International Journal of Herbal Medicine
Available online at www.florajournal.com

I J H M International Journal of Herbal Medicine

E-ISSN: 2321-2187
P-ISSN: 2394-0514
IJHM 2019; 7(3): 52-58
Received: 28-03-2019
Accepted: 30-04-2019

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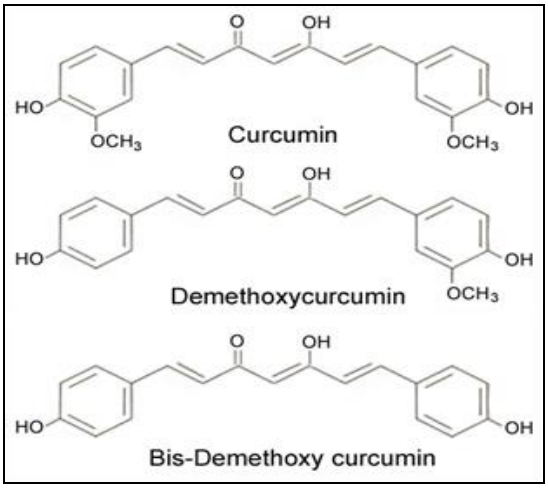
Curcumin: A multifaceted herbal medicine

Chhavi Sharma

Abstract
Curcumin, is a phenolic compounds isolated from the roots of *Curcuma longa* (Zingiberaceae), exhibit a variety of beneficial effects on health and on events that help in preventing certain diseases. These plant-derived chemicals have generated considerable interest recently for their potential to show great variety of pharmacological activities such as anti-inflammation, antioxidant, neuro protection, anti-cancer etc by modulation of several important molecular targets including transcription factors, cytokines, cell cycle proteins etc. As a result of extensive epidemiological, clinical, and animal studies, several molecular mechanisms are developed that elucidate multiple biological effects of curcumin. The purpose of this review is to provide a brief summary for research awareness of the effects of curcumin on the subject of potential health benefits.

Keywords: *Curcuma longa* L., antioxidant, cytokines, anti-inflammatory, neuro protective, anti- cancer

1. Introduction
The use of medicinal plants for the treatment of many diseases is associated to folk medicine from different parts of the world. Natural products from some plants are continued to be used in pharmaceutical preparations either as pure compound or as extract. There are variety of compounds that can be extracted and characterized from plants, one good example is curcumin. Curcumin is a chemical of the polyphenol family derived from the rhizome *Curcuma longa L.* The dried, ground product of this root is the common spice known as turmeric. Referred to as 'Haldi' in Hindi [1], this spice has been used as an aromatic and coloring in food [2], as well as having a significant role in both Asian medicine and ancient Hindu scripture. Most commercial turmeric preparations consist of ~2-8% active curcumin.
Over the last few years, a number of studies have provided evidence of important pharmacological properties of curcumin including antioxidant, anti-carcinogenic, anti-infectious, wound healing, immunomodulatory, and anti-inflammatory activities [3-6]. Curcumin is a potential natural plant antioxidant and has been found to have beneficial effects on endogenous cellular antioxidants without any side effects [7]**.** Curcumin has been shown to be effective in acute as well as chronic models.
Curcumin (di-feruloylmethane) is in the most important fraction of *C. longa* L. and its chemical structure, was determined by roughly and Whiting [8]. The other two curcuminoids are demethoxycurcumin and bis-demethoxycurcumin. The curcuminoids are polyphenols and are responsible for the yellow color of turmeric [9].



Source: Structure of the curcuminoids curcumin, demethoxycurcumin and bisdeme thoxy curcumin [10].

2. Therapeutic Implications of Curcumin

Curcumin, has been shown to target multiple signaling molecules while also signifying activity at the cellular level, which has aided to support its multiple health benefits.

