

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 an important source 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. In this review, we provide 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 be used to 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 do research across disciplines for the project to be successful in the future. 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 has the highest incidence of all types of human morbidity and mortality. In 2020, approximately 19.3 million new cancer cases were reported, and 10 million people died from cancer [1]. 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]. Considering the high incidence of cancer and the limitation of conventional treatment, one can well imagine the urgent need for effective treatment and the mandate of alternative

treatment for cancer. In other words, it is crucial to explore alternative therapeutic strategies to combat the ongoing epidemic of human cancers, and natural products offer significant potential as rich sources of anticancer compounds.

Nature produces a wide variety of chemicals, which could potentially lead to the development of numerous new medicines. These medicines could target different parts of the cancer cell or the environment around the tumor that are involved in starting the cancer, making it grow, or spreading to other parts of the body. 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. This comprehensive review points out the huge potential of natural products as the major source of anti-cancer drugs, reporting the recent findings and future trends for the discovery of novel and more efficient anticancer therapies.

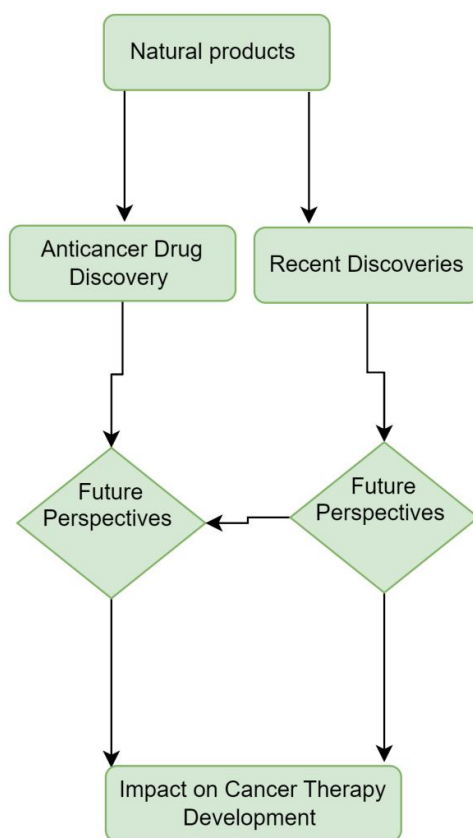


Fig 1. Natural Products as Anticancer: Recent Discovery and Future Perspectives Flowchart. This diagram highlights the interconnections of these components and emphasizes their collective contribution to the advancement of cancer therapies.

Natural Products → Anticancer Drug Discovery: Natural products provide a rich source of bioactive compounds, which can be screened and developed into potential anticancer drugs.

Natural Products → Recent Discoveries: Ongoing research in natural products continuously unveils new compounds with promising anticancer properties.

Anticancer Drug Discovery → Impact on Cancer Therapy Development: Successful drug discovery efforts lead to innovative and more effective cancer therapies.

Recent Discoveries → Impact on Cancer Therapy Development: Recent findings in natural product-based anticancer agents contribute to the development of novel cancer therapies.

Recent Discoveries → Future Perspectives: Recent discoveries shape future directions and strategies for natural product-based drug development.

Future Perspectives → Impact on Cancer Therapy Development: Future advances in natural product research and drug development will further enhance cancer therapy options.

Methodology:

This review article is based on a comprehensive literature search and analysis of scientific articles, reviews, and books related to 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 a comprehensive writing on untapped potential of natural products for targeted therapies.

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

Critical assessment and synthesis of the information to provide a comprehensive overview of the subject matter, highlighting key findings, notable examples, and potential implications for the future of natural product-based anticancer drug development.

1.1. Conventional anticancer therapies and their limitations

Conventional 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 frequently seen in breast cancer patients receiving paclitaxel and doxorubicin chemotherapies. This is sometimes because the chemo treatments 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 levels of 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 more 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 the use of 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. In any treatment area, patients can expect to develop redness or blistering skin. 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 make lymph fluid buildup in the arms or legs and cause swelling called lymphoedema. Radiation enteritis is fatigue from inflammation of the small intestine, 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. Nonetheless, skin-related issues, diarrhea, and high blood pressure are commonly seen. 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 a variety of 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.

