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INFLEASE CAPSULES: A UNIQUE ANTIINFLAMMATORY AGENT TO SUPPORT IMMUNE SYSTEM IN CANCER

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ABSTRACT

Cancer is hyperproliferative disorder that involves transformation, dysregulation of apoptosis, proliferation, invasion, angiogenesis and metastasis Cancer is one of the major threats of modern life and is considered as the second cause of death after myocardial infarction. Millions of people every year die with different types of cancer despite tremendous efforts to find methods of control and cure. Although great advances were made in modern medical science to control disease but many diseases like cancer are not yet curable fully. Curcumin, commonly called diferuloyl methane, is a hydrophobic polyphenol derived from rhizome (turmeric) of the herb *Curcuma longa*. Extensive research over the last half century has revealed important functions of curcumin. *In vitro* and *in vivo* research has shown various activities, such as anti-inflammatory, cytokines release, antioxidant, immunomodulatory, enhancing of the apoptotic process, and anti-angiogenic properties. Curcumin has also been shown to be a mediator of chemo-resistance and radio-resistance. The anti-cancer effect of INFLEASE capsules has been seen in a few clinical trials, mainly as a native chemoprevention agent in colon and pancreatic cancer, cervical neoplasia and Barrets metaplasia.

KEY WORDS: INFLEASE capsules**,** Curcumin, Anti-tumor activity, Chemopreventive.

INTRODUCTION

Curcumin [(1E,6E)-1,7-bis (4- hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is an orange-yellow active component from the herb Curcuma longa (usually known as turmeric) commonly used in the Indian and Eastern Asia. It is an orange-yellow crystalline powder with melting point of 183°C, molecular formula of C21H20O6, and molecular weight of 368.37 g/mol. The essential structure of this molecule consists of feruloylmethane skeleton**.** Curcumin is a botanical pigment derived from the ground rhizome named Curcuma species or Zingiberaceae. It is now clear that there arefour major curcuminoids namely curcumin, demethoxycurcumin, bis-demethoxycurcumin, and a new identified cyclocurcumin occurring naturally in Curcuma species.

Traditionally, curcumin has been employed as a spice, cosmetic and medicine. Extensive research has proven that most of its bioactivities are associated with the curcuminoid's content [2]. As a medicine, curcumin is shown to exhibit antioxidant, anti-inflammatory, antiviral, Antibacterial, antifungal, and anticancer activities, and thus has a potential to against various diseases including diabetes, asthma, allergies, arthritis, atherosclerosis, neurodegenerative diseases, and other chronic illnesses like cancers [3]. Furthermore, it is widely accepted of curcumin's pharmacological safety, as usually used at doses up to 100 mg/day in folk medicine for centuries [4]. In India, curcumin has been taken orally for the treatment of sore throat, exhibiting its anti-inflammatory activity significantly.

Although the inflammation is a protective effect fundamentally, the harmful residuals underline various chronic diseases. To date, persistent inflammation has been known to contribute to multistage carcinogenesis [5]. Therefore, there are extensive reports suggesting that INFLEASE capsules contains-curcumin extract has potential in the treatment of a variety of cancers.

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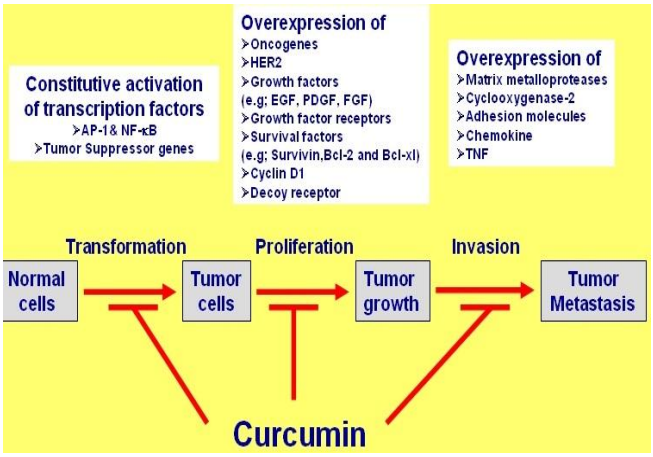


COMPOSITION OF INFLEASE capsules

Each 500 mg capsule contains-curcumin extracts 500 mg (standardized to 95% curcuminoids)

Mechanism of Action of INFLEASE capsules

Numerous animal and in vitro studies have demonstrated the ability of INFLEASE capsules and its active component, curcumin, to suppress the growth of a variety of tumor cells.

