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Curcumin: From Exotic Spice to Modern Anticancer Drug

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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 potentialility 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 ($C_{21}H_{20}O_6$), 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 focussed 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).

Turmeric Plant with Rhizome

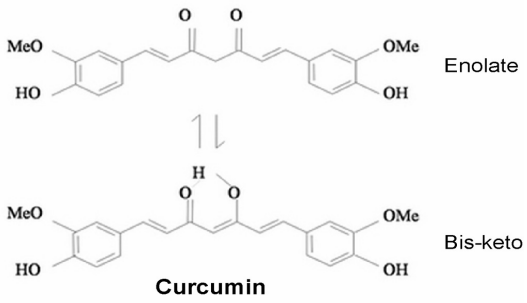

Fig 1 :*cuma longa* Plant and chemical structure of curcumin, the active ingradient of rhizome termeric.The tautomerism of curcumin is demonstrated under different physiological conditions. Under acidic and neutral conditions, the bis-keto form (bottom) is more predominant than the enolate form.

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? are gaining widespread attention in recent years to restrict the unontrolled 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,

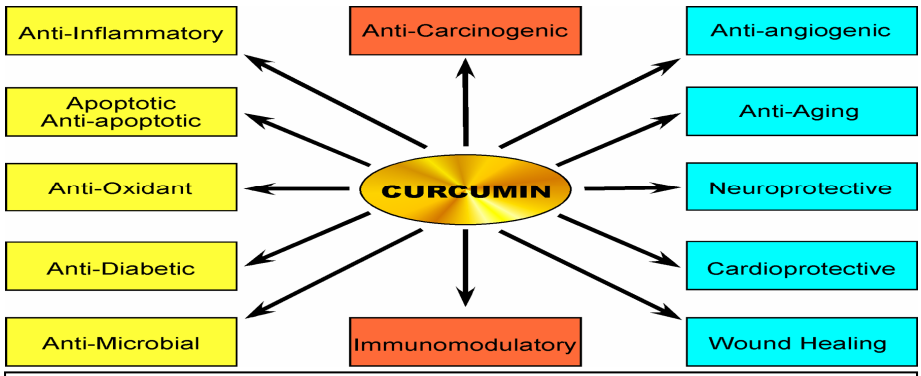

Figure-2. Biological activities of curcumin. Some biological activities of curcumin biological relevance demonstrated in preclinical models and in human studies are shown to illustrate the wide-ranging potential of curcumin to treat human diseases.

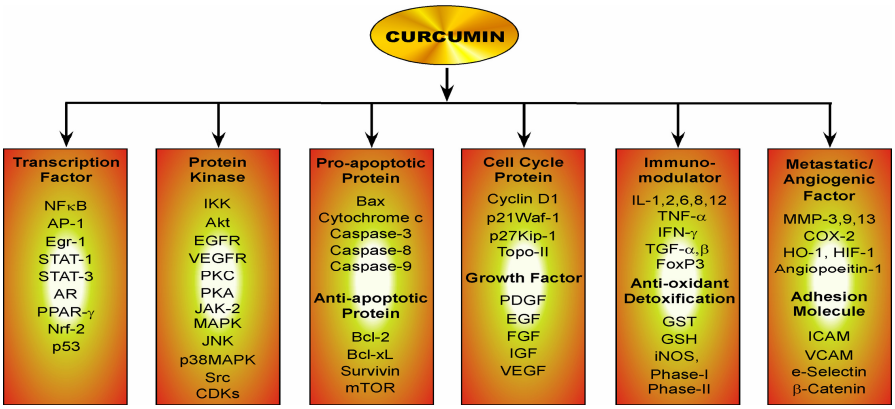

Fig-3. Molecular targets of curcumin. Curcumin enhances apoptotic death, inhibits cellular proliferation, dedifferentiation and progression towards the neoplastic phenotype by altering key signaling molecules required for cell cycle progression. Such a network organization allows the cell to sense many aspects of the intracellular and extra-cellular milieu, yet ensures that cell death proceeds efficiently once activated. Excessive oncogenic signaling is coupled to apoptosis by a complex mechanism that targets key control points in the pathways.

