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Bioactive Seed Oil Compounds Targeting Dihydroorotase for Skin Cancer Management Via *In-Silico*

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Abstract
Background*: The identification of novel, less toxic anticancer agents remain a critical priority, particularly for malignancies such as skin cancer, where rapid cellular proliferation is sustained by enhanced nucleotide biosynthesis. This study investigated the phytochemical composition and anticancer potential of seed oils from* Cocos nucifera*,* Vitellaria paradoxa*, and* Citrullus lanatus*, with a specific focus on targeting human dihydroorotase (HDE), a key enzyme in the de novo pyrimidine biosynthesis pathway.*
Methods: *The selected seed oils of Vitellaria paradoxa, Citrullus lanatus, and Cocos nucifera were extracted using N-hexane while their phytochemical profiling was conducted using Gas Chromatography- Flame Ionization Detection (GC-FID) and High-Performance Liquid Chromatography (HPLC) to identify bioactive compounds across the oils. The in-silico investigation focused on bioactive compounds present in GC-FID and HPLC analysed extracts of Vitellaria paradoxa, Citrullus lanatus, and Cocos nucifera oils, which were evaluated as potential treatments for skin cancer. Their three-dimensional structures, along with the reference drug (5-fluorouracil), were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and converted into PDB format for docking analysis. Molecular docking was performed using iGEMDock (version 2.1) to evaluate the binding interactions of the bioactive compounds with the Human Dihydroorotase Enzyme (HDE). The Lipinski's Rule of 5 (RO5) was used to evaluate the drug-likeness characteristics of the compounds. This was done using ADMET Lab 3.0. ADMETLab 3.0 and PKCSM were used to investigate the ADMET properties of possible therapeutic candidates.*
Results*: Phytochemical profiling using gas chromatography–flame ionization detection (GC-FID) and high-performance liquid chromatography (HPLC) identified a total of 45 bioactive compounds across the three seed oils. GC-FID analysis revealed 19, 15, and 17 compounds in* Vitellaria paradoxa*,* Cocos nucifera*, and* Citrullus lanatus*, respectively. HPLC analysis further confirmed and quantified key constituents, with notable abundance of quercetin (32.50%), cinnamic acid (21.57%), and cycloartenol (18.48%) in* Vitellaria paradoxa*, apigenin (30.60%) and chlorogenic acid (30.24%) in* Cocos nucifera*, and citrulline (61.51%) and rutin (7.12%) in* Citrullus lanatus*. Molecular docking analysis identified seven lead compounds—apigenin, β-sitosterol, vanillic acid, epicatechin, spinasterol, melanin, and ferulic acid—with strong binding affinities ranging from −7.3 to −8.0 kcal/mol, outperforming the reference drug 5-fluorouracil (−6.0 kcal/mol). Apigenin exhibited the highest binding affinity (−8.0 kcal/mol), indicating the strongest interaction with the HDE active site. Drug-likeness evaluation showed that all lead compounds complied with Lipinski's Rule of Five, while ADMET predictions indicated favourable absorption, low toxicity, and minimal pharmacokinetic liabilities, although minor cytochrome P450 interactions were observed in some selected compounds.*
Conclusion*: Overall, this study demonstrates that seed oil-derived phytochemicals possess significant potential as inhibitors of human dihydroorotase and prospective anticancer agents.*

Keywords*: Phytochemical profiling; Seed oils; Human dihydroorotase; Molecular docking; ADMET prediction*

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I. INTRODUCTION

Cancer constitutes an escalating global public health concern, with rising incidence and mortality attributable to demographic aging, environmental risk factors, and lifestyle-related determinants [1]. Notwithstanding significant advancements in chemotherapy, radiotherapy, and targeted therapeutic modalities, their clinical efficacy remains constrained by systemic toxicity, insufficient selectivity, and the emergence of drug resistance [2,3]. These limitations have prompted increasing interest in the development of targeted therapeutic strategies that can selectively interfere with molecular processes essential for tumor growth.

A growing body of evidence highlights the importance of metabolic enzymes as viable targets in cancer therapy [4,5]. The sustained proliferative capacity of malignant cells is fundamentally dependent upon an uninterrupted supply of nucleotide precursors to support the escalating demands of DNA replication, chromosomal duplication, and cytokinesis, necessitating marked upregulation of both de novo and salvage nucleotide biosynthetic pathways [6,7]. Human dihydroorotase (DHOase), a catalytically discrete domain within the trifunctional CAD protein complex which also harbors carbamoyl phosphate synthetase II (CPSase) and aspartate transcarbamoylase (ATCase) activities occupies a pivotal position in the de novo pyrimidine biosynthesis pathway by mediating the reversible intramolecular cyclization of N-carbamoyl-L-aspartate to L-dihydroorotate, constituting the third and rate-determining step of this pathway [8,9,10,11]. Given the heightened dependence of rapidly dividing tumor cells on pyrimidine nucleotide availability, the dihydroorotase domain of the CAD complex has emerged as a mechanistically rational and therapeutically relevant molecular target for the design and development of selective anticancer agents aimed at disrupting nucleotide biosynthetic flux in malignant cells [12,13]. Dysregulation of this pathway has been linked to enhanced tumour growth, and related enzymes such as dihydroorotate dehydrogenase (DHODH) have already been validated as therapeutic targets in cancer treatment [14]. Inhibition of pyrimidine biosynthesis disrupts nucleotide availability, thereby impairing DNA synthesis and preferentially affecting rapidly dividing cancer cells, which underscores the relevance of targeting enzymes such as HDE.

Natural products have historically constituted a principal reservoir of bioactive compounds, playing an indispensable role in the advancement of drug discovery. Notably, many clinically used anticancer agents are derived from or inspired by natural compounds, reflecting their structural diversity and biological relevance [15]. These compounds often interact with multiple molecular targets and pathways, including those involved in cell proliferation, oxidative stress, and inflammation. In addition, natural products are frequently associated with improved safety profiles compared to purely synthetic compounds, which further supports their continued exploration in anticancer research [16].

Plant-derived seed oils represent a complex and relatively underexplored source of such bioactive compounds. These oils are known to contain a diverse range of constituents, including fatty acids, sterols, tocopherols, and phenolic compounds, many of which contribute to their biological activities [17,18]. *Cocos nucifera*, *Vitellaria paradoxa*, and *Citrullus lanatus* seed oils are widely consumed and utilized in traditional medicine, and previous studies have associated their components with antioxidant and potential anticancer properties. However, while their general biological effects have been reported, there remains limited information on the specific phytochemical composition of these oils and how individual constituents interact with defined molecular targets relevant to cancer.

