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30	<b>Abstract</b>	<p>Curcumin (diferuloylmethane) is an orange-yellow component of turmeric (<i>Curcuma longa</i>), a spice often found in curry powder. Traditionally known for its anti-inflammatory effects, curcumin has been shown in the last two decades to be a potent immunomodulatory agent that can modulate the activation of T cells, B cells, macrophages, neutrophils, natural killer cells, and dendritic cells. Curcumin can also downregulate the expression of various proinflammatory cytokines including TNF, IL-1, IL-2, IL-6, IL-8, IL-12, and chemokines, most likely through inactivation of the transcription factor NF-<math>\kappa</math>B. Interestingly, however, curcumin at low doses can also enhance antibody responses. This suggests that curcumin's reported beneficial effects in arthritis, allergy, asthma, atherosclerosis, heart disease, Alzheimer's disease, diabetes, and cancer might be due in part to its ability to modulate the immune system. Together, these findings warrant further consideration of curcumin as a therapy for immune disorders.</p>	

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31 **Keywords**  
**separated by ‘-’**

Curcumin – tumor necrosis factor – nuclear factor- $\kappa$ B – interleukins – chemokines – immunomodulation

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# 1 “Spicing Up” of the Immune System by Curcumin

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3 Received December 6, 2006; accepted December 11, 2006

4 Curcumin (diferuloylmethane) is an orange-yellow component  
5 of turmeric (*Curcuma longa*), a spice often found in curry pow-  
6 der. Traditionally known for its antiinflammatory effects,  
7 curcumin has been shown in the last two decades to be a potent  
8 immunomodulatory agent that can modulate the activation of T  
9 cells, B cells, macrophages, neutrophils, natural killer cells, and  
10 dendritic cells. Curcumin can also downregulate the expression  
11 of various proinflammatory cytokines including TNF, IL-1, IL-2,  
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13 vation of the transcription factor NF- $\kappa$ B. Interestingly, however,  
14 curcumin at low doses can also enhance antibody responses. This  
15 suggests that curcumin’s reported beneficial effects in arthritis,  
16 allergy, asthma, atherosclerosis, heart disease, Alzheimer’s dis-  
17 ease, diabetes, and cancer might be due in part to its ability  
18 to modulate the immune system. Together, these findings war-  
19 rant further consideration of curcumin as a therapy for immune  
20 disorders.

21 **KEY WORDS:** Curcumin; tumor necrosis factor; nuclear factor- $\kappa$ B;  
22 interleukins; chemokines; immunomodulation.

## 23 INTRODUCTION

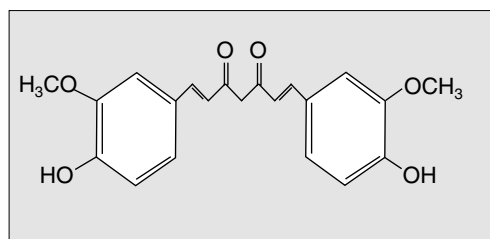
24 Turmeric (called Haldi in Hindi language) and named  
25 by British as curry, is the dried rhizome powder of  
26 *Curcuma longa*, a perennial herb of the *Zingiberaceae*  
27 (ginger) family, which is 3–5 ft tall bearing oblong,  
28 pointed, short-stemmed leaves and funnel-shaped yellow  
29 flowers. The rhizome of turmeric is a valuable cash  
30 crop, which is widely cultivated in Asia, India, China,  
31 and other tropical countries (1). Turmeric, is commonly  
32 used as a spice in curries, food additive and also, as

a dietary pigment. It has been used to treat various  
33 illnesses in the Indian subcontinent from the ancient  
34 times. Turmeric finds its use in one form or the other  
35 in the textile and pharmaceutical industries (2). It is  
36 used in Hindu religious ceremonies and Hindus also  
37 apply a mixture of turmeric and sandalwood powder on  
38 their foreheads. Turmeric has been used as a nontoxic  
39 drug in Ayurveda for centuries to treat a wide variety of  
40 disorders including rheumatism, bodyache, skin diseases,  
41 intestinal worms, diarrhea, intermittent, fevers, hepatic  
42 disorders, biliousness, urinary discharges, dyspepsia,  
43 inflammations, constipation, leukoderma, amenorrhea,  
44 and colic (3). Turmeric has been considered as an  
45 emmenagogue, diuretic, and carminative when taken  
46 orally, whereas topical application is commonly used to  
47 treat bruises, pains, sprains, boils, swellings, sinusitis, and  
48 various skin disorders (4). Turmeric is used to treat angina  
49 pectoris, stomachache, postpartum abdominal pain, and  
50 gallstones in the Chinese system of medicine (5). It seems  
51 to promote the *qi* flow, “stimulates menstrual discharge,”  
52 and relieves menstrual pain (6). The poultices prepared  
53 from turmeric are topically applied to relieve pain and  
54 inflammation (7). A mixture of turmeric powder and  
55 slaked lime is applied topically as a household remedy to  
56 cure injury-related sprains and swelling. Turmeric is also  
57 an effective household remedy for sore throat, cough, and  
58 common cold, where it is taken orally with tea or hot milk.  
59

The major chemical principles of turmeric are curcum-  
60 inoids, which impart characteristic yellow color to it. The  
61 curcuminoids can be separated from turmeric by ethanol  
62 extraction and it usually contains 0.3–5.4% curcumin (one  
63 of the major curcuminoids) depending on the season of its  
64 harvest (7). Vogel and Pellatier (8) first reported molecular  
65 formula of curcumin as C<sub>21</sub>H<sub>20</sub>O<sub>6</sub>, which was later iden-  
66 tified as diferuloylmethane (8). The IUPAC name of cur-  
67 cumin is (1,7-bis (4-hydroxy-3-methoxy-phenyl) hepta-1,  
68 6-diene-3, 5-dione) and its chemical structure (9) is de-  
69 picted in Fig. 1. Curcumin is an orange-yellow, crystalline  
70 powder and does not dissolve in water; however, it readily  
71 goes into solution in ethanol and dimethylsulfoxide.  
72

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**Structure of curcumin (diferuloylmethane)**

**Fig. 1.** Chemical structure of curcumin.

cumin is a pluripotent pharmacological agent that utilizes multiple molecular pathways to leave its imprint on biological systems (47). This review is mainly focused on curcumin's immunomodulatory activities.

## EFFECT OF CURCUMIN ON IMMUNE CELLS

Curcumin has been found to modulate the growth and cellular response of various cell types of the immune system (Fig. 2). How this agent affects T cells, B cells, macrophages, neutrophils, NK cells, and dendritic cells is discussed in the following text.

### *Effect of Curcumin on T Cells*

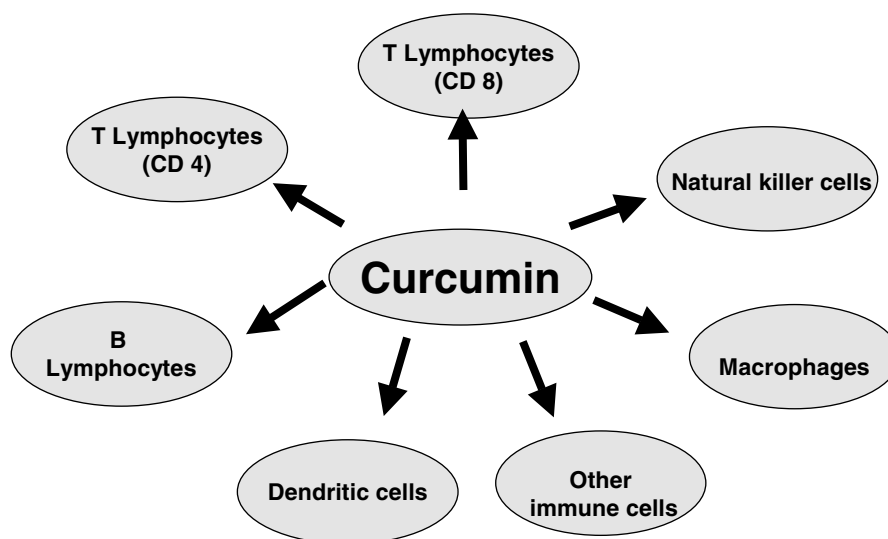
Numerous lines of evidence suggest that curcumin can modulate both the proliferation and the activation of T cells. Curcumin inhibited the proliferation induced by concanavalin A (Con A), phytohemagglutinin (PHA), and phorbol-12-myristate-13-acetate (PMA) of lymphocytes derived from fresh human spleen ((49); Table I). During these studies, curcumin also suppressed IL-2 synthesis; and IL-2 induced proliferation of lymphocytes. This correlated with suppression of NF- $\kappa$ B activation. Thus, these results suggest that curcumin exhibits immunosuppressive effects mediated through regulation of IL-2. In another study, the same group reported that curcumin inhibits the proliferation induced by PMA and anti-CD28 antibody or that induced by PHA of T lymphocytes isolated from healthy donors (50). In comparison, cyclosporine A was found to suppress PHA-induced T-cell proliferation but not that induced by PMA and anti-CD28 antibody. Thus, curcumin can overcome the resistance of PMA and CD28 pathway to cyclosporine A. These results suggest that curcumin exhibits immunosuppressive properties that are superior than cyclosporine A. Yadav and his group also reported that curcumin can suppress the PHA-induced proliferation of human peripheral blood mononuclear cells (PBMCs) and inhibit IL-2 expression and NF- $\kappa$ B (51). In still another report, curcumin inhibited the activation of human V  $\gamma$   $\delta$ T cells induced by phosphoantigens (52).

