RSC Medicinal Chemistry

ROYAL SOCIETY OF CHEMISTRY

RESEARCH ARTICLE

View Article Online
View Journal

Cite this: DOI: 10.1039/d5md00819k

Decoding the association of polycystic ovary syndrome with metabolic-associated fatty liver: insights into CK18 and LC3II/ATG7/P62 autophagy axis and adjunct therapeutics of metformin and levothyroxine

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Background: polycystic ovary syndrome (PCOS) is a common endocrine-metabolic disorder often associated with insulin resistance and metabolic-associated fatty liver disease (MAFLD), both linked to impaired autophagy. This study evaluates the effects of metformin and levothyroxine on autophagy regulation in a PCOS-induced MAFLD rat model. Materials and methods: PCOS was induced in female Wistar rats by testosterone enanthate (7.5 mg, E16–19). Post-weaning, rats were assigned to control, model, metformin (300 mg kg^{-1} per day), levothyroxine (50 μg kg^{-1} per day), or combination groups. Body/liver weight, serum markers (ALT, AST, TSH, lipid profile, testosterone, LH, estradiol), insulin sensitivity, autophagy-related proteins (LC3II, ATG7, p62, CK18), and histology were assessed. Network pharmacology, protein–protein interaction, KEGG enrichment, and molecular docking were performed. Results: combination therapy reduced body weight (10.29%) and liver weight (37.08%) and lowered ALT (26.17%), AST (42.69%), TSH (77.9%), cholesterol (41.32%), triglycerides (32.37%), and LDL (43.42%). Testosterone and LH declined (37.25%, 14.43%), while estradiol rose (37.4%). HOMA-IR decreased by 51.85%. Autophagy markers (CK18, LC3II, P62, ATG7) were suppressed, with improved hepatic and ovarian histology. Network analysis identified NOS2, KRT18, MAP1LC3B, ATG7, and SQSTM1 as key targets, with KEGG pathways implicated in autophagy, mitophagy, ferroptosis, and apelin signaling. Docking analysis showed stronger binding of levothyroxine to LC3II and ATG7, suggesting a direct modulatory role. Conclusion: metformin and levothyroxine synergistically improve PCOS-related MAFLD by restoring autophagy and metabolic-endocrine balance. System-level and docking analyses support autophagy regulation as a key therapeutic mechanism, highlighting the potential role of levothyroxine in modulating autophagy.

Received 15th September 2025,
Accepted 9th March 2026

DOI: 10.1039/d5md00819k

rsc.li/medchem

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