



A Review of the Anti-oxidation, Anti-inflammatory and Anti-tumor Properties of Curcumin

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Received: 27 Jul 2017

Revised: 28 Aug 2017

Accepted: 1 Nov 2017

Abstract

Sinafaravar pharmaceutical Company has produced Curcuma-sina that helps people have healthier lives. Curcuma-Sina shows strong anti-oxidation, anti-inflammatory and anti-tumor properties. This product is including *Curcuma longa* and *Piper nigrum*. Anti-inflammatory products are being used to remedy chronic inflammatory disorders and cancers. Thus, there is an urgent need to develop safe and effective medicines for the long-term use. Researchers have studied small molecules derived from natural sources with the aim of developing new treatments for clinical features. *Curcuma longa* and *Piper nigrum*, are well known to have beneficial clinical effects. *Curcuma longa* has various therapeutic effects on different diseases. However, it has limited tissue distribution, low serum levels and apparent rapid metabolism in human. To increase *Curcuma longa* bioavailability, *Piper nigrum*, known as a natural adjuvant increases the bioavailability of *Curcuma longa*.

Keywords: *Curcuma longa*, *Piper nigrum*, Antioxidation, Anti-inflammatory, Anti-tumor.

Citation: Mahdavi H, Hadadi Z, Ahmadi M. A Review of the Anti-oxidation, Anti-inflammatory and Anti-tumor Properties of Curcumin. Trad Integr Med 2017; 2(4): 188-195.

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Introduction

Curcuma-Sina is a drug which contains *Curcuma longa* and *Piper nigrum*. Curcuma-Sina has strong antioxidation, anti-inflammatory and anti-tumor activities. At the following, we introduce compounds of this product.

Curcuma longa is a spice of ginger family (Zingiberaceae) described as having yellow color rhizomes which are horizontal underground stems that send out shoots and leaves. The yellow color is largely derived from fat-soluble polyphenolic pigments called curcuminoids. The yellow pigment segregated from the rhizomes of *Curcuma longa* is more commonly called curcumin or turmeric [1, 2].

The dietary phytochemical curcumin has a long history of medical use in Asia for a wide variety of medical situations [3]. For hundreds of years it has mostly been part of the diet of people in a

number of countries such as Iran and India [4, 5].

Many medical researchers have studied on curcumin due to its different remedial effects on many diseases. Curcumin has received consideration mostly due to its anti-inflammatory, anti-oxidant, anti-tumoral, apoptosis-inducing and anti-angiogenesis effects, which were reported in many studies [6].

Curcumin has multilateral purpose in cellular pathways that makes this agent able to relocate multiple attempts [7]. These therapeutic influences of curcumin have been discussed in many experiments for many diseases [8-12]. (Figure. 1)

