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Turmeric: A Spice Modulating Immune Response and Combatting Cancer– literature overview

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ABSTRACT

Introduction

Curcumin, the active ingredient in turmeric, is gaining increasing attention due to its potential health benefits, especially in the context of its immunomodulatory and anticancer properties.

Aim of the study

The aim of this review was to discuss recent findings regarding the impact of curcumin on the immune system and its potential applications in anticancer therapy.

Materials and methods

The paper was created based on the Pubmed and Scholar database. The literature was reviewed using the keywords: „curcumin", „immunomodulatory effects", „cytokines", „anticancer", „apoptosis", „cell proliferation", „radiosensitizing".

Results

Studies have confirmed that curcumin, especially in the form of nanocurcumin, exhibits significant immunomodulatory effects. It reduces the number of Th17 cells, increases Treg cells, and regulates the expression of pro-inflammatory cytokines, which is crucial in controlling autoimmune reactions. Furthermore, it demonstrates anticancer activity by inhibiting the growth of cancer cells, stimulating apoptosis, and enhancing the effectiveness of anticancer therapy.

Conclusions

Despite promising results, further research on the safety of curcumin therapy, particularly in the long term, is essential. Limitations associated with bioavailability and pharmacokinetics suggest the need for the development of formulations with increased bioavailability to maximize the potential benefits of curcumin in the treatment of various disorders.

Key words: curcumin; immunomodulatory effects; cytokines; anticancer; apoptosis; cell proliferation; radiosensitizing;

INTRODUCTION

Contemporary science and medicine are increasingly emphasizing the potential health benefits derived from natural substances, such as turmeric, which has long been a significant component of spices, especially in Indian cuisine [1,2] . In addition to its role in the culinary domain, turmeric has found applications in traditional Chinese and Indian medicine, where it is utilized for the treatment of various ailments, including insect bites, wounds, urinary system disorders, and as an antiparasitic agent. Furthermore, in the literature of Indian natural medicine, anticancer properties are attributed to turmeric.[1].

Turmeric, derived from the rhizomes of Curcuma longa, is known for its content of bioactive curcuminoids, primarily curcumin, demethoxycurcumin, and bisdemethoxycurcumin. The chemical composition of turmeric comprises approximately 60-70% carbohydrates, 6-13% moisture, 6-8% protein, 3-7% essential oils, 5-10% fat, 3-7% minerals, 1-6% curcuminoids, and 2-7% fiber[1,3].

In recent years, research has been focused on curcumin, a lipophilic polyphenol exhibiting potential as an anticancer, antibiotic, anti-inflammatory, and anti-aging substance [2,4,5] . Despite its promising properties, the low water solubility, limited bioavailability, and specific pharmacokinetic profile pose certain challenges to the full therapeutic utilization of curcumin[2]. In this context, strategies aimed at enhancing bioavailability, such as the addition of piperine and nanoparticle formulations, represent promising approaches that may improve the efficacy and effectiveness of curcumin in therapeutic applications[6–8].

The research conducted in recent years through in vitro, in vivo, and clinical studies confirms the multifaceted action of curcumin on various biological targets, such as transcription factors, growth factors, inflammatory mediators, cytokines, and apoptotic proteins.[9–26]. In this review, we will discuss the current state of knowledge regarding the potential applications of curcumin in medicine, with a particular focus on its immunomodulatory properties and potential for use in oncological treatment.

IMMUNOMODULATORY PROPERTIES

The recent years have witnessed significant advancements in research on the immunomodulatory potential of curcumin. These studies have focused on various disease entities where curcumin may play a crucial role in regulating the immune response. In this chapter, we will delve into the latest findings concerning the immunomodulatory impact of curcumin, particularly in the context of rheumatic diseases, Covid-19, multiple sclerosis, and migraine.

Rheumatic diseases

Farzaneh et al., conducted a study aiming to assess the impact of nanocurcumin supplementation on the inflammatory response of Th17 helper T cells in patients with Behçet's disease (BD). A randomized, double-blind, placebo-controlled trial was carried out, involving 36 BD patients who received either 80 mg of nanocurcumin or placebo for eight weeks. At the conclusion of the study, nanocurcumin was found to significantly reduce the number of Th17 cells, along with downregulating the expression of the transcription factor RORγt, pro-inflammatory cytokines (IL-17, IL-23), and the levels of miRNA-155, miRNA-181, and miRNA-326. Furthermore, a significant reduction in disease activity was observed in the nanocurcumin-treated group compared to the placebo group[9].

