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A REVIEW ON THE USEFULNESS OF VARIOUS EUKARYOTIC PIGMENTS AND METABOLITES IN CANCER TREATMENT

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ABSTRACT

In the twenty first century, cancer has bound humanity in its shackles. Therefore various research studies are currently focussed on the development of new drugs and procedures for the treatment of cancer. Natural[1] products have always proved very fruitful in cancer research and several anti-cancer drugs have been obtained from natural products. This review focuses on the wide range of pigments and metabolites obtained from various eukaryotic sources including plants, algae, fungi, animals etc and aims to provide an idea about how they can be used as useful anti-cancer agents which may be helpful to find some innovative treatments and drugs to treat cancer.

KEYWORDS: Natural products, eukaryotes, cancer, pigments, metabolites.

INTRODUCTION

Cancer is an uncontrolled division of cells which occur mainly because a series or a combination of mutations that results in alteration of behaviour of several genes.[2] Cancer has now become the leading cause of death in the entire world. This is mainly due to ageing and growth of the world's population.[3] It is now a challenge to find some novel treatment method to fight cancer. This review gives an overall idea about various eukaryotic sources from which we can derive several anti- cancer and anti-tumor drugs. Flavonoids, curcumin, carberin, capsaicinoids, neoplacin, caroteinoids, piplartine, several types of venoms,

amsacrine, berberine, camptothecin derivatives products from aquatic eukaryotic microorganisms, plants and microalgae etc. have been known to possess a vast array of biological activities including antiviral, anti-inflammatory, antitumor, antimicrobial, estrogenic, anti-estrogenic, antioxidant and anti-mutagenic which helps in targeting different pathways involved in cancer progression.

A COMPLETE REVIEW

Aquatic eukaryotic microorganisms have always been potent sources in producing several anti-cancerous substances and metabolites that generally act as chemo-preventive agents and as factors that increase therapeutic efficacy of existing drugs which help in overcoming cancer cell drug resistance.[4-16] These organisms have developed various biochemical and physiological mechanisms which aid in surviving in highly competitive environment. They produce terpenoids, polyketides, alkaloids, sugars acid derivatives, steroids and mixed biogenesis metabolites.[17-20] *Ciliophora,* commonly called ciliates are known to produce pheromones that are responsible for the switching between the reproductive (mitotic growth) and mating (sexual) stages of ciliate life cycles.[21] A study done by Cervia et al.[22] indicates that the ciliate pheromone Er-1, may act as an immune-modulatory factor with anti-cancer properties. They found Er-1 to be active at nano-molar concentrations which indicate a high sensitivity of human T-cells to the pheromone which is probably due to an efficient activation of the intracellular cascade primed by Er-1 binding to cell membranes. It is also found that Er-1 increased the Jurkat cell production of different T helper type 1 or type 2 cytokines, including tumour necrosis factor-, IL-1, IL-2, and IL-13 and brings about an in vitro inhibition of human glioma U-373 cells growth.[22]

Flavonoids are low molecular weight poly phenolic molecules produced in the plant kingdom commonly found in fruits and vegetables and are also present in some vacuoles of flowers, leaves, stems or roots and comprise the major red, blue, and purple pigments of flowers, fruits, seeds, and leaves[23] exhibiting exhibit a vast array of biological activities including anti-inflammatory, antiviral, anti-estrogenic antitumor, antimicrobial, antioxidant, anti-mutagenic which help in targeting different pathways. Compounds like Genistein, Daidzein or its synthetic derivative Phenoxodiol as well as Luteolin and Quercetin are able to inhibit DNA topoisomerases.[24] Camptothecins.[24] Catharanthus indole alkaloids (e.g. Vincristine), epipodophyllotoxins and taxanes are some of the most important drugs used in the first line of treatment in chemotherapy that primarily target DNA topoisomerase I (Top 1) and II (Top

2), respectively.[25-27] and cause inhibition of topoisomerase catalytic (relaxation) activity.[28] .Different Flavonoids have been known to demonstrate an interaction with purified topoisomerases resulting in anti-neoplastic as well as clastogenic activity in mammalian cell systems.[29-36] Flavones, namely Chrysin, Apigenin, Kaempferol, Fisetin, and Quercetin, are more potent in poisoning Top 1 whereas Apigenin, Fisetin and Quercetin as very potent Top 2 inhibitors. Camptothecin (CPT) derivatives are found to inhibit the function of DNA topoisomerase I (top 1).[37-39] Additionally irinotecan (CPT-11) is reported most active anticancer agent in treatment of colon cancer.[40]