In recent years, computational approaches have become integral to early-stage drug discovery. Molecular docking enables the prediction of binding interactions between small molecules and target proteins, providing insight into their potential inhibitory activity [19]. Complementary to this, *in silico* tools such as SwissADME allow for the evaluation of pharmacokinetic properties and drug-likeness, including absorption, distribution, metabolism, excretion, and toxicity [20]. Such methodologies afford a financially prudent and computationally efficient framework for the high-throughput evaluation of large compound collections preceding experimental validation.

Despite the increasing interest in plant-derived bioactive and computational drug discovery, there is still a lack of studies that integrate detailed phytochemical profiling with molecular docking and pharmacokinetic evaluation of seed oil constituents targeting enzymes involved in pyrimidine biosynthesis, particularly human dihydroorotase. Therefore, this study aims to characterize the phytochemical composition of selected seed oils (*Cocos nucifera*, *Vitellaria paradoxa*, and *Citrullus lanatus*) utilizing GC-FID and HPLC chromatographic techniques, and to systematically evaluate the molecular binding interactions of the identified compounds with human dihydroorotase through computational molecular docking analysis. In addition, pharmacokinetic and toxicity profiles of these compounds are assessed using in silico tools to determine their potential as lead candidates for anticancer drug development.

II. METHODS

Sample Preparation for Phytochemical Analysis

Hexane extraction of seed oils from *Vitellaria paradoxa*, *Citrullus lanatus*, and *Cocos nucifera* was performed in accordance with the standardized protocol of the Association of Official Analytical Chemists (AOAC, 1998). One thousand grams of pulverized seed material was subjected to Soxhlet extraction with hexane over a 12-hour period. Following extraction, residual solvent was eliminated via rotary evaporation, and the recovered oil was subsequently oven-dried at 75°C for one hour. The resultant extract was equilibrated in a desiccator and preserved in airtight containers at 4°C pending further analytical procedures. For chromatographic characterization, oil samples were reconstituted in appropriate solvents and clarified by filtration through a 0.45 µm membrane filter prior to instrumental analysis.

Gas Chromatography–Flame Ionization Detection (GC-FID) Analysis

Fatty acid methyl esters (FAMEs) were prepared by transesterification. Briefly, 10 mg of oil sample was treated with 0.5 M methanolic NaOH (or methanolic H_2SO_4) and heated at 70 °C for 30 min. After cooling, n-hexane was added to extract the FAMEs, followed by the addition of saturated NaCl to facilitate phase separation. The organic layer was collected, dried over anhydrous Na_2SO_4, and filtered. GC-FID analysis was performed under standard operating conditions. Individual components were identified by comparing retention times with those of reference standards and quantified accordingly.

High-Performance Liquid Chromatography (HPLC) Analysis

For HPLC analysis, 10 g of oil sample was diluted with n-hexane or isopropanol and filtered through a 0.45 µm membrane filter. The filtrate was injected into the HPLC system.

Separation was achieved under standard chromatographic conditions which include: instrumentation, Column Selection, Mobile Phase Composition, Column Temperature, etc and compounds were identified based on retention times and comparison with available standards.

MOLECULAR DOCKING STUDIES

Protein Preparation and Active Site Identification

The three-dimensional crystallographic structure of the human dihydroorotase domain, resolved at 1.97 Å, was retrieved from the Protein Data Bank (PDB) and designated as the macromolecular receptor for subsequent molecular docking investigations. Structural preparation of the protein was conducted using Biovia Discovery Studio 2021 (Dassault Systèmes, San Diego, CA, USA), encompassing the elimination of crystallographic water molecules, incorporation of polar hydrogen atoms, and assignment of Gasteiger partial charges to neutralize potential steric clashes and electrostatic inconsistencies that could adversely influence the fidelity of the virtual screening workflow.

Identification of the putative ligand-binding site was accomplished through the Computed Atlas of Surface Topography of Proteins (CASTp) 3.0 web server (http://sts.bioe.uic.edu/castp), a computationally robust and widely validated platform for the systematic detection and topographical characterization of protein surface cavities and drug-binding pockets [21]. The three-dimensional coordinates derived from the predicted binding cavity were subsequently employed to construct the docking grid box, facilitating precise, site-directed molecular docking of the designated ligand molecules against the target receptor.

Ligand Preparation

The *in-silico* investigation was conducted on bioactive compounds previously identified through Gas Chromatography-Flame Ionization Detection (GC-FID) and High-Performance Liquid Chromatography (HPLC) analyses of ethanolic and acetonitrile extracts derived from Vitellaria paradoxa, *Citrullus lanatus*, and *Cocos nucifera*. These compounds were systematically evaluated as candidate therapeutic agents against skin carcinogenesis. The three-dimensional molecular structures of all selected bioactive compounds, inclusive of the reference standard 5-fluorouracil, were sourced from the PubChem Compound Database (National Center for Biotechnology Information, https://pubchem.ncbi.nlm.nih.gov/) in Structure Data File (SDF) format and subsequently transformed into Protein Data Bank (PDB) format employing Biovia Discovery Studio 2021. This format conversion was essential to ensure structural compatibility with the docking software and to facilitate accurate computational examination of the binding interactions between each ligand and the target receptor. All ligands were further prepared by minimizing energy, adding hydrogen atoms, and assigning Gasteiger charges prior to docking simulation, in accordance with standard molecular docking protocols.

DOCKING PROTOCOL

Molecular docking was performed using iGEMDock (version 2.1) to systematically characterize the molecular binding interactions of the identified bioactive compounds with the Human Dihydroorotase Enzyme

(HDE). The X-ray crystallographic structure of the target protein structure was imported, and the binding site was defined using a grid radius of 8.0 Å [22]. Docking parameters were set as follows: population size = 800, number of generations = 80, and number of solutions = 10 [23]. Binding interactions, including hydrogen bonding and binding energy scores, were analyzed to determine ligand affinity and stability.

Drug-Likeness Evaluation

Drug-likeness properties of selected compounds were assessed using Lipinski's Rule of Five (RO5) via the ADMET lab 3.0 web server. The physicochemical parameters evaluated encompassed molecular weight, lipophilicity (LogP), hydrogen bond donor and acceptor counts, and the number of rotatable bonds. These descriptors collectively constitute established criteria for the assessment of drug-likeness and the prediction of pharmacological suitability for oral administration in humans.

ADMET Prediction

ADMET Lab 3.0 and PKCSM were employed to examine the ADMET attributes of potential therapeutic candidates. Essential parameters such as human epithelial colorectal adenocarcinoma cells 2 (Caco2) permeability, p-glycoprotein inhibition, cytochrome P450 enzymes inhibition, Ames toxicity, carcinogenicity, hepatoxicity, human ether-a-go-go related gene (hERG) inhibition, half-life ($t^1/2$), and total clearance were assessed [24]. This was accomplished by inputting the Simplified Molecular Input Line Entry System (SMILES) of the ligands from PubChem into the web server ADMET Lab 3.0 and pkCSM respectively.

