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Anti-HIV triterpenoid components

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ABSTRACT

AIDS is a pandemic immunosuppresive disease which results in life-threatening opportunistic infections and malignancies. Exploration of effective components with anti-HIV in native products is significant for prevention and therapy of AIDS. This review will focus on the mechanisms of action of anti-HIV triterpenes and the structural features that contribute to their anti-HIV activity and site of action and compare their concrete activity.

Keywords: Triterpenes components, Anti-HIV, Activity

INTRODUCTION

HIV is the pathogenic of AIDS. In order to combat the debilitating disease acquired immune deficiency syndrome and the emergence of Anti-HIV, we search, research and develop the drug which can preventing and curing the disease. It is known that three enzyme play an important role in the development of HIV, such as nucleoside analogue HIV reverse transcriptase(RT), HIV integrase and HIV protease. However, the efficacy of these HIV enzyme inhibitors is limited by the development of drug resistance. The most potent HIV-1 protease inhibitor is components of polypeptide, however, the efficacy of components is low and expensive and the emergence of Anti-HIV is also their disadvantage.In the search of the drug of An-HIV, some triterpenoid components from nutural plant revealed good activity.

TRITERPENES CHEMICAL CONSTITUTION

The triterpenoid components distributing extensively in the nature which are consisted of thirty carbon atom are in the state of dissociation or indican, some combine with sugar are called triterpenoid saponins. A lot of Chinese traditional medicine such as *Panax, liqurice, Panax noginseng* and *highaspiration* contain a great deal of triterpeno-

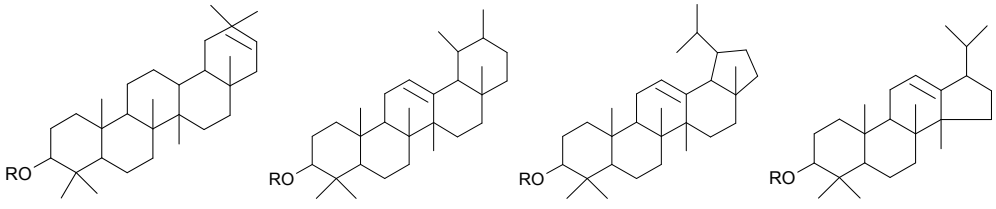


Fig. 1 Triterpenes chemical constitution

id saponins. Their aglycone mostly are pentacyclic triterpenoids and tetracyclic triterpenoids. The compotents of pentacyclic triterpenoids, the carboxyl on the C28 or C30 instead of methyl have acidity which are also called acid sapoid. Acid sapogenins such as Oleanolic acid, Ursolic acid and Maslinic acid have helpful Anti-HIV activity.

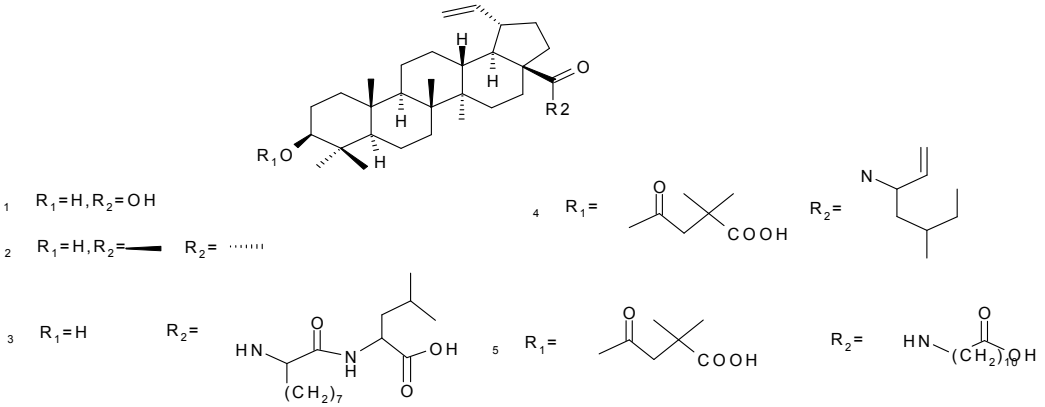
THE TRITERPENOID COMPONENTS' ANTI-HIV MECHANISM

