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Anti-cancer agents from natural sources-A review

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ABSTRACT

The most serious diseases cancer, is responsible for the death of more than 8.2 million people in the world wide in recent years. The uncontrolled growth of abnormal cells in the anywhere in the body are known to us cancer. These abnormal cells are referred to as cancer cells, malignant cells and tumor cells. There are over 200 types of cancer of them carcinoma, sarcoma, leukemia, lymphoma and myeloma, central nervous system cancers are the most common. A lump, abnormal bleeding, prolonged cough, unexplained weight loss and a change in bowel movements are the possible signs and symptoms of cancer. So in this way cancer, becomes a fearful terms in the world. Many conventional therapies such as radiation and chemotherapy are well known but they have numerous hazardous effects to the patients. Researchers are now focused to find out more effective and less toxic anti-cancer agents. In this respect natural sources are playing an important role in the development of novel anti-cancer agents. Till now various natural processes and chemical synthesis provide many anti-cancer drugs. Many active phytochemicals and dietary compound have been used for the cancer treatment and many are under human clinical trial as they can inhibit and reverse carcinogenesis by inducing detoxifying antioxidant enzyme system and inducing cell cycle arrest and apoptosis. Epidemiological studies reveals that the high intake of fruits and vegetable reduce the risk of cancer. This review will discuss the anticancer activity of natural products which are highly promising and demanding for mankind.

KEY WORDS: Anti-Cancer activity, Polysaccharides, Alkaloids, Terpenoids

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INTRODUCTION

Cancers which are the large family of diseases leading cause of mortality to the developing and developed country. Annually more than 15 million people are victim of this morbidity due to various types of cancer. Recent data accounting for more than 8.2 million deaths in recent years[1]. Six hallmarks of cancer are by the tumor cells due to the following reasons (i) cell growth and division absent the proper signals, (ii) continuous growth and division even given contrary signals, (iii) avoidance of programmed cell death (iv) Limitless number of cell divisions (v) promoting blood vessel construction (vi) invasion of tissue and formation of metastases[2,3]. Recent data showed that 22% of the total cancer patients are tobacco users. Another 10% are coming from obesity, poor diets, lack of physical activity and excess drinking of alcohol. Environmental pollutants and ionizing radiations are also responsible for invasive cancer. Helicobacter pylori, hepatitis B, hepatitis C, human papillomavirus infection, Epstein–Barr virus and human immunodeficiency virus (HIV) etc virus infections are the culprits of the 15% cancer of the developing countries[4,5]. Classification of cancers are done by the type of cell that the tumor cells resemble. The types of cancer are as follows: (i) Carcinoma: Cancers derived from epithelial cells. This group includes many of the most common cancers and include nearly all those in the breast, prostate, lung, pancreas and colon. (ii) Sarcoma: Cancers arising from connective tissue (i.e. bone, cartilage, fat, nerve), each of which develops from cells originating in mesenchymal cells outside the bone marrow. (iii) Lymphoma and leukemia: These two classes arise from hematopoietic (blood-forming) cells that leave the marrow and tend to mature in the lymph nodes and blood, respectively. (iv) Germ cell tumor: Cancers derived from pluripotent cells, most often presenting in the testicle or the ovary (seminoma and dysgerminoma, respectively). (v) Blastoma: Cancers derived from immature "precursor" cells or embryonic tissue[6,7].

Cancer prevention is defined as active measures to decrease cancer risk of which 30% could be prevented by avoiding risk factors including: tobacco, excess weight/obesity, poor diet, physical inactivity, alcohol, sexually transmitted infections and air pollution[8,9]. Current cancer therapy involves surgical removal, radiotherapy, chemotherapy, immunotherapy and so on. Albeit chemotherapy has major disadvantage such as drug resistance and severe side effect such as endocrine system problem, lungs problem, brain-spinal-nerve problems, digestion problem etc , still chemotherapy is used popularly worldwide to treat the all kind of cancer in every stage of cancer progression . And this therapy is very costly. Recently Vaccines specially Human papillomavirus vaccine (Gardasil and Cervarix) lowers the risk of developing cervical cancer and hepatitis B vaccine prevents infection with hepatitis B virus and thus decreases the risk of liver cancer[10-12]. To overcome the disadvantages of chemotherapy now the researchers are hunting novel anticancer drugs from the natural sources. From the very ancient era, natural products have been used to treat various

morbidity with no or less side effect & thus become an important and promising research area for drug discovery. Recent data showed that a various classes of natural products possessing anti-cancer activity are alkaloids, terpenoids, flavonoids, polysaccharides etc are some of the bioactive natural product with potent anticancer activity. A set of 617 approved anticancer drugs constituting active domain & a set of 2892 natural products, constituting the inactive domain, were employed to build predictive models and to index natural products for their anticancer bioactivity. The anticancer activity of most of the natural products can inhibit & reverse carcinogenesis by inducing cell cycle arrest, apoptosis & regulating immune function [1, 13-14].

