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Biological Activities and Corresponding SARs of Andrographolide and Its Derivatives

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Abstracts: In recent years, pharmaceutical chemists have synthesized large numbers of andrographolide derivatives, which bear important biological activities such as anti-inflammatory, antibacterial, antivirus, antitumor, antidiabetic, and antifeedant. Consequently, corresponding SARs were increasingly obvious. This paper aimed to review all the available literature in this field, highlighting the significant achievements on the structural modification and SARs of andrographolide and its derivatives.

Keywords: Andrographolide derivatives, biological activities, SARs.

INTRODUCTION

Andrographolide (Andro) (Fig. (**1**)) is a labdane diterpene isolated from the leaves of *Andrographis paniculata* (*A. paniculata*), a medicinal plant from Acanthaceae family, which is widely utilized as a traditional medicine in China, India, and many other countries in Asia [1]. As a major active constituent, Andro is known to possess a broad range of biological activities, such as anti-inflammatory, antibacterial, antitumor, antidiabetic, antimalarial, hepatoprotective, and others activities (see [2] for review). As shown in (Fig. **1**), Andro incorporates two double bonds ($\Delta^{12(13)}$ and $\Delta^{8(17)}$), one α-alkylidene-γ-butyrolactone, and three hydroxyl groups at C-3, C-14, and C-19, which are the main fragments for structural modification.

Given the impressive biological activities, a large number of Andro derivatives emerged and evaluated for their pharmacological activities during the past few years. However, no comprehensive summary on the structure-activity relationship (SAR) of Andro and its derivatives has yet been published. Herein, we present a systematic review on this specific field.

ANTI-INFLAMMATORY ACTIVITY

Research has shown a potential therapeutic value of Andro in the treatment of fever, asthma, pain, rheumatoid arthritis [2, 3]. Xia *et al.* [4] demonstrated that Andro could form a covalent adduct with reduced cysteine (62) of p50, thus blocking the binding process of nuclear factor-kappa B (NF-κB) oligonucleotide to nuclear proteins. Thereafter, Andro has also been testified to have the ability to inhibit gene expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) and release of nitric oxide (NO), prostaglandin E2 (PGE_2), tumor necrosis factor-alpha (TNF-α) and granulocyte macrophage colony-stimulating factor (GM-CSF) [5, 6]. However, the exact anti-inflammatory mechanism was not yet fully elucidated.

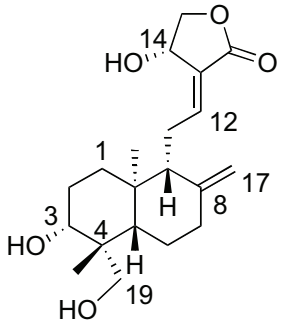

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Fig. (1). Chemical structure of Andrographolide.

Recently, Li *et al.* [7] investigated the inhibitory effects of a series of Andro derivatives (Fig. (**2**)) on lipopolysaccharide (LPS)-induced TNF-α and Interleukin 6 (IL-6) release in mouse macrophages. The results showed that compounds **12**, **14**, and **15** (the inhibiting percentage was 43.75, 36.45, and 41.60, respectively) displayed more potency than Andro (62.54) in inhibiting LPS-induced TNF-α expression. The same was true to compounds **2**, **5**, **6**, **7**, and **9** (the inhibiting percentage was 44.73, 37.53, 29.21, 32.1, and 44.64, respectively) in inhibiting LPS-induced IL-6 expression. Among the isoandrographolide derivatives (**10**-**18**), an improvement of inhibitory activity could be obtained by protecting both C-3 and C-19 hydroxyls (**12**) rather than C-3 hydroxyl (**18**). However, for compounds **13** and **14**, the opposite results appeared. The increase of water solubility of isoandrographolide would be detrimental to the inhibiting activity, as was evident from compound **15** (with hydrophilic groups) being extremely less potent. Among 12-hydroxy-14-dehydroandrographolide analogs (**2**-**9**), compounds fused with the alkyl group at C-12 (**2**, **3**, **4**, and **8**) showed weaker inhibitory effects than those fused with aryl group at C-12

