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Disrupting Cancer Metabolism: Molecular Docking Insights into Andrographolides as a Competitive Inhibitors of Selected Lipogenic Enzymes (Fatty Acid Synthase, ATP Citrate Lyase, and Acetyl-CoA Carboxylase)

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Abstract

Cancer remains a significant global health challenge, with metabolic dysregulation emerging as a critical focus in cancer research. Aberrant *de novo* lipogenesis has been identified as a hallmark of various malignancies. Key enzymes in this pathway including fatty acid synthase (FASN), ATP citrate lyase (ACLY), and acetyl-CoA carboxylase alpha (ACCα). Overexpression of these enzymes facilitate fatty acid production, supports tumor growth by contributing to membrane biosynthesis, energy storage, and signaling. Andrographolide, a bioactive compound derived from *Andrographis paniculata*, has demonstrated anti-cancer properties by inhibiting *de novo* lipogenesis. This study aimed to elucidate the molecular docking interactions and inhibitory effects of andrographolide towards lipogenic enzymes. Docking analyses revealed that andrographolide targets FASN's thioesterase (TE) domain (residues S101 and H237) and enoyl reductase (ER) domain (residues 1671–1688) with a binding affinity of -2.14 and -1.92 kcal/mol respectively. Similarly, andrographolide interacted with ACCα's carboxyltransferase (CT) domain (residues A1722, I1724, I1827, I2126, and K2127), showing a binding affinity of -1.32 kcal/mol. However, its interaction with ACLY at residue F347 yielded a binding affinity of -1.62 kcal/mol, with evidence suggesting that F347 may not be involved in stable citrate interactions due to poorly resolved electron density. The inhibition of enzyme disrupts the production of long-chain fatty acids essential for cancer cell growth, restricts the energy and structural demands of rapidly dividing cancer cells, and hinders their survival, progression, and metastatic potential, offering a promising therapeutic approach for multiple cancer types.

1. Introduction

Cancer remains a significant global health burden, accounting for substantial morbidity and mortality worldwide [1]. According to the most recent GLOBOCAN report (February 2024), six major cancer types which include lung cancer (12.4%), colorectal cancer (11.5%), breast cancer (11.5%), prostate cancer (7.3%), stomach cancer (4.8%), and liver cancer (4.3%) constitute more than half of all newly diagnosed cases globally. Despite advances in detection, diagnosis, and treatment, the incidence and mortality rates of these cancers continue to rise [2,3]. This persistent trend highlights the complexity of cancer biology, where underlying factors such as genetic predisposition, environmental exposures, and metabolic alterations converge to drive tumorigenesis [4].

An emerging area of interest in cancer research is the impact of metabolic reprogramming on tumour development and progression [5]. Notably, obesity has been recognized as a significant cancer risk factor, accounting for approximately 20% of all cancer cases [6]. Obesity fosters a pro-tumorigenic environment through mechanisms such as chronic inflammation, insulin resistance, and disrupted lipid metabolism, all of which contribute to oncogenesis [7]. Among the various metabolic pathways associated with cancer, *de novo* lipogenesis - a process involving the synthesis of fatty acids from non-lipid precursors - has recently gained attention for its critical role in supporting cancer cell proliferation and survival [8,9].

Aberrant *de novo* lipogenesis is now recognized as a hallmark of many malignancies, including lung, colorectal, breast, prostate, stomach, and liver cancers [5]. Cancer cells rely on this process to generate fatty acids

that are essential for building membrane lipids, producing signalling molecules, and providing energy reserves [10]. In contrast to normal tissues, cancer cells show a significant upregulation of lipogenic enzymes, including fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC), which are essential for fatty acid production (Figure 1) [11-13]. This enhanced lipogenesis not only meets the rapid growth requirements of tumour cells but also creates a microenvironment that supports their survival, progression, and metastasis [14,15].

