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Review Article

Fight for Cancer Diseases using Natural Compounds and Their Semisynthetic Derivatives

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Abstract
Cancer stands as one of the deadliest diseases afflicting contemporary human societies, encompassing over 100 distinct forms, including oral, salivary glands, oropharynx, nasopharynx, hypopharynx, colorectal, liver, pancreas, lung, skin, breast, cervix, ovary, prostate, kidney, brain, thyroid, and leukemia cancers. At the cellular level, the uncontrolled growth of cancerous cells can disrupt the body's normal functions. Chemotherapy, a widely recognized cancer treatment, utilizes anticancer agents to target specific cancer cell lines effectively. Natural compounds are favored for their compatibility with the body, minimal harm to healthy cells, and easy extraction from natural sources. These natural compounds and their derivatives hold promise for cancer therapy, boasting diverse structural and pharmacological characteristics. Additionally, chemical modifications can enhance their anticancer properties. This review explores the anticancer potential of terpenoids, flavonoids, alkaloids, xanthones, and epoxides, as well as elucidates their molecular mechanisms, such as their antiproliferative, apoptotic, antiangiogenic, and antimetastatic actions. Furthermore, the effect of the functional group on the anticancer activity through the structure-activity relationship will be discussed in detail, supported by molecular docking and molecular dynamic simulations. Combining experimental *in vitro* and *in vivo* assays with computational *in silico* assays significantly helps us understand how we shall fight cancer diseases in the modern era.

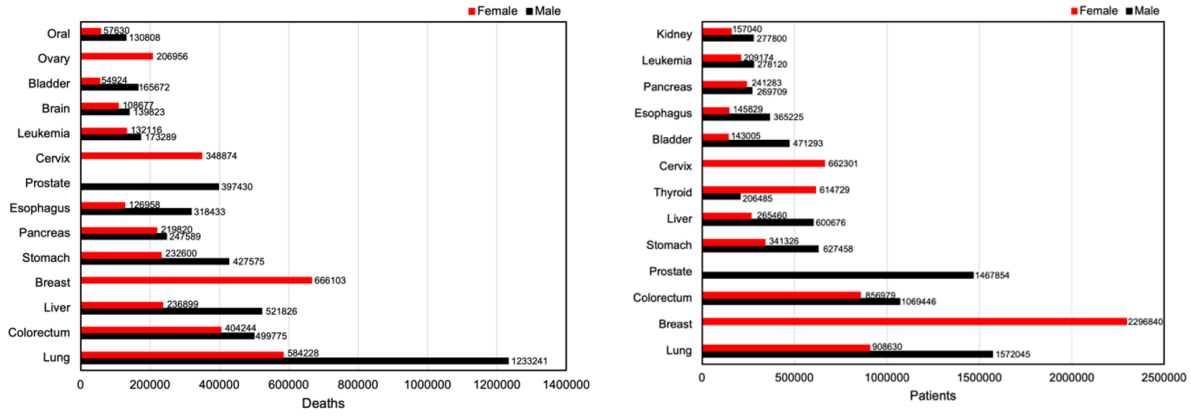
Keywords: anticancer, cancer, natural compounds, derivative

1. INTRODUCTION

Cancer is one of the most fatal diseases in recent human communities. In 2015, almost 90.5 million people in the world had cancer cells in their bodies. In 2022, almost 20 million cancer cases are reported, with 9.7 million deaths [1]. Cancer encompasses more than 100 distinct diseases, including oral, salivary glands, oropharynx, nasopharynx, hypopharynx, colorectal, liver, pancreas, lung, skin, breast, cervix, ovary, prostate, kidney, brain, thyroid, and leukemia cancers. Figure 1 shows the reported cancer cases and cancer deaths in 2022 by the International Agency for Research on Cancer, World Health Organization. The most reported cancers for males are liver, stomach, colorectal, prostate, and lung cancers. Meanwhile, thyroid, cervical, lung, colorectal, and breast cancers are the most common cancer types in females. In children, the most common are leukemia and brain cancers. The cancer diseases with the highest mortality cases for males are similar to the most reported cancer cases. On the other hand, the cancer diseases with the highest mortality cases for females are breast, lung, colorectal, cervix, and liver cancers [2].

Asia has become the top-leading cancer country, with 49.2% of global cases (9.83 million) and 56.1% of global mortality (5.46 million) in the world. In Southeast Asia, the number of prevalent cases, new cases, and deaths are 5472871, 2369106, and 1527959, respectively. The most common cancers for males are oral (11.2%), lung (11.2%), colorectal (7.5%), liver (6.6%), and esophagus (6.2%), while for females are breast (25.9%), cervix (16.2%), ovary (6.1%), colorectal (5.0%), and lung (4.6%). In Indonesia, the number of prevalent cases, new cases, and deaths are 1018110, 408661, and 242988, respectively. The most common cancers for males are lung (15.4%), colorectal (11.6%), liver (9.7%), nasopharynx (7.7%), and prostate (7.0%), while for females are breast (30.1%), cervix (16.8%), ovary (6.9%), colorectal (6.3%), and lung (4.4%). The risk for cancer diseases is linear with human age in developed countries. It was estimated that the annual economic loss due to cancer was around $1.62 trillion in 2023 [1].

The first note for cancer in the world was found



(a) (b)

Figure 1. Cancer statistics for (a) deaths and (b) patients in 2022 adopted from the International Agency for Research on Cancer, World Health Organization.

in the Edwin Smith Papyrus, an ancient Egyptian textbook for surgery. This papyrus describes eight cases of breast cancer. The name "cancer" was first introduced by Hippocrates in 460–370 BC from a Greek word, "καρκίνος" or "carcinos" with a definition of crab. This is because the cancer cells are often observed as massive flesh resembling the legs of the "crab". Afterward, Celcus (25 BC–50 AD) coined the term "cancer" as a Latin word for crab. Later, Galen (130–200 AD) used "oncos" for tumor-related diseases. This is the beginning of the "oncology" era. The world of cancer has been introduced in English since the 16th century. John Hunter, a Scottish surgeon, reported that some cancers could be handled through surgery, and from that time, cancer treatment has been quickly developed [3].

The American Cancer Society describes cancer as a complicated illness marked by the unregulated proliferation and dissemination of abnormal cells, potentially leading to fatality if left unchecked. Neoplasia, tumor, and neoplasm are related to cancer terms. Neoplasia is commonly used in medical circles for cancers, while neoplasm is a synonym for tumor, denoting "new growth". Cancer is not a transmissible disease. This means that cancers cannot be simply transferred to another human through physical contact, airborne, or droplet transmissions, except for pregnancies and organ donors. Cellular biologist elucidates the variances between normal cells and cancerous cells. Normal cells control specific bodily functions, and intricate biochemical mechanisms govern their growth. Conversely, cancer cells exhibit rapid spread and uncontrollable growth and fail to recognize natural boundaries due to genetic mutations. This contrasts with the tumor that does not invade the other parts of the human body [4].

From the cellular point of view, the human body comprises trillions of cells that typically undergo controlled growth and division. Normally, when cells become abnormal or aged, they undergo programmed cell death. However, cancer initiates when a disruption occurs in this process, causing cells to continuously reproduce, with the old or abnormal ones failing to undergo apoptosis or cell death as they should. Consequently, the uncontrolled proliferation of cancer cells can overwhelm normal cells, impeding the body's proper functioning through blood circulation or the lymph system. This phenomenon, called metastasis, is the spread distribution of cancer cells to other tissues or organs in the human body [5].

There is a common parameter to describe the level of metastasis, i.e., cancer stage. The higher stage describes the cancer cells more massively spreading in the human body. Cancer stage 4 is the highest stage of metastasis in the medical field. Information on the cancer stage is critical to determine the required treatment for cancer patients. Similarly, information on primary cancer cells is also important. Even though cancer cells have been infected into other tissues or organs, their type of cells are not transformed. For example,

breast cancer cells that invade the lungs remain as breast cancer cells and not as lung cancer cells [6].

