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Pharmacological efficacy/toxicity of drugs: A Comprehensive update about the dynamic interplay of microbes

JA Gimenez-Bastida¹, L Martinez², A Moya-Pérez³, J.M. Laparra^{2,*}

¹Division of Clinical Pharmacology, Department of Pharmacology, Vanderbilt University Medical Center, Nashville, TN, United States

²Nutrition Precision in Cancer Unit. Madrid Institute for Advanced Studies in Food (IMDEA Food), 28049 Madrid, Spain.

³Department of Developmental and Cell Biology University of California, Irvine, CA, United States

Abstract

Oral ingestion is a common, easy to access, route for therapeutic drugs to be delivered. The conception of the gastrointestinal tract as a passive physiological compartment has evolved towards a dynamic perspective of the same. Thus, microbiota plays an important role in contributing with additional metabolic capacities to its host as well as to its phenotypic heterogeneity. These adaptations in turn influence the efficacy and toxicity of a broad range of drugs. Notwithstanding, xenobiotics and therapeutic drugs affecting the microbiome's activity also significantly impact metabolism affecting different organs and tissues, and thereby drugs' toxicity/efficacy effects. Other physiological interfaces (i.e., gut, lungs, skin) also represent complex media with features about microbiota's composition. Additionally, there have been described key regulatory effects of microbes on immunotherapy, because of its potential harnessing the host immune system, mental disorders by modulating neuroendocrine systems and cancer. These alterations are responsible of physiological variations in the response(s) between individuals and populations. However, the study of population-based differences in intestinal microbial-related drug metabolism has been largely inferential. This review outlines major reciprocal implications between drugs and microbes regulatory capacities in pharmacotherapy.

Keywords

Therapeutics; microbes; efficacy; toxicity; metabolism

1. Introduction

Pharmacological efficacy of therapeutic drugs depends on drug delivery and disposition of the active form responsible for physiological effects. A major challenge of therapeutics is to tailor personalized approaches to minimize population-based differences in bioavailability and biological effects of drugs. The evidence that '*environmental*' factors greatly impact, to a different extent, drug metabolism and physiological behavior from one individual to

*Corresponding author: José Moisés Laparra Llopis moises.laparra@imdea.org Telephone: (+34) 917 278 100.

another highlight the need of changing the way the efficacy/toxicity of several drugs is being approached.

Increasing evidence demonstrates that microbiome is a critical determinant in human health. Strategies to manipulate and prevent alterations in healthy microbiota to normalize physiological manifestations of metabolic and autoimmune diseases are actively being investigated. Microbiome develops a number of protective, immune and metabolic functions, which altogether have an enormous impact on the nutritional and health status of the host providing biological functions that cannot be performed by human metabolism¹. The application of metagenomics to the gut microbial ecosystem has revealed truly remarkable correlations between imbalances in gut microbiota and metabolic diseases². It has also led to the suggestion of the existence of a '*core microbiome*' that encompasses key functions shared by each individual³. Research efforts are focused to unravel microbial partners and define the microbiome composition in the gut and other interfaces between host and the external environment, but this task remains incomplete. Gut microbiota and its microbiome exhibit a relevant participation in the development or instauration of major diseases. The latter highlights the need to understand the relationship between intrinsic human genes, its interaction with different environmental factors and the molecular basis of drug efficacy and toxicity.^{4,5} In the quest to better understand interactions between microbiota and diseases appearance and progression, new physiological information is needed. This information will contribute to implement personalized therapies tailored to the exact biology or biological state of an individual that constitutes one of the greatest challenges of modern medicine.

Microbiota plays an important role in training and modulating the immune system, preventing growth of harmful bacteria species, producing some useful vitamins and affording the extraction of energy and biotransformation of non-nutritive dietary components as well as therapeutic drugs and other xenobiotics. Besides, therapeutic agents can also end up exerting a significant impact on organs and/or tissues through their effect on gut microbiota.⁶ The metabolic capacity of the intestinal microbiota could constitute a crucial factor affecting the disposition, stability and, thereby, efficacy and/or toxicity of several different therapeutic drugs due to extensive transformation of active structures⁷⁻⁹. This metabolic activity leads to the production of metabolites, which exhibit a different behavior (i.e., solubility, disposition) than that observed for their parental compounds.