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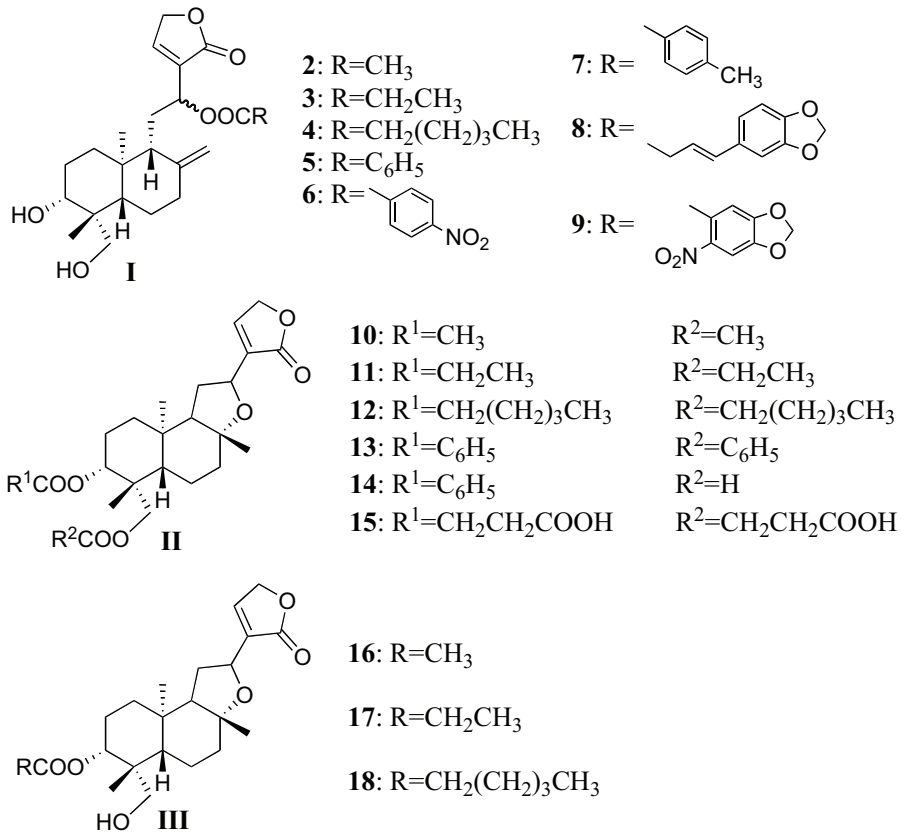


Fig. (2). Chemical of andrographolide and isoandrographolide derivatives studied for TNF-α and IL-6 expression inhibitory activities.

(**5**, **6**, and **7**) in both TNF-α and IL-6 expression, indicating that the introduction of bulky aryl group or electron-withdrawing group at C-12 may enhance the inhibitory activity of parent **I**. Generally, it became clear that $\Delta^{8(17)}$ double bond may be necessary for inhibitory activity and the structure of 12-hydroxy-14-dehydroandrograholide may be a good lead for further optimization as novel TNF-α and IL-6 expression inhibitor, considering Parent **I** being superior to parents **II** and **III** in terms of inhibitory profile.

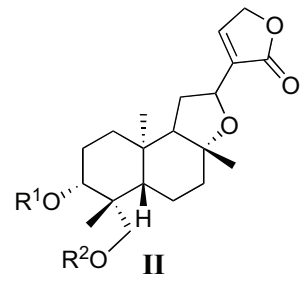
In another article, Li *et al.* [8] also reported the inhibitory activity studies of Andro derivatives (Fig. (**3**)) on LPS-induced COX-2 expression in mouse macrophages. In this study, compounds **13**, **14**, **19**, **20**, and **21** was found to display the inhibiting percentage as 51.2, 56.4, 43.0, 25.7, and 52.3, respectively. Apparently, compound **13** showed stronger inhibitory activity than compound **14**, with the same occurring to compound **19** toward **21**, suggesting that the two hydroxyls need to be converted into esters. On the other hand, parent **II** exhibited superior inhibitory activity to parent **IV**. Especially for compound **20**, which belonged to parent **II**, could significantly suppress LPS-induced COX-2 expression at 5μM. Thus, the structure of isoandrographolide may provide a good train of thought for further optimization as novel COX-2 expression inhibitor.

It was reported that Andro and compounds **30**-**36** (Fig. (**4**)) could significantly inhibit TNF-α, IL-6, macrophage inflammatory protein-2 (MIP-2), and nitric oxide secretions from LPS/IFN-γ-stimulated RAW 264.7 cells [9]. Among these Andro derivatives, compounds **34**, **35**, and **36** exerted the strongest inhibitory effect on NF-κB-dependent transactivation in the RAW 264.7 cell, with IC_{50} values of 2, 2.2, and 2.4 μg/ml, respectively. Therefore, the α-alkylidene-β, γ-unsaturated-γ-lactone side chain may be an essential group for anti-inflammatory activity. In addition, compound **30** suppressed NF-κB activation and allergic airway inflammation but devoid of cytotoxicity, making it a safer agent for the potential treatment of asthma [10]. To summarize, the number and position of double bolds in the chemical structure of Andro seems to play a key role on anti-inflammatory activity.

