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Review Article

Unlocking the Potential of *Calophyllum* Xanthones: A Review on Antileukemic Activity and Molecular Docking Insights

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ABSTRACT

The genus *Calophyllum*, a member of the Calophyllaceae family, has garnered increasing scientific attention due to its pharmacologically active constituents, particularly xanthones. This review consolidates current findings on xanthones isolated from Malaysian *Calophyllum* species, emphasizing their antileukemic potential. A total of 72 xanthones have been reported across various species, with the majority derived from stem bark and roots. Several xanthones such as caloxanthone B, ananixanthone, and brasixanthone B exhibit remarkable cytotoxic activity against leukemia cell lines, notably K562. The review also evaluates molecular docking interactions of 41 structurally characterized xanthones with two critical leukemia-related protein targets: cyclin-dependent kinase 4 (CDK4) and matrix metalloproteinase-2 (MMP2). Docking simulations revealed that calozeyloxanthone, xanthochymone B, and caloxanthone J demonstrated strong binding affinities toward these targets, by surpassing standard inhibitors abemaciclib and batimastat in silico. These findings corroborate existing in vitro data and highlight the therapeutic potential of *Calophyllum*-derived xanthones as dual-target inhibitors. The review outlines key pharmacophores contributing to bioactivity and underscores the promise of Malaysian *Calophyllum* species as reservoirs for novel antileukemic agents. Further preclinical and clinical evaluations are warranted to validate their efficacy and develop structure-optimized derivatives for cancer therapy.

Keywords: *Calophyllum*, xanthone, leukemia, cyclin-dependent kinase 4, matrix metalloproteinase-2, molecular docking

1. INTRODUCTION

The family Calophyllaceae includes about 200 species of tropical and subtropical evergreen trees and shrubs in the genus *Calophyllum*. Known by various local names, such as "Bintangor" in Malaysia, "Nyamplung" in Indonesia, "Poonagam" in India and "Guanandi" in Latin America. The name *Calophyllum*, which translates to "beautiful leaf" in Greek, explains

the reason that most of the plants in this group have beautiful leathery leaves with green and thick leaves (Mahato et al., 2024). *Calophyllum* species have significant medicinal and economical effects in addition to their ecological role in protection of biodiversity. *Calophyllum* species are widely spread in Southeast Asia, Africa, Australia, and America. They exhibit some variations in their features and are generally medium to large size trees with straight stems and yellow sticky resin which slowly flow out from girdling parts. They are leathery smooth, opposite and simple leaves with well-defined parallel veins. These trees produce single-seeded drupes and small scented white florals that form in racemose or paniculate inflorescences (Gomez-Verjan et al., 2017).

Calophyllum species have traditionally been utilized for several applications, including the production of biofuels, timber, animal feed, colors, soap, and pharmaceuticals. Various parts of *Calophyllum* species have been utilized in traditional medicine in Asia and the Pacific islands (Ong et al., 2011). *C. inophyllum*, also known as tamanu, has been utilized to treat several conditions, including rheumatism, ulcers, scabies, leprosy, skin infections, and ocular illnesses. *C. inophyllum* seed oil is renowned for its application in the treatment of dermatological diseases (Gupta and Gupta, 2020; Vittaya et al., 2023). Likewise, *C. apetalum* has historically been utilized in the treatment of leprosy through the application of its seed oil as well as scabies and others dermatological illnesses. Phytochemical studies of *Calophyllum* species have revealed several beneficial compounds, including xanthones, coumarins, and triterpenoids. These phytochemicals exhibit many pharmacological activities, including anti-inflammatory, antioxidant, and anticancer actions (Oo, 2018).

Leukemia, a type of blood cancer caused by the uncontrolled growth of abnormal white blood cells, remains a major global health concern. The two most common types are acute lymphoblastic leukemia (ALL) and chronic myeloid leukemia (CML). Although treatments are available, they often face limitations such as relapse and drug resistance (Niu et al., 2022). These challenges underscore the urgent need for novel therapeutic strategies. Natural compounds from medicinal plants like *Calophyllum* have shown potential in treating leukemia by inducing apoptosis, inhibiting cell growth, and preventing metastasis. Xanthones isolated from various Malaysian *Calophyllum* species have shown strong cytotoxic effects, especially against the K562 cell line, a standard model for CML research (Kurniawan et al., 2021). For instance, brasilixanthone has been reported to target critical pathways involved in cancer progression (Zamakshshari et al., 2019). Similarly, compounds such as ananixanthone and caloxanthone B have demonstrated notable cytotoxic activity against K562 cells (Oriola and Kar, 2024). Additionally, GUT-70, a tricyclic coumarin has been shown to strongly inhibit leukemia cell growth by activating caspase-mediated apoptosis (Jin et al., 2011).

This study explores the anti-leukemic potential of substances derived from Malaysian *Calophyllum* species by molecular docking techniques, examining their interactions with CDK4 and MMP2 in K562 leukemia cells. These studies seek to elucidate the therapeutic applications of these phytochemicals and illustrate their potential as innovative treatment alternatives for leukemia. The research will also serve as a preliminary guide for future researchers before conducting *in vitro* and *in vivo* laboratory tests. The *Calophyllum* genus serves as a significant resource for drug discovery owing to its diverse phytochemical profile, ethnomedicinal importance, and established anticancer properties.

2. SEARCH STRATEGY

A systematic literature search was conducted to identify all relevant studies on *Calophyllum* xanthones and their biological activities. PubMed, Scopus, Web of Science, and Google Scholar were queried using the terms "*Calophyllum*," "xanthone," "anti-leukemic activity," "CDK4," "MMP2" and "molecular docking." Searches were limited to peer-reviewed

articles published in English from January 1968 through January 2025. Titles and abstracts were screened for relevance, and the reference lists of selected papers were manually examined to capture any additional pertinent reports.

2.1. Preparation of the Target Protein

This study aimed to investigate the binding mechanisms and the capacity of compounds to occupy protein active sites in targeting the role in the development of leukemia. Cyclin-dependent kinase 4 (CDK4) and matrix metalloproteinase 2 (MMP2) were selected as targets due to their role in leukemia development, making them important therapeutic candidates (Bride et al., 2022). The 3D structural coordinates of CDK4 and MMP2 were sourced from the Protein Data Bank (PDB ID: 1FIN and 1HOV, respectively) (Feng et al., 2002). Before docking, water molecules, other atoms, and ligand cocrystallized with the protein were removed using Biovia Discovery Studio 2021 Client (BIOVIA 2021). Protein structures were minimized using AMBER force field conjugated gradient algorithm in UCSF Chimera 1.10.1. for smooth conformation of proteins.

2.2. Preparation of Ligands

Forty-one xanthone isolated from Malaysian genus *Calophyllum* were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) as SDF files. The reference drug used for CDK4 (abemaciclib) (PubChem CID: 46220502) and MMP2 (batimastat) (BB-94) (PubChem CID: 5362422) were also retrieved from PubChem database in sdf format and then converted to pdb files using open babel integrated in Pyrx software (Dallakyan and Olson, 2015). For each ligand an energy minimization was undertaken using OpenBabel tool in PyRx with default settings including 100 steepest descent steps, a step size of 0.02 Å, and an update interval of 10.

2.3. Molecular Docking

Molecular docking was performed within the PyRx virtual screening utilizing the AutoDock Vina Wizard 4.2 (Trott et al., 2010). The grid box was designed to encompass the binding sites, with central coordinates established at X: 27.2401, Y: 36.8107, Z: 29.9005 for CDK4, and X: 29.1324, Y: 26.4245, Z: 23.2543 for MMP2, thereby facilitating ligand flexibility within the binding pocket. An exhaustiveness parameter of 8 was utilized to enhance the accuracy of the docking outcomes and the docked compounds were evaluated based on their lowest binding energy (kJ/mol). The 2D and 3D depictions of the docking complexes were generated using Biovia Discovery Studio 2021 Client (BIOVIA 2021).

3. XANTHONES FROM THE GENUS *Calophyllum*

Xanthones are a category of polyphenolic compounds that are distinguished by their substantial biological activity and structural diversity. These compounds are distinguished by their unique tricyclic aromatic structure, which is composed of a core pyranone ring and two fused benzene rings, with a basic framework of 13 carbon atoms (C_6-C_1-C_6) (Lizazman et al., 2022). Phytochemical studies on *Calophyllum* species have identified various xanthones classified as simple, prenylated, oxygenated, and other variants based on their functional groups and substitution patterns across different plant parts, including the bark, roots, and seeds. The Malaysian *Calophyllum* species are known to be rich in bioactive xanthones with a total of 72 xanthones have been discovered based on Table 1 and their chemical structures as Figure 1.