Cerberin (CR) is a commonly known cardenolide isolated from the fruit kernel of *Cerbera odollam*. It was found to potently inhibit cancer cell growth as they are found to be cytotoxic against different cancer cell lines.[41-48] Experiments by Hossan et al. indicate that CR inhibits cancer cell proliferation, triple negative breast, non –small cell lung cancer cell lines and the migration and colony survival in human –derived pancreatic cell lines mainly by G2/M cell cycle arrest ,disruption of cytoskeletal architecture ,suppressing PI3K/AKT/mTOR and STAT 3 signal transduction , down-regulated PLK 1, c-Myc, Bcl-2 and Mcl-1 expression and increasing ROS production and caused DNA DSBs, ultimately inducing apoptosis.[48]

When eukaryotic pigments are considered, the contribution of microalgae can never be ignored. Microalgae are known to produce a variety of polysaccharides, the main producers being diatoms, chlorophytes, prasinophytes, haptophytes, rhodophytes, and dinoflagellates.[49] Microalgae mainly produce carotenoids, glycolipids, polysaccharides, and proteins.[50] Carotenoids are not only produced by microalgae but also by different photosynthetic plants, protists, bacteria, and even by some heterotrophic bacteria, fungi, and invertebrates as well. β-carotene, lutein, astaxanthin, violaxanthin, and fucoxanthin are reported to posses significant anticancer activities.[51] Palozza et al. (2005).[52] highlighted that β-carotene inhibited significantly the growth of human colon cancer cell lines and that astaxanthin has the property of inhibiting the growth of human colorectal cancer (CRC) cell lines, including human cancer cell lines HCT-116, HT-29, LS-174, WiDr, and SW-480.[53]

Pham et al. (2013) demonstrated that β-carotene decreased migration, invasion, and metalloproteinase (required for invasion of tumor cells into a new tissue) expression in colon carcinoma cells.[54] Lutein is a compound produced mainly by Dunaliella salina (Fu et al., 2013).[55] Chlorella sorokiniana (Pasquet et al., 2011).[56] and Chlorella prothecoides (Shi and Chen, 2002).[57] and it has commonly known anti-proliferative effects on the human colon

cell line HCT-116 (Cha et al., 2008).[58] Violaxanthin isolated from D. salina (Pasquet et al., 2011) and Chlorella ellipsoidea (Talero et al., 2015) is reported to demonstrate anti-proliferative and pro-apoptotic effects against human colon cancer cell line HCT-116. Fucoxanthin is known to be the most promising carotenoid for drug development against cancer. Kumar et al. (2013) have reported fucoxanthin's anti-proliferative effects against SK-Hep-1 (human hepatoma) cells, BNL CL.2 (murine embryonic liver) cells, colon cancer cell lines (Caco-2, HT-29, and DLD-1), PC-3 prostate cancer cells, and HL-60 leukemia cells. Separate studies done by (Mizushina et al., 2012)[60] and (Hossain et al., 2005)[61] concluded that mono-galactosyldiacylglycerol (MGDG) had an effect toward the HT-29 human colon adeno-carcinoma tumors. GA3P (d-galactan sulfate, associated with l-(+)-lactic acid), an extracellular polysaccharide, purified from Gymnodinium sp., can inhibit the growth of different cell lines specially the colon cancer cell lines (HCC2998, KM-12, HT-29, WiDr, HCT-15, and HCT-116) as reported by Umemura et al., 2003.[62]

Curcumin obtained from the rhizome of *Curcuma longa* is a natural yellow, orange dye .From time immemorial it is known that curcumin is associated with a large number of anti-tumor and anti cancer properties. It down-regulates the activity of two major transcriptor factors NF-κB and AP-1. It also has the capability to suppress mitogen-activated protein kinases (MAPKs) generated by inflammatory stimuli, scavenge reactive oxygen species (ROS), suppress the expression of pro-inflammatory enzymes cyclo-oxygenases (COX-2) and lipoxygenases (LOX), induce apoptosis in the cancer cells by up regulating p53 protein and induce Phase II detoxification enzymes. Owing to its different moieties in its chemical structure, curcumin has also been found to be a good antioxidant, anti-inflammatory and anti-mutagenic agent.[63] A study done by Jobin et al. using intestinal epithelial cells (IEC), showed that curcumin blocked NF-κB activation by blocking the signal leading to IKK activity[64] and suppressed many inflammatory genes that are regulated by NF-κB such as TNF, COX-2 and NOS2.[65] Curcumin is found to induce apoptosis in cancer cells taken from the colon, liver, and breast[66] Curcumin is known to promote apoptosis thus bringing a check in the promotion of uncontrolled cell division by . activating caspase 8, leading to cleavage of BID, loss of mitochondrial potential, opening of transition pores, release of cytochrome C, activation of caspase 9 and 3, activation and cleavage of PARP and finally DNA fragmentation and apoptosis. An alternate way may also be followed by curcumin like apoptosis by down-regulating anti-apoptotic proteins such as bcl-2 and bcl-xL. Study by Choudhuri et al. found that curcumin induced Bax through p53, which caused the release of

