NATURAL MEDICINES DESIGN BASED ON ENCAPSULATION TECHNOLOGY

About Us

Today, societies are facing problems with a healthy lifestyle. A change in lifestyle using natural products that are effectively healthy is greatly required. Given the significant advances in medicine, all possible capacities should be applied to reduce treatment expenses by increasing effectiveness and reducing side effects of health-oriented products. For a long time, I have felt upset about the exorbitant costs of medicines on the one hand and the low effectiveness and side effects of consuming them on the other hand. By targeting the ongoing academic research since 2016, we have used Nano encapsulation technology to form a strong, scientific and committed team to design a variety of smart medicines with the aim of increasing effectiveness and reducing side effects. So far, many projects have been successfully completed in the laboratory and the results have marked a starting point for the creation of a knowledge-based company called Mehr o Mah Pharmaceutical Company. The aim of this company is the industrial manufacturing of various medicines on the basis of encapsulation technology.

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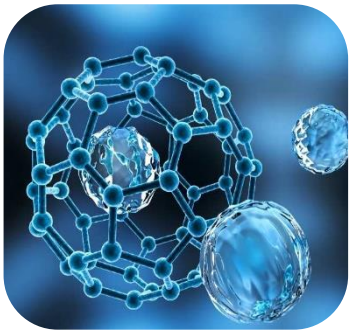

The Advantages of Encapsulated Turmeric (*Curcuma longa*)

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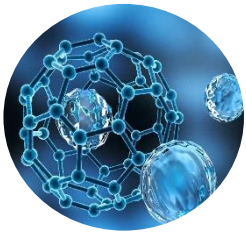

Anti-inflammatory

The effect of turmeric (*Curcuma longa*) on the prevention of Rheumatoid Arthritis

Curcumin, a nontoxic compound and the major constituent of the spice turmeric (1). In addition to antibacterial, anti-oxidant, and anti inflammatory action, curcumin exerts unique immunosuppressant properties via the inhibition of Th17 pro inflammatory responses and promotion of regulatory T cells, thus suppressing autoimmunity (Fig 1-1) (2).

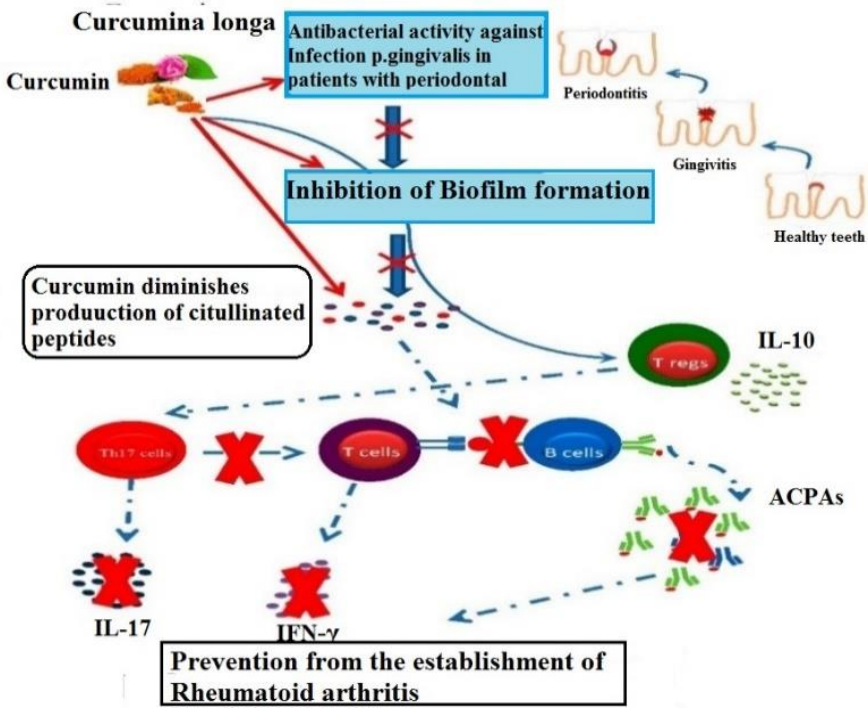

Fig 1-1. Curcumin may play a significant role in preventing from rheumatoid arthritis through its antibacterial action against *P. gingivalis* infection and biofilm formation in patients with periodontitis; and modulation of the proinflammatory immune response, such as inhibition of Th17 cells and enhancement of IL-10 producing regulatory T cells (2).

The effect of turmeric (*Curcuma longa*) on the treatment of Rheumatoid Arthritis

Curcumin inhibits these autoimmune diseases by regulating inflammatory cytokines such as IL-1beta, IL-6, IL-12, TNF-alpha and IFN-gamma and associated JAK-STAT, AP-1, and NF-kappaB signaling pathways in immune cells. Curcumin inhibits the production of several keypro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 by activated macrophages. Curcumin also suppresses activation and cytokine production of autoreactive T cell, which in downstream leading to the inhibited activation of pathologic synoviocytes and osteoclasts. Curcumin restore the TH17/Treg balance, which resulted in the increased numbers of Treg cells and subsequently production of anti-inflammatory cytokines IL-10 and TGF-β. Curcumin also suppresses production of autoantibodies by auto-reactive B cells on the one hand and increasing the numbers of Breg cells, which inhibit T cell immune responses, on the other hand. Finally, all of these immunomodulatory effects of curcumin lead to the inhibition of joint and bone destruction in RA (Fig 1-2) (3).