History of Cancer research

The inventor of chemotherapy, Paul Ehrlich made a great contribution to the cancer drug development in the early 1900s. In 1939 Charles Huggins introduced the hormonal therapy for the treatment of prostate cancer in men[15]. The sulfur mustard gas which was used in the World War-I, markedly depleted the bone marrow lymph nodes. Inspired by this observations (mainly by Milton Winternitz) US office of Scientific Research and Development found the nitrogen mustard compound was effective for the non-Hodgkin's lymphoma and other lymphoma[16,17]. Faber and coworkers developed antifolate compounds containing aminopterin and amethopterin (now a days popularly known to us as methotrexate) and used these compounds in the treatment of child leukemia[18]. In 1951 Hitchings and Elicon invented two drugs namely 6-Thioquanine and 6-Mercaptopurine in the treatment of acute leukemia[19,20]. In 1957 Heidelberger et al.,[21] synthesized 5 FU (Fluoropyrimidine-5-fluorouracil) which had a broad spectrum activity against a range of solid tumors and this makes it important for the treatment of colorectal cancer and this represents the very first example of cancer therapy become the hallmark of the recent cancer drugs[22]. In the same year another group of researchers investigated the two drugs, vincristine and vinblastine as anti-cancer agents from the periwinkle plant as they found that some of their extracts caused bone marrow suppression in animals[23]. After that in 1960s radiotherapy and surgery are playing a major role in the field of cancer treatment. The application of anticancer drugs with the combination of either radiotherapy or surgery or by both gave the new dimension to the cancer treatment. This method is applied initially for the breast cancer and field of adjuvant chemotherapy was invented[24-26]. Min Chiu Li used methotrexate in an unusual way for the treatment of rare tumor of the placenta, choriocarcinoma effectively[27]. A great breakthrough occurred in cancer therapy when the Eli Lilly company isolated plant alkaloids from *Vinca rosea* and this alkaloids had the activity in the leukemia and Hodgkin's disease[28]. Two different group of scientists De vita et al., 1966 and Brunner & Young 1967 invented the activity of the ibenzmethyzin in Hodgkin's disease [29,30].

In 1964 Skipper proposed the "Cell Kill" hypothesis, which stated that a given dose of drug killed constant fraction of tumor cells not a constant number of cells & thus it is necessary to know about the no. of cells present at the beginning of each treatment to be succeed[31,32]. The metal-based compounds including arsenic, mercury, gold and platinum showed cell killing activities although platinum -containing complexes are the supreme one[33]. In mid-1974 the idea of combination chemotherapy was introduced by Lawrence et.al. They started a series of study on the cure rate of metastatic testicular cancer going from 10% to 60% by 1978 by the use of a combination of cis-platinum, vinblastine, & bleomycin[34]. Now a days Chemotherapy is extensively used in the treatment of all stages of tumor and testicular cancer effectively[35-37].

Classification of anti-cancer drugs

In classical approach anticancer drugs were classified as chemotherapy, hormonal therapy, immunotherapy. Alkylators, anti-biotics, antimetabolites, topoisomerases inhibitors, mitosis inhibitors and others are included in the section of chemotherapy. Hormonal therapy includes steroids, anti-estrogens, anti-endrogens, LH-RH analogs and anti-aromatase agents. Interferon, interleukin 2 and vaccines are the part of the immunotherapy. After that Enrique Espinosa et al in 2003[38] proposed a new drug classification based on the targeted tumor cell. The targets are located at the DNA, RNA, or the protein level. Some chemotherapeutic agents that are directed towards the tumor DNA are as follows:-nitrogen mustards (eg., chlorambucil), Nitrosoureas (eg., BCNU) Trizenes (eg., Dacarbazine), Pt-Compouns (Oxaliplatin), DNA related proteins antibiotics (eg., Doxorubicin), podophillotoxins (eg., etoposide), topo-I inhibitors (eg., Topotecan), antimetabolites (eg., 5-FU, trimetrexate, cladribine) and other ecteinascidin. All these drugs works by breaking the DNA either by cross links or free radicals and other mechanisms. Besides this some steroids (eg., Dexamethasone) , antihormones (eg., antiestrogen), retinoids (eg., ATRA), interferon-α and gene therapy are also reported. They are probably act by the union to specific receptors and transcriptional interaction with specific genes[38].

Synthetic anticancer drugs

The number of more effective synthetic anti-cancer drugs are increases day by day because most of the patients are still die due to their advanced solid tumors. Here we discuss some of the synthetic anticancer drugs.

