Original Research Article

Exploring the Potential of Cocos nucifera Phytochemicals in the Effective Management of Breast Cancer via ER-Alpha Targeting

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Abstract : Cocos nucifera L., commonly referred to as the coconut tree, is a vital plant in tropical and subtropical regions and is often called the "tree of life" due to its many uses and health benefits. Historically, coconut products have played a key role in traditional Indian medicine for treating conditions like bronchitis, gingivitis, and tumors. Known for its rich content of medium-chain fatty acids, coconut exhibits a wide range of pharmacological properties, including antiviral, antibacterial, anti-inflammatory, and anticancer effects. This study investigates the potential of coconut-derived phytochemicals as inhibitors of Estrogen Receptor-Alpha (PDB ID: 3ERT), a key target in breast cancer therapy, through molecular docking techniques. The results identified Ar-turmerone (CID: 558221) as having a binding affinity of -5.7 kcal/mol, closely aligning with the standard breast cancer treatment drug Tamoxifen (CID: 637517), which showed a slightly higher affinity of -6.1 kcal/mol. Additionally, other coconut-based compounds, such as lauric acid, capric acid, and caprylic acid, demonstrated potential anticancer activity. These findings suggest that phytochemicals from Cocos nucifera L., particularly Ar-turmerone, hold promise for breast cancer treatment and could be further developed as therapeutic agents. Furthermore, the study also hints at possible antiviral properties of these compounds. While the docking results are encouraging, they require further validation through in vitro and in vivo research to confirm their safety, efficacy, and practical application. Overall, this research highlights the potential of coconut-derived compounds in modern medicine, especially for cancer treatment.

Keywords: Cocos nucifera; molecular docking; Estrogen Receptor-Alpha; breast cancer; Ar-turmerone; Tamoxifen; anticancer.

Citation

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Introduction

The coconut (Cocos nucifera), often referred to as the "tree of life," is a significant fruit tree with numerous applications in tropical and subtropical regions. India ranks third globally in coconut production, with the southern states contributing about 90% of the total yield [1-3]. Coconut products have long been used in traditional Indian medicine, and the plant's various parts are utilized to treat a range of health conditions, such as hair loss, burns, heart problems, and digestive issues. The coconut also holds religious significance in India and has been used in Ayurvedic practices for millennia [4-5].

Cocos nucifera phytochemicals include carotenoids, flavonoids, and phytoestrogens, which have notable health potentials [6-9]. Coconut oil, a key product of the fruit, contains high levels of medium-chain fatty acids, such as lauric acid, which are known for their antibacterial, antiviral, antifungal, and

antiprotozoal properties [10-14]. Monolaurin, a metabolite of lauric acid, plays a key role in coconut oil's health benefits [15-20]. The oil's composition provides a range of therapeutic effects, from skincare to heart disease prevention and immunity enhancement [21-25].

Cocos nucifera has also shown promise in cancer treatment, particularly for breast cancer. Coconut's phytochemicals are known to help fight malignancies, including breast cancer, by targeting estrogen receptor-alpha (ER-α). A 2020 molecular docking study published in the Journal of Ethnopharmacology identified compounds such as lauric acid, capric acid, and caprylic acid as having a significant binding affinity to ER-α, suggesting their potential as anti-breast cancer agents [26].

Molecular docking studies are essential for predicting how small molecules, like phytochemicals from coconut, interact with cancer-related proteins. In the case of breast cancer, ER-α is a critical target, and the ability of these compounds to inhibit its activity could lead to new therapeutic approaches [27]. This highlights the importance of further research into natural compounds for developing safer and more effective cancer treatments [28-29].

In the present study, coconut-derived phytochemicals exhibit strong potential as therapeutic agents against breast cancer. Their ability to inhibit ER-α and other cancer-related pathways demonstrates the versatility of coconut not just as a nutritional food but as a functional medicinal resource. Continued studies into these compounds could lead to new, natural therapies for managing breast cancer and other diseases [30].

Materials and Methods

Collection of Plant Materials: Fruits of Cocos nucifera L. were collected from Anthiyur, Erode District, Tamil Nadu for the study.

Sample Preparation: The collected seeds were washed with sterile water, shade-dried, and ground into a fine powder. The powdered sample was stored in an airtight container for further analysis. A total of 20g of the powdered seeds was soaked in 100 ml of methanol for 24 hours to extract alkaloids, terpenoids, and other phytoconstituents. The methanolic extract was filtered using Whatmann No. 41 filter paper [1].

