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Biological Activity of Curcumin in Inflammatory Diseases and Cancers: A Review

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ABSTRACT: Curcumin is an active component in *Curcuma longa which has* derivation from its Rhizome. It is a perennial plant. Curcumin has molecular formula: $C_{21}H_{20}O_6$. It is chemically, 1, 7- bis (4- hydroxy - 3 methoxyphenyl) -1, 6 - heptadine - 3, 5 – diene. It is also termed as- 'Di feruloyl methane'. It is extensively employed as a herbal drug in treatment of various diseases mainly associated with inflammatory conditions. In this review paper, mechanisms of action of Curcumin of various molecules of inflammation associated pathway has been studied. Also, few clinical trials have been researched up on which throw a light on beneficial effects of Curcumin in inflammatory conditions like- rheumatoid arthritis and malignant conditions such as colorectal carcinomas. Hence, the challenges while performing the review article were to pin-point pharmaceutical benefits of Curcumin within acceptable dosages over various inflammatory diseases and cancerous conditions affecting humans.

Keywords: Curcumin, *Curcuma*, inflammation, cancer, biological, mediators, chemokines.

INTRODUCTION

Curcumin, a derivative of *Curcumin longa* (turmeric) is main biologically active principle component of this rhizome herb which is a perennial plant. This medicinal product is used widely in traditional Indian as well as Chinese medicinal systems. This has wide consumption in Asian food (Akbar *et al.*, 2018; Alwi *et al.*, 2017). Curcumin is structurally '1,7-bis-4-hydroxy-3-methoxyphenyl 0-1,6-heptadiene-3,5-dione' and is also termed as 'diferuloylmethane'. It constitutes the primary lipophilic polyphenol, water insoluble component within turmeric. However, curcumin has stable structure in acidic gastric pH (Akbar *et al.*, 2018).

According to *Babaei et al.* (2020) curcuma longa has been as a medicinal/therapeutic agent owing to its antioxidantive and anti-inflammatory roles. Curcumin modulates various signaling molecular structures at cellular level that have a role in inflammation (Cheng *et al.*, 2018; Derosa *et al.*, 2016). However, the main issue associated with ingestion of Curcumin is its poor bio-availability (Du *et al.*, 2004).

Hence, different additive agents have been tried in order to improve the bioavailability of curcumins. Most commonly used additive agent is 'Piperine' which is an active constituent of black pepper. Piperine results in an increase of up to 2000% bioavailability of curcumin (Du *et al.*, 2004; Fan *et al.*, 2015). Also, curcumin formulation with prepared in bio-degradable 'nano particle' form by using the emulsion technique increases its bioavailability upto nine times when compared with Piperine (Ferreira *et al.*, 2015).

C REACTIVE PROTEIN (CRP) AND OTHER BIOMARKERS IN SYSTEMIC INFLAMMATORY CONDITIONS

C - reactive protein is a polypeptide molecule belonging to pentraxin family. It is primarily synthesized by liver as a response towards specific types of pro-inflammatory cytokines, for example, Interleukin-6 (IL-6). CRP is one of the main markers associated with inflammation. It is protein seen in acute inflammatory conditions of systemic origin. It is an important marker expressed in variety of inflammation associated conditions for example, cardiovascular diseases, Rheumatoid arthritis and infectious conditions (Garcea *et al.*, 2005; Ganjali *et al.*, 2014; Hosseini and Hosseinzadeh, 2018; Hanah *et al.*, 2006).

Levels of serum C-Reactive Protein show ten to hundred times rapid changes within six to seventy two hours of any inflammation associated event. Besides being a biomarker of inflammation which is used commonly due to the reason that it is inexpensive (Moghadamtousi *et al.*, 2017; Moutachakkir, 2017; Palizgir, 2018).

Elevated C-reactive protein levels show correlation with onset as well as extent of inflammatory responses (Panahi *et al.*, 2014). Healthy subjects demonstrate

minimal amount of C Reactive Protein in their blood. Its levels rise whenever there is damage to tissues and inflammation in association with episodes of trauma or any infectious condition. Hence, aim of review article is to evaluate effects of curcumin over reducing level of C reactive protein (Palizgir *et al.*,2018; Panahi *et al.*, 2014; Ridker, 2003). Karthikeyan *et al.* (2021) in their study found that curcumin interacts with a variety of cell targets such as- NF-ƙB, TNF, IL-6, TRPV1, JAKs/STATs, MAP kinases and PPAR that can reduce progression of Inflammatory Bowel Disease (Kartikeyan *et al*., 2021).

