Advances in Anticancer Drug Discovery: Exploring the Untapped Potential of Natural Products for Targeted Therapies

ABSTRACT

Natural products have long been a significant source of structurally diverse and biologically active compounds, making them important for anticancer drug development. Taxol, a natural product isolated from the bark of the Pacific yew tree, is used to treat some cancers; vincristine, a related compound that was eked out of the Madagascar periwinkle plant, treats leukemia and lymphoma. This review provides recent advances and future perspectives on developing natural-product-derived anticancer agents. We introduce celebrated examples of successfully developed natural-product-derived anticancer drugs, such as paclitaxel, doxorubicin, and camptothecin derivatives. We also discuss the hurdles of natural product-derived drug discovery, including limited availability, poor pharmacokinetics, and a lack of specificity to their intended targets.

We will talk about some examples of these types of modification, including new developments in drug delivery systems, nanotechnology, and targeted drug delivery. These show how they could make natural product-derived anti-tumor drugs more effective and less harmful. It is emphasized that researchers from different fields, such as pharmacologists, catalyst chemists, drug delivery experts, rational drug designers, and nanotechnologists, will need to work together and research across disciplines for the project to succeed. This is so that problems and bottlenecks can be solved, and natural products can be used to make new anticancer drugs. Given the continuous and increasing global demand for novel anticancer drugs in the foreseeable future, natural products will remain a critically important source for discovering novel, safe, and effective anticancer drugs.

Keywords: Natural products, Anticancer, Drug discovery, Paclitaxel, Doxorubicin, Camptothecin, Nanotechnology,

I. Introduction

Cancer remains a major global health concern, with consistently high incidence rates and significant mortality figures. In 2020, an estimated 19.3 million new cancer cases were reported, and 10 million people lost their lives to the disease [1]. As we approach 2024, current projections indicate a further increase in these numbers due to factors such as population growth and aging, highlighting the continued urgency for research, early detection, and effective treatments.The anticancer treatment strategies include surgery, chemotherapy, radiotherapy, and targeted therapy. However, the

conventional drugs used for cancer treatment often result in some inherent problems, such as drug resistance, poor efficacy, and severe adverse effects [2]. Traditional cancer therapies frequently come with a metabolic cost and an unknown side-effect profile, creating considerable treatment burdens for carriers who receive them. For example, drug resistance is commonly seen in breast cancer patients receiving paclitaxel and doxorubicin chemotherapies. The chemo treatments sometimes increase the selection pressure, which helps resistant cells survive and multiply during selection. Researchers have also identified some ways in which drugs do not function as well. These include changes to apoptotic signaling pathways and increased drug efflux transporters like P-glycoprotein [3].

Drug resistance can lead to treatment failure and disease progression. Some NSCLC patients initially responded well to treatment with EGFR tyrosine kinase inhibitors (TKIs) like gefitinib and erlotinib. However, these EGFR-specific TKIs often make people resistant by changing EGFR in secondary ways. This makes it harder for drugs targeting EGFR to bind to the receptor and restart EGFR activity. This acquired resistance leads to treatment failure and emphasizes the demand for novel therapeutic strategies [4]. Finally, resistance to endocrine therapy in breast cancer ER+ breast cancer patients is treated with endocrine treatments, including tamoxifen and aromatase inhibitors. However, 30 percent of the patients develop resistance to these agents, either by acquiring alternative signaling pathways or ER-negative cells [5]. The above demonstrates that drug resistance to chemotherapy in cancer has increased the demand for novel anticancer agents and therapeutic strategies.

In contrast to drug resistance, traditional anticancer therapies (e.g., chemotherapy, radiotherapy, and targeted therapy) often lead to a range of side effects with a potentially negative impact on patients' quality of life. Side effects can be acute or chronic, with or without management via other medical interventions. Chemotherapy refers to using drugs that act on specific cellular targets and cause damage to rapidly growing cells, including cancer cells. Because they target any rapidly growing cells, chemotherapy drugs lead to various second-order effects. The most common side effects of chemotherapy include nausea and vomiting, which could be easily alleviated using anti-emetic drugs. There is also hair loss, an expected consequence of the drugs used, which usually regrows once the treatment ends. Chemotherapy may also cause fatigue, a suppression of the immune system, or even anemia. Some chemotherapy drugs are neurotoxic, crippling the nerves and causing tingling, numbness, and pain in hands and feet (known as chemotherapy-induced peripheral neuropathy) [6]. Chemotherapy drugs may also damage the heart, leading to cardiotoxicity, cardiac dysfunction, and heart failure in patients [7].

Radiotherapy uses high-energy beams to destroy cancer cells and normal cells in the treatment area, resulting in unpleasant and sadly unremarkable side effects. Patients can expect to develop redness or blistering skin in any treatment area. Systemically, fatigue can occur and persist for weeks or months following the end of treatment. For patients receiving radiation therapy to the chest, inflammation of the lungs can occur. For other head, neck, and thoracic (chest) tumors, lymph node irradiation can cause lymph fluid buildup in the arms or legs and cause swelling called lymphoedema. Radiation enteritis is fatigue from small intestine inflammation, which causes diarrhea, abdominal pain, and nausea [9].

The therapy targets these molecular changes, which, along with its mechanisms of action, explains its name, 'targeted therapy.' Usually, side effects caused by these newer treatments are milder than the ones associated with chemotherapy and radiotherapy; sometimes, they are nonexistent. Skin-related issues, diarrhea, and high

blood pressure are common. Some targeted drugs can trigger liver damage, and immunotherapy side effects include multi-organ inflammations that can result in colitis, pneumonitis, or endocrinopathies [10]. Against the light shade, conventional anticancer therapies have various side effects that can significantly impair a patient's quality of life. To achieve the best possible outcome in a patient, oncologists must weigh the potential benefits of these treatments against their harmful side effects and adverse reactions and prevent and control them.

Considering the high incidence of cancer and the limitations of conventional treatment, one can well imagine the urgent need for effective treatment and the mandate of alternative treatment for cancer. In other words, exploring alternative therapeutic strategies to combat the ongoing epidemic of human cancers is crucial, and natural products offer significant potential as rich sources of anticancer compounds.

Nature produces various chemicals, potentially leading to the development of numerous new medicines. These medicines could target different parts of the cancer cell or the environment around the tumor involved in starting the cancer, making it grow, or spreading to other body parts. During years of natural product screening, scientists have invested much effort in determining the validity of the chemoprevention hypothesis and discovering as many anticancer compounds as possible from various plant and animal sources. According to the results obtained from numerous in vitro and in vivo studies, scientists show that a list of natural products exhibits promising anticancer activity.

Natural products have long been recognized as a valuable source of structurally diverse and biologically active compounds, making them a vital resource for anticancer drug development. The historical success of natural-product-derived drugs like Taxol and vincristine demonstrates the potential of this approach. However, several challenges impede the efficient development and application of natural-product-derived anticancer drugs.

This comprehensive review aims to analyze the recent advancements, existing hurdles, and innovative solutions in natural-product-derived anticancer drug development. Our work will contribute to a better understanding of the untapped potential of natural products and emphasize the importance of interdisciplinary collaboration in addressing the current challenges. In light of the continuous and increasing global demand for novel anticancer therapies, this review will underscore the crucial role of natural products in the quest for more effective and safer cancer treatments.

Figure 1: Charting the Path of Natural Product-Derived Anticancer Drug Development: From Discovery to Interdisciplinary Solutions

The chart represents the process and key components of developing anticancer drugs derived from natural products. Here's a brief explanation of each element in the chart:

Natural Products: This is the starting point, representing the diverse range of compounds found in nature that serve as the source for anticancer drug candidates.

Recent Advances: This box highlights some successful examples of natural-product-derived anticancer drugs, such as paclitaxel, doxorubicin, and camptothecin derivatives.

Challenges: This box lists some common obstacles encountered in developing anticancer drugs from natural products, including limited availability, poor pharmacokinetics, and lack of target specificity.
Interdisciplinary Solutions: This section emphasizes the importance of collaboration between various scientific fields to overcome the abovementioned challenges. The sub-points within this box list key areas where collaboration is essential, such as pharmacology, catalysis, drug delivery, rational drug design, and nanotechnology.

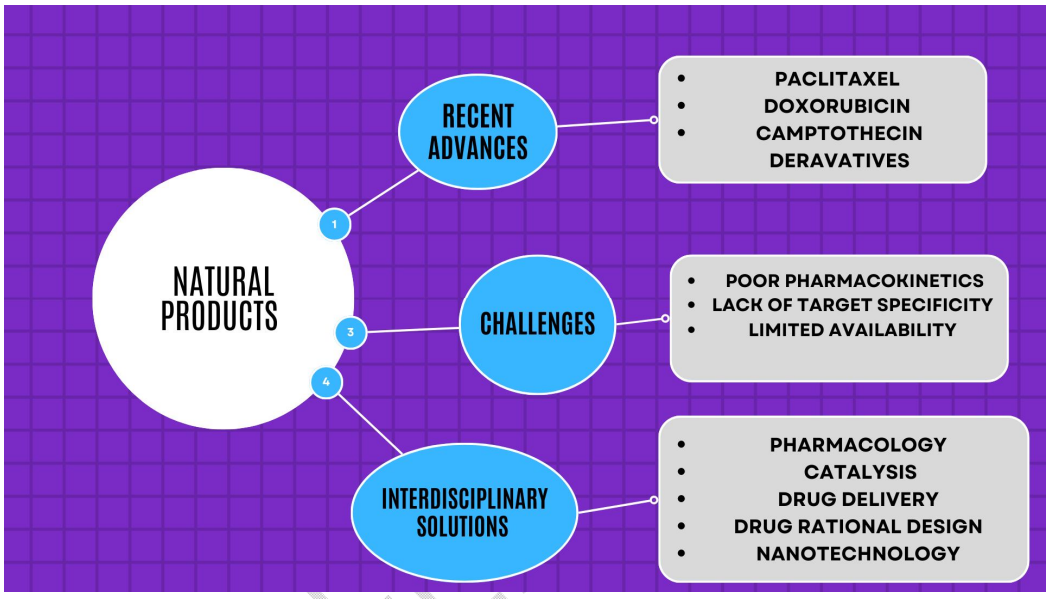

Figure 1:Charting the Path of Natural Product-Derived Anticancer Drug Development

1.1 **Natural products as a valuable resource for anticancer drug discovery**

Most anticancer drugs identified and developed to date are based on natural products. New estimates indicate that natural products and their derivatives were responsible for approximately 70 percent of all anticancer drugs approved between the 1980s and 2010s [11]. Natural products have proven to be a rich resource for anticancer agents, many deriving from plants, marine organisms, and microorganisms. The structures of the constituents often evolved over millions of years within the cells of organisms and consequently might be novel, making them useful in identifying new types of bioactive constituents that we have not come across. Additionally, the continual development in analytical screening techniques and computational methods for natural product characterization is boosting our ability to detect bioactive compounds from natural sources [12].
Several natural products and semi-synthetic or synthetic analogs are now in clinical use as anticancer agents. The most well-known is the one for the drug paclitaxel (Taxol), which is derived from a type of Pacific yew and stabilizes microtubules. This stops mitosis and then starts apoptosis [13]. Anthracycline antibiotic doxorubicin, found in Streptomyces bacteria, is another success story. It stops topoisomerase II from working and doesn't allow DNA to copy normally [14].