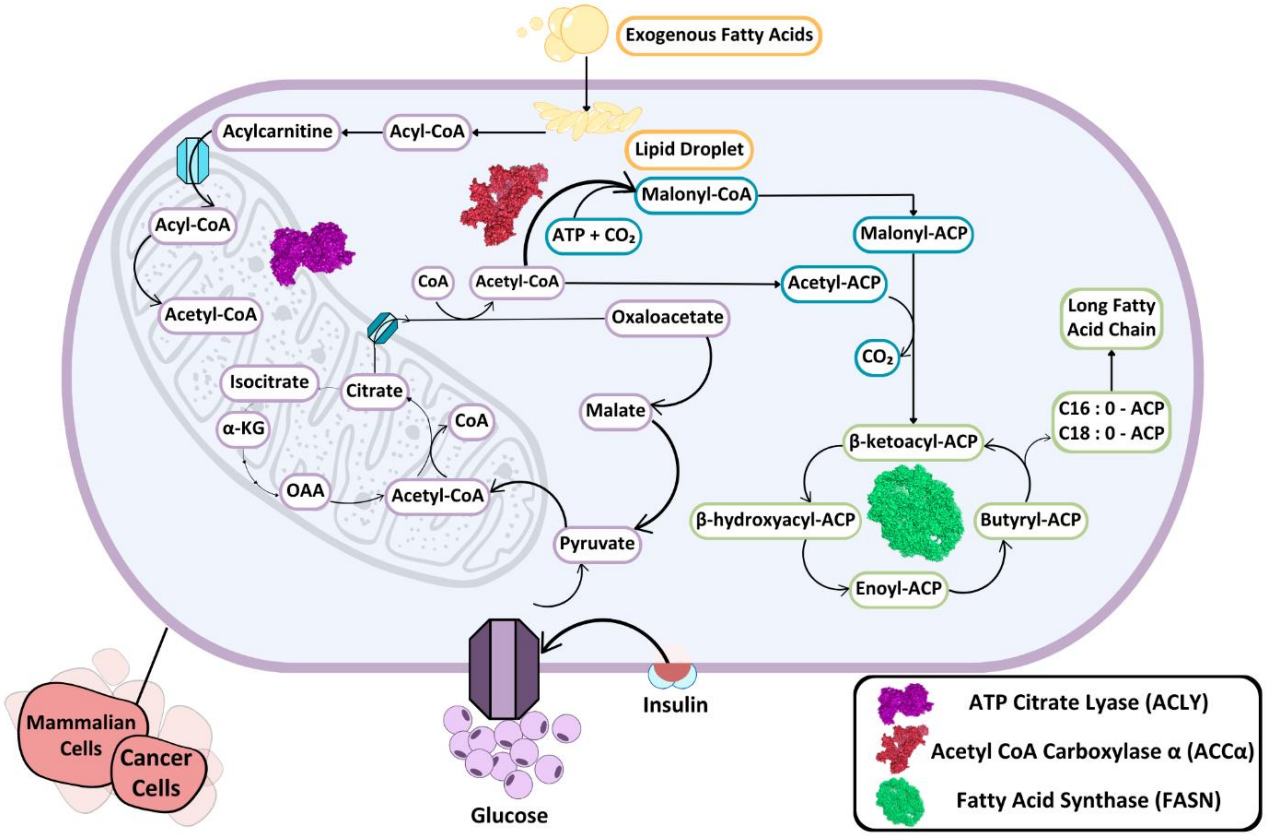

Figure 1. The overexpression of lipogenic enzymes (FASN, ACCα and ACLY) promotes the accumulation of long chain fatty acids through *de novo* lipogenesis pathway. If it is in cancer cells, it prepare the cancer cells to equip with strengthen cytoplasmic membrane to against oxidative stress and damage, and also to reserve energy for progression and metastasis.

Fatty acid synthase (FASN) is a key enzyme in lipid biosynthesis, responsible for catalysing the de novo synthesis of long-chain fatty acids from acetyl-CoA and malonyl-CoA [16]. In cancer cells, FASN is upregulated and supports tumour growth by promoting *de novo* lipogenesis [12]. FASN functions as a homodimer (~273 kDa per subunit), containing seven catalytic domains: malonyl/acetyltransferase (MAT), β-ketoacyl synthase (KS), β-ketoacyl reductase (KR), dehydrase (DH), enoyl reductase (ER), thioesterase (TE), and acyl carrier protein (ACP). These domains collectively facilitate the synthesis of 16-carbon palmitic acid using acetyl-CoA, malonyl-CoA, and NADPH [16]. These enable FASN to drive lipid synthesis, which is vital for tumour cell membrane formation and metabolic processes.

ATP citrate lyase (ACLY) is a cytosolic enzyme that plays a crucial role in linking glucose and lipid metabolism by catalysing the magnesium-ATP-dependent conversion of citrate, transported from the mitochondria, into oxaloacetate and acetyl-CoA [17]. The acetyl-CoA generated by ACLY is fundamental for various biosynthetic processes, including fatty acid and cholesterol synthesis, glutamine catabolism, and histone acetylation, underscoring ACLY's key regulatory role in cellular metabolism, deregulation of the ACLY has been reported to be related to the development of several cancers [18].

Acetyl-CoA carboxylase (ACC) is a pivotal enzyme in *de novo* lipogenesis, catalysing the ATP-dependent conversion of acetyl-CoA to malonyl-CoA, the first committed step in fatty acid biosynthesis [19]. In obesity-related cancers, ACCα, a key isoform encoded by the ACACA gene on chromosome 17q12, is often overexpressed, driving fatty acid production to support rapid cancer cell proliferation [20]. Structurally, ACCα is a 265 kDa dimer with three functional domains: the carboxyl transferase (CT) domain, the biotin carboxylase (BC) domain, and the biotin carboxyl carrier protein (BCCP) domain, which links the BC and CT domains [21]. Catalysis begins in the BC domain, where ATP and bicarbonate facilitate the carboxylation of biotin. The BCCP domain then transports the carboxylated biotin to the CT domain, which transfers the carboxyl group to acetyl-CoA, yielding malonyl-CoA, the substrate for fatty acid elongation by fatty acid synthase (FASN) [21].

Given the centrality of lipogenesis in cancer metabolism, targeting this pathway presents a promising therapeutic strategy. Several lipogenesis inhibitors, including FASN inhibitors, have shown preclinical efficacy in reducing tumour growth and enhancing sensitivity to

chemotherapy [22,23]. However, the search for novel agents with fewer off-target effects and better therapeutic indices continues.

