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Mangiferin: A promising therapeutic agent for rheumatoid arthritis treatment

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by synovial hyperplasia and progressive joint destruction. Despite aggressive treatment with anti-rheumatic drugs, progressive destruction of joints continues to occur in RA patients, who subsequently require joint surgery. A lot of evidence suggest that fibroblast-like synovial cells (FLS) play crucial role in joint degradation and the propagation of inflammation in RA. The expansion of fibroblast populations in the joint results primarily from the inhibition of pro-apoptotic pathways, rather than large scale proliferation. Because multiple factors, which contribute to fibroblast activation and enhance their destructive potential, are under control of transcription factor NF-κB, this pathway presents an interesting target for RA therapy. However, due to the lack of specificity, NF-κB inhibitors may exert severe side effects. Given the above, there has recently been more interest in natural substances of plant origin which are regarded as a safe alternatives for synthetic drugs. Mangiferin, the naturally occurring polyphenol with excellent anti-inflammatory and antioxidative properties, exhibits strong pro-apoptotic effect toward synoviocytes isolated from human synovia. Moreover, it shows no cytotoxicity toward cultivated chondrocytes and reduces the levels of matrix metalloproteinases. Considering that mangiferin is a natural constituent of foods and traditional herbal medicines, showing fewer adverse effects and low toxicity, we hypothesize that it may prove effective in the treatment of RA and prevention against joint destruction.

Introduction

Rheumatoid arthritis (RA) is a synovial inflammatory disease of unknown etiology, affecting roughly 1% of the world population. Although the etiology of RA remains unknown, a variety of studies suggest that the interaction of environmental and genetic factors is responsible for its progress. This process involves certain specific genes that can help break tolerance and lead to autoreactivity. RA frequently shows systemic involvement but primarily affects the joints, where chronic synovial inflammation and subsequent destruction of articular cartilage and bone are the main characteristics of disease [1]. As demonstrated in a number of studies, fibroblast-like synovial cells (FLS) play a pivotal role in both the initiation and perpetuation of RA and have been linked most prominently to the progressive destruction of articular structures [2]. RA synoviocytes have a transformed phenotype characterized by resistance to apoptosis and invasive ability. They directly invade cartilage and bone and destroy cartilaginous matrix [3]. Joint destruction is largely responsible for limiting the quality of life of patients with RA—after 10 years, 40% of them are already on retirement pay [4]. Thus, inhibiting progressive joint damage is a key treatment goal in RA. Data from clinical trials show that 30–50% of patients do not achieve clinically meaningful responses to standard therapies such as, e.g. the combination of a tumor necrosis alpha (TNF-α) inhibitor with methotrexate [5]. Moreover, the majority of synthetic drugs used in RA treatment exhibit adverse effects which may substantially decrease overall benefits of long-term treatment.

In recent years, there was an increased interest in natural substances of plant origin, evaluated as therapeutic agents which may interrupt the mechanism of joint destruction in rheumatic diseases. In the present work, we focus on biological activities of mangiferin, a tetraoxygenated xanthone *C*-glucoside belonging to the most extensively studied plant polyphenols. Although quite widely distributed in plant kingdom, mangiferin is present in substantial amounts only in relatively few species [6]. Mango (*Mangifera indica*) leaves and stem bark are considered its major source, with concentration ranging from ca. 2–17% and 1–7% dry weight (DW), respectively [6–8]. Other mangiferin-rich plant sources include rhizomes of Chinese medicinal plant *Anemarrhena asphodeloides* (up to 7% DW), leaves of East-African wild coffee

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species *Coffea pseudozanguebariae* (up to 6% DW) and aerial parts of the South-African shrubs of the genus *Cyclopia*, with up to 5% DW mangiferin reported in *Cyclopia genistoides* [7,9]. Mangiferin was shown to exhibit a range of biological effects, including, but not limited to antioxidant, chemopreventive, anti-cancer, anti-diabetic and anti-inflammatory [6–8,10]. Given its multidirectional activity, the above xanthone is considered a promising therapeutic agent in a number of diseases.

Hypothesis

Pro-apoptotic activity of mangiferin toward FLS, as well as its anti-inflammatory potential, manifested i.a. by modulation of nuclear factor kappa B (NF-κB) pathway and down-regulation of pro-inflammatory cytokines [6–10], suggest that the discussed xanthone may prove effective in the intra-articular treatment of rheumatoid arthritis.

Evaluation of the hypothesis

The crucial role of FLS in RA development—evaluation of potential therapeutic targets

It is now well established that synovial mesenchymal cells play a crucial role in both joint damage and propagation of inflammation. Under normal conditions, these cells are in quiescent state, but in RA the intimal lining shows a marked increase in cellularity. Surface layer of normal synovia is 20–40 μm thick and one to three cells deep. In RA, this layer expands to a depth of 15 or more cells. Synovial hyperplasia is caused by a massive influx and retention of inflammatory cells such as macrophages and lymphocytes and, more importantly, a substantial increase in the number of resident synovial cells (FLS), which are of mesenchymal origin. FLS hyperplasia has been shown to precede the accumulation of inflammatory cells, suggesting their pivotal role in RA development [11]. There is a lot of evidence demonstrating that in the course of RA, FLS undergo fundamental changes that are referred to as stable activation or tumor like transformation [12], resulting in aggressive, invasive behavior. It was shown that fibroblasts exhibit some features of tumor cells, such as anchorage-independent growth, alterations in the response to apoptotic stimuli, invasiveness toward articular cartilage and bone, and migration from joint to joint [13]. Interestingly, RA FLS are able to maintain this altered phenotype over prolonged periods of time in the absence of continuous stimulation by an inflammatory environment. The activation of RA FLS is also independent of the presence of inflammatory cells. This was demonstrated in studies conducted in the severe combined immunodeficient (SCID) mouse model of RA in which implanted isolated human RA FLS invaded co-implanted human cartilage, leading to cartilage destruction in the absence of immune cells or their soluble products [14].

RA FLS express a variety of pro-mitotic and anti-apoptotic mutations but whether these are primarily a cause or a consequence of the disease remains a matter of conjecture. The invasive front of rheumatoid pannus is composed of FLS which exhibit transformed phenotype characterized by proliferation and invasive ability. Lymphocytes are suggested to play a less important role in joint destruction, as they do not appear until blood vessels at cartilage-pannus junction are established [15]. Several in vitro studies suggest that RA FLS divide more rapidly than cells from osteoarthritis joint. Despite these observations, little evidence supports the claim that synovial hyperproliferation is sufficient to explain the accumulation of FLS. In fact, some investigators have reported that FLS divide slowly in vivo [16]. Mitotic figures are rarely seen within synovium and thymidine uptake, a marker of cell division, is observed in 1–5% of synovial cells [17]. On the other hand, human studies indicate that the accumulation of synoviocytes results from dysregulation of apoptosis. The resistance to apoptotic cell death is mainly observed in synoviocytes of the surface layer of the synovium, involved in joint destruction, whereas less than 1% of the lining cells exhibit morphological features of apoptosis, as shown by ultrastructural methods. Various studies revealed that in RA the expression of anti-apoptotic molecules such as FLICE (FADD-like interleukin-1β-converting enzyme) inhibitory protein and Bcl-2 (B-cell lymphoma 2), is increased. Furthermore, tumor necrosis factor alpha (TNF-α) cannot induce FLS apoptosis through its receptor TNFR1 due to the strong activation of the NF-κB pathway [18]. NF-κB is a key transcription factor in RA which controls transcription of inflammatory genes including TNF-α, IL-1, IL-6, IL-8 (interleukin 1, 6 and 8, respectively), COX-2 (cyclooxygenase-2), as well as anti-apoptotic molecules such as A1, XIAP (X-linked inhibitor of apoptosis protein), Flip (flice-like inhibitory protein) and Bcl-2 [19]. As demonstrated in other reports, inhibition of NF-κB sensitized RA FLS to TNF-α- and Fas (TNF receptor superfamily member 6)-induced apoptosis [20].

Not only does the synovial fibroblast population in RA increase in size, but the behavior of these cells also changes, leading to joint damage through enhanced secretion of MMPs (matrix metalloproteinases) and CTS (cathepsins) that degrade cartilage and bone tissues [3]. Due to their key role in collagenous matrix degradation, MMPs have long been the central issue in the research of RA [21]. In a healthy joint, there is a balance between MMPs and their physiologic inhibitors—TIMPs (tissue inhibitors of metalloproteinases). On the other hand, the amounts of MMPs in RA joints exceeds approximately 40-fold that of TIMPs. For this reason, MMP inhibitors have been tested in an attempt to prevent joint damage [22]. Unfortunately, these drugs exhibit only limited efficacy and have been plagued by side effects, related in part to joint fibrosis [23].

From a therapeutic point of view, the most important information arising from the experimental data is that RA synoviocytes are protected from death at different levels [18]. The apoptotic death of FLS involves several signal transduction pathways, which can thus be considered new promising targets in RA management [24]. Among these, NF-κB is of special importance, as a key factor involved in RA pathophysiology [25].

Mangiferin—a promising phytotherapeutic agent for RA treatment

As previously indicated, mangiferin, the naturally occurring xanthone *C*-glucoside, has excellent anti-inflammatory and antioxidative properties. Below, we summarize the so far available experimental data indicating the possible use of mangiferin as an anti-RA drug. Additionally, the diagram (Fig. 1) was included, in order to illustrate the multi-directional activity of the discussed xanthone on joint components.

In the study involving arthritic mice, Kumar et al. investigated the effect of mangiferin-containing aqueous extract of *Swertia chirayita* stem on the elevated pro- and anti-inflammatory cytokines balance in primary joint synovium. A dose-dependent reduction of TNF-α, IL-1, IFN-γ (interferon-gamma) and elevation of IL-10 (interleukin 10) were observed in the joint homogenates by the 12th day after extract administration [26]. Bhatia et al. reported that mangiferin inhibits COX-2 expression and prostaglandin E2 production. It was found that mangiferin markedly reduces LPS (lipopolysaccharide)-induced prostaglandin synthesis and formation of 8-iso-prostaglandin [27].

Several studies demonstrated pro-apoptotic activity of mangiferin. For instance, Cheng and co-workers found that mangiferin inhibited telomerase activity of K562 cells in a time- and concentration-dependent manner and that it could induce apoptosis and