Review

Modulation of steroid activity in chronic inflammation: A novel anti-inflammatory role for curcumin

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The expression of NF-kappaB (NF-κB)-dependent pro-inflammatory genes in response to oxidative stress is regulated by the acetylation – deacetylation status of histones bound to the DNA. It has been suggested that in severe asthma and in chronic obstructive pulmonary disease (COPD) patients, oxidative stress not only activates the NF-κB pathway but also alters the histone acetylation and deacetylation balance *via* post-translational modification of histone deacetylases (HDACs). Corticosteroids have been one of the major modes of therapy against various chronic respiratory diseases such as asthma and COPD. Failure of corticosteroids to ameliorate such disease conditions has been attributed to their inability to either recruit HDAC2 or to the presence of an oxidatively modified HDAC2 in asthmatics and COPD subjects. Naturally occurring polyphenols such as curcumin and resveratrol have been increasingly considered as safer nutraceuticals. Curcumin is a polyphenol present in the spice turmeric, which can directly scavenge free radicals such as superoxide anion and nitric oxide and modulate important signaling pathways mediated *via* NF-κB and mitogen-activated protein kinase pathways. Polyphenols also down-regulate expression of pro-inflammatory mediators, matrix metalloproteinases, adhesion molecules, and growth factor receptor genes and they up-regulate HDAC2 in the lung. Thus, curcumin may be a potential antioxidant and anti-inflammatory therapeutic agent against chronic inflammatory lung diseases.

Keywords: Asthma / Chronic obstructive pulmonary disease / Corticosteroids / Histone deacetylase / Nuclear factor-kappa B

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1 Introduction

The disease-preventing ability of a wide variety of dietary plants, tea, and wine has been attributed to polyphenols and antioxidants present in these natural resources [1, 2]. Numerous data on the beneficial effects of fruits, vegetables, and red wine on health support the notion that such effects may be associated with the polyphenols present in these dietary sources. However, the actual therapeutic potential of these compounds is yet to be translated for human use due to lack of knowledge of their complex mode of absorption, biotransformation, and bioavailability. Although several *in vitro* studies have yielded excellent results using the polyphenols from plants, more detailed investigations are still required to extrapolate these results to *in vivo* conditions.

Curcumin, a yellow polyphenolic pigment obtained from the rhizome of *Curcuma longa* Linn. (family Zingiberaceae), is a member of the curcuminoid family of compounds and several of its pharmacological activities and medicinal applications have been reported [3 – 5]. The hydroxyl and methoxy groups of curcumin have been considered to render antioxidant and anticarcinogenic activities, respectively. About 40 – 85% of the total amount of curcumin ingested remains unaltered in the gastrointestinal tract; it is, however, metabolized in the intestinal mucosa

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Abbreviations: **ARE**, antioxidant response elements; **CAM**, cell adhesion molecules; **COPD**, chronic obstructive pulmonary disease; **ERK**, extracellular signal-regulated kinase; **H_2O_2**, hydrogen peroxide; **HAT**, histone acetyltransferase; **HDAC**, histone deacetylase; **HDAC2**, histone deacetylase-2; **IL-6**, interleukin 6; **iNOS,** inducible nitric oxide synthase; **JNK**, c-Jun N-terminal kinases; **MAPK**, mitogen-activated protein kinase; **MMP-9**, matrix metalloproteinases; **NF-κB**, nuclear factor-kappa B; **$O_2^{\bullet -}$**, superoxide anion; **OH^-**, hydroxyl anion; **ROS**, reactive oxygen species; **TNF**, tumor necrotic factor

and liver [6]. Consumption of curcumin up to 10 g/day has been reported to be devoid of any direct toxicity in humans [7] and its bioavailability has been found to be increased 20-fold when consumed along with piperine (an active ingredient of pepper) [8]. A recent surge in research on oxidative stress-related diseases, along with the possibility that antioxidants may help control such diseases, has triggered a remarkable increment in scientific investigations and knowledge regarding the antioxidant role of polyphenols.

