



The integrated application of metabolites from *Avena sativa* and gut microbiota to alleviate non-alcoholic fatty liver disease: a network pharmacology study

Ki-Kwang Oh¹, Sang-Jun Yoon¹, Su-Been Lee¹, Sang Youn Lee¹, Haripriya Gupta¹, Raja Ganesan¹, Satya Priya Sharma¹, Sung-Min Won¹, Jin-Ju Jeong¹, Dong Joon Kim¹, Ki-Tae Suk^{1,*}

¹Hallym University College of Medicine, Institute for Liver and Digestive Diseases, Chuncheon, Korea

INTRODUCTION & AIM

In the incomplete project, we pioneered the secondary metabolites (SMs) from *Avena sativa* (AS; known as oat) and gut microbiota (GM) to identify the key SMs in both AS and GM for the treatment of NAFLD. Furthermore, AS has a wide spectrum of pharmacological activities such as antioxidant, anti-inflammatory, antidiabetic and anticholesterolemic efficacy. The AS is an ancient grain utilized as an important grain from primitive times, suggesting that AS can diminish cholesterol, control satiety, and even make positive effects on gastrointestinal (GI) health.

Currently, several studies have demonstrated that natural products can regulate body metabolism including anti-obesity and anti-diabetes.

It is believed that NP might be a key to decrypt the therapeutic issue in dilemma, ending up with combinatorial application. As aforementioned, our study has established that the combinatorial application of AS and GM is to be expected as an alternative therapeutic strategy for NAFLD. Thus, this approach might be given critical hints to further clinical trials and advancement of the combined applications with AS and GM.

The process of this study is displayed in **Figure 1**.

MATERIAL & METHODS

The identification of SMs and its targets from AS

Natural Product Activity & Species Source (NPASS) database (<http://bidd.group/NPASS/>) (accessed on 28 September 2022) was utilized to select the significant SMs from AS, indicating that targets related to the SMs were retrieved by Similarity Ensemble Approach (SEA) (<https://sea.bkslab.org/>) (accessed on 28 September 2022) and SwissTargetPrediction (STP) (<http://www.swisstargetprediction.ch/>) (accessed on 28 September 2022). With the exactness and rigor, the intersecting targets between SEA and STP were considered as important targets associated with SMs from AS. It was defined as AS-related targets. Crucially, SEA database is a mining platform to select some major targets linked to targets, developed by Dr Shoichet's group. It is to be specified that the number of 23 in 30 targets extracted by SEA was confirmed by experimentation. Apparently, STP has been used to identify the putative targets for ligands, for instance, the attained targets for cudraflavone C hit the mark experimentally.

The protein-protein interaction networks

We utilized String database (<https://string-db.org/>) (accessed on 01 October 2022) to identify protein-protein interaction (PPI) networks, which was described by R Package. On the PPI networks, we found a target with the highest degree value, thus it was to be defined as a key target to ameliorate NAFLD.

The construction of bubble plot

The construction of bubble plot was established by Kyoto Encyclopedia of Gene and Genomes (KEGG) pathway enrichment analysis. The signaling pathways on the bubble plot were depicted, according to Rich factor value. We discerned a key signaling pathway for the treatment of NAFLD, suggesting that the mechanism might be inhibitive effect on NAFLD. The bubble plot was constructed by R package.

The construction of GM or AS- a key signaling pathway-targets-SMs (GASTM) networks

We described GASTM network to know the relationships of each component: GM or AS, a key signaling pathway, targets, and secondary metabolites. The GASTM network was constructed by utilizing R Package. Taken together with GM or AS, a key signaling pathway, targets, and SMs as nodes, matching associations above components were assembled with Microsoft Excel, then input into R package to identify the interaction network of GASTM against NAFLD.

Molecular docking assay (MDA)

The Molecular docking assay (MDA) was implemented with AutodockTools-1.5.6 to understand what the most significant SMs in both GM and AS are. Commonly, the threshold of AutodockTools-1.5.6 was fitted as -6.0 kcal/mol or SM with lowest Gibbs energy (the greatest negative value) was regarded as the uppermost SM to have therapeutic value in the treatment of NAFLD.