In this context, *Andrographis paniculata*, a medicinal plant widely used in traditional Asian medicine (Figure 2), has emerged as a potential modulator of lipid metabolism in cancer cells [24]. Native to several Asian countries, *A. paniculata* has long been employed to treat various ailments, ranging from infections to inflammatory conditions [25,26]. The plant's principal bioactive compound, andrographolide, has demonstrated a wide array of pharmacological properties, including anti-inflammatory, antioxidant, hepatoprotective, and immunomodulatory effects, and this phytoconstituent can be found in whole plant, including aerial part, leaves and roots; and can be extracted using methanol, ethanol, hexane and acetone water [24,27]. Recent research has highlighted its potential antihyperlipidemic effects, particularly in the context of obesity-related cancers [28,29].

Figure 2. *Andrographis paniculata*, also known as green chiretta, is a plant that distributed in tropical Asian counties, used as traditional herbs in Asian family to treat fever, sore throat, diarrhoea, bug or snake bite. (picture adapted from with GNU Free Documentation License (GFDL) https://commons.wikimedia.org/wiki/File:Andrographis_paniculata_001.JPG)

Andrographolide's anticancer activity appears to be linked to its ability to inhibit the *de novo* lipogenesis pathway, thereby disrupting the metabolic processes that sustain tumour growth and progression. By targeting key lipogenic enzymes, andrographolide may reduce fatty acid availability, impairing cancer cell membrane synthesis, energy storage, and signalling pathways essential for proliferation. Emerging studies suggest that andrographolide could serve as a promising therapeutic agent for metabolic reprogramming in cancer cells, warranting further investigation into its clinical potential. Andrographolide (Figure 3), the bioactive compound derived from *Andrographis paniculata*, has shown potential as an anticancer agent.

To elucidate its therapeutic value, it is essential to explore its interactions with key lipogenic enzymes, including ATP citrate lyase (ACLY), acetyl-CoA carboxylase alpha (ACCα), and fatty acid synthase (FASN), which are crucial to the lipogenesis pathway. These enzymes support cancer cell survival and proliferation, marking them as promising targets for intervention. However, studies examining andrographolide's molecular docking properties and inhibitory effects on these enzymes remain limited. Therefore, current research aims to investigate andrographolide as a potential inhibitor of cancer-associated lipogenesis enzymes.

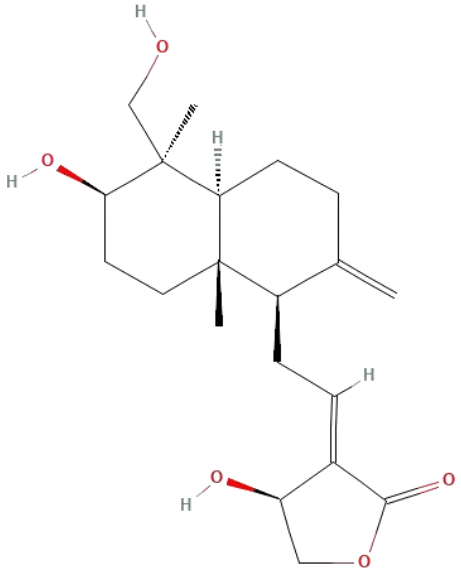

Figure 3. Chemical structure of Andrographolides (adapted from PubChem https://pubchem.ncbi.nlm.nih.gov/compound/Andrographolide)

2. Methods

2.1 Ligand Preparation

The ligand compound, Andrographolide, was downloaded in a mol file from PubChem (NIH, USA) (https://pubchem.ncbi.nlm.nih.gov/) and initially prepared and optimised using Avogadro software (Avogadro 2 1.95.1), which allows for the generation and refinement of molecular structures. The molecular geometry of the ligand was adjusted by applying the MMFF94 (Merck Molecular Force Field) force field, ensuring an accurate representation of its three-dimensional conformation. Energy minimization was performed through a series of 15 steps per update to refine the geometry and achieve a stable, energetically favourable structure. This optimization step is crucial to ensure that the ligand adopts the correct conformation for subsequent docking simulations, eliminating any steric clashes or unrealistic bond angles.

2.2 Protein Grid Configuration

For docking simulations, the receptor proteins (domains) including FASN (PDB ID: 4XJV, PDB ID: 4W82) , ACLY (PDB ID: 3MWD) and ACCa (PDB ID: 4ASI) were prepared by extracting their crystal structures from the Protein Data Bank (PDB) (https://www.rcsb.org/), and their binding sites and active sites were confirmed by searching from Uniport.org and previous published papers. The AutoDock Vina software (1.2.0 AutoDock Vina) was utilised to facilitate the docking process, as it is widely recognized for its efficient and accurate molecular docking capabilities [30]. The grid box, which defines the binding site of each protein, was configured with dimensions of 50 × 50 × 50 Å, with 0.375 spacing to adequately cover the entire binding pocket of the receptor. This ensures that all potential ligand binding sites are considered during the docking process, maximising the predictive accuracy and thoroughness of the predictions [31]. By leveraging these approaches, the grid configuration allows AutoDock Vina to perform an exhaustive search of the ligand-protein interactions by sampling various poses within the predefined binding site.

