Perturbation of Immune and Intestinal Permeability Pathways, and Microbiome Shift: Differential Effects of Corn Oil on Different Rodent Models

Gokulan K[1], **Kumar, A[1]**, Lahiani MH[1], Sutherland V[2], Cerniglia CE[1] and Khare S[1*]

1 Division of Microbiology, National Center for Toxicological Research, US Food and Drug Administration, 3900 NCTR Rd, Jefferson, AR, 72079

2 National Institute of Environmental Health Sciences, National Institute of Health, Research Triangle Park, NC. 27709

* Corresponding author: sangeeta.khare@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

National Center for Toxicological Research

Work was featured as Toxspotlight article in March 2021 issue of Toxicological Sciencee Journal , oxford academic.

ABSTRACT

The contribution of gut microbiome in maintaining human health has been widely studied in last decade. Apart from their role in human disease such as inflammatory bowel disease, non-alcoholic fatty lever disease, Alzheimer's, Parkinsons and so on, microbiomes also play important role in the metabolism of ingested xenobiotics. However, xenobiotics could also adversely affect the gut microbiome. In biomedical studies, while assessing the toxicological end-points of water insoluble xenobiotics in animal models, corn oil is one of the most commonly used non-aqueous vehicles. Outcome of toxicological end point assessment studies relies largely on diligent selection of (a) an appropriate animal model to translate toxicity assessment in predicting human exposure and (b) an appropriate non-interfering vehicle. In this study, using adult female Harlan Sprague Dawley rats and adult female CD-1 mice, we studied the gastrointestinal toxicity in the host in terms of (a) shift in gut microbiota and (b) expression of permeability related and immune related pathway genes, at transcript level. Results showed that corn oil (2mg ml-1 kg-1) tested against a water control, did not cause significant perturbation in the rat gut microbiome, intestinal cytokine/chemokine secretion, and mRNA expression of intestinal permeability, and immune response genes. Whereas mice treated with corn oil showed significant shifts in the abundance of bacterial community structures at the phyla, genera, and species levels in the ileum, as well as revealed significant changes in the mRNA expression of intestinal mucosal/epithelial permeability and immune response genes. In conclusion, our study clearly illustrated the importance of appropriate selection of a rodent model, and vehicle (like corn oil) is used to test the toxicity of water insoluble xenobiotics.

INTRODUCTION

Gut microbiome is a very dynamic microbial community which has a detrimental impacts on human health. In last decade, studies have proven roles that the gut microbiome play in inflammatory bowl disease (IBD), neurological diseases, obesity, diabetes and several other conditions. But, the underlying mechanism by which microbiome change effects the host health is not understood well. Also, the gut microbiome itself gets effected by several factors such as change in diet, sleep habits, exercise and exposure to xenobiotic etc. Therefore, to study the effects of any external factor on the gut microbiome and to obtain the results directly translatable to humans it is very important to select right animal model. Further, studying water insoluble xenobiotics require a vehicle to improve the solubility and hence, selecting a non-interfering vehicle is of utmost importance. Many vegetable oils such as olive, sunflower, corn, peanut oils are used as vehicles to many FDA approved water insoluble drugs. In our study, we tested two most common animal models that are usually used in toxicological risk assessment studies. We also chose corn oil, one of the most commonly used non-aqueous vehicles for water insoluble xenobiotics, to see if the vehicle could effect the model animals and hence the outcomes of toxicity studies.

AIMS

Aim 1: Investigate the effects of corn oil used as vehicle for water insoluble xenobiotics across different animal models.

Aim 2: Investigate and establish the animal model to be used to obtain result better translatable to humans

APPROACH

10 Adult female Harlan SD rats, 102 days
10 Adult female CD-1 mice, 92 days old
(age at the time of sacrifice)

Water or Oil (2.0 ml/kg BW); gavage from 7 days before sacrifice

Sacrifice and harvest the tissues

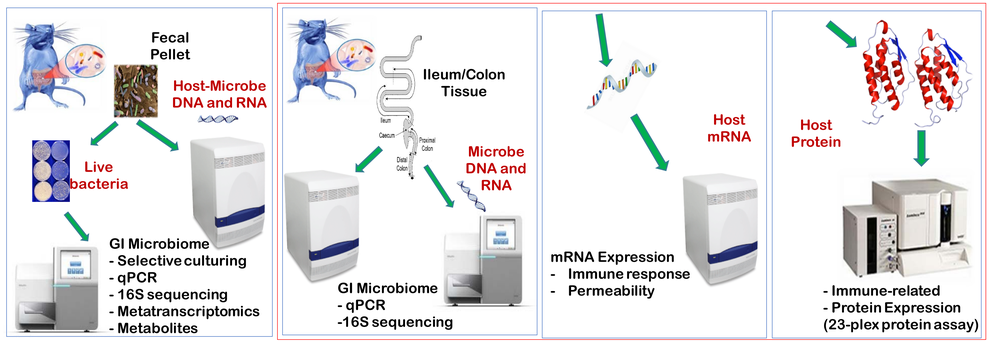


Fig 1: Schematic diagram illustrating the experimental procedure.