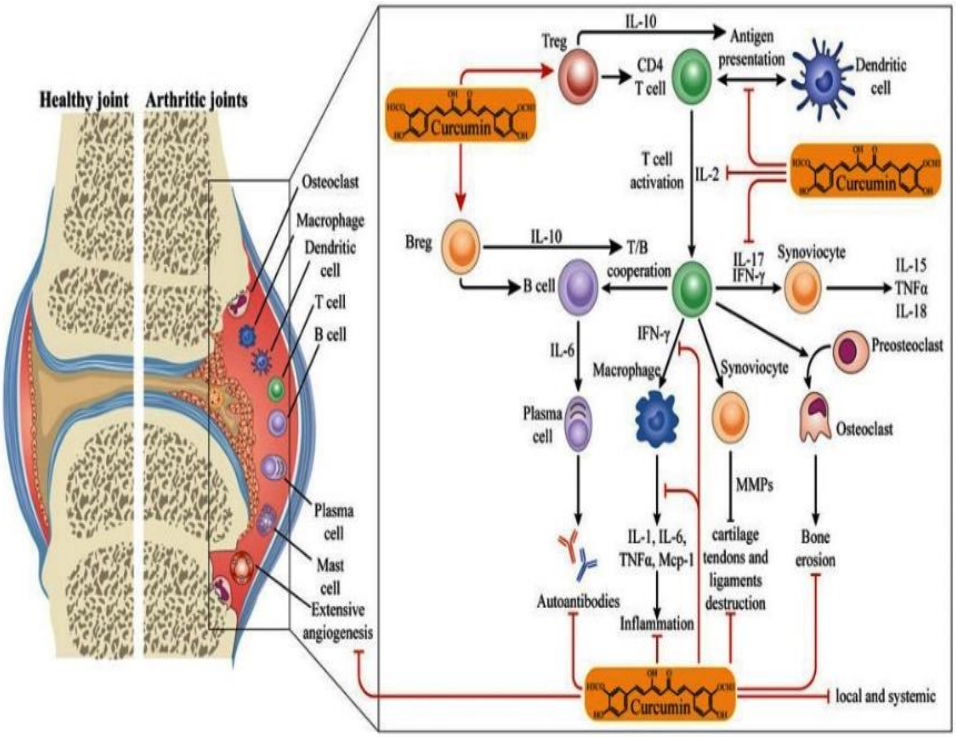

Fig 1-2. A schematic view of curcumin's immunomodulatory effects on dis regulated immune cells in RA.

Reference:

1- Rowe, S.M., 2005. Mechanisms of disease: cystic fibrosis. *N Eng J Med*, *352*, pp.1992-2001.

2-Asteriou, E., Gkoutzourelas, A., Mavropoulos, A., Katsiari, C., Sakkas, L.I. and Bogdanos, D.P., 2018. Curcumin for the management of periodontitis and early ACPA-positive rheumatoid arthritis: killing two birds with one stone. *Nutrients*, *10*(7), p.908.

3-Mohammadian Haftcheshmeh, S., Khosrojerdi, A., Aliabadi, A., Lotfi, S., Mohammadi, A. and Momtazi-Borojeni, A.A., 2020. Immunomodulatory effects of curcumin in rheumatoid arthritis: Evidence from molecular mechanisms to clinical outcomes. *Reviews of Physiology, Biochemistry and Pharmacology*, pp.1-29.

4-de Oliveira, G.V. and Alvares, T.S., 2022. Effect of curcumin on endothelial function in humans and their proposed physiological mechanism: insights in formulating curcumin products supplementation. *PharmaNutrition*, p.100313.

Curcumin ameliorates multiple sclerosis, rheumatoid arthritis, psoriasis, and inflammatory bowel disease in human or animal models (Fig1-3). Scientific studies reveal that curcumin is a potent agent in managing and preventing pain and inflammatory disorders, which are linked to its antioxidant, anti-inflammatory, analgesic, antimicrobial, and neuroprotective effects (1,2).

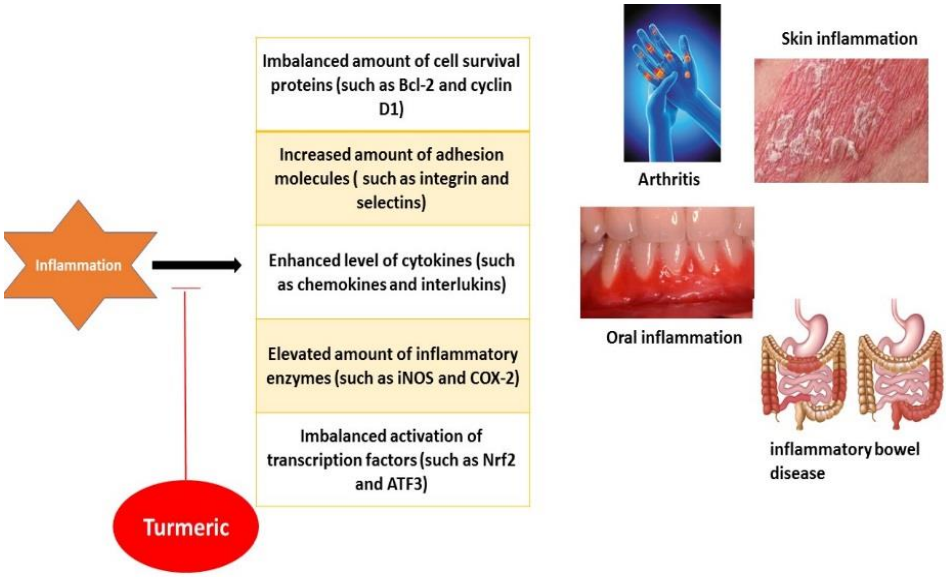

Fig 1-3. Anti-inflammatory mechanisms of turmeric.