2.3 Docking Simulations

Molecular docking simulations were performed using AutoDock Vina, a widely utilized docking tool that applies a genetic algorithm to conduct a comprehensive search of the ligand's conformational space. During each docking run, the ligand was flexibly docked to the protein, with conformations generated for the ligand and receptor binding site. The algorithm was set to perform 100 iterations per docking run, ensuring that a broad range of possible binding modes were explored to identify the most stable and energetically favourable ligand-protein interaction. Each iteration was designed to refine the ligand's position and orientation within the binding site, allowing the software to evaluate the strength and nature of the binding interactions from various perspectives.

2.4 Binding Energy Analysis

The binding energy of each docked complex was calculated to evaluate the strength and stability of the ligand-protein interactions. This parameter is essential as it represents the overall stability of the ligand-receptor binding. The lowest binding energy value from the docking simulations was selected as the most optimal pose for the ligand-protein complex. This pose represents the most energetically favourable conformation, with the lowest free energy, which suggests the highest likelihood of the ligand binding in that specific orientation. The analysis of binding energies allows for a comparative assessment of the ligand's affinity for each target protein, aiding in the selection of the most promising candidates for further experimental validation.

2.5 Interaction Visualisation

Following the docking simulations, the results were visualised and analysed using UCSF Chimera, which is a non-commercial free web resource is developed by University of California San Francisco. Chimera was used to demonstrates interactive visualization and analysis of molecular structures, assisting to analyse the data related to the results obtained by docking with ligands. Hence, Chimera was used to render the docked complexes in three dimensions, enabling a detailed examination of the ligand and protein interactions. Key molecular interactions, including the intermolecular interaction were identified and analysed. Bond lengths and binding energies between specific amino acid residues within the protein and atoms of the ligand were measured to provide insights into the molecular basis of the binding affinity. The visualisations also helped to identify crucial residues involved in the ligand-protein interaction, which can guide the design of modifications to improve binding affinity or specificity.

3. Results and Discussion

3.1 Fatty Acid Synthase (FASN)

The Thioesterase II (TE II) domain plays a pivotal role in regulating the chain length of fatty acids synthesized by fatty acid synthase (FASN) through catalyzing chain termination and the release of medium-chain fatty acids. The active sites of the human TE II domain are reported to involve a catalytic triad consisting of S101, H237, and D212 [32]. This triad is crucial for the proper positioning of the acyl-ACP substrate, aligning the acyl chain and the 4′-phosphopantetheine linker arm for catalysis, which facilitates the enzymatic reaction [1,32]. Mutagenesis studies on rodent TE II, which shares high homology with the human domain, have demonstrated that S101 and H237 are critical for enzymatic activity [33]. Substitutions at these positions result in inactive proteins, underscoring the importance of these residues in catalysis [33].

In this study, we performed in silico docking simulations of the potential anticancer agent, andrographolide, with the human FASN TE II domain (PDB ID: 4XJV). The docking analysis revealed interactions between andrographolide and multiple residues, including M35, S101, M102, Y105, S129, A130, T131, A137, W138, H139, Y155, E158, D183, L184, V187, I213, A214, K215, and H237 (Figure 4). Notably, the ligand interacts directly with the catalytic triad residues S101 and H237, suggesting potential competitive inhibition. This interaction likely prevents proper docking of the acyl-ACP substrate, thereby inhibiting the enzymatic function of TE II. The binding affinity between andrographolide and TE II was recorded -2.03 kcal/mol (Table 1). As more negative value indicates stronger binding, this further supports its potential role as a competitive inhibitor of FASN [16]. These findings provide a mechanistic basis for the anticancer activity of andrographolide via inhibition of fatty acid biosynthesis.

Table 1. The summary of binding affinity of the enzyme or its domain that is used to dock andrographolides

Enzyme/ Domain region targeted	Residues bind	Binding affinity (kcal/mol)	Comments
FASN TE II	S101, H237	-2.14	Energetically favourable
FASN ER	G1679, V1680	-1.92	Energetically favourable
ACLY	F347	-1.62	Energetically favourable
ACCα	I1724, I2126, K2127	-1.32	Energetically favourable

