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Review Article

CURCUMIN PHARMACOLOGICAL PROPERTY: A REVIEW ON ANTI-INFLAMMATORY ACTIVITY AND HUMAN HEALTH

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ABSTRACT

Turmeric has been documented as a spice and for its medicinal values; that attention has been made by both medicinal and culinary fanatics due to its polyphenol compound curcumin. It also worked as an antioxidant and anti-inflammatory, and other ailments include arthritis, diabetes, and cardiovascular diseases. Turmeric's major polyphenol compounds, curcuminoids, which include curcumin (diferuloyl methane), dimethoxy curcumin, and bisdemethoxycurcumin, have been evidenced as anti-inflammatory in human studies. The inflammation has shown different cascade mechanisms involving a number of molecules that are inhibited by curcumin, including cyclooxygenase-2, prostaglandin, phospholipase, lipoxygenase, thromboxane, nitric oxide, elastase, tumor necrosis factor (TNF), interleukin-12 (IL-12), monocyte chemoattractant protein-1 (MCP-1), and leukotrienes. The principal aim of this review paper is to evaluate curcumin's pharmacological anti-inflammatory properties in various diseases in humans with different mechanism of action.

Keywords: Curcumin, Anti-inflammation, Phospholipase, Cyclooxygenase-2 interleukin-12, Turmeric.

INTRODUCTION

Curcuma longa belongs to the ginger family, Zingiberaceae; its root powder is a bright yellow color known as turmeric. In the United States it could be used as a color agent in food. In India, turmeric has been used for a long time as a spice and food preservative, and it also has various medicinal values (Peirce,1999). Curcumin is one of the major components in turmeric, and it is used worldwide in various forms, like capsules, tablets, ointments, energy drinks, soaps, and cosmetics, for different health benefits. For instance, in China, Thailand, Korea, Japan, Malaysia, and Pakistan, curcumin is used in various fields, including as a colorant, in cosmetics, in drinks, in tea, and for antiseptic and anti-inflammatory activity, respectively (Peirce *et al*., 2013; Basnet *et al*., 2011). Curcuminoids are generally recognized as safe even at doses between 4000 and 1200 mg/day at a 95% concentration of three major bioactive constituents of curcuminoids, including curcumin, desmethoxy curcumin, and bisdemethoxycurcumin (Ruby *et al*., 1995). by Food and Drug Administration. The previous studies have been described the curcuminoids properties like antiviral, antifungal and anti-inflammatory (Apisariyakul *et al*.,1995).

The physical characters of the inflammation include swelling, redness, heat, pain and loss of function are could be major process in wound healing and infection. Inflammation also encourages the sequence of reactions in tissue injury which include heal in damaged tissue, initiates the signal transduction (Bisse, 1994). In this mechanism

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neutrophils, monocytes and eosinophils were majorly involved and endothelium and fibroblast proliferation movie for rebuilding of normal condition in the site of injured tissue (Miller and Murray, 1998). This review mainly focusses to provide embarrassment of overview on potential health benefits of curcumin regarding anti-inflammatory in various inflammation related human diseases.

Curcumin: Safety And Activity in Animal

The previous studies have demonstrated that turmeric and curcumin show no side effects at different dosage levels in animals. For instance, mice fed with 0.5% of turmeric and 0.015% of curcumin have been shown to have a protective role in chromosomal damage and mutagenic index. In another dosage study on rats and monkeys, it was also revealed that 1.8 g/kg of curcumin fed to rats and 0.8 mg/kg to monkeys in a 90-day treatment showed no adverse effect. However, in contrast to the safety of curcumin in animals was the 14-day treatment of rats and Swiss mice. They were fed with turmeric and ethanol extract of turmeric (Majeed *et al*., 1995). Any adverse effects were not observed in rats at any doses of turmeric and ethanolic extract, whereas in Swiss mice shown at 5% of both turmeric products, adverse effects like hepatotoxicity were observed (Deshpande *et al*., 1998).

Effect of curcumin in healthy peoples

The number of previous studies were documented on curcumin effects in humans existing with health problems because curcumin health benefits not be as immediate in healthy people if existence of biomarkers at baseline. However, some studies were reported that the health benefits of curcumin in normal people such as 80 mg/kg of curcumin significantly lower the triglycerides but not total cholesterol and increase the inflammation related neutrophil's function and nitrous oxide levels (Epstein *et al*., 2010). Further, it was also reduced free radical generation which were formed during the normal metabolism by increase antioxidant enzymes activity. In addition, prevent the brain aging by decreased the beta amyloid plaque and also protect the liver by regulating the release of alanine amino transferase. In another study, combination of curcumin with Boswellia serrata for three months treatment shown synergetic effects on healthy master cyclists.