A study by Sikora *et al.*, reported that curcumin treatment completely abolished the proliferation of Con A stimulated rat thymocytes and it also suppressed the dexamethasone-induced apoptosis in stimulated as well as nonstimulated rat thymocytes. This inhibition of apoptosis is accompanied by partial or complete oppression of AP-1 activity in nonstimulated or Con-A-stimulated thymocytes, respectively. A similar effect was also observable in rat thymocytes treated with dexamethasone; however, curcumin *per se* did not have any adverse effect on AP-1 activity (53). The immunomodulatory role of cur-

Curcumin as such does not possess any nutritive value however; it has been in constant use by humans as turmeric powder since Vedic times or even earlier and could be considered as pharmacologically safe. Human consumption of curcumin as a dietary spice ranges up to 100 mg/day (10) and recent phase I clinical trials indicate that humans can tolerate a dose of curcumin as high as 12 g/day, without any toxic side effects (11). The latest report has indicated safe dose of curcumin up to 12 g/day in humans (12).

The degradation kinetics of curcumin have been worked out under various pH conditions (13). Ninety percent of curcumin gets decomposed within 30 min in 0.1 M phosphate buffer and serum-free medium (pH 7.2 at 37°C). The decomposition of curcumin is pH-dependent (pH 3–10) and the rate of decomposition is higher under neutral-basic conditions. Curcumin is comparatively more stable in cell culture media containing 10% fetal calf serum and in human blood. Less than 20% of curcumin gets degraded after 1 h and approximately 50% decomposes after 8 h. The *trans*-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexenal has been reported as a major degradation product of curcumin, whereas vanillin, ferulic acid, and feruloyl methane were found to be the minor degradation products. Among all the major degradation products reported, the quantity of vanillin increases with time (13). Levels as low as 0.017 ng/mL of curcumin can be detected in aqueous solution *in vitro* by flurometric methods using mixed micelle of sodium dodecyl benzene sulfonate (SDBS) and cetyltrimethylammonium bromide (CTAB) surfactants (14).

Curcumin reportedly possesses several pharmacological properties including antiinflammatory, antimicrobial, antiviral, antifungal, antioxidant, chemosensitizing, radiosensitizing, and wound healing activities (2, 15–33). Curcumin can suppress tumor initiation, promotion, and metastasis in experimental models (34–44). It can also act as an antiproliferative agent by interrupting the cell cycle, disrupting mitotic spindle structures, and inducing apoptosis and micronucleation (45–48). Apparently, cur-



**Regulation of various immune cells by curcumin (diferuloylmethane)**

**Fig. 2.** Action of curcumin on different types of immune cells.

161 curcumin has been studied in HTLV-1-infected T-cells and  
 162 primary ATL cells, where curcumin treatment preferentially  
 163 inhibited the growth of HTLV-1-infected T-cells and  
 164 primary ATL cells, but spared the normal PMBCs. This  
 165 antiproliferative effect of curcumin on HTLV-1-infected  
 166 T-cells and primary ATL cells was directly correlated to  
 167 its ability to induce cell cycle arrest by downregulating  
 168 the expression of cyclin D1, Cdk1, and Cdc25C and induce  
 169 apoptosis by reducing the expression of XIAP and survivin.  
 170 In addition, it also suppressed the constitutive  
 171 AP-1 DNA-binding and transcriptional activity in these  
 172 cells (54, 55).

173 Another study on mouse lymphocytes has reported that  
 174 a low-dose curcumin increased the proliferation of splenic  
 175 lymphocytes, whereas high-dose curcumin depressed it  
 176 indicating its ability to differentially regulate the proliferation  
 177 of splenic lymphocytes (56). In yet another study,  
 178 curcumin treatment increased the proliferation of intestinal  
 179 mucosal CD3<sup>+</sup> T cells due to change in CD4<sup>+</sup> T subsets  
 180 in C57BL/6J-Min<sup>+/+</sup> (Min<sup>+/+</sup>) mice bearing a germline  
 181 mutation in *Apc* tumor suppressor gene (57). These studies  
 182 further demonstrate the ability of curcumin to modulate  
 183 immune functions in T cells.

184 The studies by Gerstch *et al.* on PMA-stimulated  
 185 PBMCs have revealed that the low concentrations of  
 186 curcumin significantly downregulated the expression of  
 187 PMA-induced granulocyte macrophage colony stimulating  
 188 factor (GM-CSF) mRNAs, whereas high concentrations  
 189 upregulated interferon gamma (IFN- $\gamma$ ) mRNAs.  
 190 These effects of curcumin were linked with the suppression

191 of PMA-induced activation of NF- $\kappa$ B and downregulation  
 192 of PMA-induced cyclin D1 mRNA expression in  
 193 PMBCs (58). The experiments on rat splenic lymphocytes  
 194 showed that curcumin treatment enhances the immune  
 195 response of the lymphocytes by increasing IgG production  
 196 (59).

197 The studies of ion transport enzyme activity in stimulated  
 198 T cells revealed a marked regulatory activity of turmeric  
 199 and its active principles, turmerin or curcumin.  
 200 Treatment of Con A-stimulated and control human blood  
 201 mononuclear T cells with different concentrations of  
 202 turmeric, curcumin, and turmerin reduced ATPase levels  
 203 on 3 and 5 days after treatment than the control. On the  
 204 contrary, a three and twofold elevation in Ca<sup>2+</sup>ATPase  
 205 and Na/K<sup>+</sup> ATPase activities were observed on day 7,  
 206 respectively (60). This could be one of the mechanisms of  
 207 immunomodulation by curcumin in T cells.

208 Curcumin not only plays an important role in the immunomodulation  
 209 of normal but also transformed T cells, where it adversely  
 210 affects the cell proliferation of these cells by suppression  
 211 of IL-2 gene expression and by inhibiting the activation  
 212 of NF- $\kappa$ B (58). These results indicate that the antiproliferative  
 213 activity of curcumin against T cells may be relevant for T-cell  
 214 leukemia.

