Role of Curcumin in Cancer Prevention

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Abstract **- Cancer is one of the most fatal disease worldwide and posses a big threat as a whole to mankind. Conventional chemotherapy are not much effective and can have severe implications. So, a natural noble drug is the need of the hour. Curcumin a well-known natural polyphenol compound is found to exhibit anti-cancerous property by regulating many signaling pathways. It is found that, curcumin somehow has its effect in many different kinds of cancer. It also affects the sustainability of cancer cell by increasing DNA damage and inducing apoptosis in cancerous cells. This compound alone or in combination with other drugs could represent an effective way in cancer therapy.**

Index Terms **- Cancer, curcumin, tumour, apoptosis, Chemotherapy, Carcinoma.**

INTRODUCTION

Cancer has emerged as a nearly invisible and fatal disease in modern times. It can be induced by environmental factors, oxidative stress which are characterized by genetic mutations and epigenetic changes. The main obstacle in tackling cancer cell is its drug resistant power. Therefore, to improve chemotherapy, new therapeutic drugs are required. This , require a complete understanding of tumor biology, the signaling pathways through which cell communicate and their microenvironment [1,3,12,22].

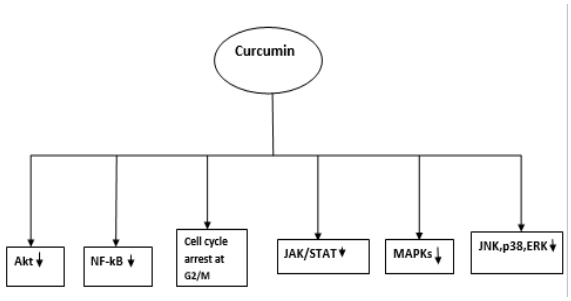

Figure 1: Downregulation of various signaling pathways in which curcumin control cancer .

So, in treating cancer curcumin has emerged as a key potential player. It is a natural polyphenol compound that is derived from the rhizome of the medicinal plant Curcuma Longa [14]. Extensive research within the last century on curcumin ha shown that it has aptitude to modulate multiple signaling pathways of multiple levels such as transcription factors NF-Kb(Nucler factor kappa B), matrix metalloproteinases(MMPs), cell cycle arrest, cytoprotective pathway(Nrf 2), cell poliferation(EGFR and Akt) [3]. Also it is found that curcumin also targets one member of STAT family i.e STAT3. STAT3 controls the activity of anti-apoptotic protein like BCL-2 and BCL-XL.It also activates Vascular endothelial growth factor(VGEF) and Basic fibroblast growth factor(bFGF).This two-growth factor promote angiogenesis in cancer cells. So, curcumin show various immunomodulatory effects [1].

Table 1: Various Molecular Targets of curcumin [1,3,12,22].

Transcription Factors	Growth Factors	Cytokines	Apoptotic Proteins	Protein Kinase	Receptors	Cell proliferative proteins
ERG-1,ERE STAT1, STAT3, STAT4, STAT5, Notch-1, NF-Kb.	FGF, VEGF, TGF-β1, EGF	Prostaglandin, TNF, INF, Interlukins, COX-2	Cytochrome c,Bax, Caspase-3, Caspase-8, Caspase-6, Caspase-10, FADD	MAPK, EGFR,ERK,IL-1, PKA/B/C, JNK, IKK	HER-2, EGFR, H2R, IL-8R, LDL-R	Survivin, Mcl-1, Bcl-XL, Bcl-2, cMyc, cyclin D1

BIOAVAILIBILITY AND METHODS OF DELIVERYING CURCUMIN INTO THE CANCER CELLS

As Curcumin is a hydrophobic polyphenol its solubility is less in water. Another challenge in using curcumin is that it degrades in physiological Ph. Also a large amount of curcumin gets used up in various metabolic pathways [3]. So to improve its bioavailability various research strategies such as preparing curcumin analogs, Adjuvant therapy, Nano particle targeting, etc are being adopted [3]. Also

methods such as microemulsions, Nanoemulsions, Micelles, etc have been used to increase its bioavailability and targeting [3].