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 p21*Waf-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.

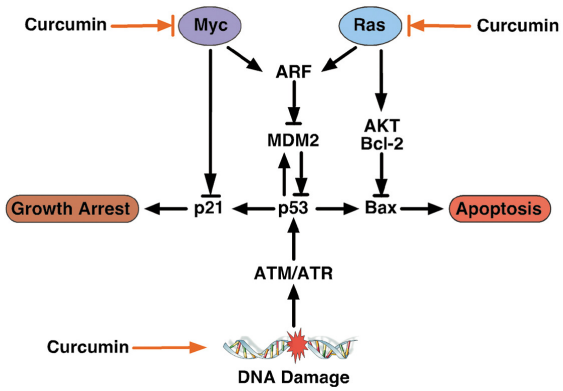

Fig 4 The p53 circuit in tumour development and therapy. Activation of Myc and Ras engage tumor-suppressor network at many points, including through the ARF-p53 circuit. Myc activates p53 to promote apoptosis while interfering with its ability to induce growth arrest by p21. Conversely, Ras activates p53 to promote growth arrest while suppressing apoptosis. This simplified view helps explain why, despite the potential of p53 to control several processes; apoptosis is primarily responsible for p53-mediated tumor suppression. DNA damage and oncogene signaling engage the tumor-suppressor network at different points and, as such, DNA-damage signaling relies more on p53 than on ARF to elicit an anti-proliferative response. Such a model explains why loss of ARF or p53 confers similar advantages during Myc-induced tumorigenesis but not following treatment with DNA-damaging drugs such as curcumin. Here, drug resistance is an unselected trait conferred by p53 mutations that provides a unique advantage as the tumor encounters a new environment (e.g., chemotherapy).

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 p21*Waf-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

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, resulted 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 *cyclin D1, p53, p21* and *16* 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–beta activation induces VEGF expression through trascriptional 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 trascriptional 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 effecter 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

(NOS). 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.

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References

1. Pal S, Bhattacharya S, Choudhuri T, Datta GK, Das T, Sa G. Amelioration of immune cell number depletion and potentiation of depressed detoxification system of tumor-bearing mice by curcumin. *Cancer Detection Prevention.,* 29: 470-478, 2005.
2. Sa G, Das T. Anti cancer effects of curcumin: cycle of life and death. *Cell Division*, 3: 14, 2008.
3. Pal S, Choudhuri T, Chattopadhyay S, Bhattacharya A, Datta G, Das T, Sa G. *Biochem. Biophys. Res. Commun.,* 288: 658-665, 2001.
4. Choudhuri T, Pal S, Das T, Sa G. Curcumin selectively induces apoptosis in deregulated cyclin D1-expressed cells at G2 phase of cell cycle in a p53-dependent manner. *J. Biol. Chem*., 280: 20059-20068, 2005.
5. Bhattacharyya S, Mandal D, Sen GS, Pal S, Banerjee S, Lahiry L, Finke JH, Tannenbaum CS, Das T, Sa G. Tumor-induced oxidative stress perturbs nuclear factor-kappaB activity-augmenting tumor necrosis factor-alpha-mediated T-cell death: protection by curcumin. *Cancer Res.,* 67: 362-70, 2007.
6. Kiuchi F, Goto Y, Sugimoto N, Akao N, Kondo K, Tsuda Y. Nematocidal activity of turmeric: synergistic action of curcuminoids. *Chem Pharm Bull (Tokyo).*, 41: 1640-3, 1993.
7. Kunnumakkara AB, Anand P, Aggarwal BB. Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. *Cancer Lett*., 2008. [Epub ahead of print]
8. Singh RP, Agarwal R. Natural flavonoids targeting deregulated cell cycle progression in cancer cells. *Curr Drug Targets*., 7: 345-54, 2006.
9. Sen S, Sharma H, Singh N. Curcumin enhances Vinorelbine mediated apoptosis in NSCLC cells by the mitochondrial pathway. *Biochem Biophys Res Commun.,* 331: 1245-52, 2005.

