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ANTICANCER THERAPEUTIC POTENTIAL OF NATURAL PRODUCTS

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Abstract

Cancer remains a significant global health concern, with millions of new cases and deaths recorded annually. The limitations of conventional therapies, including chemotherapy and radiation, have driven the search for potent and less toxic alternatives. Natural products have emerged as promising candidates for cancer treatment due to their diverse biological activities, such as antioxidant, anti-inflammatory, and immunomodulatory effects. This review explores the anticancer potential of various natural products derived from plants, marine organisms, and microorganisms. These natural compounds, including flavonoids, alkaloids, terpenoids, polyphenols, and others, have demonstrated multiple mechanisms of action, such as inducing apoptosis, inhibiting cancer cell proliferation, and modulating signalling pathways. Despite the challenges in development, such as bioavailability, regulatory hurdles, and intellectual property issues, natural products continue to offer valuable insights and opportunities for innovative cancer therapies. The review highlights the importance of integrating natural products into modern therapeutic regimens to enhance the efficacy and safety of cancer treatments, emphasizing the need for further research to realize their full potential.

Keywords: Anti-cancer therapeutics, Cancer, Natural compounds

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Introduction

In both developed and developing nations, cancer is a severe and significant health concern. Approximately 20 million new cancer cases and 9.7 million deaths were recorded in 2022, with estimates indicating that about one in five individuals will develop cancer in their lifetime, with one in nine men and one in twelve women dying from the disease. Breast cancer is most common in women, while lung cancer is in men; in both terms of incidence and mortality, followed by the most frequently diagnosed cancers with more mortalities for both genders are colorectum, prostate, and stomach (Bray et al., 2024). The global cancer burden in 2040 is expected to rise to 30.2 million incidences, with 16.3 million deaths (Sung et al., 2021). Depending on the cancer stage and type, therapies may involve surgery, hormone therapy, chemotherapy, biological therapy, and radiation therapy. Chemotherapy and radiation treatment may lead to side effects like sleep problems, nausea, loss of appetite, anxiety, hair loss, depression, fever, and infections. Detrimental side effects may also include the risk of secondary cancer, hormonal and reproductive complications, cardiopathy, neurological effects, immune system effects, and effects on the gastrointestinal system, bladder, and kidneys (Narayanaswamy et al., 2023).

The growing demand for potent and less toxic treatments has led to a renewed interest in natural products, which have fewer side effects than conventional chemotherapy agents, making them more promising for novel cancer therapeutics in the future (Welz et al., 2018). Natural products have diverse biological activities, which include antioxidant, anti-inflammatory, and immunomodulatory effects, that are particularly crucial in cancer treatment, where they can complement the direct anticancer actions of these compounds (Cooper & Nicola, 2018). The utilization of natural products has been recorded over centuries in different civilizations, with prominent examples being Egypt's "Ebers Papyrus," China's Materia Medica, and India's Ayurvedic texts (Cragg & Newman, 2005).

Natural products in allopathic medicine have a rich history, with early examples like aspirin, quinine and morphine derived from plants (Abraham, 2021; Newman et al., 2000; Mann, 1994). This tradition continues with modern medicines such as paclitaxel from the yew tree, vincristine from the periwinkle, and camptothecin from the Chinese tree *Camptotheca acuminata* (Alqahtani et al., 2019; Mcqueen, 2010; Neidle, 2008). Between 1981 and 2019, about 1881 new drugs were approved, with roughly 23.5% being natural products or their semi-synthetic versions, while approximately 25% were mimics of natural products or had pharmacophores derived from them. By 1996, about 80% of medicines were based on natural compounds or inspired by them. Additionally, about 50% of drugs validated from 1981 to 2010 had natural origins, and 48.6% of 175 anti-cancer drugs from 1940 to 2010 were derived from natural sources. Although there are over 500,000 natural products from plants, marine organisms, and microorganisms, only 5-10% have been explored for medicinal use, and merely 1% have made it to market, highlighting a significant area for more anti-cancer natural product development (Newman & Cragg, 2020; Gurnani et al., 2014; Li & Vederas, 2009; Newman & Cragg, 2007). This review aims to explore the therapeutic anticancer potential of natural products along with their mechanism of action and implied challenges during their development for clinical use.

Natural Products Vs Synthetic Products

Natural medicines refer to biologically or pharmacologically active chemical substances produced by living entities, including plants, animals, insects, marine organisms, and microorganisms, typically created through complex biosynthetic processes that demand significant resources from the organism (Koehn,

2012; Xu et al., 2011). The primary types of natural products include plant-derived compounds, marine-derived compounds, and microbial-derived compounds.

Out of the 300,000–400,000 higher plant species, only 5–15% have demonstrated pharmacological effects. Of these, 150–200 species have been incorporated into Western medicine, with plant-derived substances making up a quarter of global prescriptions (Gurnani et al., 2014).

Natural products derived from plants have played a vital role in traditional medicine and continue to offer a vast array of compounds with significant anticancer potential (Newman & Cragg, 2012). These compounds, including flavonoids, alkaloids, terpenoids, and polyphenols, have diverse mechanisms of action that make them crucial in cancer prevention and treatment (Harborne & Williams, 2000). Flavonoids are recognized for mitigating oxidative stress by neutralizing free radicals and modulating cellular signalling pathways, critical factors in cancer development (Middleton et al., 2000). Research has demonstrated that specific flavonoids can inhibit the proliferation of cancer cells and induce apoptosis, offering promising prospects for cancer therapy (Hollman et al., 1996).

Alkaloids, a class of plant compounds, are among the most potent natural anticancer agents due to their ability to interfere with cell division, a crucial process in cancer cell proliferation (Cragg & Newman, 2005). These compounds have been integral to chemotherapy regimens, demonstrating their efficacy in inhibiting cancer cell growth (Cordell, 1981). Similarly, terpenoids have been shown to exhibit significant anticancer properties by stabilizing cellular structures essential for the division and survival of cancer cells (Singh & Sharma, 2015). Polyphenols, another group of plant-derived compounds, are known for their ability to target multiple signalling pathways within cancer cells, enhancing therapeutic outcomes and reducing the risk of drug resistance (Pandey & Rizvi, 2009).