Despite the many breakthroughs witnessed in anti-cancer therapies based on conventional chemical drugs, such as chemotherapy and radiotherapy, their intrinsic limitations have forced researchers to search for alternative treatment strategies. Scientists have discovered natural products as an amazing source of potential anticancer agents, driven by the urgent need to overcome the issue of drug resistance, reduce their severe side effects, and enhance their efficacy. This "new face" of natural product-based therapies is expected to play a crucial role in the future of cancer treatment, providing patients with improved, highly personalized cancer care.

1.2 Natural products as a valuable resource for anticancer drug discovery

Most anticancer drugs identified and developed to date are based on natural products, with new estimates indicating that natural products and/or their derivatives were responsible for approximately 70 percent of all anticancer drugs approved between the 1980s and 2010s [11]. Natural products have proven a rich resource for anticancer agents, with 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, which in turn makes them useful in identifying new types of bioactive constituents that we have not previously come across. Additionally, the continual development in analytical techniques for screening, and computational methods for natural product characterization, are boosting our ability to detect bio-active compounds from natural sources [12].

Several natural products, as well as semi-synthetic or synthetic analogs, are now in clinical use as anticancer agents. The most well-known is probably 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, which was found in *Streptomyces* bacteria, is another success story. It stops topoisomerase II from working, which means it doesn't allow DNA to copy normally [14].

More recently, researchers have turned their attention to other natural sources 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, which is often found in solid tumors like sarcoma, leiomyosarcoma, and some types of lymphoma [15]. Plitidepsin is now advancing in clinical trials for multiple myeloma and angioimmunoblastic T-cell lymphoma.

Another example is the so-called endophytic fungi, which hover, literally between the cracks, being 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 stops 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 used against a wide range of 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 metaphorical dictionary hold enormous and unexplored potential in anticancer drug discovery.

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 initially into two broad categories based on their functions inside the organisms that produce them: primary metabolites 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 of great interest 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 a vast number of plants, microbes, and marine organisms. The diversity in structure and bioactivity of alkaloids is remarkable; their anticancer activity has garnered significant attention. Vinca alkaloids, along with 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 components of the cytoskeleton, which is responsible for maintaining cell shape and intracellular transport. They also assemble into the mitotic spindle, which is a key contributor to chromosome segregation during cell division (the mitosis). As a result, microtubule dynamics are influenced by several alkaloids that are 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, which is essential for strand separation processes like DNA replication and transcription. Some chemicals called alkaloids, like camptothecin and its variations like topotecan and irinotecan, stop these enzymes from working. They do this by stabilizing the DNA-topoisomerase complex. This stops 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 a wide range of 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.

