

Network Pharmacology Exploration of Ubidecarenone (Coenzyme Q10): An *In Silico*, Hypothesis-Generating Study

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Abstract: Ubidecarenone (coenzyme Q10, CoQ10) is a widely used lipophilic quinone whose therapeutic associations beyond mitochondrial electron transport remain incompletely mapped. This *in silico* study applied network pharmacology to explore its therapeutic potential. Targets were predicted with SwissTargetPrediction (100 targets; probability 0.014–0.424, only six ≥ 0.10), the Similarity Ensemble Approach (SEA) and PharmMapper; six SwissTargetPrediction targets (ALOX5, ALOX15, PPARG, PPARA, PTGES, APEX1) were also supported by SEA at $p < 0.05$. Disease associations were taken from Open Targets. A STRING network of 110 proteins (895 edges, confidence ≥ 0.40) was analysed by degree, betweenness and closeness centrality; IL6, AKT1, TNF, STAT3 and ESR1 ranked highest. GO and KEGG enrichment (FDR < 0.05) highlighted metabolic and xenobiotic pathways, arachidonic-acid metabolism, serotonergic signalling, terpenoid-backbone biosynthesis and responses to lipids and oxidative stress. The data suggest that ubidecarenone may relate to lipid-metabolic, inflammatory and oxidative-stress pathways, but they are computational predictions that do not demonstrate binding or efficacy and require experimental confirmation.

Keywords: ubidecarenone, coenzyme Q10, network pharmacology, enrichment analysis, drug repurposing

1. Introduction

Developing a new drug from discovery to approval takes many years and substantial resources. Drug repurposing, which looks for new uses of molecules whose safety and pharmacokinetics are already known, shortens this path [1]. Network pharmacology complements it by treating a compound's effects as perturbations of an interacting target network rather than of a single protein [2].

2. Literature Survey

Ubidecarenone (coenzyme Q10) is an endogenous, lipid-soluble benzoquinone with a ten-unit isoprenoid tail. It carries electrons in the mitochondrial respiratory chain and acts as a membrane antioxidant [3], and it is used in cardiovascular, neurological and metabolic settings [4].

3. Problem Definition

Its molecular targets beyond the respiratory chain are poorly defined. Here we combine ligand-based target prediction (three methods), disease-association mining, protein–protein interaction (PPI) analysis, and functional enrichment to generate testable hypotheses about its therapeutic potential, and we report the limits of each step.

4. Methodology / Approach

4.1 Ligand retrieval and properties

The structure and canonical SMILES of ubidecarenone (PubChem CID 5281915; C59H90O4; molecular weight ≈ 863 g/mol; 63 heavy atoms) were obtained from PubChem [5]. Physicochemical descriptors, solubility, drug-likeness filters (Lipinski, Ghose, Veber, Egan, Muegge),

pharmacokinetic predictions (GI absorption, blood–brain barrier permeation, P-glycoprotein substrate status, CYP inhibition) and medicinal-chemistry alerts (PAINS, Brenk) were obtained from SwissADME [6]; these were used for description only.

4.2 Target prediction

Targets of the SMILES were predicted with SwissTargetPrediction [7] (Homo sapiens), which returned 100 targets, all retained irrespective of probability because the highest value was low. The SMILES was also submitted to the Similarity Ensemble Approach (SEA) [8], which compares the ligand with sets of known ligands for each target and reports a p-value and the maximum Tanimoto coefficient (Max Tc), and to PharmMapper [9]–[11], which fits the molecule to a database of target pharmacophore models and reports a fit score and z-score. SEA hits with $p < 0.05$ and PharmMapper hits with $z\text{-score} \geq 2$ (an arbitrary cut-off chosen by us) were restricted to human proteins. Targets common to SwissTargetPrediction and SEA were treated as consensus-supported. SEA p-values are not corrected for multiple testing. The PharmMapper input was the ubidecarenone structure (PubChem CID 5281915); the server returned 281 pharmacophore-model hits (Supplementary Table S1).

4.3 Disease association

Each of the 111 targets with a gene symbol (97 from SwissTargetPrediction and 14 added from SEA and PharmMapper) was queried in the Open Targets Platform [12]. The disease with the highest overall association score (0–1) was recorded as its principal disease association. These scores reflect the evidence linking a target to a disease and do not indicate that ubidecarenone modulates that disease.