The ability of plant-derived compounds to target multiple pathways within cancer cells presents a significant advantage in cancer therapy, as it reduces the likelihood of resistance, a common challenge associated with single-target therapies (Aggarwal et al., 2003). This multitargeted approach not only disrupts several processes critical to cancer cell survival but also enhances the effectiveness of these compounds, making them valuable as both standalone therapies and in combination with other treatments (Sharma et al., 2013).

Marine environments are a rich source of bioactive compounds with potential anticancer properties, offering unique chemical diversity (Mayer et al., 2010). Seaweeds, sponges, and marine bacteria are among the marine organisms that have yielded promising compounds in preclinical studies (Blunt et al., 2007). For instance, marine sponges have provided compounds like manoalide, which inhibits inflammation and potentially prevents cancer progression (De Rosa et al., 2003). Additionally, bryostatin, a compound derived from marine bryozoans, has been found to modulate protein kinase C and has shown the potential to inhibit tumour growth and enhance the efficacy of other chemotherapy agents (Kraft et al., 2006). Marine bacteria have also contributed to the discovery of novel anticancer agents, such as marinopyrroles, which have been shown to induce apoptosis in cancer cells (Hughes et al., 2008).

Microorganisms, including fungi and actinomycetes, are essential sources of anticancer agents (Demain & Sanchez, 2009). Fungi produce taxol, a compound originally isolated from the Pacific yew tree that disrupts

microtubule function and is widely used in treating various cancers (Wani et al., 1971; Strobel et al., 1996). Actinomycetes, known for their prolific production of bioactive compounds, have yielded important anticancer drugs like doxorubicin, which intercalates into DNA and is extensively used in chemotherapy despite its associated cardiotoxicity (Minotti et al., 2004). Another promising compound is staurosporine, derived from *Streptomyces* species, which functions as a protein kinase inhibitor and has shown potential in targeting various cancer types (Ruegg & Burgess, 1989).

Synthetic drugs, designed to target specific pathways or structures within cancer cells, often have significant side effects and challenges, such as resistance development due to cancer cells' adaptability and adverse side effects due to non-specific targeting (Druker et al., 2001). However, natural products often provide a broader approach due to their complex structures and multifaceted modes of action, which result in lower rates of resistance and more favourable safety profiles (Newman & Cragg, 2020). For instance, camptothecin, a compound derived from the *Camptotheca acuminate that* originated in China, has served as a model for the development of synthetic analogues like irinotecan and topotecan, which have been successfully integrated into chemotherapy regimens (Wall & Wani, 1995).

One of the significant challenges in synthetic drug development is replicating the intricate structures of natural compounds, as synthetic versions may not exhibit the same bioactivity as their natural counterparts, potentially leading to reduced efficacy or unwanted side effects (Newman & Cragg, 2016). Additionally, the complex architecture of natural compounds, such as those found in marine organisms or certain plants, is often challenging to reproduce synthetically, which may result in analogues that do not fully replicate the therapeutic potential of the original compounds (Nicolaou & Sorensen, 1996). This limitation underscores the unique advantage of natural products, which are produced in their optimal bioactive forms by the organisms that synthesize them (Burgess et al., 2016).

While natural and synthetic products have their respective advantages, natural products remain a crucial and diverse source of anticancer agents. Their ability to target multiple pathways with fewer side effects makes them invaluable candidates in the ongoing battle against cancer (Aggarwal et al., 2003). Integrating natural products into modern therapeutic regimens could significantly enhance the efficacy and safety of cancer treatments, offering new hope for patients worldwide (Newman & Cragg, 2020).

Natural Products and Their Mechanisms of Action as Anticancer Agents

Gedunin

Gedunin (Fig.1), a natural compound found in *Azadirachta indica* (neem), *Chloroxylon swietenia* (Indian satinwood), and various *Rutaceae* family plants, has demonstrated promising anti-cancer properties (Nwokwu et al., 2017; Tharmarajah et al., 2017; Patwardhan et al., 2013). Neem is a phytochemically diverse plant, rich in secondary metabolites like gedunin (Nguyen et al., 2018). Furthermore, the *Anacardiaceae* family plants produce various phytochemicals such as polyphenols, triterpenes, amino acids, and carotenoids, contributing to their medicinal value (Ashfaq et al., 2015; Masibo & He, 2009).

Gedunin inhibits the kinases Akt, IKK, and AR and the transcription factors NF-κB and HIF-1α, essential for cancer cell survival, inflammation, and angiogenesis. This inhibition blocks tumour growth and spread. It targets several crucial cancer-related pathways and proteins, including NF-κB, Wnt/β-catenin, PI3K/Akt, MAPK, and JAK/STAT. Their ability to affect multiple cancer pathways makes them ideal for cancer

prevention and therapy. It specifically inhibits the NF-κB signalling pathway, which is important for cancer cell survival and proliferation, thereby inducing apoptosis and impeding cancer cell growth while also reducing the activity of kinases involved in tumour progression (Kishoreet al., 2015; Nagini, 2014). Liposomal encapsulation significantly enhances its bioavailability and therapeutic efficacy in NSCLC by promoting apoptosis through the mitochondrial pathway (Nwokwu et al., 2017). Additionally, Gedunin shows promise in targeting cancer stemlike cells, which could be crucial for overcoming resistance and preventing recurrence in cancer therapy (Tharmarajah et al., 2017). These findings endorse optimized delivery of Gedunin through targeting cancer stem cells, which could offer significant benefits in cancer treatment.

Beyond its anticancer properties, it exhibits significant anti-inflammatory and antimalarial activities. It helps reduce oxidative stress and regulate the immune response. Although its antimalarial effects were the most extensively studied, later studies highlighted its antiallergic and anti-inflammatory benefits in various experimental models (Ferraris et al., 2012; Brandt et al., 2008; Omar et al., 2003).

