Curcumin: From Exotic Spice to Modern Anticancer Drug
Gaurisankar Sa*, Tanya Das, Shuvomoy Banerjee and Juni Chakraborty
Division of Molecular Medicine, Bose Institute, P-1/12 CIT Scheme VII M,
Kolkata-700054, India.

Abstract
Inhibition of defined molecular steps of tumourigenesis by natural non-toxic compounds may be an efficient means to tackle the population cancer burden. Extensive research has addressed the chemotherapeutic potential of curcumin (diferuloylmethane), a relatively non-toxic plant derived polyphenol. Curcumin is used for centuries in cuisine and indigenous medicine against several major human diseases. Cancer is the second leading cause of death worldwide. Disruption of a proper regulation of cell proliferation can ultimately cause cancer. Most human malignancies are driven by chromosomal translocations or other genetic alterations that directly affect the function of critical cell cycle proteins such as cyclins as well as tumor suppressors, e.g., p53. In this regard, curcumin, the yellow pigment of the spice turmeric, has been reported to have immense potentiality for being used in cancer chemotherapy because of its control over the cell growth regulatory mechanisms and for its anti-inflammatory, anti-toxic and anti-oxidative properties. Increasingly reports are showing that curcumin can induce apoptosis in a wide variety of cancer cells. The mechanisms implicated in the inhibition of tumorigenesis by curcumin are diverse and seem to involve a combination of cell signalling pathways at multiple levels. When curcumin is combined with some cytotoxic drugs or certain other diet-derived polyphenols, synergistic effects have been demonstrated. Taken together, this review seeks to summarise the unique properties of curcumin that may be exploited for successful clinical cancer prevention.

Key Words: Antioxidant; carcinogenesis; chemoprevention; phytochemical; nutraceutical.

Introduction
Over the past decade, there has been a significant increase in public and scientific interest in the beneficial effects of chemicals derived from plants, known as phytochemicals, and their role in the maintenance of health and prevention of disease. Polyphenols are amongst the lead chemical substances that fulfill this definition. Consequently, their potential preventive and therapeutic properties have been studied extensively. Polyphenols are derived from many components of the human diet, including peanuts, green and black tea, red wine, olive oil and the spice, turmeric. Many of these natural substances, which were traditionally utilized in ancient medicines for their anti-inflammatory and antioxidant actions, are now being investigated as cardioprotective, antiproliferative, and preventive agents. In particular, traditional agents derived from ancient Hindu medicine, such as curcumin from turmeric, chemically known as diferuloylmethane (C21H20O6), has been the subject of hundreds of published papers over the past three decades, studying its antioxidant, anti-toxic, anti-inflammatory, cancer chemopreventive and potentially chemotherapeutic properties [1-3]. Because curcumin has been shown to suppress cancer cell proliferation, induce apoptosis, inhibit angiogenesis, and suppress the expression of anti-apoptotic proteins while protecting immune system of the tumor bearer, it may have untapped therapeutic value [4-5]. With regard to the chemoprevention and therapy of many diseases, particularly cancer, this article aims
to review the extensive published literature on the use of the natural polyphenol, curcumin, as a single agent and in combinatorial chemoprevention and treatment. Basic searches of the most commonly internationally accessed scientific databases using the keywords “curcumin” and “turmeric” has demonstrated that over 2600 articles have been published in English language journals since 1966. The reader should note that whereas these reviews have generally focused on the potential role of phytochemicals to treat or prevent particular diseases, the purpose of this comprehensive review is to offer a broader perspective on the potential for curcumin to prevent or treat diverse human disease pathologies, particularly cancer.

**Curcumin:** Curcumin is a component of turmeric; the yellow spice derived from the roots (rhizomes) of the plant *Curcuma longa*. *Curcuma longa* is a short-stemmed perennial, which grows to about 100 cm in height (Figure-1). *Curcuma longa* grows naturally throughout the Indian subcontinent and in tropical countries, particularly South East Asia. A traditional remedy in “Ayurvedic medicine” and ancient Indian healing system that dates back over 5,000 years, turmeric has been used through the ages as an "herbal aspirin" and "herbal cortisone" to relieve discomfort and inflammation associated with an extraordinary spectrum of infectious and autoimmune diseases. The curcuminoids, which constitute approximately 5% of most turmeric preparations, are a mixture of curcumin (sometimes referred to as “Curcumin I”), desmethoxycurcumin (Curcumin II) and bisdesmethoxycurcumin (Curcumin III) [6]. Curcumin [chemical name: (E,E)-1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3, 5 dione] is a bis-α,β-unsaturated β-diketone. It has a molecular weight (MW) of 368.38 and chemical formula C21H20O6. Under physiological conditions, curcumin appears in both an enolate and a bis-keto form, which coexist in equilibrium (Figure-1).