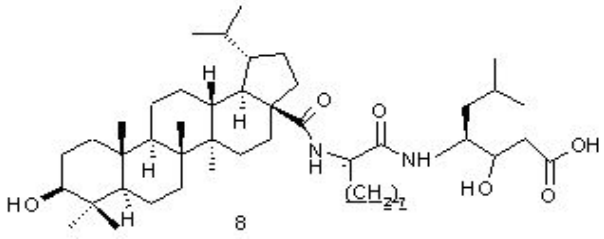
Base on their action mechanism and molecule target, the triterpenoid components'anti-HIV mechanism are classified into seven different classes. Currently approved anti-HIV drugs are either HIV-1 protease or reverse transcriptase inhibitors.

2.1 Entry Inhibitors that Block HIV Adsorption or Membrane Fusion

Betulin derivative aminooctanoyl amino-3R-hydroxy-6methylheptanoic acid (Compound 1) and its stereoisomers (Compound 8) were found equal in anti-HIV activity with an EC_{50} value of 0.4 μmol/L [1]. However, mutations in the HIV-1 envelope glycoprotein gp120 sequence makes HIV-1 resistant to it [2]. Through changing the signal between gp120 and gp41 which is essential of changing construct of acceptor gp41, those betulin derivative can block HIV adsorption [2]. In the infection trial (MAGI and Fusion) of H9 lymphocyte, compounds (Compound 8 and Compound 3) reveal best activity. In MAGI experiment, their value of EC_{50} are 0.33 and 0.46μmol/L respectively. And in the fusion assay, their value of EC_{50} are 0.40 and 0.33μmol/L respectively [2].

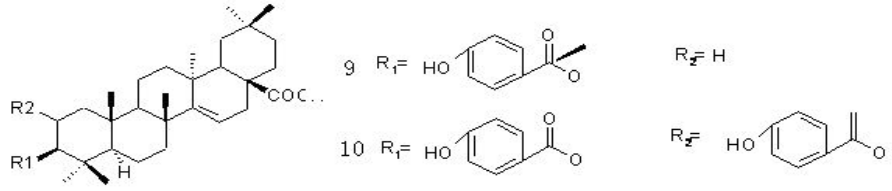
Betulin derivative which both C-3 and C-28 side chain are replaced by other group, their activity block the fusion between virus ectoblast and the host membrane. On the other hand, viruses which bypass this blockage, have to face the maturation inhibition activity of these compounds. Superior bifunctional anti-HIV compounds N[3-O(3,3-dimethylsucciny)-lup-20(29)-en-28-oyl]-L-leucine (Compound 4) and N-[3-O(3,3-dimethylsucciny)-lup-20(29)-en-28-oyl]-11-aminoundecanoic acid (Compound 5) were obtained (depending on the tested HIV-1 strain). Among this series compounds, Compound 6,7 reveal best activity with the value of EC_{50} are 0.0026 and 0.0036μmol/L respectively [2]. The saponin isolated from the fruits of *Tieghemella heckelii Pierre* was reported to have antiviral activity. It strongly inhibited the entry of HIV into cells in a cell fusion assay, and showed no significant cytotoxicity towards HeLa-CD4 cell [3].