More recently, researchers have turned their attention to other natural sources that are less well-trodden by pharmaceutical companies in search of new anticancer drugs. Marine organisms' ecological niches and biosynthetic pathways are very interesting. Plitidepsin, for example, is derived from the Mediterranean Sea squirt Aplidium albicans. It is a cyclic depsipeptide that is very good at fighting cancer. It works especially well against a group of proteins called eEF1A2, often found in solid tumors like sarcoma, leiomyosarcoma, and some types of lymphoma [15]. Plitidepsin is advancing in clinical trials for multiple myeloma and angioimmunoblastic T-cell lymphoma.

Another example is the so-called endophytic fungi, which hover between the cracks as inhabitants of or growing inside plants. By definition, there is a close relationship between the fungus and its plant host, as well as between the fungus and the botanist, because one of the most striking effects of the endophytes is that they cooperate with, protect, or participate in the lifestyle of their hosts, even though they also cause damage to them, as any symbiosis does. We previously discussed the origin of endophytic fungi, but now we are interested in some of their natural products. These products are produced by the host plant or by the fungus growing inside, and they may act as phytoalexins that protect the plant against pathogens or other environmental stresses. One of these is camptothecin (CTI), an alkaloid that was first found in the Chinese ornamental tree *Camptotheca acuminata* and then in endophytic fungi like Fusarium solani and Entrophosporainfrequens a few years later. The discovery of CTI in a tree plant is remarkable. However, its discovery in fungi is even more surprising, as this finding might have important implications for the classification of fungi and the compounds they produce. Traces of CTI had been discovered in various other species since the early 1960s, but their utility as drugs was not clear. We now know that CTI stops topoisomerase I (topo I) from breaking down DNA by slowing it down. This prevents the broken strand from being fixed and creates an irreversible "knot" in the DNA double helix, which kills the cell through apoptosis.

Today, camptothecin and its natural and semi-synthetic derivatives, like topotecan and irinotecan, are strong cancer fighters against many tumors. These drugs are known as TOP I inhibitors. With enhanced analytical methods, high-throughput screening, and computational capacity aiding the discovery, identification, and characterization of bioactive natural products, it is clear that nature and its symbolic dictionary hold enormous and unexplored potential in anticancer drug discovery.

Methodology:

This review article is based on a comprehensive literature search and analysis of scientific articles, reviews, and books on natural product-based anticancer drug discovery. The information was obtained from various sources, including peer-reviewed journals, online databases (e.g., PubMed, Google Scholar), and other relevant scientific platforms. Utilizing these resources enabled comprehensive writing on the untapped potential of natural products for targeted therapies.

We have established inclusion criteria to ensure this review includes relevant, high-quality studies. These criteria stipulated that selected studies must have been published recently in English and focus on Natural products as a source of anticancer. This review synthesizes significant findings from relevant studies, providing a comprehensive understanding of recent discoveries and future perspectives on natural products as a source of anticancer agents.

2. Natural products with anticancer properties.

2.1. Overview of major classes of anticancer natural products, their sources, and mechanisms of action

Natural products can also be split into two broad categories based on their functions inside the organisms that produce them: primary and secondary metabolites. Primary Metabolites: organic molecules that serve an essential function for the producing organism. In essence, without these metabolites, the organism would die. These metabolites, such as nucleic acids, amino acids, sugars, and fatty acids, are fundamental building blocks of life and are key to the synthesis of major macromolecules such as DNA, RNA, proteins, carbohydrates, and lipids, which are used in biologically relevant life-sustaining processes.

Primary metabolites are organic molecules with intrinsic functions, whereas secondary metabolites are organic molecules with extrinsic functions that primarily affect other organisms in the producers' ecosystems. While these are not usually essential for survival, these secondary metabolites are believed to contribute to the organism's ecological fitness. Secondary metabolites are greatly interested in medicinal chemistry and pharmacognosy because of their therapeutic potential [17]. For example, molecules of such an encouraging diversity of structural types as alkaloids, phenolics, and terpenoids demonstrate their vast role in anticancer activities.

2.1.1. Alkaloids

Alkaloids are a huge group of nitrogen-containing secondary metabolites in many plants, microbes, and marine organisms. Alkaloids' diversity in structure and bioactivity is remarkable; their anticancer activity has garnered significant attention. Vinca alkaloids and other alkaloids originating from Madagascar periwinkle serve as a crucial source for chemotherapy. The most well-known member of this family is vincristine, which inhibits microtubule dynamics [18–19]. Additionally, camptothecin, another cancer treatment, is derived from the Chinese tree *Camptotheca acuminata* and inhibits topoisomerase. This is primarily achieved by interfering with microtubule dynamics and inhibiting topoisomerase enzymes. First, as mentioned earlier, microtubules are cytoskeleton components responsible for maintaining cell shape and intracellular transport. They also assemble into the mitotic spindle, contributing to chromosome segregation during cell division (mitosis). As a result, microtubule dynamics are influenced by several alkaloids used in the clinic as anticancer drugs. These include natural products such as the vinca alkaloids (ephedrine is a natural alkaloid) like vinblastine and vincristine, as well as colchicine. When they interact with the tubulin protein subunit of microtubules, they either make microtubules polymerize or depolymerize, which can mess up the cell cycle and mitotic spindle [20]. Secondly, regarding the latter, topoisomerases play a crucial role in regulating DNA topology. They aid in the breakage and re-ligation of DNA, essential for strand separation processes like DNA replication and transcription. Some

chemicals called alkaloids, like camptothecin, and their variations, like topotecan and irinotecan, stop these enzymes from working. They do this by stabilizing the DNA-topoisomerase complex. This prevents DNA strands from being relegated, which leads to DNA damage and cell death [21].
Alkaloids, with more than 13,000 examples described so far, represent the most extensive class of naturally occurring compounds with potential anticancer activity and undoubtedly one of the most diverse classes of natural products with high pharmacological potency. They come from various biological sources, such as plants, fungi, bacteria, and animals. They also have complex chemical structures and unique biosynthetic pathways. Because of these factors, they have unique pharmacological properties that make them very appealing as starting molecules for finding new anticancer drugs. Future research that deciphers their precise mechanisms of action at molecular scales, structural activities, and 'green' synthetic strategies should enable rational capitalization of their potential therapeutic values.

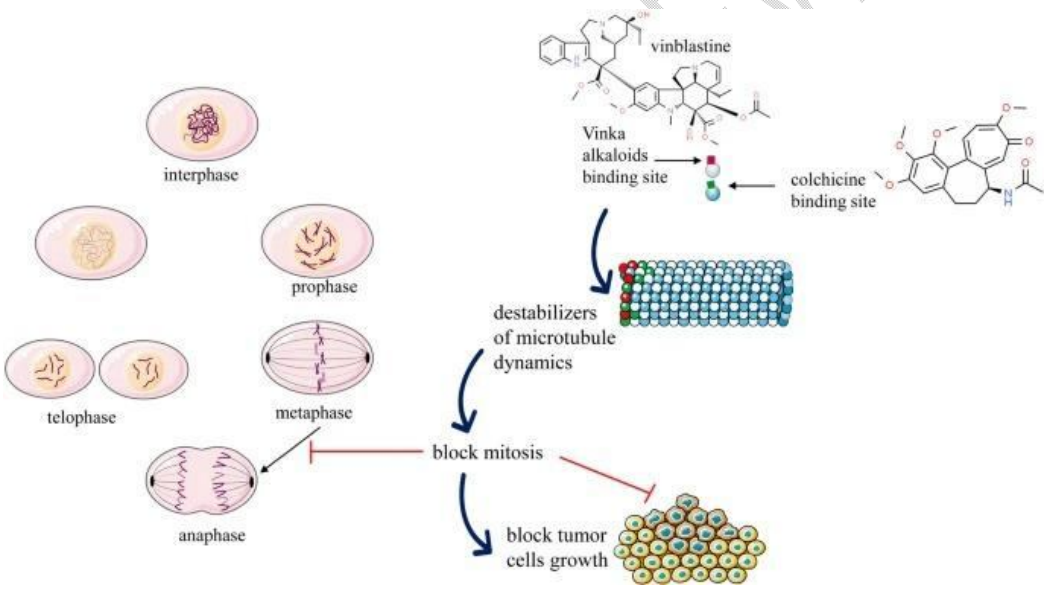

Fig 2.Summarized scheme with anticancer mechanisms of Vinca alkaloids and colchicine.

At mitosis, they stop the cell cycle by sticking to two tubulin heterodimers near a GTP-binding site that can be changed. This causes the microtubules to depolymerize. As a result, the microtubules destabilize and disrupt normal tubulin dynamics, which elicits apoptosis or programmed cell death. *Source:* *https://doi.org/10.1186/s12935-022-02624-9*

2.1.2. Terpenoids

One of the largest and most promising groups of these secondary metabolites—terpenoids—has garnered tremendous effort for their anticancer properties. This class of molecules, mainly synthesized from isoprene units assembled individually, is also remarkably relevant to medicine because they are primarily extracted from plants.

Some of these terpenoids fight cancer by messing with important steps in the growth process. For example, they stop the cell cycle in the early stages of tumorigenesis and stop cancer cells from differentiating. This makes it harder for the cancer cells to spread and grow throughout the body. At later stages of carcinogenesis, some of these terpenoids can also induce apoptosis [22]. This (programmed) cell death is a kind of cellular suicide that actively destroys the cancer cells. For example, Paclitaxel, a diterpene that was first found in the Pacific yew tree, is a well-known cancer-fighting drug that works by stopping tubulin protein from assembling into microtubules, which are an important part of the cell's cytoskeleton [23].
One of the examples of terpenoids with anticancer effects includes **Thymol** (a monoterpenoid).

Summarize the Mechanism of Action of Selected Terpenoid against Cancer Progression.