ANTIBACTERIAL ACTIVITY

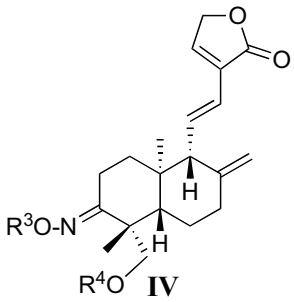
Wu *et al.* [11] first reported that Andro could recover the susceptibility of *Pseudomonas aeruginosa* (*P. aeruginosa*) to certain antibiotics, and the possible mechanism was that Andro inhibited the *mexAB-oprm*-oriented expression of the quorum sensing (QS) system. Interestingly, compounds **37**, **38**, **39** and **40** (Fig. (**5**)) were active against *Staphylococcus aureus* (*S. aureus*) including the methicillin-resistant MRSA5676 and MRSA5677 strains while Andro and compounds **41**-**43** were not [12].

Andro and its C-14 hydroxyl-modified derivatives (**37**(AL-1), **38**, **39** and **40**) inhibited both pyocyanin and protease production (two different virulence factor produced and excreted by *P. aeruginosa*) at 0.1mM, and AL-1 was the



13: R^1=COC_6H_5 R^2=COC_6H_5
14: R^1=COC_6H_5 R^2=H
19: R^1= $CO(CH_2)_4CH_3$ R^2=$CO(CH_2)_4CH_3$
20: R^1=H R^2=Tr
21: R^1=$CO(CH_2)_4CH_3$ R^2=H

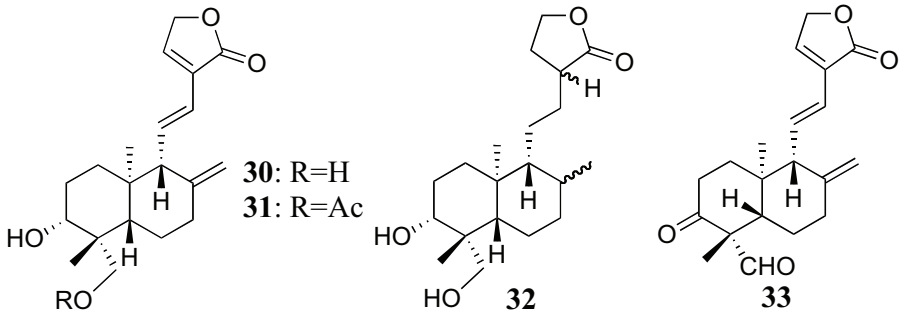
II



22: R^3=H R^4=H
23: R^3=CH_3 R^4=H
24: R^3=$COCH_3$ R^4=$COCH_3$
25: R^3=$COCH_2CH_3$ R^4=$COCH_2CH_3$
26: R^3=COC_6H_5 R^4=COC_6H_5
27: R^3=$COCH{=}CHC_6H_5$ R^4=$COCH{=}CHC_6H_5$
28: R^3=COC_6H_5-p-Cl R^4=H
29: R^3=$COCH_2C_6H_5$ R^4=H

IV

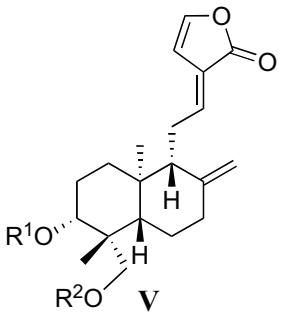
Fig. (3). Chemical structure of andrographolide and isoandrographolide derivatives studied for COX-2 expression inhibitory activities.



30: R=H
31: R=Ac

32

33



34: R^1=H R^2=H
35: R^1=Ac R^2=Ac
36: R^1=H R^2=Ac

V

Fig. (4). Chemical structure of andrographolide and its derivatives studied for NF-κB-dependent transactivation inhibitory activities in the RAW 264.7 cells.

most potent, while compounds **41**-**43** only suppressed protease production. Although Andro could inhibit biofilm formation, compounds **40** and **42** did not show any inhibitory effect. Differing from others, biofilm formation was almost completely inhibited by AL-1 at 1mM. On the other hand, compounds **44**-**52** inhibited pyocyanin production at 0.5mM, and compound **52** and AL-1 emerged as the most potent analogs [13]. Further investigation suggested that compounds **52**, **46**, **49** and AL-1 almost completely suppressed protease production at 0.5 mM; meanwhile, compounds **48**, **50**, **51** and Andro had a similar activity. Since these C-14 hydroxyl-modified analogs were tested, several SARs in terms of antibacterial and QS system activity are presented as follows:

a) Removal of the C-14 hydroxyl moiety evidently reduces the antibacterial activity and the free hydroxyls at C-3 and C-19 are important for inhibitory activity (Andro and **37**-**40** vs. **41**-**43**);