Table 1. Xanthones isolated from Malaysian *Calophyllum* species

Compounds	Species	Part	References
Jacareubin (**1**)	*C. inophyllum*	Heartwood	Goh et al., 1991
Osajaxanthone (**2**)	*C. hosei*	Stem bark	Daud et al., 2014
	C. enervosum	Stem bark	Taher et al., 2005
Caloxanthone A (**3**)	*C. hosei*	Stem bark	Daud et al., 2020
	C. depressinervosum	Stem bark	Zamakshshari et al., 2019
	C. benjaminum	Stem bark	Sahimi et al., 2013
	C. javanicum	Stem bark	Sahimi et al., 2013
	C. soulattri	Stem bark	Ee et al., 2011
	C. inophyllum	Root bark	Yimdjo et al., 2004
Caloxanthone C (**4**)	*C. canum*	Stem bark	Lizazman et al., 2022a
	C. andersonii	Stem bark	Tee et al., 2018
	C. depressinervosum	Stem bark	Zamakshshari et al., 2016
	C. soulattri	Stem bark	Mah et al., 2014
	C. gracilipes	Stem bark	Cao et al., 1997
Macluraxanthone (**5**)	*C. buxifolium*	Stem bark	Daud et al., 2016
	C. andersonii	Stem bark	Tee et al., 2018
	C. lowii	Stem bark	Jamaluddin et al., 2013
	C. sclerophyllum	Stem bark	Daud et al., 2013
	C. inophyllum	Stem bark	Ee et al., 2011
	C. soulattri	Stem bark	Ee et al., 2011
Trapezifolixanthone (**6**)	*C. macrocarpum*	Stem bark	Karunakaran et al., 2020
	C. canum	Stem bark	Taher et al., 2020
	C. depressinervosum	Stem bark	Zamakshshari et al., 2016
	C. soulattri	Stem bark	Mah et al., 2014
	C. hosei	Stem bark	Daud et al., 2014
	C. gracilipes	Bark	Nasir et al., 2013
	C. sclerophyllum	Stem bark	Daud et al., 2013
Trapezifolixanthone A (**7**)	*C. canum*	Stem bark	Taher et al., 2020
	C. nodusum	Bark	Nasir et al., 2011
Calabaxanthone (**8**)	*C. walkeri*	Stem bark	Ampofo & Waterman, 1986
Demethylcalabaxanthone (**9**)	*C. walkeri*	Stem bark	Ampofo & Waterman, 1986
Dombakinaxanthone (**10**)	*C. hosei*	Stem bark	Daud et al., 2020
	C. benjaminum	Stem bark	Sahimi et al., 2015
	C. javanicum	Stem bark	Sahimi et al., 2013
	C. sclerophyllum	Stem bark	Daud et al., 2013
Brasixanthone B (**11**)	*C. soulattri*	Stem bark	Mah et al., 2014
Caloxanthone J (**12**)	*C. depressinervosum*	Stem bark	Zamakshshari et al., 2016
Xanthochymone B (**13**)	*C. depressinervosum*	Stem bark	Zamakshshari et al., 2016
6-Deoxyjacareubin (**14**)	*C. flavoramulum*	Leaves	Ferchichi et al., 2012
	C. symingtonianum	Heartwood	Kawamura et al., 2012
	C. inophyllum	Heartwood	Goh et al., 1991
9-Hydroxycalabaxanthone (**15**)	*C. hosei*	Stem bark	Daud et al., 2020
Pyranojacareubin (**16**)	*C. andersonii*	Stem bark	Tee et al., 2018
	C. buxifolium	Stem bark	Daud et al., 2016
	C. inophyllum	Stem bark	Ee et al., 2009, 2011
	C. gracilipes	Stem bark	Cao et al., 1997
Caloxanthone I (**17**)	*C. andersonii*	Stem bark	Tee et al., 2018
	C. depressinervosum	Stem bark	Zamakshshari et al., 2016
	C. venulosum	Stem bark	Ismail et al., 2015
Thwaitesixanthone (**18**)	*C. recurvatum*	Stem bark	Firouza et al., 2024
	C. hosei	Stem bark	Daud et al., 2020
	C. buxifolium	Stem bark	Zamakshshari et al., 2019
	C. benjaminum	Stem bark	Sahimi et al., 2015
	C. teysmannii	Stem bark	Jamaluddin et al., 2013
	C. javanicum	Stem bark	Sahimi et al., 2013
	C. sclerophyllum	Stem bark	Daud et al., 2013

Ananixanthone (**19**)	*C. canum*	Stem bark	Lizazman et al., 2022a
	C. macrocarpum	Stem bark	Karunakaran et al., 2020
	C. hosei	Stem bark	Daud et al., 2014, 2020
	C. buxifolium	Stem bark	Daud et al., 2016
	C. depressinervosum	Stem bark	Zamakshshari et al., 2016
	C. venulosum	Stem bark	Ismail et al., 2015
	C. lowii	Stem bark	Jamaluddin et al., 2013
	C. teysmannii	Stem bark	Jamaluddin et al., 2013
6-Deoxyisojacareubin (**20**)	*C. canum*	Stem bark	Lizazman et al., 2022a
β-mangostin (**21**)	*C. hosei*	Stem bark	Daud et al., 2020
	C. teysmannii	Stem bark	Wei et al., 2018
	C. benjaminum	Stem bark	Sahimi et al., 2015
	C. javanicum	Stem bark	Sahimi et al., 2013
	C. lowii	Stem bark	Jamaluddin et al., 2013
Cudraxanthone C (**22**)	*C. mucigerum*	Stem bark	Ee et al., 2004
Euxanthone (**23**)	*C. havilandii*	Stem bark	Zailan et al., 2024
	C. lanigerum	Stem bark	Mokhtar et al., 2024
	C. canum	Stem bark	Lizazman et al., 2022a
	C. gracilentum	Stem bark	Lim et al., 2018, 2019
	C. castaneum	Stem bark	Lim et al., 2016, 2019
	C. andersonii	Stem bark	Tee et al., 2018
Flavoramulone (**24**)	*C. flavoramulum*	Leaves	Ferchichi et al., 2012
Fuscaxanthone C (**25**)	*C. benjaminum*	Stem bark	Sahimi et al., 2015
	C. lowii	Stem bark	Jamaluddin et al., 2013
	C. teysmannii	Stem bark	Jamaluddin et al., 2013
	C. javanicum	Stem bark	Sahimi et al., 2013
Rubraxanthone (**26**)	*C. hosei*	Stem bark	Daud et al., 2020
	C. sclerophyllum	Stem bark	Daud et al., 2013
	C. symingtonianum	Heartwood	Kawamura et al., 2012
Tovopyrifolin C (**27**)	*C. venulosum*	Stem bark	Ismail et al., 2015
	C. inophyllum	Roots	Ee et al., 2009
1-Hydroxy-7-methoxyxanthone (**28**)	*C. ferrugineum*	Stem bark	Noh & Jong, 2020
1-Hydroxy-5-methoxyanthone (**29**)	*C. scriblitifolium*	Heartwood	Jackson et al., 1968
1,3,5,6-Tetrahydroxyxanthone (**30**)	*C. buxifolium*	Stem bark	Zamakshshari et al., 2019
1,5-Dihydroxyxanthone (**31**)	*C. inophyllum*	Root bark	Yimdjo et al., 2004
4-Hydroxyxanthone (**32**)	*C. inophyllum*	Stem bark	Ee et al., 2011
8-Deoxygartanin (**33**)	*C. macrocarpum*	Stem bark	Karunakaran et al., 2020
Scriblitifolic acid (**34**)	*C. scriblitifolium*	Heartwood	Jackson et al., 1968
Calophyllin B (**35**)	*C. scriblitifolium*	Heartwood	Jackson et al., 1968
Calozeyloxanthone (**36**)	*C. hosei*	Stem bark	Daud et al., 2020
Brasilixanthone (**37**)	*C. inophyllum*	Roots	Ee et al., 2009
Brasilixanthone B (**38**)	*C. inophyllum*	Roots	Ee et al., 2004
Caloxanthone B (**39**)	*C. hosei*	Stem bark	Daud et al., 2020
	C. depressinervosum	Stem bark	Zamakshshari et al., 2019
	C. soulattri	Stem bark	Ee et al., 2011
	C. inophyllum	Roots	Ee et al., 2009
2-(3-Hydroxy-3-methylbutyl)-l,3,5,6-tetrahydroxyxanthone (**40**)	*C. inophyllum*	Heartwood	Goh et al., 1991
2-(3-Methylbut-2-enyl)-1,3,5-trihydroxyxanthone (**41**)	*C. inophyllum*	Heartwood	Goh et al., 1991
Rheediachromenoxanthone (**42**)	*C. flavoramulum*	Leaves	Ferchichi et al., 2012
Nodusuxanthone (**43**)	*C. nodusum*	Bark	Nasir et al., 2011
Soulattrin (**44**)	*C. soulattri*	Stem bark	Mah et al., 2011, 2014
5-Methoxytrapezifoli-xanthone (**45**)	*C. canum*	Stem bark	Lizazman et al., 2022a
Gracilixanthone (**46**)	*C. gracilipes*	Stem bark	Cao et al., 1997
Thwaitesixanthonol (**47**)	*C. walkeri*	Stem bark	Ampofo & Waterman, 1986
5-Methoxyananixanthone (**48**)	*C. canum*	Stem bark	Lizazman et al., 2022a
	C. teysmannii	Stem bark	Wei et al., 2018

