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Review Article

Gut *Microbiota* and Its Role in Metabolism of Common Drugs–A Short Review

Rohitash Jamwal[1] and Sumanta Kumar Goswami[2]

[1]Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, Kingston, RI 02881, United States.
[2]Department of Pharmacology, Al-Ameen College of Pharmacy, Near Lalbagh main gate, Hosur road, Bangalore, India.

ABSTRACT

Our gut is home to over a trillion of microbes existing in a symbiotic relationship with its host organ. The enzymes synthesized by gut *Microflora* have been long known to influence our health, but their role in the metabolism of drugs has not been studied to that extent. Similar to drug metabolizing enzymes in liver and intestine, gut *Microbiota* can modulate the metabolism of drugs in a number of ways including but not limited to hydrolysis, reduction, or degradation of a drug molecule. The role of liver and intestine has been extensively studied during early drug discovery for its influence on drug metabolism but very less emphasis is given to metabolism of drugs by gut *Microbiota*. This review paper discusses the role of gut *Microflora* and its role to alter drug metabolism and advocate the inclusion of microbial metabolism screening during drug development.

Key words: Digoxin, Drug Metabolism, Gut *Microbiota*, Phenacetin, Sorivudine.

INTRODUCTION

Human gastrointestinal tract is home to a diverse community of symbiotic microorganisms collectively referred as Gut *Microbiota*. Studies in past 25 years have changed our understanding of the role of human gastrointestinal (GI) tract and microbes inhabiting our intestine. This microbial community is highly plastic in nature and governed by a number of factors like diet, drugs, probiotics, environment, gender, eating behavior and microbially produced metabolites.[1] That makes human *Microbiota* of a person as diverse as a human fingerprint.[2] These microbes participate in mutualistic interaction with its host and are of immense use to humans. They regulate extraction of vital nutrients, synthesis of essential vitamins and provide resistance to colonization by pathogens.[3,4] Such is the magnitude of gut *microbiota* that some researchers consider it as a separate organ inside the human body with the metabolic potential at par to human liver or maybe even higher. Microbial genome is suggested to carry ~150 times more genes than the host human genome; hence providing *Microbiota* with extensive metabolic activity.[1]

As oral administration remains the most preferred route of drug administration due to attributes like convenience, safety, and cost, every drug has to go through GI tract before being absorbed in the small intestine. Before a drug reaches its target site, it passes through the intestinal wall and is delivered to the liver by hepatic portal vein and then finally transported to its site of action via the bloodstream. A small amount of absorption also takes place in the large intestine but it's not significant. Before absorption of the drug in the gut, it should dissolve in luminal fluids and remain intact for absorption processes. As the drug begins its journey through the gastrointestinal tract towards the site of absorption, it is exposed to harsh gastrointestinal environment and microbial metabolism. The enzymes present in the intestinal epithelia and liver also metabolize these drugs, hence, decreasing the amount of drug reaching the systemic blood circulation. Cytochrome P450 and UGT are major drug metabolizing enzymes in humans and they participate in drug metabolism by oxidation or conjugation reactions. On contrary, gut microbes tend to participate in reduction or hydrolysis reactions, including decarboxylation, dehydroxylation, and deamination[5] (Figure 1).

Like any other cell, gut microbes are capable of producing different enzymes with the ability to act on a wide array of substrates. The metabolism of xenobiotics by microbes plays a key role in the biotransformation of drugs and other xenobiotics, leading to alteration in the drug disposition and toxicity. Microbial enzymes can metabolize and transform the drugs to make them either inactive or toxic by changing its pharmacological activity. For example, a cardiac drug digoxin is metabolized by *Eggerthella lenta* (Actinobacteria) in the gut to dihydrodigoxin. The metabolite thus produced has a lower biological activity in comparison to the parent molecule.[6]

Corresponding Author :
Dr. Sumanta Kumar Goswami
Department of Pharmacology, Al-Ameen College of Pharmacy, Near Lalbagh main gate, Hosur road, Bangalore, India.
E-mail: sumantag@gmail.com

