A.A.P.

ADVANCES IN PHARMACOGNOSY AND PHYTOMEDICINE

Journal homepage: http://www.journals.wsrpublishing.com/index.php/APP

Print ISSN: 2423-706X *Online ISSN:* 2423-7078

Review Article

Curcumin: Nutraceutical and Pharmaceutical Applications

Basavaraj K. Nanjwade[*,1], Kishor A. Bellad[2], Anas S. Mohamied[3], Moftah S. Nwaji[4], Teerapol Srichana[5]

[1] Department of Pharmacy Practice, The Oxford College of Pharmacy, 6/9, 1st Cross, Begur Main Road, Hongasandra, Bangalore-560068, Karnataka, India
[2] Department of Pharmaceutics, KLE College of Pharmacy, Nipani 591237, Karnataka, India
[3] Department of Pharmaceutics, Faculty of Pharmacy, Omer Al-Mukhtar University, Bayda, Libya
[4] Department of Pharmaceutical Microbiology, Faculty of Pharmacy, Omer Al-Mukhtar University, Tobruk, Libya
[5] Drug Delivery System Excellence Centre, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat-Yai-90112, Songkla, Thailand

ARTICLE INFO

Corresponding Author:
Basavaraj K. Nanjwade
nanjwadebk@gmail.com

How to Cite this Article
Nanjwade, B.K., Bellad, K.A., Mohamied, A.S., Nwaji, M.S., & Srichana, T. (2015). Curcumin: Nutraceutical and Pharmaceutical Applications. *Advances in Pharmacognosy and Phytomedicine*, 1(1), 17-26.

Article History:
Received: 18 October 2015
Accepted: 29 October 2015

ABSTRACT

Medicinal plants can be used for the treatment of many diseases is associated to folk medicine from different parts of the world. Natural and herbal products from some plants, fungi, bacteria's and other organisms, continue to be used in pharmaceutical formulations either as pure compounds or as extracts. There is a great variety of compounds that can be extracted and characterized from plants, herbs and roots. One good example is the harmaline, one of the indole alkaloids found in Peganum harmala (Zygo-phyllaceae), used in the treatment of dermatosis. Extensive scientific research on curcumin, a natural compound present in the rhizomes of plant Curcuma longa Linn. The natural product curcumin (diferuloylmethane, 1,7-bis[4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione), obtained from the spice turmeric is a rhizomatous herbaceous plant belonging to the family Zingiberaceae, exhibits numerous biological activities. It is the major constituent of the oleoresin of turmeric. In the crude extract of rhizomes of C. longa about 70-76% curcumin is available along with about 16% demethoxycurcumin and 8% bisdemethoxycurcumin. Curcumin which is commonly used as a spice is also well documented for its medicinal properties in Indian and Chinese systems of medicine. It is extensively used for imparting color and flavor to the food. Extensive scientific research on curcumin had demonstrated a wide spectrum of therapeutic effects such as ant-inflammatory, antibacterial, antiviral, antifungal, antitumor, antispasmodic, hepato-protective, anti-angiogenic, anti-oxidant, wound healing, anti-cancer effects, nematocidal activities, anti-protozoal activity, anti-venom activity. Recently, its potential utility in Auto-Immune Deficiency Syndrome (AIDS) had been demonstrated. A number of curcumin based pyrazoles an isoxazoles and a diazepine had been synthesized and evaluated for their antibacterial activities.

Keywords: Curcumin, ant-inflammatory, antibacterial, antiviral, antifungal, antitumor, antispasmodic, hepato-protective, anti-angiogenic.

INTRODUCTION

The increasing importance in traditional medicine, chiefly plants-based medicine has headed to wide research on the potentials of natural origin substances. Large amount of studies were carried-out to explore the effects of natural origin compounds on human health and prevention and treatment of chronic diseases (Schmid *et al*., 2007). Among the various compounds studied, polyphenols are found as one of the most promising groups. In plants, polyphenols plays an important role in growth and protection against pathogens. In recent times polyphenol have received greater attention due to their demonstrated antioxidant capabilities against prevention and treatment of disease (Zern and Fernandez, 2005). Polyphenols are derived from components of the human food such as peanuts, dark chocolate, green and black tea and turmeric etc. Ayurveda, Unani, Siddha and Chinese medicines recommend turmeric for a wide range of disorders and diseases. Turmeric has been used traditionally for many ailments because of its wide spectrum of biological and pharmacological activities. Among the various polyphenols present, curcumin is currently one of the most studied substances. Curcumin has been identified as the active principle of turmeric. Curcumin has been used in traditional medicine for many centuries mainly in Asian countries such as India and China (Shishodia *et al*., 2005). It is chemically a yellow hydrophobicpolyphenol, diferuloylmethane extracted from the rhizomes of turmeric (*Curcuma longa*), it is a bis-α, β-unsaturated β-diketone that exhibits keto-enoltautomerism, which exhibits keto-enoltautomerism having a predominant keto form in acidic and neutral solutions and stable enol form in alkaline medium. Commercial curcumin contains approximately 77% diferuloylmethane, 17% demethoxycurcumin, and 6% bisdemethoxycurcumin. Curcumin has been shown to exhibit antioxidant, anti-inflammatory (Srimal and Dhawan, 1973; Sherma, 1976; Ruby *et al.,* 1995; Sugiyama *et al.,* 1996) , antimicrobial and anti-carcinogenic activities (Kuttan *et al.,* 1985; Jordan and Drew, 1996; Kim *et al*., 2003; Reddy *et al*., 2005). Additionally, the hepato-protective and nephro-protective (Kiso *et al.,* 1998; Venkatesan, 1998; Venkatesan *et al.,* 2000), thrombosis suppressing (Dikshit *et al*., 1987), myocardial infarction protective (Dikshit *et al*., 1995; Nirmala and Puvanakrishnan, 1996ab), hypoglycemic (Srinivasan, 1972 ; Babu and Srinivasan, 1995; Babu and Srinivasan, 1997; Arun and Nalini, 2002) and anti-rheumatic (Deodhar *et al*.,1980) antitumor, anti-amyloid effects of curcumin are also well established. Various animal models (Shankar *et al.,* 1980; Qureshi *et al*., 1992) or human studies (Lao *et al*., 1996ab; Shoba *et al.,* 1998; Cheng *et al*., 2000) proved that curcumin is extremely safe even at very high doses as, it possesses low intrinsic toxicity. Inspite of its efficacy and safety, curcumin has not yet been approved as a therapeutic agent. Curcumin is known to possess low systemic bio-availability (Ireson *et al*., 2001), attributed to a generally poor aqueous solubility poor absorption and faster metabolic alterations (Ireson *et al.,* 2001; 2002) and intense staining color of curcumin have been highlighted as major problems.