Cancers are categorized based on their resemblance to specific types of cells presumed to be the origin of the tumor. Carcinoma is a cancer cell that originates from epithelial cells, such as colon, pancreas, lung, prostate, and breast epithelial cells. Sarcoma is a cancer cell that arises from connective tissue, including bone, cartilage, fat, and nerve cells. Lymphoma and leukemia are types of cancer originating from hematopoietic cells, which mature in the lymph nodes and blood after leaving the marrow. Seminoma and dysgerminoma are cancers that start from pluripotent cells and often manifest in the testicle or ovary, respectively. Meanwhile, blastomas are cancer cells that develop from immature precursor cells or embryonic tissue. Therefore, cancer types are typically named with suffixes such as -carcinoma, -sarcoma, or -blastoma, along with the Latin or Greek term for the organ or tissue of origin. For example, liver cancers originating from malignant epithelial cells are termed hepatocarcinoma, while malignancies arising from primitive liver precursor cells are called hepatoblastomas. Similarly, cancers originating from fat cells are called liposarcomas [4].

An exact cause for cancer remains elusive. However, numerous factors have been identified as potential contributors to cancer, such as infectious agents, excessive alcohol consumption, limited physical activity, polluted environment, genetic mutations, unhealthy diet, obesity, ultraviolet radiation, and smoking. Smoking and obesity are the riskiest factors that contribute to 30% and 35% of cancer cases, while infectious agents contribute to 20% of cancer cases. On the other hand, genetic mutation is the number four cancer leading factor contributing to 10% of cancers, similar to ultraviolet irradiation (10%) [7].

Around 30–50% of cancer diseases are preventable. Cancer disease prevention could be performed by avoiding air pollution, protecting from sexually transmitted infections, limiting excessive alcohol consumption, doing regular exercise, doing a healthy diet, maintaining a healthy weight, doing a screening test, protecting skin from direct sunlight, and avoiding tobacco. Vaccination could also help to suppress the infection from viruses such as human papillomavirus and hepatitis B. However, it should be kept in mind that cancer prevention is an effort to lower the risk of getting cancer, and that does not guarantee that no cancer cells will develop in the human body [8].

Many cancer therapies are available nowadays. These therapies include surgery, radiation therapy, immunotherapy, palliative care, and chemotherapy. Medical experts recommend these therapies after carefully examining the patient, including the cancer type, primary type, cancer type, patient's health, and preferences. Surgery is the most straightforward cancer therapy by removing cancer cells from the human body. Unfortunately, not all cancers could be removed by surgery, such as leukemia and lymphoma. Furthermore, cancer cells could not be removed completely by surgery. Radiation therapy is cancer therapy using either ionizing or non-ionizing radiation to damage the DNA of cancer cells, leading to apoptosis. This therapy might work for an early stage of neck and

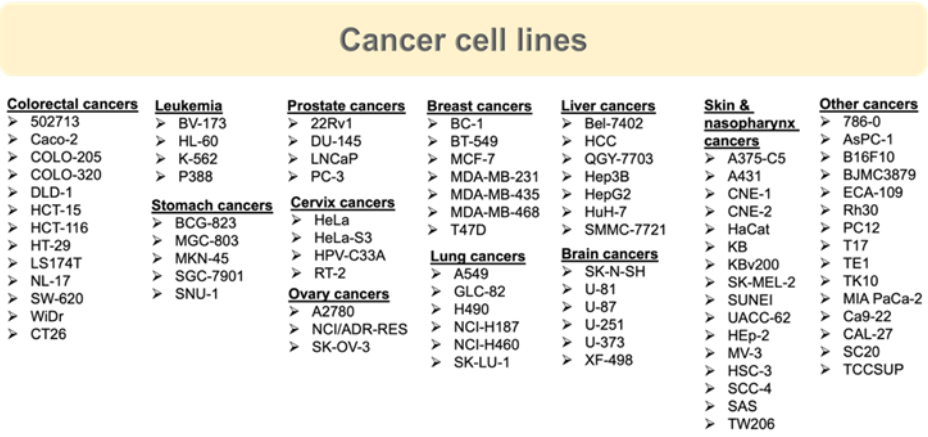


Figure 2. Commonly used cancer cells in medical research.

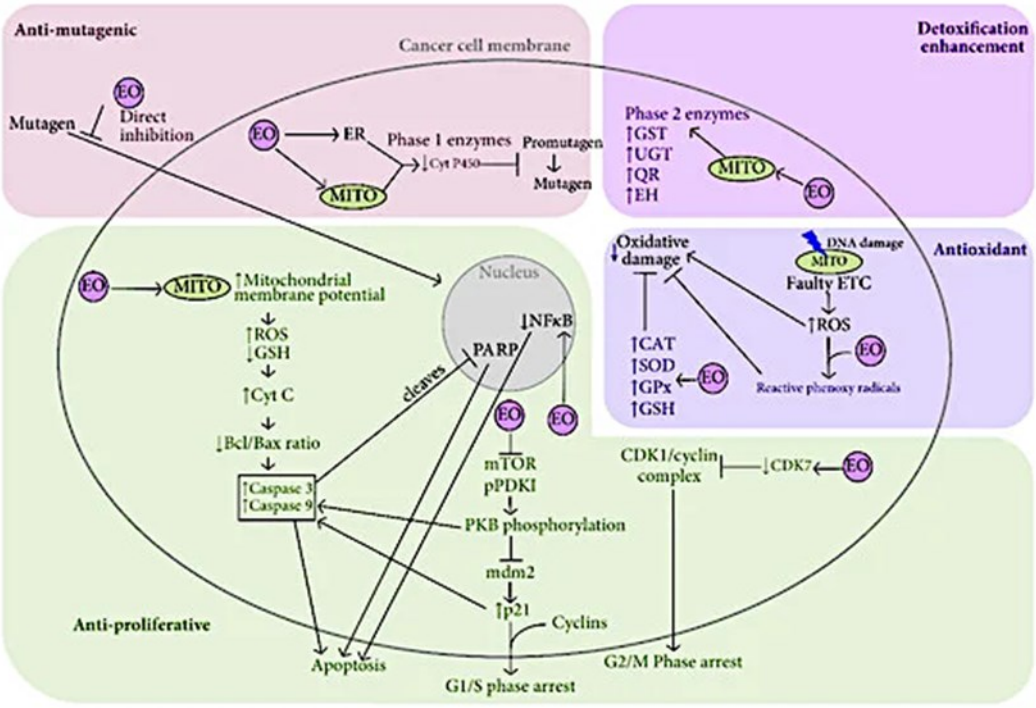


Figure 3. Mechanism of action of terpenoid essential oils as anticancer [59].

head cancers. However, the side effects of radiation therapy are skin changes, hair loss, and fatigue. Immunotherapy is a cancer therapy that stimulates the immune system by administering antibodies, adoptive cell transfer, and checkpoint therapy. Palliative care is a complementary cancer treatment that takes care of the psycho-social, spiritual, and emotional aspects of the patients [9].

Chemotherapy is one of the well-known cancer therapies employing anticancer agents with effective and selective anticancer activity against certain cancer cell lines [10]. Figure 2 shows the commonly used cancer cell lines in medical research. An effective anticancer agent is characterized by using a dosage as low as possible with a high ability to eliminate the cancer cells. For this purpose, medicinal chemists use a half-maximal inhibitory concentration (IC_{50}) to describe the required drug dosage to inhibit the growth of cancer cells by 50%. The anticancer agent can be classified as strong, moderate, weak, and inactive when the IC_{50} values are less than 5 µM, 5-10 µM, 10-50 µM, and more than 50 µM, respectively. On the other hand, selective anticancer agents noted by the targeted cells are cancer cells only, with no toxic effects on the normal cells. This approach is also well-known as targeted therapy to distinguish between cancer and normal cells [11]. The selectivity of anticancer agents is indicated by the selectivity index parameter, obtained from a division of the IC_{50} value for normal cells by the IC_{50} value of cancer cells [12]. There is an inevitable demand for research in the design and development of anticancer agents due to the ongoing suffering of cancer patients and the relentless rise in global mortality rates. The search for effective and selective anticancer agents has been attracting the world's attention to construct a sustainable health system with no cancer deaths in the future [13].

