Phytochemicals as potential antidotes for targeting NF- κ B in rheumatoid arthritis

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Abstract Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune destructive arthropathy prevalent among people in the age group of 40–70 years. RA induces severe pain, swelling and stiffness of joints resulting in bone damage. RA leads to reduced life expectancy when left untreated. RA is characterized by synovial hyperplasia, infiltration of inflammatory cells resulting in formation of pannus. Synovial hyperplasia is mediated by proinflammatory cytokines, notably IL-1 and TNF- α . NF- κ B is a predominant transcription factor in amplifying the inflammatory response. The translocation of activated NF- κ B into the nucleus triggers the transcription of several genes that induce proinflammatory cytokine production. The inhibition of NF- κ B translocation aids blocking the activation of proinflammatory cascades. The quest for more effective and side-effect free treatment for RA unveiled phytochemicals as efficacious and promising. Phytochemicals have been a source of therapeutic substances for many ailments from ancient times. Their therapeutic ability helps in developing potent and safe drugs targeting immune inflammatory diseases driven by NF- κ B including RA. This review highlights the importance of NF- κ B inflammatory cascade in RA so as to elucidate the crucial role of phytochemicals that inhibit the activity of NF- κ B.

Keywords Rheumatoid arthritis · Synovial hyperplasia · NF- κ B · Phytochemicals

Introduction

Arthritis is an age-old musculoskeletal disorder that involves joint inflammation. Of the many types of arthritis, RA is significant. RA is a non-communicable chronic multifactorial destructive arthropathy that affects diarthrodial joints. RA is a systemic inflammatory disorder prevalent in the age group of 40–70 years with male–female ratio 1/2.5 (Lee and Weinblatt 2001). Joint swelling, pain and weakness are the clinical manifestations of RA. When left untreated, RA leads to severe bone and cartilage damage resulting in disability and diminished life expectancy (Bartok and Firestein 2011). RA is characterized by inflammation of the synovial lining manifesting in formation of pannus (Traister and Hirsch 2008). Autoimmune activation triggers an inflammatory response stimulating the production of proinflammatory cytokines at synovial lining. Hyperplasia of synovial fibroblasts, infiltration of lymphocytes, macrophages, plasma cell population and dysregulated apoptosis are found to be the effects of inflammation (Mohr et al. 1975). Profound etiology of RA is not clearly understood. However, studies show that both environmental and genetic factors contribute to pathology (Bartok and Firestein 2011; Traister and Hirsch 2008; Mohr et al. 1975; McInnes and Schett 2011; Hashemi 2013; Matthey et al. 1999; Rubinstein and Weinberg 2012; Vieira et al. 2011; Song et al. 2012; Kourilovitch et al. 2014). Studies also suggest that elevated inflammatory response is due to an altered adaptive immunity and repeated activation of innate immunity prompting the breakdown of tolerance (Bartok and Firestein 2011).

Functionally, synovium encapsulates the joints providing structural support, lubrication and nutrients to the cartilage. Anatomically, the synovial lining comprises of sublining layer and intimal lining layer. Typical synovial

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sublining is acellular consisting scattered blood vessels, few fibroblasts, lymphocytes and macrophages (Smith 2011). Intimal lining layer is superficial and is in contact with the intra articular cavity. The cells of this layer produce lubricious synovial fluid. This layer is made up of two distinct cell types in equal proportions namely, Type A Macrophage-like synoviocytes (MLS) and Type B Fibroblast-like synoviocytes (FLS) (Bartok and Firestein 2011).