Reference:

1- Vollono, L., Falconi, M., Gaziano, R., Iacovelli, F., Dika, E., Terracciano, C., Bianchi, L. and Campione, E., 2019. Potential of curcumin in skin disorders. *Nutrients*, *11*(9), p.2169.

2- Aggarwal, B.B., Gupta, S.C. and Sung, B., 2013. Curcumin: an orally bioavailable blocker of TNF and other pro-inflammatory biomarkers. *British journal of pharmacology*, *169*(8), pp.1672-1692.

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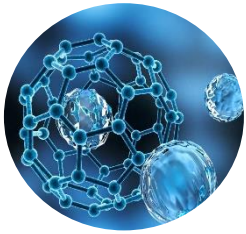

Cardiovascular Diseases (CVD)

Different studies revealed that curcumin presents anti-amyloid properties (Fig 1,2) (1,2).

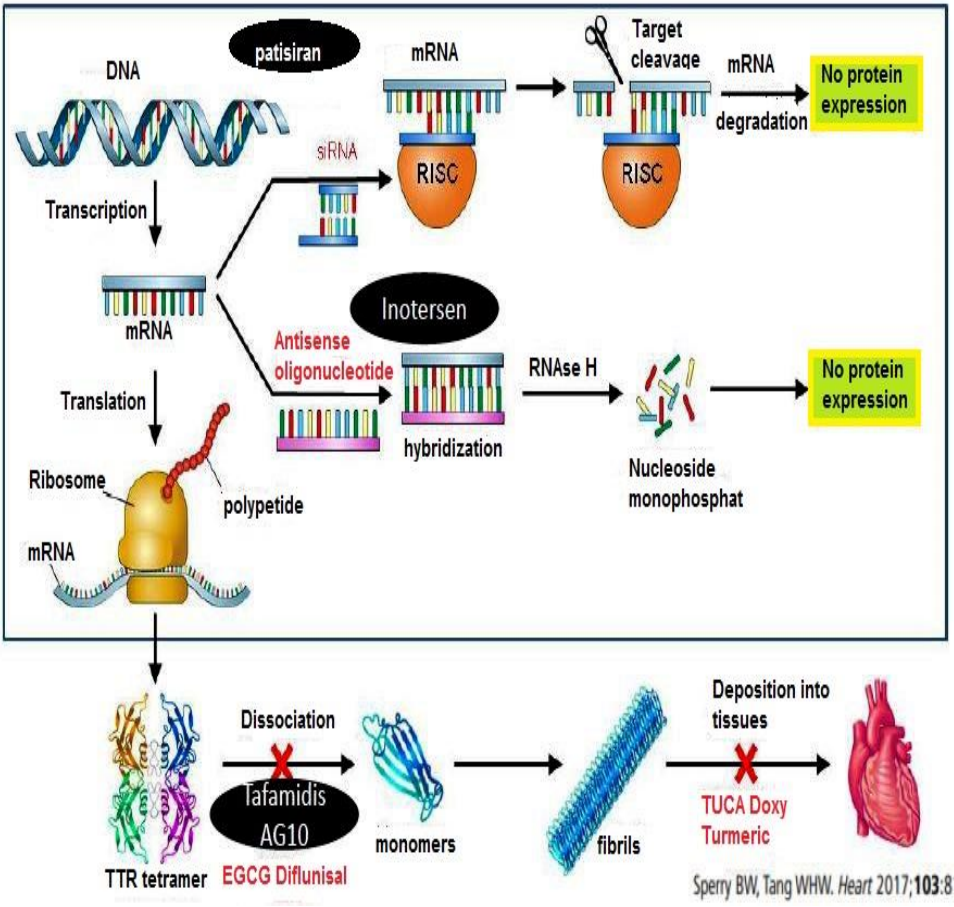

Fig 1. Mechanism of antiamyloid properties of curcumin.

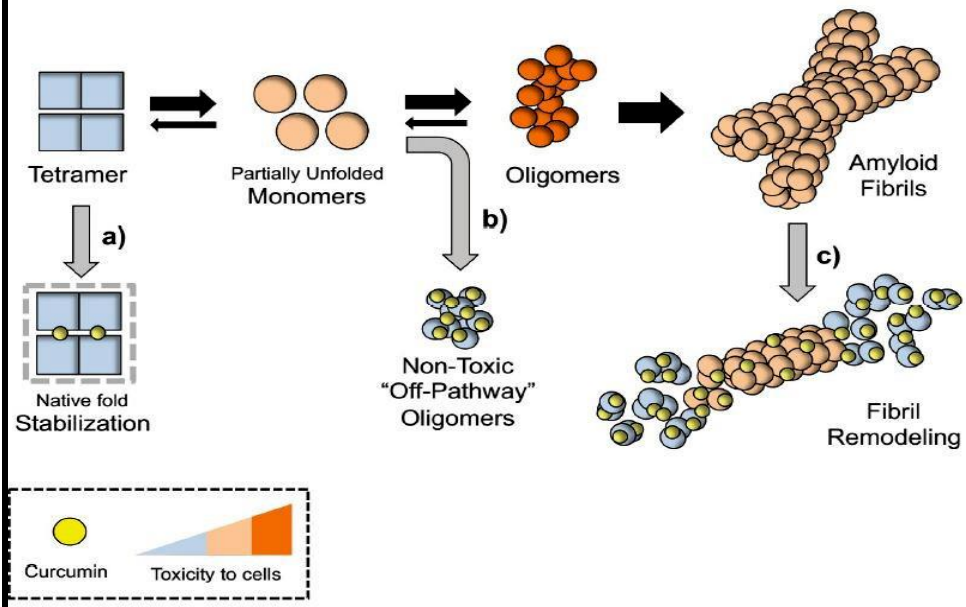

Fig 2. Proposed mechanism for Transthyretin (TTR) aggregation pathway modulation by curcumin (1,2).

