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Review Paper

Plant-Derived Anticancer Agents: From Traditional Medicine To Modern Therapeutics

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ABSTRACT

Despite significant progress in the treatment of cancer, it is still one of the major causes of morbidity and mortality worldwide, and challenges associated with drug resistance, systemic toxicity, recurrence, metastasis, poor selectivity, and high therapeutic cost persist in the treatment of cancer. The role of plant-derived anticancer agents in modern oncology has been very important as it has been used as a source of structurally diverse and biologically potent compounds which has been employed in drug discovery and development. Medicinal plants are used in traditional systems of medicine such as Ayurveda, Traditional Chinese Medicine, Unani and folk medicine for the management of abnormal growths, chronic inflammation, ulcers and tumor like conditions and provide valuable leads for scientific investigation. The main classes of plant-derived anticancer compounds are alkaloids, terpenoids, taxanes, flavonoids, polyphenols, lignans, quinones, saponins, glycosides, coumarins and others phytoconstituents.

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Several clinically approved anticancer drugs, such as vincristine, vinblastine, paclitaxel, docetaxel, irinotecan, topotecan, etoposide, and teniposide, demonstrate the therapeutic importance of plant-based molecules. They can accomplish many things such as induce apoptosis, stop the cell cycle, inhibit angiogenesis, suppress metastasis, regulate oxidative stress, inhibit topoisomerases, disrupt the dynamics of microtubules, regulate cancer signaling pathways and immunomodulation. Besides their chemotherapeutic effect, plant extracted substances have been found to be useful in adjuvant therapy, chemoprevention, multidrug resistance reversing, and synergism with conventional anticancer drugs. However there are still some limitations like poor bioavailability, toxicity, lack of standardisation and lack of clinical validation. The combination of traditional knowledge and state-of-the-art technologies like nanotechnology, molecular docking, network pharmacology, artificial intelligence, and clinical trials can help in the development of safer, effective, and affordable plant-based anticancer drugs

INTRODUCTION

1.1 Background of Cancer and Current Therapeutic Challenges

Despite the substantial advances that have been made in cancer diagnosis, treatment and prevention, cancer is still one of the most serious life-threatening diseases in the world and is a major public health burden. It is defined as the uncontrolled growth of cells, abnormal proliferation of cells, invasion of surrounding tissues, and metastasis (the spread of the cells to distant organs). Cancer is a multi-stage disease with many underlying genetic and epigenetic changes, oxidative stress, chronic inflammation, immune evasion, and cellular signaling pathways being dysregulated [1]. Cancer initiation and progression is caused by different risk factors including the use of tobacco, drinking alcohol, unhealthy food, environmental pollutants, radiation exposure, infections, genetic predispositions and lifestyle changes. Current cancer treatment primarily consists of surgery, chemotherapy, radiotherapy, immunotherapy,

targeted therapy and hormonal therapy. While these treatment strategies have led to an increase in survival in some forms of cancers, they also have significant drawbacks [2]. The conventional chemotherapy is not completely selective for the cancer cells and affects the rapidly dividing normal cells resulting in side effects like nausea, vomiting, hair loss, bone marrow suppression, mucositis, fatigue, infertility and organ toxicity. Besides this, radiotherapy can also damage other healthy tissues, and surgery can be ineffective in an advanced or metastasized cancer. A further major issue in cancer therapy is the acquisition of drug resistance. Cancer cells can develop resistance to chemotherapeutic agents in a variety of ways – such as increased drug efflux, activation of DNA repair, mutation of drug targets, inhibition of apoptosis, alteration in drug metabolism, and activation of survival pathways. The resistance to multiple drugs has a profound impact on treatment effectiveness and recurrence risk. Moreover, many of the anticancer drugs are poorly soluble, have low bioavailability, short half-life, and dose limiting toxicity, limiting their clinical use [3-5]. The expense of modern cancer therapy is a significant issue also, particularly in developing countries where access to advanced therapy is limited. Targeted therapies and immunotherapies are costly, and many patients aren't able to afford them. Hence, the need to constantly search for safer, more effective, economical and available anticancer drugs. In this context, plant-derived compounds have been the subject of much interest due to their various chemical structures, multiple biological activities and their ability to intervene in several molecular targets implicated in cancer progression [6].

1.2 Importance of Natural Products in Drug Discovery

Natural products have been important in the discovery and development of therapeutic agents



for numerous diseases such as cancer. A large variety of bioactive substances are synthesized by plants, microorganisms, marine organisms and animals, which act as defense molecules against pathogens, insects, herbivores and environmental stress [7]. The naturally occurring compounds frequently have unusual and complex chemical structures which are not easy to design synthetically. Natural products remain key sources for lead molecules in drug discovery, due to their biological specificity and structural diversity. Natural products are particularly useful in the development of anticancer drugs as many can disrupt important processes that are essential to tumor growth and survival. Plant derived compounds have the ability to trigger apoptosis, arrest the cell cycle, inhibit angiogenesis, suppress metastasis, regulate oxidative stress, modulate immune response and inhibit important enzymes including topoisomerases and protein kinases. Several phytochemicals have multiple actions, unlike many single target synthetic drugs, which could be beneficial in complex disease such as cancer where multiple signaling pathways are active. Numerous natural sources, particularly medicinal plants, have been the basis for the development of successful anticancer drugs [8]. They include vincristine and vinblastine from *Catharanthus roseus*, paclitaxel from *Taxus* species, camptothecin derivative from *Camptotheca acuminata*, and etoposide from podophyllotoxin of *Podophyllum* species. These drugs are now significant agents in modern chemotherapy and are applied to the treatment of several types of cancer including leukemia, lymphoma, breast cancer, ovarian cancer, lung cancer and testicular cancer. Natural products are also well known sources of useful chemical scaffolds for semi-synthetic modification. The structures of many naturally occurring compounds may be chemically modified to improve their pharmacokinetic properties, potency, selectivity

and safety, even though these may be limited by the properties of the naturally occurring compound. Therefore natural products are used in their own right as drugs as well as providing templates for the design of improved analogues. The role of natural products in cancer research has been further enhanced in recent years by the advent of technologies like high throughput screening, molecular docking and network pharmacology, metabolomics, genomics and nanotechnology. These tools can be used to discover active phytoconstituents, molecular targets prediction, mechanism of action studies and drug delivery. Thus, natural products are a promising and scientifically interesting source for development of new anticancer drugs [9,10].

1.3 Historical Role of Medicinal Plants in Cancer Treatment

Medicinal plants have been utilized for many centuries in traditional medicine to treat different types of disease such as tumors, ulcers, abnormal swellings and inflammatory diseases with cancer-like symptoms. The ancient medical systems like Ayurveda, Traditional Chinese Medicine, Unani, Siddha, and folk medicine, describe several plants that are used for the treatment of chronic diseases, abnormal growth, pain and inflammation, and general weakness. While popular beliefs about cancer differed from those of modern biomedicine, numerous cancer-like afflictions were treated by plant medications [11]. According to Ayurveda, there are some herbs and formulations which have been traditionally used for balancing the body systems and improving immunity, reducing inflammation, removing toxins and strengthening overall health. *Curcuma longa*, *Withania somnifera*, *Tinospora cordifolia*, *Azadirachta indica*, *Ocimum sanctum* and *Phyllanthus* species have been studied in detail for their anticancer, antioxidant, anti-inflammatory and immunomodulatory activity. Likewise, the



Traditional Chinese Medicine has been utilizing plant based formulation to enhance the body, decrease the tumor burden and improve the quality of life for cancer patients. Medicinal plants have been an important source of anticancer drug discovery, based on their historical use [12]. Ethnomedicine knowledge is valuable in identifying the plants that have a potential biological activity and choosing them for scientific evaluation. Numerous anticancer compounds from plant sources were originally identified as a result of studies on plants used to treat certain diseases or natural sources that had known biological properties. It shows the great association between traditional medicine and modern therapeutics. But the traditional claims are not scientifically valid yet for clinical use. To ensure safety and efficacy, standardization, isolation of active compounds, toxicity studies, pharmacological evaluation, clinical trials, and regulatory approval are essential [13]. While traditional medicine has provided some good leads, not all of the plant remedies are safe or effective. Hence, the proper incorporation of traditional knowledge with modern scientific approach is essential to find evidence-based anticancer agents from medicinal plants. In sum, medicinal plants have been playing a great role in cancer therapy as a source of bioactive compounds, molecules and therapeutic inspiration. They still inform modern researchers in their search for novel, safer and more effective anticancer agents [14].

2. Traditional Medicine as a Source of Anticancer Leads

2.1 Ethnomedicinal Knowledge and Cancer-Related Remedies

Traditional medicine has been an invaluable source for seeking biologically active compounds in general, and in the search for anti-cancer agents in particular. Ethnomedicinal knowledge is the

traditional knowledge and utilization of plants, minerals, animal products and natural materials for prevention as well as treatment of diseases by the local communities [15]. This knowledge is typically acquired through long-term observation, experience and cultural practices handed down from generation to generation. Many plants have been used by local healers and traditional practitioners for treating abnormal growth, chronic wounds, ulcers, swelling, pain, inflammation and non-healing lesions that may be cancer-like in many parts of the world. Traditional healers did not view cancer in a similar manner to modern medicine but used a variety of remedies for diseases that could be considered comparable to a tumor or malignant disease. Plants having bitter taste, latex, resins, alkaloids, tannins, flavonoids and other phytochemicals have been used traditionally to inhibit abnormal tissue growth, stimulate immunity, alleviate pain and promoting wound healing. These so-called uses can be useful in discovering potential anticancer agents among plants. Ethnomedicinal information will help to minimize the chance in drug discovery [16]. Given that fact, rather than scanning thousands of plants with no knowledge of their uses, researchers can focus on plants from past times that have been used for tumor-like ailments, inflammatory diseases, immune deficiency, or chronic infections. This will help to ensure that a more chance is likely in order to discover pharmacologically active plants. Numerous modern anticancer compounds have been found in traditionally used medicinal plants. Thus, ethnomedicine serves as a liaison between traditional medicine and scientific research. But, the ethnomedicinal claims have to be scientifically validated before accepting them for therapeutic use. The safety or effectiveness of traditional use is not demonstrated by the fact that it is a traditional use. Proper botanical identification, extraction, phytochemical analysis, *in vitro* and *in vivo* studies, toxicity evaluation, mechanism based



studies and clinical trials are needed. Some plants may be showing the good anticancer activity and some may be toxic and ineffective. Hence, ethnomedicinal information should be recognized as a valuable initial step, but should be assessed using the latest pharmacological and toxicological techniques [17].

