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Review

Curcumin: A natural modulator of immune cells in systemic lupus erythematosus

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ABSTRACT

Curcumin is a polyphenol natural product isolated from turmeric, interacting with different cellular and molecular targets and, consequently, showing a wide range of pharmacological effects. Recent preclinical and clinical trials have revealed immunomodulatory properties of curcumin that arise from its effects on immune cells and mediators involved in the immune response, such as various T-lymphocyte subsets and dendritic cells, as well as different inflammatory cytokines. Systemic lupus erythematosus (SLE) is an inflammatory, chronic autoimmune-mediated disease characterized by the presence of autoantibodies, deposition of immune complexes in various organs, recruitment of autoreactive and inflammatory T cells, and excessive levels of plasma proinflammatory cytokines. The function and numbers of dendritic cells and T cell subsets, such as T helper 1 (Th1), Th17, and regulatory T cells have been found to be significantly altered in SLE. In the present report, we reviewed the results of *in vitro*, experimental (pre-clinical), and clinical studies pertaining to the modulatory effects that curcumin produces on the function and numbers of dendritic cells and T cell subsets, as well as relevant cytokines that participate in SLE.

Contents

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1. Introduction

Systemic lupus erythematosus (SLE) is a debilitating autoimmune disease. Fortunately, the outlook for patients now is much better than it was 50 years ago. This is due to improved and more rapid diagnosis, renal dialysis and kidney transplant, and just better patient care in general. As an example of improved patient care, making sure that blood pressure is controlled, as well as treating osteoporosis, have been cornerstones in the treatment of SLE. Unfortunately, the progression to end-stage renal disease with SLE has not changed with improved patient care. To date, the use of corticosteroids and immunosuppressive drugs has been the foundation of drug treatment for SLE, although hydroxychloroquine, antihypertensive drugs, and anti-osteoporosis drugs also play an important role in the management of SLE. The medical community has attained a temporary plateau with regard to the treatment of SLE, because even though more steroid-sparing medications and less toxic doses of immunosuppressive drugs have improved therapeutic efficacy and reduced side effects, the use of these agents has essentially been fully optimized and promise little additional significant benefits. This has prompted the introduction of biologics (*e.g.*, monoclonal antibodies) to alter the course of SLE, but, regrettably, the results of clinical trials have been disappointing thus far. Therefore, there exists an urgent need for alternative treatments, which may include medical procedures, lifestyle changes, and the use of exogenous therapeutic compounds of both synthetic and natural origin. One such natural compound that has shown promise in the treatment of several diseases is curcumin. This review will explore the use of this natural compound to ameliorate the symptoms of SLE.

1.1. Curcumin and its immunomodulatory effects

Curcumin is one of the most well-known natural products used today. This natural compound is isolated from turmeric and is used either alone, or as adjunct therapy with other conventional medications, to treat various diseases. Curcumin is generally regarded as safe. In fact, various human clinical trials have shown no dose-limited toxicity when administered at doses up to 10 g/day [1,2]. Curcumin has also been found to have a wide range pharmacological activities, including anti- and pro-oxidant, anti-inflammatory, and antimicrobial properties, as well as chemopreventive and chemotherapeutic activity [3–16]. Of note, studies have also revealed interesting insight into the immunomodulatory potential of curcumin [17–24]. The immunomodulatory property of curcumin arises from its interaction with various immune mediators, including B and T lymphocytes, macrophage and dendritic cells, cytokines, and various transcription factors. These transcription factors include nuclear factor kappa B (NF-κB), activator protein-1 (AP-1), signal transducer and activator of transcription (STAT), and also their downstream signaling pathways [25–31].

NF-κB exerts a key role in producing pro-inflammatory cytokines such as interleukin (IL)-1, IL-2, and interferon-γ (IFNγ) in T-cells [32–35]. The pleiotropic effects of curcumin are found to originate from suppression of NF-κB activity by inhibiting I kappa B kinase-a (IKK-a) phosphorylation and preventing nuclear translocation of the NF-κB p65 subunit [36–38]. B lymphocyte stimulator (BLYS) is an important cytokine for B cell proliferation and autoantibody secretion in autoimmune diseases [39]. It has been suggested that curcumin could potentially serve as a novel therapeutic agent in the treatment of autoimmune diseases, such as SLE and rheumatoid arthritis (RA), by targeting BLYS. The inhibitory effect of curcumin on BLYS expression is due to a reduction in NF-κB activity mediated by an inhibition in DNA binding of NF-κB and the nuclear translocation of p65 [40]. Another mechanism for the immunomodulatory effect of curcumin is related to inhibition of mammalian target of rapamycin (mTOR) signaling by suppression of cytokine production, for example, IL-2 [41].

1.2. Immunopathology of SLE

SLE is an chronic, inflammatory, autoimmune-mediated disease, which primarily causes intolerance towards self-antigens [42,43]. SLE is commonly characterized by the presence of autoantibodies, deposition of immune complexes in various organs [44,45], recruitment of autoreactive and inflammatory T-cells, and excessive levels of plasma proinflammatory cytokines [46–48]. Autoantibody production by autoreactive B cells leads to the formation and deposition of immunecomplexes in multiple organs and tissues, including the heart, kidneys, brain, joints, skin, and the central nervous system [46,49]. Approximately 80–90% of cases of SLE occur in women [50], who suffer from a mixture of mild skin or musculoskeletal and hematological symptoms [44]. It is believed that heredity, viruses, ultraviolet light, hormonal factors, and drugs may all contribute to some degree in the development of SLE [45].

As it pertains to the immune-based causes of SLE, an imbalance in various T-helper cell subsets (Th1/Th17), regulatory T cells (Tregs), and dendritic cells (DCs) has been suggested to contribute to the pathogenesis of SLE [51]. An immoderate number and function of Th17 cells [52–54] is known to be a preliminary trigger of autoimmune responses, which is mediated through excessive secretion of proinflammatory cytokines, including IL-17 and IL-23. This leads to inflammation and tissue destruction in SLE patients [55,56]. The reduced number and compromised function of Treg cells and the resistance of effector T-cells to the suppressor effects of Tregs are additional mechanisms that have been identified to be involved with the immunopathology of SLE [57–59].

The dysregulated release or functions of pro/anti-inflammatory cytokines in SLE, which can stem from an imbalance among different immune cell subsets, such as Th17/Treg cells, also have a role in the pathogenesis of SLE [60]. Hence, restoring the imbalance in cytokines and deficient immune cells has the potential to be a promising therapeutic target for ameliorating the symptoms of SLE.

Accumulating evidence has demonstrated the usefulness of curcumin in alleviating the effects of several diseases, including SLE, by affecting various types of immune cell [61–63]. In this review, we focus on the positive effects of curcumin as an effective therapeutic agent with which to modulate the function of DCs, Th1, Th17, and Treg cells in SLE.

2. Overview of curcumin's effects on deficient immune cells in SLE

2.1. Role of dendritic cells in the pathogenesis of SLE

Immune cells play an important role in priming, initiating, developing, and in the functional phases of the immune response against foreign pathogens, cancer antigens, and autoantigens. DCs, as key regulatory cells in the innate and adaptive immune response, direct the primary immune response of naïve T-cells against protein antigens [64,65]. DCs, which are widely distributed in most tissues and exist in a so-called 'immature' state are unable to stimulate $CD4^+$ or $CD8^+$ T-cell responses. Immature DCs (iDCs) express low levels of major histocompatibility complex (MHC) class I and class II on the cell surface, but these cells are highly capable of capturing antigens and then processing the ingested proteins into peptides, which are present in the