History

The structure of curcumin ($C_{21}H_{20}O_6$) was first described in 1910 by Lampe and Milobedeska and shown to be diferuloylmethane (Aggarwal *et al.,* 2003). However Curcumin the major constituent of *Curcuma longa* L. (turmeric), was been isolated first early in 1815 by Vogel and Pelletier, but it has attracted few modern studies, then it was crystallized in 1870 by Daube and the structure was revealed in 1910 by Lampe and co-workers, who future completed a synthesis. Renewed interest has been evoked by the recent discovery of relative sharing the 1,7-diaryl skeleton.

Cultivation & Extraction

Turmeric (*Curcuma longa*) is a rhizomatous herbaceous plant belonging to the family Zingiberaceae. It is native to tropical South Asia and requires the temperatures in between 20-30° C and a considerable amount of yearly rainfall to flourish. Sangli a town in the southern part of the Indian state of Maharashtra is the leading and most significant trading centre for turmeric in Asia or possibly in the whole world.

Plants are collected annually for their rhizomes and re-seeded from some of those rhizomes in the following season. The gathered

rhizomes are then boiled for several hours and are dried in hot ovens after which they are pulverized into a deep orange-yellow powder i.e. turmeric powder which are commonly used as a spice in curries.

The obtained turmeric powders are then extracted with 95% alcohol in soxhlet assembly until all the coloring matter is completely extracted. The Alcoholic extracts are distilled of to a semisolid brown colored mass (about 4.5%) (Figure 1).

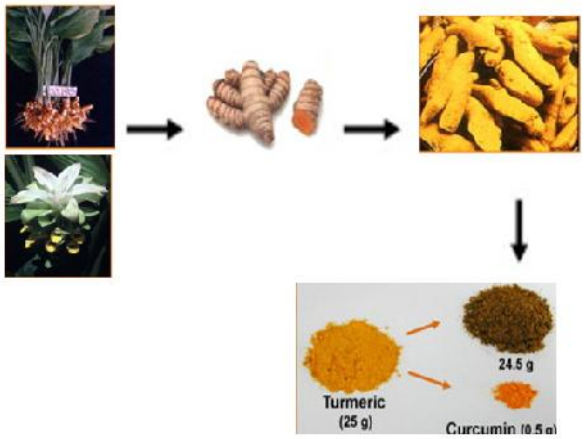

Figure 1: The extraction of curcumin

The crude extract is then dissolved in 50 ml of benzene and extracted two times with the same volume of 0.1% sodium hydroxide solution. The alkaline extracts are then combined and acidified with dilute hydrochloric acid. A yellow colored precipitate is thus formed. It is then allowed to settle down for 15 min, after settling down of precipitate (ppt). The extract is concentrated by boiling on water bath and at the same time dissolving the precipitate in boiling water. During this process of boiling the resinous material is agglomerated and lumpy mass is formed. The solution is then filtered in hot condition and the filtrate is concentrated to very small volume and finally cooled to get curcumin (1.5%). The final product obtained is recrystallized using 95% alcohol (Kokate, 1993).

Structure of Curcumin

Curcumin is an orange–yellow crystalline powder. Lampe and Milobedeska in 1910 first described the structure of curcumin ($C_{21}H_{20}O_6$) and shown to be diferuloylmethane. Curcumin 1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, is a natural polyphenolic phytochemical extracted from the powdered rhizomes of turmeric (*Curcuma longa*). Hydroxyl groups of the benzene rings, double bonds in the alkene part and the central b-diketone moiety are suggested to be likely responsible for the high beneficial activities of this polyphenolic molecule (Figure 2).

