Letter to the Editor
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Can Other Herbal Drugs Affect Signaling Pathways in Glioblastoma Cells Similar to Curcumin?

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Dear Editor,

The most malignant human brain tumor is glioblastoma multiform (GBM). The patients usually do not suffer this tumor more than one year.[1] It is also the most common tumor among primary brain tumors.[1]

Primary GBM is a condition that tumor expands as de novo without prior record of disease of low grade often in the old individuals; however, secondary GBM happens by development from astrocytoma with low grade in younger patients.[1-2]

The main genetic factors in primary GBM are epidermal growth factor receptor (EGFR) amplification, phosphatase and tensin homolog (PTEN) mutations, and p16INK4a deletion.[1] The common mutations among patients with secondary or advanced glioma are in PDGFR-a (platelet derived growth factor receptor-alpha) and tumor protein P53 (P53).[1]

The recognition of good components among herbal drugs is a main point in research for prohibition of key signaling pathways in diseases specially GBM.[1-3] Among herbal drugs, curcumin (CUR) is a natural phenolic component that is obtained from turmeric (*Curcuma longa*).[4,5] This natural drug has several main remedial acts including antiproliferative (on cells), anti-inflammatory, antioxidant, antimicrobial, and antiangiogenic effects.[1] It has been proved that CUR can prohibit different signaling pathways that are related to drug resistance in cancer cells especially GBM cells.[3]

CUR reduces livability of glioma cells via different ways such as decreasing some proteins that are effective in cell survival including activator protein 1(AP1), nuclear

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factor κB (NFκB), and phosphoinositide 3 kinase. It also performs this act by upregulating some factors like p53, p21, and executor caspase 3 that are apoptotic agents.[6] Generally, CUR prohibits cell proliferation and stimulates apoptosis in glioblastoma tumors.[6-7]

CUR stimulates autophagy process by repression of the protein kinase B (AKT)/mammalian target of rapamycin (mTOR)/p70S6K that are key factors in GBM cell proliferation and also can activate the extracellular-signal regulated kinase (ERK1/2) signaling pathway for effect on autophagy.[8] CUR is also an inhibitor of migration and because of its inhibitory act on the JAK/STAT3 pathway, reduces aggressive condition in glioma cells.[8] According to the studies performed about application of CUR and its effect on signaling pathways of glioma cells, it could be a hypothesis that other herbal drugs can be useful materials for more research works about investigation of their effect on main signaling pathways in this disease in future.

GBM cells by CUR were sensitized to radiation and several clinically used chemotherapeutic drugs such as cisplatin, camptothecin, etoposide, and doxorubicin that these effects were related to decreased expression of some DNA repair enzymes including Ku70, MGMT, Ku80, and ERCC-1 and also bcl-2 family.[9]

CUR stimulates reactive oxygen species (ROS), advances activation of MAPK pathway, decreases STAT3 act and expression of inhibitors of apoptosis proteins family.[10]

It has been proved that CUR can neutralize glioma cell proliferation via prohibition of signaling pathway of the Sonic Hedgehog/glioma-associated oncogene homolog 1 (SHH/GLI1).[11]

P53-dependent manner of CUR causes cell cycle arrest that is related to enhancement expression of p21 and ING4 factors.[12] During this process, high expression of ING4 will enhance the binding to p53; afterwards, enhanced p21 expression decreases cell proliferation by stimulating cell cycle arrest in human GBM cells.[12] In addition, CUR stimulates G2/M arrest of cell cycle and induces apoptosis through FoxO1 signaling pathway in U87 human glioblastoma cells.[13]

CUR is an effective natural drug for activating both mitochondria-mediated proteolytic and the receptor-mediated pathways for apoptosis process in human glioblastoma cells.[13] On the other hand, CUR causes an enhancement in Bax: Bcl-2 proportion, and releasing cytochrome c from mitochondria that help to apoptosis.[14]

CUR causes sensitization to temozolomide in glioblastoma cells by producing ROS and interrupting AKT/mTOR signaling pathway.[15]

An oncogenic role in tumorgenesis is attributed to Skp2 (S-phase kinase associated protein 2). It has been shown that CUR repressed cell proliferation and stimulated apoptosis by decreasing expression of Skp2 in human GBM cells.[16]

Autophagy is a key process for regulation of glioma-initiating cell (GIC) differentiation and self-renewal. It shows that autophagy can be a beneficial therapeutic aim in glioblastoma tumors.[17] Moreover, CUR in this subject is stimulating differentiation of GICs and prohibiting glioma cells growth. It means that its act is related to the stimulation of autophagy process.[17]

Migration capability of malignant glioma tumors and their invasiveness condition is related to key factors named matrix metalloproteinases (MMPs).[6] The existence of some MMPs in higher rates in human glioma tissue samples toward healthy astrocytes has been proved.[6] CUR prohibits the high activity of MMPs as migration agents in GBM.[6]

Another effect of CUR is the expression of Notch1 decrease, NEDD4 and AKT signaling factors and its result is inhibition of GBM cell growth, apoptosis and repression of migration and invasion.[18]

Generally, CUR effects on main signaling pathways of GBM cells via inhibition of several key proteins that is shown in figure 1.

