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Review Article

A Short Review on Anticancer Phytochemicals

Md Kalimuddin Mandal, Mukti Mohammad, Syed Ismattowaha Parvin, Md Maidul Islam*, Harun Al Rasid Gazi*

Department of Chemistry, Aliah University, New Town, Kolkata, West Bengal, INDIA.

ABSTRACT

Cancer has been regarded as one of the leading causes of mortality and has distressed people globally. There are many conventional treatments like chemotherapy, radiotherapy, surgery, hormone therapy etc. But these treatments have many harmful side effects, which have restricted conventional treatments efficacy. Many phytochemicals found in various plants have been studied largely for their anticancer properties. Many phytochemicals present in ayurvedic and homeopathic medicines have also been determined as good anticancer drugs. Hence, there are lots of opportunities for researchers to develop potent anticancer drugs from medicinal plants available in several countries. Researchers also need to acquire knowledge on the action of phytochemicals to develop more potent anticancer drugs. The present review discussed systematically the anticancer activities of different class of phytochemical compounds.
Keywords: Anticancer, Phytochemicals, Cumarin derivatives, Quinoline and Isoquinoline derivatives, Macrocycle, Vinblastin.

Correspondence:
Md Maidul Islam
Department of Chemistry, Aliah University, New Town, Kolkata 700 160, West Bengal, INDIA.
Email id: maidulaliah@gmail.com

Harun Al Rasid Gazi
Department of Chemistry, Aliah University, New Town, Kolkata 700 160, West Bengal, INDIA.
Email id: harun@aliah.ac.in

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INTRODUCTION

Cancer is the second leading cause of death globally. In 2018, there were 18.1 million new cases and 9.5 million cancer-related deaths worldwide. It is expected that by 2040, the number of cancer cases per year will rise to 29.5 million and the number of cancer-related deaths will be 16.4 million.

The first recorded matter of cancer hails in 1600 B. C. in ancient Egypt[1] and was thoroughly recorded on papyrus, documenting eight cases of breast tumors. It was also written that no treatment available for cancer, palliative care only. There is proof that ancient Egyptians could differentiate between benign tumors and malignant tumors.

The word cancer came from the Greek word, *Karkinos* to describe carcinoma tumor. Around 400 BC., Hippocrates, the Greek physician known as the father of medicine, is said to have first given its name: *Karkinos*.[1] Celsus (25 BC – 50 A D) translated karkinos into cancer.[1] The word comes from crab, and there was something about tumors as they sent their fingers or fingerlings into the body.

Through the centuries it was discovered that cancer could occur anywhere in the body, but Hippocrates' humor-theory[2] based treatment remained popular till the 19th century. According to this theory, there were four humors (fluids of the body) blood, yellow bile, phlegm, and black bile. Any type of imbalance of body fluids will cause disease and a surplus of black bile in a certain organ site was considered to create cancer. The Lymph theory was discovered in the 17th century, putting back Hippocrates', theory of black bile on the origin of cancer. Marilyn Yalom gave a new idea on the cause of cancer after discovering of lymphatic system.[3] Latter on Rudolph Virchow discovered in the 19th century that cells, even cancer cells, may create from other cells.[2] Karl Thiersel, a German surgeon concluded that cancer may spread from malignant cells.[2] The genetic concept of cancer was recognized by another German scientist Theodor Bovery, in 1902.[4] He gave the idea of checkpoints of the cell cycle, oncogenes, and tumor suppressor genes and proposed that mutation in genes due to radiations, chemicals, and pathogenic micro-organisms may increase the chance of cancers in the human body.[4]

Healthy cells can destroy themselves when they become damaged and new healthy cells replace them, sometimes changes in cells make them grow uncontrollably resulting in a mass or tumor. A comparison between normal and cancer cells is given below (Figure 1).

Self-sufficiency in growth signals

Typically, normal cells require hormones and other molecules that act as signals for them to increase and create a new one. However, cancer cells can grow without these signals. There are multiple ways in which cancer cells can grow and known as autocrine signaling. Permanently activating the signaling pathways or by the destruction of 'off switches' which stops unnatural growth of cell from negative feedback. Normal cell

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division is firmly controlled but cancer cell division is deregulated due to a change of controlling proteins.[5]

Uncaring attitude to signals of anti-growth

The cell has some methods that prevent cell division for controlling cell division tightly. These methods are done by some proteins which are called tumor suppressor genes. In cancer cells, tumor suppressor genes change such a way that they cannot prevent properly cell division.[5]

Avoiding apoptosis

Normal cells generally have the capability to self-destruct which is called apoptosis. But cancer cells do not have this type of ability to apoptose.[5]

Unlimited replicative potential

Normal cells of our body can't divide indefinitely and they die or get unable to cell division after occurring of a limited number of cell division because telomeric DNA becomes shorter for every division. But cancer cells avoid this hurdle by controlling enzymes that make longer the length of telomeres. As a result, they can divide into infinite numbers.[5]

Sustained angiogenesis

The method which forms new vessels of blood is called angiogenesis.

An expanding tumor needs new adequate blood vessels to supply oxygen to cancer cells and thus maintain these physiological processes normally for its need. For this purpose cancer cells obtain the capability to produce new vessels by activating the 'angiogenic switch'.[5,6]

Tissue invading and metastasis

An important feature of cancer cells is their capability to invade other neighbouring tissues. Multiple changes are occurring in the cancer cell and as result cancer cells obtain the capability to metastasize. It is a multistep procedure that begins locally into the surrounding tissues.[5]

Unique morphological feature

Cancer cells have an asymmetrically large shaped nucleus and small cytoplasm in the cell. An abnormal change is observed on the chromatin of cancer cells nuclei which are called the miotic spindle. The miotic spindle helps to divide cells and causes different genetic abnormalities like a mutation of gene sequencing.[7]

PROCEDURES FOR THE TREATMENT OF CANCER

The types of treatment depend on the type of cancer and stages of cancer. In some cases, only one method is applied, while in most cases amalgamation of treatments, such as surgery with radiation therapy and or chemotherapy is used.