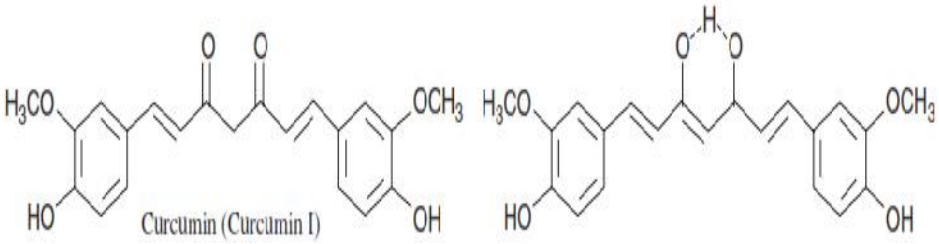

Figure 2: Structure of Curcumin (Keto form of curcumin and Enol form of curcumin

Properties of Curcumin

Curcumin belongs to the linear diarylheptanoid class of natural products in which two oxy-substituted aryl moieties are joined together by a seven-carbon chain. The C7 chain of linear diarylheptanoids is known to have unsaturation, oxo functions, enone moiety, and a 1,3-diketone group. Excluding for the oxo and hydroxy functions, the C7 chain is usually unsubstituted. This unsaturation in the linker unit has an E-configuration (trans C C bonds). The aryl rings could be substituted symmetrically or unsymmetrically; the most prevalent natural substituents are of the oxy type, such as hydroxy or methoxy elements (Anand *et al*., 2008). Curcumin which has a molecular formula ($C_{21}H_{20}O_6$) is chemically known as 1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione, it has a molecular weight of 368.37 g/mol and melting point of 183°C. Curcumin is poorly soluble in water (Zaveri *et al.*, 2011), however it completely dissolves in methanol which is

further followed by acetone, normal amyl methyl ketone, ethanol, tetrahydrofuran, acetylacetone, chloroform, aceticacid, dimethyl sulfoxide, benzene, toluene, and CCl_4. Lamda max of curcumin in UV-Vis spectrophotometric investigation,where maximum light absorption of curcumin occurs around 400-430 nm dependings upon organic solvent (Ganpati *et al*., 2011).