In this study curcumin and serrata decreased the oxidative stress by reduce the lipid peroxidation and positive effect on glycoxidation with 10 mg of curcumin and 140 mg of Boswellia extract (Sahebkar *et al*.,2013). In India, the people with 60kg body weight average intake of turmeric are 2-2.5g that means approximately 60-100 mg of curcumin daily consumed. However, the FDA was classified the turmeric as Generally Recognized as Safe (GRAS) substances. The previous studies reported that when intake of 8000 mg of curcumin was available in serum only 1-2hrs and gradually declined within 12 hrs in humans and not found any toxic effects. However, 1200mg of curcumin treatment for 12 weeks in rheumatoid arthritis in humans at the age of between 22-48 years has not shown any adverse effect (Chilelli *et al*., 2016; Shah *et al*., 1999; Cheng *et al*., 2001).

When compared to the rats, the humans are able to tolerate high doses of curcumin due to differences in curcumin metabolism in intestine and liver, because of curcumin conjugation was found greater in intestine than the rats whereas less extensive in liver than the rats. Thus, in humans' curcumin conjugate and curcumin reduction in gastrointestinal tract was greater than in rat intestinal tissue (Mittal *et al*., 2014).

Assessing Parameters Involved in Inflammation

Reactive oxygen species (ROS) play a crucial role in formation of inflammation when they are in higher concentration due to oxidize lipid and proteins result DNA damage, whereas in lower concentration ROS act as signaling molecules in cell growth and apoptosis. The construction of inflammation by ROS mediated through NADPH oxidase interaction with thioredoxin-interacting proteins (TXNIP) and Trx complex which direct the binding of NLRP3 (NOD like receptor pyrin domain containing inflamosome) to TXNIP then it was construct the inflammasome by activation of NLRP3 and association of ASC and procaspase 1/12 protein and release the IL-1β and IL-18 from inflammatory cell (Zhou *et al*., 2010; Zhou *et al*., 2011; Dal Secco *et al*., 2006).

Anti-Inflammatory Mechanism of Curcumin

Executing of inflammation in four stages which include inducers, sensors, mediators and effectors. There are different inflammatory triggers involved in the physiological and pathological of mechanism of inflammation. Most of the anti-inflammatory drugs effects on the receptor, signaling pathway and regulated the target tissue to response to the inflammatory mediators. In similar way, Curcumin exerts anti-inflammatory activity by inhibition of inflammatory mediators' production and regulating inflammatory signaling pathway (Ozaki *et al*., 2002). Curcumin reduced the inflammation in diseases by regulating the inflammatory mediators include IL-1,IL-1β,IL-6, 8,17,27 and tumor necrosis factor (TNF-α) through binding to Toll-like receptors (TLRs) and activate the downstream cascade of nuclear factor-kappa (NF-kB) through acting on Peroxisome proliferator-activated receptor gamaa (PPARγ), Activator Protein (AP-1) and Mitogen activated protein kinase reactions. In addition, curcumin also regulating the activator of Janus kinase/ signal transducer (JAK/STAT) and inhibit the inflammation process (Zhang *et al*., 2019; Rahimifard *et al*., 2017). In the most of the cases recruitment of inflammation was carried out by involvement of the NLRP3 complex, however, curcumin prevents the inflammation process through restrain the assembly of NLRP3 or inhibits the activation of NLRP3 by impedes NF-kB pathway. Daily 80 mg of curcumin nano -micelle significantly reduced the plasma levels of C-reactive protein (CRP) and TNF-α (Ashrafizadeh *et al*., 2020; Kahkhaie *et al*., 2019).

Curcumin shown anti-inflammation through regulation of immune cells involvement in inflammation includes T-helper cell, T-regulatory cells and dendritic cells. In this process, curcumin mainly inhibit the T-helper 17 cell (Th17) differentiation which mainly produce the IL-17,22 and 23 promote the inflammation (Hasanzadeh *et al*.,2020; Olcum *et al*., 2020; Chowdhury *et al*., 2019). ROS associated oxidative stress play a crucial role in the activating of inflammation related transcription factors. However, antioxidant activity of curcumin prevents the formation of ROS production by inhibition of NADH oxidase activity reflects reduce the inflammation (Panahi *et al*., 2016; Alizadeh *et al*., 2018).

