TARGETING THYROID HORMONE RECEPTOR ALPHA WITH NATURAL POLYPHENOLS: A NOVEL STRATEGY FOR NAFLD MODULATION

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Introduction and Aim

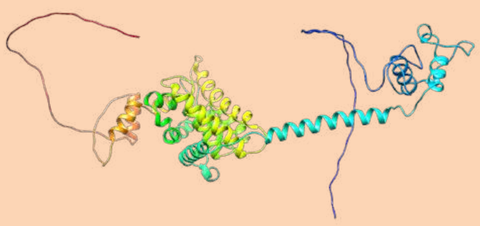
Non-alcoholic fatty liver disease (NAFLD) is a metabolic disorder described by the deposition of triglycerides in the liver, which primarily occurs due to insulin resistance and obesity. Thyroid hormone receptor alpha (THRA) is involved in metabolic pathways that promote lipolysis, which can prevent the accumulation of liver fat. As a possible treatment for NAFLD, this in silico study examines the binding interactions between THRA and polyphenols and flavonoids present in fruits and vegetables. Including caffeic acid, curcumin, and chlorogenic acid, the binding affinities of the natural substances to THRA were found comparable to the hormone T3, boosting the THRA–TRAP220 complex, promoting fatty acid oxidation, while decreasing lipid accumulation in the liver. **Aim: to evaluate the molecular docking and lipolytic effects of natural compounds from peaches on the THRA receptor. By examining their role in modulating THRA/TRAP220 binding, the study identifies compounds capable of improving lipid metabolism and offering therapeutic potential for NAFLD.**

Results and Discussion

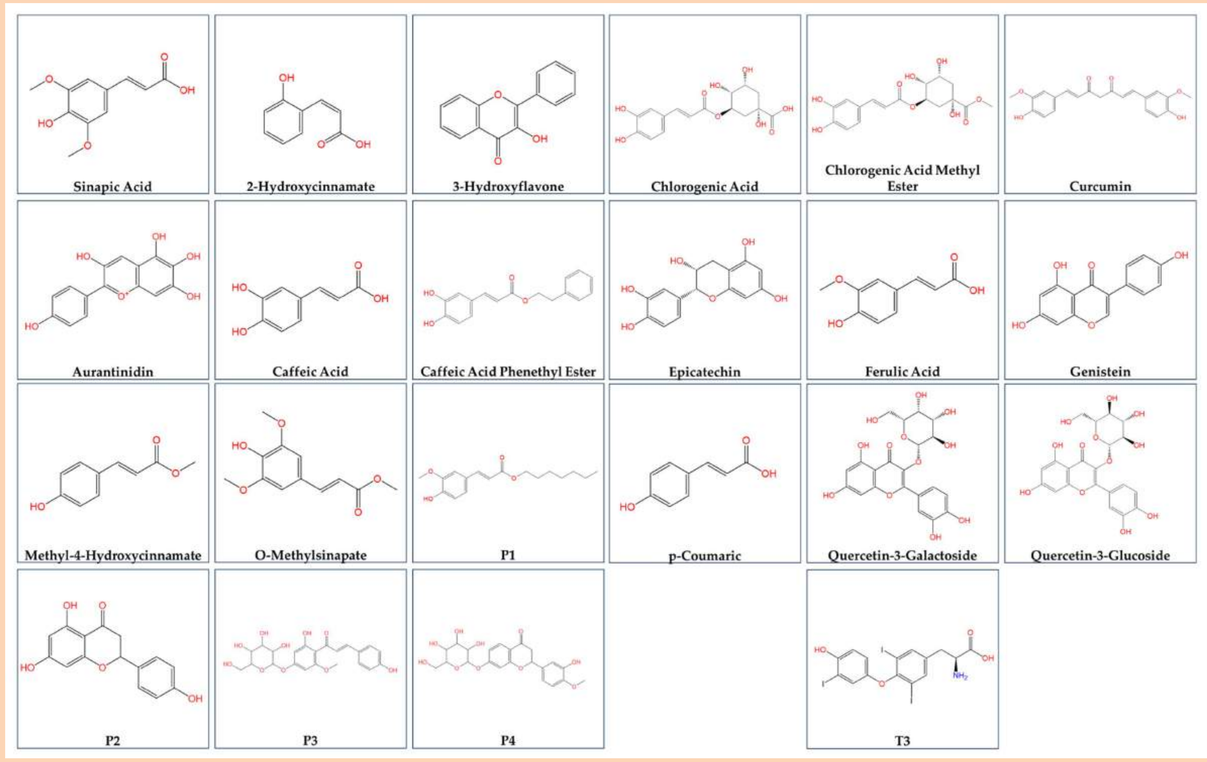
1. Protein Target

THRα

Thyroid Hormone Receptor Alpha is a nuclear receptor critical for regulating lipid and glucose metabolism, activated by the thyroid hormone T3, and plays a key role in promoting lipolysis and reducing triglyceride accumulation in the liver.