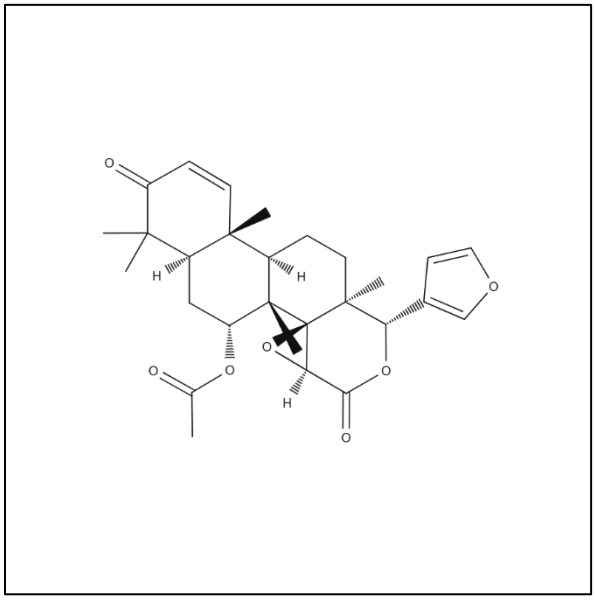

Figure 1: Structural Formula of Gedunin.

3.1 Alpha Hederin

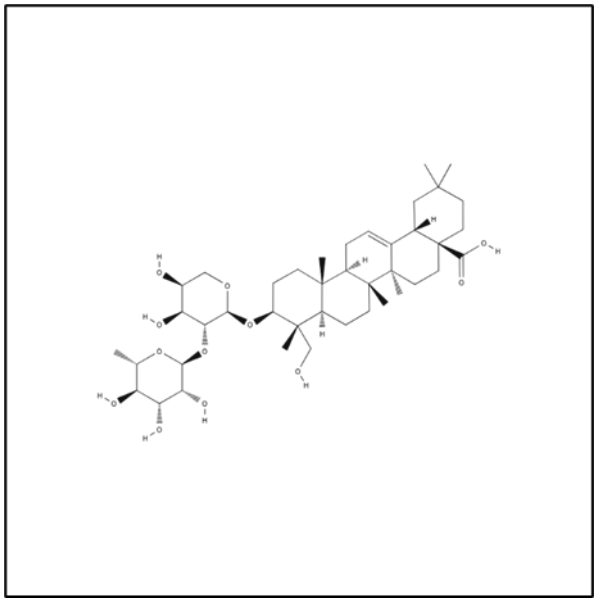

Figure 2: Structural Formula of Alpha Hederin.

Alpha Hederin (Fig.2) is a saponin glycoside found in multiple plants such as English ivy (Hedera helix), Nigella sativa, Lens culinaris, and Pulsatilla chinensis(Pham et al., 2022; Dagtas & Griffin, 2021; Jin et al., 2017; Taylor et al., 2007). English ivy is a common source of α-Hederin, especially from its leaves and stems (Bezruk et al., 2020).

Alpha Hederin triggers cancer cell apoptosis by activating the caspase cascade and changing mitochondrial membrane potential, generating reactive oxygen species (ROS) while also blocking cancer growth and invasion by disrupting NF-κB, MAPK and PI3K/Akt/mTOR pathways (Wang et al., 2019b; Wang et al., 2019; Sun et al., 2018a). Its primary anticancer mechanisms include inducing apoptosis, halting the cell cycle, decreasing ATP production, and inhibiting autophagy, cell proliferation, invasion, and metastasis (Adamska et al., 2019; Sun et al., 2019; Wang et al., 2019a; Wang et al., 2019; Sun et al., 2018a).

Alpha Hederin is under investigation for its potential use in cancer therapy, particularly in breast and colorectal cancers (Jin et al., 2024; Saliu et al., 2024; Sun et al., 2018b). The study by Saliu et al. (2024) highlights alpha-hederin as a potent inhibitor of the Wnt/β-catenin signaling pathway in breast cancer stem cells. In silico analyses and in vitro experimental models demonstrated that alpha-hederin effectively disrupts this pathway, reducing β-catenin activity, cell proliferation, and stem cell properties. These findings suggest alpha-hederin as a potential targeted therapeutic agent for breast cancer, especially in targeting resistant cancer stem cells. Alpha hederin possesses notable antiviral, antimicrobial, and anti-inflammatory properties (Rooney & Ryan, 2005). Due to these properties, it has been studied for its potential to treat respiratory diseases and skin conditions (Palma et al., 2021; Hong et al., 2015; Greunke et al., 2015).

3.2 Thymoquinone

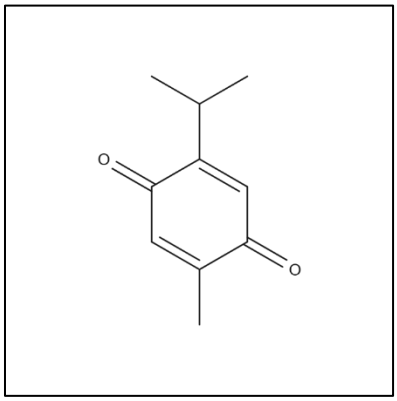

Figure 3: Structural Formula of Thymoquinone.

Thymoquinone (Fig.3) is the main biologically active compound of Nigella sativa oil, a plant in the Ranunculaceae family commonly referred to as black cumin/black seed (Roychoudhury et al., 2022). Thymoquinone hinders cancer progression by targeting various tumorigenic processes such as tumour growth, invasion, metastasis and angiogenesis and enhances the efficacy of other anticancer agents (Yi et al., 2008).

It induces apoptosis in cancer cells through intrinsic and extrinsic pathways and modulates several signalling pathways such as PI3K/Akt/mTOR and MAPK (He et al., 2023; Motaghed et al., 2013). Additionally, it up-regulates miR-34a, regulates the p53 pathway, suppresses Rac1, and manages apoptosis-related gene expression while reducing NF-κB, IKK, ERK1/2, and PI3K activity (Jehan et al., 2020; Khan et al., 2019; Yu & Kim, 2014; Sethi et al., 2008). Thymoquinone's potential to enhance the effectiveness of conventional chemotherapy is also being investigated in preclinical studies for various types of cancer, including breast, prostate, and colorectal cancers (El-Far et al., 2021; Gholamnezhad et al., 2016; Samarakoon et al., 2010; Kaseb et al., 2007).