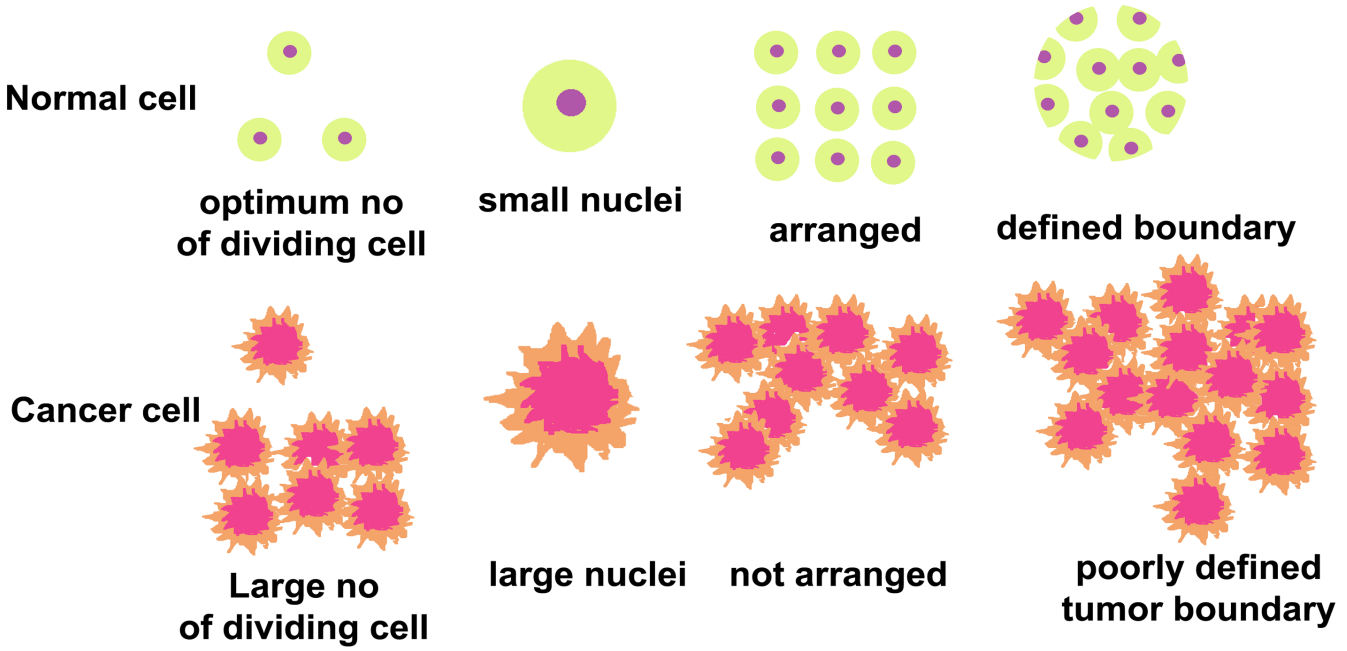

Figure 1: A comparison between normal cell and cancer cell.

Surgery

The surgical method aims to remove cancer-affected tissues completely.[8] However, if the vital organs such as the liver, lungs, brain are affected, complete removal may not be possible to prevent organ damage. For these cases, other procedures may be applied followed by surgery.

Radiation therapy

Radiation therapy works by damaging the DNA of cancer cells. DNA damage is caused by direct or indirect ionization. Linear accelerators, Cobalt-60 units, Caesium-137 therapy units, low to orthovoltage x-ray units, high dose and low dose rate brachytherapy units and conventional brachytherapy units are used for radiation therapy.[9]

Immunotherapy

Immunotherapy is a type of treatment that helps your immune system to fight against cancer. Immune Checkpoint Inhibitors, Adoptive Cell Therapies, Monoclonal Antibodies, Oncolytic Virus Therapy, Cancer Vaccines, Immune System Modulators are used for immunotherapy.[10]

Targeted therapy

There is another type of cancer treatment which is known as targeted therapy. Targeted therapy is a cancer treatment that uses drugs to target specific genes and proteins involved in the growth and survival of cancer cells. In Targeted therapy used drugs can either affect the environmental tissues that help cancer growth or it can target cells related to cancer growth.[11]

Hormone therapy

This treatment reduces or completely terminates the growth of prostate and breast cancer which apply hormones for growth. Aromatase inhibitors (AIs), such as anastrozole, exemestane, and letrozole and Selective estrogen receptor modulators (SERMs), such as tamoxifen and raloxifene and Estrogen receptor antagonists, such as fulvestrant and toremifene are used in hormone therapy.[12]

Transplant of stem cell

Stem cell therapy promotes the repair of diseased, dysfunctional or injured tissue using stem cells or their derivatives. Stem cells are used in cancer patients to treat certain cancer like leukemia. These are processes that restore blood-forming stems cells in patients for whom these are damaged by heavy doses of radiation or chemotherapy.[13]

Chemotherapy

Chemotherapy is a very effective cancer treatment that applies specific drugs to destroy cancer cells. In the current application, the word "chemotherapy" generally indicates cytotoxic drugs that influence quickly dividing cells, in contrast to targeted therapy. Chemotherapy drugs prevent cell division in different possible mechanisms. In most cases of chemotherapy, not only cancer cells but also normal cells are affected. Often more than one drug is referred together because a few drugs' responses are better in combination. This type of chemotherapy is known as "combination chemotherapy".[14]

SIDE EFFECTS OF CANCER TREATMENT

It can take time to get over the side effects of treatment. Side effects depend on the type of cancer, cancer stage and type of treatment. Side effects may be both physically and mentally. Few problems are solved quickly, others may take a long time (might be a year) to improve. Side effects generally include:[15]

i. Feeling of tiredness.

ii. Pain.

iii. Loss of self–esteem and confidence.

iv. Changes in sexual desire.

v. Menopausal symptoms for women.

vi. Fertility problems.

vii. Lymphoedema.

viii. Cognitive changes.

ix. Depression.

x. Other side effects.