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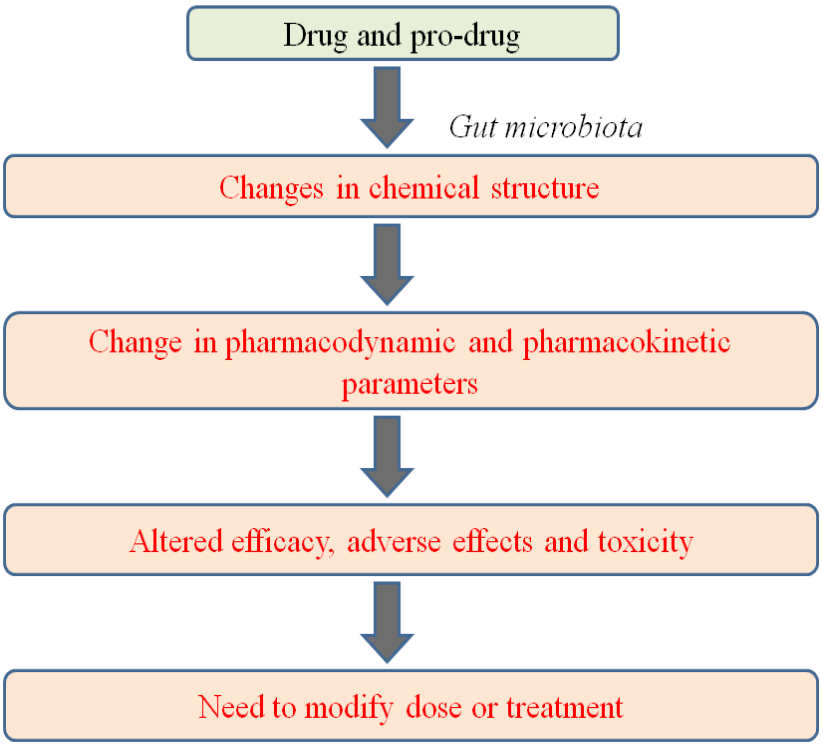

Graphical Abstract

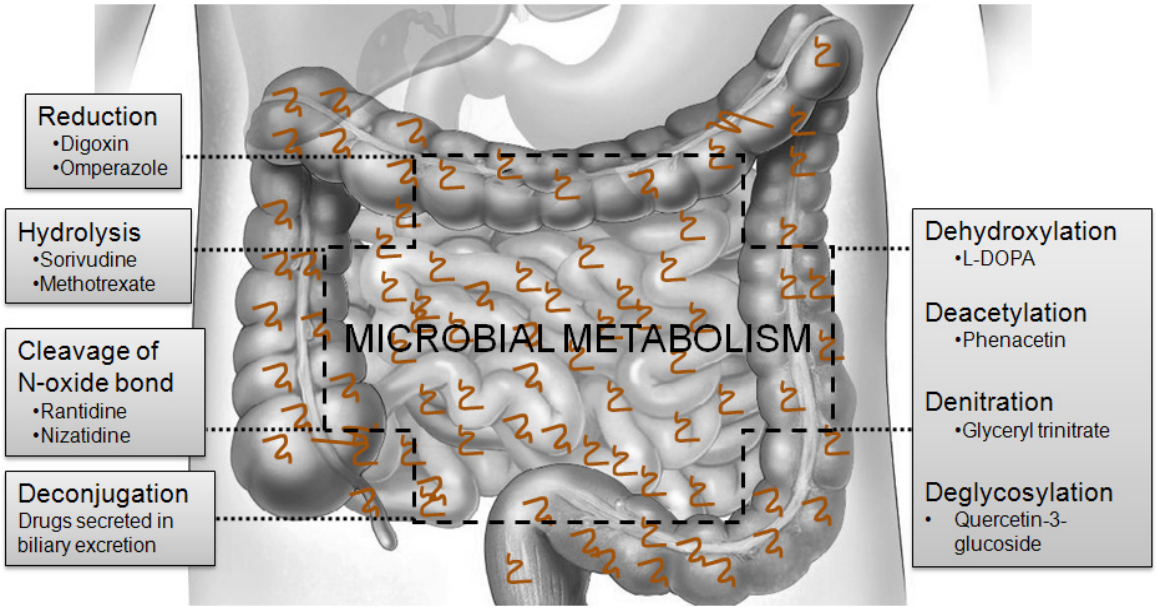

Figure 1: Key microbial metabolism reactions of drugs and major drugs which are undergo microbial metabolism in the GI tract

