Frontiers in Chemical Sciences (FCS) **2021, 2(1); 59-72**

Phytopharmaceuticals as Important Anticancer Therapeutic Agents

Kiran Mustafa[1*], Imama Fayyaz[1]
[1]Govt. Post Graduate College (W) Khanewal, Higher Education Department Punjab, Pakistan
***Corresponding email:** kiranmustafa100@gmail.com

Abstract

Cancer is usually referred to group of diseases which are associated with abnormal growth of cells in different parts of the body. It is presenting serious threat to the global health since decades. Different phytochemicals obtain from an array of plants have offered a treatment route to the varying sorts of cancers. The phytochemicals have been shown to be effective against cancer individually as well as in combination with other therapeutic technologies. Phytochemicals like curcumin, thymol, and rosmarinic acid is clinically found to effective against bladder cancer, apoptotic death and colon carcinoma. Each phytochemical has its own mechanism for fighting with particular cancer, for instance curcumin is capable of increasing histologic parameters which are helpful in the fight against bladder cancer. This study is focused on elaboration of some vital phytochemicals which are proven to be effective against some sort of cancer (or carcinogenic elements), their mechanism of action, origin and clinical data against the disease.

Keywords: Phytopharmaceuticals, Anticancer, Medicinal plants, Therapeutic agents

I. Introduction

Cancer involves in category of serious ailments and presents a serious threat to the global health. In 2018, evaluated new cases of 18.1 million as cancer ailment appeared at global level which is probably to extend to cancer cases of 23.6 million annually by 2030. Considering the hazardous character of the disease, the cure has been an unbroken effort with very little attainment. In order to treat cancer, choices are available involving radiotherapy of the tumors and surgical excision, classically succeeded by treatment of chemotherapy. The commonly used chemotherapeutic agents consists of many other agents those are interactive to DNA (such as cisplatin, doxorubicin), antimetabolites (involving methotrexate), hormones, anti-tubulin and molecular targeting agents (like taxanes). However, the medical applications of these drugs are consistent with many side effects like hair shedding, brain disorders, cardiac toxicity, myelosuppression, resistant to drug and gastrointestinal lesions (Nussbaumeret al., 2011). To beat the complications of current remedy, quest for noval agents against cancer disease with desirable potency and minor unwanted actions continues.

Plants derived phytochemicals are favorable choices to reinforce the remedy power in patient of cancer as they persuade the apoptotic actions, retard the angiogenesis, decrease the proliferation of cells and blocked metastasis process (Ghorbani, 2012). As naturally occurring compounds, phytochemicals, deemed to be biologically active and consistent with functionality of powerful antitumor actions.

Currently, variety of compounds derived from plants has been used for cancer therapy. Prominent examples are taxol and its analogs, vinca alkaloids, podophyllotoxin analogues etc. (Saklani and kutty, 2008). From the literature it is

found that several plants like *allium sativum*, resveratrol, curcumin, *panax ginseng*, *rhus verniciflua*, campotothecin and *viscum album* have promising anticancer potential which is also supported by satisfactory clinical evidence. Inclusion of phytopharmaceuticals in the cancer treatment will result in cost reduction, lesser or no side effects alongside the prevention against drug resistance. This chapter will elaborate different phytochemicals and the plants which possessed the anti-cancer abilities while focusing on their clinical trials, *in vitro* studies and therapeutic value.

1.1 Curcumin

A yellow polyphenol i.e. diferuloylmethane referred to curcumin that is released from turmeric rhizome, green tea, white willow bark, maritime pine bark etc. During past decade experimental and clinical works proved its therapeutic effects against various diseases it has also been reported for its anticancer effects because of its action on metastasis, cell cycle regulation, mutagenesis, oncogene expression and apoptosis. It can affect variant cancer phases including initiation, development and progression. Moreover, it exhibits antitumor ability due to its antiproliferative effect, retarding effects on factors of transcription and products of downstream gene, regulatory actions on receptors of growth factor and molecules of cell adhesion that included in metastasis, angiogenesis and tumor growth [1]. In a study, curcumin was found to enhance histologic characters in single patient out of 2 with resection of bladder tumor. It was also found that lymphocytic glutathione S-transferase (GST) actions decrease significantly by the ingestion of the curcumin. The GSTs belong to phase II detoxification enzymes family that are included in the progress of opposition to chemotherapeutic agents[2].

1.2 Thymol

Cymene ($C_{10}H_{14}O$) derived monoterpene phenolic compound i.e. 2-isopropyl-5-methylphenol commonly referred as thymol. The transformation of gamma-terpinene to p-cymene results in the biosynthesis of an essential oil which is thymol. It is approved by EU and FDA as a safe food enhancer [3]. Thymol is obtained from different plants such as *Monarda didyma*, *Nigella sativa*, *Origanum compactum*, *Thymus glandulosus*etc.[4]. Thymol has capability to catalyze the oxidative stress-associated mitochondrial dysfunction and other natural and induced apoptotic death of cancerous cells coupled with the antiproliferative action. Binding potency and molecular interactions of thymol were examined against proteins receptor 17 to discover proteins with considerable potency for thymol. Advanced research offers suggestion that thymol-6BHV (−6.9 kcal/mol) complicated compound having prime structure of ligand-receptors relied on the minimum energy and how many H-bonds exist between the ligand and target. So, 6BHV could be well thought-out as effective proteins for thymol in averting cancer at initiation and promotion stages, as a conceivable choice to control cancer strategies {ref}.

1.3 Rosmarinicacid

Rosmarinic acid (RA) is a phenolic compound formed through esterification of 3, 4-dihydroxyphenyllactic acid and caffeic acid. Plants belonging to the Boraginaceae commonly contain RA. RA has shown several biological activities against virus, bacteria. Moreover, it show actions like anti-inflammatory, anticancer, and antioxidant [5]. RA has been found to be operative against diversity of neoplastic cell lines hence can be employed as latent therapeutic agent against these cancer types. RA mechanism of action on cancerous cells involves different approaches such as anti-inflammatory action, antioxidant activities, impeding cell proliferation and selective neoplastic cell apoptosis. Furthermore, the compound has been revealed to own antiangiogenic action as confirmed by repression of cell division, adherence capacity, migration and tube formation of cells derived from the endothelium of the veins from the umbilical cord which may be useful in avoiding tumor growth and metastasis[6]. RA has also been found to inverse the multi-drug resistance in

SGC7901/Adr cells and enhance the in cell buildup of adriamycin and rhodamine 123 and lessen MDR1 gene transcription and P-gp in SGC7901/Adr cells expression. RA are proven to be wonderful therapeutic agent against cure of diverse cancers primarily colon carcinoma[7].

