23-VI-10

The synchronized feature of *Saururus Chinensis* and gut microbiota against T2DM, NAFLD, obesity, and hypertension via integrated pharmacology

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Introduction

Commonly, type 2 diabetes mellitus (T2DM) nonalcoholic fatty liver disease (NAFLD), and obesity (OB) have been strongly linked to its occurrence and development; furthermore, hypertension (HT) causes T2DM, NAFLD, and OB without consistent patterns. Its etiological spectrum involves in the intersecting target(s) in the context of therapeutics. In this unexplored project, we focused on medicinal plants to unravel complicated syndromes because the multiple chemicals can exert multiple effects via interactions between two plant species. Among the medicinal plants, *Saururus chinensis* (SC) is an invaluable resource to for treating four diseases: T2DM, NAFLD, OB, and HT. Notably, SC has been utilized as a traditional medication in Asia for a long time without any specific toxicity. It is believed that the gut microbiota (GM) might be a significant agent for ameliorating metabolic disorders due to its anti-inflammatory, antioxidant, and anticholesterolemic effects. Additionally, our previous study has been revealed its combined effects (OB, NAFLD, alcoholic liver disease (ALD), and liver regeneration) in combination with the use of favorable natural herbal plants. In fact, the GM plays important roles in modulating the physiological system of the host via certain mechanisms. Some probiotics metabolize fewer drug-like molecules into more drug-like molecules via their own biosynthetic pathway. For instance, *Bifidobacterium dentium* can metabolize rutin (molecular weight: 610.52 g) into quercetin (molecular weight: 302.24 g), implying that quercetin might have better bioavailability than rutin. As a flavonoid derivative can produce from isoflavone via *Lactobacillus paracasei JS1*, revealing that equol has the greatest antioxidant effect on all isoflavone species. Some studies confirming the efficacy of metabolites (known as postbiotics) via inflammatory mechanisms have reported inconsistent experimental results due to diverse metabolites and their derivatives.
Accordingly, key prebiotics, probiotics, and metabolite(s) need to be established for administration in the context of therapeutics.
In this study, significant components were revealed to maintain the consistency of the experimental results in the selection of the bioactive compounds from SC and favorable metabolite(s) via potential GM. Accordingly, our study aimed to determine the key bioactive compounds produced by SC and the GM to confirm the lack of effects on T2DM, NAFLD, OB, and HT. To perform the project, we adopted the network pharmacology (NP) concept to decode the critical elements: key molecule(s), target(s), mechanism(s), and GM. NPs might serve as a decoder to elucidate the orchestration of multiple-compounds-targets-mechanisms-GM. As previously mentioned, our analysis revealed that combination treatment with SC and GM might be an alternative therapeutic for treating T2DM, NAFLD, OB, and HT. Hence, this analysis might provide crucial insight for the clinical tests and the development of combined SC and GM treatments. The workflow of this study is depicted in **Figure 1**.

Materials and methods

SC, GM- signaling pathway-target-metabolite (SGSTM) network

We constructed SGSTM networks to decipher the interconnections of each element: SC or GM, key signaling pathways, targets, and metabolites. Collectively, each element is represented as a node with a circle, and their relationships are represented as edges with a gray line. The above elements were merged with Microsoft Excel, and then, the SGSTM networks were constructed by using the R program to identify their interconnectedness against the four diseases via the incorporation of SC, or GM.

Molecular docking test (MDT)

The MDT was conducted with AutodockTools-1.5.6 to identify the most stable conformer between key target(s) and molecule(s) (or metabolites) in both SC and GM. As a rule, the threshold of AutodockTools-1.5.6 was –6.0 kcal/mol [34] and the ligand with the lowest binding energy value on each target was considered the most significant effector. The molecules were gathered as .sdf files from PubChem(https://pubchem.ncbi.nlm.nih.gov/) (accessed on 6 October 2023), and converted into .pdb file through the PyMOL visualizer. The .pdb file was translated into an .pdbqt file via AutodockTools-1.5.6 to dock on each target (or protein). Taken together with each .pdbqt file, the docking site was formatted in a square box (x = 40 Å,
y = 40 Å, and z = 40 Å)

