Cancer Letters xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

Oleanolic acid and its synthetic derivatives for the prevention and therapy of cancer: Preclinical and clinical evidence

Muthu K. Shanmugam [a], Xiaoyun Dai [a], Alan Prem Kumar [a,b,c,d], Benny K.H. Tan [a], Gautam Sethi [a,b,*], Anupam Bishayee [e,*]

[a] Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[b] Cancer Science Institute of Singapore, National University of Singapore, Centre for Translational Medicine, Singapore
[c] School of Biomedical Sciences, Faculty of Health Sciences, Curtin University, Western Australia, Australia
[d] Department of Biological Sciences, University of North Texas, Denton, TX, USA
[e] Department of Pharmaceutical Sciences, School of Pharmacy, American University of Health Sciences, Signal Hill, CA, USA

ARTICLE INFO

Article history:
Received 30 November 2013
Received in revised form 6 January 2014
Accepted 20 January 2014
Available online xxxx

Keywords:
Oleanolic acid
Synthetic triterpenoids
CDDO
Pentacyclic triterpenoids
Inflammation cancer

ABSTRACT

Oleanolic acid (OA, 3β-hydroxyolean-12-en-28-oic acid) is a ubiquitous pentacyclic multifunctional triterpenoid, widely found in several dietary and medicinal plants. Natural and synthetic OA derivatives can modulate multiple signaling pathways including nuclear factor-κB, AKT, signal transducer and activator of transcription 3, mammalian target of rapamycin, caspases, intercellular adhesion molecule 1, vascular endothelial growth factor, and poly (ADP-ribose) polymerase in a variety of tumor cells. Importantly, synthetic derivative of OA, 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO), and its C-28 methyl ester (CDDO-Me) and C28 imidazole (CDDO-Im) have demonstrated potent antiangiogenic and antitumor activities in rodent cancer models. These agents are presently under evaluation in phase I studies in cancer patients. This review summarizes the diverse molecular targets of OA and its derivatives and also provides clear evidence on their promising potential in preclinical and clinical situations.

1. Introduction

Triterpenes have existed in nature from ancient times and have been identified in prehistoric geological sediments [1]. Triterpenes are widespread in nature and are highly abundant in medicinal plants especially in the leaves, bark, fruits and seeds of the herbs [2,3]. Based on the number of isoprene units, triterpenes can be acyclic, mono-, bi-, tri-, tetra- and pentacyclic. Pentacyclic triterpenes have six isoprene units with a basic formula of $C_{30}H_{48}$. They are synthesized in plants by cyclization of squalene. Latest estimate indicates the existence of approximately 20,000 different triterpene saponins from various sources [1,3,4]. The most studied triterpenes are the tetracyclic triterpenes, such as cycloartanes, dammaranes, euphanes and protostanes, and pentacyclic triterpenes, such as gammaceranes, hopanes, lupanes, oleananes and ursanes. In the past decade, numerous publications have indicated the various bioactivities of pentacyclic triterpenoids. Pentacyclic triterpenes in general possess unique biological properties. These bioactivities include antitumor, anti-inflammatory, antiviral, antidiabetic, antimicrobial, antiparasitic, cardioprotective, hepatoprotective, gastroprotective and wound healing effects [5]. The antitumor and anti-inflammatory effects of pentacyclic triterpenoids have received the most attention and a couple of synthetic oleanolic acid derivatives are now in clinical trials [3,4,6–9].

