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Plant-Derived Anticancer Agents: A Sustainable Approach to Combating Cancer

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Abstract

The great structural diversity found in natural resources makes them an invaluable source of new, innovative chemical molecules with potential applications in medicine. The need for new and better pharmaceuticals has experienced a growth in investigating and utilizing nature especially for development of antibacterial, antidiabetic and anticancer compounds. Nature has historically provided us with potent anticancer agents which include vinca alkaloids (Vincristine (VCR), vinblastine, vindesine, vinorelbine), taxanes (Paclitaxel (PTX), docetaxel), podophyllotoxin and its derivatives (Etoposide (ETP), teniposide), Camptothecin (CPT) and its derivatives (topotecan, irinotecan), anthracyclines (doxorubicin, daunorubicin, epirubicin, idarubicin) and others. Approximately 50% of all anti-cancer medications that are approved globally are derived from natural chemicals or their derivatives and were produced using the knowledge gathered from small molecules or macro-molecules providing.

Keywords: Cancer • Chemotherapy • Proliferation • Anticancer

Introduction

Cancer is the most significant health complication that affects people worldwide. It is estimated that 19.3 million new cases and approximately 10.0 million deaths from cancer will occur in 2020. A significant number of cancer patients are believed to take herbal medications. These medications may be used to prevent or reduce some of the cancer's symptoms; to reduce some of the adverse impacts of cancer treatments like chemotherapy or radiation; to reduce a related illness like anxiety or despair or to give cancer patients a sense of empowerment or active participation treatment. Humans can develop many different types of cancer; among these, lung cancer is said to be the most common in men, then breast cancer in women. It is a significant public health burden that is regularly addressed by medicinal plants as a whole or by its phytochemicals in both developed and developing nations. Chemically, phytomedicines consist of biologically active secondary metabolites like alkaloids, phenols, flavonoids, tannins or terpenoids, which are isolated by different chemical extraction procedures. Shikonin, found in herbal medicine, exhibited synergistic effects when combined with anticancer drugs [1].

Herbal medicine's clinical applications with anti-cancer effects

Many research studies have demonstrated that a variety of herbal medications can exhibit a spectrum of anticancer effects. The therapeutic use of certain herbal remedies has been categorized and arranged in this section based on their ability to prevent specific cancer types (Table 1) [2].

Herbal medicine	Inhibitory effects on the development and spread of cancer
Alkaloids	Inhibition of cancer cell growth
Coumarin	Inhibition of cancer cell growth
Terpenoids	MCF-7 cell apoptosis
Curcumin	Induce apoptosis and inhibiting proliferation
Ginseng	Antiproliferation, apoptosis

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Vitamin A (Fenretinide)	Consumed either 200 mg/day Prep to reduce breast cancer in premenopausal women

Table 1. Herbal medicine's clinical applications with anticancer effects.

Materials and Methods

Phytomedicine in cancer treatment

The type, stage and location of the cancer determine the treatment options. Chemotherapeutic agents comprise cytostatic and cytotoxic medications that, either used alone or in combination with other cancer treatments, have had encouraging outcomes. Topoisomerase inhibitors (such as doxorubicin (side effects include cardiotoxicity), diarrhoea, neuropenia and sensory neuropathy), alkylating agents (such as oxaliplatin, melphalan, carboplatin, cisplatin and cyclophosphamide (side effects include nephrotoxicity, gastrointestinal toxicity, cardiovascular toxicity, pulmonary and hematologic toxicity) and microtubules acting agent (such as vincristine, vinblastine, docetaxel and paclitaxel, etc.) are among these chemotherapeutic agents [3].

Bioactive herbal medicines

Vinca alkaloids: They are isolated from the Apocynaceae family plant *Catharanthus roseus* (L.) G. Don, also known as "periwinkles." The four distinct vinca alkaloids-Vincristine (VCR), Vinblastine (VLB), vindesine and vinorelbine are utilized in clinical practice to treat different types of cancer. Vinca alkaloids have semi-synthetic analogs in vindesine and vinorelbine [4].

Vinca alkaloid cytotoxicity primarily results via interactions with tubulin that disrupt microtubule function, especially in the case of microtubules that make up the mitotic spindle apparatus, which in turn causes metaphase arrest.

By attaching to microtubules, vinca alkaloids prevent cell proliferation by blocking mitosis and inducing apoptosis. Microtubule instability is caused by VCR and similar chemicals binding to tubulin and preventing polymerization. Vinca alkaloids are so important for being combating cancer [5].