LIMITATION OF CONVENTIONAL TREATMENTS

Chemotherapeutic drugs do not work all the time and surprisingly, they may not fully destroy cancer when it is needed. Patients often may miss realizing its drawbacks.[16] The blood-brain barrier creates a difficult obstacle to pass to deliver chemotherapeutic drugs to the brain. This is the reason the brain has a major system in position to prevent it to form harmful chemicals. Drug carriers can discharge the drugs from the brain and blood vessel cells of brains and decrease their efficiency for brain tumor treatments.[17] Tumor blood vessels are very dissimilar from those which are present in normal tissues. Tumor cells furthermost apart from blood vessels become short in oxygen because of tumor growth. For that reason, blood vessels are created poorly and do not deliver sufficient blood to all fields of the tumors. Surgery of disturbing larger, and few parts are tough, not reasonable for sub-clinical metastases. There are a few drawbacks to this type of treatment. It can't fully remove the cancer cells. Sometimes this surgery can eliminate the entire organ.[8]

Radiation therapy has a lot of side effects. Radiation therapy directly can either harm DNA or produce free radicals within the cells which can damage the DNA. Dry mouth is created on the

Table 1: Structural Class wise distribution of Anticancer Phytochemicals.

Sl. No.	Structural class of Compound	Phytochemicals	Activity
1.	Coumarin derivative	Kaempferol	It has anticancer activity on breast cancer, ovarian cancer, leukemia, bladder cancer, prostate cancer, gastric cancer, lung cancer, pancreatic cancer and colorectal cancer.
		Isopimpinellin	It is inhibitor of skin tumor and breast cancer.
		Myricetin	It is effective in protecting cells from carcinogenic mutation. It decreases the possibility of skin tumorigenecity.
		Apigenin	It induces autophagy in leukemia cells, which may support a possible chemopreventive role.
		Taxifolin	It acts as effective chemo-preventive agent by regulating genes via an ARE(antioxidant response element)–dependent mechanism.
2.	Quinoline and Isoquinoline derivatives	Sanguinarine	It has antitumor property and also good DNA and RNA binder.
		Coralyne	It is also good DNA and RNA binder and it has high antitumor potentiality compared to others protoberberine alkaloids.
		Camptothecin	It has anticancer activity against many types of cancers *in vitro*.
3.	Steroidal Compounds	Cucurbitacin	The development of drugs for cancer, inflammation, diabetes and cardiovascular disease. It has anticancer activities *in vitro* and *in vivo*.
		Withaferin A	It is effective on pancreatic cancer, cervical cancer, lungs cancer, medullary thyroid cancer.
		Oleandrin	It may be able to inhibit the proliferation of tumor cells and stimulate their apoptosis as a result of the high concentration of intracellular calcium.
4.	Carbohydrate and macrocyclic derivatives	Saponin	It enhance the cytotoxicity of immunotoxins and other targeted toxins against cancer cells in humans.
		Paclitaxel	It is used as a chemotherapeutic drug to treat cancer like breast cancer, ovarian cancer, cervical cancer, lung cancer.
		Caryophyllene	It exhibited synergy with Paclitaxel which is used as a chemotherapy drug on human tumor cell lines, and it works alone in the stimulation of apoptosis and suppression of tumor growth.
		Alpha- Amanitin	It has activity in therapy-resistant tumor cells e.g. cells expressing multidrug-resistant transporters, tumor-initiating cells and non-dividing cells at picomolar concentrations.
		Vincristine	It is a chemotherapy medication applied for the treatment of acute lymphocytic leukemia, myeloid leukemia, Hodgkins' disease, neuroblastoma, and lung cancer.
		Vinblastine	It is a chemotherapeutic drug, generally applied with other medicine for the treatment of Hodgkin's lymphoma, specific kinds of lung cancer, bladder cancer, brain cancer, testicular cancer and melanoma.

5.	Other Anticancer phytochemicals	Terpinolene:	It is a potent antiproliferative compound for brain tumour cells.
		Ajoene	It has been investigated as an anti–leukemia agent for acute myeloid leukemia therapy.
		S-Allyl cysteine	It works as a potential lowering agent of cholesterol and as a chemopreventive.
		6-Pentadecyl salicylic acid	It is a potent HAT inhibitor and cancer cell sensitizer.
		12-Deoxyphorbol 13-Palmitate	It is a potential preventative and or cancer therapeutic agent.
		Beta-boswellic acid	It has been pointed to cancer cell apoptosis, specifically brain tumors and cells attacked by colon cancer or leukemia.
		Plumbagin	It may use as a potential anticancer drug and its mechanism may be related to the down-regulation of focal adhesion kinase expression.
		Lupeol	It has been exhibited to activate arresting of cell cycle and apoptosis in many cancer cell lines including lung, melanoma, breast etc.
		Thymoquinone	It acts as a useful therapeutic candidate for suppressing tumor development and metastasis for a large scale of cancerous tumors.
		Ursolic acid	It plays remarkable anticancer effects on cells of metastatic melanoma by activation of apoptotic cell death and cell cycle arrest.
		Carvacrol	It stimulates prostate cancer cell apoptosis.

subjection of salivary glands to radiation in radiation therapy. The salivary glands grease the mouth with spit or moisture. After the therapy, salivary glands will restart work but seldom in the same way. Dry mouth created by radiation therapy may be a lifelong issue. In addition, radiation creates remarkable side effects which impact the lifestyle of young patients. The high-energy rays are used in radiation therapy such as X-rays and similar rays for the treatment of cancer. It destroys cancer affected cells in the region that's treated. If the tumor was noticed in the late stage, it needs to give higher radiation exposure that may be dangerous for the organs of patients. Radiation mostly creates long-term side effects for children such as blindness and hearing loss. Children who take scalp radiation are expected at a big risk for educational failure and mental delay.[18]

Targeted therapy is expected to be more efficient than other treatments and less harmful to normal cells. Yet, targeted therapies have some limitations. The specific studies that manifested that targeted therapy would alter tumor cell malignant phenotype connected treating Her 2/neu converted cells in both in vivo and in vitro with monoclonal antibodies by the laboratory of Mark Greene in 1985.[19]