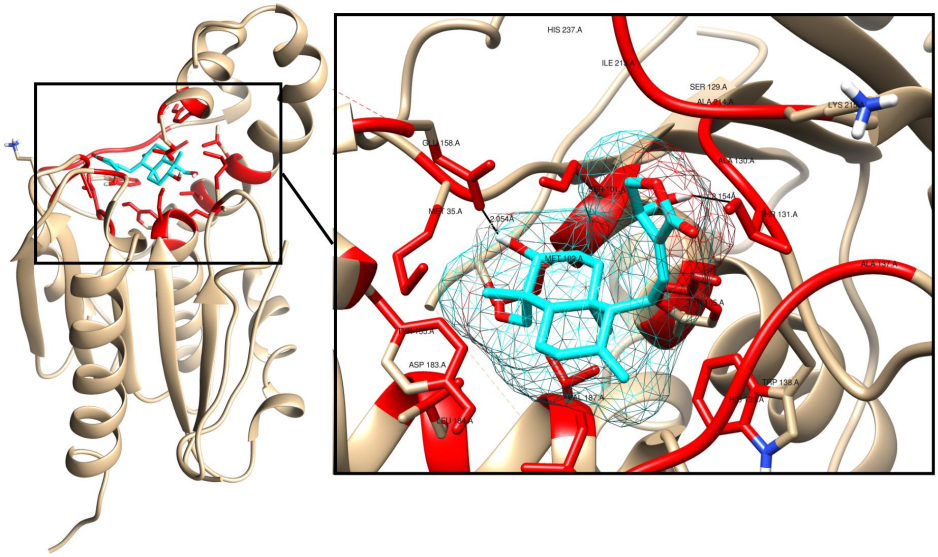

Figure 4. Molecular interaction of Andrographolides against Human FASN TE II domain (PDB ID: 4XJV), the binding of the ligand occurs at the catalytic triad residues S101 and H237. The binding affinity is -2.03 kcal/mol.

The human enoyl-acyl carrier protein reductase (ER) domain is a key catalytic region of fatty acid synthase (FASN), responsible for reducing the double bond of the enoyl-ACP intermediate to a saturated acyl-ACP through the use of NADPH as a reducing agent. The ER domain spans residues 1529–1867. This domain includes a subdomain of NADPH-binding region located between residues 1671–1688. Previous studies have demonstrated that triclosan, a known ER domain inhibitor, binds specifically to residues L1753, L1780, I1784, and F1791, inducing conformational changes that alter the orientation of the dimer and reconfigure key catalytic residues in the NADPH-binding site [34]. This conformational shift obstructs NADPH binding, thereby preventing the reduction of enoyl-ACP to acyl-ACP and halting fatty acid elongation.

To explore alternative inhibitory mechanisms, we conducted in silico docking simulations of andrographolide with the ER domain of human FASN (PDB ID: 4W82). Docking analysis revealed that andrographolide interacts with a distinct set of residues, including L1571, N1572, F1573, D1575, M1601, V1651, G1679, V1680, I1769, G1770, L1795, M1843, H1848, G1850, K1851, and V1852 (Figure 5). Notably, although the binding mode of andrographolide differs from

triclosan, it still targets the NADPH-binding site (residues 1671–1688). This suggests that andrographolide may inhibit the ER domain through a mechanism distinct from that of triclosan, potentially interfering with NADPH utilization. The calculated binding affinity of -1.92 kcal/mol supports the notion that this interaction is energetically favourable, indicating potential for strong inhibitory activity (Table 1).