In the article from the journal Evidence-Based Complementary and Alternative Medicine, "Therapeutic Potential of Certain Terpenoids as Anticancer Agents: A Scoping Review" by Kamran et al. (2022), a new perspective of selected terpenoids against anticancer activity, its molecular mechanism, signaling pathways, and clinical trials are explained with great details.

It has been demonstrated that terpenoids inhibit tumor progress and cytotoxic effects. Some terpenoids can exogenously stimulate immune cells to enhance immune surveillance function and may have potential as innovative cancer treatment options. Two terpenoids are specifically described as monoterpenoids, which are α-thujene and γ-terpinene, whereas one is a sesquiterpenoid, which is α-humulene, and another two are diterpenoids, which are thymol and kaurenol.

Recent cancer research has focused on therapeutic agents to increase tumor surveillance, induce tumor regression, and suppress the metastasis of cancer cells. Kamran et al. (2022) review discussed that specific terpenoids such as α-thujene, γ-terpinene, α-humulene, thymol, and Lauren can suppress all the pathways above at different stages of cancer progression to support further the notion that terpenoids are potential anticancer agents. The mechanism of action for Thymol as monoterpenoids against cancer progress is explained below.

Thymol

In the leukemia cells (HL-60) model, thymol stops the cell cycle at the G0/G1 phase, creating reactive oxygen species (ROS) that depolarize mitochondria. This is how it kills cells. Thymol-mediated mitochondrial breakdown caused lipid degeneration and cell disruption. Because it is an antioxidant agent, it inhibits cell proliferation and kills cancer cells by increasing the level of Bax and decreasing Bcl-2 protein. Increased Bax favors a cascade of signaling molecules and proteins, ultimately leading to apoptosis [24]. In the second ultrastructural study, it was discovered that thymol treatment led to mitochondrial depolarization, lipid degeneration, and the movement and separation of cells that were dying and making mitochondrial energy in Caco-2 colorectal cancer cell lines. Though this ultrastructural study demonstrated that thymol is cytotoxic to carcinoma cells, additional studies are required to determine the mechanisms of thymol-mediated cytotoxicity [25].

The endoplasmic reticulum-mediated effects of thymol on cancer cells are triggered by phospholipase C-dependent Ca2+ and store-operated calcium entry [26, 27, 28]. The question now arises whether thymol may induce apoptosis in calcium-entry-mediated death signaling in MG63 osteosarcoma, DBTRG-05MG glioblastoma, or PC3 prostate cancer cells. Also, releasing Ca2+ by thymol increases the production of reactive oxygen species. This means Ca2+-mediated cell death may be more complicated [26] than apoptosis. Their ability to inhibit multiple steps in cancer cell formation makes terpenoids a promising candidate for the next generation of anticancer drugs. Future research into terpenoids' therapeutic mechanisms and applications will guide the development of new cancer drugs.

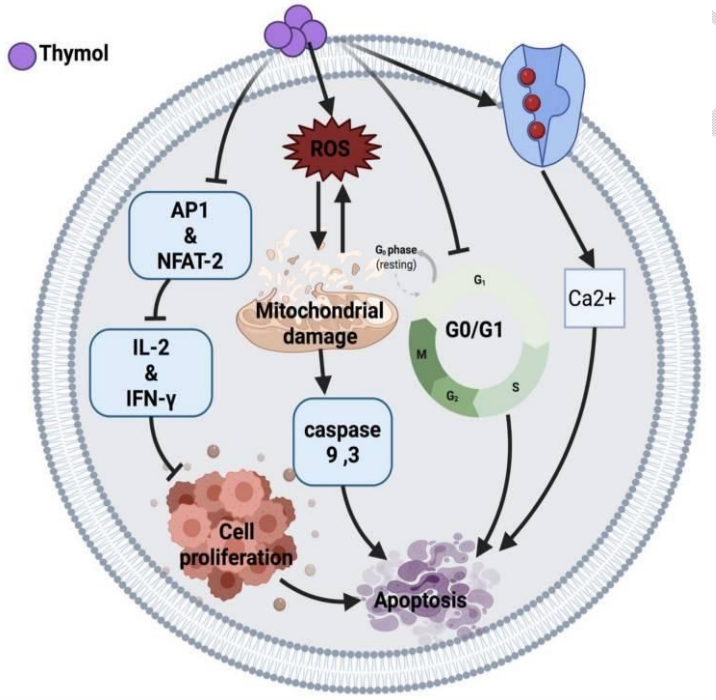

Figure 3: An overview of the potential anticancer mechanisms of thymol. (Kamran et al., 2022)

Phenolic

Phenolic compounds play an important role in the treatment of different diseases, such as diabetes, cardiovascular and neurodegenerative diseases, and cancer, due to their medicinal potency. These compounds predominantly exert their antidiabetic activity by modulating glucose metabolism [29]. Their anticancer activity is mainly due to their antioxidant activity, as they are strong radical scavengers, chelate metals, and modulate endogenous defense transcription factor-mediated antioxidant responses like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidases (GPx). They ameliorate glutathione (GSH) redox status

and regulate a diverse number of proteins or transcription factors like nuclear factor erythroid 2-related factor (NRF2) [29, 30]. Their anticarcinogenic efficacy is also attributed to their capabilities to inhibit cell proliferation markers such as extracellular signal-regulated kinase (Erk)1/2, D-type cyclins, and cyclin-dependent kinases (CDKs), angiogenic factors (vascular endothelial growth factor (VEGF) and MIC-1), oncogenic signaling cascades (phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt) and causing apoptosis and restrain cell migration and metastasis [29]. Plant phenolics can act as 'anticancer agents' by utilizing one, a combination, or all of the previously suggested mechanisms, as detailed below: Plant phenolics interfere and inhibit the following three universal hallmark capabilities of cancer: 1. block cell adhesion 2. Disrupt the cell cycle. 3. inhibit DNA binding 4. interfere with signaling transduction→ block cell proliferation and receptor binding. The fourth and final pillar of the hallmark capabilities of cancer involves metabolism', in which the anaerobic 'Warburg effect' represents the hallmark metabolic disorder in cancer.

Flavonoids, a subclass of phenolics, are some of the most promising agents to be studied for their anticancer activity. Well-known examples of anticancer flavonoids are quercetin, genistein, and curcumin. Flavonoids have been shown to have anticancer activity by directly targeting key molecules or regulating critical cell signaling pathways, as well as by inducing apoptosis and inhibiting metastasis.

Key Mechanisms Flavonoids exert their anticancer effects.

1. Modulation of Cell Signaling Pathways

Flavonoids modulate multiple cells and signaling pathways that control cell proliferation, cell survival, and cell death: PI3K/Akt, MAPK, and NF-κB signaling cascades are among the most investigated. Modification of these pathways results in an inhibition of proliferation and promotion of apoptosis of cancer cells. Quercetin, for example, has been shown to inhibit the PI3K/Akt pathway, consequently reducing cancer cell proliferation and increasing apoptosis [31].

2. Apoptosis Induction

The apoptotic response can be harnessed to promote the selective death of specific cell populations, and one of the mechanisms frequently utilized by flavonoids to kill Cancer cells appears to be edema-dependent apoptosis (programmed cell death). The induction of apoptosis is mediated by flavonoids' ability to activate caspases, increase the expression of pro-apoptotic proteins such as Bax, and decrease the expression of anti-apoptotic proteins, for example, Bcl-2. For instance, genistein can induce the selective death of estrogen receptor-positive breast cancer cells through the modulation of the Bax and Bcl-2 expression [32].

3. Metastasis Inhibition

Metastasis is the spread of tumor cells from the primary tumor site (where cancer originated) to other body organs. In this context, flavonoids can suppress metastasis

by inhibiting cell migration, invasion, and angiogenesis (blood vessel formation) by targeting the expression and actions of multiple proteins, including MMPs, vascular endothelial growth factor (VEGF), and hypoxia-inducible factor-1α (HIF-1α), and also their enzymatic activities. For example, the migration and invasion of colorectal cancer cells were repressed by curcumin by downregulation of MMP-2 and MMP-9 expression. [33]

The anticancer actions of flavonoids are mediated through multiple mechanisms of action, such as modulation of cellular signaling pathways, induction of apoptosis, and inhibition of metastasis; flavonoids and other phenolic compounds will likely be developed as novel anticancer therapeutics.

Podophyllotoxin

Podophyllotoxin comes from the rhizomes of Podophyllum hexandrum, also known as "Bankakri" or the Himalayan mayapple. It is a lignan, a compound used to make new cancer-fighting drugs. The mayapple, a perennial herb found in Central Asian mountains, including the Himalayas, has been used for centuries in Ayurvedic medicine in India, Central Asia, and elsewhere for various therapeutic purposes [34]. Chemically, podophyllotoxin is made up of four fused rings. A lactone ring connected to the central core may contribute to the compound's biological activity [34]. As an antimitotic compound [35], it stops the microtubules from coming together. Microtubules are the main parts of the mitotic spindle, which changes shape during mitosis to separate the chromosomes. The derivatives of podophyllotoxin are among the most intriguing aspects.

Over the ensuing years, several other anticancer drugs based on podophyllotoxin were developed – etoposide, teniposide, and etopophos (Fig 4) – but the side effects associated with these often precluded their use, thus initiating the design and synthesis of less toxic derivatives. In recent years, newer therapeutics, including TOP-53, NK611, GL-331, azatoxin, and others, have been reported, showing that efforts to unravel clinically more effective and better-tolerated anticancer agents in the podophyllotoxin family are still in high demand.

