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A SYSTEMATIC REVIEW ON CHEMICAL ACTIVES FROM NATURAL SOURCES FOR CANCER TREATMENT

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ABSTRACT

Cancer, a severe metabolic syndrome, is the leading cause of mortality and morbidity worldwide and the numbers of cases are continuously rising. A natural product in chemoprevention is beneficial, because of fewer side effects and low toxicity profile compared to compounds of synthetic origin. In the present review, we summarize natural products with chemo preventive activities against cancer target. We also covered targets of cancer Vascular endothelial Growth factor Receptor (VEGFR), epidermal growth factor receptor (EGFR) and Poly(ADP-ribose) polymerase-1 and their mechanism of action. The present review may provide information on the use of these compounds for the prevention of cancer.

Keywords*:* - Phytochemicals; Chemotherapy; Targets

INTRODUCTION

Cancer, a severe metabolic syndrome, is the leading cause of mortality and morbidity worldwide and the number of cases is continuously rising. The cancer phenomenon is described by uncontrolled proliferation and dedifferentiation of a normal cell. Cancer cells have some marked features i.e., they tune out the signals of proliferation and differentiation, they are capable to sustain proliferation, they overcome the apoptosis, and they have power of invasion and angiogenesis. Sequential genetic alterations which produce genetic instabilities accumulate in the cell and a normal cell transforms into a malignant cell. These alterations include mutations in DNA repair genes, tumor suppressor genes, oncogenes and genes involve in cell growth & differentiation. Various types of cancer forms exist in human and the lung, breast and colorectal cancer being the most common forms. Among these the lung cancer is reported the most in men and the breast cancer in women. Several genes coordinate together for the growth & differentiation of a normal cell. In the cancer, one or group of these genes get altered and express aberrantly. These genes can be targeted for the development of anticancer therapeutics. Modifications of epigenetic processes involved in cell growth and differentiation also lead to the development of a cancer.

Targets for cancer Treatment:

1. Epidermal growth factor receptor (EGFR)

The epidermal growth factor receptor (EGFR)s a receptor tyrosine kinase that is commonly upregulated in cancers such as in non-small-cell lung cancer, metastatic colorectal cancer, glioblastoma, head and neck cancer, pancreatic cancer, and breast cancer. Various mechanisms mediate the upregulation of EGFR activity, including common mutations and truncations to its extracellular domain, such as in the EGFRvIII truncations, as well as to its kinase domain [1].

2.Poly(ADP-ribose) polymerase-1

Poly(ADP-ribose) polymerase-1 (PARP-1) is a nuclear enzyme which binds DNA via two zinc finger motifs and transfers chains of ADP-ribosyl moieties (PARs) from nicotinamide-adenine-dinucleotide (NAD+) to chromatin-associated acceptor proteins,including PARP-1 itself. This post-translational modification playsan important role in promoting DNA repair by releasing PARP-1 from DNA and allowing for recruitment of proteins involvedin both base excisional repair (BER) and homologous recombination (HR) [2]. Accordingly, PARP-1 is an attractive anticancer target, and poly(ADP-ribose) polymerase (PARP) inhibitors havebeen identified as chemo- and radiation-sensitizing agents in anarray of cancers [3],

including our report on the sensitization of head and neck cancer to radiotherapy following PARP inhibition [4]. Found inhibition of PARP-1in cells containing BRCA mutations resulted in the generation ofchromatid breaks, G2 cell cycle arrest, and enhancement of apoptosis, results which have been confirmed in early phase clinicaltrials [5,6].