**Crossroads of alternative and mainstream medicine:** Turmeric has been used for thousand of years in Ayurvedic and traditional Chinese medicine. In modern times, curcumin continues to be used as an alternative medicinal agent in many parts of South East Asia for the treatment of common ailments such as stomachic upset, flatulence, jaundice, arthritis, sprains, wounds and skin infections among many others. Curcumin and turmeric products have been
characterized as safe by health authorities such as the Food and Drug Administration in United States of America, Food and Agriculture Organization/World Health Organization. Curcumin has entered scientific clinical trials at the phase I and II level for its therapeutic efficacy [7]. A phase III study of gemcitabine, curcumin and celecoxib has recently started at the Tel-Aviv Sourasky Medical Center for patients with metastatic colorectal cancer.

Curcumin - the curry to cure cancer: Controlled cell cycle progression is an important biological event in normal cells, which almost universally becomes abnormal in transformed and neoplastic cells. In this regard, targeting deregulated cell cycle progression and its modulation by various natural agents are gaining widespread attention in recent years to restrict the uncontrolled growth and proliferation in cancer cells. In fact, a vast number of experimental studies convincingly show that many phytochemicals halt uncontrolled cell cycle progression in cancer cells [8]. Among these phytochemicals, curcumin has been identified as one of the major natural anticancer agents exerting anti-neoplastic activity in various types of cancer cells.

Mechanisms of action: Compatible with the range of activity, curcumin has been shown to affect many cellular and molecular pathways. The complexity of the pleiotropic activity of curcumin may account for its efficacy in combating human diseases such as cancer, which are usually multifactorial in nature and usually involve cellular or molecular defects at more than one level. The main molecular targets of curcumin appear to be gene expression, transcription factors, growth factors and their receptors, nuclear factors, hormones and hormone receptors. In cancer, such targets have been implicated in all stages of carcinogenesis (initiation,
promotion and progression). In Figure-2, some of the important biological properties of curcumin are listed. Figure-3 highlights some of the molecular targets of curcumin relevant to the therapy and prevention of cancer.

**Oncogenes and tumor suppressor genes:** Curcumin can alter the expression of genes involved in tumor growth and apoptosis, evident by the down regulation of the survival genes, early growth response-1 (egr-1), c-myc, bcl-2, Bcl-xL etc. and up-regulation of apoptotic genes, p53, bax, Bcl-xs etc. [9]. The tumor suppressor gene p53, acknowledged as the “guardian of genome”, is situated at the crossroads of a network of signaling pathways that are essential for cell growth regulation and apoptosis [10]. Under normal conditions, p53 inhibits proliferation and growth of cells with abnormal or damaged DNA, as seen in ageing and cancer. Mutations of this gene can be found in many cancers and may lead to resistance to chemotherapy treatments due to impaired p53-induced apoptosis [11]. In basal cell carcinoma, curcumin promotes de novo synthesis of p53 protein or some other proteins for stabilization of p53, and hence enhances its nuclear translocation to transactivate Cip1 and Gadd45 indicating that p53-associated signaling pathway is critically involved in curcumin-mediated apoptotic cell death. Curcumin has been found to block Mdm2- and E6-dependent p53 degradation [12].