III. RESULTS

RESULTS FOR GC-FID OF SELECTED SEED OILS.

The GC-FID and HPLC Analysis of ethanoic and acetonitrile extracts of *Vitellaria paradoxa*, *Citrullus lanatus*, and *Cocos nucifera* oil revealed 45 bioactive compounds in the three seed oils. GC-FID analysis revealed 19, 15, and 17 compounds in *Vitellaria paradoxa*, *Cocos nucifera*, and *Citrullus lanatus*, with their retention time and percentage area as follows: Dammaradienol (8.550 min, 1.23%), Butyrospermol (9.750 min, 4.14%), Gallic Acid (10.133 min, 3.17%), Alpha-Amyrin (11.283 min, 1.71%), Beta-Amyrin (11.600 min, 5.49%), Catching (12.500 min, 3.94%), Epicatechin (12.983 min, 8.21%), Epicatechin gallate (13.816 min, 6.32%), Gallocatechin (14.283 min, 9.41%), Epigallocatechin gallat (14.933 min, 4.16%), Stigmasterol (15.516 min, 12.36%), Quercetin (16.250 min, 8.36%), Lupeol (16.666 min, 7.97%), Cinnamic Acid (17.400 min, 2.02%), Taraxastenol (17.766 min, 6.65%), Parkeol (18.816 min, 5.19%), Cloartanol (19.816 min, 5.33%), Cycloartenal (20.333 min, 0.88%), Spinasterol (20.783 min, 2.65%).; Beta- carotene (3.300 min, 3.57%), phenol (4.033 min, 1.86%), Lycopene (4.316 min, 0.99%), Citrulline (5.016 min, 17.61%), Anthocyanin (6.033 min, 0.88%), Sapogenin (6.450 min, 2.42%), Catechin (7.150 min, 2.72%), Epicatechin (7.533 min, 8.68%), Beta-Sitosterol (7.816 min, 9.47%), Kaempferol (8.600 min, 10.12%), Rutin (9.200 min, 37.42%), Lunamarine (11.016 min, 0.87%), Vanillin (11.483 min, 2.32%), Coumarin (11.916 min, 0.28%), Ribalindine (12.233 min, 0.09%), Curcubutacin B (12.550 min, 0.37%), Melanin (14.566 min, 0.32%).; Chlorogenic Acid (7.016 min, 4.83%), Beta-Caryophylline (9.133 min, 24430.68%), Benzoic Acid (9.816 min, 0.589%), Caffeic Acid (11.283 min, 100401.28%), Vanillic Acid (11.550 min, 0.56%), Catechin (12.350 min, 339102.33%), Epicatechin (12.650 min, 0.10%), Epigallocatechin (13.416 min, 1327470.85%), Rutin (14.233 min, 0.13%), Betanin (15.216 min, 1283381.0 %), Apigenin (15.866 min, 0.41%), P-Coumaric Acid (16.366 min, 109100.58%), Cinnamic Acid (16.816 min, 0.17 %), Ferulic Acid (17.150 min, 725969.52 %), Geranoil (17.433 min, 0.02%) respectively.

HPLC analysis further confirmed and quantified key constituents, with notable abundance of Butyrospermol (1.300 min, 16.64%), Gallic Acid (1.850 min, 8.00%), Alpha-Amyrin (2.183 min, 6.33%), Catechin (3.050 min, 5.12%), Epicatechin (4.000 min, 8.627%), Stigmasterol (5.316 min, 0.09%), Quercetin (6.200 min, 32.49%), Lupeol (8.166 min, 3.39%), Cinnamic Acid (10.616 min, 21.57%), Taraxastenol (10.916 min, 6.99%), Parkeol (11.283 min, 8.03%), Cloartanol (12.750 min, 1.87%), Cyclocloartenol (13.433 min, 18.48%), Spinasterol (13.983 min, 2.25%), Methylene-dihydroparl (14.333, 2.38%) in *Vitellaria paradoxa*,; chlorogenic Acid (3.700 min, 30.24%), Beta- Caryophylline (5.883 min, 4.85%), Benzoic Acid (7.966 min, 10.43%), Gallic Acid (9.116 min, 1.71%), Caffeic acid (9.950 min, 1.%), Vanilla acid (10.550 min, 1.08%), Catching (11.300 min,1.45%), Epicatechin (11.850 min, 1.68%), Rutin (13.466, 1.20%), Betanin (15.500 min, 11.04%), Apigenin (17.233 min, 30.60%), P-Coumaric acid (19.616 min, 1.63%), Cinnamon Acid (20.500 min, 1.19%), Ferulic acid (21.416 min, 1.69%), chlorogenic Acid (3.700, 30.24%), Beta- Caryophylline (5.883 min, 4.85%), Benzoic Acid (7.966 min, 10.43%), Gallic Acid (9.116 min, 1.71%), Caffeic acid (9.950 min, 1.19%) in *Cocos nucifera*, and Beta-Carotene (1.350 min, 2.26%), Phenol (1.650 min, 3.16%), Citrulline (1.983 min, 61.51%), Lycopene (3.166 min, 10.08%), Catechin (4.016 min, 10.98%), Epicatechin (5.05 min, 1.33%), Beta-Sitosterol (5.766 min, 0.29%), kaempferol (6.350 min, 1.60%), Rutin (7.350 min, 7.11%), Lunamarine (8.616 min, 0.81%), Vanillin (9.616 min, 0.66%), Ribalindine (10.566 min, 0.20%) in *Citrullus lanatus*.