Metabolic activity of gut microbiota has led to consider it as a '*supraorgan*' likely comparable to the liver⁸⁻¹⁰. Notably, gut microbiome exhibits high variability between individuals (i.e., genders) and can constitute a source of variation of the effects observed. In fact, experimental studies have evidenced differences in the efficacy or toxicity of therapeutic drugs because of differences in microbial-mediated drug metabolism¹¹⁻¹³. These diverse and complicated interactions between the microbiome, drugs, and host still constitute a novel aspect that should not be ruled out when evaluating the potential, positive or negative, biological effects of drugs^{8,14-17}. The interaction between microbes and their metabolites with the main physiological interfaces seems to be necessary for health and wellbeing maintenance.¹⁸

The study of human intestinal microbiota is one of the most challenging tasks for the scientist community because of its high complexity. The latter led to join efforts within international collaborative research projects to define microbial composition and characterize their genotype.¹⁹ Additionally, there are intense research programs to develop animal models, including germ-free, antibiotic-treated, and disease-resistant mice as a landmark to unravel the role of the microorganisms that modulates host intestinal physiology.^{20,21}

This review helps to expand the knowledge about the role of microbiota as important contributor to delivery, disposition and co-metabolism of drugs. To this end, a comprehensive update of the different independently reported aspects about the dynamic interplay between drugs and microbes is reported and completed with current knowledge on novel clinical fields.

2. Impact of microbes on drug disposition.

Limited knowledge exists concerning potential metabolic reactions performed by the bacteria to metabolize therapeutic drugs^{7,22,23}. The existing studies are mostly related to drugs administered orally, whereas there is a lack of data about the efficacy of drugs administered by several other ways.

Currently, many different therapeutic drugs have been identified as susceptible of biotransformation by microbiota's metabolism. There have been revealed significant differences in the metabolic activation or inactivation of drugs causing important variations of efficacy^{8,24}. However, there is scarce evidence that does demonstrate the population-based differences in microbial-related drug metabolism^{11–12}. Examples of the distinct reactions that have been described (Figure 1) affecting several drugs (Figure 2.) are briefly detailed below.

Reductive metabolism

A well-known example of reductive metabolism is the marked decrease in the efficacy of cardiac glycoside drugs such as digoxin^{22,23}, which is particularly important because of its narrow therapeutic interval. In this sense, comparative studies performed on healthy volunteers from southern India and the United States revealed differences in drug metabolism of digoxin associated to the presence of *Eubacterium lentum*¹¹. Similarly, *in vitro* studies showed that therapeutic drugs such as misonidazole²⁵, sulfinpyrazone²⁶, and sulindac are susceptible to undergo reductive-mediated inactivation in the gastrointestinal tract by gut microbiota showing aldehyde oxidase activity. Similarly, studies on rabbits reported the incomplete bioavailability and greater formation of the active metabolite of these drugs when are administered (orally).²⁷ Similarly, some other *in vitro* studies have demonstrated the capability of different microbial (*Bacillus subtilis* MTCC 619, but not *Escherichia coli* MTCC 118), and fungi (*Beauveria bassiana* NCIM 1216 used as biological insecticide) cultures to produce the biotransformation of valdecixib²⁸. The metabolism of metronidazole²⁹ and zonisamide³⁰ has also been evaluated in germ-free and antibiotic-treated animals, respectively. These studies displayed that caecal contents of conventional animals had significant reductase activity, whereas slight or no activity was observed in

germ-free and antibiotic-treated animals. In germ-free and antibiotic-treated rats, bacterial nitroreductase activities have also been associated with an increased toxicity and teratogenic potential of drugs such as nitrazepam and clonazepam^{31,32}. These effects concluded that gut microbiota is essentially involved in the activation of nitroreductase activity. However, these reductive metabolic features of gut microbiota could also be advantageously used when administering pro-drugs to deliver the active structures to the precise location where they are required. For example, the metabolic activation of antimicrobial or anti-inflammatory drugs such as prontosil or sulfasalazine³³, respectively, and their derivatives³⁴ occurs through the reduction of the “azo” bond in their structures minimizing side effects. The strategy of pro-drugs is also useful for poorly absorbed drugs from the gastrointestinal tract as succinylsulfathiazole, which is activated by elimination of the succinyl group acquiring efficacy as antibacterial.³⁵

