ISSN 2249-622X

Asian Journal of Biomedical and Pharmaceutical Sciences

Insights on Cancer Preventive Approaches Using Plant Based Extracts

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Abstract

Cancer is one of the fatal diseases, and it continues to pose a significant health problem worldwide. Although great efforts are being done to discover a cure, cancer still remains a very prominent cause of mortality in humans, and its effective treatment is a formidable challenge. Although cancer therapies have been performed throughout the history, the efficacy of the treatment still remains a challenge. In recent years, natural product compounds have become the first choice of treatment in many cases. Gene therapy, in addition, is offering selective new methods for treatment.

This review emphasizes the advancements cancer treatment using naturally derived products with significantly less toxicity and more efficacies; thereby enhancing the understanding of different cancers and potential of the plant based extract in the anti-cancer field.

Accepted on July 02, 2018

Introduction

With an increasing worldwide population coupled with medical intervention and sedentary lifestyles, the mortality has shifted gradually towards non-communicable diseases like cancer and cardiovascular disease. Based upon the WHO statistics, about 12.7 million cancer cases and 7.6 million cancer deaths occurred in 2008, the number of deaths between 2005 and 2015 was reported to be 84 million [1,2]. Cancer can be treated by chemotherapy, surgery, hormonal therapy, targeted therapy (monoclonal antibody therapy) and use of naturally derived products [3,4]. Other experimental cancer treatments are still under development [5]. Significant attention has been gained by the natural product compounds from the scientific community respectively for their potent effects against cancer [6]. A research (including preclinical, clinical, and epidemiological studies), has indicated that the dietary consumption of polyphenol, (in cereals, pulses, vegetables, and fruits), can prevent the evolution of cancer [7,8].

Since ancient times, natural products have been known to prevent several chronic diseases, like cancer. A revived interest in different phytochemicals obtained from dietary/medicinal plant sources has proved to be the alternative sources of bioactive compound that can be used as therapeutic or preventive agents against many diseases [9-11]. The application of substances to prevent or delay the development of carcinogenesis is commonly termed as chemoprevention. There is an interest for the use of natural compounds as a means of possible chemo-preventive and therapeutic agents for humans [12].

Interestingly, Chinese traditional medicine also contain such natural compounds, mainly the extracts (such as obtained from *Polygonum cuspidatum*) [13,14]. As these compounds have shown a high potency in the tumor treatment; these medicines have shown to be accepted by doctors, experts, and patients [15]. The traditional medicines have shown significant effects in the patients with late-stage cancers; which helped the increase the prognosis and diagnosis [16]. Despite of the various conventional methods, the detection of the cancer at an early stage is necessary for inhibiting the tumor progression and metastasis. Biomarkers have shown a great potential in the detection of tumors, which has aided in the improvement of the prognosis and diagnosis of the disease [17]. Chinese traditional medicine majorly plays a significant role in protecting cancer patients who suffer from severe complications, and helping them to live well. In addition, Chinese medicine also assists in a palliative care by reducing the side-effects of conventional treatment or improving patient's quality of life [18]. It is estimated that the National Cancer Institute (NCI) invests around $120 million each year on related research projects [19,20].

Plant Extracts as Anti-Cancer Agents

The traditional method of the cancer therapy involves the plant extracts or their active principles. The use of plant derived natural products is beneficial to act against cancer [21]. The

vinca alkaloids, and the cytotoxic podophyllotoxins isolation was marked by the search for anti-cancer agents from various plant sources [22,23]. Bioavailability of the isolated anti-cancer drugs, has been enhanced by pharmacokinetic models which improve the drug absorption and affinities, by modulating the structural chemistry of the anti-cancer compounds [24].

Plant Derived Anti-Cancer Agents in Clinical Use

Vinca Alkaloids

Vinca alkaloids, namely vinblastine (VLB) and vincristine (VCR), isolated from the *Catharanthus roseus* G. Don. (Apocynaceae) were the first to be in the clinical use [25,26]. These drugs were serendipitously found during an investigational procedure on the oral hypoglycemic agents. These plant extracts has shown to increase the life-span of the mice affected with lymphocytic leukemia [27,28]. Vinorelbine is cell cycle specific and act on mitosis phase [29,30]. The vinblastine has shown effectiveness on the leukemias, lymphomas, testicular cancer, lung cancer, breast cancers and sarcoma, whereas, vincristine on the acute lymphocytic leukemia. [31-33]. However, adverse effects of vincristine drug such as myelosuppression, abdominal pain, alopecia, autonomic dysfunction, paralytic ileus, urinary retention, seizures and prominent bone marrow depression, less neurotoxicity of vinblastine are observed [34,35].