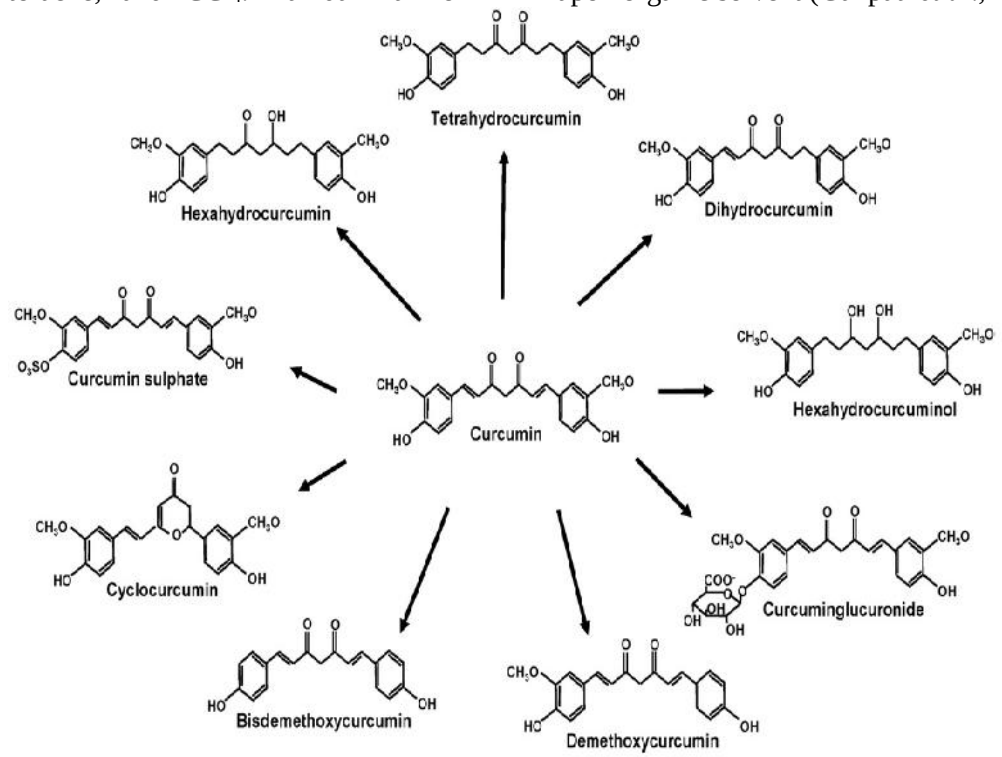

Figure 3: Structure of Curcumin and its metabolites

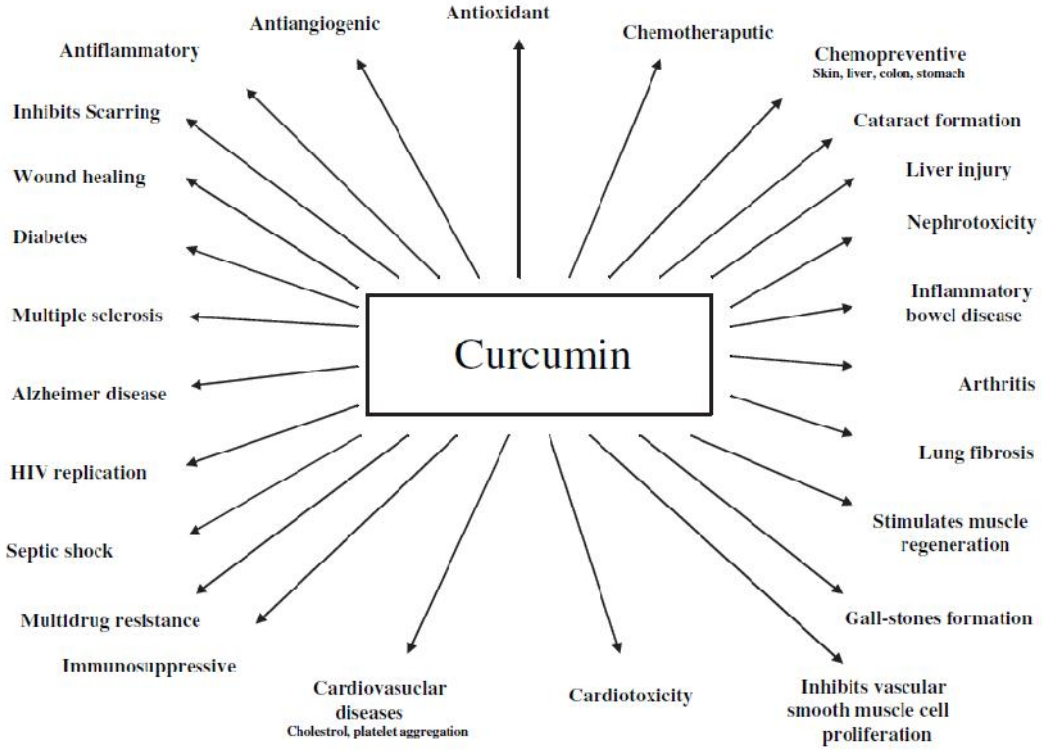

Figure 4: Biological properties of Curcumin

Metabolism and Elimination

The orally administered curcumin is absorbed from the alimentary tract and present in the general blood circulation after mainly being metabolized to the form of glucuronide/sulfate conjugates (Asai and Miyazawa, 2000). Once absorbed, Curcumin is subjected to conjugations like sulfation and glucuronidation at various tissue sites. Curcumin undergoes rapid metabolism in the liver particularly via glucuronidation, while curcumin given intraperitoneally or systemically undergoes reduction (Aggarwal and Sung, 2009). Metabolites produced from these pathways show low or no pharmacological activity (Aggarwal *et al*., 2007; Aggarwal and Harikumar, 2009). The major billiary metabolites of curcumin are glucuronides of dihydrocurcumin (DHC), tetrahydrocurcumin (THC) and hexahydrocurcumin (HHC). A minor biliary metabolite was dihydroferulic acid together with traces of ferulic acid (Holder *et al*., 1978). Various other metabolites of curcumin that have been reported, includes, octahydrocurcumin (OHC), curcuminglucuronide and curcumin sulfate. Tetrahydrocurcumin (THC), a partially reduced derivative of curcumin not found in turmeric, is one of the major metabolites of curcumin. Other reduced forms of curcumin, HHC and OHC, have also been considered curcumin metabolites, but have not been examined as extensively as THC. Tetrahydrocurcumin (THC) is obtained by partial hydrogenation of curcumin; it is colorless and more hydrophilic than curcumin.

A large amount of ingested curcumin is excreted mainly through the feces un-metabolized, the minor portion that is absorbed is extensively converted to its water-soluble metabolites, i.e. glucuronides and sulfate, and thus excreted. This seriously limits curcumin to reach targets distant from the gut and exert its beneficial action. The major route of eradication of the curcumin is through feces; the urinary excretion of curcumin is very low regardless of the dose. The elimination pattern of orally administered curcumin exhibit's unchanged excretion mostly in the feces of the single oral administration over a period of 8 days. Maximum fecal excretion of curcumin occurs during first 24 h and gradually declines thereafter. Excretion of intact curcumin in the urine is only minimal (Suresh and Srinivasan, 2010) (Figure 3).

Safety Evaluation

Human clinical trials indicate that curcumin has no toxicity when administered at dose of 1-10g/day.

Stability

Curcumin has a poor light stability. It suffers photo-degradation when being exposed to light in solution as well as in solid form. curcumin is unstable at basic pH and undergoes alkaline hydrolysis in alkali (higher pH) solution. Hydrolytic decomposition also occurs even in in-vitro physiological condition (isotopicphosphate buffer. pH 7.2). Under acidic conditions, the degradation of curcumin is much slower. Curcuminin basic pH solution degrades with in 30 min to form trans- 6(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexanal, ferulic acid, feruloylniethane and vanillin. Whereas in acidic conditions the degradation is less than 20% of total curcumin at 1 hour. When being exposed to sun light, both in ethanolic and methanolic extracts and as a solid curcumin degrades to give vanillin, vanillic acid, ferulic aldehyde and ferulic acid as final products (wikipededia.org/ wiki/ curcumin).

Adverse Reaction

No major side effect has been noted for curcumin for higher dose. Curcumin have shown few side effects, with some subjects reporting mild nausea or diarrhea.

