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Natural Compounds Targeting Cancer Stem Cells for Chemotherapy

Misfiqua[1]* Dr. Ashiya Fatima[2]

[1] Student

[2] Azteca University

Abstract – Cancer Stem Cells are a subpopulation of cancer cells straightforwardly associated with drug opposition, inaccessible organ metastases, and cancer repeat (CSCs). In the current investigation, a systemic writing search was performed through different electronic information bases, including Pubmed, Scopus, Google researchers, utilizing the watchwords "cancer stem cells" and "natural compounds" Between 1999 and 2019, it inspected articles distributed. All openings identified with CSCs identified with cancer pathogenesis and treatment obstruction and targeting these properties of CSCs by natural compounds were chosen for the current investigation. Natural compounds have consistently been viewed as a rich wellspring of organically dynamic rules that target abnormally actuated flagging pathways and other CSC modalities, though first-line and second-line chemotherapy are usually connected with agonizing results. The key flagging pathways actuated in CSCs to keep up their endurance were portrayed in this audit and featured how natural compounds intrude on these flagging pathways to limit the protection from treatment, pathogenesis and cancer repeat properties of CSCs, accordingly giving valuable systems to cancer therapy or assisting with improving cancer treatment. Like typical stem cells, CSCs depend on various flagging pathways and different properties for their support. Therefore, the achievement of cancer therapy relies upon the advancement of suitable enemy of neoplastic medications fit for catching those flagging pathways and different properties of CSCs to annihilate this sly subpopulation of cancer cells. Natural compounds may act as an outstanding source of novel therapies for cancer stem cells.

Keywords – Cancer Stem Cells, Natural Compounds, Cancer Therapy, Therapy Resistance, Signaling Pathways

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INTRODUCTION

Malignancy is considered by general supposition to be an inexorably undermining ailment, influencing individuals, everything being equal. It is the subsequent driving reason for death among the worldwide populace, following cardiovascular maladies (1, 2). Individuals will in general acknowledge disease with emotionlessness and submit to delayed treatment periods that are not generally compelling (2). The word cancer-causing has been characterized as the capacity of a compound to follow up on one of a few organs or tissues to unchain the cycle of malignancy improvement in people and creatures under fitting conditions (3, 4). This definition is presently inadequate, with the revelation of different systems associated with carcinogenesis (5). A compound is viewed as cancer-causing from an exploratory perspective when its organization to research facility creatures initiates a factually critical increment in the frequency of at least one histological sorts of neoplasia contrasted with creatures not presented to the substance in the benchmark group (6).

Dangerous development is an assortment of ailments that are brought about by acquired and epigenetic changes that are totaled. These progressions cause one or a couple of cells to develop and duplicate inconclusively without control, prompting an unusual development called a tumor or neoplasm (7). In spite of progress in understanding the atomic premise, analysis and therapy of malignancy, it is important to accomplish long haul endurance rates for disease patients (8, 9). Protection from first-line and second-line chemo-radiotherapy and disease repeat have added to the restricted generally speaking endurance of malignant growth patients (10).

Natural compounds targeting cancer stem cells

Traditional cancer therapies such as chemotherapy and radiation therapy fail to target stem cells of cancer and, moreover, non-specificity of these therapies causes normal cell toxicity (11). Interestingly, both in vivo and in vitro, many natural compounds have already shown anti-CSC properties (11). The results indicated that natural compounds may have the potential to induce CSC death. Natural compounds could likewise sharpen them to regular treatments, forcing them to re-separate or keep them from entering a torpid or safe state, empowering them to improve cancer the board in clinical settings (11). In the accompanying segments, the jobs of natural compounds against CSCs in different cancers are depicted.

Natural Compounds Targeting Signaling Pathways in CSCs

In CSCs, multiple signaling pathways such as Wnt/β-catenin, Notch, Hedgehog signaling are overactivated. Various changes in these signaling pathways accumulated in CSCs and led to the initiation, progression and recurrence of cancer (11). Natural compounds show anti-CSC activity by interrupting various signaling pathways or are summarised in Table 1 by their components.

