Review Article

Role of Curcumin in Disease Prevention and Treatment

Abstract

Treatment based on traditional medicine is very popular in developing world due to inexpensive properties. Nowadays, several types of preparations based on medicinal plants at different dose have been extensively recognized in the diseases prevention and treatment. In this vista, latest findings support the effect of *Curcuma longa* and its chief constituents curcumin in a broad range of diseases cure via modulation of physiological and biochemical process. In addition, various studies based on animal mode and clinical trials showed that curcumin does not cause any adverse complications on liver and kidney function and it is safe at high dose. This review article aims at gathering information predominantly on pharmacological activities such as anti-diabetic, anti-microbial, hepato-protective activity, anti-inflammatory, and neurodegenerative diseases.

Keywords: *Anti-inflammatory and anti-tumor activity, curcumin, health management*

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Introduction

The plants and its constituents based remedies are very popular in health management since ancient time. Numerous studies based on animal model and clinical trials have shown beneficial effect of medicinal plants in diseases control through modulation of various biological activities. Natural products or natural products based remedies are very popular in health management and its importance in health cure documented in religious literatures including Bible and Quran. In this vista, Prophet Mohammad (Peace Be Upon Him) has recommended various plants in the diseases cure and prevention.[1,2] In this view, turmeric and its constituents curcumin derived from turmeric (*Curcumin longa*) has been used for thousands of years in the treatment of various diseases due to efficacy, affordable, and rich source of antioxidant. In addition, toxicity studies showed that it is quite safe even in high doses (up to 12 g in humans).[3,4] Curcumin, a chief constituents of turmeric has been proven to have clinical therapeutic and its antioxidant properties play an important role in the management of chronic inflammation diseases.[5] Previous finding has proven that curcumin has a therapeutic potential as antifungal, antiviral, antioxidant, anti-inflammatory, and management of other pharmacological activities.[5-9] In this review, we summarized the therapeutics role of curcumin in diseases prevention such as cancer, diabetes, cardiovascular, and other diseases together with modulation of biological activities.

Possible Mechanism of Action of Curcumin in Health Management

Curcumin shows a pivotal role in the diseases prevention through the modulation of biological processes. It shows role in the prevention of pathogenesis due its effective scavenger of reactive oxygen species (ROS). Curcumin is an effective scavenger of ROS and reactive nitrogen species[10,11] and in other finding, the antioxidant activity was established by inhibition of controlled initiation of styrene oxidation.[12]

The effective anticancer property of curcumin is attributed to its antioxidant effect that control DNA damage and free radical–mediated lipid peroxidation.[13]

Curcumin also have an important in the health management through its anti-inflammatory effects. However, the exact mechanism by which curcumin shows its anti-inflammatory effects are not entirely understood. But, it is believe that curcumin shows role as anti-inflammatory via inhibition of enzymes such as cyclooxygenase-2 (COX-2) and 5-lipooxygenase. It was confirmed that its role in the management of diseases via inhibition of pathogenesis of diseases.

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Role of Curcumin in the Diseases Management Described as Following

Anti-oxidant activity

Antioxidant activity of herbs shows function in health management via its role in neutralization of free radical species. Finding based on *in vitro* showed that curcumin is an effective scavenger of ROS and reactive nitrogen species[10,11] and in other finding, the antioxidant activity was established by inhibition of controlled initiation of styrene oxidation.[12] The effective anticancer property of curcumin is attributed to its antioxidant effect that control DNA damage and free radical–mediated lipid peroxidation.[13]

It also exerts powerful inhibitory effect against hydrogen peroxide-induced damage in human keratinocytes and fibroblasts.[14] In addition, curcumin, chief constituents of turmeric shows role in the improvement of the activities of detoxifying enzymes such as glutathione-S-transferase (GST).[15] Earlier study reported that curcumin efficiently inhibits intracellular amyloid toxicity at low dosages based on rats through its free radical scavenging activity.[16]

Experiment based on rat model confirmed that oral administration of curcumin showed noteworthy reversal in lipid peroxidation, brain lipids as well as produced enhancement of glutathione.[17]

Anti-diabetic activity

Study was performed to check the effects of curcumin and it was found that administration of curcumin enhanced the activities of all antioxidant enzymes.[18] Furthermore, curcumin treated rats has shown noteworthy increase in gene expression such as insulin-like growth factor-1, B-cell lymphoma 2, superoxide dismutase and GST as compared groups such as nondiabetic and diabetic untreated rats.[18] Another study based on rat showed that insulin secretion, heme oxygenase (HO)-1 gene expression and HO activity were significantly increased after isolated islets of Langerhans treated in curcumin.[19] Recent study summarized the role of curcumin in the prevention or delaying of diabetic retinopathy via modulation of various biological activities[20] and oral administration of curcumin with dose 0.05% w/w in diets for 9 weeks showed role in the inhibition of diabetes-induced increase in acetylated histones in the retinas.[21]

Anti–inflammatory activity

Nonsteroidal anti-inflammatory drugs are most commonly used drugs worldwide in the treatment of inflammation and are approved for orthopedic conditions and wound. However, such drugs show an adverse side effect and causes gastric ulcer. Curcumin have shown a vital effect in the prevention of inflammatory process via modulation or inhibition of various molecular pathways [Figure 1 and Table 1]. A study based on animal model,

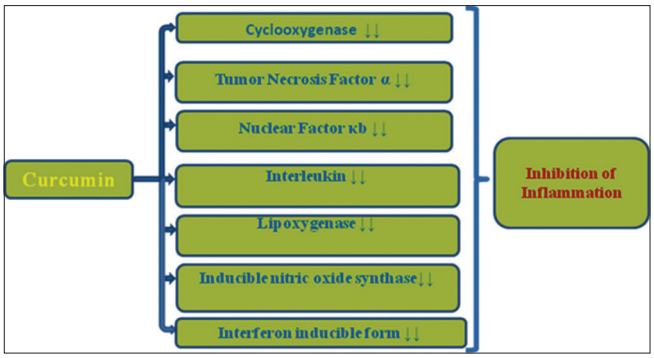

Figure 1: Curcumin shows role as anti-inflammatory via inhibition of various genetic pathways

curcumin, a chief ingredient of turmeric inhibited arachidonic acid metabolism and inflammation in skin epidermis through downregulation of the pathways of cyclooxygenase and lipoxygenase and other study reported that curcumin possesses anti-inflammatory activity.[22-23]