Podophyllotoxin Derivatives

Podophyllum peltatum Linn., P. *emodii Wallich* (Podophyllaceae family) have been reported to treat skin cancers and warts [36]. The dried root extracts from these plants has shown to cure the venereal warts [37]. Other podophyllotoxins such as lignans were also used in the clinical trials, but it has shown low efficacy and high toxicity.

Taxanes

A recent development of plant-derived agents is the development of taxanes [38]. Paclitaxel is one of the taxanes and is also named as taxol [39]; isolated from the bark of *Taxus brevifolia* Nutt. (Taxaceae). Paclitaxel from various Taxus species, and the semisynthetic conversion of baccatins to paclitaxel, its analogs, has provided a major source of this class of drugs [40]. Paclitaxel has shown effectiveness in the treatment of breast, ovarian and non-small-cell lung cancer, and has also shown low efficacy against Kaposi sarcoma [41,42]. Paclitaxel exhibits reversible myelosuppression (granulocytopenia), anthralgia, myalgia and edema [43]. Docetaxel, which is a paclitaxel analog and a semisynthetic derivative, primarily used in the ovarian and breast cancer, small cell cancer, lung, pancreatic, gastric, head/neck carcinoma [44]. Adverse drug reactions are also associated with this drug like neutropenia, neuropathy, arrhythmias, fall in BP, fluid retention.

Campothecin derivatives

Another advancement made in the anti-cancer agents was campothecin derivatives, isolated from *Camptotheca acuminata* Decne (Nyssaceae). The *C. acuminate* extract has shown an effective anti-tumor activity. Extensive investigations are still in pursuit in search of more effective camptothecin derivative. Certain compounds such as Topotecan- developed by SmithKline Beecham (now known as Glaxo SmithKline) and Irinotecan- developed by Yakult Honsha (Japanese company); are now in therapeutic use [45,46]. Topotecan has shown effectiveness and it is extensively used for the small-cell lung cancers, while Irinotecan for the colorectal cancer treatments. Of the NCI-enlisted clinical trials (2069) on cancer, approximately 4.5% are listed as camptothecin-derived drugs, including 26 with topotecan, 64 with irinotecan (CPT-11). In addition to these investigations, about 15 other camptothecin derivatives are still in preclinical development [47].

Homoharringtonine

Homoharringtonine is another plant-derived extract that are in clinical development [48]; isolated from the *Cephalotaxus harringtonia* var. drupacea (Cephalotaxaceae) [49]. Elliptinium is another plant derivative isolated from the Apocynaceae species, has shown promising results on the breast cancer treatmant. In China, the acute and chronic myelogenous leukemias were been treated successfully by the mixture of harringtonine and homoharringtonine (HHT) [50,51].

Investigational Studies on Cancer

Cancers can be grouped based upon the origin. For example, lung cancer arises from the lung, and brain cancer starts in cells of the brain.

Lung cancer

Globally, the lung cancer is one of the primary causes of death. In an effort towards improvement of treatment using drug delivery, a redox-sensitive nanocarrier system was developed which has shown potential for targeted delivery and localized release of the paclitaxel. [52]. The PTX-loaded redox-sensitive nanoparticles has shown greater *in vitro* cytotoxicity and apoptosis-inducing ability against CD44 over-expressed A549 tumor cells in comparison to the redox-insensitive nanoparticles [53]. In an *in-vivo* study, the PTX-loaded HSV nanoparticles exhibited an enhanced antitumor efficacy in a A549 mouse xenograft model [54].

In another research study, the development of new medicinal parts of ginseng and the search for new alternatives have been done. The production of ginseng is increasing gradually with growing awareness of health care and the continuous improvement of people's living standards. Ginseng constituents- ginsenosides Rb2 and Rg3 can inhibit the angiogenesis, thereby inhibiting tumor growth and metastasis. It enhances immune activity and it is now used in the treatment of lung cancer [55].

Currently, lung cancer is treated mostly by combined radiotherapy and chemotherapy. However, these therapies have large toxic side effects, where patients can hardly adhere to the treatment. Therefore, a research study was conducted to explore the effects of *Stephania kwangsiensis* root tubers on the proliferation and apoptosis of the NCI-H446 cells- a lung adenocarcinoma model. The results demonstrated that corydine has marked cytostatic and proapoptotic effects on human small cell lung cancer [56,57].