2.1 Anti-inflammatory and Antioxidant Properties

Unnikrishnan and Rao [11] studied the antioxidant properties of curcumin and its derivatives. The discovery of the antioxidant properties of curcumin explains many of its wide ranging pharmacological activities. Curcumin is an effective antioxidant and scavenges superoxide radicals, hydrogen peroxide, and nitric oxide from activated macrophages [12] In fact, curcumin has been found to be at least 10 times more active as an antioxidant than even vitamin E [13]. The phenolic and the methoxy groups on the benzene rings and the 1,3-diketone system are the two important structural features that contribute to its antioxidant properties [14-18]**.** The highest antioxidant activity was obtained when the phenolic group was sterically hindered by the introduction of two methyl groups at the ortho position. The H-donating phenolic group is essential for free radical scavenging activity [19] and the presence of the methoxy group further increases the activity. Curcumin shows both antioxidant and pro-oxidant effects [20]. Ahsan *et al* [21] have shown that both of these effects are determined by the same structural moieties of the curcuminoids.

The anti-oxidation process is thought to be divided into two stages as shown in following schemes:

(1) Radical trapping stage

S-OOe- (or Se-) + AH → S-OOH (or SH) + A

(2) Radical termination stage

Ae-→ non-radical materials

S is the substance for oxidation, AH is the antioxidant, and A→ is the antioxidant radical. Recent mechanistic studies of a plant phenolic antioxidant have been focused on the trapping stage using a kinetic approach or a structure-activity relationship approach [22, 23]**.** Vajragupta *et al*., [24] have evaluated the free radical-scavenging and neuroprotective potential of the manganese complexes of curcumin.

The antioxidant activity of curcumin could be mediated through antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. Curcumin has been shown to serve as a Michael acceptor reacting with glutathione and thioredoxin 1 [25]**.** Reaction of curcumin with these agents reduces intracellular GSH in the cells.

Curcumin can lower lipid peroxidation by maintaining the activities of antioxidant enzymes like superoxide dismutase, catalase and glutathione peroxidase at higher levels. These enzymes play an important role in the regulation of lipid peroxidation [26]. Pulla Reddy and Lokesh [26] observed that curcumin is capable of scavenging oxygen free radicals such as superoxide anions and hydroxyl radicals, which are important to the initiation of lipid peroxidation. The suppression of lipid peroxidation by curcumin could lead to suppression of inflammation. Another article about curcuminoids as potent inhibitors of lipid peroxidation was described by Sreejayan Rao [14], in which the authors showed that three curcuminoids were inhibitors of lipid peroxidation in rat brain homogenates and rat liver micro somes.

Elizabeth [27, 28], also reported a better correlation between anti-inflammatory activity and superoxide scavenging property. In the literature Arora *et al*., [29] investigated the anti-inflammatory activity in different fractions of the petroleum ether extract of the rhizomes of turmeric (two constituents) in animals. They found that the extracts reduced the granuloma growth and no toxic effects were observed. Chandra and Gupta [30] demonstrated the anti-inflammatory and anti-arthritic actions of volatile oil of *C. longa* L. Non-steroidal anti-inflammatory agents may act via single or combination of any of the mechanism involving inhibition of arachadonic acid metabolism, inhibition of cyclo-oxygenase(COX)/inhibition of PG synthesis, inhibition of lipo-oxgenase (LOX),inhibition of cytokines(IL, TNF, etc)release of steroidal hormone from adrenals, stabilization of lysosomal memberane and uncoupling of oxidative phosphorylation, etc.

Kiuchi *et al*., [31, 32] and Iwakami *et al*., [33] associate the anti-inflammatory activity of curcumin and its derivatives to the presence of hydroxyl and phenol groups in the molecule, being essential for the inhibition of prostaglandins (PG synthetase) and leucotrienes (LT). On the other hand, some authors suggested that the anti-inflammatory action is associated to the existence of the β-dicarbonylic system, which has the conjugated double bonds (dienes), being responsible for this activity [34, 35]. This system seems to be responsible not only for anti-inflammatory power, but also to antiparasitic activity [36]. The presence of diene ketone system provides a lipophylicity to the compounds, and thus probably better skin penetration.