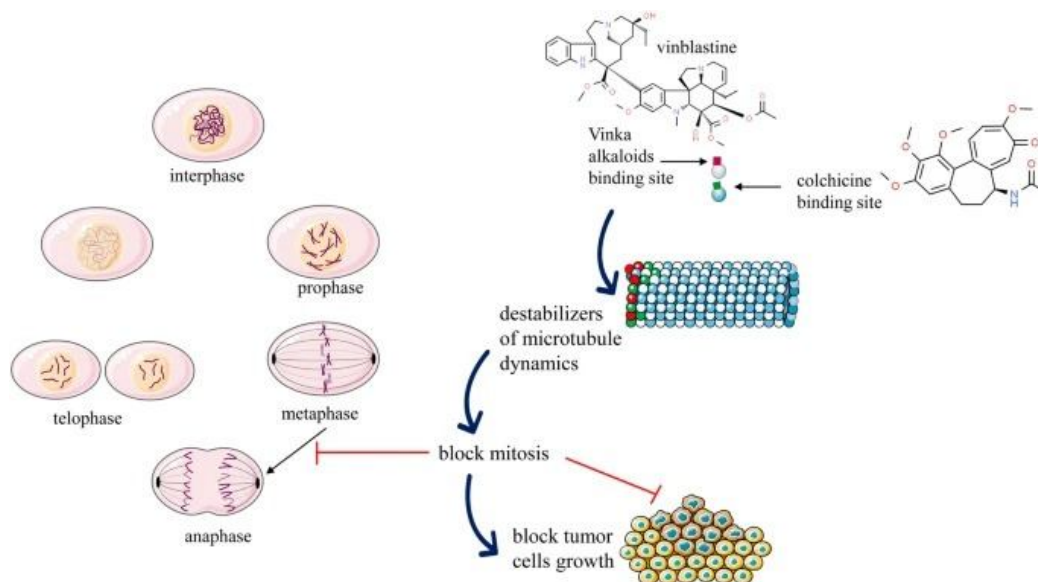


Fig 2. Summarized scheme with anticancer mechanisms of Vinca alkaloids and colchicine.

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—known as terpenoids—has garnered tremendous effort for their anticancer properties. This class of molecules, which is mainly synthesized from isoprene units assembled one by one, 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 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 efficacy in the inhibition of tumor progress and cytotoxic effect. 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 kaurenol can suppresses all the aforementioned pathways at different stages of cancer progression, to further supporting the notion that terpenoids are potential anticancer agents. Mechanism of action for Thymol as monoterpenoids against cancer progress explained below.

Thymol

In the leukemia cells (HL-60) model, thymol stops the cell cycle at the G0/G1 phase and then creates 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 that ultimately lead 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 Ca^{2+} and store-operated calcium entry [26, 27, 28]. The question now arises as to whether thymol may induce apoptosis in calcium-entry-mediated death signaling in MG63 osteosarcoma, DBTRG-05MG glioblastoma, or PC3 prostate cancer cells. Also, the release of Ca^{2+} by thymol increases the production of reactive oxygen species. This means that Ca^{2+} -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.

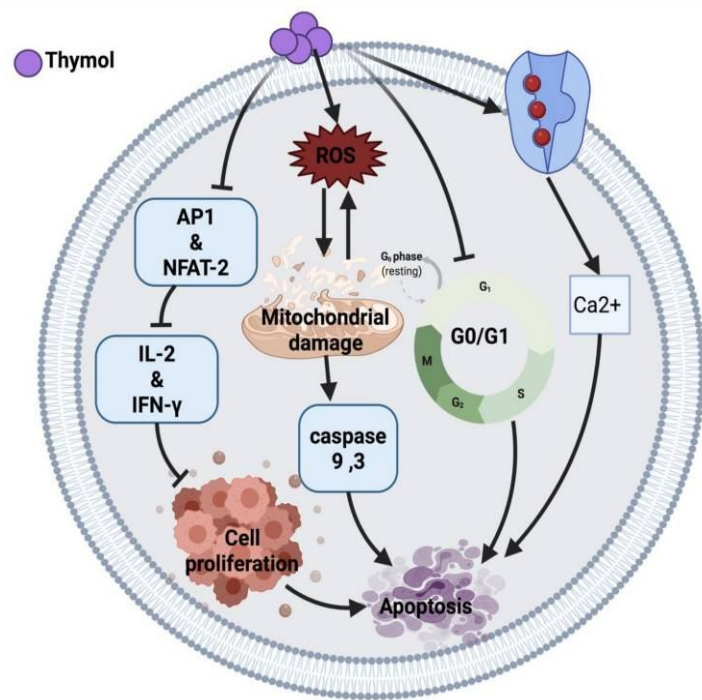


Figure 3: An overview of the potential anticancer mechanisms of thymol. (Kamran et al., 2022)

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 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 through regulation of critical cell signaling pathways, as well as by inducing apoptosis and inhibiting metastasis.

Key Mechanisms Flavonoid exert their anticancer effects.