Immune-based therapy for treating solid cancer remains an exciting approach. It is quickly making headway to the clinic from the laboratory. Surprisingly, with the recent treatment autoimmune vitiligo is facing difficulty for immunotherapy for melanoma of malignant and application of allogeneic bone marrow transplantation. An action procedure of immunotherapy of leukemia is frequently complex by graft vs. host disease.[20] It is crucial to record that multiple recent trials of immunotherapy enlist patients with remaining big primary or metastatic disease. The statistics demonstrate that size of tumor straight impacts the capability to climb fruitful tumor-specific immune response.[21] The growth of some cancers can be inhibited by blocking or proving certain hormones. So, the use of hormonal therapy is limited. So it is an urgent need to search for a new treatment line with higher activity and lower side effects. Presently researchers show that phytochemicals may be an important source of anticancer drugs and its use as the anticancer drug became a hot area of research in the past few years.[22] The source, structure and activity of some phytochemicals are discussed here.

ANTICANCER PHYTOCHEMICALS

Anticancer phytochemicals work in different pathways like DNA binding, protein binding, etc.[23] The activities of different phytochemicals may differ, but a similar mechanism may be observed in the phytochemicals with similar structures. In general, the phytochemicals may be divided into several structural groups having the same activity (Table 1).

Coumarin derivatives

This group of phytochemicals (Figure 2) contains a coumarin ring which may be an important pharmacophore of the drug.

Kaempferol

Kaempferol is an active compound present in Thuja Occidentalis and a variety of plants and plant-derived foods,[24]

such as Pteridophyta. It has anticancer activity on breast cancer,[25] ovarian cancer, leukemia, bladder cancer, prostate cancer, gastric cancer, lung cancer, pancreatic cancer and colorectal cancer. It has been also observed to induce apoptosis in breast cancer cells through extracellular signal-regulated kinase ½ activation,[25] and up-regulation of p53.[22] It interacts with the Estrogen receptors and changes the signalling pathway which in turn reduces cancer cells growth. VEGF (Vascular endothelial growth factor), also known as VPF (vascular permeability factor), sigma protein is produced by cells that acts as a reduce MMP-3 protein activity inferring potential ability to reduce metastasis,[23] stimulating agent to form blood vessels. Chen SS *et al.* showed that Kaempferol can act as an anticancer drug by inhibiting VEGF production.[26]

Isopimpinellin

Plant Ruta Graveolens is the source of the anticancer compound isopimpinellin.[27] There have been several studies looking into the effects of isopimpinellin as anticarcinogens. It is an inhibitor of skin tumor,[29] and breast cancer.[28] Mistry Prince *et al.* showed naturally occurring coumarins (isopimpinellin) are anti-carcinogenic in the study of mouse skin models. They also evaluated the inhibition of 7, 12-dimethylbenz [a] anthracene (DMBA) and DNA adduct formation by this.[28] The study by Heather E. Kleiner *et al.* evaluated the effects of orally administered isopimpinellin on skin tumor initiated by applying benzo[a]pyrene(B[a]P) and 7,12-dimethylbenz[a]anthracene(DMBA). In the first dose it inhibited significantly the formation of B[a]P-DNA adduct by 37% and in the second dose oral administration of it (35,70 and 150 miligram per kg) inhibited the formation of DMBA-DNA complex by 23,56 and 69 respectively in response study.[29]

Myricetin

Myricetin is also present in Thuja Occidentalis,[30] and it is commonly derived from vegetables, fruits, nuts, berries, tea,[31] and is also found in red wine. It is effective in protecting cells from carcinogenic mutation. It decreases the possibility of skin tumorigenicity which is produced by polycyclic aromatic compounds such as benzo (a) pyrene, known as an extremely carcinogenic compound. It also protected against the development of skin tumors after tumour-initiating and promoter mediums were used to the skin in mice model. It was observed that topical use of myricetin created inhibition to bind benzo (a) pyrene with DNA and native protein of epidermal skin cells.[32] It has also been evaluated that it inhibits the role of genetic mutation as demonstrated by the Ames test. This test exhibited that it effectively prevented mutagenesis started by specific carcinogenic aromatic polycyclic hydrocarbons (benzo (a) pyrene, dibenzo (a,h) pyrene and dibenzo (a,i) pyrene as compared to other compounds in which it prevented less effectively against mutagénesis.[32] This data proves that myricetin is not effective unilaterally to prevent the carcinogenic role of all aromatic polycyclic hydrocarbons.

Apigenin

Apigenin, a phytochemical, is present in many plants like *Bacopa monnieri* (brahmi).[33] It induces autophagy in leukemia cells, which may support a possible chemopreventive role. Induced autophagy interferes with the role of the chemotherapeutic drug vincristine.[34] Apigenin dimmers can alter the maximum level of drug resistance shown in cancer cells. Through results on cell cycle, inflammation, cell signalling and protease production apigenin have exhibited usefulness against the large scale of types of cancer while not exhibiting toxicity on normal cells.[35] It is capable to stop the phosphorylation of specific proteins in the route in which cases of cancer are expressed like NF-kB, P13K, etc. This has been demonstrated to prevent cancer cell invasion and migration *in vivo* and *in vitro* animal models. Y Zhu *et al.* proved in prostate cancer DU145 cells, apigenin firmly inhibited tumor cell migration and invasion in a dose-dependent fashion.[36]

Taxifolin

Taxifolin, flavanonol can be produced from conifers like Cedar deodara.[37] Saet Byoul Lee *et al.* proved that it acts as an effective chemopreventive agent by regulating genes via an ARE (antioxidant response element)–dependent mechanism. It has been exhibited to forbid the growth of ovarian cancer cells in a dose-dependent route.[38] In many studies, it was observed that it is also effective for anti-proliferation of many different types of cancer cell lipogenesis by inhibition of fatty acid synthase in the