2. Natural Products

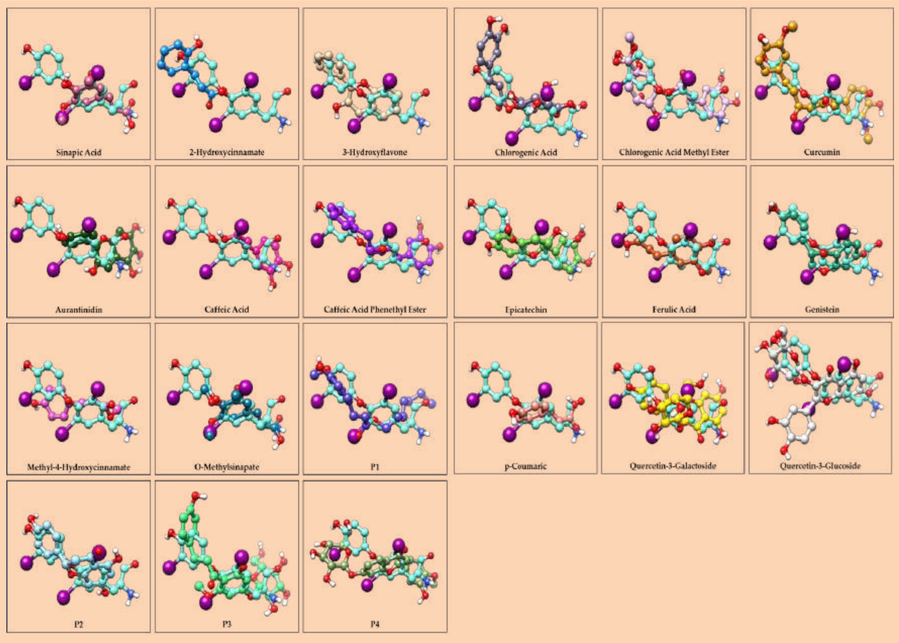


The chemical structures of the natural products used in the present study.

4. *In silico* action of THRα in NAFLD

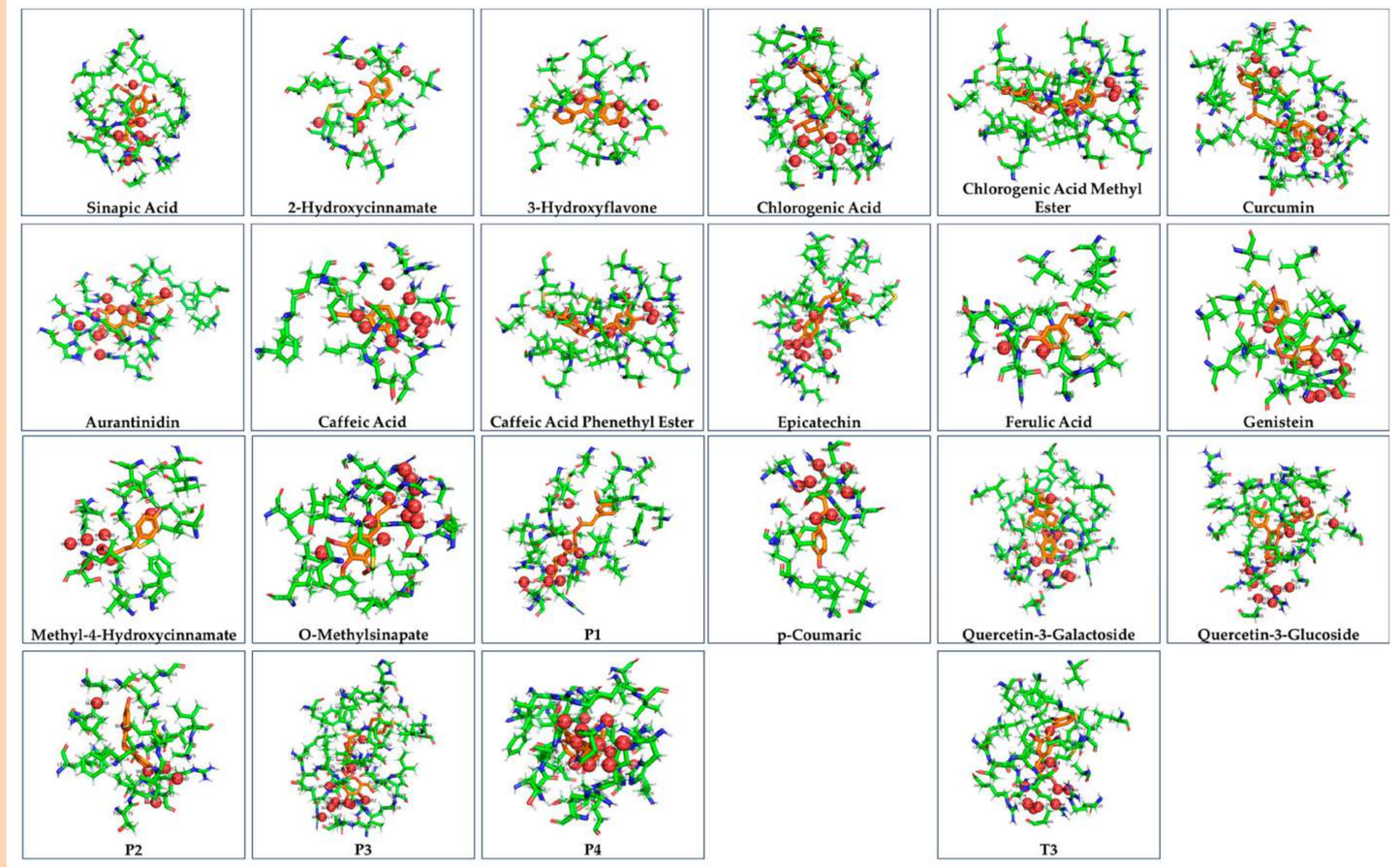
The arrangement of THRA receptor amino acids 350-400, which are located at the C-Terminal of the receptor, is critical for their binding to the TRAP220 receptor. As shown in Table, natural compounds bind strongly to the THRA receptor, leading to modifications in its C-Terminal region. This fact results in a different ability to bind the TRAP220 receptor. In general, the compounds that led to the binding of THRA to the TRAP220 receptor with a ΔG value < -582.45 Kcal/mol (corresponding to T3) through the program HEX 8.0.0., show quite promising for the process of reducing NAFLD.

