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Review article

Discovery and development of natural product oridonin-inspired anticancer agents

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ABSTRACT

Natural products have historically been, and continue to be, an invaluable source for the discovery of various therapeutic agents. Oridonin, a natural diterpenoid widely applied in traditional Chinese medicines, exhibits a broad range of biological effects including anticancer and anti-inflammatory activities. To further improve its potency, aqueous solubility and bioavailability, the oridonin template serves as an exciting platform for drug discovery to yield better candidates with unique targets and enhanced drug properties. A number of oridonin derivatives (e.g. HAO472) have been designed and synthesized, and have contributed to substantial progress in the identification of new agents and relevant molecular mechanistic studies toward the treatment of human cancers and other diseases. This review summarizes the recent advances in medicinal chemistry on the explorations of novel oridonin analogues as potential anticancer therapeutics, and provides a detailed discussion of future directions for the development and progression of this class of molecules into the clinic.

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1. Introduction

Natural products extracted from microbes, plants, and animals have remarkable structural diversity and biological characteristics, providing researchers with exciting possibilities to develop novel molecular entities for human therapeutics [1–5]. Of the 112 first-in-class drugs approved by Food and Drug Administration (FDA) between 1999 and 2013, 31 (28%) are developed based on natural pharmacophores (Fig. 1A) [6]. Notably, the 2015 Nobel Prize in Physiology or Medicine highlighted the significant importance of natural products (e.g. Artemisinin) in the treatment of devastating parasitic infections [7,8].

In the kingdom of natural products, diterpenoids have emerged as one of the most important families given their distinct biological activities and drug-like properties as demonstrated by the success of taxane-type diterpenoids in preclinical studies and clinical treatments [9,10]. Besides the taxanes, the kaurane-type diterpenoid, oridonin (**1,** Fig. 1B), has attracted an increasing amount of attention in recent years, due to its impressive pharmacological activities and a safety profile necessary for developing new therapeutics (Figs. 1C and D).

Oridonin, initially isolated from various *Isodon* species which are commonly used as a home remedy herb in China and Japan, was proven to possess considerable anticancer effects [11–13]. Despite a promising safety and efficacy profile for cancer treatment, the relatively moderate potency, limited aqueous solubility and bioavailability, as well as imprecise mechanisms of action have greatly hindered its further preclinical development and clinical applications. To overcome such disadvantages and yield better drug candidates with enhanced activity, a number of oridonin derivatives have been designed and synthesized. Substantial progress has been achieved in the identification of new agents and relevant molecular mechanistic studies towards the treatment of human cancers and other diseases over the past decade. As one of the major milestones achieved (Fig. 2), L-alanine-(14-oridonin) ester trifluoroacetate (**2**, HAO472) [14] was recently advanced into a Phase I human clinical trial (CTR20150246; www.chinadrugtrials.org.cn) in China by Hengrui Medicine Co. Ltd, for the treatment of acute myelogenous leukemia. Herein, we seek to briefly overview the biological and pharmacological investigations of oridonin, and summarize the recent medicinal chemistry advances of novel oridonin analogues, aiming to appreciate the therapeutic potential and value of the oridonin template serving as an exciting platform for drug discovery.

2. The natural product oridonin and its mechanisms of action

Isodon rubescens (a.k.a. "*Rabdosia rubescens*", traditional Chinese medicine name "*Donglingcao*"), the primary natural source of oridonin, has been used for the treatment of inflammation and cancer in Asian countries for hundreds of years [15]. To date, *Donglingcao* remains a commonly available over-the-counter (OTC) herbal medicine for the treatment of inflammation in China [16,17]. Mechanistic studies reveal that the herbal extract can suppress breast cancer *in vitro* and *in vivo* by regulating the MAPK and the Akt signaling pathways [18], and control aortitis inflammation through its anti-TNF-α effect, as seen in a United Kingdom patient study [19].

Oridonin is one of the major efficacious components of the herbal extract with an elucidated chemical structure that has attracted considerable interest [20–22]. Accumulating evidence suggests that oridonin triggers autophagy, inhibits angiogenesis, arrests cell cycle progression and promotes apoptosis through several major molecular mechanisms by modulating the relevant signaling pathways involved in the regulation of intracellular reactive oxygen species (ROS), Bcl-2/Bax, NF-κB, p53/p21, MAPK, PI3K, microRNA and fatty acid synthase pathways. These pathway modulations may be levied for the treatment of broad-spectrum cancers, as demonstrated both *in vitro* and *in vivo* (Table 1). These studies support the idea that cross-talk amongst these targets and signaling pathways are critically associated with the pharmacological effects of oridonin for human cancer treatment [23–26].

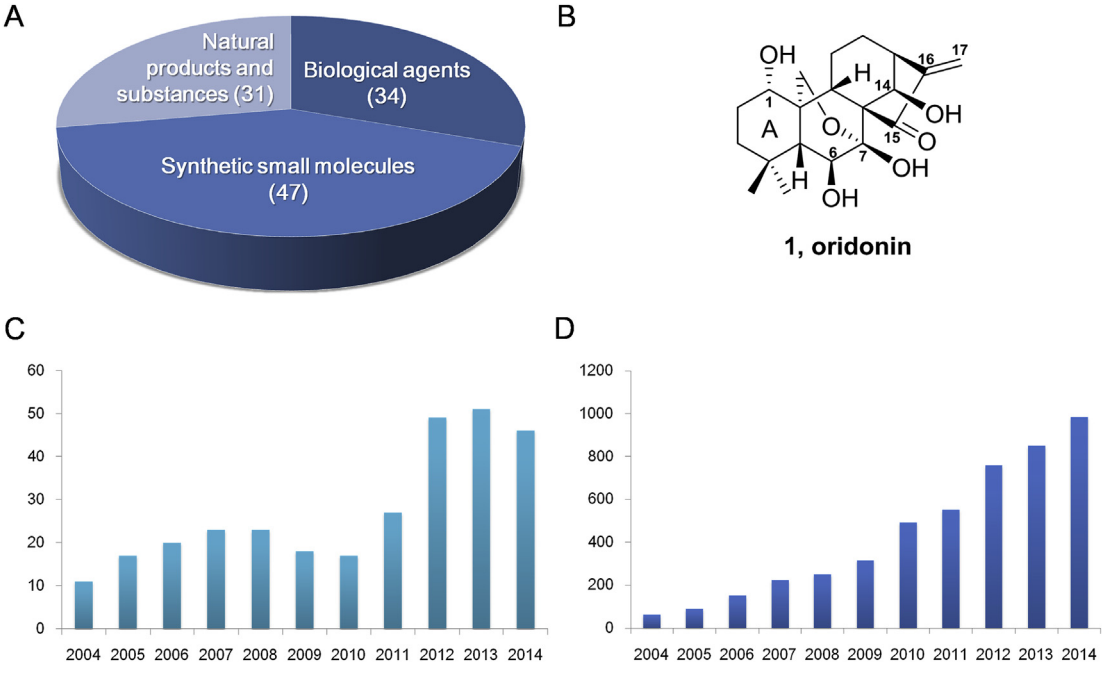

Fig. 1. A) Of the 112 FDA-approved first-in-class drugs from 1999 to 2013, 31 drugs (28%) originated from natural products and substances versus 47 drugs (42%) which are synthetic small molecules, and 34 drugs which are biological agents. **B**) The structure of the natural diterpenoid oridonin. **C**) Number of papers published between 2004 and 2014 containing the keyword "oridonin" according to the Web of Science search. **D**) Citations between 2004 and 2014 according to the Web of Science search using the keyword "oridonin".