cytochrome c from the mitochondria, thus leading to apoptosis.[67] Treatment of cells done with curcumin is found to arrest the cell cycle at the G 2 - M stage in several cell types, and this results in reduction in the expression of genes such as p53, p21, Bcl-xl and up-regulation of Bax.[68]

Fruits and vegetables that we normally consume in our diet contain varieties of phytochemicals having anticancer properties.[69] Capsaicinoids present in the genus Capsicum *(Solanaceae*) are naturally occurring phenolic compounds possessing remarkable anti-mutagenic and anti-tumour properties.[70-72] The highest concentration of capsaicinoids is found in C. Chinense among the chilli varieties.[73] Diverse studies have shown that capsaicin has anti-proliferative effect on several human cell lines derived from multiple myeloma,[74] gastric cancer,[75] pancreatic cancer.[76] breast cancer[77] and prostate cancer[78] etc. Capsaicin shows anti-proliferative effects on various human cancer cell lines by apoptosis mediated cell death,[79] It suppresses the expression of the inhibitor of caspase activated DNase to induce apoptosis of human melanoma cells.[80] Capsaicin induces apoptosis by bringing an elevation in the levels of intracellular ROS and Ca2+, promoting the levels of Bax, GADD153 and GRP78, decreasing membrane potential, Bcl-2 XIAP and CIAPI. ROS play significant role in the induction of apoptosis in HepG2 cells by capsaicin.[80]

Neplanocin A isolated from the culture filtrate of *Ampullariella regularis* A11079 by means of ionexchange, carbon, silica gel adsorption, or partition chromatography is a novel carbocyclic analog of adenosine. It demonstrates cytotoxicity against L5178Y cells in culture and shows a remarkable effect on the life prolongation of mice infected with L1210 leukemia. It demonstrates cytotoxicity at 0.2 mcg/ml against lymphoma cell line L5178Y cell in culture. The acute toxicity (LD50) in mice was 13.7 mg/kg when administered intra-peritoneally.[81]

Piplartine{5,6-dihydro-1-[(2E)-1-oxo-3-(3,4,5-trimethoxyphenyl)-2-propen-1-yl]-2(1H)-pyridinone} isolated from the roots of *Piper tuberculatum* , is an alkamide present in Piper species that exhibits promising anticancer properties , anti-inflammatory, insecticidal, anti-hypertensive, anti-diabetics, immune-modulating, antifungal properties, anti-platelet aggregation, as well as anxiolytic, antidepressant and antitumor activities in murine models . Piplartine is mutagenic in yeast and genotoxic in mammalian cultured cells due to the increased incidence of DNA double strand breaks (DSBs). Anticancer effect in vivo was

evaluated in mice by transplanting with sarcoma 180 and in vitro anti-leukemic activity in HL-60, K562, Jukart, and Molt-4 cell lines by Bezerra et al.[82-94]

W. somnifera L. is reported to have several anti-carcinogenic properties .It decreases the expression of nuclear factor-kappaB, suppressing intercellular tumor necrosis factor, and potentiating apoptotic signaling in cancerous cell lines.[95] L-Asparaginase purified from *W. Somnifera* has been reported for many years as effective drugs in the treatment of acute lymphoblastic leukemia.[96] L-asparaginase is also produced by endophytes. Endophytic bioactive compounds were gradually integrated in novel drug discoveries due to their wide variety of biological activities as antibiotic, anticancer, antioxidant, and anti-inflammatory agents.[97] This anticancer agent was formerly extracted from the Pacific yew tree, and with this discovery, more taxol was produced without the mass destruction of the yew trees. With the discovery of taxol-producing endophyte T. andrenae from yew trees, it is hypothesized that endophytes have potential to synthesize compounds like campthothecin.[98] maytansine[99] and cajanol[100] possessing anticancer properties. In cancer treatment, L-asparaginase removes L-asparagine in the serum, depriving tumor cells from large amounts of asparagine required for growth [101] thus controlling tumor growth effectively.[102]