With elegant time-lapse video-micrography and quantitative imaging approach we have demonstrated that in deregulated cyclin D1-expressing cells, curcumin induces p53 dramatically at G2 phase of cell cycle and enhances p53 DNA-binding activity [4,13] resulting in apoptosis at G2 phase. An interesting finding in this study was that curcumin appeared to be sparing the normal epithelial cells by arresting them at the G0 phase of the cell cycle via down-regulation of cyclin D1 and its related protein kinases (Cdk4/Cdk6) or up-regulation of the inhibitory protein p21Waf-1. In cancer cells where cyclin D1 was overexpressed, curcumin down-regulates cyclin D1
expression through activation of both transcriptional and post-transcriptional mechanisms, and this may contribute to the antiproliferative effects of curcumin [14]. Works from our laboratory as well as from other laboratories suggest that curcumin predominantly acts in a p53-dependent manner as careful analysis of the effect of curcumin in various cells expressing wild-type or mutated p53 as well as cells transfected with dominant-negative p53, revealed that the cells expressing high levels of wild-type p53 were more sensitive to curcumin toxicity [4]. On the other hand, p53-knock out as well as p53-mutated cells also showed toxicity; although the apoptotic-index is lower [13]. Search for downstream of p53 revealed that curcumin could increase the expression of the pro-apoptotic protein Bax and decrease the anti-apoptotic protein Bcl-2 and Bcl-xL through the phosphorylation at Ser15 and activation of p53. On the other hand, c-Abl, a non-receptor tyrosine kinase, has been reported to play an important role in curcumin-induced cell death through activation of JNK and induction of p53 [15]. Other potential targets of curcumin are oncoproteins implicated in carcinogenesis, such as beta-catenin, which is often over-expressed in cancers and regulates transcription of genes such as T-cell factor, lymphoid enhancer factor and c-myc [16-17]. In a recent study, it was demonstrated that curcumin may execute its anticancer activity by blocking the mammalian target of rapamycin (mTOR) [18], which regulates translation and cell division and enhances growth by stimulating cells to pass from G1 to S phase of the cell cycle.

All these reports indicate that curcumin can induce cancer cell killing predominantly via p53-mediated pathway, p53 not only controls apoptotic pathways but also acts as a key cell cycle regulatory protein as it can transactivate cell cycle inhibitors like p21Waf-1 on the event of DNA damage and when the damage is irreparable it induces apoptosis by inducing the expression of pro-apoptotic proteins like Bax (Figure-4). So far our discussion thus clearly

© 2010, Al Ameen Charitable Fund Trust, Bangalore
indicates the involvement of the guardian of genome, p53, in curcumin-induced cancer cell apoptosis and cell cycle regulation.

**Nuclear factors:** An example of a cellular target with a central role in the pathogenesis of multiple pathogeneses, particularly cancer and inflammatory disease, is the cell survival-signaling transcription factor, nuclear factor kappa B (NF-κB). Under normal conditions, NF-κB is sequestered and bound in the cytoplasm by inhibitory proteins called IκBs. The IκB kinase (IKK) phosphorylates IκBs, resulting in degradation of IκB so that NF-κB is released and can translocate to the nucleus, where it stimulates the transcription of many of the key genes responsible for inflammation, proliferation, invasion, metastasis and inhibition of apoptosis. NF-κB activation results in transcriptional activation of cyclin D1, Bcl-2 and Bcl-XL proteins, matrix metalloproteinases, growth factor receptors, survivin, inducible nitric oxide synthase (iNOS), interleukins, activator protein-1 (AP-1), heme oxygenase-1 (HO-1) and many others which links between the pathogenesis of many malignant, inflammatory and degenerative conditions. Curcumin is a strong suppressor of NF-κB activation by inhibiting the activity of IKK and preventing the phosphorylation of IκB and the subsequent translocation of NF-kB to the nucleus [19]. Inhibition of NF-κB activation by curcumin is implicated as a mechanism by which curcumin suppresses the induction of *cox-2* gene expression, resulting in inhibition of the transcription of Cox-2 protein [20].

Curcumin cause direct suppression of the activator protein-1 (AP-1), which regulates genes responsible for cell apoptosis and proliferation such as *cyclin D1, p53, p21* and *i6* genes [21-22]. Suppression of AP-1 has been linked with anti-carcinogenesis and tumor anti-angiogenesis [23]. Recently, it has been postulated that curcumin upregulates nuclear factor erythroid 2-related factor 2 (Nfr-2) and promotes increased Nfr-2 binding to antioxidant response elements (ARE) which mediates induction of phase 2 detoxifying and antioxidant enzymes, including glutathione-S-transferase (GST), NAD(P)H:quinone oxidoreductase and heme oxygenase-1 (HO-1).  