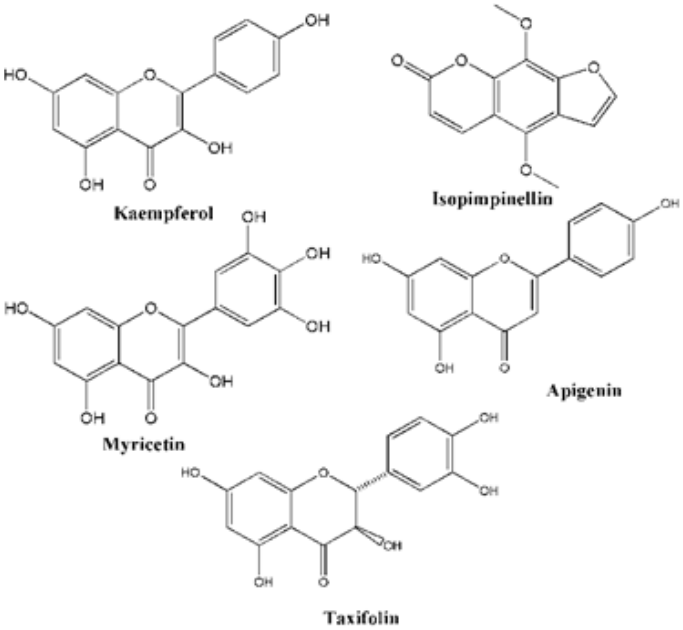

Figure 2: Structures of Coumarin Derivatives.

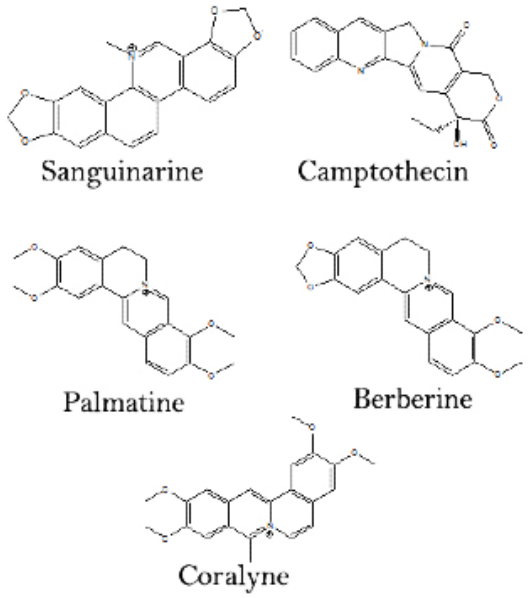

Figure 3: Structures of quinoline and isoquinoline.

cancer cell. So, it is capable to prevent the growth and spread of cancer cells.[39]

Quinoline and Isoquinoline derivatives

Several phytochemicals belonging to the quinoline and isoquinoline group has been proved to have anticancer activities. Some important derivatives are detailed here (Figure 3).

Sanguinarine

It is a polycyclic ammonium ion that is present in the plant Chelidonium majus, used as homoeopathic medicine.[40] It has been promoted to treat or cure human cancer recently. Sanguinarine acts as a promising anticancer therapeutic and shows very good nucleic acid binding properties.[41]

G. Suresh Kumar and his group showed sanguinarine derivative protoberberine alkaloids like berberine and palmatine have antitumor potential and they are also good DNA and RNA binder.[42] They studied the binding affinity of berberine and palmatine to single-stranded polyribonucleotides like polyguanylic acid [poly (G)], polyinosinic acid [poly (I)], polycytidylic acid [poly (C)] and polyduridylic acid [poly (U)]. A study showed that berberine, palmatine and ethidium bound strongly with poly (G) and poly (I) with affinity in the order 105 M-1 while their binding poly(C) and poly (U) were very weak or practically nil.[42]

Coralyne

Protoberberine alkaloids coralyne is also good DNA and RNA binder,[43] and they have high antitumor potentiality compared to others protoberberine alkaloids. Rahul Bhattacharyya *et al.* showed in their study that it has the potential to treat human skin cancers as a photo-chemotherapeutic agent.[44]

Camptothecin

It is isolated from the stem and bark of the tree *Camptotheca acuminata*. Wang Xian H *et al.* showed in their study that it has anticancer activity against many types of cancers *in vitro*.[45] A study by WK Eng *et al.* demonstrated that camptothecin and its analogues act as an inhibitor of topoisomerase 1 (Top1).[46]

Steroidal Compounds

Several phytochemicals containing steroidal structural (Figure 4) moiety can act as anticancer drug.

Cucurbitacin

Cucurbitacins are chemically classified as steroids, found in many plants like *Bacopa monnieri* (Brahmi).[47] The basic research on this is continuing for their biological characters, including toxicity and uses in pharmacology in the development of drugs for cancer, inflammation, diabetes and cardiovascular disease.[48] Fang *et al.* reported that it has anticancer activities *in vitro* and *in vivo* studies.[49]

Withaferin A:

Withaferin A, steroidal lactone is extracted from *Withania somnífera*,[50] (Indian winter cherry or *Ashwagandha* in Sanskrit), *Acnistus arborescens* and other members of the *Solanaceae* family. It has been traditionally used in ayurvedic medicine. This natural product has a large-scale pharmacological role including cardioprotective, anti-inflammatory, immune-modulatory, anti-angiogenesis, anti-metastasis and anti-carcinogenic properties.

Withaferin A is a potent drug to treat cancer. Studies in mouse models by Jose T. Thaiparambil observed that it has shown promising results for breast cáncer.[51] It is also effective on pancreatic cancer, cervical cancer, lungs cáncer,[52] medullary thyroid cancer among others.