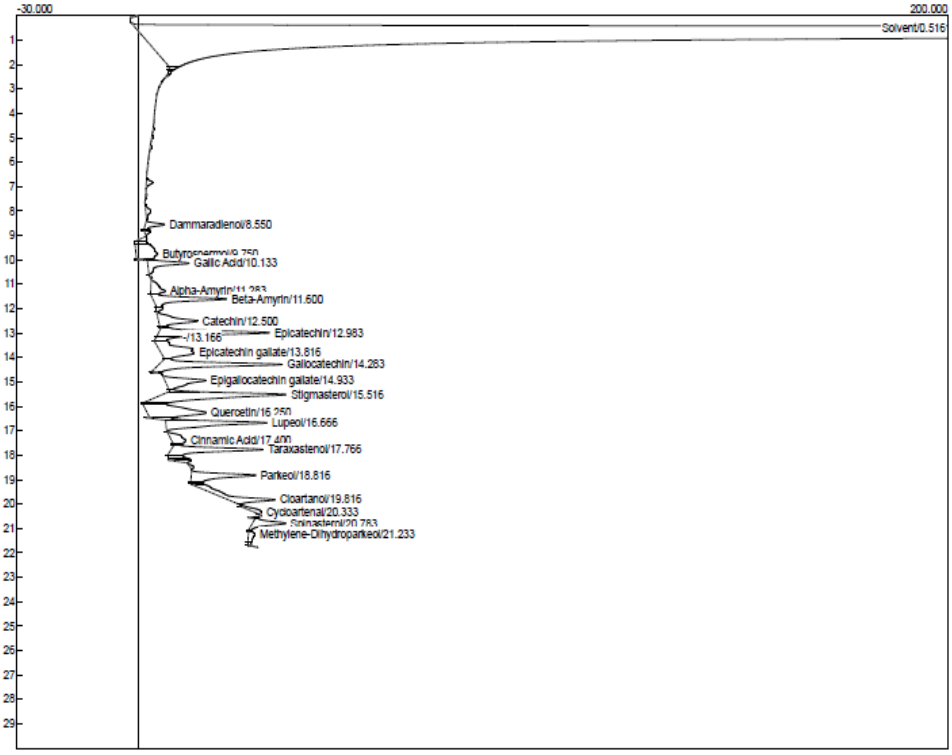


Figure 1: GC-FID Chromatogram of *VITELLARIA PARADOXA* seed oil illustrating their percentage chemical composition, retention periods and area.

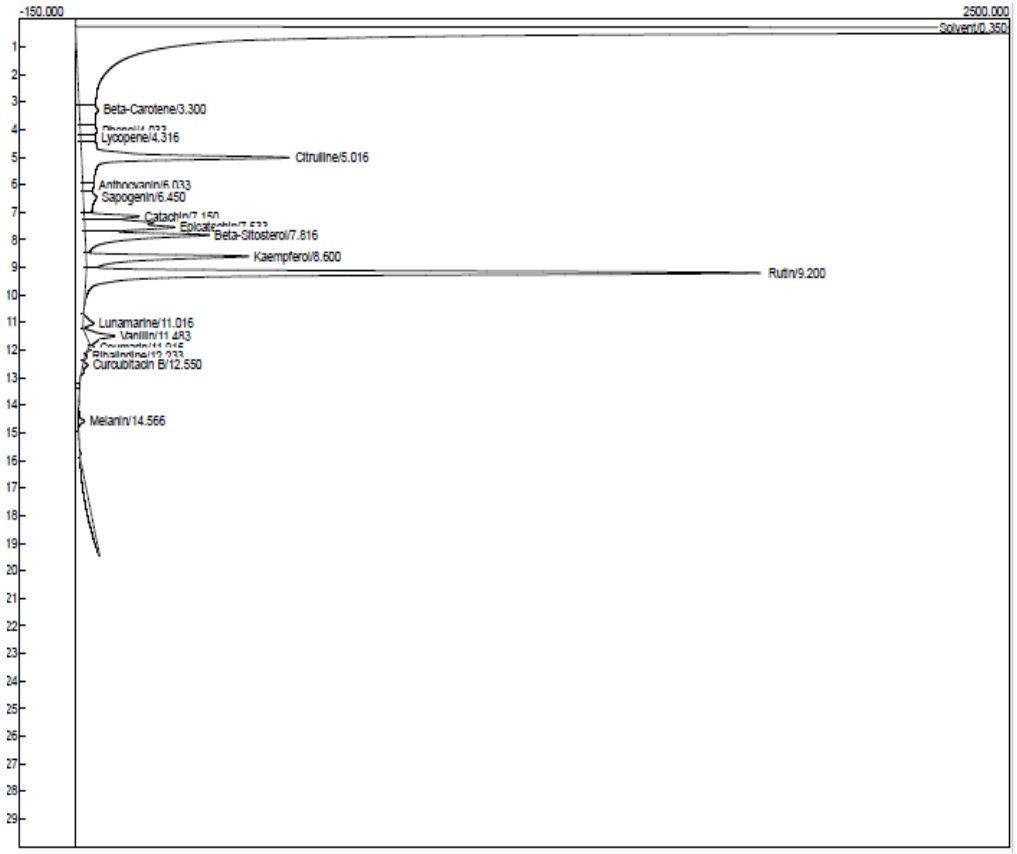


Figure 2. GC-FID Chromatogram of *CITRULLUS LANATUS* seed oil illustrating their percentage chemical composition, retention periods and area.