Crizotinib- an anti-cancer drug has been used for the treatment of non-small cell lung cancer (NSCLC). There are many evidences suggesting that there is development of resistance against crizotinib action, developing necessity to develop potent anti-cancer drugs for the treatment of crizotinib resistance. A traditional plant source have a potential to inhibit (EML4)-ALK fusion protein which is responsible for lung cancer. ALK inhibitor is certainly helpful to overcome the drug resistance in NSCLC [58]

Colon cancer

To investigate the efficacy of an ethanolic Extract of gamboge (EEG), a TCM, a study was conducted, both *in vitro* on colon cancer cells and *in vivo* in an orthotopic mouse model of human colon cancer. This study demonstrates anti-tumor efficacy of EEG on colon cancer through inducing proliferation, inhibition and apoptosis of SW480 colon cancer cells and tumor growth inhibition, respectively. EEG exerts anti-tumor activity at least partly via down-regulation of the Wnt/β-catenin signaling pathway [59,60]. Another TCM, Hu Zhang (driedroots and rhizomes of *Polygonum cuspidatum* Sieb.et Zuc) was identified as an anti-cancer substance. It contains anthraquinones and stilbenes. The extract of *Polygonum cuspidatum* enriched and purified with resin has shown inhibitory effect on human colon cancer SW480 cells in different concentrations. This drug has potential action against colorectal cancer [61].

Pancreatic cancer

In most of the cancers including pancreatic cancer, the cancer progression is largely ascribed to a phenomenon known as epithelial-mesenchymal transition (EMT). Toosendanin (TSN), an active component in TCM, has shown an enhanced attenuation towards the progression of pancreatic cancer [62-64]. In a dose-dependent manner TSN suppresses the viability and growth of pancreatic cancer cells in a dose-dependent manner. The migration and invasion of pancreatic cancer cells were also consistently inhibited dose-dependently. TSN can reverse the TGF-β induced EMT and morphological change in pancreatic cancer cells by increasing E-cadherin expression while reducing Vimentin, ZEB1 and SNAIL levels [65]. Furthermore, TSN evidently repressed xenograft tumor growth in mouse pancreatic cancer models without significant toxic side effects. Mechanistic studies suggested that TSN mediated pancreatic cancer inhibition by blocking Akt/mTOR signaling pathway. TSN inhibits pancreatic cancer progression via downregulating Akt/mTOR signaling [66]. Since TSN inhibits pancreatic cancer progression at a very low concentration ot can be used as a potential pharmacological agent especially in treatment of pancreatic cancer.

Breast cancer

Among women, breast cancer is the most common cancer. Based on the statistics, this is the second-most leading cause of cancer mortality [67]. With improving awareness and screening techniques, the mortality rate of the breast cancer has been declined. The risks pertaining to the breast cancer is preventable. Of course, one cannot control every variable that may influence the risk. The primary risk factors are the age and gender. family history, a breast cancer gene mutation, breast changes and conditions, race/ethnicity, hormones, weight, alcohol consumption, radiation exposure, pregnancy history, DES exposure. The treatment depends on the stage of cancer which may consist of chemotherapy, radiation, hormone therapy and surgery [68].

Certain studies have demonstrated that the *Sophora alopecuroides* L. has a variety of pharmacological actions and inhibitory effect on the proliferation of the breast cancer MCF-7 cell lines, and thereby can induce the apoptosis [69].

Prostate cancer

Prostate cancer is also considered as one of the detrimental cancer among men. Several investigations is underway into other techniques such as gene therapy and monoclonal antibodies to treat and eliminate cancer cells. Due to these improvements in the techniques, fewer non-cancerous cells are harmed, thereby reducing the risk of harmful side effects. Chinese herbs and specifically the secondary metabolites found in them look to be effective at destroying cancer cells [70,71].

Melanoma

Melanoma, a malignant tumor that originates from the melanocytes. The primary source of the melanomas are the pigment-producing melanocytes. Although, its incidence is growing rapidly at an annual rate of 3-5%, its incidence remains low in china, with approx. 20,000 new cases reported per year [72]. *Polygonum cuspidatum* as discussed above also acts against on melanoma A375 cells. Resveratrol from the Polygonu cuspidatum has shown in the inhibition of the proliferation of human melanoma A375 cells [73,74].

Leukemia

Leukemia is mostly diagnosed in children accounting for greater than 30% of all childhood cancers and it originates in the bone marrow. The subtype of leukemia, Acute Lymphoblastic Leukemia (ALL) is the most prevalent cancer in childhood and also the first leading cause of death from cancer within 20 years of age. It is observed that TCM has more utilization in pediatric leukemia patients rather than adults. As children cannot tolerate extreme uncomfortable symptoms associated with chemotherapy. Many studies have shown that TCM alleviates adverse effects of western medicine

and improves prognosis in the cancer patients [75]. Certain investigations have been performed for development of a method for determining tubeimoside I content in the *Bolbostemma paniculatum*. It has shown that its bulb has an anti-proliferative effect on human erythroleukemia K562 cells, providing conclusive evidence in the inhibition of the cell differentiation [76].