CONCLUSION

In conclusion, our study highlights the therapeutic effects and mechanisms of the treatment on NAFLD via combinatorial application: gut microbiota (GM), and *Avena sativa* (AS), indicating antagonists (myricetin, quercetin, diosgenin, and vestitol) to inhibit PI3K-Akt signaling pathway. These findings provide a new insight to utilize the endogenous species (gut microbiota) and exogenous species (*Avena sativa*) on microbiome-based therapeutics. However, this study should be taken *in vitro* or *in vivo* experimentation into consideration to uncover bona fide pharmacological efficacy.

RESULTS

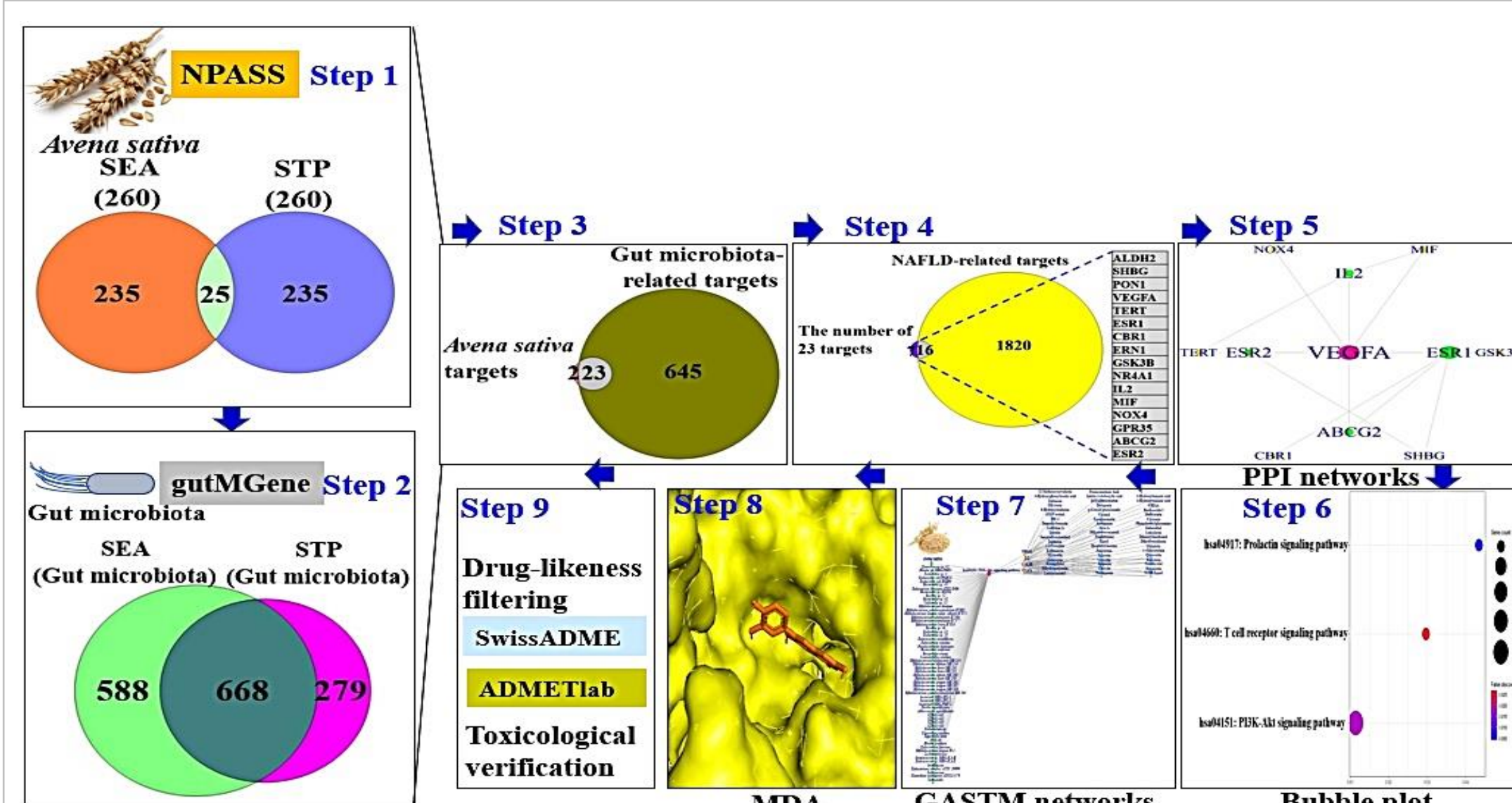


Figure 1. The workflow of this study.

