Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 10, No. 4, 473-491
2026
Publisher: Learning Gate
DOI: 10.55214/2576-8484.v10i4.12701

Molecular docking insights into *Calophyllum*-derived chromanones as potential EGFR and STAT3 inhibitors in cervical cancer: A review

Nur Nabilah Mohd Zaini[1], Wan Mohd Nuzul Hakimi Wan Salleh[1*], Nurunajah Ab Ghani[2,3], Abubakar Siddiq Salihu[1,4], Bodee Nutho[5], Farkhoed Eshboev[6], Alfred Ngenge Tamfu[7]
[1]Department of Chemistry, Faculty of Science and Mathematics, Universiti Pendidikan Sultan Idris, Tanjong Malim, Perak, Malaysia; wmnhakimi@fsmt.upsi.edu.my (W.M.N.H.W.S.).
[2]Atta-ur-Rahman Institute for Natural Product Discovery (AuRIns), Universiti Teknologi MARA, Puncak Alam Campus, Puncak Alam, Selangor, Malaysia.
[3]Faculty of Applied Sciences, Universiti Teknologi MARA, Shah Alam, Selangor, Malaysia.
[4]Department of Pure and Industrial Chemistry, Faculty of Natural and Applied Science, Umaru Musa Yar'adua University, Katsina, Nigeria.
[5]Department of Pharmacology, Faculty of Science, Mahidol University, Bangkok, Thailand.
[6]Institute for Advanced Studies, New Uzbekistan University, Tashkent, Uzbekistan.
[7]Department of Chemical Engineering, School of Chemical Engineering and Mineral Industries, University of Ngaoundere, Ngaoundere, Cameroon.

Abstract: Recently, chromanone compounds obtained from the *Calophyllum* species were found to exhibit anticancer properties in cervical cancer by inhibiting key cancerous proteins that are essential to cervical cancer progression and development. In this docking study, experiments were conducted against two key oncogenic targets in cervical cancer: the epidermal growth factor receptor (EGFR, PDB ID: 8A27) and STAT3 (PDB ID: 6NUQ). For EGFR, the mutant-selective allosteric inhibitor EAI045 was used as the positive control to match the allosteric conformation of the 8A27 structure. For STAT3, the SH2-domain suppressor STAT3 Inhibitor VII served as the control, consistent with the binding site captured in 6NUQ. Favorable interactions were observed with several compounds showing docking scores indicating strong binding affinity for EGFR kinase and STAT3 SH2 domain. Structural interaction analysis additionally exposed essential hydrogen bonding and hydrophobic contacts in the active sites. The results favor *Calophyllum*-derived chromanones as interesting lead compounds for dual targeting of EGFR and STAT3 pathways as an additional alternative for targeted therapies in cervical cancer. More importantly, it supports the ethnobotanical importance of *Calophyllum* species and illustrates the potential of computational techniques in converging traditional medicine for contemporary drug discovery.

Keywords: *Bioactivity, Calophyllum, Cervical cancer, Chromanones, Molecular docking.*

1. Introduction

Calophyllum is a large genus of tropical trees and shrubs with over 200 species forming the family Calophyllaceae; many of them can be found in Southeast Asia, the Pacific Islands, and many parts of Africa [1]. *Calophyllum* species have been a promising reservoir of novel bioactive secondary metabolites for drug discovery, both due to their ethnopharmacological relevance and specific chemical profiles [2]. They show a diverse therapeutic spectrum, which ranges from antiviral to antibacterial, anti-inflammatory, or anticancer effects. Alternatively, traditional medicine is widely used in many cultural areas to treat peptic ulcers, malaria, tumors, infections, venereal diseases, hypertension, pain, and inflammation, among other health problems [3]. *Calophyllum* is a well-known source of natural products that has been explored as the topic of various phytochemical investigations, leading to the isolation of

History: Received: 2 February 2026; Revised: 2 April 2026; Accepted: 6 April 2026; Published: 16 April 2026
* Correspondence: wmnhakimi@fsmt.upsi.edu.my

several key classes, including xanthones, coumarins, triterpenoids, and chromanones [4]. Chromanones have recently become prevalent because their fused-ring structures are remarkably unique. Chromanones have different structures because the substitution patterns on both the aromatic and heterocyclic rings are different. This leads to a wide range of pharmacological effects, including the ability to fight cancer. Many of these chromanone derivatives exhibit key in vitro biological activities, and their occurrence within *Calophyllum* provides support for the ethnobotanical uses of these plant species as anti-inflammatory, anti-bacterial, and anti-tumor agents. These data closely parallel the most recent pharmacological studies, which show that several chromanones demonstrate cytotoxic activity for various cancer cell lines [5-7].

Cervical cancer is a significant public health issue for women globally, with over 500,000 annual diagnoses and at least 300,000 cases requiring surgical procedures each year [8, 9]. Ovarian cancer has a high fatality rate since it is generally diagnosed late, and there are limited treatment options. It is the fourth most prevalent cause of cancer-related death in women. There is an urgent need to develop new, safe, and effective drugs for treating cervical cancer that can specifically target cancer cells. HeLa cells are the most extensively studied among cervical cancer cell lines [10-12]. Derived from a cervical cancer patient named Henrietta Lacks in 1951, HeLa cells are invaluable for understanding cancer mechanisms, drug screening, and molecular characterization that drive the progression of malignancy. This makes them a crucial experimental system for cancer research and the screening of novel anticancer compounds. Recent studies have highlighted the potential of natural compounds, such as those derived from *Calophyllum* species, in providing promising solutions for disease treatment [13, 14].

The groundwork for this discovery began with the two proteins responsible for maintaining the aggressive nature of cancer, called EGFR (Epidermal Growth Factor Receptor) and STAT3 (Signal Transducer and Activator of Transcription 3) in HeLa cells. When EGFR is overexpressed, it is present in excessive and abnormally high amounts. This overexpression causes constant activation of growth signals even without external stimulation, which contributes to uncontrolled cancer cell division. One of the major downstream effects of EGFR activation is the phosphorylation and activation of STAT3. It activates STAT3, a transcription factor that goes to the nucleus of cancer cells and turns on genes that help them survive and be resistant to treatment [15-18]. For STAT3 to become active, it must be phosphorylated (especially at tyrosine 705), and then two STAT3 proteins bind together (dimerize) through a specific region called the SH2 domain (Src Homology 2). This SH2 domain is necessary for STAT3 to dimerize and then translocate into the nucleus, where it can colonize the promoter of genes [19-21]. Therefore, in the HeLa cells, both EGFR and STAT3 pathways are spontaneously active, implying that these two pathways cooperate functionally as a dual target for anticancer therapy. Inhibiting both proteins can more effectively disrupt cervical cancer progression than targeting either alone.

Molecular docking simulations employ real 3D protein structures and are widely used in hit identification in drug discovery. This computational protocol allows researchers to predict how well a small molecule (ligand) will bind and interact with its protein or receptor, thereby facilitating the identification of potential drug candidates [22, 23]. In this study, molecular docking simulations were employed to study the interactions of chromanones with target proteins associated with cancer progression. Thus, by providing deeper insights into their mode of action, it can be emphasized that molecular docking has the potential to improve the exploration of anticancer compounds from *Calophyllum* species.

This review aims to critically evaluate the anticancer properties of chromanones derived from *Calophyllum* species, focusing on cervical cancer and HeLa cells. Using a combined in silico approach of molecular docking, we seek to identify dual-targeted chromanone leads with potential therapeutic value. This provides evidence supporting *Calophyllum*'s ethnomedicinal uses and offers a new perspective for cancer chemotherapy.

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 10, No. 4: 473-491, 2026
DOI: 10.55214/2576-8484.v10i4.12701

2. Experimental

2.1. Preparation of the target protein

This study aims to explore the binding affinity and interactions of two major oncogenic proteins involved in cervical cancer progression: Epidermal Growth Factor Receptor (EGFR) and Signal Transducer and Activator of Transcription 3 (STAT3) [24, 25]. The 3D crystal structures of the EGFR kinase domain (PDB ID: 8A27) and the STAT3 SH2 domain (PDB ID: 6NUQ) were obtained from the RCSB Protein Data Bank (https://www.rcsb.org/) and pre-processed by removing all co-crystallized ligands, water molecules, and heteroatoms using BIOVIA Discovery Studio Visualizer 2021 before docking. Structural minimization was performed with the AMBER force field in UCSF Chimera 1.15 using the conjugate gradient algorithm to ensure protein stability and avoid steric clashes, enabling accurate docking [26, 27].

2.2. Preparation of Ligands

This study was conducted based on a total of 55 chromanones that have been isolated and identified from *Calophyllum* species. Two main sources were used to prepare these ligands: The SDF (Structure Data File) format of some compound structures was obtained directly from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), and ChemDraw Ultra 12.0 was also used to manually sketch the structures of compounds not found in PubChem. The ligands were manually imported into PyRx 0.9.8 and converted to PDBQT format through Open Babel for each compound. Energy minimization of the ligands was performed with the Universal Force Field (UFF) in each receptor, using an energy convergence criterion of 0.1, a maximum of 100 steepest descent steps, and a step size of 0.02 Å. Energy minimization is a crucial step before or during molecular docking to loosen the structure and eliminate steric interference for more accurate results [22]. This stage maintains the ligand's optimal shape and conformational stability for effective docking. EAI045 (PubChem CID: 121231412) and STAT3 Inhibitor VII (PubChem CID: 24905707) were selected as positive controls, respectively [28]. Since 8A27 represents an allosteric conformation of EGFR, the allosteric inhibitor EAI045 was used instead of ATP-site inhibitors. For STAT3, STAT3 Inhibitor VII (Calbiochem, Merck, Cat. No. 573103) was chosen because it is described by the manufacturer as a selective SH2-domain inhibitor, aligning with the well-established role of the SH2 domain as a therapeutic target for STAT3 inhibition [29]. For consistency, these control ligands were prepared similarly to the potential test compounds and downloaded from PubChem.