Another study on the role of curcumin in Behçet's disease was conducted by Abbasian et al., focusing on the assessment of the impact of nanocurcumin supplementation on the population and function of regulatory T cells (Treg) in patients with Behçet's disease (BD). In a randomized, double-blind, placebo-controlled trial, 36 BD participants received either 80 mg of nanocurcumin or placebo for 8 weeks. Disease activity, Treg frequency, and the expression of associated immunological parameters, such as the transcription factor FoxP3 mRNA, microRNAs (miRNA) miRNA-25 and miRNA-106b, as well as levels of cytokines such as transforming growth factor (TGF)-β and interleukin (IL)-10, were analyzed. The results demonstrated a significant increase in the number of Treg cells, as well as elevated levels of FoxP3, TGF-β, IL-10, miRNA-25, and miRNA-106b in the nanocurcumin group compared to the placebo group. Additionally, a significant increase in serum levels of TGF-β

and IL-10 was observed in the nanocurcumin group. A substantial decrease in disease activity was also noted in this group compared to the placebo group[10].

In a study investigating the impact of nanocurcumin on patients with ankylosing spondylitis (AS), 12 patients received nanocurcumin for 4 months, while 12 patients constituted the control group, receiving a placebo. Following nanocurcumin treatment, a significant increase in the frequency of regulatory T cells (Treg) was observed in AS patients. Real-time PCR analysis revealed significant changes in the expression of microRNAs (miR-17, miR-27, miR-146a) and the FoxP3 gene after nanocurcumin therapy. The nanocurcumin-treated group also exhibited higher levels of interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), along with lower levels of interleukin-6 (IL-6) compared to the control group[11].

Another study by Atabaki et al., aimed to investigate the effects of curcumin, an active component of turmeric, on immune responses in osteoarthritis (OA) patients. Thirty participants were divided into intervention (received Sinacurcumin® 80 mg daily) and placebo groups, monitored for 3 months. The intervention group showed significant improvements in Visual Analog Score (VAS), C-reactive protein (CRP), CD4+ and CD8+ T cells, Th17 cells, and B cells frequency. Treg cells increased significantly, and Treg/Th17 ratio shifted towards Treg lymphocytes, indicating a notable immunomodulatory effect of curcumin. Additionally, curcumin significantly decreased B cell activities, providing a novel insight into its potential role in regulating B cell functions in OA patients[12].

The study conducted by Wang et al. confirms the potent therapeutic effect of curcumin in the context of joint inflammation in collagen-induced arthritis (CIA) rats. Curcumin demonstrates strong pharmacological activity in reducing the inflammatory response of macrophages by inhibiting the NF-κB signaling pathway. It has been shown that curcumin regulates the IκBα protein, a key inhibitor of NF-κB, which may have therapeutic significance in rheumatoid arthritis (RA). During the study, curcumin limited the degradation of IκBα, resulting in reduced COX-2 expression. Treatment with curcumin led to a reduction in the severity of inflammation, joint damage, and histopathological changes, such as swelling or bone/cartilage destruction. Additionally, curcumin inhibited the release of pro-inflammatory cytokines and demonstrated the ability to induce macrophage apoptosis at safe concentrations. The study findings suggest that curcumin may represent a promising therapy for RA by simultaneously reducing the inflammatory response in the joints and inducing macrophage apoptosis, contributing to the improvement of rheumatoid arthritis symptoms in rats[13].

Covid-19

The triple-blind, placebo-controlled, randomized clinical trial conducted by Hassaniazad et al. aimed to investigate the therapeutic role of nanomicelles containing curcumin as a modulator of inflammatory immune responses in patients with Covid-19. Participants were divided into two groups: one receiving a placebo and the other nanocurcumin. The expression of genes and levels of cytokines in serum, associated with subgroups of the cellular immune response such as Th1, Th2, Th17, and Treg, were analyzed. The results indicate that nanocurcumin appears to modulate the immune response by reducing Th1 and Th17, increasing Treg responses, and decreasing IL-17 and IFN-γ, while simultaneously elevating levels of suppressive cytokines TGF-β and IL-4. Conclusions from the study suggest that nanocurcumin may expedite the recovery process after the acute inflammatory phase of Covid-19[14].