Previous studies has shown that its effect in the reduction of neutrophil infiltration in inflammatory conditions.[24-26] Other results showed that curcumin inhibited arthritis at a dose of 40 mg/kg, and acute toxicity was not noticed at doses up to 2 g/kg body weight.[23] Earlier finding has shown that curcumin exerts its anti-inflammatory effects in murine colitis models via inhibition of COX-2-and pro-inflammatory cytokine expression[27-29] and suppression of nuclear factor kappa B (NF-κB) activation.[30,31] Curcumin, chief constituents of turmeric shows a role in the suppression of both acute and chronic inflammation as it block the formation of enzymes such as COX-2 involved in inflammation.[57] Curcumin supplementation is linked with lowered plasma levels of tumor necrosis factor-alpha (TNF-α), interleukin-6, and monocyte chemoattractant protein-1 in diabetic rats and in high glucose treated monocytes.[32]

Anti-microbial activity

The frequency of drug resistance against microorganism is rapidly growing worldwide and resistance against antimicrobial agents is one of the main culprits of the treatment disintegrate. A safe and effective natural source is needed to overcome such types of problem. Curcumin, a chief ingredient of turmeric has been confirmed to have antibacterial, antiviral, and antifungal activities.[8] A study finding revealed that curcumin exhibited inhibitory activity on methicillin-resistant *Staphylococcus aureus* strains with minimum inhibitory concentration value of 125–250 μg/Ml.[58] Curcumin, chief ingredients of turmeric showed role in the inhibition of growth of all *Helicobacter pylori* strains *in vitro* that were isolated from infected patients suffering from gastrointestinal disorders.[33] Curcumin possesses antibacterial property against a number of Gram-positive and Gram-negative bacteria[59] and study finding revealed that curcumin and its new derivatives such

Table 1: Pharmalogical activities

Activities	Outcome/findings	References
Scavenger of reactive oxygen	Curcumin is an effective scavenger of ROS and reactive nitrogen species	[10,11]
Antioxidant activity	Antioxidant activity was established by inhibition of controlled initiation of styrene oxidation and anticancer property of curcumin is attributed to its antioxidant effect that control DNA damage and free radical-mediated lipid peroxidation.	[12,13]
Anti-diabetic	*Curcuma longa* rhizomes have anti-diabetic properties as its alcohol extract contains active constituents showed blood glucose lowering activity	[20]
Anti-inflammatory	Anti-inflammatory activity of curcumin has been demonstrated in acute and chronic models of inflammation in rats and mice	[23-24]
	Curcumin reduces the neutrophil infiltration in inflammatory conditions	[24,25-29]
	Curcumin exerts its anti-inflammatory effects via inhibiting COX-2-and pro-inflammatory cytokine expression and suppressing NF-κB activation	[27-31]
Anti-microbial	Curcumin exhibited inhibitory activity on MRSA with MIC value of 125-250 µg/Ml	[32]
	Curcumin potentially inhibited the growth of all 65 *Helicobacter pylori* strains *in vitro* that were isolated from infected patients suffering from gastrointestinal disorders	[33]
Anti-ulcer	Antiulcer activity of curcumin in indomethacin-induced gastric ulceration and its association with down-regulation of MMP-9 activity and up-regulation of MMP-2 activity and oral dose of 60 mg/kg blocks 85% of gastric damage caused by indomethacin	[34]
Prevention of gastric lesions	Curcumin potentially preventing gastric lesions development in the gastric wall during the acute phase of gastric ulcer diseases	[35]
Hepato-protective	Curcumin at 200 mg/kg dose for four consecutive days not only protected against DMN-induced hepatic injury, but also showed more than 3-fold induction of HO-1 protein expression and activity in rat liver	[36]
Cardio-preventive	Curcumin inhibit p300-HAT and that finally prevent the development of heart failure	[37]
Neuro-protective	Curcumin improves survival of cortical neurons induced by OGD/R and reduced OGD-induced cell injury	[38]
Anti-obesity	Curcumin at cellular and whole organism levels shows potential health benefits for prevention of obesity and associated metabolic disorders through suppressing angiogenesis in adipose tissue, up regulating adipocyte energy metabolism	[39]
Hypertension reducing	Curcumin showed that hypertension reducing effect	[40]
Anti-cancer activity	Curcumin increased the activity of phase II enzymes, such as GSTs and down regulated VEGF through inhibition of PPARδ in colon cancer cells	[41-44]
Role in respiratory system	Curcumin has inhibited bleomycin-induced pulmonary fibrosis in rats	[45]
	Curcumin significantly inhibited the release of TNF-α and prevented the respiratory and cardiovascular effects	[46]
Immounomodulatory	Curcumin imparted immunosuppression by mainly down-regulating the expression of CD28 and CD80 and up-regulating CTLA-4	[47]
	Modulation of activation of T cells, B cells, macrophages, dendritic cells, cell cycle protein, cell mediated and humoral mediated immunity	[48-50]
Anti-malarial	Oral administration of curcumin to mice infected with malaria parasite showed reduced blood parasitemia by 80-90% and enhances their survival significantly	[51]
Anti-malarial activity	Turmeric showed a cytotoxic effect in *Giardia lamblia* inhibiting the parasite growth and adherent capacity, induced morphological alterations and provoked apoptosis-like changes	[52]
Nephrotoxicity effect	Curcumin showed protection of diabetic nephropathy and oxidative stress against streptozotocin-induced and showed protective effects against nephrotoxicity	[53-55]
Reduction in sperm motility	Incubation of normal human sperm with curcumin resulted in a dose-and time-dependent loss of sperm motility	[56]