Firstly we will start with Procarbazine HCl which is a 'nonclassical' oral alkylating antineoplastic agent that belongs to the same family as dacarbazine and hexamethylamine approved since 1969 in United States. It is used as a chemotherapy medication for the treatment of Hodgkin's

lymphoma and brain cancers, multiple myeloma,melanoma, lung cancers. It is frequently used together with chlormethine, vincristine, and prednisone for Hodgkin's whilst for brain cancers such as glioblastoma multiforme it is used with lomustine and vincristine [39].

The second antineoplastic drug of the family of alkylating agents is cyclophosphamide which is also known as cytophosphane. It is used in the chemotherapeutic agents to suppress the immune system and for the treatment of the lymphoma, multiple myeloma, leukemia, overian cancer, breast cancer, small cell lung cancer, neuroblastoma, sarcoma, as chemotherapy, & as an immune suppressor it is used in nephrotic syndrome, etc. mechanistically they work by forming DNA cross links between & with in DNA strands at guanine N-7 position lead to the cell apoptosis[40]. The third one anti-cancer agent in the class of alkylating agent is BCNU (bis-chloroethylnitrosourea) used to treat several types of brain cancer including glioma , glioblastoma multiforme , astrocytoma , etc multiple myeloma , lymphoma . they leads to cell apoptosis by forming crosslinks in DNA[41]. The fourth anti-cancer agent is Oxaliplatin, a platinum based antineoplastic compound used to treat advanced cancer of colon & rectum alomg with folinic acid & 5-FU in a combination known as FOLFOX . It forms inter & intra strands cross links in DNA which prevent DNA replication & transcription causing cell death[42]. The fifth one is 6-Mercaptopurine, w is used to treat leukemia and autoimmunodiseases and lymphosarcoma and lymphoma. It is generally inhibit the nucleic acid synthesis [43]. The sixth one is fenretinide , a semi synthetic retinoid related to Vit-A . It is used to treat prostate cancer, controlateral breast cancer T-cell lymphoma (cutaneous, peripheral) malignant bone tumors. Fenretinide activates retinoic acid receptors , as a result it induce cell differentiation & apoptosis in some tumor cell types[44-46]. The seventh one is methotraxate previously known as amethopterin, used in the treatment of the breast cancer, leukemia, lung cancer, lymphoma, osteosarcoma. Methotraxate acts by the prevention of the incorporation of the purine and pyrimidine to the DNA during the S-phase and thereby stopping normal development and division[47].

The side effects of the synthetic anticancer drugs

All types of synthetic anticancer drugs show adverse effects because of their mode of action on growing normal cells such as hair follicle cells and gastrointestinal, surface epithelial cell and stem cell. So it is necessary to design more effective and less toxic drugs to minimize the side effects of synthetic anticancer drugs. Some of the common side effects of synthetic anticancer drugs are as follows: 1. Alopecia (loss of hair) 2. skin rashes, 3. changes in the color and texture, 4. loss of fingernails and toenails 5. nausea, 6. vomiting, 7. diarrhea, 8. Constipation, 9. liver and kidney damage, 10. peripheral neuropathy 11. Cardiotoxicity etc.

Table-1:- Some of the characteristics of the synthetic anticancer drugs

NAME OF DRUG	Mode Of Action	Type Of Cancer	Side Effect	Reference
Procarbazine	DNA crosslinking / alkylation	Hodgkin's disease (III & IV stages) non-hodgkin's lymphomas , multiple myeloma , primary brain tumors ,melanoma ,lung cancer	Gastrointestinal disturbances, myelosuppression, nervousness, and insomnia, Azoospermia	Aramand J P et al.., 2007[39]
Cyclophosphamide	DNA cross- linking / alkylation	Lymphoma , multiple myeloma , leukemia , Overian cancer , breast cancer , small cell lung cancer , neoroblastoma , sarcoma	Cardiotoxicity , nausea , vomiting, bone marrow suppression , stomach ache , hemorrhagic cystitis , alopecia ,syndrome of inappropriate antidiuretic hormone secretion	Bogatyrenko T. N. et al., 2014[40]
BCNU	DNA cross- linking / alkylation	Brain cancer including Glioma, glioblastoma multiforme and multiple myeloma and lymphoma	myelosuppres-sion, hepatic toxicity, and pulmonary fibrosis	Li Y., et al., 2005[48]
Oxaliplatin	Cross linking in DNA	Advanced cancer of colon & rectum, pancreatic, gastric, breast and non small cell lung cancer	peripheral neuropathy, myelosuppression, nausea, and vomiting thrombocytopenia	Beypinar, I., et al 2017[49] Dilruba , S, 2016[50].
Mercaptopurine	Nucleic acid synthesis inhibitor	Leukemia , autoimmune diseases, lymphosarcoma, lymphoma	Bone marrow suppression, Myelotoxicity, Asymptomatic leucopenia	Nielsen, O. H. et al., 2001[51].
Fenritinide	Union to retinoic acid receptors	Prostate cancer, controlateral breast cancer , T-cell lymphoma , malignant bone tumours.	Rheumatoid arthritis, acne, psoriasis, skin dryness and night-blindness	Espinosa, E., 2003[38]; Radu, R A., et al., 2005[52].
Methotrexate	Cross linking in DNA	Breast cancer , leukemia, lung cancer, lymphoma, osteo sarcoma	Pancytopenia , renalfailure, hypoalbuminemia, aplastic anemia, osteopenia, damages bine growth in children, steonecrosis of the jaw,	Sato T . et al. 2018[53].

