased immune function, increasing susceptibility to infections	41-42
2	Proton Pump Inhibitors	Small Intestinal Bacterial Overgrowth, which can cause bloating, diarrhea, and abdominal pain	43-44
3	NSAIDs	gastrointestinal bleeding, ulcers	45-46
4	Metformin	gastrointestinal side effects such as diarrhea and discomfort	47-48
5	Chemotherapy	Impair immune function, increase the risk of infections, nausea, vomiting, and diarrhea	49
6	Selective serotonin reuptake inhibitors	gastrointestinal disturbances, including nausea and diarrhea, affecting mood and cognition	50

Microbiome as a Therapeutic Target

Emerging evidence highlights the significance of gut microbiome in many diseases like liver disease, Alcohol-related liver disease, Depression, Anxiety, Inflammatory Bowel Diseases, Diabetic, Cancer Immunotherapy and Gastrointestinal Infectious Diseases, which the current review aim to focus on.

Probiotics and prebiotics show an important benefit for gut and liver health by regulating homeostasis system of the microbiota [51].

I. Hepatic failure is a prominent problem affecting many people in several forms worldwide. It is well known that dysbiosis of the gut microbiota influence the development of liver disease signs and symptoms like Non-alcoholic fatty liver disease. In many animal models and recent clinical studies, the incorporation of probiotics, prebiotics, fecal microbiota transplants, and other targeted therapeutics has been advantageous in treating various liver disease etiologies and halting the course of liver disease [52]. Although microbial engineering treatments are still in their infancy, they may prove to be a helpful tactic to eradicate the microorganisms causing gut dysbiosis linked to the advancement of liver disease [53].

II. Depression and anxiety are frequently linked to dysbiosis and inflammatory bowel disorder. Low-grade widespread inflammation and the stress response are both exacerbated by dysbiosis, and vice versa. Depression may develop as a result of this vicious cycle. Dysbiosis should be eradicated in conjunction with antidepressant medication. Prebiotics, probiotics, nutrition, and transplantation of fecal microbiota can all be used for these aims [54].

III. Crohn's disease and ulcerative colitis are two different illnesses and share the characteristic of chronic inflammation: they are both included in Inflammatory Bowel Disease (IBD). Additionally, there is rising evidence linking gut dysbiosis to IBD and its side effects, including colorectal cancer [55]. According to foppa et al, existence of some strains of mucolytic microorganisms have been showed extra in individuals with Crohn's and ulcerative colitis [56]. According to various reviews, the gut microbiota may act as a non-invasive biomarker for the existence and the harshness of inflammatory bowel disease. As well, IBD may be caused by a disparity in the gut microbiota [57].

IV. Based on the articles that are currently available, it showed that lowering dysbiosis and preserving a well balance system of gut flora may assist decrease exaggerated immune responses, which will lessen flare-

ups and sustain remission. The gut microbiome's architecture, taxonomic makeup, and molecular mechanism of action have been found to be key biomarkers for predicting immunotherapy reaction and immune-related adverse events (irAEs). They also serve as a prime target to alter the efficacy of immunotherapy [(58)]. Both adaptive and innate immunity might be controlled by the gut microbiome and their metabolites[(59)]. Since probiotics can add precise change to the composition of the gut microbiome, it is really desirable to add-on with them to improve the outcomes of immunotherapy in conditions when the processes underlying the gut microbiome's influence on immunotherapy are well assumed and understood. potentially yet, probiotics that have been used traditionally should be utilized carefully because improper use can undercut immunotherapy's effectiveness and possibly encourage the tumors growth [(60)].

V. For people with diabetes, primarily type 2, and overweight, the gut microbiome level and diversity are another area of interest. Unique significant discovery is that *Bifidobacterium animalis ssp*., a highly worthwhile and proliferative probiotic, improves metabolic disorders by modifying the gut flora species, which raises systemic concentrations of short-chain fatty acids, particularly acetate [(61)]. These understandings aids and directs toward better guidance of therapy.

Emerging Trends and Outlook

Priorities should be considered as follows:

A. Analytical Diagnostics: A specialized test should be taken in consideration to evaluate and determine the diversity of microbiome, this is going to make it clearer and flawless to physician to choose best allowed medication and avoid possible adverse effects.
B. Studying should continue to update and keep informed gut microbiome health culture and specified enzyme interactions
C. Therapeutics level-up: Future targeting on microbiome manipulation to boost the response by probiotics next generation with modified (engineered) activity to control medications kinetics, interventions within food and prebiotics to maintain normal flora surveillance and best promising outcomes.
D. Customized Medicine Integration: Gut microbiome could be added to patient profile and synchronized with personalized medicine to develop better pharmacological attention.
E. Artificial intelligent (AI): AI break through most sciences fields, so gathering information, updating many algorithms paths and determine genomics variations could be analyzed with AI to yield better management, less undesirable interactions and improved quality of life.