Table 1: Different natural compounds target different pathways in various cancer types.

Natural Compounds	Source	Target Pathway (s)	CSCs in Cancer Types	References
EGCG	*Camellia sinensis*	Wnt/ β-catenin	Colon	(11)
DATS	*Allium sativum*	Wnt/ β-catenin	Colon	(12)
BLP	*Morella rubra*	Wnt/ β-catenin	Ovarian	(13)
Compound k	*Panax quinquefolius*	Wnt/ β-catenin	Ovarian	(14)
Isoliquiritigenin	*Glycyrrhizaglabra*	Wnt/ β-catenin	Breast	(15, 16)
Sulforaphane	*Brassica oleracea var.*	Wnt/ β-catenin, Notch, Hedgehog	Breast, Pancreatic	(17, 18)
Alpinetin	*Alpinia zerumbet*	Notch	Glioblastoma	(19)
Eckol	*Ecklonia cava*	Notch, PI3K-Akt and Ras-Raf-1-Erk	Glioblastoma	(20)
Genistein	*Glycine max*	Hedgehog	Breast	(21)
Honokiol	*Magnolia officinalis*	Notch	Melanoma	(22)
Cyclopamine	*Veratrum californicum*	Hedgehog	Leukemia	(23)
Nitidine chloride	*Zanthoxylum nitidum*	Hedgehog	Breast	(24)
Hinokitiol	*Chamaecyparis taiwanensis*	Nrf2	Glioblastoma	(25)
Plumbagin	*Plumbago zeylanica*	Nrf2	Squamous carcinoma	(26)
Triptolide	*Tripterygium wilfordii*	Nrf2	Leukemia	(27)
BBMD1, synthetic derivative of Berbamine	*Berberis amurensis*	JNK/AP-1	Glioblastoma, Osteosarcoma	(28, 29)
Compound 2	*Garcinia hanburyi, Garcinia Morella*	Akt/Erk	Head and neck	(30)
BMR270 (extract)	Medicinal Plants	NF-kβ	Osteosarcoma	(31)
Nutraceuticals	Medicinal Plants	-	-	(32)

Note- DATS: Diallyl trisulphide; **EGCG:** Epigallocatechin-3-Gallate; **PI3K**: Phosphatidylinositol 3-kinase; **Akt**: Protein kinase B; **BLP**: Bayberry leaf proanthocyanidins; **Nrf2**: NF-E2-related factor 2; **JNK**: c-Jun NH_2-terminal kinase (JNK); **Raf**: Rapidly Accelerated Fibrosarcoma; **Erk**: Extracellular-regulated kinase; **AP-1**: Activator protein-1; **NF-kβ**: Nuclear factor kappa β.

Natural Compounds Targeting the Notch Signaling Pathway

Notch signalling, an evolutionarily preserved pathway, plays a pivotal role in normal stem cells in embryonic growth, organ development and self-renewal regulation and subsequently maintains tissue homeostasis. However, this signalling is intensively activated in CSCs in the context of disrupting signalling pathways and mediates the critical processes of carcinogenesis, including angiogenesis, EMT and tumour metastatic spread. By targeting CSCs in numerous cancers, various natural compounds disengaged from therapeutic and eatable plants, for example, Alpinetin, Eckol, Sulforaphane, and Honokiol, demonstrated enemy of tumor exercises by stifling the Notch single pathway (Figure 1). Alpinetin detached from palatable plants, for example, Alpinia zerumbet, for instance, in the orthopic GSC xenograft model, can decrease obtrusiveness, multiplication and initiate apoptosis in a portion and time-subordinate way. Alpinetin induced proteolytic cleavage of Notch protein in GSC, thus reducing Notch target gene expression, i.e. About HES and c-Myc. Another natural compound isolated from the brown algae Ecklonia cava, Eckol, showed the activity of anti-CSCs by reducing Notch protein expression in GSC.