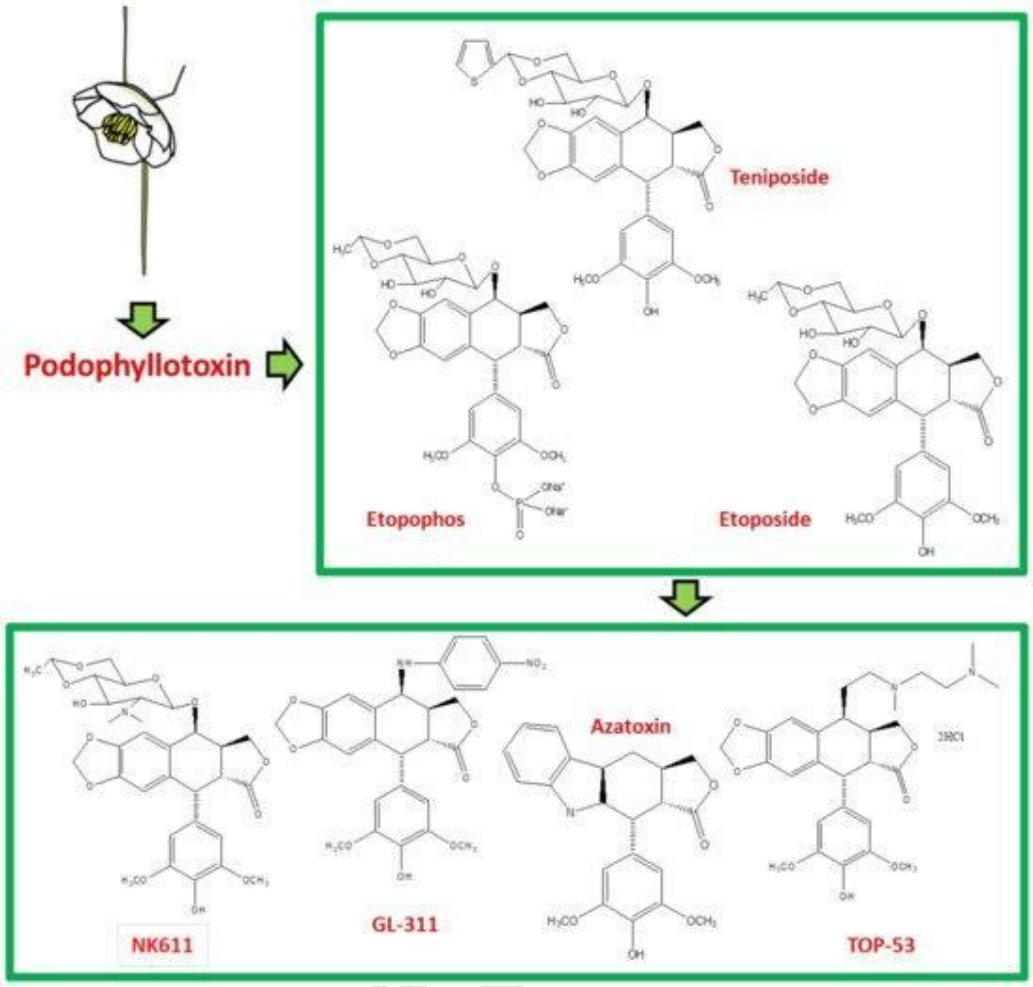

Figure 4. Chemical structure of etoposide, teniposide and etopophos
Source: Shah, Z., Gohar, U. F., Jamshed, I., Mushtaq, A., Mukhtar, H., Toma, S. I., Manea, R., Moga, M., & Popovici, B. (2021). Podophyllotoxin: History, Recent Advances and Future Prospects. Biomolecules, 11(4), 603. https://doi.org/10.3390/biom11040603

Homoharringtonine

Homoharringtonine (HHT) is a natural compound extracted from the tree Cephalotaxus Harrington. It selectively works on multiple mechanisms by affecting a variety of important molecules. HHT has demonstrated significant cancercidal activity in most cancers, particularly many hematological malignancies. So far, the main ways that HHT fights cancer are by stopping protein synthesis, halting the cell cycle at G2/M, and inducing apoptosis by changing proteins related to apoptosis, like Bcl-2 and Bax [36]. As we understand, HHT essentially binds shut the A site of the large ribosomal subunit, interrupting protein synthesis and ultimately causing cancer cells to die through various signaling pathways [37]. For example, HHT can change Bcl-2 and Bax, which help control and speed up cell growth [38]. This can stop the cell cycle in the G2/M phase and lead to apoptosis.

Additionally, its antitumor effects or cidal activity are not limited to this; reports suggest it also affects the entire microenvironment of malignancies. For instance, recent research has shown that HHT inhibits tumor angiogenesis by repressing vascular endothelial growth factor (VEGF) and its receptor (VEGFR) [36]. It is highly effective in treating CML and AML patients who are resistant to conventional therapies. HHT received its second approval, this time in the US by the Food and Drug Administration (FDA) in March 2012, under the trade name Omacetaxine mepesuccinate for the treatment of adult patients with CML resistant or intolerant to two or more TKI [39].

Betulinic acid

Betulinic acid is one of the plants' most common organic secondary metabolites, mainly from Betula species (Betulaceae) [40]. Betulinic acid came from Zizyphus species (Rhamnaceae), e.g., Mauritiana rugosa and Mauritiana oenophilia [41, 42]. It has different biological properties, including anti-HIV, anti-inflammatory, antioxidant, antiretroviral, and antibacterial [43, 44, 45, 46, 47]. It was primarily used as an antitumor agent in recent years because it inhibits topoisomerase [48, 49, 50]. Betulinic acid was designed to increase this compound's activity. These compounds' unpleasant pharmacological and physicochemical properties led to some problems encountered during the clinical development of BetA derivates. The new BetA derivative NVX-207 is well tolerated. It showed amazing anti-tumor activity in clinical studies of canine cancer patients with naturally occurring malignancies that are resistant to treatment. Apoptosis, or programmed cell death, was caused by NVX-207. This was done by starting the intrinsic apoptotic pathway, which includes caspases-9, -3, and -7 cleavage and poly (ADP-ribose) polymerase (PARP) [51]. Five of the dogs in a phase I/II study with cancer that went away on its own after receiving local treatment (intramuscular implantation) of the BetA derivative (10 mg mL^{-1}) have shown great clinical response, with signs of complete remission in all five of them.

Subtopic 2.1 summarizes anticancer natural products in several groups, such as alkaloids, terpenoids, phenolics, and other specific compounds, including podophyllotoxin, homoharringtonine, betulinic acid, etc. These cancer-inhibitory natural products are produced by various plants and exert anti-cancer activity in multiple ways. An accurate understanding of the mechanism of action is indispensable for developing therapies.

Alkaloids, terpenoids, and phenolics are representative natural products with highly diverse chemical structures and biological activities. The inhibition of DNA

replication and microtubule dynamics in alkaloids play a major role in the anticancer activities induced by these agents. Meanwhile, terpenoids harmonizing the tubulin binding with microtubules (such as paclitaxel or Taxol) or with topoisomerase, such as in betulinic acid, will be consequently inhibited to induce apoptosis. In an epidemiological study, a wide variety of constituents in five-flavor herbal drugs are proven to possess phenoloxidase and anti-inflammation activities, causing antitumorigenic effects by inhibiting cancer cell proliferation and inducing apoptosis via multiple signaling pathways. These evident examples, represented by podophyllotoxin,homoharringtonine, and betulinic acid, indicate that anticancer natural products from traditional medicine might no longer be regarded with a fuzzy concept. It is also certainly a deep and wide pool of drug discovery.
Many cancer cells are in the human body, but the survival rate is very low. As cancer is an abnormal reproduction of cells, these natural products could clarify several molecular targets of cancer cells, as betulinic acid targets topoisomerase in addition to the tubulin in paclitaxel, leading to varieties of possible molecular targets of natural products.

Overall, the subtopic highlights the abundance of natural anticancer products and the hope for their use as valuable assets in the constant endeavor to develop new cancer treatments. To gain new insights into novel and effective anticancer natural products, researchers should continue to explore their unique mechanisms of action and seek novel and diverse sources to mine for new natural products.

3.Preclinical and clinical development of anticancer natural products

3.1. Overview of preclinical studies in cell lines and animal models

As part of the preclinical phase, the first step in using natural products as possible anticancer drugs is to test them on a cell line and an animal model. This is done to learn more about the compound's toxicity and identify the most promising ones for further development. As more molecular targets in cancer are found and tumors are said to be very different from one another, natural products, with their complicated chemical structures and wide range of biological activities, are great places to get anticancer drugs that work on many molecular targets involved in cancer signaling pathways [19].
Natural products' anticancer potential is first assessed vitro using cancer cell lines. In such studies, a compound is typically tested for inhibition of cancer cell proliferation and cell death and modulation of specific signaling pathways. High-throughput screening assays allow us to quickly assess the cytotoxic activity of multiple natural products in various cell lines [52]. Once a natural product has been shown to have exciting activity in cancer cell lines, it is subjected to further in vivo studies using animal models such as mice or rats. Xenografts, in which human cancer cells are put into an animal with weak immune systems or genetically modified animals that grow tumors independently, make these in vivo studies possible. Researchers assess the antitumor efficacy of a compound against tumor growth in vivo studies; they also check the compound's pharmacokinetics, evaluate toxicity, look for side effects, and so on [52]. Several natural products from preclinical studies have been identified, which has compelled researchers to take them into the clinic recently. For example, studies on curcumin, a naturally occurring compound from turmeric, have

demonstrated curcumin's potential to inhibit cancer cell growth (by blocking proliferation and inducing cell death or apoptosis) in various cell lines [53]. Studies in animal cancer models have shown robust curcumin activity against breast, colon, and pancreatic cancers. Others, like resveratrol, a polyphenol from grapes and red wine, are another family of chemicals where decades of research have established their anticancer attributes. Preclinical studies on resveratrol have demonstrated its ability to inhibit cancer cell growth (by blocking proliferation and inducing apoptosis) in a wide variety of cancer cell lines, as well as its ability to suppress the development of blood vessels that feed tumors (a process we call angiogenesis). Studies in animal cancer models have demonstrated this compound's chemopreventive activity against breast, prostate, colon, and lung cancers, amongst others [56].
The reasons behind these examples were that they would unearth the anticancer potential of natural products in their preclinical studies through careful investigations into their actions on cancer cell lines and animal models. Such investigations were intended to generate information to design applicable clinical trials and guide the development of new anticancer therapies from natural sources.

3.2. Clinical trials and regulatory approval process

After showing anticancer activity and safety in preclinical trials, the compounds move on to human volunteers for clinical trials. This pivotal phase of drug development has multiple stages where different compound properties are evaluated. They evaluate Phase I, during which a natural product is given to only-stage or terminal cancer patients who have exhausted other therapies. The focus for Phase I trials is on safety: the maximum tolerated dose and side effects. Phase II also relies on a limited number of patients with a specific type of cancer, but the goal is to assess safety and determine whether the compound has any efficacy against the cancer of interest.
Phase III mega-studies compare the natural product with standard treatments or placebo in a large, randomized, placebo-controlled trial. If the natural is effective and safe, it is submitted for regulatory approval. Regulatory agencies like the U.S. Food and Drug Administration (FDA) are crucial to the process, where anticancer drugs from natural products are tested on people. Drugs are approved if the FDA determines that enough data from clinical studies, preclinical studies, and manufacturing designs assure the drug's safety, efficacy, and quality [57]. Paclitaxel (Trade name Taxol) was the first natural product to complete the approval route, starting with extraction from the bark of the Pacific yew tree. After promising to cure cancer in preclinical studies, paclitaxel was tested on patients, and significant therapeutic benefits in Phase III trials led to FDA approval2 for women with ovarian cancer and later for breast cancer and non-small cell lung cancer [58].
Clinical trials and regulatory approval are required to validate natural products as anticancer agents. When placed under the scrutiny of clinical and regulatory science, natural products are thoroughly screened for their safety, efficacy, and reproducible quality from batch to batch, while the strongest contenders make their way to patients seeking innovative treatments.