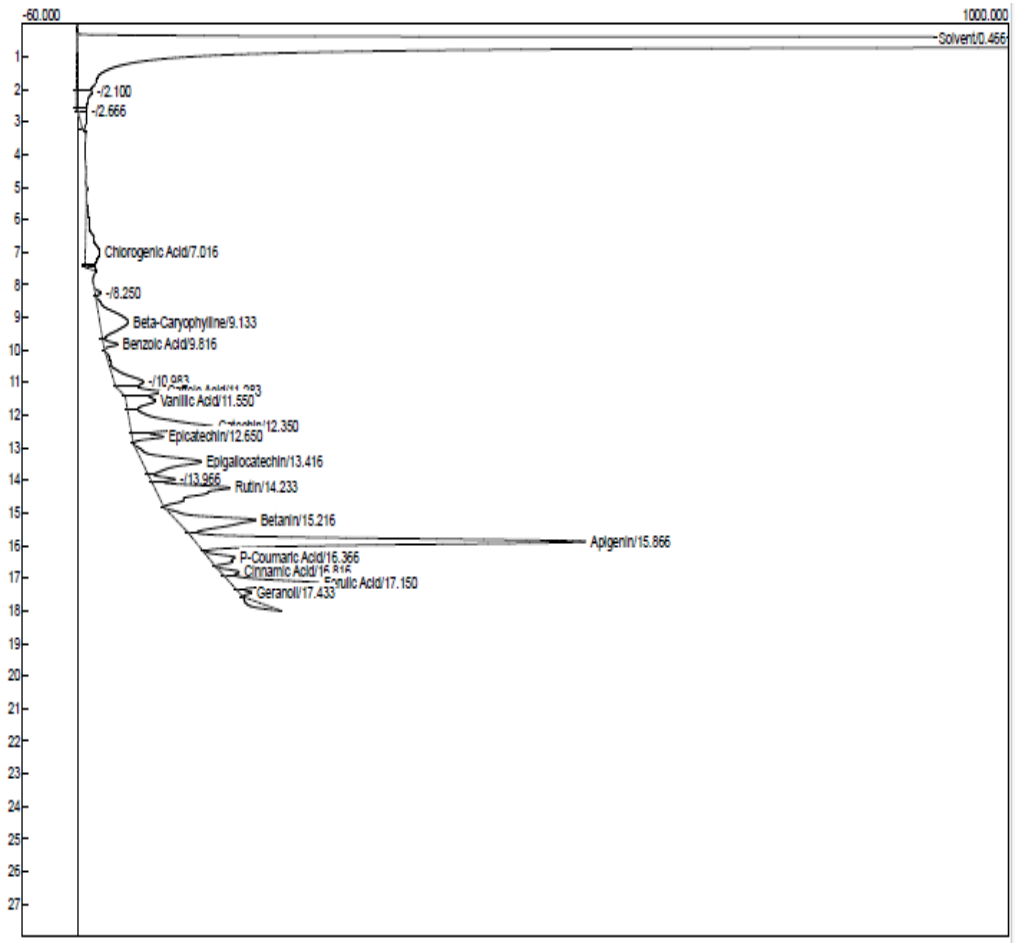


Figure 3. GC-FID Chromatogram of *COCOS NUCIFERA* seed oil illustrating their percentage chemical composition, retention periods and area.

RESULTS FOR HPLC OF SELECTED SEED OILS

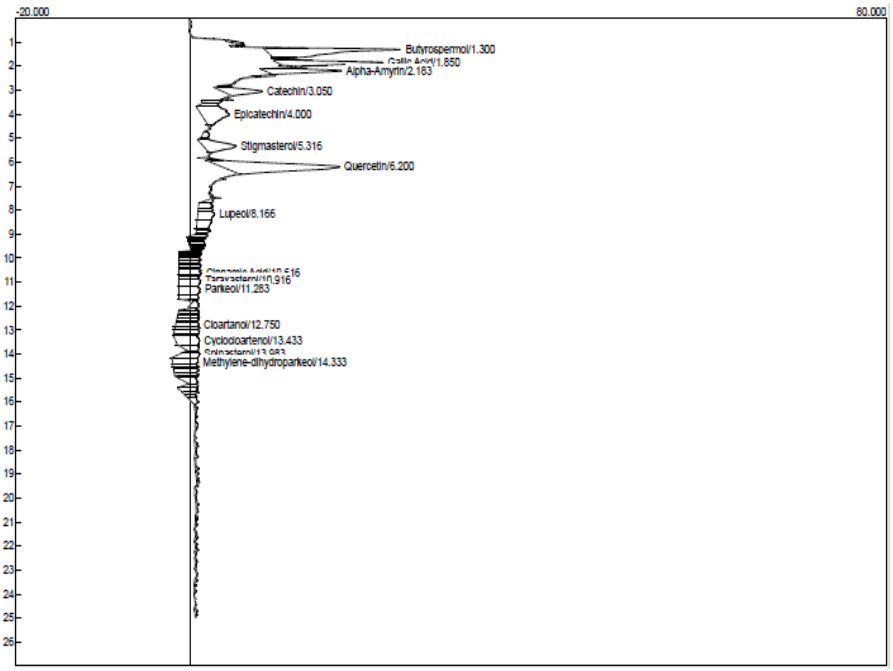


Figure 4. HPLC Chromatogram of *VITELLARIA PARADOXA* seed oil illustrating their percentage chemical composition, retention periods and area.

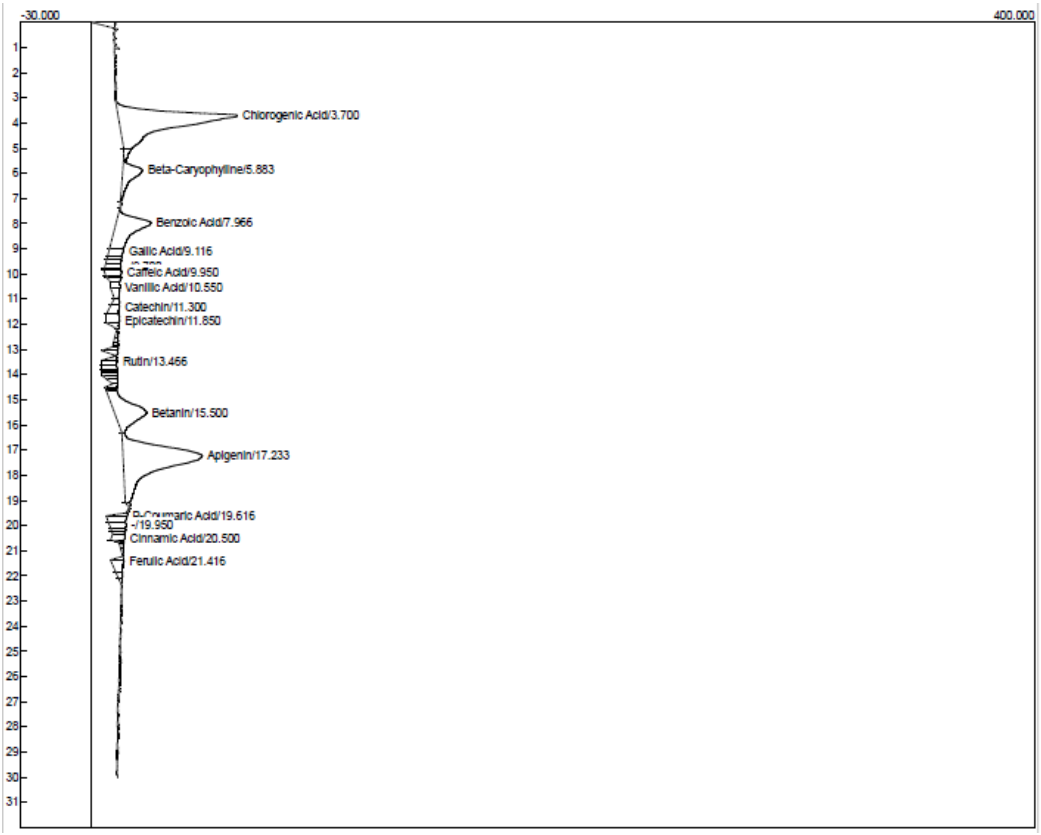


Figure 5. HPLC Chromatogram of *COCOS NUCIFERA* seed oil illustrating their percentage chemical composition, retention periods and area.

