

Elucidation of Anticancerous Potential of Plant Extracts Against Cervical Cancer



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Abstract

Cancer has been a public health problem that has gained a lot of death. However, in spite of the advances in the diagnosis and treatment of cervical cancer, women follow the struggle versus this disease. Also, those patients suffer from limited efficacy and specificity, undesirable effects, drug resistance, and a high cost of treatments. Early detection and affordable drugs that have clinical efficacy have to go simultaneously in order to seriously address this health challenge. Plant-based drugs with potent anticancer effects should add to the efforts because it will find a cheap drug with limited clinical side effects. So, keeping this in mind, an attempt has been made to explore the potential of plant extracts or constituents known to exhibit anticancerous activity or exert cytotoxic effect in human cervical cells. Alkaloids such as those isolated from *C. vincetoxicum* and *T. tanakae* naurorals A and B, isolated from the roots of *N. orientalis*, (6aR)-normecambroline isolated from the bark of *N. dealbata* can be promising in different human cervical carcinoma cells with the IC₅₀ of 4.0-8µg/mL. However, other compounds such as rhinacanthone and neolignans isolated from different plants are not far behind and kill cervical cancer cells at a very low concentration. Among plant extracts that enhance the effect of known anticancer drugs aloe vera perhaps is the best one. The cytotoxic capability and apoptotic index of certain plant extracts were found to be significant in further enhancing the combination of different human cervical carcinoma cells and therefore they are considered as a promising herbal-based anticancer agent. However, further research needs to be further investigated in various cervical cell lines and most importantly, in *in vivo* cervical culture for possible use as an alternative and safe anticancer drug.

Keywords: Cancer; Carcinoma cells; IC₅₀; Alkaloids; *N. dealbata*; *N. orientalis*; Rhinacanthone; Neolignans

Introduction

A human adult consists of about 10¹⁵ cells; which divide and differentiate in order to refurbish organs and tissues [1]. However, if the cells do not stop dividing, they may lead to cancer. Characteristically, cancer is an uncontrolled proliferation of cells which become structurally abnormal and possess the ability to detach them from a tumor and establish a new tumor at a remote site [2]. Every year over 200,000 people are diagnosed with cancer in the United Kingdom only, and approximately 120,000 die as a result of this disease [2]. According to the International Agency for Research on Cancer, in 2002, cancer killed more than 6.7 million people around the world and another 10.9 million new cases were diagnosed [3]. According to World Health Organization, cancer is the second cause of death globally after cardiovascular diseases. An estimated 8.2 million people die from cancer each year, that represents 13% of all deaths worldwide. Cancer basically results from the uncontrolled rapid division of malignant cells that grow beyond their usual limits. Unlike normal cells, cancerous cells do not respond to the controlling signals and consequently, they grow and divide in an uncontrolled manner, infecting normal tissues and organs.

There can be many different types of cancers. The type of the cell from where the tumors originate classifies the cancers. Cancers derived from epithelial cells of breast, prostate, lung, pancreas and colon, cause approximately 90% of all human deaths from cancer; lymphomas are cancers of the immune organs such as spleen, white blood cells and lymph glands; leukemias causes the cancers of blood forming bone marrow; while sarcomas are cancers of fibrous connective tissues of bone, cartilage, fat tissue, muscle and neurons; and germ cell tumors are derived from pluripotent stem cells presented in the testicles and ovary. Early detection and effective treatment can help to increase survival rates of cancer patients. So therefore, deliberative plans are needed to improve prevention and treatment of cancer. As we all know cancer rates continue to rise, particularly in the developed world, becoming one of the leading public health problems in many countries [4]. Many of the cancers are associated with longevity, and the possibility of their appearance increases as the life expectancy of individuals increases [5]. Cervical cancer (CC) is a principal cause of death in women in the whole world [6-8]. The research done up to date indicated that this cancer

