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ANTICANCER APPROACH WITH NATURAL PRODUCT

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ABSTRACT

The control of cancer, the second largest cause of death in the world, may benefit from the potential that resides in alternative therapies. The primary carcinogens stem from a variety of agricultural, industrial, and dietary factors. A number of natural products have been implicated as anticancer agents. Many anticancer molecules such as vincristine, vinblastine, combretastatins, taxol, podophyllotoxin, camptothecin, etc. have been isolated from plants and many of them have been structurally modified to yield better analogues for better anticancer activity with minimum toxicity. Several successful molecules like etoposide, topotecan, irinotecan, teniposide, etc. also have emerged as drugs upon modification of these natural leads and many more are yet to come. Thus there is more need to utilise alternative concept and approaches for prevention of cancer. This review focused on natural products has been implicated in cancer prevention and promoting human health.

INTRODUCTION: Cancer is a disease of misguided cells which have high potential of excess proliferation without apparent relation to the physiological demand of the process. Cancer is the second leading causes of death in the United States, with one of every four deaths attributable to cancer. Deaths from cancer worldwide are projected to continue rising, with an estimated 12 million deaths in 2030 [1].

Cancer is one of the most dreaded diseases of the 20th century and spreading further with continuance and increasing incidence in 21st century. In the United States, as the leading cause of death, it accounts for 25% of all the deaths in humans presently. It is considered as an adversary of modernization and advanced pattern of socio-cultural life dominated by Western medicine. Multidisciplinary scientific investigations are making best efforts to combat this disease, but the sure-shot, perfect cure is yet to be brought into world medicine. Recently, a greater emphasis has been given towards the researches on complementary and alternative medicine that deals with cancer management. Several studies have been conducted on herbs under a multitude of ethno botanical grounds.

For example, Hartwell has collected data on about 3000 plants, those of which possess anticancer properties and subsequently been used as potent anticancer drugs. Ayurveda, a traditional Indian medicine of plant drugs has been successful from very early times in using these natural drugs and preventing or suppressing various tumors using various lines of treatment [2]. Many therapeutic advances in the understanding of the processes in carcinogenesis, overall mortality statistics are unlikely to change until there is a reorientation of the concepts for the use of natural products as new chemo-preventive agents.

Natural or semi synthetic compounds may be used to block, reverse, or prevent the development of invasive cancers. Cellular carcinogenesis forms the biologic basis for the identification of preventive products, the assessment of their activity, and ultimately the success or failure of a therapy.

Cancers may be caused in one of three ways, namely incorrect diet, genetic predisposition, and via the environment. At least 35% of all cancers worldwide are caused by an incorrect diet, and in the case of colon cancer, diet may account for 80% of the cases. When one adds alcohol and cigarettes to their diet, the percentage may increase to 60%. Genetic predisposition to cancer lends itself to 20% of cancer cases, thus leaving the majority of cancers being associated with a host of environmental carcinogens.

Carcinogens: The majority of human cancers occur by environmental carcinogens; these include both natural and manmade chemicals, radiation, and viruses. Carcinogens may be divided into several classes.

1. Genotoxic carcinogens - they react with nucleic acids. These can be directly acting or primary carcinogens, if they are of such reactivity so as to directly affect cellular constituents.

2. Alternatively - they may be procarcinogens that require metabolic activation to induce carcinogenesis.

3. Epigenetic carcinogens are those that are not genotoxic. Molecular diversity of the cancer-initiating compounds ranges from metals to complex organic chemicals and there is large variation in potency. The variation in structure and potency suggests that more than one mechanism is involved in carcinogenesis.

Carcinogens in the diet that trigger the initial stage include moulds and aflatoxins, nitrosamines, rancid fats and cooking oils, alcohol, and additives and preservatives. A combination of foods may have a cumulative effect, and when incorrect diet is added to a polluted environment, smoking, UV radiation, free radicals, lack of exercise, and stress, the stage is set for DNA damage and cancer progression.

On the protective side, we know that a diet rich in fruit, vegetables, and fiber is associated with a reduced risk of cancer at most sites [3].

Cell Cycle: Cancer is a disease occurs in the normal process of cell division, the process of cell division is controlled by genetic material of cell (DNA). For a cell to replicate, it must

- Faithfully reproduce its DNA.
- Manufacture sufficient cellular organelles, membranes, soluble proteins, etc., to enable the daughter cells to survive.
- Partition the DNA and cytoplasm (containing organelles) equally to form two daughter cells.