#### Effect of Curcumin on B Cells

215 In addition to affecting T cells, curcumin can also influence  
 216 the proliferation of B cells and B lymphocyte-mediated  
 217 immune function. Curcumin has been reported  
 218

**Table I.** Modulation of Immune Cells by Curcumin

<i>T lymphocytes</i>	
Inhibits the proliferation of human spleen T cells induced by PHA, PMA, and CON-A (49).	
Inhibits the proliferation of human T cells induced by PMA and anti-CD28 (50).	
Inhibits the proliferation of human T cells induced by PHA (51).	
Inhibits the proliferation of human PBMC induced by PHA (51).	
Inhibits the activation of human $V\gamma\delta$ T cells induced by phosphoantigens (52).	
Inhibits IL-2 expression in various T cells (50).	
Inhibits proliferation of Con-A stimulated rat thymocytes and dexamethasone-induced apoptosis in stimulated as well as unstimulated rat thymocytes (53).	
Inhibits the proliferation of HTLV-1 infected T cells and ATL cells but not normal PMBCs, induces apoptosis in infected cells, and downregulates the expression of cyclin D1, Cdk1, and Cdc25C (54, 55).	
Increases cell proliferation of splenic lymphocytes and CD4 <sup>+</sup> T cells (56, 57).	
Decreases ATPase early (3 & 5 days), whereas increases by 7 days in Con-A stimulated T cells (60).	
<i>B cells</i>	
Inhibits Epstein bar virus-induced B-cell proliferation and immortalization (61).	
Increases B-cell proliferation in intestinal mucosa of mice (57).	
<i>Macrophages</i>	
Increases phagocytosis of macrophages and differentially regulates splenocyte proliferation (56).	
Reduces the ROS generation ability of macrophages and secretion of lysosomal enzymes (63, 64).	
Differentially activates macrophages by downregulating Th1 and NO production (65).	
<i>NK Cells</i>	
Low dose enhances proliferation of YAC-1 cells but not of splenocytes or EL4 cells (66).	
Decreases proliferation of splenic lymphocytes, cytotoxic T lymphocytes (CTLs), lymphokine-activated killer (LAK) cells, and macrophages (67).	
Increases NK-cell cytotoxicity (51).	
<i>Effect on dendritic cells</i>	
Suppresses expression of CD80, CD86, and MHC class II antigens in GM-CSF/IL-4 stimulated DCs without affecting MHC class I antigens (73).	
Inhibits LPS-induced IL-12, IL-1 $\beta$ , IL-6, and TNF- $\alpha$ and the phosphorylation of MAPK and NF- $\kappa$ B nuclear translocation (73).	
<i>PMN</i>	
Increases total white blood cell count, circulating antibody titer, plaque-forming cells, $\alpha$ -esterase-positive cells, and phagocytic activity of macrophages (75).	
Induces reaginic antibody in $\beta$ -lactoglobulin-challenged brown Norway rats (76).	
Inhibit 5-hydroxyeicosatetraenoic acid in human neutrophils (77).	

219 to block Epstein-bar virus (EBV) induced immortaliza-  
 220 tion of human B cells. This effect of curcumin ap-  
 221 pears to be mediated through downregulation of oxidative  
 222 stress induced by cyclosporine and hydrogen peroxide.  
 223 Thus, posttransplant lymphoproliferative disorder (PLTD)  
 224 associated with the use of cyclosporine during organ trans-  
 225 plantation, can be reversed by curcumin (61). Churchill  
 226 *et al.*, have reported that curcumin treatment stimulates  
 227 proliferation of B cells in the mucosa of intestine of  
 228 C57BL/6J-Min<sup>+</sup> (Min<sup>+</sup>) mice indicating its immunos-  
 229 timulatory activity (57).

230 Apart from affecting normal B-cells, curcumin has been  
 231 found to differentially reduce the proliferation of imma-  
 232 ture B-cell lymphoma (BKS-2) cells, but not of normal  
 233 cells, by inducing apoptosis and this is associated with  
 234 downregulation of *egr-1*, *c-myc*, *bcl-XL*, and the tumor  
 235 suppressor gene *p53*, and almost complete inhibition of  
 236 NF- $\kappa$ B activity (62). These studies indicate that curcumin  
 237 differentially regulates the immune function in normal as

well as tumor cells, which could confer advantage in a 238  
 therapeutic setting. 239

#### *Effect of Curcumin on Macrophages* 240

241 Many studies have shown curcumin's ability to mod-  
 242 ulate the activation of macrophages. For example, cur-  
 243 curcumin seems to regulate the immune function of mice in a  
 244 dose-dependent fashion as curcumin treatment enhanced  
 245 the phagocytosis of peritoneal macrophages and differ-  
 246 entially regulates the proliferation of splenocytes (56).  
 247 Apart from cell proliferation, a daily diet of curcumin  
 248 (30 mg/kg body weight/day) for 2 weeks in rats report-  
 249 edly attenuated the ability of macrophages to generate  
 250 ROS, (63) and secrete lysosomal enzymes collagenase,  
 251 elastase, and hyaluronidase (64). The ability of curcumin  
 252 to downregulate Th1 and NO production has been directly  
 253 correlated to its ability to differentially activate the host  
 254 macrophages (65).

255 *Effect of Curcumin on Natural Killer Cells*

256 Curcumin can also apparently modulate the activation  
257 of natural killer (NK) cells. Studies by South and his  
258 colleagues, in rats showed that curcumin at a dose of 1  
259 and 20 mg/kg body weight could not enhance the IgG lev-  
260 els in the NK cells, whereas a higher dose (40 mg/kg) did  
261 elevate IgG levels significantly. More importantly, none of  
262 the three doses of curcumin significantly enhanced either  
263 delayed-type hypersensitivity or NK cell activity (66).  
264 The extended studies by these authors on YAC-1 and EL4  
265 tumor cells and normal splenocytes *in vitro* showed that  
266 curcumin treatment exerted differential effects on cell vi-  
267 ability and proliferation. Treatment with low-dose cur-  
268 curmin (1.25  $\mu\text{g}/\text{mL}$ ) enhanced the proliferation of YAC-1  
269 cells but not that of either splenocytes or EL4 cells (66).  
270 A similar differential effect has been reported on NK cells  
271 by curcumin and it was linked to its ability to upregulate  
272 Th1 and NO production (65). In yet another study, cur-  
273 curmin treatment retarded the proliferation of splenic lym-  
274 phocytes, cytotoxic T lymphocytes (CTLs), lymphokine-  
275 activated killer (LAK) cells, and macrophages (67). In one  
276 of the investigations, curcumin has been found to augment  
277 NK-cell cytotoxicity (51). All these studies indicate that  
278 curcumin acts like a good immunomodulatory agent.

279 In addition to its immunomodulation of normal NK  
280 cells, curcumin could also increase cell death of refrac-  
281 tory natural killer/T-cell lymphoma (NKTL) cell lines  
282 (i.e., NKL, NK-92, and HANK1), which are resistant to  
283 other therapies. This was directly linked to the suppres-  
284 sion of the NF- $\kappa$ B activation including the constitutively  
285 expressed NF- $\kappa$ B and also blockage of Bcl-xL, cyclin D1,  
286 XIAP, and c-FLIP expression and the subsequent cleav-  
287 age and activation of caspase-8 and poly (ADP-ribose)  
288 polymerase (68). These observations indicate its potential  
289 as an antiproliferative agent that could play an important  
290 and decisive role in cancer chemotherapy.

291 *Effect of Curcumin on Dendritic Cells*

292 Dendritic cells are professional antigen-presenting cells  
293 that play a key role as immune sentinels in the initiation of  
294 T-cell responses to microbial pathogens, tumors, and in-  
295 flammation (69, 70). Peripheral DCs are generally imma-  
296 ture both phenotypically and functionally (71). They nev-  
297 ertheless have clinical potential as cellular adjuvants in the  
298 treatment of chronic infectious diseases and tumors (72).  
299 There is only one report to date on immune modulation  
300 of murine DCs using curcumin by Kim *et al.*, who found  
301 that curcumin significantly depressed the expression of  
302 CD80, CD86, and MHC class II antigens in GM-CSF/IL-4  
303 stimulated DCs without affecting MHC class I antigens.  
304 They also found that curcumin efficiently blocked the

LPS-induced expression of IL-12 and inflammatory cy- 305  
tokines including IL-1 $\beta$ , IL-6, and TNF- $\alpha$ . Curcumin 306  
treatment enhanced the Ag capturing ability of DCs via 307  
mannose receptor-mediated endocytosis. However, their 308  
Th1 and normal cell-mediated immune response was very 309  
poor. Further studies showed that treatment of DCs with 310  
curcumin before LPS stimulation completely suppressed 311  
the LPS-induced phosphorylation of MAPK and NF- $\kappa$ B 312  
nuclear translocation (73). The direct suppression of these 313  
activities by curcumin in DCs may lead to the attenuated T- 314  
cell-mediated immune responses by interfering with han- 315  
dling and presentation of antigens by DCs. 316

317 *Effect of Curcumin on Other Immune Cells*

318 Apart from affecting T cells, B cells, macrophages, and  
319 NK cells, curcumin has also been reported to affect other  
320 immune cells such as neutrophils, etc. In one of the stud-  
321 ies, curcumin inhibited the FMLP (a chemotactic peptide)  
322 and zymosan-activated plasma (ZAP)-induced aggrega-  
323 tion of monkey neutrophils. However, such an action was  
324 absent in serum-treated zymosan (STZ) and arachidonic  
325 acid (AA) treated neutrophils. Curcumin also blocked the  
326 production of O<sub>2</sub><sup>-</sup> radicals, and myeloperoxidase, in AA-,  
327 STZ-, and fmlp-stimulated cells, except lysozymes, which  
328 were mildly affected (74). The studies on Balb/c mice  
329 spleen immunized with sheep red blood cells have shown  
330 several immunostimulatory actions of curcumin includ-  
331 ing increase in total white blood cell count, circulating  
332 antibody titer, and plaque-forming cells (75). In addition,  
333 curcumin also raised bone marrow cellularity,  $\alpha$ -esterase-  
334 positive cells, and phagocytic activity of macrophages  
335 (75).

