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Review Article

Pharmacomicrobiomics: An Insight to Clinical Applications

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Abstract:

Pharmacomicrobiomics is an emerging branch of Pharmacology, which deals with effect of variations in microbiome on drug related pharmacokinetics and pharmacodynamics. Gut microbes are of numerous types and millions in numbers. Studying alteration of these microbes and its effect on modifying drugs response and disease prognosis has opened many gateways of treatment in many difficult to treat chronic diseases. Cancer, diabetes mellitus, hypertension, rheumatoid arthritis are certain examples of such diseases. Recent advancement like organ-on-chips and bacterial culturomics may allow pharmacomicrobiomics to completely revolutionize the concept of personalized medicine. Present article is about current and possible future clinical applications of pharmacomicrobiomics.

Keywords: Pharmacomicrobiomics, Gut Microbes, Drug-Microbe Interaction, Clinical Applications.

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Introduction

Pharmacomicrobiomics is defined as effect of variations in microbiome on the drug disposition, action and toxicity.[1,2] The human microbiome project was launched in 2007 with intention of identifying and characterizing collections of human associated microorganisms at multiple anatomical sites and to ascertain influence of these variations on human health and immunity.[2,3] This project laid down the basis of pharmacomicrobiomics.[3] Since then, efforts are being made to understand role of human gut microbes on drug metabolism and how alteration in microbiome flora can alter disease outcome.

Pharmacogenomics concept, which studies genetic analysis of drugs metabolizing enzymes and human genome have not been broadly translated in to clinics.[4] Various studies establishing metabolic capabilities of gut microbes and evolution of microbial genomics from culture based to culture free strategies allowed identification of gut microbe associated with certain disease or with altered drug response.[5] Pharmacomicrobiomics is emerging as an essential component of personalized medicine and modulating the gut microbe has the potential to become a very attractive approach to manage drug efficiency and safety at individual level.[6] Many review articles have been written describing interaction of gut microbe with drug and possible role of pharmacomicrobiomics in individual disease entity, but it was rare to found article reviewing all the current and possible future clinical applications of pharmacomicrobiomics in single article.

Primary aim of this review is to provide overview of future possibilities of utility of pharmacomicrobiomics in various clinical diseases. Concurrently role of gut microbes in metabolism and drug metabolism has been outlined, but primary focus of this article is to encapsulate clinical applications of pharmacomicrobiomics.

Gut microbes and metabolism

The primary site of drug metabolism is the liver. Drugs are either metabolized by conjugation, reduction, oxidation, isomerization, hydrolysis, or condensation; regardless of the metabolism phases, the aim is to ensure that the drug can be easily excreted.[7] Most drugs are metabolized in two phases. In the first phase, the reactions are mainly about forming a new or modified functional via non-synthetic reactions. The second phase reactions are mainly about conjugating with an endogenous substance in a synthetic reaction such as glucuronic acid, sulfate, or glycine. Synthetic reactions produce water-soluble metabolites that are more easily to be execrated by the kidneys via urine and

by the liver via bile, than those formed in reactions that are non-synthetic.[8]

Orally ingested drugs may pass through the upper GI tract and small intestine into the large intestine, where they encounter the thousands of microbial species that reside in the human gut. Complex drug-microbial interactions occur mainly in the colon. Drugs may change intestinal microenvironment, alter microbial metabolism or affect bacterial growth, thereby altering microbial community composition and function. Conversely, the gut microbiome can also participate directly in chemical transformation of drugs.

Chemical modifications carried out by gut bacteria are very different from these hepatic processes. Gut microbes primarily conduct hydrolytic and reductive reactions to metabolize xenobiotics, while enzymes in the liver typically conduct oxidative and conjugative reactions.[9]

Upon metabolism in the gut and/or the liver, drug metabolites are either transported to targeted tissues or excreted by the kidneys into the urine or by the liver via the biliary system back into the gut lumen. In the gut, drugs or their drug metabolites can be subjected again to bacterial metabolism (e.g., deconjugation) and (re)absorption.[10] These complex reactions and its results can be utilized to modify treatment outcome of various diseases and that is the basic concept behind all the clinical applications of pharmacomicrobiomics.