Kezia et al.,[103] investigated the in vitro and in vivo antitumor properties of a sulfated polysaccharide isolated from the seaweed *C. feldmannii*. It showed in vivo antitumor effect. The extract from a red alga, *Amphiroa zonata* exhibited strong cytotoxicity to all human leukemic cell lines[104] Fascaplysin is a red pigment isolated from marine sponge *Fascaplysinopsis sp*. It is found to have a significant cyclin-dependent kinase inhibitor activity.[105] Fascaplysin, carboline class alkaloid showed highly selective CDK4/D1 and CDK6/D1 inhibition in the high nanomolar range.[106] Arctigenin is a novel anti-inflammatory lignan obtained mainly from the seeds of *Arctium lappa*.[107] The anti-carcinogenic activity of Arc has been demonstrated in vitro and in a few animal studies in several cancers, including pancreatic, breast, and lung cancer, associated with the induction of apoptosis, inhibition of proliferation and modulations of multiple signaling pathways.[108-109] A strong induction of the tumor suppressor TIMP3 and ZNF185 was observed in both LNCaP and LAPC-4 cells.[110] TIMP3 is an inhibitor of matrix metallo-proteinases (MMPs), and it also blocks the binding of VEGF to VEGF receptor-2 to inhibit angiogenesis. A study demonstrates that treatment with Arc significantly decreased the expression of pro-angiogenic miR-126-5p and miR-21-5p in tumors, and increased the expression of five putative tumor suppressor

miRNAs, including miR-135a-5p.[111] miR-205-5p,[112] miR-22-3p,[113] miR-455-5p,[114] and miR-96-5p.[115]

Extracts of different macrophytes and microphytes are known to possess cytotoxic activities. The extracts of Polysiphonia urceolata are found to be active against HT-29 cells while the extracts from *Symphyocladia latiuscula, Rhodomela confervoides* and *Punctaria latifolia* showed cytotoxic activities towards HT-29 and KB cells.[116] Nine species (*Leathesia difformis, Polysiphonia urceolata, Scytosiphon lomentaria, Gloiopeltis furcata, Dictyopteris divaricata, Punctaria latifolia, Symphyocladia latiuscula, Rhodomela confervoides*, and *Gracilaria verrucosa)* showed antineoplastic activities. The extracts of *Leathesia difformis* were more toxic against KB cells.[116] The selective cytotoxic activity of extracts from two marine green algae, *Cladophoropsis vaucheriaeformis* and *Halimeda discoidea*, were examined via a dose response assay against mouse leukemia L-1210 cells and normal NIH-3T3 cells. The MeOH extract of *C. vaucheriaeformis* showed selective cytotoxicity to L-1210 cells at concentrations ranging from 50 to 100 μg/mL.[118] An extract of the red marine alga Liagora farinose (Rhodophyta, Nemaliales), was reported to possess cytotoxic activity. The ethanolic extract of C. prolifera exhibited antitumor activity against Ehrlich ascites carcinoma in vitro.[119-122]

Some plants are known to produce a variety of toxins, but in reduced amounts, *C. taxifolia* synthesizes a single major secondary metabolite, caulerpenyne which was found to be cytotoxic to several cell lines. Caulerpenyne generally blocks polymerization of pure tubulin with an IC50 of 21 μM, presumably by inducing its aggregation after a short incubation in vitro. Cells of colorectal cancer origin were the most sensitive to caulerpenyne, with IC50 values from 6.1 to 7.7 μM.[123] Tubulin may represent just one of the targets of caulerpenyne.[124] Marine red algae of the genus *Laurencia* (order *Ceramiales*, family *Rhodomelaceae*) are widely distributed in temperate and tropical waters .Their crude extracts showed cytotoxic activity against the U937 tumor cell line in the range 0.5 to 40 μg/mL, and strong activity against *leishmania* in vitro.[124] Antitumor bioassay-guided fractionation of the organic extract of the marine Brown Bowl Sponge (*Cribrochalina vasculum*) resulted in the isolation of several closely related cytotoxic acetylenic alcohols.[125] Isolated compounds selected from this series showed selective in vitro antitumor activity against H-522 non-small cell lung line and IGROV-1 ovarian line.[126] Five acetylenic alcohols with immunosuppressant and antitumor activity were isolated from the sponge *Cribrochalina*