2.3. Molecular Docking Protocol

AutoDock Vina calculations were performed using the PyRx 0.9.8 interface for molecular docking computations. Grid box parameters were adjusted to fully cover the active sites of each protein to ensure accurate binding predictions: for EGFR (8A27), grid center coordinates were set at X:22.1529, Y:14.2328, Z:18.5351, and for STAT3 (6NUQ), X:11.3875, Y:22.7651, Z:12.8498, based on the location of co-crystallized inhibitors. The grid box size was optimized to allow full ligand flexibility within the binding pocket. The exhaustiveness value was 8 to ensure reliable sampling of binding poses. The top-ranked complexes, selected based on the lowest binding energy (kcal/mol), were further evaluated and visualized. Discovery Studio Visualizer 2021 was used to assess the binding interactions (2D and 3D) between protein and ligand [30].

3. Results and Discussion

3.1. Chromanones

Many chromanone derivative compounds have been isolated from different species of the *Calophyllum* genus. The nature of bioactivities within these chromanones obtained from different plant parts, e.g., stem bark, fruit kernels, and pericarps of the genus, certainly reflects the richness of this genus as an excellent source for pharmaceutical drug development. Chromanones are among the

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 10, No. 4: 473-491, 2026
DOI: 10.55214/2576-8484.v10i4.12701

flavonoid family of compounds, which is a large group of closely related polyphenolic metabolites collectively that are well represented in plants. Chromanone, also known as chroman-4-one (2,3-dihydro-1-benzopyran-4-one), has a privileged bicyclic heterocycle in medicinal chemistry. It is composed of a benzene ring fused to a 2,3-dihydro-γ-pyran-4-one moiety (Figure 1). One of the central structural elements that sets chromanones apart from scaffolds like chromones, chromenes, and robustols is their lack of a C2-C3 double bond, which affects chemical reactivity and biological properties associated with in vitro assays. Chromanones can be subdivided into simple chromanones and more complex derivatives, including pyranochromanones and furanochromanones, based on substitution patterns and extra ring fusion. This high diversity makes these molecules possess a wide dispersion of pharmacological activities, including anticancer potential [31, 32].

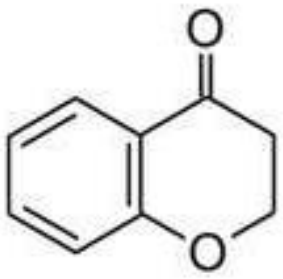

Figure 1.
Structural framework of chromanone skeleton.

This unusual chemical structure plays an important role in the bioactivity of chromanones, and thereby the variety of natural activities. Chromanones are typically present in the plant families Calophyllaceae, Rutaceae, and Leguminosae and are often found as secondary metabolites from plants traditionally used for medicinal purposes, such as anti-inflammatory agents, antitumor activity, or treatments of bacterial infections [33]. For example, species of *Calophyllum* have a history of use in traditional medicines as treatments for wounds, skin infections, and fever. The antimicrobial and immune support properties found in these plants have led some cultures to use them, while others use them internally to treat chronic diseases [34]. These historical uses of plants containing chromanones emphasize the continual human concern for this class of bioactive compounds and their future in medicine.

The molecular modification of chromanones can be achieved through various substitutions on the aromatic ring, pyran ring, or ketone group, leading to a variety of derivatives. These structural variations are significant, as they influence the biological activity of chromanones. Depending on the nature of these modifications, chromanones can exhibit a broad spectrum of biological effects [35]. For instance, chromanones from *Calophyllum* species exhibit significant inhibitory activities in the proliferation of cancer cell lines, such as HeLa cells (cervical), leading to apoptosis and cell cycle arrest. Therefore, these compounds are also shown to have potential as novel anti-cancer agents. In addition to their anticancer activity, chromanones have also been demonstrated to possess significant antibacterial and antifungal activities, making them of great interest in bactericidal-fungicidal drugs [36]. Furthermore, chromanones can act as antioxidants by reducing oxidative stress, which is often associated with chronic and age-related disorders. Recent studies suggest that chromanones might also be neuroprotective, as emerging evidence indicates they could be a possible treatment for neurodegenerative disorders such as Alzheimer's disease [37]. Their potential as medicinal agents is further emphasized by their anti-inflammatory properties, opening additional possibilities for treating ailments such as arthritis and cardiovascular diseases.

Chromanones are mainly produced via the polyketide pathway, which generates an array of aromatic and heterocyclic compounds. The initial step involves the condensation of acetyl-CoA and

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 10, No. 4: 473-491, 2026
DOI: 10.55214/2576-8484.v10i4.12701

malonyl-CoA units to form a polyketide chain that cyclizes into the chromanone core. The key enzymes involved are polyketide synthases, cyclases, and methyltransferases, which perform cyclization, hydroxylation, and methylation, respectively, during modification. These changes promote structural variability in chromanones produced by various plant species. After the core structure is formed, hydroxylases and methyltransferases are used to enhance several positions by adding hydroxyl and methyl groups, resulting in various chromanone derivatives [38]. Thus, chromanones are a significant group of natural products with diverse bioactive properties. Their unique chemical structure, combined with their biological effects, makes them promising candidates for developing new therapeutic agents. Further research into their biosynthesis, structural diversity, and pharmacological activities may provide insights into their mechanisms of action and facilitate the development of more potent agents with fewer side effects.

3.2. Active Chromanones from Calophyllum Species

The presence of chromanones in several species of the genus *Calophyllum* demonstrates their broad distribution in tropical and subtropical regions globally. Table 1 lists active chromanones isolated from different *Calophyllum* species from 1968 to 2024 [39].

Ethical approval for this study is based on data from the Scopus database. *Calophyllum* species are an abundant source of chromanones, which have been reported from several countries worldwide, and the structure is shown in Figure 2. This broad distribution of chromanones in different tissues suggests that the plant can produce these unique compounds not only in the stem bark but also in other parts such as leaves, fruit kernels, resin, and pericarps. The diversity of plant parts accumulating these compounds implies important functions in the plant's metabolic pathways, such as defense mechanisms against herbivores, pathogens, and environmental stressors.

Table 1.
Chromanones isolated from *Calophyllum* species.

Compounds	Species	Locality	Part	References
Calolongic acid	*C. havilandii*	Malaysia	Stem bark	Zailan, et al. [39]
	C. teysmannii	Malaysia	Stem bark	Lim, et al. [40]
	C. pinetorum	Havana	Resin	Piccinelli, et al. [41]
Isocalolongic acid	*C. havilandii*	Malaysia	Stem bark	Zailan, et al. [39]
	C. lanigerum	Malaysia	Stem bark	Mokhtar, et al. [42]
	C. teysmannii	Malaysia	Stem bark	Lim, et al. [40]
	C. pinetorum	Havana	Resin	Piccinelli, et al. [41]
	C. recedens	French	Bark	Guerreiro, et al. [43]
Caloteysmannic acid	*C. havilandii*	Malaysia	Stem bark	Zailan, et al. [39]
	C. lanigerum	Malaysia	Stem bark	Mokhtar, et al. [42]
	C. teysmannii	Malaysia	Stem bark	Lim, et al. [40]
Blancoic acid	*C. castaneum*	Malaysia	Stem bark	Gan [44]
	C. castaneum	Malaysia	Stem bark	Lim, et al. [45]
Isoblancoic acid	*C. castaneum*	Malaysia	Stem bark	Lim, et al. [45]
Calophynic acid	*C. inophyllum*	Malaysia	Fruit kernel	Zakaria, et al. [46]
Apetalic acid	*C. polyanthum*	China	Pericarps	Wang, et al. [47]
Apetalic acid methyl ester	*C. blancoi*	Taiwan	Seeds	Shen, et al. [48]
Isoapetalic acid	*C. polyanthum*	China	Pericarps	Wang, et al. [47]
	C. blancoi	Taiwan	Seeds	Shen, et al. [48]
Isoapetalic acid methyl ester	*C. blancoi*	Taiwan	Seeds	Shen, et al. [48]
Chapelieric acid	*C. polyanthum*	China	Pericarps	Wang, et al. [47]
Isochapelieric acid	*C. calaba*	Sri Lanka	Leaves	Gunatilaka, et al. [49]
Isocordato-oblongic acid	*C. cordatooblongum*	Sri Lanka	Stem bark	Dharmaratne, et al. [50]
Cordato-oblongic acid	*C. cordatooblongum*	Sri Lanka	Bark	Dharmaratne, et al. [50]
Cordato-oblongic acid methyl ester	*C. cordatooblongum*	Sri Lanka	Bark	Dharmaratne, et al. [50]
Isocordato-oblongic acid methyl ester	*C. cordatooblongum*	Sri Lanka	Bark	Dharmaratne, et al. [50]
Calofolic acid A	*C. scriblitifolium*	Malaysia	Bark	Nugroho, et al. [51]

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 10, No. 4: 473-491, 2026
DOI: 10.55214/2576-8484.v10i4.12701