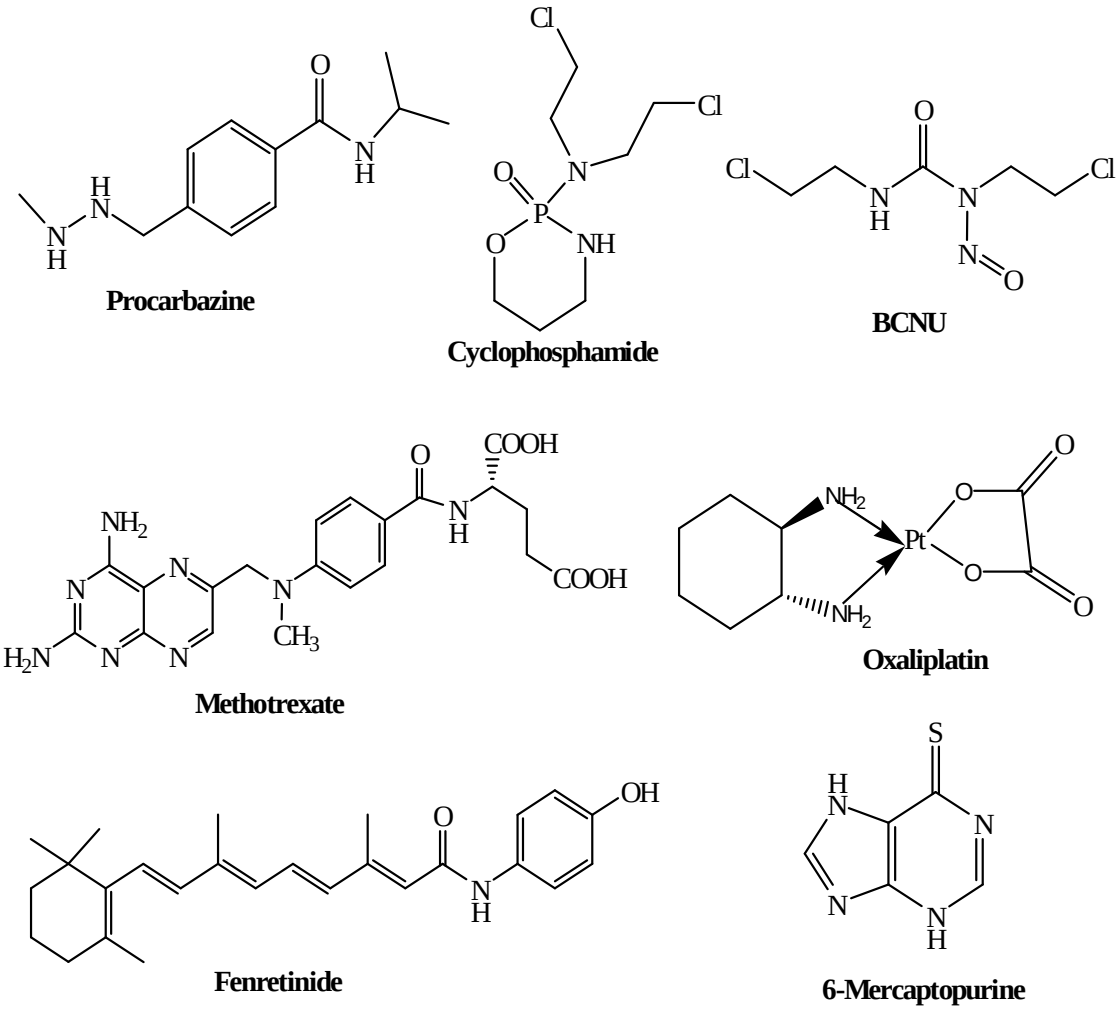

Figure-1:- The structures of the discussed synthetic anti-cancer drugs:

Search for the novel less toxic targeted anticancer drugs from nature

In spite of the invention and synthesis of many synthetic anticancer drugs, chemotherapy, radiotherapy, surgery, cancer threatens the mankind till now. It has been already discussed the adverse effects and toxicity of synthetic anticancer drugs. For this still now morbidity and mortality due to cancer is a worldwide problem in the developing countries. Researchers are now looking for targeted, less toxic anticancer drugs from the nature. In this respect researchers are now used pharmacotherapy which can be currently regarded as a very talented future substitute to conventional therapy for the treatment of cancer. Phramoctherapy includes the natural substances i.e., biological macromolecules, polysaccharide together with protein and polynucleotide. These biomacromolecules

have a major role in the growth and development of living organism. Besides this Pharmacotherapy also includes some pharmacologically active alkaloids, terpeneoids from plant sources [1,54].