LUNG CANCER

Lung cancer has proven to be a major cause of cancer coupled mortality in men worldwide. The survival rate of men who are suffering from men cancer varies from 4%-17% [8].

Curcumin has been seen to down regulate NF-Kb in Lung cancer cell line A549 and also by acting on JAK 2/STAT 3 activity in its therapeutic efficiency [1]. In a wide range of cancer including lung cancer high level of expression of STAT 3 activities is seen when we compare them with normal cells. It helps in angiogenesis . VGEF and bFGF have been marked as an important regulator of angiogenesis [12]. When certain inhibitors like AG 490 or one pair of siRNA specific to STAT 3 were introduced in lung cancer cells, it was seen that there is notable decrease in VGEF and bFGF mRNA levels [12]. Also it is found that various signaling pathways like Hedgehog (Hh) and Wnt/β-catenin play a key role in development of cancer cells . When wnt is present β-catenin activates various transcription factors like C-Myc , cyclin D1, CD 44 and ALDH which helps in development of cancer stem cells . Similarly open Hh binding , Gli-1 and Gli-2 transcription factors is activated which regulate cancer stem cell activity [10]. Curcumin was able to regulate these pathways . Upon treatment curcumin increase the level of GSK-3β which degrade the β catenin . Also the level of Gli-1 and Gli-2 were decreased upon application of curcumin [10]. It induced G0/G1 arrest of cell cycle in lung cancer cell by mediating the Wnt/ β catenin pathways [1]. In addition to these an elevated level of expression of AKR1C1. AKR1C1 is a aldo-keto reducatase composed of 4 enzymes . It plays a vital role in in the drug resistance activity of cancer cells . Its expression is also important in metastasis of non small cell lung cancer(NSCLC) . AKR1C1 propel the metastasis of cancer in NSCLC by increasing the interaction of JAK 2 and STAT 3 [8]. Curcumin was found to reduce the efficacy of AKR1C1 and the malignancy of cancer when introduced in high amount .It was also able to reduce the malignancy of cancer cells by inhibiting the expression of mi-RNA-196 [12].

It was also found that Cancer people were quite vulnerable to COVID-19 than normal people [2]. Also the epitome of COVID-19 and caner are common to some extent. Among signaling cytokine signaling is common to both of them. The level of IL-6 and Tumor necrosis Factor α was observed to be very high in COVID-19 and cancer patients. IL-6 regulates JAK/STAT signaling in cancer cells [2]. While in COVID-19 patients it causes the cytokine storm which lead to lung injury and multiple organ failure. NF-Kb controls the levels of IL-6. So curcumin can play a major role in blocking NF-Kb and thereby reducing the amount of IL-6 in both cancer and COVID-19 patients [2,23].

CERVICAL CANCER

Cervical cancer is one of the most fatal cancer in woman worldwide [15]. It is caused by Human Papiloma Virus(HPV) [14]. It contains two viral proteins i.e E6 and E7 which play a key role in cervical cancer. It upregulates various types of signaling pathways, transcription factors, proteins, etc which drives the metastatis [13].

From in vitro analysis, it is shown that curcumin can show effect these cancer cells in dose dependent manner [14]. It can be inserted by means of liposomal or nano-cur based targeting [3,14]. Cucumin was able to induce DNA damage in Human cervical cancer HeLa cells. It also repressed the proliferation and induce apoptosis by means of downregulting NF-Kb, Akt pathway and tubulin polymerization [9]. The amount of BRCA1, P53, P-H2A.X in HeLa also increased which bring about the DNA damage and disruption of the cancer cells [9].Caspase 3 is a executioner caspase which play a pivotal role in inducing apoptosis. From experiments it is found that it upregulates the concentration of caspase 3 in the cancer cells in which it was targeted [19].