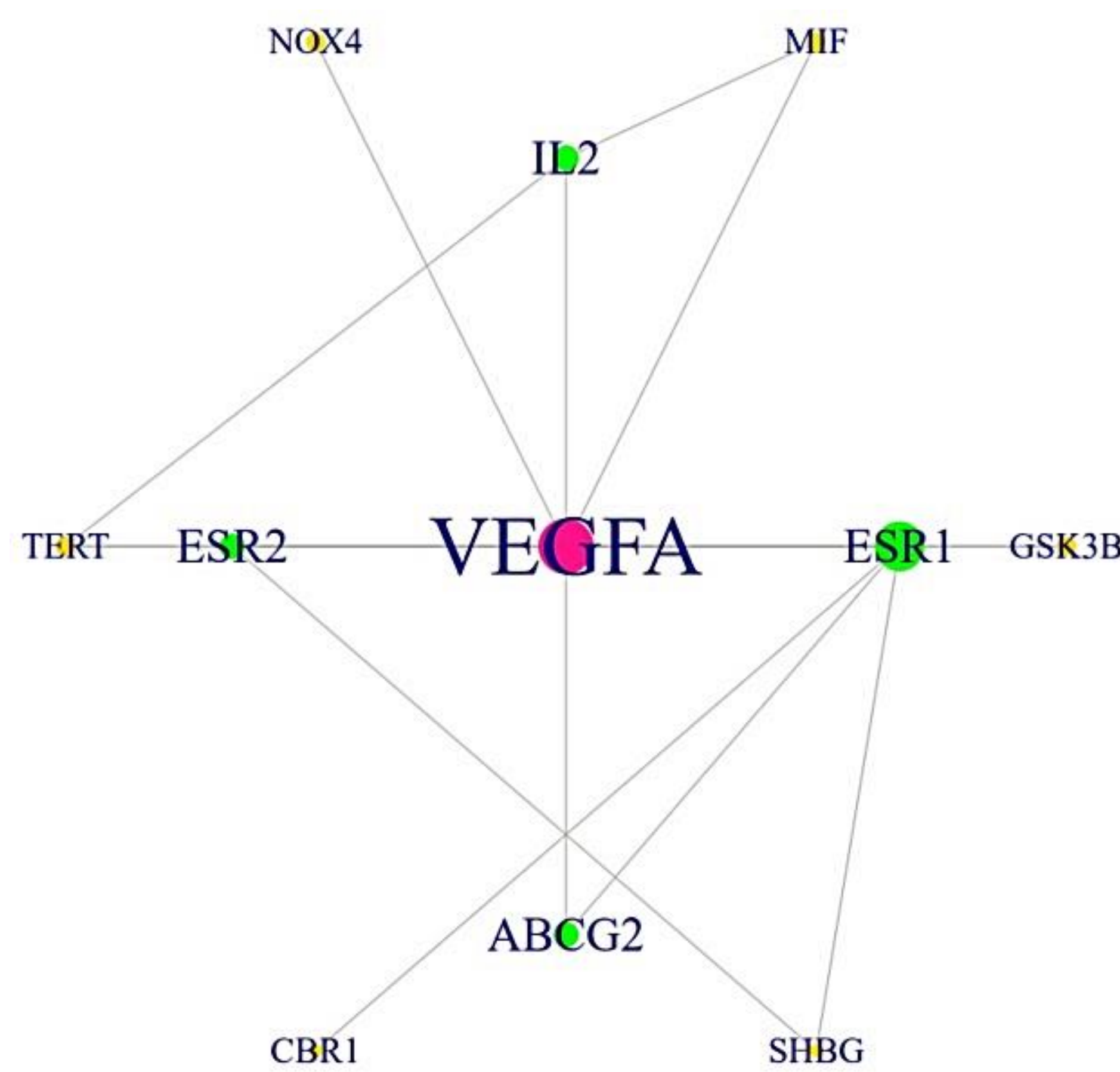


Figure 2. PPI networks.