2.2 Ayurveda, Traditional Chinese Medicine, Unani, and Folk Medicine

In fact, several traditional systems of medicine have played a great role in identifying anticancer medicinal plants. According to the ancient system of medicine, Ayurveda, health is a balance of body, mind, and spirit. While there is no one to one correspondence between the modern term 'cancer' and the classical term in Ayurveda, abnormal swellings, abnormal enlargement of glands, non-healing ulcers, and abnormal growth of tissue have been described in the Ayurvedic texts. The antioxidant, anti-inflammatory, immunomodulatory and anticancer activities of the Ayurvedic herbs, *Curcuma longa*, *Withania somnifera*, *Tinospora cordifolia*, *Azadirachta indica*, *Ocimum sanctum*, *Phyllanthus emblica* and *Andrographis paniculata* have been well studied [18-21]. The use of herbal formulations by traditional Chinese medicine (TCM) has also a long history in regard to chronic diseases, tumors, immune regulation and supportive cancer care. It aims to balance the body and enhance resistance to diseases. Instead of taking individual herbs, plants are frequently used to make complicated formulations for use in Traditional Chinese Medicine. Numerous Chinese medicinal plants display anti-cancer activities, such as apoptosis regulation, angiogenesis inhibition, immune modulation and inflammation control [22]. These are *Camptotheca acuminata* (where camptothecin was found) and some supportive oncology herbs. Unani medicine is another traditional system of medicine which involves the use of herbal, mineral

and animal substances to re-establish harmony in the body and cure chronic ailments. According to the Unani system of medicine, disease can be understood in terms of imbalance of humors and temperament. A lot of Unani herbs are utilized for enhancing the resistance, minimizing the swelling, purifying the blood, alleviating pain and treating the abnormal swellings of the body [23]. The pharmacological activities of plants like *Nigella sativa*, *Aloe vera*, *Glycyrrhiza glabra*, and *Terminalia* species have been studied for anticancer and chemopreventive activities. Folk medicine is also important in the discovery of anticancer drugs. Traditional treatments are typically followed by traditional healers, villagers, and tribal people. Many of these remedies are the extracts, juices, powders, pastes and decoctions of locally available plants [24]. Many folk medicinal plants are scientifically not explored and could be good candidates for future investigations. The documentation of folk medicinal knowledge is important since with the process of modernization, deforestation and loss of traditional practices, this information could be lost forever. In combination, Ayurveda, Traditional Chinese Medicine, Unani and folk medicine offer a vast pool of knowledge related to plants. These systems are of particular value in providing clues for modern cancer research along with traditional claims, phytochemical, molecular and pharmacological studies [25].

2.3 Selection of Plants for Anticancer Screening

Plant selection is an important step in screening of natural products for anticancer activity in natural product drug discovery. There are thousands of medicinal plants and researchers need to take a systematic approach to select the most promising ones. Ethnomedicinal selection is one common approach, which involves selecting plants that have been traditionally used for tumors, ulcers, swellings, chronic inflammation, immune



disorders or cancer-like diseases [26]. The use of this method has greater possibility of obtaining biologically active compounds since the plant has been used as therapy in the past. Phytochemical composition is another important criterion. Plants that are abundant in various classes of compounds that are known to show anticancer mechanisms like alkaloids, flavonoids, terpenoids, lignans, quinones, coumarins, saponins, tannins, and phenolic compounds are often chosen. Alkaloids, for instance, can disrupt the replication of DNA or the formation of microtubules, while flavonoids can help mitigate oxidative stress and regulate signaling pathways, and terpenoids can induce apoptosis or inhibit tumour growth [27]. Flowchart of Anticancer Drug Development Process mentioned in Fig.1.

Thus, preliminary phytochemical screening assists in picking up the plants containing possible anticancer constituents. Availability and sustainability together with correct botanical authentication are also crucial. Plant species should be properly identified and a voucher specimen retained for future reference. Sustainable harvesting is crucial as excessive collection of medicinal plants can lead to the loss of biodiversity. The accessibility and culturability of the selected plant should also be taken into consideration, and its suitability for large-scale extraction if the activity is promising,

should be considered [28]. The part of the plant used is another important factor. Different phytoconstituents may occur in leaves, roots, bark, seeds, flowers, fruits, latex and whole plants and these may exhibit different biological activities. The type of compounds extracted also depends on the solvent that is used. Polar solvents can remove phenolics and glycosides, and non-polar solvents can remove lipids, terpenoids and other hydrophobic compounds. Thus, suitable extraction procedures are needed to be able to extract the active fractions. Plants are selected and usually tested *in vitro* with cancerous cell lines by MTT, SRB, neutral red uptake and trypan blue exclusion assays [29]. Encouraging extracts are then subjected to tests to see if they are selective for cancer cells, specifically, or for normal cells. Fractions containing active extracts can then be further fractionated, compounds can be isolated, mechanisms can be studied and animal models can be used. Overall, the scientific approach using traditional medicine as a starting point for the discovery of potential anticancer drugs is beneficial, however, careful selection of plants, standardization, pharmacological screening, and evaluation of their safety are required to transform traditional knowledge into modern therapeutic leads [30].

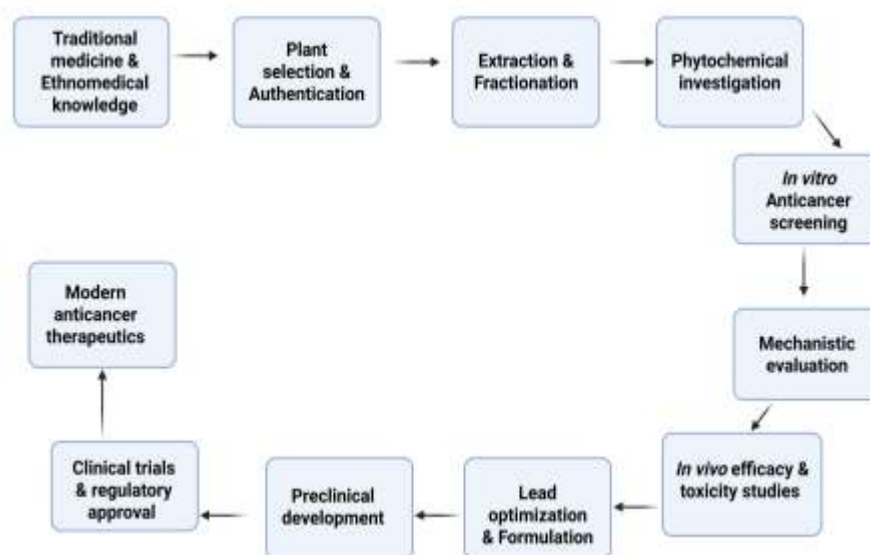


Fig.1: Flowchart of Anticancer Drug Development Process

3. Major classes of plant-derived anticancer compounds

Plant-derived anticancer compounds belong to different phytochemical classes with diverse chemical structures and biological activities. These compounds can act on multiple cancer-related targets such as DNA replication, cell division, apoptosis, angiogenesis, oxidative stress, inflammation, metastasis, and signaling pathways.

The major classes include alkaloids, terpenoids, taxanes, flavonoids, polyphenols, lignans, quinones, saponins, glycosides, coumarins, and other secondary metabolites mentioned in Table 1. Many clinically used anticancer drugs have originated from these phytochemical groups, proving the strong therapeutic value of medicinal plants in oncology [31].

Table 1: Major Phytochemical Classes with Anticancer Mechanisms

Phytochemical Class	Important Examples	Major Plant Sources	Main Anticancer Mechanisms	Anticancer Significance
Alkaloids	Vincristine, vinblastine, camptothecin, berberine	<i>Catharanthus roseus</i> , <i>Camptotheca acuminata</i> , <i>Berberis</i> species	Inhibit microtubule formation, inhibit topoisomerases, induce apoptosis, arrest cell cycle	Important source of clinically approved anticancer drugs
Terpenoids	Paclitaxel, docetaxel, ursolic acid, betulinic acid, andrographolide	<i>Taxus</i> species, <i>Ocimum</i> species, <i>Betula</i> species, <i>Andrographis paniculata</i>	Stabilize microtubules, induce apoptosis, inhibit inflammation, suppress angiogenesis	Useful in chemotherapy and experimental anticancer research
Flavonoids	Quercetin, kaempferol, apigenin, luteolin, genistein	Onion, apple, tea, soybean, parsley, citrus fruits	Antioxidant activity, apoptosis induction, cell cycle arrest, inhibition of angiogenesis and metastasis	Important chemopreventive and supportive anticancer compounds
Polyphenols	Curcumin, resveratrol, epigallocatechin	<i>Curcuma longa</i> , grapes, green tea,	Regulate NF- κ B, STAT3, PI3K/Akt, oxidative	Strong potential in chemopreventio