vasculum and characterized.[127] The alcohols displayed immunosuppressive activity in mixed lymphocyte reaction and CV-1 cytotoxicity assays. Being tested in vitro on P388 leukemia cells, and cells from human lung (A549) and colon (HT-29) tumors, these compounds had IC50 values that varied from 0.86 to 90 µg/mL.[128] *Adociacetylenes* A, C, and D exhibited inhibitory activity in the in vitro endothelial cell-neutrophil leukocyte adhesion assay. All acetylenes were highly cytotoxic to P388, A-549, HT-29, and MEL-28 melanoma cells.[129] The sponge *Strongylophora durissima* yielded two new acetylenic derivatives, durissimols A and B, and duryne. Durissimol B and duryne showed potent cytotoxicity against human gastric tumor (NUGC) cells.[130] Duryne, a cytotoxic metabolite that inhibits the growth of both mouse and human tumor cell lines in vitro was previously isolated from the marine sponge *Cribrochalina dura*.[131,132]

A new C43 acetylenic alcohol, vasculyne was isolated by cytotoxicity-guided fractionation of the Caribbean sponge *Cribrochalina vasculum*. It is found to exhibit modest differential cytotoxicity toward the melanoma and colon tumor cell-line subpanels when tested against the NCI's 60-cell antitumor screening panel.[133] *Osirisynes* A-F are highly oxygenated C47 polyacetylenes, isolated from the sponge *Haliclona osiris* are found to exhibit moderate cytotoxicity against a human leukemia cellline (KS62).[134] *Callyspongamide A* isolated from the marine sponge *Callyspongia fistularis* showed a moderate cytotoxicity against HeLa cells with an IC50 value of 4.1 µg/mL.[135] Frozen marine sponge *Petrosia* sp. produces methanol-soluble extract that shows cytotoxic activities against a panel of human solid-tumor cells.[136] The marine sponge, *Prianos osiros* from Pohnpei, gave a new cytotoxic acetylenic carotenoid, which was cytotoxic toward cultured human colon tumor cells, HCT 116.[137] Two new carotenoids, the neoplasm inhibitors, 19-hexanoyloxymytiloxanthin and 19-butanoyloxymytiloxanthin isolated from the marine sponge *Phakellia Stelliderma* showed mild cytotoxic activity against P388 mouse leukemia cells. Callipeltoside A the first member of a novel class of marine glycoside macrolides, was isolated from the lithistid sponge *Callipelta* sp. by Minale and co-workers in 1996 exhibited cytotoxic activity against NSCLC-N6 human bronchopulmonary non-small-cell lung carcinoma and P388 cell lines moderately cytotoxic against NSCLC-N6 cells.[138-140]

The genus *Montipora* is very rich in acetylenic compounds and many of them were shown to be Cytotoxic properties, against P-388 murine leukemia cells, with IC50 values of 5 and 12 µg/mL.[141] Coral metabolites and two known diacetylenes have been isolated from the

methanolic extract of the stony coral *Montipora* sp. exhibited significant cytotoxicity against a small panel of human solid tumor cell lines.[142] Six acetylenic compounds, montiporyne A-F with cytotoxic activities against human solid tumor cell lines SK-OV-3, SKMEL- 2, XF498, and HCT15, have been isolated from the stony coral *Montipora sp*.[143] Callysponginol sulfate A a sulfated C24 acetylenic fatty acid from the marine sponge *Callyspongia truncata*, is a membrane type 1 matrix metalloproteinase (MT1- MMP) inhibitor and sodium 1-(12-hydroxy) octadecanyl sulfate was isolated from a marine tunicate as a matrix metalloproteinase 2 (MMP2) inhibitor,[144] The carotenoids of the muscles and tunic of the tunicates *Halocynthia aurantium*, *H. roretzi*, *Styela clava*, and *Styela plicata*, were isolated and identified, Antimutagenic activities of the carotenoids towards *S. typhimurium* TA 98 and cytotoxic activity for cancer cell lines were detected.[145,146] Halocynthiaxanthin were isolated from Halocynthia roretzi inhibited growth of HeLa, COLO32ODM, HGC-27, PANC-I, and GOTO cells, in vitro halocyanthiaxanthin also inhibited the growth of other human malignant tumor cells. Thus halocyanthiaxanthin seems to be a promising antineoplastic agent.[144-146]