Chemotherapy could be performed using natural and/or synthetic compounds [14]. Nature is an untapped source of biological and functional compounds [15]-[19]. However, natural compounds are preferable due to their high biocompatibility, low cytotoxicity to normal cells, and ease of access from plants' extraction and isolation [20]. Unfortunately, the anticancer activity of some natural compounds is not satisfactory; thus, further modification through synthetic procedures is necessary to enhance their anticancer activity [21]-[23]. This approach is known as a semisynthetic anticancer agent [24]. This review will focus on the potency of natural compounds and their semisynthetic derivatives to fight cancer disease from a molecular point of view.

2. THE POTENCY OF NATURAL COMPOUNDS AS ANTICANCER AGENTS

Active compound products from natural ingredients contribute to the discovery of new drugs, tracers, and chemical entities available for treating of various cancer diseases [25]-[28]. Natural compounds and their derivatives have shown great potential for the development of chemotherapy in the treatment of various cancers and show a wide diversity of structural, pharmacological, and molecular characteristics that support the development of treatment [29]. Around 80% of drugs used as active ingredients in chemotherapy come from natural ingredients. Natural bioactive compounds exhibit cytotoxic effects by attacking macromolecules expressed by cancer, such as oncogenic signal transmission pathways [25][30][31]. Besides, bioactive compounds also function as agents to suppress the proliferation, angiogenesis, and metastasis of cancer cells and, at the same time, prevent immunosuppression without damaging normal cells [32][33]. Classes of natural compounds reported to have potential for treating various cancers include terpenoids [34]-[39], flavonoids [38]-[42], and alkaloids [43]-[50]. Some of the descriptions below show scientific evidence of the potential of groups of active compounds from natural ingredients in cancer treatment.

2.1. Terpenoids

The terpenoid group of compounds is often called isoprenoids, which are the most abundant natural products and have diverse structures in plants [51]. Terpenoids play an essential role in plants as a response to the environment and physiological processes. This group shows diverse pharmacological effects such as antitumor, antiviral, antimalarial, anti-inflammatory, antibacterial, anticancer effects, preventing and treating cardiovascular diseases, and hypoglycemic activity [52]-[55]. The class of compounds that include terpenoids includes monoterpenes, sesquiterpenes, diterpenes, sesterpenes, triterpenes, and tetraterpenes in plants synthesized with the C5

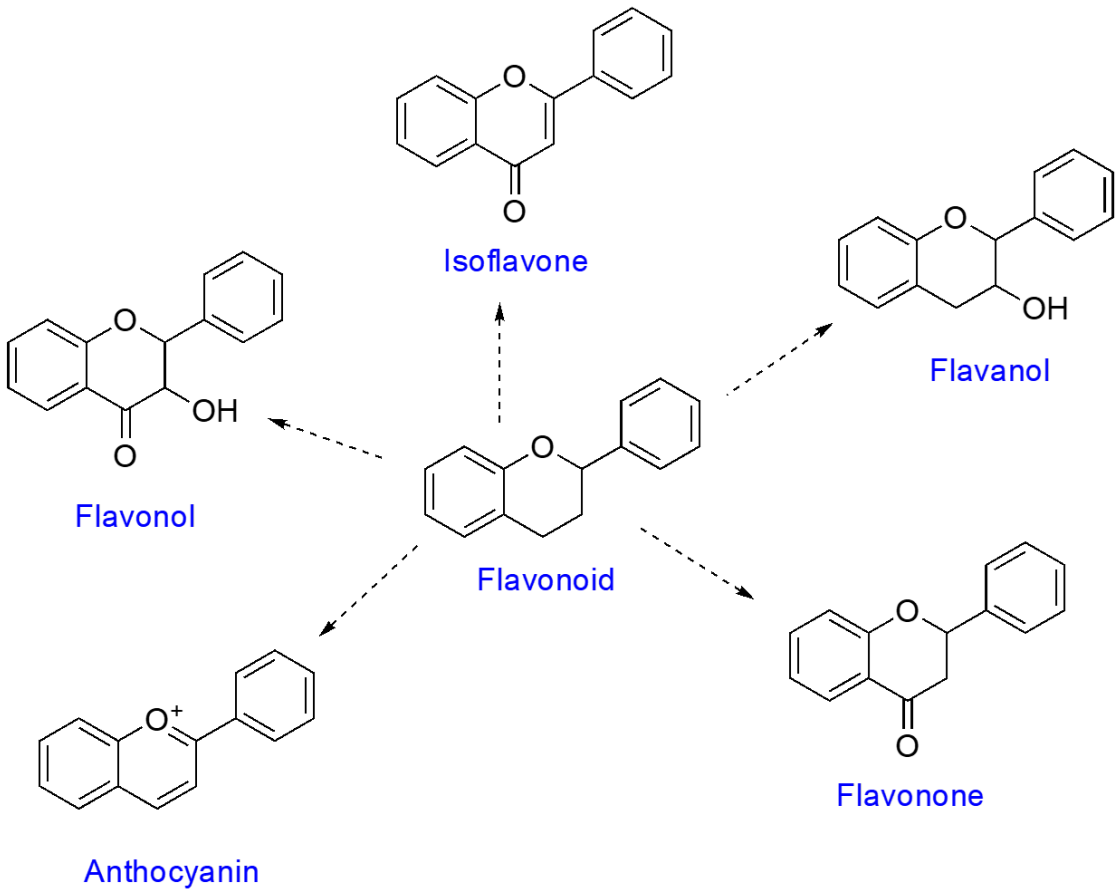


Figure 4. The flavonoid framework and the types of classes included.

Table 1. Potential anticancer activity of the terpenoid group based on the classification of the number of carbon units.

Compound Name	Cancer Cell Line	IC_{50}	Ref.
Carvacrol	U-87	322.0 µM	[62]
	MDA-MB-231	199.0 µM	
	MCF-7	46.5 µg/mL	
	HeLa	550.0 µM	
Citral	MCF-7	140.7 µg/mL	
	HT-29 and HCT-116	50–200 µg/mL	
Thymol	HL-60	20–100 µM	
	B16F10	88.0 µg/mL	
Linalool	HEp-2	25.2 µg/mL	
	PC-3	46.0 µg/mL	
	A549	141.0 µg/mL	
	HCT-116	100–200 µM	
Limonene	A375-C5	9.8 µg/mL	
	Caco-2	90.0 µg/mL	
(*R*)-(-)-Carvone	HT-29	475.0 µg/mL	[63]
(*S*)-(+)-Carvone	HT-29	310.0 µg/mL	
Ferutinin	HT-29	29.0 µg/mL	
	CT26	26.0 µg/mL	
β-Caryophyllene	HCT-116	19.0 µM	[64]
	HepG2	4.0 µM	
	DU-145	210.0 µM	
β-Ionone	LNCaP	130.0 µM	
	PC-3	130.0 µM	
Isoalantolactone	SGC-7901, HeLa, U-87 and A549	4.4–10.2 µM	
7α-acetoxyroylcanone	MIA PaCa-2	4.7 µM	[65]
	MV-3	7.4 µM	
Horminone	MIA PaCa-2	27.5 µM	
	MV-3	16.7 µM	
	MCF-7	9.6 µg/mL	[66]
	K-562	5.1–9.6 µg/mL	
Royleanone	MIA PaCa-2	32.5 µM	
	MV-3	>80 µM	
7α-ketoroyleanone	MIA PaCa-2	30.2 µM	[65]
	MV-3	65.8 µM	
7α-ethoxyroyleanone	MIA PaCa-2	>100 µM	
	MV-3	>80 µM	
7α-acetoxy-6β-hydroxyroylcanone	MCF-7	7.9 µM	
	HCT-116	7.9 µM	
6β,7α-dihydroxyroylcanone	MCF-7	26.0 µM	[67]
	HCT-116	>50 µM	
	A549	25.0 µM	