1.4 β-carotene

β-Carotene (BC) is used as a precursor of vitamin A. The fruits and vegetables with deep orange and green color contain β-Carotene[8]. BC tends to decrease the occurrence of epithelial carcinoma which is responsible for greater than 90% deaths from cancer [9]. Furthermore, it is found that excessive uptake of vegetables and fruits enriched with BC, reduce the chances of cancer in numerous organs, particularly in lungs[10].*Pradeep et al*. have also reported the similar results by showing that β-Carotene lessens the occurrence of metastasis cancer to lungs caused by B16F-10 skin cancer cells [11]. These results are supported by additional study Studies have also shown that β-Carotene controls cell division and apoptosis process in various cell lines of cancer inclusive of melanoma, lung, leukemia and colon cancer cells lines [12-14].

1.5 Quercetin,

Quercetin i.e. 3, 3′, 4′, 5, 7-pentahydroxyflavone as a flavonoid present in kinds of fruits, plants, and vegetables like buckwheat, onion and broccoli. Quercetin used for functional foods as an economic nutritional supplement for treatment of different disorders like cancer[15]. Quercetin possesses several biological abilities against cancer, inflammation and oxidizing agent. (Li et al., 2016). Quercetin is poisonous less and has different retarding actions on variant tumor formation ways. *In vivo* and *in vitro* study, have shown that it plays a promising function in developing apoptosis action, retarding metastasis, and has potency to modulate tumor angiogenesis and cell cycle. Furthermore, Quercetin regulate the epigenetics that effect the progress of tumor, in its turn, it directly modulate the micro RNA expression and the level of DNA methylation to apply anticancer action and increase the sensation of tumor cells for chemotherapy (Kim et al.,2019; Kedhari et al., 2019). With the advancement of medical research, the high potency of quercetin for treatment of cancer has been confirmed more and more. Thus, few restriction are yet in the scope and the number of medical research included in the present medical study, and further extensive medical research are required to confirm their remedial actions on cancer and the effects they develop.

1.6 Rutin

Rutin i.e. 3,3′,4′,5,7-pentahydroxyflavone-3-rhamnoglucoside as a glycoside consist of flavonolic aglycone quercetin along with disaccharide rutinose. Rutin is present in plants like apple, passion-flower, apple, buckwheat and tea. Rutin has been used as an important supplement food. [16]. Furthermore, it shows biological actions involving anticancer, antioxidant, cardio protective, vasoprotective and neuroprotective [17]. Widely studied that rutin has been used for cancer. In an investigation, human blood cancer HL-60 cells were inserted in a murine, and after that rutin was introduced which caused a clear depletion in size of tumor defending anticancer potency [18]. In another research, when rutin injected to human cell line of colon cancer, less deleterious actions on the human body were appeared with an elevation of average time of 50 days[19]. Rutin has been used to retard growth of cancer cell by cell cycle capture and cell death, together with retardation of cell division, angiogenesis, or metastasis in colorectal cancer cell lines (Araújo et al., 2011). Furthermore, rutin believe to be functional as a supporter in radioiodine treatment (Gonçalves et al., 2013).

1.7 Allicin

Allicin i.e. diallyl-thiosulfinate believe to be most important pharmacologically active compound of garlic. Allicin is rapidly produced by activity of CS-lyase (allinase) on allicin, not in raw garlic. As a result of crushing of garlic cloves, allinase become active (Block et al., 1985; Cavallito et al., 1944; Caporaso et al., 1983; Stoll et al., 1949). By the mechanical crushing of garlic cloves, allicin constitute about 70% of the total thiosulfinates stuffed in cloves (Block et al., 1992; Han et al., 1995; Lawson et al., 1998). Allicin perform a chief function against cell division action of garlic prepration and this action in the antiproliferative effect of water-soluble garlic preparations and this effect may be ascribed to the capability of allicin to briefly reduce the intracellular gluthathione (GSH) level. Sulphur containing allyl compounds acts as anticarcinogenic (Dirsh et al., 1998). Diallyl disulfide condensed the number and size of preneoplastic foci in liver of rat persuaded by AFB1 (Haber et al., 1996). The shield of garlic as anticancer stimulated from numerous procedures counting the obstruction of nitrosamines production and bio activation (Atanasova-Goranowa et al., 1997).

Garlic consumption can adapt the chances of colorectal cancer to female as diallyl disulfide as an active retarder of the development of neoplastic CMT-13 cells and of N-acetyltransferase action in cell line of human colon adenocarcinoma (Chen et al., 1998; Sundaram et al., 1993). Additionally, diallyl disulfide exposed as an active retarder for the advancement stage of 9, 10-dimethyl-1, 2-benzanthracene tempted skin tumors in the mouse (Belman et al., 1989). Allicin presented actions on processing of DNA, synthesis of RNA, (Feldberg et al., 1988) signal transduction and apoptosis (Zheng et al., 1997). Absolute actions of allicin are facilitated through formation of nitric oxide (Dirsch et al., 1998). Oommen et al., considered the chemo-preventive effect of allicin on cancer cell growth of rat and human origin by cell capability analysis. It is also observed that allicin reserved the cancer cell division and persuaded apoptosis action with classic structures like apoptotic items, fragmentation of DNA, activation of caspases and poly (ADP-ribose) polymerase cleavage, so these actions of allicin include incompletely for the anticarcinogenic components of garlic .Park et al., displayed that allicin persuaded cell apoptosis through caspase-independent pathway of apoptosis, that was coupled with the mitochondrial discharge of AIF and protein kinase A and functions as caspase-independent apoptotic action.