Reference:

1- Ferreira, N., Saraiva, M.J. and Almeida, M.R., 2019. Uncovering the neuroprotective mechanisms of curcumin on transthyretin amyloidosis. *International journal of molecular sciences*, *20*(6), p.1287

2- Cardiac Amyloidosis: early diagnosis and novel *treatments https*://www.heart.org (MWA) 9-Amyloid-Sperry

Curcumin has anti atherosclerotic effects via the modulation of cholesterol efflux in macrophage foam cells through signaling AMPK/SIRT1/LXRα. AMPK pathway is also involved in the regulation of hyperlipidemia. Activated AMPK protects the myocardium through improved energy utilization, enhanced mitochondrial biogenesis, and inhibiting cell apoptosis. In endothelial cells, curcumin regulates uncoupling protein 2 and activates the AMPK pathway by inhibiting excessive ATP production in endothelial cells (Fig2-3) (1).

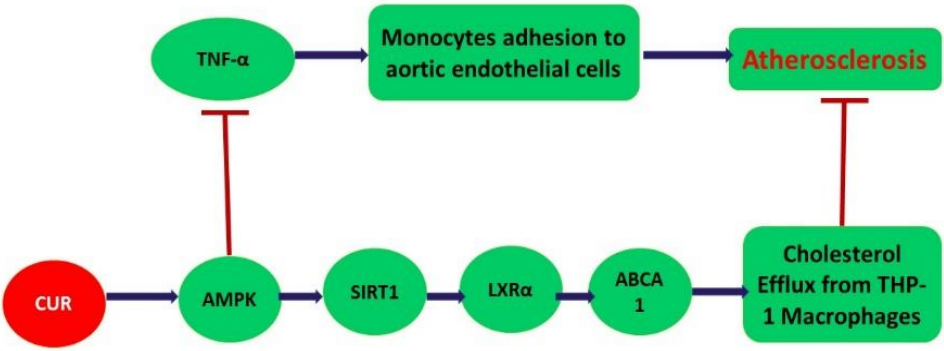

Fig 3. Effects of curcumin on AMPK signaling pathway in development of atherosclerosis. CUR: Curcumin; TNF-α: Tumor necrosis factor alpha; AMPK: 5′ AMP-activated protein kinase; LXRα: liver X receptor alpha; ABCA1: ATP Binding Cassette Subfamily a Member 1 (1).

Reference:

1- Pourbagher-Shahri, A.M., Farkhondeh, T., Ashrafizadeh, M., Talebi, M. and Samargahndian, S., 2021. Curcumin and cardiovascular diseases: Focus on cellular targets and cascades. *Biomedicine & Pharmacotherapy*, *136*, p.111214.

Inhibitors of the TLR4/MyD88/NF-κB signaling pathway show protective effects against CME-induced myocardial injury in vivo (1). curcumin exhibited myocardial protection by suppressing the myocardial inflammation via inhibiting the TLR4/MyD88/NF-κB signaling pathway (Fig 4) (2).

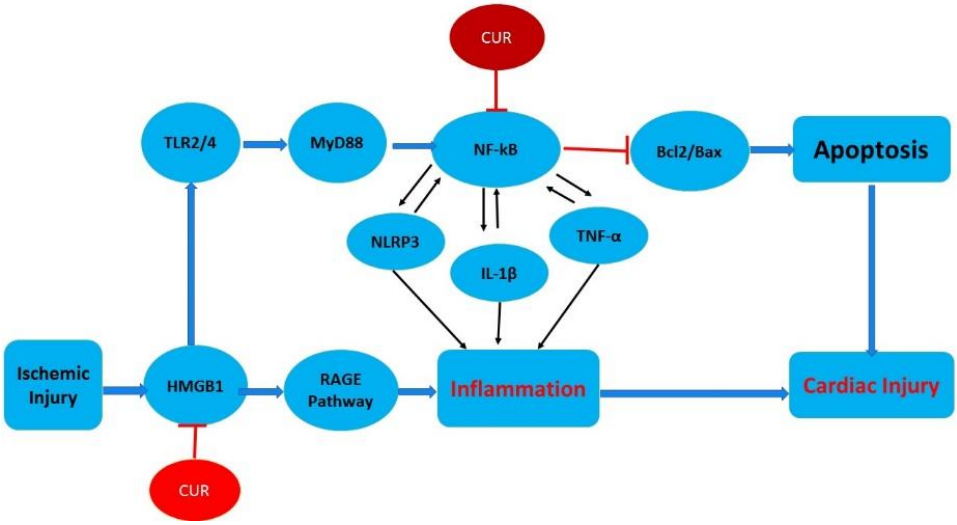

Fig 4. Effects of curcumin on Toll-like receptors mechanism involved in development of cardiac injury following ischemic injuries. CUR:Curcumin; TLR: Toll-like receptors; HMGB1: High mobility group box 1; Nf-kB: Nuclear Factor kappa-light-chain-enhancer of activated B cells; NLRP3: NOD-, LRR- and pyrin domaincontaining protein 3; Il-1β: Interleukin 1 beta; TNF-α: Tumor necrosis factor alpha (2).