10. Lim YP, Lim TT, Chan YL, Song AC, Yeo BH, Vojtesek B, Coomber D, Rajagopal G, Lane D. The p53 knowledgebase: an integrated information resource for p53 research. *Oncogene.,* 26: 1517-21, 2007.
11. Scata KA, El-Deiry WS. p53, BRCA1 and breast Cancer chemoresistance. Adv Exp Med Biol., 608: 70-86. 2007.
12. Bech-Otschir D, Kraft R, Huang X, Henklein P, Kapelari B, Pollmann C, Dubiel W. COP9 signalosome-specific phosphorylation targets p53 to degradation by the ubiquitin system. *EMBO J.*, 20: 1630-9, 2001.
13. Choudhuri, T, Pal, S, Agwarwal, ML, Das, T, Sa, G. Curcumin induces apoptosis in human breast cancer cells through p53-dependent Bax induction. *FEBS Lett*., 512: 334–340, 2002.
14. Mukhopadhyay A, Banerjee S, Stafford LJ, Xia C, Liu M, Aggarwal BB. Curcumin-induced suppression of cell proliferation correlates with down-regulation of cyclin D1 expression and CDK4-mediated retinoblastoma protein phosphorylation. *Oncogene.,* 21: 8852-61, 2002.
15. Kamath R, Jiang Z, Sun G, Yalowich JC, Baskaran R. c-Abl kinase regulates curcumin-induced cell death through activation of c-Jun N-terminal kinase. *Mol Pharmacol.,* 71: 61-72. 2007.
16. Jaiswal, AS, Marlow, BP, Gupta, N, Narayan, S. Beta-catenin-mediated transactivation and cell-cell adhesion pathways are important in curcumin (diferuylmethane)-induced growth arrest and apoptosis in colon cancer cells. *Oncogene*,. 21: 8414-8427, 2002.
17. Park CH, Hahm ER, Park S, Kim HK, Yang CH. The inhibitory mechanism of curcumin and its derivative against beta-catenin/Tcf signaling. *FEBS Lett.,* 579: 2965-71, 2005.
18. Beevers CS, Li F, Liu L, Huang S. Curcumin inhibits the mammalian target of rapamycin-mediated signaling pathways in cancer cells. *Int J Cancer* 119: 757-64, 2006.
19. Singh S, Aggarwal BB. Activation of transcription factor NF-kappa B is suppressed by curcumin (diferuloylmethane). *J Biol Chem.,* 270: 24995-5000, 1995.
20. Plummer SM, Holloway KA, Manson MM, Munks RJ, Kaptein A, Farrow S, Howells L. Inhibition of cyclo-oxygenase 2 expression in colon cells by the chemopreventive agent curcumin involves inhibition of NF-kappaB activation via the NIK/IKK signalling complex. *Oncogene.,* 18: 6013-20, 1999.
21. Divya CS, Pillai MR. Antitumor action of curcumin in human papillomavirus associated cells involves downregulation of viral oncogenes, prevention of NFkB and AP-1 translocation, and modulation of apoptosis. *Mol Carcinog.,* 45: 320-32, 2006.
22. Eferl R, Wagner EF. AP-1: a double-edged sword in tumorigenesis. *Nat Rev Cancer.,* 3: 859-68, 2003.
23. Shih SC, Claffey KP. Role of AP-1 and HIF-1 transcription factors in TGF-beta activation of VEGF expression. *Growth Factors.,* 19: 19-34, 2001.
24. Chen A, Xu J. Activation of PPAR{gamma} by curcumin inhibits Moser cell growth and mediates suppression of gene expression of cyclin D1 and EGFR. *Am J Physiol Gastrointest Liver Physiol.*, 288: G447-G456, 2005.
25. Hussain AR, Al-Rasheed M, Manogaran PS, Al-Hussein KA, Platanias LC, Al KK, Uddin S. Curcumin induces apoptosis via inhibition of PI3'-kinase/AKT pathway in acute T cell leukemias. *Apoptosis.,* 11: 245-54, 2006.