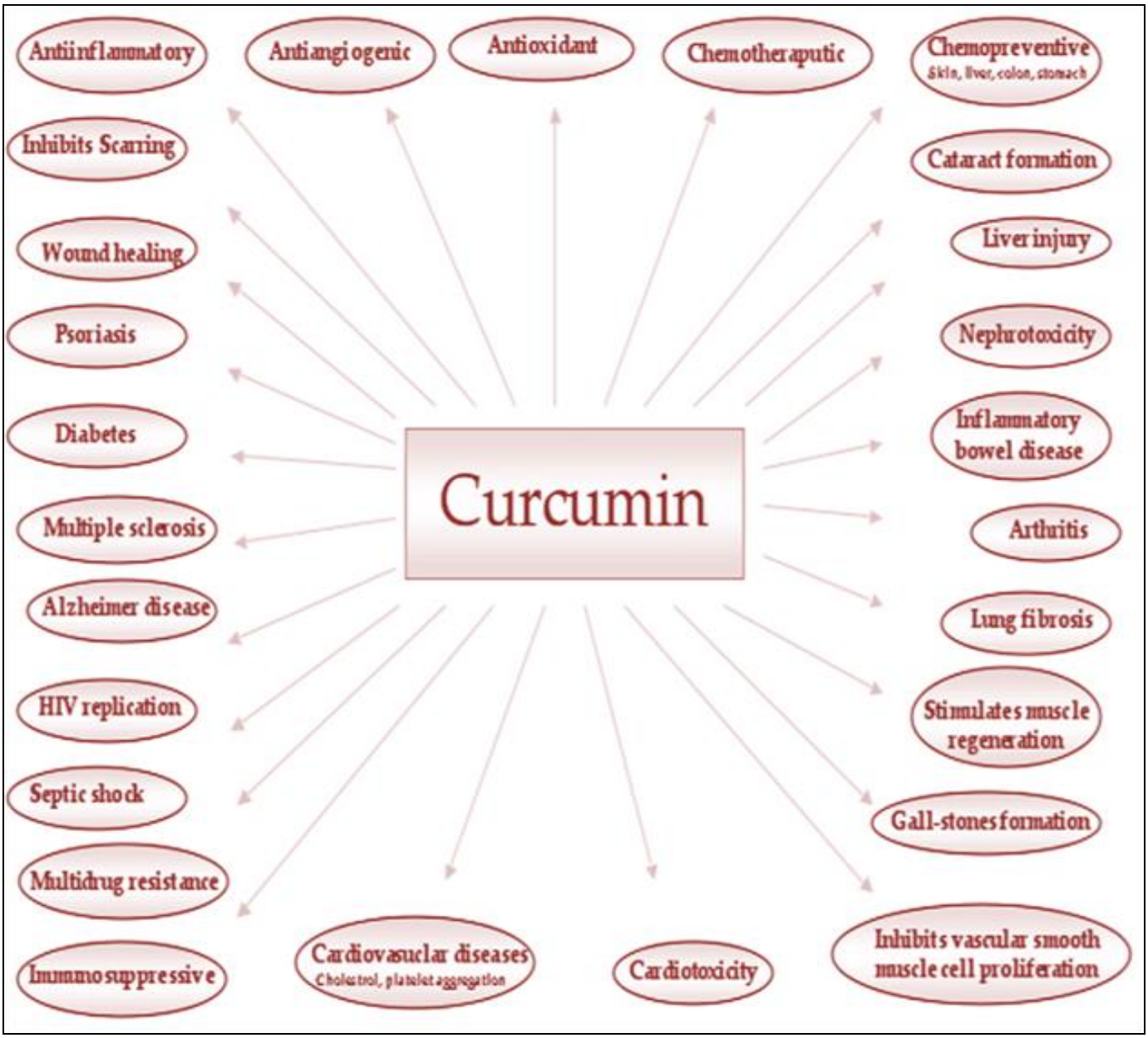


Fig 1: Disease targets of curcumin

2.2 Neuroprotective effect of Curcumin

Neurodegenerative diseases, ischemia, and trauma are among the major causes of morbidity and death, yet there are no reliable methods of preventing nerve cell loss in these conditions. Although there are innumerable insults that lead to nerve cell death, ranging from aberrant protein aggregation in the amyloid diseases [37] to the loss of neuro trophic support [38], it is very likely that there is a much smaller subset of mechanisms responsible for the ultimate demise of the cell. If this assumption is valid, then it should be possible to identify drugs that block the common pathways leading to nerve cell death. A good starting point for the identification of such lead compounds is the enormous family of natural products which form the basic scaffolds for the majority of our most widely used drugs [39-41].