Defect in normal cell cycle or failure to control cell cycle process may lead carcinogenesis.

Carcinogenesis: The transformation of a normal cell into a cancer cell is proceeds through many stages over a number of years or even decades.

Stages of carcinogenesis;

- Initiation,
- Promotion,
- Progression

The first stage involves a reaction between the carcinogen and genetic materials of cell. This stage may remain dormant, and the subject may only be at risk for developing cancer at a later stage. The second stage occurs very slowly over a period of time from several months to years. During this stage, a change in diet and lifestyle can have a beneficial effect so that the person may not develop cancer during his or her lifetime. The third and final stage involves progression and spread of the cancer, at which point diet may have less of an impact. Preventing initiation is an important anticancer strategy, as are the opportunities to inhibit cancer throughout the latter stages of malignancy.

One of the most important mechanisms contributing to cancer is considered to be oxidative damage to the DNA leads to be a permanent genetic defect and mutagenic changes in the components of signaling pathways lead to cellular transformation (cancer) [4].

Globally Cancer Incidence: Modern man is confronted with an increasing incidence of cancer and cancer deaths annually. Statistics indicate that men are largely plagued by lung, colon, rectum, and prostrate cancer, whilst women increasingly suffer from breast, colon, rectum, and stomach cancer [5].

Plant-derived Anti-Cancer Agents in clinical use: The vinca alkaloids (vinblastine and vincristine) was the first anticancer agent under clinical use, isolated from the Madagascar periwinkle, *Catharanthus roseus* G. Don. (Apocynaceae), which was found to be active against lymphatic leukemia in mice. The semi synthetic compounds like vinorelbine and vindesine is the analougs of vinca alkaloids and recently these agents are primarily used in combination with other for treatment of a variety of cancers, including leukemias, advanced testicular cancer, lymphomas, Kaposi's sarcoma, and breast and lung cancers [6].

The two clinically active agents, etoposide and teniposide, which are semi-synthetic derivatives of the natural product, epipodophyllotoxin (an isomer of podophyllotoxin), may be considered as being more closely linked to a plant originally used for the treatment of cancer [7].

In addition to the anti-cancer drug armamentarium is the class of clinically active agents derived from camptothecin, which is isolated from the Chinese ornamental tree, *Camptotheca acuminata* Decne (Nyssaceae) [8]. Other plant-derived agents in clinical use are homoharringtonine, isolated from the Chinese tree, *Cephalotaxus harringtonia* var. and elliptinium, a derivative of ellipticine, isolated from species of several genera of the Apocynaceae family, including *Bleekeria vitensis* a Fijian medicinal plant with reputed anti-cancer properties [9].

Plant-derived Anticancer Agent under clinical evaluation: Natural products continue to be an invaluable resource of anticancer drug discovery in recent years, by considering the comparatively large number of chemical entities of natural origin currently under clinical trial [10].

Presently, a large number of derivatives of paclitaxel and camptothecin are in clinical trials to treat various types of cancer, with, among these, several taxanes [ABI-007 (suspension), DHA paclitaxel, RPR-116278A, paclitaxel poliglumex, XRP-9881 (RPR109881A)] and camptothecin derivatives [exatecin mesylate, 9-aminocamptothecin, oral topotecan, rubitecan (9-nitrocamptothecin)] being the most advanced, and in Phase III clinical trials. Two additional vinca alkaloid derivatives are also in phase clinical trials (vinflunine ditartrate and anhydrovinblastine) as well as two epipodophyllotoxin derivatives (NK-611 and tafluposide) [11].

A broadspectrum of activities has been attributed to curcumin including antioxidant, anti-inflammatory, antimicrobial, and immunomodulatory effects as well as potential antitumor effects. A Phase II clinical trial of curcumin (8) in patients with advanced pancreatic cancer has been launched at the M.D. Anderson Cancer Center in Houston, Texas [12]. Homoharringtonine (9, HHT, Ceflatonin) is a Cephalotaxus alkaloid isolated from several Cephalotaxus species indigenous to eastern Asia. Homoharringtonine (9) as a single chemical entity is currently under Phase II/III clinical trials for the treatment of patients with chronic myeloid leukemia (CML) in the United States and Europe [9, 13].