2 Antioxidant properties of curcumin

Free radicals (reactive oxygen species, ROS and reactive nitrogen species, RNS) such as superoxide anion ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and nitric oxide (NO), have now been reported to be scavenged by curcumin (in the micro- to millimolar range) both *in vitro* and *in vivo* [9]. Curcumin has been shown to be particularly protective against H_2O_2-induced damage as demonstrated in human keratinocytes, fibroblasts, and in NG 108-15 cells (a mouse neuroblastoma–rat glioma hybrid cell line) [10]. Findings from our own laboratory indicate that curcumin, up to 1–50 μM, could scavenge ROS in 1–4 h as determined by electron paramagnetic resonance spectroscopy (unpublished observation). Curcumin was found to be much faster in terms of quenching ROS when compared with other polyphenols tested (resveratrol and quercetin). The antioxidant properties of curcumin are evident from its ability to lower lipid peroxidation and maintain the activity status of various antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase [11]. In addition, the ability of curcumin to lower ROS production has been attributed to its ability to increase intracellular reduced glutathione levels and its biosynthesis *via* Nrf2 [12]. Since ROS have been implicated in the pathogenesis of various chronic and inflammatory conditions, curcumin has the potential to control these diseases through its potent antioxidant activity. Curcumin can have a contradictory pro-oxidant role which was evidenced in view of its failure to prevent H_2O_2-mediated single-strand DNA breaks, a damage that was prevented by vitamin E [13]. The pro-oxidant property is believed to be due to the generation of phenoxyl radicals of curcumin by the peroxidase–H_2O_2 system, which co-oxidizes cellular glutathione or NADH, accompanied by O_2 uptake to form ROS [14]. Thus curcumin may not be a complete antioxidant under situations of oxidative stress.

3 Curcumin and inflammation

Inflammation is a complex process initiated by either bacterial infection and/or tissue injury resulting in a series of chain reactions ultimately leading to accelerated development of certain chronic diseases [15, 16]. While inflammation may be initiated by primary oxidative stress existent in a cell or tissue, it may also lead to oxidative stress in a system. Thus, both inflammation and oxidative stress are uniquely coupled with each other. Tissue injury induced by trauma releases inflammatory mediators including pro-inflammatory cytokines, and tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1) from leukocytes, monocytes, and macrophages [17]. These cytokines further trigger the up-regulation of other pro-inflammatory cytokines and chemokines, and they increase the expression of many cellular adhesion molecules (CAMs), selectins, integrins, and immunoglobulins [18]. On the other hand, phagocytosis of bacteria or foreign particles is associated with an increase in oxygen uptake by neutrophils, called a respiratory burst. This phase is characterized by generation of high amounts of ROS, such as $O_2^{\bullet -}$, hydroxyl anion (HO^-), singlet oxygen ($^1O_2$), and H_2O_2 [19], and an increase in the expression of phospholipase A2, 5-lipoxygenase (5-LOX), and cyclooxygenase-2 inducible nitric oxide synthase (iNOS) [20, 21] as well as a host of other ROS-generating enzymes, along with the activation of the transcription factor nuclear factor kappa B (NF-κB) [22]. Ultimately, the activation of the transcription factor NF-κB appears to play a pivotal role in the regulation of inducible enzymes, inflammatory cytokines, CAMs, and other substances that are initiators or enhancers of the inflammatory process.

4 Effect of curcumin on NF-κB

Curcumin has been reported to inhibit NF-κB activation, with concomitant suppression of IL-8 release in lung cells [22]. The inhibition of cigarette smoke-induced NF-κB activation by curcumin is believed to be *via* inhibition: of the regulatory Iκ-Bα kinase, NF-κB binding to the DNA, IκBα phosphorylation and degradation, as well as NF-κB p65 translocation [23, 24]. Curcumin basically inhibits NF-κB transactivation by inhibiting the nuclear translocation of the p65 subunit of NF-κB, in association with the sequential suppression of IκBα kinase phosphorylation, IκBα degradation, p65 phosphorylation, and p65 acetylation. A host of other NF-κB-regulated genes involved in inflammation and cellular proliferation have been reported to be down-regulated by curcumin. Furthermore, curcumin was shown to inhibit TNF-α-induced NF-κB-dependent reporter gene expression and also suppressed NF-κB reporter activity induced by TNFR1 and -2, NF-κB-inducing kinase (NIK) and I-kappa kinase [25]. Since NF-κB regulates expression of a wide variety of genes intimately involved in the process of inflammation, inhibition of NF-κB by curcumin may be an interesting prospect in controlling chronic inflammatory diseases involving the NF-κB signaling pathway [25].