Curcumin's neuro protective role has recently been demonstrated in a fluoride exposed neuronal developmental [42] and adult hippocampal neurogenesis, and a biological activity that may enhance neuronal plasticity and repair [43-45]. The structure of curcumin, which has two methoxylphenol groups separated by a β-diketone bridge, allows it to chelate iron, and free iron has been implicated in a variety of neurodegenerative diseases [46]. Tripathy and Sharma *et al*., [47] demonstrate the anti-oxidative, anti-lipofuscinogenesic and anti-ageing effects of curcumin in the brain. It also improves learning and memory deficits by protecting the nervous system against oxidative stress [48]. Thiyagarajan and Sharma [49] have demonstrated the neuro protective effects of curcumin against the effects of middle cerebral artery occlusion.

Table 1: Ten Neuroprotective effects of curcumin

LIMITS	MECHANISM
Pro-inflammatory cytokine induction	Inhibition of AP-1, NF-κB, HAT, HDAC stimulation?
Reactive oxygen species (ROS)	Scavenger, metal/Fe chelator, induces AO defense enzymes
Aβ production	Suppresses cholesterol, BACE1 induction
Amyloid aggregates	Congo red mimetic/aggregate inhibitor
Misfolded protein accumulation	Potentiates HSPS
Neurotoxicity	JNK pathway
Excitotoxicity	COX-2 induction via AP-1, NF-κB
Toxicity	Phase II inducer, HO-1
Particulate toxins	Increases phagocyte clearance
Neuron loss	Stimulates neurogenesis

Source: Adv Exp Med Biol. Author manuscript; available in PMC 2008 September 1. Published in final edited form as: Adv Exp Med Biol. 2007; 595: 197–21

2.3 Multiple Sclerosis

Multiple sclerosis is characterized by the destruction of oligodendrocytes and myelin sheath in the CNS. Curcumin inhibits experimental allergic encephalomyelitis by blocking interleukin (IL)-12 signaling in T cells, suggesting it would be effective in the treatment of multiple sclerosis [50].

2.4 Alzheimer's disease

Curcumin can suppress oxidative damage, inflammation, cognitive deficits, and amyloid accumulation in Alzheimer's disease [51]**.** Curcumin has gained importance because of its antioxidant and antiplatelet aggregating qualities. Curcumin's ability to control platelet aggregation appears directly to be related to thromboxane inhibition (a promoter of aggregation) and an increase in prostacyclin activity, an inhibitor of aggregation [52, 53].

2.5 Head Trauma

Head trauma is a severe test of neuro protective activity and a validated environmental risk factor for AD. Cummings, [54] repeated head trauma is also the cause of boxer's dementia (dementia pugilistica), which involves both tangles.

2.6 Anticancer Properties

Aggarwal, [25] reviewed the anticancer potential of curcumin in number of systems. Curcumin has been shown to block transformation, tumor initiation, tumor promotion, invasion, angiogenesis, and metastasis. Curcumin in *In vivo* conditions suppresses carcinogenesis of the skin, fore-stomach, colon, and liver in mice. Mammary carcinogenesis is also suppressed by Curcumin. Curcumin has been shown to inhibit the proliferation of a wide variety of tumor cells, including B-cell and T-cell leukemia, colon carcinoma, epidermis carcinoma, and various breast carcinoma cells.

2.7 Cardio protective Effect

The study of Aggarwal, [50] clearly demonstrated the effectiveness of curcumin against atherosclerosis and myocardial infarction. The proliferation of peripheral blood mononuclear cells (PBMCs) and vascular smooth muscle cells (VSMCs), which are hallmarks of atherosclerosis, is inhibited by curcumin. Curcumin prevents the oxidation of low density lipoproteins (LDLs), inhibits platelet aggregation, and reduces the incidence of myocardial infarction.

2.8 Skin Diseases

Curcumin has emerged as effective protectant against different skin diseases including skin carcinogenesis, psoriasis [55]**,** scleroderma [56] and dermatitis. Numerous studies advocate that curcumin accelerates wound healing. In addition, curcumin also prevents the formation of scars and plays a role in muscle regeneration following trauma [50]**.**

2.9 Diabetes

In type II diabetes, administration of curcumin reduced the blood sugar, hemoglobin, and glycosylated hemoglobin levels significantly in an alloxan-induced diabetic rat model. Diabetic rats when given curcumin diet for 8 weeks excreted less albumin, urea, creatinine, and inorganic phosphorus. Dietary curcumin also partially reversed the abnormalities in plasma albumin, urea, creative, and inorganic phosphorus in diabetic animals [50]**.** Diabetic rats fed a curcumin diet had a lower relative liver weight at the end of the study, compared to other diabetic groups. The mechanism by which curcumin improves this situation is probably by virtue of its hypocholesterolemic influence [57]**,** antioxidant nature, and free radical scavenging property [58].