The study by Samarakoon et al. (2010) reveals that the ethanolic extract of *Nigella sativa* seeds exhibits substantial cytotoxicity against cancer cell lines, demonstrating a more pronounced effect once compared with aqueous extract. The ethanolic extract was more effective in extracting the bioactive compounds responsible for the cytotoxic effects, suggesting that *N. sativa* seeds, when processed with ethanol, have significant potential as an anticancer agent. The results highlight the enhanced potency of the ethanolic extract and support its use in developing therapeutic agents from *N. sativa*. Phase I studies investigated its safety and tolerability in combination with other anticancer drugs. The outcomes of these studies are promising, showing potential benefits in cancer treatment, but further trials are needed to confirm its efficacy and safety (Al-Amri & Bamosa, 2009).

Thymoquinone exhibits anti-inflammatory, antioxidant, and antimicrobial properties, along with antineoplastic effects observed both in vitro and in vivo (Bian & Pei, 2021, pp.395–409). It has been studied for its potential therapeutic benefits in asthma, diabetes, and cardiovascular diseases (Gholamnezhad et al., 2016).

3.3 Halichondrin B

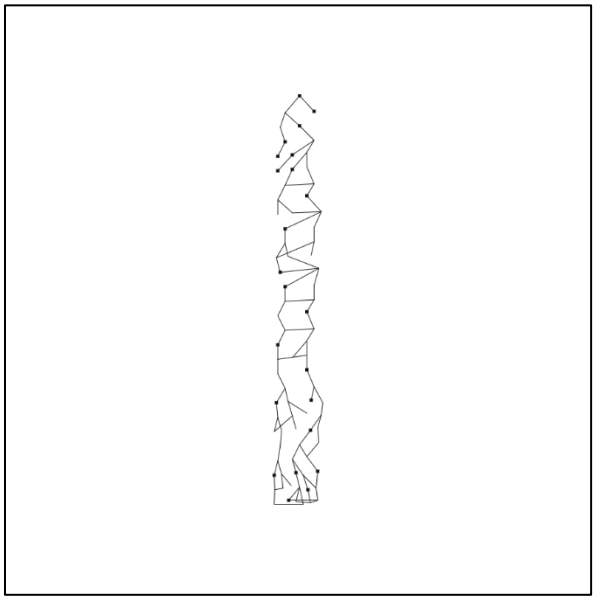

Figure 4: Structural Formula of Halichondrin B.

Halichondrin B (Fig.4) is a potent marine natural product from *Halichondria okadai*, a type of marine sponge. It belongs to the polyether macrolide family, which includes compounds found in various marine sponges (Hearn et al., 2007). Halichondrin B acts as a potent microtubule inhibitor by binding to tubulin subunits. This results in mitotic spindle disruption, cell cycle arrest in the M phase, apoptosis in cancer cells, and tumour growth inhibition (Reilly, 2020; Kuznetsov et al., 2007; Towle et al., 2001).

Besides its anticancer effects, halichondrin B has shown potential anti-inflammatory activity (Mayer & Hamann, 2005). The development of eribulin mesylate (Halaven™), a synthetic version of halichondrin B, has been approved by the US FDA for the treatment of metastatic breast cancer and soft tissue sarcoma (Osgood et al., 2017; FDA, 2010). Eribulin has been extensively studied in clinical trials. It has been shown to provide clinical benefits in terms of progression-free survival and overall survival in patients with breast cancer and soft tissue sarcoma, with promising efficacy and safety profiles (Schöffski et al., 2011; Cortes et al., 2010).

Bleomycin

Bleomycin (Fig.5) is a glycopeptide antibiotic with anti-tumor properties, originating from the bacterium *Streptomyces verticillus* (Tamzali & Kemp-Symonds, 2015). Bleomycin interferes with DNA replication and cell growth by binding to DNA and inducing single and double-strand breaks. It binds transition metals such as Fe(II) and Cu(I), generating free radicals that cause oxidative stress. This process leads to DNA strand breaks during the S and G2 phases, resulting in apoptosis and effectively inhibiting tumour proliferation (Czaja et al., 2022; Dziegielewski et al., 2000); (Latta et al., 2015). Bleomycin also exhibits antimicrobial properties (Yagoda, 1972). It is often part of combination chemotherapy regimens used in the treatment of several cancers, including Hodgkin's lymphoma, testicular cancer, and certain types of head and neck cancers (Brandt & Gerriets, 2023).

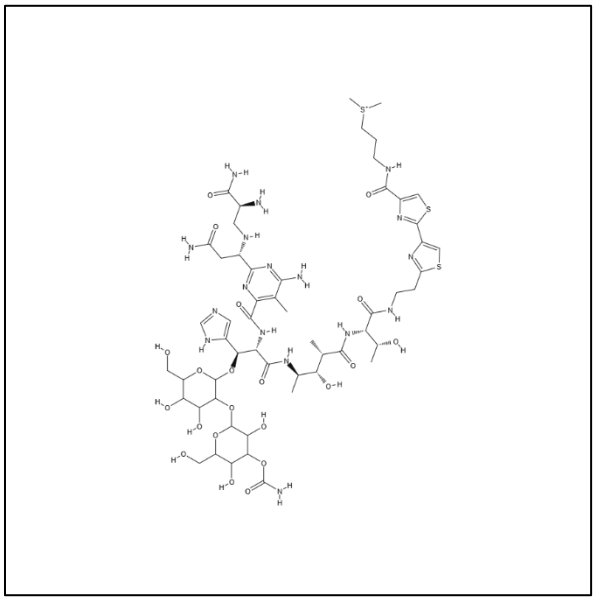

Figure 5: Structure of Bleomycin.