1.8 Gingerol

Gingerol is an important naturally occurring compound isolated from Zingiber officinale and has been reported to exhibit antitumor action against variant kinds of cancers, which include, but are not limited to, colon and breast cancer (Lee et al., 2008a; Lee et al., 2008b). Gingerol applied time and dose dependent growth retarding actions in the cancer cell of eye. Though, the development retarding actions of gingerol were less marked counter to normal cells of fr2. As related to the purified control cells, cells treated with gingerol at variant concentrations i.e. 25, 75, and 150 μM severe variations in morphology of cell, as well as ciruiting and scorching of cells, with disordered layers of cell. Cells treated with Gingerol displayed bright fluorescence, signifying cell membrane rupture. Depending on dose, gingerol causes G2-M phase of cell cycle capture in RB355 retinoblastoma cells i.e. RB355 cell line, along with dose depending activation of PI3K-associated expression of protein. Gingerol prove to be effective in human retinoblastoma i.e. RB355 cancer cells and these properties were facilitated through initiation stage of apoptosis, arrest of cell cycle, and variation of the PI3K-Akt pathway of signal.

1.9 Epigallocatechin gallate

Green tea contains certain types of catechin. Epigallocatechin gallate is a health enhancing specie having numerous antidiabetics, antitumor, antiobesity and anti-inflammatory functions. The structure of epigallocatechin gallate comprises three

aromatic rings joined together through a pyran ring. The health encouraging functions of epigallocatechin is ascribed to its special structure. E.g. epigallocatechin gallate has antioxidizing property due to allocation of single electron or hydrogen atoms in a reaction, inclusive of hydroxyl group of the B and D rings (Lambert et al., 2010). The epigenetic reactions attribute to the initiation and development of cancer, involving abnormal DNA acetylation and methylation. EGCG averts lung tumor formation, prostate and oral-digestive tract. In A-J mice, EGCG retard the tobacco related nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone persuaded lung tumor formation though retardation of 8-hydroxydeoxyguanosine production by antioxidizing function (Xu et al., 1992). In addition, EGCG retard dimethylarsinic acid or cisplatin that persuade formation of lung tumor (Mimoto et al., 2000, An et al., 2008) and diethyl nitrosamine-induced formation of liver tumor through the retardation of signal of insulin like growth factor in diabetic and obese C57BL-KsJ-db-db mice.23 N-methyl-N′-nitro-N-nitrosoguanidine- persuaded carcer that is also stopped by EGCG therapy in glandular stomach (Yamane et al., 1995). Oral administration of EGCG is administrated orally to retard prostate cancer cell growth in xenograft models though the stimulation of apoptosis (Khan et al., 2014). However, mechanisms of EGCG against cancer or tumor formation is unclear, the anticancer action of EGCG has been noted in variant cancers.

1.10 Coumarin

Coumarin is 1, 2-Benzopyrone or 2H-1-benzopyran-2-one, or phenylpropanoids, 1. Coumarins as a derivatives are widely spread across the environment and several display valuable and different pharmacological activities (Egan et al., 1990; Borges et al., 2005). Coumarins are secondary metabolites and exist in seeds, leaves and roots of several plant species, especially in large amount in bean of tonka and so, its name derived from a French word, coumarou, for the tonka bean. Derivatives of coumarin deemed to be important as they have been used for medicinal uses involving anti-HIV, antitumor and photochemotherapy (Harvey et al., 1988; Kostova et al., 2006). Moreover it functions as booster for central nervous system (CNS) (Moffet et al., 196. Also, Coumarin show biological activities against bacteria (Al-Haiza et al.,2003; Musiciki et al.,2000) inflammation (Fylaktakidou et al., 2004), coagulants (Jung et al., 2001) and dyes (Wang et al., 2005). Major reason of death in western countries is breast cancer. It has been observed that approximately 1/3 of postmenopausal breast cancer sufferer have tumors depending on tumor including estrogen receptor stimulant (Henderson et al., 1980). During the last 30 years, a large focus is placed on the remediation beside with avoidance in clinical investigation and laboratory research. In breast cancer treatment, curative agents helpful in the prevention of estrogens production and activities prove to be beneficial (Hamelers et al., 2003). In consequence of in-situ synthesis, estrogen produced at high degree that related with tumor growth in tissues depending on endocrine. Estrogens produced entirely in peripheral tissues. Synthesis of estrogen in tissues related with 2 pathways i.e. sulfatase and aromatase. The aromatase route include transformation of androgen precursor, androstenedione, released primarily via adrenal cortex, to estrone via the complex aromatase (AR) enzyme. Whilst, estrone sulfatase (E1-STS) route include the transformation of estrone produced by the aromatase pathway to estrone sulfate (E1S) via enzyme sulfotransferase (Strott et al., 2002). In tumor of breast, action of the last enzyme is greater as compared to first enzyme that results in bad recovery chances. (Utsumi et al., 1999; Miyoshi et al., 2003; Suzuki et al., 2003; Yoshimura et al., 2004). Estrone sulfatase is the main reason that lead to estrogen production, in its turn, that cause low rate of response in estrogen level breast tumor sufferer to powerful AR retarder(Castiglione et al.,1996; Jonat et al., 1996; Santner et al.,1984; Yamamoto et al.,1993). Furthermore, recent study show that endocrine

treatment includes the retardation of enzymes within the steroid biosynthetic torrent may be single pathway to control the disorder. This route lead to the progress of new coumarins as STS (Purohit et al., 2003) and AR inhibitors as well as (Chen et al., 2004).

1.11 Fluorouracil

5-Fluorouracil (5-FU) is well known as the first option for colorectal cancer treatment owing to understanding of its reaction mechanisms of activity (Longley et al., 2003). As metabolites, 5-FU is integrated into DNA and RNA and act as thymidylate synthase retarder that prevent the development of cancer cell by activation of apoptosis process and stoppage of cell division (Longley et al., 2003). Though, in view of integrated retardation of colorectal cancer cells to 5-Fluorouracil and malignity to normal surrounding cells, attainment by the chemotherapeutic treatment of 5-Fluorouracil are insufficient in patients affected with CRC (Ohtsu et al., 2004). Moreover, only 10–15% patients suffering with cancer at initial level rapidly response to an early stage cancer actively response to 5-Fluorouracil separately. Preventive action enhances up to 50% when 5-Fluorouracil and other chemopreventive agents coupled with each other (Reglero et al., 2013). Activation of multiple existence and proliferative signaling route, involving receptor of epidermal growth factor (EGFR), nuclear related factor 2 (Nrf2), speedly accelerated fibrosarcoma nuclear factor kappa B (NF-κB), mitogen-activated protein kinase (MAPK), rat sarcoma virus oncogene, speedly accelerated fibrosarcoma and protein kinase B (Akt) etc. causing increase in growth of tumor and chemoinhibitors (Nakanishi et al., 2005; Jin et al., 2005; Akhdar et al., 2008). When complexity and affordability problem coupled with high rate of drug resistance made colorectal cancer treatment challenging at the global level, so the urgent study action should be taken. However, modulation of molecular targets with chemopreventives is an efficious mechanism to control the chemoinhibitors by coupling of natural compounds and 5-FU.