2.10 Cystic Fibrosis

Cystic fibrosis, the most common lethal hereditary disease in the white population, is caused by mutations in the cystic fibrosis transmembrane conductance regulator gene. In a recent report, Egan *et al*., [59] demonstrated that curcumin corrected the cystic fibrosis defects in Delta F508 CF mice.

3. Multiple Molecular Targets of Curcumin

Through various studies it has been concluded that curcumin modulates numerous molecular targets, it directly bind and modulate the activity, or indirectly regulate their functions including: regulating several cytokines and fibroblast growth factor-2 (gene expression), growth-factor receptors including modulation of androgen receptors (protein kinases), transcription factors, neuro tranmitters (Nitric oxide) pro-inflammatory enzymes (including suppression of COX-2, 5-LOX and iNOS and regulation of NF-κB), modulation of cell-cycle-related gene expression, blocking the adhesion molecules, downregulating anti-apoptic proteins and inhibiting multi-drug resistance [44,45,60,61], thus providing a strong scientific basis for its effectiveness in number of diseases. Extensive research shows most diseases are caused

by dysregulation of multiple signaling pathways--casting doubt on the effectiveness of monotherapy, which is limited to a single target [60, 61].

3.1 Cytokines and Growth Factors

In the growth and promotion of various tumors number of growth factors is responsible. Curcumin has been shown to down regulate the expression of several cytokines including TNF, IL-6, IL-8, IL-12, and fibroblast growth factor-2. [50]

3.2 Receptors

Aggarwal, [50] showed down regulation of both the epithelial growth factor receptor: (EGFR) and HER2/neu receptors on Curcumin administration. It also modulates androgen receptors.

3.3 Protein Kinases

In the study by Aggarwal, [50] Curcumin suppressed a number of protein kinases including mitogen-activated protein kinases, JNK, PKA, PKC, src tyrosine kinase, phosphorylase kinase, IκBα kinase, JAK kinase, and the growth factor receptor protein tyrosine kinases.

3.4 Cell Cycle and Anti-Apoptotic Proteins

Curcumin modulates cell-cycle related gene expression. Specifically, curcumin induces G0/G1 and/or G2/M phase cell cycle arrest, upregulates CDKIs, p21WAF1/CIP1, p27KIP1, and p53, and slightly down regulates cyclin B1 and cdc2. Down regulation of cyclin D1 at the transcriptional and post-transcriptional levels has been observed on curcumin administration, it also induces apoptosis by releasing cytochrome *c* [62-64]. caspase 9 and 3 activation and by down regulation of the anti-apoptotic proteins Bcl-2 and BclXL has also been observed by Aggarwal [25] on curcumin administration**.**