Reference:

1- Su, Q., Lv, X., Sun, Y., Ye, Z., Kong, B. and Qin, Z., 2018. Role of TLR4/MyD88/NF-κB signaling pathway in coronary microembolization-induced myocardial injury prevented and treated with nicorandil. *Biomedicine & Pharmacotherapy*, *106*, pp.776-784.

2- Liu, Y., Liu, Y., Huang, X., Zhang, J. and Yang, L., 2019. Protective effects and mechanism of curcumin on myocardial injury induced by coronary microembolization. *Journal of Cellular Biochemistry*, *120*(4), pp.5695-5703.

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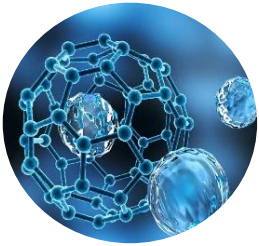

Liver

Curcumin and Non-Alcoholic Steatohepatitis (NASH)

The relationship between steatosis and fibrosis, hepatic cell injury and lobular inflammation is recognized as NASH (Fig 1) (1).

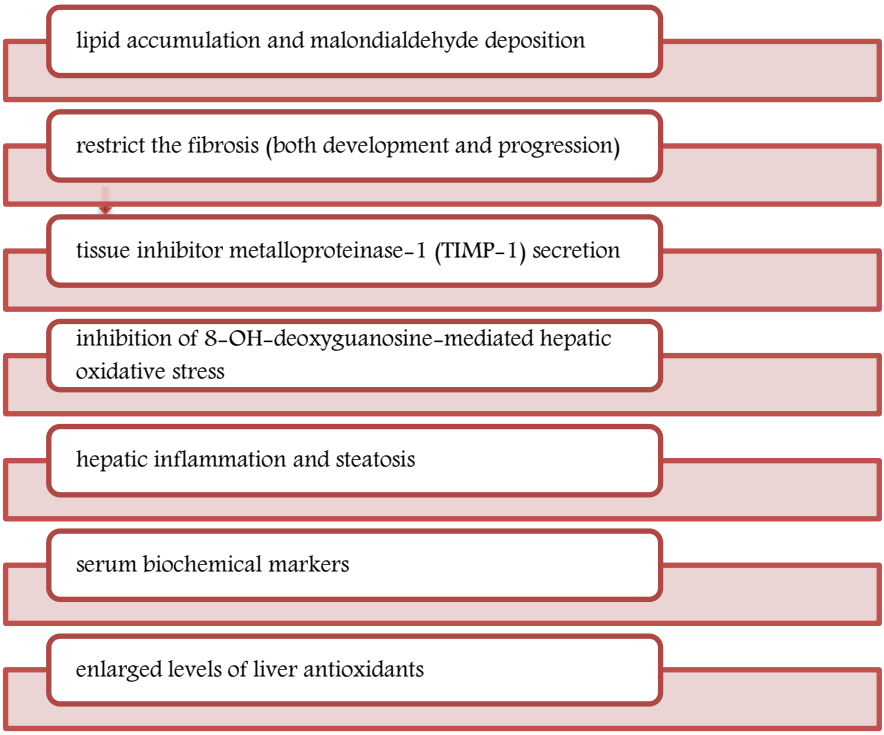

Fig 1. The effect of curcumin on Non-Alcoholic Steatohepatitis.

Reference:

1- Vizzutti, F., Provenzano, A., Galastri, S., Milani, S., Delogu, W., Novo, E., Caligiuri, A., Zamara, E., Arena, U., Laffi, G. and Parola, M., 2010. Curcumin limits the fibrogenic evolution of experimental steatohepatitis. *Laboratory Investigation*, *90*(1), pp.104-115.

Curcumin and Alcoholic Liver Disease (ALD)

The turmeric compound bisacurone can protect liver cells from alcohol-induced damage (Fig 2) (1).

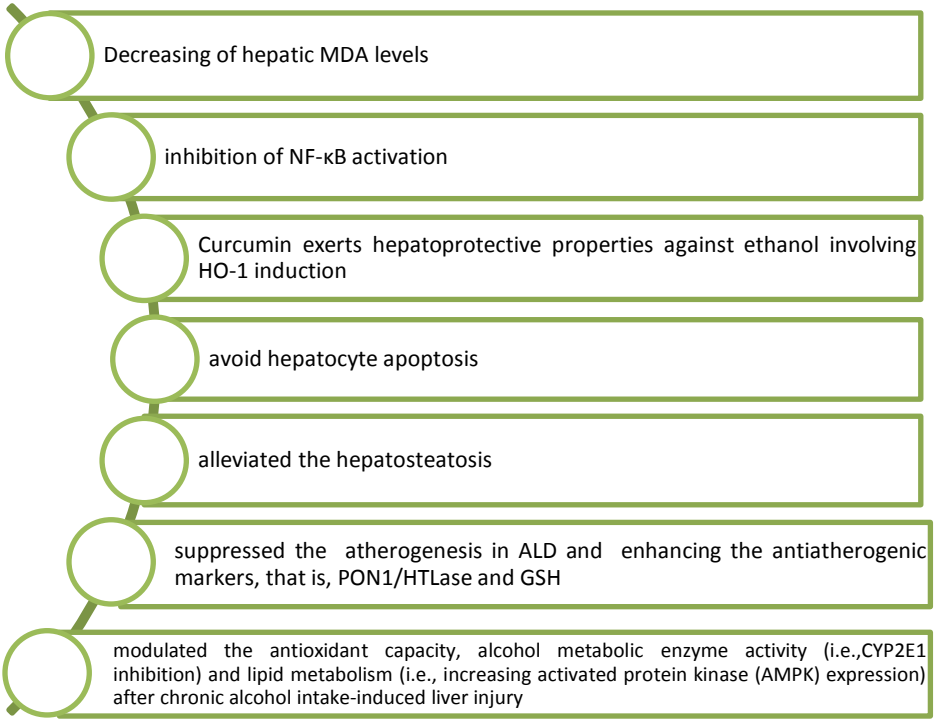

Fig 2. The effect of curcumin on Alcoholic Liver Disease

Reference:

1- Plus, S.B.S. and Style, A.B.H., Smart foods for an aging population.