Curcumin anti-inflammatory effects on inflammatory diseases in humans

Curcumin significant effect on inflammation that has been documented by several preclinical or clinical research studies in inflammatory diseases of humans among them atherosclerosis, bowel disease and arthritis. Recent data have been describing that curcumin anti-inflammatory activity was mainly due to effectively reducing the levels of inflammatory mediators. In the present review, curcumin anti-inflammatory mechanism and their therapeutic effects in the above diseases were briefly documented.

Effect of Curcumin on Inflammatory Bowel Disease (IBD)

IBD is a chronic and recurrent gastrointestinal inflammatory disease which is mainly form the Ulcerative colitis (UC) and Crohn's disease (CD). Transmural inflammation from mouth to anus was mainly observed in CD whereas epithelium of large intestine mainly colon and rectum was inflamed in UC. IBD was observed in World Wide and it became as global economic burden. However, aetiology of IBD has not been described well it may be genetic or environment factor and immunity. Intestinal barrier was mainly damaged in UC due to excessive production of pro-inflammatory factors which in turn aggravates the inflammatory symptoms (Atabaki *et al*., 2020; Fallahi *et al*., 2021)**.** In IBD treatment, curcumin could act as safe and effective adjuvant agent and it was significantly reduced the clinical symptoms like endoscopic relief, inflammatory markers and oxidative stress. However, some studies described there is no significant evidence related to prove that curcumin is a therapeutic agent for IBD but curcumin used as adjuvant therapy when mesalazine used for the treatment of IBD (Zhang *et al*., 2021; Yousefian *et al*., 2019)

Effect of Curcumin on Arthritis

There are various types of arthritis are present which includes rheumatoid arthritis (RA), gouty arthritis and osteoarthritis. Osteoarthritis is a common degenerative joint disease associated with inflammation was mainly observe in the age 50 years old females. Pathogenesis of osteoarthritis was mainly involvement of synovial inflammation, subchondral bone and cartilage. The clinical symptoms of osteoarthritis was joint swelling and pain found due to destruction of joint by production of inflammatory cytokines like IL-6, TNF-α and IL-1β and matrix degrading enzymes Matrix metalloproteinase (MMP)1, Metalloproteinase with thromobospondin-like motifs (ADAMTS)-5 from the stimulation of osteoblasts, chondrocytes and synovial cells (Coelho *et al*., 2020; Kumar *et al*., 2012). Protective effect of Curcumin on cartilaginous and its anti-inflammatory activity reduce the joint inflammation and pain symptoms. However, in chondrocytes culture inhibit the pro-inflammatory mediators mRNA expressions which include IL-1β and TNF-α, MMPs 1.3and 13 whereas upregulate the chondroprotective transcriptional regulator Cbp/p300 (Glyn-Jones *et al*., 2015).

Effect of Curcumin on Atherosclerosis

In the present days, Atherosclerosis is one of the common incidences of cardiovascular diseases seriously affected human health. Atherosclerosis has complex pathogenesis mainly accompanied with hypertension, hyperlipidaemia and coronary heart disease. In Atherosclerosis, arterial wall inflamed chronically and forms atherosclerosis plaque and rupture. Atherosclerosis plaques were mainly form due to activation of endothelial cells by modified lipoproteins and released the chemokines mainly attract and adherent the monocytes and lymphocytes to the lesion site where cytokines and growth factors released and differentiated the monocytes into macrophages. In addition to that upregulation of the scavenge receptors and TLR (T-cell receptors) accompanied with activation of macrophages made foam-like cells and activate the inflammatory cascade in turn leads to atherosclerotic plaque formation (Seo *et al*., 2018)**.**

In human beings, normal tissue maintains homeostasis in the case of macrophages by balance the two types of macrophages include proinflammatory (M1) and anti-inflammatory (M2). In the formation of atherosclerotic plaque M1 macrophages were dominant which was accumulated with lipoproteins along with in dendritic cells increased the inflammatory cytokines IL-6, iNOS and IL-1β through the expression of NLRP3 inflammasome-related genes. Atherosclerotic plaque mainly contained macrophage, T cells and monocytes when it was activated secrete the protease which was rupture the plaque and finally produce the ischemia and infarction (Yan *et al*., 2019; Lepetsos *et al*., 2019). The clinical trials studies were described Curcumin significantly reduced lipid levels and inflammatory response in non-atherosclerotic populations which was like in mouse model. In other clinical studies were also reported that curcumin reduced concentration of triglycerides in plasma as well as increased the high-density lipoprotein cholesterol levels (HDL). However, to date, there is no strong evidence on effect of curcumin on

atherosclerosis in humans, so that need more comprehensive clinical trials to better effects of curcumin on atherosclerosis.

