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Review

Is there a future for andrographolide to be an anti-inflammatory drug? Deciphering its major mechanisms of action

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ABSTRACT

Andrographis paniculata has long been part of the traditional herbal medicine system in Asia and in Scandinavia. Andrographolide was isolated as a major bioactive constituent of *A. paniculata* in 1951, and since 1984, andrographolide and its analogs have been scrutinized with modern drug discovery approach for anti-inflammatory properties. With this accumulated wealth of pre-clinical data, it is imperative to review and consolidate different sources of information, to decipher the major anti-inflammatory mechanisms of action in inflammatory diseases, and to provide direction for future studies. Andrographolide and its analogs have been shown to provide anti-inflammatory benefits in a variety of inflammatory disease models. Among the diverse signaling pathways investigated, inhibition of NF-κB activity is the prevailing anti-inflammatory mechanism elicited by andrographolide. There is also increasing evidence supporting endogenous antioxidant defense enhancement by andrographolide through Nrf2 activation. However, the exact pathway leading to NF-κB and Nrf2 activation by andrographolide has yet to be elucidated. Validation and consensus on the major mechanistic actions of andrographolide in different inflammatory conditions are required before translating current findings into clinical settings. There are a few clinical trials conducted using andrographolide in fixed combination formulation which have shown anti-inflammatory benefits and good safety profile. A concerted effort is definitely needed to identify potent andrographolide lead compounds with improved pharmacokinetics and toxicological properties. Taken together, andrographolide and its analogs have great potential to be the next new class of anti-inflammatory agents, and more andrographolide molecules are likely moving towards clinical study stage in the near future.

Contents

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1. Introduction

The plant *Andrographis paniculata* (Burm. f.) Wall. ex Nees (Acanthaceae) has long been a part of the traditional medicine in Asia [1] and Scandinavia [2] for the treatment of flu, upper respiratory tract infection and sore throat. There are up to 44 species in the *Andrographis* genus, of which *A. paniculata* is a branched, erect dark green stem and annual herbaceous plant [3]. *A. paniculata* is known by many names, in China *Chuan-Xin-Lian*, in India *Kalmegh*, in Scandinavia countries 'green chiretta', in Japan *Senshinren*, in Malaysia *Hempedu bumi* and in Thailand *Fah Talai* [4]. The whole plant has medicinal value, but the leaves contain the highest level of andrographolide [5]. Andrographolide (PubChem CID: 5318517), a labdane diterpenoid lactone, was first reported in the Indian Medical Gazette in 1951 as an active constituent of *A. paniculata* [6]. However, it was not until 1984 that andrographolide was first described as a potential therapeutic for liver injury [7]. It has since been shown to possess anti-viral [8], anti-thrombotic [9], hepatoprotective [10], anti-cancer [11] and anti-inflammatory [12] properties. In this review, the effectiveness of andrographolide or its analogs in experimental inflammatory disease models (Fig. 1) will be assessed to determine if andrographolide has a future perspective as an anti-inflammatory drug, and to sort out its major anti-inflammatory mechanisms of action.