3.3. Challenges and strategies for optimizing the pharmacokinetics, pharmacodynamics, and toxicity profiles of natural product-based drugs

The pharmacokinetic optimization of natural product-based oncology drugs can enhance the therapeutic index by improving pharmacological quality while minimizing toxicity and adverse effects. The challenges include but are not limited to solubility, bioavailability, metabolism, and toxicity. Several new approaches have been proposed by researchers to tackle these challenges [59]. One method involves structural modification, which can also improve bioavailability. There are several ways to improve the physicochemical properties of these drugs: esterification, glycosylation, or adding ionizable functional groups. Formulation development is another synthetic way to improve the pharmacokinetics of product-based natural medicines. Designer formulations such as nanoparticles, liposomal encapsulated formulations, or polymer conjugates can not only enhance the solubility and stability of natural product-based medication but they can also be used to target tumors, improving bioavailability as well as local interaction and reducing systemic toxicity [61].

Furthermore, to achieve the goal of delivering the drug to the tumor with minimal release while maintaining drug safety, it is necessary to design formulations that regulate the drug's release. Drug metabolism could also be targeted to improve therapeutic indices, such as developing drugs that produce less toxicity towards normal cells and more exhaustive potential to kill cancer cells. In addition, understanding drug pharmacokinetics, including drug-drug interactions, is an important treatment. This can be exploited in vitro and in vivo studies to identify strategies to improve natural product-based drugs' absorption, distribution, metabolism, and elimination (ADME). For example, metabolites found in the faces of cancer patients can be used in xenograft mouse models made from cancer patients to study how drugs might interact badly [57]. In the same way, using human liver microsomes lets researchers quickly guess how drugs will interact with each other in the liver through cytochrome P450.

Finally, it is often necessary to reduce the toxicity of natural products. To solve the first problem, we could use prodrugs, which are inactive starting materials that are turned into active drugs when they are broken down, and targeted delivery systems, which limit systemic toxicity by releasing drugs only where they are needed [59]. For example, clinically approved camptothecin derivatives have been synthesized, a potent anticancer plant alkaloid poorly soluble in water and presenting toxic effects. These derivatives, irinotecan, and topotecan, were originally developed to treat colorectal and ovarian cancers [62].

Their pharmacokinetic, pharmacodynamic, and toxicological profiles need to be optimized to make clean, useful, and safe anticancer drugs from natural products. However, these active ingredients and their derivatives still have the potential to be important drugs. By applying novel methods, endeavors can be made to re-investigate the promising natural products for their anticancer activities.

4. Future perspectives

4.1. The potential of novel natural product sources, such as marine organisms and endophytic fungi

Interest in discovering and developing anticancer natural products, particularly those derived from terrestrial plants, remains high. Besides traditional plant sources, marine

natural products, particularly endophytic fungi, represent new sources that have already delivered interesting anticancer leads.

Marine Organisms:

Ocean biodiversity contains many organisms that produce bioactive compounds of various chemical structures. Many of these compounds are cytotoxic, which is one of their features. For instance, sponges are filter-feeding sessile animals that have evolved to produce a variety of cytotoxic chemicals against predators and other environmental threats. They are a prolific source of bioactive marine molecules because their survival depends on generating novel molecules to defend themselves from their natural predators. These compounds typically show selective toxicity against cancer cells and are thus attractive starting points in drug discovery [63]. This is an example of a depsipeptide compound called didemnin B. It was taken from the straggly globular siphonophore of the squirt Tridemnum solidum, which lives in the Caribbean Sea. It showed potent in vitro and in vivo antitumor activity in some cancer cell lines and mouse models with induced tumors [64]. Despite its numerous advantages, its use in cancer treatment was thwarted because it was too toxic for cancer patients. Didemnin B is a marine product that provides a valuable lead compound for developing more effective and less poisonous analogs, such as tamandarin A and plitidepsin [65].

Endophytic Fungi:

Endophytic fungi are microbes that live inside the tissues of living plants. They are also a great source of natural products that may help fight cancer because they produce many secondary metabolites with strong biological effects. This category includes the anticancer drug taxol, originally isolated from the Pacific yew tree, Taxus brevifolia, and subsequently discovered to be produced by many endophytic fungi inhabiting the tree [66]. The discovery of taxol (paclitaxel), which came from endophytes in the western yew tree Taxus brevifolia, may be one of the best examples of how endophytic fungi can be used to make anticancer drugs. Paclitaxel, which disrupts the dynamic function of microtubules by binding to tubulin, is now widely used for the treatment of ovarian, breast, and non-small cell lung cancers. It was the first taxane to be used for chemotherapeutic purposes. The search for endophytic fungi in other plants has yielded additional anticancer compounds since the discovery of paclitaxel, such as camptothecin from the lignum vitae tree and vincristine from the periwinkle [67]. Novel natural product sources, such as marine organisms and endophytic fungi, are great prospects for anticancer drug research. The number of novel compounds from underexplored natural product sources, such as marine organisms and endophytic fungi (nonpathogenic fungi that reside inside plants), is a huge resource of highly novel chemical entities.
Nevertheless, new interdisciplinary areas like synthetic biology and genome mining allow researchers to explore new avenues for natural product discovery from novel sources, including marine organisms and endophytic fungi. Synthetic biology and genome mining work together to reveal untapped biosynthetic potential, which increases the range of biochemicals that can be used to find new drugs. Synthetic biology is a discipline that combines engineering and biology to construct new biological systems or modify existing biological systems (some of which are natural) by designing those systems to have novel functions or behaviors. Synthetic biology

can be used in various ways in marine organisms and endophytic fungi. First, it can be employed to enhance the production of bioactive compounds that are already known. For instance, a well-known way that a bioactive compound comes from marine organisms or endophytic fungi can be found and expanded, making it easier to make the active ingredient. Second, synthetic biology in aquatic biota and endophytic fungi can translate a biosynthetic pathway of one organism into another organism's manufacture. This entails the creation of new interactions among workhorse organisms that enable biosynthesis. These new biosynthetic pathways lead to new natural products derived from natural products with unique bioactivities.
This approach to natural product discovery captures what synthetic biology tries to engineer and reveals unseen potential. Finally, synthetic biology for marine organisms or endophytic fungi can be used to create novel biosynthetic pathways that have not been known before. The act of engineering synthesis ultimately results in the creation of novel natural products with previously untapped bioactivities. Synthetic biology improves already-known compounds and enables the discovery of new natural products. Genome mining is another new area of research that involves the analysis of genomic data to identify biosynthetic gene clusters, which are clumps of genes that produce bioactive compounds in a particular organism. The minerals can help find new biosynthetic pathways in marine organisms and endophytic fungi by looking at how well they can make these well-known natural products from their genomic information. Genome mining can also help guide or speed up the isolation and characterization of known compounds, saving time and money. It can also find "silent" or "cryptic" gene clusters that can be turned on or expressed heterologously, which means "out of context," in this case, to make a new natural product.
More and more marine or endophytic fungal genomes are being sequenced. Combining synthetic biology and genome mining lets us use the full bio-synthetic potential of marine sources to find new medicines and natural products. Natural product biosynthesis gene clusters' discovery potential harnesses the power of predictive genome-mining approaches. The engineering potential of synthetic biology takes advantage of the chemical knowledge from whole-organism lead optimization.

4.2. The role of drug delivery systems and nanotechnology in improving the efficacy and safety of natural product-based anticancer drugs.

We hypothesize that drug delivery systems and nanotechnology can alleviate the solubility, bioavailability, and systemic toxicity associated with natural product-based anticancer drugs because they have the potential to offer both enhanced delivery and improved targeting properties.
Drug delivery systems can release therapeutic agents in a controlled manner at the right target. This improves the compound's pharmacokinetics and pharmacodynamics, making it more effective overall and less harmful than giving the natural product in its raw form. These systems could be liposomes, micelles, or nanoparticles. Different drug delivery systems, like liposomes, micelles, and nanoparticles, are viable options for delivering natural anticancer drugs. Such liposomal formulations of the natural product vincristine, a widely used drug for anticancer treatment, enhance its therapeutic index. Vincristine, also derived from the Madagascan found in the Madagascar periwinkle (Catharanthus roseus), is a medicine that combats various types of cancer. While vincristine is necessary for optimal activity, its dose-limiting neurotoxicity poses a significant risk. Therapeutic options have become available for

the treatment of cancers using a liposomal formulation of vincristine that is not only more effective but also less toxic in the treatment of certain forms of leukemia. This liposomal vincristine (Marqibo) was approved for use in adult patients with acute lymphoblastic leukemia that is resistant or relapsing after treatment with two or more anticancer agents [68].

Nanotechnology allows us to manipulate matter at the nanoscale (1–100 nm). It is, therefore, useful for developing new drug delivery platforms with unique physical, chemical, and biological properties that can help enhance efficacy and reduce toxicity. Nanocarriers, such as polymeric and inorganic nanoparticles, have been developed to encapsulate or conjugate natural product-based anticancer drugs to improve their stability, solubility, or targeting capabilities. Nanotechnology applications have contributed significantly to the success of numerous natural product-based anticancer therapies. For example, paclitaxel is a diterpenoid compound found in the yew tree's bark and needles (Taxus brevifolia). It has very strong anticancer properties and has been used as a semisynthetic anticancer drug for a long time. However, this compound has limited water solubility and serious side effects due to a formulation that induces hypersensitivity. Paclitaxel is, therefore, typically administered with dextran and ethanol, which increase toxicity and reduce the maximum tolerated dose. To overcome these problems, an albumin-bound paclitaxel nanoparticle (Abraxane) formulation that shows 130-nm-sized particles was developed in the 1990s. Albumin, a protein normally found in plasma, is modified with paclitaxel molecules so that the drug can reach the needed places. Compared to the standard paclitaxel formulation, Abraxane is more effective and less harmful, and the highest dose that can be tolerated is raised four times [69].

So, drug delivery systems and nanotechnology have been very promising approaches for overcoming the major problems associated with anticancer drugs formulated from natural products, especially enhancing their bioavailability, reducing their water-solubility, and improving their ultimate localization to the target place. Thus, it might promote natural compounds as a safe, effective, and reliable alternative therapy, potentially reducing patients' pain, prolonging patient survival, and decreasing host-systemic toxicity. In the future, drug delivery systems and nanotechnology will be increasingly prominent in developing safer and more effective natural product-based anticancer therapies.