Chemical reactivity description via frontier molecular orbitals

The chemical reactivity of a key molecules was determined by LEE-Yang-Parr (LYP) correlation functional analysis at the 6-31G++(d,p) optimized geometry level [35]. The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) were also obtained in the optimized geometry via frontier molecular orbital (FMO) theory. To determine the energy gap (E_{gap}) of each molecule, the LUMO energy was deducted from HOMO energy value. The following formula was used to determine the key parameters for evaluating the chemical reactivity level.

Energy gap (E_{gap}) = HOMO – LUMO

Hardness (η) = (LUMO – HOMO)/2

Softness (S) = 1/ η

Electronegativity (χ) = – (LUMO – HOMO)/2

As mentioned above, the parameters were calculated and visualized by GaussView 6.0 and Gaussian 09 W to determine the electron donor or acceptor. Pinpointedly, a molecule with the lowest energy gap (E_{gap}) and the highest softness (S) was confirmed to be a promising agent for the treatment of these four diseases.

The key findings of this study were represented in **Figure 2**.

Abstract

Type 2 diabetes mellitus (T2DM), nonalcoholic fatty liver disease (NAFLD), obesity (OB), and hypertension (HT) are categorized as metabolic disorders (MDs), which develop independently without distinct borders. Herein, we examined the gut microbiota (GM) and *Saururus chinensis* (SC) to confirm their therapeutic effects via integrated pharmacology. The overlapping targets from the four diseases were determined to be key protein coding genes. The protein–protein interaction (PPI) networks, and the SC, GM, signaling pathway, target, and metabolite (SGSTM) networks were analyzed via RPackage. Additionally, molecular docking tests (MDTs) and density functional theory (DFT) analysis were conducted to determine the affinity and stability of the conformer(s). TNF was the main target in the PPI analysis, and equol derived from *Lactobacillus paracasei JS1* was the most effective agent for the formation of the TNF complex. The SC agonism (PPAR signaling pathway), and antagonism (neurotrophin signaling pathway) by SC were identified as agonistic bioactives (aromadendrane, stigmasta-5,22-dien-3-ol, 3,6,6-trimethyl-3,4,5,7,8,9-hexahydro-1H-2-benzoxepine, 4α-5α-epoxycholestane, and kinic acid), and antagonistic bioactives (STK734327, and piclamilast), respectively, via MDT. Finally, STK734327-MAPK1 was the most favorable conformer according to DFT. Overall, the 7 bioactives from SC and equol that can be produced by *Lactobacillus paracasei JS1* can exert synergistic effects on these four diseases.

Keywords: *Saururus chinensis*; *Lactobacillus paracasei JS1*; PPAR signaling pathway; Neurotrophin signaling pathway; STK734327; MAPK1