ROS: Reactive oxygen species, NF-κB: Nuclear factor kappa B, MRSA: Methicillin-resistant *Staphylococcus aureus*, MIC: Minimum inhibitory concentration, DMN: Dimethylnitrosamine, OGD/R: Oxygen-glucose deprivation/reoxygenation, GSTs: Glutathione S transferases, VEGF: Vascular endothelial growth factor, PPARδ: Peroxisome proliferator-activated receptor δ, TNF-α: Tumor necrosis factor alpha, CTLA: Cytotoxic T lymphocyte antigen 4, MMP-9: Matrix metallopeptidase-9, HO: Heme oxygenase, COX-2: Cyclooxygenase-2

as gallium-curcumin and Cu-curcumin have remarkable antiviral effects on HSV-1 in cell culture.[7] Moreover, other investigators have also reported that anti-bacterial activity of curcumin.[60-62]

Gastro-protective effect

Curcumin show gastroprotective effect and also reduced peptic ulcer and its associated complications [Figure 2 and Table 1]. Earlier investigation has shown

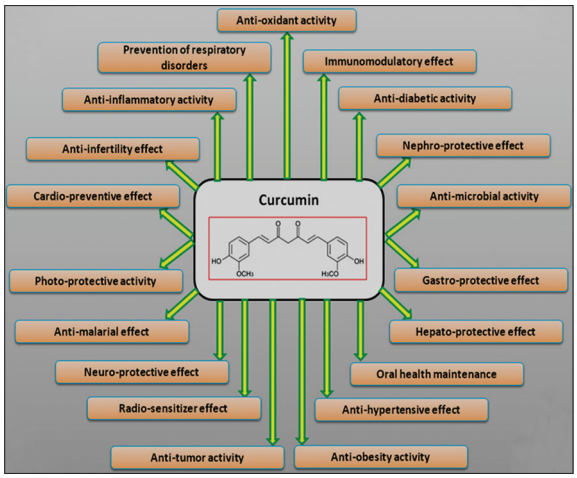

Figure 2: Pharmalogical activities of curcumin

that curcumin increases mucin secretion and may hence act as a gastroprotectant against irritants.[63] Administration of acetylsalicylic acid on an empty stomach has shown severe gastric lesions and serious damage to the internal lining of the gastric mucosa, whereas administered with curcumin in the fasting condition did not show reddish lesions or swelling of the gastric mucosa.[64] Another vital study demonstrated that antiulcer activity of curcumin in indomethacin-induced gastric ulceration and its association with down-regulation of matrix metalloproteinase (MMP)-9 activity and up-regulation of MMP-2 activity[34] and oral dose of curcumin (60 mg/kg) blocks 85% of gastric damage.[34] Study reported that curcumin and omeprazole showed role in the prevention of gastric lesions development in the gastric wall during the acute phase of gastric ulcer diseases.[35]

Hepato-protective effect

Liver is one of the important human organs, which play a major role in detoxification of xenobiotics. Various factors are responsible for the hepatic complications such as parasitic and viral infections, autoimmune diseases and intoxication with various xenobiotics including chlorinated solvents, alcohol, drugs, fungal toxins, industrial pollutants, and radioactive isotopes.[65] In this vista, curcumin-based therapeutics for a liver disorder has been in use in different part of the world for a long time.

Study based on rat model demonstrated that oral administration of curcumin with a dose of 200 mg/kg not only protected against dimethylnitrosamine-induced hepatic injury but also showed more than 3-fold induction of HO-1 protein expression and activity in rat liver.[36]

An experiment based on mice model via carbon tetrachloride 4 (CCl4) induced liver toxicity has proved that pretreatment with picroliv, curcumin, and ellagic acid normalized serum aminotransferase activities, decreased levels of malondialdehyde, improved the antioxidant status and also normalized the hepatic histo-architecture.[66] Other study reported that administration of *C. longa* was found to provide noteworthy protection in CCl4 induced increases in the level of serum glutamic oxaloacetic transaminase and serum glutamate pyruvate transaminase and serum bilirubin[67] and curcumin treatment protected the liver from the arsenic-induced deterioration of antioxidant levels.[68]

Cardio-preventive effect

Cardiovascular diseases are a major global health problem and one of the major causes of death worldwide. Previous investigation based on two different heart failure model *in vivo*-hypertensive salt-sensitive rats and surgically induced rat model of myocardial infarction has shown that curcumin inhibit p300-HAT and that finally prevent the development of heart failure.[37] Another study based on male rat reported that curcumin possesses a potential cardioprotective effect against sodium fluoride intoxication.[69] A study finding reported that curcumin, chief constituent of turmeric pre- and co-treatment decreased the severity of pathological changes and therefore, could have a protective effect against the damage caused by myocardial infarction (MI).[70] A recent study reported that curcumin prevented ISO-induced cardiac hypertrophy, oxidative stress, inflammatory events, necrosis, and neutrophil infiltration and protected cardiomyocytes from cellular injury.[71]

Photo-protection activity

Medicinal plants are rich source of antioxidant and antioxidant activity of plants shows importance in the neutralization of adverse effect of ultraviolet (UV) light. Curcumin plays an important role in control of various types of pathogenesis and also shows a role in skin protector due to antioxidant activity. The previous study based on flow cytometric analysis revealed that increase in intracellular oxidative stress caused by UV irradiation could be abolished by curcumin.[72] Earlier study data clearly showed that topical application of curcumin inhibits UVB-induced carcinogenesis and also decreases various UVB-induced biomarkers.[73]