Buxixanthone (**49**)	*C. buxifolium*	Stem bark	Daud et al., 2016
Inophyllin A (**50**)	*C. inophyllum*	Stem bark	Ee et al., 2011, 2016
Inophyllin B (**51**)	*C. inophyllum*	Roots	Ee et al., 2004
Gracixanthone (**52**)	*C.gracilipes*	Bark	Nasir et al., 2013
Phylattrin (**53**)	*C. soulattri*	Stem bark	Mah et al., 2012, 2014
1,5-Dihydroxy-3-methoxy-4-isoprenylxanthone (**54**)	*C. canum*	Stem bark	Lizazman et al., 2022a
1,7-Dihydroxy-6-methoxyxanthone (**55**)	*C. inophyllum*	Fruit kernel	Zakaria et al., 2014
3-Methoxy-2-hydroxyxanthone (**56**)	*C. flavoramulum*	Leaves	Ferchichi et al., 2012
6-Hydroxy-2-methoxyxanthone (**57**)	*C. ferrugineum*	Bark	Aminudin et al., 2016
1,5-Dihydroxy-6-(4-hydroxy-3-methylbutyl)xanthone (**58**)	*C. scriblitifolium*	Heartwood	Jackson et al., 1968
l,5-Dihydroxy-6-(4-hydroxy-3-methylbut-2-enyl)xanthone (**59**)	*C. scriblitifolium*	Heartwood	Jackson et al., 1968
2"-Isopropenyl-3"-hydroxy-dihydrofurano-demethylcalaba-xanthone (**60**)	*C. walkeri*	Stem bark	Ampofo & Waterman, 1986
Zeyloxanthone (**61**)	*C.gracilipes*	Bark	Nasir et al., 2013
Biscaloxanthone (**62**)	*C. canum*	Stem bark	Taher et al., 2020
Inophinone (**63**)	*C. inophyllum*	Stem bark	Mah et al., 2014
Caloxanthone L (**64**)	*C. lowii*	Stem bark	Jamaluddin et al., 2013
Inophinnin (**65**)	*C. inophyllum*	Stem bark	Ee et al., 2011
Rheediaxanthone A (**66**)	*C. inophyllum*	Stem bark	Mah et al., 2014
Venuloxanthone (**67**)	*C. venulosum*	Stem bark	Ismail et al., 2015
Ananixanthone monoacetate (**68**)	*C. teysmannii*	Stem bark	Wei et al., 2018
Ananixanthone diacetate (**69**)	*C. teysmannii*	Stem bark	Wei et al., 2018
5-Obenzylananixanthone (**70**)	*C. teysmannii*	Stem bark	Wei et al., 2018
1,3,5-Trihydroxy-2-(3-methylbut-2-enyl)xanthone (**71**)	*C. symingtonianum*	Heartwood	Kawamura et al., 2012
2-(3-Methylbut-2-enyl)-1,3,5,6-tetrahydroxyxanthone (**72**)	*C. inophyllum*	Heartwood	Goh et al., 1991

C. inophyllum is the most known one with over 20 xanthones discovered, jacareubin (**1**), caloxanthone B (**39**), brasilixanthone (**37**), and inophinnin (**65**) to name a few. *C. soulattri* and *C. depressinervosum* have also been important additions and are responsible for producing many xanthones in several works. A substantial number of research studies have reported caloxanthone A (**3**) as the compound which has been extracted from *C. hosei, C. depressinervosum*, *C. benjaminum*, *C. soulattri*, *C. inophyllum* and is one of the most found compounds as it has been extracted from thirteen species. The compound is mostly found in the stem bark of the plant depicting it as a vital source of xanthones. Others compound such as caloxanthone C (**4**), macluraxanthone (**5**) and trapezifolixanthone (**6**) have been widely documented. *C. depressinervosum* and *C. soulattri* frequently yield these xanthones.

Notably, the stem bark is the most extensively studied part and has yielded the majority of the identified xanthones, including brasixanthone B (**11**), pyranojacareubin (**16**) and ananixanthone (**19**). The focus on the stem bark is most likely highly concentrated with secondary metabolites which make it easier for extraction. In addition, the leaves and fruit kernels are less studied but still provide valuable xanthones. For instance, the leaves of *C. flavoramulum* yielded flavoramulone (**24**) and 3-methoxy-2-hydroxyxanthone (**56**) and *C. inophyllum* fruit kernel were found to contain 1,7-dihydroxy-6-methoxyxanthone (**55**). The increasing number of xanthones realized from Malaysian *Calophyllum* species indicates the enormous pharmaceutical potential that this group has, especially as anticancer, antioxidant and antimicrobial agents. This is a starting point for researchers to conduct an additional

investigation for further studies, especially, the leaves and fruit kernels parts, to unlock the full spectrum of bioactive compounds of these plant species.