	gallate, gallic acid, ellagic acid	berries, pomegranate	stress, inflammation, and apoptosis	n and combination therapy
Lignans	Podophyllotoxin, etoposide, teniposide, secoisolariciresinol	<i>Podophyllum</i> species, flaxseed, sesame seed	Inhibit topoisomerase II, cause DNA strand breaks, induce apoptosis	Source of clinically approved anticancer drugs such as etoposide and teniposide
Quinones	Plumbagin, shikonin, juglone, emodin	<i>Plumbago zeylanica</i> , <i>Lithospermum erythrorhizon</i> , walnut, <i>Rheum</i> species	Generate reactive oxygen species, induce apoptosis, inhibit NF- κ B, damage DNA	Promising cytotoxic compounds, but toxicity requires careful evaluation
Saponins	Ginsenosides, diosgenin, saikosaponins	<i>Panax ginseng</i> , <i>Dioscorea</i> species, <i>Bupleurum</i> species	Induce apoptosis, disrupt cancer cell membranes, inhibit angiogenesis, modulate immunity	Useful as anticancer, immunomodulatory, and adjuvant agents
Glycosides	Cardiac glycosides, anthraquinone glycosides, flavonoid glycosides	<i>Digitalis</i> species, <i>Aloe vera</i> , <i>Senna</i> species, medicinal herbs	Inhibit Na ⁺ /K ⁺ -ATPase, regulate signaling pathways, induce apoptosis	Show experimental anticancer potential but may have narrow safety margin
Coumarins	Esculetin, umbelliferone, scopoletin, osthole	<i>Angelica</i> species, citrus plants, <i>Artemisia</i> species	Induce apoptosis, inhibit cell proliferation, reduce inflammation, suppress angiogenesis	Useful in cancer prevention and preclinical anticancer studies
Other Phytoconstituents	Tannins, carotenoids, organosulfur compounds, essential oil constituents	Garlic, tomato, clove, thyme, medicinal plants	Antioxidant activity, detoxification enzyme modulation, apoptosis induction, anti-inflammatory action	Supportive role in cancer prevention and complementary research

3.1 Alkaloids

Alkaloids are a subclass of plant secondary metabolites containing N which exhibit strong pharmacological activity. They are one of the most significant groups of plant-based anticancer drugs. A number of alkaloids disrupt cell division, DNA replication and cell signaling. Vinca alkaloids (e.g., vincristine and vinblastine) derived from *Catharanthus roseus* are archetypal examples of plant-derived anticancer agents. These compounds

disrupt the formation of microtubules, which hinders the development of the mitotic spindle and thus stalls cancer cells in metaphase. Consequently, cancer cell division is halted and the cancer cells undergo apoptosis. Camptothecin, which is derived from *Camptotheca acuminata*, is another alkaloid which inhibits the enzyme topoisomerase I that is essential for DNA replication and transcription. Two semi-synthetic derivatives of camptothecin, irinotecan and

topotecan, have been used clinically in colorectal, ovarian and lung cancers. Although the alkaloids are of value in cancer therapy, due to their potent cytotoxic effects, they can also induce dose limiting toxicities, including neurotoxicity, myelosuppression, and gastrointestinal toxicity. To overcome these safety and therapeutic effects, however, they are often modified structurally and subjected to targeted delivery systems [32].

3.2 Terpenoids and Taxanes

There is a large class of naturally occurring compounds that are based on isoprene units, called terpenoids. These are monoterpenes, diterpenes, triterpenes and sesquiterpenes. Numerous terpenoids have been reported to have anticancer activity, such as inducing apoptosis, inhibiting cell proliferation, suppressing inflammation, preventing angiogenesis, and regulating oxidative stress. Taxanes are the most clinically important anticancer agents of terpenoids. The well-known taxane, paclitaxel, isolated from the bark of *Taxus brevifolia*, is used in the treatment of breast, ovarian, lung and other cancers. Paclitaxel does not inhibit microtubule formation like vinca alkaloids, but rather it stabilizes microtubules and interferes with their normal breakdown. This disturbs mitosis and results in the arrest of the cell cycle and apoptosis. Semi-synthetic analogue of paclitaxel, docetaxel, has better pharmacological properties and is widely used in cancer chemotherapy. Some other terpenes, like limonene, ursolic acid, betulinic acid and andrographolide, have exhibited encouraging anticancer activity in laboratory experiments. These compounds are capable of regulating the molecular targets like NF- κ B, PI3K/Akt, MAPK, Caspases and Bel-2 family proteins. Thus, terpenes are significant not only as anticancer agents but also as effective precursor molecules for developing therapeutic agents with better activity [33].

3.3 Flavonoids and Polyphenols

Flavonoids and polyphenols are plant compounds that are common in fruits, vegetables, tea, spices and medicinal herbs. They have long been recognized for their antioxidant, anti-inflammatory, immunomodulatory and chemopreventive activities. Some of the more common flavonoids include quercetin, kaempferol, luteolin, apigenin, genistein, naringenin and catechins. Polyphenols are curcumin, resveratrol, epigallocatechin gallate, gallic acid, ellagic acid and tannins. These compounds exhibit anticancer effects in various ways. They have the ability to combat free radicals, minimize oxidative damage to DNA, curb chronic inflammation, promote apoptosis, stop the cell cycle, prevent the formation of new blood vessels and suppress metastases. Curcumin, for instance, from *Curcuma longa* has been extensively investigated for its NF- κ B, STAT3, COX-2 and other apoptotic protein regulating properties. The bioactive compound resveratrol in grapes and berries have been found to be active against tumor growth, inflammation and the pathways of cancer cell survival. Green tea extract (EGCG) has been shown to suppress cancer cell growth and regulate signaling pathways that play a role in cancer development. Flavonoids and polyphenols are particularly relevant with respect to cancer prevention since they are widely consumed in the human diet and potentially can lower the risk of cancer with long-term effects. But many of these compounds have poor bioavailability, fast metabolism and poor stability. New methods like nanoformulation, structural modification, and combination therapy are being investigated to enhance their clinical utility [34].

3.4 Lignans

Lignans are phenolic compounds present in seeds, grains, fruits, vegetables and medicinal plants. They have been the subject of interest due to their

antioxidant, hormonal, and anticancer activity. Podophyllotoxin from Podophyllum species is one of the key lignans that has proven important for anticancer drug development. Podophyllotoxin is quite toxic to be used directly in the clinic, however, its semi-synthetic derivatives, etoposide and teniposide, are widely used anti-cancer drugs. Etoposide interferes with the function of topoisomerase II causing breaks in the DNA and cell death. Used to treat testicular cancer, small cell lung cancer, lymphoma and leukemia. Other food-based lignans, including secoisolariciresinol and matairesinol, are converted by gut bacteria to enterolignans that may have protective effects against hormone-dependent cancers like breast and prostate cancer. Lignans also have the potential to regulate estrogen receptors, to suppress proliferation and to decrease oxidative stress. Lignans are thus significant as clinically useful drug precursors and as dietary chemopreventive compounds [35].

3.5 Quinones

Quinones are those molecules with a quinone ring system that have been identified for their redox activity. They can produce Reactive Oxygen Species (ROS) and can disrupt cellular respiration, DNA replication and enzyme activity. Among the various quinones, several have demonstrated anticancer activity and have been found to kill cancer cells through oxidative stress mediated pathway, inhibition of topoisomerases and DNA damage. The quinones found in plants are such as plumbagin from *Plumbago zeylanica*, juglone from walnut species, shikonin from *Lithospermum erythrorhizon* and emodin from *Rheum* species. Plumbagin has been shown to cause apoptosis, suppress NF- κ B signaling, inhibit angiogenesis, and decrease metastasis in experimental models. Shikonin has demonstrated effects on apoptosis, necroptosis and tumor metabolism. The reduction-oxidation (redox) potential of quinones is both

promising for their anticancer use and a potential source of toxicity to normal cells. Thus, for their therapeutic use to be safe, careful optimization of the dose and targeted delivery are needed [36].

3.6 Saponins and Glycosides

The saponins are glycosidic compounds with a sugar part and a triterpenoid or steroidal aglycone. They are known for their foaming property and membrane-interacting ability. Many of the plant saponins have anticancer activity, causing cancer cells to die, making cancer cells permeable, blocking the growth of new blood vessels, stimulating the immune system and increasing the action of chemotherapeutic drugs. These are such as ginsenosides of *Panax ginseng*, diosgenin of *Dioscorea* species and saikosaponins of *Bupleurum* species. Glycosides are compounds in which a sugar molecule is attached to a non-sugar part. Several cardiac glycosides, like digoxin, digitoxin, and ouabain have been demonstrated to possess anticancer activity in experimental studies through their interaction with Na⁺/K⁺-ATPase and the regulation of cancer cell signaling pathways. Anthraquinone glycosides and flavonoid glycosides also exhibit anti-cancer and chemopreventive effects. Some glycosides however, particularly cardiac glycosides, have a narrow therapeutic range, and can cause serious toxicity. So their anticancer applications are to be carefully evaluated [37].

3.7 Coumarins and Other Phytoconstituents

Coumarins are derivatives of benzopyrone which are present in numerous medicinal plants. They have antioxidant, anti-inflammatory, anticoagulant, antimicrobial and anticancer properties. Coumarins might have anti-proliferative activities, pro-apoptotic effects, cell cycle arrest and anti-angiogenic and anti-metastatic properties against cancer cells. Some of the compounds, including esculetin,

umbelliferone, scopoletin, imperatorin, and osthole have been demonstrated to possess anticancer activity in preclinical studies. Certain coumarins have also been found to help regulate enzymes responsible for the metabolism of carcinogens and thus are being pursued in cancer prevention studies. In addition to the major classes listed above, there are several other phytoconstituents that help to provide anticancer activity. These are tannins, phenolic acids, stilbenes, organosulfur compounds, carotenoids, phytosterols and essential oil components. For instance, organosulfur compounds found in garlic can affect detoxification enzymes and apoptosis, and carotenoids like lycopene and beta-carotene are known to inhibit oxidative damage and promote chemoprevention. Furthermore, in experimental studies, the components of essential oils such as eugenol, thymol, and carvacrol have exhibited cytotoxic and anti-inflammatory activity. As a whole, the plant origin anticancer compounds are a group of natural products found to be chemically diverse and of therapeutic value. They can target multiple molecular targets that make them highly important in cancer therapy and prevention. But there are many challenges that phytochemicals encounter, including small solubility, poor bioavailability, toxicity, and the lack of clinical validation. Hence, there is a need

for additional research to translate these potential natural products into modern anticancer drugs: standardization, mechanistic studies, pharmacokinetic evaluation, nanoformulation and clinical trials [38-40].

