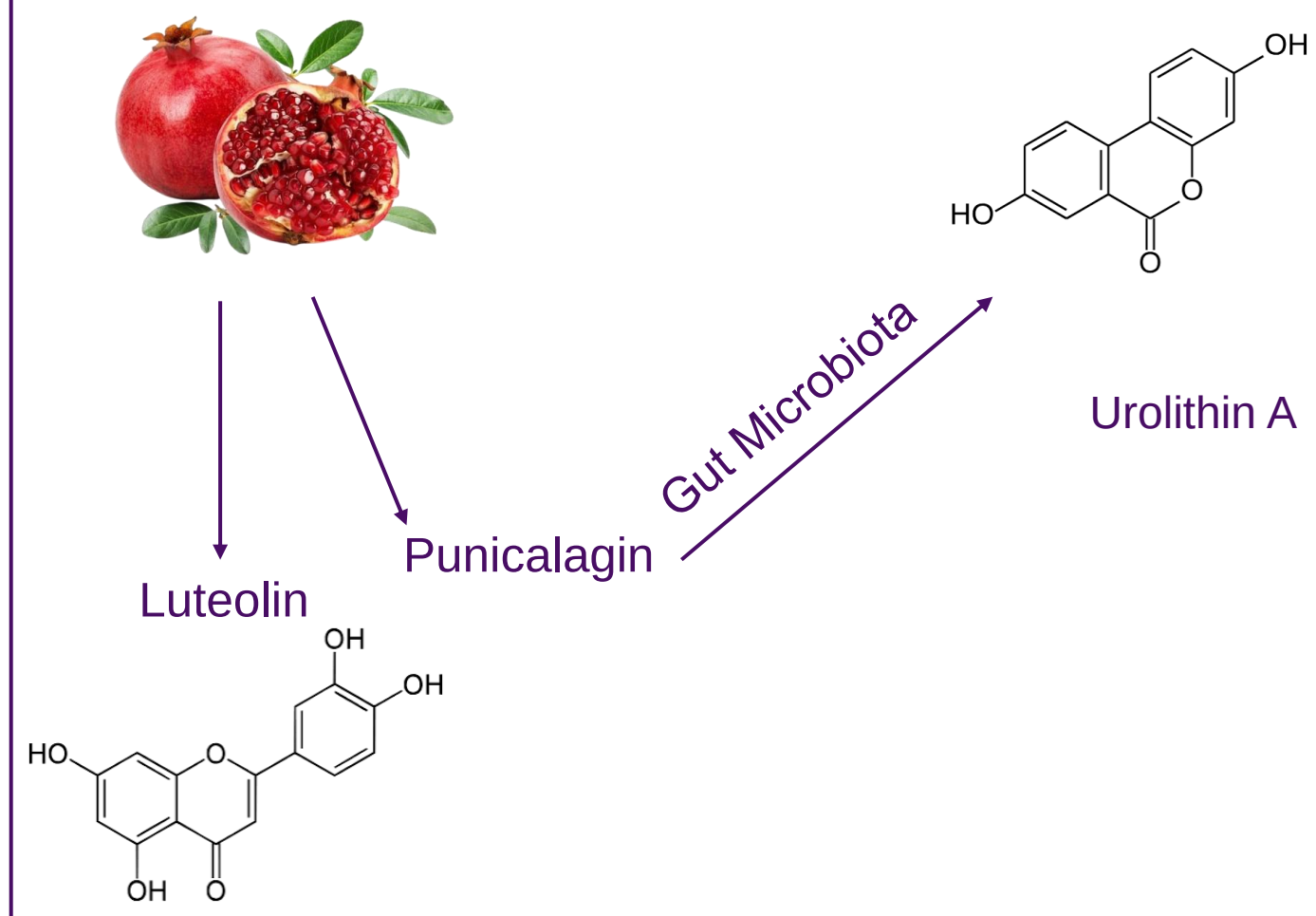
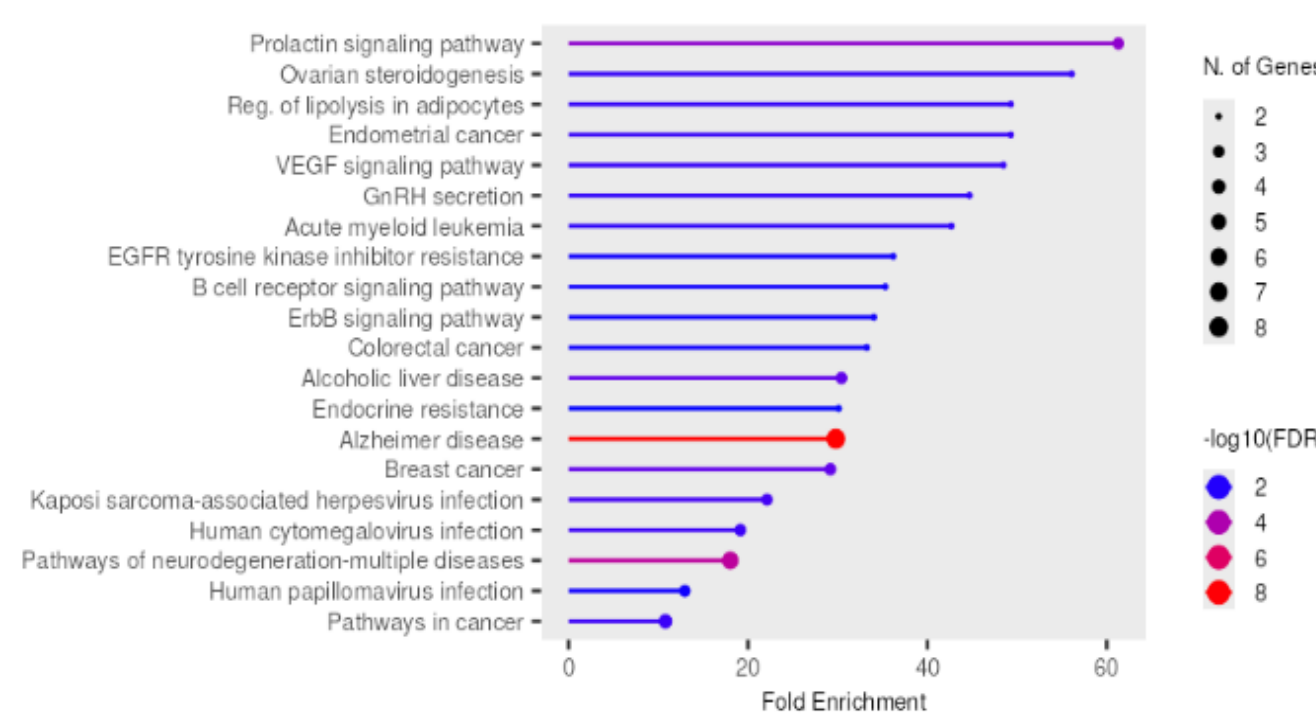
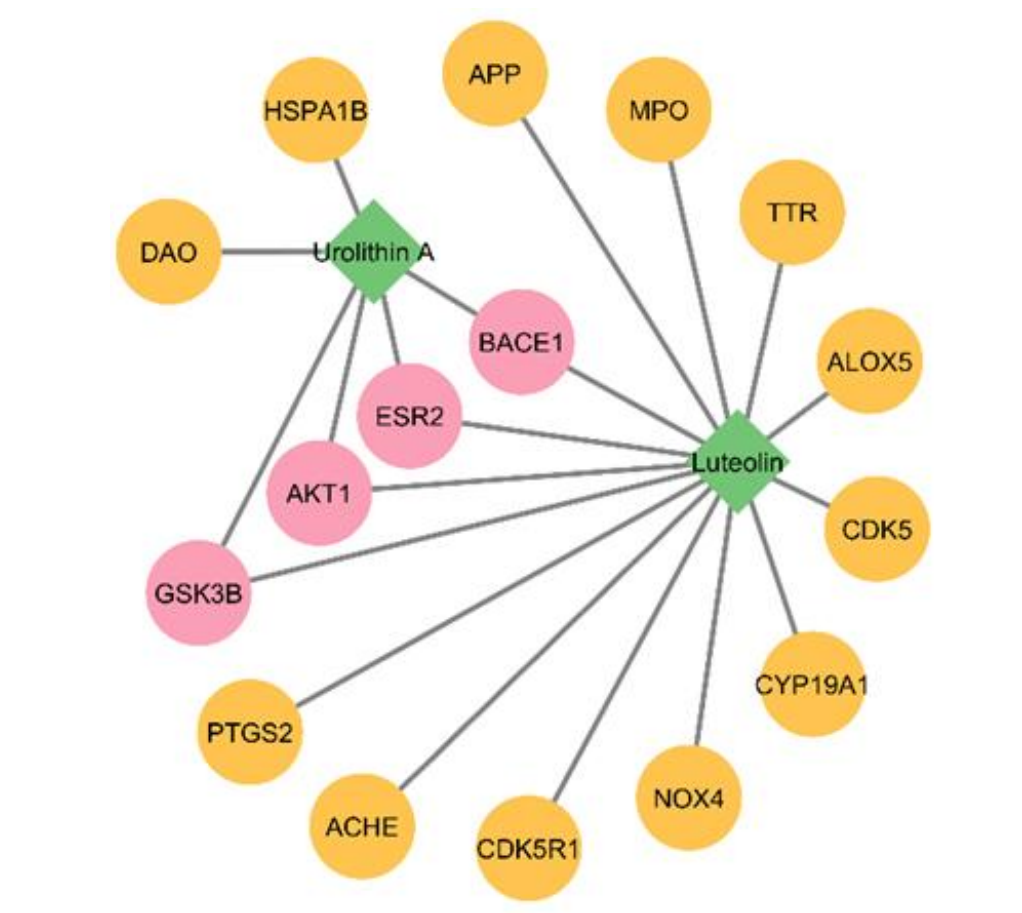


# NETWORK PHARMACOLOGY APPROACH FOR THE COMBINED EFFECT OF LUTEOLIN AND UROLITHIN A AGAINST ALZHEIMER'S DISEASE

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Nutraceuticals, luteolin and urolithin A, collectively modulate multiple AD-related targets and pathways, supporting their potential utility in combination therapy for Alzheimer's Disease.