Neuro-protective effect

Turmeric and its chief constituents such as curcumin show a role as neuro-protector [Figure 2 and Table 1], but the exact mechanism of action is not fully understood. It is considered that due to the phenolic compound present in turmeric shows neuroprotective effect. *In vitro* based study has confirmed that curcumin improves survival of cortical neurons induced by oxygen-glucose deprivation (OGD)/reoxygenation and reduced OGD-induced cell injury.[38] Furthermore, results also revealed that curcumin decreases infarct volume and inhibits oxidative stress after focal cerebral ischemia/reperfusion injury in middle cerebral artery occlusion rats.[38]

Another study based *in vitro* showed that levels of the active oxygen decreased in chronic ischemic PC12 cells

when treated with curcumin, and expression of uncoupling protein 2 notably increased after treated with curcumin.[74] A study result suggests that curcumin, the chief component of turmeric significantly modulates arsenic-induced cholinergic dysfunctions in the brain and also demonstrated neuroprotective efficacy of curcumin[75] and curcumin modulates the levels of norepinephrine, dopamine, and serotonin in the brain.[76,77]

Anti-obesity effect

Obesity is a major health problem worldwide, and it is also causes various types of pathogenesis. A study results demonstrated that curcumin improves insulin signaling, glucose disposal, as well as blocks obesity during high-fat diet consumption.[78] Curcumin therapy ameliorates the inflammatory consequences of obesity in murine obesity models as compared to control obese animals. In addition, curcumin treated obese animals also showed decreased NF-κB activity in liver tissue.[79] Oral curcumin supplementation was shown to prevent the development of obesity-associated inflammation, insulin resistance, and diabetes.[79] Curcumin at cellular and whole organism levels shows potential health benefits for prevention of obesity and associated metabolic disorders through suppressing angiogenesis in adipose tissue, up-regulating adipocyte energy metabolism.[39]

Effect on hypertension

Hypertension and associated complication is a one of the culprits in the pathogenesis of diseases. In this concerned, curcumin has proven an important role in the prevention of hypertension [Figure 2]. Earlier finding concluded that increase of blood pressure due to N-nitro-L-arginine-methylester can be partially prevented by piperine or curcumin, the result of combination of curcumin and piperine being less significant[80] and other finding showed that hypertension reducing the effect of curcumin.[40]

Anti-tumor activity

Numerous natural products or products based on plant seed, flower, leaves, and stem have confirmed their role in tumor prevention. Curcumin, chief constituent of turmeric has been shown to inhibit the activity of the drug-metabolizing enzymes (cytochrome p450 and p450 reductase).[81] Numerous studies based on animals model found that dietary curcumin increased the activity of Phase II enzymes, such as GSTs[41-43] and downregulated vascular endothelial growth factor through inhibition of peroxisome proliferator-activated receptor δ in colon cancer cells.[44] A study results noticed that noteworthy reduction in cell viability in curcumin-treated cells, which was consistent with induction of apoptosis and associated with down-regulation of Notch-1 and NF-κB.[82] A study finding reported that curcumin is able to induce apoptosis and inhibit the proliferation of melanoma cells.[83]

Effect on respiratory disorder

Respiratory disorder such as asthma, bronchitis, and cold coughs rapidly increasing worldwide due to the continuous increasing of environmental pollutants. Currently used drugs in this prospective are not a permanent solution and also causes other adverse complications. Curcumin shows a valuable role in the control of respiratory related complications [Figure 2 and Table 1].

A study results demonstrated that curcumin increases the expression of cathepsins K and L in lung which an effect on lung fibroblast cell behavior.[84] Oral administration of curcumin has inhibited bleomycin-induced pulmonary fibrosis in rats[45] and cigarette smoke-induced lung inflammation and emphysema in mice.[85] Study finding suggested that curcumin is a potent anti-inflammatory agent that prevents the release of TNF-α and protects against the pulmonary and cardiovascular effects of diesel exhaust particle.[46]

Immunomodulatory effect

Immunomodulatory process plays an important role in the modulations of immune system either by enhance the immune response or suppressing the immune response. Curcumin, active compound of turmeric shows pivotal role in the modulation of immune system. A study was performed to check the effect of curcumin on T, B cells and macrophages and results showed that curcumin imparted immunosuppression by mainly down-regulating the expression of CD28 and CD80 and up-regulating cytotoxic T-lymphocyte antigen 4 (CTLA-4).[47] Other study confirmed that curcumin inhibited the proliferation induced by concanavalin A, phytohemagglutinin (PHA), and phorbol-12-myristate-13-acetate of lymphocytes derived from fresh human spleen.[86,87] Experiment results noticed that curcumin, chief ingredients of curcumin inhibits PHA-induced T-cell proliferation, interleukin-2 production, NO generation, and lipopolysachharide-induced NF-κB and augments NK cell cytotoxicity.[88] Numerous previous results have shown that curcumin role as immunomodulatory that shows an important effect in the modulation of activation of T cells, B cells, macrophages, dendritic cells, cell cycle protein, cell-mediated and humoral mediated immunity.[48-50]

Anti-malarial activity

Malaria is infectious diseases caused by blood parasites and a major health problem in the terms of morbidity and mortality. Plants such as carica papaya show an important role in the prevention of malaria[89] and it is affordable and also shows fewer side effects. The experiment was performed on mice, and results confirmed that oral administration of curcumin to mice infected with malaria parasite showed role in the reduction of blood parasitemia by 80%–90% and enhance their survival significantly.[51] Other study results concluded that

curcumin, chief ingredient of spice turmeric showed a cytotoxic effect in *Giardia lamblia* inhibiting the parasite growth and adherent capacity, induced morphological alterations and provoked apoptosis-like changes.[52]

Nephro-protective effect

Effect of curcumin on renal function and oxidative stress in streptozotacin-induced diabetic rats was examined, and study results showed that treatment with curcumin for 2 weeks significantly attenuated both renal dysfunction and oxidative stress in diabetic rats.[53] Previous studies confirmed that curcumin showed protective effects against nephrotoxicity.[54,55]