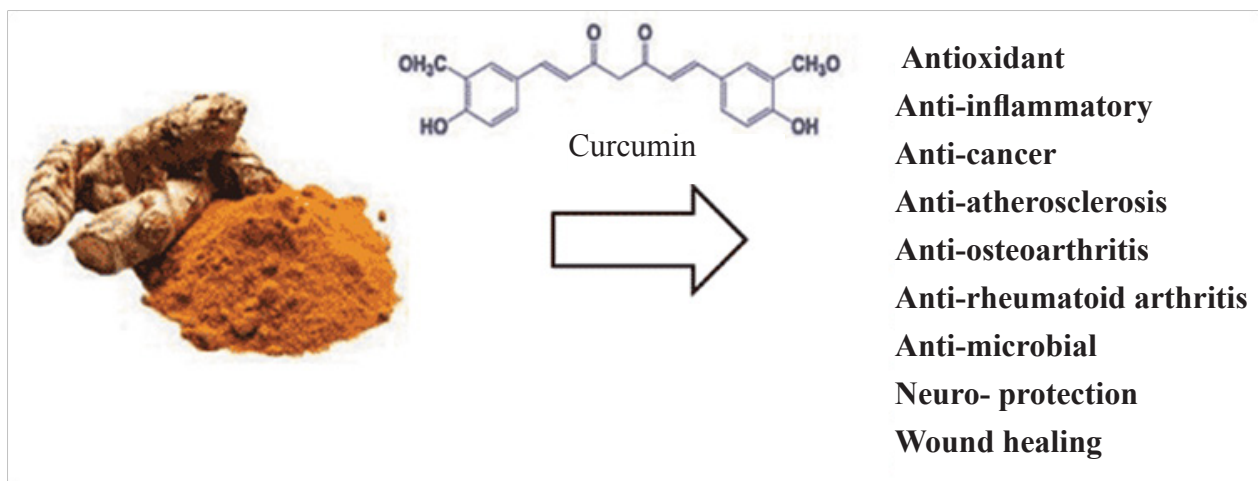


Figure 1: The therapeutic influences of curcumin

The antioxidant activity

Oxidative stress has an important role in the cause of various diseases including inflammation, cancer, diabetes, cardiovascular diseases, cell injury and liver disorders. Experimental models have been reported to consider the therapeutic effects on various materials as well as curcumin in this matter [13].

Antioxidants are materials which destroy or postpone oxidation of oxidative stratum such as carbohydrates, amino acids, lipids and genome damage in cells. Various diseases may be occurred if the rate of free radicals and antioxidants becomes off balanced [14]. Natural antioxidants play a major role in the preservation of health and in cure of various disorders [15, 16]. Curcumin is one of the most important indigenous antioxidants with a broad aspect of medical properties. Various research using various models have confirmed curcumin conservation despite oxidative factors for the whole body [17-20].

Curcumin is a free radical scavenger and a suppressor of genome injury, particularly in attendance of some particles such as Cu or Fe ions [21-23]. Curcumin is adherent to many ions that modulates the antioxidant attributes and radical scavenging effects [24, 25].

The anti-inflammatory activity

Curcumin has been well known with anti-inflammatory capability. Many of the activities associated with curcumin are related to its ability to inhibit inflammations [26].

Anti-inflammatory mechanisms of curcumin including inhibition of nuclear factor kappa-B

(NF- κ B) that plays an important role in signal transduction pathways preoccupied in diseases and various cancers, inhibited metabolism of arachidonic acid with lipoxygenase and scavenging of free radicals beget in this pathway. Also, it reduces expression of inflammatory cytokines such as IL-1b, IL-6 and TNF- α , eventuating in growth inhibition of cancer cell lines and down-regulation of enzymes such as protein kinase C, that interfere inflammation and abnormal cell proliferation [27-30].

The anti-cancer activity

Cancer is a high proliferative disturbance of a normal cell with missed cellular homeostasis. It inchoates to fundamentally activate an extravagance of genes that are convicted in cell cycle, invasion, survival, metastasis and angiogenesis. A study suggests that arranged inflammatory pathways play a major function in regiment of chronic diseases especially cancer [31]. The chronic inflammation drives cancer initiation and development whit increased production of pro inflammatory mediators, such as cytokines, chemokines, reactive oxygen species (ROS), over expression of oncogenes, cyclooxygenase (COX-2), matrix metalloproteinase (MMPs), intracellular signaling pathway mediators, transcription factors such as nuclear factor κ B (NF- κ B), signal transducer, activator of transcription 3 (STAT3), protein kinaseB (AKT), activator protein 1 (AP1) that drive tumor cell proliferation, transformation, invasion, metastasis, angiogenesis, chemoresistance and radio resistance [32, 33]. It has been proven that pro-inflammatory mediators are linked to tu-

mor formation. Curcumin's anti-tumoral effects have been shown in many of preclinical cancer models, including colorectal, pancreatic, gastric, prostate, hepatic, breast, oral cancers, leukemia and at various cell lines of carcinogenesis [34]. In addition, curcumin confiscates cell cycle's advancement independent of prevention of prostaglandin synthesis [35].

According to this different finding, curcumin engages with plenty of extracellular and intracellular molecules that are actively involved in cancer initiation and progression [36-39].