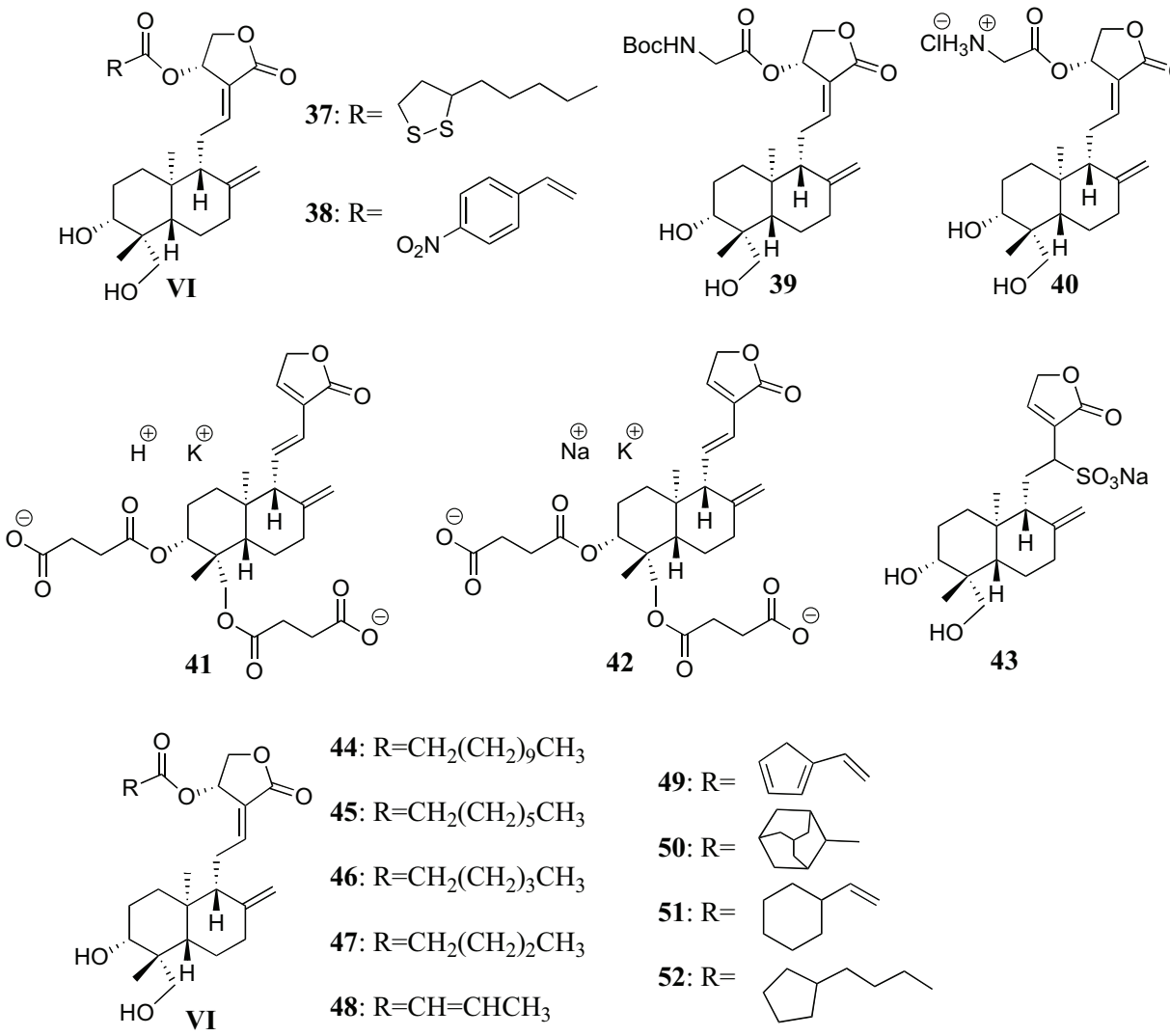


Fig. (5). Chemical structure of andrographolide derivatives studied for antibacterial activities.

b) The lipophilic group, aliphatic straight or cyclic, at C-14 increase the inhibitory activity;

c) Inhibition process of pyocyanin and protease production of these compounds is carried out through different pathways. (e.g., compound **46** is potent at different levels on the inhibition of pyocyanin and protease production);

d) A disulfide bond plays a negligible role for antibacterial activity (AL-1and **52** with identical effect).