4 References

1. Eigner D, Scholz D. Ferula asa-foetida and *Curcuma longa* in traditional medical treatment and diet in Nepal. J Ethnopharmacol. 2003; 67:1-6.
2. Singh S. From exotic spice to modern drug?, Cell. 2007; 130:765-8.
3. Ramsewak RS, DeWitt DL, Nair MG. Cytotoxicity, antioxidant and anti-inflammatory activities of curcumins I-III fromn Curcuma longa. Phytomedicine. 2000; 7:303-308.
4. Leu TH, Maa MC. The molecular mechanisms for the antitumorigenic effect of curcumin. Curr Med Chem Anticancer Agents. 2002; 2:357-370.
5. Balasubramanyam M, Koteswari AA, Kumar RS, Monickaraj SF, Maheswari JU. Curcumin-induced inhibition of cellular reactive oxygen species generation. Novel therapeutic implications. J Bio sci. 2003; 28:715-721.
6. Johnson JJ, Mukhtar H. Curcumin for chemoprevention of colon cancer. Cancer Lett. 2007; 255:170-181.
7. Inano H, Onoda M, Inafuku N, Kubota M, Kamada Y, Osawa T *et al*. Potent preventive action of curcumin on radiation-induced initiation of mammary tumorigenesis in rats. Carcinogenesis. 2000; 21:1835-1841.
8. Roughley PJ, Whiting DA. Experiments in the biosynthesis of curcumin. J Chem Soc. 1973; 20:2379-2388.
9. Calabrese V, Butterfield DA, Stella AM. Nutritional antioxidants and the heme oxygenase pathway of stress tolerance, novel targets for neuroprotection in Alzheimer's disease. Ital J Bio-chem. 2003; 52:177-181.
10. Wilken R, Veena MS, Wang MB, Srivatsan ES. Curcumin A review of anti-cancer properties and therapeutic activity in head and neck squamous cell carcinoma. 2011; 10:12. doi: 10.1186/1476-4598-10-12.
11. Unnikrishnan MK, Roa MN. Inhibition of nitrite induced oxidation of haemoglobin by curcuminoids. Pharmazie. 1995; 50:490-492.
12. Joe B, Lokesh BR. Role of capsaicin, curcumin and dietary n-3 fatty acids in lowering the generation of reactive oxygen species in rat peritoneal macrophages. Biochim. Biophys. Acta. 1994; 1224:255-263. DOI:10.1016/0167-4889(94)90198-8.
13. Khopde SM, Priyadarshni KI, Venkatesan P. Free radical scavenging ability and antioxidant efficiency of curcumin and its substituted analogue. Biophys. Chem. 1999; 80:85-91.
14. Sreejayan N, Rao MN. Free radical scavenging activity of curcuminoids. Arzneimittelforschung. 1996; 46(2):169-171.
15. Sreejayan N, MNA Rao. Nitric oxide scavenging by curcuminoids. J Pharm. Pharmacol. 1997; 49:105-10.
16. Barclay LR, Vinqvist MR, Mukai K, Goto H, Hashimoto Y, Tokunaga A *et al*. On the antioxidant mechanism of curcumin: classical methods are needed to determine antioxidant mechanism and activity. Org. Lett., 2000; 2:2841-2843.
17. Masuda T, Nisbett RA. Attending holistically versus analytically: Comparing the context sensitivity of Japanese and Americans. Journal of Personality and Social Psychology. 2001; 81:922-934.
18. Sun YM, Zhang HY, Chen DZ, Liu CB. Theoretical elucidation on the antioxidant mechanism of curcumin: a DFT study. Org. Lett. 2002; 4:2909-2911.
19. Ruby AJ, Kuttan G, Babu KD, Rajasekharan KN, Kuttan R. Antitumour and antioxidant activity of natural curcuminoids. Cancer Lett. 1995; 94:79-93.
20. Banerjee A, Kunwar A, Mishra B, Priyadarsini KI. Concentration dependent antioxidant/pro-oxidant activity of curcumin studies from AAPH induced hemolysis of RBCs. Chem Biol Interact. 2008; 174(2):134-9. doi: 10.1016/j.cbi.2008.05.009
21. Ahsan, Parveen H, Khan NU *et al.* Pro-oxidant, anti-oxidant and cleavage activities on DNA of curcumin and its derivatives demethoxycurcumin and bisdemethoxy curcumin. Chem. Biol. Interact. 1999; 121:161-175.
22. Aruoma OI. Free radicals, oxidative stress, and antioxidants in human health and disease. J Agric. Food Chem. 1999; 47:397-492.
23. Hall CA, Cuppett Sl. Structure-activities of natural antioxidants, in Antioxidant Methodology In Vivo and in Vitro Concepts, Ed by Auroma OI and Cuppett SL, AOCS Pres, Champaign, IL, 1997, 141-170.
24. Vajragupta O, Boonchoong P, Watanabe H, Tohda M, Kummasud N, Sumanont Y. Manganese complexes of curcumin and its derivatives: evaluation for the radical scavenging ability and neuroprotective activity. Free Radic Biol Med. 2003; 35:1632-1644.
25. Aggarwal BB, Kumar A, Bharti AC. Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Res. 2003; 23:363-398.
26. Pulla R ACh, Lokesh BR. Effect of dietary turmeric (*Curcuma longa*) on iron-induced lipid peroxidation in the rat liver. Fd Chem Toxic. 1992; 32:279-283.

