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Invited Review

Labdane diterpenoids as potential anti-inflammatory agents

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ABSTRACT

The search for new anti-inflammatory agents is challenging due to the complexity of the inflammatory process and its role in host defense. Over the past few decades, a significant body of evidence has emerged, supporting the prominent role of labdane diterpenoids in therapeutic interventions of various inflammatory diseases. The anti-inflammatory activity of labdane diterpenoids has been attributed mainly to the inhibition of nuclear factor-κB (NF-κB) activity, the modulation of arachidonic acid (AA) metabolism and the reduction of nitric oxide (NO) production. This article provides extensive coverage of naturally occurring labdane diterpenes, discovered between 1981 and 2016, which have been verified as NF-κB, NO, or AA modulators. Herein, we also discuss the role of Michael acceptor, a common structural feature present in most of the active labdane diterpenes, and its association with NF-κB signaling inhibition. In the cases where a sufficient amount of data exists, structure-activity relationship (SAR) studies and clinical studies performed on the anti-inflammatory labdane diterpenoids are also discussed.

Contents

Abbreviations: AA, arachidonic acid; AP-1, activator protein-1; BAFF, B cell-activating factor; cAMP, cyclic adenosine monophosphate; COX, cyclooxygenase; HLO, human lipoxygenase; IDO, indoleamine 2,3-dioxygenase; IκB, inhibitory kappa B; IKK, inhibitory kappa B kinases; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; LOX, lipoxygenase; LT, leukotriene; LT-β, lymphotoxin-β; LX, lipoxin; MAPK, mitogen-activated protein kinase; Mac-1, macrophage-1 antigen; MPO, myeloperoxidase; NIK, NF-kappa-B-inducing kinase; NF-κB, nuclear factor-kappaB; NO, nitric oxide; PBMC, peripheral blood mononuclear cell; PDE, phosphodiesterase; PG, prostaglandin; PHA, phytohemagglutinin; PLA_2, phospholipase A2; TAK1, transforming growth factor beta-activated kinase 1; TLR, toll-like receptor; TNF-α, tumor necrosis factor; TNFR, tumor necrosis factor receptor; TX, thromboxane.

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1. Introduction

Inflammation, under normal physiological condition, is one of the most important protective mechanisms of the body against irritation, injury, or infection [1]. However, excessive inflammation can be a cause of many chronic diseases, ranging from arthritis [2], irritable bowel syndrome [3] to degenerative inflammatory diseases [4]. These conditions can be severely debilitating and tend to gradually worsen with age, affecting a larger and ever-growing population. The search for effective agents against inflammation remains a challenge due to the complexity of the inflammatory processes [5]. Corticosteroids and non-steroidal anti-inflammatory drugs remain the most effective therapeutics for a wide range of inflammatory conditions. However, these drugs are inherently associated with a variety of unwanted side effects [6], and a large number of patients are steroid-resistant [7]. Thus, there is an unmet medical need for developing more effective anti-inflammatory drugs to complement or replace the current therapies. Small molecule natural products provide an incomparable source of inspiration for advances in alternative anti-inflammatory drug development. Many drugs used today for the treatment of various human diseases have been developed from natural products [8–12].

Labdane diterpenoids have emerged as novel lead compounds for modern drug discovery. The interest in studying labdanes was heightened in the past decades due to a wide range of biological activities associated with these compounds, such as anti-bacterial and anti-fungal [13], anti-mutagenic [14], cytotoxic and cytostatic effects [15], and anti-inflammatory modulation of immune cell functions. Several success stories of traditional remedies derived from plant labdane diterpenoids have been reported, with andrographolide [16,17], forskolin [18], sclareol [19], and (+)-polyalthic acid [14], being representatives of this class of compounds. Many of these compounds have been explored as potential anti-inflammatory agents.