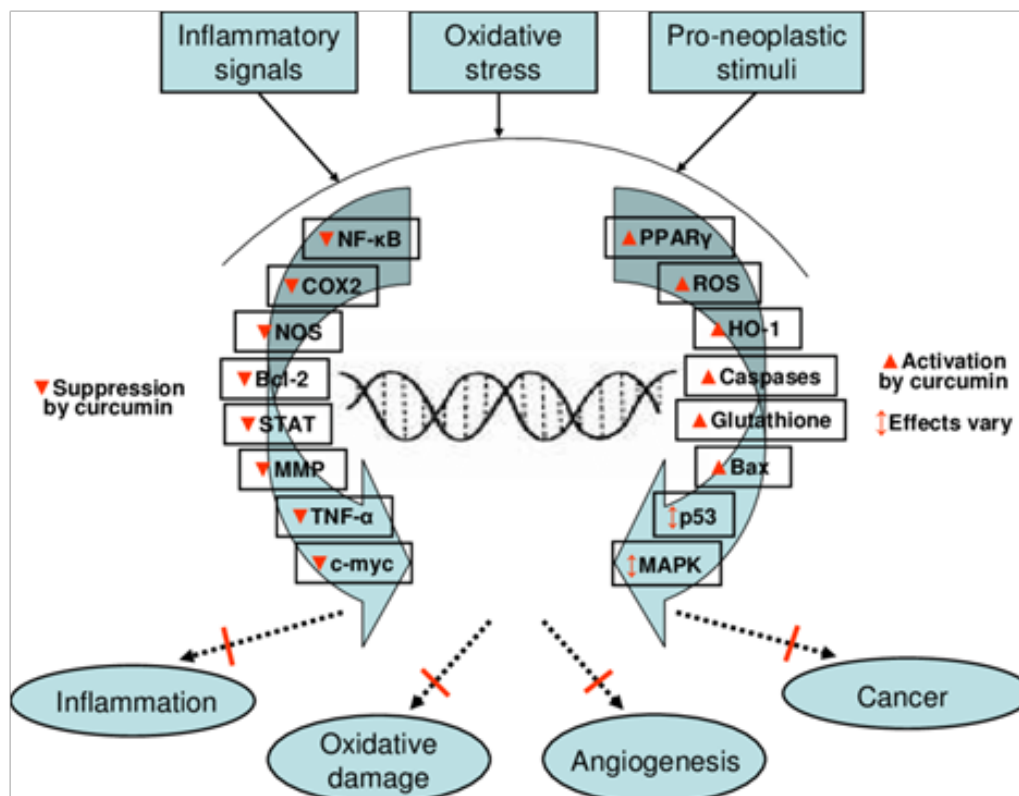


Figure 2: Cellular activities of curcumin and molecular mechanisms of action

Bioavailability of Curcumin

Curcumin bioavailability is so poor in humans. Although curcumin has hopeful features for prevention and treatment of various disorders, clinical uses have been bereaved by insignificant absorption, fast metabolism, short biological half-life and down oral bioavailability [40, 41]. The main problems of bioavailability of curcumin are low serum levels, limited tissue

broadcast and rapid metabolism [42]. Therefore, superior doses are urgent to make many drugs [43]. Studies on curcumin have detected some potential ways to improve the bioavailability, boost circulation, improve penetrance and resistance to metabolic proceedings. Multiple formulations have helped including nanoparticles, phospholipid complexes, liposomes, micelles, and adjuvants [44-49].

One of the natural adjuvants is piperine, the main part of *Piper nigrum*, known to improve the bioavailability of curcumin. This effect of piperine on the pharmacokinetics of curcumin has been shown to be much greater in humans than in animal study. A study shows that piperine increases the serum compactness, measure of absorption and bioavailability of curcumin in both animal and humans with no deleterious effects [50].

Increased bioavailability of curcumin has been found to be associated with piperine. Intestinal sorption of curcumin was also detected comparatively higher when provided concomitantly with piperine, and has constancy significantly longer in the body tissues [51, 52].

Combination therapy including curcumin and a bio activator such as piperine could promote the cellular uptake of curcumin and modulate the pharmacokinetics effect of curcumin which may cause to albumin binding interactions which are expected to increase the efficacy of curcumin [53, 54].