The metabolism of the drug by microbes may lower the stability of the drug, make it unsuitable for absorption, lower the bioavailability or may reduce the activity of the parent drug molecule. In addition, compounds of microbial origin can compete and interfere with absorption and metabolism of the drug molecule in the intestine. Microbial derived compounds or drug metabolites can also cause serious drug-drug interaction if they alter the pharmacokinetics and pharmacodynamics of the co-administered drugs.[7,8] Recent studies have also highlighted the role of *Microbiota* in disease conditions like diabetes, obesity, and allergies.[8,9]

A large amount of research emphasis is given to the intestinal (enterocyte) and hepatic metabolism (ADME studies) but metabolism of drugs by microbes is not a part of the screening. The main emphasis of this review article is to review the studies on the biotransformation of a few of the commonly used drugs. In addition, it also emphasizes the consideration (inclusion) of drug metabolism by gut microbes during early drug development along with ADME studies.

Microbial Metabolism of Drugs By Hydrolysis

Hydrolysis is one of the most common types of reaction by which a large number of drugs are metabolized by gut flora. β-glucuronidase, β-glucosidase, azoreductase, nitrate reductase, nitroreductase, and phosphorylases are some of the key hydrolytic enzymes produced by gut microbes.

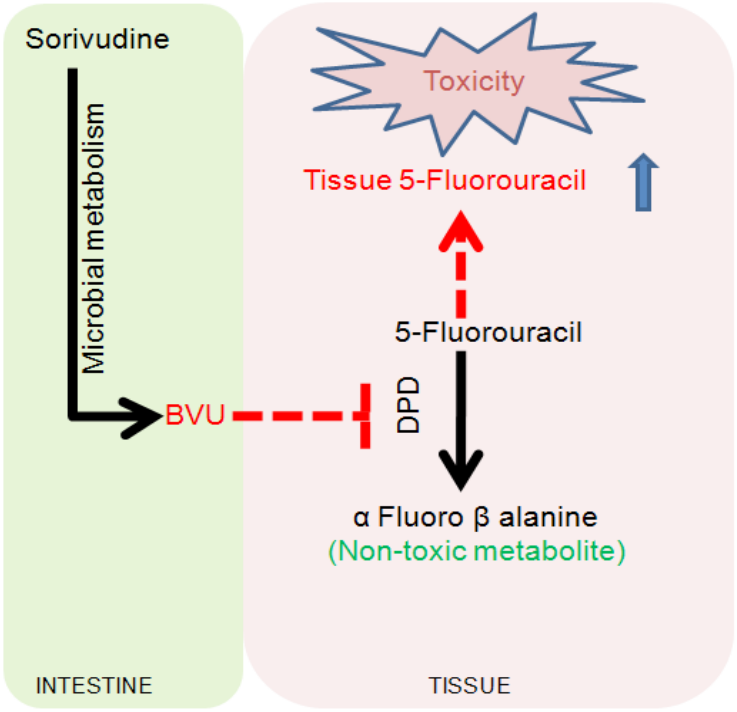

Figure 2: Hydrolysis of Sorivudine to BVU by gut *Microflora*

Sorivudine (SRV, 1-β-D-arabinofuranosyl-(E)-5-(2-bromovinyl) uracil) toxicity remains as one of the earliest studies which changed our perspective towards microbial metabolism of the drugs and drug interactions.[7] Sorivudine was an antiviral launched in Japan in 1993 for the treatment of viral herpes zoster disease, but was withdrawn from the market within one month of its launch due to lethal side effects.[7] In a tragic event, 18 patients in Japan died due to acute toxicity when SRV was administered to cancer patients who had received previous doses of 5-fluorouracil (5-FU). 5-FU is an anticancer drug which is usually administered as a part of chemotherapy.[10] A toxicology study was performed in rats to ascertain the cause of human toxicity. A number of studies were performed, and it was found that SRV gets metabolized in the intestine to a reactive drug metabolite (E)-5-(2-bromovinyl) uracil (BVU) by bacterial enzyme pyrimidine nucleoside phosphorylase. BVU permeates through intestinal membrane (BVU) and binds covalently to hepatic dehydrogenase (DPD). (Figure 2), an enzyme required for the catabolism of 5-FU in rats and humans. This binding led to irreversible inhibition of the DPD that in turn resulted in a significant increase in the 5-FU concentration when it was administered concomitantly with SRV in patients suffering from cancer and viral disease.[11,12] Nakayama *et al*. identified that *Bacteroides eggerthii* and *Bacteroides vulgates* present in the human intestine were responsible for the conversion of SRV into BVU. Hence, it was shown that inhibition of DPD by gut *Microflora* generated BVU led to the deaths when SRV was co-administered with the 5-FU.[13]