In vitro studies have described a significant decline in ranitidine and nizatidine levels because of the microbiota-mediated *in vitro* cleavage of the *N*-oxide bond in these molecules³⁶. However, if these transformations take place *in vivo* is not clear as the highest rates of absorption (medians 160–923 $\mu\text{g} \times 30 \text{ cm}^{-1} \times \text{min}^{-1}$) are found in the most proximal region (duodeno/jejunal junction), where bacteria are present at low proportions, and not in the distal part of the intestine or colon³⁷. Similarly, it has been reported that omeprazole is susceptible of bacterial reduction *in vitro*³⁸, but its efficacy should not be affected as it is mostly absorbed before reaching the lower intestine. Animal studies documented that omeprazole administration to rats caused marked shifts in the numbers and genus of enteric bacteria, including a significant reduction (~80%) of jejunal Actinobacteria, particularly *Bifidobacterium* spp.³⁹ considered beneficial to the host's health.

Hydrolysis / Immunotherapy

The dramatic impact of microbial metabolism on the toxicity of metabolites derived from drugs was clearly manifested in the death of fifteen patients, who were orally administered with sorivudine (SRV, 1-b-d-arabinofuranosyl-(*E*)-5-(2-bromovinyl) uracil) within forty days⁴⁰. This effect was attributed to the enterobacteria-mediated SRV hydrolysis, thus leading to the formation of 5-(2-bromovinyl) uracil. This transformation is mainly carried out by *E. coli*⁴⁰ and *Bacteroides* spp. (*B. vulgatus*, *B. thetaiotaomicron*, *B. fragilis*, *B. uniformis* and *B. eggerthii*)⁴¹ and increases toxicity of the anticancer chemotherapy with 5-fluorouracil pro-drugs. The anticancer activity of 5-fluorouracil relies on the restoration of T-cell immunity following the elimination of myeloid-derived suppressor cells. In this context, coadjuvant strategies to restore the population of those microbial groups considered as healthy could provide additional benefits to the pharmacological intervention. For example, recent data provided convincing evidences about the promising potential of defined commensal bacteria (*Bifidobacterium longum*) as part of immunotherapy because of its potential harnessing the host immune system favoring anti-PD-L1 efficacy⁴². The scarce existing data allow us to hypothesize that immune-metabolic activity of microbes could have an important impact favoring antigen presenting processes, thus preventing T cell anergy or exhaustion. In relation to cancer chemotherapy efficacy and toxicity a recent review has focused on defining tools for manipulating microbiota in the clinical practice⁴³.

Intestinal bacteria can also mediate the conversion of a nitro group to a primary aromatic amine with further hydrolysis of the amide linkage as occurs from orally administered chloramphenicol to conventional, but not antibiotic-treated, animals producing *p*-aminophenyl-2-amino-1,3-propanediol ⁴⁴. It is noteworthy to mention that this reaction is not produced by beneficial lactic acid bacteria, which are highly sensitive to chloramphenicol ⁴⁵.

Denitration, decarboxylation

Denitration of glyceryl trinitrate, commonly used for the treatment of angina pectoris, has also been reported after incubation of this drug with rat colonic contents ⁴⁶ as well as mixed cultures with wastewater (*Pseudomonas putida* and *Pseudomonas fluorescens*) ^{47,48} in anaerobic and aerobic conditions, respectively. This observation could motivate an important decline on drug delivery, since glyceryl trinitrate is mainly administered through transdermal patches; however, it is difficult to draw out any conclusion due to the lack of studies evaluating the potential impact of skin microbiome on drug metabolism. Another important reaction reported is the reaction of decarboxylation of dyhydroxyphenylalanine residues of L-DOPA, effective in the therapy of Parkinson's disease, undertaken by bacteria. This biotransformation highlights aspects such as whether variations on the concentrations of L-DOPA reaching the central nervous system affect its desired bioactivity ⁴⁹.