2.2 Reverse Transcriptase Inhibitors

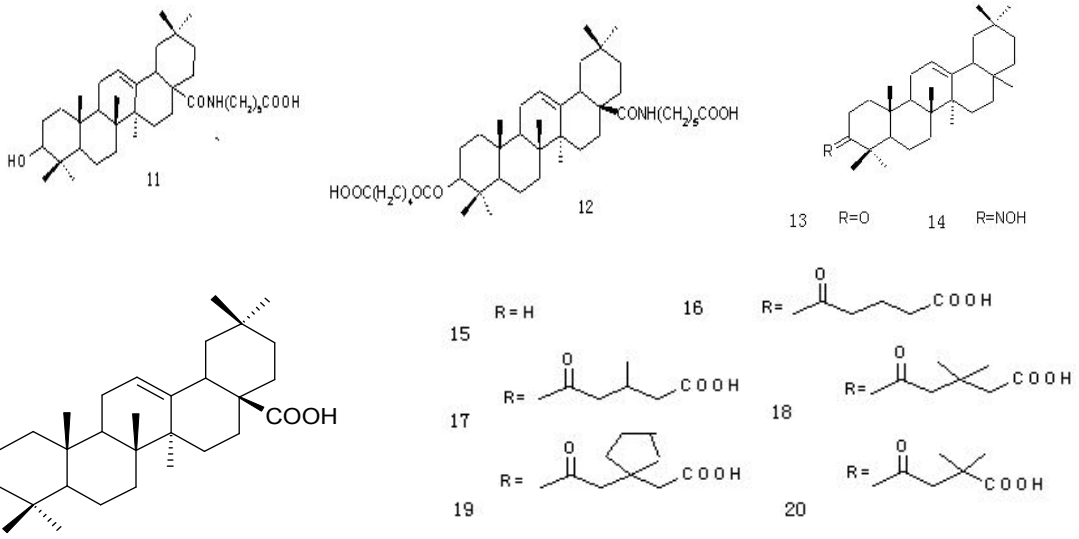
Pentacyclic triterpenes, 1b-hydroxymaprounic 3-p-hydroxybenzoate (Compound 9) and 2a-hydroxymaprounic acid 2,3-bis-p-hydroxybenzoate (Compound 10) isolated from the root of *Maprounea Africana Muell.-Arg*, inhibited HIV-1 RTase with a value of IC_{50} 3.7μmol/L [4]. 1β-hydroxy-aleruitolic acid-3-p-hydroxybenzoate, isolated from *Swertia franchetiano*, inhibited HIV-1 RTase with a IC_{50} value of 3.7μmol/L [5].



2.3 Protease Inhibitors

In the series of C-3 acid group of triterpene derivative, such as malonate mono-ester, reveal obvious anti-protease activity. The polar-fuction group of C-3 side chain of triterpene derivative play an important role in the process of interactional with enzyme. When both the carboxyl of C-17 methylation and was replaced with methyl, their inhibition was rudused. So the polar-fuction group of C-17 side chain of triterpene derivative play an important role in the process of interactional with enzyme. We can conclude that the polar-fuction group of C-3 or side chain interact with some amino-adid residue of protease through hydrogen bond and electrostatic interaction to inhibit the HIV-1 protease activity. Mekkawy isolated two triterpenoid components, ganoderiol and ganodermanotriol, with IC_{50} value of 1.0 μmol/L anti-HIV-1 protease [6].

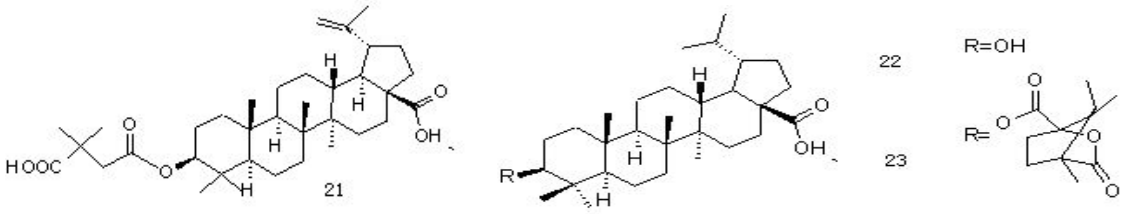
Ursolic acid and its malonate mono-ester have fort function in inhibiting HIV-1 protease, with a EC_{50} value of 8 and 6μmol/L respectively [7]. Gymonocladus saponin G and gleditisa saponic C were isolated from *Gymnocladus chinensis* and *Gleditsiajaponica* respectively. They are polycose triterpenoid saponin which constructed with oleanane triterpene and seven to nine sugar, have activity of inhibiting protease, with a EC_{50} value of 1.1 and 2.7μmol/L respectively [8]. We can obtain ursolic acid, maslinic acid and 2α, 19α-dihydroxy-3-carboxide-ursolic-12ene-28acid from Geum japonicum which can inhibit HIV-1 protease. Among them, maslinic acid revealed best activity [9]. The C-3 hydroxy group of oleanolic acid (Compound 13) was oxidized with a IC_{50} value of 5.5μmol/L, the it react with hydroxylamine, the created compound (Compound 14) with a IC_{50} value of 5.5 μmol/L [10]. The C-28 carboxy group of oleanolic acid was linked with long amino acids chin produce compound (Compound 11), then its C-3 hydroxy group react with hexanedione produce compound ether (Compound 12), with a IC_{50} value of 1.7 μmol/L. The bouble bond of C12-C13 of oleanolic acid was deoxidized to single bond come into being of new compound (Compound 15) with a EC_{50} value of 0.5 μmol/L. The series of compound were produced when reacting with corresponding acid anhydride. Among these compounds which inhibit HIV protease, Compound 16 has a EC_{50} value of 2.6 μmol/L, Compound 17,18,19 have a EC_{50} value of 0.1μmol/L, and Compound 20 has a EC_{50} value of 0.0039 μmol/L [11].