Sarcoma Cancer

In adults, the osteosarcoma is one of the most common bone cancers, which is primarily treated by surgery and chemotherapy (Cisplatin). The application of the cisplatin has been restricted clinically, due to its systemic side-effects and drug resistance. As an effective substituent, the active substances present in *Taxus Cuspidata* (Family- Taxiceae), also known as Zishan, was discovered to possess an anti-osteosarcoma acivity. Taxus species are further classified into subspecies, *T. cuspidata* Sieb. et Zucc. and *T. cuspidata* Sieb. et. Zucc. var. nana Rehder. Certain preliminary studies have shown that *T. cuspidate* has relatively higher paclitaxel content compared to other species of the Taxane family. Since 1922, research on Taxus plants has been increasing and a variety of other compounds have been isolated from *T. cuspidate* like, flavonoids, glycoside, taxane diterpenoids, steroids, sesquiterpenoids, lignans. Paclitaxel acts by inhibiting the cell division and proliferation. It has significant effects on other cancers such as nasopharyngeal cancer, esophageal cancer, lymphoma, bladder cancer, prostate cancer, malignant melanoma, gastrointestinal cancer [77]. Certain flavonoids such as morin have shown a therapeutic effectiveness on the eradication of spectrum of diseases including cancer. Studies have corroborated the efficacy of morin on disease pathologies [78].

Bladder cancer

Bladder cancer is considered to be the fourth common cancer in men and the eighth most in women. There are three types of bladder cancer namely, Urothelial carcinoma which accounts for about 90% of all bladder cancer and seriously threat the survival of patients. Secondly, squamous cell carcinoma which accounts for 4% of all bladder cancers. Adenocarcinoma is the third type of bladder cancer and accounts for least percentage of cancer that is only 2%. Studies have shown a apoptotic phenomenon by the resveratrol on human bladder cancer T24 cells. MTT assay results show that the test concentrations of resveratrol can effectively inhibit the proliferation of T24 cells and has a certain anti-cancer activity [79].

Liver Cancer

Pharmacological studies have shown that allicin, a sulfur compound; in the bulb extract of Liliaceae plant garlic- has varying degrees of inhibitory effects on diverse cancers such as stomach, colon, liver and lung cancers while basically having no toxic side effects. One study investigated the anti-proliferative effect of allicin on human hepatoma HepG2 cells using MTT assay. Within the experimental dose range, ethanol extract of Radix Astragali (Chinese herbal medicine) also has a proliferation inhibitory effect on HepG2 cells. In experimental settings, Radix Astragali showed an anti-inflammatory effect using RAW 264.7 cell lines and anticancer effects on A549 cells and these were influenced by extraction methods used for determining content of Radix. An absolute ethanol extract of Radix showed the highest anti-inflammatory and anticancer effects [80]. More potent anti-inflammatory activity was driven by the ethanol extract of Cimicifugae rhizome towards human cancer cell.

Gastric Cancer

Combined with chemotherapy and radiotherapy, TCM can achieve efficacy enhancing effects, not only by inhibiting tumors, but also improving immunity [81]. One such benefiting medicine known as *Astragalus membranaceus*, the dried root of leguminous plant *Astragalus membranaceus* in different concentrations of astragalosides have marked anti-proliferative effects on gastric cancer SGC-7901 cells, which strengthen with increasing dose and medication time, showing dose- and time-dependence [82]. Other naturally occurring medicine like Banxia which is obtained from the tuber of *Pinellia ternate*, was recorded to have similar pharmacological actions as astragalosides. With the cutting-edge discovery of the CRISPR/Cas 9 gene editing system, the diagnosis and treatment of the cancer has been improved [83].

Conclusion

This review has tried to summarize the research studies done in the discovery of naturally derived medicines and their effective utilization in the treatment of different types of cancer. This also provides information about herbs and natural products that potentially decrease the growth of cancer. In addition to chemotherapy, and all other therapies, new therapies are now at different stages of development to decrease drug toxicity in humans and increase efficacy by directly targeting the tumor. More studies are required but these new ways of treatment are opening doors to hope for many patients waiting for a successful therapy for cancer disease. Healthcare and clinical professionals can play clinical roles as knowledge resources for masses, by generating awareness on usage of herbs. Natural drugs also serve as a chemical model for the design, synthesis, and semisynthesis of novel substances, such as paclitaxel (Taxol), vincristine (Oncovin) and camptothecin, in the treatment of human cancer. Taken together, the anti-cancer compounds derived from the extracts has proven to be effective in the prognosis and diagnosis of the cancer and its recurrence.

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