Functional groups

The bacteria-mediated inactivation of the active component of sulfasalazine (i.e., 5-aminosalicylic acid) has been reported to take place through the incorporation of an acetyl group in the drug's structure by a plethora of bacteria (*Citrobacter amalonaticus*, *Citrobacter farmeri*, *Citrobacter freundii*, *Klebsiella ozaenae*, *Klebsiella oxytoca*, *Klebsiella rhinoscleromatis*, *Morganella morganii*, *Serratia marcescens*, *Shigella flexneri*, *Plesiomonas shigelloides*, and *Vibrio cholerae*) commonly present in the gut ⁵⁰. The elimination of the acetyl group from another analgesic such as phenacetin leads to the formation of *p*-phenetidin, and exacerbates the *in vitro* toxic effects ⁵¹, which are connected with methemoglobinemia and nephritis.

N-demethylation seems to be the molecular mechanism by which gut microbiota mediate the alteration of methamphetamine ⁵². Notably, this reaction has only been reported *in vitro* using caecal contents of guinea pigs. This alteration can have little or no effect on drug efficacy as methamphetamine is mainly absorbed in the duodenal/jejunal sections of the intestine. In addition, the alteration of amine/amide groups by bacterial metabolism can also take place when they are present as thiazole ring, for example, the biotransformation of levamisole - coadjuvant in vaccines - mainly due to *Bacteroides* and *Clostridium* spp. ⁵³. Similarly, the isoxazole ring of risperidone resulted metabolized by gut microbiota showing oxidative dealkylation at the piperidine nitrogen and the scission of the isoxazole in the benzisoxazole ring system ⁵⁴.

Among all the bacteria-mediated alterations on drugs' structure, there can be particularly highlighted two major metabolic reactions. These changes are associated with the alteration of bile acid metabolites and derived conjugates affecting drug disposition ⁵⁵. Additionally,

expression and activity of major drug-metabolizing enzymes have also a significant effect on drugs' efficacy⁵⁶. These interactions are especially relevant in the case of parent molecules that render highly toxic metabolites delaying its elimination from blood circulation. Irinotecan is a pro-drug that renders the SN-38 metabolite (7-ethyl-10-hydroxycamptotecin). SN-38, which exerts much more antitumor activity, is eliminated by conjugation with a glucuronide group in the liver. However, this metabolite is majorly deconjugated by the β -glucuronidase activity of gut microbiota, thus contributing to exacerbate intestinal toxicity (structural and functional injuries)^{22,57}. Other well-known examples of drugs suffering bacteria-mediated deconjugation and enterohepatic recycling are digitoxin⁵⁸ or morphine that results in reduced phagocytosis of Gram-positive in comparison to Gram-negative bacteria⁵⁹. In addition to classic deglycosylation processes^{59,60}, human-derived data demonstrate the positive effects of polysaccharides, from ginsenosides used in traditional medicine, recovering the microbiota (i.e., *Lactobacillus spp.* and *Bacteroides spp.*) responsible for its metabolism²¹. These products have been identified as probably responsible for the bioactivity of ginsenosides in humans.⁶⁰ Similarly, bacterial-mediated metabolism also occurs on pharmacologically active natural glucuronides such as biacalin (from *Scutellariae radix*)⁶¹ and glucosinolates like glucorapharin (found in Cruciferous vegetables) with anticarcinogenic properties²³. The bacterial-mediated metabolism favors their rapid appearance in the systemic circulation, as demonstrated in conventional rats in comparison to germ free animals⁶¹. However, there have been identified species- and substrate-specific differences in the capacity of the caecal microbiota to hydrolyze different glucuronide conjugates (phenolphthalein glucuronide, 4-methylumbelliferone glucuronide, morphine-3-glucuronide)⁶² pointing to the importance of gut microbiota composition in the disposition and efficacy of these pro-drugs.