Reduction in sperm motility

The study was made to investigate the sperm-immobilizing effects of curcumin, and it was found that incubation of normal human sperm with curcumin resulted in a dose-and time-dependent loss of sperm motility.[56] Another study was performed based on in male albino rats to examine the contraceptive effect of the crude extracts of *C. longa* and results of the study showed a reduction in sperm motility and density was observed in both the treated groups.[90]

Radiosensitizer effect

Prostate cancer cell line PC3 based study confirmed that curcumin, is a major chemical component of turmeric confer radiosensitizing effects in prostate cancer cell line through inhibiting the growth of human prostate PC-3 cancer cells[91] and other studies based on cancer cells confirmed curcumin role as a promising radiosensitizer.[85]

Conclusion

The health-promoting effects of curcumin are well recognized and are in practice in traditional medicine since ancient time. Ayurveda and Unani based preparation of curcumin are popular in the diseases management due to its nontoxic and fewer side effect properties. A considerable number of *in vitro, in vivo* and clinical trials based studies revealed that turmeric and its ingredients are effective modulator of biological process. Curcumin shows a pivotal role in diseases cure through the modulation of various genes and enzymes involve in the pathogenesis. Further details studies based on animal models and clinical trials are required to improve the efficacy, safety, and mode of action of curcumin in diseases prevention and management.

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Conflicts of interest

There are no conflicts of interest.

References

1. Rahmani AH, Shabrmi FM, Aly SM. Active ingredients of ginger as potential candidates in the prevention and treatment of diseases via modulation of biological activities. Int J Physiol Pathophysiol Pharmacol 2014;6:125-36.
2. Al-Bukhari MI, Al-Bukhari S. The Collection of Authentic Sayings of Prophet Mohammad (Peace Be Upon Him), Division 71 on Medicine. Ankara, Turkey: Hilal Yayinlari; 1976.
3. Wahlström B, Blennow G. A study on the fate of curcumin in the rat. Acta Pharmacol Toxicol (Copenh) 1978;43:86-92.
4. Lao CD, Ruffin MT 4th, Normolle D, Heath DD, Murray SI, Bailey JM, *et al.* Dose escalation of a curcuminoid formulation. BMC Complement Altern Med 2006;6:10.
5. He Y, Yue Y, Zheng X, Zhang K, Chen S, Du Z, *et al.* Curcumin, inflammation, and chronic diseases: How are they linked? Molecules 2015;20:9183-213.
6. Ghosh S, Banerjee S, Sil PC. The beneficial role of curcumin on inflammation, diabetes and neurodegenerative disease: A recent update. Food Chem Toxicol 2015;83:111-24.
7. Zandi K, Ramedani E, Mohammadi K, Tajbakhsh S, Deilami I, Rastian Z, *et al.* Evaluation of antiviral activities of curcumin derivatives against HSV-1 in Vero cell line. Nat Prod Commun 2010;5:1935-8.
8. Moghadamtousi SZ, Kadir HA, Hassandarvish P, Tajik H, Abubakar S, Zandi K. A review on antibacterial, antiviral, and antifungal activity of curcumin. Biomed Res Int 2014;2014:186864.
9. Sandur SK, Ichikawa H, Pandey MK, Kunnumakkara AB, Sung B, Sethi G, *et al.* Role of pro-oxidants and antioxidants in the anti-inflammatory and apoptotic effects of curcumin (diferuloylmethane). Free Radic Biol Med 2007;43:568-80.
10. Sreejayan, Rao MN. Nitric oxide scavenging by curcuminoids. J Pharm Pharmacol 1997;49:105-7.
11. Sreejayan N, Rao MN. Free radical scavenging activity of curcuminoids. Arzneimittelforschung 1996;46:169-71.
12. Barclay LR, Vinqvist MR, Mukai K, Goto H, Hashimoto Y, Tokunaga A, Uno H. On the antioxidant mechanism of curcumin: Classical methods are needed to determine antioxidant mechanism and activity. Org Lett. 2000 7;2(18):2841-3.
13. Shukla PK, Khanna VK, Khan MY, Srimal RC. Protective effect of curcumin against lead neurotoxicity in rat. Hum Exp Toxicol 2003;22:653–8.
14. Phan TT, See P, Lee ST, Chan SY. Protective effects of curcumin against oxidative damage on skin cells *in vitro*: Its implication for wound healing. J Trauma 2001;51:927-31.
15. Piper JT, Singhal SS, Salameh MS, Torman RT, Awasthi YC, Awasthi S. Mechanisms of anticarcinogenic properties of curcumin: The effect of curcumin on glutathione linked detoxification enzymes in rat liver. Int J Biochem Cell Biol 1998;30:445-56.
16. Ye J, Zhang Y. Curcumin protects against intracellular amyloid toxicity in rat primary neurons. Int J Clin Exp Med 2012;5:44-9.
17. Rajakrishnan V, Viswanathan P, Rajasekharan KN, Menon VP. Neuroprotective role of curcumin from *Curcuma longa* on ethanol-induced brain damage. Phytother Res 1999;13:571-4.
18. El-Bahr SM. Curcumin regulates gene expression of insulin like growth factor, B-cell CLL/lymphoma 2 and antioxidant enzymes in streptozotocin induced diabetic rats. BMC Complement Altern Med 2013;13:368.
19. Abdel Aziz MT, El-Asmar MF, El Nadi EG, Wassef MA, Ahmed HH, Rashed LA, *et al.* The effect of curcumin on insulin release in rat-isolated pancreatic islets. Angiology 2010;61:557-66.
20. Aldebasi YH, Aly SM, Rahmani AH. Therapeutic implications of curcumin in the prevention of diabetic retinopathy via