4. Clinically approved plant-derived anticancer drugs

Clinically approved plant-derived anticancer drugs represent one of the strongest examples of how traditional knowledge, natural product chemistry, and modern pharmacology can be integrated to develop effective cancer therapeutics. Several important anticancer agents used in modern chemotherapy were originally isolated from medicinal plants or developed as semi-synthetic derivatives of plant constituents. These drugs act through well-defined mechanisms such as inhibition of microtubule function, stabilization of microtubules, inhibition of topoisomerase enzymes, interference with DNA replication, and suppression of protein synthesis. Their clinical success proves that plants are not only sources of traditional remedies but also valuable reservoirs of structurally unique and pharmacologically potent anticancer molecules [41]. Clinically approved plant-derived anticancer drugs and their sources mentioned in Table 2.

Table 2: Clinically approved plant-derived anticancer drugs and their sources

Drug	Plant Source / Parent Compound	Class	Main Mechanism of Action	Major Clinical Applications
Vincristine	<i>Catharanthus roseus</i> / Madagascar periwinkle	Vinca alkaloid	Inhibits microtubule formation and blocks mitosis	Acute lymphoblastic leukemia, Hodgkin/non-Hodgkin lymphoma, pediatric solid tumors
Vinblastine	<i>Catharanthus roseus</i> / Madagascar periwinkle	Vinca alkaloid	Disrupts microtubule formation during mitosis	Hodgkin lymphoma, testicular cancer, Kaposi sarcoma, breast cancer
Vinorelbine	Semi-synthetic derivative of periwinkle vinca alkaloids	Vinca alkaloid	Inhibits tubulin polymerization and spindle formation	Non-small cell lung cancer, breast cancer

Paclitaxel	<i>Taxus brevifolia</i> / Pacific yew bark	Taxane	Stabilizes microtubules and prevents depolymerization	Breast, ovarian, lung cancer, Kaposi sarcoma
Docetaxel	Semi-synthetic analogue of paclitaxel; developed from taxane precursors of <i>Taxus</i> species	Taxane	Stabilizes β -tubulin and inhibits microtubule disassembly	Breast, lung, prostate, gastric, head and neck cancers
Cabazitaxel	Semi-synthetic taxane analogue	Taxane	Inhibits microtubule depolymerization and cell division	Metastatic castration-resistant prostate cancer after docetaxel therapy
Topotecan	Semi-synthetic derivative of camptothecin from <i>Camptotheca acuminata</i>	Camptothecin derivative	Inhibits topoisomerase I and causes DNA damage	Small cell lung cancer, ovarian cancer, cervical cancer
Irinotecan	Semi-synthetic derivative of camptothecin from <i>Camptotheca acuminata</i>	Camptothecin derivative	Inhibits topoisomerase I through active metabolite SN-38	Colorectal cancer and other gastrointestinal cancers
Etoposide	Semi-synthetic derivative of podophyllotoxin from <i>Podophyllum peltatum</i>	Podophyllotoxin derivative	Inhibits topoisomerase II and causes DNA strand breaks	Testicular cancer, small cell lung cancer, lymphoma, leukemia
Teniposide	Semi-synthetic derivative of podophyllotoxin from <i>Podophyllum</i> species	Podophyllotoxin derivative	Inhibits topoisomerase II and DNA re-ligation	Refractory childhood acute lymphoblastic leukemia
Omacetaxine mepesuccinate	Semi-synthetic form of homoharringtonine from <i>Cephalotaxus</i> species	Cephalotaxine alkaloid	Inhibits protein synthesis/translation elongation	Chronic or accelerated phase chronic myeloid leukemia resistant/intolerant to ≥ 2 TKIs; current market availability may vary

4.1 Vinca Alkaloids: Vincristine and Vinblastine

The Vinca alkaloids are some of the first and most effective plant-derived anti-cancer drugs. Vincristine and vinblastine are originally extracted from a plant called Madagascar periwinkle (*Catharanthus roseus*). These compounds are part of the class of alkaloids that are commonly utilized in hematological malignancies as well as selected

solid tumors. Their discovery constituted a turning point in natural product oncology since it showed that higher plants could furnish highly active compounds that would prove suitable for clinical cancer therapy [42]. The main mechanism of action of vinca alkaloids is inhibition of microtubule formation. Microtubules are critical part of the mitotic spindle that is needed for proper separation of chromosomes during cell division.



Vincristine and vinblastine bind to tubulin and prevent its polymerization into microtubules. Consequently, the formation of the spindle apparatus is impaired, the cancer cells are blockaded in the metaphase and the cancer cells are induced to die by apoptosis. Because cancer cells divide quickly, they rely heavily on mitosis so that disruption of the dynamics of the microtubules is highly active against cancer. According to NCI, vincristine and vinblastine are called vinca alkaloids and they inhibit the functioning of the micro tubes and prevent cells from undergoing mitosis. Vincristine is part of a number of chemotherapy combination drug regimens, particularly for acute leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, neuroblastoma, rhabdomyosarcoma and Wilms tumor. It is often used in combination therapy since it has a unique mechanism and it has been shown to increase therapeutic response when combined with other anticancer drugs. Vincristine is especially useful in children's oncology and haematological malignancies. Its major problem is neurotoxicity, however, mainly peripheral neuropathy, constipation, autonomic dysfunction and rarely severe neurological complications. Given this toxicity, careful dose monitoring is needed. Vinblastine acts by a similar mechanism but has a different clinical use and toxicity profile. Used in the treatment of Hodgkin and non-Hodgkin lymphoma, advanced testicular cancer, Kaposi's sarcoma, mycosis fungoides, choriocarcinoma, and certain breast cancers. Vinblastine causes more bone marrow suppression, particularly leukopenia, than vincristine. Both drugs have significant clinical usefulness due to their strong antimitotic activity but their narrow therapeutic index, neurotoxicity, myelosuppression and the ability to develop resistance are significant limitations. Nevertheless, vinca alkaloids are still important

drugs in many current chemotherapy regimens [43].

4.2 Taxanes: Paclitaxel and Docetaxel

Taxanes Another important group of plant-derived anti-cancer drugs are the taxanes. Paclitaxel was first found in the bark of the Pacific yew tree, *Taxus brevifolia*. Docetaxel is a semi-synthetic analogue derived from precursors from the European species of yew. Taxanes are common drugs in contemporary oncology and have demonstrated excellent clinical activity in breast, ovarian, lung, prostate, gastric, and head and neck cancer. Taxanes' mode of action involves stabilizing microtubules. Taxanes bind to the β -tubulin and stabilize microtubules against depolymerization, while vinca alkaloids inhibit the formation of microtubules. The huge amount of stabilisation inhibits a normal regulation of microtubule dynamics, which are essential for the function of the mitotic spindle. This results in cells being locked in the cell cycle and the cells die. NCI defines taxane chemotherapeutic drugs, such as paclitaxel and docetaxel, as drugs that disrupt the microtubules and prevent the process of mitosis [44].

Paclitaxel has been approved for use in some cancers alone, or in combination with other medications such as breast cancer, ovarian cancer, non-small cell lung cancer, and AIDS-related Kaposi sarcoma. It is commonly used in first-line and second-line therapy in various types of tumors and stages of disease. Paclitaxel has also prompted the creation of better formulations, like albumin-bound paclitaxel, which would deliver it better while minimizing the effects of solvents on the body. But, there are side effects of paclitaxel therapy, including peripheral neuropathy, myelosuppression, hypersensitivity reactions, alopecia, arthralgia, myalgia, and fatigue. Another important taxane used in breast cancer, non-small cell lung cancer, metastatic castration-resistant



prostate cancer, locally advanced head and neck squamous cell carcinoma and gastric or gastroesophageal junction adenocarcinoma is docetaxel. These are the approved uses of docetaxel, alone or in combination with other chemotherapy drugs, listed by NCI. Docetaxel is a potent agent with strong antitumor activity which may lead to neutropenia, fluid retention, hypersensitivity reactions, mucositis, changes in the nails and peripheral neuropathy [45].