Phytochemical Screening : Phytochemical screening was performed on the plant extract following standard protocols to determine the presence of various bioactive compounds. A stock solution of the plant extract (10 mg/ml) was prepared for the screening tests.

Test for Tannins: Two milliliters of the aqueous extract solution were treated with a few drops of 10% ferric chloride solution. The formation of a blackish-blue color indicated the presence of gallic tannins, while a green-blackish color indicated catechol tannins [2].

Test for Terpenoids: Five milliliters of the extract were mixed with 2 ml of chloroform, followed by the addition of 3 ml of concentrated sulfuric acid. The appearance of a reddish-brown color at the interface confirmed the presence of terpenoids [3].

Test for Carbohydrates: A few drops of Molisch’s reagent were added to 1-2

ml of the extract, followed by the careful addition of concentrated sulfuric acid to form a layer. The formation of a purple ring at the interface indicated the presence of carbohydrates [4].

Test for Saponins: The extract (5 ml) was vigorously shaken with distilled water. The formation of a persistent foam indicated the presence of saponins [5].

Test for Sterols: The extract (50 mg) was dissolved in 2 ml of acetic anhydride and carefully treated with a few drops of concentrated sulfuric acid. The presence of phytosterols was confirmed by color changes [6].

Ligand Preparation : Tamoxifen (PubChem CID: 2733526) was selected as the standard reference compound. The phytochemical compounds identified in the Cocos nucifera fruit extract through GC-MS analysis were included in the study. The 3D structures of both the standard drug and the phytochemicals were obtained from the PubChem database as SDF files and prepared for docking [7].

Target Protein Preparation : The crystal structure of estrogen receptor-alpha (ER-α) complexed with a ligand (PDB ID: 3ERT) was retrieved from the Protein Data Bank. The 3D structure of the protein was downloaded in PDB format for further docking analysis [8].

Molecular Docking : Molecular docking studies were conducted using AutoDock Vina within the PyRx 0.8 software. The docking simulations involved interactions between the phytochemicals and ER-α. The grid box was set to cover the entire protein surface, with the center coordinates X: 21.0689, Y: 6.2484, Z: 21.9622, and dimensions X: 77.9405, Y: 74.0416, Z: 56.0327 [9].

Ligand-Protein Interaction Visualization : After docking, the results were exported as zip files and unzipped. The docked ER-α and the compound scripts were merged using TextEdit software and saved as PDBQT files. These files were then imported into Biovia Discovery Studio 4.5 for visualization, allowing for the analysis of ligand interactions with the protein's active site and the identification of amino acids involved in binding [10]..

Results

The phytochemical screening of the methanolic extract of Cocos nucifera L. revealed the presence of tannins, terpenoids, carbohydrates, and steroids. However, saponins were found to be absent (Table 1).This indicates that the extract contains significant bioactive compounds such as tannins, which are known for their antioxidant properties; terpenoids, which may exhibit anti-inflammatory effects; carbohydrates, contributing to energy sources; and steroids, which are important for various physiological processes. The absence of saponins suggests that the extract may not exhibit the characteristic foaming properties or other biological activities typically associated with this group of phytochemicals.

GC-MS ANALYSIS

Gas chromatography-mass spectroscopy (GC-MS) is a combined analytical technique used to determine and identify compounds present in a plant

sample. GC-MS plays an essential role in the phytochemical analysis and chemotaxonomic studies of medicinal plants containing biologically active components.

Table 1: Phytochemical Screening of Methanolic Extract of Cocos nucifera.L

S.No	Tests	Presence of Phytochemicals
1	Tannis	Present
2	Terpnoids	Present
3	Carbohydrates	Present
4	Saponin	Absent
5	Steroids	Present