Biological Properties of Curcumin

The various medicinal properties exhibited by the curcumin are as follows: anti-inflammatory, antioxidant, anti-carcinogenic activities, antimicrobial, antibacterial, antiviral, anti-protozoan, hepato- protective, nephro-protective, thrombosis suppressing and anticoagulant, myocardial infarction protective, nematocidal activities, hypoglycemic, hypolipemic, anti-rheumatic, antitumor, anti-amyloid effects, antispasmodic, anti-angiogenic, anti-venom activity (Figure 4).

Pharmacological Effect of Curcumin

1. Anti-inflammatory

The curcumin exhibits its anti-inflammatory activities by one of the following ways.

Perhaps one of curcumin's most important activities in the human body is its ability to inhibit activation of the transcription factor, nuclear factor-kappa B (NF-kB), a potent inducer of chronic inflammation and also the anti-inflammatory effect of curcumin is mediated through its ability to inhibit COX-2, lipoxygenase and inducible nitric oxide synthase important enzyme that mediate inflammatory process. NF-kB is a protein that acts as a sort of switch, turning on inflammation by activating genes involved in the production of inflammatory compounds. As NF-kB activation has been implicated in all the stages of carcinogenesis, this transcription factor is a potential target in cancer chemoprevention and is the subject of intensive research (Kiefer, 2012). The various tumor promoters, including phorbol ester, tumor necrosis factor (TNF), and H_2O_2, activate NF-κB and that curcumin down regulates the activation. Subsequently, the curcumin-induced down regulation of NF-κB is mediated through suppression of I κB α kinase activation. It also reported that curcumin suppresses the constitutively active NF-κB activation in mantle cell lymphoma. This led to the down regulation of cyclin D1, COX-2, and matrix metalloproteinase (MMP)-9 by curcumin (Aggarwal *et al*., 2007).

The other mechanisms implicated in the anti-inflammatory potential of curcumin may include:

1) Inhibition of arachidonic acid metabolism via lipoxygenase and scavenging the free radicals generated in this pathway

2) Down-regulation of the expression of various cell surface adhesion molecules that have been linked with inflammation.

3) Decreasing the expression of various inflammatory cytokines, including TNF, IL-1, IL-6, IL-8, and chemokines.

4) Curcumin is a potent antioxidant, which contributes to its anti-inflammatory action.

All these effects are thought to lead to lowering the formation of inflammatory compounds and suppressing the inflammatory response. This outcome is considered to be beneficial in many abnormal conditions such as autoimmune diseases (Sharma, 1976).

2. Antioxidant

The various authors demonstrated that antioxidant effect of curcumin is exhibited by following ways.

The antioxidant activity of curcumin arises mainly from scavenging of several biologically relevant free radicals that are produced during physiological processes. The curcumin act by protecting haemoglobin from oxidation even at a low concentration, several authors have studied the effect of curcumin on LPO in various models. Curcumin a good antioxidant acts by inhibiting LPO in rat liver microsomes, erythrocyte membranes, and brain homogenates. The LPO plays a major role in the inflammation, in heart diseases, and in cancer. The antioxidant action is mainly mediated through the antioxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase (Ruby *et al*., 1995; Sugiyama *et al.,* 1996; Adams *et al.,* 2000). Curcumin acts as a Michael acceptor, there by reacting with glutathione and thioredoxin thus interaction of curcumin with these agents decreases intracellular GSH in the cells (Adams *et al.,* 2000). It has been demonstrated that curcumin is at least ten times more active as an antioxidant than even vitamin E (Khopde *et al*., 1999). The methoxy and phenolic group on the phenyl ring and the 1,3-diketone system may be considered important to show antioxidant property of curcumin. Additional information in the literature is exhibits that the antioxidant action of curcumin increases when the phenolic group with a methoxy group is at the ortho position (Motterlini *et al.,* 2000).

3. Anti-carcinogenic

A broad examination of the works carried on curcumin characterises it as one of the excellent molecule among many naturally occurring compounds for cancer therapeutics.

Researchers of University of Alabama have published report in the Journal of Cancer Research, describing one of possibly various mechanisms by which curcumin functions as an anticancer agent. The investigators grew prostate cancer cells in the laboratory, and exposed them to varying concentrations of curcumin. Accordingly curcumin acts by decreasing the cell's production of MDM2 a known protein, which is mainly associated with the formation of malignant tumors. Simultaneously, curcumin stimulates the cells to produce another protein which is associated with the promotion of programmed cell death (apoptosis) (Li *et al.,* 2007). MDM2 have been recommended as

innovative target for human cancer therapy. Thus the curcumin acts by reducing the expression of MDM2. This down regulation exerts its anticancer activity which is considered as one of its mechanism against cancer.