Furthermore, Zeng *et al.* [14] verified that the biofilms formation of *P. aeruginosa* was almost completely inhibited when AL-1 was combined with AZM (azithromycin), CIP (ciprofloxacin), and STR (streptomycin). The productions of both EPS (exopolysaccharide) and pyocyanin were significantly reduced under this condition compared with the case of each antibiotic being used alone. In other words, AL-1 has synergistic effects on antibiofilm and antivirulence activities when combined with AZM, CIP and STR.

ANTIVIRUS ACTIVITY

Andro and three of its derivatives (DASS (**43**), DDAS (**42**), DDAP (**41**)) have been used clinically in China over the last 30 years. Recently, the inhibitory activity of Andro, DASS, and AL-1(**37**) on influenza and avian influenza viruses *in vitro* and *in vivo* were evaluated by Chen *et al.* [15]. In particular, AL-1(EC_{50} values ranging from 7.2 to 15.2 μM) exhibited the strongest antiviral activity against avian influenza A (H9N2 and H5N1) and human influenza A (H1N1) viruses *in vitro* while the control group, ribavirin (EC_{50} values ranging from 30.3 to 42.9 μM), exhibited slightly lower potency. Although AL-1(CC_{50}, 785μM) showed high toxicity to Madin Darby canine kidney (MDCK) cells, the results demonstrated that AL-1 had the highest selective index (SI) or therapeutic index (TI). Furthermore, AL-1 could directly interfere with the viral hemagglutinin binding to cellular receptors due to its significant inhibition of viral adsorption onto red blood cells (RBCs) in the concentration range of 5.3-16.8 mM.

Currently, anti-HSV-1 activity in infected Vero cell lines *in vitro* was examined for several Andro and its derivatives (Fig. (**6**)) by Aromdee *et al.* [16, 17]. The results showed that IPAD (**54**) (IC_{50}, 8.3μM) had the strongest anti-HSV-1 activity and the inhibitory effects of all these compounds were confirmed on viral entry and replication steps (anti-replication) using pre- and post-infection assays. Although the site of action for anti-replication activity of IPAD was still unclear, it was still a promising structure for antivirus. An improvement of anti-HSV-1 activity could also be obtained by removing C-14 hydroxyl of Andro (DAD). Moreover, compounds **59-61** showed greater potency compared to Andro, DAD, and compound **30**, suggesting that acetylation of C-14 hydroxyl was essential to the anti-HSV-1 activity in virus entry step, regardless of the substitutions at C-3 and C-19 hydroxyls.

On the other hand, studies on the potential anti-HIV activity of Andro and its derivatives were relatively rare. Andro and 14-deoxy-11, 12-didehydroandrographoli-de (**30**) (EC_{50}:49.0, and 56.8μm/ml, respectively) were first evaluated for anti-HIV activity by Reddy *et al.* [18]. Since then, a series of compounds (Fig. (**7**)) were obtained and evaluated for anti-HIV activity on C8166 cells [19, 20]. When their TIs were compared, only compounds **13** and **64** (CC_{50}:100.45 and >100 μg/ml, EC_{50}:3.81 and 3.91μg/ml, TI:26.35 an d >51.19, respectively) were found to exert moderate inhibitory activity on the cytopathic effect (CPE). However, the mechanism of anti-HIV and SAR remain to be further investigated.

ANTITUMOR ACTIVITY

Antitumor mechanisms of Andro were found to be involved with both the cell-cycle regulating and immunostimulatory in tumor cells during the past few years. Rajagopal *et al.* [21] reported that Andro inhibits different tumor cell lines by inducing cell-cycle arrest at G0/G1 phase and decreasing expression of cyclin-dependent kinase 4 (CDK4). Meanwhile, Andro could increase the proliferation of lymphocytes and production of interleukin-2, which contributed to the activation of the lymphocytes against cancer cells. Thereafter, Sheeja *et al.* [22] also reported that Andro could inhibit tumor-specific angiogenesis by down-regulating various proangiogenic molecules such as VEGF, NO and proinflammatory cytokines and up-regulating antiangiogenic molecules like IL-2 and TIMP-1. More recently, Andro verified its inhibitory activity of human colorectal carcinoma Lovo cells migration and invasion via the down-regulation of MMP-7 expression, which provided a new mechanism for its antitumor activity [23].