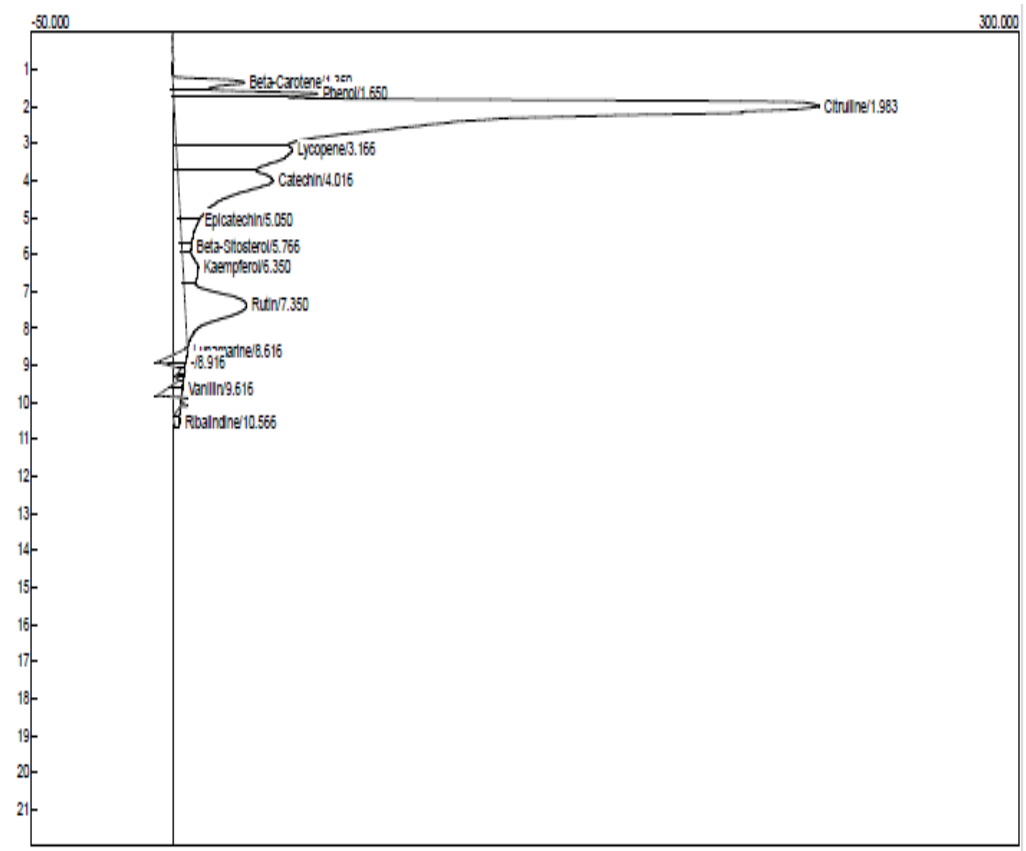


Figure 6. HPLC Chromatogram of *CITRULLUS LANATUS* seed oil illustrating their percentage chemical composition, retention periods and area.

Results for Molecular Docking

Presents the binding energy values obtained from docking programs, which determine the strength and stability of ligand-protein interactions. Among the 45 bioactive compounds tested, seven compounds (Apigenin, Beta-Sitosterol, Vanillic Acid, Epicatechin, Spinasterol, Melanin, and Ferulic Acid) exhibited higher binding affinities (lower binding energies) than the standard drug 5-FU in the docking software, making them potential hit compounds for further investigation. As shown, 5-fluorouracil exhibited binding affinities of -6.0 kcal/mol (iGEMDock). In contrast, the seven hit compounds demonstrated significantly stronger interactions with the target enzyme, with binding affinities ranging from -7.3 to -8.0 kcal/mol (iGEMDock). Among them, Apigenin displayed the highest binding affinity (-8.0 kcal/mol, iGEMDock; suggesting the strongest inhibitory potential.

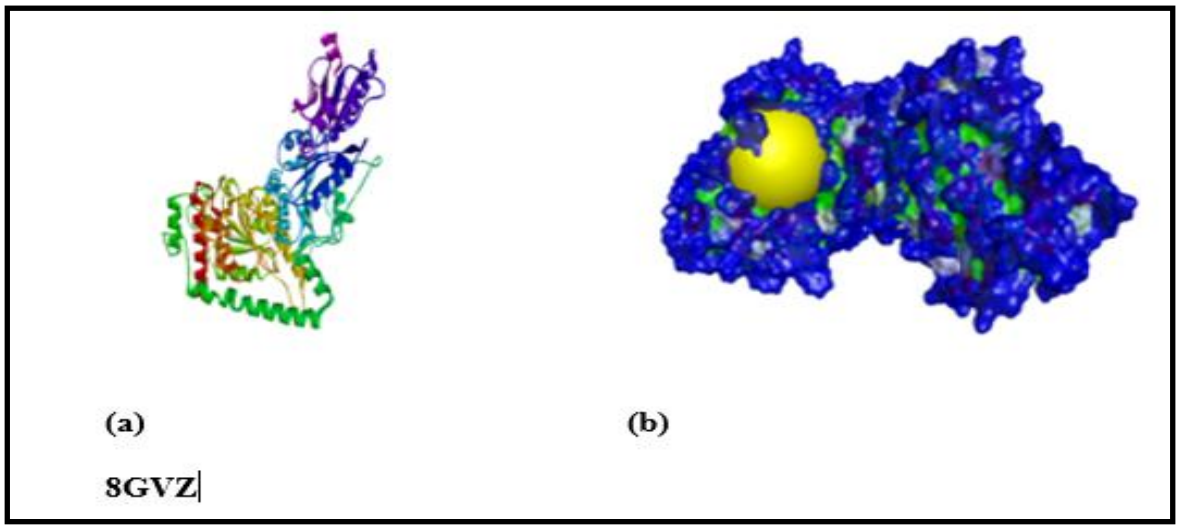
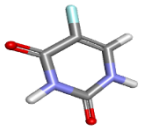
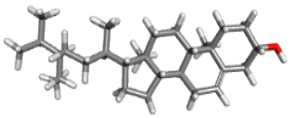
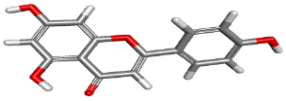
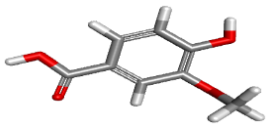
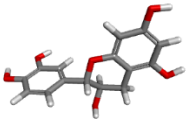
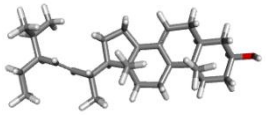
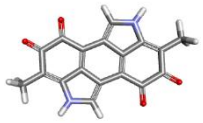
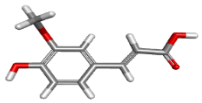


Figure 7. Visualization of the human dihydroorotase receptor (PDB ID: 8GVZ), (a) cartoon model (b) surface model with the active site colored in yellow.

Table 1. Binding affinities, hydrogen interactions, and 3D structures of 5-fluorouracil and the 7 hit bioactive compounds.