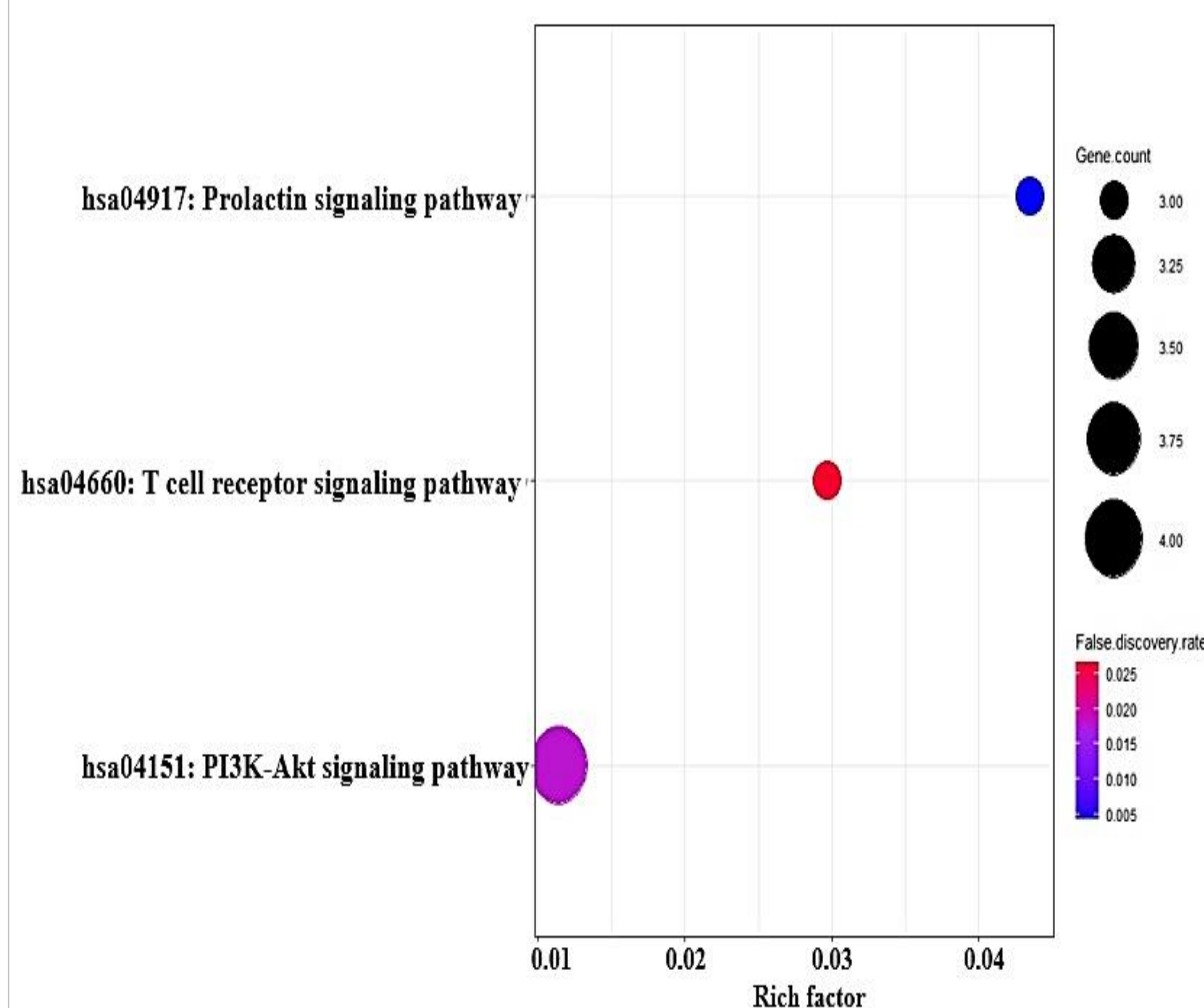


Figure 3. Bubble plot of 3 signaling pathways associated with occurrence and development of NAFLD.