2- Lee, H.I., McGregor, R.A., Choi, M.S., Seo, K.I., Jung, U.J., Yeo, J., Kim, M.J. and Lee, M.K., 2013. Low doses of curcumin protect alcohol-induced liver damage by modulation of the alcohol metabolic pathway, CYP2E1 and AMPK. *Life Sciences*, *93*(18-19), pp.693-699.

3- Bao, W., Li, K., Rong, S., Yao, P., Hao, L., Ying, C., Zhang, X., Nussler, A. and Liu, L., 2010. Curcumin alleviates ethanol-induced hepatocytes oxidative damage involving heme oxygenase-1 induction. *Journal of ethnopharmacology*, *128*(2), pp.549-553.

Curcumin for the Prevention of the Oxidative Stress in Liver

Curcumin can suppress lipid peroxidation and recover chemically induced oxidative stress (OS) as well as increase xenobiotic detoxifying enzymes' activities in both the liver and kidneys (1). Some of the important mechanisms of curcumin in the prevention of oxidative associated liver disease are shown in (Fig 3).

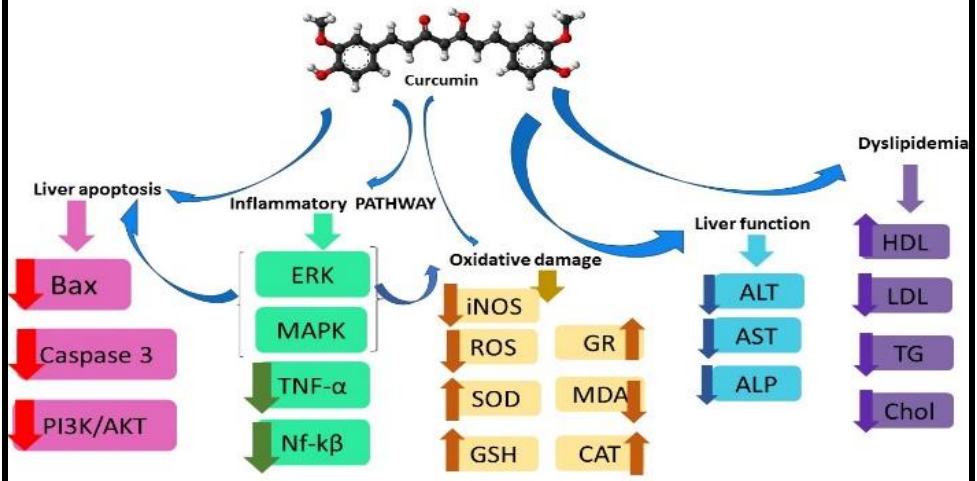

Fig 3. Cellular and molecular mechanisms of curcumin in the prevention of oxidative-associated liver disease.

Reference:

1-Abdel-Daim, M.M. and Abdou, R.H., 2015. Protective effects of diallyl sulfide and curcumin separately against thallium-induced toxicity in rats. *Cell Journal (Yakhteh)*, *17*(2),

Oxidative associated liver diseases (epigenetic pathway)

It has been demonstrated that curcumin can reduce the occurrence and/or delay the development of HCC by epigenetic mechanisms such as DNA demethylation and histone deacetylases (HDAC)-inhibitory effect (1). Furthermore, Curcumin can modulate miRs in liver diseases (Fig 4**)** (2,3).

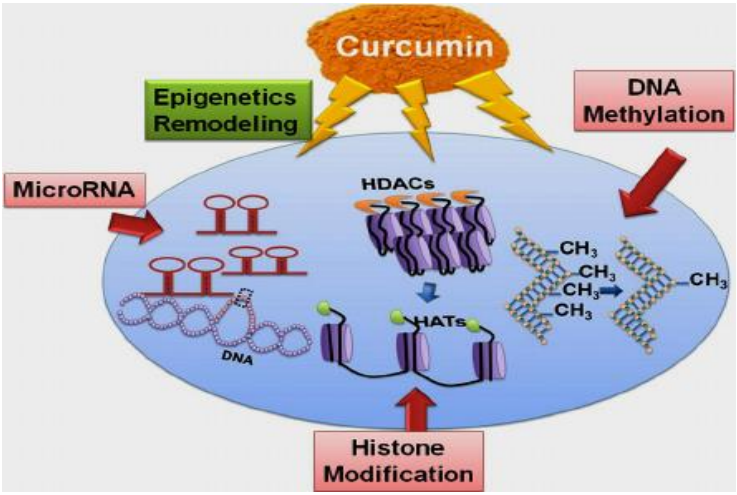

Fig 4. Curcumin-mediated epigenetic mechanisms involving DNA methylation, histone modifications and microRNA based epigenetic processes.

Reference:

1- Moreno, F.S., Heidor, R. and Pogribny, I.P., 2016. Nutritional epigenetics and the prevention of hepatocellular carcinoma with bioactive food constituents. *Nutrition and cancer*, *68*(5), pp.719-733.

2- Momtazi, A.A., and Sahebkar, A., 2016. Role of microRNAs in the therapeutic effects of curcumin in non-cancer diseases. *Molecular diagnosis & therapy*, *20*(4), pp.335-345.