Reactive oxygen species(ROS) also cause damage to the organells and DNA in the cell. It also suppresses the β-catenin and Wnt pathway. Curcumin was observed to increase the level of ROS in HeLa cells leading to damage of those cells. High level of ROS also leads to disruption of various signaling pathways. It also leads to autophagic cell death. Curcumin also downregulates the metastasis of HeLa cells by arresting the cell cycle by adding a inhibitory phosphate of CDK1, thereby inactivating Cyclin B

which is required in cell cycle progression from G2 [19].

BONE CANCER

Intrestingly, it has been found out that cucumin is able to control osteogenesis of Human adipose derived mesenchymal stem cells(hADSC) in bone cancer [7,17]. This is done by regulating expression of some mi-RNA and inhibiting signaling pathways like Wnt/β-catenin. It is found that, mi-RNA control osteogenesis, bone development, cell proliferation, growth etc by binding to 3'UTR region of target mRNAs. Elevated levels of mi-RNA-126a in hADSCs suppress bone growth and osteogenesis [7]. And upon induction of curcumin these mi-RNA levels got significantly increased. The main target of the mi-RNA-126a-3p is the receptor for LRP [7]. These results shown that curcumin was able to suppress the Wnt/β-catenin pathway by increasing the expression of mi-RNA-126a-3p which further inhibited or decreased LRP6 expression [7].

LEUKEMIA

It is responsible for 8% of all cancer and it involves the blood and bone marrow [6]. In treatment of Leukemia curcumin has emerged as an efficient anti-leukemia drug [11]. It increases the levels of ROS in cells, inhibit various signaling pathways(JAK/STAT, PI3K/Akt, NF-Kb, TRAIL) and induce apoptosis in these cells. Curcumin effect gets multiplied when it is used with lready existing therapeutic drugs such as bortezomib [11]. In vitro, they have inhibited the malignancy shown by these leukemia cells. They perform this by primarily inhibiting the NF-Kb pathway [11]. Also both curcumin and bortezomib also decreased the levels of BCL-2 which directly affects the JNK signaling pathway [11]. The level of Cyclin D1 and D2 are downregulated and BIRC3 and CASP4 were upregulated by both compounds [11]. These changes leads to the apoptosis of leukemia cells. Curcumin was also seen to be effective in acute myloid leukemia(AML). It shows its effect by regulating the MAPK and NF-kB pathway which ultimately leads to apoptosis [5]. Curcumin also reduced the concentration of Vimentin(type of intermediate Filament) in AML cells, which was fond to drive the metastasis of these cells [5].

MULTIPLE MYELOMA

It is a B-cell malignancy which is caused by the increase in no. of monoclonal plasma cells in the bone marrow. Primary cause of this type of cancer is due to increase in expression of Notch-3 and 4 receptor which activates the notch signaling pathways which in turn increases the cell proliferation. Also the expression of p53 protein was regulated by notch receptors which is a major factor in regulating cancer. So in treating this kind of cancer curcumin was found to reduce the expression of notch receptor by inhibiting notch delta pathway. Also curcumin increases the mRNA levels of p53 which is a tumor suppressing gene. All these processes ultimately leads the cell to apoptosis [21].

CONCLUSION

Cancer still remains a quite viable and dangereous threat to our lives. Preparing its drug still imposes a big obstacle for the scientists. But in treatment of cancer curcumin has emerged as one of the most encouraging compound among many. As reported in present review, curcumin controls or suppress the cancer by regulating various signaling pathways, genes, mRNAs, proteins. Also inducing apoptosis in cancer cells is a major way in which it controls cancer [12,20]. By using different curcumin analogs or by combining with other drugs, it is seen that the tumerogenesis or metastasis can be controlled in a more efficient way [12,20]. Due to this, in recent years there is increasing amount of research going on it, so that its bioavailability and its effectiveness can be used extensively in treating cancer [3].

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REFERENCES

[1] Giordano,A. and Tommonaro,G.(2019) Curcumin and Cancer. Nutrients. 2019.11,2376.1-19 .