3. Vascular Epidermal Growth Factor Receptor

VEGF is involved in tumor progression indicates that the signaling mechanism of VEGF is due to its interaction with some tumor-cell-expressed receptors. These include the RTKs VEGFR1, VEGFR2, and VEGFR3, which are known as Flt-1, Flk-1, and Flt-4, respectively **[7]**. Initially, the VEGF binding site was identified to be present on the surface of endothelial cells, but other evidence later reported indicates that the receptor of VEGF is also present in bone marrow. These receptors contain a domain that binds to a specific VEGF ligand. This ligand–receptor interaction is responsible for stimulating the tyrosine kinase domain of VEGFR. This stimulation induces an intracellular signaling transduction pathway involved in the regulation of cell proliferation, which ultimately leads to cancer progression [8, 9]. Blockage of VGFR1 prevents cancer pain in diverse mouse models. Therefore, we can conclude from this finding that VGFR1 can promote cancer symptoms, and the development of a VGFR1 inhibitor can improve antiangiogenic cancer therapies [10-12]. In various cancers, an elevated VEGFR level has been observed, which is correlated with metastasis and a poor diagnosis. Deregulation of receptor tyrosine kinases (RTKs) leads to the formation and progression of cancer. Thus, by blocking the signal of RTK, cancer formation can be prohibited. Various VEGFR inhibitors have been introduced to overcome the angiogenesis and lymph angiogenesis linked with tumor development [13]. Initially, the VEGF binding site was identified to be present on the surface of endothelial cells, but other evidence later reported indicates that the receptor of VEGF is also present in bone marrow cells [14]. These receptors exhibit overlapping, but the expression pattern is different: VEGFR2 in vascular endothelial cells [15], and VEGFR3 in lymphatic endothelial cells [16]. VEGFA plays the main role in angiogenesis by binding with two receptors: VEGFR1 and VGFR2. The juxta membrane domain of VEGFR1 is involved in the suppression of kinas way that checks the contact of regulatory sequences in the kinase domain's activity [11].

Phytochemicals used in Cancer Treatment

There are different phytochemicals recently used in cancer treatment. These Possess complementary and overlapping mechanisms to Slow down the carcinogenic process by scavenging free Radicals, suppressing survival and proliferation of Malignant cells, as well as

diminishing invasiveness and Angiogenesis of tumors. They exert wide and complex Range of actions on different molecular targets and signal Transduction pathways including membrane receptors, Kinases, downstream tumor-activator or -suppressor Proteins, transcriptional factors, microRNAs (miRNAs), Cyclins, and caspases.[17]

PHYTOCHEMICALS:

ALKALOIDS:

THEOBROMINE: Theobromine is remarkable natural agents in the class of methyl xanthines and flavonoids. These bioactive molecules have several biological activities, for instance, antioxidant, anti-inflammatory, and antitumor capacity. In this sense, studies focusing on these molecules have been performed to discover new treatments against diseases, such as cancer. Cancer is a serious public health problem worldwide responsible for more than 70% of all deaths globally. Therefore, revealing new strategies to block cancer growth is one of the biggest challenges to science [18-20].

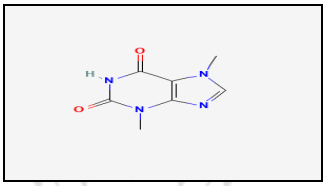

Fig No. 1: Theobromine

BERBERINE: Berberine (BBR) has been extensively studied in vivo and vitro experiments. BBR 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 microRNAs and suppressing telomerase activity. BBR exerts its anti-inflammation and antioxidant properties, and also regulates tumor microenvironment. This review emphasized that BBR as a potential antiinflammation and antioxidant agentz also as an effective immune modulator, is expected to be widely used in clinic for cancer therapy [21].

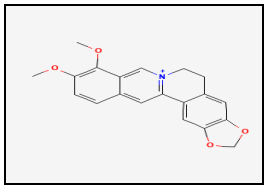

Fig No. 2: Berberine

BETA-SITOSTEROL: β-sitosterol restricts proliferation and induces apoptosis in different cancer cell lines, including gastric, colon, prostate, lung, and breast cancer [22]. Numerous

studies have evidenced that the anticancer effect of BS is related to the induction of apoptosis through blockade of multiple cell signaling mechanisms [23]. For instance, anticancer effects of BS are executed via increasing the levels of first apoptotic signal (Fas), caspase-8 activity, β-catenin activity, phosphorylation of extracellular-signal regulating kinase (ERK), p38 mitogen-activated protein kinase (MAPK), and proliferating cell nuclear antigen (PCNA) [24] . Molecular studies have shown that BS induces endoreduplication in U937 and HL60 cells through the PI3K/Akt and Bcl-2 signaling pathways to promote spindle microtubule dynamics [25].