3. Dynamic interplay between microbes and drugs.

The mechanisms commonly involved in the host-drug interaction are: **i)** delayed gastric emptying, **ii)** alteration of the “first step” of drug metabolism in the intestine and/or liver, **iii)** increased bile flow, **iv)** formation of complexes and non-absorbable chelates, **v)** increased splanchnic blood flow, **vi)** alteration of intestinal transit time, and **vii)** modification of gastrointestinal and/or urine pH. In the intestine, detoxifying systems (multidrug resistance, cytochrome P450 or ABC transporters - ATP-binding cassette transporters - in general) work in conjunction metabolizing the administered drugs or xenobiotics by introduction of functional groups. This modification favors their excretion or accumulation into the entero-hepatic circulation of polar metabolites.

Nutrients and metabolites are transported from the intestine to the liver establishing a way of interconnection, known as ‘*gut-liver axis*’, whereby microbiota-biotransformed metabolites interact with liver metabolism jointly with those compounds transported in the bile (Figure 2.). Liver cells respond to these compounds via different nuclear receptors “xenosensors” that have been demonstrated, in animal studies, be susceptible of regulation by the microbiota^{12,17}. These comprehensive analyses revealed transcriptional and protein changes in a network connected with the hepatic metabolism of xenobiotics affecting the activity of cytochrome P450, fatty acids and lipid metabolism, amino acid metabolism and bile acid synthesis. A clear example is the recently demonstrated effect of the probiotic

microorganism *Lactobacillus casei* decreasing the expression (mRNA and protein) levels of cytochromes P450 in male rats, an effect that could prevent the development of colorectal cancer and some other interactions with the concurrent administration of pharmacotherapeutic agents ⁶³.

The potential bacteria-mediated modulation in the activity of organs such as the gut and liver, and thereby drugs disposition and metabolism affects the dosage of therapeutic compounds. For example, gut microbiota has been identified as responsible of a less efficient metabolism of pentobarbital ¹². The impaired metabolism is reflected in a longer time of anesthesia in conventionally-raised animals compared to germ-free animals. Indeed, there have been reported moderate effects of gut microbiota in the modulation the levels of phase II metabolizing enzymes in germ-free rats ^{16,64}. Intestinal bacteria have shown an important regulatory effect on glutathione S-transferases (p1 and p2), as well as major bile acid transporters (i.e., Na⁺-taurocholate cotransporting polypeptide and organic anion-transporting polypeptide 1b2), and the cholesterol transporter Abcg5/Abcg8 ⁶⁴.

The bacterial-mediated differences in metabolizing enzymes in conventionally raised animals, as concluded from comparison to germ-free rats, were low protein levels of glutathione transferases, gastrointestinal glutathione peroxidase, epoxy hydrolases and N-acetyltransferases. These results evidence the participation of gut microbiota metabolism to reduce drugs concentration available after oral administration. However, the effects observed displayed a high variability based on the animal model (mouse or rat) and diet ¹⁶. The bacteria-mediated modulation of metabolizing systems in complement organs has also been associated with the bioactivation of toxic molecules, for example cycasin – a carcinogenic glycoside from cycads hydrolytically activated - or heterocyclic amines ^{63,65}. In this sense, bacterial metabolizing enzymes can hydrolyze the conjugates produced in the liver and excrete them into bile, thus delaying their elimination and, thereby, exacerbating the potential cytotoxic effects. A growing body of evidence indicates that gut microbiota also impacts on intestinal and hepatic expression and function of transporters (uptake and efflux) ^{64,66}. Notably, the direction of these responses suggests that microbiota-mediated modulation of host's gene expression and/or function in the gut and/or liver can greatly impact, worsening or improving, drugs' efficacy/toxicity in mice and patients.