26. Woo JH, Kim YH, Choi YJ, *et al*. Molecular mechanisms of curcumin-induced cytotoxicity: induction of apoptosis through generation of reactive oxygen species, down-regulation of Bcl-XL and IAP, the release of cytochrome c and inhibition of Akt. *Carcinogenesis.,* 24: 1199-208, 2003.
27. Chen A, Xu J, Johnson AC. Curcumin inhibits human colon cancer cell growth by suppressing gene expression of epidermal growth factor receptor through reducing the activity of the transcription factor Egr-1. *Oncogene.,* 25: 278-87, 2006.
28. Collett GP, Campbell FC. Curcumin induces c-jun N-terminal kinase-dependent apoptosis in HCT116 human colon cancer cells. *Carcinogenesis,* 25: 2183-9, 2004.
29. Javvadi P, Segan AT, Tuttle SW, Koumenis C. The chemopreventive agent curcumin is a potent radiosensitizer of human cervical tumor cells via increased reactive oxygen species production and overactivation of the mitogen-activated protein kinase pathway. *Mol Pharmacol*., 73: 1491-501, 2008
30. Liu JY, Lin SJ, Lin JK. Inhibitory effects of curcumin on protein kinase C activity induced by12-O-tetradecanoyl-phorbol-13-acetate in NIH 3T3 cells. *Carcinogenesis* 14: 857-61, 1993.
31. Brennan MJ. Endocrinology in cancer of the breast. Status and prospects. *Am J Clin Pathol*., 64: 797-809, 1975.
32. Rao CV, Rivenson A, Simi B, Reddy BS. Chemoprevention of colon carcinogenesis by dietary curcumin, a naturally occurring plant phenolic compound. *Cancer Res.,* 55: 259-66, 1995.
33. Sharma RA, Farmer PB. Biological relevance of adduct detection to the chemoprevention of cancer. *Clin Cancer Res.,* 10: 4901-12, 2004.
34. Kawamori T, Lubet R, Steele VE, Kelloff GJ, Kaskey RB, Rao CV, Reddy BS. Chemopreventive effect of curcumin, a naturally occurring anti-inflammatory agent, during the promotion/progression stages of colon cancer. *Cancer Res.,* 59: 597-601, 1999.
35. Deeb, D., Xu, Y.X., Jiang, H., *et al.* Curcumin (Diferuloyl-Methane) enhances tumor necrosis factor-related apoptosis-inducing ligand-induced apoptosis in LNCaP prostate cancer cells. *Mol. Cancer Ther*., 2: 95-103,2003.
36. Dorai, T., Gehani, N., Katz, A. Therapeutic potential of curcumin in human prostate cancer- I. Curcumin induces apoptosis in both androgen-dependent and androgen independent prostate cancer cells. *Prostate Cancer Prostatic. Dis*., 3: 84-93, 2000.
37. Huang MT, Newmark HL, Frenkel KJ. Inhibitory effects of curcumin on tumorigenesis in mice. *Biochem. Suppl*., 27: 326-34, 1997.
38. Greene HSN. Heterologous transplantation of mammalian tumors: II. The transfer of human tumors to alien species. *J Exp Med*., 73: 475-86, 1941.
39. Folkman J. Clinical applications of research on angiogenesis. *N Engl J Med.,* 333: 1757-63, 1995.
40. Shih SC, Claffey KP. Role of AP-1 and HIF-1 transcription factors in TGF-beta activation of VEGF expression. *Growth Factors.,* 19: 19-34, 2001.
41. Choi H, Chun YS, Kim SW, Kim MS, Park JW. Curcumin inhibits hypoxia-inducible factor-1 by degrading aryl hydrocarbon receptor nuclear translocator: a mechanism of tumor growth inhibition. *Mol Pharmacol.,* 70: 1664-71, 2006.
42. Mohan R, Sivak J, Ashton P, Russo LA, Pham BQ, Kasahara N, Raizman MB, Fini ME. Curcuminoids inhibit the angiogenic response stimulated by fibroblast growth factor-2, including expression of matrix metalloproteinase gelatinase B. *J Biol Chem.,* 275: 10405-12, 2000.