So far, we have seen that drug delivery systems and nanotechnology can help overcome the common problems associated with natural product-based anticancer drugs. The major topic of targeted drug delivery lies at the heart of cutting-edge drug delivery strategies, which aim to divert the therapeutic agent to the site of cancer, thereby significantly improving therapeutic efficacy, causing minimal damage to normal tissues and, thus, reducing the incidence of common adverse side effects caused by conventional cancer treatments.

The following paragraphs will summarize the different targeted drug delivery approaches and their relevance concerning natural product-based anticancer drugs.

Targeted drug delivery

Nanotechnology-designed drug delivery systems can deliver anticancer drugs to tumor sites. Particularly, these technologies enhance the effectiveness of traditional natural product-based anticancer drugs by enabling targeted drug delivery. Instead of providing the drug to all tissues, targeted drug delivery can specifically deliver the drug to the tumor site, achieving higher therapeutic efficacy with minimal off-target effects and potentially reducing conventional cancer therapy's severe adverse side

effects. Passive targeting, active targeting, and stimuli-responsive delivery are some strategies for targeted drug delivery.
Passive targeting is based on the unique features of solid tumors: their leaky vasculature, which allows large dyes and macromolecules to extravasate and accumulate in the tumor because of impaired lymphatic drainage (the so-called enhanced permeability and retention [EPR] effect). By collecting at the disease site because of the EPR effect, a drug can achieve increased local accumulation and higher concentrations, leading to improved therapeutic effects. Liposomal doxorubicin (Doxil) is a clinically successful formulation of the natural product doxorubicin that passively targets solid tumors via the EPR effect [70].

Approaches to active targeting include targeting the ligands or antibodies to tumor-specific antigens or receptors by conjugation to nanoparticles; for example, Mylotarg, an antibody-drug conjugate against CD33, an antigen expressed on leukemic cells, binds selectively by its antibody moiety, and this improves the anticancer activity of its conjugated drug, the cytotoxic calicheamicin, a natural product of a bacterium [71]. They have found that when nanoparticles are actively targeted, the drug accumulates in the tumor cells selectively and is taken up by receptor-mediated endocytosis, improving the anticancer activity while significantly reducing the toxicity to normal healthy cells. For example, Chen et al. reported the synthesis of the folate-conjugated paclitaxel-loaded nanoparticles to target the folate receptor-overexpressing cancer cells, which showed that it could improve the anticancer activity by achieving higher cellular uptake.

According to what was said above, stimuli-responsive delivery is the process of making drug delivery systems that can react to changes in pH, temperature, or enzyme activity that happen a lot in the tumor microenvironment. These systems release their drug payload only when they encounter the desired stimulus; this allows for site-specific drug release and reduces off-target effects. For example, pH-responsive nanoparticles have been developed to deliver doxorubicin to the acidic tumor microenvironment for enhanced anticancer efficacy. [72]
Purposely, targeted drug delivery can provide the key to overcoming the weaknesses of natural product-based anticancer drugs like poor metabolic stability and toxicity towards normal cells. Simultaneously, it can enhance the strength of these drugs, such as higher efficacy and less toxicity, by delivering the drug to only the target location (tumor). In line with the goal of targeted drug delivery, controlled release systems are critical for achieving the required objectives. By precisely releasing the therapeutics at the desired target site, their spatiotemporal releases are well-defined, offering improved drug pharmacokinetics, pharmacodynamics, and other benefits in NP-based anticancer chemotherapy.

Controlled release systems

Controlled release systems are becoming important parts of targeted drug delivery systems. These systems are very important for improving anticancer drugs from natural products by releasing therapeutic agents locally or systemically at the site of action. This improves the pharmacokinetics and pharmacodynamics of these drugs. The release of the drug at a controlled rate will not only enhance the bioavailability but will also help to reduce the side effects in the body and improve the pharmacokinetic responses, resulting in more patient compliance. They are easily put

into various drug delivery platforms, such as nanoparticles, hydrogels, and microspheres. These platforms can react differently to temperature, pH, magnetic fields, or other physiological or environmental stimuli or to the tumor's physiology to give precise control over when and where they are released.
Controlled release systems could help solve some of the problems we have seen with natural product-based cancer drugs, including:

1. Side effects that happen when too much of the drug is given;

2. The drug becoming inactive through metabolism or known detoxification processes in the body;

3. The drug leaves the bloodstream before it can do its job of fighting cancer.

In the context of natural product-based anticancer drugs, controlled-release systems can offer several advantages:

Sustained drug release: Controlled release systems can maintain therapeutic concentrations (including absorption) of the drug within the target tissue over an extended period, avoiding frequent drug administration and fluctuations in the drug concentration. This is especially important for natural products (such as TNUs) that have short half-lives or are quickly cleared from the body.

Stability: encapsulation of natural product-based anticancer drugs in controlled release systems ensures drug stability, preventing degradation or inactivation of the drug before it reaches the target.

Improved uptake in the cell: Incorporated drug release into controlled systems can improve the drug uptake into the cell, which leads to a high concentration of the drug at the intracellular level and a better therapeutic outcome.
An excellent example of a controlled release system for natural product-based anticancer drugs is designing poly (lactic-co-glycolic acid) (PLGA) nanoparticles to deliver curcumin, a natural compound with strong anticancer activity. Encapsulation of curcumin into PLGA nanoparticles led to its release in a controlled manner, thereby improving the anticancer activity while curtailing toxic effects in systemic organs compared with free curcumin [74].

Hence, controlled release systems play an important role in achieving spatiotemporal controlled release and targeted drug delivery, which offers a relatively effective means of optimizing the pharmacokinetics and pharmacodynamics, especially the drug's water solubility and bioavailability. By further optimizing the therapeutic efficacy and safety of natural product-based anticancer drugs, the control release systems could become an important way of treating patients and improving the therapeutic outcome of cancer.

To sum up, natural product-based anticancer drugs face bias because of their poor water solubility and low bioavailability, which often cause side effects, including further systemic toxicity. Such drawbacks can be alleviated by DDSs and nanotechnology that can improve the abovementioned major issues by enhancing the bioavailability and targeting capacity of those compounds. As a result, the efficacy of

these systems should be better than that of current natural product-based anticancer drugs, making DDSs and nanotechnology an important addition to the development and use of safer and cleaner natural product-based anticancer therapies.

4.3. The importance of interdisciplinary collaboration in advancing natural product-based anticancer drug discovery

Finding new anticancer drugs from natural products is a complicated process that requires the assistance of numerous experts with a wide range of skills. These skills span from animal behavior to medicinal plant extraction, from chemical synthesis to bioassay-guided fractionation, from computational chemistry to drug metabolism and pharmacology, from physiology to pharmacology, from in vitro to in vivo, from preclinical to clinical testing—in essence, the entire process of discovering a new anticancer drug. The whole field, therefore, demands interdisciplinary collaboration with many different areas of expertise, rapidly moving between isolation, purification, chemical synthesis, animal testing, and clinical trials to make the discoveries of one team applicable to the next.

Perhaps most importantly, natural product-based drug discovery requires a constant and fruitful dialogue between chemists and biologists to develop and use innovative methods to efficiently extract, purify, and characterize bioactive compounds from natural sources of complex chemical diversity [75]. In this regard, collaborative efforts between chemists and biologists can be greatly beneficial in uncovering novel anticancer lead compounds from nature by optimizing their structural diversity and access. Identifying a novel lead compound from natural sources can pave the way for interdisciplinary collaboration to improve it as a drug candidate in terms of potency, selectivity, and pharmacological properties. Chemists can apply their expertise in medicinal chemistry to enhance the drug-like properties of natural products by optimizing their structure-activity relationship (SAR) and making analogs using various chemical approaches. At the same time, biologists and pharmacologists can determine the mechanism of the compound's anti-tumor action, investigate its potency in pre-clinical models, and study its mechanism of drug resistance [52]. Unavoidably, clinical translation requires that natural product-based anticancer drugs be assessed and evaluated by physicians, oncologists, and clinical pharmacologists. By working together with clinicians, efforts may be made to perform clinical trials to elucidate optimal dosing for natural product-based drugs in cancer patients, as well as their toxicity and efficacy [76]. Such an interdisciplinary approach is instrumental in bringing novel natural products from the bench to the bedside and ultimately improving cancer treatment outcomes for patients.

Taxanes, like paclitaxel and their derivatives, are a good example of a natural product-based anticancer drug discovery and development project that works well across disciplines. Paclitaxel, a natural compound extracted from a yew tree (Taxus brevifolia), was discovered by chemists and biologists in the 1960s [58, 69]. Based on this discovery, more research across different fields led to the creation of docetaxel, a semisynthetic taxane derived from the compound paclitaxel. Interdisciplinary research also found albumin-bound paclitaxel nanoparticles (Abraxane), which made paclitaxel much easier to dissolve and change its form in the body. Such taxanes have been widely used to treat various types of cancer.

Another best example of fruitful interdisciplinary collaboration in natural product-based anticancer drug discovery is the family of camptothecin derivatives. The natural product camptothecin was first extracted from the Chinese tree Camptotheca acuminata by an interdisciplinary team consisting of medicinal chemists and botanists in the 1950s [77]. However, poor solubility and severe toxicity have made the early clinical development of camptothecin futile. Scientists from different fields worked together several times to make camptothecin-based anticancer drugs possible. First, medicinal chemists improved the pharmacological properties of the natural compound by synthesizing different camptothecin derivatives. This was a successful way to find drugs like topotecan and irinotecan, which are now used in clinical settings to treat ovarian cancer, small-cell lung cancer, and colorectal cancer [62, 78]. Next, pharmacologists and oncologists figured out how it worked, how well it worked, and how dangerous it was in both preclinical and clinical settings [79]. The clinical translation of natural product-based anticancer drugs requires the involvement of physicians, oncologists, and clinical pharmacologists to ensure the safe and effective evaluation of these compounds in patients. By collaborating with clinicians, researchers can design and conduct clinical trials that explore the optimal dosing, safety, and efficacy of natural product-based drugs in cancer patients [76]. This interdisciplinary effort is essential for advancing novel natural products from the bench to the bedside and ultimately improving treatment outcomes for cancer patients. Examples of successful interdisciplinary collaborations in natural product-based anticancer drug discovery include the development of paclitaxel and its derivatives. Paclitaxel, a natural compound isolated from the yew tree (Taxus brevifolia), was identified through collaborative efforts between chemists and biologists in the 1960s. Subsequent interdisciplinary research led to the development of docetaxel, a semisynthetic taxane derived from paclitaxel, and the discovery of albumin-bound paclitaxel nanoparticles (Abraxane), which improved the drug's solubility and pharmacokinetics [58,69]. These collaborative efforts have significantly advanced the use of taxanes in the treatment of various cancers.