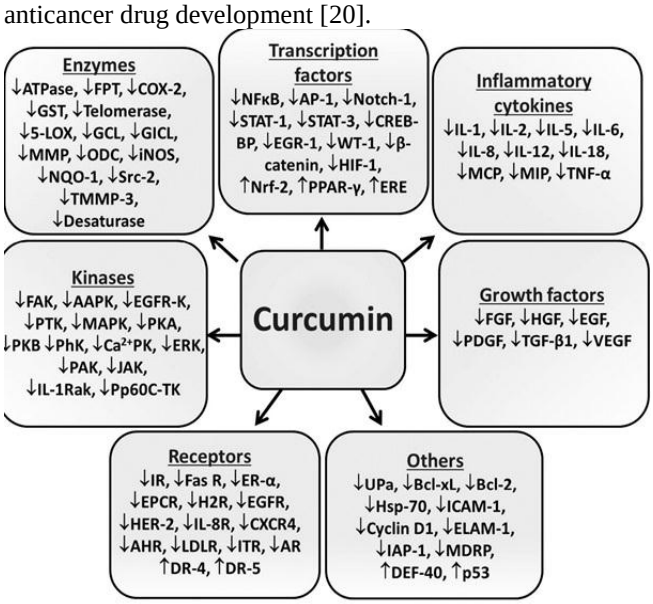
* **Antiproliferative effects**: induction of apoptosis (at high concentrations), suppression of proteins that regulate apoptosis, modulation of transcription factors.
* **Suppression of cyclooxygenase-2 (COX-2)** and lipooxygenase expression, which blocks production of prostaglandins and leukotrienes, respectively.
* **Suppression of cyclin D1** which is a proto-oncogene overexpressed in many cancers (e.g., breast, esophagus, lung, liver, head and neck, colon, and prostate).
* **Suppression of adhesion molecules** that play an important role in tumor metastasis.
* **Suppression of various inflammatory cytokines**, including tumor necrosis factor.
* **Suppression of angiogenesis**, a crucial step in the growth and metastasis of many cancers.
* **Competition with carcinogens** that use the aryl hydrocarbon and cytochrome P450 pathway.

Anticancer effects of INFLEASE capsules

Cancers, with diverse histological origin, have therapeutic specific targets as well as common molecular markers involved in their initiation and progression. Based upon this concept, curcumin has been shown to affect several intracellular targets regulating survival or death of cancer cells.

To exert its anticancer activity, curcumin was considered to counteract the altered functionality of proliferative and apoptotic pathways. Interestingly, accumulating evidence suggests that curcumin shows anticancer effects at lower doses compared to other anticancer drugs. These effects are mediated through the regulation of numerous biochemical cascades, including various transcription factors, growth factors, inflammatory cytokines, protein kinases, and other enzymes [6]. Among these molecular targets, particularly, curcumin is apparently a highly effective molecule to interact with several inflammatory targets. This suggests that curcumin's reported beneficial effects might be due in part to its ability in modulating the immune system.

In principle, curcumin has been widely demonstrated to have potent antioxidant activities. It is well known that reactive oxygen species (ROS) play a key role in enhancing inflammation through the activation of stress kinases and redoxsensitive transcription factors such as NF-κB. Oxidative stress activates NF-κB-mediated transcription of proinflammatory mediators either through the activation of its activating inhibitor IKK or the enhanced recruitment or activation of transcriptional co-activators. Although numerous different pathways are activated during the inflammatory response, NF-κB is thought to be of the most importance in cancer-related inflammation [16]. However, curcumin acts as ROS scavenger, increases antioxidant glutathione levels by induction of glutamate cysteine ligase, and acts as an anti-inflammatory agent through inhibition of NF-κB signaling [17]. Persistent activation of NF-κB has been observed in many different cancers. Interestingly, recent works have identified that the sustained IKK activation is achieved to activate NF-κB pathway in many types of human cancer, indicating the activation of NF-κB is likely to result from alterations in its upstream signaling components [18]. In addition, cytotoxic studies in different cell lines have indicated that the toxicity of curcumin was significantly higher in tumor cells if compared to the normal cells [19]. Considering these recent discoveries, therefore, curcumin can be considered as an ideal lead compound for anticancer drug development [20].