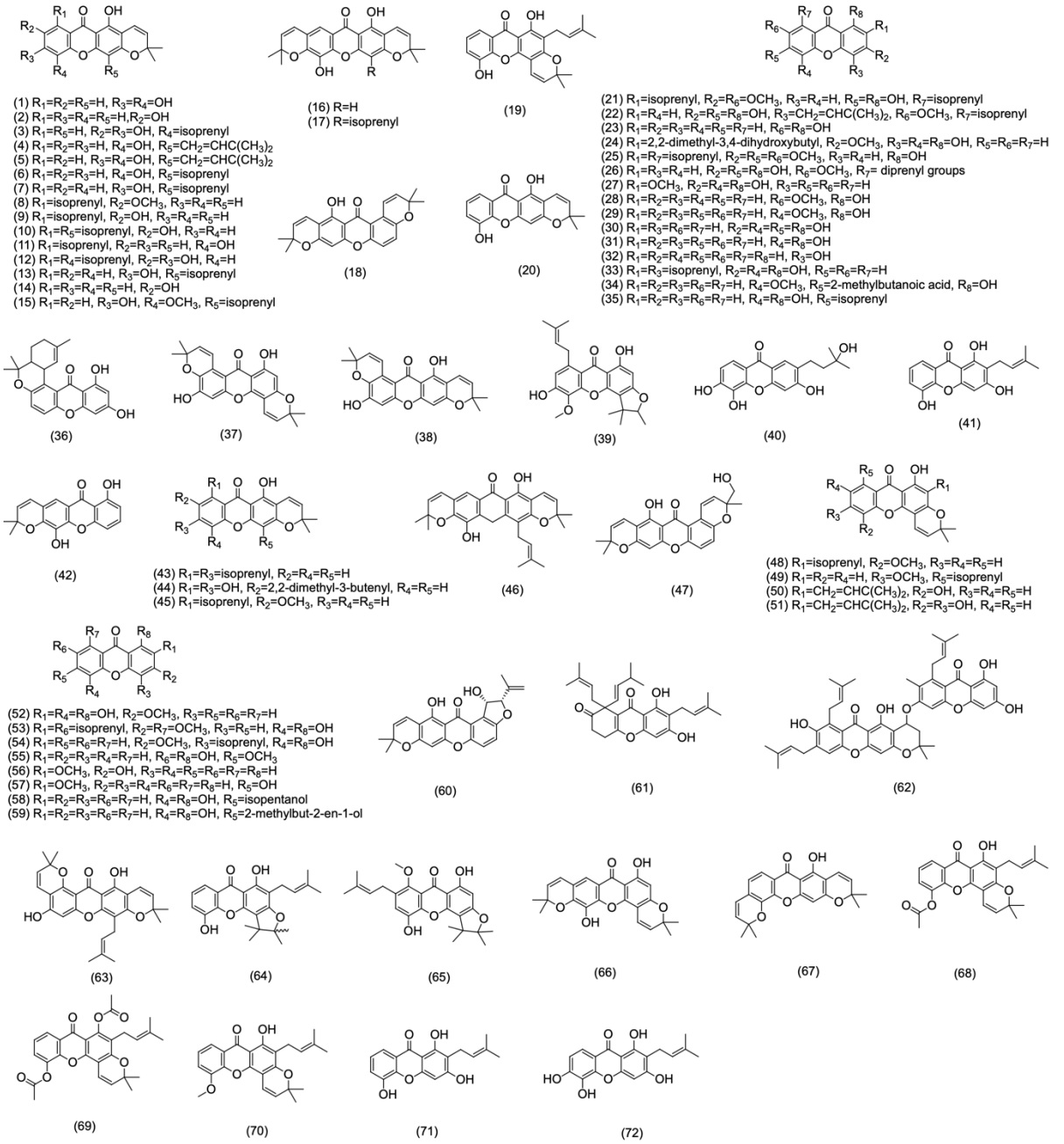


Figure 1. Chemical structures of isolated xanthones

4. PHARMACOLOGICAL ACTIVITIES OF XANTHONES

The broad range of pharmacological activities attributed to xanthones has received considerable interest. Because xanthones are able to interact with a wide variety of biological targets, there has been a lot of research done on how they could be used as potential treatments for a variety of disorders. Table 2 provides a complete overview of the pharmacologically active xanthones isolated from various Malaysian *Calophyllum* species between 1968 and 2024. This information was extracted from the Scopus database.

Table 2. Biological activities of xanthones from *Calophyllum*

Compounds	Biological activities
Caloxanthone A (**3**)	**Cytotoxicity**: Display potent activity against human epidermoid carcinoma of the nasopharynx cell (KB) with IC_{50} value 7.4 µM (Yimdjo et al., 2004)
	Antimicrobial: Displayed potent against *Staphylococcus aureus* with IC_{50} value 9.0 µM (Yimdjo et al., 2004)
Caloxanthone C (**4**)	**Cytotoxicity**: Inhibited strongly the proliferation rate of HeLa, and HEP G2 cells at IC_{50} values 6.8 and 6.2 µM, respectively (Mah et al., 2015a); Significant activity in MTT assay against Raji, LS174T and IMR-32 of human cancer cell lines with IC_{50} values 5.8, 10.9 and 7.0 µg/mL, respectively (Mah et al., 2015b)
Macluraxanthone (**5**)	**Cytotoxicity**: Inhibited significantly active against proliferation human cancer cell lines of SNU-1, HeLa, NCI-H23, Hep G2 and K562 at IC_{50} values 4.95, 6.95, 4.62, 11.12 and 5.28 µM, respectively (Mah et al., 2015a); Showed highly active in MTT assay against Raji, LS174T and IMR-32 human cancer cell lines with IC_{50} values 1.75, 5.94 and 1.95 µg/mL, respectively, while in SK-MEL-28 it showed moderate activity with IC_{50} value 15.62 µg/mL (Mah et al., 2015b)
	Antiplatelet aggregation: Showed inhibitory activity against ADP-induced platelet aggregation with an IC_{50} value 47.0µM (Jantan et al., 2009)
Trapezifolixanthone (**6**)	**Cytotoxicity**: Strongly inhibited the proliferation rate of HeLa cells at IC_{50} value 7.57 µM (Mah et al., 2015a); Significant activity in MTT assay against Raji, LS174T and SK-MEL-28 of human cancer cell lines with IC_{50} values 7.29, 14.58 and 7.80 µg/mL, respectively (Mah et al., 2015b); Moderate activity at concentrations <100 µM on MCF-7 breast cancer cell and 3T3L1 preadipocyte cell lines with IC_{50} value 88.7 and 47.8 µM, respectively (Taher et al., 2020)
Trapezifolixanthone (**6**)	**Cytotoxicity**: Significant activity in human cancer cell lines against SNU-1 and HeLa with IC_{50} value 15.7 and 7.5 µg/mL, respectively (Daud et al., 2020)
Trapezifolixanthone A (**7**)	**Cytotoxicity**: Showed moderate activity at concentrations <100 µM against A549 lung cancer cell line with IC_{50} value 50.2 µM (Taher et al., 2020)
Dombakinaxanthone (**10**)	**Anti-inflammatory**: Showed considerable NO activity against LPS induced RAW 264.7 murine macrophages with IC_{50} value 7.57 µg/mL (Daud et al., 2020)
	Anticancer: Showed the significant activity level towards K562 cells with IC_{50} value 17.44 µg/mL (Zamakshshari et al., 2019)
Brasixanthone B (**11**)	**Cytotoxicity**: Showed significant activity in MTT assay against Raji, LS174T and SK-MEL-28 of human cancer cell lines with IC_{50} values 9.89, 13.75 and 10.93 µg/mL while in IMR-32 it showed low activity with IC_{50} value 35.0 µg/mL (Mah et al., 2015b)
Xanthochymone B (**13**)	**Anticancer**: Showed the significant activity level towards K562 cells with IC_{50} value 17.55 µg/mL (Zamakshshari et al., 2019)
6-Deoxyjacareubin (**14**)	**Antifungal**: Showed higher activity against a white-rot fungus *P. sanguineus* with MIC value 50 µg/disk (Kawamura et al., 2012)
	Antimicrobial: Showed significant activity against *P. sanguineus* with MIC value 0.16 µg/mL (Kawamura et al., 2012)
Pyranojacareubin (**16**)	**Cytotoxicity**: Inhibited significant activity against proliferation human cancer cell lines of HeLa, Hep G2 and K562 at IC_{50} values 13.95, 14.59 and 8.62 µM respectively (Mah et al., 2015a); Moderate activity in MTT assay against Raji and LS174T of human cancer cell lines with IC_{50} value 7.0 and 15.6 µg/mL, respectively (Mah et al., 2015b)
Thwaitesixanthone (**18**)	**Anti-inflammatory**: Showed considerable NO inhibitory activity against LPS induced RAW 264.7 murine macrophages with the IC_{50} value 17.9 µg/mL (Daud et al., 2020)
Ananixanthone (**19**)	**Cytotoxicity**: Exerted the highest activity against nasopharyngeal cancer cell lines (SUNE1, TW01, CNE1, HK1) with IC_{50} values <30 µM (Lim et al., 2016); Exhibited appreciable activity with IC_{50} value 11.08 µM against HeLa Chang liver cell line and moderate against HEK-293 cell line (Karunakaran et al., 2020); Good activity in MTT assay against SNU-1, LS174T and K562 cell lines with IC_{50} values 8.97, 7.48 and 2.96 µg/mL, respectively (Wei et al., 2018)
	Anticancer: Showed good activity level towards K562 cells than the standard with IC_{50} value 2.96 µg/mL (Zamakshshari et al., 2019)