Calofolic acid B	*C. incrassatum*	Indonesia	Stem bark	Hasanah, et al. [52]
Calofolic acid C	*C. scriblitifolium*	Malaysia	Stem bark	Nugroho, et al. [51]
Calofolic acid D	*C. scriblitifolium*	Malaysia	Stem bark	Nugroho, et al. [51]
Calofolic acid E	*C. scriblitifolium*	Malaysia	Stem bark	Nugroho, et al. [51]
Brasiliensic acid	*C. brasiliense*	Brazil	Stem bark	Lemos, et al. [53]
Isobrasiliensic acid	*C. brasiliense*	Brazil	Stem bark	Lemos, et al. [53]
Inophylloidic acid	*C. inophyllum*	Cameroon	Root bark	Yimdjo, et al. [54]
Recedensic acid	*C. polyanthum*	China	Pericarps	Wang, et al. [47]
Isorecedensic acid	*C. polyanthum*	China	Pericarps	Wang, et al. [47]
Calopolyanic acid	*C. polyanthum*	China	Pericarps	Wang, et al. [47]
Isocalopolyanic acid	*C. polyanthum*	China	Pericarps	Wang, et al. [47]
Calopolyanic acid methyl ester	*C. membranaceum*	China	Stem	Ming, et al. [55]
Isopinetoric acid methyl ester	*C. membranaceum*	China	Stem	Ming, et al. [55]
Apetalolide	*C. inophyllum*	China	Leaves	Zou, et al. [56]
Inophynone	*C. inophyllum*	Pakistan	Leaves	Ali, et al. [57]
Isoinophynone	*C. inophyllum*	Pakistan	Leaves	Ali, et al. [57]
Brasiliensophyllic acid A	*C. brasiliense*	Mexico	Bark	Cottiglia, et al. [7]
Isobrasiliensophyllic acid A	*C. brasiliense*	Mexico	Bark	Cottiglia, et al. [7]
Brasiliensophyllic acid B	*C. brasiliense*	Mexico	Bark	Cottiglia, et al. [7]
Isobrasiliensophyllic acid B	*C. brasiliense*	Mexico	Bark	Cottiglia, et al. [7]
Caloverticillic acid C	*C. verticillatum*	French	Stem bark	Ravelonjato, et al. [58]
Brasiliensophyllic acid C	*C. brasiliense*	Mexico	Bark	Cottiglia, et al. [7]
Isobrasiliensophyllic acid C	*C. brasiliense*	Mexico	Bark	Cottiglia, et al. [7]
Calophyllic acid	*C. pinetorum*	Cuba	Leaves	Alarcón, et al. [59]
Isocalophyllic acid	*C. inophyllum*	India	Leaves	Prasad, et al. [60]
Calozeylanic acid	*C. lankaensis*	Sri Lanka	Leaves	Ranjith, et al. [61]
Thwaitesic acid	*C. lankaensis*	Sri Lanka	Leaves	Ranjith, et al. [61]
Isothwaitesic acid	*C. lankaensis*	Sri Lanka	Leaves	Ranjith, et al. [61]
	C. thwaitesii	Sri Lanka	Leaves	Ranjith, et al. [61]
Caloinophyllin A	*C. inophyllum*	Thailand	Roots	Ponguschariyagul, et al. [62]
Pinetoric acid I	*C. antillanum*	Cuba	Resin	Cuesta-Rubio, et al. [63]
Pinetoric acid II	*C. antillanum*	Cuba	Resin	Cuesta-Rubio, et al. [63]
	C. pinetorum	Cuba	Resin	Piccinelli, et al. [41]
Pinetoric acid III	*C. antillanum*	Cuba	Resin	Cuesta-Rubio, et al. [63]
Isopinetoric acid III	*C. antillanum*	Cuba	Resin	Cuesta-Rubio, et al. [63]
	C. membranaceum	China	Stem	Ming, et al. [55]
Decipic acid	*C. decipiens*	India	Bark	Ajithabai, et al. [64]
12-Acetyl apetalic acid	*C. decipiens*	India	Bark	Ajithabai, et al. [64]
Papuanic acid	*C. papuanum*	New Guinea	Bark resin	Stout, et al. [65]
Isopapuanic acid	*C. papuanum*	New Guinea	Bark resin	Stout, et al. [65]
Calofloride	*C. verticillatum*	French	Stem bark	Ravelonjato, et al. [66]

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 10, No. 4: 473-491, 2026
DOI: 10.55214/2576-8484.v10i4.12701

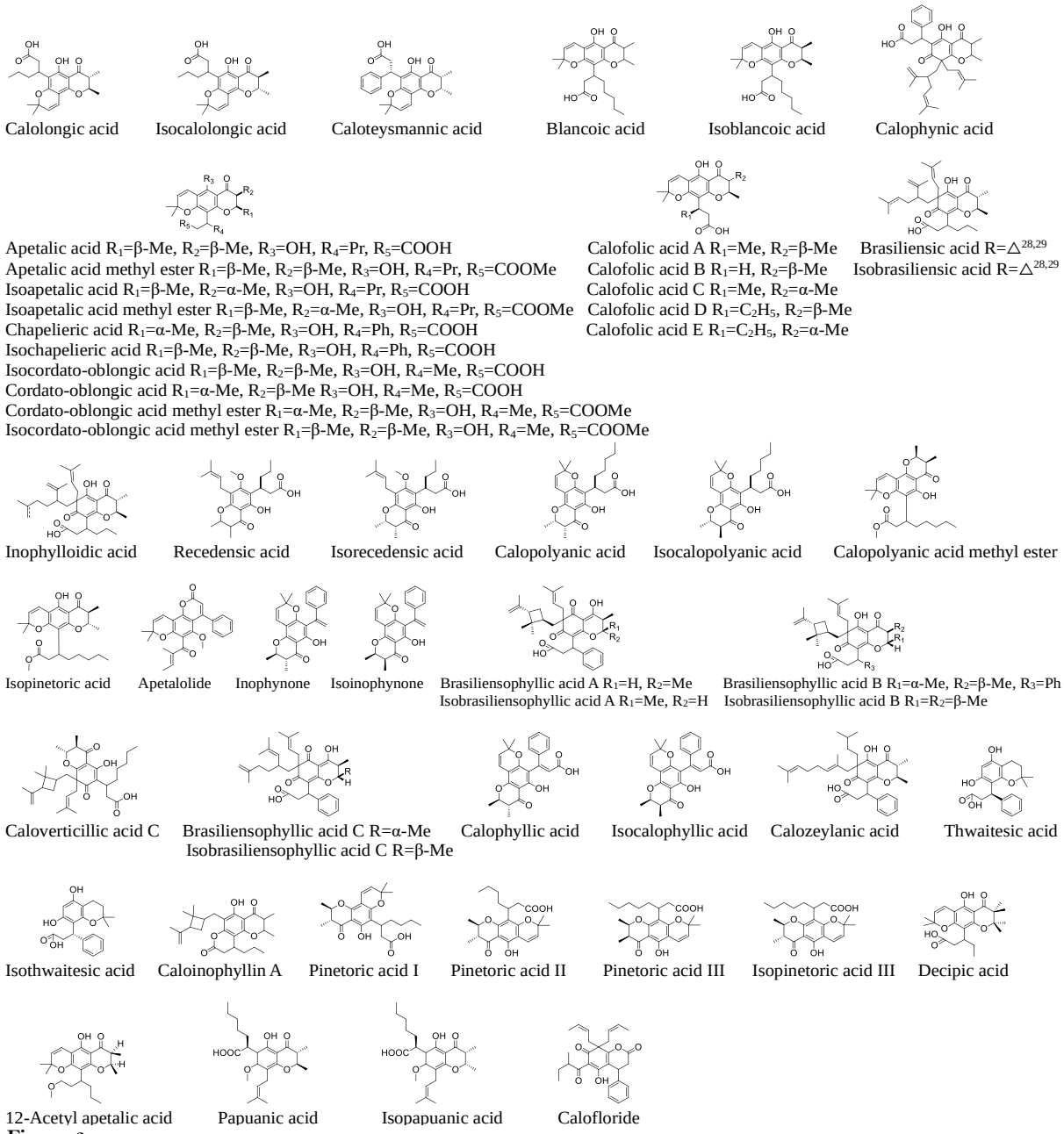

Figure 2.
Chemical structures of isolated chromanones from *Calophyllum* species

One such trend is the high accumulation of chromanones in Southeast Asia, especially in Malaysia, where several species, including *C. havilandii*, *C. teysmannii*, and partially *C. lanigerum* and *C. inophyllum*, are well-documented for their wealth of chromanones. This shows the significance of finding potential medicinal compounds from *Calophyllum* species as part of the tropical ecosystem. For example, chromanones such as calolongic acid, isocalolongic acid, and caloteysmannic acid are isolated from the stem bark of *C. havilandii* and *C. teysmannii*, indicating the medicinal importance of these species [40, 67]. These molecules are frequently associated with the traditional use of the plant species as a remedy for many ailments, including inflammation, infections, or even cancer. In addition to Southeast Asia,

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 10, No. 4: 473-491, 2026
DOI: 10.55214/2576-8484.v10i4.12701

chromanones have also been isolated from *Calophyllum* species in other tropical regions. In Brazil, species like *C. brasiliense* produced compounds such as brasiliensophyllic acid and its isomers, demonstrating the global distribution of chromanones [53]. This widespread dispersion of bioactive compounds over several geographic regions emphasizes how *Calophyllum* species may be able to adapt to environmental stressors and produce distinct classes of secondary metabolites. The plants most likely to withstand environmental stressors or illnesses, such as microbial and herbivore infections, are thought to synthesize those compounds.

The distribution of chromanones has been further extended in China with the isolation of apetalic acid, isoapetalic acid, and calopolyanic acid from species including *C. polyanthum* and *C. membranaceum* [47, 55]. The variety of chromanones found in the pericarps and stems of *Calophyllum* species in China indicates the region's potential for discovering additional bioactive substances with therapeutic potential. The fact that chromanones were isolated from this area also raises the possibility that these compounds may be used in traditional Chinese medicine, which has long utilized plant-derived substances for their medicinal properties, particularly in the treatment of cancer and other chronic diseases [55]. The chemical diversity and broad distribution of chromanones from *Calophyllum* species hint at a pharmacological future. From the data, these compounds, which are isolated in a wide range of geographical regions and plant species, may offer significant medicinal capacity. Their presence in regions as diverse as Southeast Asia, South America, and China highlights the importance of these plants as sources of natural products for drug discovery. Ongoing research into the bioactivity of these chromanones, combined with their global distribution, can provide a valuable basis for further studies aimed at developing new therapies for diseases like cancer and other significant illnesses.