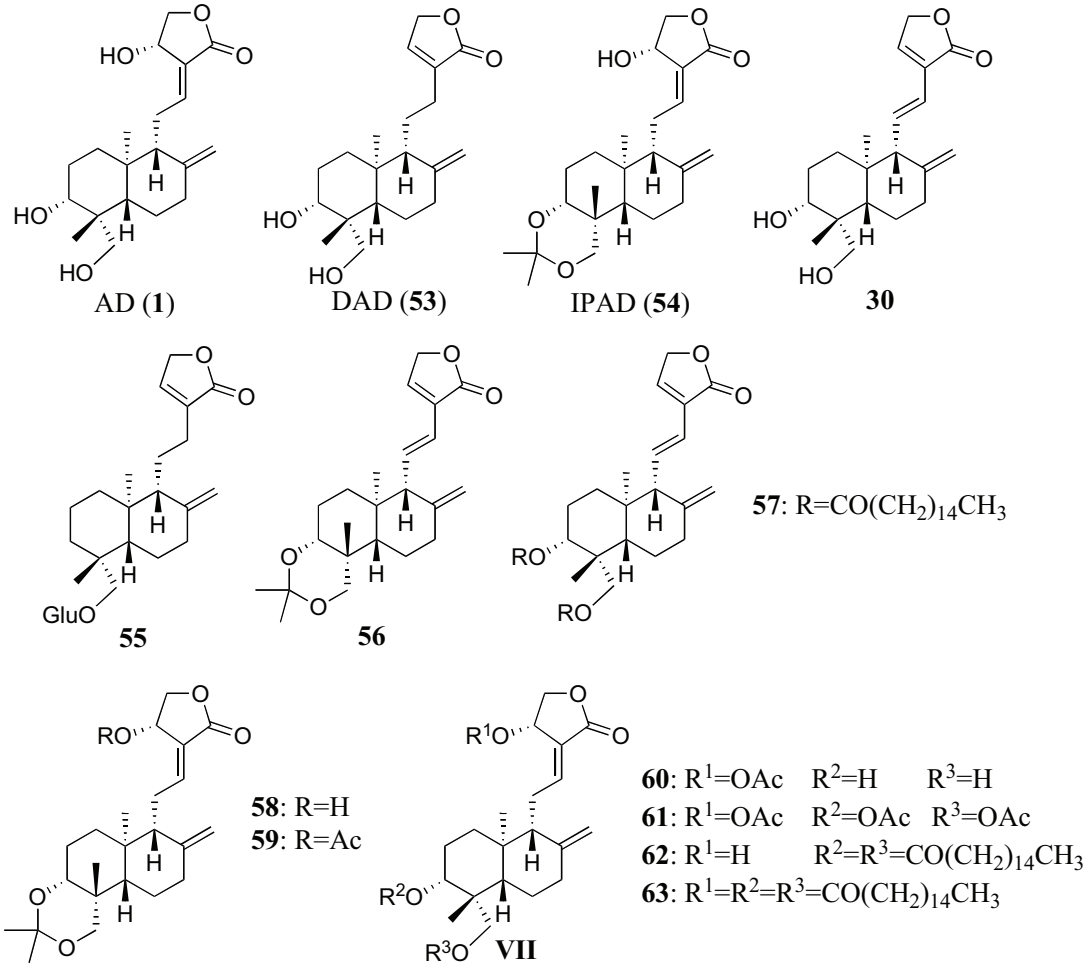


Fig. (6). Chemical structure of Andro analogues studied for antivirus activity *in vitro*.