4.3 Camptothecin Derivatives: Topotecan and Irinotecan

Topotecan and Irinotecan are derivatives of camptothecin. Camptothecin is a plant alkaloid that was first isolated from the Chinese happy tree (*Camptotheca acuminata*). Camptothecin had high anticancer activity but was not used directly in the clinic because of low solubility and toxicity. To address some of these issues, semi-synthetic derivatives like irinotecan and topotecan were created. These agents proved to be clinically useful examples of the ability of natural plant compounds to be chemically modified to enhance therapeutic performance. Topotecan and irinotecan are topoisomerase I inhibitors. Topoisomerase I is an enzyme that makes some transient single strand breaks in DNA during replication and transcription to relieve DNA supercoiling. The derivatives of camptothecin prevent re-ligation of the DNA breaks and stabilize the topoisomerase I-DNA complex. These unrepaired breaks become lethal DNA damage during the DNA replication process and this leads to tumour cell proliferation inhibition and induction of tumour cell apoptosis [46]. According to NCI, irinotecan is a topoisomerase I inhibitor which blocks the growth of cancer cells by interfering with the ability of the cells to repair these breaks, which leads to cell death. Topotecan is primarily used for small cell lung cancer and cervical cancer. According to the FDA label, topotecan injection is a topoisomerase

inhibitor indicated for chemotherapy-sensitive small cell lung cancer (SCLC) following failure of first-line chemotherapy and in combination with cisplatin for treatment of stage IVB, recurrent, or persistent cervical carcinoma that is not appropriate for curative surgery or radiotherapy. Major toxicities are bone marrow suppression in particular neutropenia, anaemia and thrombocytopenia, which need careful monitoring of the haematology. Irinotecan is primarily indicated for the treatment of colorectal cancer, including metastatic colorectal cancer (mCRC), alone or in combination with other drugs, including FOLFIRI. It is a prodrug that can be metabolized to SN-38, which has strong topoisomerase I inhibiting activity. Irinotecan has substantially enhanced therapeutic possibilities in colorectal cancer, but is accompanied by specific side effects including severe diarrhoea, neutropenia, nausea, vomiting, fatigue and cholinergic symptoms. UGT1A1 genetic variability may affect the toxicity of irinotecan. Therefore, camptothecin derivatives may be effective plant-based anticancer drugs, which need to be carefully dosed, toxicity monitored, and supported [47].

4.4 Podophyllotoxin Derivatives: Etoposide and Teniposide

Podophyllotoxin is a naturally-occurring lignan extracted from Podophyllum species. The parent compound is very cytotoxic, but not suitable for direct systemic use as an anticancer agent. Hence, the synthesis of semi-synthetic derivatives like etoposide and teniposide was prepared to enhance the clinical usefulness. These derivatives are not only significant examples of the use of medicinal chemistry in naturally occurring toxic compounds to become more effective and safer chemotherapeutics but also examples of the mechanism of action of the naturally occurring compounds. Etoposide and Teniposide work



primarily by blocking topoisomerase II. Topoisomerase II is crucial for DNA replication; it transiently breaks both strands of DNA to remove supercoiling and then joins them together again. Etoposide and teniposide bind to topoisomerase II-DNA complex and inhibit re-ligation resulting in increased number of DNA strand breaks. This results in cell cycle arrest in particular during the S and G2 phases and ultimately leads to cell death through apoptosis [48].

Teniposide is a semi-synthetic podophyllotoxin derivative that binds to topoisomerase II and DNA, resulting in DNA breakdown and cytotoxicity, as defined by NCI. Etoposide is commonly used in small cell lung cancer, testicular cancer, lymphomas, leukemias, ovarian cancer and other cancers, typically in conjunction with other chemotherapy drugs. According to DailyMed, etoposide is a semi-synthetic derivative of podophyllotoxin and is indicated for refractory testicular tumour and small cell lung cancer in combination with approved chemotherapeutic agents, in certain neoplastic diseases. It has a wide range of clinical applications and is active in combination therapy, and is thereby an important drug. The main side effects are, however, myelosuppression, alopecia, mucositis, nausea and vomiting, hypotension during infusion, hypersensitivity reactions, and a possibility of secondary leukemia in long term or high cumulative doses. Teniposide is similar to etoposide and is primarily used with other anti-cancer drugs for the treatment of children with resistant ALL. Teniposide is listed on the FDA Orphan Drugs Information Page for approval as induction therapy in children with refractory acute lymphoblastic leukemia (ALL) in combination with other drugs approved for the treatment of cancer. Teniposide shares these drawbacks such as myelosuppression, hypersensitivity reactions, mucosal toxicity and risk of infection. Its clinical application is more limited but it continues to be a

significant member of the family of anticancer drugs derived from podophyllotoxin [49].

4.5 Homoharringtonine and Other Approved Agents

Homoharringtonine is an alkaloid, first extracted from the species of *Cephalotaxus*. Semi-synthetic form omacetaxine mepesuccinate has been employed as an anti-cancer drug, particularly for chronic myeloid leukemia. Omacetaxine is not a microtubule targeting agent (like vinca alkaloids, taxanes or camptothecin derivatives) or topoisomerase inhibitor (like podophyllotoxin derivatives). Rather, it blocks protein synthesis by blocking the first elongation step of the translation process. This results in short-lived oncoproteins that promote leukemic cell survival being depleted. Omacetaxine is approved by the FDA for use in adult patients with chronic or accelerated phase chronic myeloid leukemia who are resistant or intolerant to at least two tyrosine kinase inhibitors (TKIs). This indication is listed as 26 October 2012 in the FDA orphan drug information. Subsequent sources report that availability in the U.S. market has altered; the availability and regulatory status should be verified before it is described as available in a particular country. However, omacetaxine is still of scientific interest as proof that plant alkaloids can be of use other than for classical DNA or microtubule targeting. Other plant-based (or plant-inspired) anticancer drugs include vinorelbine, a semi-synthetic vinca alkaloid for non-small cell lung cancer and breast cancer, and cabazitaxel, a semi-synthetic taxane primarily in use for metastatic castration-resistant prostate cancer. New drug formulations of paclitaxel, such as the nanoparticle albumin-bound paclitaxel, are also modern drug advances of plant molecules. These examples demonstrate that the development of anticancer drugs from plants is not limited to the parent compound, but is further extended by semi-



synthesis, formulation optimization and targeted delivery [50].

4.6 Clinical Applications and Limitations

The clinically approved plant-derived anticancer drugs have been applied in diverse types of cancers such as leukemia, lymphoma, breast cancer, ovarian cancer, lung cancer, colorectal cancer, prostate cancer, testicular cancer, cervical cancer, gastric cancer, Kaposi sarcoma, neuroblastoma, Wilms tumor and other solid and haematological malignancies. The clinical relevance of these is related to their potent cytotoxicity, well characterized mechanisms and proven efficacy in combination chemotherapy. They are still used in many conventional chemotherapy regimens as they disrupt vital cellular functions needed for tumor cell proliferation. But they have certain drawbacks as well. Most anticancer drugs from plant sources are not completely selective against cancer cells, but are cytotoxic. Thus, they are able to affect rapidly growing tissues like bone marrow, gastrointestinal epithelium, hair follicles and reproductive cells. Myelosuppression, nausea and vomiting, mucositis, alopecia, neuropathy, diarrhoea, fatigue, hypersensitivity reactions, and organ-specific toxicity are common toxicities. Special precautions are needed with some of the agents, including monitoring for neurotoxicity with vincristine; hypersensitivity with taxanes; diarrhea with irinotecan; and bone marrow suppression with topotecan and etoposide. Another significant drawback is drug resistance. Cancer cells can decrease the amount of drugs available by expressing efflux pumps that pump the drug out of the cell; change the target of the drug, such as the protein that tubulin or topoisomerases are, so that the drug no longer affects the drug target; increase the capability of DNA repair; prevent cells from dying when the drug causes cell death; or activate alternative survival pathways. The low solubility and

formulation-related toxicity of a number of natural products such as paclitaxel and camptothecin derivatives also posed a challenge, with the result that a range of semi-synthetic analogues and advanced delivery systems have been developed. Sustainability is also an issue as some of the sources used by plants (e.g. yew bark in paclitaxel) have raised ecological concerns prior to the development of semi-synthetic and biotechnological processes. In spite of these difficulties, plant-based drugs for cancer treatment are still essential in oncology. Their success has spurred further research into medicinal plants, the isolation of new phytoconstituents, modification of the structure, the use of nanotechnology to deliver the plant's products and mechanism-based drug development. The story of vincristine, vinblastine, paclitaxel, docetaxel, irinotecan, topotecan, etoposide, teniposide, and omacetaxine, all drugs derived from plants, illustrates the potential for natural products to advance from traditional medicine and natural product discovery to evidence-based modern therapeutics [51].

5. Mechanisms of Anticancer Action

The anticancer properties from plants work through various biological mechanisms which disrupt the initiation, progression, survival, invasion and metastasis of cancer cells. The uncontrolled proliferation of cells, failure to undergo apoptosis, angiogenesis, inflammation, oxidative stress, genetic instability, immune escape and activation of survival signaling pathways all contribute to cancer. Many phytochemicals have multiple target actions, and thus are very useful in cancer prevention and treatment. Various agents present in plants, such as alkaloids, taxanes, flavonoids, terpenoids, lignans, quinones, saponins, and polyphenols, can act as modulators of molecular targets associated with cancer. Mechanisms of Action of Plant-Derived



Anticancer Compounds mentioned in Fig.2. They have been shown to exert their anticancer effects by inducing apoptosis, arresting cell cycles, inhibiting angiogenesis, blocking metastasis, and

regulating oxidative stress, topoisomerases, microtubules, signal transduction, and immune responses [52].