4.4 PPI network and hub selection

The union of the SwissTargetPrediction targets that had a single gene symbol (97 of 100; the other three were the protein complexes IKK, HSP60/HSP10 and AP-1), the six human SEA-only hits and the eight additional PharmMapper hits (111 unique genes) was submitted to STRING [13] (*Homo sapiens*; minimum interaction score 0.40). MAPK10 could not be resolved by STRING (only the phosphatases DUSP16 and DUSP23 were offered); DUSP16 is a different protein and was removed, so the network analysed contained 110 proteins and MAPK10 is absent from it (Section 5.6). Degree (from STRING), betweenness and closeness centrality (NetworkX) were calculated for each node, and a composite score was defined as the mean of the three min-max normalised centralities. Proteins were ranked by this score. Centrality values for all 110 nodes are given in Supplementary Table S2.

4.5 GO and KEGG enrichment

The submitted proteins were analysed in STRING for enrichment of GO Biological Process, Molecular Function, Cellular Component and KEGG pathways against the whole-genome background. Terms with FDR < 0.05 were retained and are reported with observed gene count, strength (log10 of observed/expected) and FDR. The enrichment run used the 111-protein input in which DUSP16 stood in for the unresolved MAPK10. Terms containing DUSP16 (e.g. efferocytosis and MAPK signalling) were not interpreted, and the gene counts of the 43 terms that include it (22 Biological Process, 7 Molecular Function, 12 Cellular Component and 2 KEGG terms) are inflated by one; the only such term discussed below is the generic component cytoplasm.

5. Results and Discussion

5.1 Physicochemical profile, predicted targets and SEA cross-check

SwissADME showed ubidecarenone (C59H90O4) to be a very large, highly lipophilic molecule: molecular weight 863.34 g/mol, 63 heavy atoms, 31 rotatable bonds, 4 hydrogen-bond acceptors, no hydrogen-bond donors, TPSA 52.60 Å² and consensus Log Po/w 15.57. It was predicted to be insoluble in water (Log S -15.38, ESOL). It violated Lipinski's rule twice (MW > 500, MLOGP > 4.15) and also the Ghose (4 violations), Veber (1), Egan (1) and Muegge (3) filters; the bioavailability score was 0.85. Gastrointestinal absorption was predicted to be low, blood-brain barrier permeation absent, and the molecule a P-glycoprotein substrate that does not inhibit CYP1A2, CYP2C19, CYP2C9, CYP2D6 or CYP3A4. SwissADME raised one PAINS alert (quinone_A) and two Brenk alerts (chinone_1, isolated alkene), and the synthetic accessibility score was 8.28.

SwissTargetPrediction returned 100 targets, mainly oxidoreductases (16), kinases (14), lyases (10), cytochrome P450 enzymes (8) and nuclear receptors (7). Probabilities were low (0.014–0.424); only ALOX5 (0.42) exceeded 0.40, and six targets (ALOX5, IDO1, CYP3A4, CYP2C19, CYP2C9, CYP2D6) reached 0.10. For 85 of 100 targets no

similar known active ligand was found, so the list is low-confidence, as expected for a large lipophilic molecule outside the chemical space of most known ligands.

SEA returned 7,746 target scores. Fifteen reached $p < 0.01$, but most were non-human proteins (e.g. rat squalene synthase, $p = 7 \times 10^{-14}$; rat TRPA1; Trypanosoma alternative oxidase), and Max Tc was ≤ 0.43 for most. Twelve human targets had $p < 0.05$ (Table 1). Six of them (ALOX5, ALOX15, PPARG, PPARA, PTGES, APEX1) also occur in the SwissTargetPrediction list and are treated as consensus-supported; the pig HMG-CoA reductase hit ($p = 0.003$) corresponds to HMGCR in that list. The SEA hits cluster in isoprenoid and lipid metabolism (GGPS1, SQLE, ICMT, lipoxygenases, PPARs), which is chemically plausible for an isoprenoid-tailed quinone, but Tc values of 0.31–0.47 indicate only modest similarity to known ligands.