modulation of anti-oxidant activity and genetic pathways. Int J Physiol Pathophysiol Pharmacol 2013;5:194-202.
21. Wang LL, Sun Y, Huang K, Zheng L. Curcumin, a potential therapeutic candidate for retinal diseases. Mol Nutr Food Res 2013;57:1557-68.
22. Huang MT, Lysz T, Ferraro T, Abidi TF, Laskin JD, Conney AH. Inhibitory effects of curcumin on *in vitro* lipoxygenase and cyclooxygenase activities in mouse epidermis. Cancer Res 1991;51:813-9.
23. Srimal RC, Dhawan BN. Pharmacology of diferuloyl methane (curcumin), a non-steroidal anti-inflammatory agent. J Pharm Pharmacol 1973;25:447-52.
24. Ukil A, Maity S, Karmakar S, Datta N, Vedasiromoni JR, Das PK. Curcumin, the major component of food flavour turmeric, reduces mucosal injury in trinitrobenzene sulphonic acid-induced colitis. Br J Pharmacol 2003;139:209-18.
25. Lukita-Atmadja W, Ito Y, Baker GL, McCuskey RS. Effect of curcuminoids as anti-inflammatory agents on the hepatic microvascular response to endotoxin. Shock 2002;17:399-403.
26. Gukovsky I, Reyes CN, Vaquero EC, Gukovskaya AS, Pandol SJ. Curcumin ameliorates ethanol and nonethanol experimental pancreatitis. Am J Physiol Gastrointest Liver Physiol 2003;284:G85-95.
27. Sugimoto K, Hanai H, Tozawa K, Aoshi T, Uchijima M, Nagata T, *et al.* Curcumin prevents and ameliorates trinitrobenzene sulfonic acid-induced colitis in mice. Gastroenterology 2002;123:1912-22.
28. Camacho-Barquero L, Villegas I, Sánchez-Calvo JM, Talero E, Sánchez-Fidalgo S, Motilva V, *et al.* Curcumin, a *Curcuma longa* constituent, acts on MAPK p38 pathway modulating COX-2 and iNOS expression in chronic experimental colitis. Int Immunopharmacol 2007;7:333-42.
29. Ung VY, Foshaug RR, MacFarlane SM, Churchill TA, Doyle JS, Sydora BC, *et al.* Oral administration of curcumin emulsified in carboxymethyl cellulose has a potent anti-inflammatory effect in the IL-10 gene-deficient mouse model of IBD. Dig Dis Sci 2010;55:1272-7.
30. Jobin C, Bradham CA, Russo MP, Juma B, Narula AS, Brenner DA, *et al.* Curcumin blocks cytokine-mediated NF-kappa B activation and proinflammatory gene expression by inhibiting inhibitory factor I-kappa B kinase activity. J Immunol 1999;163:3474-83.
31. Jian YT, Mai GF, Wang JD, Zhang YL, Luo RC, Fang YX. Preventive and therapeutic effects of NF-kappaB inhibitor curcumin in rats colitis induced by trinitrobenzene sulfonic acid. World J Gastroenterol 2005;11:1747-52.
32. Jain SK, Rains J, Croad J, Larson B, Jones K. Curcumin supplementation lowers TNF-alpha, IL-6, IL-8, and MCP-1 secretion in high glucose-treated cultured monocytes and blood levels of TNF-alpha, IL-6, MCP-1, glucose, and glycosylated hemoglobin in diabetic rats. Antioxid Redox Signal 2009;11:241-9.
33. De R, Kundu P, Swarnakar S, Ramamurthy T, Chowdhury A, Nair GB, *et al.* Antimicrobial activity of curcumin against *Helicobacter pylori* isolates from India and during infections in mice. Antimicrob Agents Chemother 2009;53:1592-7.
34. Swarnakar S, Ganguly K, Kundu P, Banerjee A, Maity P, Sharma AV. Curcumin regulates expression and activity of matrix metalloproteinases 9 and 2 during prevention and healing of indomethacin-induced gastric ulcer. J Biol Chem 2005;280:9409-15.
35. Abdul-Aziz K. Comparative evaluation of the anti-ulcer activity of curcumin and omeprazole during the acute phase of gastric ulcer-efficacy of curcumin in gastric ulcer prevention against omeprazole. Food Nutr Sci 2011;2:628-40.
36. Farombi EO, Shrotriya S, Na HK, Kim SH, Surh YJ. Curcumin attenuates dimethylnitrosamine-induced liver injury in rats through Nrf2-mediated induction of heme oxygenase-1. Food Chem Toxicol 2008;46:1279-87.
37. Morimoto T, Sunagawa Y, Kawamura T, Takaya T, Wada H, Nagasawa A, *et al.* The dietary compound curcumin inhibits p300 histone acetyltransferase activity and prevents heart failure in rats. J Clin Invest 2008;118:868-78.
38. Wu J, Li Q, Wang X, Yu S, Li L, Wu X, *et al.* Neuroprotection by curcumin in ischemic brain injury involves the Akt/Nrf2 pathway. PLoS One 2013;8:e59843.
39. Ejaz A, Wu D, Kwan P, Meydani M. Curcumin inhibits adipogenesis in 3T3-L1 adipocytes and angiogenesis and obesity in C57/BL mice. J Nutr 2009;139:919-25.
40. Nakmareong S, Kukongviriyapan U, Pakdeechote P, Donpunha W, Kukongviriyapan V, Kongyingyoes B, *et al.* Antioxidant and vascular protective effects of curcumin and tetrahydrocurcumin in rats with L-NAME-induced hypertension. Naunyn Schmiedebergs Arch Pharmacol 2011;383:519-29.
41. Singh SV, Hu X, Srivastava SK, Singh M, Xia H, Orchard JL, *et al.* Mechanism of inhibition of benzo[a] pyrene-induced forestomach cancer in mice by dietary curcumin. Carcinogenesis 1998;19:1357-60.
42. Iqbal M, Sharma SD, Okazaki Y, Fujisawa M, Okada S. Dietary supplementation of curcumin enhances antioxidant and phase II metabolizing enzymes in ddY male mice: Possible role in protection against chemical carcinogenesis and toxicity. Pharmacol Toxicol 2003;92:33-8.
43. Susan M, Rao MN. Induction of glutathione S-transferase activity by curcumin in mice. Arzneimittelforschung 1992;42:962-4.
44. Wang JB, Qi LL, Zheng SD, Wang HZ, Wu TX. Curcumin suppresses PPARdelta expression and related genes in HT-29 cells. World J Gastroenterol 2009;15:1346-52.
45. Punithavathi D, Venkatesan N, Babu M. Curcumin inhibition of bleomycin-induced pulmonary fibrosis in rats. Br J Pharmacol 2000;131:169-72.
46. Nemmar A, Subramaniyan D, Ali BH. Protective effect of curcumin on pulmonary and cardiovascular effects induced by repeated exposure to diesel exhaust particles in mice. PLoS One 2012;7:e39554.
47. Sharma S, Chopra K, Kulkarni SK, Agrewala JN. Resveratrol and curcumin suppress immune response through CD28/CTLA-4 and CD80 co-stimulatory pathway. Clin Exp Immunol 2007;147:155-63.
48. Gautam SC, Gao X, Dulchavsky S. Immunomodulation by curcumin. Adv Exp Med Biol 2007;595:321-41.
49. Gao X, Kuo J, Jiang H, Deeb D, Liu Y, Divine G, *et al.* Immunomodulatory activity of curcumin: Suppression of lymphocyte proliferation, development of cell-mediated cytotoxicity, and cytokine production *in vitro*. Biochem Pharmacol 2004;68:51-61.
50. Kim GY, Kim KH, Lee SH, Yoon MS, Lee HJ, Moon DO, *et al.* Curcumin inhibits immunostimulatory function of dendritic cells: MAPKs and translocation of NF-kappa B as potential targets. J Immunol 2005;174:8116-24.
51. Reddy RC, Vatsala PG, Keshamouni VG, Padmanaban G, Rangarajan PN. Curcumin for malaria therapy. Biochem Biophys Res Commun 2005;326:472-4.
52. Pérez-Arriaga L, Mendoza-Magaña ML, Cortés-Zárate R, Corona-Rivera A, Bobadilla-Morales L, Troyo-Sanromán R, *et al.* Cytotoxic effect of curcumin on *Giardia lamblia* trophozoites. Acta Trop 2006;98:152-61.