RA manifests in the form of synovitis. It also inflicts considerable changes in both layers of synovial membrane. In RA synovium, the sublining layer shows rise in T cells (30–50%), B cells (5%), lymphoid aggregation around dendritic cells and fall in neutrophils. Also, localized antibody production may be observed in patients, e.g.: rheumatoid factors, citrullinated peptide and anti-collagen antibodies. In RA synovium, the intimal lining layer exhibits hypercellularity due to increase in MLS and FLS leading to the expansion of lining depth from 1–2 cells to 10–20 cells. FLS not only express markers of mesenchymal origin that resemble fibroblasts in several characteristics, but also express Cadherin 11, Intercellular Adhesion Molecule 1 (ICAM), Vascular Cell Adhesion molecule (VCAM), integrin and CD55 (decay accelerating factor) (Kiener and Brenner 2005). The early MLS predomination in RA, in turn activates local FLS in the lining by secretion of proinflammatory cytokines, chemokines and growth factors that induce the production of intermediary cytokines, prostanooids, matrix metalloproteinases (MMPs), etc. The production of ample assortment of cytokines eventually leads to synovial inflammation and joint destruction due to the imbalance between the pro and anti-inflammatory cytokines. Although several mediators play a seminal role in the inflammatory cascade IL-1, IL-6 and TNF- α are found to be the main causative agents of amplified inflammation as these trigger the pathways that degrade the bone and cartilage (Epstein et al. 2001). The confluence of such activities starts a paracrine or autocrine network that perpetuates synovitis and destruct the bone cartilage. The synovial environment of RA intimal lining facilitates the survival of FLS by inhibiting apoptosis (Firestein et al. 1996). Despite the genotoxicity of RA synovium, cell proliferation occurs due to the increased expression of anti-apoptotic proteins such as Bcl-2 family proteins (Bartok and Firestein 2011).

Several therapies for treating RA are depicted in Fig. 1. Biological therapies that target proinflammatory cytokines (such as TNF- α , IL-1 and IL-6) have assumed significance in the past two decades. Biological compounds, namely, etanercept, infliximab, adalimumab, certolizumab pegol, golimumab are effective in treating RA. Also, a group of therapeutic agents called disease-modifying antirheumatic drugs (DMARDs) have shown significant results when

used alone or in combination with other biological agents. The effect of methotrexate, an active member in DMARD family is pronounced in combination therapy either with other DMARDs or with a biological agent. Likewise, nonsteroidal anti-inflammatory drugs (NSAIDs) are also commonly used for the treatment of RA. NSAIDs do not provide therapeutic healing but relieve symptomatic discomforts such as pain, swelling and inflammation associated with RA. Prolonged usage of NSAIDs results in side effects such as gastrointestinal bleeding, hypertension, congestive heart failure and renal insufficiency. Whereas, repeated usage of DMARDs leads to soreness of stomach and mouth, swollen lymph nodes, myelotoxicity, myelosuppression, pyrexia, infections and damage to lungs or liver (Vollenhoven 2009; Kahlenberg and Fox 2011).

Albeit several advancements in the field of medicine, no promising treatment exists for the treatment of immune and inflammatory disorders, especially RA. Conventional therapies were found to be ineffective due to symptomatic relief, sometimes accompanied by side effects as mentioned above. Hence, it is all more important to find a holistic and comprehensive therapeutic approach. Hence, a review exploring the importance of phytochemicals as antidotes for the treatment of RA has been presented.

NF- κ B: a regulatory transcription factor

Nuclear factor- κ B (NF- κ B), a predominant transcription factor in vertebrates, intervenes the activation of assorted pathways related to basic cellular functions including immune and inflammatory responses (Roman-Blas and Jimenez 2006). The NF- κ B family comprises five different types of proteins viz., p105 (processed to p50), p100 (processed to p52), p65 (RelA), RelB and c-Rel which share 300 amino acid residues called Rel homology region (RHR) whose crystal structure exhibit a tripartite organization. The first 180 amino acids that form the amino-terminal region fold into an immunoglobulin-like domain. A second immunoglobulin-like domain of approximately 100 amino acids is linked to the first domain through a flexible linker consisting of 10 amino acids. The NF- κ B family proteins act either as homo or heterodimers to initiate transcriptional cascade. The most prevalent activating form of NF- κ B found in stimulated cells is the p65/p50 heterodimer (also called 'classic NF- κ B'). The C-terminal domain regions of the RHR are important for dimerization. DNA binding specificities vary with the type of dimer formed. These homo/heterodimers bind to the NF- κ B consensus sequence 5'-GGGRNYYYCC-3' thereby regulating transcription of target genes. Despite both RHR domains contact DNA, only N-terminal domains form sequence specific interactions. About 150 NF- κ B

Fig. 1 Various therapies for RA treatment. *COX* cyclooxygenase, *PGE2* prostaglandin E2, *MMPs* matrix metalloproteinases, *DMARDs* disease-modifying antirheumatic drugs, *NSAIDs* nonsteroidal anti-inflammatory drugs, *FLS* fibroblast-like synoviocytes, *TNF- α* tumor necrosis factor alpha

responsive genes have been identified so far (Baeuerle 1998; Jaffray et al. 1995; Huxford et al. 1998; Jacobs and Harrison 1998; Makarov 2001).