336 Moreover, curcumin has been found to induce reaginic  
337 antibody in  $\beta$ -lactoglobulin-challenged brown Norway  
338 rats maintained on diets comprising 10% coconut oil  
339 (CO), high oleic safflower oil, safflower oil (SO), or fish  
340 oil. Curcumin also reduced the secretion of rat chymase  
341 II (RChyII) in rats fed with SO and 0.5% curcumin, indi-  
342 cating variable effect on the synthesis of immunoglob-  
343 ulin E and the degranulation of intestinal mast cells  
344 (76). Curcumin treatment has been reported to inhibit  
345 5-hydroxyeicosatetraenoic acid in human neutrophils in  
346 one of the studies (77).

347 In yet another study, curcumin caused cell death by  
348 apoptosis in both normal and transformed human (HL  
349 60) and rodent cells despite the lack of oligonucleosomal  
350 DNA fragmentation (DNA "ladder"). However, curcumin  
351 blocked HL-60 in sub-G1 and increased caspase-3 activity  
352 (78). These results indicate that curcumin exerts its im-  
353 munomodulatory action on other immune cells described  
354 earlier.

## 355 EFFECT OF CURCUMIN ON IMMUNE CYTOKINES

356 *Effect of Curcumin on Expression and Action of*  
357 *TNF/TRAIL and Their Receptors*

358 Cytokines are autocrine, paracrine, and acrine cell sig-  
359 naling molecules that play a crucial role in acquired  
360 as well as innate immunity. TNF- $\alpha$  is one of the most  
361 versatile pleiotropic cytokine that induces growth stimu-  
362 lation as well as inhibition by self-regulatory mechanisms  
363 of its own and plays a crucial role as an immunostimulant  
364 and mediator of host resistance to many infectious agents.  
365 Curcumin exerts its profound effects on various cytokines  
366 of the TNF superfamily. Curcumin can modulate the ex-  
367 pression of both TNF and TNF-induced signaling and can  
368 also inhibit LPS-induced expression of TNF- $\alpha$  (79–81).  
369 It has also been reported to inhibit LPS or PMA-induced  
370 TNF- $\alpha$  in dendritic cells, macrophages, monocytes, alve-  
371 olar macrophages, and endothelial and bone marrow  
372 cells (73, 82, 83). An almost identical observation has  
373 been made in rats, where curcumin treatment attenuated  
374 TNF- $\alpha$  in sodium taurocholate-induced acute pancreatitis  
375 (84).

376 In another study, curcumin treatment blocked the ex-  
377 pression of TNF- $\alpha$  mRNA in the rat model of hemor-  
378 rhage and resuscitation (85). Studies by Siddiqui *et al.*, on  
379 septic rats revealed that curcumin treatment both before  
380 and after the onset of sepsis could reduce tissue injury,  
381 mortality, and decrease TNF- $\alpha$  expression (86). The anal-  
382 ysis of molecular pathways revealed that curcumin re-  
383 stores PPAR- $\gamma$  expression in the liver of septic rats within  
384 20 h. Similar results were obtained in endotoxin-treated  
385 cultured RAW 264.7 cells, where curcumin suppressed  
386 endotoxin-induced TNF- $\alpha$  expression and markedly ele-  
387 vated PPAR- $\gamma$  expression (86).

388 Experiments on HT29 intestinal epithelial cells (IECs)  
389 stimulated with TNF- $\alpha$  and IL-1 $\beta$ , showed that curcumin  
390 can block the binding of Shiga-like toxins (Stx) to IECs by  
391 inhibiting Gb3 synthase (GalT6) mRNA expression (83).  
392 In another set of experiments, three major active principles  
393 namely, 1,7-bis (4-hydroxyphenyl)-1,4,6-heptatrien-3-  
394 one, procurcumenol, and epiprocurcumenol isolated from  
395 the crude methanol extract of the rhizomes of *Curcuma*  
396 *zedoaria* were reported to suppress the production of  
397 TNF- $\alpha$  in LPS-stimulated macrophages (87). These stud-  
398 ies suggest that antiinflammatory activity of curcumin  
399 could well be correlated to its ability to inhibit inflam-  
400 matory cytokines at protein as well as mRNA levels.

401 TNF-related apoptosis-inducing ligand (TRAIL) is an-  
402 other member of TNF superfamily that has been found to  
403 be markedly influenced by curcumin treatment in various  
404 investigations. Experiments conducted on the androgen-

405 sensitive human prostate cancer cell line LNCaP have  
406 shown that curcumin increases cell death-promoting ac-  
407 tivity of TRAIL by inducing DNA fragmentation even  
408 though neither agent alone is significantly cytotoxic to  
409 LNCaP cells at low concentrations (10  $\mu$ M curcumin and  
410 20 ng/mL TRAIL). Further analysis of molecular mech-  
411 anisms showed that combination treatment resulted in  
412 cleavage of procaspase-3, procaspase-8, and procaspase-  
413 9; truncation of Bid, and release of cytochrome c from the  
414 mitochondria (88, 89) and could be responsible for the  
415 observed increase in cytotoxicity.

416 Another study has reported the effect of curcumin on  
417 death receptor DR5 (DR5/TRAIL-R2) in Caki, HCT 116,  
418 HT 29, HepG2, and Hep 3B cells. This study clearly  
419 demonstrated that curcumin and TRAIL treatment syn-  
420 ergistically increased the death of TRAIL-resistant Caki  
421 cells in a curcumin concentration-dependent manner,  
422 which could be directly correlated to the upregulated ex-  
423 pression of DR5 and proapoptotic gene, C/EBP homol-  
424 ogous protein (CHOP), at both the mRNA and protein  
425 levels in HCT 116, HT29, and HepG2 cell lines after cur-  
426 cumin treatment. This upregulation of DR5 and CHOP  
427 and cytotoxic effect of curcumin were due to its ability  
428 to generate ROS (90, 91). The combination studies on  
429 curcumin and TRAIL point that curcumin enhances the  
430 effect of TRAIL and could make TRAIL-resistant cells  
431 amenable to TRAIL therapy.

432 *Effect of Curcumin on Interleukins*

433 Interleukins are a group of cytokines that are secreted  
434 by leukocytes and act as communication channels be-  
435 tween them. Curcumin can also alter the expression and  
436 activity of a variety of interleukins, especially IL-1, IL-2,  
437 IL-6, IL-8, IL-10, and IL-12 and thus can influence func-  
438 tions of different cells in a variety of ways (Table II). For  
439 example, treatment of PMBCs with curcumin inhibited  
440 LPS-induced IL-1 $\beta$ , IL-6, and TNF- $\alpha$ . Similarly, in rab-  
441 bit experiments, curcumin reduced LPS-induced fever by  
442 attenuating the expression of IL-1 $\beta$ , IL-6, and TNF- $\alpha$  in  
443 the serum (81). This action of curcumin was mediated by  
444 suppression of NF- $\kappa$ B activation and downstream events  
445 that blocked these cytokines (81). Curcumin reportedly  
446 reduced PMA- or LPS-stimulated production of IL-1 and  
447 IL-8 in human peripheral blood monocytes and alveo-  
448 lar macrophages in a concentration- and time-dependent  
449 manner (79). A similar effect was observed for IL-2 pro-  
450 duction in PHA-stimulated human PMBCs (51).