Results

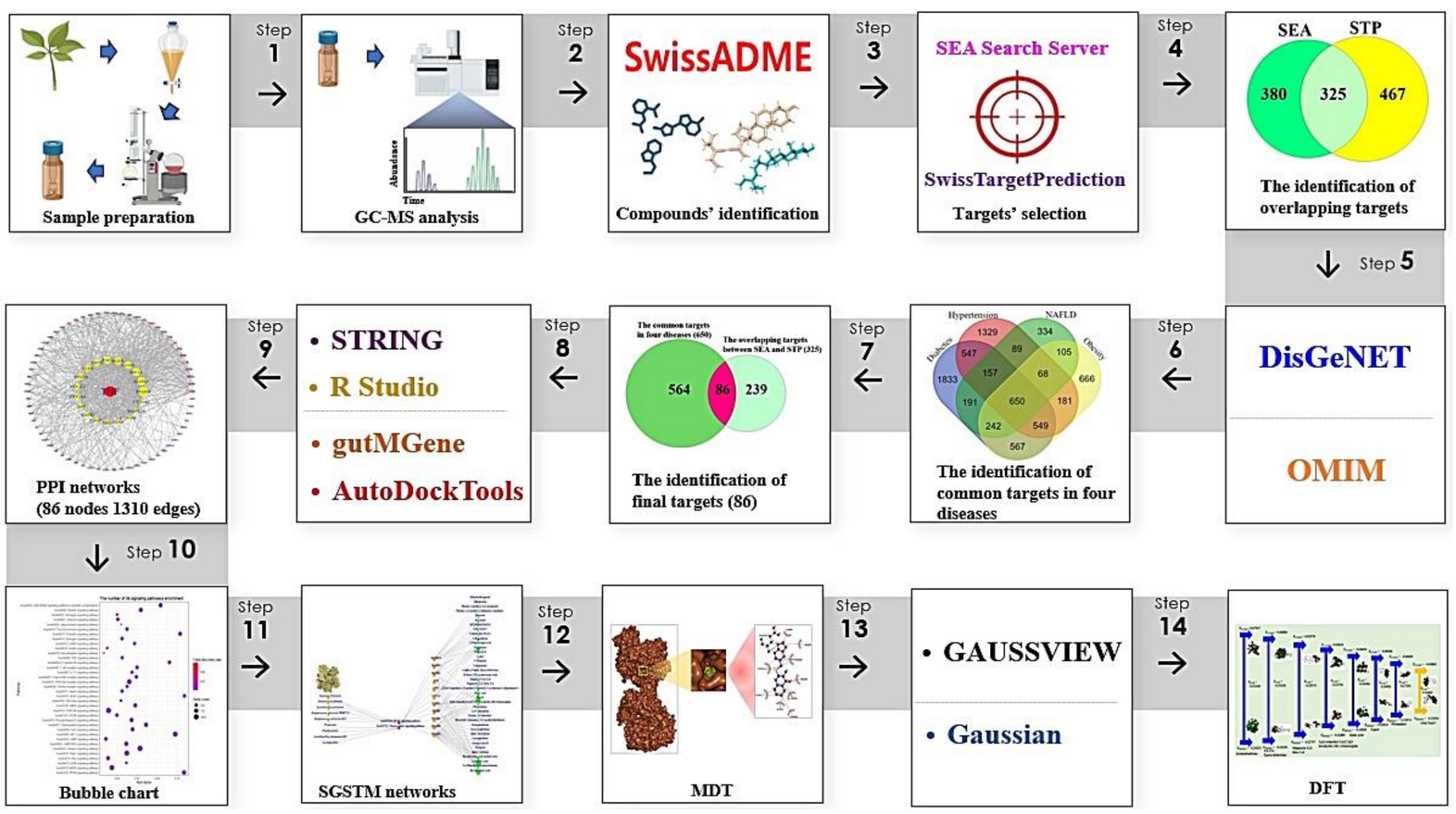

Figure 1. The workflow of this study.