| INTRODUCTION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | METHODS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | RESULTS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | REFERENCES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| <p>While definitive treatments for Alzheimer’s Disease (AD) remain unavailable, plant-derived multi-target-directed ligands (MTDLs) offer a promising strategy to modulate its complex pathogenesis. Luteolin (LUT) and urolithin A (UA) are two nutraceuticals that have demonstrated individual therapeutic benefits against AD. This study examines the combined effects and multi-target mechanisms of LUT and UA against AD using network pharmacology incorporated with molecular docking.</p> <div></div> | <ul style="list-style-type: none"><li>Pharmacokinetic and toxicity evaluations of LUT and UA were performed using SwissADME and ProTox 3.0, respectively.</li><li>The potential targets of nutraceuticals were identified using SwissTargetPrediction and PharmMapper.</li><li>AD-associated targets were obtained from the OMIM and GeneCards databases.</li><li>Overlapping targets between the LUT-UA combination and AD were identified using Venny 2.1.0.</li><li>A protein–protein interaction network was constructed using STRING and analysed in Cytoscape using several plug-ins.</li><li>Gene Ontology (GO) and KEGG enrichment analyses were performed using ShinyGO 0.82.</li><li>Molecular docking was conducted using UCSF ChimeraX, PyRx 0.8 and Discovery Studio on selected targets.</li></ul> | <ul style="list-style-type: none"><li>Luteolin and UA exhibited favourable ADMET profiles.</li><li>BACE1, GSK3β, AKT1, PTGS2, APP and ACHE were identified as key targets.</li><li>The AD pathway was identified as the top-enriched pathway.</li><li>Binding affinities of LUT to both BACE1 and GSK3β were -8 and -8.3 (kcal/mol), respectively.</li><li>Binding affinities of UA to both BACE1 and GSK3β were -7.9 and -8.2 (kcal/mol), respectively.</li></ul> <p>AD pathway as the top enriched pathway</p> <div></div> | <div><p>Compound-target network of LUT-UA combination</p></div> <p>Noor, F., Qamar, M.T.U., Ashfaq, U.A., Albutti, A., Alwashmi, A.S.S., Aljasir, M.A., 2022. Network Pharmacology Approach for Medicinal Plants: Review and Assessment. Pharmaceuticals. <a href="https://doi.org/10.3390/ph15050572">https://doi.org/10.3390/ph15050572</a>.</p> <p>Daina, A., Michielin, O., Zoete, V., 2019. SwissTargetPrediction: updated data and new features for efficient prediction of protein targets of small molecules. Nucleic Acids Res 47, W357 W3664. <a href="https://doi.org/10.1093/nar/gkz382">https://doi.org/10.1093/nar/gkz382</a>.</p> <p>Hampel, H., Hardy, J., Blennow, K., Chen, C., Perry, G., Kim, S.H., Villemagne, V.L., Aisen, P., Vendruscolo, M., Iwatsubo, T., Masters, C.L., Cho, M., Lannfelt, L., Cummings, J.L., Vergallo, A., 2021. The Amyloid-β Pathway in Alzheimer's Disease. Mol Psychiatry. <a href="https://doi.org/10.1038/s41380-021-01249-0">https://doi.org/10.1038/s41380-021-01249-0</a>.</p> |
| CONCLUSIONS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | CONTACT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <ul style="list-style-type: none"><li>Luteolin and urolithin A may collectively modulate multiple AD-related targets and pathways, including the amyloidogenic pathway and the PI3K/Akt signalling pathway.</li><li>Experimental validation is essential to confirm the predicted molecular activities and safety profiles.</li></ul>                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <p><a href="mailto:reshsirimalwatta@gmail.com">reshsirimalwatta@gmail.com</a></p> <p><a href="mailto:pamoda@sci.sjp.ac.lk">pamoda@sci.sjp.ac.lk</a></p> <div></div>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |