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Review Article

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Exploring the Potential of Secondary Metabolites as Anticancer Agents: Mechanisms, Efficacy, and Future Perspectives

Akanksha Kulshreshtha, Dr. Mahendra Singh Ranawat

Faculty of Pharmacy, Bhupal Nobles' University, Udaipur (Raj.)

Abstract Cancer is a complex and multifaceted biological phenomenon characterized by the dysregulation and excessive proliferation of cells, ultimately leading to uncontrolled growth. It represents a significant contributor to global mortality rates. The documented cases and projected outcomes for the immediate future are beyond imagination. According to statistics from the FDA, it has been observed that 40% of the molecules that have received approval are either natural compounds or have been derived from them. Furthermore, it has been shown that out of these molecules, around 74% are utilized in the context of anticancer therapy. Indeed, natural goods are perceived to possess a higher degree of biological compatibility, resulting in reduced toxicity towards typical cellular structures. This study focuses on discussing the latest and effective instances of secondary metabolites, comprising polyphenolic, diterpene, triterpene, and alkaloid chemicals, which exhibit significant potential in the field of anticancer research. This analysis will mostly concentrate on compounds that are either through clinical trials or are already being utilized in anticancer therapy. Consequently, we will examine successful instances for ex. paclitaxel and homoharringtonine, which are currently in clinical use. Additionally, we will discuss curcumin and ingenol mebutate, both of which are currently being investigated in clinical trials. This paper aims to examine the natural sources of various compounds, the key methods involved in their development, their therapeutic targets, and primary structural alterations which can enhance their anticancer capabilities. The objective is to highlight the significance of plants as a valuable reservoir of potent and non-toxic anticancer medications.

Keywords Anticancer Agents, Secondary Metabolites, Mechanisms, Efficacy

1. Introduction

Cancer, a highly destructive illness that surpasses both coronary heart diseases and strokes in terms of mortality, was accountable for 8.2 million fatalities amongst 14.1 million new cases in the year 2012 [1]. However, there exists a documented trend of decreasing cancer mortality rates, leading to an overall reduction of 23% since 1991 [2]. In spite of the advancements made, the global mortality count in 2015 amounted to 8.8 million individuals, with cancer emerging as the primary cause of death in 21 states within the USA [2]. According to a study, the aggregate yearly economic burden associated with cancer in the year 2010 amounted to around $1.16 trillion [3]. It is anticipated that this burden will continue to increase, as there is a projected global incidence of over 20 million additional cancer cases by the year 2025 [4]. Furthermore, there has been a notable rise in the incidence and mortality rates of certain forms of cancer, such as liver and pancreatic cancer [2]. In lower as well as middle-income nations, situation is notably more unfavorable, with cancer diseases accounting for nearly 70% of mortality. Furthermore, only one out of every five nations possess the requisite data to inform cancer policy [3,5]. In order to make progress in combating

cancer, it is imperative to allocate further resources towards cancer pathology research and the development of novel anticancer drugs that are not only safe and effective, but also affordable and associated with low side effects.

Throughout the course of history, various indigenous societies across the globe have employed traditional herbal medicine as a means to address a wide range of ailments. Plants are frequently utilized as a viable option for cancer therapy in numerous nations, with over 3000 plant species globally documented to possess anti-cancer characteristics [6,7].

While there is evidence indicating a decline in the utilization of traditional medicines in contemporary times, particularly in densely populated middle-income nations [8], the use of herbal medicine remains prevalent in oncology treatment on a global scale [6,7,9–11]. Over the past twenty years, the use of herbal treatments as a form of complementary and alternative medicine has gained significant acceptance in numerous affluent nations. However, this trend has been accompanied by stringent regulations and close monitoring [12]. Usage of natural products in cancer management has gained significant interest due to their perceived biological compatibility, as they are believed to have co-evolved with their target sites and exhibit lower toxicity towards normal cells [13]. Additionally, it has been demonstrated that anticancer medicines derived from natural products exhibit various mechanisms for inducing cell death [14,15]. In light of these empirical findings, a considerable number of scholars are currently focusing their inquiries on exploring the capacity of plants to provide natural substances that hold promise for application in pharmaceutical sector [16–18]. Usage of natural items as a foundation for exploration and advancement of pharmaceutical compounds remains a prominent area of research. Approximately 49% of the small molecules that were granted approval for cancer chemotherapy from 1940 to 2014 are classified as natural products [19].

Despite the numerous potential benefits of medicinal plants as well as their products, there remains a lack of sufficient monitoring to ensure their effectiveness as well as safety [20,21].

Subsequent sections provide a comprehensive overview of plant-derived compounds that have demonstrated efficacy against various forms of cancer. These compounds have either been approved as anticancer drugs and are currently available on the market, or they are currently undergoing clinical trials, representing the final phase of drug development for clinical use. Hence, the ensuing discussion will provide a concise overview of these substances, which have demonstrated efficacy in cancer treatment.

2. The utilization of secondary metabolites derived from plants as potential agents for fighting cancer.

Plants have long served as a valuable reservoir of cost-effective natural compounds, particularly secondary metabolites, which are characterized by intricate structures that present challenges for synthesis, often remaining unachieved to date. Furthermore, these chemicals exhibit a diverse array of biological functions, including antitumor properties [22,23]. Secondary metabolites are predominantly comprised of tiny organic compounds that are synthesized by an organism and are not considered vital for its development, growth, and reproductive processes. The classification of these entities can be determined according to the specific process by which they are generated (Reference 24). In addition, a basic categorization comprises three primary categories: terpenoids (which are polymeric derivatives of isoprene and are synthesized from acetate through mevalonic acid pathway), phenolics (which are synthesized from shikimate pathways and contain atleast one hydroxylated aromatic rings), along with highly varied alkaloids (which are nitrogen-containing compounds that do not belong to proteins and are synthesized from amino acids like tyrosine, with a longstanding usage in medicine) [24,25]. Every year, numerous cytotoxic secondary metabolites are discovered and extracted from plants, offering a promising avenue for further investigation in the battle against malignant ailments.

Despite the presence of distinctive anticancer activities in certain natural compounds, their application in clinical settings is hindered by their physicochemical characteristics, such as poor bioavailability, and/or their potential toxicity. Conversely, secondary metabolites found in plants frequently serve as promising starting points for the development of pharmaceutical drugs. Therefore, altering the chemical composition of these compounds with greater potential is a strategic approach to enhance their effectiveness against cancer and specificity, enhance their absorption, distribution, metabolism, as well as excretion characteristics, also reduce their toxicity in addition to

adverse reactions [26,27]. In this paper, we will discuss notable advancements in field of plant secondary metabolites, including those that have been successfully employed in clinical settings and those now undergoing clinical trials as potential anticancer treatments. Additionally, we will explore the most effective derivatives of these metabolites, which have been generated by structural alterations.

Metabolites used in Cancer Therapy:

Over past few decades, a diverse array of cytotoxic agents has been identified from plants. However, only a limited compounds have successfully navigated the extensive, rigorous, costly, and administrative process from initial chemical identification to demonstrating efficacy in clinical cancer treatment. All these chemical possesses a distinct historical background, along with documented accounts of their successes and limitations. Numerous writers have extensively discussed these aspects, which will be subsequently examined from a molecular, historical, pharmacological, as well as clinical perspective.

Vincristine

Vincristine possesses a dimeric structure that is asymmetrical in nature. This structure is comprised of 2 indole-type nuclei connected by a C-C bond, specifically referred to as vindoline portion as well as catharanthine type portion (as depicted in Fig 1). Clinical application of cancer treatment was approved by the FDA in 1963. Indeed, this particular drug was among the initial plant-derived anticancer substances that received approval from the aforementioned regulatory agency [19]. The substance in question is an alkaloid that occurs naturally and is derived from leaves of Catharanthus roseus (L.) G.Don, also known as Vincarosea L. It has been employed in the field of chemotherapy, primarily in management of acute lymphoblastic leukemia, with a focus on pediatric patients. The inclusion of this element in the therapeutic protocol leads to a significant improvement in the survival rate, reaching 80% [28]. Furthermore, it has been employed in the treatment of neuroblastoma, rhabdomyosarcoma, nephroblastoma, and lymphomas, [29,30].

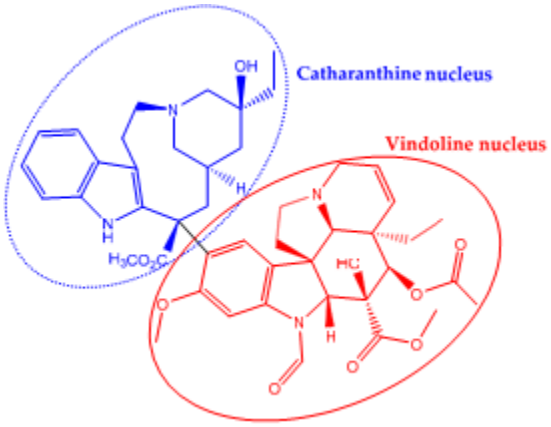


Figure 1: The chemical structure of vincristine (1), a naturally occurring anticancer drug, is responsible for its ability to inhibit cell development by modulating microtubular dynamics.

The significant level of interest surrounding vincristine is in stark contrast to its limited natural abundance, resulting in a high cost associated with its extraction. The present scenario has sparked a vigorous research endeavor with the objective of identifying effective techniques to enhance the production of vincristine (along with other vinca alkaloids). The application of genetic engineering techniques to manipulate specific enzymes and utilization of elicitors to activate genes associated with vincristine metabolic pathways have been identified as efficient approaches for enhancing the biotechnological production of this molecule [30,31]. Nevertheless, several enhancements are required prior to achieving economic feasibility for these procedures. An alternative approach for increasing the yield of vincristine involves the utilization and refinement of high-yield extraction techniques, such as -ve-pressure cavitation extraction [32].

Vincristine has the ability to impact cellular division in a concentration-dependent manner. Nevertheless, the primary method through which vincristine exhibits its anticancer effects is by its interaction with tubulin, the fundamental component of microtubules in the mitotic spindle. This interaction hinders the polymerization of tubulin, ultimately leading to the inhibition of mitosis. Consequently, it interferes with formation of mitotic spindle, leading to death of cells that are undergoing active division [33]. Several authors have reported that the anti-proliferative effect occurs at the minimum effective concentration, which is attributed to a subtle alteration in the dynamics of tubulin addition and loss at the microtubules of mitotic spindle. This alteration ultimately causes stabilization of the assembly and disassembly processes of mitotic spindle, resulting in metaphase arrest [30]. The disruption of microtubule dynamics, which is essential for cell division, can be achieved by inhibiting polymerization or depolymerization of tubulin in microtubules. This impairment of mitotic spindle assembly appears to be the mechanism by which vincristine acts, with its effectiveness dependent on concentration level. Additionally, a molecular docking analysis provided proof indicating that every component of vincristine dimeric structure plays a distinct function in its anticancer action upon binding to tubulin heterodimers. Specifically, the vindoline nucleus is responsible for the binding process, while catharanthine nucleus contributes to the cytotoxic effect [34].

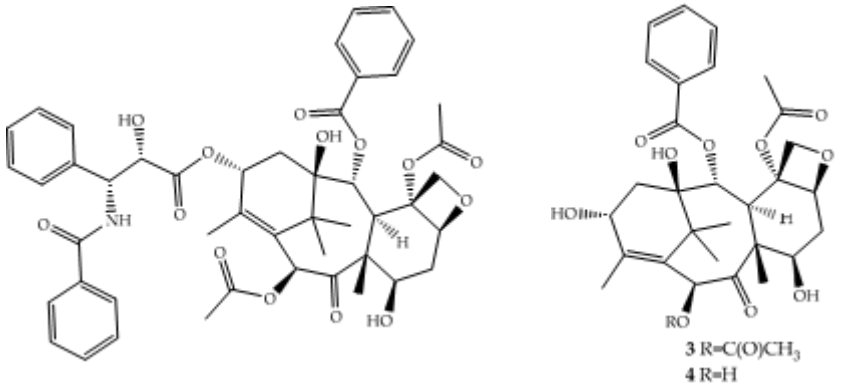
Despite its lengthy history of therapeutic use in cancer treatment, vincristine's impact in therapeutics is diminished by three factors. Firstly, its antitumor mechanism is cell-cycle-specific, meaning that period of its exposure to tumor cells can considerably affect its antitumor activity. Secondly, pharmacokinetic behavior of vincristine in human blood follows a bi-exponential elimination pattern, characterized by a faster initial distribution half-life followed by a lengthier elimination half-life. Additionally, vincristine has a large volume of distribution, suggesting diffuse distribution and tissue binding. Lastly, vincristine may lead to permanent or temporary peripheral neuropathy, which is a side effect and is dose-dependent influenced by various variables like genetic profile, race, age, and method of administration. Grownup children, particularly those of Caucasian ethnicity, appear to be more susceptible to this side effect. The mitigation of certain aspects can potentially be achieved through the process of encapsulating vincristine into liposomes. This method aims to enhance the duration of circulation, improve the targeting of specific tissues, and enable the intensification of dosage without a corresponding increase in toxicity [35].

The approval of sphingomyelin/cholesterol (SM/Chol) liposomal vincristine (Marqibo®) for treatment of relapsed acute lymphoblastic leukemia in adults was granted by the FDA in 2012 (New Drug Application: 202497). Vincristine has been successfully incorporated into conventional liposomes like SM/Chol liposomes. However, alternative liposomal formulations, such as PEGylated liposomes, have also been investigated. It has been observed that SM/Chol liposomal vincristine exhibits a lower leakage rate from liposomes, longer circulation time, as well as enhanced antitumor efficacy compared to PEGylated liposomal vincristine [33]. Clinical trials are now being conducted to assess the efficacy of Marqibo® in pediatric patients who have relapsed or have solid tumors and leukemia that are resistant to chemotherapy. There are ongoing clinical trials investigating the efficacy of various formulations containing vincristine in treatment of different cancer types, including liver cancer, advanced cervical cancer, small-cell lung cancer. Administration of Vincristine in conjunction with other anticancer medicines often results in enhanced efficacy. Indeed, the utilization of combination chemotherapy has been shown to not only augment eradication of tumor cells, but also counteract drug resistance and mitigate toxicity by employing medications that operate through distinct mechanisms of action. Hence, ongoing clinical trials are being conducted to evaluate efficacy of combination vincristine therapy. A recent case report examined treatment of infantile fibrosarcoma by the use of adjuvant therapy following surgical removal. The adjuvant therapy consisted of dactinomycin, and vincristine with duration of chemotherapy being selected based on the response of the tumor. After the conclusion of the treatment, there were no observable functional impairments and no indications of the condition recurring within a span of 18 months, as reported in reference [37].

Paclitaxel

The identification of previously unknown natural structures that possess notable biological significance and exhibit unique modes of action holds immense implications for the pharmaceutical sector. The identification of (2) serves as

a noteworthy illustration. The high level of activity exhibited by this compound, together with its unique mechanism of action involving the encouragement of tubulin assembly, represents a significant breakthrough in the field of anticancer drug research. Paclitaxel, which is derived from bark of Taxus brevifolia Nutt. It is commercially marketed as Taxol® since 1993, is a highly potent cancer chemotherapeutic agent that has gained significant recognition [38,39]. The compound in question is a tricyclic diterpenoid, which is sometimes classified as a pseudo alkaloid. It possesses an intricate 6,8,6-tri-cycle-fused skeleton known as "taxane ring system". This system is connected to a 4-membered oxetane ring and exhibits many functional groups including amide, ester, alcohol, and ketone groups (Fig 2).



Paclitaxel (2) it's precursors (3) and (4)

Figure 2: The chemical structure of paclitaxel (2), a naturally occurring microtubule inhibitor, as well as its precursors baccatin III (3) and 10-deacetylbaccatin III (4)

Paclitaxel is characterized as a non-ionic compound possessing significant lipophilic properties, as evidenced by its high lipophilicity value (log P = 3.20). Moreover, it exhibits limited solubility in aqueous environments, with an approximate solubility range of 0.3-0.5 µg/mL [40]. The administration of this substance, owing to its hydrophobic nature, is typically carried out in a solution that includes alcohol and polyoxyethylated castor oil in order to improve its delivery. Biosynthesis pathway of paclitaxel is an intricate process that commences with the precursor geranylgeranyl diphosphate. This pathway encompasses a total of 19 stages, which are regulated by a variety of enzymes. While some of these enzymes have been previously defined, our understanding of the entire process remains incomplete [41].

The sole utilization of pure paclitaxel component derived from the bark of Pacific Yew for medical purposes has led to significant efforts in seeking other sources due to the plant's limited quantity and the environmental consequences associated with its extraction. The successful complete synthesis of paclitaxel did not occur until 1994 [42]. Despite further advancements [43,44], the process continues to be arduous, impeding its feasibility for industrial-scale production. There is a growing utilization of more sustainable alternatives in the production of paclitaxel. These alternatives include: (i) the implementation of fermentation technology using microbes or plant cell culture [45]; (ii) the application of protein engineering techniques to enhance the catalytic efficiency for paclitaxel synthesis [46]; (iii) the utilization of semisynthesis methods involving baccatin III [47] or 10-deacetylbaccatin III [48], which are precursors of paclitaxel. These precursor molecules, found in high amounts, are non-cytotoxic and are freely available in needles of Taxus baccata, Taxus brevifolia, as well as other Taxus species [49]. Last methodology is one utilized by pharmaceutical sector.

Advent of paclitaxel in recent decades has significantly broadened range of therapeutic possibilities, mostly owing to its potent anticancer properties. Substantial advancements have been made in treatment of breast, ovarian, as well as lung malignancies, resulting in notable achievements [39]. Furthermore, the success of this treatment can be attributed to its efficacy in treating both solid and disseminated tumors, as well as its wide range of antitumor activity, which is facilitated by its distinctive mechanism of action. This mechanism specifically targets fundamental aspects of cancer phenotype, such as cell proliferation as well as DNA repair [38]. The paclitaxel skeleton contains functional groups strategically positioned to specifically target β-tubulin, thereby inhibiting the dynamic

disassembly of microtubules necessary for the accurate construction of the mitotic spindle and segregation of chromosomes during cellular division. As a result, cellular demise occurs in a manner that is contingent upon both the duration of exposure and the concentration of the agent [38].

The ongoing investigation into mechanism of action of paclitaxel, in conjunction with analysis of its structure-activity relationship (SAR) and quantitative SAR (QSAR), has led to identification and characterization of pharmacophores, in addition to structural components which should not be altered (Fig 3). This enabled development of innovative derivatives that exhibit superior efficacy and a reduced incidence of adverse effects [26,50].Based on the existing body of knowledge, two semi-synthetic derivatives, namely docetaxel (5) and cabazitaxel (6) (as seen in Fig 3), were created and demonstrated significant efficacy. The structural adjustments were limited to variable regions of original structure, resulting in their acquisition, and they are presently accessible for clinical use (Fig 3).

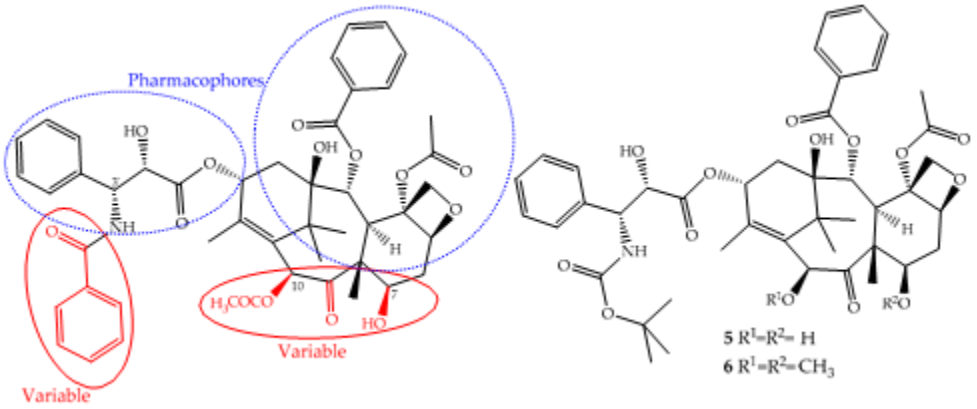


Figure 3: Structural components of paclitaxel (2) that can be altered without compromising its efficacy, as well as two commercially available derivatives, namely docetaxel (5) and cabazitaxel (6), intended for clinical application

Despite the successful application of paclitaxel in the treatment of several cancer types, its therapeutic effectiveness is becoming increasingly constrained as a result of the emergence of multidrug resistance (MDR) [51,52]. The precise cellular mechanisms underlying multidrug resistance (MDR) remain incompletely elucidated. However, current evidence suggests that the primary contributing factors include the upregulation of ABCB1 (also known as P-glycoprotein) and ABCC10 (also referred to as multidrug resistance protein 7) efflux transporters, as well as mutations or modifications in binding regions of α-/β-tubulin [51,52].

Advancement of novel drug delivery technologies and formulations has facilitated the targeted administration of paclitaxel to tumor tissue, hence enhancing its anticancer efficacy and overcoming challenges such as multidrug resistance, limited solubility in water, clinical neurotoxicity, and neutropenia [53–55].One instance of an injectable medication called Lipusu®, which is composed of paclitaxel, lecithin, and cholesterol liposomes, has been available in China since 2006. This medication is utilized in the therapeutic management of several types of cancers, including ovarian, gastric, head and neck, breast, as well as non-small cell lung cancers [39]. The liposomal formulation Lipusu® demonstrated comparable anticancer efficacy to paclitaxel, while exhibiting reduced toxicity compared to paclitaxel at equivalent dosages [39,56]. One more illustration is “Abraxane®, an injectable nanoparticle albumin-bound paclitaxel, also known as nab-paclitaxel”, which was designed to enhance solubility of paclitaxel. It received approval from the FDA in 2005 and from EMA in 2012 [57]. The administration of high dosages of nab-paclitaxel within a shorter infusion period has been found to result in a reduction in neuropathy side effects following end of therapy [57]. However, it should be noted that peripheral sensory neuropathy occurred more frequently with nab-paclitaxel in comparison to paclitaxel [55].

Discovery of docetaxel (5, Fig 3), which has been commercially available since 1995 under trade name “Taxotere®”, was made possible through the creation of simpler paclitaxel-mimics. This medicine exhibits enhanced pharmacological qualities and a reduced incidence of side effects [58]. The compound is derived through a process of semisynthesis using 10-deacetylbaccatin-III. It has a similar mechanism of action and identical affinity

for ABCB1 as paclitaxel. However, it differs in terms of pharmacokinetics and adverse effects, as stated in reference 49.The structural dissimilarity between the compound and paclitaxel lies primarily in the modifications made at C-10 and C-3r positions. Specifically, acetyl group at C-10 has been eliminated, and N-C(O)Ph group has been substituted with an N-tert-butyl acetate group. These changes have been implemented to enhance the compound's solubility in water and reduce its lipophilicity, as evidenced by a log P value of 3.20. This information is illustrated in Fig 3. This compound is classified as a member of the initial taxane generation and is commonly employed in the therapeutic management of prostate, ovarian, non-small cell lung, in addition to breast cancers. In comparison to paclitaxel, it has a lengthier duration of action, enhanced cellular absorption kinetics, and prolonged intracellular persistence [59].

The FDA granted approval to Cabazitaxel (Jevtana®) (6, Fig 3) in 2010 for therapeutic management of individuals diagnosed with hormone-refractory metastatic prostate cancer as well as for tumors which exhibit resistance to paclitaxel or docetaxel [60]. Additionally, it can be acquired through semisynthesis and is classified as a dimethoxyl derivative of docetaxel. This modification enhances its lipophilicity (log P = 3.90), hence facilitating its cellular permeation through passive influx. This effect is attributed to the changing of P-gp affinity [61].Drug's ability to accumulate intracellularly at higher concentrations compared to docetaxel is a contributing factor to its enhanced cytotoxicity and efficacy in patients with taxane resistance [27,49].

Paclitaxel has become a highly successful drug in the pharmaceutical industry, primarily attributed to advancements in delivery systems for cancer therapy [62]. Additionally, its effectiveness has been demonstrated when used in combination with other anticancer drugs, as evidenced by many clinical trials [63,64, 65] and botulinum neurotoxin inhibition [66], exemplifying its versatility and widespread application. These examples serve to underscore the compound's remarkable achievements.

Homoharringtonine

Homoharringtonine is an alkaloid compound possessing a cephalotaxine nucleus, specifically referred to as “cephalotaxine 4-methyl-2(R)-hydroxy-2-(4-hydroxy-4-methylpentyl)succinate”, as depicted in Fig 4. The compound in question was initially obtained from the plants Cephalotaxus harringtonii, K.Koch and Cephalotaxus fortunei Hook. The bark extracts of both trees have been historically employed in Chinese traditional medicine for the treatment of cancer. Homoharringtonine, along with other derivatives of cephalotaxine, can also be observed in the foliage, bark, and seeds of several Cephalotaxus species [67]. Cephalotaxine compound is found in high quantities within the leaves of Cephalotaxus species. It can be extracted and converted into homoharringtonine through a straightforward esterification process. Consequently, this method serves as a semisynthetic approach employed in the industrial production of homoharringtonine [50, 68].

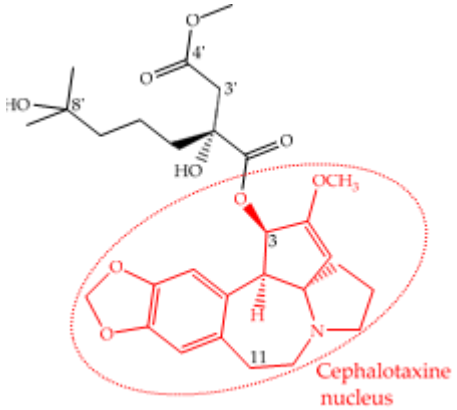


Figure 4: The chemical structure of homoharringtonine, (7), features an alkaloid nucleus called cephalotaxine (highlighted in red).

The investigation into homoharringtonine was initiated upon the discovery of its significant antiproliferative effects against murine P-388 leukemia cells, as evidenced by IC_{50} values of 17nM [69]. Indeed, the utilization of

homoharringtonine or a combination of cephalotaxine esters for the treatment of hematological malignancies has been practiced in China since the 1970s [70]. Nevertheless, it was not until advent of aforementioned semisynthetic process that homoharringtonine garnered the interest of Western medicine.

Homoharringtonine is classified as a pioneering protein translation inhibitor, as it effectively hinders elongation phase of protein synthesis. Homoharringtonine has been observed to bind to the A-site of large ribosomal subunit, thereby impeding entry of charged tRNA molecules then subsequently inhibiting peptide bond formation [71]. The efficacy of this medicine primarily stems from its ability to disrupt proteins with high turnover rates, like the elevated short-lived oncoproteins BCR-ABL1 and antiapoptotic proteins (Mcl-1, Myc), which are present in leukemic cells. Consequently, this disruption induces death in the cells [71]. In recent studies, it has been observed that this phenomenon has the potential to impact several signaling pathways, including as the Jak-stat5 system, by modulating the phosphorylation of protein tyrosine kinases [72]. Additionally, it has been found to activate TGF-β pathway by inducing phosphorylation of smad3 [73].

Chang et al. recently conducted a comprehensive study and discussion on the structure-activity correlations of many natural cephalotaxine esters that bear resemblance to homoharringtonine and other derivatives generated through semisynthesis. This identification has facilitated the establishment of these links. The cephalotaxine nucleus exhibits lower activity against P388 cell line compared to its ester derivatives, highlighting their significance in SAR studies. Additionally, the presence of an aliphatic side chain attached to hydroxyl group at C-3 appears to be crucial for enhancing compound's activity. Conversely, presence of hydroxyl groups at either C-11 or C-3r leads to a decrease in activity. Furthermore, the introduction of a free carboxylic acid at C-4r results in a sudden decline in activity. However, the substitution of the methyl group with other alkyl groups, including bulky ones, does not lead to a loss of activity and may even enhance it in certain cases. Moreover, the inclusion of bulky groups attached to 8r-OH is also well-tolerated. Conversely, substituents attached to 2r-OH significantly diminish the compound's activity (Fig 4).

The utilization of homoharringtonine in management of chronic myeloid leukemia has been extensively studied and has demonstrated a substantial history of clinical effectiveness and safety. Presently, there is a significant emphasis on utilizing this treatment in individuals who have demonstrated intolerance or resistance to several tyrosine kinase inhibitors, specifically those targeting imatinib and sorafenib [74]. Additionally, it has been explored in patients with T315I mutation, a genetic variant that renders them insensitive to tyrosine kinase inhibitors [74-76]. Indeed, FDA granted approval to homoharringtonine in 2012, which is marketed under trade name “Synribo®”, for purpose of treating chronic myeloid leukemia in individuals who exhibit intolerance or resistance to two or more tyrosine kinase inhibitors. It is worth noting that homoharringtonine is the sole naturally occurring therapeutic agent that has been authorized as a commercial medication for treatment of chronic myeloid leukemia.

Endorsement of homoharringtonine in commercial settings, along with the ongoing preclinical as well as clinical examinations of this substance, suggest potential applications for its usage in various hematological malignancies. For example, observed lasting cytogenetic and hematologic responses, irrespective of mutational status (76, 77), demonstrate capacity to efficiently eliminate stem/progenitor cells (77, 78), and play a significant role in context of acute myeloid leukemia (79).

Therapeutic efficacy of homoharringtonine is now under evaluation, and its potential utilization in other hematologic malignancies is anticipated in the near future. The investigational treatment is currently undergoing evaluation in a total of 20 clinical trials. These trials encompass both mono and combined therapy approaches, and involve various patient populations. Examples of these populations include individuals with newly-diagnosed acute myelogenous leukemia, those with relapsed/refractory acute myeloid leukemia carrying FLT3-ITD, and individuals with myelodysplastic syndrome. Additionally, the treatment is being studied in combination with other medications like imatinib mesylate, quizartinib, and cytarabine and idarubicin. In addition, bioavailability of homoharringtonine remains unaffected by its subcutaneous administration, as observed in a clinical trial [80]. Furthermore, this mode of administration has been found to reduce the cardiac toxicity associated with homoharringtonine [77]. Furthermore, in 2014, FDA granted approval for administration of homoharringtonine at home by either patient or a caretaker. This development represents a notable advancement as it allows patients to independently administer their own

medication. Moreover, the stability of homoharringtonine further enhances its suitability for home-based administration [81].

Despite the potential hematologic toxicity, such as myelosuppression, associated with homoharringtonine medication, its use should not be discouraged. The benefits of this drug outweigh the adverse effects, and the latter can be mitigated through appropriate dose adjustments and patient education regarding symptom management [82]. The aforementioned statistics present numerous instances in which homoharringtonine has been utilized, as well as indicating potential future applications that may get permission in the foreseeable future. These findings underscore the enduring significance of homoharringtonine in the field of cancer therapy.

2.2 Metabolites in Clinical Trials

In Sep 2007, a study reported that there were 91 plant-derived substances undergoing clinical studies [83]. However, by the end of 2013, the number had increased to 100 unmodified natural products and their derivatives being investigated in clinical trials, with a significant proportion focused on oncology [68].

Numerous semisynthetic compounds derived from plants, such as daidzein (e.g., phenoxodiol) rohitukine (e.g., riviciclib, alvocidib), combretastatin A (e.g., combretastatin A1 diphosphate; fosbretabulin tromethamine), camptothecin (e.g., gimatecan), and triptolide (e.g., minnelide) [50, 68, 83], are currently undergoing clinical trials. However, primary compounds themselves, despite exhibiting significant cytotoxic properties, have not been investigated in clinical studies as anticancer agents. Currently, clinical studies are exclusively focused on lead compounds produced from plants as potential anticancer medicines. The subsequent discussion will delve into the derivatives of these compounds.

Ingenol Mebutate

The investigation of the phytochemical composition of the latex sap from Euphorbia peplus L. resulted in the discovery of many macrocyclicditerpenes [84]. Among these compounds, ingenol mebutate (8, Fig 5) (also referred to as PEP005, ingenol-3-angelate, and 3-ingenyl angelate) was subsequently discovered as most potent antitumor constituent [85]. Efficacy of Euphorbia peplus sap against human non-melanoma skin cancer has been demonstrated in a recent phase I/II clinical research (86).The diterpene depicted in Fig 5 is a type of ingenene and can also be obtained from various other Euphorbia species, including , Euphorbia helioscopia L, Euphorbia millii Des Moul., Euphorbia paralias L., Euphorbia marginata Pursh, and Euphorbia palustris L. However, it is particularly abundant in lower leafless stems of Euphorbia myrsinites L., where it has been found in a significant extent (upto 547 mg/kg of dry weight) [68,87]. The preparation of ingenol mebutate involves a semisynthesis process utilizing ingenol, which is extracted from seeds of Euphorbia lathyris L. The yield of ingenol from this source is approximately 100 mg/kg. Technology encompasses a targeted esterification process of hydroxyl group located at 3rd position using (Z)-2-methylbut-2-enoic acid (angelate nucleus) as seen in Fig 5 [88]. Several attempts have been undertaken to achieve whole synthesis of ingenol; however, these endeavors have proven unsuitable for implementation within the pharmaceutical sector, thereby leaving the total synthesis of ingenol mebutate unfinished. In pharmacological terminology, ingenol mebutate is classified as a small molecule monoester. The stability of the compound is influenced by the pH of the environment and it has the capacity to easily undergo acyl migration, specifically involving hydroxyl groups, particularly 5- and 20-OH groups (see Fig 5). The presence of free hydroxyl groups and ester moiety at position 3 is crucial for anticancer activity, since it is significant from a biological activity perspective [89].

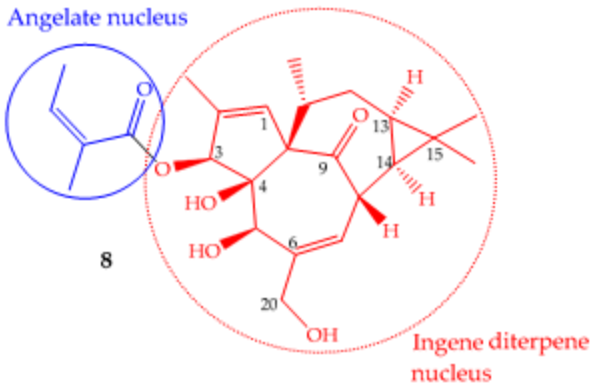


Figure 5: Chemical structure of the diterpene ingenol mebutate (8).

In a study conducted, it was observed that ingenol mebutate exhibited significant antiproliferative effects against various cell lines in a manner that was reliant on both the dosage and duration of exposure [90, 91]. Notably, it displayed particularly strong activity against the colon 205 cell line, with an IC50 value of 10 nM. This level of activity surpassed that of staurosporine (IC_{50} = 29nM) and doxorubicin (IC_{50} = 1.5µM), which are recognized as active compounds commonly employed as reference standards [90].Evidence suggests that the success of the treatment in causing damage to the tumor vasculature is associated with its ability to be transferred from epidermis to deep dermis by a P-glycoprotein [92]. The administration of this compound at concentrations of 230µM in vitro and 42 nmol in vivo resulted in the prompt enlargement of mitochondria, likely due to the disruption of mitochondrial membrane potential. Consequently, cell death occurred through primary necrosis. As a result, it is improbable that the compound's effectiveness would be hindered by advent of apoptosis resistance in tumor cells [86]. The quick efficacy of ingenol mebutate can be attributed to its dual mechanism of action, which involves both cytotoxic and immunomodulatory actions. This combination leads to the swift necrosis of lesions and the activation of neutrophils-mediated antibody-dependent cellular cytotoxicity [93]. The partial relationship between ingenol mebutate and its mode of action involves the modification of protein kinase C (PKC). Ingenol mebutate has a strong binding affinity to PKC, leading to the activation of PKCδ and the inhibition of PKCα [91,94]. The isozyme selectivity was assessed in an in vitro experiment, and it was found to be modest, as shown by a Ki range of 0.105–0.376 nM [95].

The aforementioned findings provide evidence of potential of ingenol mebutate in advancing cancer therapy. Specifically, topical application of ingenol mebutate gel was approved by FDA as well as EMA in 2012 for the treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis. This condition is considered precancerous and if left untreated, it often progresses to melanoma. The gel formulation, formerly known as PEP005 and marketed as Picato®, has shown promise in addressing this condition.Regrettably, there have been reports of adverse reactions connected with the utilization of this treatment. However, it is important to note that these reactions are limited to moderate "local skin responses." These responses encompass crusting, swelling, flaking/scaling, erythema, erosion/ulceration, and vesiculation/postulation. Nevertheless, the results indicate a positive safety and tolerability profile, as there is no evidence of systemic absorption and photosensitivity [92,97].

Curcumin

Curcumin, also known as diferuloylmethane or bis-α,β-unsaturated β-diketone (9, Fig 6), is a polyphenolic chemical derived from the rhizome of Curcuma longa L., a plant native to tropical Southeast Asia. This plant is primarily utilized as a culinary spice. Utilization of turmeric powder, including around 2-5% curcumin, is prevalent in the ancient medicinal practices of China and India [98]. A multitude of advantageous qualities, such as antioxidant, chemo-sensitizing, chemotherapeutic, chemo preventive, and anti-inflammatory action have been ascribed to this age-old treatment [98]. Curcumin is a lipophilic phenolic molecule that has an orange-yellow crystalline appearance. When dissolved, it undergoes an equilibrium with its keto-enol tautomeric forms (Fig 6). The compound has limited

solubility in water and demonstrates moderate stability. However, its disintegration rate is shown to escalate under alkaline conditions [99].

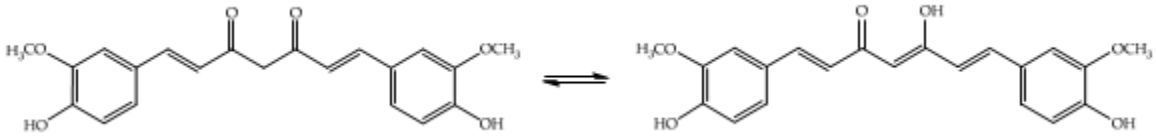


Figure 6: Chemical structure of the polyphenol curcumin (9)

The research interest in the anticancer qualities of curcumin has emerged due to the very low incidence of gastrointestinal mucosal malignancies in Southeast Asian communities, which has been linked to the regular consumption of turmeric in their diet [100].

A substantial body of experimental data has demonstrated therapeutic effectiveness of curcumin at the cellular level in laboratory settings, along with certain tumor-derived cancer cells and solid tumors such as pancreatic cancer, brain tumors, breast cancer, lung cancer, prostate cancer, leukemia, skin cancers, and hepatocellular cancer. Studies have shown that curcumin exhibits cytotoxic effects on cancer stem cells and displays antimetastatic activity [101–103]. In the present year, a comprehensive evaluation was conducted on the potential application of this treatment in the context of colorectal and head and neck cancer chemotherapy [104,105]. Equally significant were the assays that provided evidence indicating that curcumin did not exhibit cytotoxicity towards normal cells when administered at the dosages necessary to achieve therapeutic effectiveness against cancer cell lines [106,107]. Scientific significance and pharmacological promise of curcumin's anticancer properties are further substantiated by the substantial figure of patents on therapies based on curcumin that have been registered within the past five years [108].

Multiple investigations have demonstrated that curcumin possesses the ability to regulate many targets or pathways associated with cancer [102,103,109,110], potentially accounting for its efficacy in addressing cancer-related ailments. Recent studies have provided evidence indicating that curcumin operates through various mechanisms, one of which involves

(i) The manipulation of CYP enzymes. This modulation is achieved by increasing the levels of the transcription factor Nrf2 through the activation of both mitogen-activated protein kinase signaling pathway and the Akt pathway [111].

(ii) The induction of mitotic catastrophe is caused by the activation of caspases and the polarization of mitochondrial membranes [14].

(iii) The stimulation of autophagic cell death, which is a significant mechanism for inducing cell death in cancer cells that are resistant to apoptosis, occurs through both beclin-1-dependent and beclin-1-independent pathways [14,112].

(iv) Cell cycle can be halted at specific checkpoints, including S-phase, G1, and G2/M phase, by process of arrest. This arrest is achieved by regulating the cell cycle regulators, which involves the overexpression of cyclin-dependent kinase inhibitors [113].

(v) Objective is to promote inhibition of the transcription factor NF-κB by impeding its nuclear translocation and reducing its DNA binding capacity. This approach aims to address the issue of chemoresistance [114].

(vi) The inhibition of key processes in angiogenesis can be promoted through the downregulation of PDGF, VEGF, and FGF expression, as well as the downregulation of MMPs, achieved by inhibiting NF-κB, ERKs, MAPKs, PKC, and PI3K [115].

(vii) Curcumin has been found to inhibit tubulin polymerization and bond with DNA [116,117].

Despite present understanding regarding various methods of action of curcumin, there remains a lack of comprehensive understanding regarding its biological qualities. For instance, does the survival and proliferation effects of curcumin rely on factors such as its concentration, duration of treatment, and the specific types of cells being studied? Conversely, investigations have been conducted on the administration of curcumin dosages.In vivo doses ranging from 300 mg to 3.5 g per kilogram of body weight, administered for a duration of 14 to 90 days, or

clinical studies involving oral intake of 1.2 to 12 g per day for a period of 6 weeks to 4 months, did not exhibit any adverse effects on animals, as well as patients [118]. It is worth noting that these dosages exceed the normal consumption levels, which are considered acceptable by Joint FAO/WHO Expert Committee on Food Additives, with an established daily intake level of 0.1 to 3 mg per kilogram of body weight. Furthermore, typical intake of Indian population, which ranges from 60 to 100 mg per day, is also lower than the aforementioned doses.

Additionally, it has been documented that curcumin functions as a chemo sensitizer for certain established anticancer medicines in clinical settings, such as gemcitabine, paclitaxel, 5-fluorouracil, and doxorubicin. Furthermore, curcumin demonstrates a synergistic effect when combined with other natural substances like honokiol, resveratrol, omega-3, licochalcone, and epigallocatechin-3-gallate. These observations suggest that curcumin could serve as an effective approach to overcome tumor resistance and minimize the likelihood of recurrence [108, 119, 120]. Hence, these data indicate that the utilization of curcumin in combination therapies may lead to a more favorable therapeutic index, thereby offering potential advantages in treatment of certain malignancies. Further research is required to evaluate precise mechanism underlying the synergistic action of curcumin.

However, the clinical application of curcumin has faced substantial obstacles due to its limited absorption, inefficient metabolism, and low systemic bioavailability. As a result, patients are required to orally consume a substantial amount of free curcumin, ranging from 8 to 10 grams per day, in order to achieve detectable levels in bloodstream [109,118]. Therefore, various approaches have been suggested to address challenge of curcumin's bioavailability. These include the utilization of adjuvants such as piperine, which hinders curcumin metabolism through glucuronidation. Additionally, nanotechnology-based curcumin formulations involving liposomes, micelles, phospholipids, and other techniques have been proposed. Furthermore, the use of curcumin analogues has also been explored [117,121–123]. Due to the recognized anticancer properties of curcumin, there is ongoing interest in its clinical application, despite certain limits in its therapeutic efficacy. Presently, there are a total of 17 active clinical trials investigating curcumin, primarily focusing on its combined therapeutic use with other agents, aiming to address various forms of cancer.

Betulinic Acid

Betulinic acid, also known as 3β-hydroxy-lup-20(29)-en-28-oic acid, is a pentacyclic triterpene of the lupane-type (10, Fig 7). It is produced through the biosynthesis of six distinct isoprene units. The initial discovery and isolation of betulinic acid occurred in Gratiola officinalis L., where it was given the name "graciolon". Furthermore, it was obtained in a state of isolation from various species, albeit designated by distinct nomenclatures (referred to as "platanolic acid" from bark of Platanus acerifolia (Aiton) Willd. and "cornolic acid" from Cornus florida L.), so causing certain levels of ambiguity. Subsequently, it was verified that each possesses an identical structure, leading to the nomenclature of the substance as betulinic acid. Currently, it is widely acknowledged that this triterpene is widely distributed across various plant species, such as Diospyros spp., Betula spp., Ziziphus spp., Syzygium spp., Sarracenia flava L., Paeonia spp., Lycopodium cernuum L., and Anemone raddeana Regel, among others. Furthermore, it is found in significant quantities, reaching up to 2.5% [124]. Nevertheless, the aforementioned sources fail to adequately fulfill the increasing need for betulinic acid. Hence, it is possible to acquire it by a targeted oxidation process of betulin (lup-20(29)-en-3,28-diol) [125], which is considerably more prevalent (upto 30%) in the bark of birch trees compared to betulinic acid [126].

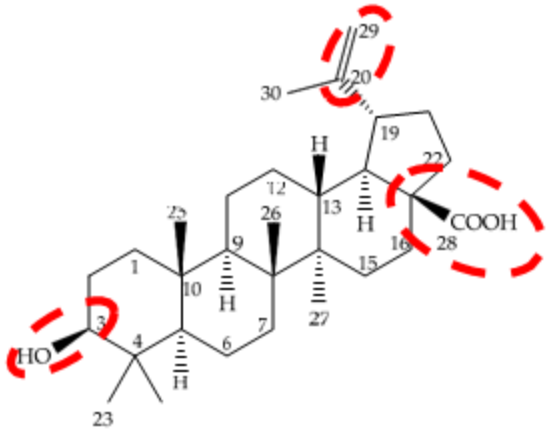


Figure 7: Chemical composition of betulinic acid (10), a pentacyclic triterpene, and its primary focus for structural alterations (highlighted in red) are depicted.

The initial documentation of betulinic acid's anticancer action was published in 1995 by a researcher affiliated with the University of Illinois. The study demonstrated the efficacy of the treatment in eliminating melanoma cells in mice, as evidenced by low IC_{50} values ranging from 0.5 to 1.5 µg/mL [127]. Subsequently, several researchers have undertaken laboratory experiments to investigate the anticancer characteristics of betulinic acid, particularly in relation to melanoma cells [128]. Latest research have indicated that betulinic acid exhibits a wider range of effectiveness against many types of cancer cells. As a result, the National Cancer Institute has chosen to include betulinic acid in Rapid Access to Intervention in Development program.

Betulinic acid has noteworthy cytotoxicity in vitro against many tumor cell lines and effectively impedes formation of solid tumors in vivo. Its efficacy is equivalent to certain medications now employed in clinical settings, and it exhibits a favorable selectivity index by exerting its anticancer effects while sparing normal cells, even at dosages as high as 500mg/kg body weight [14,127,129,130]. The anticancer properties of the substance have been proven in various types of cancer, including cervical carcinoma, breast, ovarian, lung, colon, colorectal, hepatocellular, bladder, prostate, pancreatic, stomach, head and neck, chronic myeloid leukemia cells, glioblastoma, and human melanoma. The effectiveness of the substance is indicated by IC50 values ranging from 1 to 13.0 µg/mL, as reported in multiple studies [14,124,128–132].

Betulinic acid demonstrates significant efficacy against cancer through various molecular targets. Among these targets, the most extensively studied mechanism involves induction of apoptosis by directly modulating mitochondrial apoptotic pathway. This process is related to the collapse of mitochondria through the direct opening of the permeability transition pore, leading to a decrease in mitochondrial outer membrane potential. Additionally, betulinic acid downregulates Bcl-2 family members, resulting in the release of pro-apoptotic factors like cytochrome c. Furthermore, it enhances caspase activities, thereby promoting apoptosis. Moreover, betulinic acid attenuates both constitutive and inducible phosphorylation of STAT3, inhibiting its nuclear translocation and DNA binding. These findings have been supported by multiple studies [124, 130, 133]. Nevertheless, there exists supporting data indicating that in certain instances, apoptosis can be triggered by the stabilization of p53 and the suppression of NF-kB-mediated signaling [124,134].

Potential antimetastatic mechanism of betulinic acid appears to involve inhibition of epithelial-to-mesenchymal transition in melanoma cells with high aggressiveness [131]. Conversely, in breast cancer cells, the antimetastatic activity may be attributed to the downregulation of matrix metalloproteinases expression [133]. Betulinic acid has been found to have the ability to elicit an antiangiogenic reaction in hypoxic conditions through the involvement of STAT3/HIF-1α/VEGF signaling pathway [124,130]. Additionally, it has been observed that betulinic acid can impede the progression of cell cycle at G1 phase by inhibiting Cyclin B1 and Hiwi mRNA. Furthermore, betulinic acid can effectively induce autophagy as a means of cellular survival in response to the opening of permeability transition pores and mitochondrial damage [14,133]. In a recent study, it was discovered that betulinic acid is

associated with a novel mechanism of cell death. This mechanism involves inhibition of an enzyme (stearoyl-CoA-desaturase) which is found to be overexpressed in tumor cells [135]. According to proteasome inhibition studies, it was suggested that betulinic acid primarily targets the proteasome [136]. Nevertheless, the precise regulatory mechanisms by which betulinic acid affects NF-κB pathway as well as modulates the production of Bax or Bak remain poorly elucidated [130].

Betulinic acid has demonstrated significant efficacy as a chemosensitizer in treatment of cancer with chemoresistant cell lines. This is attributed to its ability to decrease multidrug resistance proteins both in vitro and in vivo. Notably, betulinic acid has shown promising results when used in combination with 5-fluorouracil and oxaliplatin [133,137]. The findings presented in this study provide compelling evidence that, under certain circumstances, acquired chemoresistance can be overcome through the utilization of combination therapy involving anticancer medicines and chemosensitizers such as betulinic acid. Furthermore, it has been observed that betulinic acid exhibits a robust synergistic effect when combined with mithramycin A in terms of inhibiting migration as well as invasion of pancreatic cancer cells. This effect is observed even at concentrations that are not hazardous, and it is achieved by lowering the levels of Sp1 and uPAR [138]. Moreover, a study by [139] demonstrated that the combination of betulinic acid and tumor necrosis factor-related apoptosis-inducing ligand exhibits a synergistic effect in inhibiting progression of liver cancer both in vitro as well as in vivo. This effect is achieved by targeting the p53 signaling pathway. These findings suggest that the combination of betulinic acid and TRAIL holds promise as a probable therapeutic line for liver cancer.