Clinical Applications

Cancer: In spite of advances in treatment, cancer still remains in difficult to treat zone and carries significant mortality rate. Adverse effects, resistance and unpredictable outcome are the main obstacles in successful treatment of cancer. These obstacles can be overcome by utilizing pharmacomicrobiomics. Microorganism induced modification in drug biotransformation may lead to either increased or decreased bioactivity.[11] There are evidences suggesting beneficial partnership between gut microbiota and anticancer treatment including chemotherapy, radiotherapy, targeted therapy and immunotherapy.[12]

Concomitant administration of probiotics, prebiotics, synbiotics, postbiotics or antibiotics with anticancer treatment can yield added advantages.[13] Significant association has been revealed between gut microbiota and Immune check point inhibitors (ICPIs) which targets programmed cell death protein (PD-1)/programmed cell death ligand (PD-L1) and cytotoxic T lymphocyte associated protein (CTLA-4).[14] These association can be modulated to get favourable outcome in ICPIs. Fecal microbiota transplantation (FMT), probiotics, bacteriophage, minimizing use of antibiotics are some pharmacomicrobiomics strategies to improve outcome of cancer treatment.[15] Potential anticancer drug targets for pharmacomicrobiomics are summarized in Table-1.

Table 1: Correlation between pharmacomicrobiomics and anticancer drugs [12,15-17]:

Anticancer drug	Involved microbes	Modified therapeutic response
Irinotecan	Clostridium clusters	Probiotics can decrease Diarrhoea
5-fluorouracil	Fusobacterium nucleatum	Responsible for resistance
Gemcitabine	Mycoplasma hyorhinis	Responsible for resistance
Cyclophosphamide	Enterococcus hirae, Barnesiella intestinohominis	Responsible for progression free survival
CTLA-4 inhibitors	Bacteroides species	Facilitate antitumor response
PD-1/PDL1 inhibitors	Bifidobacterium species	Facilitate antitumor response
EGFR inhibitors	Commensal skin microbiota	Increased skin toxicity
Oxaliplatin	Ileal microbiota	Facilitate antitumor response
Cisplatin	Unspecified	Responsible for progression free survival
Radiotherapy	Gram positive intestinal flora	Facilitate antitumor response

Metabolic disorders: Gut microbiota and its disturbance also appear to be involved in the pathogenesis of metabolic disorders.[18] Prebiotics promote SCFA (Short Chain Fatty Acid) production and the growth of beneficial bacteria, especially Bifidobacterium and Lactobacillus.[19]

Studies have demonstrated that prebiotic consumption reduces hunger and enhances satiety.[20] This modulation of ingestive behavior is mediated by SCFA-induced changes in gut peptide secretion by promoting Bifidobacterium populations and prebiotics improve gut barrier function.[21]

Probiotic also shows to improve obesity and metabolic disorders by inhibition of the pathogen adhesion to gut mucosa, stabilization of the microbial community, or improvement of the mucosal integrity and barrier function.[22]

- **Diabetes mellitus (DM)**

DM type 2 carries major burden of health related issues of modern world. Many treatment options are available to control, but there are still many