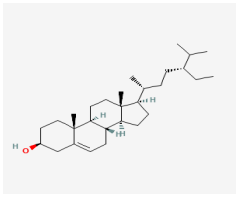

Fig No. 3: β-sitosterol

GINGEROL: Gingerol is also a group of bioactive compound isolated from the fresh rhizome of Zingiberofficinale containing [6]-gingerol, [8]-gingerol and [10]-gingerol with marked anticancer properties in colon, pancreas, ovarian and breast cancers. It downregulates the expression of iNOS and TNF-alpha through suppressing NF-kB nuclear translocation and IkBa phosphorylation [26].Oyagbemi et al. summarized the mechanisms of action of gingerol onK562 cells, MOLT4 cells with high reactive oxygen species, induced apoptosis in leukemia cells by mitochondrial pathway [26]. [. The inhibitory effect of [10]-gingerol on MDA-MB-231 cells was related with the reduction of number of cell divisions, cell cycle arrest, induces apoptosis and releases proapoptotic mitochondrial cytochrome c [27]. Gingerol mechanism of action on different molecular targets.

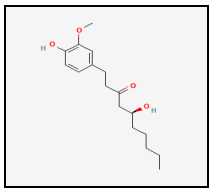

Fig No. 4: Gingerol

LYCOPENE: Lycopene is a bright red pigment with anticancer potential isolated from tomatoes, watermelons, red papayas and red carrots and plays significant role in targeting PI3K/Akt signaling pathway in pancreatic and stomach cancer by down-regulating Erk and Bcl-2 proteins [28]. It up-regulates anti-oxidant enzymes (GSH, GST and GPxn) and removes oxidative damage caused by the carcinogens in breast, endometrial, prostate and colon cancer [29]. HT-29 colorectal cancer cells and animal models have shown that lycopene has also

effect on cell proliferation and progression by interacting with various cellular signaling pathways like, NF-kB and JNK [30]. Lycopene also inhibited invasion, metastasis and proliferation in human SW480 colorectal cancer cells by restraining NF-kB and JNK activation, causes inflammation and suppresses the expression of COX-2, iNOS IL-1b, IL-6, and TNF-a [31]. Lycopene and its different nuclear and cellular targets.

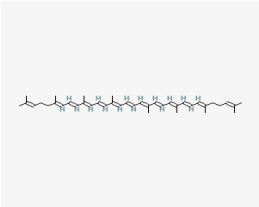

Fig No. 5: Lycopene

RESVERATROL: Resveratrol is also a naturally occurring polyphenol and has been identified in mulberries, peanuts, grapes, bilberries and blueberries. Resveratrol play substantial role in curing a wide range of cancers including breast, colorectal, liver, pancreatic, prostate cancer and lung carcinoma by up-regulating p53 and Bcl-2 associated X proteins and down-regulating MMPs, NFkB, AP-1, Bcl-2, cyclins, cyclin dependent kinases, cytokines, and COX-2 proteins [32]. Resveratrol is known to inhibit angiogenesis, suppressing VEGF protein action by reducing MAP kinase phosphorylation [33]. The mechanism of action of resveratrol on different nuclear and cellular factors.

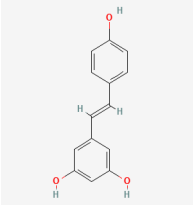

Fig No. 6: Resveratrol

CHALCONES: Chalcone is also a naturally occurring anticancer flavonoid in fruits and vegetables. It is responsible for activation of different caspases (caspase-8, 9, 12 enzymes), upregulate the of proapoptotic proteins expression (Bid, Bax, and Bak proteins), decreases anti-apoptotic Bcl-2 gene expression and have been used for the treatment of the treatment of colon, lung, breast, liver and prostate cancer [34]. Chalcone targeted different nuclear and cellular factors (Bax, Bid, and Bak, Bcl-2 proteins, caspase-8, 9, 12 enzymes are illustrated.

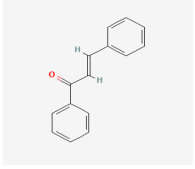

Fig No. 7: Chalcone

GENIPIN: Genipin is a natural phytochemical isolated from Gardenia jasminoides and is used to treat breast cancer [35]. In breast cancer, genipin regulates different protein and enzymes as for examples, caspase-3, Bax, Bcl-2, JNK, p38, MAPK. Genipin has anti-proliferative activity in MDA-MB-231 breast cancer cells by down-regulating Bcl-2 expression and up-regulating Bax and caspase-3, pro-apoptotic signaling cascades such as JNK and p38 MAPK.