RESULTS

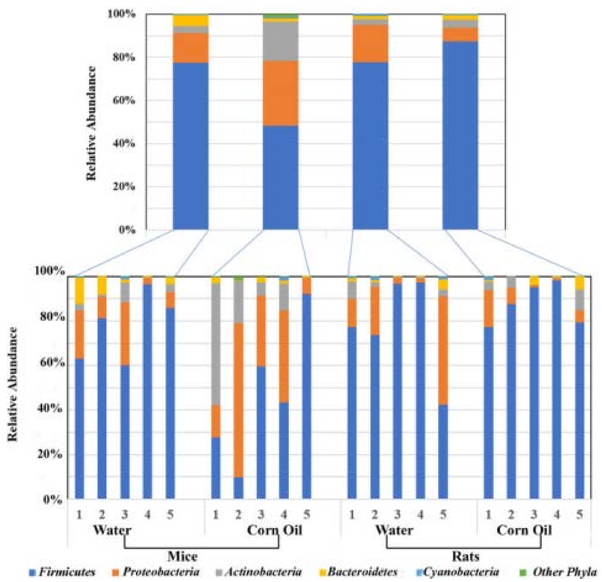


Fig 2: Phyla level analysis of gut microbiome, identifying the shift in microbiome constitution upon corn oil treatment. Showing the microbiome shift in mice and rats .

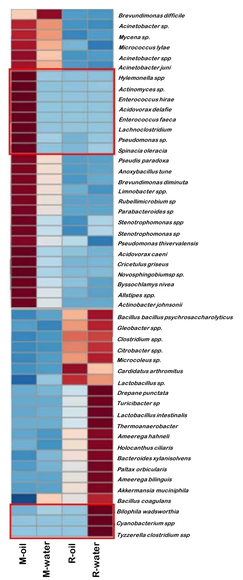
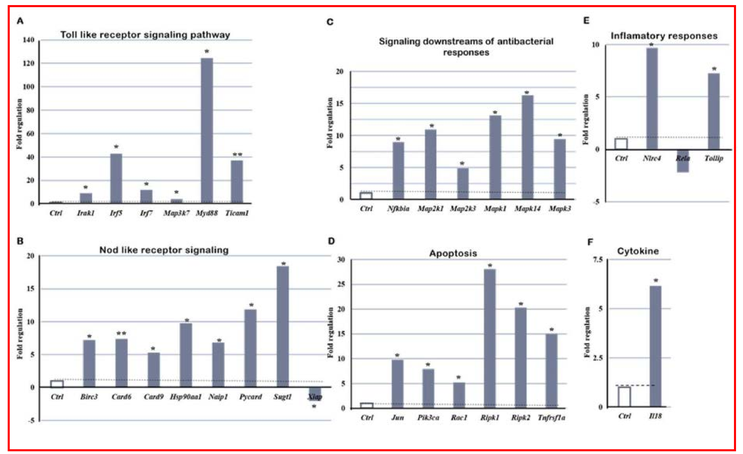
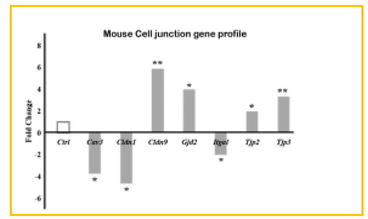


Fig 3: Showing the top 50 common species and the shift upon corn oil treatment.

RESULTS Cont.





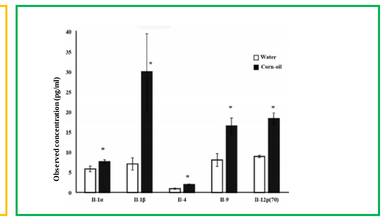


Fig 4: Host immune pathway (Red panel), cell junction pathway (Yellow panel) genes transcripts and cytokines (Green panel; protein) expression analysis. Genes expression with >2 fold expression and p-value < 0.05 only are shown; * and ** signify p < 0.05 and p < 0.001, respectively.

CONCLUSION & FUTURE STUDIES

- Selection of an appropriate animal model and the most non-interfering vehicle is very important to understand the true effects of xenobiotics.
- Further dose dependent studies using different animal models and vehicles combinations could help to establish standard animal model-non aqueous vehicle combinations for xenobiotic toxicity studies.

ACKNOWLEDGEMENT

This work was supported by National Institute of Environmental Health Sciences/Division of the National Toxicology Program, National Institutes of Health (FDA IAG # 224-17-0502 and NIH IAG #AES12013).

Reference

Gokulan et al, TOXICOLOGICAL SCIENCES, 180(1), 2021, 89–102
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