451 In endothelial cell-based experiments, curcumin sig-  
452 nificantly retarded the transcriptional upregulation of IL-  
453 1 $\alpha$  and TNF- $\alpha$ -induced HO-1 (an inducible form of  
454 hemeoxygenase that is upregulated in oxidant and inflam-

**Table II.** Modulation of Various Cytokines by Curcumin

---

*TNF- $\alpha$*   
 Inhibits LPS-induced expression of TNF- $\alpha$  and IL-1 (80, 81).  
 Decreases sepsis-induced TNF- $\alpha$  and restores PPAR- $\gamma$  expression (86).  
 Inhibits endotoxin-induced TNF- $\alpha$  in RAW 264.7 cells (86).  
 Suppression of TNF- $\alpha$  mRNA in hemorrhage and resuscitation rat model (85).

*TRAIL*  
 Increases activity of TRAIL in LNCaP cells by cleavage of procaspase-3, procaspase-8, and procaspase-9; truncation of Bid, and release of cytochrome c from the mitochondria (88, 89).  
 Increases expression of DR5 and proapoptotic gene, C/EBP homologous protein (CHOP), at both the mRNA and protein levels in HCT 116, HT29, and HepG2 cells (90, 91).

*Interleukins*  
 Inhibits LPS-induced IL-1 $\beta$ , IL-6, and TNF- $\alpha$  in PMBCs and rabbit serum and also inhibits NF- $\kappa$ B activation (81).  
 Decreases PMA- or LPS-stimulated IL-1 and IL-8 in human peripheral blood monocytes and alveolar macrophages (79, 82).  
 Inhibits PHA-stimulated IL-2 production in human PMBCs (51).  
 Decreases the transcriptional upregulation of IL-1 $\alpha$  and TNF- $\alpha$ -induced HO-1 mRNA in endothelial cells (92).  
 Reduces IL-8 production in human pancreatic cells (94, 95).  
 Inhibits expression of IL-6 in WI-38 VA13 cells, dendritic cells, and sodium taurocholate-induced pancreatitis rats (73, 84, 95).  
 Inhibits IL-2 synthesis in Con A-, PHA-, and PMA-stimulated human splenocytes by blocking NF- $\kappa$ B activation (49).  
 Inhibits IL-1 $\beta$ -stimulated IL-8 gene expression in human bone marrow stromal cells (97).  
 Inhibits mRNA transcripts of IL-1 $\alpha$ , IL- $\beta$ , IL-2, and IL-6 in hemorrhage/resuscitation rat model by suppressing the activation of NF- $\kappa$ B and AP-1 (85).  
 Inhibits IL-12 p40 promoter activation in RAW264.7 monocytic cells transfected with p40 promoter/reporter constructs by blocking the activation of NF- $\kappa$ B (98).  
 Decreases IL-12 production and Th1 cytokine profile in CD4<sup>+</sup> T cells stimulated with either LPS or heat-killed *Listeria* monocytogenes (99).

*Toll-like receptors*  
 Inhibits LPS-induced mRNA expression of TLR2 and blocks NF- $\kappa$ B activation in C3H/HeN mouse splenic macrophages (103).

*Chemokines*  
 Inhibits constitutive production of IL-8 and increases the expression of IL-8 receptors CXCR1 and CXCR2 in pancreatic cells (93).  
 Inhibits IL-1 $\beta$ -stimulated and neurotensin receptor-induced expression of IL-8 in human colorectal cancer cells (94).  
 Decreases expression of IL-6 in WI-38 VA13 and dendritic cells and also in sodium taurocholate-induced acute pancreatitis in rats (73, 84, 95).  
 Inhibits IL-8 secretion by blocking nuclear translocation of NF- $\kappa$ B in BCG-stimulated human monocytes (104).  
 Inhibits LPS-induced expression of MCP-1 and IP-10 mRNA in mouse bone marrow stromal cells (105).  
 Reduces P-LPS-induced expression of MCP-1 gene and activation of AP-1 and NF- $\kappa$ B in human gingival fibroblasts (108).  
 Inhibits the proliferation of lymphocytes and their ability to secrete IL-2, IL-5, GM-CSF, and IL-4 (109).

*Adhesion molecules*  
 Inhibits transcription of ICAM-1, VCAM-1, and E-selectin in human umbilical vein endothelial cells (110).

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455 matory settings) mRNA (92). Curcumin can also report-  
 456 edly block the activity of interleukin-1 (IL-1) receptor-  
 457 associated kinase (IRAK) thiols in murine EL4 thymoma  
 458 cells. It also abrogates the recruitment of IRAKs to the  
 459 IL-1RI followed by the phosphorylation of IRAK and  
 460 IL-1RI-associated proteins (93). In other studies, the pro-  
 461 duction of IL-8 was abolished by curcumin in a dose  
 462 and time-dependent fashion (93, 94). In experiments  
 463 with SV40-transformed embryonic (WI-38 VA13) cells,  
 464 dendritic cells and sodium taurocholate-induced pancre-  
 465 atitic rats, curcumin was able to arrest the expression  
 466 of IL-6 (73, 84, 95). The studies conducted on IEC-6,  
 467 HT-29, and Caco-2 cells showed that curcumin treatment  
 468 represses the IL-1 $\beta$ -mediated ICAM-1 and IL-8 gene ex-  
 469 pression (96) and this action of curcumin was a result of  
 470 suppression of NF- $\kappa$ B activation, RelA nuclear translo-  
 471 cation, I $\kappa$ B $\alpha$  degradation, I $\kappa$ B serine 32 phosphorylation,  
 472 and I $\kappa$ B kinase activity (96).

In still another study, curcumin depressed IL-2 synthe- 473  
 474 sis in Con A-, PHA-, and PMA-stimulated human spleno-  
 475 cytes in a concentration-dependent manner by blocking  
 476 NF- $\kappa$ B activation (49). Similarly, curcumin successfully  
 477 blocked the IL-1 $\beta$ -stimulated IL-8 gene expression in hu-  
 478 man bone marrow stromal cells (97). A study on a rat  
 479 model of hemorrhage and resuscitation reported that cur-  
 480 cumin treatment suppresses the production of multiple  
 481 mRNA transcripts of IL-1 $\alpha$ , IL- $\beta$ , IL-2, IL-6, and IL-10 at  
 482 2 and 24 h after hemorrhage/resuscitation and this action  
 483 is mediated through the inhibition of NF- $\kappa$ B activation  
 484 and AP-1 (85). In another study, curcumin was found to  
 485 exert a repressive effect on IL-12 p40 promoter activa-  
 486 tion in RAW264.7 monocytic cells transfected with p40  
 487 promoter/reporter constructs by blocking the activation  
 488 of NF- $\kappa$ B (98). Similarly, curcumin pretreatment signifi-  
 489 cantly suppressed IL-12 production and Th1 cytokine pro-  
 490 file (i.e., decreased IFN- $\gamma$  and increased IL-4 production)

in CD4<sup>+</sup> T cells stimulated with either LPS or heat-killed *Listeria monocytogenes* and ability of macrophages to induce IFN- $\gamma$  (99). These studies show that one of the most important mechanisms of immunoregulation by curcumin is suppression of activation of NF- $\kappa$ B.

#### Effect of Curcumin on Toll-Like Receptors

Toll-like receptors (TLRs) are, type I transmembrane proteins that are key regulators of innate and adaptive immune responses in mammals that can recognize distinct pathogen-associated molecular signatures (100). A few studies have reported the influence of curcumin on TLRs. In one such study with Ba/F3 cells, curcumin abated LPS-induced IRF3 activation and LPS-induced TLR4 signaling by arresting both myeloid differentiation factor 88 (MyD88)- and the TIR domain containing adaptor inducing IFN- $\beta$  (TRIF)-dependent pathways. However, curcumin could not abrogate the IRF3 activation in 293T cells caused by increased expression of TRIF, indicating that curcumin also targets the TLR4 receptor complex in addition to IKK $\beta$  (101). In studies using peritoneal mesothelial cells from C3H/HeN mice, curcumin has been shown to suppress lipid A-induced NF- $\kappa$ B, MCP-1, and MIP-2 mRNA, implying its role in TLR4 signaling (102). In still another experiment, treatment of C3H/HeN mouse splenic macrophages with curcumin was found to abrogate LPS-induced mRNA expression of TLR2 and block NF- $\kappa$ B activation (103). Studies on TLRs indicate that immunomodulatory activity of curcumin may also be due to its ability to target TLRs.