	Anti-inflammatory: Showed considerable NO inhibitory activity against LPS induced RAW 264.7 murine macrophages with IC_{50} value 7.14 µg/mL (Daud et al., 2020)
β-Mangostin (**21**)	**Anti-inflammatory**: Considerable NO activity against LPS induced RAW 264.7 murine macrophages with IC_{50} value 11.68 µg/mL (Daud et al., 2020)
	Cytotoxicity: Displayed appreciable activity against HL-60 cell line with the IC_{50} value of 7.16 µg/mL (Daud et al., 2020); Showed a significant activity in human cancer cell lines against HL-60 with IC_{50} value of 16.86 µg/mL (Daud et al., 2020)
Rubraxanthone (**26**)	**Anti-inflammatory**: Considerable NO inhibitory activity against LPS induced RAW 264.7 murine macrophages with IC_{50} value 6.45 µg/mL (Daud et al., 2020)
	Cytotoxicity: Displayed appreciable activity against HL-60 cell line with IC_{50} value 10.53 µg/mL (Daud et al., 2020)
	Antimicrobial: Showed significant activity against *G. trabeum* with MIC value 0.080 µg/mL (Kawamura et al., 2012)
	Antiplatelet aggregation: Showed inhibitory activity against collagen-induced platelet aggregation with IC_{50} value 47.0µM (Jantan et al., 2009)
4-Hydroxyxanthone (**32**)	**Cytotoxicity**: Showed inactive activities in MTT assay against Raji, LS174T, IMR-32 and SK-MEL-28 of human cancer cell lines with IC_{50} value >40 µg/mL (Mah et al., 2015b)
Caloxanthone B (**39**)	**Anticancer**: Showed good activity towards K562 cells with IC_{50} value 1.23 µg/mL (Zamakshshari et al., 2019)
Soulattrin (**44**)	**Cytotoxicity**: Showed significant activity in MTT assay against Raji, LS174T, IMR-32 and SK-MEL-28 of human cancer cell lines with IC_{50} values 1.01, 1.25, 0.27 and 0.57 µg/mL, respectively (Mah et al., 2015b); Inhibited strongly the proliferation rate of SNU-1, HeLa, NCI-H23 and K562 cells with IC_{50} values 1.98, 2.77, 2.64 and 2.23 µM, respectively (Mah et al., 2015a)
5-Methoxyananixanthone (**48**)	**Cytotoxicity**: Showed greater inhibition against LS174T cell lines with IC_{50} value 5.76 µg/mL (Wei et al., 2018)
Inophyllin A (**50**)	**Anti-leukemia**: Induces oxidative stress mediated apoptosis in Jurkat-T lymphoblastic leukemia cells with IC_{50} value 50 µM (Chan et al., 2012)
Phylattrin (**53**)	**Cytotoxicity**: Showed significant activity in MTT assay against Raji, LS174T, IMR-32 and SK-MEL-28 of human cancer cell lines with IC_{50} values 4.95, 4.68, 7.81 and 4.68 µg/mL, respectively (Mah et al., 2015b)
3-Methoxy-2 hydroxyxanthone (**56**)	**Antioxidant**: Potent against anti-AGEs properties with IC_{50} value 0.06 µM (Ferchichi et al., 2012).
Inophinone (**63**)	**Cytotoxicity**: Showed significant activity in MTT assay against Raji of human cancer cell lines with IC_{50} value 8.33 µg/mL (Mah et al., 2015b)
Inophinnin (**65**)	**Anti-inflammatory**: Showed potent activity in LPS-induced NO production assay at concentration 100 µM with 61.42% of inhibition (Ee et al., 2011)
	Cytotoxicity: Significant activity in MTT assay against Raji, LS174T, IMR-32 and SK-MEL-28 of human cancer cell lines with IC_{50} values 8.33, 13.75, 13.75 and 13.75 µg/mL, respectively (Mah et al., 2015b); Significant activity against proliferation human cancer cell lines of SNU-1, HeLa, NCI-H23 and K562 with IC_{50} values 13.32, 9.51, 14.29 and 16.76 µM, respectively (Mah et al., 2015a)
Rheediaxanthone A (**66**)	**Cytotoxicity**: Showed significantly active against proliferation human cancer cell lines of HeLa, Hep G2 and K562 with IC_{50} values 13.95, 25.51 and 17.53 µM respectively (Mah et al., 2015a); Showed moderate activity in MTT assay against Raji, LS174T and SK-MEL-28 of human cancer cell lines with IC_{50} values 7.29, 14.58 and 7.80 µg/mL, respectively (Mah et al., 2015b)
Ananixanthone monoacetate (**68**)	**Cytotoxicity**: Potent activity in MTT assay against K562 cell lines with IC_{50} values of 7.94 µg/mL while for SNU-1 and LS174T cell line it shows moderate activity with IC_{50} values 11.6 and 11.7 µg/mL, respectively (Wei et al., 2018)
5-*O*-Benzylananixanthone (**70**)	**Cytotoxicity**: Show potent activity in MTT assay against LS174T and K562 cell lines with IC_{50} values 8.02 and 7.34 µg/mL, while for SNU-1 cell line it shows moderate activity with IC_{50} value 19.48 µg/mL (Wei et al., 2018)
1,3,5-Trihydroxy-2-(3-methylbut-2-enyl) xanthone (**71**)	**Antifungal**: Showed higher activity against a brown-rot fungus *G. trabeum* with MIC value 25 µg/disk (Kawamura et al., 2012)

Euxanthone (**23**) has the rather remarkable property of being a potent antioxidant, which serves to shield cells against oxidative stress. On the other hand, caloxanthone B (**39**) has been reported to have potent cytotoxic activity on leukemia cancer cell lines, particularly K562 cells with low IC_{50} values which imply potential as an anti-cancer agent (Kilus et al., 2023; Zamakshshari et al., 2019). The mode of action of this compound is based upon the induction of apoptosis and inhibition of cell growth as a result of alteration of specific signaling pathways and enzymes such as cyclin dependent kinases (CDKs). In other studies, caloxanthone B (**39**), and its derivatives have shown significant promising in inhibiting matrix metalloproteinase (MMPs) activity and thereby reducing the metastasis of cancer cells. Likewise, brasixanthone B (**11**), extracted from *C. brasiliense*, has shown impressive anticancer effect in breast, lung, and leukemia cancer cell lines (Mah et al., 2015b). Because of its capacity to hit two cell-cycle regulators and apoptosis pathways at the same time, however, is a need for more investigation on the compound. Besides, xanthones have the ability to interact with the main cell cycle regulators such as CDKs (Nauman et al., 2021). By acting to inhibit CDK4 and CDK6, xanthones are able to block cell cycle progression mainly at G1/S phase transition thus preventing cancer cell growth (Shan et al., 2011). Furthermore, the xanthone groups of *Calophyllum* species have potential in targeting CDKs and MMPs and this can be effective in the management of various types of cancer including leukemia.

Ananixanthone (**19**) stands to being the most dominant type of xanthone derived from *C. depressinervosum* as it has demonstrated desirable anticancer activity including leukemia cell lines. Moreover, ananixanthone (**19**) disrupts the cell cycle and brings about apoptosis and has an IC_{50} value of about 2.96 µg/mL which is an improvement on the means of typical reference drugs (Zamakshshari et al., 2019). Further, the ananixanthone (**19**) obtained from *C. teysmannii* showed good activity in cytotoxicity assays with cell line K562 showing a 2.96 µg/mL IC_{50} value, SNU-1 8.97 µg/mL, and LS174T 7.48 µg/mL which conclusively depicts the anticancer activity rather positively (Wei et al., 2018). Apart from being used for cancerous purposes, ananixanthone (**19**) can significantly mitigate inflammation as demonstrated by studies conducted. In addition to being an anti-inflammatory agent, ananixanthone (**19**) was obtained from *C. hosei* and inhibited NO at an IC_{50} of 7.14 µg/mL. This is particularly effective against RAW 264.7 cells exposed to LPS (Daud et al. 2020). Brasixanthone B (**11**) and ananixanthone (**19**), both prenylated xanthones, are distinguished by their significant anticancer activities. These compounds exhibit significant cytotoxic effects against multiple cancer cell lines, including leukemia, via regulating apoptosis and efficiently suppressing cell proliferation (Zamakshshari et al., 2019; Gómez-Verjan et al., 2017). These properties significantly enhance the bioavailability of these compounds as well as their efficacy in targeting cancerous cells. Besides, there are specific studies that have revealed that jacareubin (**1**) has interesting combinatorial properties since it possesses both antibacterial as well as anticancer actions (Garcia-Nino et al., 2017).

In particular, the xanthones derived from the *Calophyllum* genus have considerable pharmacological potential. Due to the variations in their structure and the mechanisms of action exhibited, they are of interest in the field of anticancer drug development, especially against leukemias. The study of these compounds does not only enhance our understanding of their therapeutic mechanisms but highlights the need to conserve the genetic resources of the *Calophyllum* species for the purpose of the development of new medicinal compounds in the future.