In vivo studies has shown that CUR is an effective herbal drug in inhibiting tumor growth and has a vital role in increasing resistance of TMZ in the xenograft mouse models.[19, 20]

Other studies on animal models revealed that

this drug had an antiangiogenic effect on GBM tumor.[21]

CUR also effects on cancer repression via autophagy in mouse xenograft with GICs. Only one clinical trial has been performed about CUR effect on patients with GBM that has represented in these patient's oral treatment with micellar curcuminoids led to quantifiable concentrations of total curcuminoids in glioblastomas and may alter intratumoral energy metabolism.[22]

Remedy of glioblastoma cells with garlic combinations induces production of ROS that stimulates apoptosis via the p38 MAPK phosphorylation and by inducing the redox-sensitive JNK1 pathway. ROS creation, p38 MAPK phosphorylation, and JNK1 activation reduced by treating cells with ascorbic acid. In addition, treating by JNK1 inhibitor can significantly decrease cell death. Involvement of endoplasmic reticulum stress in apoptosis has been demonstrated by enhancement of intracellular free, calreticulin expression, and stimulation of caspase-4.[23]

Several studies have advised that drinking black and particularly green tea is related to a decreased risk of several types of cancer in humans. In addition, there are proofs from experimental animal studies that drinking green tea prevents many tumors.[3-5] Green tea includes catechins for example 2-(3, 4-dihydroxyphenyl)-3, 4-dihydro-2H-1-benzopyran-3, 5, 7-triol (catechin), epicathechin and epigallocathechin-3 gallate (EGCG). Recently, chief consideration has been centralized on the anticancer act of the green tea combination EGCG. In order to give details about the anticancer action of EGCG, diverse mechanisms have been suggested, e.g. EGCG might reduce enzyme urokinase function, one of the most often overexpressed enzymes in cancers.[24]

The useful functions of flavonoids about the lessening the risk of chronic diseases such as cancer have been stated in some studies. Furthermore, it has been revealed that flavonoids, including quercetin in apple, genistein in soya, and epigallocatechin-3-gallate in green tea stimulate apoptosis. This function has a key role in physiological acts; however, there is basic dysregulation of apoptosis in many pathological conditions including Parkinson and Alzheimer's diseases, and cancers.[25]

Several natural molecules such as dauricine, isoliensinine, and cepharanthine induce MAPK-mTOR dependent stimulation of autophagy that the following result is cell death by autophagy process in a panel of resistant cells against apoptosis.[26]

Death and survival control of cancerous cell is a vital process in managing and treating cancer. Anticancer materials should eradicate the cancerous cell with the least side effects on healthy cells that is probable by the stimulation of apoptotic mechanisms. Apoptosis is recognized as programmed cell death in both healthy and injured tissues. Stimulation of apoptosis is one of the main mechanisms of cytotoxic anticancer compounds. Several natural agents such as plants stimulate apoptotic ways that are closed in cancer

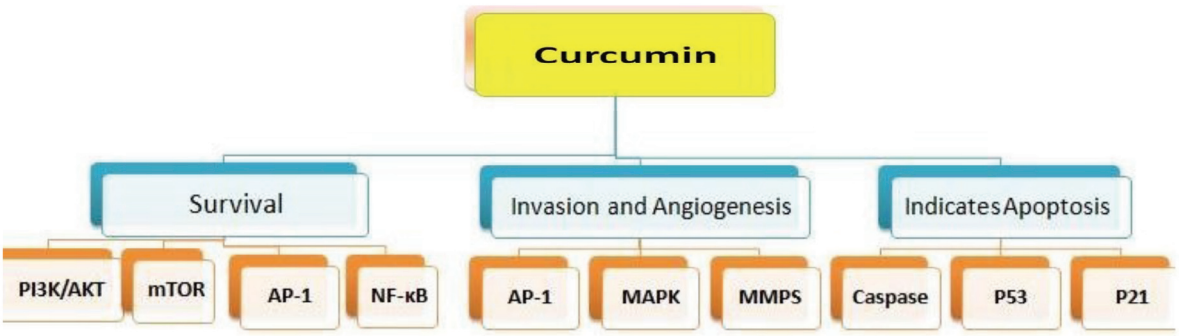

Figure1. Curcumin effects on key proteins of the main signaling pathways in GBM cells.

cells via different mechanisms. One of the main roles of CUR in treating of glioblastoma is apoptosis induction. Many studies have demonstrated that other herbal drugs apply as stimulators of apoptosis in cancers treatment.[26-28]

Totally, results represent the inhibitory function of CUR on various signaling pathways which have a key role in treatment of glioblastoma. We also suggest that herbal drugs can affect glioblastoma cells similar to CUR. Therefore, other herbal drugs can be useful for treating gliobalstoma.

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