#### Effect of Curcumin on Chemokines

Chemokines are small, chemotactic cytokines, which direct leukocyte migration, activate inflammatory responses, and help regulate tumor growth. A number of studies in various study systems have confirmed curcumin's potential to suppress various chemokines. In experiments with human pancreatic carcinoma cell lines, curcumin abated the constitutive production of IL-8 while raising the expression of IL-8 receptors CXCR1 and CXCR2 (93). Similarly, in human colorectal cancer cells, curcumin blocked in a time- and dose-dependent manner the IL-1 $\beta$ -stimulated and neurotensin receptor-induced expression of IL-8 (94). In other studies, curcumin blocked the expression of IL-6 in WI-38 VA13 and dendritic cells and also in sodium taurocholate-induced acute pancreatitis in rats (73, 84, 95, 96). The studies by Mendez-Samperio *et al.*, on *Mycobacterium bovis* Calmette-Guerin (BCG)-stimulated human monocytes reported that curcumin abated BCG-induced IL-8 secretion by blocking nuclear translocation of NF- $\kappa$ B (104).

Curcumin reportedly arrests the expression of the chemokines MCP-1 (105) and interferon-inducible protein-10 kDa (IP-10) in mouse bone marrow stromal cells. This effect is apparently mediated by curcumin's ability to prevent TNF, IL-1, and LPS-induced expression of MCP-1 and IP-10 mRNA, and it is completely reversible within 24 h after removing curcumin from the cell culture medium. The inhibition of AP-1 and NF- $\kappa$ B activation are responsible for this activity of curcumin (106, 107).

Studies on human gingival fibroblasts have shown that curcumin impedes the chemotactic activity of monocytes isolated from the culture supernatant of *Porphyromonas gingivalis* LPS (P-LPS)-treated cells (108). This effect of curcumin seems to be mediated by blocking the P-LPS-induced expression of MCP-1 gene and AP-1 and NF- $\kappa$ B activation in human gingival fibroblasts (108). Experiments by Kobayashi *et al.* have shown that curcumin arrests in a concentration-dependent manner the proliferation of lymphocytes from common house dust mite (*Dermatophagoides jhrinea*) atopic asthmatics and also their ability to secrete IL-2, IL-5, GM-CSF, and IL-4 (109). The immunomodulatory activity of curcumin may also be due to its ability to alter chemokine expression as indicated earlier.

#### Effect of Curcumin on Adhesion molecules

Experiments on human umbilical vein endothelial cells demonstrated that curcumin blocks the steady-state transcription of ICAM-1, VCAM-1, and E-selectin both temporally and reversibly (110).

#### EFFECT OF CURCUMIN ON INFLAMMATORY ENZYMES

Curcumin can markedly influence the activities of enzymes that are hallmark of inflammation and subsequently various disease states in humans (Table III). Curcumin can differentially block inflammatory enzymes involved in inflammation and extracellular matrix degradation at both the mRNA and protein levels (111–127). In several murine studies, curcumin has been shown to abate TPA-induced epidermal inflammation, and inhibit epidermal lipooxygenase and cyclooxygenase (COX) activities in dose-dependent fashion by downregulating TPA-induced NF- $\kappa$ B activation (111–113). Another study has also reported suppression of TPA-induced COX-2, prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), and MMP-9 expression. This was in direct correlation with the inhibition of ERK1/2 phosphorylation and NF- $\kappa$ B activation (114). A similar effect has been reported in Colo 205 colon carcinoma cells, where cur-

**Table III.** Modulation of Inflammatory Enzymes and Other Inflammatory Mediators by Curcumin

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*Cyclooxygenase*  
 Inhibits TPA-induced COX-2, prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), and MMP-9 expression, ERK1/2 phosphorylation, and NF-κB activation in mouse (114).  
 Inhibits COX-2, PGE<sub>2</sub>, matrix metalloproteinase (MMP)-2, COX-1, and MMP-9 levels, without affecting MMP-7 levels in Colo 205 colon carcinoma cells (115).  
 Inhibits the expression of COX-2 mRNA but had no effect on COX-1 mRNAs (116, 117, 126).  
 Inhibits LPS-induced COX-2 and PGE<sub>2</sub> in human leucocytes in a dose-dependent manner (118).  
 Inhibits IL-1β or IFN-α-induced PGE<sub>2</sub> and COX-2 at the protein and the mRNA levels (119, 120).  
 Inhibits expression of COX-2 and inflammatory cytokines while increasing PGE<sub>2</sub> levels in TNBS-induced colitis in rats (121).  
 Inhibits cigarette smoke or smokeless tobacco-induced NF-κB activation and COX-2 expression in human lung epithelial cells (122, 123).  
 Inhibits MAPK and JNK activity in HaCaT cells (124).  
 Inhibits TNF-α, and fecapentaene-12-induced COX-2 by blocking NF-κB activation and IKK activity in human colon epithelial cells (125).  
 Inhibits LPS-induced COX-2 expression, PGE<sub>2</sub> formation, and the catalytic activities of 5-LOX in RAW-264.7 cells (127).

*Nitric oxide*  
 Inhibits LPS- and IFNγ-induced NO production at low doses but not at higher doses (128).  
 Inhibits production of LPS-induced iNOS mRNA in cultured BALB/c mouse peritoneal macrophages *ex vivo* and mouse liver *in vivo* (129).  
 Inhibits NO production in activated macrophages (130).  
 Inhibits LPS-induced NO production in mouse macrophages (51).

*Transcription factor NF-κB*  
 Inhibits TNF-α, PMA, or H<sub>2</sub>O<sub>2</sub>-induced NF-κB activation by blocking the phosphorylation of IκKα (131).  
 Inhibits tobacco smoke-induced NF-κB activation and the phosphorylation and degradation of IκBα in myeloblastic and mantle cell lymphoma cells (132).  
 Downregulates IL1 or TNF-α or LPS-induced NF-κB activation (51, 99, 133, 134).  
 Inhibits TRAIL-induced apoptosis by blocking IκBα phosphorylation and degradation and NF-κB activation in LNCaP cancer cells (88, 89).  
 Inhibits UVB-induced NF-κB activation in NCTC 2544 keratinocytes (135).  
 Inhibits degradation of IκBα, NF-κB DNA-binding activity and NF-κB-dependent expression of IL-6 in WI-38 VA13 cells (95).  
 Inhibits NF-κB and Ap-1 activation induced by hemorrhage/resuscitation injury in rats (85).  
 Inhibits TPA-induced NF-κB activation and degradation of IκBα in cultured HL-60 cells (136).  
 Inhibits cytokine-induced NF-κB DNA binding activity, RelA nuclear translocation, IκBα degradation, IκB serine 32 phosphorylation, and IKK activity in EC-6, HT-29, and Caco-2 cells (96).  
 Inhibits TNBS-induced intestinal inflammation by simultaneously blocking NF-κB activation, degradation of cytoplasmic IκBα protein, and cytokine mRNA expression (137).  
 Inhibits LPS-mediated TLR2 mRNA induction by inhibiting NF-κB activation (102, 103).  
 Inhibits BCG-induced IL-8 production in human monocytes and gingival fibroblasts by blocking NF-κB activation (108).  
 Inhibits constitutive activation of NF-κB in HTLV-1 infected T-cell lines and primary ATL cells, by inhibiting phosphorylation of IκBα and Tax-induced NF-κB transcriptional activity (55).