53. Sharma S, Kulkarni SK, Chopra K. Curcumin, the active principle of turmeric (*Curcuma longa*), ameliorates diabetic nephropathy in rats. Clin Exp Pharmacol Physiol 2006;33:940-5.
54. Ghoniem MH, El-Sharkawy NI, Hussein MM, Moustafa GG. Efficacy of curcumin on lead induced nephrotoxicity in female albino rats. J Am Sci 2012;8:502-10.
55. Sangartit W, Donpunha W, Kukongviriyapa U, Pakdeechote P, Kukongviriyapan V, Surawattanawan P. Effect of curcumin on kidney function and arterial blood pressure in rats with long-term and low level exposure of lead and cadmium. Srinagarind Med J 2012;27:107-10.
56. Rithaporn T, Monga M, Rajasekaran M. Curcumin: A potential vaginal contraceptive. Contraception 2003;68:219-23.
57. Aggarwal BB, Harikumar KB. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. Int J Biochem Cell Biol 2009;41:40-59.
58. Mun SH, Joung DK, Kim YS, Kang OH, Kim SB, Seo YS, *et al*. Synergistic antibacterial effect of curcumin against methicillin-resistant *Staphylococcus aureus*. Phytother Res 2013;19:599-604.
59. Negi PS, Jayaprakasha GK, Jagan Mohan Rao L, Sakariah KK. Antibacterial activity of turmeric oil: A byproduct from curcumin manufacture. J Agric Food Chem 1999;47:4297-300.
60. Chattopadhyay I, Biswas K, Bandyopadhyay U, Banerjee RK. Turmeric and curcumin: Biological actions and medicinal applications. Curr Sci 2004;87:44-53.
61. Di Mario F, Cavallaro LG, Nouvenne A, Stefani N, Cavestro GM, Iori V, *et al.* A curcumin-based 1-week triple therapy for eradication of *Helicobacter pylori* infection: Something to learn from failure? Helicobacter 2007;12:238-43.
62. Rai D, Singh JK, Roy N, Panda D. Curcumin inhibits FtsZ assembly: An attractive mechanism for its antibacterial activity. Biochem J 2008;410:147-55.
63. Lee CJ, Lee JH, Seok JH, Hur GM, Park YC, Seol IC, *et al.* Effects of baicalein, berberine, curcumin and hesperidin on mucin release from airway goblet cells. Planta Med 2003;69:523-6.
64. Haider S, Naqvi F, Tabassum S, Saleem S, Batool Z, Sadir S, *et al.* Preventive effects of curcumin against drug- and starvation-induced gastric erosions in rats. Sci Pharm 2013;81:549-58.
65. Evans WC. An overview of drugs with anti hepatotoxic and oral hypoglycaemic activities. In: Trease and Evans Pharmacognosy. Edinburgh: W.B. Saunders; 2002. p. 414-20.
66. Girish C, Pradhan SC. Hepatoprotective activities of picroliv, curcumin, and ellagic acid compared to silymarin on carbon-tetrachloride-induced liver toxicity in mice. J Pharmacol Pharmacother 2012;3:149-55.
67. Sengupta M, Sharma GD, Chakraborty B. Hepatoprotective and immunomodulatory properties of aqueous extract of *Curcuma longa* in carbon tetra chloride intoxicated Swiss albino mice. Asian Pac J Trop Biomed 2011;1:193-9.
68. Mathews VV, Binu P, Paul MV, Abhilash M, Manju A, Nair RH. Hepatoprotective efficacy of curcumin against arsenic trioxide toxicity. Asian Pac J Trop Biomed 2012;2:S706-7.
69. Nabavi SF, Nabavi SM, Ebrahimzadeh MA, Eslami S, Jafari N, Moghaddam AH. The protective effect of curcumin against sodium fluoride-inducedoxidative stress in rat heart. Arch Biol Sci Belgrade 2011;63:563-9.
70. Nirmala C, Puvanakrishnan R. Protective role of curcumin against isoproterenol induced myocardial infarction in rats. Mol Cell Biochem 1996;159:85-93.
71. Izem-Meziane M, Djerdjouri B, Rimbaud S, Caffin F, Fortin D, Garnier A, *et al.* Catecholamine-induced cardiac mitochondrial dysfunction and mPTP opening: Protective effect of curcumin. Am J Physiol Heart Circ Physiol 2012;302:H665-74.
72. Chan WH, Wu CC, Yu JS. Curcumin inhibits UV irradiation-induced oxidative stress and apoptotic biochemical changes in human epidermoid carcinoma A431 cells. J Cell Biochem 2003;90:327-38.