43. Thaloor D, Singh AK, Sidhu GS, Prasad PV, Kleinman HK, Maheshwari RK. Inhibition of angiogenic differentiation of human umbilical vein endothelial cells by curcumin. *Cell Growth Differ.,* 9: 305-12, 1998.
44. Bae MK, Kim SH, Jeong JW, Lee YM, Kim HS, Kim SR, Yun I, Bae SK, Kim KW. Curcumin inhibits hypoxia-induced angiogenesis via down-regulation of HIF-1. *Oncol Rep.,* 15: 1557-62, 2006.
45. Jaiswal AS, Marlow BP, Gupta N, Narayan S. Beta-catenin-mediated transactivation and cell-cell adhesion pathways are important in curcumin (diferuylmethane)-induced growth arrest and apoptosis in colon cancer cells. *Oncogene.,* 21: 8414-27, 2002.
46. Park CH, Hahm ER, Park S, Kim HK, Yang CH. The inhibitory mechanism of curcumin and its derivative against beta-catenin/Tcf signaling. *FEBS Lett.,* 579: 2965-71, 2005.
47. Gupta B, Ghosh B. Curcuma longa inhibits TNF-alpha induced expression of adhesion molecules on human umbilical vein endothelial cells. *Int J Immunopharmacol.,* 21: 745-57, 1999.
48. Bhaumik S, Jyothi MD, Khar A. Differential modulation of nitric oxide production by curcumin in host macrophages and NK cells. *FEBS Lett*., 483: 78-82. 2000.
49. Joe B, Lokesh BR. Role of capsaicin, curcumin and dietary n-3 fatty acids in lowering the generation of reactive oxygen species in rat peritoneal macrophages. *Biochim Biophys Acta.,* 1224: 255-63, 1994.
50. Khopde M, Priyadarsini KI, Venkatesan P, Rao MN. Free radical scavenging ability and antioxidant efficiency of curcumin and its substituted analogue. *Biophys Chem.,* 80: 85-91, 1999.
51. Kunchandy E, Rao MNA. Oxygen radical scavenging activity of curcumin. *Int J Pharmaceutics,* 58: 237-40, 1990.
52. Barik A, Mishra B, Shen L, Mohan H, Kadam RM, Dutta S, Zhang HY, Priyadarsini KI. Evaluation of a new copper(II)-curcumin complex as superoxide dismutase mimic and its free radical reactions. *Free Radic Biol Med*., 39: 811-22, 2005.
53. Nair J, Strand S, Frank N, Knauft J, Wesch H, Galle PR, Bartsch H. Apoptosis and age-dependant induction of nuclear and mitochondrial etheno-DNA adducts in Long-Evans Cinnamon (LEC) rats: enhanced DNA damage by dietary curcumin upon copper accumulation. *Carcinogenesis.,* 26: 1307-15, 2005.
54. Lala PK, Chakraborty C. Role of nitric oxide in carcinogenesis and tumour progression. *Lancet Oncol.,* 2: 149-56, 2001.
55. Graziewicz M, Wink DA, Laval F. Nitric oxide inhibits DNA ligase activity: potential mechanisms for NO-mediated DNA damage. *Carcinogenesis.,* 17: 2501-5, 1996.
56. Chan MM, Huang HI, Fenton MR, Fong D. *In vivo* inhibition of nitric oxide synthase gene expression by curcumin, a cancer preventive natural product with anti-inflammatory properties. *Biochem Pharmacol.,* 55: 1955-62, 1998.
57. Garcea, G, Berry, DP, Jones, DJ, Singh, R, Dennison, A. R., Farmer, PB, Sharma, RA, Steward, WP, and Gescher, AJ. Consumption of the putative chemopreventive agent curcumin by cancer patients: assessment of curcumin levels in the colorectum and their pharmacodynamic consequences. *Cancer Epidemiol Biomarkers Prev.*, 14: 120-125, 2005.
58. Sheweita SA. Drug-metabolizing enzymes: mechanisms and functions. *Curr Drug Metab.,* 1: 107-32, 2000.
59. Ciolino HP, Daschner PJ, Wang TT, Yeh GC. Effect of curcumin on the aryl hydrocarbon and cytochrome P450 1A1 in MCF-7 human breast carcinoma cells. *Biochem. Pharmacol.,* 56: 197-206, 1998.