6β-Cinnamoyl-7α-hydroxyvouacapen-5α-ol

6β-Cinnamoyl-7α-hydroxyvouacapen-5α-ol (Fig.6) is isolated from the bark of *Trichiliacatigua*, a tree commonly found in the Amazon rainforest and other tropical regions of South America. The extraction process typically involves organic solvents like methanol or ethanol, followed by chromatographic techniques for purification (Sakurai et al., 2020; Oliveira et al., 2018). Research has indicated that 6β-cinnamoyl-7α-hydroxyvouacapen-5α-ol exhibits significant anticancer activity against various cancer cell lines, including breast, lung, and colon cancers. Research highlights its ability to induce apoptosis by activating caspase-3 and caspase-9, increasing pro-apoptotic Bax, and decreasing antiapoptotic Bcl-2 proteins, collectively promoting cancer cell death (Lopes et al., 2019). Additionally, it causes cell cycle arrest at the G2/M phase, thereby inhibiting cancer cell proliferation by modulating cyclin-dependent kinases and their inhibitors (Silva et al., 2021). This compound also hinders angiogenesis by downregulating vascular endothelial growth factor (VEGF) and other angiogenic factors essential for tumour growth and metastasis (De-Silva et al., 2022). Furthermore, 6β-cinnamoyl-7α-hydroxyvouacapen-5α-ol increases reactive oxygen species (ROS) levels in cancer cells, leading to oxidative stress and apoptosis (Sakurai et al., 2020).In vitro studies have shown that this compound inhibits cell proliferation, induces apoptosis, and reduces the viability of cancer cells (Lopes et al., 2019; Silva et al., 2021). *In vivo* studies further support these findings, demonstrating that treatment with 6β-cinnamoyl-7α-hydroxyvouacapen-5α-ol reduces tumour growth and metastasis in animal models. A study by De-Silva et al. (2022) reported a marked decrease in tumour volume in mice treated with this compound, highlighting its potential as a therapeutic agent.

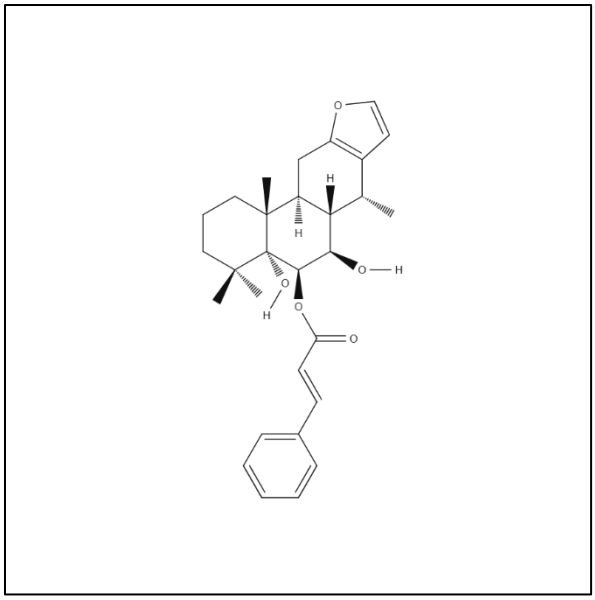

Figure 6 : Structure of 6β-Cinnamoyl-7α-Hydroxyvouacapen-5α-Ol.

Curcumin

Curcumin (Fig.7), a polyphenolic compound extracted from the rhizomes of the turmeric plant (*Curcuma longa*), has been extensively studied for its anticancer properties (Alibeiki et al., 2017). Curcumin exhibits its anticancer effects through multiple mechanisms, including inhibiting nuclear factor-kappa B (NF-κB) signalling, which reduces inflammation and hinders cancer cell proliferation. Furthermore, it inhibits cancer proliferation by interfering with the action of intercellular transcription factors, including activator protein 1 (AP-1), matrix metalloproteinase-9 (MMP-9), cyclooxygenase II (COX-2), nitric oxide synthase (Lee et al., 2014). Curcumin also induces apoptosis by modulating various apoptotic proteins and enhances the sensitivity of cancer cells to chemotherapeutic agents. The anticancer potential of curcumin has been studied on several cell lines, including prostate cancer, lung cancer, breast cancer, head and neck squamous cell carcinoma, and brain tumour (Tomeh et al., 2019).

Furthermore, it has been observed that curcumin has a synergistic effect when combined with other chemotherapeutic agents. A study reported that combining curcumin with docetaxel decreases drug resistance in breast cancer cells (Aung et al., 2017). In addition to anticancer properties, curcumin has also been examined to possess anti-inflammatory and antioxidant properties (Nagahama et al., 2016).

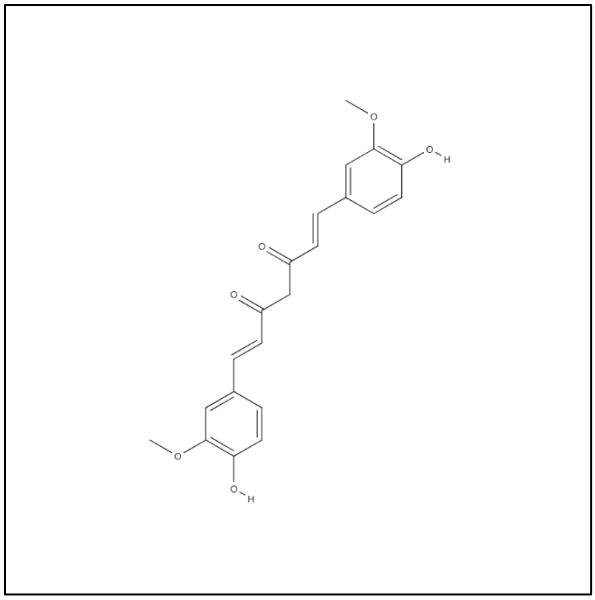

Figure 7 : Structure of Curcumin.

Resveratrol

Resveratrol (Fig.8), a natural stilbene and a non-flavonoid polyphenol found in grapes, berries, and other plant sources, has gained significant interest in cancer prevention and treatment. The major organelle in which this natural product exerts its anti-cancer effect is the mitochondria (Abate et al., 2020; Kursvietiene et al., 2023). Its anticancer activities are attributed to its ability to modulate various molecular pathways, such as inhibiting the phosphoinositide 3-kinase (PI3K)/Akt pathway, which is crucial for cancer cell survival and growth. Resveratrol also induces cell cycle arrest at the G1/S phase and promotes apoptosis by activating p53 and Bax proteins (Kursvietiene et al., 2023). It has shown potential in reducing the risk of colorectal and lung cancers. Furthermore, resveratrol has antioxidant, anti-inflammatory, anti-ageing and neuroprotective activity (Pezzuto, 2018; Meng et al., 2020).

The combinatorial approach of resveratrol with conventional chemotherapeutics has shown promising advantages. For example, in vitro assays and mouse models have shown a synergistic effect of resveratrol used as an adjuvant of chemotherapeutic drugs, such as temozolomide, paclitaxel and doxorubicin (Rai et al., 2016).