In addition, sulforaphane induced Notch-1 expression down-regulation in pancreatic CSC. Downregulation of Notch-1 consistently inhibited the expression of c-Rel (a transactivation-potent NF-3B transcription factor subunit), resulting in inactivation of NF-3B signalling in pancreatic CSC. Thus, through Notch-1 downregulation, sulforaphane could potentially inhibit NF-μB signalling in CSC (Figure 1). Also, a new report has indicated that honokiol, a biphenolic compound separated from Magnolia Officinalis, smothers the unusual enactment of Notch motioning in the mesenchymal stem cell line B16/F-10 and SKMEL-28 melanoma cells (34). Notch receptor proteolytic cleavage is crucial to inactivating Notch signalling and it was interestingly noted that honokiol treatment induced Notch-2 receptor proteolytic degradation in melanoma CSCs (34). Subsequently, the expression of downstream Notch signalling targets such as Hes-1 and cyclin D1 was decreased in mesenchymal stem cells treated with honokiol, inhibiting the growth and proliferation of stem cells of melanoma (Figure 1) (34). As the Notch signalling pathway is deeply associated with cancer progression, a fruitful way to treat cancer may be to target this pathway through these natural compounds.

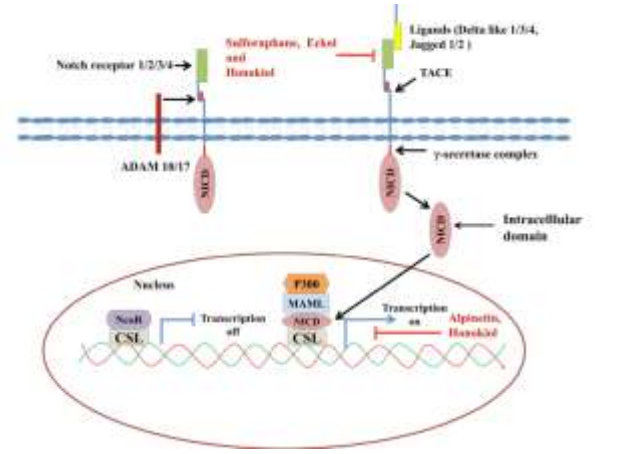

Figure 1: The Notch signaling and its interference natural compounds.

Natural Compounds in CSCs Targeting Other Pathways

Additionally associated with CSCs are some other flagging pathways, for example, NF-E2-related factor 2 (Nrf2), JNK/AP-1, NF-eterB, and so on. The targeting of these pathways by naturally occurring compounds is therefore also of great importance. Nrf2 is considered a useful factor that protects humans from chemicals that are carcinogenic. It is a transcription factor that helps to protect the cells from carcinogenic insults by chemotherapy compounds such as detoxifying enzymes, antioxidants, and transporters. In addition, it is evident that Nrf2 plays a dual role in the pathogenesis of cancer, i.e. protecting normal cells from transformation into cancer cells and nourishing the survival of cancer cells in the microenvironment of tumours.

Increasing evidence suggests that increased Nrf2 activity due to mutations in NFE2L2 or KEAP1 (Kelch-like ECH related protein 1) plays an important role in the pathogenesis of many solid tumours. It has recently emerged as one of the main pathways implicated in renal carcinoma, for example. In addition, it was also shown that the polymorphism of KEAP1-Nrf2 also occurred in breast cancer. Besides, Nrf2 advances metastatic bosom cancer cell movement through upregulation of glucose-6-phosphate dehydrogenase (G6PD), hypoxia-prompting factor 1 a (HIF-1 a) in MCF-7 and MDA-MB-231 cells. In addition, Keap1-Nrf2 flagging has been seen to assume a basic job in reacting to oxidative pressure in cellular breakdown in the lungs. Transformations in the KEAP1/NFE2L2 qualities consistently cause diligent Nrf2 actuation in cellular breakdown in the lungs cells that presents restorative opposition and forceful tumorigenic movement. Along these lines, Nrf2 concealment with compound specialists that cause improved oxidative unevenness or unusual digestion would be promising in the treatment of lung adenocarcinoma. Natural compound targeting of Nrf2 could induce down-regulation of Nrf2, thereby inhibiting its tumor-promoting activity. Nrf2 expression in Glioma stem cells has been reported to be upregulated (36).