1. Modulation of Cell Signaling Pathways

Flavonoids modulate multiple cells, signaling pathways involved in controlling cell proliferation, cell survival and cell death: PI3K/Akt, MAPK and NF- κ B 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 with consequent reduction of cancer cell proliferation and increase of 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 through 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 organs of the body. 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-1 α (HIF-1 α), 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]

Given that 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*, which is also known as "Bankakri" or the Himalayan mayapple. It is a lignan, a type of compound used to make new cancer-fighting drugs. The mayapple, a perennial herb found in the mountains of Central Asia, including the Himalayas, has been used for centuries in Ayurvedic medicine in India, Central Asia, and elsewhere for a variety of therapeutic purposes [34]. Chemically, podophyllotoxin is made up of four rings that are fused. A lactone ring connected to the central core may contribute to the compound's biological activity [34]. As an antimetabolic 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.

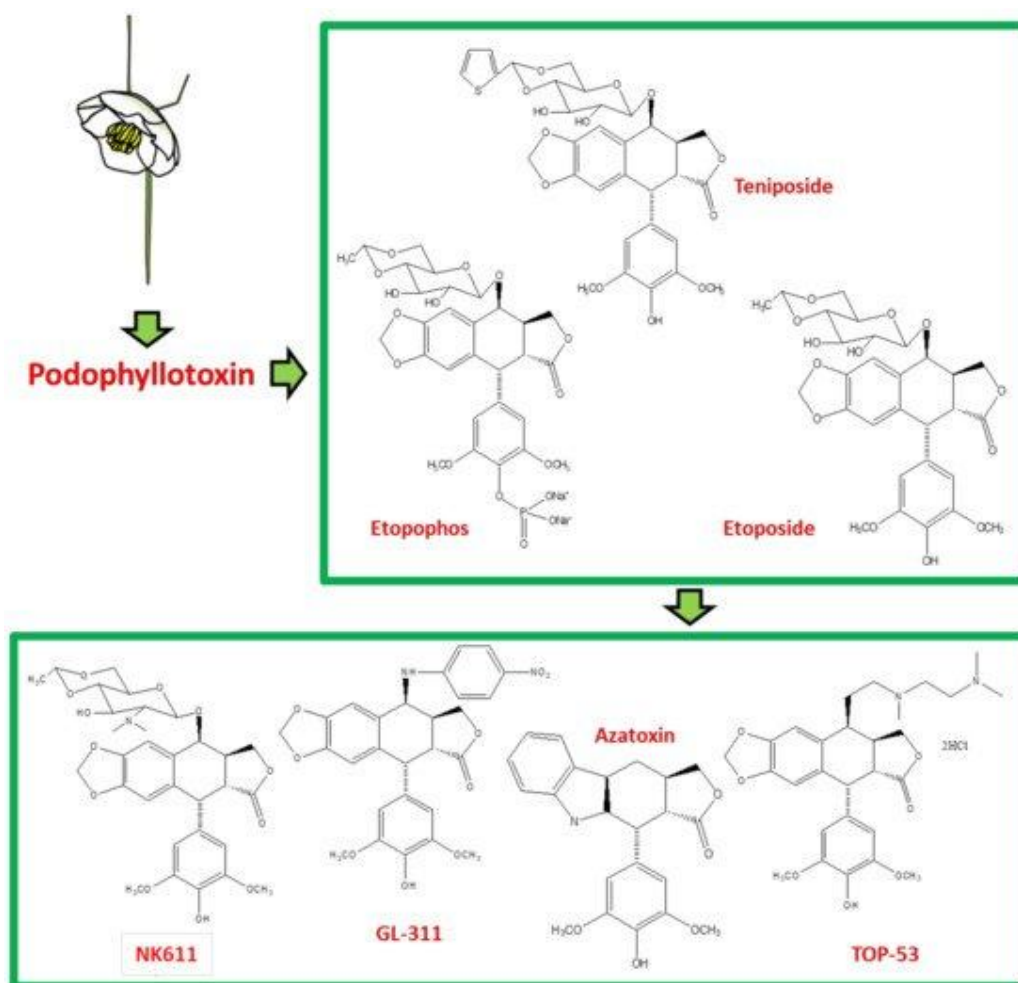


Fig 4. Chemical structure of etoposide, teniposide and etopophos

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 *Cephalotaxusharringtonia*. It selectively works on multiple mechanisms by affecting a variety of important molecules. HHT has demonstrated significant anticancer activity in most cancers, particularly many hematological malignancies. So far, the main ways that HHT fights cancer are thought to be by stopping protein synthesis, stopping the cell cycle at G2/M, and inducing apoptosis by changing proteins related to apoptosis, like Bcl-2 and Bax [36]. As far as we currently 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, two molecules that 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 anticancer effects or activity are not limited to this, as

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 treatment of adult patients with CML resistant or intolerant to two or more TKI [39].

Betulinic acid

Betulinic acid is one of the most common organic secondary metabolites of higher plants, mainly from *Betula* species (Betulaceae) [40]. Betulinic acid came from *Zizyphus* species (Rhamnaceae), e.g., *Mauritiana rugosa* and *Mauritiana oenophila* [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 of its ability to inhibit topoisomerase [48, 49, 50]. Betulinic acid was designed to increase this compound's activity. These compounds' unpleasant pharmacological and physicochemical properties led to some of the problems encountered during the clinical development of BetA derivatives. 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 existing 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 a wide variety of 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-flavour herbal drugs are proved to possess phenoloxidant and anti-inflammation activities causing the antitumorigenic effects through inhibiting the cancer cell proliferation and inducing apoptosis via multiple signalling pathways. These evident examples represented by podophyllotoxin, homoharringtonine and betulinic acid indicate that anticancer natural products from traditional medicine might be no longer regarded with a fuzzy concept. It is also certainly a deep and wide pool of drug discovery.