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587 cumin reduced COX-2, PGE<sub>2</sub>, matrix metalloproteinase  
 588 (MMP)-2, COX-1, and MMP-9 levels, but had no effect  
 589 on MMP-7 levels (115). Other studies have reported that  
 590 curcumin blocked the expression of COX-2 mRNA (116,  
 591 117) but had no effect on COX-1 mRNAs (116). Plummer  
 592 *et al.* observed that curcumin suppressed the protein levels  
 593 of LPS-induced COX-2 and PGE<sub>2</sub> in human leucocytes  
 594 in a dose-dependent manner (118). A similar effect was  
 595 reported in A549 human lung epithelial cells, where cur-  
 596 curcumin inhibited IL-1β or IFN-α-induced prostaglandin  
 597 E<sub>2</sub> and cyclooxygenase-2 at both the protein and the  
 598 mRNA levels (119, 120). In rats with TNBS-induced col-  
 599 itis, curcumin blocked the expression of COX-2 and in-  
 600 flammatory cytokines while increasing PGE<sub>2</sub> levels (121).  
 601 Various studies on human lung epithelial cells exposed  
 602 to cigarette smoke have shown that curcumin inhibited  
 603 NNK-induced activation of NF-κB and COX-2 expression  
 604 (122, 123). Similarly, in HaCaT cells, curcumin abol-  
 605 ished UVB-induced COX-2 expression by suppressing  
 606 p38 MAPK and JNK activity (124).

In human colon epithelial cells, curcumin arrested the  
 TNF-α, and fecapentaene-12-induced COX-2 by blocking  
 NF-κB activation and IKK activity (125). A similar effect  
 has been observed in HT-29 colon cancer cells, where cur-  
 cumin arrested the mRNA and protein expression of COX-  
 2 but not of COX-1 (126). Studies on LPS-stimulated  
 RAW-264.7 cells indicate that curcumin reduces COX-2  
 expression, PGE<sub>2</sub> formation, and the catalytic activities  
 of 5-LOX (127).

The studies on mouse peritoneal exudates have revealed  
 that low-dose curcumin reduces LPS- and IFNγ-induced  
 NO production, whereas higher doses do not (128). In  
 another investigation, curcumin reduced the production  
 of iNOS mRNA in cultured BALB/c mouse peritoneal  
 macrophages *ex vivo* in a concentration-dependent man-  
 ner and also iNOS mRNA expression in the livers of mice  
 receiving two oral doses of 0.5 mL of a 10-μM curcumin  
 (92 ng/g of body weight) and LPS (129). Similarly, in  
 studies using activated macrophages, low-dose curcumin  
 inhibited NO production at 24 h (IC<sub>50</sub> of 6 μM) and 10 μM

627 curcumin also reduced NOS activity than noncurcumin-  
628 treated activated macrophages (130). In another study,  
629 curcumin has been reported to reduce LPS-induced NO  
630 production in mouse macrophages (51). These studies  
631 affirm that curcumin acts as a strong antiinflammatory  
632 agent.

#### 633 EFFECT ON CURCUMIN ON TRANSCRIPTION FACTOR 634 NF- $\kappa$ B

635 The nuclear factor NF- $\kappa$ B is a ubiquitous transcrip-  
636 tion factor important for its pleiotropic effects, inducible  
637 expression patterns, unique regulatory mechanisms, and  
638 involvement in a large number of signaling and gene ex-  
639 pression pathways (Table III). The activation of NF- $\kappa$ B is  
640 crucial to innate and adaptive immunity and it plays an  
641 important role in inflammation, autoimmune diseases, and  
642 cancer. As shown in a seminal study performed in our labo-  
643 ratory, curcumin abrogates NF- $\kappa$ B activation induced by  
644 TNF- $\alpha$ , PMA, or H<sub>2</sub>O<sub>2</sub>, by blocking the phosphorylation  
645 of IKK $\alpha$  (131). Moreover, our studies on tobacco smoke-  
646 induced NF- $\kappa$ B activation in myeloblastic and mantle cell  
647 lymphoma cells revealed that curcumin blocks NF- $\kappa$ B ac-  
648 tivation by inhibiting the phosphorylation and degradation  
649 of I $\kappa$ B $\alpha$  (132). Curcumin also reportedly abrogates LPS-  
650 induced MAPK activation and the translocation of NF- $\kappa$ B  
651 p65 in DCs (73). In several other experiments, curcumin  
652 has been reported to downregulate IL1 or TNF- $\alpha$  or LPS-  
653 induced NF- $\kappa$ B activation (51, 99, 133, 134). A study with  
654 A549 cells has reported that the ability of curcumin to ar-  
655 rest NF- $\kappa$ B binding activity is reversible within 30 min  
656 after IFN- $\alpha$  administration (134). In studies on LNCaP  
657 cancer cells, curcumin mediated TRAIL-induced apop-  
658 tosis by blocking I $\kappa$ B $\alpha$  phosphorylation and degradation  
659 and subsequently abrogated NF- $\kappa$ B activation (88, 89).  
660 The studies with NCTC 2544 keratinocytes have shown  
661 that curcumin can inhibit UVB-induced TNF- $\alpha$ , IL-6, and  
662 IL-8 by impeding NF- $\kappa$ B activation (135).

663 The studies with WI-38 VA13 cells have revealed that  
664 curcumin can also inhibit the degradation of I $\kappa$ B $\alpha$  up-  
665 stream and subsequent NF- $\kappa$ B DNA-binding activity and  
666 NF- $\kappa$ B-dependent expression of IL-6 downstream (95).  
667 Curcumin treatment also repressed NF- $\kappa$ B and Ap-1 ac-  
668 tivation induced by hemorrhage/resuscitation injury in rats  
669 (85). Similar to this, curcumin has also been found to  
670 arrest the TPA-induced NF- $\kappa$ B activation by attenuating  
671 the degradation of I $\kappa$ B $\alpha$  and the subsequent translocation  
672 of the p65 subunit in cultured HL-60 cells. Alternatively,  
673 curcumin also repressed the TPA-induced activation of  
674 NF- $\kappa$ B through direct interruption of the binding of NF-  
675  $\kappa$ B to its consensus DNA sequences (136). The exper-

676 iments on EC-6, HT-29, and Caco-2 cells revealed that  
677 curcumin blocks cytokine-induced NF- $\kappa$ B DNA binding  
678 activity, RelA nuclear translocation, I $\kappa$ B $\alpha$  degradation,  
679 I $\kappa$ B serine 32 phosphorylation, and IKK activity (96).

680 Furthermore, as already mentioned earlier, curcumin  
681 can prevent and treat wasting and histopathologic symp-  
682 toms associated with TNBS-induced intestinal inflam-  
683 mation by simultaneously blocking NF- $\kappa$ B activation,  
684 degradation of cytoplasmic I $\kappa$ B $\alpha$  protein, and cytokine  
685 mRNA expression (137). The experiments on mouse  
686 splenic macrophages have shown that high-dose curcumin  
687 can abrogate LPS-mediated TLR2 mRNA induction by  
688 inhibiting NF- $\kappa$ B activation (102, 103). The studies by  
689 Watanabe *et al.* have shown that curcumin can also arrest  
690 BCG-induced IL-8 production in human monocytes and  
691 gingival fibroblasts by inhibiting NF- $\kappa$ B activation (108).  
692 Finally, curcumin abolished constitutive activation of NF-  
693  $\kappa$ B in HTLV-1 infected T-cell lines and primary ATL cells,  
694 by inhibiting phosphorylation of I $\kappa$ B $\alpha$  and Tax-induced  
695 NF- $\kappa$ B transcriptional activity (55). The various studies  
696 outlined earlier indicate that suppression of NF- $\kappa$ B ac-  
697 tivity may be one of the most important properties of  
698 curcumin that could be responsible for its various immune  
699 functions.