In addition to the suppression of pro-inflammatory genes by curcumin, several other secondary genes involved in the

process of inflammation and its effects are also modulated by curcumin. For instance, curcumin down-regulates the expression of iNOS, matrix metalloproteinase (MMP)-9, TNF-α, chemokines, cell surface adhesion molecules, and growth factor receptors (such as EGFR) [26]. In addition, curcumin also modulates a number of other kinase signaling pathways such as c-Jun N-terminal kinases (JNK), p38, AKT, JAK, extracellular signal-regulated kinase (ERK), and PKC in a wide variety of cell types [27]. Interestingly, curcumin and TNF-related apoptosis-inducing ligand have been reported to promote cell death in a cooperative manner [28]. Considering the large array of signaling pathways modulated by curcumin, it becomes apparently difficult to attribute specific pathway(s) for the anti-inflammatory effects of curcumin. In line with this thought process, it may also be possible that curcumin might act by preventing cross-talk between the myriad of signaling pathways to exert its anti-inflammatory properties. The propriety of this contention will require further systematic investigation.

5 Curcumin and glucocorticoid signaling

Corticosteroids have been a therapeutic mainstay for various inflammatory conditions such as asthma and other immune diseases. To the dismay of physicians, a small proportion of asthmatics still remain unresponsive to glucocorticoids, even at higher oral doses, and such a resistance to corticosteroid therapy has also been reported for other inflammatory and immune diseases, including rheumatoid arthritis and inflammatory bowel disease. Such patients present a considerable challenge as to the management of their pathology and episodic exacerbations. Chronic obstructive pulmonary disease (COPD), which is widespread among smokers, is highly unresponsive to corticosteroids and exhibits a largely steroid-resistant pattern of inflammation [29].

Oxidative stress is known to play a conspicuous role in the pathogenesis of COPD [30] and is now widely believed to play an insidious role in downplaying the efficacy of corticosteroids as a therapy for COPD and severe asthma. Recent investigations into how oxidants and oxidative stress bring about enhanced expression of inflammatory genes have revealed that histone acetylation and deacetylation processes may play an important role in determining the efficacy of glucocorticoids [31, 32]. Histones are DNA-binding proteins and play a temporal role in gene expression by regulating and modulating gene accessibility to specific transcription factors. Acetylation of histones by histone acetylases (HATs) allows dissociation of histones from the DNA and makes way for the transcription factors to interact with specific gene(s) leading to their expression (Fig. 1). On the other hand, deacetylation of histones by histone deacetylases (HDACs; there are several isoforms of these enzymes and are classified accordingly) allows re-

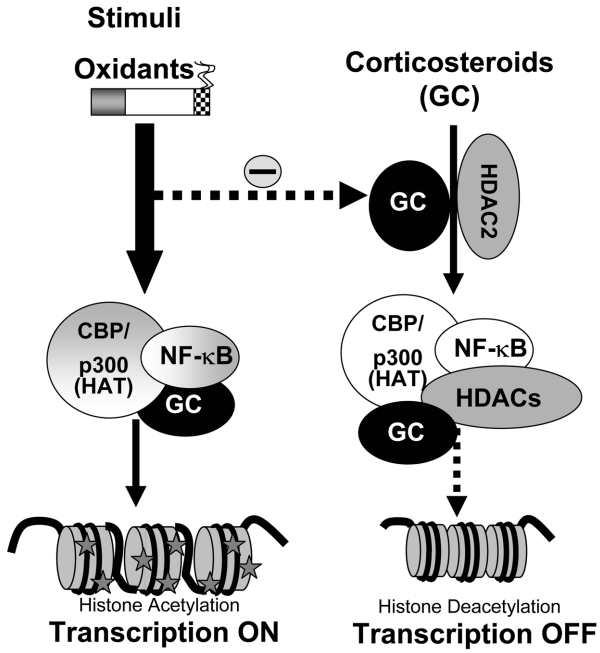

Figure 1. Impact of oxidative stress on the regulation of chromatin structure and pro-inflammatory gene expression. Pro-inflammatory cytokines activate transcription factors, such as NF-κB, recruiting transcriptional co-activator molecules CBP/p300 containing intrinsic HAT activity resulting in histone acetylation and DNA unwinding, allowing DNA polymerases access to the DNA and pro-inflammatory gene expression. Activated glucocorticosteroid receptors (GC) recruit HDAC2 into the transcriptome complex promoting histone deacetylation, chromatin condensation, and expulsion of RNA polymerases, shutting off gene expression. Oxidative stress inhibits HDAC2 activity as well as activating NF-κB, facilitating histone acetylation by the transcriptome complex even in the presence of activated glucocorticoid receptor. Minus sign represents the inhibitory effect of oxidants on GC function.