There are lots of cancer cells 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 in vitro using cancer cell lines. In such studies, a compound is typically tested for inhibition of cancer cell proliferation and/or cell death, as well as 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 on their own make these in vivo studies possible. Researchers assess the antitumor efficacy of a compound against tumor growth in 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, amongst others. 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 models of animal cancers have demonstrated the

chemopreventive activity of this compound 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 as well as 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 properties of the compound 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 and placebo-controlled trial. If the natural 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 safety, efficacy and quality of the drug [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].

To summarize, 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 natural product-based drugs. Designer formulations such as nanoparticles, liposomal encapsulated formulations, or polymer conjugates can not only enhance the solubility and stability of natural product-based drugs, 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. The drug metabolism could also be targeted to improve therapeutic indices, such as designing drugs that would result in 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 aimed at identifying strategies that would improve the absorption, distribution, metabolism, and elimination (ADME) of natural product-based drugs. 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 with each other [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 derivatives of camptothecin, a potent anticancer plant alkaloid that is poorly soluble in water and presents toxic effects, have been synthesized. These derivatives, named irinotecan and topotecan, were originally developed to treat colorectal and ovarian cancers [62].

To make clean, useful, and safe anticancer drugs from natural products, their pharmacokinetic, pharmacodynamic, and toxicological profiles need to be optimized. However, these active ingredients and their derivatives still have potential as 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 the discovery and development of anticancer natural products, particularly those derived from terrestrial plants, remains high. Besides traditional plant sources, marine natural products, in particular endophytic fungi, represent new sources that have already delivered interesting anticancer leads.