Classification of anticancer agents from the nature

From the study of the bioactive anticancer agents from the nature it can categorized into three categories 1. Polysaccharides, 2. Alkaloids, 3. Terpenoids.

Polysaccharides as anticancer agent

Firstly starting study with the polysaccharides, it is found that marine resources are one of the source of the novel compounds having antitumor activities. Jiao, et al., 2011[55] studied on the brown algae which contains biologically active alginic acids, laminarans, and fucoidans. From which fucoidans showed anticancer activity. Fucoidans works by the mediated different signal pathway to regulating cell apoptosis by the inhibiting tumor metastasis and potentiating the toxic effect of chemical drugs[56-58]. The use of the following anticancer polysaccahrides: (i) Lentinan from *Lentinus edodes*, (ii) D-fraction from *Grifola frondosa*, (iii) schizophyllan from Schizophyllum commune, (iv) polysaccharide-K (PSK) from *Trametes versicolor* were done in clinical tumor immunotherapy[59]. Peng et al., 2012[60] reports that Polysaccharides from *Laminaria japonica* showed significant anti-tumor activity against A375 and BGC823 cells and low cytotoxicity to vascular smooth muscle cells. Maxwell et al., 2016[61] informed that the complex polysaccharide pectin has inhibitory activity towards several cancer cell lines. Fan, Wang and his group in 2012[62] study the significant inhibitory effect of the isolated acidic polysaccharide from *Gracilaria lemaneiformis* on the growth of transplanted H22 hepatoma in vivo. According to Hazama et al., 2009[63]; Bisen, et al., 2010[64], in the treatment of gastric cancer, pancreatic cancer, colorectal cancer and hepatocellular carcinoma, the Lentinan injection was used as an adjuvant therapy. It is to be noted that the application of lentinan injection can develop the cellular immune function of blood cancer patients[1]. Lins et al., 2009[65] studied on the combination therapy of sulfated polysaccharides from the red seaweed *Champia feldmannii* with 5-FU. This therapy enhance the anti-cancer efficiency of 5-FU and prevent leucopenia. Zhang, et al., 2010[66] showed that *Bletilla striata* polysaccharide gum poessess broad-spectrum antitumor activity. The gum is mainly composed with mannose and glucose. This gum has significant inhibitory effect on the tumor development. The use of this gum as a carrier of the chemotherapy drugs can be done. Cai et al., 2012[67] isolated an antitumor polysaccharide from the root of *Sanguisorba officinalis L.* This polysaccharide show anticancer activity by rejuvenating the immunity of mice that are inhibited by tumor cells. Lee et al., 2006[68] extracted Polysaccharopeptide (PSP) from the *Coriolus versicolor,* medicinal mushroom. This PSP fraction arrested the Molt4

leukemic cells in the S-phase. It leads finally apoptosis. Xie et al., 2006[69] reported about the inhibition of the growth of human breast malignant carcinoma cells MT-1 by the polysaccharides from the *Ganoderma lucidum*. This polysaccharide reduce the expression of Erk, through the Erk signaling pathway to inhibit tumor cell proliferation. More work on this polysaccahrides reveals that it can inhibit the growth of human breast cancer cells MDA-MB-231 in a dose-dependent manner by activating macrophage cell[70]. Synytsya and his groups in 2010[71] study the anticancer activity of the polysaccharides extracted from sporophyll of Korean brown seaweed *Undaria pinnatifida*. This polysaccharide significantly inhibit the PC-3 human prostate cancer cells, HeLa human cervical cancer cells and A549 human lung cancer cells. Wu and his coworkers in 2017[72] reported the anticancer polysaccharide (SpaTA) from *Sparganii Rhizoma*. This polysaccharide showed its anticancer activity on the ZR-75-1 breast cancer cells by the ERα mediated apoptosis pathway.

Mechanism of action

Yue Yu et al., 2018[1] classified the mechanism of the anti-tumor activities of polysaccharides mainly into three categories.

Firstly by the inducing the apoptosis of tumor cells or inhibition of the expression of cellular oncogenes to kill tumors directly. Pectin, *Ganoderma lucidum* polysaccharide; MD fraction; *Lycium barbarum* polysaccharides; Sulfated polysaccharide PKG03, Polysaccharopeptide (PSP) [68,69,73,74,75,55.]