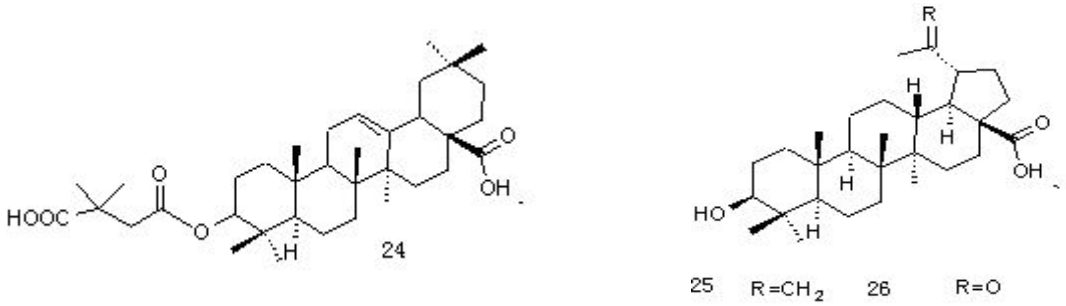
2.3 Virus Maturation Inhibitors

In particular, a mechanism is proposed, where DSB (Compound 21) acts late in the HIV-1 life cycle and binds to the CA-p2 junction of Gag polyprotein (single polyprotein which is sufficient for virus particle assembly) by viral protease during HIV-1 particle assembly and sterically inhibits cleavage of this site [12]. Dimethyl-succinyl-betulinic-acid whose C-3 hydroxy group of betulic acid was improved, is a special virus maturation inhibitor. The virus of HIV-1 which produce drug fast to the inhibitor of both protease and RT-transcriptase is still sensitive to dimethyl-succinyl-betulinic-acid [2].

