International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

The Efficacy of Microbiome-Targeted Therapy in Modulating Gut Health in Alcohol-Induced Liver Injury: A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - Adelaide Graduate Research Scholarship.

Review Stage at time of this submission - Formal screening of search results against eligibility criteria.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202490059

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 September 2024 and was last updated on 16 September 2024.

INTRODUCTION

Review question / Objective Is using microbiome-targeted therapy useful in modulating gut and liver health in the case of alcoholic liver disease?
The objective of this study is to review and analyse what kind of changes the microbiome-targeted therapies induce in alcoholic liver injury. In addition to that, we also aim to understand if these therapies change liver markers in these pre-clinical mice and clinical studies in human clinical trial-based studies. We will also conduct group and sub-group analysis of different microbial cultures and identify which therapy was more helpful in modulating gut and liver health.
• Participants: Mice (Pre-clinical studies), Humans (Clinical trials)
• Intervention: use of any microbiome-targeted therapy
• Control: Non-exposure group (mice), standard of care/ SOC (Humans)
• Outcome: comparing the changes in the gut microbiome in the intervention and control groups (Mice), comparing the gut microbiome changes in intervention and SOC (Humans)
• Study design: Preclinical studies (Mice), Clinical Trials (Humans).

Rationale Previous studies have reported dysbiosis in the gut microbiota (GM) in alcoholic liver diseases, indicating GM to be a factor in driving recovery in liver diseases via gut modulation. ALD is a major disease burden worldwide in the case of liver diseases. However, there are limited studies that report the overall effect of microbiome-targeted therapies on alcoholic liver disease. Therefore, this study aims to carry out a systematic review and meta-analysis on the studies that analyse GM changes in alcohol-induced liver injury and after Microbiome targeted therapies (such as the use of probiotics, prebiotics, and faecal microbiome transplant) to treat and manage alcoholic liver diseases. For this,

we will look at the preclinical studies on mice using MTT in alcohol-induced liver injury and human clinical trials. We will perform a meta-analysis on the changes in microbial communities based on the alpha diversity in the case of mice-based studies and will do the same in the case of human clinical studies if the authors come in contact. In case we have insufficient data, we will include the human studies only in the systematic review.

Condition being studied Alcoholic liver disease model, alcohol-induced liver injury (Mice); Alcoholic liver disease (Humans).

METHODS

Search strategy "Fecal Microbiota Transplantation"[mh] OR "probiotics"[mh] OR "Saccharomyces"[mh]
OR fecal microbiota transplant*[tiab] OR faecal microbiota transplant*[tiab] OR fecal
microbiome transplant*[tiab] OR faecal microbiome transplant*[tiab] OR fecal
microflora transplant*[tiab] OR faecal microflora transplant*[tiab] OR Fecal
transplant*[tiab] OR faecal transplant*[tiab] OR Donor Infusion*[tiab] OR Feces
Infusion*[tiab] OR Faeces Infusion*[tiab] OR Donor Feces transplant*[tiab] OR Donor
Faeces transplant*[tiab] OR Intestinal Transplant*[tiab] OR Intestinal Microbiome
Transplant*[tiab] OR Microbiota Transfer*[tiab] OR Intestinal Transfer*[tiab] OR
Intestinal Microbiota*[tiab] OR Intestinal Microbiome Transplant*[tiab] OR Intestinal
Microbiota transplant*[tiab] OR Intestinal microbiome transfer*[tiab] OR Faecal
Microbiota Transfer*[tiab] OR Fecal microbiota transfer*[tiab] OR Probiotic*[tiab] OR
symbiotic*[tiab] OR Probiota[tiab] OR symbiota[tiab] OR Saccharomyce*[tiab] OR
prebiotic*[tiab] OR yogurt[tiab] OR inulin[tiab] OR oligosaccharide*[tiab] OR
Lactobacillus[tiab] OR Bifidobacterium[tiab] OR Enterococcus[tiab] OR
Streptococcus[tiab] OR synbiotic*[tiab] OR "Microbiota therapy"[tiab:~3] OR
"microbiome therapy"[tiab:~3] OR "microbiota therapies"[tiab:~3] OR "microbiome
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supplements"[tiab:~3] OR "microbiomes supplement"[tiab:~3] OR "microbiomes
supplements"[tiab:~3] "Gastrointestinal Microbiome"[mh] OR gut microbi*[tiab] OR gastrointestinal
microbi*[tiab] OR gut microflora[tiab] OR gastrointestinal microflora[tiab] OR gut
flora[tiab] OR gastrointestinal flora[tiab] OR gastric microbi*[tiab] OR intestinal
microbi*[tiab] OR intestinal microflora[tiab] OR intestinal flora[tiab] OR enteric
bacteria[tiab] "liver diseases, alcoholic"[mh:noexp] OR "hepatitis, alcoholic"[mh] OR "alcohol
hepatitis"[tiab:~3] OR "alcoholic hepatitis"[tiab:~3] OR "alcohol liver disease"[tiab:~3]
OR "alcoholic liver disease"[tiab:~3] OR "alcohol liver diseases"[tiab:~3] OR "alcoholic
liver diseases"[tiab:~3] OR "alcohol liver disorder"[tiab:~3] OR "alcoholic liver
disorder"[tiab:~3] OR "alcohol liver disorders"[tiab:~3] OR "alcoholic liver
disorders"[tiab:~3]
fecal microbiota transplantation.sh OR ((donor OR f?eces OR intestinal OR microbio*
OR f?ecal) adj3 (infusion OR transplant* OR transfer*)).ti,ab,kf OR Exp Probiotic
agent OR exp Saccharomyces OR (Probiotic* OR symbiotic* OR Probiota OR symbiota
OR Saccharomyce* OR prebiotic* OR yogurt OR inulin OR oligosaccharide* OR
Lactobacillus OR Bifidobacterium OR Enterococcus OR Streptococcus OR
synbiotic*).ti,ab,kf OR ((Microbiot* OR microbiome*) adj3 (therap* OR treatment*
OR intervention* OR supplement*)).ti,ab,kf
Exp intestine flora OR ((Gut OR gastro* OR gastric* OR intestin* OR bowel OR digest*
OR alimentary OR enteric) adj3 (flora OR microbi* or microflora OR bacteria)).ti,ab
alcohol liver disease.sh OR exp alcoholic hepatitis OR (alcohol* adj3 (hepatitis OR
liver disease* OR liver disorder*)).ti,ab,kf
[mh "fecal microbiota transplantation"] OR [mh probiotics] OR [mh saccharomyces]OR
((donor OR feces OR faeces OR intestinal OR microbio* OR fecal OR faecal) NEAR/3 (infusion
OR transplant* OR transfer*)):ti,ab OR (Probiotic* OR symbiotic* OR Probiota OR symbiota