2. Oleanolic acid

Oleanolic acid (OA, 3β-hydroxyolean-12-en-28-oic acid) (Fig. 1A) is a bioactive pentacyclic triterpenoid belonging to the family Oleaceae and has been isolated from more than 1600 plant species, the majority of them are edible plants and medicinal herbs [5,10,11]. OA is abundant in ginseng root [12] and in olive plant (*Olea europaea*) from which the compound derives its name [13]. The olive plant is the primary commercial source for the compound but other sources include *Arctostaphyllos uva-ursi* (Bearberry), *Calluna vulgaris* (Heather), *Crataeva nurvala* (Three leaved caper)

* Corresponding authors. Address: Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore. Tel.: +65 65163267; fax: +65 68737690 (G. Sethi). Address: Department of Pharmaceutical Sciences, School of Pharmacy, American University of Health Sciences, 1600 East Hill Street, Signal Hill, CA 90755, USA. Tel.: +1 (562) 988 2278x2038; fax: +1 (562) 988 1791 (A. Bishayee).
E-mail addresses: phcgs@nus.edu.sg (G. Sethi), abishayee@auhs.edu (A. Bishayee).

http://dx.doi.org/10.1016/j.canlet.2014.01.016
0304-3835/

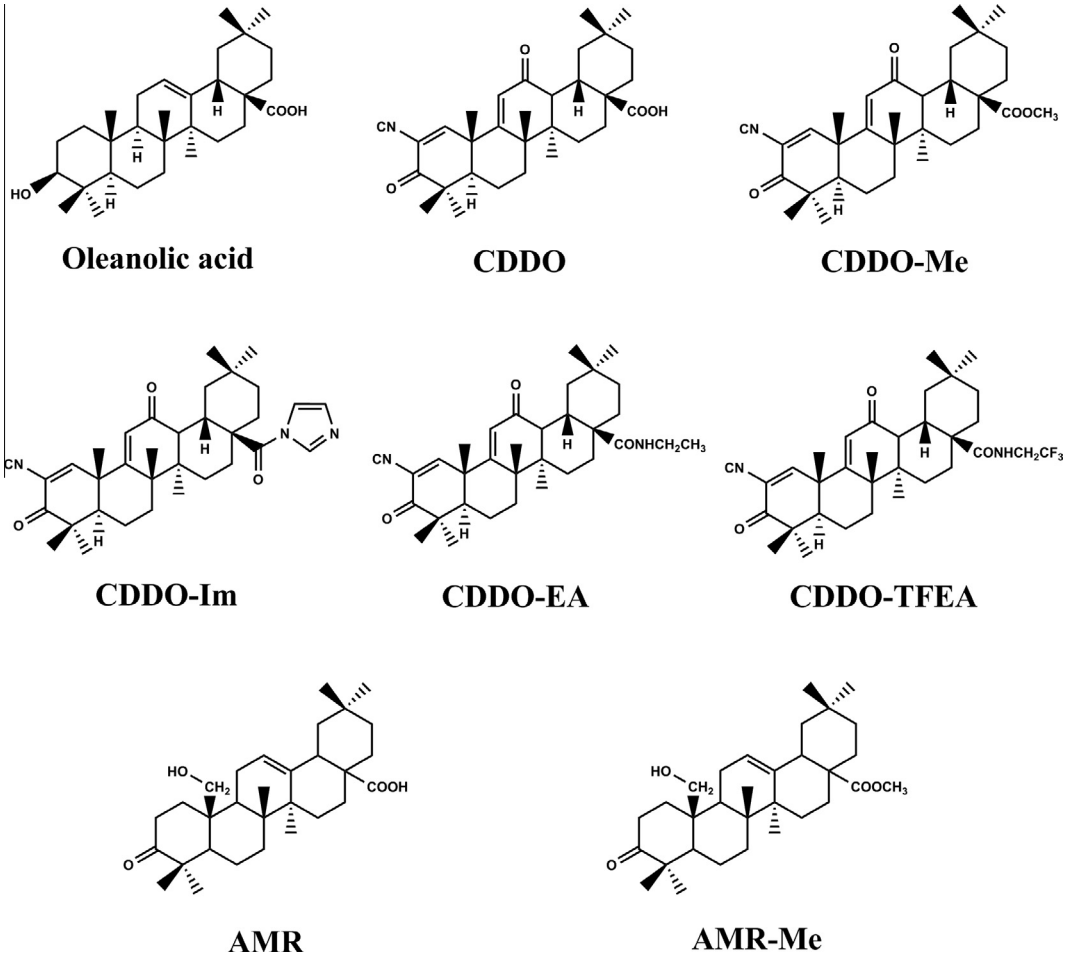

Fig. 1. The chemical structures of oleanolic acid and its derivatives. (A) natural oleanolic acid; B, synthetic oleanane triterpenoids.