Piperine is a promising natural source with potential for therapeutic use. Piperine is also known to promote the bioavailability of some pharmacological agents by inhibiting drug metabolism or increasing absorption [55, 56]. Piperine has antioxidant ability, it scavenge free radicals and reactive oxygen species against oxidative injury that might be due to the presence of flavonoids and phenolic contents.

Piper nigrum inhibit the oxidative stress by preventing lipid peroxidation, lipoxygenase and arresting hydroxyl and superoxide free radicals and decreasing carcinogenesis [57-64]. Also,

piperine has effective immunomodulatory and antitumor activities with inhibit tumors formation [65-67]. According to studies, the antitumor activity of piperine may be related to its immunomodulatory properties that involves the activation of cellular and humoral immune responses [68, 69]. Piperine inhibits the production of proinflammatory mediators including, IL6 and PGE2, furthermore by inhibiting tumor necrosis factor- α (TNF- α) it can induce activation of NF- κ B via blocking I κ B α kinase activation [70-72].

Conclusion

Since earliest times, curcumin has been used in Asian countries against human affliction. Contemporary science has describe the molecular basis for the pharmaceutical uses of curcumin. Numerous studies over the past decade have demonstrated the safety and efficacy of this phenol and have provided a solid basis for evaluating its efficacy in human clinical trials. Despite its efficacy and safety, limited curcumin bioavailability continues to be highlighted as a major concern. However, in attempting to improve the bioavailability of curcumin, several strategies have been explored such as blocking of metabolic pathways by concomitant administration with other agents like piperine.

Conflict of Interest

None.

Acknowledgment

None.

