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BENEFICIAL ROLE OF CURCUMIN IN DISEASES TREATMENT

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ABSTRACT: Curcumin regulates cellular signaling pathway related to cancer growth, inflammation and apoptosis and due to biological activities can be target DNA, RNA and enzymes. In addition, curcumin has inhibitory effect against MARK, P53, β -catenin and AKT. It can be consider as a promising agent to treat many diseases but it is important that should be acceptably carried out cellular targeting with curcumin. Here, we reviewed beneficial effects of curcumin in treatment of diseases. Our review study was confirmed that curcumin has potential effect in diseases treatment but there is a dire need for increase of its bioavailability in order to promotion of its efficacy. We suggest that should be design the methods for increase of cellular targeting by curcumin in further studies.

INTRODUCTION: Curcumin is considered as a phenolic compound with therapeutic properties including anti-inflammation, antioxidant and anticancer ¹. In previous studies, it has been found that it is safe compound for the body following its administration in patients with cancer and healthy individuals. In fact, its therapeutic effects is more than its side effects ^{2, 3}. However, despite having such a beneficial effect on human biological, it has not very high bioavailability in human due to poor absorption and fast metabolism ^{4, 5}.

In animal and human, major amount of curcumin is excreted as urine and feces and is absorbed only a small portion of curcumin that combines with glucuronide and sulfate in order to create its conjugated forms in liver. These events lead to reduction of plasma concentrations of free curcumin ^{2, 5-9}.

In addition, curcumin is an insoluble compound in water at neutral and basic conditions due to production of phenolate that leads to poor availability in aqueous systems ^{10, 11}. Using nanoparticles can increase cellular uptake and stability of curcumin so that solid lipid nanoparticles promote distribution and stability of curcumin in aqueous solutions that lead to improvement of the anticancer effect of curcumin ¹². In addition, silica nanoparticle can be a suitable delivery system for curcumin because it has been

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demonstrated that silica nanoparticle increase anti-tumor properties of curcumin¹³. In this study, we reviewed the beneficial effect of curcumin in order to treatment of diseases.

2. Review Method: Here, we searched paper related to role of curcumin treatment of diseases with keywords such as curcumin and cancer, curcumin and Parkinson's diseases, curcumin and Alzheimer disease, curcumin and histone acetyl transferase (HAT), curcumin and diabetes in databases include web of science, PubMed and Scopus. Then, the papers were fully read and summarized here.

3. Curcumin Beneficial Effects in Diseases

Treatment: According to a study Yallapu *et al.*, 2014, PLGA or poly (lactic-co-glycolic acid) combined with curcumin leads to a reduction of tumor cells growth (prostate cancer). Poly (lactic-co-glycolic acid) combined with curcumin had pivotal role in inhibition of beta-catenin expression in tumor cells. In addition, it led to inhibition of anti-apoptotic proteins (Mcl-1, Bcl-xL) through suppression of STAT3 and AKT phosphorylation. Down-regulation of miR21 and up-regulation of miR-205 also were showed after treatment with poly (lactic-co-glycolic acid) combined with curcumin. Given that this effects poly (lactic-co-glycolic acid) combined with curcumin can be consider as a promising agent to treat cancer due to good delivery into tumor cells¹⁴. Thiolated chitosan nanoparticle can promote anticancer effect of curcumin because it increases curcumin bioavailability. In addition, treatment of mice with colon cancer by curcumin loaded with thiolated chitosan nanoparticle led to dramatically reduction of cancer cells¹⁵.

Kumar *et al.*, 2014 examined that treatment of ovarian cancer cells (SKOV-3) with curcumin-loaded polymer of 2-hydroxy methyl methacrylate resulted in decrease of cancer cells by arresting of cell cycle in G0/G1 and induction of apoptosis¹⁶. It has been reported that curcumin-combined silica nanoparticle conjugated with hyaluronic acid results in cytotoxic effects on human colon carcinoma (colo-205) that is due to appropriate delivery of curcumin in to cancer cells through silica nanoparticle conjugated with hyaluronic acid¹⁷. Curcumin-loaded PLGA-PEG nanoparticle has