OR Saccharomyce* OR prebiotic* OR yogurt OR inulin OR oligosaccharide* OR Lactobacillus OR Bifidobacterium OR Enterococcus OR Streptococcus OR synbiotic*):ti,ab OR ((Microbiot* OR microbiome*) NEAR/3 (therap* OR treatment* OR intervention* OR supplement*)):ti,ab
[mh ^"gastrointestinal microbiome"] OR ((Gut OR gastro* OR gastric* OR intestin* OR bowel OR digest* OR alimentary OR enteric) NEAR/3 (flora OR microbi* or microflora OR bacteria)):ti,ab
[mh ^"liver diseases, alcoholic"] OR [mh ^"hepatitis, alcoholic"] OR (alcohol* NEAR/3 (hepatitis OR "liver disease" OR "liver disorder" OR "liver diseases" OR "liver disorders")):ti,ab.

Participant or population Alcohol-induced liver injury (Mice model-based studies)
Patients with alcoholic liver diseases receiving microbiome-targeted therapy/ MTT (Human clinical trial-based studies).

Intervention Faecal microbiome transplant, probiotics, prebiotics, synbiotics, symbiotics, and other microbiome-targeted therapies other than fungal and bactreriophages.

Comparator A control group with alcohol-induced liver injury not exposed to any interventions (in the case of mice)
Standard of care group receiving medical treatment as per the medical standards of treatment (in case of humans).

Study designs to be included We will include pre-clinical animal intervention-based studies (mice), and clinical trial-based studies (humans) to address the objective of the review.

Eligibility criteria Inclusion criteria: Mouse model-based studies with alcohol-induced liver injury being treated with microbiome-targeted therapies. Original research articles only.
Exclusion criteria: Studies other than original research studies (Systematic review, meta-analysis, review, case report, comment, editorial), studies with non-bacterial outcomes/ fungal or viral outcomes, studies using bacteriophages, studies not reporting microbiome-based changes, studies with no control or baseline microbiome outcomes, non-alcoholic liver injury or non-alcoholic liver diseases (both human and mice), Non-alcoholic Fatty Liver Disease, Viral Hepatitis, Autoimmune Hepatitis, non-alcoholic fatty liver, studies using animals other than mice (for animal studies), studies using sequencing techniques other than 16S rRNA gene sequencing or shot-gun/ metagenomic sequencing, studies not reporting alpha diversity data.

Information sources Electronic databases (Embase, Pubmed, Cochrane Central) will be systematically searched. The corresponding authors will be contacted for any data missing and needed for the meta-analysis in case of insufficient data.

Main outcome(s) The primary outcomes will include the changes in gut microbiome outcomes post-MTT treatment (16S rRNA gene sequencing/ Metagenomic sequencing). Secondary outcomes will include changes in taxonomic abundance post-treatment. The outcome reported will be a baseline gut microbiome profile compared to gut microbiome profile post-treatment.

Additional outcome(s) Other outcomes will include bioinformatics details, study details, and changes in liver markers (if reported). Functional pathway changes post-treatment will be reported (For metagenomic studies).

Data management Covidence will be used to screen and select the studies as well as to record the study data.

Quality assessment / Risk of bias analysis SYRCLE's risk of bias tool will be used for mice studies - primary studies.
The Newcastle-Ottawa scale will be used for human studies.

Strategy of data synthesis Meta-analysis of Alpha diversity post-treatment will be compared to baseline when at least two studies are reporting the same index of measure in same microbiome-targeted therapy. The Q and I square statistics will be used to test heterogeneity between the studies. Publication bias will be assessed using funnel plots. Egger's test will be used to test the symmetry statistically if we have enough studies (>10). All analyses planned to be performed using RevMan 5.3 (Cochrane).

Subgroup analysis Subgroup analyses will be conducted (Treatment based sub-grouping).

Sensitivity analysis Planned if there is significant heterogeneity.

Language restriction English.

Country(ies) involved Australia.

Keywords gut microbiome; microbiome target therapy; alcoholic liver disease.

Dissemination plans Plans on presenting at conference and submitting for publication.

Contributions of each author

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