CONCLUSION

Every human body is different, and every person's gut microbiota is unique as well. Variations include the type of microorganisms and their enzyme levels. Gut microbiota eubiosis is directly influenced by a number of factors, including nutrition and medical conditions. Likewise, gut microbiome presents as crucial determinant in therapy design (Pharmacodynamics and pharmacokinetics). As shown in the current review, gut microbiome (by direct and indirect way) has the ability to some extent to affect and deactivate or boost up commonly used drug resulting in variable therapeutic response that swing from expectations among individuals. This review mentioned important clinical examples such as decreased digoxin efficacy and reduced levodopa in the CNS, while gut microbiota could enhance Irinotecan activation. Targeting gut microbes and taking into account all of these variables offer a promising way to modify treatment and influence the result. Prebiotics, probiotics, dietary invasions, fecal microbiota transplantation, and microbial engineering therapy are just a few of the methods that have been investigated and tried both in vivo and in vitro, with good success rates. At the same time, pharmacogenomics and gut microbe profiling can be combined to create fully tailored therapy. Anyway, many obstacles remained to limit clinical outcomes, like high degree of inter-individual variability in microbiome

composition, the deficiency of consistent analytical and practical methods, and existence of few studies with large sample size with well control clinical studies. Therefore, by concentrating on all of these gaps and offering a genuine answer through creative methods, new trustworthy diagnostic tools, and microbiome targeted therapy, it is hoped to reduce response fluctuation and improve quality of life. To put it briefly, the gut microbiota should be viewed as necessary rather than optional.

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الميكروبيوم في الجهاز الهضمي وعلاقته بعلم الأدوية: الآثار المترتبة على استقلاب الأدوية والنتائج العلاجية

احمد محمد محمود[1]، إبراهيم عامر سلمان [1]

[1]كلية الصيدلة, جامعة الفارابي, بغداد, العراق.

الخلاصة

تم إجراء بحث شامل في المقالات والابحاث باستخدام قواعد بيانات عالميه مثل Google Scholar وشملت الدراسة تحليل الأعمال المنشورة بين عامي 2013 و 2025 لضمان حداثة النتائج واستنتاجاتها. تستقر الكائنات الحية الدقيقة (الميكروبيوم) على جميع أسطح جسم الإنسان، بما في ذلك القناة الهضمية، حيث تؤثر في العديد من الجوانب الفسيولوجية للجسم مثل التوازن الداخلي، والتمثيل الغذائي، والاستجابات الالتهابية، والأهم من ذلك هو التفاعل بين إنزيمات الميكروبيوم المعوي والأدوية الفموية.

تناقش هذه المراجعة مجموعة من التداخلات المرتبطة بتأثير الميكروبيوم على العلاجات، والتي قد تؤدي إلى إعاقة أو تقلب التوافر الحيوي وفعالية الدواء وتسبب انخفاضًا في فعالية الأدوية، بينما قد يؤدي بعضها الآخر إلى تعزيز التأثير العلاجي من خلال تأثيرها على امتصاص الدواء، واستقلابه، إعادة معالجته.

تُظهر البيانات المتاحة أمثلة عديدة لتفاعلات الأدوية مع الميكروبيوم عبر آليات مختلفة، وتم ذكر عددا من هذه الأمثلة لتوضيح مفهوم هذه التفاعلات بشكلٍ أدق. ومن الجدير بالاهتمام ان استهداف الميكروبيوم المعوي والتأثير على بيئته في أمراض مختلفة كما هو موضح، للمساعدة في إبطاء تقدم بعض الامراض وتحسين فعالية العلاج.

من خلال التركيز على هذه الفجوات والسعي لتقديم حلول حقيقية عبر تقنيات مبتكرة وأدوات تشخيصية موثوقة وعلاجات موجهة نحو الميكروبيوم، نأمل في تقليل التفاوت في الاستجابة العلاجية وتحسين جودة الحياة.

الكلمات المفتاحية: الميكروبيوم المعوي، تفاعل الدواء مع الميكروبيوم، التوافر الحيوي للدواء، الإنزيمات الميكروبية، العلاج الموجه نحو الميكروبيوم