Neuroprotective and anti-inflammatory effects of curcumin in Alzheimer's disease

Alzheimer's disease (AD) is one kind of intensified neurodegenerative disorder; it is one of the major threats in the healthcare system throughout the world (Yiannopoulou *et al*., 2020) In AD, the brain memory region and language centers are going to be severely affected due to the progressive degeneration of neurons in those regions (Li *et al*., 2023). The major symptoms of AD are loss of short-term memory and, more frequently, long-term memory also being affected (. The major causative factors, including inflammation and oxidative stress, are involved in the development of AD (Nussbaum *et al*., 2017). Curcumin is a natural polyphenol compound derived from turmeric. It has potent antioxidant and anti-inflammatory activity due to two methoxyl phenols that are lin Peng ked by alpha and beta unsaturated carbonyl groups in their structure (Chainoglou *et al*.,2020; Peng *et al*., 2021)**.**

Pre clinical studies have stated that curcumin alleviates the symptoms of AD through the activation of the Nrf2 signaling pathway, which results in reducing the oxidative stress and inflammation response and inhibiting the activity of Aβ formation and Tau hyperphosphorylation (Davies *et al*., 2020; Sidiropoulou *et al*., 2023) . Curcumin can also mitigate the neuroinflammation via acting as an agonist of the PPAR-γ signaling pathway and inhibiting the TLR4 signaling pathway, which was mainly involved in inducing the inflammation (Silva-Abreu *et al*., 2020)**.** HMGB1 expression and release through the activation of Aβ in microglia and increased AchE majorly contribute to the neuronal damage in AD. Curcumin alleviates neuronal damage in AD via inhibition of HMGB1 expression and release and decreases the AchE level (He *et al*., 2020)**.** AD also developed due to the malfunctioning of mitochondria and Abeta and heme complex formation, which contributes to the overproduction of ROS and enhances the inflammation process. However, curcumin prevents the complex formation between Abeta and heme and also Abeta-heme with peroxidase. Curcumin also improved the mitochondrial function through the activation of AMPK and SIRT1 and prevented the oxidative stress and neuroinflammation (Sade *et al*., 2023).

Curcuminoids anti-inflammatory activity in cardiovascular diseases

Cardiovascular diseases (CVD) threaten the human healthcare system and mortality worldwide. Today, fortunately, the individuals manage the CVD through modification of their lifestyle and drug therapies, but it can't decrease the mortality rate in CVD worldwide (Humphries *et al*., 2017)**.** Inflammation and reactive oxygen species are major causative agents for the progression of CVD. Prolonged persistence of oxidative stress induced the inflammation and Therapies that are mainly focused on antioxidants and anti-inflammatories for prevention and treatment of CVD. Myocardial injury by ischemic reperfusion (IR) is the main pathological manifestation to develop the coronary heart disease. Myocardial IR injury reduced the curcumin by mitigating the inflammation and declining the oxidative stress (Mokhtari-Zaer *et al*., 2018). Curcumin at dose 300mg/kg exerts inhibition of expression of Tolk like receptor-2 and monositic chemotatic protein1 and decreases macrophage infiltration via CD68 and also lessens of fibrotic response in cardiac tissue, arterial wall remodelling and obstruction of blood flow leading to the CVDs (He *et al*., 2015). Hyperglycemia-induced proinflammatory cytokines were reduced by curcumin analogue C66 via regulation of the NF-kB and c-Jun N-terminal kinase (JNK) signaling (Pan *et al*., 2014). J17 is another analogue of curcumin that reduced renal and cardiac dysfunction markers in diabetic conditions by suppressing the hyperglycemia-induced inflammation, hypertrophy, and fibrosis. Under diabetic conditions, cardiac microvascular destruction took place, while curcumin treatment restored and redeveloped the cardiac microvasculature (Chen *et al*., 2017)