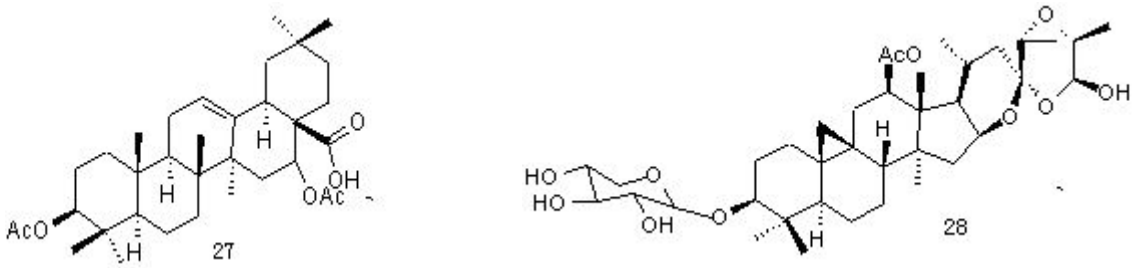
2.4 H9 Lymphocyte Inhibitors



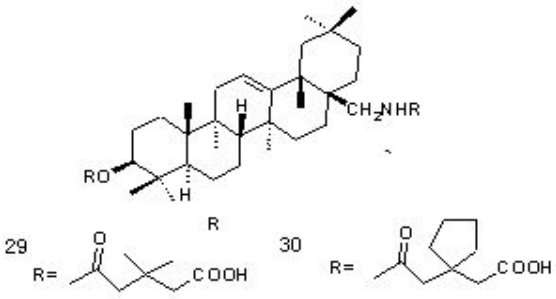
Betulinic acid isolated from the leaves of *Syzigium claviflorum*, exhibited anti-HIV activity in H9 lymphocyte cell. Betulinic acid demonstrated an anti-HIV activity with an EC_{50} value of 1.4μmol/L and a IC_{50} value of 13 μmol/L. Dihydrobetulinic acid (Compound 22) showed EC_{50} value of 0.9 μmol/L and a IC_{50} value of 13 μmol/L [13]. Oleanolic acid isolated from methanolic extract of wood of *Xanthoceras sorbifolia*, inhibited HIV-1 replication in acutely infected H9 cell growth. Esterification at C-3 hydroxyl of oleanolic resulted in 3-oxotirucalla-7,24-dien-21-oic acid (Compound 24) with improved activity(EC_{50} 0.0039 g/mL, TI 3750) [14].



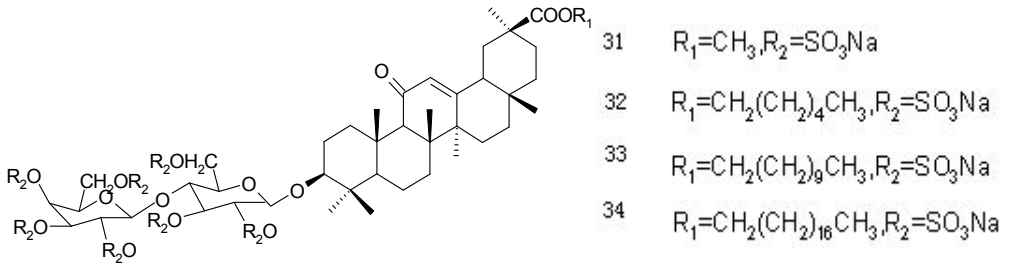
Toshihiro Fujilka found the methanol leaching liquid from the leaf of Syzigium daviflorum have anti-HIV activity. From it, we can obtain triterpene and kata-triterpene. 3-Hydroxy-20-oxonorlupan-28-oic acid,3.beta (Compound 25) inhibit the replication of HIV in H9 lymphocyte, with a EC_{50} value of 1.4 μmol/L, and inhibit the growth of uninfected H9 lymphocyte, with a IC_{50} value of 13 μmol/L. The corresponding value of kata-triterpene (Compound 26) are EC_{50} value of 6.5 μmol/L, IC_{50} value of 90 μmol/L [15]. The gleditschisaponin echinocystic acid derivative of Gleditsia japonica, 3,16-diacetyl- echinocystic acid (Compound 27) has a EC_{50} value of 2.3 μmol/L, IC_{50} value of 13 μmol/L [16].



Actein (Compound 28) isolated from methanolic extract of rhizome of *Cimicifuga racemosa*, showed activity against HIV replication in H9 lymphocytes, with an EC_{50} of 0.375 μg/mL and TI of 144 [17]. Converting the C3-carboxyl of Oleanolic acid, then introducing 3,3-dimethylglutaryl or 3,3-tetramethylglutaryl group at both the C3 and C28 positions produced two new compounds (Compound 29, 30) with an EC_{50} 0.1μg/mL, IC_{50} 21.2 and 19.5 μg/mL respectively [14].

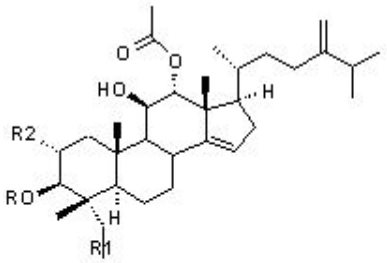


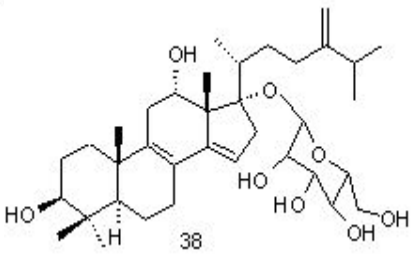
Sulfurized triterpene (Compound 31,32,33,34) effects on the inhibition of replication of HIV, with EC_{50} of 5, 4, 6, 30μg/mL respectively [16].