Ligand	ΔG of binding to THRA (kcal/mol)	ΔG of THRA-liganded binding to TRAP220 (kcal/mol)
T3	-13.388	-582,45
Sinapic Acid	-9.274	-559,81
2-Hydroxycinnamate	-5.804	-669,50
3-Hydroxyflavone	-9.231	-570,24
Aurantinidin	-14.221	-559,73
Caffeic Acid	-8.499	-651,59
Caffeic Acid Phenethyl Ester	-12.300	-562,89
Chlorogenic Acid	-13.616	-627,93
Chlorogenic Acid Methyl Ester	-15.155	-617,52
Curcumin	-15.491	-649,71
Epicatechin	-11.952	-596,21
Ferulic Acid	-8.980	-563,35
Genistein	-9.671	-595,28
Methyl-4-Hydroxycinnamate	-7.914	-641,87
O-Methylsinapate	-9.628	-588,62
P1*	-10.579	-654,50
P2*	-12.110	-665,11
P3*	-18.465	-525,58
P4*	-17.269	-694,70
p-Coumaric	-7.948	-812,60
Quercetin-3-Galactoside	-17.321	-599,31
Quercetin-3-Glucoside	-15.370	-576,29



Comparison of the three-dimensional structure of T3 with the natural products used in this work. The structures have been extracted from Chimera program as they bind to the THRA binding pocket.

3. *In silico* docking of THRα with dietary polyphenols



Hydrasized binding pocket of THRA receptor with the natural products.

Green color shows the amino acids, which form strong intermolecular forces with the ligands, which are shown in orange. Red spheres show the water molecules, which participate in hydrogen bonds, enhancing the binding of the ligands to the receptor binding site (PHE_{218}, ILE_{222}, ALA_{225}, MET_{256}, MET_{259}, SER_{260}, ALA_{263}, LEU_{276}, SER_{277}, LEU_{292}, ILE_{299}, VAL_{395}, and LEU_{403}).

Conclusions

This study demonstrates that natural compounds, particularly those derived from peaches, have significant potential as therapeutic agents for Non-Alcoholic Fatty Liver Disease (NAFLD). By targeting the thyroid hormone receptor alpha (THRA), these compounds mimic the action of thyroid hormone T3, enhancing its interaction with the coactivator TRAP220. This interaction promotes lipolysis, fatty acid oxidation, and triglyceride clearance, which are critical in reducing hepatic lipid accumulation.

The computational analyses revealed that several bioactive compounds show strong binding affinities to THRA, comparable to T3, and effectively activate the THRA/TRAP220 complex. These findings support the role of natural products in modulating metabolic pathways and provide a foundation for developing safer, more effective NAFLD treatments with minimal side effects. Future research should focus on validating these findings through in vivo studies and exploring the clinical applicability of these compounds.

References

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Acknowledgments

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