3.3. Biological Activity

The chromanones from *Calophyllum* species have demonstrated significant biological activities, highlighting their potential for diverse therapeutic applications, particularly in the treatment of cancer, infections, and inflammation. Chromanones exhibiting various pharmacological activities are summarized in Table 2. For instance, calolongic acid and isocalolongic acid showed significant antioxidant activity; the inhibition was against HeLa cancer cell proliferation with IC_{50} values of 10.0 μM for calolongic acid and 7.8 μM for isocalolongic acid, respectively [40]. These findings suggest that chromanones, being a type of flavonoid, might have a significant effect on diseases related to oxidative stress, donate electrons to neutralize free radicals, and prevent cell damage. The antioxidative and anticancer properties suggest these compounds could be potential therapeutic agents against oxidative-stress-related diseases [68, 69]. Caloteysmannic acid and calophynic acid both display potent anticancer properties on HeLa cells, besides possessing antioxidant activities. The IC_{50} value of caloteysmannic acid was 7.3 μM, indicating its potential as a therapeutic agent for cervical cancer [40]. Additionally, other compounds like isoblancoic acid showed remarkable anti-cancer activity against nasopharyngeal cancer cell lines, including SUNE1, TW01, CNE1, and HK1, with IC_{50} values ranging from 15.19 to 25.86 μM [45]. This implies that chromanones might exert potential anti-proliferative and apoptosis-inducing effects not only on HeLa cells but also on other distinct types of cancer. The ability of chromanones to target diverse cancer cell lines expands their potential application in treating a range of cancers beyond cervical cancer. Furthermore, other compounds such as apetalic acid and isoapetalic acid have antimicrobial effects, which could strengthen their therapeutic value. These showed significant antibacterial activities against *Staphylococcus aureus* and *Bacillus subtilis* with MIC values of 31.25 μg/mL [70]. Given the challenges in treatments available due to multidrug resistance in pathogens, these compounds might be a novel and promising class of antimicrobial agents. Moreover, these two compounds showed cytotoxicity against the MCF-7 and A-549 tumor cell lines with IC_{50} values of 3.79 μM for apetalic acid and 26.64 μM for isoapetalic acid, respectively [70]. In this respect, the chromanones exhibit dual bioactivity, antibacterial and anticancer, further underscoring the wide range of applicability of these classes for cancer targeting and other infections. Aside from their anticancer and

antimicrobial properties, chromanones such as calofolic acid A, B, and C showed vasorelaxant activity with IC_{50} values of 6.0 to 18.9 μM, which can be considered as a treatment option in cardiovascular cases, specifically hypertension, since they relax blood vessels [51]. Together, vasorelaxant effects further extend the therapeutic potential of chromanones beyond cancer and infectious diseases.

Therefore, the chromanones from *the Calophyllum* genus exhibit a wide range of biological activities such as antioxidant, anticancer, antimicrobial, and vasorelaxant effects. They could be particularly relevant for drug development, as these compounds seem capable of enhancing cancer therapies, antimicrobial treatments, and improving cardiovascular health. In addition to eliciting a significant cytotoxic response against HeLa cells, the potent activity of chromanones is highly relevant for their application in cancer research, as it reveals how chromanones could modulate the hallmarks of cancer by providing invaluable information on their ability to target critical pathways and control cancer cell proliferation. With ongoing research, these phytochemicals could be developed into novel therapeutic agents addressing various health issues, from cancer to infectious diseases and cardiovascular disorders.

Table 2.
Biological activities of chromanones from *Calophyllum* phytochemicals.

Compounds	**Biological activities**
Calolongic acid	Antioxidant: Displayed potent activity against HeLa cancer cell line with IC_{50} value 10.0 μM [40]
	Antifungal: Exerts strong activity against *Aspergillus fumigatus* with MIC_{80} values 4 μg/mL [67]
Isocalolongic acid	Antioxidant: Displayed potent activity against HeLa cancer cell line with IC_{50} value 7.8 ± 0.2 μM [40]
	Antifungal: Exerts strong activity against *Aspergillus fumigatus* with showing MIC_{80} values of 2 μg/mL [67]
	Cytotoxic: Showed significant activity against MDA-MB-231 and MG-63 cell lines with IC_{50} value 57.88 and 53.04 μM respectively [42]
Caloteysmannic acid	Antioxidant: Displayed potent activity against HeLa cancer cell line with IC_{50} value 7.3 μM [40]
	Anticancer: Exhibited potent activity against HeLa cancer cells IC_{50} value 7.3 μM [40]
Isoblancoic acid	Cytotoxicity: Exerted the activity against nasopharyngeal cancer cell lines SUNE1, TW01, CNE1, HK1 with IC_{50} values ranging from 15.19 to 25.86 μM [45]
Calophynic acid	Cytotoxicity: Displays potent activity against human epidermoid carcinoma of the nasopharynx cell (KB) with IC_{50} value 10.5 μM [54]
Apetalic acid	Antibacterial: Exhibit potent activity against *S. aureus* and *B. subtilis* with MIC value 31.25 μg/mL [70]
	Cytotoxic: Exhibit significant activity towards MCF-7 and A-549 cell line with IC_{50} value 3.79 μM [70]
	Antioxidant: Displayed an appreciable activity in DPPH free radical assays with inhibition of 22.64% [64]
Isoapetalic acid	Antibacterial: Exhibit potent activity against *S. aureus* and *B. subtilis* with MIC value 31.25 μg/mL [70]
	Cytotoxic: Exhibits significant cytotoxic activities towards MCF-7 and A-549 cancer cell lines with IC_{50} value of 26.64 μM [70]
Isocordato-oblongic acid	Antimicrobial: Significant activity against *B. subtilis* with a MIC value 62.5 μg/mL, while when against *S. aureus* it showed a MIC value of 125 μg/mL [71]
Calofolic acid A	Vasorelaxant: Potent activity on isolated rat aorta with phenylephrine the IC_{50} value 6.07 μM [51]
Calofolic acid B	Vasorelaxant: Showed potent activity on isolated rat aorta with phenylephrine the IC_{50} value 10.3 μM [51]
	Cytotoxic: Showed an active activity against P-388 cells, with IC_{50} value of 1.14 μg/mL [52]
Calofolic acid C	Vasorelaxant: Showed potent activity on isolated rat aorta with phenylephrine the IC_{50} value 10.4 μM [51]
Calofolic acid D	Vasorelaxant: Showed significant activity on isolated rat aorta with phenylephrine the IC_{50} value 18.9 μM [51]

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 10, No. 4: 473-491, 2026
DOI: 10.55214/2576-8484.v10i4.12701

Calofolic acid E	Vasorelaxant: Showed high activity on isolated rat aorta with phenylephrine the IC_{50} value 13.8 µM [51]
Brasiliensic acid	Antibacterial: Potent activity against *Helicobacter pylori* with MIC value 50 µg/mL [53]
	Cytotoxicity: Potent activity against human epidermoid carcinoma of the nasopharynx cell (KB) with IC_{50} value 11.0 µM [54]
	Antibacterial: Showed significant activity against *Helicobacter pylori* with MIC value 50 µg/mL [53]
Isobrasiliensic acid	Antibacterial: Displays potent activity against *Helicobacter pylori* with MIC value 12.5 µg/mL [53]
Inophylloidic acid	Cytotoxicity: Potent activity against human epidermoid carcinoma of the nasopharynx cell (KB) with IC_{50} value 9.7 µM [54]
	Antimicrobial: Shows potent against *S. aureus* with IC_{50} value 9.0 µM [54]
Calophyllic acid	Antioxidant: Showed significant activity in hyperlipidemia model at 200 g/mL concentration with -24 to -30% [60]
Isocalophyllic acid	Antioxidant: Showed significant activity in hyperlipidemia model at 200 g/mL concentration with -18 to -19% [60]

3.4. Molecular Docking Studies

The chromanones were further analyzed to predict their binding affinity and interaction profile against two target proteins using molecular docking analysis. The ability of each ligand to occupy the ATP-binding cleft was evaluated with AutoDock Vina, integrated into PyRx, using the positive control as the reference standard. Binding affinities in kcal/mol were predicted for the lowest energy conformations. Table 3 presents the docking scores for each tested ligand, while the interaction profiles between the ligands and active site residues are shown in Figures 3 and 4.

Table 3.
Ligand binding energies (LBE) in kcal/mol of xanthone derivatives against 8A27 and 6NUQ.

Compound	**8A27**	**6NUQ**
EAI045	-8.1	-
STAT3 Inhibitor VII	-	-6.3
Calolongic acid	-7.0	-6.2
Isocalolongic acid	-6.6	-5.9
Caloteysmannic acid	-8.6	-6.7
Blancoi acid	-7.4	-6.3
Isoblancoi acid	-7.4	-6.2
Calophynic acid	-7.0	-6.2
Apetalic acid	-7.0	-5.7
Apetalic acid methyl ester	-7.1	-6.1
Isoapetalic acid	-6.7	-5.9
Isoapetalic acid methyl ester	-7.2	-6.0
Chapelieric acid	-7.8	-6.4
Isochapelieric acid	-8.1	-6.4
Isocordato-oblongic acid	-6.9	-5.9
Cordato-oblongic acid	-7.2	-6.2
Cordato-oblongic acid methyl ester	-7.5	-5.9
Isocordato-oblongic acid methyl ester	-6.7	-6.2
Calofolic acid A	-7.3	-6.2
Calofolic acid B	-7.6	-6.1
Calofolic acid C	-7.3	-6.2
Calofolic acid D	-7.7	-6.3
Calofolic acid E	-7.7	-6.4
Brasiliensic acid	-7.4	-5.3
Isobrasiliensic acid	-7.1	-5.8
Inophylloidic acid	-6.4	-5.7
Recedensic acid	-6.4	-5.6
Isorecedensic acid	-6.4	-5.7

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 10, No. 4: 473-491, 2026
DOI: 10.55214/2576-8484.v10i4.12701

Calopolyanic acid	-7.4	-5.8
Isocalopolyanic acid	-7.2	-6.5
Calopolyanic acid methyl ester	-7.3	-5.8
Isopinetoric acid methyl ester	-6.4	-5.6
Apetalolide	-7.1	-7.0
Inophynone	-8.9	-6.9
Isoinophynone	-8.9	-7.0
Brasiliensophyllic acid A	-7.8	-5.9
Isobrasiliensophyllic acid A	-7.5	-6.2
Brasiliensophyllic acid B	-7.0	-6.1
Isobrasiliensophyllic acid B	-6.7	-5.1
Caloverticillic acid C	-7.3	-6.4
Brasiliensophyllic acid C	-7.0	-5.8
Isobrasiliensophyllic acid C	-7.7	-5.5
Calophyllic acid	-7.7	-6.4
Isocalophyllic acid	-7.7	-6.5
Calozeylanic acid	-8.4	-6.7
Thwaitesic acid	-7.3	-5.6
Isothwaitesic acid	-7.3	-5.7
Caloinophyllin A	-9.0	-6.9
Pinetoric acid I	-7.8	-5.8
Pinetoric acid II	-7.0	-6.0
Pinetoric acid III	-6.6	-5.8
Isopinetoric acid III	-6.5	-5.9
Decipic acid	-7.4	-6.3
12-Acetyl apetalic acid	-7.2	-5.5
Papuanic acid	-6.3	-5.6
Isopapuanic acid	-5.9	-5.4
Calofloride	-6.6	-5.8