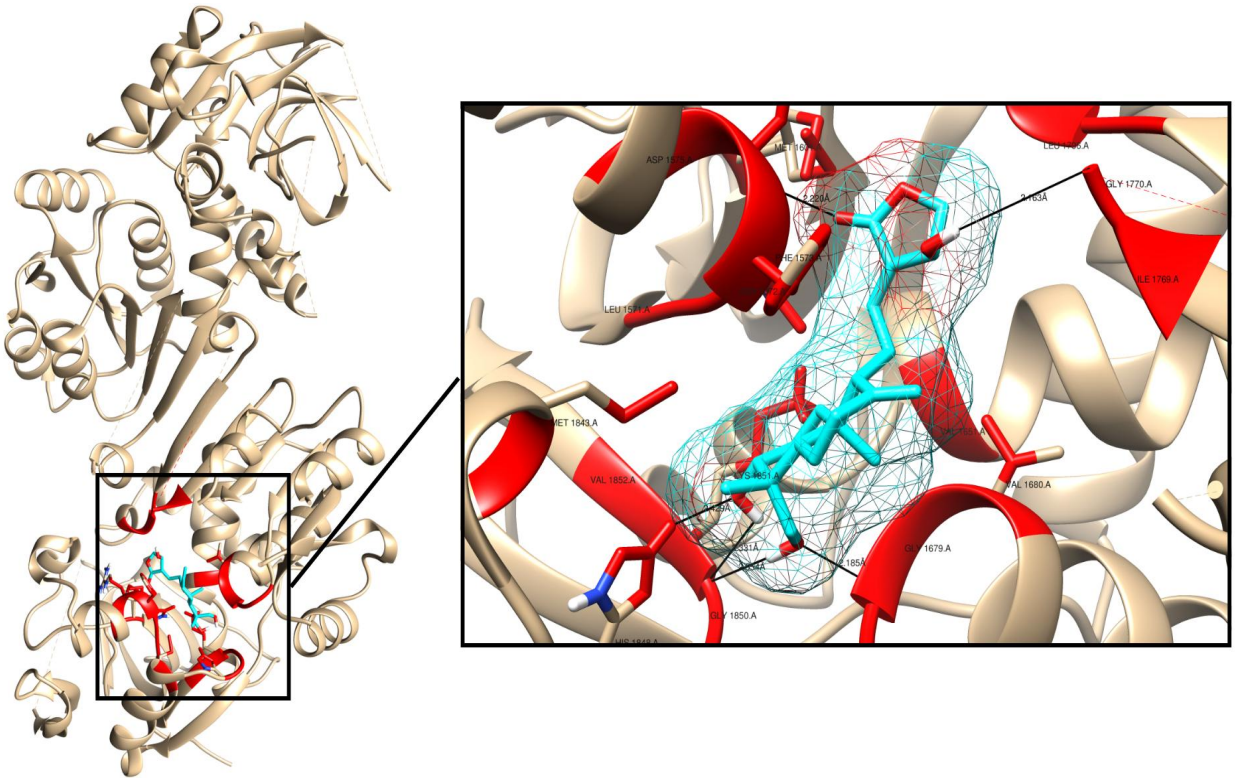

Figure 5. Molecular interaction of Andrographolides against Human FASN enoyl-acyl carrier protein reductase (ER) domain (PDB ID: 4W82), the binding at the G1679 and V1680 residues in NADPH-binding site (residues 1671–1688) were recorded. The binding affinity is -1.92 kcal/mol.

3.2 ATP Citrate Lyase (ACLY)

ATP-citrate lyase (ACLY) is a key enzyme that catalyzes the conversion of citrate and CoA into acetyl-CoA and oxaloacetate, with the reaction coupled to ATP hydrolysis. In humans, ACLY plays a crucial role in lipid biosynthesis by providing acetyl-CoA, an essential substrate for the synthesis of fatty acids and cholesterol. ACLY acts as a metabolic link between carbohydrate-derived energy and lipid production, as citrate is derived from the tricarboxylic acid (TCA) cycle. By directing acetyl-CoA into lipid biosynthesis, ACLY integrates energy metabolism with lipid anabolism in the cytoplasm.

In the structure of ACLY complexed with citrate, the citrate ligand binds to a loop comprising residues S-343 to T-348 [35]. This interaction is facilitated by specific hydrogen bonds between the hydroxyl and carboxyl groups of citrate's prochiral center and key active site residues. Specifically, the pro-R carboxyl group of citrate forms robust hydrogen bonds with R-379, while the central carboxyl group establishes hydrogen bonds with the side chain of T-348 and the backbone nitrogen atoms of N-346 and T-348. Additionally, the hydroxyl group of citrate interacts with the side-chain hydroxyl group of T-348 and the backbone nitrogen of G-309. Interestingly, the pro-S carboxyl group does not engage in hydrogen-bonding interactions with the protein, and its electron density is less defined compared to the other carboxyl groups.

While F-347 lies near the pro-S carboxyl group of citrate, its electron density is poorly resolved, suggesting that the side chain of F-347 may be flexible or disordered in this configuration. This flexibility implies that F-347 may not participate in stable interactions with citrate. However, structural studies using tartrate, a competitive inhibitor of citrate, revealed that F-347 forms a hydrogen bond with the backbone nitrogen of the phenylalanine residue in tartrate, and exhibits stronger, more continuous electron density. This observation suggests that F-347 may play a role in catalysis when bound to alternative ligands, such as tartrate.

To explore alternative inhibitory mechanisms, we performed in silico docking simulations of andrographolide with ACLY (PDB ID: 3MWD). The docking analysis revealed that andrographolide interacts with a distinct set of residues, including F347, R507, Q510, G511, D514, M642, L643, D644, P822, M823, D824, S826, W827, and R835 (Figure 6). Notably, andrographolide binds specifically to F347, but does not interact with the CoA or ATP binding regions of ACLY. This suggests that andrographolide may not function as a competitive inhibitor, as it does not effectively block the

substrate's catalytic binding sites. The binding affinity of andrographolide for ACLY was calculated to be -1.62 kcal/mol (Table 1). While this is lower than the binding affinities observed for andrographolide with the thioesterase II (TE II) and enoyl-reductase (ER) domains of fatty acid synthase (FASN), it still indicates a favourable interaction with the enzyme. However, more experiments (mutagenesis experiments) are needed to validate the result and provide a conclusion on this.