1.12 Polyphenols

Polyphenols encompass a various type of secondary metabolites stuffed in plants. Polyphenols in concentration of more than 8000 have been recognized in numerous species of plants (Scalbert et al., 2005). Specific attention in these naturally produced plant elements has been sparked by the quest for new chemopreventive agents that are more effective and harmless as compared to traditional treatment. Polyphenols has been considered active against carcinogenic qualities, like regulating cell division, growth of tumor, inflammation, angiogenesis, metastasis, and apoptosis (Ramos et al., 2008; Fantini et al., 2015). Polyphenolic compounds are categorized on the basis of number of phenolic rings and structural elements that joints other rings to each other. Following groups involve flavonoids, lignans, stilbenes and phenolic acids. Flavonoids found in vegetables, fruits, legumes, green tea and red wine and it has both property of antioxidant and anti-inflammation. Flavones consist primarily of luteolin glycosides and parsley and celery consider being important palatable origin of flavones (Manach et al., 2004). Flavanones stuffed in tomatoes and other specific aromatic plants like mint. Also, they found in citrus fruit in large amount.

Catechins are present in several kinds of red wine, green tea, fruits and chocolate. Epigallocatechin, gallocatechin and epigallocatechin gallate (EGCG) are present in grapes, teas and seeds of leguminous plants (Arts et al., 2000a; Arts et al., 2000b). Green tea is a rich source of catechins consists of 200 mg in a single cup of tea (Lakenbrink et al., 2000). As other clases of flavonoids, Flavanols food is not glycosylated in nature. Hence, heating under acidic pH, tea epicatechins become very stable. At pH 5, only 15% of these substances are destroyed after 7 h boiling (Zhu et al., 1997). Hydroxybenzoic acids are the only acid among phenolic acids that present

in tea and more familiar hydroxycinnamic acids that present in coffee, cinnamon, kiwis, apples, blueberries, plums, and cherries. The acids are commonly found in form of glycosylated derivatives of esters of quinic acid, tartaric acid and shikimic acid (Manach et al., 2004). Among the phenolic acid, Ferrulic acid is the most abundantly found acid that present in wheat and cereal grains. Ferrulic acid characterize up to approximately 90% polyphenols (Lempereur et al., 1999). Stilbenes is present in low amount in our food and is not adequate to exercise substantial medicinal action; large amounts available in concentrate or present in pure c; pound. Resveratrol exist as a specific stilbene and present in peanuts and red wine that has been extensively searched for its anticarcinogenic and other medicinal actions (Bhat et al., 2002). Lignans are present in legumes, flax seeds, cereals, grains, fruits, algae, and specific vegetables (Manach et al., 2004). Lignans amount in linseed is approximately 1000 times more as in other eatable sources (Adlercreutz et al., 1997). Secoisolariciresinol diglycoside (SDG), Plant lignin, and its metabolites played a promising role in preventing carcinogenic tumors, especially those which are hormone sensitive including breast, endometrium and prostate tumors (Tourė et al., 2010). Initiation, development and progression are different stages include in the development of cancer. Dietary polyphenols regulate several variant biochemical processes and routes include in cancer formation (Han et al., 2007). Furthermore, they also functions as biological response modifiers supportive in function of immune system and provide protection to living cells from the damage of free radicals. Though, polyphenols in vegetables and fruits are extensively concerned in prevention of cancer, some protective actions of each compounds have been definitely established in medicinal investigation owing to alterations in timing, dosing and other amazing factors.

1.13 Vinca alkaloids

Vinca alkaloids are basically organic compounds that is often extracted from plant named as alkaloid (Sahelian et al., 2011). They are present in nature and are semi synthetic nitrogenous bases of partly synthetic nature take out from plant Catharanthus roseus G, pink periwinkle. Don (Kufe et al., 2003). Vinca alkaloids has effective role in preventing cancer. Following four chief vinca alkaloids have been used for medicinal application: Vincristine (VCR), vinorelbine (VRL), vindesine (VDS) and vinblastine (VBL), but in United States, vindesine are not in use because of its disapproval (Kufe et al., 2003). The interactions of vinca alkaloids with disordering of microtubule function and tubulin is the chief mechanism of cytotoxity of vinca alkaloids, mainly of microtubules encompassing the mitotic spindle apparatus that cause metaphase blockage directly (Himes et al., 1991). However, there is an effect of vinca alkaloids and other antimicrotubular agents on both malignant and unmalignant cells in the non-mitotic cell cycle, by dint of involvement of microtubules in various non-mitotic activities (Kufe et al., 2003). On tubulin Vinca alkaloids joint to binding spot. Binding may happen speedly or not. Present confirmation established the presence of two binding sites of vinca alkaloid with tubulin dimer of 1 mole (Correia et al.,2001) Each microtubule has about 16 to 17 high power binding site existing at the ending point of 1 microtubule. Vinca alkaloids connection to these sites break off microtubule assembly, but most valuable action of low concentration of drug may be reduce the both growth rate and contraction at the end of congregation of the microtubule that producing a “kinetic cap” and reduce the activity (Jordan et al., 1992). They connect to microtubule that inhibits cell division, in its turn, causing mitotic arrest and apoptotic cell death. VCR and associated compounds destabilize the microtubules by connecting to tubulin and inhibiting the process of polymerization (Wang et al., 1999). They have been primarily involved in combine chemotherapy schemas for clinical treatment. Vinca alkaloids do not