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 10, No. 4: 473-491, 2026
***DOI:** 10.55214/2576-8484.v10i4.12701*

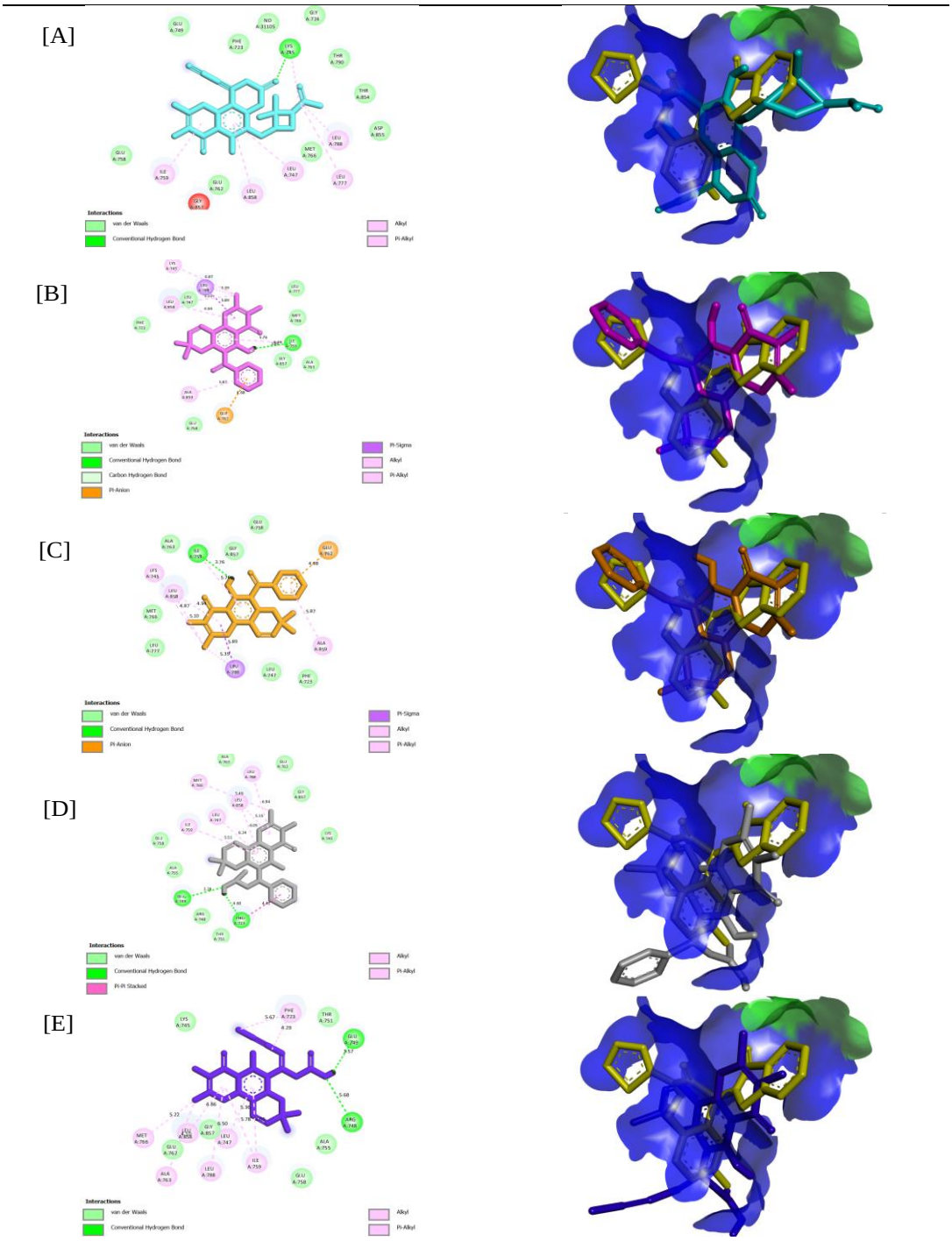

Figure 3.
2D and 3D conformation view of Caloinophyllin A [A], Inophynone [B], Isoinophynone [C], Calotesymannic acid [D] and Pinoteric acid I [E] superimposed with control onto the 8A27-EGFR complex.

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 10, No. 4: 473-491, 2026
DOI: 10.55214/2576-8484.v10i4.12701

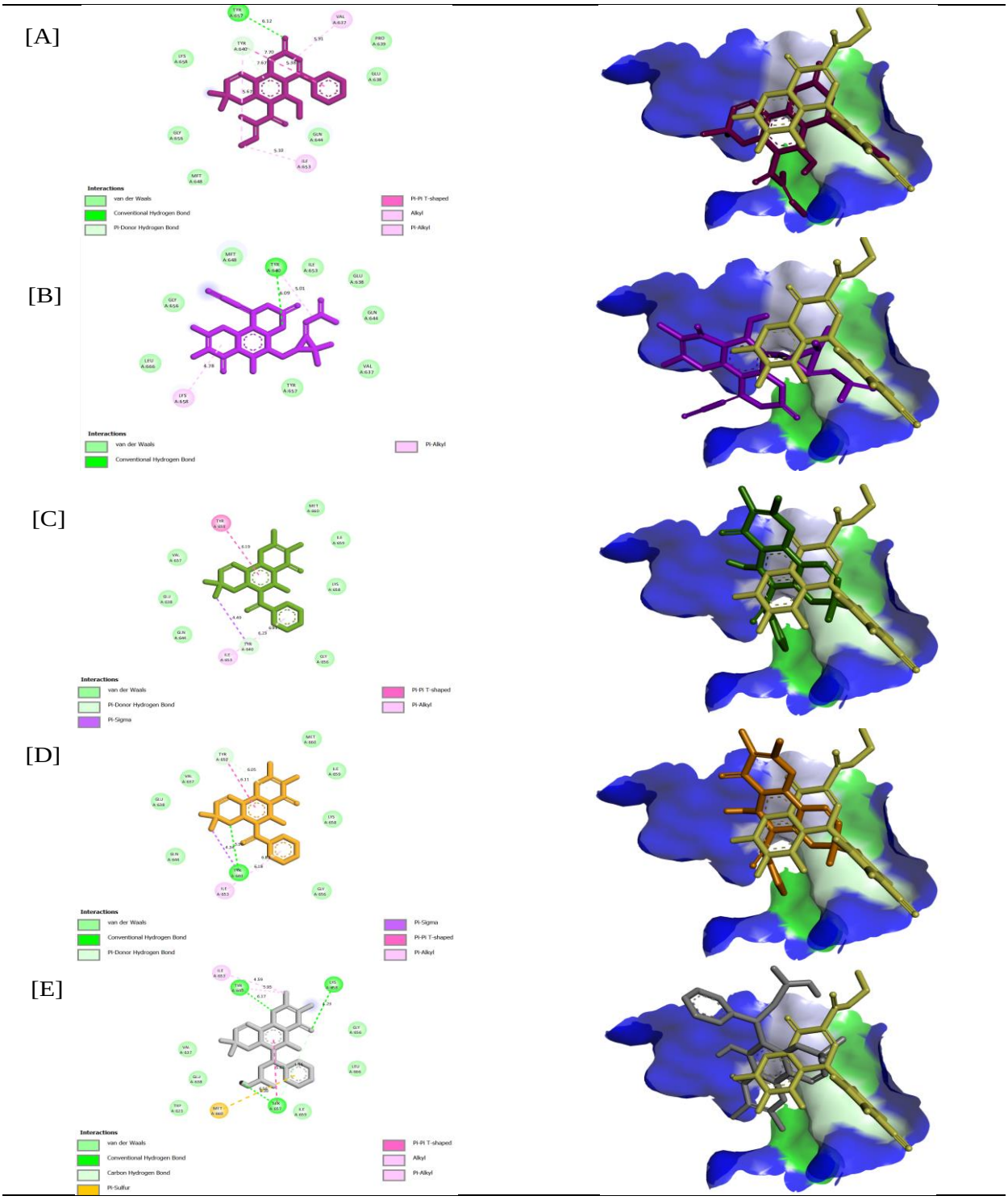

Figure 4.
2D and 3D conformation view of Apetalolide [A], Caloinophyllin A [B], Inophynone [C], Isoinophynone [D] and Calotesymannic acid [E] superimposed with control unto the 6NUQ-STAT3 complex

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 10, No. 4: 473-491, 2026
DOI: 10.55214/2576-8484.v10i4.12701

For 8A27, the inhibitory molecule EAI045 (-8.1 kcal/mol) showed the anticipated binding profile, as its aromatic rings were stabilized through π-alkyl and π-sigma interactions with Met766, Leu777, Leu747, and Leu858, while the terminal hydroxyl group formed a conventional hydrogen bond with residue Gly857 (2.62 Å). Among the chromanones, caloinophyllin A (-9.0 kcal/mol) surpassed the control through extensive hydrophobic anchoring of its three rings: the A-ring engaged Leu858 (π-alkyl, 4.59 Å) and Leu747 (π-alkyl, 5.43 Å), the B-ring made contact with Ile759 (π-alkyl, 4.80 Å), and the methyl group at C-3 formed alkyl contacts with Leu777 (5.59 Å) and Leu788 (4.18 Å). The C=O group contributed to a conventional hydrogen bond with Lys745 (4.02 Å), supported by widespread van der Waals interactions across the binding surface.