To activate the transcriptional events, NF- κ B has to get translocated into the nucleus. This translocation is hindered by the binding of inhibitory proteins such as I κ B. I κ B masks the nuclear localization signal (NLS) and also interferes with the capacity of NF- κ B to bind with DNA. There are six I κ B family proteins in higher eukaryotes viz., I κ B α , I κ B β , I κ B ϵ , p105, p100 and Bcl-3. All these proteins contain a centrally located 33 amino acid ankyrin repeat (AR) domain. Activation of NF- κ B involves the release of I κ B from NF- κ B exposing NLS. Release of I κ B from NF- κ B involves phosphorylation followed by ubiquitin mediated proteasome degradation. The signal receiving domain present towards the AR domain possesses the amino acids that are activated by the phosphorylation and ubiquitination signals. I κ B is phosphorylated by specific kinases called IKK (I κ B Kinase) complex. IKK complex is a high molecular weight protein complex embracing at least three subunits IKK1 (also called IKK α), IKK2 (also called IKK β) and NF- κ B essential modulator (NEMO, also called IKK γ). IKK complex phosphorylates I κ B at two sites near the N-terminus (Ser-32, Ser-36). IKK2 is linked to RA as it activates NF- κ B by phosphorylating I κ B. IKK1 has a negative regulatory role as checkpoint in NF- κ B activation. NEMO is less significant as it does not have kinase activity.

However, it is required for the phosphorylation by the IKK complex (Fig. 2) (Solt and May 2008; Golden et al. 2013; Miyakoshi and Yagi 2000; Müller and Harrison 1995).

Role of NF- κ B in RA

Activation of NF- κ B triggers several cascades that induce the inflammatory and immune responses. NF- κ B activation has been observed in RA synovial tissue in early as well as later stages. Immunohistochemical studies have revealed the presence of nuclear NF- κ B in both RA endothelium and synovial lining. Chronic inflammation through NF- κ B activation in RA is initiated by the interaction of T cells and antigen presenting cells (APC). Recognition of the molecules expressed by MHC class-II followed by interaction of receptors (TCR and CD80) with their ligands leads to an induction of NF- κ B-dependent genes namely IL-2, IL-2R and IFN- γ for the activation and proliferation of T cells. Activated T cells express molecules of TNF superfamily, CD40 ligand and RANKL (receptor activator of NF- κ B ligand). Interaction of these molecules with APC receptors induces NF- κ B activation that triggers the ability of APC to activate T-cell proliferation and survival. Moreover, NF- κ B activation also guides toward Th1 response which leads to secretion of proinflammatory cytokines (Makarov 2001).

Fig. 2 NF- κ B signaling cascade. *NEMO* NF- κ B essential modulator

Current approaches targeting NF- κ B

Conventional therapies targeting NF- κ B include gene transfer and usage of several inhibitors that cease either the nuclear translocation of NF- κ B or the binding of NF- κ B to DNA. The events that phosphorylate and degrade I κ B have also received greater attention to regulate NF- κ B signaling in immune inflammatory diseases and cancer. Adenoviral gene transfer of an undegradable “super-repressor” I κ B α (srI κ B α) suppressed the constitutive activation of NF- κ B which in turn decreased the production of proinflammatory cytokines in synovial fibroblasts in vitro (Kabouridis et al. 2002). In streptococcal cell wall (SCW) and pristane-induced rats, suppression of NF- κ B by proteasomal inhibitors and Adenoviral gene transfer of srI κ B α profoundly induced apoptosis in synovium. The administration of liposomal complexes of NF- κ B decoys (short double stranded oligonucleotide sequences that contain NF- κ B binding sites) decreased the severity of inflammation and disease recurrence. Glucocorticoids like dexamethasone and prednisone are one of the widely used anti-inflammatory drugs. These increase the expression of I κ B α that enhances the cytosolic retention of NF- κ B. NF- κ B is a pivotal regulator in multitude cellular processes and can activate almost 200 genes. As, it is the converging point of

several signaling pathways it may be difficult to find the exact pathway to target. Because of its involvement in various cellular functions, care must be taken to avoid unwanted and toxic effects.

Inhibitory effects of phytochemicals on NF- κ B

Inflammation is a complex biological response of body to endogenous or exogenous stimuli. Inflammation is tightly regulated by controlling the mediators that initiate, maintain and shut down the process. Antigen activated T_H cells stimulate FLS, monocytes and macrophages to secrete multitude proinflammatory cytokines viz., IL-1, IL-6 and TNF- α . TNF- α and IL-1 are potent inducers of cells of mesenchymal origin such as synovial fibroblasts, osteoclasts and chondrocytes. These cells secrete MMPs leading to cartilage and bone destruction. The overexpression of proinflammatory genes is associated with the activation of transcription factor NF- κ B. Nuclear translocation of NF- κ B induces expression of proinflammatory cytokines, COX (cyclooxygenase), PGE2 (prostaglandin E2), etc. Therefore, inflammatory mediators are considered as potential targets in the treatment of many diseases including RA.

Plants and plant products are being explored for their potential therapeutic benefits in and around the globe. Chemical compounds from plants in particular steroids, terpenoids, sterols, flavonoids, sesquiterpene lactones, curcuminoids, thymoquinones, triterpenes, phytoalexins

were proven to exhibit antioxidant, anti-inflammatory, anti-arthritic effects, etc. The chemical structures of above-mentioned bioactive compounds are depicted in Fig. 3 and are reviewed below.

Fig. 3 Structures of phytochemicals inhibiting NF- κ B

Withania somnifera

Withania somnifera (Ashwagandha, WS), a potent plant that inhibits the activation of NF- κ B, is used in the treatment of RA by Ayurveda practitioners (Mishra et al. 2000; Ichikawa 2006; Venkatesha et al. 2011). About 35 chemical compounds have been identified and characterized in WS extract. Biologically active compounds in WS include alkaloids (isopelletierine, anaferrine), steroidal lactones (withanolides) and sitoindosides. Withanolides fall under the group of ergostane-type steroids with atoms C-22 and C-26 bridged by a D-lactone functional group and oxidized C-1 position. Withaferin A, an effective withanolide is a prominent inhibitor of NF- κ B activation (Grover et al. 2010; SoRelle et al. 2013; Heyninck et al. 2014). The effect of crude ethanol extract of WS on spontaneous and LPS (Lipopolysaccharide) induced proinflammatory cytokines was analyzed at transcript and protein levels. This was studied in healthy individuals as well as RA patients. WS crude extract at 1 mg/ml inhibited the production of proinflammatory cytokines by ceasing the translocation of NF- κ B and Activator Protein 1 (AP-1) into the nucleus. WS extract (1 mg/ml) also inhibited LPS activated NF- κ B and AP-1 whereas no considerable effect was observed on the basal levels of these transcription factors. Furthermore, Withaferin A at a concentration of 10 μ g/ml inhibited spontaneous and LPS activated NF- κ B. However, no such effect has been observed when the concentration is 1 or 0.1 μ g/ml (Singh et al. 2007).

Tripterygium wilfordii

Tripterygium wilfordii Hook F (TWHF) also known as Thunder God Vine is a well known Chinese medicinal herb. TWHF is found to be effective in treating various immune inflammatory diseases (Bao and Dai 2011). Recent placebo controlled clinical trials confirmed the efficacy of TWHF extract against RA. TWHF extract contains more than 70 compounds including diterpenoids, triterpenoids, sesquiterpenoids, β -sitosterol, dulcitol and glycosides. Triptolide, a diterpene triepoxide, is a major component of TWHF extract and mainly responsible for its therapeutic properties. Several studies suggest that TWHF has inhibitory effects on various transcription factors like NF- κ B, AP-1, and NF-AT (Nuclear factor of activated T cells) (Matta et al. 2009). The effect of triptolide on NF- κ B expression in the joints of collagen-induced arthritis (CIA) mice was immunohistochemically examined. Triptolide at concentrations 8, 16 and 32 μ g/kg/day were orally administered to CIA mice. In the synovial cells of CIA mice, triptolide treatment at above concentrations decreased both the total cells and NF- κ B-p65 transcript. In

all the cases triptolide suppressed both gene and protein expression of NF- κ B. Triptolide at 32 μ g/kg/day has shown more effect on inhibition of NF- κ B activation and translocation in comparison with remaining concentrations (Lin et al. 2007).

Commiphora mukul

Guggulsterone (4,17(20)-pregnadiene-3, 16-dione), is a plant sterol derived from gum resin (guggulu) of *Commiphora mukul*. This gum resin has been used for centuries in Ayurvedic medicine to treat arthritis, hyperlipidemia and obesity. The anti-inflammatory property of guggulsterone is attributed to the inhibition of NF- κ B signaling by direct suppression of IKK (Xiao and Singh 2008; Patel and Shah 2013; Shishodia and Aggarwal 2004). The ability of guggulsterone to inhibit IL-1 β -mediated inflammatory responses by inhibiting NF- κ B in FLS has been studied. FLS were collected from 12 RA patients and the cells were grown in high glucose containing-DMEM supplemented with 10% fetal bovine serum, 2 mM glutamine, 100 units/ml of penicillin, 100 μ g/ml of streptomycin, and 2.5 μ g/ml of amphotericin B. The cells were exposed to IL-1 β (5 ng/ml) for 24 h and this induced the production of cytokines. The presence of guggulsterone inhibited the production of cytokines. It suppressed the nuclear translocation of NF- κ B by inhibiting the degradation of I κ B α that occurred as a result of IL-1 β exposure (Lee et al. 2008).

Camellia sinensis

Epigallocatechin-3-gallate (EGCG) is an effective antioxidant and anti-inflammatory compound extracted from *Camellia sinensis* (green tea). The inhibition of apoptosis in RA-FLS is due to overexpression of anti-apoptotic proteins such as the members of Bcl-2 family, for instance Mcl-1 (myeloid cell leukemia 1). Recent studies have shown that RA-FLS resistance to TNF- α and Fas-mediated apoptosis is also due to overexpression of Mcl-1. This overexpression results in disease progression, therapy resistance and reduced clinical outcome. EGCG was effective in abrogation of Mcl-1 expression in RA-FLS. Further, EGCG inhibited IL-1 β -induced chemokine production and activation of MMP-2 in RA-FLS. In an incubation period of 0.5–24 h, EGCG was effective in inhibiting the constitutive and TNF- α -induced nuclear translocation of NF- κ B-p65. EGCG also inhibited the DNA binding capacity of TNF- α -induced NF- κ B-p65 by >50% when compared to samples treated with TNF- α alone (Ahmed et al. 2010). EGCG is known to downregulate NF- κ B pathway by decreasing the large numbers of NF- κ B that translocate into the nucleus, thereby inhibiting DNA binding activity in RA. EGCG is also known to suppress

OSM (oncostatin M, member of IL-6 family) induced degradation of I κ B α and nuclear translocation of NF- κ B (Wu et al. 2012).

Saposhnikovia divaricata

Sesquiterpene lactones of some Mexican Indian plants could also inhibit the activation of NF- κ B (Bork et al. 1997; Hehner et al. 1998; Rüngeler et al. 1999). *Saposhnikovia divaricata* also called “fangfeng” in China exhibits anti-inflammatory effect. It is the typical medication that has been used for the treatment of arthritis. The dry root extract of the plant contains essential oils, coumarins, mannitol, glycoside, polyacetylenes and bioactive chromones. These chromones in particular, prim-*O*-glucosylcimifugin manifested potent anti-inflammatory function against xylene induced mouse ear inflammation. *S. divaricata* chromone extract (SCE) impeded expression of NF- κ B and its DNA binding activity in CIA rats. This regulated the production of proinflammatory cytokines in RA synovium of CIA rats. SCE also inhibited ERK, JNK and p38 MAPK (Mitogen-activated protein kinase) phosphorylation that activate NF- κ B (Dai et al. 2008; Gui et al. 2011; Kong et al. 2013).

Curcuma longa

Curcumin, an active anti-inflammatory ingredient of rhizome turmeric has been reported to have anti-arthritis effect (Basnet and Skalko-Basnet 2011; Sharma et al. 2005; Jurenka 2009; Schulze-Tanzil et al. 2004; Buhrmann et al. 2010, 2013; Mobasheri 2012). Curcumin, a diaryl heptanoid is one of the three major phenolic curcuminoids that constitute 3–4% of turmeric. Curcuminoids are natural phenols that give turmeric its distinctive yellow hue. The inhibitory effects of curcumin on NF- κ B have been adequately studied (Funk et al. 2008). Anti-arthritis effects of turmeric extract on SCW-induced arthritis have been reported. Female Lewis rats were induced with RA by administering a single intraperitoneal injection of peptidoglycan polysaccharides isolated from the sonicated cell wall of Group A *Streptococcus pyogenes*. These animals were then treated with turmeric intraperitoneally at a concentration of 0.5–1.0 μ g/ml at regular intervals. Chemiluminescence and Pathway Assistant software results have shown that administration of turmeric extract suppressed the activation and expression of NF- κ B-regulated genes. Results were promising as at least 42 NF- κ B-regulated genes were targeted. Furthermore, the expression of genes controlled by NF- κ B-regulated gene products were also affected by turmeric treatment in SCW-induced arthritis model (Funk et al. 2006).

Andrographis paniculata

Andrographis paniculata (AP), a shrub from Acanthaceae family has extensive usage against several diseases like inflammation, digestive disorders, etc. These therapeutic properties are attributed to andrographolide, a labdane diterpene present in the aerial part of the plant. Andrographolide, the bioactive compound in the AP extract inhibits NF- κ B activation by blocking the binding of NF- κ B to its consensus sequence. The ability of AP extract to reduce joint stiffness, pain, swelling and impairing has been evaluated in 60 female patients after 14 weeks of treatment with the extract. 60 RA affected women were divided into two groups; ‘placebo’ and ‘active’ based on the date and time of arrival to the post screening clinic. Several clinical parameters of pain and swollen joints were evaluated. When each treatment was evaluated separately, a significant reduction in the tender and swollen joints has been observed. Treatment with AP formulation (30% andrographolide) can reduce the symptoms associated with RA. This beneficial effect of the formulation is because of its ability to inhibit NF- κ B binding to DNA (Burgos et al. 2009).

Nigella sativa

Nigella sativa (NS) also known as black cumin is a herbal plant belonging to Ranunculaceae family. NS oil and seeds can be used for medicinal purposes (Al-Ghamdi 2001). Active compounds of NS oil extract include thymoquinone (TQ), dithymoquinone, thymohydroquinone, thymol, *p*-cymene, 4-terpineol, *t*-anethol. NS seeds also contain nigellidine, nigellicine, nigellimine, saponin and water-soluble triterpene. Among these, TQ is the most abundant and potent pharmacologically active compound (Shuid et al. 2012). Recent reports suggest that TQ suppressed Adjuvant arthritis (AA) an action similar to that of methotrexate. The effects of TQ on NF- κ B were elucidated using western blotting with protein samples from RA-FLS. RA-FLS have been pre-incubated with 10 μ M TQ for 1 h, followed by 15, 30, 60 and 120 min of stimulation with 1 μ M LPS. At 10 μ M of TQ no effect was observed on basal MAPKs and NF- κ B-p65. Whereas, at 10 μ M concentration, TQ blocked LPS-induced p38 MAPK and NF- κ B-p65 phosphorylation (Vaillancourt et al. 2011).

Glycine max

Genistein (4',5,7-trihydroxyisoflavone) is a predominant isoflavone present in soy beans (*Glycine max*). It has inhibitory effects on several degenerative diseases viz., osteoporosis, hormone-related cancers and cardiovascular diseases. The attention drawn by genistein is accredited to

its anti-inflammatory properties (Verdrengh et al. 2003). Studies revealed the suppressive effects of genistein on inflammatory cascade in CIA (Li et al. 2013b). The inhibitory effects of genistein on TNF- α -induced inflammation in human synovocyte MH7A cells have been studied. MH7A cells were pretreated with TNF- α to induce the production of proinflammatory cytokines such as IL-1 β , IL-6 and IL-8. The levels of proinflammatory cytokines significantly increased when stimulated with TNF- α . These cells when treated with genistein (20 μ M) for 2 h prior to the incubation of TNF- α decreased the release of proinflammatory cytokines. It also inhibited TNF- α -induced phosphorylation of Ser536 of NF- κ B-p65 as well as nuclear translocation of NF- κ B (Li et al. 2014b).

Salvia miltiorrhiza

Cryptotanshinone (CTS) is an active quinoid diterpene derived from the roots of a Chinese herb *Salvia miltiorrhiza* Bunge. It has anti-inflammatory, antibacterial and anti-cancer properties (Tang et al. 2010). Studies reported the ability of CTS in the attenuation of severity in AA (Zheng et al. 2011). The mechanisms for the protective effects of CTS in RA were elucidated using IL-1 β and TNF- α -induced FLS. RA-FLS from CIA induced rats were pre-treated with CTS (5 and 20 μ M) for 2 h followed by stimulation of IL-1 β and TNF- α . Nuclear extracts were separated and analyzed. Histological studies indicated reduced pathological scores in the cells incubated with CTS. After 24 h of incubation, CTS (20 μ M) significantly inhibited the secretion of IL-1 β and IL-17 α . While CTS at a concentration of 10 μ M inhibited LPS-induced I κ B α degradation, 20 μ M CTS inhibited the nuclear translocation of NF- κ B. Also, CTS at higher concentration (18 mg/kg/day) decreased arthritic symptoms in CIA induced rats (Wang et al. 2015).

Celastrus orbiculatus

Celastrol, a bioactive triterpene from the extracts of Celastraceae family plants exhibits antioxidant, anti-inflammatory and anti-rheumatic properties (Li et al. 2014a; Park et al. 2011). It is a cell permeable quinone methide triterpenoid that inhibits the release of proinflammatory cytokines from macrophages and monocytes in LPS-induced RA-FLS invasion. Pretreatment of LPS-induced RA-FLS with celastrol at 0.05 μ M, 0.1 μ M and 0.2 μ M concentrations had no effect on MMP-1 and MMP-2 mRNA expression. However, experiments have revealed the effect of celastrol on inhibition of LPS-induced MMP-9 expression. This was accomplished by suppressing the binding of NF- κ B to the MMP-9 promoter. Treatment of RA-FLS with 0.05–0.2 μ M celastrol has no effect, whereas 0.4 and

0.8 μ M decreased cell viability by one and twofold, respectively. In addition, celastrol inhibited TLR4/MyD88/NF- κ B signaling pathway. Furthermore, celastrol suppressed nuclear translocation of NF- κ B through inhibition of LPS-induced phosphorylation of I κ B α and its degradation (Li et al. 2013a).

Vitis vinifera

Resveratrol (trans-3, 4'-hydroxystilbene) is a polyphenolic phytoalexin predominantly found in the skin of red grapes (*Vitis vinifera*) that exhibits anti-inflammatory, antioxidant, anti-arthritic and immunomodulatory properties. Resveratrol displayed chondroprotective activity by suppressing IL-1 β and ROS (reactive oxygen species) production (Shakibaei et al. 2008; Csaki et al. 2008). Resveratrol inhibited the nuclear translocation of NF- κ B by stabilizing I κ B. Resveratrol (50 nM) also prevented the acetylation of NF- κ B subunit RelA/p65 in 3T3 cells in Sirt-1 (Sirtuin 1)-dependent manner. Recent studies showed the suppression of TNF- α -induced MMP-9, IL-1 and iNOS (inducible nitric oxide synthase) by resveratrol (50 nM) (Zhu et al. 2011). Resveratrol (50 μ M) along with curcumin (50 μ M) blocked IL-1 β -induced nuclear translocation of NF- κ B in chondrocytes. Pretreatment of resveratrol (50 μ M) for 4 h inhibited IL-1 β -induced activation of I κ B α . Noticeably, resveratrol (50 μ M) arrested NF- κ B activation by preventing the phosphorylation, ubiquitination and degradation of I κ B α (Csaki et al. 2009).

Conclusion

The conventional strategies for RA treatment have produced mixed results with some of them causing undesirable side effects while few others may even worsen the disease. Even a low occurring side effect needs to be carefully weighed against the therapeutic potential of the drug. Conventional drugs that pass the initial scrutiny and are approved for human use may not guarantee total relief from RA. The path to successful development of a safe and effective therapy for RA involves significant research efforts. Plants provide abounding compounds effective in target based therapies that counteract the disease. NF- κ B has a decisive role in eliciting the secretion of proinflammatory cytokines that assist the chemotaxis of plethora of cells. Phytochemicals that interfere with the activation, translocation and DNA binding of NF- κ B are perhaps superior antidotes for the alleviation of the disease. Development of promising therapies for RA that improve the quality of life is desirable. The need for research towards natural products as a therapeutic alternative for the treatment of RA cannot be understated.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest in the publication.

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