3- Kalani, A., Kamat, P.K., Kalani, K. and Tyagi, N., 2015. Epigenetic impact of curcumin on stroke prevention. *Metabolic brain disease*, *30*(2), pp.427-435.

Curcumin and Liver Injury

Antioxidant Potential

The curcumin is found to be 10 times more antioxidant than vitamin E. Curcumin up regulates Nrf2 genes, which leads to rise in GSH concentration and activity of glutathione peroxidase and superoxide dismutase (SOD). SOD scavenges superoxide radicals by converting superoxide free radicals into H2O2 while preventing formation of OH radicals (Fig 1) (1,2,3).

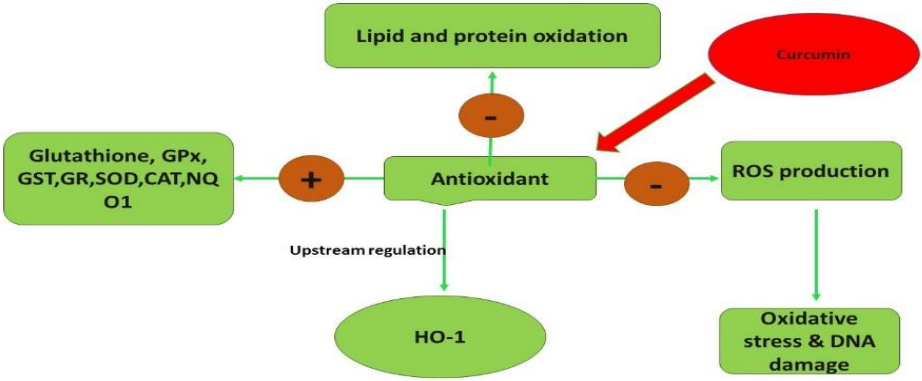

Fig 1. Curcumin decreases ROS inhibits lipid and protein oxidation and up regulates GSH, NQO1, GST, GR, GPx, CAT, SOD and HO-1expression.

Reference:

1- Liczbiński, P., Michałowicz, J. and Bukowska, B., 2020. Molecular mechanism of curcumin action in signaling pathways: Review of the latest research. *Phytotherapy Research*, *34*(8), pp.1992-2005.

2- Abdel-Daim, M.M. and Abdou, R.H., 2015. Protective effects of diallyl sulfide and curcumin separately against thallium-induced toxicity in rats. *Cell Journal (Yakhteh)*, *17*(2), p.379

3- Bavarsad, K., Riahi, M.M., Saadat, S., Barreto, G., Atkin, S.L. and Sahebkar, A., 2019. Protective effects of curcumin against ischemia-reperfusion injury in the liver. *Pharmacological research*, *141*, pp.53-62

The effect of curcumin against heavy metals-induced liver damage

The antioxidant, anti-inflammatory, anti-fibrogenic and anti carcinogenic activities of curcumin may confer therapeutic efficacy against different environmental or occupational hepatic toxins. In this manner, curcumin can protect against the toxic effects of heavy metals on the liver by reducing the structural damage, preventing lipid peroxidation, avoiding GSH depletion, maintaining he activity of SOD, CAT, GPx, GR, GST and NQO1 and protecting against the following liver mitochondrial alterations: oxidative phosphorylation-disruption, decrease in the cellular ATP levels mitochondrial permeability transition, calcium homeostasis disruption and apoptosis (fig 3-6). Oxidative stress induced by heavy metals exposure leads to the activation of the Nrf2/Keap1/ARE pathway. Protective effects of curcumin were attributed to its ability to scavenge free radicals, to act as an chelating agent and/or its capacity to induce detoxifying enzymes by the up regulation of Keap1/Nrf2/ARE pathway (Fig 1) (1).

Reference:

1- Kukongviriyapan, U., Apaijit, K. and Kukongviriyapan, V., 2016. Oxidative stress and cardiovascular dysfunction associated with cadmium exposure: beneficial effects of curcumin and tetrahydrocurcumin. *The Tohoku journal of experimental medicine*, *239*(1), pp.25-38.

2- García-Niño, W.R. and Pedraza-Chaverrí, J., 2014. Protective effect of curcumin against heavy metals-induced liver damage. *Food and Chemical Toxicology*, *69*, pp.182-201.