**Growth factor receptors and protein kinases:** Curcumin can also interfere with the activation of other key cellular mediators involved in cancer and inflammation. This yellow pigment stimulates the activity of peroxisome proliferator-activated receptor γ (PPAR-γ), which mediates the suppression of gene expression of *cyclin D1* and the epidermal growth factor receptor (*EGFR*) and induces cell differentiation and cell cycle arrest [24]. Curcumin also appeared to inhibit the Akt/PI3K pathway, which transmits signals received by the EGFR [25-26]. A recent study in human colon cancer-derived cell lines has shown that curcumin inhibits cell growth by interference with the EGFR signaling pathway via downregulation of egr-1 [27]. Curcumin has also been shown to suppress the mitogen activating protein (MAP) kinases pathway, which includes p42/p44 MAP kinases, c-Jun N-terminal kinases and p38 MAP kinases [28-29]. Inhibition of PKC function by curcumin has been documented in several independent studies [30]. Curcumin inactivates Protein kinase C by reacting with the vicinal thiols of its catalytic domain.
**Anti-carcinogenic activity:** Carcinogenesis is the complex process by which normal cells develop into a malignant tumor. In traditional descriptions, it has been divided into 3 stages: *initiation*, during which normal cells become transformed, *promotion* where transformed cells become preneoplastic and *progression*, which is the final step when the preneoplastic cells become neoplastic [31]. The ability of curcumin to induce apoptosis in cancer cells without cytotoxic effects on healthy cells contributes to the understanding of the anti-cancer potential of curcumin. Curcumin can interfere in the described processes of carcinogenesis by inhibiting the initiation step or suppressing the promotion and progression stages. Curcumin has been shown to have effects relevant to all three stages of carcinogenesis. Oral curcumin administration has been shown to prevent the development of cancers of the skin, soft palate, stomach, duodenum, colon, liver, lung, and breasts of rodents [32]. Inhibition of initiation has been demonstrated in chemical models, incorporating the measurement of DNA adducts formed by benzo[α]pyrene or by aflatoxin B1, which have been linked with this stage of carcinogenesis [33]. Chemical models of the promotion and progression of colon cancer have also been used to study the effects of oral curcumin. In mice model curcumin inhibits colon tumorigenesis in the initiation and the promotion/progression stages [34]. Other than cancer of GI tract, curcumin has been reported to enhance TNF-α-induced apoptosis in prostate cancer cells [35]. In fact, curcumin induces apoptosis in both androgen-dependent and androgen-independent prostate cancer cells [36]. Topical application of curcumin has been also shown to inhibit the initiation and promotion stages of chemically induced skin cancer [37].

**Effects on angiogenesis and cell adhesion:** It has been well known for more than half a century that angiogenesis is linked to neoplasia [38]. Angiogenesis, meaning the formation of new vessels, is generally considered to be a crucial step in tumor survival and growth beyond a certain size (about 1-2 mm in diameter) [39]. Tumors produce growth factors that stimulate vasculature formation, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor and epidermal growth factor (EGF). The density of the vasculature and the intensity of angiogenesis act as prognostic factors for many solid tumors. Curcumin may inhibit angiogenesis directly and via regulation of these angiogenic growth factors, as well as the genes, *angiopoietin 1* and 2, *HIF-1*, *HO-1*, and the transcriptional factors like NF-κB. It is known that hypoxic stress and transforming growth factor–β activation induces VEGF expression through transcriptional activation of AP-1 and Hypoxia-inducible factor-1 (HIF-1) [40]. Curcumin is a potent inhibitor of AP-1 activation and recently it has also been found that curcumin is a direct inhibitor of the activity of the HIF-1 transcriptional factor [41], which induces transcription of many genes involved in angiogenesis in tumors. Inhibition of angiogenic growth factor production and metalloproteinase generation, both integral to the formation of new vasculature, has also been influenced by curcumin in non-malignant and malignant cells growth [42-43]. Curcumin can thus interfere with tumor survival, metabolism and progression [44].
Cancer progression, local invasion and metastasis also require the involvement of molecules produced by the tumor or via its interaction with the surrounding matrix. These molecules influence cellular interaction and adhesion. Similar to the inhibition of angiogenic factors, curcumin has been shown to regulate proteins related to cell-cell adhesion, such as β-catenin, E-cadherin and APC and to inhibit the production of cytokines relevant to tumor growth, e.g. tumour necrosis factor-α (TNF-α) and interleukin-1 [45-46]. Additionally, curcumin has been shown to reduce the expression of membrane surface molecules such as intracellular adhesion molecule-1, vascular cell adhesion molecule-1 and E-selectin that play a role in cellular adhesion [47]. This effect was achieved via inhibition of gene expression at a transcriptional level. Collectively, these results pertaining to direct and indirect inhibition of angiogenesis and attenuation of cell-cell adhesion necessary for malignant behavior render curcumin a promising agent for altering the invasive and metastatic behavior of established malignancy.