Curcuminoids anti-inflammatory activity in HIV-infected individuals

In HIV conditions, the consequences that arise include insulin resistance and pancreatic beta cell dysfunction through the action of the virus as well as cART and inflammation. The mainly pro-inflammatory markers like TNF alpha and IL-6 elevated in HIV was developed alteration in intracellular signaling of insulin receptor and reduce the tissue sensitivity to its action (Caron-Debarle *et al*., 2010; Ivanov *et al*., 2016). The studies of the therapeutic effect of curcumin are optimistic about restricting the HIV replication because it has limitations regarding antioxidant dosages and is related to the stage of infection. Further, the results of the pro-oxidant activity of curcumin also depend on the amount of intake and the presence of transition metal ions present in the organism (Ferreira *et al*., 2015).

Therapeutic effects of curcumin in reproductive disorders by anti-inflammatory activity

Pre- and post-testicular abnormalities are the main cause of infertility in men. Pre-testicular abnormalities were associated with hormonal disorders and testicular problems with spermatogenesis, whereas post-testicular abnormalities in the epididymis result in failure in transportation of sperm and fertilization. However, in women, infertility is associated with multifactorial disorders, which are related to ovulatory disorders, chronic diseases, sexual infections, and reproductive-associated endocrine disruption (Esteves *et al*., 2019)**.** A number of previous studies speculated that curcumin is a potent bioactive compound and significantly reduces infertility in men by affecting testicular cells and sperm parameters and male hormonal levels through their antioxidant capacity and reduction in malonaldehyde, creatine protein, and

TNF-alpha levels (Chaithra *et al*., 2020). Curcumin's antioxidant activity and anti-inflammatory activity resolve the disorders in ovaries and pregnancy and positively affect sexual glands (Mahriani *et al*., 2020). A recent study reported that curcumin protectively activates the follicle and maintains the ovarian reserve by inhibiting the PTEN-AKT-FOXO3 pathway (Filardi *et al*., 2020) Curcumin significantly ameiolarate the pregnency's advers out come by inhibit the upregulation of phosphorylation of Akt and pro-inflammatory mediators, inflammation, and migration of macrophages into the placenta (Zhou *et al*., 2016)

Three-quarters of infertility took place in reproductive-age women due to polycystic ovary syndrome (PCOS), which is a common endocrinopathy and heterogeneous syndrome. In this condition, anovulation is common, and also it has significant characteristics like a thinned granulosa cell layer and a thickened theca layer (Chen *et al*., 2015). In PCOS, there seems to be low-grade inflammation due to enhancement of visceral fat, which triggers the development of TNF-alpha, IL-6, and CRP. Curcumin's anti-inflammatory and antioxidant activity impacts the reduction the development of TNF-alpha, IL-6, and CRP. Curcumin treatment also enhances the PPAR-gamma, LDLR, and PGC1-alpha gene expression (Heshmati *et al*., 2021; Jamilian *et al*., 2020)**.** Chronic pelvic pain and infertility are main symptoms of endometriosis, and it is a kind of gynecological disease where endometrium tissue forms outside the uterus. Approximately 10% of childbearing-age women are bearing this disease; these women have 30-50% of infertility (Bina *et al*., 2019).

The peritoneal cavity is a major site for inflammation and immune response in endometriosis. Infiltrated macrophages and other inflammatory immune cells upregulate the production of cytokines, including TNF-alpha, IL-1, 4, 5, 6, 8, 10, 13, 15, and INF-gamma, and transforming growth factor beta (TGF-beta) in the peritoneum. Peritoneal fluid contains elevated levels of IL-6, IL-8, and MCP-1, indicating the severity of endometriosis. However, curcumin regulates the inflammation and inflammatory cytokines by inhibiting the activation and translocation of NF-kB (Arablou & Kolahdouz-Mohammadi, 2018; Devi *et al*., 2015)

CONCLUSION

In conclusion, curcumin significantly regulates the NF-kB, MAPK, AP-1, JAK/STAT, PTEN-AKT-FOXO3 and inhibiting the production of inflammatory mediators. Curcumin could reduce the inflammatory response in IBD, arthritis and atherosclerosis, CVD, HIV, AD and reproductive disorders. Small structural modifications may could also enhance the pharmacokinetics and anti-inflammatory effects of curcumin. At present curcumin more feasible used as dietary supplement or adjuvant drug for significant therapeutic effect.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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