Berberine (BBR) obtained from various plants inhibits cell proliferation by regulating cell cycle and cell autophagy, and promoting cell apoptosis. BBR also inhibits cell invasion and metastasis by suppressing EMT and down-regulating the expression of metastasis-related proteins and signaling pathways. In addition, BBR inhibits cell proliferation by interacting with micro RNAs and suppressing telomerase activity. BBR also exerts anti-tumor effects against lung cancer, cervical cancer, liver cancer, leukemia, and other malignancies and commonly demonstrates anti-inflammation and antioxidant properties, playing a crucial role in regulating tumor micro-environment.[147] BBR is found to reduce lipid levels and glycemic index.[148-152] Studies showed that a combination of an Hsp90 inhibitor and BBR inhibited cell growth via inhibition of CDK4 expression and modulation of cyclin D1 in colorectal cancer cells. In HepG2 human hepatoma cells, BBR suppressed cyclin D1 expression in vitro and in vivo. BBR is found to arrest the cell cycle at G1 via reduced expression of cyclin B1 and indirect inhibition of CDC2 kinase in several cancer cells. In HBT-94 chondrosarcoma cells, BBR upregulated the expression of p53 and p21 by modulating activation of the PI3K/Akt and p38 signaling pathways, which resulted in G2/M phase arrest. In MDA-MB-231 breast cancer cells, BBR arrested cells in S phase, which contributed to high sensitivity of cancer cells to chemotherapy. Experiments indicate BBR influences cell cycle through regulation of Rb (Retinoblastoma) gene. In a separate study it was found that BBR inhibited

phosphorylation of Rb protein, which prevented dissociation of the transcriptional activator E2F from Rb, and resulted in inhibition of the transition from G1 to S phase. In leukemia. BBR also contributed to cell apoptosis by increasing the expression of caspase-8 and caspase-9, and inhibiting the expression of bcl-2 through activation of caspase-3. In MDM2-overexpressing tumor cells, BBR treatment led to the degradation of MDM2, which induced cell apoptosis in acute lymphoblastic leukemia. Interestingly BBR is capable in undergoing reverse drug resistance by regulating autophagy through activation of AMPK. A study showed that BBR promoted binding of the miR30 family with the beclin1 3′UTR region, which resulted in the inhibition of autophagy in adipocytes. BBR Inhibits Cell Invasion and Metastasis .In triple negative breast cancer cells, BBR inhibited cell proliferation by down-regulating IL8 expression through inhibiting the EGFR/MEK/ERK signaling pathway. In addition, BBR has been shown to inhibit the COX-2/PGE2-JAK2/STAT3 signaling pathway, which resulted in reduced expression of MMP2 and MMP9. In addition, BBR inhibited tumor metastasis by reducing the expression of the transcription factor snail-1. In osteo-sarcoma, BBR altered the inflammatory microenvironment by down regulating the caspase-1/IL-1β signaling pathway, which resulted in cell apoptosis. BBR has been shown to improve osteoarthritis through inhibition of IL-1β signaling, and inhibition of cartilage damage. BBR has been shown to improve osteoarthritis through inhibition of IL-1β signaling, and inhibition of cartilage damage. In all, BBR regulates tumor microenvironment by affecting inflammatory response and immune molecules. BBR induced and inhibited inflammation. BBR Acts as an Effective Candidate for tumor Immunotherapy by inducing Nrf2 activation in an AMPK-dependent manner. It is also demonstrated that BBR can act as a dopamine D1- and D2-like receptor antagonist to inhibit secretion of IFN-γ, TNF-α, IL-6, and IL-1β from LPS stimulated lymphocytes , improve autoimmune neuropathy by down-regulating TNF-α and IL-1 levels, and by inhibiting proliferation of CD4+ T cells.[152-173]

CONCLUSION

Nature is a beautiful and excellent source of potential chemotherapeutic agents.[1] A complete and a clear study of such natural sources can help us to develop some novel anti-cancer drugs. Natural compounds can be used alone or in combination with other natural products or standard anti-neoplastic drugs to improve the efficiency of the later. Berberine along with various eukaryotic products like amsacrine has provided high hopes in the development of some novel anti-tumor compounds but the efficacy of BBR is limited by poor solubility in water, rapid metabolism, and low absorption rate in intestines. Therefore, development of

formulations that improve absorption of BBR in the intestines may have great potential for treatment of cancer.[146-152] This review mainly focuses on the different types of pigments and metabolites from a wide range of eukaryotic compounds which may help us to develop novel chemotherapeutic agents. Further research is required to understand whether such compounds would be efficient in vivo conditions as well. Also there is need to understand the importance of targeted drug delivery which can be an efficient way in treating cancer with these compounds.

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