Solubility of betulinic acid in water is limited, which poses a challenge in terms of its absorption and bioavailability, necessitating the need for strategies to enhance its aqueous solubility. The primary focal points for conducting structure-activity investigations were C-20 vinyl, C-3 hydroxyl, as well as C-28 carboxyl groups, as depicted in Fig 7. The cytotoxic activity was shown to be enhanced by the oxidation of the 3-OH group, albeit at the cost of lower selectivity. The introduction of functional groups, like amine or hydroxyl, at position C-28 resulted in improved activity. Conversely, changes at the position C-20 did not yield any significant improvement in cytotoxicity [14,124,140]. It can be inferred that alterations have the potential to enhance cytotoxicity and/or water solubility, although they do not appear to affect the selectivity. The primary factors of significance appear to be the existence of carboxyl group at C-28 and hydroxyl group at C-3.

In a recent study, the authors employed the 3D-QSAR method, specifically CoMFA and CoMSIA, to investigate structure-cytotoxicity relationship of betulinic acid derivatives against the A2780 human ovarian cancer cell line. Findings of this study indicate several key conclusions. Firstly, the presence of an electropositive group at C-2 α-site is favorable for cytotoxic activity. Secondly, an electronegative group that can act as a H bond acceptor at C-2 β-site is also beneficial. Thirdly, the inclusion of bulky groups at the C-3 β-site is associated with increased cytotoxicity. Additionally, the presence of bulky and electronegative groups at the C-3 α-site further enhances the antitumor potency. Moreover, the attachment of bulky, electronegative, and hydrogen bond donor or acceptor groups to C-28 side chain is found to be advantageous for antitumor activity [130].

Betulinic acid, owing to its remarkable potential as an anticancer drug, underwent phase I/II clinical trials to assess both its efficacy as well as safety.The research conducted in this study focused on the utilization of topical treatments containing 20% betulinic acid in ointment form for treatment of dysplastic nevi, which has the potential to undergo transformation into melanoma. Regrettably, the trial was terminated at the conclusion of 2013 as a result of financial constraints, as indicated by the Clinical Trials database.

Berries and fungi as chemotherapeutic agents

Weber et al., (2001) prepared Fruit extracts from four raspberry cultivars, Rubus idaeus L., 'Heritage', 'Kiwigold', 'Goldie', and 'Anne' were evaluated for total antioxidant capacity and cancer cell antiproliferative activity to study the health benefits of raspberries. The total amount of phenolics and flavonoids for each of the raspberry cultivars was determined. 'Heritage' had the highest total phenolic content (512.70±4.66mg/100g fruit) followed by 'Kiwigold' (451.06±4.45mg/100g fruit), 'Goldie' (427.51±7.51mg/ 100g fruit) and 'Anne' (359.19±3.35mg/100g fruit). Similarly, 'Heritage' contained the highest total flavonoids (103.41±2.04 mg/100g fruit) followed by 'Kiwigold'

(87.33±1.83mg/100g fruit), 'Goldie' (84.16±1.82mg/100g fruit) and 'Anne' (63.53±0.65mg/100g fruit). The color of the raspberry juice correlated well to the total phenolic/flavonoid content. 'Heritage' had the highest a/b colorimeter ratio and the darkest colored juice with the highest phenolic/flavonoid content, and 'Anne' had the lowest phytochemical content, the palest color, and lowest a/b ratio. 'Heritage' had the highest total antioxidant activity, followed by 'Kiwigold' and 'Goldie'. 'Anne' had the lowest antioxidant activity of the cultivars tested. The proliferation of HepG2 human liver cancer cells was significantly inhibited in a dose-dependent manner after exposure to the raspberry extracts. The extract equivalent to 50 mg 'Goldie', 'Heritage', and 'Kiwigold' fruit inhibited the proliferation of those cells by 89.43±0.11%, 87.96±0.19% and 87.55±0.98, respectively. 'Anne' had the lowest antiproliferative activity of the cultivars measured, but exhibited a significant inhibition of 70.33±1.15% with an extract equivalent to 50 mg of fruit. The antioxidant activity of each of the cultivars was directly related to the total amount of phenolics and flavonoids ($p<0.01$), but no significant relationship was found between antiproliferative activity and the total amount of phenolics/flavonoids ($p>0.05$) [141].

Bowen-Forbes et al., (2010) described that many people see fresh or processed berries as having health benefits. The phytochemistry and biological activity of fruits from closely related species of plants can exhibit notable variations. Hence, despite the existence of earlier research on several Rubus berries, there is considerable significance in exploring species that have not before been examined. The present study examined the anthocyanin contents, lipid peroxidation levels, cyclooxygenase enzyme activity, and inhibitory effects on human tumor cell proliferation of three wild Jamaican species (Rubus jamaicensis, Rubus rosifolius, and Rubus racemosus) and three Michigan-grown species (Rubus acuminatus, Rubus idaeus cv. Heritage, and Rubus idaeus cv. Golden). The study unveiled that the fruits exhibited elevated concentrations of anthocyanins (ranging from 146 to 2199 mg/100 g fresh weight) surpassing those previously documented for other raspberry and blackberry species. Additionally, the hexane, EtOAc, and MeOH extracts derived from these fruits demonstrated notable antioxidant properties, with a majority of the extracts displaying more than 50% inhibition of lipid peroxidation at a concentration of 50 μg/mL. The hexane extracts derived from the Rubus spp. plants found in Jamaica displayed a moderate level of inhibitory activity against COX enzymes, ranging from 27.5% to 33.1% at a concentration of 100 μg/mL. Additionally, these extracts demonstrated significant promise in inhibiting the growth of several cancer cells, including colon, breast, lung, and stomach tumor cells, with inhibition rates of 50%, 24%, 54%, and 37% correspondingly. The fruits mentioned exhibit a notable concentration of anthocyanins and possess various biological properties, suggesting that their consumption could have positive effects on health. Additionally, these fruits have the potential to be utilized in the development of functional meals that include an effective amount of anthocyanins [142].

Dai et al (2009) examined the composition, stability, antioxidant and anticancer characteristics, as well as the underlying mechanisms, of blackberry extracts containing anthocyanins (referred to as ACEs). This investigation involved the utilization of several extraction methods and the selection of certain cultivars. The analysis of ACEs encompassed the examination of their total anthocyanin and phenolics content, polymeric color, and total antioxidant capacity (TAC). The evaluation was conducted to assess the impact of water content on the extraction system. The stability of the extract was assessed using a 90-day study and a 48-hour investigation in biologically relevant buffers. The study aimed to assess the cytotoxic impacts of ACEs on HT-29, MCF-7, and HL-60 cell lines. The quantification of hydrogen peroxide (H_2O_2) production in the culture media and the measurement of intracellular reactive oxygen species (ROS) levels were performed. In contrast to ACEs obtained from powder, ACEs formed from puree exhibited comparable levels of anthocyanins but higher concentrations of phenolics. Additionally, puree-derived ACEs demonstrated improved total antioxidant capacity (TAC), dramatically elevated generation of hydrogen peroxide (H_2O_2), and significantly enhanced cytotoxicity across all cell lines. The protective effect of catalase against ACE-induced cell death was not observed. The anticancer effect of cyanidin 3-glucoside was observed to be enhanced by synergistic or additive interactions with other active components present in the extracts. The studies presented indicate that the combined presence of anthocyanins and non-anthocyanin phenolics in ACEs may exhibit a synergistic or additive effect in the manifestation of anticancer properties [143].

Wang et al., (2007) studied that the inhibitory effects of fruit extracts derived from 17 to 18 individuals representing three distinct strawberry species, namely Fragaria virginiana Mill., F. chiloensis (L.) Mill., and F. ×ananassa

Duchesne ex Rozier, were evaluated in relation to their potential to impede the proliferation of A549 human lung epithelial cancer cells. The activities of various fruit extracts against different types of free radicals (peroxyl radicals, hydroxyl radicals, singlet oxygen, and superoxide radicals) were also assessed. Additionally, the effects of these extracts on the activities of antioxidant enzymes (glutathione peroxidase, superoxide dismutase, guaiacol peroxidase, ascorbate peroxidase, monodehydroascorbate reductase, dehydroascorbate reductase, and glutathione reductase) as well as non-enzyme antioxidant components (ascorbic acid and glutathione) were examined. The study involved the calculation of correlations between the proliferation of cancer cells and the antioxidant activities. At the level of species, the fruit extract of F. virginiana demonstrated a considerably higher suppression (34%) of the proliferation of A549 human lung epithelial cancer cells compared to the fruit extracts of F. chiloensis (26%) or F. ×ananassa (25%) ($P < 0.0001$). The antioxidant activity of extracts derived from the fruit of F. virginiana were shown to be significantly stronger compared to extracts obtained from the other two species. Additionally, these extracts exhibited higher levels of antioxidant enzymes and nonenzyme components. A strong positive association was observed among individual genotypes in terms of the antiproliferative effects on A549 cancer cells, antioxidant activities against free radicals, activities of antioxidant enzymes, and activities of non-enzymatic components. While the fruit extracts of many strawberry genotypes had the ability to inhibit the proliferation of A594 cancer cells, it was observed that the fruit extracts derived from seven genotypes of F. virginiana exhibited notably stronger antiproliferative effects compared to the genotypes of F. chiloensis. The genotypes CFRA 0982, JP 95-1-1, NC 95-19–1, RH 30, NC 96-48-1, JP 95-9-6, and LH 50-4 exhibit promising characteristics that could be advantageous in the development of cultivars with enhanced anticancer properties [144].