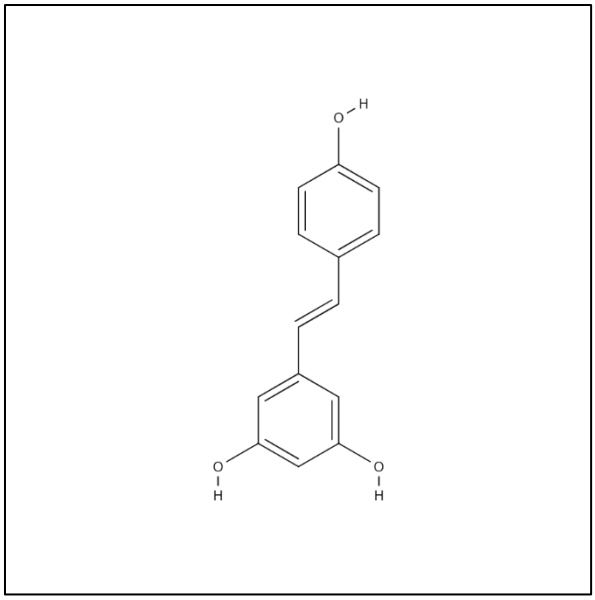

Figure 8 : Structure of Resveratrol.

Quercetin

Quercetin (Fig.9), a bioflavonoid found in many fruits and vegetables, including tomatoes, onions, broccoli, apples, and citrus fruits, has been recognized for its cancer chemo-preventive properties. It inhibits cancer cell proliferation by blocking the cell cycle at the G2/M phase through induction of p73 and p21 and inhibiting cyclin B. It also induces apoptosis through the mitochondrial pathway. Depending on the cell type, such as Hep G2, quercetin has been studied to also initiate cell cycle arrest at the G1 phase by induction of p21, p27 and p53 (Mu et al., 2007; Rather & Bhagat, 2020).

Due to its ability to interact with various intracellular targets, quercetin also modulates key signalling pathways, such as the PI3K/Akt, mitogen-activated protein kinases (MAPK), β-catenin/Tcf signalling pathways, which play critical roles in cancer initiation, progression and induction of apoptosis. Quercetin also shows selective degradation of oncogenic Ras proteins, not wild-type Ras, in combination with Raf and MEK protein kinases (Russo et al., 2012; Rather & Bhagat, 2020). This suggests that this natural product can be used to treat Ras-driven tumours. The apoptotic ability of quercetin on cancer cells is attributed to its ability to inhibit the P13k/Akt pathway and the generation of reactive intermediates (Huang, 2013; Rather & Bhagat, 2020). Furthermore, it has been demonstrated to have antioxidant/pro-oxidant action, regulation of redox homeostasis, anti-inflammatory action, and modulation of drug-metabolizing enzymes, all of which synergistically helps to retard cancer growth and proliferation (Rather & Bhagat, 2020).

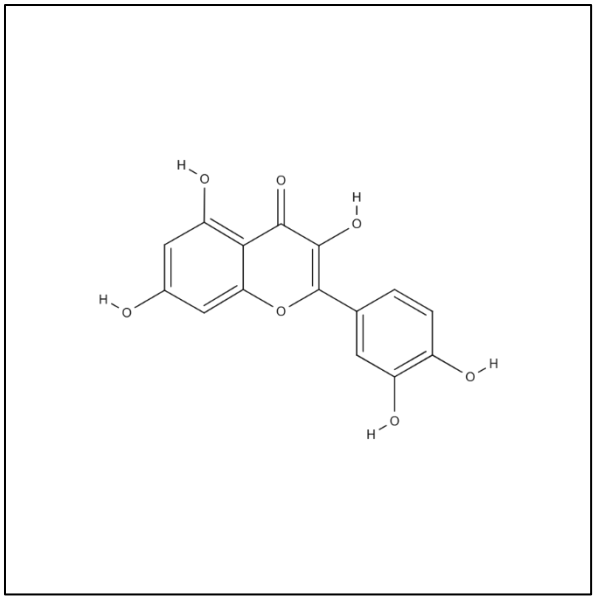

Figure 9: Structure of Quercetin.

Trabectedin (ET743)

Trabectedin (Fig.10), derived from the sea squirt *Ecteinascidia turbinata*, was one of the first marine-derived anticancer alkaloids to be identified. It binds to the minor groove of DNA, causing DNA strand breaks and inhibiting DNA repair mechanisms and transcription factors, leading to apoptosis. Trabectedin was approved in 2007 by the European Medical Agency for treating advanced soft tissue sarcoma with resistance to doxorubicin either alone or in combination with ifosfamide (Nakamura & Sudo, 2022). Successful clinical trials have also led to the approval of trabectedin by the Food and Drug Administration (FDA) for treating patients with unresectable or metastatic liposarcoma or leiomyosarcoma (Barone et al., 2017). Clinical studies have demonstrated its efficacy in patients with advanced sarcomas and relapsed platinum-sensitive ovarian cancer, showing improved progression-free survival rates (Nakamura & Sudo, 2022).

Lurbinectedin, a synthetic analogue of trabectedin, has been proven effective in treating small-cell lung carcinoma. Both lurbinectedin and trabectedin have similar mechanisms of action by binding guanines at the N2 position in the DNA minor groove. It inhibits active transcription and induces DNA damage, leading to apoptosis (Allavena et al., 2022).

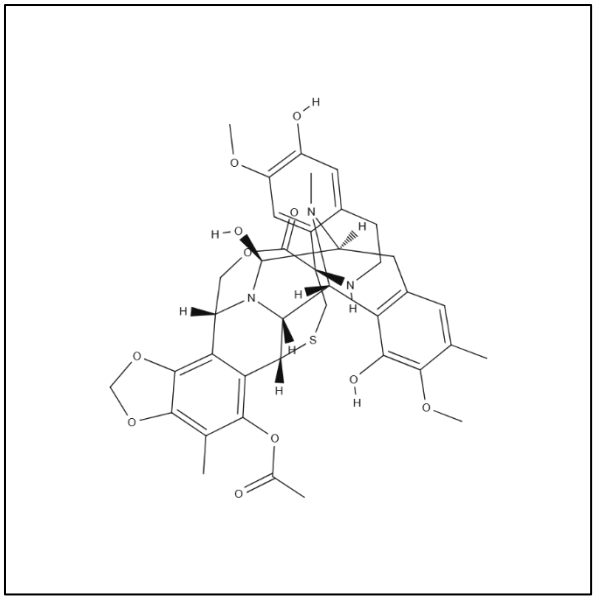

Figure 10: Structure of Trabectedin.