Secondly by the improvement the immune function of the host Astragalus polysaccharide, Lentinan, D-fraction from *Grifola frondosa*, PSP; PSK (polysaccharide–protein complex); Schizophyllan[59,68,76,77.]

Thirdly the Synergistic effect with traditional chemotherapy drugs from the fucoidans, *Ganoderma lucidum* polysaccharide, Astragalus polysaccharides; *Polyporus umbellatus* polysaccharide, Lentinan; polysaccharide-K (PSK) from *Trametes versicolor*[1].

Clinical trials of the pharmacologically active polysaccharides can progress the physical condition of cancer patients and thereby make longer the life of cancer patients[1].

Alkaloids as anticancer agent

Alkaloids from the natural herbs serve as a rich source for drug discovery. Several alkaloids namely berberine, evodiamine, matrine, piperine, sanguinarine, and tetrandrine exhibit antiproliferation and antimetastasis effects on various types of cancers both in vitro and in vivo[14]. Camptothecin (CPT) and Vinblastine has been successfully used as a chemotherapeutic agent [78,79].

Here we will discuss some of the anticancer alkaloids. The first example of anticancer alkaloid is Berberine which shows anticancer activity. It is an isoquinoline alkaloid widely spread in

natural Chinese herbs including *Rhizoma Coptidis*[80]. Berberine interferes the multiple aspects of tumorigenesis and tumor progression in both *in vitro* and *in vivo* conditions through the proliferation of multiple cancer cell lines by inducing cell cycle arrest at the G1 or G2/M phases and by apoptosis[81,82]. According to Manoharan, S., et al., 2012[83], Berberine also shows potential chemopreventive efficacy in hamster buccal pouch carcinogenesis. Singh, T, et al., 2011[84] reports about the inhibitory effect of Berberine upon the melanoma cancer cell migration by reducing the expressions of cyclooxygenase-2, prostaglandin E and prostaglandin E receptors. The second anticancer alkaloid is Sanguinarine, a benzophenanthridine alkaloid isolated from the *Sanguinaria canadensis L.* and *Chelidonium majus L.* Sanguinarine shows anticancer activities on the skin cancer prostate cancer, breast cancer [85-87]. The third anticancer alkaloid is Matrinein, isolated from *Sophora flavescens* Ait[88]. It shows anticancer activity on the gastric carcinoma cells, pancreatic cancer cells, human osteosarcoma cells in vitro and in vivo[89-91].The fourth anticancer alkaloid is Piperine, a piperidine alkaloid isolated from *Piper nigrum* and *Piper longum*[92]. Piperine shows its anticancer potentials upon the growth of Sarcoma 180 in vivo, breast stem cancer cells, lung cancer cells[93-95]. The fifth one is Evodiamine. a quinolone alkaloid, isolated from the Chinese herb *Evodia rutaecarpa*[96]. The use of this alkaloids as anticancer agents on the human cervix carcinoma HeLa cells, human prostate cancer cell line LNCaP, human leukemic Tlymphocytes[97-99]. Besides these discussed alkaloids other anticancer alkaloids are chelerythrine chelidonine fagaronine lycorine, nitidine chloride solanine, sophocarpine, trigonelline also from various natural herbs [100-103].

Mechanism of action

Berberine, evodiamine, matrine, piperine, sanguinarine, and tetrandrine fights against cancer by modulating multiple signaling pathways, resulting in the inhibition of the initiation of carcinogenesis, induction of cell cycle arrest, apoptosis, autophagy, or differentiation, and inhibition of metastasis, angiogenesis, and so on. Albeit the mechanism of anticancer activity of these alkaloids are not clearly known. More studies are required to understand the mechanistic routes of anticancer activities of anticancer alkaloids from the natural herbs. In this context new pharmacological techniques, effective combinational therapy, effective drug delivery system, additional clinical anticancer trials for these alkaloids need to be performed[14].

Terpenoids as anticancer agent

Lastly in this section we will discuss about the anti-cancer activities on terpenoids. Naturally occurring anticancer terpenoid compounds particularly classified into monoterpenoids, sesquiterpenoids, diterpenoids, triterpenoids, and tetraterpenoids. Some of the important anticancer

terpenoids are Limonene, Cantharidin, Artemisinin, Tanshinone IIA, Triptolide, Pseudolaric acid B, Andrographolide, Oridonin, Celastrol, Cucurbitacin, Alisol B, Pachymic acid, Lycopene etc[104].