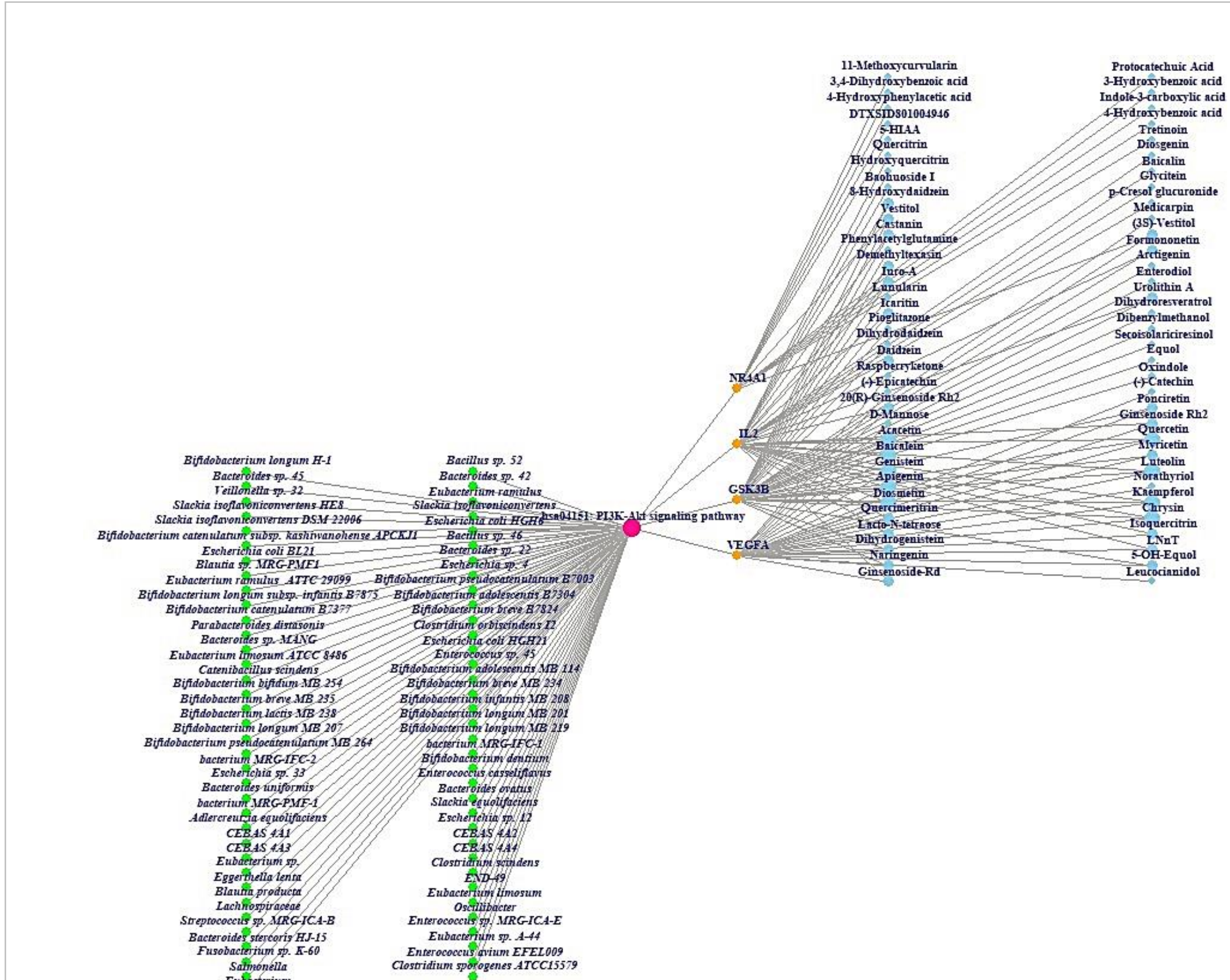


Figure 4. The GM or AS- a key signaling pathway-targets-SMs (GASTM) network (122 nodes and 155 edges).