Another good example of successful interdisciplinary collaboration in natural product-based anticancer drug discovery is the development of camptothecin derivatives. Camptothecin, a natural compound isolated from the Chinese tree Camptotheca acuminata, was initially discovered through joint efforts between chemists and botanists in the 1950s [77]. However, its poor solubility and severe side effects hampered its clinical development. Interdisciplinary collaboration played a crucial role in overcoming these challenges and developing effective camptothecin-based anticancer drugs. Chemists synthesized various camptothecin derivatives to improve the compound's pharmacological properties, leading to the development of topotecan and irinotecan, two clinically approved drugs for the treatment of ovarian cancer, small-cell lung cancer, and colorectal cancer [62, 78]. Furthermore, researchers from different disciplines, including pharmacologists and oncologists, collaborated to understand the mechanism of action of camptothecin derivatives, which target the enzyme topoisomerase I, and to evaluate their efficacy and safety in preclinical and clinical settings [79].
Recently, research from different fields has been focusing on making new camptothecin analogues and different targeted delivery systems to make this group of compounds more useful for therapy. Some examples are liposome forms of camptothecin derivatives, like liposomal irinotecan (Onivyde), which was recently approved by the FDA to treat pancreatic cancer [80].

5. Conclusion

In this review article, we have highlighted the crucial role of natural products in discovering anticancer drugs. Natural products are a unique source of structurally diverse and biologically active molecules, making them an invaluable resource for identifying lead compounds in drug discovery. Several natural product-derived anticancer drugs, such as paclitaxel, doxorubicin, and camptothecin derivatives, have been successfully applied in clinics to treat various cancers.

Despite the significant achievements, natural product-oriented drug discovery faces challenges, including inconsistent drug supply, poor pharmacokinetics, and off-target effects. Next-generation strategies involving delivery systems, nanotechnology, and targeted drug delivery have been developed to overcome these limitations. These innovative approaches improve the pharmacokinetics, bioavailability, and safety of natural product-based anticancer drugs, paving the way for more effective and well-tolerated cancer therapies.

The success of natural product-based anticancer drugs can be attributed to the commitment of researchers across multiple disciplines and the recent advances in cancer biology and precision medicine. As the global incidence of cancer rises, the demand for structurally diverse and biologically active compounds from natural sources will continue to grow. By fostering interdisciplinary collaborations and embracing technological innovations, we can harness the full potential of natural products in cancer drug discovery.

In conclusion, natural products will remain an indispensable source of novel anticancer agents. Continued exploration and development of these compounds and advancements in drug delivery systems and precision medicine will lead to more effective and safer cancer therapies. This, in turn, will improve outcomes for cancer patients worldwide and contribute to the ongoing battle against cancer.

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REFERENCES

1. Sung, H., et al. "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries." CA: A Cancer Journal for Clinicians, vol. 71, no. 3, 2021, pp. 209-249.

2. Sharma, V., et al. "Chemotherapy-Induced Peripheral Neuropathy: Molecular Pathophysiology, Chemotherapeutic Drugs Inducing Neuropathy, Current Management Strategies, and Future Perspectives." Cancers, vol. 14, no. 10, 2022, p. 2225.

3. Vasan, S., et al. "Combination of Natural Products with Chemotherapy for Overcoming Drug Resistance in Breast Cancer: An Overview." Biomedicine & Pharmacotherapy, vol. 118, 2019, p. 109294.

4. Yu, S., et al. "Mechanisms and Biomarkers of EGFR TKI Resistance in NSCLC." Cancers, vol. 13, no. 10, 2021, p. 2208.

5. Musgrove, E. A., et al. "Mechanisms of Endocrine Resistance in Breast Cancer." Nature Reviews Cancer, vol. 21, no. 2, 2021, pp. 99-117.

6. Chirik, E., et al. "Emerging Biomarkers in Cardiotoxicity From Anticancer Therapies." JACC: CardioOncology, vol. 3, no. 2, 2021, pp. 307-318.

7. Harrington, A., et al. "A Mobile Phone App for Nausea and Vomiting in Patients Receiving Chemotherapy: Results from a Mixed Methods Study." European Journal of Oncology Nursing, vol. 32, 2018, pp. 52-60.

8. Khoja, L., et al. "Navigating Toxicities of Precision Oncology: Adverse Effects of Targeted Anticancer Therapies and Immune Checkpoint Inhibitors." Expert Review of Anticancer Therapy, vol. 21, no. 6, 2021, pp. 627-646.

9. Kumar, A., et al. "Targeted Therapies for Cancer: Present Scenario and Future Perspectives." Cancer Cell International, vol. 21, no. 1, 2021, pp. 1-20.

10. Verma, V., et al. "Radiotherapy in Skin Cancer: Review of Current Standards and Practical Guidelines." Dermatology and Therapy, vol. 10, no. 3, 2020, pp. 1075-1098.

11. Newman, D. J., et al. "Natural Products as Leads to Anticancer Drugs." Future Medicinal Chemistry, vol. 11, no. 6, 2019, pp. 751-758.

12. Harvey, A. L., et al. "Natural Products as a Source of New Drugs: A 2020 Update." Journal of Antibiotics, vol. 73, no. 5, 2020, pp. 272-279.

13. Deng, Y., et al. "Doxorubicin: A Classical Drug at the Forefront of Tumor Chemotherapy." Acta Pharmaceutica Sinica B, vol. 10, no. 11, 2020, pp. 1877-1892.

14. García-Fernández, L., et al. "Plitidepsin in Oncology: Mechanisms of Action and Therapeutic Potential in Cancer Treatment." Biochemical Pharmacology, vol. 175, 2020, p. 113857.

15. Kusari, S., Singh, S., &Jayabaskaran, C. "Plant-Endophytic Fungi Interactions: A Source of Novel Metabolites with Anticancer Properties." Biomolecules, vol. 11, no. 5, 2021, p. 684.

16. Xiao, Z., et al. "Paclitaxel Induces Apoptosis by Regulating Death Receptor 4-Mediated Mitochondrial Pathways in Human Colon Cancer Cells." European Journal of Pharmacology, vol. 909, 2021, p. 174497.

17. Zhao, J., et al. "Natural Products from Endophytic Fungi: A Promising Source of Anticancer Agents." Frontiers in Pharmacology, vol. 12, 2021, p. 637703.

18. Kusari, S., et al. "Alkaloids as Anticancer Agents." Anti-Cancer Agents in Medicinal Chemistry, vol. 21, no. 9, 2021, pp. 1155-1216.

19. Cragg, G. M., Newman, D. J., & Snader, K. M. "Natural Products in Drug Discovery and Development." Natural Product Reports, vol. 26, no. 7, 2009, pp. 897-921.

20. Feng, M., et al. "Anti-Cancer Natural Products Isolated from Traditional Chinese Medicine: Pharmacological Mechanisms and Potential as Lead Compounds." Journal of Traditional and Complementary Medicine, vol. 11, no. 3, 2021, pp. 307-326.

21. Pommier, Y., et al. "DNA Topoisomerases and Their Poisoning by Anticancer and Antibacterial Drugs." Chemistry & Biology, vol. 17, no. 5, 2010, pp. 421-433.

22. Chen, Y., Wu, X., & Zhou, B. "Terpenoids as Potential Anticancer Agents: A Comprehensive Review of Their Molecular Targets and Mechanisms." Cancer Medicine, vol. 9, no. 15, 2020, pp. 5235-5246.

23. Huang, Y., et al. "Anticancer Terpenoids from Medicinal Plants: Structures, Sources, and Mechanisms." Natural Product Communications, vol. 16, no. 1, 2021, p. 193201172096518.

24. Deb, D. D., et al. "Effect of Thymol on Peripheral Blood Mononuclear Cell PBMC and Acute Promyelotic Cancer Cell Line HL-60." Chemico-Biological Interactions, vol. 193, 2011, pp. 97-106.

25. Llana-Ruiz-Cabello, M., et al. "Cytotoxicity and Morphological Effects Induced by Carvacrol and Thymol on the Human Cell Line Caco-2." Food Chemistry and Toxicology, vol. 64, 2014, pp. 281-290.

26. Chang, H.-T., et al. "Effect of Thymol on Ca2+ Homeostasis and Viability in MG63 Human Osteosarcoma Cells." Pharmacology, vol. 88, 2011, pp. 201-212.

27. Hsu, S.-S., et al. "Effect of Thymol on Ca2+ Homeostasis and Viability in Human Glioblastoma Cells." European Journal of Pharmacology, vol. 670, 2011, pp. 85-91.

28. Yeh, J.-H., et al. "Effect of Thymol on Ca2+ Homeostasis and Viability in PC3 Human Prostate Cancer Cells." Chinese Journal of Physiology, vol. 60, 2017, pp. 32-40.

29. Rajashekhar, L., and Nja, S. "Anticancer Properties of Phenolic Acids in Colon Cancer – A Review." Journal of Nutrition and Food Science, vol. 6, 2016, p. 10-4172.

30. Chander, M. "Anticancer Efficacy of Some Plant Phenolics - A Recent Scenario." International Journal of Contemporary Medical and Applied Sciences, vol. 7, 2018, pp. 1746-1768.

31. Jiang, S., et al. "Curcumin Inhibits Migration and Invasion via Modulating MMP-2/9 Expression in Colorectal Cancer Cells." Frontiers in Oncology, vol. 10, 2021, p. 591372.

32. Kuo, C. H., et al. "Genistein Induces Apoptosis through the Modulation of Bax/Bcl-2 Expression and MAPK Signaling Pathway in Human Breast Cancer Cells." Journal of Food and Drug Analysis, vol. 26, no. 1, 2018, pp. 101-110.

33. Li, Y., et al. "Quercetin, a Flavonoid with Ubiquitin-Dependent Degradative Activity against Cell Cycle Regulatory Proteins, Suppresses Growth of Human Colon Cancer Cells." Food & Function, vol. 7, no. 5, 2016, pp. 2255-2264.

34. Katiyar, S., Tanveer, A., and Gupta, V. "Podophyllotoxin: A Novel Anticancer Agent." International Journal of Pharmacy and Pharmaceutical Sciences, vol. 4, suppl. 5, 2012, pp. 10-15.

35. Kunert, O., Chan, H. P., and Ng, S. C. "Microtubule-Targeted Anticancer Agents: Mechanisms of Action and Resistance Pathways." Current Cancer Drug Targets, vol. 8, no. 1, 2008, pp. 19-35.