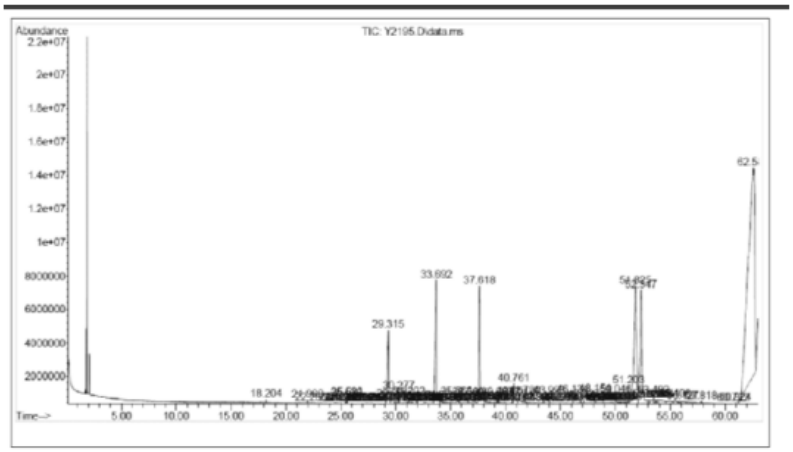

Fig1: GC-MS Results Phytochemical compounds identified for Fruit Methanolic extract of Cocos nucifera.L

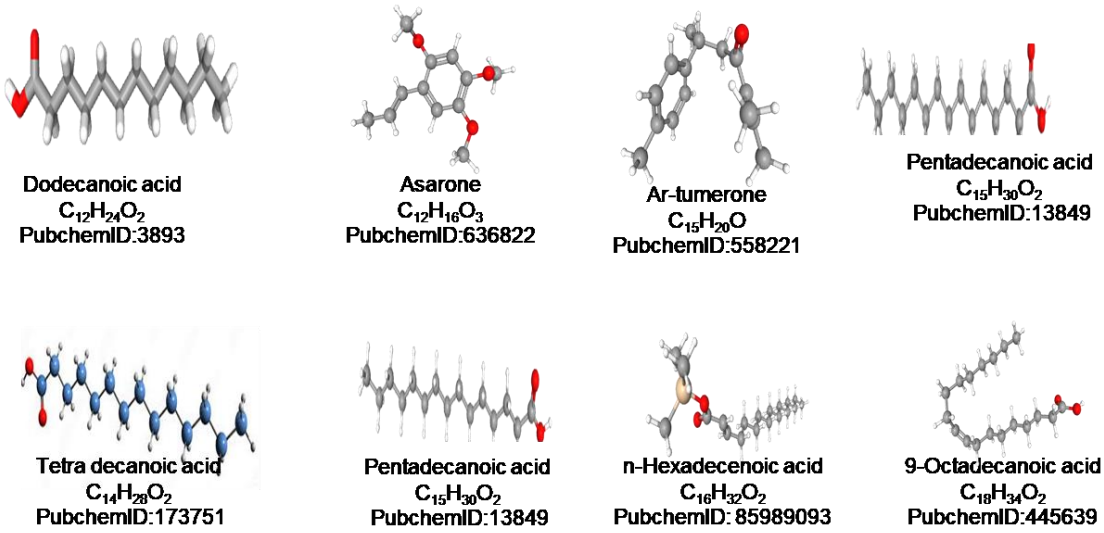

Fig2: Active compounds present in seed extracts of through Cocos nucifera.L GC-MS

Estrogen receptors (ERs) and their estrogen ligands play a crucial role in the initiation and progression of breast cancer. ERs exhibit genomic activity by modulating the expression of genes essential for cell growth and survival through their classic nuclear receptor pathways. In this study, the 3D structure

of Estrogen Receptor-Alpha was modeled using the Protein Data Bank (PDB) server, based on its X-ray crystallography structure (PDB ID: 3ERT). The binding interactions of an antiviral drug, along with the phytochemical compounds extracted from Cocos nucifera L. fruit via GC-MS analysis, were assessed as ligands. Virtual screening of the antiviral properties of these Cocos nucifera L. phytochemicals was conducted using the PyRx tool to evaluate their binding affinities and potential as therapeutic agents

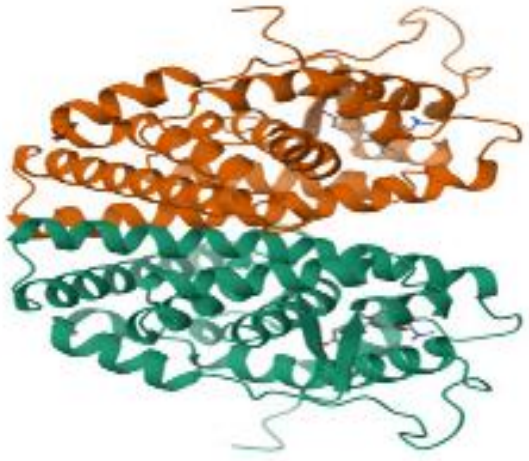

Fig3: The 3D structure of modelled Estrogen Receptor-Alpha shown in ribbons representation