Table 1: Human SEA hits ($p < 0.05$), overlap with SwissTargetPrediction (STP) and PharmMapper z-score where present

Target	SEA p	Max Tc	In STP	Pharm Mapper z	Consensus
IMPDH2	1.6×10^{-10}	0.31	No	-0.99	No
MPEG1	1.1×10^{-9}	0.62	No	—	No
GGPS1	1.5×10^{-8}	0.36	No	—	No
ALOX5	2.3×10^{-5}	0.62	Yes	—	Yes
ALOX15	9.8×10^{-4}	0.47	Yes	—	Yes
TRPV1	6.7×10^{-3}	0.37	No	—	No
APEX1	8.0×10^{-3}	0.36	Yes	—	Yes
PPARA	0.014	0.4	Yes	1.36	Yes
ICMT	0.015	0.34	No	—	No
PPARG	0.023	0.41	Yes	-0.10	Yes
PTGES	0.028	0.36	Yes	—	Yes
SQLE	0.029	0.37	No	—	No

PharmMapper returned 281 pharmacophore-model hits for ubidecarenone (Supplementary Table S1), of which only eight had a z-score ≥ 2 : nuclear receptor subfamily 1 group I member 3 (NR1I3, CAR; z 3.48), flavin reductase (BLVRB, 2.90), caspase-1 (2.58), MAPK10 (2.44), TRAPPC3 (2.41), SEC14L2 (2.25), CYP2C8 (2.09) and endothelial protein C receptor (PROCR, 2.00). None of these is among the targets supported by SwissTargetPrediction and SEA. Of the consensus-supported targets, PPARA (z 1.36) and PPARG (-0.10) were returned but weakly, and ALOX5, ALOX15, PTGES and APEX1 were not returned. Among other targets discussed here, MAOA (0.98), ESR1 (0.96), FGFR1 (0.79), ABL1 (1.18), MAOB (0.43) and EGFR (0.31) had positive but sub-threshold z-scores, whereas AKT1 (-1.64), GSTT2 (-1.78), angiogenin (-1.27), IMPDH2 (-0.99), CDK6 (-0.38), HRAS (-0.40) and mitochondrial SOD2 (-0.55) were negative; HMGCR, PTGS2, CLK1, GSTZ1, CYP3A4 and the GGPS1/ICMT/SQLE isoprenoid enzymes were not returned. PharmMapper is therefore treated as weak supporting evidence only, and PPARA and PPARG remain the only targets that appear in all three methods, although with low PharmMapper scores.

5.2 Disease associations

Open Targets association scores for the top disease of each of the 111 queried targets ranged from 0.09 to 0.88 (HSD17B3 and CA5B had no association). Table 2 lists eight

representative SwissTargetPrediction targets (four network hubs and four metabolic enzymes) with their strongest disease and Table 3 the 14 targets added from SEA and PharmMapper. Several top associations are rare monogenic disorders (Proteus syndrome for AKT1, Brunner syndrome for MAOA) that reflect genetic evidence, not relevance to ubidecarenone, and should not be over-interpreted.

Table 2: Strongest Open Targets disease association for eight representative SwissTargetPrediction targets.

Gene	STP prob.	Top disease (score)
AKT1	0.034	Proteus syndrome (0.76)
ESR1	0.023	Breast adenocarcinoma (0.74)
PPARG	0.018	Type 2 diabetes mellitus (0.86)
PTGS2	0.032	Rheumatoid arthritis (0.63)
HMGCR	0.024	Hypercholesterolaemia (0.74)
MAOB	0.019	Parkinson disease (0.63)
MAOA	0.018	Brunner syndrome (0.77)
CYP3A4	0.109	HIV infectious disease (0.66)

Table 3: Strongest Open Targets disease association for the 14 targets added from SEA and PharmMapper (PharmMapper rows are the eight hits with $z \geq 2$).

Gene	Top disease	Score	Source
IMPDH2	Acute lymphoblastic leukemia	0.53	SEA
MPEG1	Immunodeficiency	0.7	SEA
GGPS1	Muscular dystrophy; congenital hearing loss; ovarian insufficiency syndrome (three diseases tied)	0.7	SEA
TRPV1	Migraine disorder	0.63	SEA
ICMT	Cancer	0.38	SEA
SQLE	Neurodegenerative disease	0.52	SEA
NR1I3	Neurodegenerative disease	0.27	PharmMapper
BLVRB	Neurodegenerative disease	0.12	PharmMapper
CASP1	Severe acute respiratory syndrome	0.37	PharmMapper
MAPK10	Gout	0.53	PharmMapper
TRAPPC3	Neurodegenerative disease	0.55	PharmMapper
SEC14L2	Neurodegenerative disease	0.4	PharmMapper
CYP2C8	Abnormality of the skeletal system	0.27	PharmMapper
PROCR	Venous thromboembolism	0.55	PharmMapper