Monoterpenoids

Limonene, a monocyclic monoterpene is found as a major constituents in the several citrus oils e.g., lemon, orange, mandarin, lime, and grapefruit. D-limonene possesses broad spectrum anticancer activity upon the pancreas, stomach, colon, skin, and liver cancers. D-limonene exerts anticancer activity by preventing carcinogen-induced mammary cancer at both the initiation and the promotion/progression stages. It also raises the levels of hepatic enzymes. As a result it can detoxify the carcinogens and acts as chemopreventive agent as against liver cancer. It is also effectively used in the combinational therapy with the 5-FU and docetaxel in the cancer treatment than their single treatment via Reactive Oxygen species generation mechanism[105,106]. Another non-plant derived terpenoids Cantharidin is isolated from Chinese blister beetles *Mylabris phalerata* or *Mylabris cichori*. Cantharidin acts as an anticancer agents against leukemia, colorectal carcinoma, hepatoma, bladder carcinoma, and breast cancer[107-109].

Sesquiterpenoid

Artemisinin an anticancer terpenoids extracted from the Chinese medicinal herb *Artemisia annua L.* Artemisinin and its derivatives shows potential anticancer activities upon the proliferation of various types of cancer cells, including leukemia, breast cancer, ovarian cancer, prostate cancer, colon cancer, hepatoma, gastric cancer, melanoma, and lung cancer. It also inhibits angiogenesis, metastasis, and invasion [110-114].

Diterpenoids

Tanshinones, a diterpenoids isolated from *Salvia miltiorrhiza* Bunge. Tanshinone IIA has anticancer activities in various human carcinoma cells, including leukemia, breast cancer, colon cancer, and hepatocellular carcinoma. It is also used in the combinational therapy with combined doxorubicin and cisplatin[115-120]. Second diterpenoids Pseudolaric acid B shows anticancer activity against lung, colon, breast, brain,and renal cancer[121]. Third anticancer diterpenoids Oridonin shows potential anticancer activity on different types of cancer on various solid tumors, including liver cancer, skin carcinoma, osteoma, and colorectal cancers[122].

Triterpenoid

Lanostane-type anticancer triterpenoid Pachymic acid, is a derived from *Poria cocos*. It is used in the treatment of the human lung cancer A549 cells, human prostate cancer DU145 cells, and colon carcinoma HT29 cells[123,124]. Other anticancer triterpenoids are Celastrol, Cucurbitacins, Alisol [104].

Tetraterpenoid

According to Tanaka T, and his coworkers (2012)[125] reported that the most common tetraterpenoids are carotenoids, such as β-carotene, α-carotene, lycopene, lutein, zeaxanthin, β-cryptoxanthin, fucoxanthin, canthaxanthin and astaxanthin exhibiting anti-carcinogenic activity. Lycopene is used in the treatment of hormone sensitive prostate cancer[126]. β-carotene possesses anticancer activity against the breast cancer cell lines[127].

Mechanism of action

Although a large number of terpenoids shows promising anti-cancer activities but due to lack of Structure-Activity-Relationships (SAR) the mechanistic routes of the anticancer activities of these class of compound is still not clearly understood. Different types of terpenoids act by the different pathways. Huang, M., and his coworkers in 2012[104] have summarized few of the anticancer terpenoids and their mechanism of actions. Such as (i) D-limonene works by the Inhibition of HMG-CoA reductase and CoA synthesis, etc[128]. (ii) Cantharidin show its activity by the inhibition of serine/threonine PP1 and PP2A, etc[129]. (iii) Artemisinin and its derivatives play its activity by the cleavage of iron- or heme-mediated peroxide bridge, etc[111]. (iv) Tanshinone IIA acts as a DNA minor groove binder, etc[118]. (v) Triptolide inhibits XPB ATPase and transcription factors, etc[130]. (vi) Oridonin down regulates AP-1 and inhibits NF-κB signaling, etc[131]. (vii) Andrographolide also inhibits of NF-κB, JAK-STAT, PI3K, HSP90 and MMPs, etc[132]. (viii) Celastrol acts as an chempreventive agent by the inhibition of the IKK α,β kinases and proteasomes, etc[133]. (ix) Alisol exerts its activity inhibition of sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase, etc[134]. (x) Pachymic acid inhibits of DNA topoisomerase I and II, MMP9 and NF-κB, etc[135]. (xi) Lycopene scavenges of ROS and inhibits of MMP2 and u-PA, etc (Chen et al., 2012). More studies are needed to understand the Structure Activity Relationships (SAR) as well as the mechanistic routes of the terpenoids as an anticancer agents.