5. MOLECULAR DOCKING STUDIES

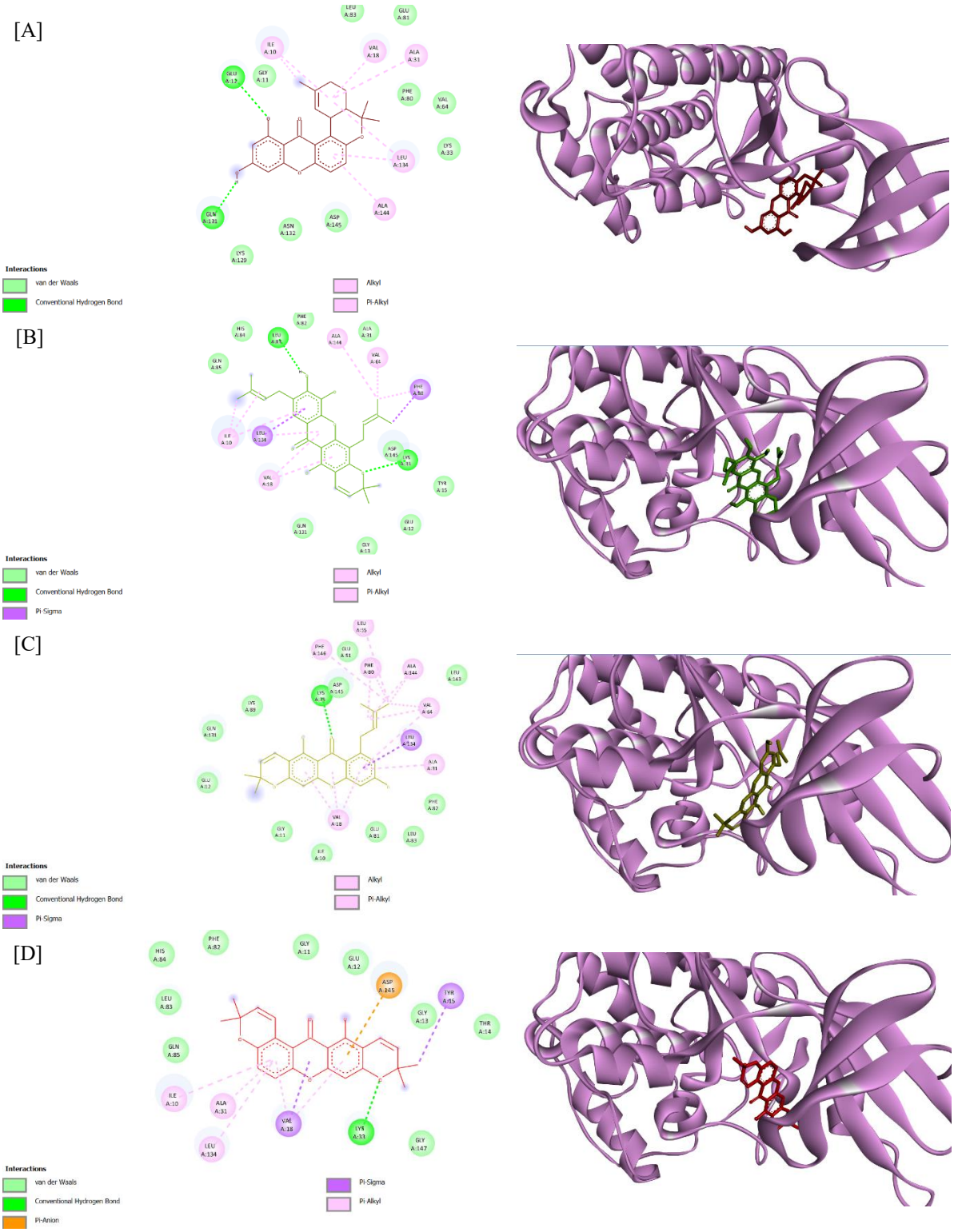
In this review, we calculated the molecular docking interactions of xanthones derived from Malaysia *Calophyllum* with two pivotal anti-cancer targets, cyclin-dependent kinase 4

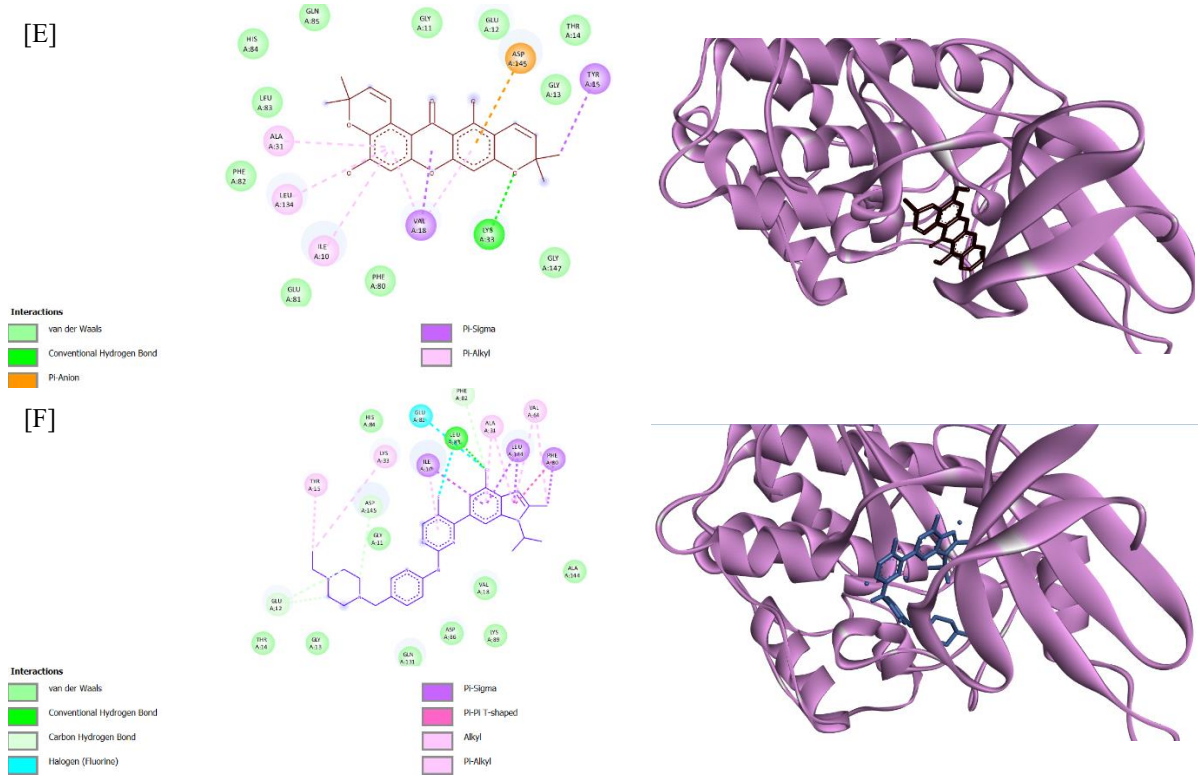
(CDK4) and matrix metalloproteinase-2 (MMP2) using docking simulations. Both enzymes are important for the regulation of cell proliferation and tumor invasion, respectively. CDK4, which is often over-expressed in many forms of leukemia, is one of the master regulators during the G1/S phase of the cell cycle. MMP2 was also one of the enzymes that degrade the extracellular matrix, allowing cancer cells to migrate and undergo metastasis (Bride et al., 2022). Only 41 out of 72 *Calophyllum* compounds could be docked because 3D structures for the others were not available in PubChem.The docking scores of xanthones showed a different range of binding affinities for CDK4 (-44.35 to -31.8 kJ/mol) and MMP2 (-34.73 to -25.1 kJ/mol) as given in Table 3. In addition, Figures 2 and 3 illustrate the 2D and 3D conformations of compounds in molecular docking studies against CDK4 and MMP2, respectively.