Radha Munagala *et al.* demonstrated in their study that it remarkably downregulates the expression of oncogenes HPV E6/E7 and repair the p53 route, outcoming in apoptosis of cervical cancerous cells.[53]

Oleandrin

It is a toxic glycoside found in *Nerium Indicum* (synonym is *Nerium oleander*).[54]

It has been applied for both suicidal and therapeutic purposes as in medication for cardiac insufficiency. It may be able to inhibit the proliferation of tumor cells and stimulate their apoptosis as a result of the high concentration of intracellular calcium. This is a promising agent for anti-cancer. Experiments exhibit potential effects *in vitro* for cancer of non-small cell lung cancer, leukemia,

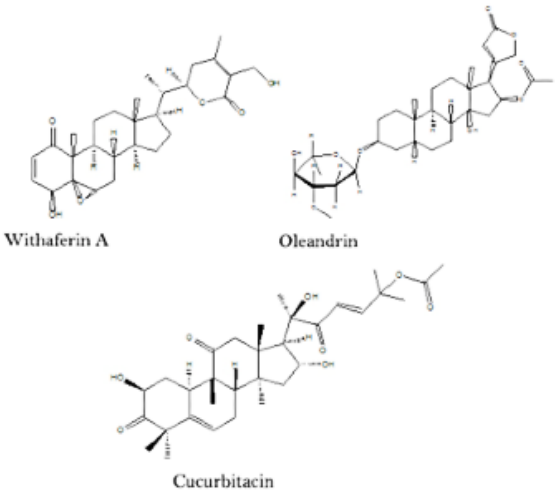

Figure 4: Structures of steroidal compounds.

colon, melanoma, prostate and páncreas.[55] S Pathak *et al.* evaluated that it Oleandrin was able to induce the death of cells in human cancerous cells. They also proved that cell-killing ability was greater than Anvirzel.[56]

Carbohydrate and macrocyclic derivatives

Several plants contain carbohydrate derivatives and compounds having macrocylic strucutre. These phytochemicals are also good sources of anticaner drug (Figure 5).

Saponin

Saponins, a class compound is in particular abundance in various plants like polygala senega,[57] that is utilized as homoeopathic medicine. It has been observed to remarkably enhance the cytotoxicity of immunotoxins and other targeted toxins against cancer cells in humans. The research groups led by Prof. Hendrik Fuchs (Charite University, Berlin, Germany) and Doctor David Flavel (United Kingdom) are doing together to develop the Gypsophila saponins for application in combination with immunotoxins and other targeted toxins for leukaemia, lymphoma and other cancer patients. There is also evidence of anticancer and anticholesterol activity of it.[58] A study by K Xu *et al.* evaluated the cytotoxic activity of saponin extracted from Pulsatilla chinensis on human cancer cell lines (A549, SGC-7901) and this showed remarkable cytotoxic activity.[59]

Paclitaxel

It is a phytochemical which is used as a chemotherapeutic drug to treat cancer like breast cancer, ovarian cancer, cervical cancer, lung cancer etc.[60] Paclitaxel whose brand name is taxol is produced from the bark of the tree *Taxus bravifolia*. In 1979 it was reported that it decreases assembled tubulin subunits' critical concentration and gets larger the percentage of assembled tubulin subunits.[61] It was also showed paclitaxel treatment raises tubulin polymerization and inhibits mitosis progression.[62] This is known as the cytoskeletal drug which targets tubulin. Cells of paclitaxel-treated have faults in miotic spindle gathering, segregation of chromosomes and cell division. It also inhibits the assembly of microtubules and makes stable microtubule polymer.

Caryophyllene

Caryophyllene, natural bicyclic sesquiterpene, is present in homoeopathic medicine *Phytolacca decandra*,[63] and many essential oils. It is an anti-inflammatory and anti-carcinogen.[64] It exhibited synergy with Paclitaxel which is used as a chemotherapy drug on human tumor cell lines, and it works alone in the stimulation of apoptosis and suppression of tumor growth (Legault and Pichette, 2007). Saad S Dahham *et al.* showed that beta-caryophyllene induces apoptosis with nuclear condensation and fragmentation routes including mitochondrial membrane potential disruption. Furthermore, beta-caryophyllene exhibited potent prevention against clonogenicity, invasion, migration and spheroid formation in cells of colon cáncer.[65]

Alpha-amanitin

Alpha-Amanitin, a cyclic peptide of eight amino acids is found in Amanita Phalloides.[66] Amanitin based ADCs have shown outstanding activity in therapy-resistant tumor cells e.g. cells expressing multidrug-resistant transporters, tumor-initiating cells and non-dividing cells at picomolar concentrations.[67] In preclinical prostate cancer mouse models, it conjugated to an antibody directed against prostate-specific membrane antigen (PSMA; FOLH; GCPII) showed high antitumoral activity and caused complete remission at single i.v. doses of 150 micro-gram/kg. Also, amanitin based antibody-drug conjugates using an anti-HER2 antibody such as trastuzumab showed a high antitumoral role in groups of models of preclinical oncology designed to establish the efficacy of the trial drug to treat HER2+breast cancer. Inhibition of RNA polymerase II amanitin-binding not only leads to apoptosis of cells that are dividing but also of slowly growing cells-which is often observed in prostate cancer.[68]

Vincristine

Vincristine is a vinca alkaloid that can be collected from Madagascar periwinkle Catharanthus roseus.[69] This is a chemotherapy medication that is applied for the treatment of types of cancer. This includes acute lymphocytic leukemia, myeloid leukemia, Hodgkins' disease, neuroblastoma, and lung cancer of small cells among others. It is delivered via intravenous infusion using different types of chemotherapy regimens.[70] Its main uses are in non-Hodgkins lymphoma as an element of chemotherapy regimen CHOP, Hodgkin's lymphoma as an element of MOPP, COPP, BEACOPP, or the less popular Stanford V chemotherapy regimen in acute lymphoblastoma leukemia and treatment for nephroblastoma.[71] It acts in part to bind with tubulin protein