Marine Organisms:

Ocean biodiversity contains a large number of 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 is dependent 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 *Trididemnum 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 the development of more effective and less toxic 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 make many secondary metabolites that have 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 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 are allowing 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 then expanded, which makes it easier

to make the active ingredient. Second, the use of synthetic biology in marine organisms 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 that are derived from existing natural products with possibly 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, which can save 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 types of 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 Madagascar 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 nanoparticles and inorganic nanoparticles, have been developed for encapsulating or conjugating natural product-based anticancer drugs to enhance their stability, solubility, or targeting capabilities. Applications of nanotechnology have contributed significantly to the success of numerous natural product-based anticancer therapies. For example, paclitaxel is a diterpenoid compound that was found in the bark and needles of the yew tree (*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 as a result of 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 that is normally found in plasma, is modified with paclitaxel molecules so that the drug can get to the right places where it's needed. When compared to the standard paclitaxel formulation, abraxane is more effective, less harmful, and the highest dose that can be tolerated is raised by 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 in terms of enhancing their bioavailability and reducing their water-solubility, as well as improving their ultimate localization to the target place. Thus, it might promote natural compounds as a safe, effective and reliable alternative therapy with the potential to reduce patients' pain, to prolong patient survival, and to decrease host-systemic toxicity. In the future, drug delivery systems and nanotechnology will have an increasingly prominent role in the development of safer and more effective natural product-based anticancer therapies.

What we have seen so far suggests 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 the 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.

In the following paragraphs, we will summarize the different targeted drug delivery approaches as well as 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 delivering 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 the severe adverse side effects of conventional cancer therapy. Passive targeting, active targeting, and stimuli-responsive delivery are some of the strategies for targeted drug delivery.

Passive targeting is based on the unique features of solid tumor: 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 accumulating at the site of disease because of the EPR effect, a drug can achieve increased local accumulation and higher concentrations that leads 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 tumorespecific 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 a 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 for 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 and pharmacodynamics, along with 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 making anticancer drugs from natural products better 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 the 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 easy to put into a variety of drug delivery platforms, such as nanoparticles, hydrogels, and microspheres. These platforms can be made to 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 leaving 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 are able to maintain therapeutic concentrations (including absorption) of the drug within the target tissue over an extended period of time, 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 the designing of 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 by 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.