**Immunomodulator:** Curcumin has been shown to have immunomodulatory effects, including activation of host macrophages and natural killer (NK) cells and modulation of lymphocyte-mediated functions [48]. Studies from our laboratory showed that curcumin neutralized tumor-induced oxidative stress, restored back NF-kB activity, and inhibited TNF-α production, thereby minimizing tumor-induced T-cell apoptosis [5]. Further work suggests that curcumin helps in T cell survival both in primary and effector immune compartments of tumor-bearing hosts by normalizing perturbation of Jak-3/Stat-5 activity via restoration of IL2-receptor γc chain expression [5]. Curcumin was found to prevent tumor-induced loss of T-effector cells, reverse type-2 cytokine bias and blocks T-regulatory cell augmentation in tumor-bearing hosts via down-regulation of TGF-β in cancer cells (Bhattacharyya et al. unpublished data). From all these observations it is suggested that curcumin may be used alone or can be combined with classical anti-tumor drugs so as to sustain the immune capacity of the host, which can be affected by the disease or the treatment or may be the both.

**Anti-oxidant:** Oxidative stress and oxidative damage are involved in the pathophysiology of many cancers. The generation of reactive oxygen species (ROS) induced activation of AP-1 play pivotal roles in the development of cancer. Consequently, “quenching” of activated oxygen species or preventing the cellular damage they cause to proteins and DNA is an important mechanism to potentially prevent diseases like cancer. An early study in rat peritoneal macrophages grown in vitro demonstrated impairment of reactive oxygen species generation by curcumin [49]. Curcumin has also been shown to scavenge superoxide anion radicals and hydroxyl radicals [50-51]. Similar to other dietary phytochemicals, curcumin may possess pro-oxidant activity or antioxidant effects, dependent on dose and the chemical environment [52]. The balance between anti-oxidant and pro-oxidant activity has to be carefully considered when planning intervention trials in healthy volunteers, particularly if pro-oxidant activity results in potentially damaging effects, as suggested by biomarkers such as oxidative DNA adduct levels [53]. Nitric oxide (NO) is a short-lived, lipophilic molecule generated by enzymes called NO synthases.
Its bioactivity is related to the production of many reactive intermediates. Some of these nitrogen species intermediates can damage DNA directly or interfere with DNA repair via protein damage [54-55]. It has been shown that curcumin strongly inhibits lipopolysaccharide-induced iNOS gene expression [56]. In clinical studies of colorectal cancer patients, orally administered curcumin have achieved pharmacologically active levels in the colorectum, associated with a decline in oxidative DNA adducts in colorectal tumours [57].

Detoxifyer: One of the body’s cellular defence mechanisms against environmental toxicants, drugs, carcinogens or xenobiotics occurs via metabolism of potentially toxic agents by metabolising enzymes. The phase I enzymes consist of cytochrome P450 isoforms, the P450 reductase, the cytochrome b5 and the epoxide hydrolase. The phase II enzymes include glutathione-S-transferase (GST), aryl sulfatase, UDP-glucuronic transferase and NAD(P)H:quinone reductase [58]. Inhibition of the phase I enzymes system may protect organisms from the toxic effects of chemicals and carcinogens. In a mammary carcinoma cell line, curcumin’s inhibition of cytochrome P450-mediated activation of dimethylbenzanthracene resulted in diminished DNA adduct formation, providing an indication of its protective role against carcinogens [59]. Induction of these detoxifiers is believed to confer benefit in the prevention of the early stages of carcinogenesis. Epoxide hydrolase (EH) and various hepatic GST isoenzymes were significantly increased upon curcumin feeding in mice [60]. The ability of curcumin to induce phase II enzymes appears to be associated with the presence of the hydroxyl groups at ortho-positions on the aromatic rings and the β-diketone functionality [61]. Though glutathione (GSH) plays a protective role against toxins, carcinogens and reactive oxygen species, it may also be linked with multidrug resistance through its spontaneous reactions with drugs as a co-factor for GST isoenzymes. In contrast to the early stages of carcinogenesis in advanced tumors, GST isoenzymes (π, α and µ) are aberrantly over-expressed and linked with resistance to chemotherapy [62]. In contrast to total induction of GST activity, curcumin appears to be capable of inhibiting specific GST isoenzymes [63-64]. In these studies of GST isoenzymes, there was a linear association between the level of inhibition by curcumin and the induction of apoptosis.