possess resistance to drugs alkylating deoxyribonucleic acid (DNA) and possess a variant reaction mechanism of activity (Kufe et al., 2003). VBL is used as an important component of clinical cure schemas for medicinal testicular cancer and both Hodgkin lymphoma and non-Hodgkin lymphoma. (Rowinsky et al., 1995). It has been used in cancer of breast and germ cell. VBL has side-effects in reference to toxicity to leucocytes, vomiting, nausea, dyspnea, constipation, chest or pain of tumor, and fever. Also, it is infrequently related with anti-secretion of diuretic hormone (Kufe et al., 2003).VRL is similar to VBL. It believe to be important in reference to antitumor actions for the treatment of breast cancer and also used for osteosarcoma i.e. bone tumor cell. Moreover, VRL has tendency to reduce lipid bilayer membranes stability. In US, VRL has been certified for the primary treatment of advanced lung carcinoma patient (Gregory et al., 2000). VRL's has some bad-effects like reducing the retardation to infection, nausea, constipation, ecchymoses or bleeding, diarrhea, unconsciousness or paresthesia in the hands and feet, peripheral neuropathy, and swelling at the site of injection. Allergic reaction and hair shedding are example of least frequent side-effects by VRL (Kufe et al., 2003). VCR thought to be vital for treatment of severe leukemia, has been approved to treat acute leukemia, Hodgkin's disease, rhabdomyosarcoma i.e. skeletal muscle tissue carcinoma. Neuroblastoma i.e. nerve tissue carcinoma and Wilm's tumor. Recent study shows that VCR has been used for treatment of multiple non-malignant blood disease like refractory autoimmune thrombocytopenia, hemolytic uremic syndrome and thrombotic thrombocytopenia purpura. VCR has some common side-effects like Peripheral neuropathy, constipation, nausea, retardation of bone marrow action, nervous system toxicity and vomiting (Kufe et al., 2003; Rowinsky et al., 1995). VDS and VBL have some similar action. Antineoplastic action of VDS prove to be useful in severe lymphocytic leukemia, pediatric solid tumors, blast crisis of chronic myeloid leukemia (CML), breast, malignant melanoma, colorectal carcinomas, pediatric solid tumors and metastatic renal, esophageal carcinoma(Joel et al., 1996). In a recent study, a noval synthetic vinca alkaloid known as vinflunine was produced by addition of two fluorine molecules through super acidic chemistry (Schutz et al., 2011). Vinflunine, a vinca alkaloid, is well known for first fluorinated microtubule retarder. In Europe, Vinflunine has been applied for second-line transitional cell carcinoma of the urothelium (TCCU) treatment, and is under observed for other malignant tumors. Furthermore, it has been used for medicinal development of broad ranging solid tumors. Medicinally, vital action believes to be useful in cure of transitional cell cancer of urothelial tract, non-small cell lung and breast carcinoma. Vinflunine has been evaluated in transitional cell carcinoma of the urothelium and first-line advanced breast carcinoma patients (Bennouna et al., 2008).

1.14 Colchicine

Colchicine as an alkaloid is released from Colchicum automnale plant. It is well known as an anti-inflammatory agent to improve severe gout arrest and other inflammatory diseases for hundreds of years (Dudkiewicz et al., 2005). Colchicines not only used in treatment of severe hepatitis, biliary and alcoholic cirrhosis but used in treatment of cancer i.e. breast, cervical, esophageal and lung cancinoma, and chronic granulocytic leukemia (Kalpan et al., 1986). However, antitumor action of Colchicine is not completely known, it is broadly thought that the activation of programmed cell death is likely single cause. In a worthwhile record, numerical reverse transcriptase PCR and microarray research show that exclusively regulated DUSP1 gene may participate in blockage action of cell division of Colchicines on GC cells and a prominent retarding action on GC xenograft growth was noticed in bare mice followed by administration of Colchicine (Lin et al., 2016). Yet, according to the available data, their possible anticarcinomic molecular procedure for GC remains vague. After 48 h of drug exposure, the growth of both cells was

significantly inhibited in a dose-dependent manner in vitro analysis show that growth of both cells was considerably blocked depending on dose when 48 h of drug exposure occur. Cell survival reduced with increase of each Colchicine amount, Cells of NCI-N87 GC prominent more responsive to Colchicine as compare to AGS cells. In order to analyze, anti-clonogenic action of Colchicine on cells, test for colony formation are applied. Treatment with Colchicine clearly attenuated the colony-forming tendency of NCI-N87 GC and AGS cells, as proved by reducing the number and size of cell colonies treated with Colchicine than the control (Figure 2B). In addition, the retarding outcome of Colchicine on NCI-N87 GC cell colony formation was warrior than that in AGS cells. So, the outcomes exposed that Colchicine had a durable cyto toxic and static actions toward GC cells, especially for cells of NCI-N87 GC.

The action of Colchicine depending on dose reserved the transfer of AGS and NCI-N87 cells by 85.37% and 80.48% in AGS and NCI-N87 cells respectively at 2 ng/ml concentration; by 56.35% and 43.42% in AGS and NCI-N87 cells respectively at 5 ng/ml concentration; by 33.15% and 21.7% in AGS cells and NCI-N87 cells at 10 ng/ml concentration. Remarkably, the number of transfer NCI-N87 cells was low as compared to AGS cells followed by action of Colchicine at each same dose (Figure 2D), though it was numerically inconsiderable ($P>0.05$). Inclusively, consequences designated that Colchicine could overpower GC cells division and migration.