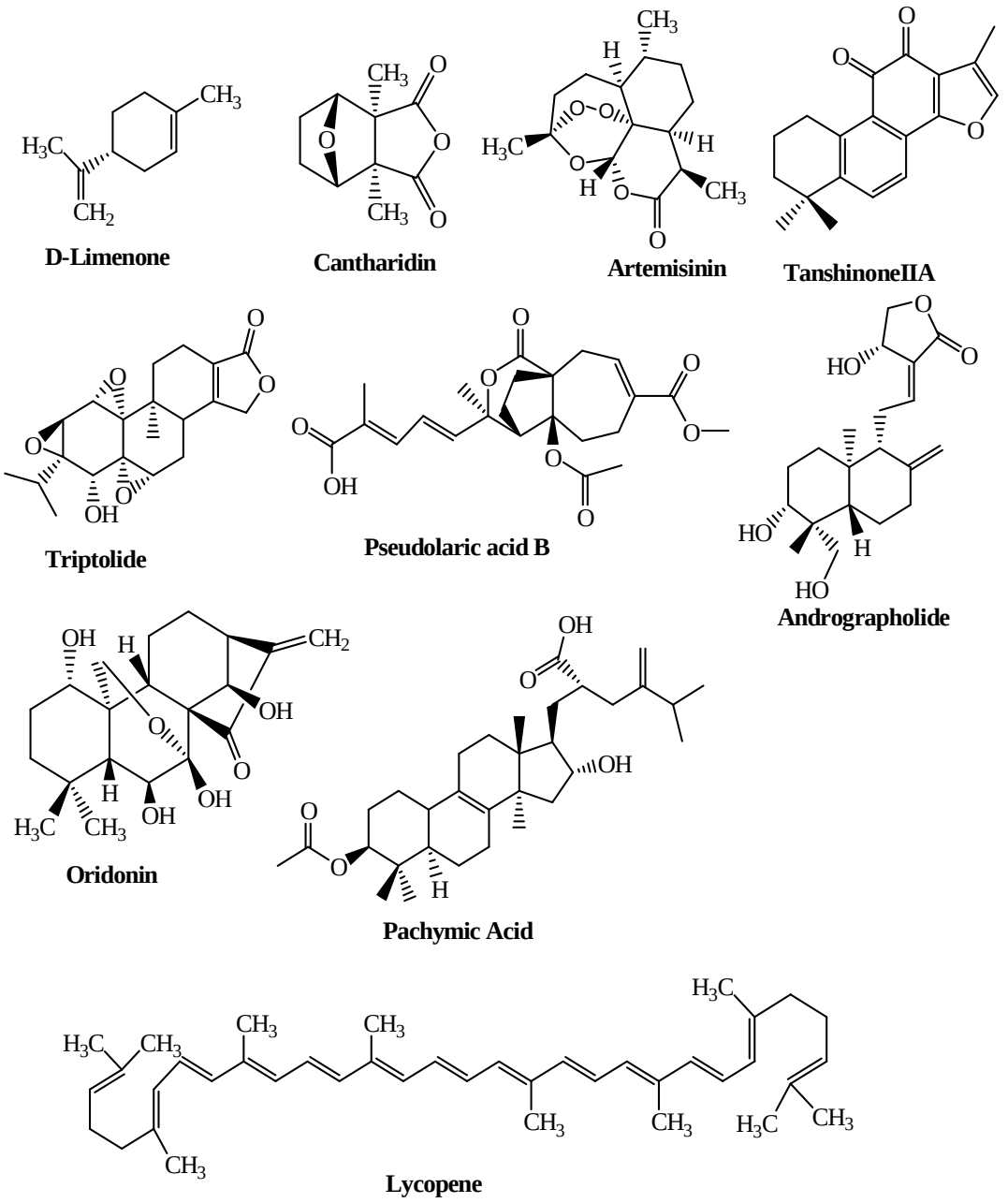

Figure-2:- Structures of the some of the Anti-cancer Terpenoids

CONCLUSION

Although developing and developed countries are doing enormous research in the field of anticancer drug development, now a days Cancer is still responsible for the mortality in the world wide. It is already been discussed about the synthetic anticancer drugs and their side effects. The limitations of use of the synthetic anti-cancer agents into the market are due to the production costs and the inherent complexity and toxicity. Researchers are now looking for novel targeted anticancer

drugs from the nature mainly from the botanical sources as well as animals, marine organisms and microorganisms. Recent data shows that nature supplies 49%-60% of currently used anti-cancer agents. Nature offers new therapeutic candidates which has a tremendous chemical diversity. It is important to note that, 19 natural product-based drugs have been approved in the year between 2005 and 2010. Out of this 19 natural product based drugs 7 are from natural product (NP), 10 from semi-synthetic NPs and rest 2 from NP-derived drugs respectively. Mechanism based investigation will guide to identify the novel anticancer compounds. In this context molecular mechanism of the compound derived from the specific plant will lead to discover the targeted novel anticancer agents. In this way researchers get a valuable platform from the nature with the help of plant biotechnology, bioprocess design and plant molecular farming to invent the individualized medicines for the cancer treatment in near future.

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