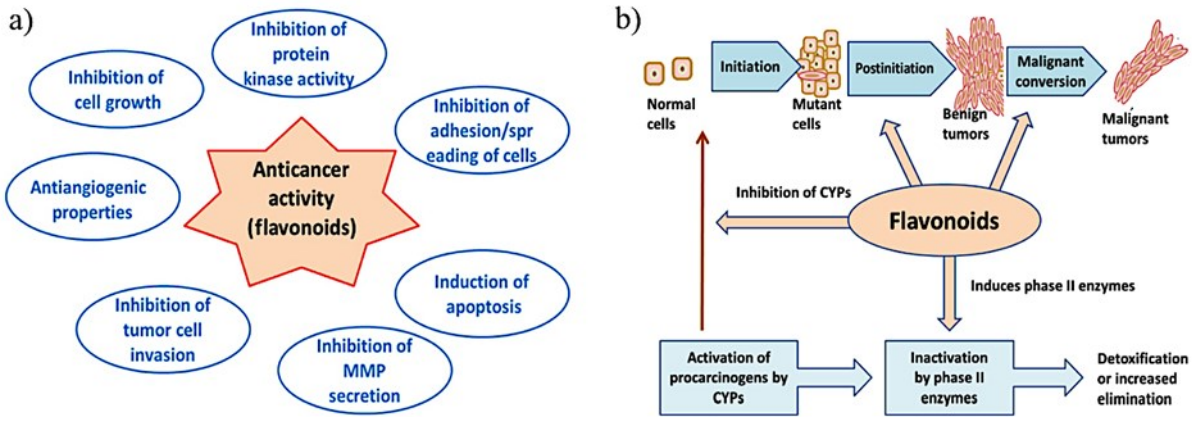


Figure 5. Anticancer (a) activity and (b) molecular mechanism of action of flavonoids.

precursor of isopentenyl diphosphate (IPP) and the allylic isomer dimethylallyl diphosphate (DMAPP) [56][57]. Several terpenoid compounds that have potential as anticancer agents are presented in Table 1.

The pathways of the terpenoid compound class in providing anticancer effects are very diverse, including antiproliferative, apoptotic, antiangiogenic, and antimetastatic, which have been tested through *in vitro* and *in vivo* research. The antiproliferative pathway is carried out by inhibiting the NF-KB pathway and increasing phosphorylation of JNK and ERK (mitogen-activated protein kinases (MAPK)) in colon cancer through freezing the cell cycle and targeting the PI3K and EGFR/MMP-9 signaling pathways in cancer cells (PC3) and bladder cancer cells (GBC-SD). The apoptotic pathway activates caspases and provides an anti-apoptotic response through the Bcl-2/Bax pathway in cervical squamous carcinoma and cervical cancer cells. In lung cancer (A549 and H1299), some compounds in this group provide an autophagy response through the pro-apoptotic agent Atg5, which interacts with the Bcl-XL transmembrane, resulting in the activation of caspases involved in apoptosis and causing cell death [37]. Angiogenesis pathway by suppressing VEGFR and downstream phosphorylation of Akt and Erk [37][58][59]. Antimetastatic pathways in cervical cancer investigated *in vivo* suppress COX-2 expression at the transcriptional level and suppress HOX antisense intergenic RNA (HOTAIR) expression [37].

The terpenoid compound group can inhibit angiogenesis and metastasis through different intracellular signaling pathways. The terpenoid group also has a mechanism to cause epigenetic and cell death targeted at kB (NF-kB), Janus kinase signal transducer and activation of transcription protein (JAK-STAT), activator protein-1 (AP-1), metalloproteinases (MMPs), DNA topoisomerase I and II, inhibits the endoplasmic reticulum (ER) ATPase calcium pump, inhibits the proteasome, activates p53, and modulates the DNA minor groove [60]. In particular, the terpenoid group (essential oils) plays an anticancer role with preventive mechanisms (Figure 3), direct effects on existing cancer cells, and direct interaction with the tumor microenvironment. Essential oils have antimutagenic, antiproliferative, antioxidant, and detoxifying abilities on various cancer cell lines and can prevent cancer. Terpenoid essential oils can inhibit the occurrence of mutagens, reduce phase I enzymes (such as Cytc), and increase phase II enzymes (such as GST, UGT, QR, and EH) while increasing detoxification [61].

2.2. Flavonoids

The flavonoid group generally has a basic framework of 15 carbons (C6-C3-C6) with two aromatic rings formed from each C6 (A and B) connected to a heterocyclic pyran ring (C3). The large groups included in the flavonoid group (Figure 4) are flavanones, isoflavonoids, flavanols, flavones, flavonols, and anthocyanidins [40]. Flavonoids have various properties, one of which is that they act as an anticancer agent but also have neuroprotective and cardioprotective effects. This depends on the type of flavonoid, which determines how it works and its bioavailability [42]. Anticancer

agents that have been reported are against lung, breast, glioblastoma, prostate, colon, and pancreatic cancer, both *in vitro* and *in vivo*, by inhibiting tumor cell proliferation, providing protection from carcinogenicity, stopping the cancer cell cycle, and inducing apoptosis through different signals [41]. The activity of anticancer agents is shown in Figure 5(a), and the anticancer mechanism of the flavonoid group is shown in Figure 5(b).

The type of compound that is widely used as an anticancer agent is the aurone compound (a benzo-furanone). The mechanism as an anticancer with many targets includes cyclin-dependent kinase, adenosine receptor, histone deacetylase, sirtuin, telomerase, and microtubules [42]. Aurone, a benzo -furanone, is another flavonoid widely used as an anticancer agent. Various aurone analogs display different mechanisms against cancer cells due to their multiple possible targets. These targets include cyclin-dependent kinases, histone deacetylases, adenosine receptors, telomerase, sirtuins, and microtubules [56]. Another type of flavonoid compound, namely luteolin, inhibits the development of carcinogenesis (cell transformation, metastasis, invasion, and angiogenesis) by various mechanisms, including suppressing kinases, cell regulation, inducing apoptotic cell death, and suppressing the transcription of cancer cells [41]. Several flavonoid compounds that have potential as anticancer agents are presented in Table 2.

2.3. Alkaloids

Alkaloid groups are often classified based on the heterocyclic ring and precursors in their biosynthesis. The alkaloid groups included are tropane, purine, isoquinoline, pyrrolidine, quinolizidine, imidazole, piperidine, indole, and pyrrolizidine. Chemical entities from the alkaloid group have shown various biological activities, including anticonvulsant, analgesic, anthelmintic, anti-inflammatory, antibacterial, antifungal, antimalarial, anticancer, and cardiotonic [72]. The

Table 2. Potential anticancer activity of several flavonoid compounds.

Compound Name	Cancer Cell Line	IC_{50}	Ref.
Fisetin	Ca9-22	50 µM	[68]
	CAL-27	200 µM	
	HSC-3	40 µM	
Kaempferol	SCC-4	< 100 µg/mL	
	MCF-7	17.5–70 µM	
	SAS	40 µM	
Quercetin	SC20	160 µM	
	HSC-3	20 µM	
	TW206	45 µM	
Cyanidin	HeLa	5.8 µM	[69]
	MCF-7	47.2 µM	
Delphinidin	MCF-7	120 µM	
Hesperetin	HT-29	29 µg/mL	[64]
	CT26	26 µg/mL	
Naringenin	HCT-15	19 µM	
	HepG2	4.0 µM	
(+)-Cathecin	HT-29	0.4 µg/mL	[70]
	A549	25 µg/mL	
	HCT-116	200–600 µM	
Epicathecin	HepG2	50 µM	[71]
	TCCSUP	20 µg/mL	

Table 3. Potential anticancer activity of several alkaloid compounds.