contributed with approximately 500,000 new cases and produced about 300,000 deaths in 2015. In general, the susceptibility to the pathogens as human papillomaviruses (HPV), lifestyle and cultural factors and inadequate medical system contribute to the development of cervical cancer [9]. Current information suggested that almost 100 serotypes of HPV exist. But, out of these two, 16 and 18 serotypes are important ones and related to the development of cervical cancer. Cervical cancer could produce free radicals that induce damage to the cells, tissues and organs [10]. However, the proper functioning of cells depends on the mitochondria's ability to regulate metabolic processes and produce molecules, including free radicals as reactive oxygen species (ROS) [11]. ROS controls both physiological as well as pathological process related to cell proliferation, invasion cell, and drug resistance. Several studies have also shown that the cancer risk at the point of specific organs is due to exposure to specific environmental chemicals, biological agents (as Human Papilloma virus, Epstein Barr Virus, HIV1, HCV, *Helicobacter pylori*) or physical agents (such as ionizing radiation, UV). Chemotherapy and radiotherapy, the conventional cancer treatments used nowadays, are expensive and cause many side effects, including such minor ones like vomiting, diarrhea, constipation, and major ones such as myelosuppression, neurological, cardiac, pulmonary and renal toxicity. All these side effects reduce the quality of life and discourage the patients to follow the medication protocols that further leads to the progression of cancer and future complications. Resection surgery procedures are a major concern because of functional deficiencies or esthetic discomfort. Therefore, there is a need

to produce alternative anticancer drugs, which can be more potent and effective, as well as more selective and less toxic than those of currently in use. In spite of the advances in the diagnosis and treatment of cervical cancer, women follow the struggle related to this disease. Also, the patients suffering from cervical cancer have limited scope and specificity, undesirable effects, drug resistance, and a very high cost of treatments. So therefore, demand of plants and its extracted compounds was increased rapidly. Currently, several studies have demonstrated the efficiency of plant extracts, against cervical cancer cell lines. Certain plant extracts have both antioxidant and pro-oxidant properties. They show high specificity because generally they act as an anti-oxidant and pro-oxidant. Approximately 60% of drugs currently used for cancer treatment have been isolated from natural products and the plant kingdom has been the most significant source. These include *Vinca* alkaloids, Taxus, diterpenes, *Camptotheca* alkaloids, Saffron, *Bonellia albeflora* etc. The pro-oxidant activity is the major reason for obstructing the growth factors related to different signaling pathways that initiates cancer. Although, usually these kind of plant extracts helps for dispatching the apoptosis in cervical cancer cell. Apoptosis describes the programmed cell death. The initial screenings for plants used for cancer treatment are cell-based assays using prepared cell lines, in which the toxic effects of plant extracts or isolated compounds can be measured. According to the National Cancer Institute (NCI), plant extracts and pure compounds with cytotoxic ED₅₀ (Effective Dose 50) values between 4g/l to 30g/l, are generally considered as active (Table 1).

Table 1: Some common plant extracts and their mechanism of action.

Plant extract	Botanical name	Mechanism of action
Ashwagandha (Roots)	<i>Withania somnifera</i>	Proliferation of abnormal cells with high capacity for replication and invasion
Aloe vera (leaves)	<i>Aloe barbadensis miller</i>	It inhibits the proliferation of cervical cancer cells and involved in apoptosis and cell cycle regulation
Blueberries	<i>Cyanococcus</i>	Blueberries generally contains flavonoids that may have antioxidant, anti inflammatory properties
Cinnamon	<i>Cinnamomum verum</i>	Cinnamon extract induces apoptosis in the cervical cancer lines through increase in intracellular calcium signaling and mitochondrial membrane potential
Green tea extract	<i>Camellia sinensis</i>	Green tea contains polyphenols which can have antioxidant activities
Saffron	<i>Crocus sativus</i>	These generally interact with topoisomerase enzymes & disrupts DNA replication which results in apoptosis and cell death
Solanum extract	<i>Solanum nigrum</i>	Immunomodulating effects, including radical scavenging and antimutagenic properties

Since time immemorial, plants have always been a very good source of drugs and many beneficial uses of medicinal plants are extensively mentioned in the traditional system of medicine of many cultures. Traditional medicines from plants offer great potential for the discovery of novel anti-cervical cancer drugs. There are several sources of anti-cervical cancer drugs: plants, vegetables, herbs and spices used in folk medicine. The combined synergistic effect of the individual active components of these extracts and their molecular mechanisms involved need further investigation in order to evaluate the potential of these compounds as anticancer agents. The protective effects of plant

extracts have been related to the presence of phytochemicals, bioactive non-nutrient plant compounds which commonly have complementary and overlapping mechanisms of action, including free radical scavenging, anti-mutagenesis, induction of apoptosis in cancer cell lines.