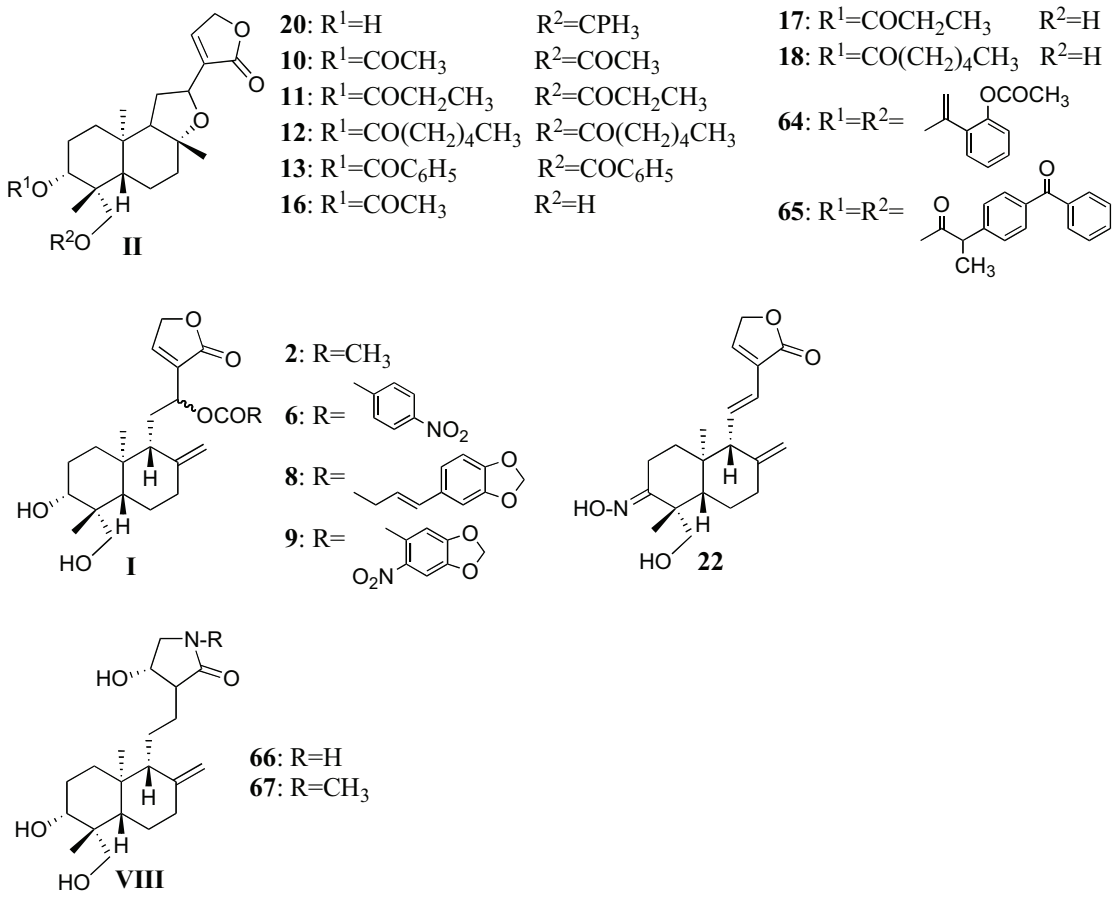


Fig. (7). Chemical structure of Andro analogues studied for anti-HIV activity *in vitro*.

As previously described, Andro contains two double bonds ($\Delta^{12(13)}$ and$\Delta^{8(17)}$), one α-alkylidene-γ-butyrolactone, and three hydroxyl groups at C-3, C-14, and C-19. Nanduri *et al.* [24] obtained large amounts of Andro derivatives (Fig. (**8**):**30**, **53**, **68-76**) through the modification of the above functional groups. Meanwhile, breast (MCF-7/ADR), CNS (U251), colon (SW620), lung (H522), ovarian (SKOV3), prostate (DU145), and renal (A498) cancer cell lines were also tested to check the cytotoxic activity of these compounds. As a result, compounds **72**, **74**, **75**, and **76** showed excellent cytotoxic activity (GI_{50} values less than 8μM against most of the cell lines) while compounds **30**, **53**, and **68-70** exhibited poor cytotoxic activity. Furthermore, the epoxidation of $\Delta^{8(17)}$ double bond gave rise to an equal potent analog of Andro (**71**). Das *et al.* [25] believed that ester derivative might be a prodrug on condition that esterases cleaved the ester bond releasing Andro *in vivo*. Then a series of C-14 ester analogs (Fig. (**8**):**77-84**) were synthesized and evaluated for their cytotoxic activity against human leukemic cell lines (U937, K562, and THP1) and normal cell lines (NIH3T3 and L132). Generally, the enhancement of lipophilicity at C-3 and C-19 hydroxyl groups had detrimental effects on cytotoxic activity, as was evident from the comparison of compounds **77-80** with the analogs **81-84**. Among all these C-14 modified derivatives, the most outstanding compounds were **77** and **80** (with IC_{50} values of 5.84 and 5.68 μM against THP1, respectively). In summary, SAR of Andro and its analogs become clear as follows:

a) Removal of C-14 hydroxyl is detrimental to the activity profile while esterification of C-14 hydroxyl is favorable to cytotoxic activity (e.g., **53** vs. Andro);

b) The $\Delta^{12(13)}$ double bold is essential for cytotoxic activity (e.g., **68** vs. Andro);

c) The $\Delta^{8(17)}$ double bold or epoxy moiety are responsible for cytotoxic activity (**69** and **70** vs. **72**);

d) The free or protected hydroxyls of C-3 and C-19 show similar cytotoxic activity (**71** vs. **72**);

e) The intact α-alkylidene-γ-butyrolactone is indispensible for activity profile (**69** and **70** vs. Andro).