MATERIALS AND METHODS

A total of 2 scientific databases were selected for article search i.e., PubMed and MedLine. Following Medical Subject Headings or MeSH were employed: curcumin, bio-active curcumin, curcuminoids systemic inflammation, C - reactive protein, CRP and hs-CRP only full text research articles were reviewed. Inclusion criteria for article search were- a) only human research based studies which had study participants between age range of 18 to 80 years and b) randomized clinical control trials on curcumin, nano-curcumin and bioperine /curcumin. Exclusion criteria for study were- a) Non-primary research b) if full article was not available and c) animal studies.

BENEFICIAL EFFECTS OF CURCUMIN USAGE

According to a systematic review, it was concluded that supplementing curcumin 'C3' complex along with bioperine as well as nano-curcumin causes lowering of C Reactive protein (Sugimoto *et al.*, 2020).

In another systematic review analysis, it was observed that approximately 1000 mg per day of curcumin or turmeric extract demonstrated significant efficacy in treating arthritis which is an inflammatory condition of knee joint (Soleimani *et al.*, 2018).

In another clinical trial, curcumin was seen to stabilize disease progress in patients suffering from advanced stages of pancreatic carcinoma. In this study, 21 patients were given 8 grams of curcumin on a daily basis. Serum levels of cytokines, NF-ƙβ and COX-2 were monitored in peripheral blood cells. 1 patient was seen to achieve stabilization of disease after a period of 18 months. One patient expressed significantly higher level (four to thirty five times) of serum cytokine which was associated with brief yet significant regression (73%) of tumour. Also, down-regulation of NF- ƙβ and COX-2 were also seen (Sahebkar *et al.*, 2016).

Garcea *et al.* (2005) observed that 3.6 grams of curcumin when administered to patients with various stages of colo-rectal carcinoma for a duration of 7 days demonstrated pharmacologically effective levels of curcumin i.e., 12.7 ± 5.7 nmol/grams in malignant as well as normal colon-rectal tissues (7.7 ± 1.8 nmol/g). this demonstrates anti-inflammatory advantages of curcumin diseases of gastro-intestinal tract. A clinical trial analyzed effect of Curcumin over malignancies and associated tumour marker levels. In first clinical trial fifteen patients diagnosed with advanced colorectal carcinoma were provided with low dose of curcumin(i.e., 440 to 2,200 mg/day) for 4months. It was seen that serum levels of carcinoembryonic antigen (CEA) showed a reduction in levels from 310 ± 15 µg/L till 175 ± 9 µg/L following 2 months of treatment. Stabilization of disease was observed through Computed Tomography scan was in 5 patients (Sproston and Ashworth 2018).

Curcumin has been demonstrated to exert a protective function against various inflammation associated free radical scavengers and causes suppression of cyclo-oxygenase (COX), LOX, inducible nitrous oxide synthetase (iNOS) besides various mediators of inflammation (Sproston and Ashworth 2018; Saji *et al.*, 2021).

The main disadvantage of curcumin is its poor bio-availability, hence, various formulations have been tested that may include- use of nano-particles or making use of Polar-Non-polar Sandwich technique accompanied with complete natural matrix of turmeric (Seo, 2012).

Prostaglandin is a by-product of two formed different and correlated enzymes, Cycloxygenase-1 (COX-1) and Cycloxygenase-1 (COX-2). COX-1, a constitutive enzyme reacts by maintaining haemostasis whereas, its inducible enzyme, COX-2 remains unregulated within inflamed tissues. COX-2 is thus, responsible for an increased synthesis of various prostaglandins (Liu *et al.*, 2016). Saji *et al.* (2021) in their study demonstrated a significant reduction in levels of both COX-1 and COX-2 following Curcumin administration.