Both inophynone and isoinophynone exhibited strong binding to EGFR (-8.9 kcal/mol), stabilized through a network of hydrophobic, aromatic, and polar interactions. Both ligands of the B-ring were observed, anchoring via π-alkyl contact with Ala859 and π-anion interaction with Glu762. Additionally, Ile759 provides dual stabilization through π-alkyl contacts and conventional hydrogen bonding to the hydroxyl group. The C-3 methyl substituent was further secured by alkyl interactions with Leu788, Leu858, and Lys745, while the A-ring contributed additional π-sigma contacts to Leu788. An extensive van der Waals force reinforced the complex formation, explaining their nearly identical docking energies and strong affinity.

Calotesymannic acid (-8.6 kcal/mol) achieved dual stabilization through conventional hydrogen bonds with the hydroxyl group to Glu749 (3.28 Å) and Phe723 (4.42 Å), which was also complemented by π-π stacking of the B-ring to Phe723. Extensive π-alkyl contacts involving Leu747, Leu788, Leu858, and Ile759 within the range of 5.15 Å - 6.94 Å, thus explaining its near-control binding energy. Pinetoric acid I (-8.1 kcal/mol) matched the control energy, driven strongly by conventional hydrogen bonding to Glu749 and Arg748, while the aromatic rings were anchored from Leu747, Ile759, Leu788, Leu858, and Gly857. While at position C-3 methyl of the ligands, there are interactions with residues Ala763 (4.10 Å) and Met766 (5.22 Å). Considering these data, it is evident that bulky chromanones, especially those discussed above, form highly beneficial hydrophobic and polar interactions within the EGFR allosteric pocket.

For 6NUQ, the reference ligand, STAT3 Inhibitor VII had a binding energy of -6.3 kcal/mol, stabilized through numerous interactions. Halogen bonding was established between the terminal fluorophenyl ring and residues Gln644 (5.68 Å), Pro639 (5.23 Å), and Glu638 (4.49 - 4.92 Å) within the binding pocket. Additionally, the central phenyl ring engaged in π-π T-shaped stacking with Tyr640 (6.16 Å) and Glu638 (4.26 Å). Further stabilization was provided by the carbonyl moiety with Tyr657 at distances of 4.65 Å, forming conventional hydrogen bonds. Besides, the cooperative binding was also provided by an alkyl contact through Trp623 and Val637, as well as van der Waals forces. Apetalolide (-7.0 kcal/mol) achieved a stronger affinity by forming a triad of interactions with Tyr640 (π–π stacking, π-donor hydrogen bond, and alkyl contact), reinforced by a carbonyl hydrogen bond with Tyr657, thus explaining its superior docking score. These interactions were stabilized by van der Waals forces.

While screening a variety of potential tested chromanone derivatives, it displayed superior attraction compared to the control. Caloinophyllin A (-6.9 kcal/mol) stabilized through alkyl interactions between residues Lys658 (4.78 Å) and Tyr640 (5.01 Å), along with a conventional hydrogen bond within the carbonyl at C-4 to Tyr640. Inophynone and Isoinophynone (6.9 and -7.0 kcal/mol) shared a highly similar binding pattern within the STAT3 SH2 pocket, anchored primarily by π-π T-shaped (Tyr657), π-alkyl (Ile653), and π-donor hydrogen bonds (Tyr640) within the chromanone aromatic system. In both ligands, the interaction involves the A-ring methyl group within π-sigma and Tyr640. Additionally, in isoinophynone, there is an extra interaction of Tyr650 at a distance of 5.96 Å through a conventional hydrogen bond. These overlapping interactions, Tyr-mediated aromatic stacking, methyl anchoring, and hydrogen bonding, account for their nearly identical docking scores, with Isoinophynone achieving a marginally stronger affinity due to the more optimal geometry of its Tyr640 interactions.

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 10, No. 4: 473-491, 2026
DOI: 10.55214/2576-8484.v10i4.12701

Calotesymannic acid (-6.7 kcal/mol) formed various connections with the STAT3 pocket to bind it tightly. Tyr657 had π-π stacking and a conventional hydrogen bond within the aromatic ring and the methyl group, respectively. The C-3 of the methyl group created two hydrophobic contacts with Ile653 (4.59 Å) through alkyl interaction and with Tyr640 (5.95 Å) through π-alkyl contact. Meanwhile, Met660 established a π-sulfur interaction with the chromanone benzene ring (6.56 Å).

The chromanone derivatives exhibited potent dual-targeting activity against both EGFR and STAT3, with several ligands outperforming standard inhibitors. Among the tested compounds, Caloinophyllin A, Inophynone, and Isoinophynone interacted most strongly with EGFR, while Isoinophynone and Apetalolide bound most tightly to STAT3. The crucial anchoring residues Leu858 in EGFR and the tyrosine residues Tyr657 and Tyr640 in STAT3 consistently facilitated binding, highlighting the important roles of aromatic stacking, hydrogen bonding interactions, and hydrophobic contacts. These results position chromanones as promising frameworks for developing multi-targeted therapeutics against these activities.

4. Conclusions and Prospects

This review consolidates current knowledge on *Calophyllum*-derived chromanones and highlights their strong potential as dual-target inhibitors of EGFR and STAT3, two key oncogenic drivers in cervical cancer progression. The phytochemical evidence, combined with reported biological activities and molecular docking outcomes, clearly indicates that chromanones possess a privileged structural scaffold capable of forming stable and meaningful interactions within the EGFR allosteric site and the STAT3 SH2 domain. Several compounds, particularly caloinophyllin A, inophynone, isoinophynone, and apetalolide, demonstrated binding affinities comparable to or exceeding those of standard inhibitors, supporting their candidacy as promising lead molecules for multitarget anticancer drug development. The dual-inhibition strategy is of particular significance, as EGFR and STAT3 signaling pathways are functionally interconnected and jointly contribute to tumor growth, survival, and resistance to therapy. Targeting both pathways simultaneously offers a more comprehensive and potentially more effective therapeutic approach than single-target inhibition. The recurrent involvement of critical residues such as Leu858 in EGFR and Tyr640 and Tyr657 in STAT3 also provides valuable structural insight that can guide rational drug design and structure–activity relationship (SAR) optimization of chromanone derivatives.

Beyond their anticancer potential, chromanones exhibit a broad pharmacological spectrum, including antioxidant, antimicrobial, and vasorelaxant activities, further emphasizing their versatility as medicinal scaffolds. Their widespread distribution across *Calophyllum* species and strong correlation with traditional medicinal uses reinforce the ethnopharmacological relevance of this genus and validate its importance as a reservoir of bioactive natural products. From a prospective standpoint, although molecular docking provides compelling theoretical support, experimental validation remains essential. Future studies should prioritize in vitro enzyme inhibition assays, cell-based evaluations in HeLa and other cervical cancer models, and in vivo investigations to confirm efficacy and safety. Additionally, pharmacokinetic profiling, toxicity assessment, and chemical modification aimed at improving selectivity, solubility, and metabolic stability are critical steps toward clinical translation. The integration of molecular dynamics simulations, ADMET prediction, and medicinal chemistry optimization would further strengthen the development pipeline. In conclusion, *Calophyllum*-derived chromanones represent a scientifically robust and forward-looking platform for discovering novel dual-acting anticancer agents. Their ability to modulate EGFR and STAT3 pathways simultaneously positions them as highly attractive candidates for targeted cervical cancer therapy, bridging traditional natural product research with modern computational and molecular drug discovery strategies.

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 10, No. 4: 473-491, 2026
DOI: 10.55214/2576-8484.v10i4.12701

Transparency:

The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

Acknowledgements:

This research was supported by the Geran Penyelidikan Universiti (Kecemerlangan@UPSI) under grant number 2025-0012-103-01, funded by Universiti Pendidikan Sultan Idris. The author would like to thank the Department of Chemistry, Faculty of Science and Mathematics, Sultan Idris Education University, for research facilities.

References

[1] P. F. Stevens, "A revision of the old world species of *Calophyllum* (Guttiferae)," *Journal of the Arnold Arboretum*, vol. 61, no. 2, pp. 117-424, 1980.

[2] J. Gómez-Verjan, K. Rodríguez-Hernández, and R. Reyes-Chilpa, "Bioactive coumarins and xanthones from *Calophyllum* genus and analysis of their druglikeness and toxicological properties," *Studies in Natural Products Chemistry*, vol. 53, pp. 277-307, 2017. https://doi.org/10.1016/B978-0-444-63930-1.00008-9

[3] V. Cechinel Filho, C. Meyre-Silva, and R. Niero, "Chemical and pharmacological aspects of the genus *Calophyllum*," *Chemistry & Biodiversity*, vol. 6, no. 3, pp. 313-327, 2009. https://doi.org/10.1002/cbdv.200800082

[4] D. N. A. A. Heilman *et al.*, "Unlocking the antibacterial potential of xanthone from *Calophyllum* species: Inhibition of nucleic acid synthesis," *ChemistrySelect*, vol. 8, no. 46, p. e202302737, 2023. https://doi.org/10.1002/slct.202302737

[5] A. Gaspar, E. M. P. Garrido, F. Borges, and J. M. Garrido, "Biological and medicinal properties of natural chromones and chromanones," *ACS Omega*, vol. 9, no. 20, pp. 21706-21726, 2024. https://doi.org/10.1021/acsomega.4c00771

[6] X. H. Su, M. L. Zhang, L. G. Li, C. H. Huo, Y. C. Gu, and Q. W. Shi, "Chemical constituents of the plants of the genus *Calophyllum*," *Chemistry & Biodiversity*, vol. 5, no. 12, pp. 2579-2608, 2008. https://doi.org/10.1002/cbdv.200890215

[7] F. Cottiglia, B. Dhanapal, O. Sticher, and J. Heilmann, "New chromanone acids with antibacterial activity from *Calophyllum brasiliense*," *Journal of Natural Products*, vol. 67, no. 4, pp. 537-541, 2004. https://doi.org/10.1021/np030438n

[8] E. R. Allanson, S. N. Zafar, C. P. Anakwenze, K. M. Schmeler, E. L. Trimble, and S. Grover, "The global burden of cervical cancer requiring surgery: Database estimates," *Infectious Agents and Cancer*, vol. 19, no. 1, p. 5, 2024. https://doi.org/10.1186/s13027-023-00562-3