Table 3. Ligand binding energies (LBE) in kJ/mol of xanthone derivatives against CDK4 and MMP2

Compounds	PubChem ID	1FIN	1HOV
Jacareubin (**1**)	5281644	-41.42	-32.22
Osajaxanthone (**2**)	6064803	-36.40	-30.12
Caloxanthone A (**3**)	1011852087	-44.35	-30.12
Caloxanthone C (**4**)	11703574	-41.84	-29.71
Macluraxanthone (**5**)	5281646	-42.68	-28.87
Trapezifolixanthone (**6**)	188341	-40.17	-30.12
Trapezifolixanthone A (**7**)	1004214676	-41.00	-33.47
Calabaxanthone (**8**)	341188	-40.58	-29.29
Demethylcalabaxanthone (**9**)	509270	-40.17	-30.54
Dombakinaxanthone (**10**)	10765794	-42.68	-29.71
Brasixanthone B (**11**)	10362269	-40.58	-30.12
Caloxanthone J (**12**)	1083283101	-44.35	-33.05
Xanthochymone B (**13**)	1106863981	-42.68	-34.31
6-Deoxyjacareubin (**14**)	5281629	-39.33	-30.54
9-Hydroxycalabaxanthone (**15**)	5495929	-38.07	-29.71
Pyranojacareubin (**16**)	15307925	-38.49	-32.22
Caloxanthone I (**17**)	1103488886	-42.26	-30.96
Thwaitesixanthone (**18**)	5281631	-32.64	-25.94
Ananixanthone (**19**)	493305	-41.42	-32.64
6-Deoxyisojacareubin (**20**)	5464641	-38.49	-29.29
β-mangostin (**21**)	5495925	-36.82	-29.29
Cudraxanthone C (**22**)	44405862	-38.49	-28.45
Euxanthone (**23**)	392169	-42.68	-32.64
Flavoramulone (**24**)	1102883848	-36.40	-26.78
Fuscaxanthone C (**25**)	231412	-40.58	-31.38
Rubraxanthone (**26**)	9953366	-37.66	-30.12
Tovopyrifolin C (**27**)	5480342	-33.05	-25.10
1-Hydroxy-7-methoxyxanthone (**28**)	12214329	-32.64	-26.78
1-Hydroxy-5-methoxyanthone (**29**)	86168207	-33.05	-27.20
1,3,5,6-Tetrahydroxyxanthone (**30**)	5479774	-33.89	-26.36
1,5-Dihydroxyxanthone (**31**)	5480299	-33.05	-25.94
4-Hydroxyxanthone (**32**)	611428	-31.80	-27.20
8-Deoxygartanin (**33**)	392450	-38.91	-30.54
Scriblitifolic acid (**34**)	1069349565	-35.56	-29.71
Calophyllin B (**35**)	5281624	-39.75	-28.45
Calozeyloxanthone (**36**)	5495849	-42.68	-34.73
Brasilixanthone (**37**)	139079252	-40.17	-31.38
Brasilixanthone B (**38**)	5324261	-42.68	-32.64
Caloxanthone B (**39**)	102066908	-40.58	-30.96
2-(3-Hydroxy-3-methylbutyl)-1,3,5,6 tetrahydroxyxanthone (**40**)	14804158	-35.15	-27.61
2-(3-Methylbut-2-enyl)-1,3,5-trihydroxyxanthone (**41**)	9995643	-37.24	-29.29
Abemaciclib	46220502	-41.84	-29.92
Batimastat (BB-94)	5362422	-40.35	-28.45

Figure 2. 2D and 3D conformation of calozeyloxanthone (**36**) [A], caloxanthone J (**12**) [B], xanthochymone B (**13**) [C], euxanthone (**23**) [D], brasilixanthone B (**38**) [E] and control [F] against CDK4