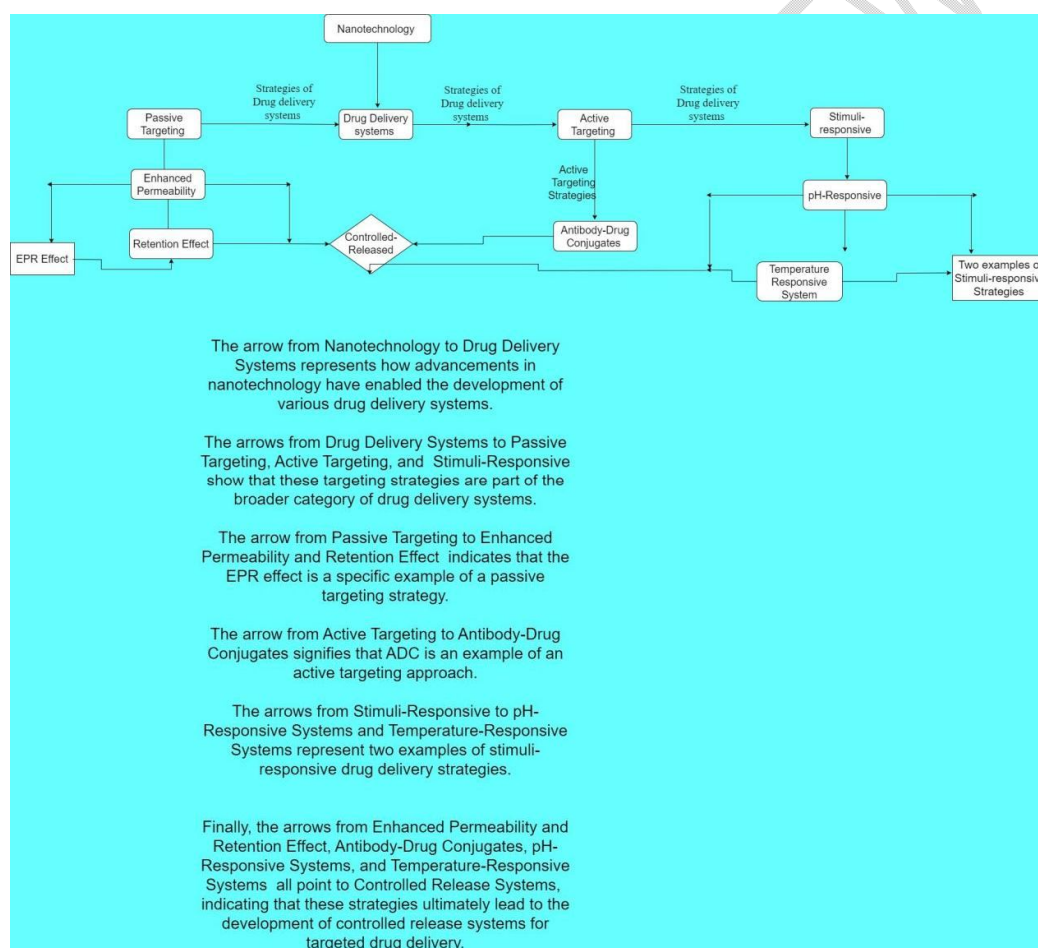


Fig.5 Natural product-based anticancer drugs

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 entire 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 bio active 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. Identification of 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 analogues using various chemical approaches. At the same time, biologists and pharmacologists can determine the mechanism of anti-tumor action of the compound, 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. 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 forward novel natural products from the bench to bedside, and ultimately to improve the 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 a collaboration between the chemists and the biologists in the 1960s [58, 69]. Based on this discovery, more research across different fields led to the creation of docetaxel, a semisynthetic taxane that is 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].

6. Conclusion

6.1. Summary of key points discussed in the review article.

We have presented the critical role of natural product in the discovery of anticancer drugs throughout this review article and illustrated that natural product is a unique source of highly structurally diverse and biologically active small organic molecules, especially for a lead compound in drug discovery. Several natural product-derived anticancer drugs have successfully been applied in clinics to cure various cancers, such as paclitaxel, doxorubicin, camptothecin derivatives and so forth.

Moreover, we put light on the shortcomings of natural product-oriented drug discovery – inconsistent drug supply, poor pharmacokinetics and off-target effects – and suggested next-generation strategies to overcome these limitations, such as delivery systems, nanotechnology and targeted drug delivery. The broad interdisciplinary recipe for success of natural product-based drugs for cancer could be attributed to a combination of favorable circumstances – including the increasing appreciation of the challenges of drug discovery and development, the innovative interdisciplinary strategies to better harvest the therapeutic potential of natural products, the recent advances in the cancer biology and precision medicine, and, most importantly, the commitment and determination of several generations of researchers.

This review presented the importance of natural products in anticancer drug discovery and novel strategies for maximizing both efficacy and safety of these natural products.

6.2. Emphasis on the continuing importance of natural products as a source of novel anticancer agents

As the global incidence of cancer rises and anticancer drug discovery is under resurgence, structurally diverse and biologically active compounds from natural sources are in great demand, as they can contribute to the growth of novel and efficacious anticancer therapy. The early success of clinically approved natural product-derived anticancer drugs, including paclitaxel, doxorubicin and camptothecin derivatives, have set examples for the role of natural products in anticancer treatment. Remarkably, recent advances in drug delivery systems, nanotechnology and targeted drug delivery have further broadened the therapeutic potential of natural products, although inevitable problems associated with natural product-based anticancer drugs during preclinical and late-stage clinical drug development. These innovative approaches allow researchers to improve the pharmacokinetics, bioavailability and safety of natural product-based anticancer drugs, which are expected to open the door to more effective and well-tolerated cancer therapies.

Overall, natural products will continue to serve as a vital, undeniable and invaluable source to support the search for novel anticancer drugs; collaborations involving multiple disciplines, and constant technological innovations, will only accelerate the role of natural products as an integral part of cancer drug discovery. Utilizing the promising potential of natural products will continue to supply unsurpassed resources for the development of transformative therapeutic strategies, thereby opening a new world of effective cancer treatments, thus enabling better outcomes for cancer patients everywhere.

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