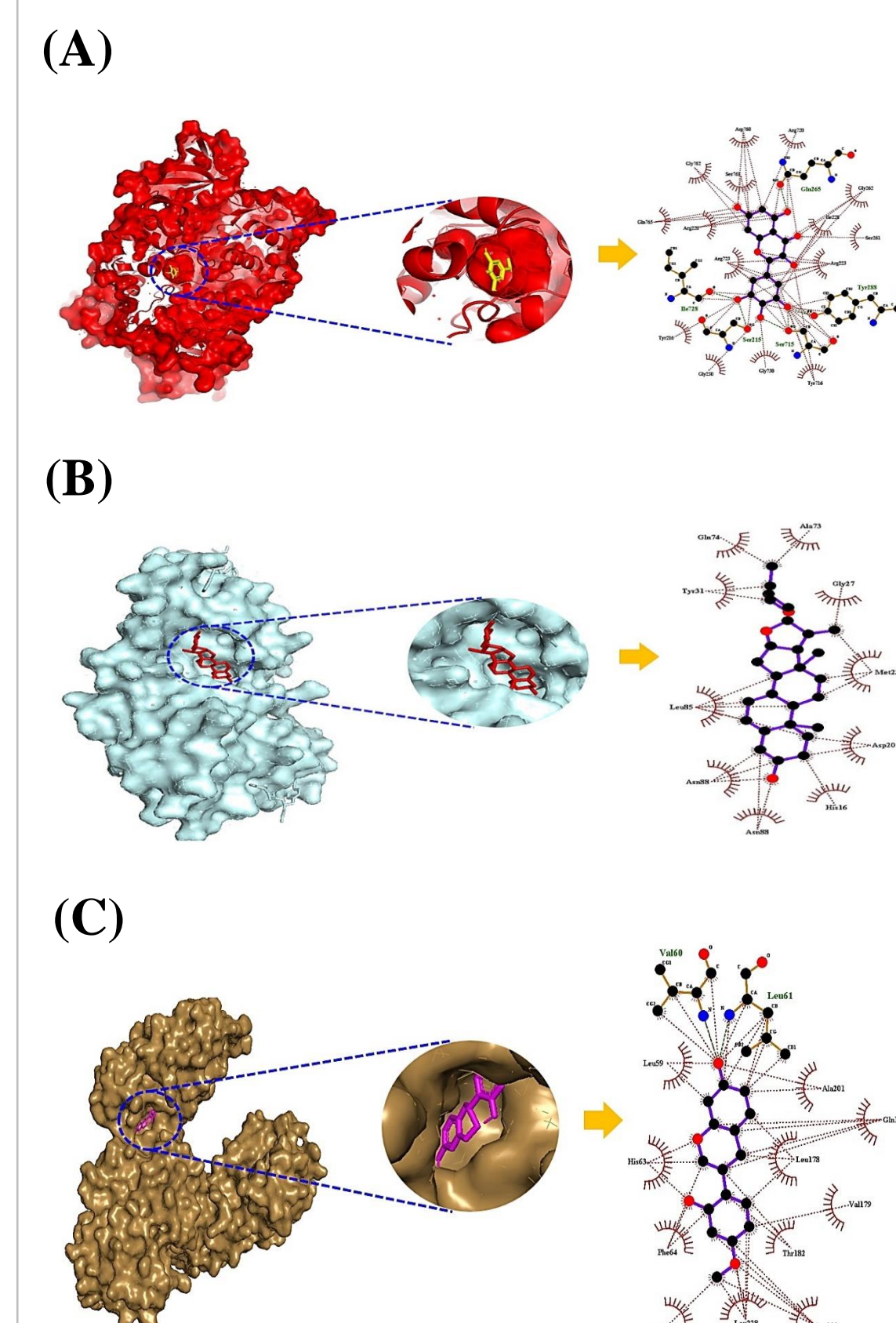


Figure 5. The results of molecular docking assay (MDA). (A) myricetin-GSK3B. (B) diosgenin-IL2. (C) vestitol-NR4A1.

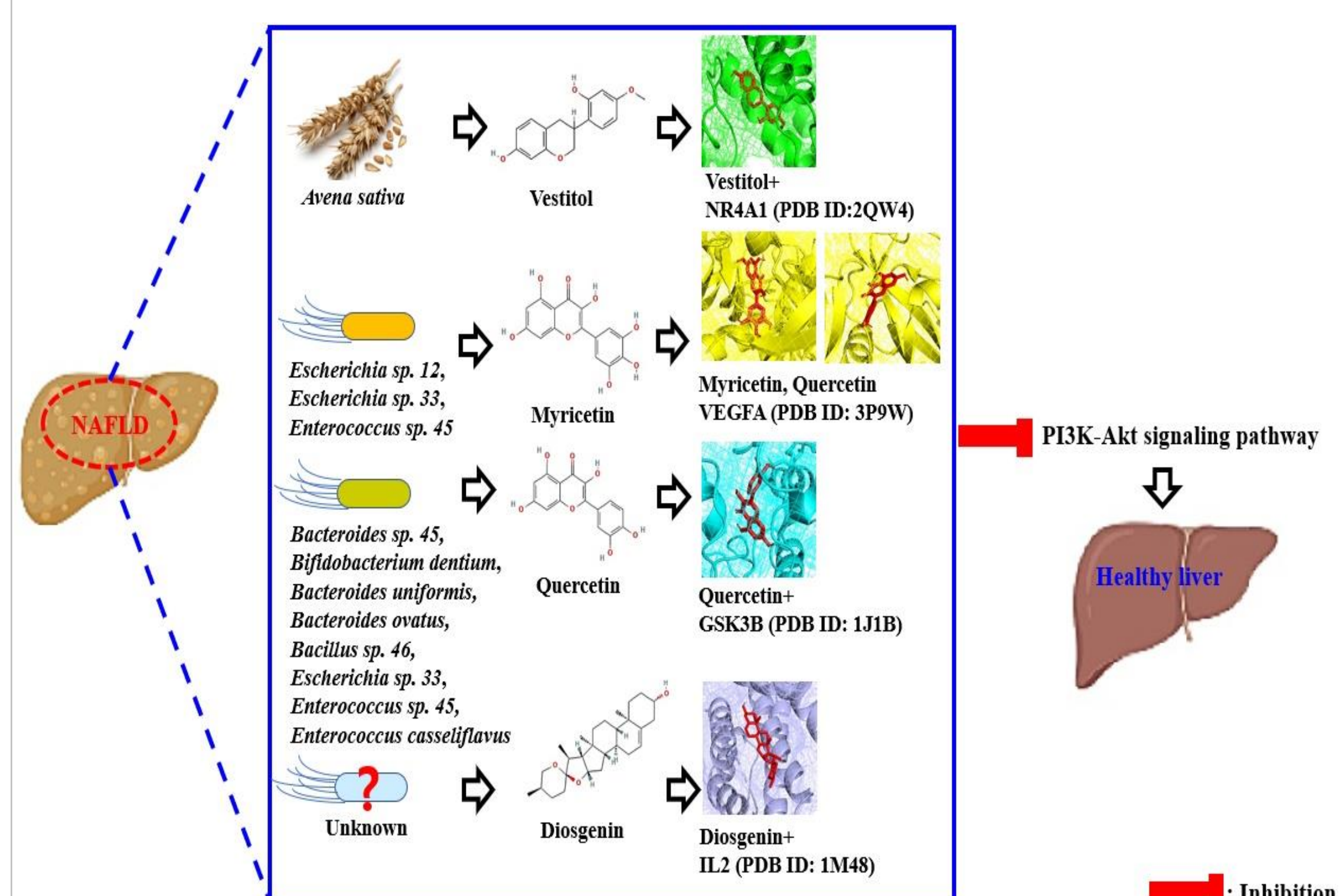


Figure 6. Key findings of this study.

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REFERENCE

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