Despite a large number of studies and scientific publications on naturally occurring secondary metabolites, such as terpenoids [20,21] or diterpenoids [22,23], there has been no report summarizing and critically evaluating the experimental findings pertaining to the anti-inflammatory activity of labdane-type compounds. This article fills the gap in the literature and discusses the recent contributions of naturally occurring labdane diterpenoids to the treatment of acute and chronic inflammatory processes, with a critical focus on the mechanisms of action underlying the anti-inflammatory activities of these compounds.

A systematic search of published literature was conducted on the following databases: PubMed, PubChem, SciDirect, and SciFinder. Search term 'labdane' was used in combination with 'anti-inflammatory', 'inflammatory', 'nuclear factor-kappa B', 'nitric oxide', and 'cyclooxygenase'. The applied search strategy is limited to English-language publications and excludes research that is currently underway or not yet available in the mentioned databases. The reviewed labdane diterpenoids are divided into groups based on whether they exhibit their modulatory activities via interference with the transcriptional NF-κB signaling, NO, or AA metabolite pathways [24]. It should be noted that some of these compounds might inhibit more than one pathway. Other natural labdane diterpenes that show anti-inflammatory effects via undefined mechanisms are also discussed.

2. General characteristics of labdane diterpenoids

2.1. The basic structures of labdane diterpenes

Naturally occurring labdane diterpenes are bicyclic diterpenoids, which comprise four isoprene units (Fig. 1). The basic skeletal structure can be fragmented into two parts: a fused decalin system (C1–10) and a branched six-carbon side chain (C11–16, with C16 attached to C13) at C9. The remaining four carbons (C17–20) are attached at C8, C4 (with C18 and C19 being attached), and C10 of the decalin system, respectively, as illustrated in Fig. 1. Labdanes are classified and named according to the general rules for nomenclature of diterpenoids. The majority of labdanes have a *trans* stereochemistry at the 5:10 junction of the ring as exemplified by Andrographolide (Fig. 1), whereas labdanes with a 5:10 *cis* ring junction are found to a much lesser extent. Their existence in nature is still in question. In addition to the stereochemistry at the ring junction, labdanes can be further classified by their stereochemistry at C9 and C10, according to their orientations. Consequently, the nomenclatures of labdane skeletons are defined according to the configuration of the ring junction and the substituents at C9 and C10. As a result, the terms, '*normal*-', '*ent*-', '*syn*-', and '*syn-ent*-', are used [25]. The chemistry of labdane-type diterpenes has been reviewed [26].

2.2. Isolation and biotransformation routes of labdane diterpenes

The isolation, chemical, and bio-manipulation of diterpenoids, particularly for labdanes, were reviewed in an excellent article published by Frija et al. in 2011 [27]. Additional reviews on their biogenetic origins are also available [25]. Generally, the biogenesis of labdane-related diterpenoids is initiated by a defining step called class II diterpene (bi)cyclization, which is essentially a protonation-initiated cyclization of Geranylgeranyl pyrophosphate (GGPP), followed by class I diterpene synthase transformations to form a variety of labdane compounds.

The extraction of labdane diterpenoids from different parts of plants was facilitated by the use of organic solvents such as hexane, methanol, butanol, ethyl acetate, or chloroform. The resulting plant extracts were then fractionated using different chromatographic methods followed by crystallization to yield the isolated compounds [28]. The elucidation of the chemical structures was furnished by the use of various spectroscopic techniques including IR, UV, MS, one-dimensional NMR, and two-dimensional NMR such as NOESY, COSY, HSQC, HMBC, and so on.

3. Labdane diterpenoids as anti-inflammatory compounds

At a molecular level, inflammation and related diseases involve the following mechanisms and molecules: the production and/or action of various inflammatory mediators (*e.g.* kinins, cytokines, vasoactive amines, and eicosanoids), cell-signaling messengers (*e.g.* protein kinases, NO, cAMP, and cGMP), the activation of NF-κB [29] and MAPK pathways [30], the expression of pro-inflammatory