The chemical compounds from Cocos nucifera L. were retrieved from the PubChem database and converted into the required format (PDBQT) using Open Babel, integrated within the PyRx tool. Molecular docking was performed by setting the grid to encompass the entire protein, targeting Estrogen Receptor-Alpha. The docking analysis aimed to explore the potential of Cocos nucifera L. phytochemicals for antiviral activity against Estrogen Receptor-Alpha in breast cancer, compared to the standard drug, Tamoxifen.

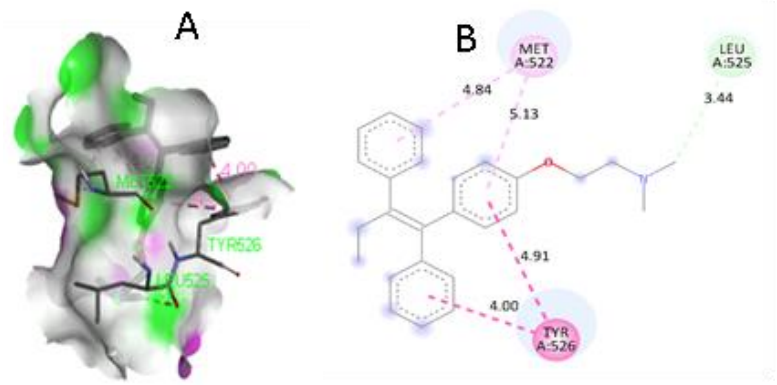

Fig 4: The docking analysis of human estrogen receptor alpha Dodecanoic acid, (CID: 3893) dock score of -5.2 kcal/mol. A. Docking Complex B. Ligand receptor interaction

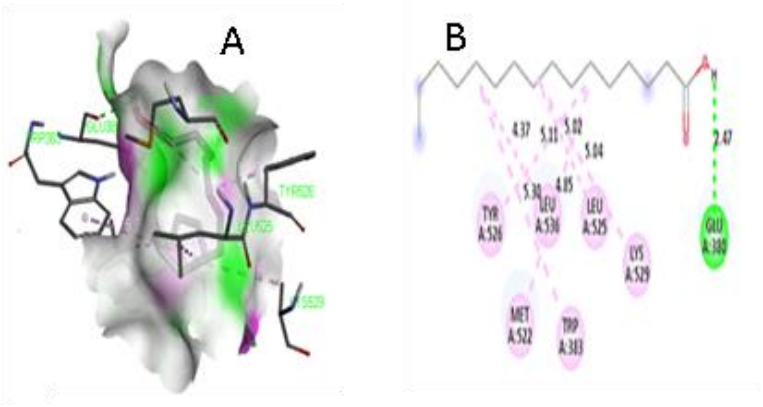

Fig 5: The docking analysis of human estrogen receptor alpha 4-hydroxytamoxifen,Asarone(CID: 636822) dock score of -5.0 kcal/mol. A. Docking Complex B. Ligand receptor interaction

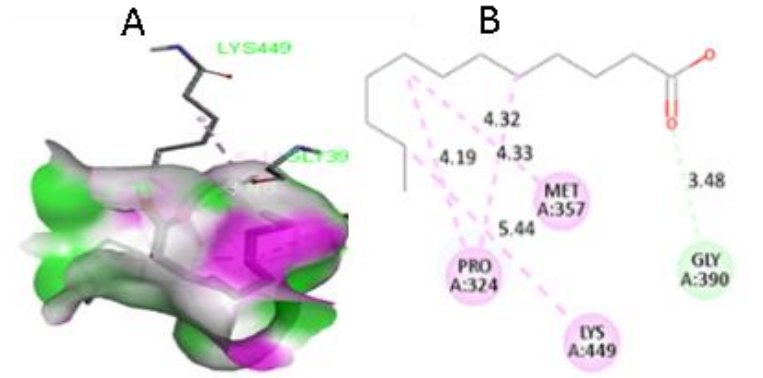

Fig 6: The docking analysis of the human estrogen receptor alpha 4-hydroxytamoxifen, Ar-turmerone (CID: 558221), dock score of-5.7 kcal. A. Docking Complex B. Ligand receptor interaction