73. Tsai KD, Lin JC, Yang SM, Tseng MJ, Hsu JD, Lee YJ, *et al.* Curcumin protects against UVB-induced skin cancers in SKH-1 hairless mouse: Analysis of early molecular markers in carcinogenesis. Evid Based Complement Alternat Med 2012;2012:593952.
74. Minna G, Li L, Peng Z, Gang Y, Yu L. Neuroprotective effect of curcumin involved in increasing the protein levels of UCP2 and inhibiting oxidative stress induced by chronic cerebral ischemia *in vitro*. Mol Neurodegener 2012;7 Suppl 1:S26.
75. Yadav RS, Chandravanshi LP, Shukla RK, Sankhwar ML, Ansari RW, Shukla PK, *et al.* Neuroprotective efficacy of curcumin in arsenic induced cholinergic dysfunctions in rats. Neurotoxicology 2011;32:760-8.
76. Kulkarni SK, Bhutani MK, Bishnoi M. Antidepressant activity of curcumin: Involvement of serotonin and dopamine system. Psychopharmacology (Berl) 2008;201:435-42.
77. Xu Y, Ku BS, Yao HY, Lin YH, Ma X, Zhang YH, *et al.* The effects of curcumin on depressive-like behaviors in mice. Eur J Pharmacol 2005;518:40-6.
78. Shao W, Yu Z, Chiang Y, Yang Y, Chai T, Foltz W, *et al.* Curcumin prevents high fat diet induced insulin resistance and obesity via attenuating lipogenesis in liver and inflammatory pathway in adipocytes. PLoS One 2012;7:e28784.
79. Weisberg SP, Leibel R, Tortoriello DV. Dietary curcumin significantly improves obesity-associated inflammation and diabetes in mouse models of diabesity. Endocrinology 2008;149:3549-58.
80. Hlavacková L, Janegová A, Ulicná O, Janega P, Cerná A, Babál P. Spice up the hypertension diet-curcumin and piperine prevent remodeling of aorta in experimental L-NAME induced hypertension. Nutr Metab (Lond) 2011;8:72.
81. Thapliyal R, Maru GB. Inhibition of cytochrome P450 isozymes by curcumins *in vitro* and *in vivo*. Food Chem Toxicol 2001;39:541-7.
82. Liao S, Xia J, Chen Z, Zhang S, Ahmad A, Miele L, *et al.* Inhibitory effect of curcumin on oral carcinoma CAL-27 cells via suppression of Notch-1 and NF-κB signaling pathways. J Cell Biochem 2011;112:1055-65.
83. Jiang AJ, Jiang G, Li LT, Zheng JN. Curcumin induces apoptosis through mitochondrial pathway and caspases activation in human melanoma cells. Mol Biol Rep 2015;42:267-75.
84. Zhang D, Huang C, Yang C, Liu RJ, Wang J, Niu J, *et al.* Antifibrotic effects of curcumin are associated with overexpression of cathepsins K and L in bleomycin treated mice and human fibroblasts. Respir Res 2011;12:154.
85. Suzuki M, Betsuyaku T, Ito Y, Nagai K, Odajima N, Moriyama C, *et al.* Curcumin attenuates elastase- and cigarette smoke-induced pulmonary emphysema in mice. Am J Physiol Lung Cell Mol Physiol 2009;296:L614-23.
86. Javvadi P, Segan AT, Tuttle SW, Koumenis C. The chemopreventive agent curcumin is a potent radiosensitizer of human cervical tumor cells via increased reactive oxygen species production and overactivation of the mitogen-activated protein kinase pathway. Mol Pharmacol 2008;73:1491-501.
87. Ranjan D, Chen C, Johnston TD, Jeon H, Nagabhushan M.

Curcumin inhibits mitogen stimulated lymphocyte proliferation, NFkappaB activation, and IL-2 signaling. J Surg Res 2004;121:171-7.
88. Yadav VS, Mishra KP, Singh DP, Mehrotra S, Singh VK. Immunomodulatory effects of curcumin. Immunopharmacol Immunotoxicol 2005;27:485-97.
89. Rahmani AH, Aldebasi YH. Potential role of carica papaya and their active constituents in the prevention and treatment of diseases. Int J Pharm Pharm Sci 2015:8:11-5.
90. Ashok P, Meenakshi B. Contraceptive effect of *Curcuma longa* (L.) in male albino rat. Asian J Androl 2004;6:71-4.
91. Chendil D, Ranga RS, Meigooni D, Sathishkumar S, Ahmed MM. Curcumin confers radiosensitizing effect in prostate cancer cell line PC-3. Oncogene 2004;23:1599-607.