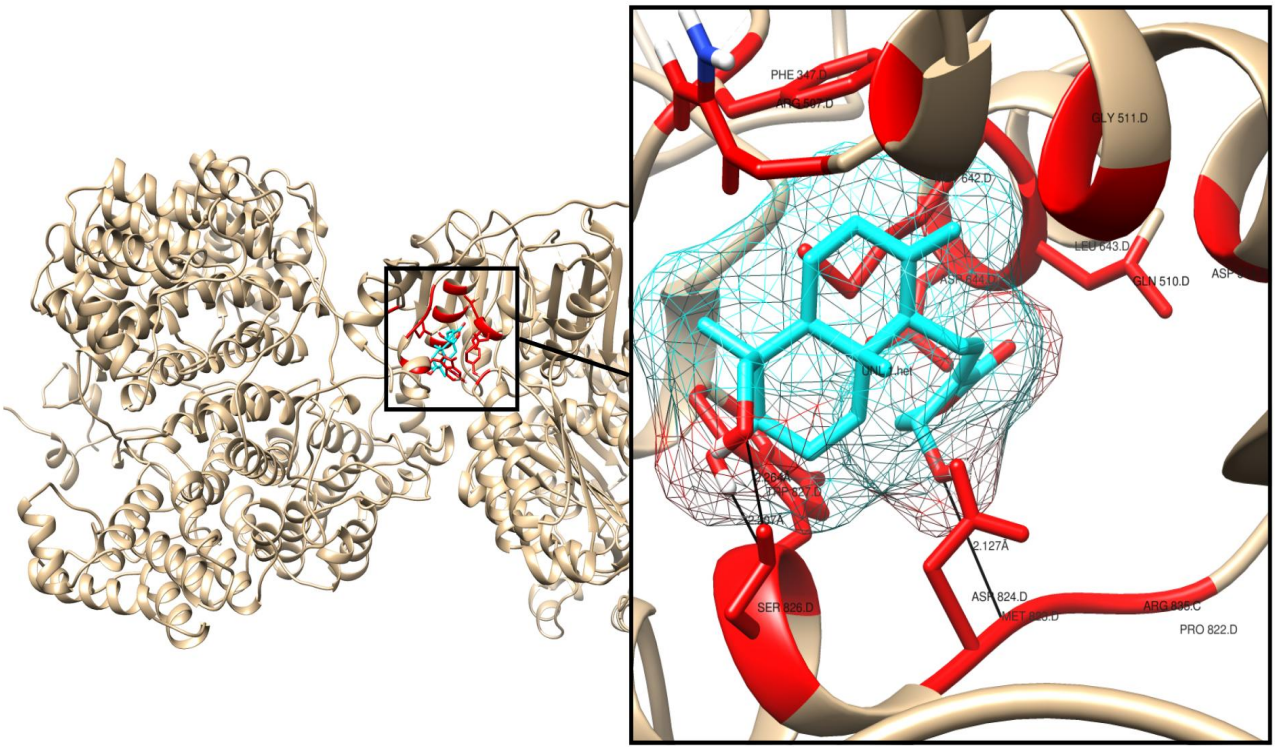

Figure 6. Molecular interaction of Andrographolides against ATP citrate lyase (ACLY) (PDB ID: 3MWD). The residue that ligand bind towards the receptor at the binding groove is at F347. The binding affinity is -1.62 kcal/mol.

3.3 Acetyl CoA carboxylase (ACCα)

Acetyl-CoA carboxylase (ACCα) is a key enzyme that is mainly found in the liver, adipose tissue and mammary gland, involved in fatty acid biosynthesis. It catalyses the carboxylation of acetyl-CoA to form malonyl-CoA, which is the first committed step in fatty acid biosynthesis to provide "raw ingredients" for FASN to generate a long fatty acid chain. ACCα plays a crucial role in regulating lipid synthesis and is essential for energy homeostasis in the body. This protein consists of biotin carboxyl carrier protein (BCCP), biotin carboxylase (BC), and carboxyltransferase (CT) domains. According to Zhou et al. (2024), the acetyl CoA ligand was found to bind towards the human ACCα at the same binding groove as previously seen from *Saccharomyces cerevisiae* ACC protein structure [36]. In human ACCα, the ligand was inserted into the binding pocket and had intermolecular interaction with residues including A1722, R1723, I1724, I1827, I2126, K2127, and R2129. The Carboxyltransferase domain (CT) in the protein aids in the transfers of the carboxyl group from biotin to acetyl-CoA, generating the final product, the malonyl-CoA.

To explore alternative inhibitory mechanisms, we conducted in silico docking simulations of andrographolide with the human ACCα (PDB ID: 8XL1). Docking analysis revealed that andrographolide interacts with a distinct set of residues, including I1688, S1720, G1721, A1722, I1724, S1800, I1825, I1827, G1826, G1828, L1848, G2090, G2091, V2117, L2118, I2126, and K2127 (Figure 7). Interestingly, andrographolides bind towards the binding groove of acetyl CoA and target the same binding site that acetyl CoA binds, including I1724, I2126 and K2127. This suggests that andrographolide may inhibit the binding of acetyl CoA, thus preventing the carboxylation of acetyl CoA into Malonyl CoA, which may hinder the downstream of the lipid biosynthesis. The calculated binding affinity of -1.32 kcal/mol supports the notion that this interaction is energetically favourable, indicating potential for strong inhibitory activity (Table 1).