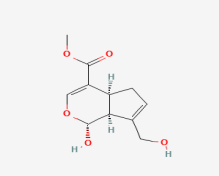

Fig No. 8: Genipin

GOSSYPOL: Gossypol is also a natural phytochemical found in cotton seeds (Gossypium) and Thespesiapopulnea, displays potential anti-cancer activities, has completed phase II clinical trials for treatment of human breast and prostate cancer. Its antitumor properties have been studied in a variety of tumors (lymphoid, hematologic and solid tumors). Gossypol suppresses cell proliferation, induces autophagy and apoptosis in colorectal cancer, HT-29, HCT116 and RKO cancer cell lines [36].

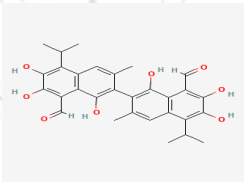

Fig No. 9: Gossypol

SAPONINS: Saponin is a diverse group of compounds widely distributed in the plant kingdom, which are usually characterized by their structure containing a steroidal or triterpenoid aglycone and one or more sugar chains [37]. Saponins possess antitumor properties in HT-29 human colon cancer cells and tumor xenografts. They inhibit cell proliferation through accumulation in S phase and G2/M arrest, with concomitant suppression of p21 expression and inhibition of cyclin-dependent kinase activity. Besides, AST promotes apoptosis in HT-29 cells through caspase 3 activation and poly (ADP-ribose) polymerase cleavage, which is indicated by DNA fragmentation and nuclear chromatin condensation [38].

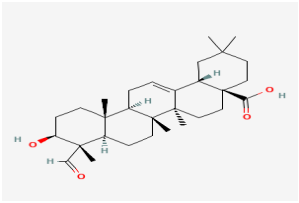

Fig No. 10: Saponin

CURCUMIN: Curcumin (diferuloylmethane), a polyphenol derived from the plant Curcuma longa (commonly called turmeric), has emerged as one of the most powerful chemopreventive and anticancer agents [39]. curcumin could inhibit tumor angiogenesis and this mechanism might be mediated through reduction of COX-2 and VEGF.

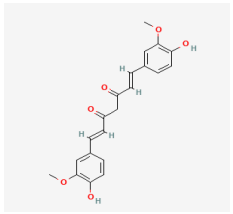

Fig No. 11: Curcumin

MISCELLANEOUS COMPOUNDS:

Alliin demonstrated a potent inhibition of VEGF-induced angiogenesis in the CAM model. Emodin in a dose-dependent manner inhibited proliferation, migration and tube formation of HUVECs stimulated with VEGF. It also suppressed bFGF-induced proliferation and migration of HUVECs and VEGF-induced tube formation of human dermal microvascular endothelial cells. Emodin on VEGF-receptor (VEGFR) phosphorylation was studied. Emodin caused a dose-dependent inhibition of VEGFR phosphorylation in HCT116 cell (colon cancer cells)[40].

FLAVONOIDES:

Flavonoids are able to attenuate NAD+ depletion by inhibiting PARP-1 hyper activation. , apigenin and luteolin) inhibit tankyrases (TNK), the proteins of the PARP family, which are attractive targets in cancer treatment. Green tea contains epigallocatechin gallate (EGCG), which is considered one of the most powerful dietary antioxidants. Tea polyphenols affect regulatory systems of cells and may produce an inhibitory effect on various stages of carcinogenesis: inflammatory processes, cell transformation, proliferation, apoptosis, metastasis, and invasion [41]. It was found that EGCG and TF cause synthetic lethality in

BRCA2-deficient cells through a PARP-dependent mechanism [42]. EGCG inhibits PARP-1 more effectively than TF, which is probably due to the presence of a haloyl group. Moreover PARP-1, the targets of tea polyphenols are histone deacetylases[43], transcription factors [44], DNA topoisomerase II [45] and ABC transporters responsible for the development of multidrug resistance.

CONCLUSION

In this review, recent discoveries of pure anticancer natural products active against triple negative breast cancer were categorized by their chemical structures. Overall, traditional herbal medicine has been used to treat breast cancer for decades. As scientific technologies have been developed and the pathological pathways of triple negative breast cancer discovered, specific study can be done to interpret the traditional usage of herbal medicines, identify the active constitutions for the TNBC, and explore the possible mechanisms of action. These studies will significantly help research areas to discover novel anticancer drugs from novel natural product leads by using medicinal chemistry approaches and to explore their mechanistic pathways through study of pharmacological activity.

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