60. Singh SV, Hu X, Srivastava SK, Singh M, Xia H, Orchard JL, Zaren HA. Mechanism of inhibition of benzo[a]pyrene-induced forestomach cancer in mice by dietary curcumin. *Carcinogenesis.*, 19: 1357-60, 1998.
61. Dinkova-Kostova AT, Talalay P. Relation of structure of curcumin analogs to their potencies as inducers of Phase 2 detoxification enzymes. *Carcinogenesis.*, 20: 911-4, 1999.
62. Hayes JD, Pulford DJ. The glutathione S-transferase supergene family: regulation of GST and the contribution of the isoenzymes to cancer chemoprotection and drug resistance. *Crit Rev Biochem Mol Biol.*, 30: 445-600, 1995.
63. Duvoix A, Schnekenburger M, Delhalle S, Blasius R, Borde-Chiche P, Morceau F, Dicato M, Diederich M. Expression of glutathione S-transferase P1-1 in leukemic cells is regulated by inducible AP-1 binding. *Cancer Lett*, 216: 207-19, 2004.
64. Hayeshi R, Mutingwende I, Mavengere W, Masiyanise V, Mukanganyama S. The inhibition of human glutathione S-transferases activity by plant polyphenolic compounds ellagic acid and curcumin. *Food Chem Toxicol.*, 45: 286-95, 2007.
65. Chainani-Wu N. Safety and anti-inflammatory activity of curcumin: a component of tumeric (Curcuma longa). *J Altern Complement Med.*, 9: 161-8, 2003.
66. Sharma RA, Ireson CR, Verschoyle RD, Hill KA, Williams ML, Leuratti C, Manson MM, Marnett LJ, Steward WP, Gescher A. Effects of dietary curcumin on glutathione S-transferase and malondialdehyde-DNA adducts in rat liver and colon mucosa: relationship with drug levels. *Clin Cancer Res.*, 7: 1452-8, 2001.
67. Deodhar SD, Sethi R, Srimal RC. Preliminary study on antirheumatic activity of curcumin (diferuloyl methane). *Indian J Med Res.*, 71: 632-4, 1980.
68. Cheng AL, Hsu CH, Lin JK, *et al*. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. *Anticancer Res.*, 21:2895-900, 2001.
69. Sharma RA, Euden SA, Platton SL, *et al*. Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. *Clin Cancer Res.*, 10: 6847-54, 2004.
70. Goh CL, Ng SK. Allergic contact dermatitis to Curcuma longa (turmeric). *Contact Dermatitis.*, 17:186, 1987.
71. Liddle M, Hull C, Liu C, Powell D. Contact urticaria from curcumin. *Dermatitis.*, 17: 196-7, 2006.
72. Verma SP, Salamone E, Goldin B. Curcumin and genistein, plant natural products, show synergistic inhibitory effects on the growth of human breast cancer MCF-7 cells induced by estrogenic pesticides. *Biochem Biophys Res Commun.*, 233: 692-6, 1997.
73. Khafif A, Schantz SP, Chou TC, Edelstein D, Sacks PG. Quantitation of chemopreventive synergism between (-)-epigallocatechin-3-gallate and curcumin in normal, premalignant and malignant human oral epithelial cells. *Carcinogenesis.*, 19: 419-24, 1998.
74. Liu Y, Chang RL, Cui XX, Newmark HL, Conney AH. Synergistic effects of curcumin on all-trans retinoic acid- and 1 alpha,25-dihydroxyvitamin D3-induced differentiation in human promyelocytic leukemia HL-60 cells. *Oncol Res.*, 9: 19-29, 1997.
75. Du B, Jiang L, Xia Q, Zhong L. Synergistic inhibitory effects of curcumin and 5-fluorouracil on the growth of the human colon cancer cell line HT-29. *Chemotherapy.*, 52: 23-8, 2006.
76. Pan MH, Huang TM, Lin JK. Biotransformation of curcumin through reduction and glucuronidation in mice. *Drug Metab Dispos.*, 27: 486-94, 1999.

77. 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. *PlantaMed.,* 64: 353-6,1998.

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