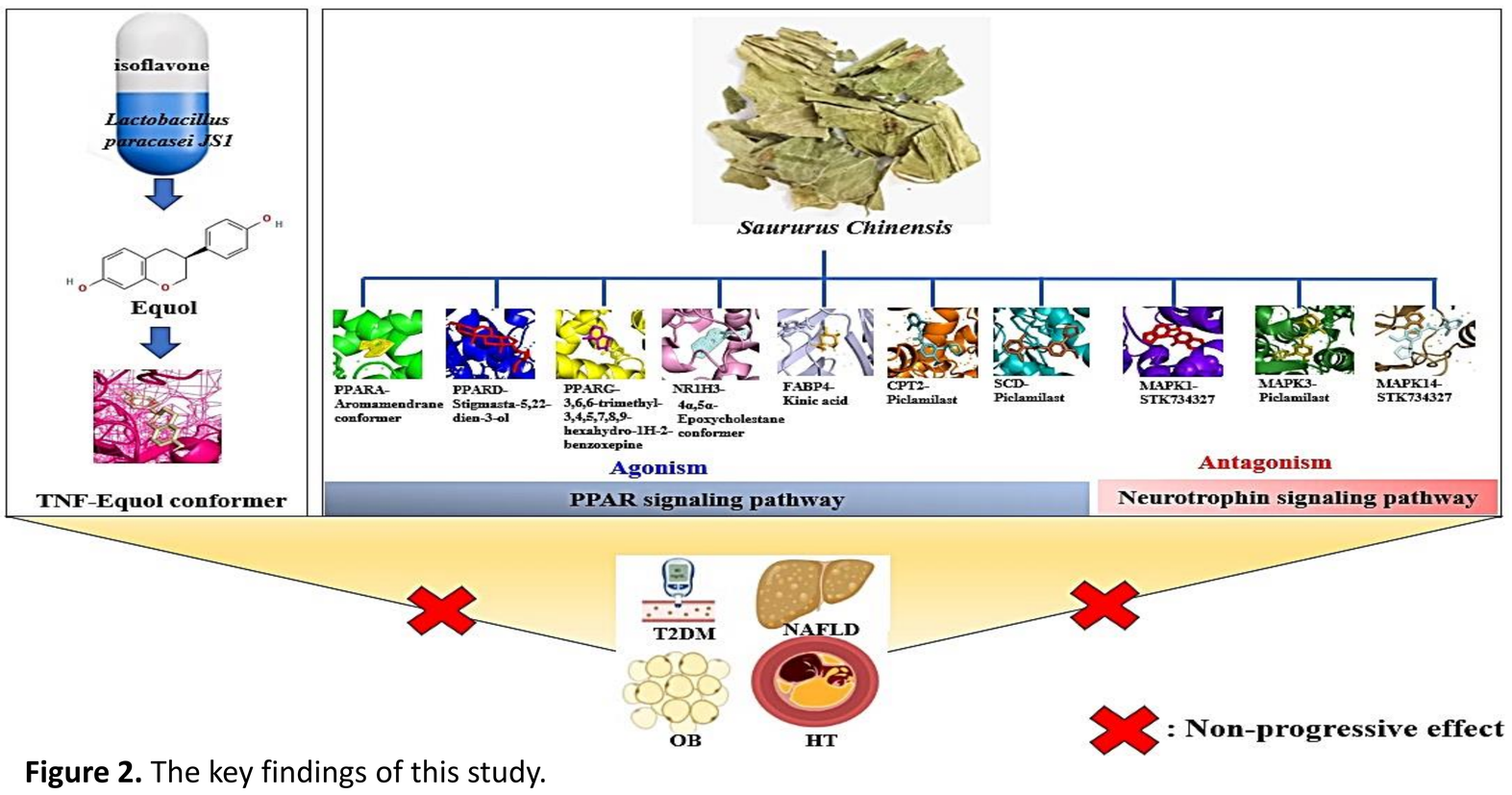

Figure 2. The key findings of this study.

Conclusion

The synchronization of the SC and GM might be an optimal therapeutic strategy to drive the nonprogressive phase against T2DM, NAFLD, OB, and HT. This study sheds light on the use of prebiotics (isoflavone), probiotics (*Lactobacillus paracasei JS1*), and postbiotics (equol). In parallel, all seven chemical compounds from SC had drug-like potency, notably, MAPK1- STK734327 (antagonism in the neurotrophin signaling pathway) was the most promising conformer in terms of MDT, and DFT theory.

Reference

Ki-Kwang Oh, Sang-Jun Yoon, Seol Hee Song, Jeong Ha Park, Jeong Su Kim, Dong Joon Kim & Ki-Tae Suk, The synchronized feature of Saururus chinensis and gut microbiota against T2DM, NAFLD, obesity and hypertension via integrated pharmacology, Artificial Cells, Nanomedicine, and Biotechnology, 2024, Vol. 52, No. 1, 278–290, https://doi.org/10.1080/21691401.2024.2350475