Treatment of these cells with Hinokitiol, a natural bioactive compound isolated from Chamacyparis taiwanensis, induces dose-dependent downregulation of Nrf2 in Glioma stem cells. In addition, the expression of Nrf2 target genes such as heme oxygenase 1 (HO-1) and glutathione S-transferase was inhibited, thereby nullifying carcinogenic insults mediated by Nrf2 in stem cells of Glioma. Plumbagin, a natural naphthoquinone detached from Plumbago zeylanica, repressed the atomic movement of Nrf2, bringing about the inactivation of the Nrf2-interceded oxidative pressure flagging pathway in cells of squamous cell carcinoma. Treatment of Plumbagin squamous cell carcinoma cells was noted to induce decreased proliferation, activated death receptor mediated apoptosis and inhibited epithelial to mesenchymal transition, thereby reducing the properties of CSCs of squamous cell carcinoma cells. Also, Triptolide (a bioactive diterpenoid triepoxide of the Chinese therapeutic plant Tripterygium wilfordii) was discovered to be powerful against leukemia stem-like cells by means of downregulation of the Nrf2 pathway. The pressure responsive JNK/AP-1 flagging pathway is engaged with cell development, transformation, and apoptosis. The key mediators of this pathway are JNK-1 and JNK2, which induce phosphorylation of c-Jun, a major protein of the activator protein-1 complex. JNK/AP-1 signalling pathway activation usually induces apoptosis. Through interaction with the components, a bioactive natural compound can activate this pathway and could induce anti-CSC activity in cancer. For example, Berbamine isolated from Berberis amurensis and its synthetic derivative BBMD3 exhibited anti-cancer effects through activation of the JNK/AP-1 signalling pathway in glioblastoma-derived cancer stem-like cells.

In addition, via JNK/AP-1 activation, BBMD3 inhibited cell viability and induced apoptosis in human osteosarcoma cells. When EGFR, an intrinsic tyrosine kinase, binds to its EGF ligand, it results in the autophosphorylation of EGFR tyrosine residues and subsequently activates signal transduction pathways involved in the regulation, differentiation, and survival of cell proliferation. Compound 2, a Chinese medicine derivative called gambose (prepared from Garcinia hanburyi, Garcinia Morella like plants), has exerted a dose-dependent inhibitory effect on the squamous cancer stem of the head and neck! Like cells in the xenograft tumour model via EGFR downregulation and Akt and Erk phosphorylation.

Expression of antiapoptotic genes is stimulated by the transcription factor NF-egB. Therefore, over-articulation of NF-nB prompts tumorigenesis in osteosarcoma-inferred cell stem-like cancer cells in relationship with Cdk6 and p655 (29). Treatment

with plant extract BMR270 dramatically inactivates NF-βB signalling cascade in MDR-induced stem-like cancer-initiating cells in CSCs derived from osteosarcoma (29). In addition to Wnt/β-catenin, Notch, Hedgehog signalling, other pathways such as Nrf2, EGFR and NF-egB are therefore also involved in the properties of CSCs. Therefore, natural compound inhibition of these pathways or their components may provide a way to treat cancer.

CONCLUSION:

Advances in the understanding of the initiation and maintenance of cancer by CSCs show that due to their multiple survival mechanisms, this sup-population of cells is the main culprit of cancer treatment failure. The lack of unique, ubiquitous and single molecular targets that affect CSCs is becoming the main concern of cancer therapy, despite the emergence of some promising treatment options aimed at normal cancer cells. In light of this, we have tried to analyse natural compounds that have a wide range of anti-CSC activities. Most of the compounds have been in vitro tested, however.

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Corresponding Author

Misfiqua*

Student