Molecular basis of NF-κB inhibition by curcumin in cancer treatments

NF-κB was initially reported in 1980s as a regulator of immunoglobulin gene transcription in B lymphocytes [21]. Currently, five mammalian NF-κB family members have been discovered, including p50, p52, p65 (RelA), c-Rel and RelB. To activate specific downstream gene expression, NF-κB molecules form dimers, dissociate with I-κB inhibitor proteins, enter the nucleus upon activation and bind DNA Curcumin inhibits inducible NF-κB activation and suppresses cancer cell proliferation in breast cancer [22], ovarian cancer [23], pancreatic cancer [24],leukemia and multiple myeloma [25], oral cancer [26], bladder cancer [27], and prostate cancer [28]. Most biological effects of curcumin are through NF-κB-regulated gene products, including apoptosis-related proteins (Bcl-2, Bcl-XL, TRAF), cell cycle regulators (cyclin D1, cyclin D2), growth factors (interleukin, TNF-α, VEGF), receptors (CD40, CD44, CD86, CCR7, CXCL) and matrix metalloproteinases (MMP-2, MMP-9). Curcumin sensitizes human cancer cells tocell-killing agents through NF-κB pathway. In human pancreatic cancer, the curcumin combination therapy with TNF-related apoptosis inducing ligand (TRAIL) suggests that inhibition of NF-κB stimulates TRAIL-induced apoptosis [29].

Moreover, Notch-1, Hes-1, and Bcl-XL expression levels can be concomitantly down-regulated by curcumin treatment, which is correlated with the inactivation of NF-κB activity in increasing apoptosis [30]. In human prostate cancer, curcumin induces apoptosis through Bax translocation to mitochondria [31] and caspase activation [32], which enhances the therapeutic efficacy when combined with TRAIL. Similarly, it has also been reported that curcumin induces sensitization to TRAIL by inhibiting Akt-regulated NF-κB and NF-κB-dependent antiapoptotic targets Bcl-2, Bcl-XL, and XIAP in LNCaP and PC3 prostate cancer cells [33]

Thus, curcumin may play an adjuvant role in treating inducible cancer chemoresistance by inhibition of NF-κB signaling. Curcumin has also been shown to interfere with the functions of Akt and mitogen-activated protein kinases (MAPKs), two key molecules for survival signaling. Because NF-κB is a downstream target of Akt and MAPK, the inhibition of Akt and MAPK by curcumin is implicated in mediating the beneficial effects in anticancer therapy. Curcumin has been shown to decrease expression and activation of EGFR, HER- 2, HER-3 and IGF-1R as well as their downstream effectors Akt and cyclooxygenase-2 (COX-2) in HCT-116 and HT-29 colon cancer cells [34].