association of histones with the DNA thus blocking transcription factor binding and gene expression. However, the specific signaling mechanism in regulation of histone acetylation/deacetylation is still largely unknown. It is therefore noteworthy that oxidants have been shown to play an important role in the modulation of HDAC both *in vivo* and *in vitro* [31 – 33]. Oxidants inhibit HDAC activity and therefore maintain the histones in an acetylated state, thus exposing the genes for transcription. Furthermore, work from our own laboratory has lent further support to this mechanism by showing that both cigarette smoke/H_2O_2 and the cytokine TNF-α could significantly increase HAT activity. Such an activation of HAT activity resulted in increased expression of IL-8 in monocytes and alveolar epithelial cells *in vitro* [34].

The suppression of inflammatory genes by glucocorticoids involves recruitment of HDAC2 into the pro-inflammatory transcriptosomal complex, a process mediated by glucocorticoid receptor [32]. This results in deacetylation

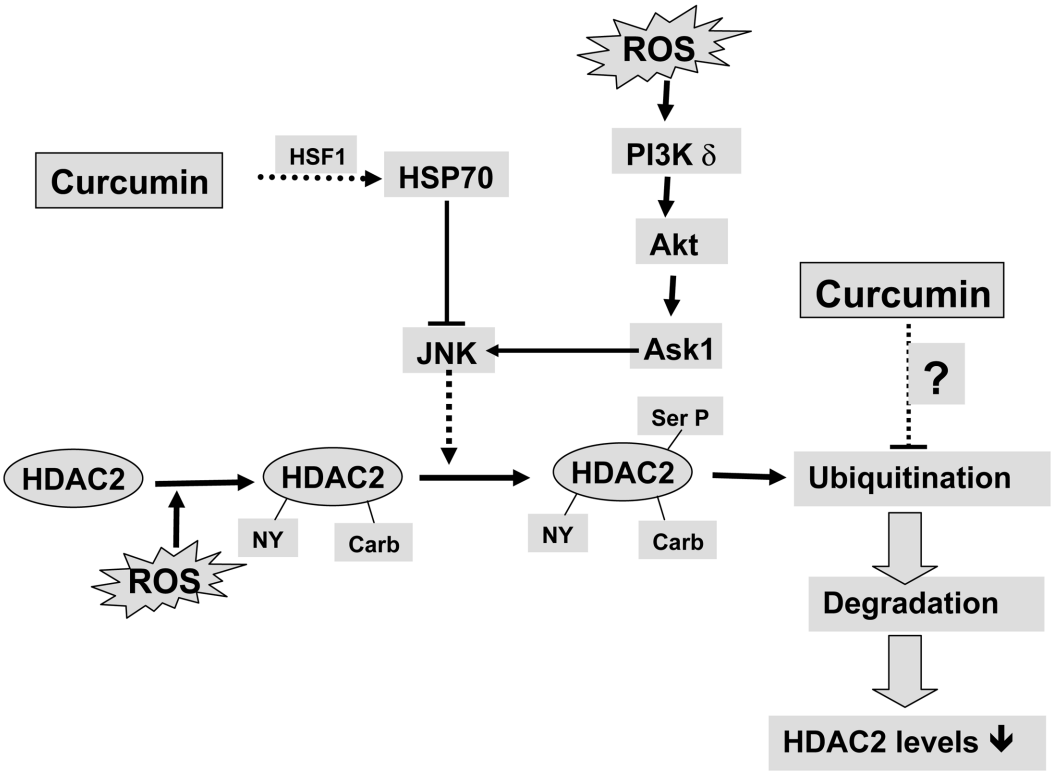

Figure 2. Modulation of HDAC2 by reactive oxygen species and counter regulation by curcumin. HDAC2 is a major component in modulation of chromatin remodeling. ROS can alter the activity status of HDAC2 *via* a host of signaling pathways or by direct oxidative modification. The modification of ROS dependent HDAC2 either by nitrosylation of tyrosine (NY) or carbonylation (Carb) subjects HDAC2 to ubiquitination and further degradation in the proteasomes. Curcumin, due to its ability to directly interfere with ubiquitination and proteasomal mechanisms of protein degradation and by blocking HDAC2 modifications *via* JNK signaling, not only protects the loss of HDAC2 but also maintains the enzyme's native activity.

of histones and a consequent decrease in inflammatory gene transcription. Bronchial biopsies and alveolar macrophages from COPD patients and smoking controls demonstrated significant decrease in HDAC2 activity and HDAC2 protein levels, the magnitude of which is determined by the severity of disease [35]. Therefore, it may not be premature to consider that finding ways to enhance HDAC2 expression would render the steroids more effective for treatment against inflammatory diseases such as COPD. This notion is supported by the finding that theophylline, a methyl xanthine tea polyphenol, increased HDAC2 activity and expression in lung macrophages and also increased the sensitivity of the cells to steroid treatment [36].