Compound Identifier	Binding affinity (iGEMDock) Kcal/mol)	H-bond Interaction	3D Structure
5-fluorouracil (Standard Drug)	-6.0	4	
Apigenin	-8.0	1	
Beta-Sitosterol	-7.9	1	
Vanillic Acid	-7.8	2	
Epicatechin	-7.5	3	

Spinasterol	-7.5	3	
Melanin	-7.4	2	
Ferulic Acid	-7.3	2	

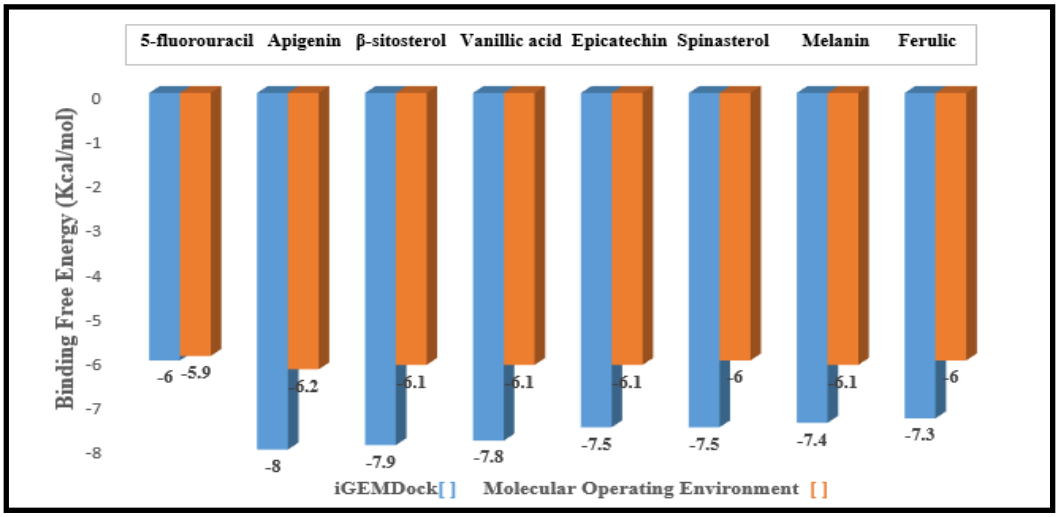


Figure 8. Binding energies of 5-fluorouracil and the 7 hit bioactive compounds

Pharmacokinetic Evaluation

Drug-likeness Prediction

Table 2. Drug-likeness (Rule of 5) evaluation of 5-fluorouracil and the seven bioactive compounds.

Ligands	Molecular Weight	H-bond donor	H-bond acceptor	Log p	Rotatable Bond	Inference
Compound ID	**< 500**	**< 5**	**< 10**	**< 5**	**< 10**	**MEET R05**
5-fluorouracil (Standard Drug)	130.02	2	4	-0.674	0	Accepted
Apigenin	270.05	3	5	2.98	1	Accepted
Beta-Sitosterol	414.39	1	1	8.00	6	Accepted
Vanillic Acid	168.04	2	4	1.34	2	Accepted
Epicatechin	290.08	5	6	0.94	1	Accepted
Spinasterol	412.37	1	1	7.70	5	Accepted
Melanin	318.06	2	6	1.53	0	Accepted
Ferulic Acid	194.06	2	4	1.65	3	Accepted

ADMET Prediction

Table 3. ADMET properties of 5-fluorouracil and the seven lead bioactive compounds.

Ligands		Absorption and Distribution			Metabolism						Excretion and Toxicity							
Compound Identifier		Caco2 permeability	Human Intestinal absorption	P-glycoprotein Inhibitor	CYP2D6	CYP3A4	CYP1A2	CYP2C19	CYP2C9	Half-life	Total Clearance	Nephrotoxicity	Acute oral toxicity	AMES toxicity	Carcinogenicity	HERG inhibitor	Hepatoxicity	Hema toxicity
5-fluorouracil (Standard Drug)		R	R	G	G	G	G	G	G	2.15	G	R	G	G	G	G	R	G
Apigenin		G	G	G	G	G	G	G	G	1.203	G	G	G	G	R	G	G	G
Beta-Sitosterol		G	G	G	G	G	G	G	G	0.541	G	G	G	G	G	G	G	G
Vanillic Acid		G	G	G	G	G	G	G	G	1.978	G	G	G	G	G	G	G	G
Epicatechin		R	G	G	G	G	G	G	G	2.218	G	G	G	G	G	G	G	G
Spinasterol		G	G	G	G	G	G	G	G	0.677	G	G	G	G	R	G	G	R
Melanin		G	R	R	G	G	G	G	G	0.529	G	G	G	R	R	G	G	G
Ferulic Acid		G	G	G	G	G	G	G	G	1.689	G	G	G	G	G	G	R	G

G = Pass R = fail

IV. DISCUSSION

Skin cancer constitutes one of the most frequently occurring malignancies on a global scale, with its incidence continuing to escalate in association with heightened ultraviolet (UV) radiation exposure and a range of environmental determinants [1, 25]. The condition is defined by the unregulated multiplication of epidermal cells, driven in part by DNA damage and the subsequent activation of pathways that support rapid cell division. This heightened proliferative demand places significant pressure on nucleotide biosynthesis pathways, including de novo pyrimidine synthesis, which are essential for sustaining DNA replication in cancer cells [6, 11]. As a result, enzymes involved in these pathways, such as human dihydroorotase (HDE), represent promising therapeutic targets. Within this context, the exploration of plant-derived bioactive compounds capable of modulating HDE activity offers a relevant and targeted approach to the development of novel interventions for skin cancer management.

The integration of phytochemical profiling with computational analysis in this study provides a targeted framework for identifying bioactive compounds capable of modulating cancer-related metabolic pathways. In line with the growing emphasis on enzyme-targeted therapy, the present findings support the relevance of plant-derived compounds as potential inhibitors of key enzymes involved in nucleotide biosynthesis, particularly human dihydroorotase (HDE). This approach is consistent with current strategies in anticancer drug discovery, which increasingly focus on disrupting metabolic dependencies that sustain tumor growth [26, 3].

Comprehensive phytochemical characterization using GC-FID and HPLC revealed a chemically diverse profile across the three seed oils, with a predominance of flavonoids, phenolic acids, and phytosterols. The detection of compounds such as apigenin, quercetin, catechin, epicatechin, ferulic acid, and β-sitosterol is particularly significant, as these classes of molecules are widely recognized for their ability to interfere with cancer-associated pathways. Flavonoids have been demonstrated to regulate critical intracellular signaling cascades implicated in cellular proliferation and survival, notably the PI3K/Akt and MAPK pathways, while concurrently exerting antioxidant activity that attenuates oxidative DNA damage [27, 28]. Similarly, phenolic acids such as ferulic and vanillic acids contribute to cellular redox balance and have been implicated in the suppression of tumor initiation and progression [29,30]. The presence of phytosterols, including β-sitosterol and spinasterol, further enhances the biological relevance of these oils, given their reported roles in inducing apoptosis and modulating membrane dynamics in cancer cells [31].