Baby *et al*., (2018) state that the longstanding association between dietary patterns and human health has prompted extensive research into the bioactive constituents found in fruits and vegetables. Berries, including well-known varieties such as strawberry, raspberry, blueberry, blackberry, and the Indian gooseberry, are well recognized as valuable dietary sources due to their abundance of diverse bioactive nutritional constituents. Berries are known to include many bioactive constituents, such as phenolic compounds, flavonoids, and tannins, in addition to essential nutrients including vitamins, minerals, carbohydrates, and dietary fibers. Both individually and in combination, these factors have been demonstrated to offer protection against many illnesses. There is an increasing body of research indicating that the consumption of berries provides antioxidant and anticancer benefits to both people and animals. Several important biological effects can be attributed to the compounds under investigation, including free radical scavenging, protection against DNA damage, activation of apoptosis, and reduction of growth and proliferation in cancer cells, among others. This research provides a complete overview of the phytochemical composition of berries and their biological mechanisms in mitigating oxidative stress and inhibiting carcinogenesis [145].

Wedge et al., (2001) studied that the freeze-dried fruits of two strawberry cultivars, namely Sweet Charlie and Carlsbad, as well as two blueberry cultivars, Tifblue and Premier, were subjected to sequential extraction using various solvents including hexane, 50% hexane/ethyl acetate, ethyl acetate, ethanol, and 70% acetone/water at room temperature. The individual extracts were subjected to independent testing to evaluate their in vitro anticancer efficacy against cervical and breast cancer cell lines. The ethanol extracts derived from all four fruits had significant inhibitory effects on the CaSki and SiHa cervical cancer cell lines, as well as the MCF-7 and T47-D breast cancer cell lines. The mutagenic effects of both direct-acting and metabolically activated carcinogens were greatly reduced by an unfractionated aqueous extract of raspberry and an ethanol extract of Premier blueberry [146].

Cooney et al., (2004) performed the analysis of the anthocyanin composition of boysenberry (Rubusloganbaccus × baileyanus Britt) extract was conducted using LC-ESI-MS. A total of four anthocyanins were detected, all characterized by a cyanidin-anthocyanidin-type framework. The two primary constituents were determined to be the disaccharide cyanidin-3-O-sophoroside and the monosaccharide cyanidin-3-O-glucoside. The two components with lower abundance were determined to be the rutinosides, specifically cyanidin-3-O-2G-glucosylrutinoside and cyanidin-3-O-rutinoside, respectively. The aforementioned four anthocyanins were also identified in human urine subsequent to a dosing research including boysenberry extract, suggesting that anthocyanins with glycosylation can be assimilated from the gastrointestinal tract and eliminated in their original form through urine. LC-ESI-MS

analysis revealed the presence of various anthocyanin metabolites in the urine, specifically monoglucuronides of peonidin, cyanidin, and pelargonidin [147].

Cho et al., (2015) state that the seeds of black raspberry (BRB) represent a significant byproduct resulting from the preparation of the fruit. The seeds contain a significant amount of ellagitannins (ET), a type of hydrolysable tannins. These ellagitannins can be hydrolyzed into ellagic acid (EA), which can then be further metabolized into urolithin A (UA) and urolithin B (UB). It is known that these metabolites are accessible in both the colon and the prostate. This study aimed to assess the anti-cancer properties of the aforementioned substances on HT-29 colon cancer cells. The proliferation of cancer cells was decreased by ET, EA, UA, and UB. Ellagic acid (EA) induced a modest yet noteworthy interruption of the cell cycle progression specifically at the G1 phase. On the other hand, urolithins led to cell cycle arrest at the G2/M phase and exhibited an upregulation of p21 expression. The chemicals induced the detection of apoptotic cells by the Annexin V-FITC/PI test. The observed perturbation in mitochondrial membrane potential and subsequent activation of caspases 8 and 9 indicate probable involvement of both extrinsic and intrinsic apoptotic pathways. The confirmation of apoptosis induction was further supported by the activation of caspase 3 and subsequent cleavage of PARP. The compounds ET, EA, UA, and UB exhibited anti-cancer effects on HT-29 human colon cancer cells by causing cell cycle arrest and promoting apoptosis. This study posits that the seeds of BRB have the potential to serve as a source of anti-cancer ellagitannins [148].

Liu and Zhang., (2005) stated that Ganoderma lucidum (Leyss. ex Fr.) Karst., commonly referred to as "Lingzhi" in China, has a long history of utilization in traditional Chinese medicine for the purpose of preventing and treating a diverse range of ailments. These include but are not limited to cancer, hepatopathy, arthritis, hypertension, neurasthenia, and chronic hepatitis. The primary contributors to the anticancer properties of G. lucidum are the polysaccharides and/or triterpenoids present in the fungus. Nevertheless, the precise mechanism underlying the anticancer properties of G. lucidum remains poorly elucidated. Formerly, it was often believed that the activation of the host's immune response was the sole method by which G. lucidum exerted its preventive and therapeutic effects against cancer. Nevertheless, the current paper examines recent studies that have demonstrated various potential mechanisms of anticancer action. These mechanisms encompass not only the activation of the host's immune response, but also the induction of cell differentiation, the activation of Phase II-metabolizing enzymes, the suppression of angiogenesis, and the inhibition of the expression of the urokinase-type plasminogen activator (uPA) and the uPA receptor in cancer cells. In order to enhance our understanding of the underlying mechanisms of G. lucidum, it is imperative to conduct additional in vivo experiments and randomized controlled clinical trials. Furthermore, it is crucial to undertake comprehensive investigations into the molecular pathways involved. Furthermore, it is imperative to conduct further research to determine whether the anticancer chemicals found in Ganoderma lucidum exhibit synergistic effects or work independently [149].

3. Conclusion

Cancer is increasingly gaining prominence as a prevalent ailment in both developed and emerging nations, necessitating arduous efforts in its treatment, albeit with notable instances of success. However, the medications synthesized and employed in chemotherapy exhibit some limits mostly attributed to their adverse effects on non-targeted tissues, hence exacerbating health difficulties. Hence, there exists a need for alternate therapeutic interventions, with naturally-derived anticancer medicines being widely considered as the optimal selection. This study provides evidence, supported by a selection of illustrative instances, that secondary metabolites possess inherent properties that make them effective in combating cancer. Consequently, this has paved the way for the creation of novel therapeutic medications with distinct modes of action specifically designed for anticancer treatment. Certain instances within the pharmaceutical business have already emerged as notable success stories. Furthermore, these compounds have exceptional properties as lead compounds. Through structural alterations, alternate formulations, and the utilization of more advanced delivery systems, their pharmacological potential can be further optimized. In the realm of cancer therapy, there is a burgeoning optimism surrounding the emergence of novel biotechnological advancements that employ nanotechnology methodologies. Notably, the utilization of nanodiamonds infused with plant-derived pharmaceuticals, as well as other nanocarriers incorporating anticancer

agents, has emerged as a promising avenue for potential therapeutic interventions. Concurrently, these findings represent a significant advancement in the effective utilization of secondary metabolites for the goal of cancer therapeutics [150–153]. In certain instances, the culmination of success for a particular narrative has not yet been attained upon its release to the market. However, the more recent investigations provided and deliberated over in this manuscript unequivocally demonstrate that this objective is progressively drawing near. However, the increasing demand for pharmaceuticals generated from plants is exerting significant strain on valuable medicinal plant species, thereby jeopardizing their biodiversity. Consequently, it is imperative to implement effective management strategies to ensure that the utilization of these resources remains sustainable and capable of meeting the growing demands. Fortunately, there have been recent advancements in the field of biotechnology that have led to the creation of sustainable alternative techniques for producing valuable plant metabolites.

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