Dietary polyphenols such as curcumin and resveratrol have been shown to exert their antioxidant/anti-inflammatory effects *via* modulation of NF-κB activation or chromatin remodeling through modulation of HDAC activity. Such a modulation of HDAC subsequently leads to control of inflammatory gene expression in lung epithelial cells. The authors have recently shown that curcumin was able to restore glucocorticoid function by up-regulating HDAC2 expression and activity in U937 cells exposed to oxidative stress by cigarette smoke or hydrogen peroxide (unpublished observation) and, interestingly, in MonoMac6 cells this was also associated with restoration of HDAC1 and HDAC3 levels by thiols [37]. Clearly then, the fulcrum of the HAT–HDAC balance, which is impaired by oxidants, may thus be restored by strategic use of dietary polyphenols (Fig. 2). Such a mechanism would facilitate steroid-mediated HDAC2 recruitment leading to attenuation of NF-κB-mediated chromatin acetylation and therefore suppression of pro-inflammatory gene expression. The concept that HAT–HDAC imbalance regulates inflammatory gene expression and that this could be modulated by dietary polyphenols is corroborated by the findings that curcumin (100 μM) could inhibit HAT activity; preventing NF-κB-mediated chromatin acetylation [38]. However, other possible mechanisms such as stalling or reversing post-translational protein modifications induced by oxidants *via* which polyphenols inhibit inflammatory response should not be overlooked. It might be reasonable to propose that in addition to their role as antioxidant/anti-inflammatory agents, dietary polyphenols (particularly curcumin) may also assist in increasing the efficacy of steroids *via* modulation of HDAC and HAT expression and activity. To this extent, the beneficial anti-inflammatory effect of polyphenols was

demonstrated by a Finnish study involving over 10 000 participants, wherein a significant inverse correlation was observed between polyphenol intake and the incidence of asthma [39]. Similar beneficial associations were also observed for COPD in a study encompassing over 13 000 adults by Tabak *et al.* [40]. Two more studies have also supported the above findings [41, 42]. However, no single polyphenol was able to control all the symptoms and pathologies of the diseases considered in these studies. Such studies therefore indicate that further multinational clinical studies should be undertaken in order to demonstrate the beneficial effects of a high intake of polyphenols against COPD and other inflammatory diseases.

Another aspect which needs immediate attention is an answer to the question: Does curcumin act only *via* the NF-κB signaling pathway or does it also exert effects independent of this pathway? This is a pertinent question, especially in light of recent reports on the involvement of curcumin in histone acetylation–deacetylation and pro-inflammatory gene transcription. Phosphorylation, glutathiolation, proteasome-ubiquitination (degradation), sumoylation and nitration are also other processes that may, in tandem with acetylation–deacetylation, decide the ultimate outcome for oxidative stress cell signaling. Much knowledge regarding the above processes with respect to curcumin is not available. Therefore, it is possible that curcumin may not only modulate the above-mentioned processes (which are oxidative stress-dependent), but it may also exert its action *via* a direct interaction either with the histones or with component(s) of various other signaling pathways. It would therefore be prudent to practice caution before drawing any firm conclusions as to the anti-inflammatory action of curcumin and its potential as a therapeutic agent.

