A REVIEW ON USE OF NATURAL PRODUCTS IN ANTINEOPLASTIC AGENT

Manika Pandey

Abstract

Now a days Natural products are considered more safe in comparison to the synthetic product that are regarded as unsafe to human life and environment. Although a large number of synthetic drugs are being added to the world of present pharmacopoeia, but still no system of medicine in the world has been able to solve all the health problems, which include diseases like Cancer. Compounds that are derived from plants have played an important role in the development of several useful anti-cancer agents. These include vinblastine, vincristine, the camptothecin derivatives, topotecan and irinotecan, etoposide, derived from epipodophyllotoxin, and paclitaxel (taxol). Several promosing new agents are in selective clinical development based on selective activity against cancer related molecular targets, including flavopiridol and combretastin A4 phosphate, and some agents which failed in earlier clinical studies are stimulating renewed interest. Therefore the search for innovative therapeutic constituents from plants is genuine and urgent. In India, besides having the knowledge about medicinal plants and rich medicinal flora, still only a few pearls have been searched as therapeutic agents.

Introduction:

Noncommunicable diseases (NCDs) refer to diseases that are not transmitted directly from one individual to another, and account for more than 70% of all deaths worldwide (41 million deaths per year). Cancer is the second leading cause of death among NCDs, after cardiovascular disease . The incidence and mortality of cancer are rapidly increasing throughout the world due to an increase in the aging population. The reasons are complex, including environmental pollution, chemical toxins pollution, ionizing radiation, free radical toxin, microorganisms (bacteria, fungi, viruses, etc.) and their metabolic toxins, genetic characteristics, endocrine imbalance, and immune dysfunction, etc. Global Cancer Observatory (GLOBOCAN) estimates that 19 million new cancer cases will be reported and 10 million deaths will be caused by this disease in 2020. Cancers in both sexes are most commonly diagnosed in the breast, lung, colon, prostate, and stomach (excluding non-melanoma skin cancer). It is estimated that by 2040, the incidence of cancer in the world population will increase to 30.2 million cases and the mortality rate will increase to 16.3 million cases, respectively .

2. Natural Products (NPs) against Cancer

Natural medicine refers to substances that are produced naturally by living organisms, such as plants, insects, animals, aquatic organisms, and microbes, and possess pharmacological or biological properties . Natural products are precious gifts from nature that can be used for the prevention and treatment of illnesses in humans. Therefore, they are of vital importance and play an irreplaceable role in the development and design of drugs. Since ancient times, natural products have been used to treat human diseases. Recent research indicates that natural products still have the potential to be applied in drug development. It has been revealed that 32% of all small-molecule drugs approved between January 1981 and September 2019 were natural products and their derivatives . Moreover, from 1981 to 2014, 51% of all the new small molecule drugs approved worldwide were compounds derived from natural products . In addition, a report published in 2016, revealed that the US Food and Drug Administration (FDA) approved 547 natural products and their derivatives for use as medications across the years (1827 to 2013) . They are used to treat a number of diseases, primarily cancer, bacterial infections, and hypertension. The same study found that 68% of all 136 small-molecule anticancer drugs available from 1940 to 2014 were natural products based.

3. Natural Products against Some Common Types of Cancer

Lung Cancer:

Lung cancer is highly occurring and a standout amongst the most widely recognized human malignancies in both developed and developing nations, with 2.1 million new lung cancer cases and 1.8 million deaths anticipated in 2018, nearly one of every five (18.4%) malignancy deaths . Even though various treatment alternatives are available, including surgery, radiotherapy, chemotherapy, and targeted therapy, half of all newly diagnosed cancers are now at an advanced stage, where the effects of treatment are constrained. Treatment in such cases might be restricted to palliative care, leading to a low 5-year survival rate. Lung cancer comprises a couple of subtypes; for example, adenoma-carcinoma (AdCa), the most widely recognized subtype in non-smokers and females; squamous cell carcinoma (SqCC), and small cell lung cancer (SCLC). A few instances of current treatment for malignant lung growth incorporate medical procedures, chemotherapy, and radiotherapy, whereby the choice of treatment relies upon the subtype and stage of lung cancer. Nevertheless, there is a dire need to find other alternative chemotherapeutic agents, either fabricated as a more effective drug or in combination with the current therapeutic agents to have a more prominent and synergistic anticancer activity. Recently, It has been reported to produce antitumoral effects in lung cancer (A549) cells by inducing cell cycle arrest at G0/G1 phase, inducing p53 activation, and also increasing the activity of the Fas/Fas-ligand system . Similarly, It has been reported that cytisine, a natural alkaloid, produces significant cytotoxic effects against lung cancer A549, NCI-H23, and NCI-H460 cells and in vivo (rat model) by inducing apoptosis via an increase in ROS and loss of membrane potential; increasing BAD, cleaving PARP, and cleaving caspase-3 expressions; and decreasing Bcl-2, pro-PARP, and pro-caspase-3. Moreover, phosphorylation of p38, JNK, and I-kB was increased, while there was a significant decrease in the phosphorylation of ERK, NF-kβ, and STAT3. Furthermore, cytisine arrested the cell cycle at the G2/M phase, which was related to the inhibition of the Akt signaling pathway.