Abbaspour-Aghdam et al. also investigated the immunomodulatory properties of curcumin in COVID-19. Their study demonstrated that nanocurcumin positively influences the immune system of COVID-19 patients by enhancing NK cell functions and reducing pro-inflammatory cytokine levels. In COVID-19 infection, a decreased number of NK cells and reduced cytotoxicity are observed. Administration of nanocurcumin resulted in an increase in both the number and cytotoxicity of NK cells. Analysis of the expression levels of activating and inhibitory NK cell receptors mRNA revealed significant differences between the patient group and the control group. COVID-19 patients exhibited lower expression levels of activating receptors and elevated levels of inhibitory receptors. After curcumin administration, there was an increase in the levels of activating receptors and a decrease in the levels of inhibitory receptors. In terms of cytokines, COVID-19 patients had significantly higher levels of IL-1β, IL-6, TNF-α, and C5a in serum. However, nanocurcumin intake significantly reduced these levels post-treatment, suggesting potential benefits in inflammation reduction[15].

The results of the study conducted by Valizadeh et al. suggest that nanocurcumin may effectively modulate the inflammatory response in patients with Covid-19 by regulating the expression and secretion of key inflammatory cytokines. In the study, forty Covid-19 patients were recruited and divided into two groups: 20 receiving Nano-curcumin and 20 receiving a placebo. Levels of mRNA expression and cytokine secretion, such as IL-1β, IL-6, TNF-α, and IL-18, were assessed using Real-time PCR and ELISA, respectively. The evaluation of mRNA expression levels in the group treated with nanocurcumin and the placebo group showed a significant reduction in the expression level of IL-1β and IL-6 after nanocurcumin treatment

compared to baseline. Results from the cytokine secretion assessment using ELISA between Covid-19 patients treated with nanocurcumin and the placebo group in serum demonstrated a decrease in levels of IL-1β, IL-6, and TNF-α after Nano-curcumin treatment, as well as IL-18 compared to the placebo group[16].

Multiple sclerosis

In a study examining the impact of nanocurcumin on patients with relapsing-remitting multiple sclerosis (RRMS), it was observed that the proportions of Th17 cells and the levels of cytokine expression associated with them were significantly higher in patients compared to a healthy control group. Following nanocurcumin treatment in RRMS patients, a significant reduction in the frequency of Th17 cells, the transcription factor RORγt expression, and cytokine levels such as IL-17A were observed. However, nanocurcumin had no impact on IL-23 mRNA expression and IL-23 concentration. The placebo group did not exhibit significant changes in these parameters. These findings suggest that nanocurcumin may lead to a substantial decrease in Th17-related parameters in RRMS patients, indicating its potential therapeutic effect on the disease[17].

In this study, the impact of Nanomicelle-formulated nanocurcumin on the balance of Treg cells in patients with multiple sclerosis (MS) was examined in comparison to a placebo group. Treg lymphocytes, which play a crucial role in maintaining self-tolerance in the body, are dysfunctional in the course of multiple sclerosis, leading to an aberrant immune response. Nanocurcumin demonstrated a favorable effect on MS patients by increasing the number of circulating Treg lymphocytes. Following nanocurcumin treatment, a significant elevation in the frequency of Treg lymphocytes and an increase in the FoxP3 protein level (regulating Treg function) were observed in both stimulated and unstimulated cells. Levels of cytokines (TGF-β and IL-10), which were lower in MS patients, were significantly elevated after nanocurcumin treatment in both serum and peripheral blood cells. These results suggest that nanocurcumin may have a beneficial impact on the immune system and symptoms of patients with MS[18].