The other mechanism involves pleiotropic properties of the curcumin which permit it to target the genome (DNA), messengers (RNA) and enzymes (proteins) within cells, actions that can be consecutive or instantaneous. Unlike other chemotherapeutic agents, curcumin exhibits pleiotropic properties that includes the modulation of nuclear factor-kappaB (NF-kB), transcription factor activator protein-1 (AP-1), tumor protein 53 (p53), mitogen-activated protein kinase (MAPK), nuclear b-catenin signaling and serine/threonine protein kinase (AKT) signalling pathways (Hatcher *et al.*, 2008). It also down regulates the expression of estrogen receptors and epidermal growth receptor that are cancer-associated growth factors (Kunnumakkara *et al.*, 2008). It has also been verified that it sensitizes tumor cells to first-line chemotherapies and radiation (Landis-Piwowar *et al.*, 2010; Page and Yang, 2010; Maher *et al.*, 2010). In cancer therapy development of multidrug resistance (MDR) causes minimal responses to regular cytotoxic agents and targeted biological therapies (Ejendal and Hrycyna, 2002; Loo and Clarke, 1999; Szakács *et al*., 2006). This result's due to over expression of ATP-binding cassette transporters, which performs as drug-efflux pumps involved in the aggressive exclusion of drug molecules from the cells, thereby reducing the intracellular levels of these therapeutic molecules. This mechanism can be overcome by curcumin treatment, which reduces P-glycoprotein (P-gp), breast cancer resistance protein (ABCG2) and multidrug resistance protein (MRP-1) expression (Um *et al.*, 2008).

4. Protection against Alzheimer's disease

Curcumin also provides protection against the most common cause of dementia: Alzheimer's disease. This disease is mainly characterized by the accumulation of amyloid-beta a malformed protein. generally, immune cells known as macrophages recognizes these defective proteins, engulf them, and kills them. In Alzheimer's disease macrophages proves incompitent to perform this crucial function (Fiala *et al.*, 2005).

CLCLUSION

The curcumin works by enhancing the clearance of amyloid-beta, and reducing fibrils, which are also associated with Alzheimer's pathology. Curcumin's ability of curcumin to cross the blood-brain barrier and to bind directly toplaques plays an important role in its anti-amyloid activity.

REFERENCES

Adams, B. K., Cai, J., Armstrong, J., Herold, M., Lu, Y. J., Sun, A., & Shoji, M. (2005). EF24, a novel synthetic curcumin analog, induces apoptosis in cancer cells via a redox-dependent mechanism. *Anti-cancer drugs*, *16*(3), 263-275.

Aggarwal, B. B., & Harikumar, K. B. (2009). Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. *The international journal of biochemistry & cell biology*, *41*(1), 40-59.

Aggarwal, B. B., & Sung, B. (2009). Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets. *Trends in pharmacological sciences*, *30*(2), 85-94.

Aggarwal, B. B., Bhatt, I. D., Ichikawa, H., Ahn, K. S., Sethi, G. S. S. K., Sandur, S. K., & Shishodia, S. (2007). Curcumin–biological and medicinal properties. *Turmeric: the genus Curcuma*, *45*, 297-368.

Aggarwal, B. B., Kumar, A., & Bharti, A. C. (2003). Anticancer potential of curcumin: preclinical and clinical studies. *Anticancer research*, *23*(1A), 363-398.

Aggarwal, B. B., Sundaram, C., Malani, N., & Ichikawa, H. (2007). Curcumin: the Indian solid gold. In *The molecular targets and therapeutic uses of curcumin in health and disease* (pp. 1-75). Springer US.

Anand, P., Thomas, S. G., Kunnumakkara, A. B., Sundaram, C., Harikumar, K. B., Sung, B., & Aggarwal, B. B. (2008). Biological activities of curcumin and its analogues (Congeners) made by man and Mother Nature. *Biochemical pharmacology*, *76*(11), 1590-1611.

Arun, N., & Nalini, N. (2002). Efficacy of turmeric on blood sugar and polyol pathway in diabetic albino rats. *Plant Foods for Human Nutrition*, *57*(1), 41-52.

Asai, A., & Miyazawa, T. (2000). Occurrence of orally administered curcuminoid as glucuronide and glucuronide/sulfate conjugates in rat plasma.*Life sciences*, *67*(23), 2785-2793.

Babu, P. S., & Srinivasan, K. (1995). Influence of dietary curcumin and cholesterol on the progression of experimentally induced diabetes in albino rat.*Molecular and cellular biochemistry*, *152*(1), 13-21.

Babu, P. S., & Srinivasan, K. (1997). Hypolipidemic action of curcumin, the active principle of turmeric (*Curcuma longa*) in streptozotocin induced diabetic rats. *Molecular and cellular biochemistry*, *166*(1-2), 169-175.

Cheng, A. L., Hsu, C. H., Lin, J. K., Hsu, M. M., Ho, Y. F., Shen, T. S., ... & Hsieh, C. Y. (2000). Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. *Anticancer research*,*21*(4B), 2895-2900.

Deodhar, S. D., Sethi, R., & Srimal, R. C. (1980). Preliminary study on antirheumatic activity of curcumin (diferuloyl methane). *The Indian journal of medical research*, *71*, 632-634.

Dikshit, M., Rastogi, L., Shukla, R., & Srimal, R. C. (1995). Prevention of ischaemia-induced biochemical changes by curcumin & quinidine in the cat heart. *Indian Journal of Medical Research*, *101*, 31-35.

Dikshit, M., Srivastava, R., Kar, K., & Srimal, R. C. (1987). Antithrombotic effect of some platelet modifying drugs. *Thrombosis research*, *46*(2), 397-403.