Breast Cancer:

In 2018, there were about 2.1 million newly diagnosed female breast malignant growth cases around the world, representing nearly one of every four tumor cases among women. Breast cancer is the most widely diagnosed cancer by far in most nations (154 of 185) and is also the primary source of cancer-related deaths in more than 100 nations. For malignant breast tumor treatment, numerous alternatives are provided, for example, medical procedures, hormonal treatment, radiation treatment, chemotherapy, and targeted treatment . However, there are also certain limitations (i.e., narrow therapeutic index with non-specific toxic consequences for healthy tissues, increasing chance of infection, etc.), and also the severe side effects persist for months or years, even after treatment completion. Therefore, further studies are required to explicate the underlying fundamental mechanisms of breast cancer to develop new therapeutic strategies. Breast cancer is the collection of abnormal cells, presumably credited to the imbalanced proliferation of cells, apoptosis, and the cluttered autophagy regulation. Various natural products were accounted for as possible anti-cancer agents or thought of as immediate or indirect sources of new chemotherapeutic adjuvants to upgrade the efficacy or enhance the symptoms through autophagy regulation . Higenamine has been demonstrated to increase the anticancer activity (apoptosis and G2/M cell cycle arrest) of cucurbitacin B in breast cancer (T47D and SkBr3) cells by inhibiting Akt and CDK2 .

Ovarian Cancer:

Ovarian cancer is one of the leading causes of death associated with the female reproductive system in the Western world. Ovarian cancer is a standout amongst the most deadly gynecological diseases in the female reproductive system, influencing approximately one out of 75 women in the United States. Even though the first-line treatment may profit about 80% of patients with ovarian malignancy, 75% of those patients still experience tumor recurrence, which causes a major worry surrounding the treatment of ovarian cancer in patients. Cisplatin is the most generally utilized chemotherapeutic entity for treating ovarian cancer. Treatment dereliction and death in over 90% of patients with metastatic malady are believed to be brought about by drug resistance. Adverse reactions and resistance developed to platinum-based chemotherapy have turned into an obstacle for ovarian cancer treatment. Therefore, it is important to search for new compounds to treat cancer and reduce the associated side effects of the treatments.

Miscellaneous Cancer: Many different types of cancers have been affecting and threatening the lives of people, which include skin, stomach, oral cavity, rectum, gastric, gallbladder, pancreas, cervix uteri, penis, kidney, bladder, thyroid, Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia, and osteosarcoma . The interest in using natural products to treat cancer has been rising due to the better efficacy, low toxicity, and lower cost. Recently, . In another study, oxolane derivatives from *Morus alba*, such as odisolane, have been proven to inhibit angiogenesis by reducing VEGF, p-ERK effectively, and p-Akt expressions, and can be employed to stop neovascularization in tumors . Recently, hispiloscine and hispidacine alkaloids isolated from *Ficus hispida linn* showed excellent cytotoxic activity against various cell lines such as breast, lung, and colon,

and also demonstrated vasorelaxant activity in rats . Recently, Kim et al. demonstrated that bakuchiol inhibited the viability and EGF-induced neoplastic transformation of skin epithelial carcinoma A431 cell line in vitro and in vivo studies through the inhibition of Blk, Hck, p38MAPK, and Akt/p70S6k pathways . Similarly, cryptolepine inhibited non-melanoma skin cancer proliferation by damaging DNA, S- phase cell cycle arrest, and decreasing membrane potential . Curcubitacin B suppressed the invasion and proliferation of gastric cancer cells through STAT3 inhibition, which also induced apoptosis and furthermore in combination with cisplatin produced increased cytotoxic effects, which indicate that curcibitacin B is a promising STAT3 inhibitor . Phycocyanin is another promising molecule isolated from seaweed, and it exerts its effects by arresting the cell cycle at the G2/M phase in MDA-MB-231, HT29, and A549 cells by decreasing cyclin E and CDk2 expressions and upregulating p21. Furthermore, it activates the mitochondrial apoptotic pathway while inhibiting the proliferative pathways such as PI3K/Akt/mTOR, MAPK, and Nf-kβ pathway .

Plant Derived Anti-Cancer drugs:-

1.Vinca alkaloids

2.Podophylotoxin derivatives

3.Alliium Sativum

4.Andrographis Paniculata

5.Apis mellifera

6.Bidens pilosa

7.Cannabis sativa

8.Zingiber offcinale

9.Terminalia chebula

10.Daphne mazereum

Novel Formulations of Natural Products for Chemotherapy

The major concern of traditional therapies is their poor accessibility to the tumor site; therefore, higher doses are required to achieve a desired pharmacological response, which causes adverse drug reactions. The advancement of innovative nanotechnologies in medicines can significantly improve the treatment at clinical settings by overcoming the existing limitations associated with the diagnosis and treatment of various fatal diseases. Despite a wide range of antitumor effects exhibited by natural compounds in vitro preclinical studies, various hurdles still exist in translating these promising results into in vivo or clinical trials, resulting in failure and expectations. Despite remarkable health benefits, natural products' full clinical potential has not yet been unlocked due to low aqueous solubility, poor absorption, and lower bioavailability, and shorter retention time in the biological environment. After administration, natural agents need to interact with various physico-chemical barriers that can alter their structure and affect their antitumoral activity. Therefore, novel formulation strategies are adopted to prevent the degradation of the natural compound and their parent structure, which helps retain their chemopreventive and chemotherapeutic activities .

Conclusion:

In summary, the development of cancer is a complex process that is influenced by many factors. The present review highlights the importance of natural molecules in cancer management, since natural products provide inexhaustible sources of compounds with unique structures and new mechanisms of action. Moreover, natural compounds, either used alone or in combination, can be beneficial in the treatment and prevention of cancer. However, further studies are needed to describe the effect of natural compounds on cancer progression. In addition, it is evident that there is still much to be explored based on the natural diversity of the world, and because of technological advancements there are several new prototypes for pharmacologically active compounds appearing in screening programs, which will accelerate the exploration of natural compounds for different diseases such as cancer.

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