36. Konopleva, M., et al. "Homoharringtonine and Related Compounds: A Novel Class of Antineoplastic Drugs Targeted to Protein Synthesis." Drug Resistance Updates, vol. 36, 2018, pp. 22-33.

37. Kim, H. S., et al. "Homoharringtonine Exerts Its Anticancer Activity through Inhibition of Protein Synthesis and Induction of Apoptosis via Endoplasmic Reticulum Stress Pathway." Experimental & Molecular Medicine, vol. 48, no. 3, 2016, p. e209.

38. Wang, X., et al. "Homoharringtonine: A Promising Therapeutic Agent for Blood Tumors." Chinese Medicine, vol. 16, no. 1, 2021, pp. 1-13.

39. Omacetaxine Mepesuccinate. Drug Information. Eds. C. A. N. Center, H. S. A. Information, and A. M. D. Association. American Medical Association, 2012, pp. 74-76.

40. Cichewitz, R. H., and Kouzi, S. A. "Chemistry, Biological Activity, and Chemotherapeutic Potential of Betulinic Acid for the Prevention and Treatment of Cancer and HIV Infection." Medical Research Reviews, vol. 24, no. 1, 2004, pp. 90-114.

41. Pisha, E., et al. "Discovery of Betulinic Acid as a Selective Inhibitor of Human Melanoma that Functions by Induction of Apoptosis." Nature Medicine, vol. 1, no. 10, 1995, pp. 1046-1051.

42. Shoeb, M. "Betulinic Acid, a Novel Apoptosis Inducing Compound, Inhibits Growth of Murine Melanoma B16F0 and B16F10 Cells in Culture and in Vivo through Induction of Apoptosis." Molecular Cancer Therapeutics, vol. 5, 2006, pp. 1740-1747.

43. Fujioka, T., et al. "Anti-AIDS Agents, 11. Betulinic Acid and Platanic Acid as Anti-HIV Principles from SyzigiumClaviflorum, and the Anti-HIV Activity of Structurally Related Triterpenoids." Journal of Natural Products, vol. 57, no. 2, 1994, pp. 243-247.

44. Nguemfo, E. L., et al. "Cytotoxicity and Antioxidant Activity of Triterpenes from the Stem Bark of Albizia Adianthifolia (Mimosaceae)." Journal of Ethnopharmacology, vol. 122, no. 2, 2009, pp. 324-328.

45. Tzakos, A. G., et al. "Betulinic Acid, a Natural Compound with Potent Anticancer Effects: A Mini-Review." Molecules, vol. 17, no. 3, 2012, pp. 3736-3746.

46. Onwuchekwa, C., and Oluwole, E. F. "Antioxidant, Antibacterial and Pro-Oxidant Activities of Phenolics from Moringa Oleifera Lam. Leaves." Brazilian Journal of Pharmacognosy, vol. 20, no. 4, 2010, pp. 594-600.

47. Yogeeswari, P., and Sriram, D. "Betulinic Acid and Its Derivatives: A Review on Their Biological Properties." Current Medicinal Chemistry, vol. 12, no. 6, 2005, pp. 657-666.

48. Chowdhury, A. R., et al. "Betulinic Acid, a Potent Inhibitor of Eukaryotic Topoisomerase I: Identification of the Inhibitory Step, the Major Functional Group Responsible and Development of More Potent Derivatives." Med. Sci. Monit, vol. 8, no. 9, 2002, pp. BR279-BR286.

49. Mukherjee, S., et al. "Betulinic Acid Isolated from Vitex Negundo Exerts Anti-Inflammatory and Anticancer Activity in Skin Carcinogenesis." Cancer Letters, vol. 236, no. 2, 2006, pp. 260-267.

50. Mullauer, F. B., et al. "Betulinic Acid, a Natural Compound with Potent Anticancer Effects." Anticancer Drugs, vol. 21, no. 3, 2010, pp. 215-227.

51. Willmann, M., et al. "Topical Application of the Novel Betulinic Acid Derivative NVX-207: Results of a Phase I/II Clinical Trial in Canine Cancer Patients." Veterinary and Comparative Oncology, vol. 7, no. 2, 2009, pp. 126-136.

52. Koehn, F. E., and Carter, G. T. "The Evolving Role of Natural Products in Drug Discovery." Nature Reviews Drug Discovery, vol. 4, no. 3, 2005, pp. 206-220.

53. Ganjali, S., et al. "Advances in Preclinical and Clinical Studies on Curcumin as a Therapeutic and Bioactive Molecule: A Comprehensive Review." The Journal of Alternative and Complementary Medicine, vol. 28, no. 10, 2022, pp. 2484-2524.

54. Shankar, S., et al. "Natural Products and Cancer Cell Biology: A Re-Emerging Link." Current Topics in Medicinal Chemistry, vol. 21, no. 1, 2021, pp. 80-99.

55. Zhang, C., et al. "The Therapeutic Efficacy and Underlying Mechanisms of Resveratrol Supplementation in the Treatment of Cancer and Cardiovascular Disease: A Systematic Review." Nutrition Reviews, vol. 79, no. 10, 2021, pp. 1144-1161.

56. Deng, Y., et al. "Resveratrol and Inflammation: A Review of Mechanistic Insights Based on Preclinical Models and Clinical Trials." Nutrients, vol. 12, no. 7, 2020, p. E2105.

57. DiMasi, J. A., et al. "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs." Journal of Health Economics, vol. 47, 2016, pp. 20-33.

58. Rowinsky, E. K., et al. "Microtubule Changes and Cytotoxicity in Leukemic Cell Lines Treated with Taxol." Cancer Research, vol. 50, no. 5, 1990, pp. 1576-1580.

59. Li, J., et al. "Pharmacokinetic Properties and Synergistic Anticancer Effects of Combined Therapy with Paclitaxel and Camptothecin Co-Loaded Solid Lipid Nanoparticles." International Journal of Pharmaceutics, vol. 466, no. 1-2, 2014, pp. 260-269.

60. Bhatia, S. "Natural Polymer-Based Nanocomposites for Delivery of Anticancer Drugs." Novel Approaches for Drug Delivery, edited by A. M. Grumezescu, Academic Press, 2016, pp. 547-587.

61. Tang, C., et al. "Optimization of Nanoparticle-Based Drug Delivery Systems to Modulate Pharmacokinetics and Pharmacodynamics in Anticancer Therapy." Journal of Controlled Release, vol. 314, 2019, pp. 93-108.

62. Hsiang, Y. H., et al. "Camptothecin Induces Protein-Linked DNA Breaks via Mammalian DNA Topoisomerase I." Journal of Biological Chemistry, vol. 264, no. 3, 1989, pp. 1436-1440.

63. Carroll, A. R., et al. "Natural Product Discovery from the Australian Marine Environment." Journal of Natural Products, vol. 82, no. 5, 2019, pp. 1144-1167.

64. Rinehart, K. L., et al. "Didemnins: Antiviral and Antitumor Depsipeptides from a Caribbean Tunicate." Science, vol. 212, no. 4500, 1981, pp. 933-935.

65. Zhai, H., et al. "The Potential and Challenges of Developing Natural Products and Their Derivatives as Anticancer Drugs: An Update over the Last Ten Years." Biomedicine & Pharmacotherapy, vol. 146, 2022, p. 112804.

66. Kusari, S., et al. "Biotechnological Potential of Plant-Associated Endophytic Fungi: Hope Versus Hype." Trends in Biotechnology, vol. 32, no. 6, 2014, pp. 297-303.

67. Rathod, D., B. Kapadiya, A. Gopale, S. Pathak, S. Sharma, and A. Kulkarni. "Endophytic Fungi: A Promising Source of Anticancer Agents." Journal of Fungi, vol. 8, no. 4, 2022, p. 355.

68. Allen, T. M., and P. R. Cullis. "Liposomal Drug Delivery Systems: From Concept to Clinical Applications." Advanced Drug Delivery Reviews, vol. 65, no. 1, 2013, pp. 36-48.

69. Desai, N., et al. "Increased Antitumor Activity, Intratumor Paclitaxel Concentrations, and Endothelial Cell Transport of Cremophor-Free, Albumin-Bound Paclitaxel, ABI-007, Compared with Cremophor-Based Paclitaxel." Clinical Cancer Research, vol. 12, no. 4, 2006, pp. 1317-1324.

70. Gabizon, A., et al. "Targeting of Liposomes to Tumors Using Peptides Grafted onto Liposome-Associated Polymers." International Journal of Cancer, vol. 56, no. 4, 1994, pp. 591-596.

71. Appelbaum, F. R. "Anticancer Drugs: 5. Antibody-Drug Conjugates." Clinical Cancer Research, vol. 7, no. 12, 2001, p. 4175.

72. Leamon, C. P., et al. "Folate-Targeted Nanoparticles for Enhanced Photodynamic Therapy." Journal of Controlled Release, vol. 124, no. 1-2, 2007, pp. 88-96.

73. Meng, F., et al. "Reduction-Sensitive Polymers and Bioconjugates for Biomedical Applications." Biomaterials, vol. 68, 2015, pp. 81-98.

74. Yallapu, M. M., et al. "Curcumin Nanoformulations: A Future Nanomedicine for Cancer." Drug Discovery Today, vol. 17, no. 1-2, 2010, pp. 71-80.

75. Cragg, G. M., and D. J. Newman. "Natural Products: A Continuing Source of Novel Drug Leads." Biochimica et Biophysica Acta (BBA) - General Subjects, vol. 1830, no. 6, 2013, pp. 3670-3695.

76. Szakács, G., et al. "Targeting Multidrug Resistance in Cancer." Nature Reviews Drug Discovery, vol. 3, no. 5, 2004, pp. 459-476.

77. Wall, M. E., et al. "Plant Antitumor Agents. I. The Isolation and Structure of Camptothecin, a Novel Alkaloidal Leukemia and Tumor Inhibitor from Camptotheca Acuminata." Journal of the American Chemical Society, vol. 88, no. 16, 1966, pp. 3888-3890.

78. Rothenberg, M. L. "Topoisomerase I Inhibitors: Review and Update." Annals of Oncology, vol. 7, no. 8, 1996, pp. 837-845.

79. Pommier, Y. "Topoisomerase I Inhibitors: Camptothecins and Beyond." Nature Reviews Cancer, vol. 6, no. 10, 2006, pp. 789-802.

80. Von Hoff, D. D., et al. "Increased Survival in Pancreatic Cancer with Nab-Paclitaxel Plus Gemcitabine." New England Journal of Medicine, vol. 375, no. 18, 2016, pp. 1720-1