1.15 Cabazitaxel

Inborn brain tumors are referred as malignant gliomas. Fatal intrinsic tumors of brain are released from glial cell and this type of tumor are most common (Abbott et al., 2012). Furthermore, gliomas possess greater efficiency to disperse in nearby areas wherein satellite colonies are formed (Friedl et al., 2011). Chemotherapy is the first-line basic therapy for gliomas when neurosurgery is not used (Han et al., 2015; wu et al., 2015). Therefore, the properties of tumor angiogenesis depict a barrier for treatment of neuro tumors by dint of disputed permeability and blood-brain retarder function (Girard et al., 2015, Donnem et al., 2013). Brain tumors' capillary endothelial cells are clinically under study in such a manner that they causes shortage of penetration and avoiding the passive diffusion of treatment into the brain (Furuse et al., 1993; Kniesel et al., 2000). So, finding and usage of agents or small molecules with greater efficiency for passive diffusion across the blood-brain barricade would enhance treatment of glioma. Cabazitaxel is well known as second generation taxane which is used for treatment of prostate cancer (Tsao et al., 2011; Semiond et al., 2013; Ecstein-Fraisse et al., 2014]. Basically, the tendency of several drug efflux pumps for first generation taxanes is a hurdle that contracts the potency in tumors of brain. However, cabazitaxel's connection to these pumps shown to be relatively low (Semiond et al., 2013; Mizutani et al., 2015). Furthermore, cabazitaxel share with regular standard across the brain (Semiond et al., 2013). However, these properties make cabazitaxel a powerful choice for first- and second-line therapy of glioma. Recent research shows that, it acts as a powerful cytotoxic agent for brain and spinal cord tumor. Outcomes disclose that treatment of cabazitaxel notably decrease glioma life and cell division. Furthermore, it is illustrated that low amount of cabazitaxel was adequately sufficient to affect cells of glioma. In addition, primary neurons and astrocytes treatment with cabazitaxel not influence cell life and cell shape or structure. In the VOGiM analysis, cell survival did not alter in non-tumoral region under cabazitaxel therapy. Although, regarding unintentionl side effects; two antagonistic data files have been issued. Girard and his fellows determined (Girard et al., 2015) the maximally tolerated concentration for C57BL/6 mice. Mice affected with Smo-Smo flank allograft tumors have been medicated with concentration of 9, 15, or 25 mgkg-1 cabazitaxel in peritoneal cavity for 3 days. However, mice treated

with cabazitaxel in concentration of 25 mgkg-1 lost notably body weight, and after 20 days, all mice gain starting weight (Girard et al., 2015). Conversely, Karavelioglu's colleagues (Karavelioglu et al., 2016) treated the Wistar rats with cabazitaxel in peritoneal cavity. Treatment with cabazitaxel (1.0 mg/kg) is administered via injection at a one time in one week and repeated this for four week that result in neurotoxicity in brain of rats with programmed cell death. However, in pathological stage I trial involving 21 sufferer with colorectal, cervical, endometrial and lung carcinoma attain rapidly increasing concentration of cabazitaxel (Diéras et al., 2013). Finally, cabazitaxel at a safe drug point of 25 mgm-2 was suggested for future medicinal investigation. Research analysis show the concurrent existence of tumor and normal cells and show that cabazitaxel has a high influence on tumor cells without neurotoxic sign. Focus is placed to explore best way of cabazitaxel usage and differences of species in order to elucidate antagonistic reports.

1.16 Bullatacin

Bullatacin, a latent antitumor ingredient secluded from Annonaceae plants, and correspondents of bullatacin. It is generally known as acetogenins and stated formerly to display effective actions in the retardation of murine tumor growth and human tumor xenografts that developed in athymic mice as well as ability to retard mitochondrial electron transport. For retardation of NADH oxidase action of plasma membrane vesicles the capability of bullatacin is secluded from HL-60 and HeLa cells but not with vesicles of plasma membrane secluded from liver of rat that diverse the retardation of mitochondrial action, associated with the capability of the acetogenins to destroy tumor cells. Moreover, it is active against cell line (HL-60) that is unaffected to Adriamycin that commend usefulness of bullatacin in direction of medicine resistant cell lines and cells.

The uniqueness of NADH oxidase activity of liver plasma membranes amongst oxidoreductase actions is not merely as a result of hormones and growth factors but, also by dint of its retarder and activators except for hormones and growth factors (MORRÉ et al., 1990; MORRÉ et al., 1992; MORRÉ et al., 1998). The NADH oxidase action of liver plasma membrane of rat was mainly uninfluenced by bullatacin, while the NADH oxidase activation of plasma membranes of HL-60 and HeLa was powerfully retarded. The outcomes show a notable difference as a result of bullatacin between the NADH oxidase action of liver and that of HeLa cells that associated with the recently noted powerful retardation of transformed cell growth (JOLAD et al., 1982; RUPRECHT et al., 1990; FANG et al., 1993).

1.17 Harmine

As a β-carboline alkaloid, Harmine (HM) was formerly secluded from and Banisteriopsis caapi and Peganum harmala seeds in 1847 (Patel et al., 2012). HM is generally present in numerous pathological plants and has extensively applied in traditional medicine in the Middle East and Asia (Berrougui et al., 2006). In vitro and in vivo analysis show that HM depicts notable antitumor actions (Chen et al., 2005), including inhibiting proliferation (Chen et al., 2005), migration (Zhang et al., 2014) and invasion (Dai et al., 2012)), promoting programmed cell death (Li et al., 2017)) and avoiding tumor formation. HM hinders the progress of numerous kinds of carcinoma, involving lung (Abe et al., 2009)), gastric (Li et al., 2017), breast (Hasheimi et al., 2015) and hepatic cancer (Zhang et al., 2015). It seizures the cell cycle at the G0-G1 stage (Hamsa et al., 2011)) and declines the cyclin-dependent kinase action (Song et al., 2004). HM involve cell eating and programmed cell through the protein kinase B (Akt)/mammalian target of rapamycin (mTOR) and extracellular signal-regulated kinase (ERK)1/2 signaling routes that enhance the expression of pro-apoptotic factors, involving P53, B-cell lymphoma 2 (Bcl-2)-associated X protein (Bax), caspases 3-8-9, and BH3-interacting domain death agonist (Bid), and decreases the pro-inflammatory cytokines level, involving TNF-α,

IL-6 and granulocyte-macrophage colony-stimulating factor, in skin and gastric carcinoma (Zhang et al., 2013). HM persuade autophagocytosis through enhancing LC3-II and regulating P62 in concentration depending way in B16 cells (Zou et al., 2017). HM retard the expression of pro-metastatic genes expression, involving matrix metalloproteinase-9, ERK and vascular endothelial growth factors, to suppress skin cell invasion (Hamsa et al., 2010).