problems associated with current treatment options. Interaction of gut microbiota with antidiabetic drugs can play pivotal role in treatment of diabetes.[23] Present scenario of DM and pharmacomicrobiomics can be better understood by three different aspects: 1) various gut microbes play important role in glycemic control by different mechanisms. For example Roseburia intestinalis increases insulin sensitivity by increasing IL-22 production; while Lactobacilli have acarbose mimetic action by inhibiting alpha glucosidase enzyme.[24] Probiotics containing these organisms can be a potential adjuvant treatment. 2) Current antidiabetic drugs may have interactions with various gut microbes which might be a part of their glucose control mechanism. For example Metformin increases abundance of Akkermansia muciniphila, Bifidobacterium adolescentis, Lactobacillus fermentium etc., which ultimately helps in controlling fasting glucose and HbA1c in DM.[25] Exploring these can give new insight in treatment of diabetes. 3) Interaction of drug with microbiota may be a cause of certain adverse effect. For example Metformin reduces abundance of certain microbes like Intestinibacter spp. and Clostridium spp., which may contribute to gastrointestinal distress leading to Metformin intolerance.[26] There are preclinical evidence suggesting use of probiotics along with antidiabetic can improve glycemic control in in mice.[27] Various clinical trials also have demonstrated antidiabetic role of gut microbes.[24] Administration of probiotics along with antidiabetic drug may be future trend of DM treatment.

Cardiovascular diseases: Cardiovascular diseases are the leading cause of mortality all over the world. Available treatment options have some lacking points which can be fulfilled by pharmacomicrobiomics knowledge. Organisms like Chlamydia pneumioniae and Helicobacter pylori have been demonstrated to have pivotal role in atherosclerotic heart diseases and acute myocardial infarction.[28,29] Utility of pharmaco microbiomics in cardiovascular conditions can be rightly explained by example of Digoxin which is an important inotropic drug used in congestive heart failure. Gut bacteria named Eggethhela lenta reduces digoxin in to inactive metabolite dihydrodigoxin leading to treatment failure in individuals having abundance of this organism.[30] Amino acid arginine, which is important for this organism can also inhibit this inactivation of digoxin.[31] Thus knowledge of pharmacomicrobiomics can alter treatment outcome. Gut microbes produces Trimethylamine-N-oxide (TMAO) from dietary amines such as choline, betaine and L-carnitine, which can be used as biomarker for various cardiovascular conditions.[32]

- **Hypertension**

Hypertension is a major non-communicable disease and leading cause of cardiovascular diseases.[33] There are numerous types of available treatment options and still new are being invented. In spite of medications 70% patients cannot achieve target BP with single drug.[34] It will be better if natural mechanism can help rather than adding other drugs. Pharmacomicrobiomics can play pivotal role in treatment of hypertension. There are studies showing significant interaction between various antihypertensive drugs like calcium channel blockers, angiotensin receptor blockers, ACE inhibitors and gut microbes.[35] Their interactions can be utilized to modify treatment response. Furthermore certain gut microbes like Lactobacillus. Helveticus, Saccharomyces. Cerevisiae and Lactobacillus. Plantarum have been claimed to reduce blood pressure by themselves.[36,37] Combination of probiotics and antihypertensive drugs might be a future of hypertension treatment.

Depression: Depression is an important CNS disorder and major concern of present generation. Various studies have demonstrated bidirectional interaction between gut microorganisms and CNS activities (e.g. stress, mood, behavior) through immune and neuroendocrine pathway.[38] Abnormal intestinal microbiota leads to a decline in the stability of the gastrointestinal barrier, resulting in an increase of lipopolysaccharide (LPS) entering the body, which activates systemic inflammation and promotes the stress response.[39] However, the treatment of probiotics can effectively prevent intestinal barrier damage and work through multiple mechanisms of action to reduce the response of the HPA axis to stress.[40] It has been demonstrated that the mechanisms of interaction between the gut microbiome and nervous system include: serotonin and tryptophan metabolism, the immune system, gut hormonal response, and short-chain fatty acids from bacterial metabolites.[41] This may provide a new therapeutic idea to enable engineered strains to continuously express therapeutic metabolites after intestinal colonization, so as to achieve therapeutic effects.[42] FMT has shown outstanding results in the treatment of depression.[43] Existing alleviating regimens and antidepressant treatment associated with gut microbes include traditional microbial-targeting drugs, dietary therapy, prebiotics, probiotics, engineered bacteria that express antidepressants, and fecal microbiota transplantation. Acceptable outcomes can be achieved in the prevention and remission of depression by regulating the intestinal microbiota and utilizing the mechanism of action of the gut–brain axis. Moreover, these measures are more flexible and maneuverable, which allows

patients to use non-drug measures to relieve symptoms and improve their quality of life.[44]

