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Pharmacomicrobiomics: A novel way towards personalized medicine

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Introduction:

Pharmacomicrobiomics studies how gut microbes interact with drugs and influence their absorption, action and toxicity (Rizkallah *et al*., 2023). It combines microbiology, genomics and pharmacology to predict individual drug responses based on their gut microbiome composition. The concept was proposed by Prof. Marco Candela and popularized in 2010 by Ramy K. Aziz.

Subfields include: Pharmacomicrobiomics (drug-microbiome interactions), Pharmacoecology (drug effects on microbiota), Toxicomicrobiomics (microbe-related drug toxicity), and Pharmacoinfection (drug-induced infections). Both genetic variation and gut microbiota determine individual drug responses.

Composition of cattle and human gut microbiome:

The gut microbiome, also known as the "second genome," (bacteria, fungi, viruses and protozoa) which contains over 100 trillion microbes and 5 million genes. Major bacterial phylum are Firmicutes, Proteobacteria, Bacteroidetes and Actinobacteria are present in the gut (Amat *et al*., 2022).

In humans, about 3.8×10^{13} microorganisms weighing nearly 1.8 kg

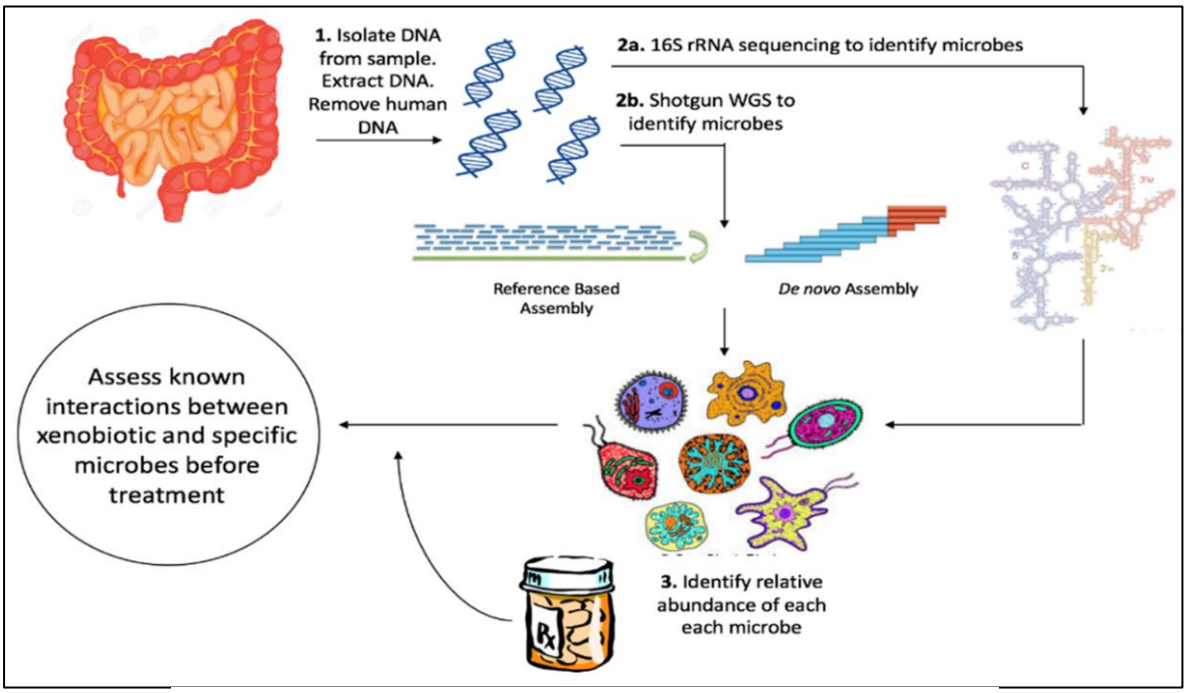

Fig. 1: Pharmacomicrobiomics analysis workflow

live mainly in the intestine. Identification of microbes is done through 16S rRNA (up to genus or species level) and shotgun genome sequencing methods (up to strain level).

Animal models:

Drug-microbiome interactions are studied using *in vivo* (germ-free, gnotobiotic and antibiotic-treated mice) model and *in vitro* (batch, semi-continuous and continuous culture systems) techniques.

In vivo models closely mimic natural conditions but are time-consuming and require ethical approval. *In vitro* techniques make the different part of large intestine *viz*., caecum, colon and rectum environment and continuous culture models maintain pH and temperature which is present normal gut of animal automatically, which enabling long-term experiments with small drug quantities.

Multi-omics strategies:

Multi-omics approaches help to integrate microbial and drug data for personalized therapy: Metagenomics: identifies all microbial genes, Metatranscriptomics: examines active gene expression, Metaproteomics: studies microbial proteins in drug metabolism, Metabonomics: detects drug and bacterial metabolites (Zhao *et al*., 2023). These techniques improve drug efficacy and minimize adverse reactions.