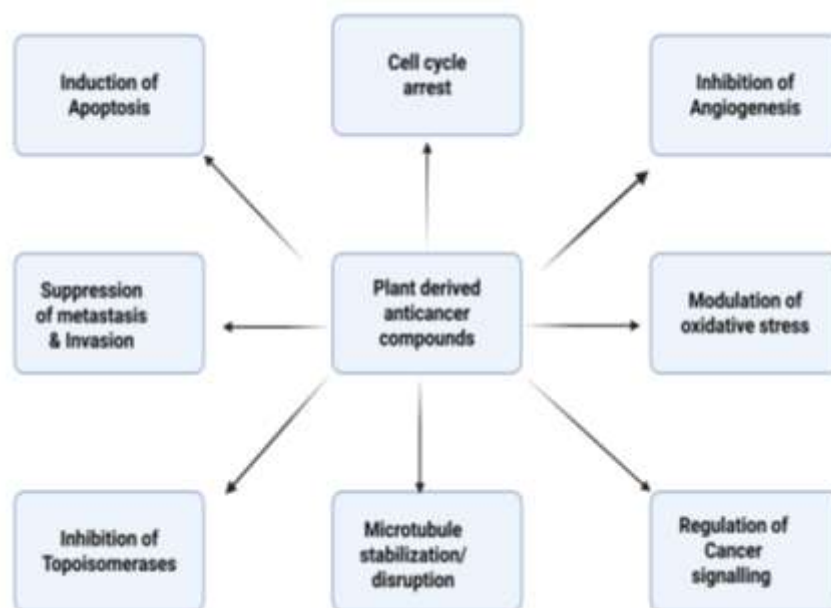


Fig.2: Mechanisms of Action of Plant-Derived Anticancer Compounds

5.1 Induction of Apoptosis

Plant-derived compounds kill cancer cells through the mechanism of programmed cell death (apoptosis), which is one of the most significant mechanisms. Apoptosis occurs in normal tissues to eliminate damaged, old or abnormal cells. Cancer cells, however, are frequently resistant to apoptosis, thereby surviving, proliferating and being able to withstand treatment. Numerous phytochemicals used to inhibit cancer restore apoptotic signaling and selectively kill cancer cells. There are two main pathways of inducing apoptosis: the intrinsic mitochondrial pathway and the extrinsic death receptor pathway. Phytochemicals may open up the permeability of the mitochondrial membrane, release cytochrome c, activate the caspase enzymes and induce cell death in intrinsic pathway. They can also act as regulators of proteins like Bax, Bcl-2, Bcl-xL and p53. An increase in Bax and decrease in Bcl-2 is proapoptotic. In the extrinsic pathway, compounds

could be able to activate death receptors, like Fas and TRAIL receptors, resulting in the death of cancer cells by caspase-mediated mechanisms. Some of the plant based compounds that cause apoptosis include curcumin, resveratrol, quercetin, paclitaxel, vincristine, camptothecin derivatives and podophyllotoxin derivatives. These agents induce activation of caspase-3, caspase-8 and caspase-9, DNA fragmentation, and decreasing of the survival signal. The induction of apoptosis is crucial because it allows the destruction of cancer cells without triggering a lot of inflammation, as would necrotic cell death [53].

5.2 Cell Cycle Arrest

One of the characteristics of cancer is uncontrolled cell growth. The cell cycle has several phases, G₀, G₁, S, G₂ and M phase. Cell cycle checkpoints help ensure the accurate replication of DNA and division of cells in normal cells. Because of mutations in checkpoint proteins, cyclins, cyclin-

dependent kinases, and p53, cancer cells can evade these checkpoints. Plant-based anticancer agents may stall cancer cells in various stages of the cell cycle and stop them from dividing. For instance, vinca alkaloids and taxanes are typical inhibitors of the M-phase of the cell cycle, which block the function of the microtubules. Camptothecin derivatives could block the cells in the S phase as a result of damage to DNA replication, and podophyllotoxin derivatives could arrest cells in the S phase and G2 phase by inhibiting the activity of topoisomerase II. Quercetin, apigenin, luteolin, curcumin, and epigallocatechin gallate are flavonoids and polyphenols that can help control cyclins, CKs and checkpoint proteins. They can also cause them to up-regulate the expression of the natural inhibitors of cell cycle progression, p21 and p27. These compounds block cancer cells at certain checkpoints, which slow their proliferation and helps to promote cell death. Therefore, the ability to arrest the cell cycle is a major way by which phytochemicals can inhibit the growth of tumors [54].

5.3 Inhibition of Angiogenesis

Angiogenesis the development of new blood vessels from the existing blood vessel. Tumors need angiogenesis to get oxygen, nutrients and remove waste. Tumor growth is limited without the formation of new blood vessels. Pro-angiogenic factors like vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and matrix metalloproteinases (MMPs) are secreted by cancer cells to promote blood vessel growth. Plant-derived compounds can inhibit angiogenesis by decreasing the production or action of these pro-angiogenic factors. A large number of phytochemicals are known to block expression of vascular endothelial growth factor, inhibit proliferation of endothelial cells, decrease migration, and prevent tube formation. This

restricts the blood flow to tumors and helps to reduce the growth of cancerous cells. Plant-derived substances that have anti-angiogenic properties include curcumin, resveratrol, genistein, epigallocatechin gallate, luteolin, apigenin and plumbagin. They may exert their effects through the inhibition of various pathways such as the VEGF pathway, the hypoxia-inducible factor 1 alpha (HIF-1 α) pathway, the NF- κ B pathway, the PI3K/Akt pathway, and the MAPK pathway. Other compounds also inhibit inflammation-mediated angiogenesis; chronic inflammation is a key element in supporting vascularization of tumors. Plant-based agents can prevent the development of new blood vessels, which can help to inhibit the growth of tumors and limit their spread [55].

5.4 Suppression of Metastasis and Invasion

The spread of cancer cells from the primary tumour to other parts of the body is called metastasis. It is responsible for most cancer-related deaths. The process of metastasis requires several steps: loss of cell to cell adhesion, degradation of extracellular matrix, invasion into surrounding tissue, entry into blood or lymph vessels, survival in blood or lymph, attachment to distant tissues, formation of secondary tumors. Cancer-causing compounds in plants can inhibit cell migration and invasion, epithelial–mesenchymal transition, extracellular matrix degradation, and adhesion molecule changes, which are all mechanisms that prevent metastasis. The extracellular matrix-degrading enzymes known as matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, play a significant role in the process of invasion and metastasis of cancer cells. A number of phytochemicals have been found to decrease the expression and activity of MMPs. Experimental studies have demonstrated anti-metastatic effects for compounds like curcumin, resveratrol,

quercetin, epigallocatechin gallate, berberine, plumbagin and ursolic acid. They are able to block EMT process via modulating proteins like E-cadherin, N-cadherin, vimentin and transcription factors like Snail, Slug and Twist. They may also inhibit pathways like NF- κ B, Wnt/ β -catenin, STAT3, and PI3K/Akt related to invasion and metastasis. Hence, the inhibition of metastasis is an added favorable effect of plant based anticancer drugs [56].

5.5 Modulation of Oxidative Stress

Oxidative stress is a double edged sword in the fight against cancer. When excess amounts of ROS are produced they can damage DNA, proteins and lipids causing mutations and the initiation of cancer. On the other hand, the very high level of ROS may destroy cancer cells through oxidative damage and apoptosis. Compounds from plants may be able to modulate oxidative stress in the context of each cell, depending on the concentration and depending on the type of cancer. Numerous flavonoids, polyphenols, tannins and phenolic acids are antioxidants. They neutralize free radicals, decrease DNA damage, block lipid peroxidation and improve cellular antioxidant defense systems. Compounds like curcumin are known to enhance the activity of antioxidant enzymes like Superoxide Dismutase, Catalase and Glutathione Peroxidase. Compounds like curcumin are known to enhance the activity of antioxidant enzymes like Superoxide Dismutase, Catalase and Glutathione Peroxidase. This anti-oxidative effect is significant especially in cancer prevention. Some anticancer agents derived from plants, however, when applied to the cancer cell become pro-oxidants. Reactive oxygen species and/or oxidative stress-mediated apoptosis can be produced by quinones like plumbagin and shikonin. Basal reactive oxygen species (ROS) levels are already high in cancer cells, and increasing ROS may further drive them toward

cell death. So, the action of modulation of oxidative stress is a complicated but significant mechanism which may prevent the development of cancer or even eliminate existing cancer cells by plant compounds [57].

5.6 Inhibition of Topoisomerases

Topoisomerases are important enzymes that control DNA topology in a wide range of biological processes such as replication, transcription, recombination, and chromosome segregation. They open up the DNA and create temporary breaks in the strands of the DNA to relieve supercoiling and then re-join the fragments. Topoisomerases are critically involved in the proliferation of cancer cells. Thus, the inhibition of topoisomerase is one of the important anticancer mechanisms. Plant-based compounds have been very important for the development of topoisomerase targeting chemotherapy. Topoisomerase I inhibitors include camptothecin derivatives like topotecan and irinotecan. They block the re-ligation of single strand DNA breaks and stabilize the topoisomerase I-DNA complex. These lesions are converted into double strand breaks during replication, which causes damage to the DNA, cell cycle arrest and apoptosis. Etoposide, Teniposide, etc. are derivatives of podophyllotoxin that act as inhibitors of topoisomerase II. These drugs block the re-ligation of double-strand DNA breaks, leading to the buildup of DNA damage and killing of cancer cells. Other phytochemicals, such as flavonoids, quinones, and alkaloids, have been reported to have an impact on topoisomerase function in experimental models. Inhibitors of topoisomerases are very potent, but can also be toxic to normal proliferating cells, particularly bone marrow cells. However, topoisomerase inhibitors are still important anti-cancer drugs that are derived from plants [58].



5.7 Microtubule Stabilization and Disruption

Tubulin proteins are the components of microtubules and they are dynamic structures. They are vital to cell shape, to moving material within a cell and to separating chromosomes in mitosis. Cancer cells grow quickly and are very sensitive to substances that interfere with the dynamics of microtubules. Microtubule targeting agents are one of the most effective clinically used anticancer drugs derived from plants. Vincas interfere with microtubules by binding tubulin and inhibiting the ability of tubulins to polymerize, including vincristine, vinblastine and vinorelbine. This prevents the formation of mitotic spindle and prevents cancer cells entering metaphase. Cells die as a result of unsuccessful mitosis. Taxanes like paclitaxel and docetaxel work in a reverse manner. They inhibit depolymerization and help to stabilize microtubules. They act in a different way than vinca alkaloids but produce a similar effect of abnormal microtubule dynamics resulting in cell death and mitotic arrest. This mechanism is particularly crucial in breast, ovarian, lung and prostate cancers. The most effective agents are those that target the microtubules, but although these drugs are effective, they have drawbacks, such as causing peripheral neuropathy, myelosuppression, hypersensitivity reactions, and drug resistance by changes in tubulin and/or increased drug efflux [59].