[2] Passaro,A., Bestivina,C., Velez,M.V., Garassino, M. C., Peters, E. G, S. (2021) Severity of COVID-19 in patients with lung cancer:evidence and challenges. Journal for Immuno Therapy of Cancer. 2021.9:e002266.1-10

[3] Mohanty, C.,Das,M., and Sahoo, S. K.(2012). Emerging role of nano carriers to increase the solubility and bioavailability of curcumin. Expert opin. Drug Deliv. 2012.1-18

[4] Ghasemi,F., Shafiee,M., Banikazemi,Z., Pourhanifeh,M.H., Kanbabaei,H. Shamshirian, A., Moghadam,S.A., Nezad,R.A, Sahebkar,A , Avan,A.(2019) Curcumin inhibits NF-Kb and Wnt/β-catenin pathways in cervical cancer cells. Pathology- Research and Practice 215. 2019. 152556. 1-6.

[5] Zhu,G., Shen,Q, Jiang,H. Ji,O., Zhu,L. and Zhang,L.(2020) Curcumin inhibited the growth and invasion of human monocytic leukemia SHI-1 cells in vivo by altering MAPK and MMP signaling. Pharmaceutical Biology. 2020. 58:1. 25-34.

[6] Kouhpeikar,H., Butler,A.E., Bamian,F., Barreto,G.E., Majeed,M., Sahebkar,A.(2019) Curcumin as a therapeutic agent in leukemia. Journal of Cellular Physiology. 2019.1-11.

[7] Li,H., Yue,L., Xu,H., Li,N., Li,J.,Zhang,Z., .Zhao, R.C.(2019) Curcumin suppresses osteogenesis by inducing miR-126-3p and subsequently suppressing the WNT/LRP pathway. 2019.11. 6983-6998.

[8] Zhu, H., Chang,L.L., YAN,F-J., Hu,Y., Zeng,C-M., Zhou,T-Y. ,Yuan,T., Ying,M-D. Cao,J., HE,Q-J., Yang.B.(2018) AKR1C1 Activates STAT3 to promote the metastasis of Non-Small Cell Lung Cancer. Theranostics. 2018.8(3). 676-692.

[9] Shang,H.S., Chang,C-H., Chou,Y-R., Yeh,M-Y., Au,M-K., Lu,H-E., Chu, Y-L., Chou,H.M., Chou, H.C., Shih,Y.L. and Chung,J.G.(2016) Curcum in causes DNA damage and affects associated protein expression in HeLa humn cervical cancer cells. Oncology Reports 36. 2016. 2207-2215.

[10] Zhu, J.Y., Yang, X., Chen,Y., Jiang,Y. ,Wang,S-J., Li,Y., Wang,X. Meng,Y. Zhu,M-M., Ma,X.,Wu,C.H.R., Xie,C-F., Li, X-T.(2017). Curcumin suppresses Lung Cancer Stem Cells via Inhibiting Wnt/β-catenin and Sonic Hedgehog Pathways. Physiotherapy Research. 20 17.

[11] 11. Nagy, L.I., Feher, L.Z., Szebeni, G.J., Gyuris,M., Sipos,P., Alfoldi, R., Ozsvari, B.,.Hackler Jr.L., Balazs, A., Batar,P., Kanizasai,I. and Puskas,L.G... Curcumin and its Analogue Induce Apoptosis in Leukemia Cells and have Additive Effects with Bortezomib in Cellular and Xenograft Models. BioMed Research International. 2015.1-11.

[12] Zhao,M., Gao, F-H., Wang,J-Y., Liu,F., Yuan,H-H., Zhang ,W.W.,and Jiang,B.,(2011). JAK2/STAT3 signaling pathway activation mediates tumor angiogenesis by upregulation of VGEF and bFGF in non-small-cell lung cancer. Lung Cancer. 2011.73. 366-374.

[13] Pouhanifeh,M.H., Darvish,M., Tabatabaeian,J., Fard,M.R., Mottaghi,R., Azadchehr,M.J., Jahanshahi,M. Sahebkar,A. and Mirzaei,H.(2020). Therapeutic role of curcumin and its novel formulations in gynecological cancer. Journal of Ovarian Research. 2020. 13:130.1-16.