Saprorthoquinone (20), a diterpenoid quinone isolated from *Salvia prionitis* Hance (Lamiaceae), a native herb in the southern part of mainland China. Salvicine (21), a semi-synthetic analoug of saprorthoquinone, was found significant growth inhibitory effect against human cancer. Salvicine (21) has entered Phase II clinical trials for the treatment of solid tumors in mainland China [14].

Another synthetic agent based on a natural product model is roscovitine which is derived from olomucine, originally isolated from the cotyledons of the radish, *Raphanus sativus* L. (Brassicaceae). Olomucine was shown to inhibit cyclin-dependent kinases (Cdk), proteins which play a major role in cell cycle progression, and chemical modification resulted in the more potent inhibitor, roscovitine, which currently is in Phase II clinical trials in Europe. Further development of this series, following synthesis of a focused library via combinatorial chemistry techniques, has led to the purvalanols which were even more potent, and are in preclinical development [15].

Approach to the discovery of Anticancer Agents from plants: While the pharmaceutical industry had a long track record of success in developing natural product drugs for the oncology market, for more than half a century there has also been an active interest in the systematic screening of extracts from plants and other organisms for their potential anticancer activity by the U.S. National Cancer Institute (NCI). In initial work during the period 1960–1982, over 114,000 plant-derived extracts were screened through a combination of prescreens, cell-based (cytotoxicity) screens, and in vivo testing in mice implanted with tumors.

During the period 1986–2004, the Natural Products Branch of the Developmental Therapeutics Program (DTP) at NCI organized the collection of some 60,000 higher plant samples in various targeted tropical locations of the world. Extracts of these plant samples were evaluated first against a pre-screen, with active samples then tested against a 60-cell line tumor panel derived from nine cancer types, followed by further in vivo evaluation when merited. Since 1999, the prescreen was modified to screening through a three-cell panel, constituting MCF-7 breast, NCI-H460 lung, and SF-268 CNS cancer cells.

Although taxol (now known as paclitaxel) was discovered in the laboratory of the late Dr. Monroe Wall and Dr. Mansukh Wani at Research Triangle Institute, North Carolina, the plant of origin of this compound (the bark of Taxus brevifolia Nutt.) was collected in Washington State initially as part of a plant collection program organized by the USDA for the NCI. In the 1980s, the U.S. National Cancer Institute set up a process for funding collaborative teams from academia and industry via the ‘‘National Cooperative Drug Discovery Groups’’ (NCDDG) mechanism, directed toward the discovery of novel anticancer agents of synthetic and natural origin.

While at the University of Illinois at Chicago, the senior author of this review served as a Principal Investigator for a NCDDG project (1995–2005) aimed at investigating new cancer chemotherapeutic agents from mainly tropical plants, with the other partners being Research Triangle Institute, Research Triangle Park, North Carolina and Bristol-Myers Squibb, Princeton, New Jersey. For an initial 5- year period of this NCDDG funding award (1990–1995), the industrial partner was Glaxo-Wellcome Medicines Research Center, Greenford, Middle sex, U.K. In previous reviews, our group has described the general technical approaches taken towards plant collections (including intellectual property agreement development), phytochemical procedures, known compound de-replication methods, in vitro cell-based and mechanism-based bioassay systems, and in vivo assays that were used in our NCDDG project, as well as those used in a follow-up program project, also funded by the U.S. NCI.

We have found the *in vivo* hollow fiber assay useful as a discriminatory procedure in helping to prioritize compounds active in preliminary in vitro biological test systems for evaluation in mouse xenograft systems. The in vivo hollow fiber assay was originally developed at the U.S. NCI. While a large number of compounds were obtained from tropical plants in our work that showed activity in one or more in vitro or in vivo bioassays, two examples of promising antineoplastic compounds that were obtained will be featured in the following paragraphs. The lupane-type triterpenoid, betulinic acid (22) was isolated in our NCDDG project from *Ziziphus mauritiana* Lam. (Rhamnaceae), collected in Zimbabwe.