Taxanes: Other most powerful plant derived chemotherapeutic drugs generated from plants are called taxanes. In *Taxus baccata* Thunb. and *T. canadensis* Marshall, the leaves and bark isolated the first taxane, paclitaxel, (it referred to as taxol). By binding to beta-tubulin, paclitaxel inhibits microtubule mobility, causing mitotic arrest. Moreover, it attaches itself to the Bcl-2 protein, inhibiting its activity and causing apoptotic cell death. A semisynthetic derivative of paclitaxel, docetaxel stabilizes microtubules by binding to them. As a result, the mitotic cell division process is inhibited from metaphase to anaphase. Microtubule accumulation also causes apoptosis, which lowers the proliferation of cancer cells. Whereas docetaxel is mostly used to treat breast cancer, paclitaxel is utilized to treat lung cancer, ovarian cancer and breast cancer [6].

Vitamin A: Derivatives of vitamin A affect cell differentiation, proliferation and death and are crucial to many physiological processes in biology. Foods derived from animals contains retinol. Provitamin A carotenoids or preformed vitamin A (mostly as retinyl ester, retinol and in much lower amounts as retinoic acid) are the two forms of vitamin A that can be obtained by diet. After the absorption by the mucosal cells, provitamin A carotenoid first convert to retinaldehyde and then to retinol. Retinoids, both natural and synthetic, have been researched as possible chemotherapeutic or chemopreventive drugs due to their antioxidant, proapoptotic, antiproliferative and differentiation properties. The CRBP-1 gene's role in regulating the amount of retinol that cells can absorb implies that the product of this gene is particularly significant to the prevention of early stages of transformation. In breast and ovarian cancers, CRBP-1 decreased levels impairs RAR action, which results in cellular differentiation loss and cancer advancement [7].

Secondary metabolites with anticancer property

Flavonoids: Flavonoids are a type of phenolic compounds that are produced by plants and are categorized as secondary metabolites.

The peels of grapefruit, orange, lemon and lime are very high in the flavanone the compound. It caused a range of human cancer cells to undergo programmed cell death and inhibition of cell growth.

Flavonoids, found in various forms like flavones, chalcones, isoflavones, anthocyanins, flavonols and flavanones, exhibit anticancer properties by targeting inflammation, cancer cell migration, invasiveness and metastasis. Consuming flavonoids is known to lower cancer risk. Their application in diet emphasizes a personalized and targeted approach for chemoprevention and chemotherapy [8].

Polyphenols: Curcumin is an active hydrophobic polyphenol extracted from the rhizomes of the turmeric plant, *Curcuma longa* belongs to the ginger family which has anti-inflammatory and anticancer properties. Numerous secondary metabolites, including as flavonoids, alkaloids, tannins and phenolic acids, are produced by the plant. Curcumin inhibits proliferation of tumors and induces apoptosis through its inhibitory action on the NF-κB-dependent pathway. It has been discovered that curcumin inhibits a few of the most important side effects caused by chemotherapy. Curcumin, when combined with cisplatin, elevated the levels of the hepatoprotective enzyme Superoxide Dismutase (SOD) [9].

Terpenes: Terpenes, along with terpenoids, are a group of secondary metabolites that are generated by both insects and plants. Terpenoids, derived from hydrocarbons called terpenes, including ursolic acid, corosolic acid, oleanolic acid, 3-epi-corosolic acid, maslinic

acid and 3-epi-maslinic acid, were isolated from *Perilla frutescens*. A study by Cho, et al. revealed their potential in preventing skin cancers by reducing epidermal proliferation, cellular signaling, and inflammation induced by 12-O-tetradecanoylphorbol-13-acetate (TPA). Cancer therapy already makes use of terpenes such as monoterpenes, sesquiterpenes, diterpenes, triterpenes and tetraterpenes [10].

Brassinosteriods: Plants produce secondary metabolites called Brassinosteroids (BRs), which are crucial for hormone signaling, stem and root cell elongation, cell growth, differentiation and development and a host of other functions like stress and disease resistance.

Cancerous cells possess the ability to proliferate uncontrollably and can evade apoptosis. BRs have been shown to interact with cell cycle proteins and cause apoptosis in order to elicit the proper anti-cancerous responses against a variety of cancer cells [11].