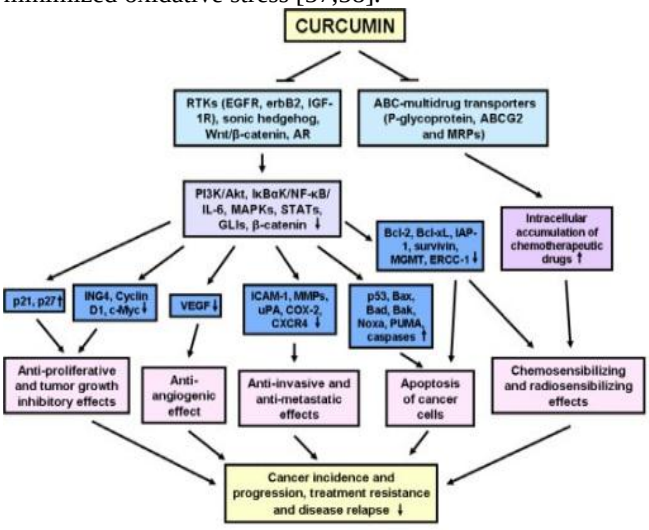
The observation that curcumin inhibits EGFR and Akt can account for reduced NF-κB activity and cancer cell apoptosis induced by curcumin at low concentrations [35]. Curcumin also interrupts extracellular signal-regulated kinase (ERK) signaling, reduces NF-κB activity and results in suppression of connective tissue growth factor (CTGF) expression in activated hepatic stellate cells [36]. Likewise, TNF-α stimulates activation of Akt cascade and the recruitment and assembling of NF-κB p65 to induce MMP-9 expression [37]. In consequence, curcumin treatments block Akt nuclear translocation and thus inhibit MMP-9 expression. Curcumin has also been reported to inhibit histone deacetylase (HDAC) and p300/Notch 1 signaling by preventing the degradation of I-κBα in leukemia [38]. Moreover, in C6 glioma cells, curcuminreduced cell survival is correlated with the inhibition of NF- κB signaling pathways via prevention of constitutive JNK and Akt activation [39]. It is conceivable that the activated NF-κB may mediate tumor cell invasion and metastasis as well, such that suppression of NF-κB by curcumin may actually increase chemotherapeutic effects. In MDA-MB-231 breast cancer cells, curcumin decreases the metastatic activity and two inflammatory cytokines CXCL1 and CXCL2 by down-regulating NF-κB activation [40]. In colon cancer cells, curcumin suppresses neurotensin-stimulated IL-8 expression and secretion, and blocked neurotensin-stimulate Cancer.

Curcumin is known to exert anti-inflammatory effects significantly by interrupting NF-κB signaling at multiple levels. For example, ROS mediate inflammation through the activation of stress kinases and redox-sensitive transcription factors such as NF-κB, however, curcumin is a ROS scavenger and thus prevents the inflammatory signaling. In addition, curcumin can interfere with the functions of Akt and MAPKs, and in turn down-regulate the downstream molecule, NF-κB. lated migration [41]. In epithelial cells, curcumin inhibits the TPA-induced up-regulation of COX-2 and MMP-9 through suppressing ERK1/2 phosphorylation and NF-κB transactivation[42]. Furthermore, curcumin exerts anti-inflammatory and growth-inhibitory effects through inhibition of NF-κB and MAPK pathways [43]. By inhibition of NF- κB DNA binding ability, curcumin treatments lead to a downregulation of UV-enhanced IL-18 expression in NCTC 2544 skin cell [44]. In addition, curcumin inhibits the extracellular stimulation of upstream protein kinase Akt, which is correlated with down-regulation of the NF-κB targets including COX-2 and MMP-9 [45]. Besides, the neutralization of tumorinduced oxidative stress and restoration of NF-κB activity along with the re-education of the TNF-α signaling pathway can be the mechanism. Some results suggest that unlike other anticancer agents, curcumin is not only devoid of immunosuppressive effects but also acts as immunorestorer in tumor-bearing subjects [46]. Overall, all of these observations provide evidence of curcumin's potent anti-inflammatory and anti-carcinogenic effects.

It is also known that curcumin with its potent antioxidant property is anticipated to exert its bioactivities. In K562 leukemia cells, curcumin-induced topoisomerase I- and IIDNA complexes are prevented by the antioxidant Nacetylcysteine; this suggests ROS may directly mediate

the formation of these complexes [47]. However, the suppression of TNF-α-induced NF-κB activation by curcumin suggests a critical role of its structural signature rather than its ROS scavenger ability [48]. Curcumin acts through the inhibition of I-κB phosphorylation and thus prevents I-κB degradation by the proteosome**.** The work from Marin et al. [49] indicates that curcumin induces apoptosis and NF-κB inhibition in melanoma cells but not normal cells, which is correlated with decrease of phospho-I-κBα level. Furthermore, the inhibition of I-κB degradation leads to a downregulation of COX-2 expression [50]. By inhibition of I-κB degradation, curcumin suppresses the expression of NF-κB, COX-2 and MMP-9, and indeed suppresses the incidence of breast cancer metastasis [51]. Other than inhibiting I-κB degradation, curcumin has also been reported to inhibit ligand-independent dimerization such as TLR4 receptor complex [52]. In MDA-MB-468 breast cancer cells and HT29 colon cancer cells, curcumin treatments inhibit Stat3 phosphorylation, resulting in reduction of nicotinamide Nmethyltransferase (NNMT) level [53]. In human endometrial cancer cells, curcumin down-regulates Ets-1 and Bcl-2 expression and induces apoptosis, suggesting a novel molecular mechanism for the antitumor activity [54] Curcumin also inhibits acid sphingomyelinase (ASPMase), and the effect might be involved in its anti-proliferative property against colon cancer cells [55]. Furthermore, it has also been reported that curcumin induces apoptosis selectively in human papilloma virus (HPV)-associated cervical cancer cells [50].