Compound Name	Cancer Cell Line	IC_{50}	Ref.
Caffeine	RT-2	0.5 mM	[70]
	HCC	100 mM	
	MCF-7 and MDA-MB-231	5 mM	
Theobromine	HT-29	1.22 µg/mL	
	HT-29	0.67 µg/mL	
	U-87	3–10 mM	
	Ovarian	20 µg/mL	
Sarcovagine D	MCF-7	16.2 µM	[69]
	A549	11.2 µM	
Solasonine	HT-29	1.4 µM	
	MCF-7	16.0 µg/mL	
	HeLa	22.7 µg/mL	
	HT-29	52.2 µg/mL	

alkaloid group is the most active natural ingredient in anticancer agents and is considered to have fewer side effects and cause lower resistance compared to existing chemotherapy agents. Mechanism of action of alkaloid groups and derivative compounds (berberine, matrine, evodiamine, piplartine, piperine, sanguinarine, aporphine, tetrandrine, harmine, harmalacidine, harmaline, and vasicinone. *In vitro* and *in vivo* test results for several groups of alkaloid compounds show activity against cancer, which causes apoptosis and arrest in the G1 and G2/M phases of cancer cells [72]. Several groups of alkaloids show stronger activity compared to controls (such as aporphine, isooxoaporphine, bisbenzylisoquinoline, oxoaporphine, and protoberberine compounds showing anticancer activity or anti-effects). Multidrug resistance (MDR) is stronger than positive control, thus encouraging the potential for the development of new cancer drugs [73].

In vitro and *in vivo* experiments on berberine have demonstrated anticancer activity by causing cell cycle arrest in the G1 or G2/M phase, apoptosis, inhibition of metastasis, invasion of tumor cells, and inhibition of cyclooxygenase-2 (COX-2), *N*-acetyltransferase (NAT), and telomerase enzymes [72]. The mechanism of the alkaloid group (indole compounds) regulates autophagy in the PI3K/Akt/mTOR signaling pathway, MAPK signaling pathway, ROS signaling pathway, and Beclin-1, leading to antitumor activity (Figure 6). Several alkaloid compounds that have potential as anticancer agents are presented in Table 3.

3. THE PROMISING APPLICATION OF SEMISYNTHETIC DERIVATIVES FROM NATURAL COMPOUNDS AS ANTICANCER AGENTS

The semisynthetic derivatives from natural compounds will be focused on xanthones and epoxides. Xanthones with dibenzopyrone structure are generated through mixed shikimic acetate and acetate polymalonic pathways. From 2012–2019, around 1200 xanthones have been isolated from natural sources. Natural xanthones are found in Polygalaceae, Logniaceae, Leguminosae, Moraceae, Hypericae, Guttiferae, Gentianaceae, Filicineae, Fabaceae, Eriocaulaceae, Clusiaceae, Asteraceae, Annonaceae, Anacardiaceae, and Amaranthaceae. From their chemical structures, xanthones are classified as (i) oxygenated xanthones, (ii) glycosylated xanthones, (iii) prenylated xanthones, (iv) xanthone dimers, (v) xanthonolignoid, and (vi) miscellaneous xanthone [75]. Xanthones exhibit anticancer activities

through various mechanisms. Firstly, they are able to activate caspase proteins, triggering the apoptosis of cancer cells. They are also able to inhibit protein kinases, impeding the proliferation of cancer cells. Xanthones also inhibit prostaglandin PG-E2, a lipid involved in inflammation, angiogenesis, apoptosis, and anti-proliferation. They also could inhibit topoisomerase, a crucial protein for halting DNA replication in cancer cells. Xanthones also inhibit P-glycoprotein, which is crucial for combating multidrug resistance in cancer cells. Xanthones also suppress the replication of cancer cells by binding to RNA and forming DNA crosslinks [76].

Sometimes, natural xanthones suffer from weak anticancer activity with high toxicity to normal cells. Sterigmatocystin isolated from *Aspergillus versicolor* gave the IC_{50} value of up to 14.2 µM against HCT-15, SK-OV-3, A549, XF-498, and SK -MEL-2 cancer cells [77]. On the other hand, schomburgones A and B isolated from *Garcinia schomburgkiana* showed weak and negligible anticancer activity with IC_{50} values of 45.05-69.22 µM against HepG2, MCF-7, HeLa S-3, and KB cancer cells [78]. Furthermore, natural xanthones are found in very low amounts in natural sources, which require tedious and complicated separation and purification processes. Therefore, modification of natural xanthones through a semisynthetic approach is required [79]. The semisynthetic approach serves as an untapped source for an unlimited variation of chemical compounds that may not be found in natural compounds and allows researchers to design the target compounds based on structure-activity relationships for better anticancer activity.

Salicylic acid is a natural compound that could be used as the starting material for xanthone synthesis. We reported a one-pot reaction method to obtain hydroxyxanthones from the salicylic acid and phenolic compounds. In this protocol, benzoic acid was protonated using methylsulfonic acid to form the inorganic ester as the intermediate. Afterward, the acylation reaction takes place, followed by the dehydration reaction to build the cyclic structure of xanthone [79]. The reaction mechanism is shown in Figure 7. By using this method, we have synthesized various hydroxyxanthones, i.e., 1-hydroxyxanthone, 1,3-dihydroxyxanthone, 1,6-dihydroxyxanthone, 3,6-dihydroxyxanthone, 1,3,8-trihydroxyxanthone, and 1,5,6-trihydroxyxanthone have been successfully obtained in up to 46.50% yield [80][81]. These xanthone derivatives showed potential anticancer activity through topoisomerase and epidermal growth factor receptor inhibition, as revealed by molecular docking and molecular dynamic investigations [82].

Table 4 illustrates the anticancer effects of hydroxylated xanthones. Among these compounds, 1-hydroxyxanthone, 1,3-dihydroxyxanthone, 1,6-

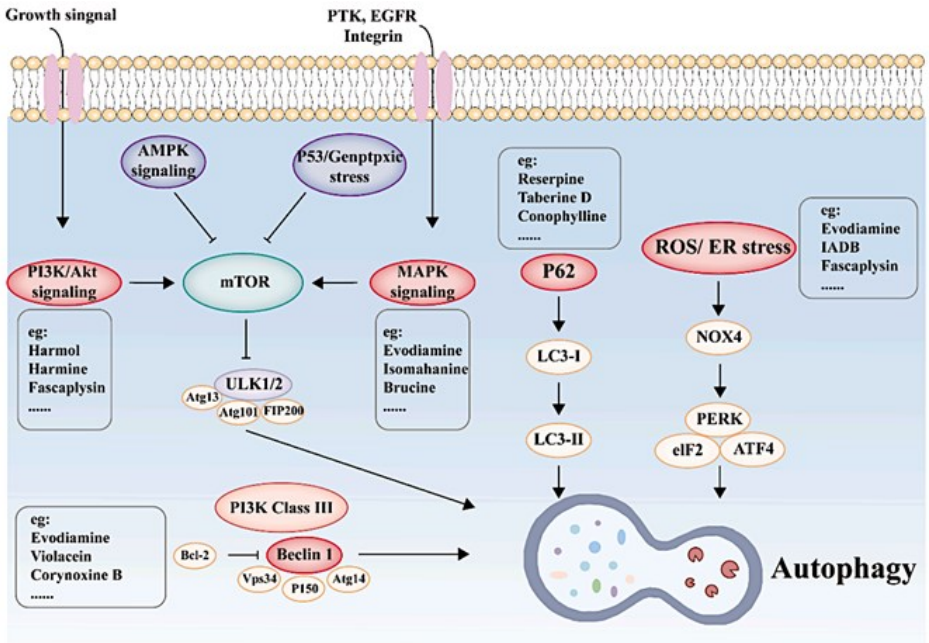


Figure 6. Mechanism of the alkaloid (indole) pathway as an anticancer agent [74].