Ganoderma lucidum (Reishi), *Sambucus chinensis* (Chinese elder), *Solanum incanum* (Sodom's apple). OA occurs in olive leaves as almost pure crystals that prevent fungal attack [14] and function as a defense compound against herbivores or pathogens or as allelopathic agents. OA exists in nature as the free acid, but also serves as an aglycone of triterpenoid saponins linked with one or more sugar moieties to form glycosides [1,4–6]. Often OA and its isomer, ursolic acid (UA) are found in combination and have similar pharmacological properties [6,7,10,11]. UA is easily obtained in very high purity by methanol extraction of rosemary leaf while OA can be easily obtained in high yield from olive pulp remaining after crushing of the olive fruit and also from olive leaves [3,15]. Thus naturally abundant OA serves as scaffolds for additional modifications to achieve semi-synthetic pentacyclic OA triterpenoids. Among all the triterpenes, pentacyclic OA triterpenoid have been shown to have unique biological activities such as anti-inflammatory, cardio-, hepato-, and gastro-protective, antitumor, antiviral, antidiabetic, antimicrobial, antiparasitic, analgesic and wound-healing effects as well as inducing apoptosis in cancer cells [5,16]. Major advancements in triterpenoid research during the current decade have been made in the synthesis of synthetic triterpenoids. For example, the OA derivative, 2-cyano-3, 12-dioxoolean-1,9(11)-dien-28-oic acid (CDDO, Fig. 1B) and its C-28 methyl ester (CDDO-Me or bardoxolone methyl, Fig. 1B) and C28 imidazole (CDDO-Im) demonstrated potent anti-inflammatory and antitumor activities [17,18]. In addition to these three derivatives, others such as di-CDDO (nitrile at C17 position of CDDO) and various amides such as CDDO-MA (methyl amide), CDDO-EA (ethyl amide), and CDDO-TFEA (trifluoroethyl amide) were synthesized and tested for their antitumor properties. All these molecules affect multiple intracellular processes such as blocking various pro-inflammatory cytokines and chemokines, repressing tumor cell proliferation and inducing tumor cell apoptosis [16,19–23] (Fig. 2). This review will mainly focus on OA and its derivatives.

3. *In vitro* effects of OA and its synthetic derivatives on cancer cells

3.1. Breast cancer

The role of triterpenoids in the chemoprevention and therapy of breast cancer has been excellently reviewed previously [24]. OA isolated from *Glossogyne tenuifolia* showed weak antitumor activity against MCF7 and MDA-MB-231 breast cancer cells [25]. Several investigators confirmed antiproliferative effect of OA against several breast carcinoma cell lines [26,27] (Table 1).

A novel synthetic OA derivative, achyranthoside H methyl ester (AH–Me) exhibited significant cytotoxicity against human breast cancer MCF-7 and MDA-MB-453 cells, with respective IC_{50} values of 4.0 and 6.5 μM. AH-Me-induced apoptosis was supported by dose- and time-dependent increases in the sub-G_1 population and activation of caspase-3 [28]. CDDO was shown to inhibit proliferation and induce peroxisome proliferator-activated receptor-γ (PPAR-γ) in human epidermal growth factor receptor 2 (HER2) overexpressing breast cancer cells [29,30]. CDDO-Im induced

Please cite this article in press as: M.K. Shanmugam et al., Oleanolic acid and its synthetic derivatives for the prevention and therapy of cancer: Preclinical and clinical evidence, Cancer Lett. (2014), http://dx.doi.org/10.1016/j.canlet.2014.01.016