5.3 PPI network and hub proteins

The STRING network contained 110 proteins and 895 interactions (Fig. 1). One component held 104 proteins, CLK1 and CLK4 formed a separate pair, and DYRK3, MPEG1, SEC14L2 and TRAPPC3 were isolated. IL6 had the highest degree (60), followed by AKT1 (57), TNF (54) and PTGS2 (47); STAT3 and NFKB1 had 46 each. By composite centrality the top ten were IL6, AKT1, TNF, STAT3, ESR1, MAPT, PTGS2, EGFR, NFKB1 and JUN (Table 4). Of the targets in Table 2, AKT1 (rank 2), ESR1 (5), PTGS2 (7), HMGCR (12) and PPARG (15) are among the leading hubs, while CYP3A4 (19), MAOA (26) and MAOB (27) rank lower. The consensus-supported ALOX5 (rank 58; degree 14) and ALOX15 (rank 55; degree 15) are peripheral, so network position and prediction support select different targets. Among the PharmMapper additions, CASP1 is well connected (degree 26, rank 24), CYP2C8 (degree 16) and

NR1I3 (12) are peripheral (ranks 56 and 67), and BLVRB, PROCR, SEC14L2 and TRAPPC3 have at most three links.

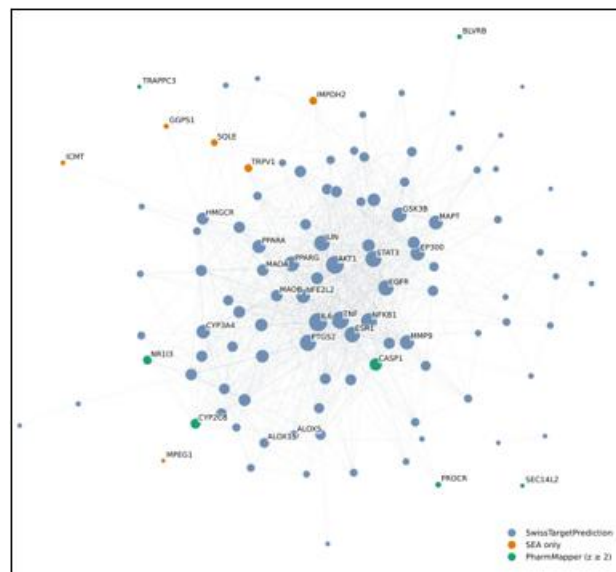


Figure 1: STRING PPI network of the 110 mapped targets (confidence ≥ 0.40 ; 895 edges; MAPK10 could not be mapped and is not shown). Node size is proportional to degree; colour shows the prediction source.

Table 4: Centrality measures and composite rank (110-node network; top ten and other targets discussed; all nodes in Supplementary Table S2).

Gene	Rank	Degree	Betw.	Close.	Comp.
IL6	1	60	0.072	0.649	1
AKT1	2	57	0.059	0.636	0.917
TNF	3	54	0.055	0.628	0.879
STAT3	4	46	0.043	0.586	0.756
ESR1	5	43	0.047	0.566	0.75
MAPT	6	34	0.059	0.541	0.742
PTGS2	7	47	0.03	0.597	0.709
EGFR	8	42	0.035	0.569	0.687
NFKB1	9	46	0.026	0.586	0.677
JUN	10	43	0.026	0.579	0.658
HMGCR	12	25	0.052	0.507	0.643
PPARG	15	41	0.024	0.566	0.628
GSK3B	17	38	0.024	0.559	0.608
CYP3A4	19	32	0.018	0.515	0.526
MAOA	26	23	0.009	0.497	0.424
MAOB	27	23	0.009	0.497	0.424

5.4 GO and KEGG enrichment

Enrichment returned 658 GO Biological Process, 116 Molecular Function, 36 Cellular Component and 141 KEGG terms at FDR < 0.05 . The strongest GO Biological Process terms were broad (cellular response to chemical stimulus, 57 genes, FDR 1.6×10^{-23} ; response to chemical, 70 genes; response to oxygen-containing compound, 45 genes; response to lipid, 33 genes, FDR 7.7×10^{-15}), followed by regulation of apoptotic process (36 genes). More specific terms included steroid metabolic process (19 genes, FDR 1.8×10^{-12}), arachidonate metabolic process (12 genes, FDR 4.3×10^{-12}), long-chain fatty-acid biosynthetic process (11 genes, FDR 6.6×10^{-12}), xenobiotic catabolic process (10 genes, FDR 1.3×10^{-11}), isoprenoid metabolic process (11 genes, FDR 3.6×10^{-8}) and response to oxidative stress (13 genes, FDR 1.8×10^{-5}) (Fig. 3). Molecular Function terms

were dominated by oxidoreductase activity (34 genes, FDR 3.3×10^{-19}), small-molecule and ion binding, carbonate dehydratase activity (9 genes), and heme and iron binding. Cellular Component terms were weak (best FDR 4.9×10^{-7}) and mainly cytoplasm, organelle lumen and endoplasmic reticulum (33 genes).