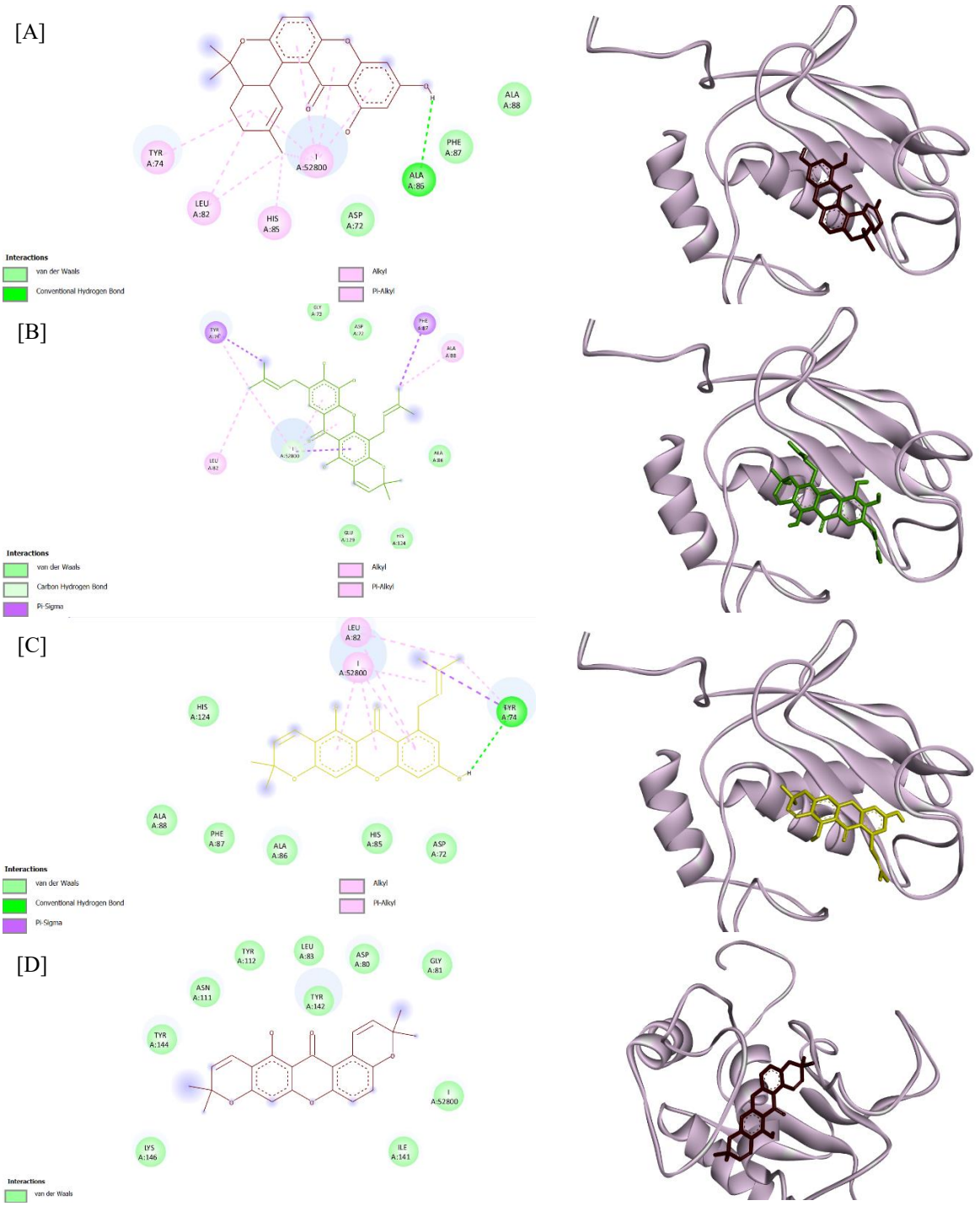


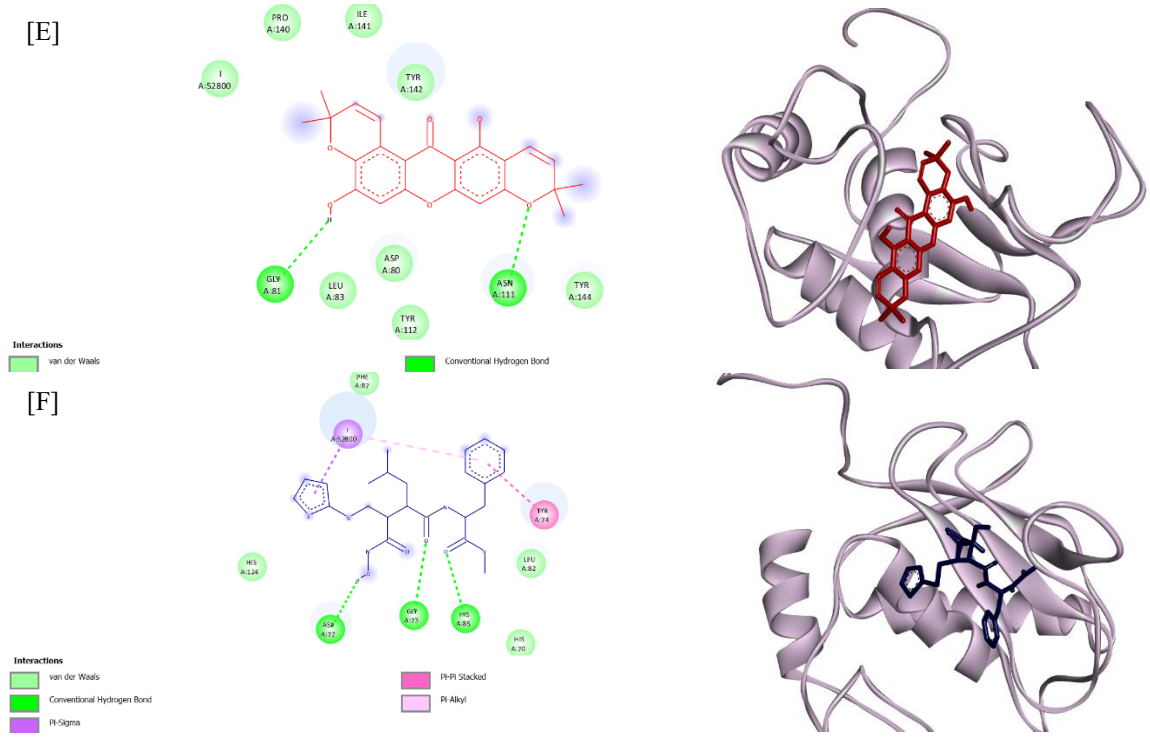


Some compounds were found to have dual inhibitory activity with high binding energy for both targets. Out of these, calozeyloxanthone (**36**) displayed the most binding energies of -42.68 kJ/mol for CDK4 and -34.73 kJ/mol for MMP2. These values are significantly better than reference compounds abemaciclib (-41.84 kJ/mol - CDK4) and Batimastat (-28.45 kJ/mol - MMP2). Additionally, some other compounds were found to exhibit significant docking scores such as xanthochymone B (**13**) which yielded -42.68 kJ/mol and -34.31 kJ/mol for CDK4 and MMP2 respectively. These computational assumptions correspond with observable in vitro cytotoxicity data, where xanthochymone B was shown to inhibit K562 leukemia cells with an IC_{50} value of 17.55 µg/mL (Zamakshshari et al., 2019). These degrees of binding are likely attributed to the presence of prenylated side chains and hydroxyl groups which may contribute for lipophilicity as well as enhanced the hydrogen bonding and improving ligand complementarity with target residues.

Interestingly, a majority of the xanthones demonstrated stronger binding affinities toward CDK4 compared to MMP2. This is probably due to the planar xanthone scaffold being compatible with the hydrophobic aromatic binding pocket of CDK4 which accepts and makes use of aromatic systems. Compounds like ananixanthone (**19**) and caloxanthone B (**39**) showcase that tendency with -41.42 and -40.58 kJ/mol binding energy for CDK4, while for MMP2 the values are -32.64 and -30.96 kJ/mol, respectively. This differential binding behavior is likely due to the unique structural configuration of the MMP2 catalytic domain which has a narrower, more solvent-accessible active site that appears to be less favorable to rigid aromatic scaffold-bound ligands. Significantly, both ananixanthone (**19**) and caloxanthone B (**39**) are potent compounds which were previously reported to demonstrate strong cytotoxic activity with 2.96 and 1.23 mg/mL IC_{50} values respectively, thus confirming their pharmacological significance and the credibility of the docking results (Wei et al., 2018).

Figure 3. 2D and 3D conformation of calozeyloxanthone (**36**) [A], caloxanthone J (**12**) [B], xanthochymone B (**13**) [C], euxanthone (**23**) [D], brasilixanthone B (**38**) [E] and control [F] against MMP2





Based on Figure 2 and 3, calozeyloxanthone (**36**) showed binding poses with stronger binding energies due to crucial interactions, which included conventional hydrogen bonds with Glu12 (2.38 Å) and Gln131 (1.96 Å). These residues are located within the CDK4 active site. Furthermore, calozeyloxanthone (**36**) stabilised π-alkyl interactions involving residue Ile10 and Val18. On the other hand, binding poses with MMP2 were characterized by only one hydrogen bond with Ala86 (2.58 Å) and weak hydrophobic interactions, suggesting a less optimized fit within the enzyme's binding pocket. In addition, caloxanthone J (**12**) was shown to increase binding with CDK4 by forming hydrogen bonds with Lys33 (2.50 Å) and Glu2 (2.04 Å) which is a position favorable for such interactions. This was further supported by several Van der Waals and hydrophobic bonds with Leu134, Phe80, and Val18. When interacting with MMP2, however, the weaker hydrophobic interactions without any non-polar bonds significantly decreased the binding score.

Xanthochymone B (**13**) formed a stable complex with CDK4 through a hydrogen bond with Lys33 (2.08 Å), π-alkyl interactions with Phe80 and Val18, and Van der Waals stabilization. In contrast, the engagement of euxanthone (**23**) with MMP2 was less thorough, consisting of only Van der Waals interactions. This may have resulted in moderate selectivity. Another promising candidate exhibited broadened interactions in the CDK4 binding region, including π–anion interaction with Asp145 (4.21 Å) and π-sigma contacts with Tyr85 and Val18, while forming a hydrogen bond with Lys33 (2.27 Å). These diverse non-covalent interactions contribute to a high binding energy and suggest strong potential as a CDK4 inhibitor. However, the interactions with MMP2 were limited to Van der Waals contacts, lacking significant polar or π-stacking interactions, resulting in a comparatively lower binding affinity.

Similarly, brasilixanthone B (**38**) demonstrated notable binding with CDK4 that included a hydrogen bond with Lys33 (1.79 Å) as well as π-anion interaction with Asp145 (4.21 Å) and additional π-alkyl interactions with Val18, Leu134, and Ile10. These interactions are likely to account for the high stability of the ligand within the binding cavity of CDK4. Concerning MMP2, the interactions were more restricted and were framed by hydrogen bonds to Gly81 and Asn111, without the additional hydrophobic or π type interactions that defined CDK4 binding. This could suggest less favorable or weaker potency towards MMP2. Other noteworthy

compounds include dombakinaxanthone (**10**), docking assessment with the CDK4 receptor had a significant docking score of -42.68 kJ/mol and demonstrated moderate cytotoxicity with an IC_{50} value of 17.44 µg/mL (Zamakshshari et al., 2019). This highlights the effectiveness of molecular docking techniques for predicting biological activity. Macluraxanthone (**5**) showed high binding scores of –42.68 kJ/mol for CDK4 and strong cytotoxicity against leukemia cells (IC_{50} value 5.28 µM) (Mah et al., 2015a). Pyranojacareubin (**16**) also emerged as a potential dual-target ligand, showing binding energies of -38.49 and -32.22 kJ/mol for CDK4 and MMP2, respectively, consistent with its reported anticancer activity (IC_{50} value 8.62 µM) (Mah et al. 2015a). CDK4 was shown to have more prominent interactions than MMP2. This suggests that some levels of structural optimization may provide more active derivatives with better dual-target action.

6. CONCLUSION

To the best of our knowledge, this review may contribute new insights into the underexplored area of molecular docking involving xanthones from *Calophyllum* species. The present study's results are important for understanding the biological potential of xanthones. The investigation identified several xanthones, including calozeyloxanthone (**36**), caloxanthone J (**12**), and xanthochymone B (**13**), as compounds exhibiting high binding affinities to CDK4 and MMP2, which are crucial regulatory proteins of the cell cycle and metastasis, respectively. These xanthones also inhibited the CDK4 protein exhibiting strong binding energies when compared to standard controls which confirm their potential as dual inhibitors. Studies suggest that xanthones can be considered as suitable candidates for the development of new drugs against leukemia. Nevertheless, for their clinical efficiency to be fully optimized, this should be supplemented by in vivo studies and several preclinical leukemia model studies.

Conflict of Interest
The authors declare no conflicts of interest.

Author Contribution Statement
Nur Nabilah Mohd Zaini: Conceptualization and writing original draft. Abubakar Siddiq Salihu: Formal Analysis. Wan Mohd Nuzul Hakimi Wan Salleh and Bunleu Sungthong: Reviewing and editing.

Data Availability Statement
The authors confirm that the data supporting the findings of this study are available within the article.

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