Ejendal, K. F., & Hrycyna, C. A. (2002). Multidrug resistance and cancer: the role of the human ABC transporter ABCG2. *Current Protein and Peptide Science*, *3*(5), 503-511.

Fiala, M., Lin, J., Ringman, J., Kermani-Arab, V., Tsao, G., Patel, A., & Bernard, G. (2005). Ineffective phagocytosis of amyloid-beta by macrophages of Alzheimer's disease patients. *Journal of Alzheimers Disease*, *7*(3), 221.

Ganpati, K. S., Bhaurao, S. S., Iranna, K. K., Dilip, C. R., & Nilkanth, Y. P. (2011). Comparative studies on curcumin content in fresh and stored samples of turmeric rhizomes. *IRJP*, *2*(4), 127-129.

Hatcher, H., Planalp, R., Cho, J., Torti, F. M., & Torti, S. V. (2008). Curcumin: from ancient medicine to current clinical trials. *Cellular and Molecular Life Sciences*, *65*(11), 1631-1652.

Holder, G. M., Plummer, J. L., & Ryan, A. J. (1978). The metabolism and excretion of curcumin (1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) in the rat. *Xenobiotica*, *8*(12), 761-768.

http:// en.wikipededia.org/ wiki/ curcumin.

Ireson, C. R., Jones, D. J., Orr, S., Coughtrie, M. W., Boocock, D. J., Williams, M. L., & Gescher, A. J. (2002). Metabolism of the cancer chemopreventive agent curcumin in human and rat intestine. *Cancer Epidemiology Biomarkers & Prevention*, *11*(1), 105-111.

Ireson, C., Orr, S., Jones, D. J., Verschoyle, R., Lim, C. K., Luo, J. L., & Gescher, A. (2001). Characterization of metabolites of the chemopreventive agent curcumin in human and rat hepatocytes and in the rat in vivo, and evaluation of their ability to inhibit phorbol ester-induced prostaglandin E2 production. *Cancer Research*, *61*(3), 1058-1064.

Jordan, W. C., & Drew, C. R. (1996). Curcumin--a natural herb with anti-HIV activity. *Journal of the National Medical Association*, *88*(6), 333.

Khopde, S. M., Priyadarsini, K. I., Venkatesan, P., & Rao, M. N. A. (1999). Free radical scavenging ability and antioxidant efficiency of curcumin and its substituted analogue. *Biophysical chemistry*, *80*(2), 85-91.

Kiefer, D. (2012). Novel turmeric compound delivers much more curcumin to the blood. *Life Extension Magazine*.

Kim, M. K., Choi, G. J., & Lee, H. S. (2003). Fungicidal property of Curcuma longa L. rhizome-derived curcumin against phytopathogenic fungi in a greenhouse. *Journal of agricultural and food chemistry*, *51*(6), 1578-1581.

Kiso, Y., Suzuki, Y., Watanabe, N., Oshima, Y., & Hikino, H. (1983). Antihepatotoxic principles of Curcuma longa rhizomes. *Planta med*, *49*(3), 185-187.

Kokate, C. K. (1993). Practical Pharmacognosy, Vallabh Prakashan. 4th ed., 138.

Kunnumakkara, A. B., Anand, P., & Aggarwal, B. B. (2008). Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. *Cancer letters*, *269*(2), 199-225.

Kuttan, R., Bhanumathy, P., Nirmala, K., & George, M. C. (1985). Potential anticancer activity of turmeric (*Curcuma longa*). *Cancer letters*, *29*(2), 197-202.

Landis-Piwowar, K. R., Milacic, V., Chen, D., Yang, H., Zhao, Y., Chan, T. H., & Dou, Q. P. (2006). The proteasome as a potential target for novel anticancer drugs and chemosensitizers. *Drug resistance updates*, *9*(6), 263-273.

Lao, C. D., Demierre, M. F., & Sondak V. K. (2006a). Targeting events in melanoma carcinogenesis for the prevention of melanoma. Expert ReV. Anticancer Therapy, 6 (11), 1559–1568.

Lao, C. D., Ruffin, M. T., Normolle, D., Heath, D. D., Murray, S. I., Bailey, J. M., & Brenner, D. E. (2006b). Dose escalation of a curcuminoid

formulation.*BMC complementary and alternative medicine*, *6*(1), 10.

Li, M., Zhang, Z., Hill, D. L., Wang, H., & Zhang, R. (2007). Curcumin, a dietary component, has anticancer, chemosensitization, and radiosensitization effects by down-regulating the MDM2 oncogene through the PI3K/mTOR/ETS2 pathway. *Cancer Research*, *67*(5), 1988-1996.

Loo, T. W., & Clarke, D. M. (1999). The human multidrug resistance P-glycoprotein is inactive when its maturation is inhibited: potential for a role in cancer chemotherapy. *The FASEB journal*, *13*(13), 1724-1732.

Maher, D., Yallapu, M. M., Sundram, V., Bell, M. C., Jaggi, M., & Chauhan, S. C. (2010). Curcumin induces chemo/radio-sensitization in ovarian cancer cells and curcumin nanoparticles inhibit ovarian cancer cell growth. *Cancer Research*, *70*(8 Supplement), 5381.