Emerging data have identified the intestinal microbiota as a regulatory component of the intestinal endocannabinoid system (eCB) increasing the expression of endocannabinoid-1 agonist receptor ⁶⁷. This microbial influence on the eCB system can be hypothesized as responsible of the dyskinetic behavior observed in 6-hydroxyphenylalanine-treated rats ⁶⁸. In addition, endocannabinoid system participates in the regulation of energy homeostasis and gut permeability. ⁶⁹ As described, there could be expected inflammatory and hypoxic conditions derived from the endogenous anandamide- and 2-arachidonoyl glycerol-mediated CB1 activation. Thus, the deregulation of cellular energetic metabolism could impair the activation of ABC transporters, which play an important role in the regulation of nutrients and xenobiotics accumulation into cells. The impairment of ABC transporters activity, in conjunction with alterations of gut permeability, condition drugs disposition increasing their toxic effects. There are some examples illustrating how bacteria can influence the regulation (either up or down) of ABC transporters in the duodenum and colon. These sections of the

intestine exhibit ability to modulate the absorption, distribution, metabolism, secretion and, thereby the impact of drugs and xenobiotics on human health ⁷⁰. Besides their role in drug disposition, the hypothesis that ABC transporters can act as potential receptors for pathogenic bacteria to cause infection is gaining strength.

Although it has been demonstrated the important impact of microbiome in host's phenotype ¹⁷, recent comprehensive analyses revealed different transcriptional response(s) to several Lactobacilli (*L. acidophilus*, *L. casei*, and *L. rhamnosus*) ⁷¹. These authors evidenced, in a modest number of volunteers, response(s) related to the regulation of major basal mucosal processes with reasonable similarity to response profiles obtained for specific bioactive molecules and drugs ⁷². These results are in agreement with the previously described microbial modulation of host's metabolic and detoxifying phenotypes. However, these authors also indicated large person-to-person variations in response to transcriptomes that may lead to measurable effects in some volunteers, but not in others. All these aspects should not be ruled out in research efforts to modeling mammalian biocomplexity ⁷².

Besides the impact of microbes in drugs disposition and biotransformation, there have also been reported changes in microbiota diversity and numbers as consequence of the drugs-mediated modifications in the internal milieu ^{39,73}, inhibition of intracellular physiological processes ⁷³, deregulation of intestinal homeostasis and/or even modulation of the expression of several different receptors ^{74,75}. Additionally, the microbiota-mediated bioactivation of anti-inflammatory drugs such as mesalazine has also been associated with lower faecal bacteria abundances and rebalancing of the major constituents of the microbiota ⁷³.

A novel area where microbiota composition has emerged as a relevant factor influencing physiological responses is mental disorders. At present, drugs belonging to new classes of antidepressants still have antimicrobial effects. Desipramine is an important antidepressant psychotherapeutic drug that causes important side-effects like dysfunction of salivary gland (i.e., oral dryness, xerostomia). This alteration generates a decrease in amylase protein levels, but an increase of the synthesis of proline-rich proteins and lysozyme as a function of the treatment and the subject's age ⁷⁶. Subsequently, oral microbiota changes with the administration of desipramine result in a higher incidence of infections generating gingivitis. However, fundamental questions concerning the microbial taxa that result affected remain unsolved. In this sense, a recent informative review summarized current data concerning the implication of dysbiosis of gut microbiota in the development or exacerbation of mental disorders ⁷⁷.

The effects of opioids on gut microbiota have been described *in vivo* and *in vitro*. Morphine can alter gut microbiota by inducing dissemination of Gram-positive intestinal bacteria (*Staphylococcus sciuri*, *S. cohnii*, *S. aureus*, *Enterococcus durans*, *E. casseliflavus*, *E. faecium* and *E. faecalis*) in C57BL/6J mice ⁷⁸. This effect was exerted through the activation of innate immune Toll-like receptor (TLR)-2 and up-regulation of interleukin (IL)-17A ⁷⁹. There have also been reported morphine-induced inhibitory effects on the *in vitro* production of interleukins and signaling of the innate immune toll like receptors, thus increasing susceptibility to bacterial infections. Morphine impaired mucosal host defense innate

immune signaling processes to *Streptococcus pneumoniae*-induced IL-23 production through MyD88-IRAK1/4-dependent TLR2 and Nod2 signaling in dendritic cells ⁷⁴. Similarly, it has been shown the morphine-mediated modulation of gut immunity and homeostasis ⁸⁰ and the depletion of lymphoid subsets ⁷⁸. These data point to the impact of opioids on the internal milieu favoring infections and alterations of the health status.