Results and Discussion

Phytomedicinal compounds: Isolation, purification and their characterization

Bioactive chemicals are found naturally in these plants. In the field of drug development, it is still very difficult to isolate, purify, characterize and evaluate these compounds activities *in vitro* or *in vivo*. The isolation, purification and characterisation of phytomedicinal substances can be done using a variety of techniques. The first stage in creating phytomedicine from conventional plants is called phytoextraction. Pre-washing, allowing the sample dry in the shade and grinding the sample into a fine powder are the fundamental processes in phytoextraction. After that, several solvent systems are employed to make the crude extract using the fine powder. Also, the polarity of the chosen bioactive component should be taken into consideration while choosing the solvent. These are the most generally used and appropriate methods for analyzing, identifying and frequently purifying particular chemicals according to their polarity and Retardation factor (Rf). Different analytical techniques, such as Liquid Chromatographic Mass Spectrometry (LC–MS), Gas Chromatographic–Mass Spectrometry (GC–MS), Nuclear Magnetic Resonance (NMR) and Fourier–Transform Infrared Spectroscopy (FTIR), are typically used to further elucidate the structure of pure phytocompounds. All these techniques are used for the structural identification of bioactive compounds before their testing in the *in vitro*/*in vivo* biological assays (Figure 1) [12].

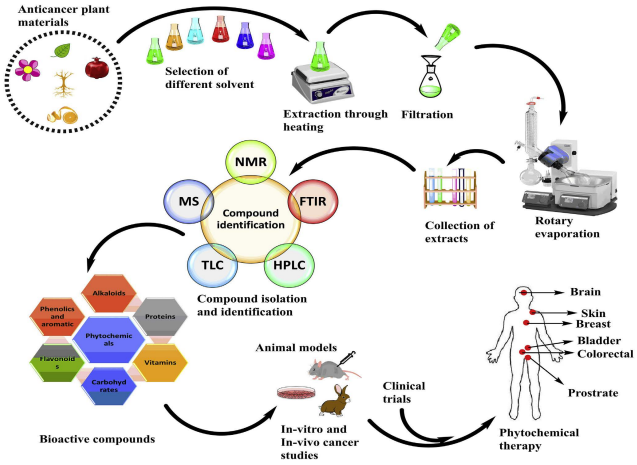

Figure 1. Challenges and future direction for the use of herbal medicine in cancer therapy.

While the use of traditional herbal medicines, phytomedicines, medicinal foods and complementary and alternative medicines has increased in Europe and North America over the past ten years, main stream medical practitioners in western countries do not appear to be interested in or accepting of these practices, especially when it comes to standard care for cancer patients. The main concern of many biomedical professionals has been the absence of evidence-based data or guidelines for the regular and legal use of herbal remedies as "drugs" in public health settings. Six main problems are the main causes of the challenges preventing the use of phytomedicines [13].

Inaccuracy in dependable and reliable sources of genuine medicinal plant materials, concerning species identification and authentication, growing through sound agricultural practice guidelines and technology and procedures for standardizing/normalizing plant extraction/mixture preparation.

Lack of standardization in the identification of metabolite profiles, index compounds, and putative active compounds or metabolites in the biochemical/biological components and compositions of herbal medicines or the phytochemicals/phytocompounds derived from medicinal plants.

General and particular safety concerns, such as acceptable high dosage, lowest effective dosage and particular use [14].

The proof of efficacy in treating or supporting particular cancer patients, such as data from preclinical animal studies lacking results, proper double-blind clinical trial studies with placebo included and statistician assistance.

Highly complex "per-sonalized" prescriptions or formulations for the use of certain traditional medicines (e.g., in Traditional Chinese Medicine) that may be enigmatic due to a "secret ingredient" in particular formulations; and

The illegal technique of "spiking" or supplementing extremely powerful western pharmaceutical medications into traditional treatments. We cannot tackle the challenges of modernizing herbal medicines if we do not address all of the above issues [15].

A variety of omics studies conducted recently have strongly suggested that a multifactorial mode of action and multitarget pharmaceutical activity may already be "standard" for a number of clinical medications now in use. Therefore, as we previously shown in a cancer cell line investigation, there may be considerably less difference than first thought in terms of the complexity of molecular targets targeted by single-compound medications against complex herbal medicine extracts.

Synergistic and/or additive effect of phytomedicines

Chemotherapies are currently the most effective cancer treatments available, despite their serious side effects and inescapable difficulties. Natural products and chemotherapy chemicals together have the potential to maximize treatment efficacy while reducing side effects in a synergistic way. *Ficus carica* plant extract was tested against Rhabdomyosarcoma (RD) cells both with and without therapeutic modalities. The results showed that the phytoextract combined with a therapeutic modality improves the treatment efficacy of RD metastasis. Resveratrol and curcumin are well-known, powerful chemotherapeutic agents that, when combined with clinically proven anticancer medications like doxorubicin, paclitaxel and cisplatin, exhibit a synergistic effect. They also reduce the toxicity associated with chemotherapy by modifying the pathways involved in autophagy and apoptosis. Despite the fact that curcumin by alone was shown to be an effective anticancer medication in the majority of trials, curcumin in combination with arctigenin and epigallocatechin gallate shown a synergistic impact against human prostate cancer and breast cancer, respectively. Another study demonstrated the synergistic effects of phytocompounds anethole anddoxorubicin against triple negative breast cancer cells by enhancing the cytotoxic effect, which was evaluated by various parameters including cell proliferation, cell cycle analysis, DNA damage and apoptosis [16].