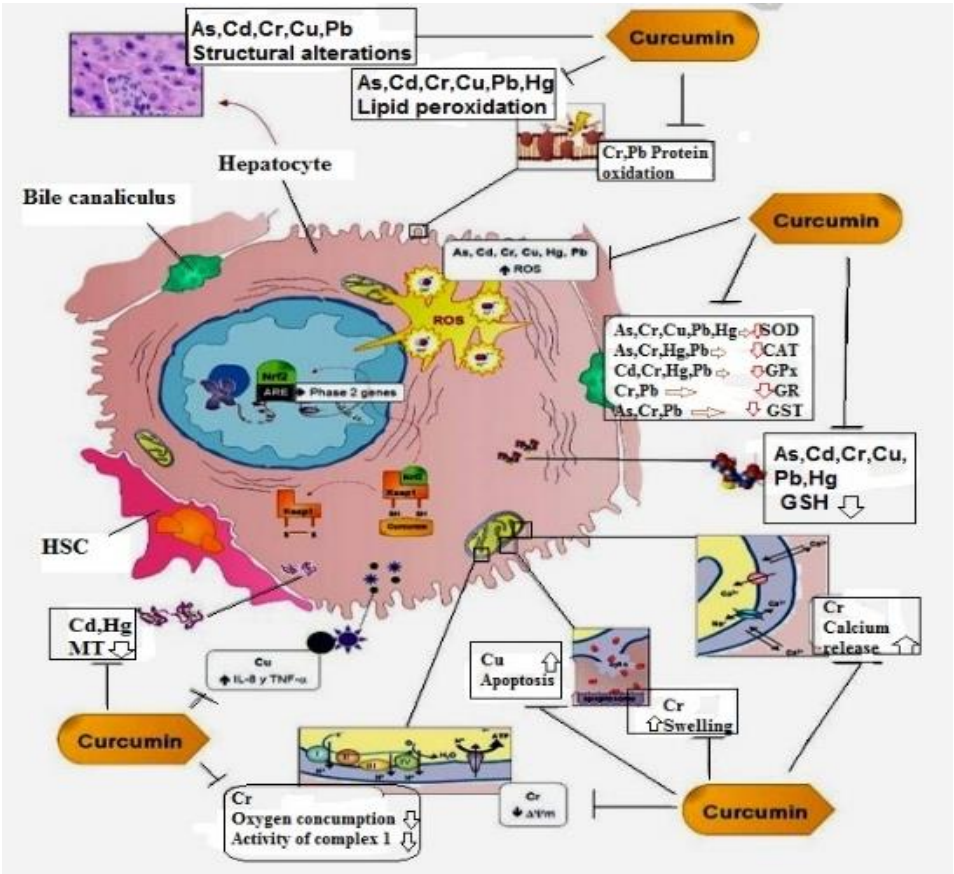

Fig 1. Protective effect of curcumin against heavy-metals induced-hepatic damage. Arsenic (As), cadmium (Cd), chromium (Cr), copper (Cu), mercury (Hg), lead (Pb), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-S-transferase (GST), glutathione (GSH), reactive oxygen species (ROS), nuclear factor (erythroid-derived 2)-like 2 (Nrf2), antioxidant responsive element (ARE), Kelch-like ECH-associated protein 1 (Keap1), hepatic stellate cells (HSC), mitochondrial membrane potential (DWm), metallothionein (MT), tumor necrosis factor-a (TNF-a) and interleukin-8 (IL-8).

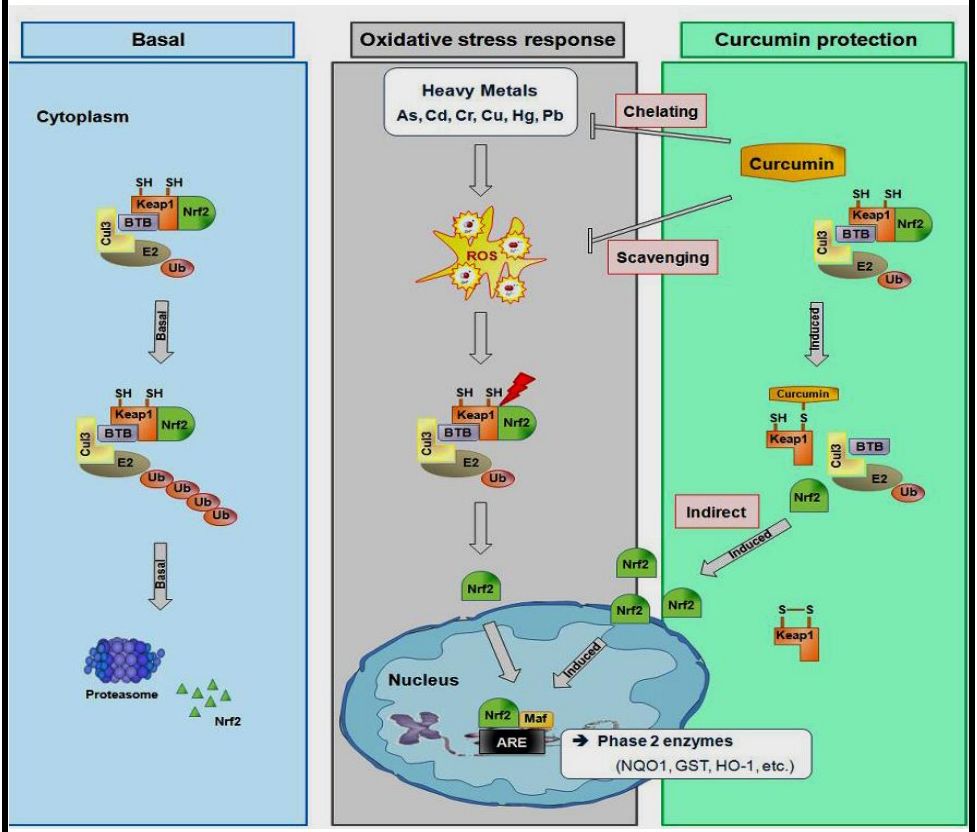

Fig 2. General scheme for the induction of gene expression through Keap1/Nrf2/ARE pathway. Nrf2 is a redox-sensitive transcription factor which, under basal conditions, is bound to its repressor Keap1 in the cytoplasm. Keap1 serves as an adaptor protein between Nrf2 and the Cul3 complex, leading to ubiquitylation of Nrf2 and subsequent degradation by the 26S proteasome. Reactive oxygen species (ROS), Kelch-like ECH-associated protein 1 (Keap1); nuclear factor (erythroid-derived 2)-like 2 (Nrf2); antioxidant responsive element (ARE); cullin-3 (Cul3); NADPH: quinone oxidoreductase 1 (NQO1); Glutathione-S-transferase (GST); heme oxygenase-1 (HO-1).

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