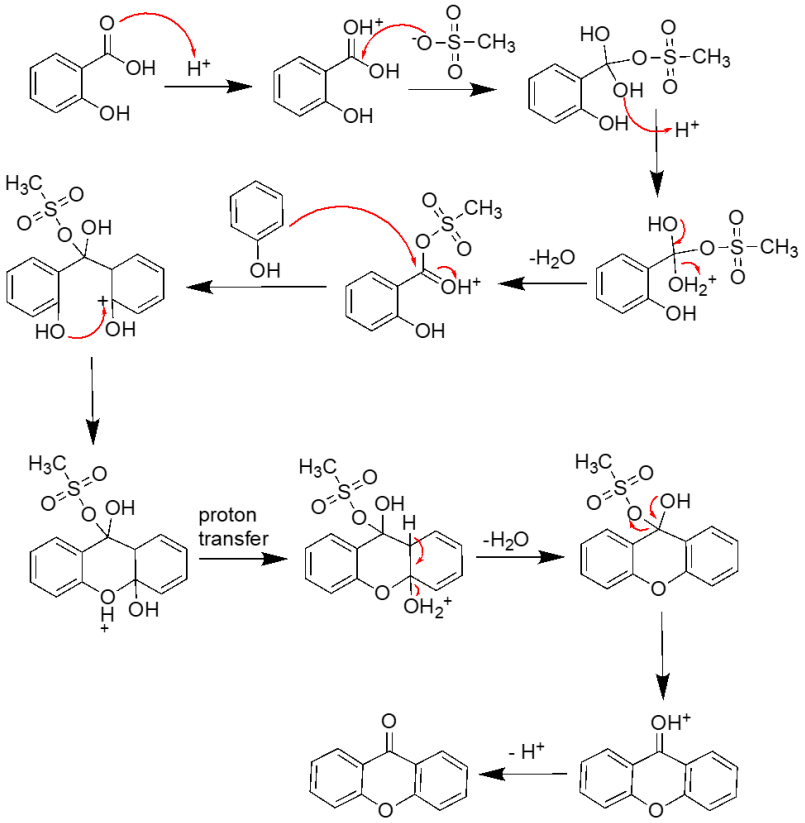


Figure 7. One pot synthesis mechanism for xanthone synthesis.

dihydroxyxanthone, 3,6-dihydroxyxanthone, 1,3,6-trihydroxyxanthone, 1,3,8-trihydroxyxanthone, and 1,5,6-trihydroxyxanthone exhibited varying degrees of efficacy against HeLa cancer cells, with IC_{50} values ranging from 86.0 to more than 200 µM. Lower IC_{50} values signify greater anticancer potential. In particular, 1-hydroxyxanthone demonstrated the least efficacy against HeLa cancer cells (IC_{50} = >200 µM) due to its single hydroxyl group. Conversely, additional hydroxyl groups, as seen in 1,3-dihydroxyxanthone, 1,6-dihydroxyxanthone, 3,6-dihydroxyxanthone, 1,3,6-trihydroxyxanthone, 1,3,8-trihydroxyxanthone, and 1,5,6-trihydroxyxanthone, significantly enhanced their anticancer. Notably, the position of the hydroxyl group influenced efficacy; for instance, 1,3-dihydroxyxanthone (IC_{50} = 86.0 µM) was more potent than 1,6-dihydroxyxanthone. Furthermore, the combination of hydroxyl groups in 1,3,6-trihydroxyxanthone and 1,5,6-trihydroxyxanthone slightly augmented their anticancer activity, while similar additions to 1,3-dihydroxyxanthone attenuated its efficacy. This outcome suggests the importance of hydrogen bonding in their activity. Against WiDr cancer cells, a similar trend in anticancer activity was observed, with 1,3-dihydroxyxanthone displaying the highest efficacy (IC_{50} = 114 µM) [80].

Likewise, the anticancer potential of hydroxyxanthones against HepG2 cancer cells varied based on the number and position of hydroxyl groups. A xanthone lacking hydroxyl substituents served as a control, exhibiting an IC_{50} value of 85.3 µM. Introducing a hydroxyl group at the 1-position notably enhanced anticancer activity to an IC_{50} of 43.2 µM, whereas addition at the 3-position showed no effect. Further addition of hydroxyl groups yielded 1,X-dihydroxyxanthones, which generally displayed stronger anticancer effects compared to xanthones without hydroxyl groups. Notably, 1,6-dihydroxyxanthone and 1,7-dihydroxyxanthone were particularly potent. Similarly, 2,X-dihydroxyxanthones exhibited enhanced anticancer activity, except for 2,7-dihydroxyxanthone, indicating that the 7-position was unfavorable. The 3,X-dihydroxyxanthone group also demonstrated increased activity, except for 3,4-dihydroxyxanthone, suggesting that additional hydroxyl groups at the 4-position were

inactive. Trihydroxyxanthones generally displayed stronger anticancer activity than xanthones without hydroxyl groups, except those with hydroxyl groups at the 4- and 7-positions. Notably, 1,3,5-trihydroxyxanthone and 1,3,6-trihydroxyxanthone showed substantial efficacy against HepG2 cancer cells. Evaluation of tetrahydroxyxanthones and pentahydroxyxanthones revealed even greater anticancer activity compared to xanthone without hydroxyl groups or monohydroxyxanthone. Notably, 1,3,6,8-tetrahydroxyxanthone displayed exceptional potency, surpassing the effectiveness of doxorubicin [83].

In general, the order of anticancer activity of hydroxyxanthones was monohydroxyxanthone < trihydroxyxanthone < dihydroxyxanthone < pentahydroxyxanthone < tetrahydroxyxanthone. Trihydroxyxanthones were expected to exhibit greater activity than dihydroxyxanthones, while pentahydroxyxanthones were more potent than tetrahydroxyxanthones. However, the arrangement of hydroxyl groups was critical to avoid intramolecular hydrogen bonding, which could hinder interaction with protein receptors in HepG2 cancer cells. Overall, 1,3,6,8-tetrahydroxyxanthone emerged as the most promising anticancer agent against HepG2 cancer cells, displaying remarkable efficacy with an IC_{50} value of 9.18 μM, surpassing the activity of doxorubicin by 5.11-fold. The molecular docking studies revealed that 1,3,6,8-tetrahydroxyxanthone interacted by hydrogen bonding with Adenine12, Guanine13, Cytosine14, Arginine503, Lysine505, and Alanine521 amino acids in the active site of topoisomerase IIα protein. 1,3,6,8-tetrahydroxyxanthone could also interact with Lysine721, Threonine766, Glutamine767, and Methionine769 through hydrogen bondings in the active site of epidermal growth factor receptor (EGFR). Our previous study also found that 1,3,6,8-tetrahydroxyxanthone interacted with Threonine670, Glutamic acid671, Cysteine673, and aspartic acid810 in the active site of platelet-derived

Table 4. Summary on the anticancer activity of semisynthetic xanthones.

Compound	IC_{50} (μM)		
	WiDr	HeLa	HepG2
xanthone	-	-	85.3
1-hydroxyxanthone	> 200	> 200	43.2
3-hydroxyxanthone	-	-	85.3
1,3-dihydroxyxanthone	114	86.0	71.4
1,6-dihydroxyxanthone	> 200	> 200	40.4
1,7-dihydroxyxanthone	-	-	13.2
2,5-dihydroxyxanthone	-	-	23.8
2,6-dihydroxyxanthone	-	-	52.2
2,7-dihydroxyxanthone			> 200
3,4-dihydroxyxanthone			89.7
3,5-dihydroxyxanthone			23.7
3,6-dihydroxyxanthone	> 200	162	61.7
1,3,5-trihydroxyxanthone	-	-	15.8
1,3,6-trihydroxyxanthone	141	> 200	45.9
1,3,7-trihydroxyxanthone	-	-	33.8
1,3,8-trihydroxyxanthone	> 200	> 200	63.1
1,5,6-trihydroxyxanthone	> 200	> 200	-
2,3,7-trihydroxyxanthone	-	-	63.3
3,4,6-trihydroxyxanthone	-	-	87.3
3,4,7-trihydroxyxanthone	-	-	> 200
1,3,6,7-tetrahydroxyxanthone	-	-	23.7
1,3,6,8-tetrahydroxyxanthone	-	-	9.18
1,3,4,5,6-pentahydroxyxanthone	-	-	12.6