27. Elizabeth K, Rao MNA. Effect of curcumin on hydroxyl radical generation through Fenton reaction. Int J Pharm. 1989; 57:173-176.
28. Elizabeth K, Rao MNA. Oxygen radical scavenging activity of curcumin. Int J Pharm. 1990; 58:237-240.
29. Arora R, Basu N, Kapoor V. Anti-inflammatory studies on *Curcuma longa* (turmeric). Indian J Med Res. 1971; 59:1289-95.
30. Chandra D, Gupta SS. Anti-inflammatory and anti-arthritic activity of volatile oil of Curcuma longa (Haldi). Indian J Med Res. 1972; 60:138-142.
31. Kiuchi F, Iwakami S, Shibuya M, Hanaoka F, Sankawa U. Inhibition of prostaglandin and leukotriene biosynthesis by gingerols and diarylheptanoids. Chem Pharm Bull. 1992; 40:387-391.
32. Kiuchi F, Shibuya M, Sankawa U. Inhibitors of prostaglandin biosynthesis from Alpinia officinarum. Chem Pharm Bull. 1982; 30:2279-2282.
33. Iwakami S, Shibuya M, Tseng CF, Hanaoka F, Sankawa U. Inhibition of arachidonate 5-lipoxygenase by phenolic compounds. Chem Pharm Bull. 1986; 34:3960-3963
34. Claeson P, Panthong A, Tuchinda P, Reutrakul V, Kanjanapothi D, Taylor WC *et al*. Three non-phenolic diarylheptanoids with anti-inflammatory activity from Curcuma xanthorrhiza. Planta Med. 1993; 59:451-454.
35. Claeson P, Pongprayoon U, Sematong T, Tuchinda P, Reutrakul V, Soontornsaratune P *et al*. Non-phenolic linear diarylheptanoids from Curcuma xanthorrhiza: a novel type of topical anti-inflammatory agents: structure-activity relationship. Planta Med. 1996; 62:236-240.
36. Araújo CAC, Alegrio LV, Castro D, Lima MEF, Leon LL. *Leishmania amazonensis*: *in vivo* experiments with diarylheptanoids from Leguminosae and Zingiberaceae plants. Mem Inst Oswaldo Cruz. 1998; 93:306.
37. Lansbury PT, Lashuel HA. A century-old debate on protein aggregation and neurodegeneration enters the clinic. Nature. 2006; 443:774-779.
38. Pezet S, Malcangio M. Brain-derived neurotrophic factor as a drug target for CNS disorders. Exp. Opin. Ther. Targets. 2004; 8:391-399.
39. Harvey A L. Medicines from nature: are natural products still relevant to drug discovery? Trends Pharmacol. Sci. 1999; 20:196-198.
40. Paterson I, Anderson EA. The renaissance of natural products as drug candidates. Science. 2005; 310:451-453.
41. Corson TW, Crews CM. Molecular understanding and modern application of traditional medicines: triumphs and trials. Cell. 2007; 130:769-774.
42. Basha MP, Madhusudan N, Rai P, Ahmed F, Prasad RG. Effect of maternal fluoride exposure on developing CNS of rats: Protective role of *Aleo vera*, *Curcuma longa* and *Ocimum sanctum*. Indian J of Exp.Biology. 2010; 48:830-836.
43. Leu TH, Maa MC. The molecular mechanisms for the antitumorigenic effect of curcumin. Curr Med Chem Anticancer Agents. 2002; 2:357-370.
44. Sharma C, Suhalka P, Sukhwal P, Jaiswal N, Bhatnagar M. Curcumin attenuates neurotoxicity induced by fluoride: An in vivo evidence. Pharmacogn Mag. 2014; 10(37):61-65. doi:10.4103/0973-1296.126663
45. Sharma C, Suhalka P, Sukhwal P, Bhatnagar M. Curcumin and resveratrol rescue cortical–hippocampal system from chronic fluoride-induced neurodegeneration and enhance memory retrieval, Int Jour. of Neuroscience. 2018; 128:11, 1007-1021. DOI: 10.1080/00207454.2018.1458727
46. Molina-Holgado F, Hider RC, Gaeta A, Williams R, Francis P. Metals ions and neurodegeneration. Biometals. 2007 2:639-654**.**
47. Tripathy BC, Sharma D. Kiran Bala. Neuroprotective and anti-ageing effects of curcumin in aged rat brain regions. Bio gerontology. 2006; 7:81-89.