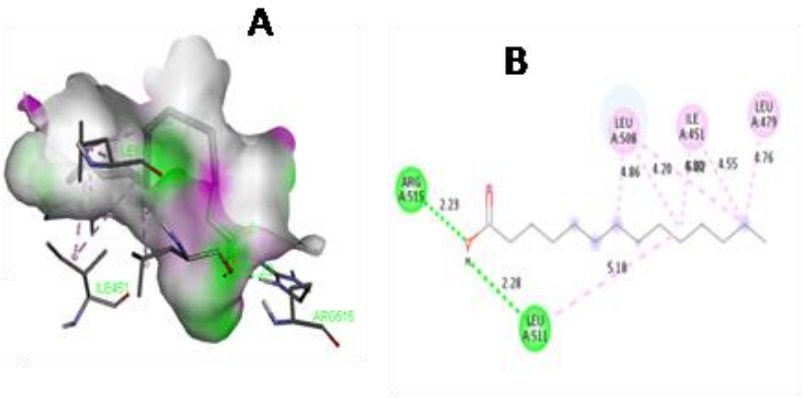

Fig 7: The docking analysis of the human estrogen receptor alpha 4-hydroxytamoxifen, Tetradecanoic acid (CID: 11005), dock score of -4.5 kcal/mol. A. Docking Complex B. Ligand receptor interaction

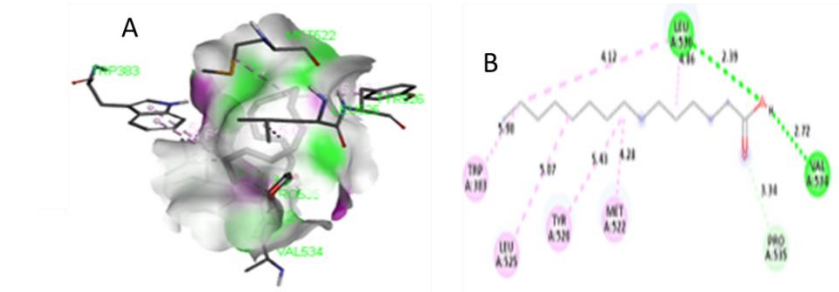

Fig 8: The docking analysis of the human 4-hydroxytamoxifen, Pentadecanoic acid (CID: 13849), dock score of -3.8 kcal/mol. A. Docking Complex B. Ligand receptor interaction

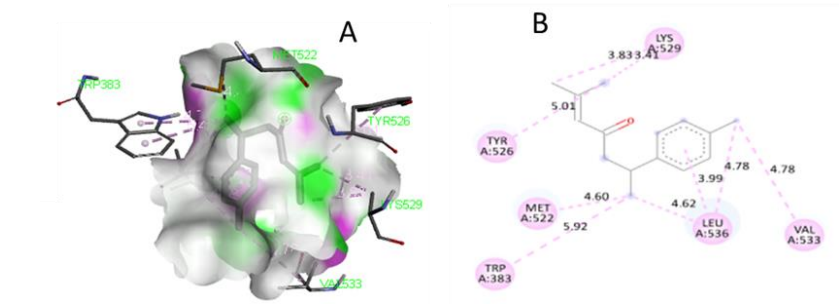

Fig 9: The docking analysis of the human estrogen receptor alpha 4-hydroxytamoxifen,n-Hexadecanoic acid (CID: 985) dock score of -3.8 kcal/mol. A. Docking Complex B. Ligand receptor interaction

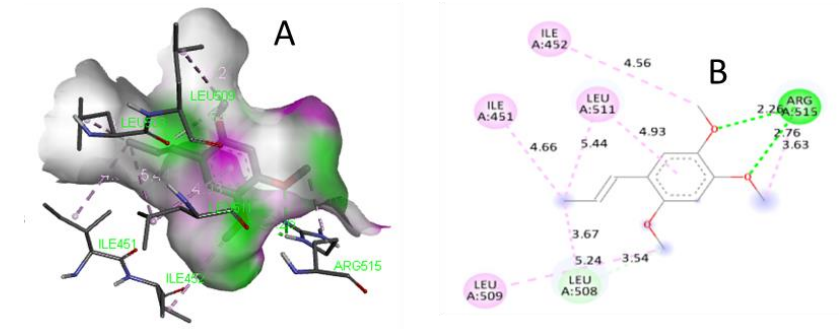

Fig 10: The docking complex of human estrogen receptor alpha 9-Octadecanoic acid (CID: 11005) with dock score of -4.7 kcal/mol. A. Docking Complex B. Ligand recptor interaction