3.11 Salinomycin

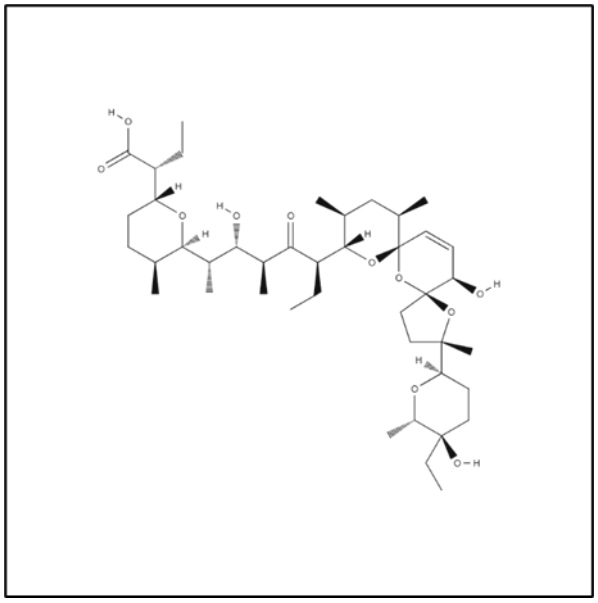

Figure 11: Structure of Salinomycin.

Salinomycin (Fig.11), a polyether ionophore antibiotic produced by the bacterium *Streptomyces albus*, has shown potent anticancer activity, particularly against cancer stem cells (CSCs) (Qi et al., 2022). It disrupts the Wnt/β-catenin and MAPK signalling pathway and induces apoptosis in CSCs, reducing tumour recurrence and metastasis. Salinomycin has further been demonstrated to trigger DNA damage, prevent DNA repair, elevate reactive oxygen species (ROS) levels, and induce stress in the endoplasmic reticulum (Huang et al., 2018; Lim et al., 2020). A study by Qi et al. revealed that salinomycin can suppress the expression of the CSC marker via the interaction with its cellular binding target nucleolin. Preclinical studies have demonstrated its effectiveness in various cancers, including breast, colorectal, and multiple myeloma (Kastritiset al., 2010; Klose et al., 2019). Salinomycin has also shown synergistic effects when

combined with conventional chemotherapeutics such as doxorubicin, gemcitabine, trastuzumab, temozolomide and tamoxifen (Sommer et al., 2016; Qi et al., 2022).

Developing Anti-Cancer Natural Products as Nutraceuticals

Nutraceuticals derived from anti-cancer natural products offer a promising approach to cancer prevention and therapy. *Panax ginseng* is commercially available in Asia as ginseng capsules or tablets as supplements. Metabolites from this plant, such as ginsenoside Rh1 and Rg3, have effectively treated lung, breast and colon cancer (Kim et al., 2021). A clinical trial study by Kim et al. (2017) reported that ginsenoside Rh1 improved the quality of life after chemotherapy in patients with epithelial uterine cancer. In vivo and in vitro studies revealed that ginseng arrests cancer by regulating apoptosis, angiogenesis, epithelial-mesenchymal transition (EMT), cell cycle arrest and multidrug resistance (MDR) (Kim et al., 2021). Ginsenoside Rg3, gotten from the ginseng plant, was approved by the China Food and Drug Administration (CFDA) in 2000 as an anti-cancer drug and was listed for the treatment of non-small cell lung cancer in the Clinical Practice Guide of the National Comprehensive Cancer Network (Chinese version) in 2006 and 2007 (Wang et al., 2018). However, certain negative side effects have been reported from drug-drug interaction with the use of ginseng. A case report revealed that the administration of ginseng and imatinib could induce hepatoxicity in patients with chronic myelogenous leukaemia (Bilgi et al., 2010). Hence, it is advised that this ginseng be strictly based on clinical prescription.

In Sri Lanka, Vernolac is a commercially available nutraceutical formulated from five different herbal plants, including *Nigella sativa*, *Hemidesmus indica*, *smilax glabra, Leucas zeylanica*, and *Verrnonia zeylanica*- which is the main ingredient from which the name was coined (Fadna, 2023). Based on extensive studies using in-vitro assays on several cell lines, this product was confirmed to demonstrate anti-cancer, pro-apoptotic, autophagic and antioxidant properties to halt abnormal proliferation of cells. For example, research by Abeysinghe et al. (2019) and Mendis et al. (2018) demonstrated that *V. Zeylanica* was able to induce antiproliferative effect and apoptosis in NTERA-2 cells, breast cancer cell lines (MCF -7, MDA-MB-231, SKBR-3) in a time-and dose-dependent manner. Furthermore, toxicity studies using mice models have revealed no toxicity, and clinical trials are underway (Fadna, 2023).

Dietary nutraceuticals have been demonstrated to be a potent preventive and management approach against cancer. These are a rich source of minerals, vitamins, amino acids and other micronutrients, which are non-toxic to normal cells (Kuppusamy et al., 2014). The majority of fruits and vegetables taken as/with food contain various natural products (such as polyphenols, flavonoids, carotenoids, and stilbenes) with anti-cancer potential, including Curcumin, Quercetin, Resveratrol, Gedunin, Oleuropein amongst others (Maiuolo et al., 2021). R

Challenges and Limitations for Therapeutic Use of Natural Products

While promising, the development of natural anticancer products faces several significant challenges and compromises their widespread use. These challenges span the discovery, formulation, synthesis, preclinical, and clinical phases of drug development (Paller et al., 2016). We discuss the primary obstacles and outline recent findings and ongoing efforts to resolve them.

Complexity of Natural Products

Natural products often possess complex molecular structures, which makes their extraction, separation, synthesis and modification complex and resource-intensive. The structural complexity of natural compounds can hinder large-scale production and limit the ability to perform structure-activity relationship (SAR) studies. Therefore, improvement in analytical technologies, such as mass spectrometry (MS), nuclear magnetic resonance (NMR), and computational methodologies, is essential to enhance the precise identification of natural products, optimize their extraction and facilitate their chemical synthesis or modifications (Garcia-Oliveira et al., 2021).