References

- [1] Henrotin Y, Clutterbuck AL, Allaway D. Biological actions of curcumin on articular chondrocytes. *O A R S J* 2010;18:141-149.
- [2] Shen L, Ji H-F. The pharmacology of curcumin: is it the degradation products. *Trends Mol Med* 2012;18:138-144.
- [3] Goel A, Kunnumakkara AB, Aggarwal BB. Curcumin as "Curecumin": from kitchen to clinic. *Biochem Pharmacol* 2008;75:787-809.
- [4] Aggarwal BB, Sung B. Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets. *Trends Pharmacol Sci* 2009;30:85-94.
- [5] Sharma R, Gescher A, Steward W. Curcumin: the story so far. *Eur J Cancer* 2005;41:1955-1968.
- [6] Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. *Mol Pharm* 2007;4:807-818.
- [7] Hatcher H, Planalp R, Cho J, Torti FM, Torti SV. Curcumin: From ancient medicine to current clinical trials. *Cell Mol Life Sci* 2008;65:1631-1652.
- [8] Kumaravel M, Sankar P, Latha P, Benson CS, Rukkumani R. Anti proliferative effects of an analog of curcumin in Hep-2 cells: a comparative study with curcumin. *N P C J* 2013;8:183-186.
- [9] Masuelli L, Benvenuto M, Fantini M. Curcumin induces apoptosis in breast cancer cell lines and delays the growth of mammary tumors in neu transgenic mice. *J B R H A* 2012;27:105-119.
- [10] Link A, Balaguer F, Shen Y. Curcumin modulates DNA methylation in colorectal cancer cells. *PLoS One* 2013;8:57709.
- [11] Peng F, Tao Q, Wu X. Cytotoxic, cytoprotective and antioxidant effects of isolated phenolic compounds from fresh ginger. *Fitoterapia* 2012;83:568-585.
- [12] Avasarala S, Zhang F, Liu G, Wang R, London SD, London L. Curcumin Modulates the Inflammatory Response and Inhibits Subsequent Fibrosis in a Mouse Model of Viral-induced Acute Respiratory Distress Syndrome. *PLoS One* 2013;8:57285.
- [13] Jovanovic S, Boone CW, Steenken S, Trinoga M, Kaskey RB. How curcumin works preferentially with water soluble antioxidants. *J Am Chem Soc* 2001;123:3064-3068.
- [14] Halliwell B, Whiteman M. Measuring reactive species and oxidative damage in vivo and in cell culture: how should you do it and what do the results mean. *Br J Pharmacol* 2004;142:231-255.
- [15] Burlakova EB. *Russ J Gen Chem* 2007;77:1983-1993.
- [16] Kancheva VD, Kasaikina OT. *Curr Med Chem* 2013;20:4784-4805.
- [17] Aggarwal BB, Sung B. *Trends Pharmacol Sci* 2009;30:85-94.
- [18] Goel A, Kunnumakkara AB, Aggarwal BB. *Biochem Pharmacol* 2008;75:787-809.
- [19] Joe B, Vijaykumar M, Lokesh BR. *Crit Rev Int J Food Sci Nutr* 2004;44:97-111.
- [20] Marchiani A, Rozzo C, Fadda A, Delogu G, Ruzza P. *Curr Med Chem* 2014;21:204-222.
- [21] Vajragupta O, Boonchoong P, Berliner LJ. Manganese complexes of curcumin analogues: Evaluation of hydroxyl radical scavenging ability, superoxide dismutase activity and stability towards hydrolysis. *Free Radic Res* 2004;38:303-314.
- [22] Barik A, Mishra B, Kunwar A. Comparative study of copper(II) curcumin complexes as superoxide dismutase mimics and free radical scavengers. *Eur J Med Chem* 2007;42:431-439.
- [23] Sreejayan RM. Nitric oxide scavenging by curcuminoids. *J Pharm Pharmacol* 1997;49:105-107.
- [24] 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. *Biochem Biophys Acta* 1994;1224:255-263.
- [25] Lin J, Shih CA. Inhibitory effect of curcumin on xanthine dehydrogenase/oxidase induced by phorbol-12-myristate-13-acetate in NIH3T3 cells. *Carcinogenesis* 1994;15:1717-21.
- [26] Thangapazham R, Sharma A, Maheshwari RK. Multiple molecular targets in cancer chemoprevention by curcumin. *A A P S J* 2006;8:443-449.
- [27] Huang MT, Lysz T, Ferraro T. Inhibitory effects of curcumin on in vitro lipoxygenase and cyclooxygenase activities in mouse epidermis. *Cancer Res* 1991;51:813-819.
- [28] Cho JW, Lee KS, Kim CW. Curcumin attenuates the expression of IL-1beta, IL-6, and TNF-alpha as well as cyclin E in TNF-alpha-treated HaCaT cells; NFkappaB and MAPKs as potential upstream targets. *Int J Mol Med* 2007;19:469-474.
- [29] Liu JY, Lin SJ, Lin JK. Inhibitory effects of curcumin on protein kinase C activity induced by 12-O-tetradecanoyl-phorbol-13-acetate in NIH 3T3 cells. *Carcinogenesis* 1993;14:857-861.
- [30] Mann J, DuBois RN. Cyclooxygenase-2 and gastrointestinal cancer. *Cancer J* 2004;10:145-152.
- [31] Amit S, Ben-Neriah Y. NF-kappaB activation in cancer: A challenge for ubiquitination- and proteasomebased therapeutic approach. *Semin Cancer Biol* 2003;13:15-28.
- [32] Bennett A. The production of prostanoids in human cancers, and their implications for tumor progression. *J Lipid*