Curcumin also participates in non-cancer treatments related to NF-κB. The mechanisms of curcumin for treating other diseases have also been mentioned for decades. For example, it has been reported of hypolipidemic and hypercholesterolemic effects by dietary curcumin supplement [56]. Basically, curcumin prevents tissue damage by at least two mechanisms: acting as an antioxidant and by inhibiting NF-κB activation to minimized oxidative stress [57,58].



Human Clinical Studies

In a Phase I clinical trial, Sharma et al gave curcuma extracts (containing 36-180 mg of curcumin) to 15 patients with refractory colorectal cancer. (59) The curcuma extracts were well-tolerated orally and no dose-limiting toxicity was observed. Radiologically stable disease was demonstrated in five patients during 2-4 months of treatment. The study showed that curcuma extract can be safely administered in doses of up to 2.2 g/d (180 mg of curcumin), has low oral bioavailability in humans, and may undergo intestinal metabolism.

The review article by Aggarwal et al examining the anticancer effect of turmeric/curcumin reported a study in China by Cheng et al of 25 patients with one of five high-risk conditions: recently resected bladder cancer, arsenic Bowen's disease of the skin, uterine cervical intraepithelial neoplasm (C1N), oral leucoplakia, and intestinal metaplasia of the stomach. (60) Curcumin was administered orally for three months with doses ranging from 500 to 12,000 mg/d. Curcumin were found to be non-toxic in doses of up to 8,000 mg/d orally for three months. The results also showed that one of four patients with C1N and one of seven patients with oral leucoplakia developed frank malignancies in spite of treatment with curcumin. However, histological improvement was seen in one of two patients with bladder cancer, two of seven patients with leucoplakia, one of six patients with intestinal metaplasia, one of four patients with C1N, and two of six patients with Bowen's disease. Turmeric given to 16 chronic smokers in doses of 1.5 g/d for 30 days reduced the urinary excretion of mutagens in a controlled trial. (61) There was no change in mutagen excretion in the urine of controls. Although suggestive, measuring surrogate outcomes, such as urinary mutagens, does not necessarily correlate with reduction in cancer incidence. In a follow-up to pharmacological research on the effects of curcumin on HIV cell replication, 18 HIV-positive patients were given an average dose curcumin of 2 g/d for 127 days. (61) There was a significant increase in CD4 and CD8 lymphocyte counts. The subsequent phase I/II study using doses of 2.7-4.8 g/d of curcumin failed to show any benefit on viral loads or CD4 count in HIV-positive individuals, It was

Suggested that the poor bioavailability of curcumin could be a factor in these negative results.

Dosage

1-2 INFLEASE capsules twice a days or as directed by healthcare specialist.

Adverse Effects

As a dietary supplement, turmeric has Generally Recognized as Safe (GRAS) status.

Drug and Herb Interactions

Because of turmeric's reported inhibition of platelet aggregation, turmeric theoretically may potentiate the

Effects of other agents that increase bleeding risk such as anticoagulants, NSAIDs, and antiplatelet medications, as well as herbs with anticoagulant activity.

CONCLUSION

INFLEASE capsules are safe and non-toxic for most **patients**, It has been shown to have diverse biological effects in humans and animals. Turmeric/curcumin is a potent anti-inflammatory and antioxidant. The evidence suggests that it can suppress tumorigenesis, tumor promotion, and metastasis and, therefore, has enormous potential as an anticancer agent. Further study is needed to determine whether it, like other antioxidants, should be avoided during chemotherapy.

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