[9] S. Pimple and G. Mishra, "Cancer cervix: Epidemiology and disease burden," *Cytojournal*, vol. 19, p. 21, 2022. https://doi.org/10.25259/CMAS_03_02_2021

[10] U. Sarı, F. Zaman, İ. Özdemir, Ş. Öztürk, and M. C. Tuncer, "Gallic acid induces heLa cell lines apoptosis via the P53/Bax signaling pathway," *Biomedicines*, vol. 12, no. 11, p. 2632, 2024. https://doi.org/10.3390/biomedicines12112632

[11] C. A. Burmeister *et al.*, "Cervical cancer therapies: Current challenges and future perspectives," *Tumour Virus Research*, vol. 13, p. 200238, 2022. https://doi.org/10.1016/j.tvr.2022.200238

[12] L. Liu, M. Wang, X. Li, S. Yin, and B. Wang, "An overview of novel agents for cervical cancer treatment by inducing apoptosis: Emerging drugs ongoing clinical trials and preclinical studies," *Frontiers in Medicine*, vol. 8, p. 682366, 2021. https://doi.org/10.3389/fmed.2021.682366

[13] N. N. M. Zaini, W. M. N. H. W. Salleh, A. S. Salihu, and B. Sungthong, "Unlocking the potential of *Calophyllum* xanthones: A review on antileukemic activity and molecular docking insights," *Journal of Science and Mathematics Letters*, vol. 13, no. 1, pp. 168-186, 2025.

[14] R. Chinthu, B. P. Kumar, and M. Raveendran, "A review on the genus *Calophyllum* (Clusiaceae): A potential medicinal tree species," *Plant Science Today*, vol. 10, no. 3, pp. 1-5, 2023.

[15] J. Zhu, Z. Wu, G. Shan, Y. Huang, J. Liang, and C. Zhan, "Nuclear epidermal growth factor receptor (nEGFR) in clinical treatment," *Heliyon*, vol. 10, no. 21, p. e40150, 2024. https://doi.org/10.1016/j.heliyon.2024.e40150

[16] P. Wee and Z. Wang, "Epidermal growth factor receptor cell proliferation signaling pathways," *Cancers*, vol. 9, no. 5, p. 52, 2017. https://doi.org/10.3390/cancers9050052

[17] C. Edmonds, S. Hagan, S. M. Gallagher-Colombo, T. M. Busch, and K. A. Cengel, "Photodynamic therapy activated signaling from epidermal growth factor receptor and STAT3: Targeting survival pathways to increase PDT efficacy

in ovarian and lung cancer," *Cancer Biology & Therapy*, vol. 13, no. 14, pp. 1463-1470, 2012. https://doi.org/10.4161/cbt.22256

[18] J. V. Alvarez, H. Greulich, W. R. Sellers, M. Meyerson, and D. A. Frank, "Signal transducer and activator of transcription 3 is required for the oncogenic effects of non–small-cell lung cancer–associated mutations of the epidermal growth factor receptor," *Cancer Research*, vol. 66, no. 6, pp. 3162-3168, 2006. https://doi.org/10.1158/0008-5472.CAN-05-3757

[19] S. Aznar, P. F. Valeron, S. V. del Rincon, L. F. Pérez, R. Perona, and J. C. Lacal, "Simultaneous tyrosine and serine phosphorylation of STAT3 transcription factor is involved in Rho A GTPase oncogenic transformation," *Molecular Biology of the Cell*, vol. 12, no. 10, pp. 3282-3294, 2001. https://doi.org/10.1091/mbc.12.10.3282

[20] G. Huang, H. Yan, S. Ye, C. Tong, and Q. L. Ying, "STAT3 phosphorylation at tyrosine 705 and serine 727 differentially regulates mouse ESC fates," *Stem Cells*, vol. 32, no. 5, pp. 1149-1160, 2014. https://doi.org/10.1002/stem.1609

[21] A. Xiong, Z. Yang, Y. Shen, J. Zhou, and Q. Shen, "Transcription factor STAT3 as a novel molecular target for cancer prevention," *Cancers*, vol. 6, no. 2, pp. 926-957, 2014. https://doi.org/10.3390/cancers6020926

[22] P. C. Agu *et al.*, "Molecular docking as a tool for the discovery of molecular targets of nutraceuticals in diseases management," *Scientific Reports*, vol. 13, no. 1, p. 13398, 2023. https://doi.org/10.1038/s41598-023-40160-2

[23] L. Pinzi and G. Rastelli, "Molecular docking: shifting paradigms in drug discovery," *International Journal of Molecular Sciences*, vol. 20, no. 18, p. 4331, 2019. https://doi.org/10.3390/ijms20184331

[24] T.-R. Min, H.-J. Park, K.-T. Ha, G.-Y. Chi, Y.-H. Choi, and S.-H. Park, "Suppression of EGFR/STAT3 activity by lupeol contributes to the induction of the apoptosis of human non-small cell lung cancer cells," *International Journal of Oncology*, vol. 55, no. 1, pp. 320-330, 2019. https://doi.org/10.3892/ijo.2019.4799

[25] N. M. Jackson and B. P. Ceresa, "EGFR-mediated apoptosis via STAT3," *Experimental Cell Research*, vol. 356, no. 1, pp. 93-103, 2017. https://doi.org/10.1016/j.yexcr.2017.04.016

[26] N. N. M. Zaini *et al.*, "Chemical constituents from *Lindera subumbelliflora*," *Chemistry of Natural Compounds*, vol. 60, no. 5, pp. 940-941, 2024. https://doi.org/10.1007/s10600-024-04485-2

[27] E. F. Pettersen *et al.*, "UCSF Chimera-a visualization system for exploratory research and analysis," *Journal of Computational Chemistry*, vol. 25, no. 13, pp. 1605-1612, 2004. https://doi.org/10.1002/jcc.20084

[28] Y. Jia *et al.*, "Overcoming EGFR (T790M) and EGFR (C797S) resistance with mutant-selective allosteric inhibitors," *Nature*, vol. 534, no. 7605, pp. 129-132, 2016. https://doi.org/10.1038/nature17960

[29] K. Siddiquee *et al.*, "Selective chemical probe inhibitor of Stat3, identified through structure-based virtual screening, induces antitumor activity," *Proceedings of the National Academy of Sciences*, vol. 104, no. 18, pp. 7391-7396, 2007. https://doi.org/10.1073/pnas.0609757104

[30] S. S. Butt, Y. Badshah, M. Shabbir, and M. Rafiq, "Molecular docking using chimera and autodock vina software for nonbioinformaticians," *JMIR Bioinformatics and Biotechnology*, vol. 1, no. 1, p. e14232, 2020.

[31] S. Kamboj and R. Singh, "Chromanone-A prerogative therapeutic scaffold: An overview," *Arabian Journal for Science and Engineering*, vol. 47, no. 1, pp. 75-111, 2022. https://doi.org/10.1007/s13369-021-05858-3

[32] Y. Amen, M. Elsbaey, A. Othman, M. Sallam, and K. Shimizu, "Naturally occurring chromone glycosides: Sources, bioactivities, and spectroscopic features," *Molecules*, vol. 26, no. 24, p. 7646, 2021. https://doi.org/10.3390/molecules26247646

[33] Y.-d. Duan *et al.*, "The antitumor activity of naturally occurring chromones: A review," *Fitoterapia*, vol. 135, pp. 114-129, 2019. https://doi.org/10.1016/j.fitote.2019.04.012

[34] Shanmugapriya, Y. Chen, S. L. Jothy, and S. Sasidharan, "*Calophyllum inophyllum*: A medical plant with multiple curative values," *Research Journal of Pharmaceutical Biological and Chemical Sciences*, vol. 7, no. 4, pp. 1446-1452, 2016.

[35] L. Feng *et al.*, "Synthesis, structure-activity relationship studies, and antibacterial evaluation of 4-chromanones and chalcones, as well as olympicin A and derivatives," *Journal of Medicinal Chemistry*, vol. 57, no. 20, pp. 8398-8420, 2014. https://doi.org/10.1021/jm500853v

[36] M. Sobiesiak, N. Fatyga, A. Brzozowski, A. Sikora, B. Kupcewicz, and M. Maj, "Chromanone derivatives: Evaluating selective anticancer activity across human cell lines," *European Journal of Medicinal Chemistry*, vol. 295, p. 117771, 2025. https://doi.org/10.1016/j.ejmech.2025.117771

[37] U. Agarwal, S. Verma, and R. K. Tonk, "Chromenone: An emerging scaffold in anti-Alzheimer drug discovery," *Bioorganic & Medicinal Chemistry Letters*, vol. 111, p. 129912, 2024. https://doi.org/10.1016/j.bmcl.2024.129912

[38] M. Costa, T. A. Dias, A. Brito, and F. Proença, "Biological importance of structurally diversified chromenes," *European Journal of Medicinal Chemistry*, vol. 123, pp. 487-507, 2016. https://doi.org/10.1016/j.ejmech.2016.07.057

[39] A. A. D. Zailan *et al.*, "Phytochemicals from the stem bark of *Calophyllum havilandii* PF Stevens and their biological activities," *Chemistry & Biodiversity*, vol. 21, no. 3, p. e202301936, 2024. https://doi.org/10.1002/cbdv.202301936

[40] C. K. Lim, H. Subramaniam, Y. H. Say, V. Y. M. Jong, H. Khaledi, and C. F. Chee, "A new chromanone acid from the stem bark of *Calophyllum teysmannii*," *Natural Product Research*, vol. 29, no. 21, pp. 1970-1977, 2015. https://doi.org/10.1080/14786419.2015.1015020

[41] A. L. Piccinelli, A. O. Kabani, C. Lotti, A. B. Alarcon, O. Cuesta-Rubio, and L. Rastrelli, "A fast and efficient HPLC-PDA–MS method for detection and identification of pyranochromanone acids in *Calophyllum* species," *Journal of Pharmaceutical and Biomedical Analysis*, vol. 76, pp. 157-163, 2013. https://doi.org/10.1016/j.jpba.2012.12.028

[42] N. Mokhtar, T. Karunakaran, R. Santhanam, M. H. Abu Bakar, and V. Y. M. Jong, "Phenolics and triterpenoids from stem bark of *Calophyllum lanigerum* var. *austrocoriaceum* (Whitmore) PF Stevens and their cytotoxic activities," *Natural Product Research*, vol. 38, no. 5, pp. 873-878, 2024. https://doi.org/10.1080/14786419.2023.2196075

[43] E. Guerreiro, G. Kunesch, and J. Polonsky, "Chromanones de l'écorce de *Calophyllum recedens*," *Phytochemistry*, vol. 12, no. 1, pp. 185-189, 1973. https://doi.org/10.1016/S0031-9422(00)84644-0

[44] S. Y. Gan, "Chemical constituents from the endemic plant of Sarawak, *Calophyllum castaneum* and their antioxidant activity," Bachelor's Degree Thesis, Universiti Tunku Abdul Rahman, 2014.