5.8 Regulation of Cancer Signaling Pathways

Several abnormal signaling pathways control cancer progression, including cell growth, survival, inflammation, angiogenesis, invasion and immune escape. Compounds derived from plants may be multi-target agents that can affect several signaling pathways simultaneously. These are useful in cancer, a complex disease in which many molecular pathways are affected. Signaling pathways that are important for cancer, and impacted by phytochemicals include

PI3K/Akt/mTOR, MAPK/ERK, NF- κ B, JAK/STAT, Wnt/ β -catenin, Notch, Hedgehog and p53 pathways. As a case in point, curcumin is capable of suppressing NF- κ B, STAT3, COX-2, and inflammatory cytokines. Resveratrol is able to modulate the PI3K/Akt, p53, and apoptosis-related pathways. Quercetin and apigenin have the ability to inhibit kinase signaling, decrease cell proliferation, and cause cell death by apoptosis. Other compounds, such as berberine, plumbagin, luteolin and epigallocatechin gallate, have a range of effects on several oncogenic pathways. Plant compounds can regulate signaling pathways to inhibit the growth of cancer cells, block cancer survival signaling, suppress inflammation, induce apoptosis and limit metastasis. Multitarget action is particularly beneficial because it is possible for cells to become resistant if a single pathway is blocked. This multi-targeted nature does however pose problems in identifying exact mechanisms and setting a standard for therapeutic effects [60].

5.9 Immunomodulatory Effects

The immune system is important in identifying and destroying abnormal cells. Cancer cells, on the other hand, can evade immune surveillance via immune suppression, the expression of immune checkpoint molecules, alteration in cytokine production, and the creation of an immunosuppressive microenvironment. Natural products from plants can modulate immune responses, cytokines, inflammatory factors, and tumor-associated immune responses to promote anticancer immunity. There are a number of phytochemicals that can act to boost the activity of natural killer cells, cytotoxic T lymphocytes, macrophages and dendritic cells. They can also control cytokines like interleukins, interferons, tumour necrosis factor-alpha and transforming growth factor-beta. Some compounds are anti-inflammatory; because chronic inflammation is a risk factor for the development and progression of



cancer. Plants with immunomodulatory activities have been investigated to determine their immunoregulatory properties, including *Withania somnifera*, *Tinospora cordifolia*, *Curcuma longa*, *Panax ginseng*, *Astragalus membranaceus*, and *Ganoderma* species. Plant Extracts can also modulate the tumor environment by decreasing the number of tumor-associated immunosuppressive cells, increasing antigen presentation, and increasing the killing of tumor cells by the immune system. As part of supportive oncology, some medicinal plants are investigated for their ability to support immune function, lessen complications of therapy and improve quality of life, while reducing fatigue. Immunomodulatory effects, though, need to be thoroughly assessed as over stimulation or inappropriate immune activation can lead to undesirable effects or compromise the use of standard treatments. In conclusion, the anti cancer properties of plant based agents are multifaceted and related to each other. One compound can affect multiple biological processes, such as inducing apoptosis, arresting the cell cycle, inhibiting angiogenesis, decreasing metastasis, regulating oxidative stress, and also influencing signaling pathways. This poly-targeted nature renders plant-derived compounds good candidates for cancer prevention, as adjuvant agents and new anti-cancer drugs. Additional studies are needed to establish their safety, bioavailability, molecular targets, clinical efficacy and potential interactions with currently available anti-cancer drugs [61].

6. Role of Plant-Derived Agents in Modern Therapeutics

Herbal agents have significant applications in the modern era of cancer therapy in terms of clinically useful drugs, lead compounds, adjuvants, chemopreventive agents and combination therapy. Surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy and hormonal therapy are

just some of the many treatment methods that have been developed for cancer, but there are still some drawbacks, including toxicity, drug resistance, recurrence, metastasis and the high cost of treatment. While cancer treatment has progressed significantly through surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy, and hormonal therapy, challenges such as toxicity, drug resistance, recurrence, metastasis, and the high cost of treatment continue to drive the need for safer, more effective therapeutic approaches. Plant-derived compounds are useful due to their ability to have multiple chemical structures with the ability to work on multiple molecular targets involved in cancer growth and progression. A number of clinically used cancer therapeutics have evolved from plants or are based on naturally derived plant compounds. Besides the direct cytotoxic chemicals, there are numerous phytochemicals that are being explored for their supportive, preventive and synergic aspects in the management of cancer [62].

6.1 Chemotherapeutic Agents of Plant Origin

One of the most promising areas of natural product contributions to oncology is the use of plant-derived chemotherapies. Numerous plants have been used in the development of clinically proven anticancer drugs and currently remain in use in cancer treatment. These include vinca alkaloids, taxanes, derivatives of vinca alkaloids, derivatives of camptothecin, derivatives of podophyllotoxin and other plant based compounds. Their significance is that they exhibit strong inhibitory activity against all major processes in the cell including protein synthesis, topoisomerase activity, DNA replication and mitosis. *Catharanthus roseus* is a source or inspiration for vinca alkaloids, including vincristine, vinblastine, and vinorelbine. They work by blocking the polymerisation of microtubules to block the formation of the mitotic spindle and to stall the



development of cancer cells in the middle of their cell division. They are used to treat leukemia, lymphoma, breast cancer, lung cancer and other cancers. The taxanes, which include paclitaxel, docetaxel, are derived from the *Taxus* species, and function by stabilizing microtubules. This results in failing to breakdown normal microtubules and arrests the dividing cell in metaphase, resulting in apoptosis. Taxanes are generally used for breast, ovarian, lung, prostate, gastric and head and neck cancer [63].

Camptothecin is derived from the tree *Camptotheca acuminata* and the camptothecin derivatives irinotecan and topotecan are developed. These drugs block topoisomerase I and cause DNA damage in the rapidly growing cancer cells. Irinotecan is applied to widespread use in colorectal cancer, while topotecan is applied to small cell lung cancer and cervical cancer. Podophyllum species are the source of podophyllotoxins, which are used to make a number of drugs, including etoposide and teniposide. They are inhibitors of topoisomerase II and used in testicular cancer, lung cancer, lymphoma, leukemia and other cancers. As seen through these examples, the compounds found in plants have not just traditional or alternative medicine applications, but have also become part of the available evidence-based modern chemotherapy. They can, however, have adverse effects like myelosuppression, neurotoxicity, gastrointestinal toxicity, alopecia, hypersensitivity reactions and organ specific toxicity, as with other cytotoxic drugs. Hence, current research is directed towards increasing their selectivity, formulation, delivery and safety. The use of adjuvant therapy and combination treatment [64].

6.2 Adjuvant Therapy and Combination Treatment

Plant derived agents are also of significance in cancer management as adjuvants. Adjuvant

therapy is the use of auxiliary treatment in addition to the main treatment to improve therapeutic outcome, reduce recurrence, improve patient recovery and reduce complications. Today, in the modern field of oncology, plant-derived compounds can be utilized as supportive agents, sensitizers, protective agents or as complementary substances, if they have been scientifically proven and properly monitored. Phytochemicals possess antioxidant, anti-inflammatory, immunomodulatory and cytoprotective effects. These may play a role in minimizing treatment-related side effects and enhance cancer patients' quality of life. Some compounds like curcumin, resveratrol, quercetin, epigallocatechin gallate, withanolides, ginsenosides, and berberine are known to exert anti-inflammatory, anti-oxidative, anti-immuno, and anti-cancer effects. Certain phytochemicals can help minimize side effects of chemotherapy treatment like mucositis, fatigue, oxidative tissue damage and inflammation, but clinical trials are required before they are widely used. Another key area where plant-based agents are becoming a focus for combination treatment. Cancer is a complex disease and so may not always be possible to use only one drug. Co-treatment of plant-derived compounds with conventional chemotherapy, radiotherapy, targeted therapy and/or immunotherapy may increase anticancer effects. These combinations can make cancer cells more sensitive, lower the dose of toxic drugs needed and prevent resistance, and enhance the effectiveness of the treatment. But combination treatment should be carefully evaluated. Herbal extracts or phytochemicals can interact with anticancer drugs by changing how the drug is absorbed, metabolized, distributed or eliminated. They can affect Cytochrome P450 enzymes, drug transporters, platelet function or immune responses. Thus, chemotherapy shouldn't be used with plant-derived agents on a whim, before scientific evidence and medical guidance. Future



of adjuvant plant-based therapy relies on regulation of the extracts, identification of active compounds, precise dosage, clinical trials, and safety [65].

6.3 Chemopreventive Potential

Chemoprevention is the prevention, delay, or reversal of cancer using natural or synthetic chemicals. Plants contain compounds with high chemopreventive activity as many of them can affect early stages of cancerous process. The process of cancer develops in multiple steps, including initiation, promotion and progression. At these times, oxidative DNA damage, inflammation, abnormal cell growth, and failure of programmed cell death, or apoptosis, and genetic instability are important factors. There are many phytochemicals that could target these processes, and the risk of malignant transformation can be lowered. Cancer protective effects of polyphenols, flavonoids, carotenoids, organosulfur compounds, lignans, tannins and phenolic acids have been studied extensively. Experimental studies indicate that compounds like curcumin (from turmeric), resveratrol (from grapes), epigallocatechin gallate (from green tea), sulforaphane (from cruciferous vegetables), lycopene (from tomatoes), quercetin (from onions and apples) and genistein (from soy) have promising chemopreventive properties. They can neutralize free radicals, boost detoxification enzymes, inhibit carcinogen activation, decrease chronic inflammation, promote DNA repair, trigger the death of abnormal cells and control cell proliferation. Some phytochemicals also regulate transcription factors and signal molecules including NF- κ B, Nrf2, STAT3, COX-2, p53, PI3K/Akt and MAPK pathways. Control of these pathways could help to lower cancer risk and slow the early development of tumors, while plant-derived compounds may have beneficial effects. Chemoprevention is particularly important for the prevention of cancers in high-risk populations,

such as those with genetic susceptibility, chronic inflammation, environmental exposure, precancerous conditions, and lifestyles that increase the risk. In the case of plant derived agents as chemopreventives, however, strong evidence on clinical benefit, long-term use, effective dose and safety must be established. Eating foods with phytochemicals is good for you, but foods containing high amounts of individual phytochemicals may not be safe. Thus, there is a critical need to move beyond presumption and rely on scientific evidence for chemoprevention [66].