Motterlini, R., Foresti, R., Bassi, R., & Green, C. J. (2000). Curcumin, an antioxidant and anti-inflammatory agent, induces heme oxygenase-1 and protects endothelial cells against oxidative stress. *Free Radical Biology and Medicine*, *28*(8), 1303-1312.

Nirmala, C., & Puvanakrishnan, R. (1996a). Protective role of curcumin against isoproterenol induced myocardial infarction in rats. *Molecular and cellular biochemistry*, *159*(2), 85-93.

Nirmala, C., & Puvanakrishnan, R. (1996b). Effect of curcumin on cetrain lysosomal hydrolases in isoproterenol-induced myocardial infarction in rats. *Biochemical pharmacology*, *51*(1), 47-51.

Page, P., & Yang, L. X. (2010). Novel chemoradiosensitizers for cancer therapy. *Anticancer research*, *30*(9), 3675-3682.

Qureshi, S., Shah, A. H., & Ageel, A. M. (1992). Toxicity studies on *Alpinia galanga* and *Curcuma longa*. *Planta medica*, *58*(2), 124-127.

Reddy, R. C., Vatsala, P. G., Keshamouni, V. G., Padmanaban, G., & Rangarajan, P. N. (2005). Curcumin for malaria therapy. *Biochemical and biophysical research communications*, *326*(2), 472-474.

Ruby, A. J., Kuttan, G., Babu, K. D., Rajasekharan, K. N., & Kuttan, R. (1995). Anti-tumour and antioxidant activity of natural curcuminoids. *Cancer letters*, *94*(1), 79-83.

Ruby, A. J., Kuttan, G., Babu, K. D., Rajasekharan, K. N., & Kuttan, R. (1995). Anti-tumour and antioxidant activity of natural curcuminoids. *Cancer letters*, *94*(1), 79-83.

Schmidt, B. M., Ribnicky, D. M., Lipsky, P. E., & Raskin, I. (2007). Revisiting the ancient concept of botanical therapeutics. *Nature Chemical Biology*, *3*(7), 360-366.

Shankar, T. B., Shantha, N. V., Ramesh, H. P., Murthy, I. A., & Murthy, V. S. (1980). Toxicity studies on turmeric (*Curcuma longa*): acute toxicity studies in rats, guineapigs and monkeys. *Indian journal of experimental biology*, *18*(1), 73-75.

Sharma, O. P. (1976). Antioxidant activity of curcumin and related compounds. *Biochemical pharmacology*, *25*(15), 1811-1812.

Sharma, O. P. (1976). Antioxidant activity of curcumin and related compounds.*Biochemical pharmacology*, *25*(15), 1811-1812.

Shishodia, S., Sethi, G., & Aggarwal, B. B. (2005). Curcumin: getting back to the roots. *Annals of the New York Academy of Sciences*, *1056*(1), 206-217.

Shoba, G., Joy, D., Joseph, T., Majeed, M., Rajendran, R., & Srinivas, P. S. (1998). Log in with. *Planta med*, *64*(4), 353-356.

Srimal, R. C., & Dhawan, B. N. (1973). Pharmacology of diferuloyl methane (curcumin), a non-steroidal anti-inflammatory agent. *Journal of pharmacy and pharmacology*, *25*(6), 447-452.

Srinivasan, M. (1972). Effect of curcumin on blood sugar as seen in a diabetic subject. *Indian journal of medical sciences*, *26*(4), 269.

Sugiyama, Y., Kawakishi, S., & Osawa, T. (1996). Involvement of the β-diketone moiety in the antioxidative mechanism of tetrahydrocurcumin. *Biochemical pharmacology*, *52*(4), 519-525.

Sugiyama, Y., Kawakishi, S., & Osawa, T. (1996). Involvement of the β-diketone moiety in the antioxidative mechanism of tetrahydrocurcumin.*Biochemical pharmacology*, *52*(4), 519-525.

Suresh, D., & Srinivasan, K. (2010). Tissue distribution & elimination of capsaicin, piperine & curcumin following oral intake in rats.

Szakács, G., Paterson, J. K., Ludwig, J. A., Booth-Genthe, C., & Gottesman, M. M. (2006). Targeting multidrug resistance in cancer. *Nature reviews Drug discovery*, *5*(3), 219-234.

Um, Y., Cho, S., Woo, H. B., Kim, Y. K., Kim, H., Ham, J., & Lee, S. (2008). Synthesis of curcumin mimics with multidrug resistance reversal activities. *Bioorganic & medicinal chemistry*, *16*(7), 3608-3615.

Venkatesan, N. (1998). Curcumin attenuation of acute adriamyc in myocardial toxicity in rats. *British journal of pharmacology*, *124*(3), 425-427.

Venkatesan, N., Punithavathi, D., & Arumugam, V. (2000). Curcumin prevents adriamycin nephrotoxicity in rats. *British journal of pharmacology*, *129*(2), 231-234.

Zaveri, M., Gajjar, H., Kanaki, N., & Patel, S. (2011). Preparation and evaluation of drug phospholipid complex for increasing transdermal penetration of phytoconstituents. *International Journal of Institutional Pharmacy and Life sciences*, *1*(3), 80-93.

Zern, T. L., & Fernandez, M. L. (2005). Cardioprotective effects of dietary polyphenols. *The Journal of nutrition*, *135*(10), 2291-2294.