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Review

Control of autoimmune arthritis by herbal extracts and their bioactive components

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ABSTRACT

Autoimmune diseases such as rheumatoid arthritis (RA) cause significant morbidity and loss of productivity. Many potent conventionally used drugs are available for these diseases, but their prolonged use is accompanied by severe adverse effects besides a high cost. Therefore, there is an unmet need for effective but less expensive medications for RA and other autoimmune diseases. Natural plant products belonging to the traditional systems of medicine, such as the traditional Chinese medicine and Indian Ayurvedic medicine, offer a vast and promising resource in this regard. However, herbal medicinal products are often poorly characterized for their composition as well as mechanisms of action. We review here the results of our systematically performed studies aimed at defining the anti-arthritic activity of three herbal extracts, namely, modified Huo-luo-xiao-ling dan (HLXL), *Celastrus aculeatus* Merr., and polyphenolic fraction of green tea (*Camellia sinensis*), as well as a purified

Abbreviations: AA, adjuvant arthritis; aBhsp65, antibodies to Bhsp65; aCCP, antibodies to cyclic citrullinated peptides; Bhsp65, mycobacterial heat-shock protein 65; CAM, complementary and alternative medicine; DEG, differentially expressed genes; FLS, fibroblast-like synoviocyte; GM-CSF, granulocyte macrophage colony-stimulating factor; GRO/KC, growth regulated oncogene/keratinocyte chemoattractant (GRO/KC); HLXL, Huo-luo-xiao-ling dan; IFN-γ, interferon gamma; IL-1β, interleukin 1 beta; MCP-1, monocyte chemotactic protein-1 (MCP-1); MIP-1a, macrophage inflammatory protein-1α (MIP-1α); MMP-9, matrix metalloproteinase-9; OPG, osteoprotegerin; OPN, osteopontin; PGT, polyphenolic fraction of green tea; NO, nitric oxide; RA-FLS, Rheumatoid arthritis-fibroblast-like synoviocyte; RANKL, receptor activator of nuclear factor-κB ligand (RANKL); RANTES, regulated upon activation, normal T cell expressed, and secreted; TCM, Traditional Chinese medicine; Th17, T helper 17 cell; Treg, T regulatory cell.

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compound Celastrol, a bioactive component of Celastrus. Specifically, we examined the effects of these herbal products on the immunological, biochemical and molecular biological effector pathways in autoimmune arthritis. We have also reviewed here related studies on these herbal products by other investigators. Taken together, we suggest further testing of these herbal products in RA patients.

1. Introduction

Autoimmune diseases result from deregulated immune responses that attack the body's own tissues contrary to their traditional role in protecting the host against external infectious agents. Complex interplays among genetic and environmental factors are involved in the pathogenesis of autoimmunity [1,2]. Cell-mediated and/or antibody-mediated effector responses contribute to autoimmune inflammation and tissue damage [3,4]. These processes can either affect multiple organs (systemic autoimmunity) or be limited primarily to one organ (organ-specific autoimmunity) [3,5]. Rheumatoid arthritis (RA), multiple sclerosis (MS), systemic lupus erythematosus (SLE), and type 1 diabetes (T1D) are examples of the major human autoimmune diseases [3,5]. In general, the prevalence of these diseases is relatively higher in the developed countries compared to that in the developing countries. For example, the prevalence of RA is estimated to be approximately 1% in the United States compared to about 0.2–0.3% in China and a subset of population from rural South Africa, and the female to male ratio for RA is 2–3:1 [6]. Uncontrolled autoimmune pathology may result in severe disabilities and/or deformities, and loss of organ function. Due to their chronic nature, autoimmune diseases impose a heavy economical, psychological and social burden on the society. Therefore, effective safe therapeutic agents, and treatment regimen are critical to the management of patients with autoimmunity. The remaining section of this article will mostly cover RA and its experimental models, with some examples of other autoimmune diseases, where needed.

RA affects people all over the world, with geographical differences in prevalence [7–9]. Major advances have been made in the treatment of RA over the past couple decades. Nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., aspirin, ibuprofen, and naproxen), corticosteroids, and disease-modifying anti-rheumatic drugs (DMARDs) (e.g., methotrexate, sulfasalazine, and leflunomide) represent conventionally used (allopathic) drugs for the management of RA [10–12]. Recent additions to this arsenal against RA are the biologics composed of cytokine-/cytokine receptor-based drugs that belong to the DMARDs category [12]. The biologics work by binding either to a particular cytokine (e.g., TNF-α, IL-6, or IL-17) and neutralizing its function or to the cytokine receptor (e.g., TNF-α receptor) and preventing the binding of the endogenous cytokine ligand to its cognate receptor. Consequently, biologics are quite potent and effective in controlling the progression of RA. However, their prolonged use is associated with severe adverse reactions, including severe infections. Furthermore, these mainstream drugs, particularly biologics, are very expensive, and it is very difficult for many patients in the developing countries to afford them. Therefore, there is a continued search for relatively less expensive yet effective alternatives to conventional drugs for RA therapy. In this context, natural plant products constitute a vital and promising resource for identifying new therapeutic agents for RA that meet these criteria.

Plant products have been the source of a large number of bioactive compounds with therapeutic potential, of which many eventually have been developed into drugs that are consumed worldwide for diverse disorders, including inflammatory and autoimmune diseases, infectious diseases, and cancer [13–19]. Furthermore, a variety of herbal products belonging to the traditional systems of medicine are either already being used by patients with autoimmune diseases including RA, with or without the primary physician's knowledge, or are under investigation for their therapeutic potential [13–15,18–20]. Such medicinal herbs belong to the traditional Chinese medicine (TCM), Japanese traditional medicine (Kampo), Egyptian and other African traditional medicine, Indian Ayurvedic medicine, and other systems.

Adjuvant-induced arthritis (AA) is a well-established experimental model of human RA [21,22]. The AA model has extensively been used for studies on the pathogenesis of autoimmune arthritis, for screening of potential anti-arthritic compounds, and for defining the mechanisms of action of such compounds. AA can be induced in Lewis rats (RT.1[l]) by subcutaneous immunization with heat-killed *Mycobacterium tuberculosis* H37Ra (Mtb). The disease appears in about 10–12 days and it affects all paws. However, generally the disease is more severe in the hind paws than the fore paws. The severity of clinical arthritis can be assigned a semi-quantitative grade on a scale of 0 (no disease) to 4 (severe arthritis) on the basis of erythema and swelling of the paws as described in detail elsewhere [21,22]. Such grading is helpful in quantifying the effect of natural products on the severity of arthritis. An alternative method used by some investigators is to measure the volume of the swollen paws by using an equipment called Plethysmograph.

In our laboratory, we have tested 3 herbal extracts (*Huo-luo-xiao-ling* dan (HLXL), Celastrus, and Green tea) and one purified compound (Celastrol) derived from one of them (Celastrus) in the rat AA model of RA. We also examined the influence of these herbal products on various immunological, biochemical and molecular parameters associated with the disease process in RA (Fig. 1). We have discussed below details