Reduction of drugs by *Microbiota*

Digoxin, a cardiac glycoside is the most commonly prescribed cardiac drug which rely on binding ability with human Na^+/K^+ ATPase in cardiac myocytes for its efficacy. Researchers during late 70's found that some of the patients (10%) on digoxin failed to respond to therapy and excreted a reduced metabolite of digoxin.[14] The role of gut *microbiota* was discovered in a breakthrough study where it was found that coadministration of digoxin with antibiotics in human prevented dihydrodigoxin excretion in patients that excreted this metabolite prior to concomitant use of antibiotics. Subsequent studies by Lindenbaum *et al*. found out that *Eggerthella lenta* metabolized digoxin in gut flora and introduced a lactone ring on the metabolites formed, dihydrodigoxin.[15] About 40% of the ingested digoxin after oral intake was metabolized by anaerobic intestinal bacterial *E. lenta* into dihydrodigoxin and dihydrodigoxigenin. Presence of a lactone ring on digoxin molecule reduced the ability of the metabolite to bind to cardiac Na^+/K^+ ATPase and thereby reducing its efficacy. The reaction was also blocked when digoxin was administered with an antibacterial (tetracycline) which inhibited *E. lenta* and stopped the reduction of digoxin *in vitro* and *in vivo*. Later it was found that *E. lenta* exclusively carried out the conversion of digoxin to dihydrodigoxin in gut.[16]

In a study published in 2013, a group of scientists showed that the absence of cytochrome-encoding operon in non-metabolizing *E. lenta* strain is responsible for variation in the metabolism of digoxin by different people.[17] The same study revealed that arginine prevents the *in vivo* microbial metabolism of digoxin in mice and circulating microbial metabolite. A high protein rich diet rich in arginine corroborated the studies with a high amount of digoxin appearing in the blood, hence suggesting the prevention of metabolism of digoxin in the gut.

Cleavage of N-oxide bond

Ranitidine is a commonly used H_2 receptor antagonist for the treatment of gastric acidity, gastro esophageal reflux disease (GERD) and peptic ulcer. Williams *et al*. found that the absorption of ranitidine from stomach and jejunum is significantly higher as compared to absorption from cecum of the small intestine.[18] Earlier theories related this behavior to the availability of small surface area within cecum and also to a low paracellular transport of ranitidine.[19] However, Basit and Lacey showed that the intestinal absorption and systemic bioavailability of ranitidine are reduced by the cleavage of N-oxide bond by colonic bacteria.[20] An *in vitro* study was designed to simulate the colon conditions and evaluate the stability of ranitidine in such conditions. Mass spectrometry analysis revealed that the colonic microbial enzymes cleaved N-oxide bond resulting in a loss of an oxygen atom from the ranitidine molecule. Subsequent studies showed that nizatidine was also susceptible to significant colonic

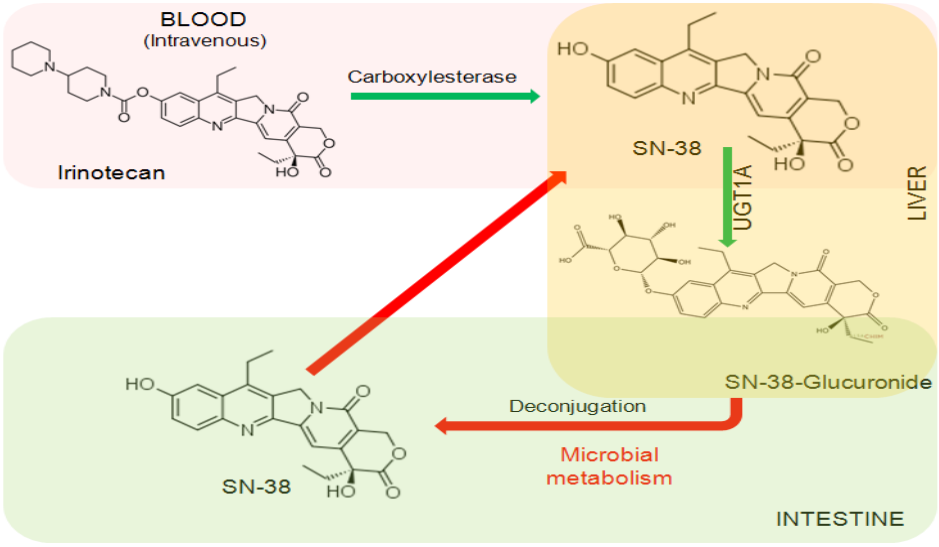

Figure 3: Deconjugation of SN-38 glucuronide to parent drug by microbial metabolism