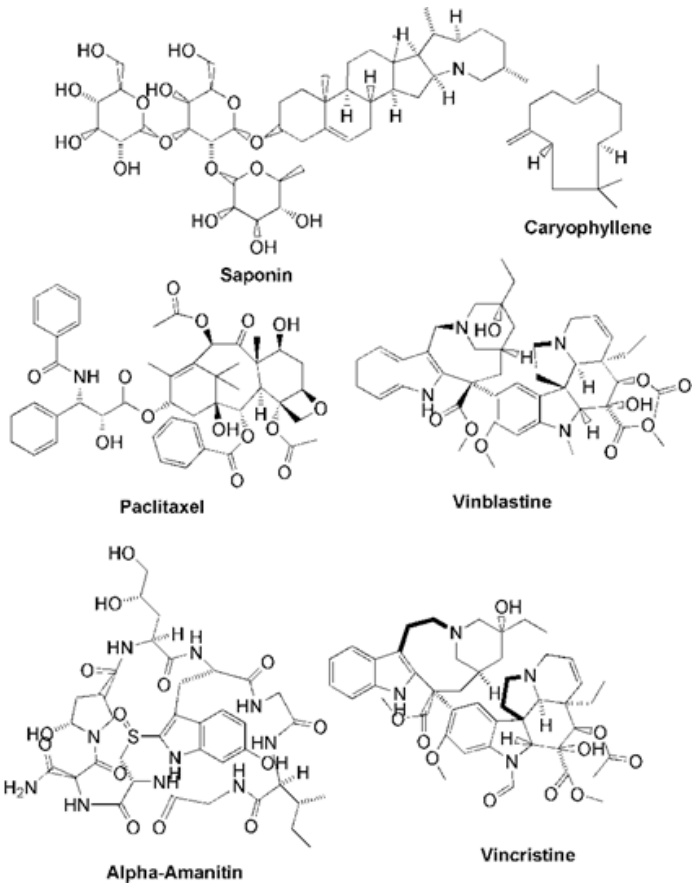

Figure 5: Carbohydrate and macrocyclic derivatives.

and to prevent the cell from its separation from chromosomes in the time of metaphase; then the cell undergoes apoptosis.[72] The vincristine molecule inhibits leukocyte production and maturation.[73]

Vinblastine

Vinblastine, a natural product was first extracted by chemist Robert Noble and Charles Thomas Beer from the Vinca *rosea* plant.[69] This is a chemotherapeutic drug, generally applied with other medicine for the treatment of different types of cancer. This includes Hodgkin's lymphoma, specific kinds of lung cancer, bladder cancer, brain cancer, testicular cancer and melanoma.[74] Vinblastine, nocodazole and colcemid are known as microtubule-disruptive drugs. The different studies showed that vinblastine, nocodazole and colcemid work with two distinct mechanisms. These drugs suppress microtubule dynamics at very low concentrations and reduce the mass of microtubule polymer at higher concentrations.[75]

Others Anticancer phytochemicals

Besides above discussed phytochemicals, lots of other phytochemicals are there which can act as anticancer agents (Figure 6).

Terpinolene

Terpinolene is antibacterial, anti-fungal, anti-insomnia, anti-proliferative and antioxidant.[76] It inhibits the growth of cancer cells.[76] This is available from a variety of plants like *Thuja occidentalis*.[30] Elanur Aydin *et al.* reported in 2013 that it is a potent antiproliferative compound for brain tumour cells and it may play as an anticancer agent.[76] Naoko Okumura *et al.* found that terpinolene noticeably decreased the protein expression level of AKT1 in K562 cells and blocked cell proliferation.[77]

Ajoene

Ajoene is an organosulfur compound found in Allium Sativum (garlic).[78] It was first isolated in 1983 by Rafael Apitz-Castro and Mahendra K. Jain.[78] It has been investigated as an anti–leukemia agent for acute myeloid leukemia therapy.[79] It has been noticed to reduce tumor size of basal-cell carcinoma by inducing apoptosis. At the same time, it also has been noticed useful in inhibiting the growth of tumor cells to target the microtubule cytoskeleton and by another mechanism.[80] CMLJ Tilli *et al.* proved *in vitro* and as well as *in vivo* studies that ajoene can prevent cancer by inducing mitochondrial-dependent pathway of apoptosis.[81]

S-Allyl cysteine

S-Allyl cysteine is an organic compound that is naturally present in fresh garlic.[82] Some studies recently evaluated that it works as a potential lowering agent of cholesterol and as a chemopreventive.[82] Both experimental and epidemiological studies have cited proof that this has anti-tumorigenic characters.[82] Ya-si Xu *et al.* determined *in vitro* that S-allyl cysteine (SAC) can suppress proliferation and induce apoptosis in A2780 ovarian cancer cells.[83]

6-Pentadecyl salicylic acid

6-Pentadecyl salicylic acid is present in *Anacardium occidentale*.[84] It is a potent HAT inhibitor and cancer cell sensitizer.[84] Yuanyuan Wu *et al.* evaluated that it plays as a potent inhibitor of tumor angiogenesis by targeting the Src/FAK/Rho GTPase signalling route, providing to remarkable suppression of growth of prostate tumor.[85] J N Rashida Gnanaprakasam *et al.* determined that it has a useful antineoplastic activity against immunocompetent animals' breast cancer cells, decreases myelosuppression and leucopenia that paclitaxel improves, produces the antitumoral immunological microenvironment and enlarges overall survival of the animals' improvement the life quality of cancer patient.[86]

12-Deoxyphorbol 13-Palmitate

It is one natural toxic compound, isolated from many plants such as *Baliospermum montanum*.[87] It is applied for cancer treatment as a folk remedy. The result of recent research showed strong proof for its application of it as a potential preventative and or cancer therapeutic agent. Hui-Yu Xu *et al.* evaluated that it may be used to target active angiogenesis through VEGF/VEGFR2 signal route for cáncer.[88] A study by Ying Yang *et al.* concluded that it inhibited the expression of VEGF and HIF-1α through the P13K/Akt/mTOR signalling route, confirming that it may be a potent therapeutic agent for breast cáncer.[89]