[45] C. K. Lim *et al.*, "In vitro cytotoxic activity of isolated compounds from Malaysian *Calophyllum* species," *Medicinal Chemistry Research*, vol. 25, no. 8, pp. 1686-1694, 2016. https://doi.org/10.1007/s00044-016-1606-y

[46] M. B. Zakaria, Z. Ilham, and N. A. Muhamad, "Anti-inflammatory activity of *Calophyllum inophyllum* fruits extracts," *Procedia Chemistry*, vol. 13, pp. 218-220, 2014. https://doi.org/10.1016/j.proche.2014.12.031

[47] H. Wang *et al.*, "Chromanone derivatives from the pericarps of *Calophyllum polyanthum*," *Helvetica Chimica Acta*, vol. 93, no. 11, pp. 2183-2188, 2010. https://doi.org/10.1002/hlca.201000066

[48] Y.-C. Shen, L.-T. Wang, A. T. Khalil, and Y.-H. Kuo, "Chromanones and dihydrocoumarins from *Calophyllum blancoi*," *Chemical and Pharmaceutical Bulletin*, vol. 52, no. 4, pp. 402-405, 2004. https://doi.org/10.1248/cpb.52.402

[49] A. L. Gunatilaka, A. J. De Silva, S. Sotheeswaran, S. Balasubramaniam, and M. I. Wazeer, "Terpenoid and biflavonoid constituents of *Calophyllum calaba* and *Garcinia spicata* from Sri Lanka," *Phytochemistry*, vol. 23, no. 2, pp. 323-328, 1984. https://doi.org/10.1016/S0031-9422(00)80326-X

[50] H. R. W. Dharmaratne, D. S. C. Perera, G. P. Marasinghe, and J. Jamie, "A chromene acid from *Calophyllum cordato-oblongum*," *Phytochemistry*, vol. 51, no. 1, pp. 111-113, 1999. https://doi.org/10.1016/S0031-9422(98)00592-5

[51] A. E. Nugroho, T. Sasaki, T. Kaneda, A. H. A. Hadi, and H. Morita, "Calofolic acids A–F, chromanones from the bark of *Calophyllum scriblitifolium* with vasorelaxation activity," *Bioorganic & Medicinal Chemistry Letters*, vol. 27, no. 10, pp. 2124-2128, 2017. https://doi.org/10.1016/j.bmcl.2017.03.071

[52] U. Hasanah, T. S. Tjahjandarie, and M. Tanjung, "Chromanone acid derivatives from the stem bark of *Calophyllum incrassatum*," in *IOP Conference Series: Earth and Environmental Science (Vol. 217, No. 1, p. 012010). IOP Publishing*, 2019.

[53] L. M. Lemos, R. B. Oliveira, B. L. Sampaio, G. V. Cana-Ccapatinta, F. B. Da Costa, and D. T. Martins, "Brasiliensic and isobrasiliensic acids: Isolation from *Calophyllum brasiliense* Cambess. and anti-*Helicobacter pylori* activity," *Natural Product Research*, vol. 30, no. 23, pp. 2720-2725, 2016. https://doi.org/10.1080/14786419.2015.1137568

[54] M. C. Yimdjo, A. G. Azebaze, A. E. Nkengfack, A. M. Meyer, B. Bodo, and Z. T. Fomum, "Antimicrobial and cytotoxic agents from *Calophyllum inophyllum*," *Phytochemistry*, vol. 65, no. 20, pp. 2789-2795, 2004. https://doi.org/10.1016/j.phytochem.2004.08.024

[55] M. Ming *et al.*, "RXRα transcriptional inhibitors from the stems of *Calophyllum membranaceum*," *Fitoterapia*, vol. 108, pp. 66-72, 2016. https://doi.org/10.1016/j.fitote.2015.11.001

[56] J. Zou, J. Wu, S. Z. Liu, and W. M. Zhao, "New coumarins and triterpenes from *Calophyllum inophyllum*," *Helvetica Chimica Acta*, vol. 93, no. 9, pp. 1812-1821, 2010. https://doi.org/10.1002/hlca.200900469

[57] M. S. Ali, S. Mahmud, S. Perveen, V. U. Ahmad, and G. H. Rizwani, "Epimers from the leaves of *Calophyllum inophyllum*," *Phytochemistry*, vol. 50, no. 8, pp. 1385-1389, 1999. https://doi.org/10.1016/S0031-9422(98)00480-4

[58] B. Ravelonjato, N. Kunesch, and J. E. Poisson, "Neoflavonoids from the stem bark of *Calophyllum verticillatum*," *Phytochemistry*, vol. 26, no. 11, pp. 2973-2976, 1987. https://doi.org/10.1016/S0031-9422(00)84574-4

[59] A. B. Alarcón, O. Cuesta-Rubio, J. C. Pérez, A. L. Piccinelli, and L. Rastrelli, "Constituents of the Cuban endemic species *Calophyllum pinetorum*," *Journal of Natural Products*, vol. 71, no. 7, pp. 1283-1286, 2008. https://doi.org/10.1021/np800079c

[60] J. Prasad, A. Shrivastava, A. Khanna, G. Bhatia, S. Awasthi, and T. Narender, "Antidyslipidemic and antioxidant activity of the constituents isolated from the leaves of *Calophyllum inophyllum*," *Phytomedicine*, vol. 19, no. 14, pp. 1245-1249, 2012. https://doi.org/10.1016/j.phymed.2012.09.001

[61] H. Ranjith, W. Dharmaratne, S. Sotheeswaran, and S. Balasubramaniam, "Triterpenes and neoflavonoids of Calophyllum lankaensis and *Calophyllum thwaitesii*," *Phytochemistry*, vol. 23, no. 11, pp. 2601-2603, 1984. https://doi.org/10.1016/S0031-9422(00)84107-2

[62] S. Ponguschariyagul, J. Sichaem, S. Khumkratok, P. Siripong, K. Lugsanangarm, and S. Tip-Pyang, "Caloinophyllin A, a new chromanone derivative from *Calophyllum inophyllum* roots," *Natural product research*, vol. 32, no. 21, pp. 2535-2541, 2018. https://doi.org/10.1080/14786419.2018.1425845

[63] O. Cuesta-Rubio, A. Oubada, A. Bello, L. Maes, P. Cos, and L. Monzote, "Antimicrobial assessment of resins from Calophyllum antillanum and *Calophyllum inophyllum*," *Phytotherapy Research*, vol. 29, no. 12, pp. 1991-1994, 2015. https://doi.org/10.1002/ptr.5506

[64] M. Ajithabai, B. Rameshkumar, G. Jayakumar, R. Luxmi Varma, S. N. Mangalam, and P. N. Gayathri, "Decipic acid and 12-acetyl apetalic acid from *Calophyllum decipiens*. Wight," *CSIR-National Institute of Science Communication and Policy Research*, vol. 51, no. 2, pp. 393-397, 2012.

[65] G. H. Stout, G. K. Hickernell, and K. D. Sears, "*Calophyllum* products. IV. Papuanic and isopapuanic acids," *The Journal of Organic Chemistry*, vol. 33, no. 11, pp. 4191-4200, 1968. https://doi.org/10.1021/jo01275a039

[66] B. Ravelonjato, F. Libot, F. Ramiandrasoa, N. Kunesch, P. Gayral, and J. Poisson, "Molluscicidal constituents of *Calophyllum* from Madagascar: Activity of some natural and synthetic neoflavonoids and khellactones," *Planta Medica*, vol. 58, no. 01, pp. 51-55, 1992. https://doi.org/10.1055/s-2006-961389

[67] A.-E. Hay, J.-J. Hélesbeux, O. Duval, M. Labaïed, P. Grellier, and P. Richomme, "Antimalarial xanthones from *Calophyllum caledonicum* and *Garcinia vieillardii*," *Life Sciences*, vol. 75, no. 25, pp. 3077-3085, 2004. https://doi.org/10.1016/j.lfs.2004.07.009

[68] K. U. Fakhri *et al.*, "The dual role of dietary phytochemicals in oxidative stress: Implications for oncogenesis, cancer chemoprevention, and ncRNA regulation," *Antioxidants*, vol. 14, no. 6, p. 620, 2025. https://doi.org/10.3390/antiox14060620

[69] A. Phaniendra, D. B. Jestadi, and L. Periyasamy, "Free radicals: Properties, sources, targets, and their implication in various diseases," *Indian Journal of Clinical Biochemistry*, vol. 30, no. 1, pp. 11-26, 2015. https://doi.org/10.1007/s12291-014-0446-0

[70] N. I. Aminudin, F. Ahmad, M. Taher, and R. M. Zulkifli, "Cytotoxic and antibacterial activities of constituents from *Calophyllum ferrugineum* Ridley," *Records of Natural Products*, vol. 10, pp. 649-653, 2016.

[71] N. I. Aminudin, F. Ahmad, M. Taher, and R. M. Zulkifli, "α-Glucosidase and 15-lipoxygenase inhibitory activities of phytochemicals from *Calophyllum symingtonianum*," *Natural Product Communications*, vol. 10, no. 9, pp. 1585-1587, 2015.