metabolism.[21] Cimetidine and famotidine were found to be resistant to colonic metabolism in the same study.

Deconjugation of drugs secreted in biliary excretion

Phase II enzymes like GST, UGT adds polar chemical moieties like glutathione and glucuronic acid to lipophilic drug molecules making them more polar and readily available for excretion through kidneys. However, some of the polar phase-II drug metabolites are often excreted back to the intestine through where the conjugates can be cleaved, and the free parent drug molecule is available for reabsorption before entering enterohepatic circulation. Bacterial enzymes remove amino acid on the carboxyl group attached to drug conjugates.[22] The reabsorption prolongs the exposure of such drugs in the body and often contribute to toxicity, more noticeably hepatotoxicity. Hence, the drugs that undergo enterohepatic circulation often exhibit a longer mean residence time in the body and a higher half-life. β-glucuronidase and β-glucosidase of bacterial origin constitutes the bulk of deconjugation reactions in the intestine. The expression of the deconjugating enzymes is markedly affected by diet and age.[23] Rats fed with meat showed an increase in activity of deconjugation enzymes while age also increased the enzymatic activity. Similar studies in human with high meat consumption showed a significant increase in fecal β-glucuronidase activity.[24]

Most steroidal sex hormones rely upon microbial deconjugation in intestine before they enter enterohepatic circulation. More than half of circulating estrogens (~60%) undergo phase II metabolism and are excreted in the bile in the form of glucuronides or sulfates.[25] The conjugate from the hormones are removed by enzymes of bacterial origin (glucuronidases and sulfatases) in the intestine with highest deconjugation in the lower small intestine and colon.[26] Deconjugation activity of *microflora* has also been implicated in exposure of morphine which enters enterohepatic circulation and is significantly deconjugated in the GI tract.[27]

Acetaminophen is another example of a drug that undergoes deconjugation in intestine upon biliary excretion. Acetaminophen is significantly conjugated by GSH forming acetaminophen-3 glutathione conjugates in hepatocytes. Glutathione conjugation results in the extensive excretion of resulting electrophile metabolite in bile. Metabolism of these conjugates by dipeptidases present in gut lumen results in the formation of cysteine conjugates. These conjugates are further cleaved by enzymes of microbial origin including β-lyases, methyltransferase and acetyltransferase in the intestine or are reabsorbed. Microbe mediated metabolism of cysteine conjugates yields toxic thiol metabolites which have been implicated for toxicity potential of acetaminophen.[28] A study showed a higher amount of urinary acetaminophen-3-cysteine in germ-free mice as compared to conventional mice.[28] In the same study, the trend was reversed for thiol metabolites of acetaminophen (acetaminophen-3-methylthiosulphoxide, 3-(methylthio) acetaminophen) highlighting the role of microbial metabolism.

Irinotecan is a chemotherapy drug widely used for the treatment of colorectal cancers and exhibits complex pharmacokinetic behavior. The drug when administered intravenously is converted into its active form, SN-38 by carboxyesterases in blood serum and tissue.[29] SN-38 is extensively glucuronidated in the liver by UDP-glucuronosyl transferase (UGT1A) before it enters the intestine through biliary secretion. SN-38-G, the glucuronidated form of SN-38 is metabolized by bacterial β-glucuronidases leading to the release of the active metabolite in the intestine Figure 3. The presence of this active metabolite is responsible for side effects of irinotecan that includes diarrhea, weight loss and anorexia. Concomitant administration of antibiotics increased efficacy of the therapy owing to a reduction in the undesirable effects of irinotecan metabolite by suppression of bacterial activity.[30] The search for bacteria specific β-glucuronidase inhibitors still remain an exciting field in cancer research.