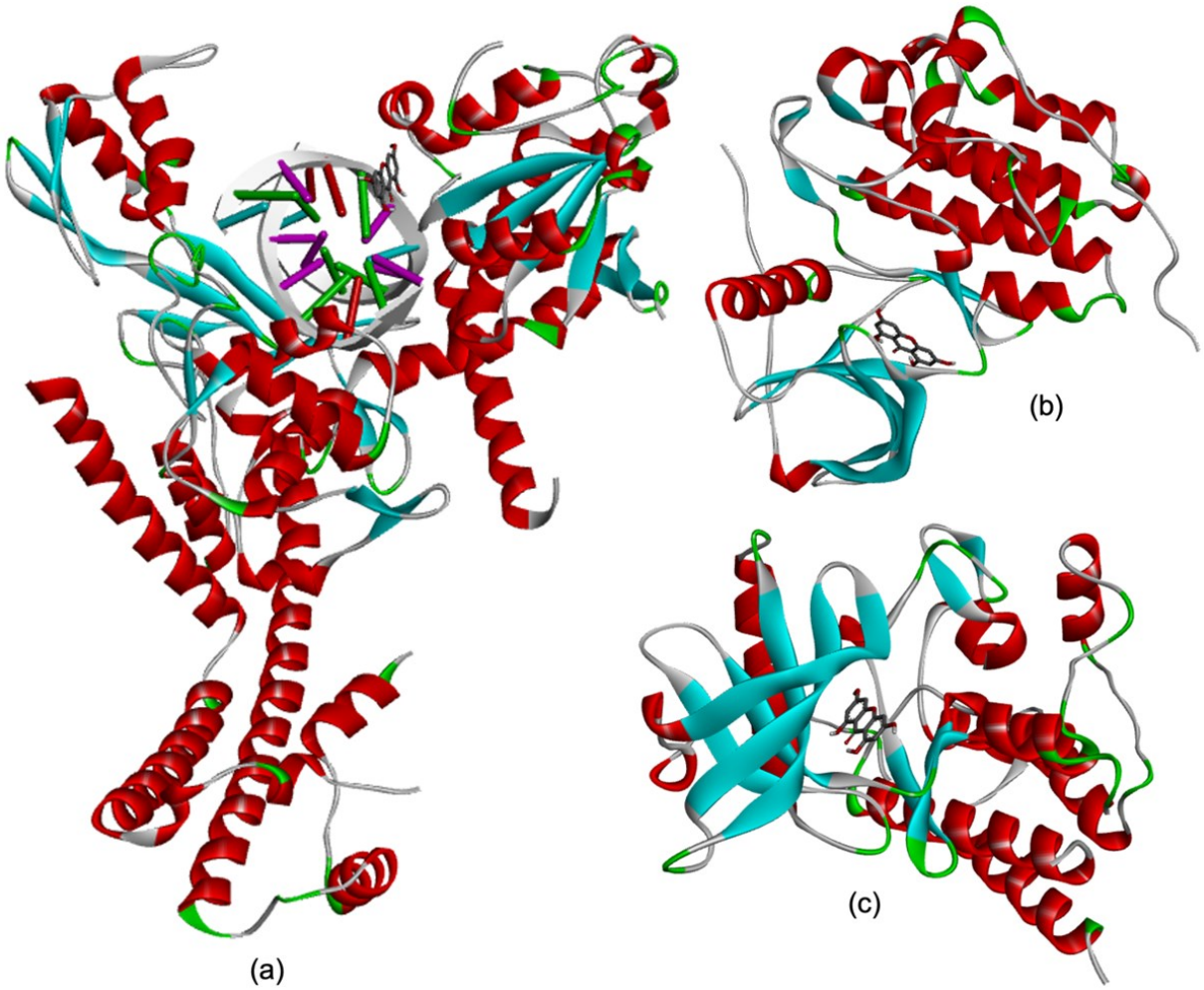


Figure 8. Molecular docking study of 1,3,6,8-tetrahydroxyxanthone against (a) topoisomerase IIα, (b) EGFR, and (c) PDGFR protein receptors.

growth factor receptor (PDGFR) (Figure 8). This multimode binding demonstrates the excellent anticancer activity of 1,3,6,8-tetrahydroxyxanthone against the HepG2 cancer cell line [83].

The semisynthetic xanthones, i.e., α-mangostin, 5,6-dimethylxanthenone-4-acetic acid (DMXAA), hycanthone, and lucanthone have been evaluated in the clinical assay. α-Mangostin in mangosteen juice is safe for 20 patients. However, the healing effect takes time because the concentration of α-mangostin is quite low (3.90 g/L). On the other hand, DMXAA exhibited no drug-related myelosuppression in 63 patients at a dosage of up to 4.9 g/m^2. However, DMXAA failed in clinical trials phase III due to no significant activity for human STING. Hycanthone and lucanthone have been assayed in clinical trials but they failed due to serious mutagenic effects. In summary, Figure 9 shows the promising xanthones as anticancer agents. These semisynthetic xanthones yielded strong anticancer activity with IC_{50} values less than 1.15 µM, which was remarkable. The brominated dihydroxyxanthone, glycosylated xanthone, prenylated xanthones, dimethylamino alkylated hydroxyxanthone, and xanthone dimer gave an IC_{50} value of 0.87, 0.19, 0.74, 0.87, 1.13, 0.47, and 0.38 µM against MDA-MB-231, NCI-H460, HeLa, PC-3, HCT-116, CNE, and HL-60 cancer cells, respectively [76].

Other utilization of phenolic compounds and oleic acids yielded new potent anticancer agents. When resorcinol compounds are cyclized with aldehyde in acidic conditions, a macrocyclic tetramer of calix[4]resorcinarene compound is generated [84]. Alkylation of calix[4]resorcinarene with epichlorohydrin led to the formation of calix [4]resorcinarene epoxide in 70% yield. This compound yielded an IC_{50} value of 3.26 µM against

MCF-7 cancer cells. The MCF-7 cancer cells were killed through the apoptotic mechanism, as shown in Figure 10. The molecular docking study revealed that the calix[4]resorcinarene epoxide could bind to the active site of EGFR through a hydrogen bond with Lysine692 and Lysine704 amino acid residues at a distance of 2.202 and 2.549 Å, respectively. Furthermore, the calix[4]resorcinarene could form a stable complex with imatinib with a binding energy of -350.4 kcal/mol and could be used for drug delivery, as revealed from the molecular dynamic study for 100 ns. At the initial point, the imatinib interacted through pi-pi interaction with calix as the host compound. At 72 ns, the imatinib started to release due to hydrogen bonds with water molecules in the simulation box. Then, a complete separation of imatinib and calix was observed imatinib and calix separated completely at 100 ns simulation time, as shown in Figure 11 [85].

Oleic acid is an unsaturated fatty acid that is beneficial to human health and has other applications [84][85]. In our latest work, we used palm oil to prepare oleate epoxides as novel anticancer agents. Palm oil contains 0.62% myristic acid, 40.48% palmitic acid, 9.05% linoleic acid, 47.30% oleic acid, and 2.55% stearic acid. After purification through urea inclusion complex, the amount of oleic acid increased to 86.06%, and the amount of myristic acid, palmitic acid, and stearic acid reached zero, as proved by gas chromatography-mass spectrometry (GC-MS) analysis. The epoxidation was successfully carried out in 85% yield with a purity of 90% using pro-analytical grade formic acid and hydrogen peroxide 30% in a mol ratio of 2:7 at room temperature for one day. The epoxidized methyl oleate showed IC_{50} values of 12.63 and 1.56 µg/mL against T47D and WiDr cancer cells. This anticancer activity is close to that of the commercial anticancer agents, i.e., doxorubicin (IC_{50} = 12.58 µg/mL against T47D) and 5-fluorouracil (IC_{50} = 1.58 µg/mL against WiDr), which were remarkable. Furthermore, the selectivity index of epoxidized methyl oleate was very high, i.e., 9.18, 17.94, and 145.13 against HeLa, T47D, and WiDr cell lines. Molecular docking investigation reveals that epoxidized methyl oleate interacted with Tyrosine2309 and Phenylalanine2371 through hydrogen bonds of fatty acid synthase protein, leading to low survival capability, low cell differentiation, limited cell migration, and poor proliferation of cancer cells [86]. A molecular hybridization strategy could enhance the anticancer activity of epoxides, terpenoids, flavonoids, alkaloids, and xanthones.