6.4 Overcoming Multidrug Resistance

One of the big reasons for cancer treatment failures is multidrug resistance. Structurally and functionally distinct anticancer drugs can become ineffective because cancer cells can become resistant to them. This resistance may be manifested in multiple ways such as the reduction of drug uptake, increase in drug efflux, activation of survival pathways, epithelial–mesenchymal transition, changes in the tumor microenvironment, mutation of drug targets, and decreased apoptosis. Compounds extracted from plants may be useful in overcoming multidrug resistance by targeting various mechanisms of resistance. Overexpression of ATP-binding cassette transporters (P-glycoprotein, multidrug resistance-associated proteins, and breast cancer resistance protein) is one of the most prevalent mechanisms of drug resistance. Such transporters actively excrete the anticancer drugs out of the cancer cells, thereby lowering the intracellular drug levels. Some phytochemicals, including curcumin, quercetin, resveratrol, berberine, piperine, epigallocatechin gallate and a few terpenoids have been studied for their drug efflux inhibitory properties and their capacity to enhance the levels of drugs within cancer cells. Plant-based compounds can also re-establish apoptosis in resistant cancer cells. The resistance of many cells



to apoptosis is mediated by increased expression of anti-apoptotic proteins like Bcl-2 and survivin, or decreased expression of pro-apoptotic proteins like Bax and caspases. Phytochemicals can alter this balance to promote apoptosis and render resistant cells more susceptible to treatment. They also can block survival pathways like PI3K/Akt/mTOR, NF- κ B, STAT3 and MAPK, pathways that are often activated in drug-resistant cancers. An additional mechanism is the inhibition of epithelial–mesenchymal transition that is associated with metastasis and resistance. Various compounds including curcumin, resveratrol, quercetin, luteolin and sulforaphane may inhibit epithelial–mesenchymal transition markers and inhibit invasion. Agents derived from plants can act on several resistance pathways at the same time, which could make them more effective than the conventional forms of chemotherapy. Yet, the majority is still preclinical and clinical trials of good design are required to validate this in overcoming MDR [67, 68].

6.5 Synergistic Effects with Conventional Anticancer Drugs

A combination of two agents acting together is more effective than each agent alone and is known as synergy. Phytochemicals may exhibit synergistic activity with the use of conventional anti-cancer agents through several mechanisms: increase in the effects of the drugs, induction of apoptosis, downregulation of survival signaling, increased delivery of the drugs and enhance sensitivity of the tumor cells to the drugs. This is desirable, as it could mean fewer doses of standard chemotherapy and thus less toxicity with equal or greater cancer-killing effects. Curcumin, for instance, has been investigated with drugs such as paclitaxel, cisplatin, doxorubicin and gemcitabine due to its ability to inhibit NF- κ B, STAT3, COX-2 and anti-apoptotic pathways. Resveratrol can also improve the effectiveness of chemotherapy,

by inducing apoptosis and decreasing damage caused by oxidative stress and inhibiting survival pathways. In experimental models quercetin has been reported to sensitize cancer cells to the action of doxorubicin, cisplatin and other chemotherapy drugs. Epigallocatechin gallate can modulate the pathways of apoptosis, proliferation and angiogenesis, thus enhancing the response to anticancer treatment. Another possible method of overcoming dose-limiting toxicity is to use synergistic combinations [69]. A phytochemical may make a cancer cell more susceptible to a chemotherapeutic agent, which could allow for a lower dose of the drug to be used. This may reduce side effects like myelosuppression, neuropathy, nephrotoxicity and gastrointestinal toxicity. Other plant-based chemicals may also help to prevent the oxidative damage of normal cells while killing cancer cells, but the selective protection needs to be carefully verified. These benefits, however, must be scientifically proven to be the case in synergy. Some of the combinations of plants and drugs are not beneficial. Others may hinder chemotherapy, via rapid metabolism of the drugs or by blocking them from getting into the cancer cells, or by shielding the cancer cells from the drug by consuming its antioxidants prior to it reaching them. A few others can make the drug more poisonous, either by interfering with how a drug is cleared from the body or by changing liver enzymes. Thus, combination therapy with plant-derived medications should be based on pharmacological evidence, standardized formulations, known dosages, and clinical trials. In general, plant derived agents have several applications in current therapies. They are directly used as chemotherapeutic agents, supportive co-adjuvants, chemopreventive agents, resistance modifying agents, and synergistic agents when used with established chemotherapy agents. They are especially useful in cancer, a disease in which multiple and interconnected molecular



abnormalities underlie the disease. They must be standardized and mechanistically evaluated, pharmacokinetically studied, safely assessed, and clinically validated, however, for their successful incorporation into modern oncology practice [70].

FUTURE PERSPECTIVES

The potential of plants as source of anticancer drugs looks bright with the rising demand for safer, effective, cost effective and multi-targeted cancer therapeutics. A number of plant-derived drugs are already in clinical use including vincristine, vinblastine, paclitaxel, docetaxel, irinotecan, topotecan, etoposide and teniposide, but many medicinal plants and phytochemicals are not yet studied. Systematic screening of traditional medicinal plants, isolation of bioactive compounds, identification of molecular targets and validation of the anticancer mechanisms through advanced experimental models, are suggested for future research. The integration of artificial intelligence, molecular docking, network pharmacology and systems biology into natural product drug discovery is one of the future directions. These tools are currently available and can be useful to predict the interaction between phytochemicals and cancer targets, discover signaling pathways and to represent and select interesting compounds for further research. In particular, the function of many plant-derived compound is multi-target and is important in a complex disease such as cancer, making network pharmacology a very useful tool. Nanotechnology will also be important in enhancing the therapeutic properties of the plant-based anticancer agents. The clinical application of many of the phytochemicals is limited by low bioavailability, rapid metabolism, poor water solubility and instability. Nanoformulations like liposomes, polymeric nanoparticles, solid lipid nanoparticles, nanoemulsions, micelles and phytosomes can help to enhance the solubility of the drug, therapeutic

efficacy, target the tumor and decrease its toxicity. These "delivery systems" could prove useful in turning beneficial phytochemicals into viable anti-cancer drugs. Combination therapy is also a field that should be explored in the future. Plant compounds can help conventional drug therapy, radiation, targeted therapy, and immunotherapy work better by promoting apoptosis, overcoming drug resistance, suppressing inflammation, and controlling immune responses. Combinations of these, however, need to be carefully assessed for safety, drug-herb interaction, optimization of dosage, and effectiveness. Production, another key area, is sustainable production. Excessive extraction of medicinal plants can be a threat to biodiversity. Hence, the development of plant tissue culture, semi-synthesis, synthetic biology and biotechnological production methods to guarantee continuous and eco-friendly supply of important anticancer compounds. Although they have promise, these plant-based agents must be thoroughly studied before they can be used clinically. Standardization of extracts, quality control, toxicity and pharmacokinetic studies as well as well-designed clinical trials are necessary. The use of traditional knowledge combined with modern pharmaceutical science in the future can potentially bring about the discovery of new plant-based anticancer drugs and enhance the efficacy of cancer treatment.

CONCLUSION

Cancer therapy has gained a tremendous boost in cancer treatment from plant-derived anticancer agents, connecting traditional and modern medicine. Medicinal plants contain a wide variety of bioactive compounds such as alkaloids, terpenoids, taxanes, flavonoids, polyphenols, lignans, quinones, saponins, glycosides, and coumarins, which can target several mechanisms involved in cancer development and progression. These compounds can act as apoptosis inducers,



cell cycle arresters, angiogenesis inhibitors, metastasis suppressors, oxidative stress regulators, topoisomerase inhibitors, microtubule disruptors, cancer signaling pathway modulators and immune response enhancers. There are several clinically used anticancer drugs such as vincristine, vinblastine, paclitaxel, docetaxel, irinotecan, topotecan, etoposide and teniposide that clearly illustrate the therapeutic relevance of plant-derived molecules. These drugs have been an indispensable part of modern chemotherapy and are employed for the treatment of different types of hematological and solid tumors. In addition to direct chemotherapy, numerous phytochemicals have been found to have a variety of other therapeutic potential as adjuvants, chemopreventive agents, resistance-modifying agents, and synergistic agents with conventional anticancer drugs. Although plant-based anticancer drugs show great potential, they have been hindered by low bioavailability, poor solubility, toxicity, lack of standardization, variability of phytochemical content, limited clinical studies and potential herb–drug interactions. Thus, before their routine clinical application, it is necessary to validate them scientifically. To overcome these challenges and facilitate clinical translation, modern techniques like nanotechnology, molecular docking, network pharmacology, artificial intelligence, metabolomics, synthetic biology, and advanced formulation strategies can be used. In general, anticancer agents derived from plants still provide an abundant and valuable source for novel anticancer agents. The use of traditional medicine in conjunction with the modern pharmacological, molecular and clinical studies can enable the development of safer, effective, cost-effective and multipurpose approaches for cancer prevention and treatment.

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