48. Sabetkasaei M, Ataie A Haghparasat A, Moghaddam HA, Ataee R, Moghaddam NS. Curcumin exerts neuroprotective effects against homocystein intra cerebroventricular injection induced cognitive impairment and oxidative stress in rat brain. J of Medicinal Food. 2010; 13:821-826.
49. Thiyagarajan M, Sharma SS. Neuroprotective effect of curcumin in middle cerebral artery occlusion induced focal cerebral ischemia in rats. Life Sci. 2004; 74:969-985.
50. Aggarwal BB, Kumar A, Aggarwal MS, Shishodia S. Curcumin derived from turmeric (*Curcuma longa*): A spice for all seasons. In: Phytopharmaceuticals in Cancer Chemoprevention. Preuss H, ed. Boca Raton: CRC Press, 2005, 349-87.
51. Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR. Curcumin inhibits formation of amyloid beta oligomers and fibrils, bind plaques and reduce amyloid *in vivo*. J Biol. Chem. 2005; 280:5892-5901.
52. McAdam BF, Catella-Lawson F, Mardini IA, Kapoor S, Lawson JA, Fitz Gerald GA. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: The human pharmacology of a selective inhibitor of COX-2. Proc Natl Acad Sci. USA. 1999; 96:272-277.
53. Zhang L, Fiala M, Cashman J, Sayre J, Espinosa A, Mahanian M. Curcuminoids enhance amyloid -beta uptake by macrophages of Alzheimer's disease patients. J Alzheimers Dis. 2006; 10:1-7.
54. Cummings JL, Vinters JHV, Cole GM, Khachaturian ZS. Alzheimer's disease: Etiologies, pathophysiology, cognitive reserve, and treatment opportunities. Neurology. 1998; 51:2-17.
55. Heng MC, Song MK, Harker J. Drug-induced suppression of phosphorylasekinase activity correlates with resolution of psoriasis as assessed by clinical, histological and immunohistochemical parameters. Br. J Dermatol. 2000; 143:937-949.
56. Tourkina E, Gooz P, Oates JC. Curcumin-induced apoptosis in scleroderma lung fibroblasts: role of protein kinase cepsilon. Am. J Respir. Cell Mol. Biol. 2004; 31:28-35.
57. Babu PS, Srinivasan K. Hypolipidemic action of curcumin, the active principle of turmeric (*Curcuma longa*) in streptozotocin induced diabetic rats. Mol Cell Bio chem. 1997; 166:169-175.
58. Babu PS, Srinivasan K. Influence of dietary curcumin and cholesterol on the progression of experimentally induced diabetes in albino rat. Mol. Cell Bio chem. 1995; 152:13-21.
59. Egan ME, Pearson M, Weiner SA. Curcumin, a major constituent of turmeric, corrects cystic fibrosis defects. Science. 2004; 304:600-602.
60. Shishodia S, Sethi G, Aggarwal BB. Curcumin: getting back to the roots. Ann. N.Y. Acad. Sci. 2005; 1056:206-217.
61. Kotwal GJ *et al*. Natural Products and Molecular Therapy, First International Conference. New York, NY: Annals of the New York Academy of Sciences. 2005;

1056:1-15.
62. Mukopadhyay A, Banerjee S, Stafford LJ. Curcumin-induced suppression of cell proliferation correlates with donregulation of cyclin D1 expression and CDK4-mediated retinoblastoma protein phosphorylation. Oncogene. 2002; 21:8852-8862.
63. Mukopadhyay A, Bueso-Ramos C, Chatterjee D. Curcumin downregulates cell survival mechanisms in human prostate cancer cell lines. Oncogene. 2001; 20:7597-7609.
64. Bharti AC, Donato N, Singh S. Curcumin (diferuloylmethane) downregulates the constitutive activation of nuclear factor-kappa B and I kappa B-alpha kinase in human multiple myeloma cells, leading to suppression of proliferation and induction of apoptosis. Blood. 2003; 101:1053-1062.