#### EFFECT OF CURCUMIN ON IMMUNE DISEASES 700

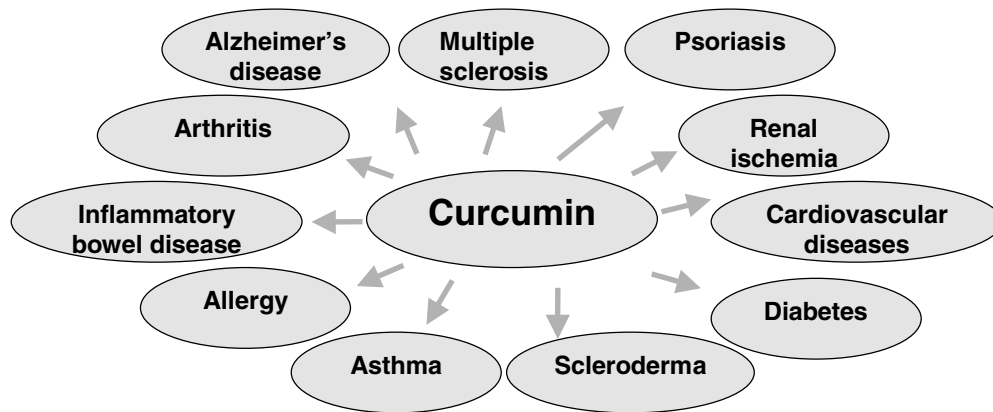
701 Because of its ability to modulate immune cells and  
702 immune cell cytokines, curcumin has been shown to af-  
703 fect several autoimmune diseases (Fig. 3). Inflammation  
704 is a critical feature of most autoimmune diseases. Thus,  
705 the role of curcumin in the therapy of such disorders is  
706 expected.

#### *Alzheimer's Disease* 707

708 Several reports suggest that curcumin has potential  
709 against Alzheimer's disease (138–141), a disease char-  
710 acterized by the amyloid-induced inflammation in the  
711 brain. The effect of curcumin in Alzheimer's disease is  
712 mediated through the downmodulation of cytokine (i.e.,  
713 TNF- $\alpha$  and IL-1 $\beta$ ) and chemokine (i.e., MIP-1b, MCP-  
714 1, and IL-8) activity in peripheral blood monocytes and  
715 reduces amyloid- $\beta$  plaque formation (138–141).

#### *Multiple Sclerosis* 716

717 There are reports that curcumin may have potential  
718 against multiple sclerosis, another autoimmune disease.  
719 In animal model of this disease, curcumin was found to  
720 inhibit IL-12-induced tyrosine phosphorylation of Janus  
721 kinase 2, tyrosine kinase 2, and STAT3 and STAT4 tran-  
722 scription factors (142).



**Regulation of autoimmune diseases by curcumin (diferuloylmethane)**

**Fig. 3.** Immune diseases that may be potentially treated with curcumin.

723 *Cardiovascular Diseases*

724 Curcumin has established antioxidant and antiinflam-  
 725 matory activities that offer promise in the treatment of  
 726 cardiovascular diseases. For example, it can inhibit lipid  
 727 peroxidation; reduce creatinine kinase and lactate dehy-  
 728 drogenase levels; and restore reduced glutathione, glu-  
 729 tathione peroxidase, and superoxide dismutase to normal  
 730 levels. Curcumin can also downregulate the expression of  
 731 myocardial TNF- $\alpha$  and MMP-2 and upregulate the ex-  
 732 pression of eNOS mRNA (143–147).

733 *Diabetes*

734 In diabetes, curcumin can suppress blood glucose lev-  
 735 els, increase the antioxidant status of pancreatic  $\beta$ -cells,  
 736 and enhance the activation of PPAR- $\gamma$  (148–153).

737 *Allergy*

738 As shown in experiments *in vivo* (in guinea pigs) and  
 739 *in vitro* (rat basophilic leukemia cells), curcumin can help  
 740 clear constricted airways and increase antioxidant levels  
 741 (154, 155).

742 *Asthma*

743 That curcumin can relieve symptoms of asthma, has  
 744 been reported. These effects are linked with reduction of  
 745 the lymphocytic production of IL-2, IL-5, GM-CSF, and  
 746 IL-4 that is associated with bronchial asthma (110, 154).

747 *Inflammatory Bowel Disease*

748 As shown *in vivo* in humans and rats, curcumin can  
 749 ameliorate inflammatory bowel disease by reducing in-

750 flammatory cytokine levels, blunting NO and O<sub>2</sub> produc-  
 751 tion, and suppressing NF- $\kappa$ B activation in colon epithe-  
 752 lium (156, 157).

753 *Rheumatoid Arthritis*

754 In rheumatoid arthritis, curcumin exerts beneficial ef-  
 755 fects by inhibiting the expression of collagenase and  
 756 stromelysin and the proliferation of synoviocytes (158,  
 757 159).

758 *Renal Ischemia*

759 In renal ischemia, curcumin can exert beneficial effects  
 760 that include reducing creatine levels; upregulating Mn-  
 761 SOD levels; and inhibiting the expression of RANTES,  
 762 MCP-1, and allograft inflammatory factor (160, 161).

763 *Psoriasis*

764 Clinical evaluation of topical application of 1% cur-  
 765 cumin gel in psoriatic areas reduced the density of CD8<sup>+</sup>  
 766 T when compared to untreated areas, where density of  
 767 CD8<sup>+</sup> T showed an elevation (162). This and other stud-  
 768 ies suggest that curcumin treatment could be an effective  
 769 paradigm in the treatment of psoriasis as it could also  
 770 reduce the activity of phosphorylase kinase (163).

771 *Scleroderma*

772 Because scleroderma is a disease that involves exces-  
 773 sive collagen deposition and hyperproliferation of fibro-  
 774 blasts, curcumin may be able to provide a therapeutic ben-  
 775 efit through its ability to suppress the proliferation of lung  
 776 fibroblasts in a process involving the inhibition of protein  
 777 kinase C $\epsilon$  (164).

778 *Acquired Immunodeficiency Disease (AIDS)*

779 There are several reports indicating that curcumin may  
 780 have potential against AIDS. These effects of curcumin  
 781 are mediated through suppression of replication of hu-  
 782 man immunodeficiency virus (HIV) by inhibition of HIV  
 783 long terminal repeat (165, 166) and HIV protease (167),  
 784 inhibits HIV-1 integrase (168, 169), inhibits p300/CREB-  
 785 binding protein-specific acetyltransferase, and represses  
 786 the acetylation of histone/nonhistone proteins and his-  
 787 tone acetyltransferase-dependent chromatin transcription  
 788 (170). Thus, curcumin has a great potential also against  
 789 AIDS.

## 790 CONCLUSIONS

791 The curcumin, an orange-yellow polyphenol present  
 792 in curry spice, *Curcuma longa* has a long history of  
 793 therapeutic use in the Ayurvedic and Chinese systems  
 794 of medicine. The wisdom and scientific credentials of  
 795 this approach have been corroborated by numerous stud-  
 796 ies conducted over the past 30 years. Indeed, curcumin  
 797 has been found to possess antioxidant, antiinflammatory,  
 798 anticancer, and several other activities listed in this re-  
 799 view. Mechanistic studies have not only confirmed beyond  
 800 doubt that curcumin employs multiple pathways to leave  
 801 its imprint on biological systems, but also warrants its po-  
 802 tential use as a modern nontoxic chemotherapy for numer-  
 803 ous disorders. Curcumin primarily exerts its therapeutic  
 804 effects by inhibiting the degradation of  $\kappa\text{B}\alpha$  and sub-  
 805 sequent inactivation of NF- $\kappa$ B, thus initiating a cascade  
 806 of downstream inflammatory and immunogenic events.  
 807 Curcumin's inhibition of NF- $\kappa$ B activation, in turn, leads  
 808 directly to the inhibition of expression of a number of  
 809 proinflammatory cytokines (e.g., TNF, IL-1, IL-2, IL-6,  
 810 IL-8, and IL-12) and downregulation of the mRNA ex-  
 811 pression of several proinflammatory enzymes (e.g., COX,  
 812 LOX, MMPs, and NOS). In addition, curcumin's immuno-  
 813 genic response is further enhanced by its ability to inhibit  
 814 TLRs. Finally, curcumin exerts proimmune activity in  
 815 several autoimmune disorders including Alzheimer's dis-  
 816 ease, multiple sclerosis, cardiovascular disease, diabetes,  
 817 allergy, asthma, inflammatory bowel disease, rheumatoid  
 818 arthritis, renal ischemia, psoriasis, and scleroderma. Over-  
 819 all, these findings suggest that curcumin warrants further  
 820 consideration as a potential immunoregulatory treatment  
 821 in various immune disorders.

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