The complementary use of GC-FID and HPLC proved valuable in capturing both volatile and non-volatile constituents, thereby providing a more complete phytochemical profile. While GC-FID facilitated the detection of lipid-soluble and derivatized compounds, HPLC enabled the identification of thermolabile and polar phenolics that may otherwise be underrepresented. Such multi-analytical approaches have been recommended in

recent studies to improve the reliability of phytochemical characterization in complex natural matrices [32]. The consistency observed between the two techniques in identifying key compounds such as catechin, epicatechin, and β-sitosterol strengthens confidence in the analytical outcomes and supports their subsequent selection for in silico evaluation.

The molecular docking results provide important mechanistic insight into the potential anticancer activity of the identified compounds. Human dihydroorotase, a critical enzyme within the CAD complex, fulfills a pivotal mechanistic function within the de novo pyrimidine biosynthesis pathway, a metabolic route that is characteristically overexpressed in highly proliferative malignant cells [11]. By catalyzing a key step in nucleotide synthesis, HDE contributes directly to DNA replication and tumor growth. Consequently, its inhibition represents a rational strategy for impairing cancer cell proliferation. In this context, the observed binding affinities of the selected phytochemicals, which ranged from −7.3 to −8.0 kcal/mol, are noteworthy, particularly when compared to the reference drug 5-fluorouracil (−6.0 kcal/mol), Lower binding energy values (more negative) indicate stronger interactions between the bioactive compounds and the enzyme. The stronger binding interactions exhibited by compounds such as apigenin and β-sitosterol suggest a higher potential for enzyme inhibition, consistent with previous reports highlighting the affinity of flavonoids for enzyme active sites through hydrogen bonding and hydrophobic interactions [14, 33].

Among the identified compounds, apigenin demonstrated the highest binding affinity, which aligns with existing literature describing its ability to interfere with multiple cancer-related targets, including enzymes involved in nucleotide metabolism [34, 35]. β-Sitosterol and vanillic acid also exhibited strong interactions, further supporting their potential as lead compounds. The convergence between phytochemical abundance and docking performance observed in this study suggests that these compounds are not only present in significant quantities but are also structurally suited for interaction with the target enzyme. This dual validation, analytical and computational, enhances the robustness of the findings.

Appraisal of drug-likeness in accordance with Lipinski's Rule of Five demonstrated that the preponderance of the identified compounds possessed physicochemical attributes consistent with adequate oral bioavailability. Although β-sitosterol and spinasterol exhibited higher lipophilicity, which may limit aqueous solubility, such deviations are not uncommon among natural products and do not preclude biological activity [36]. Indeed, lipophilic compounds may benefit from enhanced membrane permeability, which could facilitate intracellular access to enzymatic targets. These observations underscore the importance of interpreting drug-likeness parameters within the broader context of compound functionality rather than as rigid exclusion criteria.

The ADMET analysis further provided insight into the pharmacokinetic behavior and safety profiles of the selected compounds. Overall, the compounds demonstrated favorable absorption characteristics and minimal predicted toxicological profiles, reinforcing their viability as prospective drug candidates. However, the identification of possible interactions with cytochrome P450 enzymes and isolated toxicity flags highlights the need for cautious interpretation. Such findings are consistent with current perspectives in drug discovery, where early-stage ADMET screening is used to identify potential liabilities while guiding further optimization [37]. Importantly, the relatively favorable ADMET profiles observed for compounds such as apigenin and ferulic acid reinforce their suitability for further investigation.

From a clinical standpoint, the implications of these findings are particularly relevant to skin cancer, where dysregulated cell proliferation and DNA synthesis are central to disease progression. Ultraviolet (UV) radiation-induced DNA damage is a primary driver of skin carcinogenesis, and the rapid turnover of affected cells necessitates increased nucleotide synthesis [38]. By targeting HDE, the identified compounds may disrupt this metabolic requirement, thereby limiting tumor growth. In addition, the antioxidant properties of the detected phytochemicals may contribute to reducing oxidative DNA damage, providing a complementary chemopreventive effect. This dual functionality; metabolic inhibition and oxidative stress modulation, positions these compounds as promising candidates for both therapeutic and preventive strategies in skin cancer management.

The integration of phytochemical profiling, molecular docking, and ADMET prediction undertaken in this study embodies a contemporary paradigm in natural product-based drug discovery. Transcending sole dependence on empirical screening methodologies, this integrative strategy facilitates the systematic identification and prioritization of compounds exhibiting both structural appropriateness and favorable pharmacokinetic profiles. The identification of apigenin, β-sitosterol, and vanillic acid as leading candidates highlights the potential of seed oil-derived compounds as scaffolds for further drug development.

Nevertheless, it is important to acknowledge the limitations inherent in in silico studies. While molecular docking furnishes significant insight to potential ligand–protein interactions, it does not fully account for the complexity of biological systems. Factors such as bioavailability, metabolic transformation, and target accessibility can significantly influence in vivo activity. Therefore, subsequent experimental substantiation, encompassing enzyme inhibition assays and in vitro cellular investigations, is imperative to ascertain the therapeutic efficacy of these compounds.

In summary, the findings of this study demonstrate that bioactive compounds derived from *Cocos nucifera*, *Vitellaria paradoxa*, and *Citrullus lanatus* possess significant potential as inhibitors of human dihydroorotase. The strong binding affinities, favourable pharmacokinetic profiles, and established biological activities of these compounds support their candidacy as lead molecules in anticancer drug development. Hence, future work should focus on experimental validation and optimization to facilitate their translation into clinically relevant applications.

V. CONCLUSION

Seed oils from *Cocos nucifera*, *Vitellaria paradoxa*, and *Citrullus lanatus* were found to contain bioactive phytochemicals notably flavonoids, phenolic acids, and phytosterols with promising anticancer potential. Molecular docking studies identified apigenin, β-sitosterol, and vanillic acid as strong inhibitors of human dihydroorotase, an important enzyme within the de novo pyrimidine biosynthesis pathway, outperforming the reference drug 5-fluorouracil in binding affinity.

Favorable drug-likeness and ADMET profiles further support their candidacy for drug development. These compounds may be particularly relevant in skin cancer therapy, where rapidly proliferating, UV-damaged tumor cells exhibit heightened dependence on nucleotide biosynthesis. While the integration of phytochemical and computational approaches validates these plant-derived constituents as lead anticancer compounds, comprehensive in vitro and in vivo investigations are imperative to substantiate the biological activity and clinical translational potential of these findings.

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