- Res 1986;25:539-542.
- [33] Qiao L, Kozoni V, Tsioulis GJ. Selected eicosanoids increase the proliferation rate of human colon carcinoma cell lines and mouse colonocytes in-vivo. *Biochem Biophys Acta* 1995;1258:215-223.
- [34] Aggarwal BB, Kumar A, Bharti AC. Anticancer potential of curcumin: preclinical and clinical studies. *Anticancer Res* 2003;23:363-398.
- [35] Ushida J, Sugie S, Kawabata K. *Jpn J Cancer Res* 2000;91:893-898.
- [36] Anand P, Sundaram C, Jhurani S, Kunnumakkara AB, Aggarwal BB. Curcumin and cancer: An “old-age” disease with an “age-old” solution. *Cancer Lett* 2008;267:133-164.
- [37] Aggarwal BB, Gehlot P. Inflammation and cancer: How friendly is the relationship for cancer patients *Curr Opin Pharmacol* 2009;9:351-369.
- [38] Aggarwal BB, Shishodia S, Sandur SK, Pandey M K, Sethi G. Inflammation and cancer: How hot is the link. *Biochem Pharmacol* 2006;72:1605-1621.
- [39] Gupta SC, Prasad S, Kim JH, Patchva S, Webb LJ, Priyadarsini IK, Aggarwal BB. Multitargeting by curcumin as revealed by molecular interaction studies. *Nat Prod Rep* 2011;28:1937-1955.
- [40] Shehzad A, Wahid F, Lee YS. Curcumin in cancer chemoprevention: Molecular targets, pharmacokinetics, bioavailability, and clinical trials. *Arch Pharm Weinh* 2010;343:489-499.
- [41] Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: Problems and promises. *Mol Pharm* 2007;4:807-818.
- [42] Aggarwal BB, Sundaram CN, Malani H. Ichikawa, Curcumin: The Indian Solid Gold. *Adv Exp Med Biol* 2007;595:1-75.
- [43] Sharma RA, Euden SA, Platton SL, Cooke DN, Shafayat A, Hewitt HR, Marczylo TH, Morgan B, Hemingway D, Plummer SM. Phase I clinical trial of oral curcumin: Biomarkers of systemic activity and compliance. *Clin Cancer Res* 2004;10:6847-6854.
- [44] Gao Y, Li Z, Sun M, Guo C, Yu A, Xi Y. Preparation and characterization of intravenously injectable curcumin nanosuspension. *Drug Deliv* 2011;18:131-142.
- [45] Gao Y, Li Z, Sun M, Li H, Guo C, Cui J. Preparation, characterization, pharmacokinetics, and tissue distribution of curcumin nano suspension with TPGS as stabilizer. *Drug Dev Ind Pharm* 2010;36:1225-1234.
- [46] Zhongfa L, Chiu M, Wang J, Chen W, Yen W, Fan-Havard P. Enhancement of curcumin oral absorption and pharmacokinetics of curcuminoids and curcumin metabolites in mice. *Cancer chemoth oharm* 2012;69:679-689.
- [47] John MK, Xie H, Bell EC, Liang D. Development and pharmacokinetic evaluation of a curcumin co-solvent formulation. *Anticancer Res* 2013;33:4285-4291.
- [48] Saengkrit N, Saesoo S, Srinuanchai W, Phunpee S, Ruktanonchai UR. Influence of curcumin-loaded cationic liposome on anticancer activity for cervical cancer therapy. *Colloids Surf B Biointerfaces* 2014;114:349-356.
- [49] Liu CW, Xiong F, Jia HZ, Wang XL, Cheng H, Sun YH. Graphene-based anticancer nanosystem and its biosafety evaluation using a zebrafish model. *Biomacromolecules* 2013;14:358-366.
- [50] Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Med* 1998;64:353-356.
- [51] Suresh D, Srinivasan K. Tissue distribution & elimination of capsaicin, piperine & curcumin following oral intake in rats. *Ind J Med Res* 2010;131:682-691.
- [52] Moorthi C, Krishnan K, Manavalan R, Kathiresan K. Preparation and characterization of curcumin-piperine dual drug loaded nanoparticles. *Asian Pac J Trop Biomed* 2012;2:841-848.
- [53] Moorthi C, Kathiresan K. Curcumin–Piperine/Curcumin–Quercetin/Curcumin–Silibinin dual drug-loaded nanoparticulate combination therapy: A novel approach to target and treat multidrug-resistant cancers. *Med Hypotheses* 2013;7:15-20.
- [54] Doucette CD, Hilchie AL, Liwski R, Hoskin DW. Hoskin piperine, a dietary phytochemical inhibits angiogenesis. *J Nutr Biochem* 2013;24:231-239.
- [55] Selvendiran K, Banu SM, Sakthisekaran D: Oral supplementation of piperine leads to altered phase II enzymes and reduced DNA damage and DNA-protein cross links in benzo(a)pyrene induced experimental lung carcinogenesis. *Mol Cell Biochem* 2005;268:141-147.
- [56] Scholz S, Williamson G. Interactions affecting the bioavailability of dietary polyphenols in vivo. *Int J Vitam Nutr Res* 2007;77:224-235.
- [57] Acharya SG, Momin AH and Gajjar AV. Review of Piperine as A Bio-Enhancer. *Am J Pharm Tech Res* 2012;2:32-44.
- [58] Taqvi SI, Shah AJ, Gilani AH. Blood pressure lowering and vasomodulator effects of piperine. *J Cardiovasc Pharmacol* 2008;52:452-458.
- [59] Manoharan S, Balakrishnan S, Menon V, Alias L, Reena A. Chemopreventive efficacy of curcumin and piperine during 7,12-dimethylbenz[a] anthracene-induced hamster buccal pouch carcinogenesis. *Singapore Med J* 2009;50:139-146.
- [60] Parganiha R, Verma S, Chandrakar S, Pal S, Sawarkar HA, Kashyap P. In vitro anti- asthmatic activity of fruit extract of *Piper nigrum* (Piperaceae). *Int J Herb Med* 2011;1:15-18.