KEGG enrichment (Fig. 2; Table 5) was led by metabolic pathways (40 genes, FDR 2.5×10^{-14}), chemical carcinogenesis – receptor activation (17 genes), nitrogen metabolism (nine carbonic anhydrases) and pathways in cancer (22 genes), followed by lipid and atherosclerosis, serotonergic synapse (MAOA, MAOB, PTGS1/2, ALOX5/15, CYP2D6 and others), chemical carcinogenesis – DNA adducts, cytochrome P450 drug metabolism, steroid hormone biosynthesis and arachidonic-acid metabolism (8 genes, FDR 1.8×10^{-7}). Terpenoid-backbone biosynthesis (GGPS1, HMGCR, ICMT; FDR 0.0017) appeared only after the SEA-derived targets were added; this is the isoprenoid pathway that supplies the CoQ10 side chain. PI3K–Akt signalling was enriched only weakly (6 genes, FDR 0.045) despite AKT1 being a top hub.

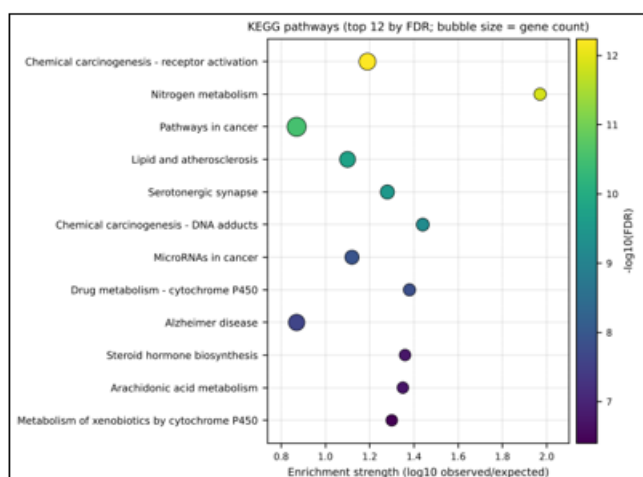


Figure 2: KEGG enrichment of the predicted targets (top 12 by FDR, excluding the generic term metabolic pathways; bubble size = gene count).

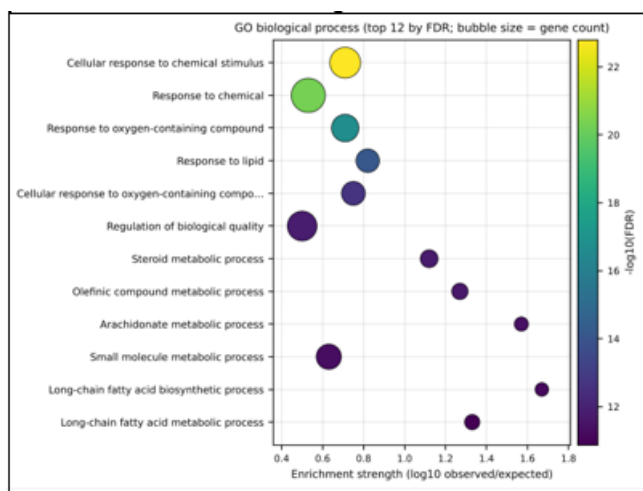


Figure 3: GO biological-process enrichment of the predicted targets (top 12 by FDR; terms containing DUSP16 omitted).

Table 5: Selected KEGG pathways (FDR < 0.05).