Autoimmune disorders

- **Systemic lupus erythematosus (SLE):**

The association between gut microbes and autoimmune disease like SLE is well understood. alteration of microbiome, 'dysbiosis' can induce autoimmune disease in people with certain genetic backgrounds and environmental factors.[45] Gut dysbiosis was partly corrected with FMT, which lead to significant enrichment of SCFAs-producing bacterial taxa and reduction of inflammation-related bacterial taxa, along with reduced levels of IL-6 and CD4+ memory/naïve ratio in the peripheral blood.[46] A mixture of 5 Lactobacillus strains (probiotics) contributed to an anti-inflammatory environment by repairing the gut permeability and decreasing IL-6 and increasing IL-10 production in the gut.[47] Modulation of gut microbiota by eliminating specific bacterial strains or communities with certain antibiotics might represents an alternative approach of microbiota manipulation.[48]

- **Rheumatoid arthritis (RA)**

RA is an immune mediated inflammatory disorder involving joints. In animal models of arthritis, L. casei was tested, it showing a decreased incidence of the diseases in association with reduced production of inflammatory cytokines.[49] Similarly in RA patients, supplementation of encapsulated, active L. casei induced a reduction of pro-inflammatory cytokines and an increase of anti-inflammatory IL-10, associated with the reduction of the disease activity scores for tender and swollen joints.[50] Another study reported that combined administration of L. casei, L. acidophilus and B.bifidum in capsules was sufficient to reduce the disease activity score; however, tender and swollen joints scores were not decreased.[51]

Administration of both L. rhamnosus GR-1 and L. reuteri RC-14 in capsules to RA patients in a randomized, double- blind, placebo-controlled clinical trial highlighted a decrease in circulating pro-inflammatory cytokines, although no overall clinical improvement was reported.[52] Combination of anti-inflammatory drugs with microbial targeted approach can be highly beneficial to RA patients.

- **Inflammatory bowel disease**

There is close connection between gut microbiota dysbiosis and the activation of the mucosal immune system in Inflammatory Bowel disease (IBD). Microbe-targeted therapies aimed at restoring gut normobiosis and immune homeostasis are promising therapeutic options.[53] The use of probiotics may modulate dysbiosis in IBD patients[54], through their strain-specific metabolisms and metabolic by-products[55]. Different strains of Lactobacillus and Bifidobacterium showed significant capability to reduce pro-inflammatory IL-6 and IL-17 levels.[56] The treatment with a multi-strain probiotics consortium has been shown to possess anti-inflammatory properties in experimental colitis[57] and in different randomized, double-blind, placebo-controlled trials. The use of this probiotics mix in Ulcerative Colitis (UC) patients showed significant effects in terms of clinical remission and clinical response during active UC with no side-effects.[58] Studies showed that therapeutic FMT administered during acute and chronic experimental colitis restores eubiosis and directly modulates both innate and adaptive mucosal immune responses towards the control of intestinal inflammation.[59] FMT not only is able to reduce colonic inflammation, by decreased levels of the pro-inflammatory cytokines, but also initiates the restoration of intestinal homeostasis through the simultaneous activation of different immune-mediated pathways.[59]

Conclusion and future aspects

After considering many of the possible applications it is worthy to say that pharmacomicrobiomics can influence future treatment. Various preclinical and clinical models are being prepared to make path for gut microbes to enter real clinical scenario.[4,60] Recent advances like organ-on-chips and bacterial culturomics which allow to study in-vitro interactions between personalized genome and cultured bacteria can revolutionize field of personal medicine.[6] However, considering complexities of gut microbiota, to make pharmacomicrobiomics a successful strategy, it will require more individualized models and more data bank on microbes and its functions. Definitely there is a huge scope for pharmacomicrobiomics in various burdensome clinical conditions, but extreme hard work at all the levels on invention is required to make this dream come true.

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