Transcriptional co-activator with PDZ-binding motif [20] was primarily recognized as a 14/3/3 binding protein (Zou et al., 2016). Owing to insuffiency of a DNA-binding domain, TAZ is not a transcription factor, but play a role as a transcriptional modulator though it's Trans activating domain. Besides its collaboration with 14/3/3 proteins, it is testified to interrelate with several proteins, involving thyroid transcription factor-1 (Park et al., 2004), myogenic differentiation 1 (Jeong et al., 2010), Smads (Varelas et al., 2010), core-binding factor α1/Runt-related transcription factor 2 (Cui et al., 2003), transcriptional enhancer factor-1 (Mahoney et al., 2005), peroxisome proliferator-activated receptor (Hong et al., 2005) and TEA domains (Zhang et al., 2009). Functioning as a transcriptional coactivator, TAZ is vital in myogenic, osteoblastic, and adipogenic distinction (Hong et al., 2006). In 2011, TAZ was initially identified as a cancer causing protein in non-small cell lung carcinoma (Zou et al., 2011). Composing research show that TAZ expression is upraised in different kinds of human carcinoma, involving colorectal carcinoma (Wang et al., 2013), brain tumor (Bhat et al., 2011) and breast carcinoma (Zhou et al., 2015; Cordenonsi et al., 2011). TAZ over expressing results in behavior of cancer cell, involving, but not restricted to, cell division that is not dependent on growth factor (Yang et al., 2012) and chemotherapeutics resistance (Zou et al., 2015). It increases cell division, epithelial-mesenchymal transition (Cordenonsi et al., 2011), migration, invasion, and tumor formation, in xenograft models (Yuen et al., 2013), signifying an oncogenic component of TAZ involve in the development of human carcinoma.

1.18 Theabrownin

Fresh leaves as a green tea are released from the everlasting plant species of Camellia sinensis, Kuntze (Theaceae). They have been extensively used as the primary health beneficial drink at the global level. They are officially recognized as a medicine by the most ancient national pharmacopeia 'Xin Xiu Ben Cao' (Newly Revised Materia Medica, AD 659) in Tang Dynasty of China. They are familiar with bitter and sweet taste. Also, they are cold and non-toxic in nature and have tendency to remove heat, sputum, and toxins from body. In the outdated Chinese medicine (TCM) theory, sputum, heat, and toxins are rated as roots of several long lasting disorder, like carcinoma that results in the use of green tea by traditional Chinese medicine for the inhibition/cure of cancer (Yang et al., 2014). Several study shows that green tea prove to be active especially for lung carcinoma (Imai et al., 1997; Yang et al., 2000; Cabrera et al., 2006; Suqanuma et al., 2011). TB is a basic portion leading the pathological actions of green tea, like cholesterol-reducing action in releasing lethargy and lowering blood lipid levels (Gong et al., 2010). Because of the crucial role of TB in green tea, it is anticipated that TB has absolute anti-lung carcinoma potency and recognized for the same action of green tea. Although, either it does is still undetermined.

Cell division is relay on development of cell cycle consisting of S, G1, G2 and M stages, and passing from the G1 to S stage is vital as it runs the alternative development of the cell cycle (Luo et al., 2016). Transition on G1 to S stage is closely monitored by the activation of CDKs that functions progressively in G1 phase to start the S phase and then G2 phase to initiate process of mitosis (Genovese et al., 2006; Lim and Kaldis, 2013). Previous research shows that several natural products could avoid movement of cell cycle (G0-G1 arrest) and cell division of the

non-small cell lung carcinoma i.e. A549 cell line, showing G0-G1 control point in cell cycle as one of the most clear goal for anti-cancer agents.

1.19 Psoralidin

Psoralidin (Figure 1) as the cheif (angular type) furanocoumarins secluded from Psoralea corylifolia seeds belong to Leguminosae, a remedial plant broadly cosmopolitan in Southeastern Asian countries (Zhao et al., 2005; Xiao et al., 2010). Induction cytotoxicity counter to gastric SNU-1 and 16, colon HT/29 and breast MCF-7 carcinoma cells are stated reported by psoralidin. Also, Psoralidin triggered apoptosis in androgen-independent DU/145, PC/3 and androgen-dependent LNCaP, C4/2B glandular carcinoma cells and repressed growth of PC/3 xenograft tumor in bare rodents (Yang et al., 1996; Mar et al., 2001; Pahari et al., 2009; Srinivasan et al., 2010; Kumar et al., 2010). Chemoprevention as an approach of tumor control during which cancer is inhibited or inverted by healthful or biological interference by use of natural or manufactured substances (Krenn et al., 2009; Ozmen et al., 2009; Ozmen et al., 2010; Szliszka et al., 2011 a, Szliszka et al., 2011b,Szliszka et al., 2011c). Numerous laboratory and epidemiological research reported the function of biological active compounds in prevention of carcinoma (Szliszka et al., 2011 c, Vanamala et al., 2006, Turner et al., 2009, Warren et al., 2009, Leonardi et al., 2010). Coumarins or other synthesized derivatives display a diversity of bioactions and have graded tremendous attention in view to powerful advantageous effects of human health and chemoprevention (Wu et al., 2009; Riveiro et al., 2010). So, natural or synthetic coumarins is becoming progressively acknowledged as an effective approach in prevention of cancer.

Tumor death factor-associated programmed cell death involving ligand (TRAIL), a powerful activator of programmed cell death in carcinoma cells, is vital immune activator molecule within the vigilance and protect against growing tumors. Endogenous TRAIL is depicted on the surface of dendritic cells, neutrophils, T lymphocytes, natural killer cells, monocytes or macrophages and might be splited into a secreted and soluble form (Szliszka et al., 2011 c, Lee et al., 2007, Szliszka et al., 2011 d). TRAIL activates programmed cell death in carcinoma cells through its correlation with specific death receptors. Two receptors i.e. TRAIL-R2/DR5 and TRAIL-R1/DR4 are extracellular domains identified and bind to ligand. Death receptors consist of complete and useful intracellular death domains responsible for the activation of route for programmed cell death in carcinoma cells (Horinanka et al., 2005; Szliszka et al., 2009). Therefore, some carcinoma cells are influenced to TRAIL-regulated death. Death receptors expression in carcinoma cells can be included in TRAIL-resistance (Lee et al., 2007; Szliszka et al., 2011 d; Horinanka et al., 2005, Szliszka et al., 2009).