Pathway	Genes	Strength	FDR
Metabolic pathways	40	0.66	2.5×10^{-14}
Chem. carcinogenesis – receptor activation	17	1.19	5.7×10^{-13}
Nitrogen metabolism	9	1.97	1.4×10^{-12}
Pathways in cancer	22	0.87	3.0×10^{-11}
Lipid and atherosclerosis	15	1.1	1.7×10^{-10}
Serotonergic synapse	12	1.28	3.0×10^{-10}
Drug metabolism – cytochrome P450	9	1.38	1.5×10^{-8}
Steroid hormone biosynthesis	8	1.36	1.8×10^{-7}
Arachidonic acid metabolism	8	1.35	1.8×10^{-7}
Terpenoid backbone biosynthesis	3	1.38	0.0017
PI3K-Akt signaling pathway	6	0.47	0.0447

Two cautions apply. First, the input list consists of predicted ligand-similar targets, rich in metabolic enzymes and cytochrome P450s, so enrichment for metabolic and xenobiotic pathways largely mirrors how the list was built and is not evidence that ubidecarenone acts on them. Second, STRING used the whole genome as background rather than a background of all druggable targets, which inflates significance; the carbonic-anhydrase signal, for example, reflects a gene family rather than a specific pathway effect.

5.5 Discussion

The workflow identified a consistent set of targets across methods. ALOX5, ALOX15, PPARG, PPARG, PTGES and APEX1 were supported by both SwissTargetPrediction and SEA, and PPARG and PPARG also returned by PharmMapper (weakly); IL6, AKT1, TNF, STAT3, ESR1 and MAPT were the highest-ranked hubs; and enrichment pointed to lipid-response, oxidoreductase, arachidonic-acid, steroid, serotonergic/MAO and terpenoid-backbone pathways. PPARG, PTGS2, ALOX5 and PTGES lie on the arachidonic-acid/inflammatory axis, and HMGCR, GGPS1, SQLE and ICMT belong to the mevalonate–isoprenoid pathway that also supplies the CoQ10 side chain. These connections are compatible with the known antioxidant, mitochondrial and lipid-metabolic roles of CoQ10 [3], [4] and suggest where its therapeutic value, if any, might be tested: oxidative-stress-related inflammatory, cardiometabolic and neurodegenerative conditions. The high-degree cytokine hubs (IL6, TNF) arise from the dense literature on inflammatory signalling and say little about ubidecarenone itself.

These are hypotheses and not findings. Target prediction probabilities and SEA similarities were modest, disease associations are not specific to ubidecarenone, enrichment mirrors the composition of the list, and no structure-based or experimental test was performed. Direct binding of ubidecarenone to any of these proteins is not shown.

5.6 Limitations

(i) Ubidecarenone is very large (863 g/mol) and flexible (31 rotatable bonds) and violates Lipinski's rule twice, so ligand-based prediction is least reliable for it. (ii) Low SwissTargetPrediction probabilities, low SEA Tc values and weak PharmMapper z-scores (only eight of 281 hits reached $z \geq 2$, none overlapping the other methods); SEA p-values are

uncorrected, its strongest hits are non-human, and the PharmMapper $z \geq 2$ cut-off is arbitrary. (iii) Whole-genome enrichment background and a metabolism-rich input list. (iv) Open Targets scores are genetic and literature evidence for a target–disease link, not evidence of an effect of ubidecarenone, and several top diseases are rare monogenic disorders. (v) No structure-based analysis (docking, molecular dynamics or free-energy calculations) and no experimental data were generated, so binding of ubidecarenone to any predicted target is untested. (vi) MAPK10 (PharmMapper z 2.44) could not be mapped to STRING and is absent from the PPI network, so the centrality values of its neighbours may be slightly underestimated; enrichment was run with DUSP16 in its place, so counts for terms containing DUSP16 may differ by one from a complete run.

6. Conclusion

Network pharmacology across three target-prediction methods, STRING centrality and GO/KEGG enrichment links ubidecarenone computationally to lipid-metabolic, arachidonic-acid/inflammatory, isoprenoid, xenobiotic-metabolism and oxidative-stress pathways, with AKT1, ESR1, PTGS2, PPARG and the lipoxygenases among the most consistently supported nodes. This indicates potential therapeutic relevance in inflammatory and cardiometabolic settings that merits investigation, but the study is hypothesis-generating only.

7. Future Scope

Structure-based validation (docking and molecular dynamics with free-energy estimation) and in vitro or in vivo testing are required before any therapeutic value can be claimed. MAPK10, which could not be mapped to STRING, should be resolved and the network and enrichment analyses repeated as a complete 111-protein run.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability

All data generated or analysed during this study are included in this article and its supplementary tables (S1 and S2, provided as a separate file). The raw outputs of the web servers used are available from the corresponding author on reasonable request.

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