[14] Zaman, M.S., Chauhan, N., Yallapu, M.M., Gara R. K., Maher, D. M., Kumari, S., Sikandar, M. Khan, S.(2016) Curcumin Nanoformulation for Cervical Cancer Treatment. Nature. 2016. 6:20051.1-14.

[15] Yadav,N., Parveen,S., Banerjee,M.(2020). Clinica Chimica Acta. 2020.505.60-72.

[16] Kundu,K., Mohanty,C., Sahoo.S.K.(2018) Antiglioma activity of curcumin-Loaded lipid nanoparicles and its enhanced bioavailability in brain tissue for effective glioblastoma therapy. Acta Biomaterialia. 2012.8. 2670-2687.

[17] Weng,Q., Ren,L., Guo,L., Hu,Y., Zhou,H., Bao,Y., Chen,L., Liang,G., Wang,Y., and Ruan,J.(2016). Curcumin analogue,A13,exhibits anti-leukemia effect via inhibing STAT3. Tumor Biology. 2016.

[18] Kamble,S., Varamini,P., Mullner,M. Pelras,T. and Rohanizadeh,R.(2020) Bisphosphonate-functionalized micelles for targeted delivery of curcumin to metastatic bone cancer. Pharmaceutical Development and Technology. 2020.

[19] Feng,T., Wei,Y., Lee,R.J., Zhao,L. Liposomal curcumin and its application in cancer.

International Journal of Nanomedicine. 2017.12. 6027-6044.
[20] Wang,T., Wu,X., rudaist,M.A., Song ,Y.,and Cheng,H.(2020). Curcumin induces G2/M arrest and triggers autophagy,ROS generation and cell senescence in cervical cancer cells. Journal of Cancer. 2020.11(22). 6704-6715.
[21] Zhang,Y., Lin,X.Y., Zhang,J-H., Xie,Z.L., Deng,H., Hyang Y.F.and Huang,X.H.(2019) Apoptosis of mouse myeloma cells induced by curcumin via the Notch3-p53 signaling axis. Oncology Letters. 2019.17:127-134.
[22] Xi,Y., Jiang,T., Yu,Y., Yu,J., Xue, M., Xu,N., Wen, J., Wen,W., He,H., Shen,Y., Chen D.(2019). Dual targeting curcumin loaded alendronate-hyaluroan-octadecanoic acid micelles forimproving osteosarcoma therapy. International Journal of Nanomedicine. 2019.14. 6425-6437.
[23] Wei,Y., Pu,X., and Zhao,L.9(2017) Preclinical studies for the combination of paclitaxel and curcumin in cancer therapy. Oncology Reports. 2017. 37. 3159-3166.
[24] Zong,Z., Wei,Y., Ren,J., Zhang and Zhou,F.(2021). The intersection of COVID-19 and cancer;signaling pathways and treatment implications. Molecular Cancer. 2021. 20:76.1-19.

ABBREVATIONS
AML-Acute Myloid Leukemia
BCL-B-Cell Lymphoma
bFGF -Basic Fibroblast Growth Factor
BRCA-Breast cancer gene
COX-Cyclooxygenase
EGFR-Epidermal Growth Factor
FGF-Fibroblast Growth Factor
hADSC-Human adipose derived mesenchymal stem cells
HeLa-Henrietta Lacks
Hh- Hedgehog
HPV- Human Papiloma Virus
IL-Inter Leukin
LDL-Low density Lipoprotein
LRP- Low density Lipoprotein Receptor
MMP-matrix metalloproteinases
NF-kB-Nuclear Factor kappa B
NF-Kb-Nucler factor kappa B
NSCLC-Non small cell lung cancer
MAPK-Mitogen-activated protein kinase
ROS- Reactive Oxygen Species
STAT- Signal Transducer and Activator of Transcription
TGF-β-Transforming Growth Factor beta
UTR- Untranslated region
VGEF-Vascular endothelial growth factor
Wnt- Wingless- related integration site