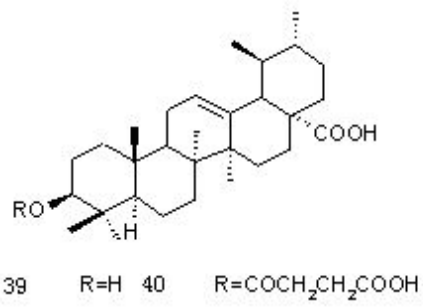


2.5 Integrase Inhibitors

Integracides were evaluated in coupled and strand transfer assays of recombinant HIV-1 integrase. Compound (Compound 35) inhibited coupled and strand transfer reactions with IC_{50} value of 4 and 9μmol/L, respectively. The desulfated compounds (Compound 36,37) and compound (Compound 38) were significantly less active in the coupled assay and showed IC_{50} value of 82, >100, 50 and >50 μmol/L, respectively. However, these compounds were completely inactive at 100 μM in strand transfer assays and thus indicated the sulfate group was important for the potency. In addition, compound (Compound 35,36,37) inhibited 3-end processing activity with an IC_{50} value of 5 μmol/L, preintegration complex(PIC) with an IC_{50} 50μmol/L and showed antiviral activity with CIC_{95} value of 25 μmol/L in the multiple cycle H9 viral spead assay. Unfortunately, it also showed toxicity at 25 μmol/L and did not exhibit any therapeutic window [18].





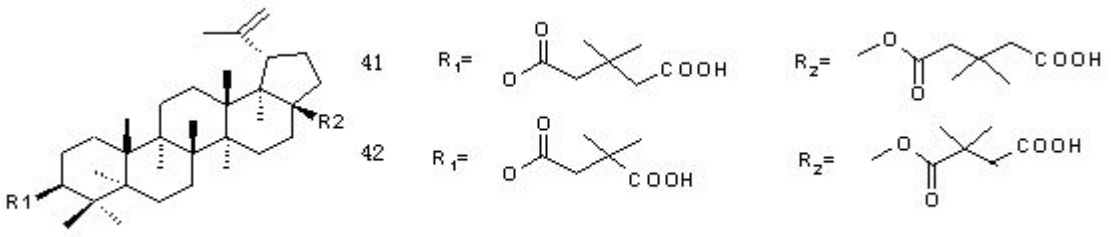


2.6 Transcriptase Inhibitors

Ursolic songaricum (Compound 39) and its malonate mono-ester (Compound 40) isolated from *Cynomorium songaricum* have anti-HIV-1 transcriptase activity, with a IC_{50} value of 8.0 and 6.0 μmol/L respectively [10].

2.7 Inhibitors with Unknown Mechanism of Action

J. Hideki N proved that glycyrrhizic sulphate is the inhibitor of reverse transcriptase [12], but Masahiko I don't think so. The major mechanism of action of glycyrrhizic acid inhibiting the replicative of HIV is cutting down the activity of protein kinase C. In addition, can inhibit the spreading of HIV, through prohibiting fusion in cells [19]. Maslinic acid has a high-performance function on all of the HIV stock which separating from all philo-CCR5 and CXCR4. Maslinic acid can restrain HSV from infecting cervix cellula epithelialis. It nearly has non-cytotoxicity, and show superiority selectivity. It prevent the connecting of HIV and HSV to cells [20]. The more high-performance is betulic acid diester derivate (Compound 41,42), their TI value are 21515 and 41400, the EC_{50} value of 0.66 and 0.87μmol/L respectively [12].



CONCLUSION

The HIV that threaten human' health heavily is the focus of our daily life at all times. To develop the drug of anti-HIV is the hotspot topic in medicinal area. Although our research is still inexploring stage, it also has some effection. Screening anti-HIV components out from triterpenoid components deserve our deeper research.

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