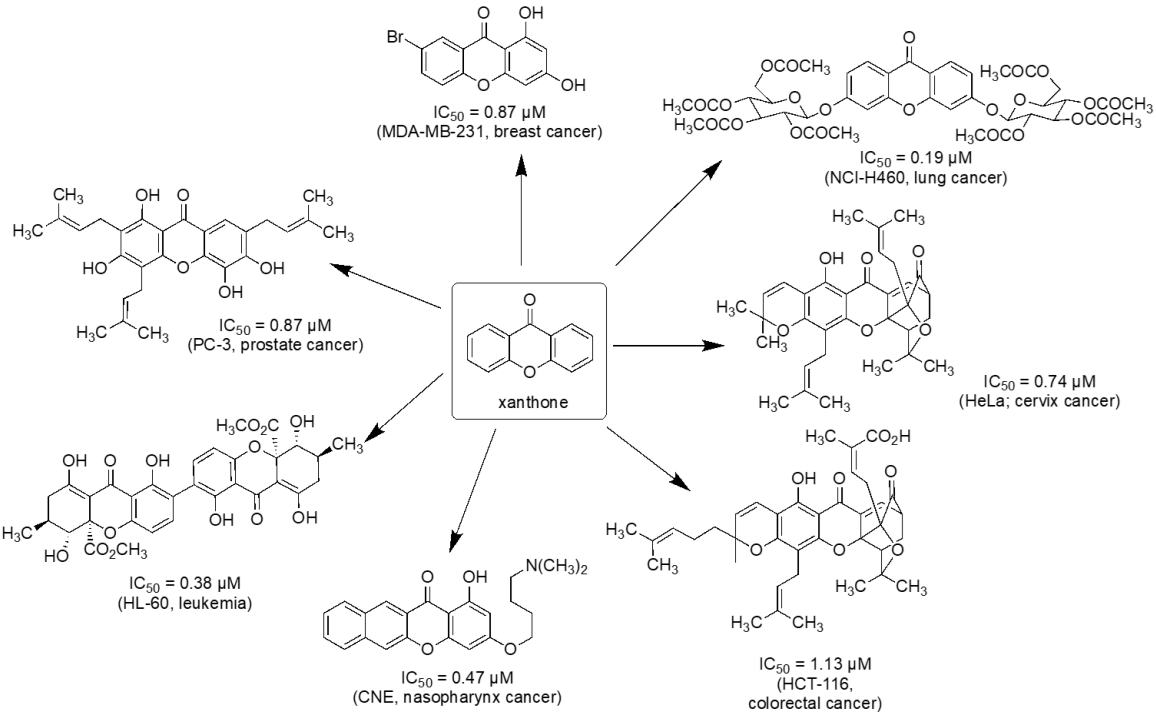


Figure 9. Summary of potential anticancer agents based on xanthone derivatives.

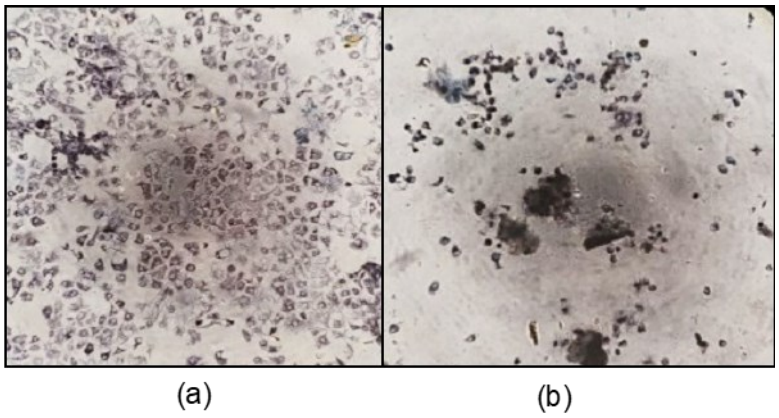


Figure 10. Microscopic observation of MCF-7 cancer cell line (a) before and (b) after the addition of calix [4]resorcinarene epoxide.

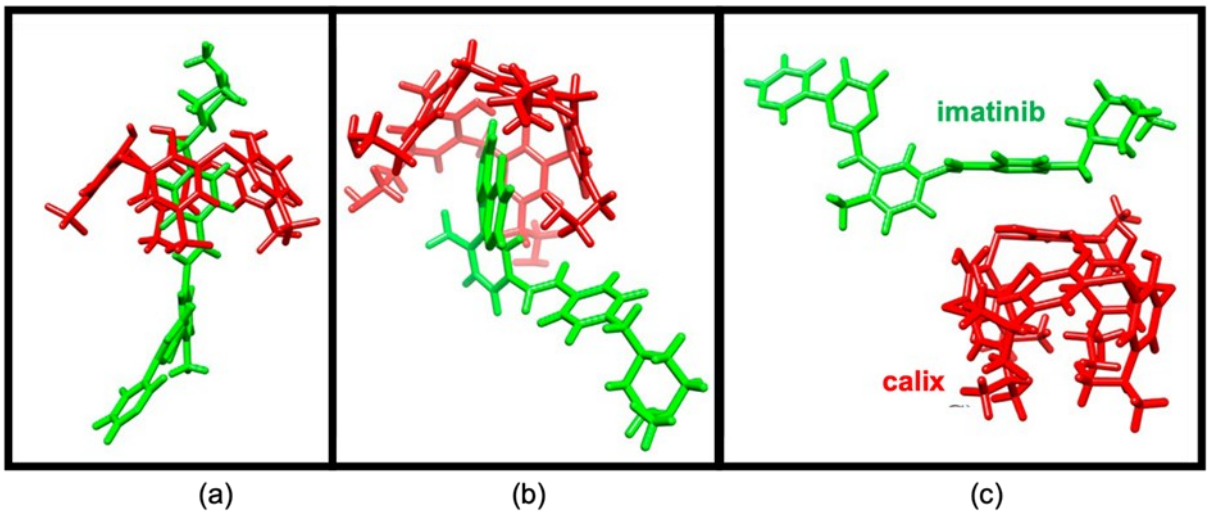


Figure 11. Molecular dynamic simulations of imatinib using calix as the host compound.

This approach combines the chemical structures of natural compounds or their semisynthetic products with commonly used anticancer drugs such as doxorubicin and 5-fluorouracil [87]-[90]. Combining two or more chemical structures will increase the molecular volume, thus giving more access to form chemical interactions with the active site of targeted protein receptors.

4. CONCLUSIONS AND FUTURE DIRECTIONS

Over the past decades, natural compounds have proven immensely valuable as anticancer agents. Many natural compounds have been developed through structural modifications of natural substances or by utilizing them as building blocks in synthesis, serving diverse purposes across wide anticancer activities. Despite the availability of numerous contemporary and expensive treatments, harnessing the potential of natural compounds remains a significant strategy in the fight against cancer. Due to several factors, the evaluation of the anticancer activity and selectivity of natural products will be widely open in the future. First, thousands of new natural compounds and their derivatives are reported nowadays with unknown anticancer activity against some cancer cell lines. Second, the anticancer activity and selectivity of new and well-known natural compounds and their derivatives could be further optimized through the structure-activity relationship of the lead compound. Lastly, interdisciplinary teamwork between chemists, pharmacists, biologists, and computational scientists are pivotal to accelerate the design and development of new anticancer drugs.

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Conflicts of Interest

The authors declare no conflict of interest.

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The first author dedicated this review article for peace memoriam to his mother that had been fighting to cancer from 2019 to 2020.

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