anti-tumor effects against breast cancer (cell line MCF-7) due to obvious reduction of cancer cells followed by treatment with curcumin-loaded PLGA-PEG nanoparticle¹⁸. The effect of polysorbate 80-coated cerasomes in order to deliver curcumin in mice with Parkinson's disease was confirmed promotion of cross of blood-brain barrier and subsequently improvement of mice with Parkinson's disease¹⁹. Curcumin and piperine coated with glycerol monooleate easily pass the blood-brain barrier and prevent formation of alpha synuclein oligomers. In addition, curcumin and piperine coated with glycerol monooleate reduce effect of rotenone as a Parkinson's disease inducer. Curcumin and piperine coated with glycerol monooleate is an important factor in reduction of oxidative stress, apoptosis and autophagy pathway and ultimately protect dopaminergic neurons against damage²⁰.

A research group was found that amine-functionalized mesoporous silica nanoparticle could be a good delivery system for curcumin in order to abrogation of Parkinson's disease complications because administration of curcumin-loaded amine-functionalized mesoporous silica nanoparticle leads to reduction of alpha synuclein accumulation²¹. Mathew *et al.*, 2012 designed a water-soluble nanoparticle (PLGA nanoparticle conjugated with Tet-1 peptide) for transferring of curcumin. Based our their study, curcumin loaded-PLGA nanoparticle conjugated with Tet-1 peptide prevents the accumulation of amyloid beta and had antioxidant effect and not cytotoxic effect therefore it can be very effective in the treatment of Alzheimer's disease²². It has been showed improvement of memory and reduction of amyloid plaques in mice with Alzheimer's disease after treatment with highly stabilized curcumin nanoparticle according to study conducted by Kin Cheng *et al.*, 2013. Meanwhile, the presence of high level of curcumin in plasma indicated enhancement of its pharmacokinetic characteristic using the nanoparticle²³.

Curcumin-loaded PLGA nanoparticle is effective in neural stem cell differentiation at rat's hippocampal and sub ventricular. In fact, injection of this compound into hippocampal leads to neurogenesis induction through expression of genes related to cell growth and proliferation (reelin, nestin and

Pax6) and differentiation of neurons, such as neurogenin, neuro D1, neuregulin, neuroligin and Stat3. These events ultimately result in improvement of learning and memory due to destruction of beta amyloid²⁴. Curcumin-coated magnetic nanoparticle has diagnostic value for Alzheimer's disease because it is a non-invasive diagnostic procedure by MRI and reduces PET disadvantages²⁵. Curcumin - loaded PLGA nanoparticle is a good agent against Alzheimer's disease due to it protects neurons against oxidative stress by up-regulation of expression of genes like APOE, APOJ, TRX, GLRX REST that indicate its high uptake in neurons²⁶. Curcumin inhibits histone acetyl transferase, a main reason of cardiac hypertrophy and heart failure, and prevents hypertrophy^{27, 28}. Furthermore, curcumin protects heart against damage caused by ischemia/reperfusion^{29, 30}.

In cells, curcumin leads to proteasome-dependent degradation of histone acetyl transferase. This event is main reason for inhibition of histone acetyl transferase by curcumin. In fact, curcumin is a selective inhibitor of histone acetyl transferase²⁸. By the mechanism, curcumin prevents excessive increase of ratio heart weight to body weight³¹. Retinopathy occurs in diabetes due to inability of body for elimination of free radicals and pro-inflammatory molecules such as NF- κ B, VEGF, and IL1 β . Curcumin prevents progression of diabetes retinopathy by inhibition of free radicals formation and reduction of inflammation³².

CONCLUSION: The use of herbal medicines is increasing in recent years. Thus, efforts to review and revive herbal medicines are reasonable so that to understand their effect mechanism lead to achieve new strategies to treat many diseases. The curcumin is most important component of turmeric. However, its low bioavailability has limited its healing properties. Today, it has been proposed several mechanisms to increase its bioavailability that can be improve its absorption. For example, the nanoparticles can significantly increase curcumin effectiveness. In this review study, we showed that to apply strategies for promotion of curcumin bioavailability lead to increase of its efficacy in treatment of diseases therefore we suggest that design further studies based on this view.

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