1.1. Chemical property of andrographolide

Andrographolide (Fig. 2A) is a diterpenoid lactone consisting of an α-alky-lidene γ-butyrolactone moiety, three hydroxyls at C-3, C-14 and C-19, together with two olefin bonds at $\Delta^{12,13}$ and $\Delta^{8,17}$. It has been shown by means of selective epoxidation on the olefin bond at $\Delta^{8,17}$, that it is not crucial towards andrographolide cytotoxic activity. Whereas, the lactone moiety, hydroxyl at C-14, and olefin bond at $\Delta^{12,13}$, all contribute to its cytotoxic activity [13]. Most modifications of andrographolide structure are performed to increase or decrease its cytotoxicity, or to enhance anti-inflammatory efficacy. One example is 12,13-dihydroandrographolide (PubChem CID: 44393988) (Fig. 2I) which was modified by removing the $\Delta^{12,13}$ olefin bond resulting in a reduction of its cytotoxicity [13]. Andrographolide, being an electrophilic α,β-unsaturated γ-lactone, is a Michael acceptor, making it capable of forming covalent bonds with nucleophilic centers in proteins, such as the Cys residues [14]. It has been shown that andrographolide which contains a substituted butenolide [15], can react with NF-κB p50 subunit nucleophilic Cys-62 residue via Michael addition on the $\Delta^{12,13}$ exocyclic double bond, forming a covalent adduct (Fig. 3) [14]. This reaction is dependent on the temporal cellular redox environment and the neighboring positively charged Arg residues. An andrographolide analog, 4-hydroandrographolide (Fig. 2J), which lacks the $\Delta^{12,13}$ exocyclic double bond has been shown to lose its ability to inhibit NF-κB and to attenuate inflammation [16]. This same structure-activity relationship is also applicable to andrographolide-mediated enhancement of quinone reductase antioxidant ability. It has been shown that andrographolide $\Delta^{12,13}$ exocyclic double bond can interact with Kelch-like ECH-associated protein 1 (Keap1), a negative regulator of nuclear factor erythroid-2-related factor 2 (Nrf2) [17]. By inhibiting Keap1, Nrf2, an antioxidant transcription factor, is released and then translocated into the nucleus to induce quinone reductase expression. The loss of the $\Delta^{12,13}$ exocyclic double bond in andrographolide analogs also led to a reduction in quinone reductase expression [17]. Besides, it has also been shown that having an α-alkylidene-β,γ-unsaturated-γ-lactone in 14-deoxy-1 4,15-dehydroandrographolide (Fig. 2E) enhances NF-κB inhibition efficacy as compared to andrographolide [18].

1.2. Toxicology of andrographolide

To-date, andrographolide and *A. paniculata* extracts are taken orally, and as such, preclinical and clinical toxicology of andro-

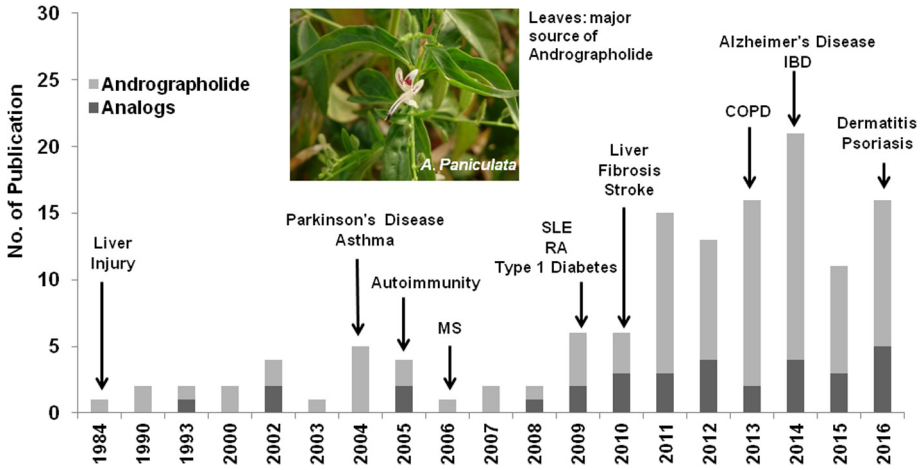

Fig. 1. Increasing trend of reports documenting anti-inflammatory actions of andrographolide or its analogs based on PubMed search. Arrows denote the years when the first report showing therapeutic potential of andrographolide or its analogs for the specified inflammatory diseases. Information was accessed on 3rd January 2017. Photo of *Andrographis paniculata* was taken from https://www.herbal-supplement-resource.com/wp-content/uploads/2016/02/andrographis-paniculata-flower-img.jpg on 12th March 2017. MS, Multiple sclerosis; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease.