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Original Research Article

Anti-inflammatory and anti-oxidative effects of herbal preparation EM 1201 in adjuvant arthritic rats

Laimis Akramas^{a,*}, Laima Leonavičienė^b, Audrius Vasiliauskas^b, Rūta Bradūnaitė^b, Dalia Vaitkienė^c, Danguolė Zabulytė^b, Teresa Normantienė^b, Audronis Lukošius^d, Irena Jonauskienė^b

^a Pharmaceutical Research Company “Aksada” UAB, Kaunas, Lithuania^b State Research Institute Center for Innovative Medicine, Vilnius, Lithuania^c Department of Pathology, Faculty of Medicine, Vilnius University, Vilnius, Lithuania^d Department of Pharmacognosy, Faculty of Pharmacy, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania

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ABSTRACT

Background and objective: The purpose of the present study was to examine the anti-arthritic and antioxidant effects of herbal and active organic ingredient complex (EM 1201) in rats with experimental adjuvant arthritis (AA).

Materials and methods: AA was induced in 30 male Wistar rats by intradermal injection of complete Freund's adjuvant into the left hind paw. The course of disease in 30 rats in response to the treatment with EM 1201 and diclofenac, the parameters including body weight, joint swelling, blood indices pro-/antioxidant status of blood serum, and histology of joints and the liver, were investigated.

Results: Preparation EM 1201 showed anti-inflammatory effect analogous to diclofenac, improved blood indices, significantly decreased joint swelling and histological changes in them. Joint swelling was suppressed by 29%–42.8% and 9.3%–34.4% in response to administration of EM 1201 and diclofenac during the entire experiment. Both preparations significantly suppressed pannus formation, general inflammatory reaction and edema in soft periarticular tissues and synovium, diminished MDA level and elevated AOA in the blood serum. Significantly lower absolute and relative weight of the liver and lower dystrophic processes in it, and general inflammatory infiltration of hepatic stroma proved the positive effect of treatment with EM 1201.

Conclusions: The present study suggests that EM 1201 has protective activity against arthritis and demonstrated its potential beneficiary effect analogous to diclofenac. Anti-inflammatory and anti-oxidative effect of EM 1201 in rats with AA support the need of further

* Corresponding author at: “Aksada” UAB, Studentų 35, 51364 Kaunas, Lithuania.

E-mail address: laimis@aksada.eu (L. Akramas).

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investigations by using it as supplementary agent alone or together with other anti-arthritic drugs in the treatment of rheumatoid arthritis.

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1. Introduction

Due to the complex etiology of rheumatoid arthritis (RA) which is characterized by excessive synovial hyperplasia, vasculogenesis, cartilage and bone destruction and joint malformation [1,2], identification of effective therapies has proven difficult. Although many of drugs used for the treatment of RA transiently suppress inflammation and ameliorate symptoms, they do not help significantly to treat the disease in the long term and may result in serious side effects. Treatments targeting cytokines, including anti-tumor necrosis factor (TNF) α antibodies, soluble TNF receptor, anti-interleukin (IL)-6 receptor antibody and IL-1 receptor antagonist, are widely used for treating RA in addition to anti-inflammatory agents and disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate, but these treatments have some problems, especially in terms of cost and the increased susceptibility of patients to infection in addition to the existence of low-responders to these treatments [1–3]. Therefore, newer drugs with low or no toxicity for the treatment of RA are actively being sought. Many patients tend to use more effective and safer therapeutic strategy to treat RA and alleviate the adverse effects of chemotherapeutic drugs [4]. Consequently, there is dramatically growing interest in herbal medicines among persons with RA and the use of complementary and alternative medicines (CAMs) for chronic conditions has increased in recent years [5–7].

CAMs are based on herbal formulas, the extracts or ingredients of herbs, and active organic ingredient which show anti-inflammatory action and used for treating arthritic diseases [5–10]. The laboratory studies have identified a number of different molecules involved in inflammation that are inhibited by curcumin including phospholipase, lipoxygenase, cyclooxygenase 2, leukotrienes, thromboxane, prostaglandins, nitric oxide, collagenase, elastase, hyaluronidase, monocyte chemoattractant protein-1 (MCP-1), interferon-inducible protein, tumor necrosis factor (TNF), and interleukin-12 (IL-12) [11]. The studies show that the isolated pure compound of *Boswellia serrata* extract is capable of carrying out a natural anti-inflammatory activity at sites where chronic inflammation is present by switching off the pro-inflammatory cytokines and mediators, which initiate the process [12]. In vitro studies and animal models show that boswellic acids inhibit the synthesis of proinflammatory enzyme, 5-lipoxygenase including 5-hydroxyicosatetraenoic acid and leukotriene B₄, which cause bronchoconstriction, chemotaxis, and increased vascular permeability [13]. The results indicate that MSM inhibits lipopolysaccharide (LPS)-induced release of pro-inflammatory mediators in murine macrophages through downregulation of nuclear factor (NF)- κ B signaling [14]. Study shows that bromelain may be effective in ameliorating physical symptoms and improving general well-being in otherwise healthy adults suffering from mild knee pain in a

dose-dependent manner [15]. Improvements in total symptom score and the stiffness, and physical function dimensions were significantly greater in the high-dose (400 mg per day) compared with the low-dose group (200 mg per day) [15]. The results indicate that the extracts and preparations of the in vitro systems had strong anti-inflammatory properties, comparable to or even higher than that of pure harpagoside (a major anti-inflammatory constituent of intact Devil's claw tubers) [16,17]. Silymarin during evaluation exhibited significant anti-inflammatory and anti-arthritic activities in the papaya latex induced model of inflammation and mycobacterial adjuvant induced arthritis in rats [18]. Results of the study indicate its action through inhibition of 5-lipoxygenase for anti-inflammatory and anti-arthritic activities [18].

The doses of active ingredients were chosen according to scientific research and publications [11–18]. Herbal anti-inflammatory medicines provide a broad-spectrum mechanism of action such as interaction with the inflammatory cascade, cytokine production, inhibition of elastase or hyaluronidase, increased anti-oxidative effectiveness and other still unidentified effects that may contribute to joint protective effects [6].

It is also known that oxygen metabolism and an increase in reactive oxygen species (ROS) have important roles in the pathogenesis of RA [19,20]. Oxygen-free radicals are implicated as mediators of joint tissue damage in RA [21] and in experimentally induced arthritis [22,23]. In addition, anti-oxidants can scavenger free radicals and limit damage. It has been suggested that the pro-oxidant/anti-oxidant imbalance in RA and arthritis models may be due to acceleration of some cellular reactions or insufficiency of the antioxidant defense system [24].

It should be noted that the most of the information about the mechanisms of action of herbal products in the experimental model of RA is relevant to arthritis patients as well. Although animal models may not reproduce all features of human RA, they are essential to facilitate understanding of the mechanisms of this disease and development of new therapies. In the present study we investigated the effects of oral administration of herbal preparation with code name EM 1201 on inflammation and antioxidant status in a rat adjuvant arthritis (AA) model, which is a T-cell dependent and immune-mediated condition characterized by hyperplasia of the synovial lining and inflammation in affected joints with pathogenesis similar to RA and serves as a vehicle to test novel therapeutic agents [25,26].

2. Materials and methods

2.1. Chemicals and drugs

Complete Freund's adjuvant (CFA), 10% formalin, spirit-formol, hematoxylin, eosin, picrofuxin, toluidine blue,

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