Safety and Toxicity: Although curcumin and turmeric are natural products used in the diet, the doses administered in clinical trials exceed those normally consumed in diet. This fact underlines the need for systematic safety and toxicity studies. Turmeric is generally recognized as safe by the USA-FDA and curcumin has been granted an acceptable daily intake level of 0.1-3 mg/kg body-weight by the Joint FAO/WHO Expert Committee on Food Additives 1996. Anecdotal reports suggest that dietary consumption of curcumin up to 150 mg/day is not associated with any adverse effects in humans [3]. In India, where the average intake of turmeric can be as high as 2.0-2.5 g per day (corresponding to approximately 60-100 mg of curcumin daily), no toxicities or adverse effects have been reported at the population level [65]. More recently, no toxicity has been observed in a preclinical study of the administration of 2% dietary curcumin (approximately 1.2 g/kg body-weight) to rats for 14 days [66]. In a study performed in India, administration of 1.2 to 2.1 g of oral curcumin to
patients with rheumatoid arthritis daily for 2 - 6 weeks did not cause any toxicity [67]. In another study of high dose oral curcumin by Cheng and colleagues in Taiwan, administration of up to 8 g daily of curcumin for 3 months to patients with pre-invasive malignant or high-risk pre-malignant conditions had no adverse effects [68]. In a phase I clinical trial of oral curcumin in patients with advanced colorectal cancer in which US National Cancer Institute criteria were used to assess potential toxicity, curcumin was well tolerated at all dose levels up to 3.6 g daily for up to 4 months [69]. Although turmeric is often used to treat inflammatory skin conditions in traditional South East Asian medical systems, it should be noted that a few reports of allergic dermatitis after contact with curcumin have been published in the scientific literature [70-71].

Synergy with other anti-cancer drugs: Potentially beneficial interactions between diet-derived polyphenols and other drugs and between individual components of the human diet have been identified. The combination of curcumin and genistein appears to inhibit growth of human breast MCF-7 cells synergistically compared to growth inhibition by each agent individually [72]. Treatment of normal oral epithelium, dysplastic leukoplakia and squamous cell carcinoma cell lines with curcumin and EGCG alone or their combination demonstrated synergistic growth inhibition, probably because these two phytochemicals block different phases of the cell cycle [73]. These findings have not been borne out by a study of the combination of curcumin with the pro-differentiation agent, all-trans retinoic acid human promyelocytic leukaemia HL-60 cells. In this study, combination treatment resulted in synergistic inhibition of the proliferation of the cells studied as well as improved induction of differentiation of these premalignant cells, both regarded as favorable effects [74].

Several investigators have studied the combination of curcumin with cytotoxic agents commonly used to treat cancer to look for additive or synergistic activity in cell kill. In a study in human colon cancer cell lines, curcumin was combined with 5-fluouracil (5-FU) to demonstrate synergistic inhibitory effects on the growth of the cancer cells in vitro, associated with reduced expression of Cox-2 protein [75]. When curcumin was co-administered with doxorubicin we observed significantly less manifestations of cardiotoxicity, measured via lesser rises of B-type natriuretic peptide mRNA level in the ventricles of the heart and lactate dehydrogenase levels in serum, than animals not receiving curcumin (unpublished data). The authors speculated that curcumin may therefore be of value to patients at risk of cardiotoxicity from high doses of anthracycline drugs. To summarize these diverse reports of combinations with cytotoxic agents, curcumin may have a role in improving the therapeutic index of drugs used routinely in the chemotherapy of cancer; either by increasing cell death in tumors or by protecting against oxidative damage induced in normal tissues.