6 Impact of curcumin in treatment of chronic inflammation in severe asthmatics and patients with COPD

Curcumin has been shown to have a wide spectrum of biological actions. These include its anti-inflammatory, antioxidant, anticarcinogenic, antimutagenic, anticoagulant, antiinfertility, antidiabetic, antibacterial, antifungal, antiprotozoal, antiviral, antifibrotic, antivenom, antiulcer, hypotensive, and hypocholesteremic activities. Its anticancer effect is mainly mediated through induction of apoptosis. Although safety evaluation studies have indicated that curcumin is well tolerated at a very high dose without any toxic effects, some workers have also reported toxic effects of curcumin *in vitro* [43, 44]. Thus, curcumin has the potential to be developed into a modern medicine for the treatment of various chronic inflammatory diseases. Earlier studies have shown that curcumin can affect a number of cellular processes including activation of apoptosis in Jurkat T cells [45], inhibition of platelet aggregation [46, 47], and inhibition of inflammatory cytokine production in macrophages [48]. Curcumin has also been shown to affect the activity of a number of key enzymes such as cyclooxygenase [49], PKC [50], and protein tyrosine kinases [51]. It is, however, important to note that curcumin, when given orally or intraperitoneally to rats, is mostly egested in the feces and only a little in the urine [52, 53]. Only traces of curcumin are found in the blood from the heart, liver, and kidney. Curcumin, when added to isolated hepatocytes, is quickly metabolized and the major biliary metabolites are glucuronides of tetrahydrocurcumin and hexahydrocurcumin [54, 55]. Curcumin, after metabolism in the liver, is mainly excreted through bile. Thus it appears that curcumin may be distributed in only a limited number of organs/tissues and that, too, in small amounts. It is therefore extremely important to investigate which tissues/organs are amenable to curcumin and the average half-life of curcumin in these tissues. However, several *in vitro* results assert that curcumin may be an important therapeutic tool for a wide range of diseases including asthma, COPD, pulmonary fibrosis and in postoperative inflammation [56, 57].

In the Indian traditional system of medicine, the Ayurveda, turmeric (curcumin) is extensively used for the treatment of sprains and swelling caused by injury [3]. Most recently, turmeric powder has been used for the treatment of biliary disorders, anorexia, coryza, cough, diabetic wounds, hepatic disorders, rheumatism, and sinusitis [27]. In view of the fact that the effect of curcumin is due to its ability to modulate oxidants and inflammatory processes in the aforementioned diseases and also since most respiratory diseases involve generation of oxidants and inflammation, the use of curcumin or turmeric extract may have a potential use in respiratory disorders too. This is supported by the more recent observations of the ability of curcumin to inhibit activation of NF-κB [22–24], decrease TNF-α-induced inflammation [25, 48], and increase glucocorticoid efficacy by restoring HDAC activity (unpublished observation). Besides, curcumin has also been shown to modulate expressions of iNOS, MMP-9, CAMs [26], AKT, p38 mitogen-activated protein kinase, ERK, PKC [27], and other inflammatory signaling pathways (Fig. 3). Incidentally, all these pathways are intimately involved in the development and progression of COPD and asthma at one stage or another. Since various studies have shown that curcumin could effectively modulate the aforesaid signaling components, it is reasonable to surmise that diseases like asthma and COPD could be effectively treated with curcumin or that their progression can be stopped. At least, curcumin could increase the efficacy of steroids as a chemopreventive neutraceutical. In fact, as discussed above, several clinical trials [39–42] have shown beneficial effects of polyphenols on subjects suffering from asthma and COPD. However, it remains to be established whether or not curcumin alone can exhibit similar beneficial effects. Future studies involving curcumin should address such questions in order to con-