1.20 Tylophorine

In East Asia, Several plants belong to Tylophora genuses have been used pathologically against arthritis, inflammation, and amebic agents (Wu et al., 2002). The phenanthroindolizine alkaloid tylophorine and its analogs are basically present in plants belong to Asclepiadaceae family, involving Tylophora genus members (Li et al., 2001). However, tylocrebrine, as a natural product associated to tylophorine, unsuccessful in anticarcinomic pathological research in 1966 in view to malignity to the central nervous system, Specific cytotoxic agents were reassessed for antitumor power by the National Cancer Institute [13] by use of tumor cell line-60. Previous study show that multiple new polar water-soluble synthesized phenanthrene-dependent tylophorine derivatives (PBTsa) prove to be powerful for cytotoxic action against the A549 human lung carcinoma cell line (Wei et al., 2006). These compounds don't possess property of toxicant to CNS toxicity, as their enhanced polarity should shield them from interruption of blood–brain barrier. In vivo analysis shows that Compound PBT-1 exhibit mild antitumor action against human A549

xenografts in bare mice and proves to be powerful for cytotoxic action in vitro study (Wei et al., 2007).

Tylophorine equivalents show efficacious growth retarding action compared to wide-spread multiple human carcinoma cells (Staerk et al., 2002; Ganguly et al.,2002;Komatsu et al.,2001; Rao et al.,2000; Rao et al., 1971) and the antitumor actions levels from the everlasting retardation of synthesis of protein at the elongation level of the translation cycle (Gupta et al., 1977; Huang et al., 1972; Donaldson et al., 1968) Several important metabolic enzymes, involving dihydrofolate reductase and thymidylate synthase (Rao et al.,1997) have been certified as tylophorine alkaloids, a biological target (Rao et al., 2000). Also, Tylophorine derivatives inhibit protein-1–mediated activator, CRE-regulated, and nuclear factor kappa B (NF-κB)-regulated transcription (Gao et al., 2008; Gao et al., 2004) the inventions clarify the tendency of tylophorine derivatives as a novel category of antitumor drugs. However, the full evaluation of antitumor actions of tylophorines has not been reported, and the approach accountable for the retarding actions of carcinoma cell growth is mainly uncommon.

II. Conclusion

The phytochemicals obtain from the plants offers significant anti-cancer effects and are proposed to be used individually or in combination with other treatments like chemotherapy for the treatment of various sort of cancer. Many phytochemicals have shown positive results in clinical trials. The current study explained various phytochemicals with anti-cancer potential, their origin and clinical effectiveness against the disease.

References

Wilken, R., et al., *Curcumin: A review of anti-cancer properties and therapeutic activity in head and neck squamous cell carcinoma.* Molecular cancer, 2011. **10**(1): p. 12.

Townsend, D.M. and K.D. Tew, *The role of glutathione-S-transferase in anti-cancer drug resistance.* Oncogene, 2003. **22**(47): p. 7369-7375.

Marchese, A., et al., *Antibacterial and antifungal activities of thymol: A brief review of the literature.* Food chemistry, 2016. **210**: p. 402-414.

Goodner, K.L., et al., *Aromatic profiles of Thymus hyemalis and Spanish T. vulgaris essential oils by GC–MS/GC–O.* Industrial Crops and Products, 2006. **24**(3): p. 264-268.

Petersen, M. and M.S.J. Simmonds, *Rosmarinic acid.* Phytochemistry, 2003. **62**(2): p. 121-125.

Huang, S.-s. and R.-l. Zheng, *Rosmarinic acid inhibits angiogenesis and its mechanism of action in vitro.* Cancer letters, 2006. **239**(2): p. 271-280.

Li, F.-R., et al., *Reversal effect of rosmarinic acid on multidrug resistance in SGC7901/Adr cell.* Journal of Asian natural products research, 2013. **15**(3): p. 276-285.

Lin, J., et al., *Vitamins C and E and beta carotene supplementation and cancer risk: a randomized controlled trial.* Journal of the National Cancer Institute, 2009. **101**(1): p. 14-23.

Pastorino, U., et al., *Vitamin A and female lung cancer: A case-control study on plasma and diet.* 1987.

Van Poppel, G. and R.A. Goldbohm, *Epidemiologic evidence for beta-carotene and cancer prevention.* The American journal of clinical nutrition, 1995. **62**(6): p. 1393S-1402S.

Pradeep, C.R. and G. Kuttan, *Effect of [beta]-carotene on the inhibition of lung metastasis in mice.* Phytomedicine, 2003. **10**(2/3): p. 159.

Bogenmann, E., *A metastatic neuroblastoma model in SCID mice.* International journal of cancer, 1996. **67**(3): p. 379-385.

Hazuka, M.B., et al., *Beta-carotene induces morphological differentiation and decreases adenylate cyclase activity in melanoma cells in culture.* Journal of the American College of Nutrition, 1990. **9**(2): p. 143-149.

Palozza, P., et al., *β-Carotene regulates NF-κB DNA-binding activity by a redox mechanism in human leukemia and colon adenocarcinoma cells.* The Journal of nutrition, 2003. **133**(2): p. 381-388.

Vargas, A.J. and R. Burd, *Hormesis and synergy: pathways and mechanisms of quercetin in cancer prevention and management.* Nutrition reviews, 2010. **68**(7): p. 418-428.

Harborne, J.B., *Nature, distribution and function of plant flavonoids.* Progress in clinical and biological research, 1986. **213**: p. 15-24.

Javed, H., et al., *Rutin prevents cognitive impairments by ameliorating oxidative stress and neuroinflammation in rat model of sporadic dementia of Alzheimer type.* Neuroscience, 2012. **210**: p. 340-352.

Lin, J.P., et al., *Rutin inhibits human leukemia tumor growth in a murine xenograft model in vivo.* Environmental toxicology, 2012. **27**(8): p. 480-484.

Alonso-Castro, A.J., F. Domínguez, and A. García-Carrancá, *Rutin exerts antitumor effects on nude mice bearing SW480 tumor.* Archives of medical research, 2013. **44**(5): p. 346-351.

Nassiri-Asl, M., et al., *The effects of rutin on the development of pentylenetetrazole kindling and memory retrieval in rats.* Epilepsy & Behavior, 2010. **18**(1-2): p. 50-53.