Beta-boswellic acid

Beta-boswellic acid, pentacyclic triterpene is extracted from the plant Boswellia serrata.[90] It has been pointed to cancer cell apoptosis, specifically brain tumors and cells attacked by colon cancer or leukemia.[91] Jian-Jun Liu *et al.* showed that it has antiproliferative and apoptotic effects in HT-29 cells of humans. This effect occurs via route dependent on depecasepase-8 activation but independent of Fas/FasL interaction.[91] Saraswati and Agrawal determined the boswellic acid as a potent anticancer candidate against MCF-7 breast cancer cell lines. Influences were examined against different intracellular targets that affect angiogenesis (VEGF), inflammation (TNF-α,IL-12) and apoptosis (casepase-3 and 9).[92]

Asiatic acid

Asiatic acid, a pentacyclic triterpene is produced from *Centella asiatica*,[93] which is used in Ayurveda treatment for multi-purposes. It may use as a potential anticancer drug and its mechanism may be related to the down-regulation of focal adhesion kinase expression. It may be an effective agent for antitumor therapy, particularly for multiple myeloma treatment.[94] Chadamas Sakonsinsiri *et al.* proved that it effectively suppressed cholangiocarcinoma (CCA) cellular viability in the induction of the apoptosis pathway.[95]

Plumbagin

Plumbagin is named after the plant genus Plumbago, from which it was originally isolated.[96] It shows many pharmacologic properties in various cellular and animal models: antimicrobial, antimalarial, anti-inflammatory, anticarcinogenic,[97] cardiotonic, immunosuppressive, antifertility action, neuroprotective and anti-atherosclerosis effects. It has been exhibited to activate arresting of cell cycle and apoptosis in many cancer cell lines including lung, melanoma, breast etc. Yi Gou *et al.* demonstrated *in vitro* study that the plumbagin-human serum albumin complex increases cytotoxicity around 2 to 3-fold in cancer cells but interestingly has no influence on normal cells.[98]

Lupeol

Lupeol is a pharmacologically active triterpenoid. It is present in different plants, including *Hygrophila spinosa, Abronia villosa*,[99] etc. It has several potential medicinal properties. This shows a complex pharmacological character, demonstrating antimicrobial, antiprotozoal, anti-inflammatory, chemopreventive and antitumor properties.[100] Sahdeo Prasad *et al.* showed in their study that it is useful in reducing oxidative stress-induced cellular injury of mouse prostate.[101] It is also a useful inhibitor in skin and cancer laboratory models.

Thymoquinone

Thymoquinone is a phytochemical compound found in the Nigella sativa plant.[102] It is derived also from specific farming *Monard fistulosa* plants grown. It has anti-oxidant and anti-inflammatory effects on animal cells and has been evaluated in models of neurodegenerative disease, cardiovascular disease and diabetes, and cancer.[103] Amin F Majdalawieh *et al.* informed that thymoquinone acts as a useful therapeutic candidate for suppressing tumor development and metastasis for a large scale of cancerous tumors.[104]

Ursolic acid

The phytochemical constituents of *Ocimum sanctum* (Tulsi) are ursolic acid, carvacrol, beta-caryophyllene, beta–elemene[105] etc. Ursolic acid is a phytochemical with pentacyclic triterpenoid. It is used for cosmetics additives. Many potential biochemical effects of ursolic acid have been evaluated, but there has been no clinical investigation exhibiting its use on human health. It inhibits *in*

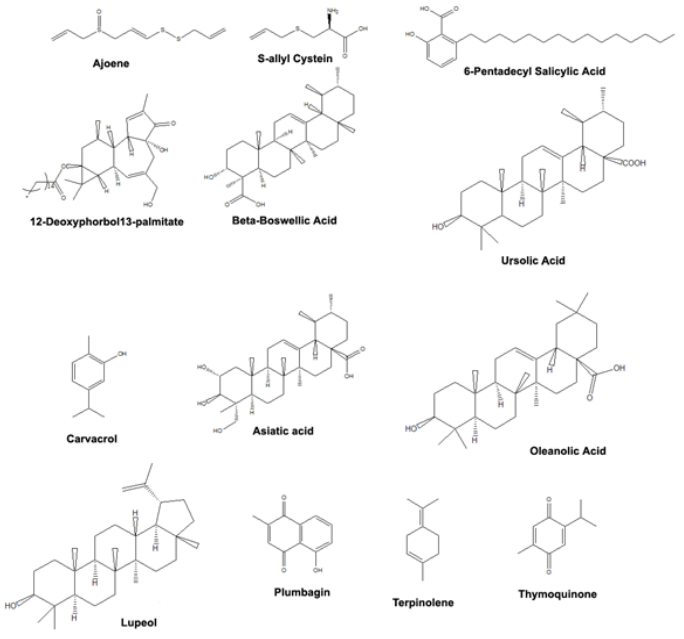

Figure 6: Structures of other compounds having anticancer activity.

vitro the proliferation of different types of cancer cells by STAT3 activation route inhibition and also may reduce the proliferation cancer affected cells and induce apoptosis.[106] Pengchen Liu *et al.* showed in their study that ursolic acid plays remarkable anticancer effects on cells of metastatic melanoma by activation of apoptotic cell death and cell cycle arrest.[107]

Carvacrol

It is a monoterpenoid phenol. It is derived from many plants like Tulsi.[105] This inhibits several bacterial growths. An investigation guided by Supriya Bavadekar reported in 2012 that it stimulates prostate cancer cell apoptosis.[108] In 2015, another study using rats with carcinogenic DMH injections showed carvacrol at 40mg/kg bt. w reversed carcinogenic effects on colon cells. However, the effects of therapy were substantially increased when combined with X-radiation treatment.[109] A follow-up study by the same lead researcher in 2016 provided additional proof for this effect.

CONCLUSION

With growing trends of cancer different new types of treatments and procedures are developing. Presently used procedures have several side effects and limitations. Use of anticancer phytochemicals may be an alternative way to fight against cancer with a small number of side effects. Therefore systematic knowledge about anticancer phytochemicals are highly needed to develop phytochemical based anticancer drugs. The present review explore the phytochemicals pharmacologically effective compounds for the treatment of different types of malignancies. In conclusion, this review provides knowledge about different classes of anticancer phytochemicals having promising anticancer activities.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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