Although, known already as a phytochemical of widespread distribution in the plant kingdom, betulinic acid was found to selectively inhibit the growth of human melanoma cell lines by causing apoptosis, and also exhibited activity in vivo for athymic mice bearing human melanoma cells. Betulinic acid has also been shown to be cytotoxic to neuroectodermal and malignant brain tumor cell lines. The compound can be produced by semi-synthesis from its abundant naturally occurring analog, betulin (23). An ointment containing 20% of betulinic acid is currently under Phase I/II clinical trials launched by NCI as a portential therapy for the treatment of dysplastic melanocytic nevi [16].

Natural products and defense against Carcinogenesis: Many natural products and naturally occurring compounds are available as chemoprotective agents against commonly occurring cancers. A major group of these products are the powerful antioxidants, others are phenolic in nature, and the remainder includes reactive groups that confer chemo protective

properties. These natural products are found in vegetables, fruits and plants. Although the mechanism of the protective effect is unclear, the fact that the consumption of fruit and vegetables lowers the incidence of carcinogenesis at a wide variety of sites is broadly supported. A host of plant constituents could be responsible for the protective effects, and it is likely that several of them play a role under some circumstances. Most of the non-nutrient antioxidants in these foods are phenolic or polyphenolic compounds, such as isoflavones in soybeans, catechins in tea, phenolic esters in coffee, phenolic acid in red wine, quercetin in onions, and rosmaric acid in rosemary.

Many anti-carcinogens already detected in plant foods, the antioxidants vitamins C and E and the pro-vitamin beta carotene have received the most attention [17]. Although there has been considered enthusiasm for the potential anti-carcinogenic properties of beta carotene, research findings suggest that several different carotenoids are likely to be associated with reduced cancer risks[18].

Mechanism of action of Natural Product against Cancer Progression: Advances in cancer research are enhancing understanding of cancer biology and genetics. Among the most important of these is that the genes that control apoptosis have a major effect on malignancy through the disruption of the apoptotic process that leads to tumor initiation, progression, and metastasis. Therefore, one mechanism of tumor suppression by natural products may be to induce apoptosis, thereby providing a genetic basis for cancer therapy by natural products.

The p53 protein, encoded by a tumor suppressor gene, mediates growth arrest or apoptosis in response to a variety of stresses. p53- dependent apoptosis, occurring in several sensitive tissues after radiation or chemotherapy, is partially responsible for the side effects of cancer treatment, making p53 a potential target for therapeutic suppression. Hypoxic stress, such as DNA damage, induces p53 protein accumulation and p53-dependent apoptosis in oncogenically transformed cells. Unlike DNA damage, hypoxia does not induce p53-dependent cell cycle arrest, suggesting that p53 activity is differentially regulated by these two stresses.

Genotoxic stress induces both kinds of interactions, whereas stresses that lack a DNA damage component, as exemplified by hypoxia, primarily induce interaction with co-suppressors. However, inhibition of either type of interaction can result in diminished apoptotic activity. Germ line mutations of the p53 tumor suppressor gene in patients with a high risk for cancer inactivate the p53 protein [19]. Lung-specific expression of the p53 and K-ras genes in mice was reported [20, 21, 22], when mice were exposed to natural products, such as myo-inositol, dexamethasone, curcumin, esculetin, resveratrol, lycopene, and butylated hydroxyanisole. The question whether any of the known natural products modulate expression of the p53 protein requires experimentation [23].

Carcinogens in the diet that trigger the initial stage include moulds and aflatoxins (for example, in peanuts and maize), nitrosamines (in smoked meats and other cured products), rancid fats and cooking oils, alcohol, and additives and preservatives. A combination of foods may have a cumulative effect, and when incorrect diet is added to a polluted environment, smoking, UV radiation, free radicals, lack of exercise, and stress, the stage is set for DNA damage and cancer progression.

In addition to the usual vitamin and mineral supplements, amino acids such as cysteine and natural antioxidants such as clove oil constituents are particularly helpful in offsetting problems caused by a variety of environmental toxins. Many diseases, including cancer, have been shown to be linked to a poorly functioning liver detoxification system. A study at an Italian chemical plant showed that workers with an inadequate liver detoxification enzyme later developed bladder cancer. Herbs that promote a healthy liver function include dandelion (taraxacum), milk thistle (silybum), and artichoke (cynara). Beetroot is particularly beneficial and may be eaten raw, cooked, or in juices.

Raw vegetable juices, which may include carrots, celery, and parsley, together with beetroot are an excellent way of providing concentrated antioxidants and plant enzymes [24]. Wheat grass is also useful. A diet rich in cruciferous vegetables and vitamins B (in whole grains and cereals) and C (cabbage, broccoli, and brussel sprouts) promotes liver detoxification.