Pharmacokinetic of Curcumin: The pharmacokinetic properties of curcumin have been studied in rodent models. When administered orally, about 75% of the curcumin was excreted in the feces and only about 35% was excreted unchanged, the remaining 65% excreted as metabolites of curcumin. Curcumin is first
Biotransformed to dihydrocurcumin and tetrahydrocurcumin, and that these compounds are subsequently converted to monoglucuronide conjugates [76] and this metabolic reduction occurred very rapidly. In contrast to the extensive studies in rodent model, less pharmacokinetic data is available from human studies. Shoba and colleagues observed low curcumin concentrations in the serum 1h post-administration of curcumin to fasting volunteers, but when 1% piperine was co-administered, bioavailability of curcumin was increased to 2000% in the serum [77]. A daily oral dose of 3.6 g of curcumin has been shown to be compatible with detectable levels of curcumin in colorectal tissue and in urine. Presence of curcumin and its metabolites in the urine offers a reliable and convenient way of potentially testing the compliance of volunteers consuming curcumin in clinical trials. Since curcumin’s poor systemic bioavailability following oral dosing compromises its potential therapeutic uses, many groups have focused on ways to improve its bioavailability. Co-administration of oral curcumin with piperine appeared to increase serum concentrations of curcumin. In more recent studies, other researchers have tried to increase curcumin’s systemic bioavailability by the application of novel delivery systems. Although systematic preclinical pharmacokinetic data are currently lacking, several research groups are currently studying liposomal formulations of curcumin in the hope that they may permit greater systemic biological effectiveness than the parent compound.

Conclusion

Curcumin: A multi-aged sword: Curcumin has been a part of the human diet since long and the subject of hundreds of published papers over the past three decades, studying its antioxidant, anti-toxic, anti-inflammatory, cancer chemopreventive properties. Given that disruption of cell cycle plays a crucial role in cancer progression, its modulation by curcumin seems to be a logical approach in controlling carcinogenesis. Most of the plant products with anti-cancer activity are effective modulators of protein kinases/phosphatases that are associated with cell cycle regulation. The broad biological activity of this phytochemical including influence upon key signal transduction pathways of cell cycle and effectiveness in animal model systems have fostered development of translational, and clinical research programs. Due to failure of conventional chemotherapy in advance stages of cancer and its enormous adverse effects, this phytochemicals could be developed as preventive and alternative medicine. There is a hope that in years to come, cancer chemoprevention by this phytochemical in a defined molecular target approach will play an important role in reducing cancer incidence as well as the number of deaths caused by this disease.

Prospects for the Future: Phase-I clinical trials have shown that curcumin is safe even at high doses (12 g/day) in humans but exhibit poor bioavailability. Major reasons contributing to the low plasma and tissue levels of curcumin appear to be due to poor absorption, rapid metabolism, and rapid systemic elimination. To improve the bioavailability of curcumin, numerous approaches have been undertaken like the use of piperine that interferes with glucuronidation, the use of liposomal curcumin; curcumin nanoparticles; curcumin phospholipid complex; and structural analogues of
curcumin. The therapeutic efficacy of curcumin against various human diseases, including cancer, cardiovascular diseases, diabetes, arthritis, and neurological diseases has been documented. Enhanced bioavailability of curcumin in the near future is likely to bring this promising natural product to the forefront of therapeutic agents for treatment of human disease. Previous seminal work, summarized above has demonstrated curcumin-mediated inhibition of key molecular mechanisms of tumorigenesis. Major advances in the understanding of cell cycle regulation mechanisms provided a better knowledge of the molecular interactions involved in human cancer. Further mechanistic work however, is required to investigate curcumin effects on switches that connect common effector pathways that regulate cell behavior, cell death and lineage commitment. Human intervention studies of curcumin, whether alone or in combination, are indicated against intermediate biomarkers and morphological stages of gastrointestinal tumorigenesis. Dietary curcumin could thus provide a useful component of dietary or pharmacological treatment aimed at reduction of the incidence of and mortality from gastrointestinal or colorectal cancer.

Acknowledgement
This work was supported by research grants from DST and ICMR, Govt. of India.

References


© 2010, Al Ameen Charitable Fund Trust, Bangalore


© 2010. *Al Ameen Charitable Fund Trust, Bangalore*

All Correspondences to: Prof. Gaurisankar Sa, Division of Molecular Medicine, Bose Institute, P-1/12 CIT Scheme VII M, Kolkata 700 054, India, E-mail: gauri@bic.boseinst.ernet.in