Dehydroxylation

L-3,4-dihydroxyphenylalanine (L-DOPA) is synthesized from tyrosine and is a precursor of majority of catecholamines (dopamine, epinephrine and norepinephrine) in humans. Dopamine secreted by brain cells control muscle movement, and death of nerve cells in Parkinson's disease leads to dopamine depletion in CNS. This leads to uncontrolled muscular movement and coordination in people with Parkinson's disease. Therapies for the treatment of the disease have been centered on drugs that increase dopamine levels in the brain. L-DOPA is one such therapy where the drug crosses blood brain barrier and undergoes decarboxylation in the brain to restore depleted dopamine[31] (Figure 4). Metabolism of orally taken L-DOPA by gut flora can result in decreased amount of drug available for absorption and hence altered pharmacokinetics and reduced efficacy of the therapy. *In vitro* incubation studies with rat fecal content demonstrated dehydroxylation of L-DOPA at para position of the catechol ring and formation of m-tyramine and m-hydrophenylacetic acid.[32] No metabolite of L-DOPA was found in urine of germ-free rats. The presence of these metabolites in urine of conventional rats corroborated the microbial metabolism of L-DOPA. Recent studies showed the interaction of L-DOPA with adhesins on surface of *Helicobacter pylori* resulting in decreased plasma concentration of L-DOPA.[33]

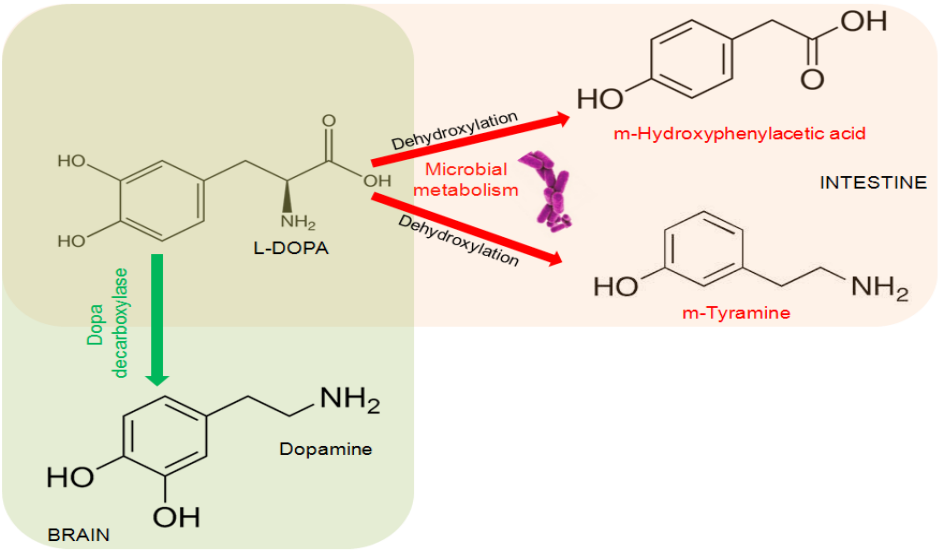

Figure 4: Dehydroxylation of L-DOPA to m-Tyramine and/or m-Hydroxyphenylacetic acid by microbes in the gut