Supply and Manufacturing Difficulties

Obtaining sufficient quantities of natural products has been challenging due to their limited availability and sustainability concerns. The extraction of natural compounds from marine or terrestrial sources often faces ecological and logistical challenges, which limits consistent mass production of these compounds for therapeutic purposes (Jing et al., 2019; Paller et al., 2016). Furthermore, manufacturing natural products in bulk is limited due to differing amounts of active ingredients from natural sources, such as pulverized muscadine grape skin harvested from different farms with different soil types under different weather conditions. The quantity of active ingredients also differs significantly from different plant parts such as leaves, fruits, roots, etc (Paller et al., 2016). However, efforts are being made to cultivate natural product-producing organisms or to use synthetic biology approaches to produce these compounds in microbial hosts (Schmidt et al., 2019).

Bioavailability and Pharmacokinetics

Many natural products have poor bioavailability and suboptimal pharmacokinetic properties, which limits their use in clinical treatment. Compounds like curcumin and quercetin exhibit low oral bioavailability and poor aqueous solubility due to poor absorption, rapid metabolism, and systemic elimination (Cai et al., 2013). The bioavailability of quercetin is highly increased when consumed in the diet. However, the current approach to enhance the bioavailability and stability of these compounds includes nanotechnology using liposomes and other nanoparticles, as well as improved formulation strategies (Garcia-Oliveira et al., 2019). A study by Ghosh et al. (2021) demonstrated that mesoporous silica nanoparticles conjugated with hyaluronic acid were used as a drug delivery system of curcumin both in vitro and in vivo on breast cancer cells, and results reported improved anticancer activity supposed to be due to higher bioavailability.

5.4 Limited Understanding of the Mechanism of Action

The precise mechanisms of action of many natural anticancer agents remain inadequately understood. At the same time, natural products like resveratrol and quercetin are known to exert anticancer effects. However, their exact molecular targets and pathways are often unclear, limiting standardized formulation and design for therapeutic use. To combat this challenge, advanced omics technologies and systems biology approaches are employed to unravel these mechanisms (Chunarkar-Patil et al., 2023).

Toxicity and Side Effects

Toxicity is an important consideration for natural products since they can have off-target effects and potential risks, limiting their therapeutic window. Compounds like artemisinin can cause neurotoxicity at high doses. Owning limited insight into their mechanism of action and challenges with bioavailability and stability, natural products' toxicity and side effects are a bit difficult to understand. Extensive preclinical

toxicology studies and the development of targeted delivery systems are crucial to mitigate these adverse effects (Wang, 2012; Chunarkar-Patil et al., 2023). Additionally, due to the rapid molecular adaptions of cancer cells, resistance to treatments derived from natural products may emerge after a while. Therefore, a thorough understanding of resistance mechanisms and developing new strategies to combat this resistance are essential to reduce unexpected side effects (Chunarkar-Patil et al., 2023).

Clinical Trials and Regulatory Burdens

The regulatory procedure for natural products can be complex and time-consuming, with stringent requirements for efficacy, patient safety, and quality control. Natural product-derived drugs must undergo rigorous clinical testing to meet regulatory standards. Furthermore, getting adequate patient volunteers who meet the specific inclusion criteria for testing might be challenging. Natural product testing, which involves a combinatorial approach, either with an existing/novel synthetic chemotherapeutic or natural product, faces significant challenges due to concerns regarding unforeseen long-term toxic effects (Goldman, 2003). To combat regulatory challenges, efforts are required to streamline the regulatory process, develop novel trial-design methodologies and implement effective patient recruitment and retention processes (Chunarkar-Patil et al., 2023).

Intellectual Property and Patent Issues

Intellectual property (IP) rights and patents related to natural products can be contentious and challenging to secure. The IP landscape for natural products is often complicated by issues of biopiracy and traditional knowledge, which arise when indigenous groups are not adequately rewarded for their contributions. In addition, complex legal processes, financial limitations, and ethical considerations impede the rapid development of natural anticancer agents. Thus, developing fair and equitable benefit-sharing arrangements is essential for the sustainable use of natural resources (Baxi et al., 2019).

Future Directions and Conclusion

Cancer is a complex disease that leads to the loss of millions of lives yearly. Hence, discovering natural products with anticancer properties as a therapeutic alternative shows promising options to combat this malignancy. Despite the significant advances in the development and analysis of the efficacy of these natural products, more investigative studies are needed to be carried out to explore the precise mechanism of action of these products and precise molecular targets of these compounds and their interaction with signalling pathways. Computational biology, such as molecular docking, offers a good advantage in understanding these interactions, as this can further facilitate the identification of related cancer biomarkers, which can be analysed using in vitro and in vivo experiments. Furthermore, to allow extensive use of a promising anticancer natural product, robust standardization is founded on modern processes involving evaluation of efficacy, composition, quality control, bioavailability, manufacturing processes, regulatory procedures, etc., which must be done to meet international standards. This is necessary to guarantee effectiveness and reduce toxicity or off-target interactions, ensuring patient safety and improving life expectancy (Naeem et al., 2021; Chunarkar-Patil et al., 2023).

New advances in drug delivery are crucial due to the limited bioavailability of natural compounds due to poor aqueous solubility, poor intestinal absorption, and rapid catabolism. Currently, nano-particle-based formulations are being used to combat this limitation, thereby allowing improved absorption and distribution in the patient's body. Incorporating advanced computer technologies, such as deep learning and

artificial intelligence, with drug development processes can also potentially improve the precision and efficacy of natural products for cancer treatments. It is postulated that machine learning algorithms in structure recognition, activity prediction, conformation simulation, and library design can improve understanding of mechanistic design and complex structures of natural products (Huang et al., 2021).

The therapeutic impact of natural products can be broadened by employing a combinatorial approach with pre-validated chemotherapeutic drugs/natural products. Natural products have a unique advantage due to their biodegradability, biocompatibility, and biodiversity. Thus, they can be explored for creating personalized cancer treatment plans based on individual genetic profiles.

In conclusion, this review underscores the relevance of natural products with potential anti-cancer effects in clinical management. Further, it emphasizes the critical challenges associated with their development and the way to face them.

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