Development of a curated hepatic steatosis (HS) database to enable Quantitative Structure-Activity Relationship modeling

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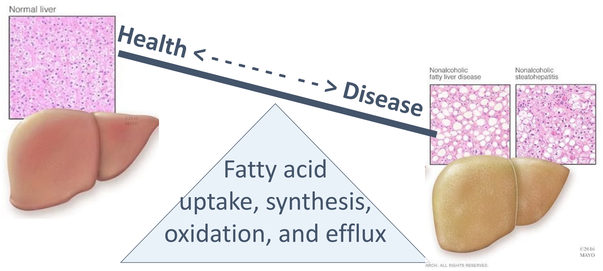
Introduction

- Hepatic steatosis, also known as non-alcoholic fatty liver disease, is characterized by abnormal fat accumulation in the liver.
- Disease spectrum impacts **one in three adults** and **one in ten children** in the US.
- It is a multifactorial disease and common causes include environment, diet, behavior, and genetics.



Four apical key events serve as the fulcrum potentiating additional disease outcomes of HS.

- HS can evolve to further adverse outcomes, including fibrosis, cirrhosis, and cancer.

This study aims to collect, curate, and integrate the largest chemogenomics HS dataset to enable the accurate identification of novel potential HS causing agents.

Materials and methods

We performed extensive literature and web search and compiled data from:

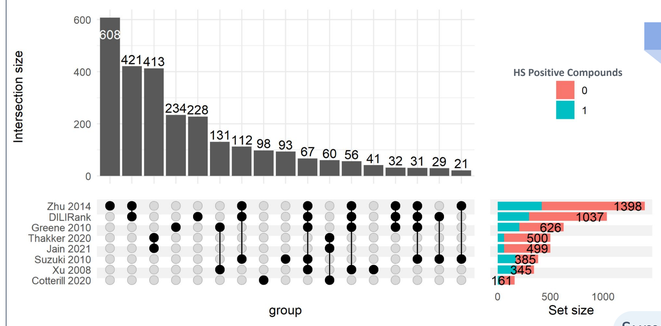
- Publications identified in PubMed
- Supplementary materials
- Publicly accessible electronic databases
- Private contributions

Data integration, curation, analysis, and visualization was executed in R.

Results and Discussion

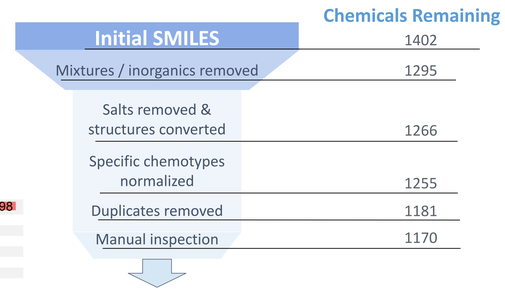
Data overview and curation

Overlapping analysis



Chemical data overlap between top source datasets, visualized by count overlapping and entire set size color coded by HS positivity (0 = negative, 1 = positive).

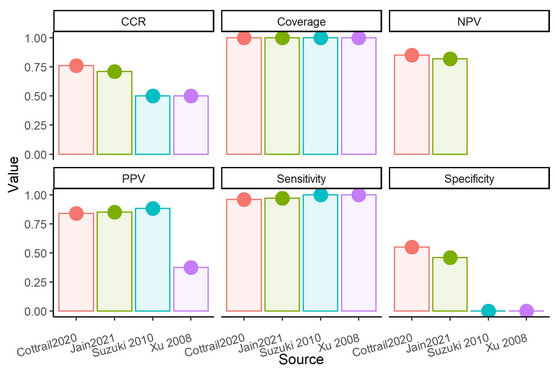
Key steps of chemical curation



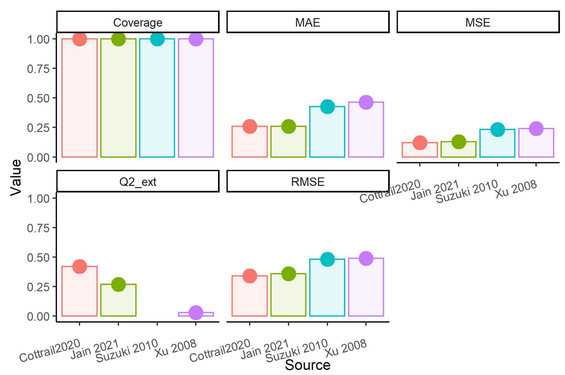
Summary of the chemical curation workflow, modified from [Fourches 2016]. Initial curation executed using subset of identified sources: Jain et al. 2021, Cotterill et al. 2020, Xu et al. 2008, and Suzuki et al. 2011.

Data analysis

Classification results



Regression results



Conclusions

Succeeded in developing the largest publicly available HS database. Using this database, we have developed QSAR HS models. Preliminary results suggest applying alternative regression strategy, as well as revisiting upstream workflow.

Future Directions

Data analysis

- Hierarchical cluster analysis to identify scaffolds associated with HS.
- Evaluation of overlap and concordance on conserved chemical subsets between data sources.

Cheminformatics analysis and modeling

- Cluster chemicals and analyze SAR to identify motifs related to HS.
- Identify representative chemicals causing additional adverse outcomes.
- QSAR Modeling
  - Virtual screening of chemicals of interest
  - Model interpretation to identify statistically validated chemical moieties associated with HS.

Experimental validation

- Validate computational models using *in vitro* assays with a collaborator at EPA.

Key References

- Angrish et al. 2016 10.1093/toxsci/kfw018
- Fourches et al. 2016 10.1021/acs.jcim.6b00129
- Tropsha 2010 10.1002/minf.201000061

virtual poster