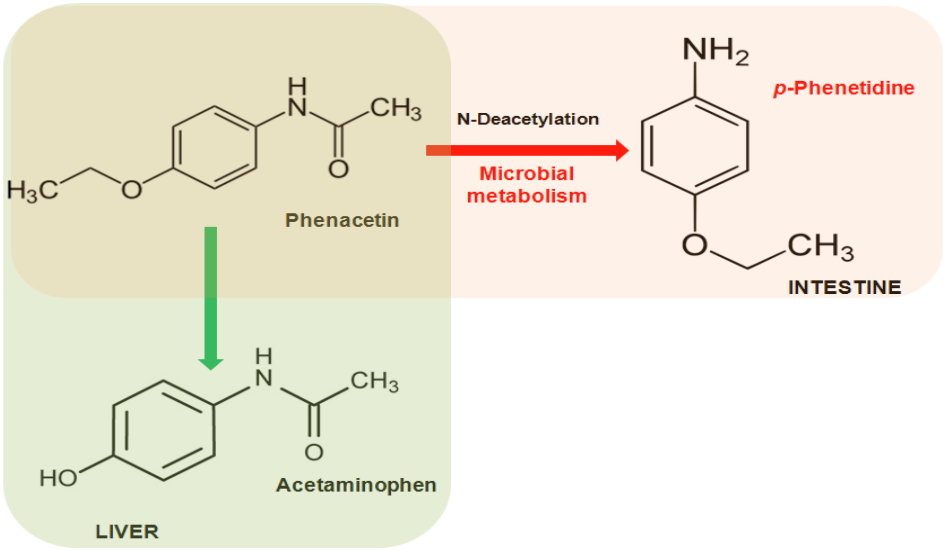

Figure 5: Deacetylation of Phenacetin to *p*-Phenetidine by gut microbes

Deacetylation

Phenacetin was a popular analgesic drug which exhibited high absorption and rapid metabolism to acetaminophen by hepatic enzymes (Figure 5). However, phenacetin is also a substrate for deacetylating enzymes in the intestine resulting in the formation of *p*-phenetidine. Smith and Griffiths incubated rat caecal contents and phenacetin to demonstrate *in vitro* formation of *p*-phenetidine under anaerobic conditions.[34] Authors also reported that formation of *p*-phenetidine was responsible for nephritis following chronic used of phenacetin and correlates with complication similar to methemoglobinemia.[34] Due to toxicity issues, phenacetin was eventually replaced by its active metabolite i.e. acetaminophen or more popularly known as paracetamol and prescribed commonly for reducing fever.

Deglycosylation

Flavonoids belong to one of the most important classes of natural compounds with vast medicinal uses. Quercetin is one such flavonoid with significant antioxidant activity responsible for its beneficial effects on the cardiovascular system and is usually present as quercetin-3-glucoside in plants. Schneider *et al*. suggested cardioprotective properties of quercetin to its inhibition of enzymes involved in platelet aggregation, i.e., cyclic phosphodiesterase and cyclooxygenase.[35] The study also showed that quercetin along with other flavonoids is metabolized by gut *Microflora* into 3,4-dihydroxyphenylacetic acid by *Eubacterium ramulus* and *Enterococcus casseliflavus*. Bacterial β-glucosidase was recently reported for the deglycosylation of glucose moieties attached to flavonoids at the C3 and C7 positions.[36]

CONCLUSION

An understanding of the implications of microbial metabolism is expected to increase with time as more and more drugs are being identified as substrates for gut *Microflora*. As discussed in this short review, a large number of drugs already in the market are substrates for microbial metabolism, and this highlights the importance of including microbial metabolism of the drug during the development phase.

CONFLICTS OF INTEREST

Authors declare no conflict of interest and any financial gains for the article.

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ABBREVIATION

ADME:	Absorption distribution metabolism excretion
GI tract:	Gastrointestinal tract
UGT:	Uridine 5'-diphospho-glucuronosyltransferase
5-FU:	5-fluorouracil
GERD:	Gastro esophageal reflux disease
GST:	Glutathione S-transferase
DPD:	Dihydropyrimidine dehydrogenase
BVU:	(E)-5-(2-bromovinyl)uracil
L-DOPA:	L-3,4-dihydroxyphenylalanine
SRV:	Sorivudine

Highlights of Paper

- Gut *microbiota* metabolizes some of the drugs and hence influence their efficacy and safety.
- Deconjugation, dehydroxylation, deacetylation, deglycosylation are common mechanisms by which gut *microbiota* alter drug efficacy and safety.
- BVU, a sorivudine metabolite produced by *B. eggerthii* and *B. vulgates*, inhibits DPD and decreases the metabolism of 5-FU.
- Reduction of digoxin in gut by *E. lenta* often leads to a decrease in its efficacy.
- Cleavage of N-oxide bond by colonic bacteria decreases the absorption of ranitidine.

Author Profile

- **Rohitash Jamwal:** Is pursuing his PhD in Pharmaceutics and Pharmacokinetics at University of Rhode Island, USA. He comes with a diverse research exposure in natural product drug discovery, applied pharmacokinetics and bioanalysis.

- **Sumanta Kumar Goswami:** Holds a PhD degree in Pharmacology and currently pursuing post doctoral training at Hammock Laboratory of Pesticide Biotechnology, University of California. His research interest includes sexual dysfunction, cardiac function, natural product development, pharmacokinetics, pain and inflammation.

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