Drugs for cancer treatment and their limitations

Many attempts have been made to reduce the negative effects of medications during the course of cancer therapy, including avoiding negative effects on surrounding tissues and cells, boosting drug efficacy and accumulation in the lesion and creating innovative drug delivery and targeting systems. Some methods exist for treating cancer, such as cancer surgery, radiotherapy, immunotherapy, chemotherapy, vaccines against cancer, photodynamic therapy, stem cell transformation or a combination of these frequently with serious side effects. Inadequate bioavailability, toxicity, nonspecificity, quick clearance, and restriction in metastasis are some examples of these negative effects. The type, stage, and location of the cancer determine the treatment strategies. Cytostatic and chemotherapeutic medications, which have demonstrated encouraging outcomes either by themselves or in conjunction with other cancer treatments, are used as chemotherapy agents. These chemotherapeutic agents include alkylating agents such as oxaliplatin, melphalan, carboplatin, isplatin and ciclophosphamide (side effects: Nephrotoxicity, gastrointestinal toxicity, cardiovascular toxicity, pulmonary and hematologic toxicity), microtubules acting agent such as vincristine, vinblastine, docetaxel and paclitaxel, etc.), and topoisomerase inhibitors (e.g. irinotecan (side effects: Neutropenia, sensory neuropathy and diarrhea) and doxorubicin (side effects include cardiotoxicity) and etc.).

The medications listed above have some negatives with their great efficacy in treating a variety of cancers (side effects, expensive, complex, non-ecofriendly and poisonous). The human body contain certain cells that divide quickly when things are normal, such as the cells in our digestive tract, bone marrow and hair follicles. Harmful side effects occur because current anticancer medications also target these quickly dividing normal cells, which is a significant issue. Reduced blood production, GIT inflammation, hair loss, immune suppression, heart disease and neurological disorders can all result from these side effects. Another disadvantage is that as a result of mutations, these cancer cells become resistant to certain medications. For example, when docetaxel was applied, the drug-resistant genes *ABCA4* and *ABCA12* were over expressed in human MCF-7 breast cancer cells, respectively. However, it was shown that the down regulation of drug resistance genes occurred when the phytochemical curcumin was used when combined with docetaxel [17].

Therefore, using a mono-target chemical agent to treat cancer cells is an ineffective approach. Thus, phytochemicals and their derived counterparts represent the most promising choice for a better and less harmful cancer treatment, according to significant research findings. A review of the literature indicates that several anticancer medications are clinically licensed and advised for the treatment of cancer.

Current cancer therapy *via* phytochemicals: A novel approach

Herbal remedies are a gift from nature to support people in the search for improved health. Since ancient times, people have used plants and their bioactive components for therapeutic purposes. Numerous types of medicinal plants and the phytochemicals they contain prevent cancer from developing and proliferating [18].

Different plant products such as alkaloids, flavonoids, lignans, saponins, terpenes, taxanes, vitamins, minerals, glycosides, gums, oils, biomolecules and other primary and secondary metabolites plays an important roles in either inhibiting cancer cell activating proteins, enzymes and signalling pathways. Only around 10% of the approximately 250 000 plant species that make up the plant kingdom have been investigated for use in the treatment of various diseases.

Conclusion

Plant derived anticancer agents offers a sustainable approach due to their natural origin, potential efficacy and reduced environmental impact compared to synthetic counterparts. The current review makes clear that phytochemicals are a useful and exciting field of research with a

right future. Compounds like vincristine, vinblastin from periwinkle and taxol from yew trees have shown promise in cancer treatment, emphasizing the importance of exploring natures resources in combating this complex disease. This thorough study paper offers details on therapeutic plants and the bioactive substances they contain that may be able to combat various cancer types. The incidence of cancer is steadily increasing worldwide and new techniques are being developed to confirm that this life-threatening condition can be treated. People are getting interested gradually to use herbal remedies as fruitful sources for cancer treatments. In the context of plant derived anticancer agents, sustainability may involve ethical sourcing of plant materials, environmentally friendly extraction and the development of cost effective and accessible treatments for a broader population.

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