Other vitamin C foods are peppers, tomatoes, oranges, and tangerines. Glutathione-rich foods, such as avocados, asparagus, and walnuts, are also good for liver detoxification. The current trend to identify natural products as new cancer preventative agents is based on a conceptual basis and understanding of their mechanisms of action in carcinogenesis.

Carcinogenesis inhibition by Antioxidant: Antioxidants are found in a wide variety fruits, vegetables and plants. They have been found to inhibit various types of cancers. One of the most important contributions to cancer is considered to be oxidative damage to DNA. Antioxidant can prevent the oxidative damage to DNA in early stage of carcinogenesis and also modified the redox environment of cancer cell and their behavior [19, 25]. Antioxidants have potential to reduce genetic instability of cancer cell and improve the efficacy of chemotherapy for example vitamin C increase efficacy of cisplatin and etopside against cervical cancer [26]. Some of flavonoids and phenolic compound can produced oxidative stress and apoptosis in cancer cell [27, 28].

Carcinogenesis inhibition by Amino Acids: Amino acids and related compounds normally found in the blood act in concert as a sort of passive defense system against the development of tumors. Cancer cells are harmed by these compounds because their uptake is unregulated, while normal cells, which carefully regulate their uptake of nutrients, are not adversely affected [29]. One of the things that is interesting in relation to natural compounds in cancer therapy is that indicated that as many as 13 compounds found in the blood act synergistically to inhibit cancer cell growth in vitro and in animals. Oral administration glutamine inhibits tumor growth in animals. Glutamine reduced the mitochondrial concentration of in cancer cell and leads to oxidative damage genetic materials of cancer cell [30, 31].

Carcinogenesis inhibition by Flavonoids: Flavonoids are the water-soluble pigments in vegetables, fruits, grains, flowers, leaves, and bark. These pigments can scavenge superoxide, hydroxy, and proxyradicals, breaking lipid peroxide chain reactions. They have also been shown to protect cells from X-ray damage, to block progression of cell cycle, to inhibit mutations, to block prostaglandin synthesis, and to prevent multistage carcinogenesis in experimental animals [5]. Flavonoids can modulate DNA synthesis of cancer cell and produced oxidative stress to cancer cell and increase natural antioxidant glutathione Nakagawa *et al* [32].

Carcinogenesis inhibition by Resveratrol: Oral administration to mice of resveratrol glycosides reduced the growth of implanted lung cancer cells and reduced metastasis [34]. Further, intraperitoneal administration inhibits tumor growth, metastasis, and tumor angiogenesis of implanted lung cancer cells in mice [34]. Oral administration of resveratrol to mice in drinking water reduced the growth of injected fibrosarcoma cells, apparently by inhibiting angiogenesis [35]. Resveratrol also inhibits growth of colon and epidermoid cancer proliferation by down-regulation of cyclin- dependent kineses.

Carcinogenesis inhibition by Alkaloids: The naturally occurring alkaloid can reverse the multidrug resistance by increasing intracellular accumulation through inhibiting the activity of P-glycoprotein. Alkaloids produced low cytotoxicity to cancer cell and could solve the problem conventional cancer chemotherapy has with multidrug resistance, which has been linked to over expression of a membrane associated with P-glycoprotein that acts as an energy-dependent drug efflux pump [36].

SUMMARY: The causes of cancer are related to dietary habits and intake of alcohol as well tobacco smoke, and as such, it is preventable disease. The incidence of cancer can be reduced by dietary modification. Such increasing diets reach in vegetable, fruits, and legumes containing large quantities of antioxidants, alkaloids, flavonoids and amino acids etc. which is giving protection against cancer.

Consumption reduced amount of meat, saturated fat, sugar and salt, as well avoidance of tobacco and alcohol that give positive effect in cancer prevention. The synthetic anticancer agent having greater chances of toxicity and nonspecific killing of cell, natural product provide protective ant therapeutic action with minimum side effect. The introduction of active agents derived from nature into the cancer armamentarium has changed the natural history of many types of human cancer.

Experimental agents derived from natural products are offering us a great opportunity to evaluate not only totally new chemical classes of anticancer agents, but also novel and potentially relevant mechanisms of action.

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