- [61] Li S, Wang C, Wang M, Li W, Matsumoto K. Antidepressant like effects of piperine in chronic mild stress treated mice and its possible mechanisms. *Life Sci* 2007;80:1373-1381.
- [62] Matsuda H, Ninomiya K, Morikawa T, Yasuda D, Yamaguchi I. Protective effects of amide constituents from the fruit of *Piper chaba* on D-galactosamine/TNF-alpha-induced cell death in mouse hepatocytes. *Bioorg Med Chem Lett* 2008;18:2038-2042.
- [63] Johnson JJ, Nihal M, Siddiqui IA, Scarlett CO, Bailey HH. Enhancing the bioavailability of resveratrol by combining it with piperine. *Mol Nutr Food Res* 2011;55:1169-1176.
- [64] Wattanathorn J, Chonpathompikunlert P, Muchimapura S, Priprem A, Tankamnerdthai O. Piperine, the potential functional food for mood and cognitive disorders. *Food Chem Toxicol* 2008;46:3106-3110.
- [65] Ahmad N, Fazal H, Abbasi BH, Farooq S, Ali M. Biological role of *Piper nigrum* L. (Black pepper): A review. *A P J T B*. 2012:1945-1953.
- [66] Selvendiran K, Sakthisekaran D. Chemopreventive effect of piperine on modulating lipid peroxidation and membrane bound enzymes in benzo(a) pyrene induced lung carcinogenesis. *Biomed Pharmacother* 2004;58:264-267.
- [67] Ahmad N, Fazal H, Abbasi BH, Rashid M, Mahmood T, Fatima N. Efficient regeneration and antioxidant potential in regenerated tissues of *Piper nigrum* L. *Plant Cell, Tissue and Organ Culture Plarma Res* 2010;102:129-134.
- [68] Sunila ES, Kuttan G. Immunomodulatory and antitumor activity of *Piper longum* Linn and piperine. *J Ethnopharmacol* 2004;90:339-346.
- [69] Pathak N, Khandelwal S. Modulation of cadmium induced alterations in murine thymocytes by piperine: oxidative stress, apoptosis, phenotyping and blastogenesis. *Biochem Pharmacol* 2006;72:486-497.
- [70] Singh R, Singh N, Saini BS, Rao HS. In vitro antioxidant activity of pet ether extract of black pepper. *Ind J Pharmacol* 2008;40:147-151.
- [71] Bang JS, Oh DH, Choi HM, Sur BJ, Lim SJ, Kim JY. Anti-inflammatory and anti-arthritic effects of piperine in human interleukin-1beta-stimulated fibroblast-like synoviocytes and in rat arthritis models. *Arthritis Res Ther* 2009;11:49.
- [72] Kumar S, Singhal V, Roshan R, Sharma A, Rembhotkar GW, Ghosh B. Piperine inhibits TNF-alpha induced adhesion of neutrophils to endothelial monolayer through suppression of NF-kappaB and IkappaB kinas