INFLAMMATION PATHO-PHYSIOLOGY

Inflammation is a process that involves multiple pathways of cell signaling molecules in response to any trauma or infectious condition. Persistent infectious state leads to development of chronic inflammatory conditions that increases the inflammatory mediators associated with diseases such as- cardiovascular diseases, inflammatory bowel diseases, neurodegenerative disorders and various cancers. Free radicals such as- reactive oxygen and nitrogen species are byproducts of inflammatory processes and are responsible for activity against various bacteria and viruses. Free radical result in oxidative stress production which damages the cell membranous proteins and nuclear proteins including DNA and RNA (Ridker, 2003).

NF-ƙβ, a pro-inflammatory signaling molecule causes macrophages and neutrophils to respond against different pathogenic micro-organisms by activating different cytokines and chemokines. These include-tumour necrosis factor – α (TNF- α), interleukins-1, -2, -6, -8 and -12 (Ridker, 2003).

C reactive protein is an acute phase reactant protein that shows an increase in response to inflammation. This protein is synthesized by hepatic tissues as a response against trauma or infection (Ridker, 2003).

Curcumin causes modulation of innate immunological responses by suppression of expression as well as synthesis of main cytokines along with chemokines for example- Interferon-γ (IFN-γ), tumour necrosis factor (TNF), Interleukins-1β, -6 and -8 and MCP-1. These

chemo attractants have a major function in development as well as pathogenesis of various inflammatory conditions via NF-κB, STAT along with AP1 signaling pathways in innate immunological antigen presenting cells such as- macrophages as well as dendritic cells (Seo, 2012; Saji *et al.*, 2021).

Immuno-modulatory activity of curcumin has been observed during transition from innate immunity to adaptive Responses by means of suppression of activation, proliferative potential as well as differentiation of naïve CD4 positive T lymphocytic cells to T helper 1 (Th-1) and Th-17 sub- types (Wu *et al.*, 2015; Zhu *et al.*, 2017).

COVID-19 is an inflammation associated viral condition which is responsible for cytokine upsurge within human body. Banerjee *et al.* (2020) observed that a 52.9 % higher positive clinical response than placebo group was observed after treatment with Curcumin in COVID-19 positive patients and was found to be statistically significant ($p = 0.001$) (Banarjee *et al.*, 2020).

Bommelaer *et al.* (2020) reported that 45% of patients in placebo group showed clinical recurrence of Crohn's Disease when compared with 30 % patients who were treated by Curcumin. However, no statistical significance was observed ($p = 0.80$).

In a similar study, Sugimoto *et al.* (2020) found that Curcumin treated individuals demonstrated significant decrease in clinical activity of Crohn's disease.

Sadeghi *et al.* (2020) demonstrated significant reduction in C-reactive proteins (CRP) and erythrocyte sedimentation rate (E.S.R.) in curcumin treated patients when compared with placebo.

Shapira *et al.* (2018) in their study found that combination of curcumin, selenium and green tea polyphenols demonstrated significantly good clinical outcomes with decreased inflammation associated symptoms and disease related activity.

However, Kedia *et al.* (2017) in their contradictory study findings on ulcerative colitis patients reported no clinically significant change in remission following curcumin administration.

Lang *et al.* (2015) in their study on ulcerative colitis patients observed clinical remission in 54% patients following treatment using curcumin compared to 0% clinical remission in placebo patients.

Hanai *et al.* (2006) in their randomized double-blinded, placebo control clinical trial reported statistically significant ($p < 0.038$) improvement in clinical activity index after Curcumin administration in ulcerative colitis. In similar study, Holt *et al.* (2005) demonstrated improvement in clinical inflammatory parameters in patients with inflammatory bowel disease after treatment using Curcumin.

CONCLUSIONS

Curcumin has been seen to target a vast variety of molecular sites or targets as it has significant potential as therapeutic drug in various inflammatory diseases and types of cancer.

The significant obstacle in utilization of curcumin in medical therapeutics is its limited bioavailability systemically. Hence, researchers all across the world are investigating large numbers of components of curcumin components and its analogous as they have greater effectiveness and have better absorption capacity. Observed results from different clinical trials have shown promising results. Henceforth, more studies are being conducted in treating inflammatory conditions and various types of cancers.

FUTURE SCOPE

Studying the effects of Curcumin in treatment of inflammatory and neoplastic conditions will enhance treatment modalities in more effective manner.

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Conflict of Interest. None.

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