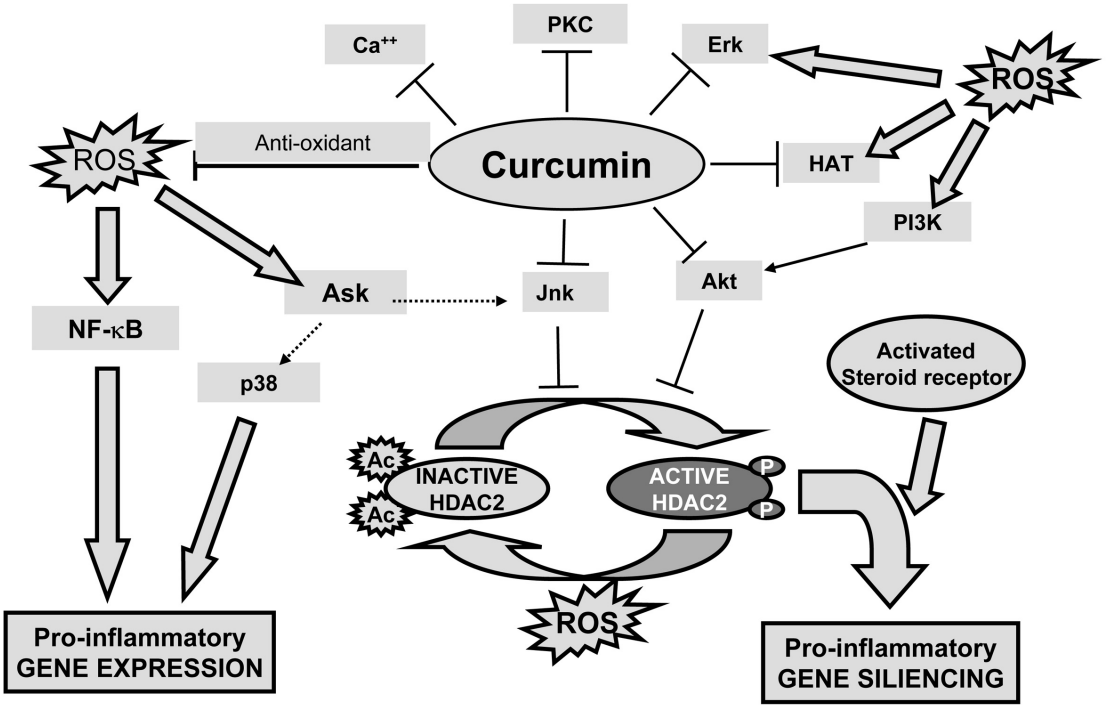

Figure 3. Role of curcumin in the regulation of pro-inflammatory gene expression. In addition to the suppression of pro-inflammatory genes by curcumin, several other secondary genes involved in the process of inflammation and its effects are also modulated by curcumin. For instance, curcumin down-regulates the expression of pro-inflammatory mediators, such as iNOS, MMP-9, TNF-α, chemokines, cell surface adhesion molecules, and growth factor receptors (such as EGFR). In addition, curcumin also modulates a number of other kinase signaling pathways such as JNK, p38, AKT, JAK, ERK, and PKC in a wide variety of cell types.

sider curcumin as a natural therapy either by inhalation or dietary supplementation (adjunct therapy with steroids) for asthma and COPD.

7 Conclusions

Curcumin is a member of the curcuminoid family of compounds and several of its pharmacological activities and medicinal applications have been reported. Curcumin has been shown to act both as an antioxidant as well as an anti-inflammatory agent. Although several studies have reported the beneficial effects of curcumin in various conditions, it is important to note that curcumin is absorbed in very low amounts and may be distributed in only a limited number of organs/tissues. It is therefore extremely important to determine which tissues/organs are amenable to curcumin and what is the average half-life of curcumin in these tissues, in other words the pharmacokinetics and pharmacology of curcumin for absorption, distribution, metabolism, and excretion (ADME). Moreover, no single polyphenol has been shown to yield total therapeutic effects individually. However, several *in vitro* studies assert that curcumin may be an important therapeutic tool for a wide range of diseases including asthma and COPD. Inflammation and oxidative stress are hallmarks of several respiratory diseases including COPD, and their control might help to prevent disease progression. Due to its dual effects, both as an antioxidant and an anti-inflammatory agent, curcumin may be an important therapeutic strategy for the control of COPD and other related diseases. Glucocorticoid resistance is one of the features that need to be immediately addressed in COPD subjects. Several reports show that curcumin is able to increase glucocorticoid efficacy *via* modulation of NF-κB activity and expression at the upstream end, as well as of HDAC2 at the downstream end, and it therefore appears promising as a novel therapeutic chemopreventive neutraceutical tool against glucocorticoid-resistant subjects. Recent observations of the ability of curcumin to inhibit activation of NF-κB, decrease TNF-α-induced inflammation, and increase steroid efficacy by restoring HDAC2 activity along with its modulation of expression of various pro-inflammatory mediators (iNOS, MMP-9, CAMs, IL-8, TNF-α, IL-1β), signaling molecules (AKT, p38 mitogen-activated protein kinase, ERK and PKC), and other inflammatory signaling pathways have added to the therapeutic potential of curcumin in chronic lung inflammation. Since all these signaling components are also involved in asthma and COPD, it is reasonable to surmise that asthma and COPD could be effectively treated with curcumin as an adjunct therapy with steroids. However, it remains to be established whether or not curcumin alone can exhibit sim-

ilar beneficial effects. Future studies involving curcumin should address the questions of its bioavailability, tissue distribution, and its effect *in vivo* in order to consider it as a neutraceutical therapy for asthma and COPD.

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