Migraine

The study aimed to investigate the impact of nano-curcumin supplementation on migraine patients. Forty participants were randomly assigned to receive either nano-curcumin or a placebo for two months. After this period, a significant increase in the expression of IL-4 and TGF-β genes was observed in the nano-curcumin group, with only IL-4 serum levels showing significant changes. Between-group comparisons did not reveal statistical differences in gene expression, but a significant increase in IL-4 serum levels was noted following nano-curcumin supplementation. The results suggest that nano-curcumin may positively influence IL-4 levels, indicating anti-inflammatory effects, while having minimal impact on TGF-β. Further studies are needed to fully understand the precise mechanism of curcumin in migraine patients[19].

CURCUMIN IN ONCOLOGY

In recent years, numerous studies have investigated the impact of curcumin on cancer cells. Diverse inhibitory mechanisms have been observed, including the inhibition of growth, proliferation, migration, stimulation of apoptosis and autophagy, as well as cell cycle blockade. Additionally, the positive effects of curcumin on alleviating side effects of anticancer therapies, synergistic actions with drugs to enhance the effectiveness of cancer pharmacotherapy, and sensitization to radiotherapy have been demonstrated.

Inhibition of growth, proliferation, and migration of cancer cells

Wang et al., investigated the tumor-suppressive effects of curcumin on SiHa human cervical cancer cells. Various concentrations of curcumin were tested for their impact on cell proliferation and apoptosis. The results demonstrated that curcumin induced ROS accumulation, apoptosis, autophagy, cell cycle arrest, and cellular senescence, accompanied by the upregulation of p53 and p21 proteins in SiHa cells. Morphological changes, such as flattened and enlarged cells, indicative of cellular senescence, were also noted upon curcumin treatment[20].

The subsequent study, conducted by Zhang et al., delved into the apoptotic effects of curcumin on human papillary thyroid carcinoma BCPAP cells. The primary objective was to elucidate the underlying mechanism, with a particular focus on endoplasmic reticulum (ER) stress pathways. The study found that curcumin increased inositol-requiring enzyme 1a (IRE1a) phosphorylation and XBP-1 mRNA splicing, inducing a subset of ER chaperones. Cleavage of activating transcription factor 6 (ATF6) and subsequent upregulation of its downstream target CHOP (C/EBP homologous protein 10 that upregulates the expression of several pro-apoptotic proteins) were observed. Additionally, curcumin induced intracellular Ca2+ influx by inhibiting the sarco-endoplasmic reticulum ATPase 2A (SERCA2) pump. The increased cytosolic Ca2+ activated calcium/calmodulin-dependent protein kinase II (CaMKII) signaling, leading to mitochondrial apoptosis pathway activation[21].

Zhou et al., investigated the expression of Enhancer of Zeste Homolog 2 (EZH2), an oncogene, and Hepatocellular Carcinoma Deletion Gene 1 (DLC1), an antioncogene, in breast cancer (BC) and assessed their regulatory association in triple-negative breast cancer (TNBC). Additionally, they examined the role of curcumin in TNBC and its potential mechanism of action.. The research reveals overexpression of EZH2 and down-regulation of DLC1 in BC tissues and cells, that may predict poor prognosis in TNBC patients. Experiments demonstrate that curcumin is identified as a potential anticancer agent, shown to restore DLC1 expression by inhibiting EZH2. This restoration leads to the inhibition of migration, invasion, and proliferation, promotion of apoptosis, and cell cycle blockade in TNBC cells[22].

Study conducted by Ainur Rahmah et al. aimed to investigate the mechanism through which curcumin induces apoptosis in breast cancer cells via the RASSF1A and Bax pathways. The tumor suppressor gene RASSF1A plays a pivotal role in regulating proliferation, promoting apoptosis, and stabilizing microtubules. Commonly observed inactivation of RASSF1A in various solid tumors, including breast cancer, underscores its significance. Additionally, Bax facilitates apoptosis by counteracting the anti-apoptotic effects of Bcl-2. The study's findings suggest that curcumin treatment effectively enhances cytotoxic activity, leading to the suppression of breast cancer cell growth in vitro. This is achieved through the reactivation of RASSF1A, upregulation of Bax, and the induction of apoptosis[23].