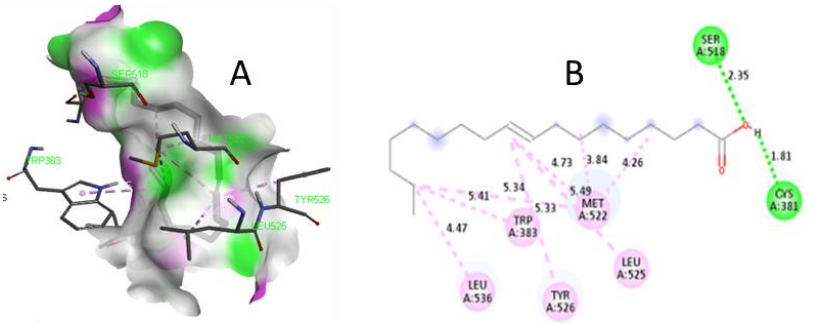

Fig 11: The docking complex of human estrogen receptor alpha and Tamoxifen (CID: 637517) with dock score of -6.1 kcal/mol. A. Docking Complex B. Ligand recptor interaction.

Discussion

From this docking analysis, the PubChem database identified seven substances with structural similarities to Tamoxifen. The binding procedure was initiated using a grid centered at coordinates X: 21.0689, Y: 6.2484, Z: 21.9622, with dimensions X: 77.9405, Y: 74.0416, Z: 56.0327. Through virtual screening, seven compounds were discovered with lower binding affinities than Tamoxifen. These compounds were selected based on Lipinski's Rule of Five, a widely accepted guideline for evaluating a compound's potential as an orally active drug, focusing on its pharmacokinetic properties—absorption, distribution, metabolism, and excretion (ADME). According to [30], a chemical is considered non-orally accessible if it violates two or more of Lipinski's rules. Compared to Tamoxifen, which shows two violations, all the selected ligands fully comply with Lipinski's Rule, suggesting that these compounds have potential for oral administration in humans based on their hydrogen bond donors and acceptors.

Among the screened compounds, the chemical with CID 558221 (Ar-tumerone) displayed the highest binding affinity, with a docking score of -5.9 kcal/mol. In contrast, the compound with CID 13849 (Pentadecanoic acid) showed the lowest binding affinity at -3.8 kcal/mol. Notably, the reference drug Tamoxifen (CID: 2733526), which binds to the estrogen receptor alpha, exhibited a higher binding affinity (-6.9 kcal/mol) than the Cocos nucifera-derived compounds.

The results indicate that Ar-tumerone, a natural compound, may serve as a promising candidate for breast cancer treatment, with fewer side effects than conventional drugs like Tamoxifen. Natural compounds often offer a therapeutic advantage by being less toxic and better tolerated by the human body [31]. However, further studies are required to validate the pharmacological efficacy of Ar-tumerone in vivo, as well as its long-term safety profile. Additionally, while Tamoxifen has been a standard therapy for estrogen receptor-positive breast cancer, its known side effects, such as the risk of endometrial cancer and thromboembolic events [32] make the search for safer alternatives essential. Future research should focus on the detailed mechanism of action of Ar-tumerone and its potential synergistic effects with other therapeutic agents, which could further enhance its efficacy in breast cancer treatment.

Conclusion

This study explores the potential of phytochemicals from *Cocos nucifera* L. in targeting Estrogen receptor-alpha through molecular docking, showing promising binding affinity. While the results suggest possible therapeutic uses, for cancer, further experimental validation is required to confirm their effectiveness against breast cancer. These findings highlight the need for *in vitro* and *in vivo* studies to assess the efficacy, and mechanisms of action. Though encouraging, these results represent an early step in understanding the broader therapeutic potential of *Cocos nucifera* L. compounds.

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