Although this review does not focus on abuse drugs, it is worth to bring here some of the potential contributions to their efficacy and toxicity. Briefly, microbial interaction with abuse drugs seems to contribute in the development of specific phenotypes. This has been identified in populations sharing a social (crack cocaine abuse) network, rather than genetic features, favoring the infection of *M. tuberculosis* ⁸¹. Similarly, cigarette smoke exposure has been linked to high risk of infections evidencing the close relationship between smoking and disruption of the fine-tuned balance of microbiota in the upper human respiratory tract ⁸². Alcohol consumption has also been identified as one of the causative factors responsible for intestinal dysbiosis as concluded from a reduced mucosal-associated microbial diversity ⁸³. Moreover, alcohol consumption on intestinal microbiota is associated with increased endotoxemia that appears as a mechanism, additional to gut leakiness, of alcoholic steatohepatitis.

Apart from the aforementioned diseases, some metabolic syndromes (i.e., non-alcoholic fatty liver, obesity, and type 2 diabetes) can significantly change bacterial composition and subsequently drug metabolism. ^{84,85} All these exhibit low-grade inflammation as a common feature, which can be significantly modulated by gut microbiota, thus affecting therapeutics efficacy/toxicity.

4. Conclusions and future perspectives.

Gut microbiota is an essential factor in the metabolic capacities of the host regulating the expression of genes and proteins. Thus, potentially affecting the biotransformation and toxicity/efficacy of therapeutic drugs. The key biological roles that gut microbiota plays in several different metabolic diseases has changed the way it is investigated, since the metabolites and effects depend on particular features of gut microbiota composition and even interindividual variability. Besides, drug-mediated changes in gut microbiota composition can also have important consequences probably modulating its functional effects in mammalian tissues. The existing scientific evidence highlights the potential importance and role of gut microbiota as a new aspect that should be taken into more consideration when establishing pharmacological therapeutic strategies. Advances on the knowledge of the interactions between bioactive food compounds and specific intestinal bacteria will help to better understand population-based differences in microbial-related drug metabolism. The latter will contribute the way for development of therapeutic applications based on personalized medicine, yet important questions such as how far and to what extent can the consequences of bacterial-related metabolic changes in efficacy/toxicity be modulated via targeted intervention.

These are novel perspectives connecting alterations in the microbiota composition of physiological interfaces to risk factors for different metabolic and/or immunological

diseases. However, current evidence for an association of these aspects with drugs' efficacy/toxicity/resistance has largely been inferential. There remain key unanswered questions that require a concerted research effort to arm the scientific and clinical communities and finally society with effective translational strategies. To this end, there is a need to overcome the usually fragmented and compartmentalized approach to evaluate the efficacy/toxicity of therapeutic drugs taking into account the role of microbiota composition in drug delivery/disposition.

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Figure 1.
Microbial-mediated biotransformation processes influencing drug disposition.

Figure 2.
Examples of drugs susceptible of microbial-mediated biotransformation.

Figure 3.

Interactions of gut microbiota with therapeutic drugs.

The black dotted arrow represented the absorption process of drugs. The bold grey arrow represented a schematic interaction of the gut microbiota with the immune-metabolic axis and the different mechanisms proposed to explain its implication in toxicity efficacy and health/disease risk. Mechanisms underlying the connection of drugs-induced host detoxifying metabolism activation influenced by gut microbiota (e.g. multidrug resistance protein, MDRs; the cytochrome P450 superfamily, CYPs; and the ATP-binding cassette transporters, ABC transporters) and microbiota biotransformations (e.g. hydrolysis, dehydroxylation, denitration, amine formation and proteolysis). Drugs metabolism occurs associated to the energetic cell metabolism; and the endocannabinoid system (eCB) participates in the regulation of energy homeostasis and gut permeability (increasing the possibility to appears a metabolic endotoxemia). The deregulation of cellular energetic metabolism could impair the activation of ABC transporters causing together inflammation (cytokines production) and alterations in gut permeability increasing the toxic effects.