Suggested Mechanism of Action

Disruption of cellular homeostasis between cell death and cell proliferation can cause cancer. In general, plant extracts cause cellular toxicity in cervical cancer cells and result in cell death by two primary pathways i.e. cell cycle arrest and

apoptosis. Inhibition of cell growth and induction of cell death are two major methods of antitumor growth [12]. Cell cycle progression and apoptosis are two important signaling mechanisms of homeostasis maintenance in healthy tissues and normal cells. The general mechanisms involved include: arrest of cell cycle in G1 phase and induction of apoptosis via the caspase-dependent intrinsic pathway.

Cell cycle arrest

Many anticancerous and DNA-damaging agents arrest the cell cycle at G0/G1, S or G2/M phase and then induce cell apoptosis. Most of the human solid tumors is genetically unstable and have defects in the cell-cycle checkpoint control mechanism. Such tumors frequently contain mutations that disrupt the G1 components of the cell cycle, which affects the abilities of chemotherapeutic drugs to inhibit cell proliferation and induce apoptosis [12]. Since cancer cells usually undergo active cell division (mitosis), a useful approach to finding anticancer drugs is to test whether a compound can selectively kill mitotic cells [13]. Therefore, cell cycle arrest is the special target for many anticancer drugs. Among them, taxols, colchicines and vinca alkaloids are the well-known examples that induce the G2/M phase arrest leading to the subsequent apoptosis [14].

Apoptosis

Apoptosis (programmed cell death) plays a crucial role in the homeostasis of organisms under both physiological and pathological conditions. Apoptosis is the most convenient manner of tumor cell elimination, as this type of cell death is a final state which does not cause any possible future danger [15]. The two major pathways leading to apoptosis in cells includes: a) extrinsic pathway which involves the activation of the TNF/Fas death receptor family and the second one b) intrinsic pathway which involves mitochondria [16]. Generally, apoptotic cells are characterized by the reduction of mitochondrial transmembrane potential, intracellular acidification, excessive production of reactive oxygen species (ROS), and externalization of phosphatidylserine residues in membrane bilayers and selective proteolysis of specific proteins and also further degradation of DNA into inter nucleosomal fragments. TRAIL (TNF related apoptosis inducing ligand) is a promising tool for cancer therapeutics due to its ability to selectively induce apoptosis in malignant tumor cells because it causes no toxicity against normal tissue. D fragmentation or degradation is considered as the hallmark of apoptosis. Agents that suppress the proliferation of malignant cells by inducing apoptosis may represent a useful mechanistic approach to both cancer chemoprevention and chemotherapy [17]. Therefore, induction of apoptosis in cancer cells is one of the useful strategies for the development of anticancer drugs [18-28].

Conclusion

Although various types of synthetic drugs are being added to this new world of health care, but still no system of medicine in the

world is there that can solve all the health problems. Therefore, the search for new therapeutic compounds from plants is genuine and urgent. Many plant-derived and natural products are being tested for their anti-cancerous activities. The mortality rate due to different types of cancer has been increasing in spite of several treatment strategies for cancer. Plant-derived molecules or drugs could be an effective alternative for the treatment of different types of cancer. This review is just an attempt to understand different types of plants and their different extracts which can be used for the cancer treatment, especially for cervical cancer. As a result of new approaches, the concept of achieving ideal health is changing, and mainly focuses on the importance of a healthy lifestyle highlighting on diet and exercise. Diet as we all know plays a crucial role in the regulation of metabolic pathways both genetically and epigenetically. By the help of modern genetics, and molecular biology, nutrition research will increasingly be able to apply new discoveries to develop designer functional foods by adding specific bioactive properties for preventing and reducing the risk of cancer development. Herbal medicines have been used since ancient times. They are usually a mixture of several compounds, which can affect cells. The information and knowledge collected so far in several civilizations needs to be utilized for the betterment of health issues. Another important problem of the treatment of cervical cancer is the resistance to chemotherapy and radiotherapy. The review focused that several bioactive polyphenols are able to sensitize cervical cancer cells to conventional chemo and radiation therapy. Therefore, this combined approach could improve the efficiency of standard therapies and allow us to decrease the heavy doses of chemotherapy drugs and irradiation leading to reduce the adverse side effects. We summarized in this article some of the polyphenolic compounds that have been studied until now for their possible anti-cancer therapeutic properties. It is crucial to continue these studies for searching therapeutic drugs from natural resource as well as for investigating their mechanism of action in cervical tumor cells.

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