Another study investigated the potential therapeutic impact of combining curcumin (CUR) and berberine (BBR) on hepatocellular carcinoma (HCC), with a specific focus on the miR-221/SRY-box transcription factor 11 (SOX11) axis. Experiments conducted on HEPG2 and Huh7 cells revealed that both CUR and BBR individually dose-dependently suppressed

HCC cell growth, and their combined effect was most potent at a 2:1 ratio. The combined effects of CUR-BBR played a significant role in inhibiting HCC cell growth by regulating the miR-221/SOX11 axis. Moreover, CUR-BBR activated pro-apoptotic proteins caspase-3/9 through the miR-221/SOX11 axis. The findings suggest a promising therapeutic approach for HCC through the targeted modulation of the miR-221/SOX11 axis using the combined treatment of CUR and BBR[24].

Synergism with medications

Martin et al. conducted an in vitro study with the objective of augmenting the effectiveness of the hypomethylating agent azacitidine (AZA), a commonly utilized treatment in myeloid neoplasms. The study proposed a novel approach by synergistically combining AZA with the natural compound curcumin (CUR). The research focused on analyzing the effects of AZA plus CUR on proliferation, apoptosis, cell cycle, and differentiation in myeloid leukemic cell lines, as well as bone marrow samples from patients. The results demonstrated a synergistic effect between AZA and CUR across all leukemic cell lines and in the majority of leukemic patient samples. This combination led to a notable decrease in proliferation and an increase in apoptosis compared to the individual activity of each drug. Importantly, AZA plus CUR exhibited low cytotoxicity in healthy samples[25].

The subsequent study was conducted by Abdallah et al. and focused on exploring the impact of combining curcumin (CUR) with celecoxib (CXB) on Hepatocellular Carcinoma (HCC) HepG2 cells. The research investigated potential synergistic interactions between CUR and CXB by treating HepG2 cells with increasing concentrations of both compounds. The study found that lower combined concentrations exhibited higher synergism and increased CXB dose reduction index. Moreover, the addition of CUR to CXB led to elevated cytotoxicity and caspase-3 activation compared to CXB alone. The combination significantly reduced cell viability and levels of Akt, nuclear factor-kappa B (NF-κB), prostaglandin E2 (PGE2), malondialdehyde (MDA), cyclin D1 (CD1), and vascular endothelial growth factor (VEGF) in comparison to individual agents. CUR enhanced CXB-mediated antitumor effects in HepG2 cells through antiproliferative, antioxidant, and pro-apoptotic mechanisms[26].

Prevention and treatment of adverse effects of anticancer therapy

The clinical study by Kia et al., aimed to evaluate the impact of nanocapsule-curcumin on oral mucositis (OM) associated with chemotherapy and radiotherapy in the head and neck region. Fifty patients undergoing chemotherapy, with or without radiotherapy, were divided into a study group and a control group. The study group received nanocapsule-curcumin, while the control group received a placebo for 7 weeks. The results revealed that the severity of OM in the study group was significantly lower than in the control group during the 1st, 4th, and 7th weeks. Moreover, the degree of pain was lower in the study group, specifically in the 7th week. The findings suggest that nanocapsule-curcumin is effective in both preventing and treating OM induced by radiotherapy, particularly in the context of chemotherapy[27].

Another study by Ramezani et al., aimed to assess the impact of curcumin on oral mucositis (OM) in patients undergoing head and neck radiotherapy. Both oral and topical curcumin were employed, compared to a placebo. Thirty-seven patients with head and neck tumors participated in the study, randomly assigned to three groups: curcumin mouthwash, curcumin nanocapsules, and placebo. Efficacy and safety were evaluated based on variables such as the severity and pain/burning associated with OM, using numerical rating scales and the WHO scale. The study results revealed a significant reduction in the severity and burning sensation of OM in patients treated with both oral and topical curcumin compared to the placebo group. At the study's conclusion, over 33% of patients using curcumin mouthwash and 15% of those using curcumin nanocapsules had no ulcers, while all patients in the placebo group experienced OM. Both forms of curcumin, oral and topical, proved to be effective, safe, and well-tolerated in the treatment of radiotherapy-induced OM[28].

Shah et al. conducted a study that compared the effectiveness and safety of a mouthwash containing 0.1% curcumin with 0.15% benzydamine in preventing and alleviating radiation-induced oral mucositis (RIOM) in patients with head and neck cancer undergoing radiotherapy. In this conducted study involving 74 patients, it was found that the curcumin mouthwash significantly delayed the onset of RIOM compared to the benzydamine mouthwash by an average of 2 weeks. The intention-to-treat (ITT) analysis showed a 50% lower risk of RIOM occurrence with curcumin. However, the per-protocol (PP) analysis did not confirm significant differences between the two mouthwashes, and the majority of patients eventually experienced the onset of RIOM. Both mouthwashes proved equally effective in alleviating severe forms of RIOM. The study's conclusion is that while neither

mouthwash completely prevented RIOM, the curcumin mouthwash demonstrated the ability to significantly delay its onset[29].

Talakesh et al. assessed the effectiveness of nanocurcumin in alleviating radiation-induced skin reactions (RISR) in breast cancer patients undergoing radiotherapy. In a randomized, triple-blind, placebo-controlled clinical trial, 42 patients were randomly assigned to receive either radiotherapy plus placebo (control group) or radiotherapy plus nanocurcumin at a dose of 80 mg/day (treatment group) for up to two weeks post-treatment. RISR assessments using the RTOG scale and pain levels were conducted at the beginning of treatment and weekly thereafter. Results showed that in the nanocurcumin-treated group, the percentage of patients with RISR grades 0, 1, and 2 were 9.52%, 47.61%, and 42.85%, respectively, whereas in the control group, these percentages were 0%, 14.28%, and 85.71%, respectively. Although a significant reduction in RISR severity was not observed from the first to the sixth week, a significant difference was noted in the seventh week. Additionally, patient-reported pain was significantly reduced in the treatment group compared to the control group[30].

Sensitization to radiotherapy

Hidayat et al. conducted a study aimed at investigating the potential of curcumin as a radiosensitizing agent in conjunction with radiation therapy for cervical cancer. The focus of the investigation was on survivin levels, an anti-apoptotic protein that plays a crucial role in both cell division and apoptosis inhibition. The results revealed notable outcomes in the curcumin + radiation group, where 75% of patients exhibited a decrease in survivin levels, while 25% showed an increase. In contrast, the placebo + radiation group demonstrated that 40% of patients experienced a decrease in survivin levels, and 60% showed an increase. In conclusion, this study suggests that curcumin proves to be an effective alternative radiosensitizer when used in conjunction with radiation therapy for cervical cancer treatment[31].

The study on sensitizing cancer cells to radiotherapy by curcumin was also conducted by Minafra et al., and the main aim of this study was to develop curcumin-loaded solid nanoparticles (Cur-SLN) to enhance curcumin bioavailability and assess their radiosensitizing capability. The effectiveness of the Cur-SLN formulation as a radiosensitizer was demonstrated on three breast cancer (BC) cell lines. The data presented suggest that SLN-curcumin exhibits a radiosensitizing effect, with its potency increasing in tandem with rising

concentrations. The radiosensitizing function of Cur-SLN, evaluated through transcriptomic and metabolomic approaches, revealed anti-oxidant and anti-tumor effects. The use of curcumin-loaded SLN is proposed for future preclinical and clinical studies, examining its concurrent application during radiotherapy. This bears the dual implications of acting as a radiosensitizing agent against cancer cells and providing a protective role against side effects of ionizing radiation[32].

CONCLUSIONS

The latest reports confirm the immunomodulatory and anticancer effects of curcumin. However, it should be emphasized that despite promising results, further research is necessary, especially regarding the safety of curcumin therapy. Limitations associated with bioavailability and pharmacokinetics suggest that additional research is essential to develop formulations with improved bioavailability, potentially maximizing the benefits of curcumin in the therapy of various medical conditions.

Author's contribution

Conceptualization, Anna Greguła, Bartosz Mazur and Karol Stachyrak; methodology, Mateusz Pawlicki; software, Dawid Mika; check, Dawid Mika, Aleksandra Kłos and Maciej Lambach; formal analysis, Aleksandra Mazurek and Wiktoria Wilanowska; investigation, Kamila Turek and Wiktoria Wilanowska; resources, Karol Stachyrak; data curation, Bartosz Mazur; writing - rough preparation, Anna Greguła; writing - review and editing, Maciej Lambach, Kamila Turek; visualization, Anna Greguła; supervision, Mateusz Pawlicki; project administration, Dawid Mika; receiving funding, Karol Stachyrak

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