Web portals:

The Pharmacomicrobiomics web portal provides information about drug-microbe interactions and microbial effects on pharmacokinetics and pharmacodynamics of drug. The Human Microbiome Project collects drug-microbes interaction data from various body sites to understand microbial roles in human health and disease.

Complex system of drug metabolism:

Drug metabolism mainly occurs in the liver, involving phase I (oxidation, reduction and hydrolysis) and phase II (conjugation) reactions that convert lipid-soluble drugs into water-soluble forms for easy excretion. Gut microbes also produce enzymes like β-glucuronidases, sulfatases, nitroreductases and azoreductases, which can activate, inactivate or make drugs toxic.

Interaction between drug and gut microbiota:

(1) Effect of drugs on gut microbiome: Drugs can alter microbial balance *i.e*., proton pump inhibitors increase the risk of *Clostridium difficile* infection by reduced stomach barrier function. Metformin increases short-chain fatty acid producing bacteria, which improving glucose tolerance effect in mice.

(2) Effect of gut microbiome on drugs:

(A) Direct effect: (i) Gut microbes can activate drugs *i.e*., prontosil converted to active sulphanilamide which shows its anti-bacterial activity. (ii) gut microbes can inactivate drugs *i.e*., in 10% human, *Eggerthella lenta* reduces digoxin activity by producton of cardiac glycosidase reductase enzyme. (iii) create toxic metabolites *i.e*., CPT-11 (irinotecan) is primarily metabolized in the liver to cytotoxic metabolite SN-38, then converted to its inactive form SN-38G by UDP-glucuronosyltransferase but in 80% human patient, β-glucuronidase reactivates SN-38G (inactive) back to SN-38 (toxic), which show toxicity toward intestinal epithelial cells and causes diarrhoea.

(B) Indirect effect: Increase drug bioavailability *i.e*., simvastatin levels correlate with microbially produced secondary bile acids and commensal *Bifidobacterium* showed association with

antitumor T cell response and showed improvement in tumor control by pd-1/pd-L1 based immunotherapy.

Effect of host diet in pharmacomicrobiomics:

Diet strongly influences drug-microbiome interaction. Polyphenols and fiber diet promote beneficial microbes like *Akkermansia muciniphila*, enhancing drug effects such as metformin. Protein-rich or arginine diets reduce *Eggerthela lenta* produce cardiac glycoside reductase enzyme activity, which enhancing digoxin effectiveness. Cytochrome P450 enzymes are highly sensitive to dietary changes.

Effect of host genetics in pharmacomicrobiomics:

Genetic variations play a key role in drug-microbiome interactions. For example, mutations in UGT1A1 reduce detoxification of irinotecan metabolite SN-38 (toxic) to SN-38G (inactive), increasing irinotecan toxicity. Similarly, lactose metabolism depends on LCT gene variants that influence *Bifidobacterium* abundance in the gut.

Pharmacomicrobiomics in different condition:

(A) Diabetes: Drugs like metformin, acarbose and SGLT2 inhibitors increase beneficial and decrease harmful gut bacteria to improve glucose control (Jia *et al*., 2023).

(B) Hypertension: Antibiotic use alters microbiota and drug metabolism, increasing amlodipine bioavailability and changing metabolism of diltiazem and metoprolol (Chen *et al*., 2022).

(C) Chemotherapy: Microbes can reduce or enhance anticancer drug effects. *E. coli* decreases gemcitabine activity but activates tretazicar. β-glucuronidase increases irinotecan toxicity, while TLR-2 activation can reduce methotrexate toxicity.

(D) Immunotherapy: Gut microbes like *Bacteroides fragilis* enhance Ipilimumab efficacy in melanoma by promoting Th1 responses but also protect against colitis.

(E) Microbial modulation strategies: Probiotics, prebiotics, synbiotics and postbiotics help to restore gut balance and improve drug safety and response.

(F) Antidepressants and gut fungi: Antidepressants such as sertraline prevent *Candida albicans* overgrowth, which reduce the toxic acetate levels and supporting gut-brain balance (Torres-Carrillo *et al*., 2023).

(G) Microbiome and CAR-T Therapy: Antibiotic use before cancer immunotherapy can reduce treatment success, suggesting careful gut microbial management before and during cancer treatment (Gosalbez and Almagro, 2023).

(H) Gut microbiome and kidney disease: A two-way relationship exists; in one direction microbial dysbiosis contributes to kidney damage, while kidney disease aggravates gut imbalance, leading to inflammation (Wehedy *et al*., 2022).

Conclusions:

Pharmacomicrobiomics studies how gut microbes influence drug response, aiming for personalized medicine. It uses sequencing, *in vivo* and *in vitro* models and multi-omics tools to explore drug-microbiome interactions. These interactions affect drug efficacy, toxicity and metabolism, while host genetics and diet further modify drug responses. Modulating the gut microbiota through probiotics, prebiotics, synbiotics or postbiotics can enhance therapeutic outcomes and reduce adverse effects.

Future prospect:

Recent advances in bacterial culturomics, organ-on-chip technology and

expanding databases to understanding of drug-microbiome interactions, but more clinical trials are needed, particularly for chronic diseases.

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