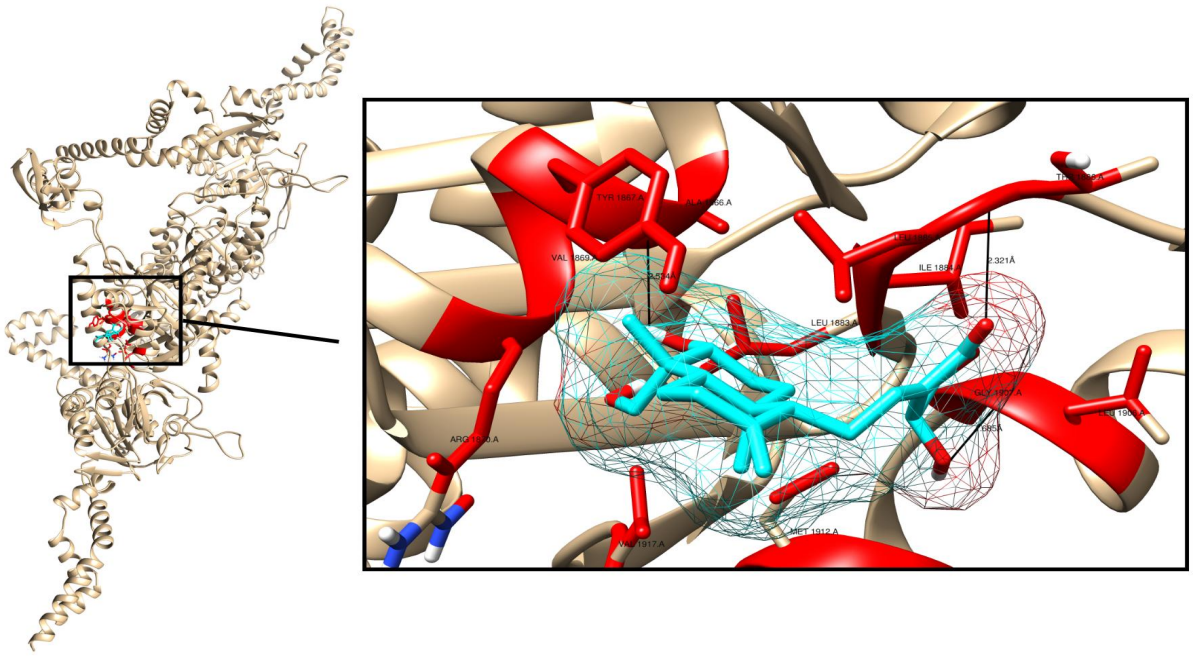

Figure 7. Molecular interaction of Andrographolides against ACCα (ACLY) (PDB ID: 8XL1). The ligand binds at I1724, I2126 and K2127 at the binding groove, with the binding affinity of -1.32 kcal/mol.

As a summary, the ligand docking results indicated that andrographolides possess excellent properties of draggability as this compound has great affinity towards the binding site of our targeted lipogenic enzymes, due to negative affinity value, indicating this binding is favourable [37]. The binding of andrographolides may further facilitate the suppression of the production of lipid droplets and accumulate in cancer cells as the substrate that originally needed to bind to the enzyme binding site to produce the end product, the long chain of fatty acids is unable to complete. Thus, this mechanism by preventing the substrate from binding towards the lipogenic enzymes, has been found to inhibit breast, lung, colorectal, prostate, stomach, and liver cancer cells taking advantage of de novo lipogenesis to aid in cancer cell proliferation and growth [5]. Moreover, downregulating lipogenesis not only inhibits the rapid growth demands of tumour cells, and would also affect the survival, progression, and metastasis of the disease [14,15].

4. Conclusion

In this study, we explored the potential inhibitory effects of andrographolide on key enzymes involved in lipid biosynthesis through in-silico docking simulations. The results suggest that andrographolide exhibits significant inhibitory interactions with several domains of fatty acid synthase (FASN), ATP-citrate lyase (ACLY), and acetyl-CoA carboxylase (ACCα).

FASN Inhibition: The docking simulations revealed that andrographolide interacts strongly with the Thioesterase II (TE II) domain and the enoyl-acyl carrier protein reductase (ER) domain of FASN. In the TE II domain, andrographolide binds to the catalytic triad, particularly residues S101 and H237, likely blocking the acyl-ACP substrate and inhibiting fatty acid chain termination. In the ER domain, andrographolide binds near the NADPH-binding site, potentially obstructing NADPH utilization and inhibiting fatty acid elongation.

ACLY Inhibition: Andrographolide binds to the ACLY enzyme, interacting primarily with F347, though it does not target the citrate, CoA, or ATP binding sites. While this suggests andrographolide may not act as a competitive inhibitor for ACLY, the favourable binding affinity indicates some inhibitory potential.

ACCα Inhibition: The docking simulations show that andrographolide binds to the same binding groove as acetyl-CoA in the carboxyltransferase domain of ACCα, potentially preventing the carboxylation of acetyl-CoA into malonyl-CoA, which is a critical step in fatty acid biosynthesis.

In conclusion, andrographolide demonstrates a promising potential to inhibit key enzymes in lipid biosynthesis, particularly FASN and ACCα, by disrupting catalytic sites or key binding regions. These findings support the notion that andrographolide may act as a competitive inhibitor of lipid biosynthesis, contributing to its potential anticancer properties.

While our study provides valuable insights through molecular docking simulations, it is important to acknowledge the inherent limitations of this approach. Molecular docking offers predictive models of ligand-protein interactions based on computational algorithms, but it cannot fully account for the dynamic nature of biological systems. Therefore, the findings presented in this study should be considered as preliminary. Further experimental validation, including *in vitro* enzyme inhibition assays and *in vivo* studies, is necessary to confirm the efficacy of andrographolides in inhibiting the lipogenic enzymes and to fully understand their potential therapeutic effects.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

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