A series of Andro derivarives (Fig. (**9**):**85-91**) which had the coupled hydroxyls of C-3 and C-19 were synthesized and evaluated for their cytotoxic activity against 60 NCI cancer cell lines by Jada *et al.* [26]. Some differences existed in the GI_{50} values of compounds **85-91**, suggesting that suitable alkyl or aryl moieties at C-3 and C-19 might be crucial in promoting anticancer activities. In contrast, introduction of phosphate at C-3 and C-19 (Fig. (**9**):**92-93**) of 14-deoxy-11,12-didehydroandrograph-olide (**30**, IC_{50} >40μg/ml) would be unfavorable for inhibitory potency against Eca109 and CNE cell lines [27]. In addition, Jada *et al.* [28] also reported that compounds **58-60** and Andro showed certain antitumor activities against a 2-cell lines panel consisting of MCF-7 and HCT-116. Screened against a panel of 60 NCI human

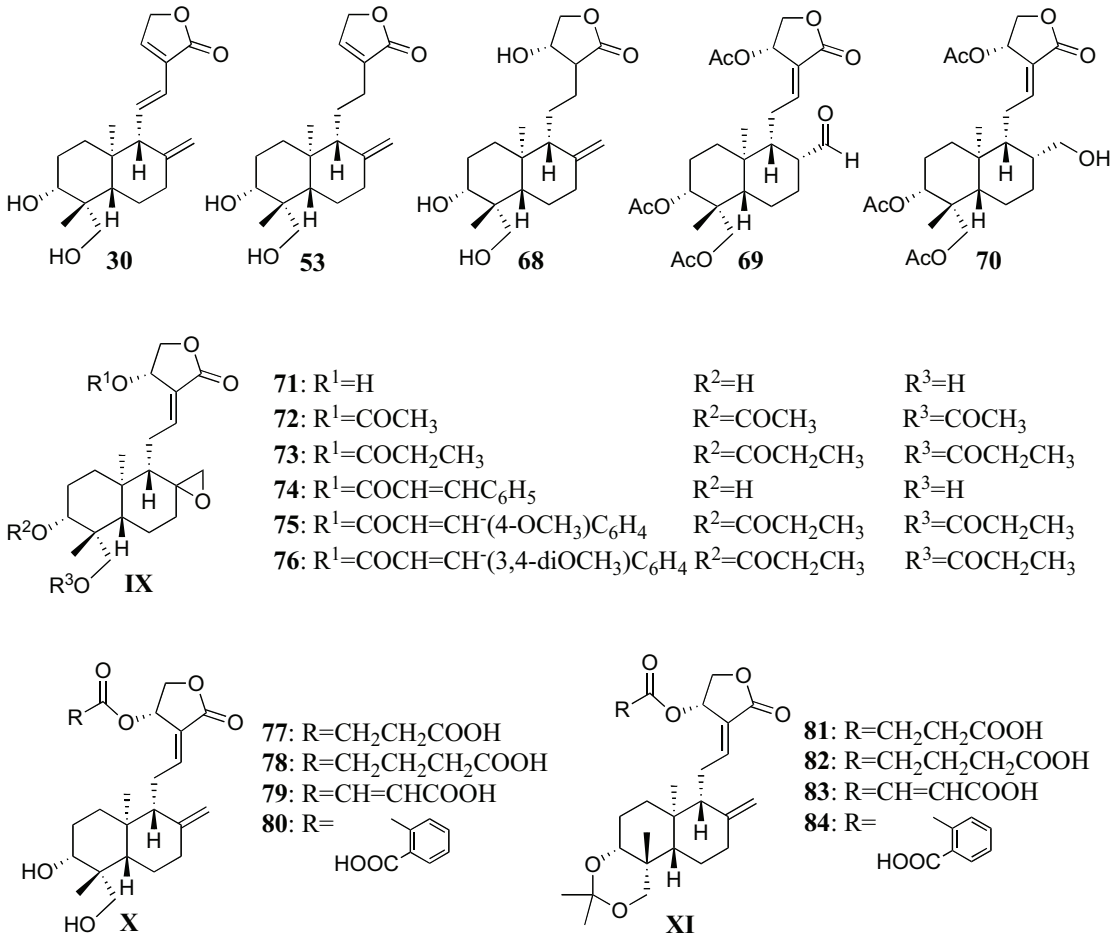


Fig. (8). Chemical structure of Andro derivatives studied for cytotoxic activities *in vitro*.

cancer cell lines derived from nine cancer types, compound **58** was found to be selective towards leukemia and colon cancer cells, and compound **60** was selective towards leukemia, ovarian and renal cancer cells.

As an endeavor to enhance water solubility of Andro, hydrophilic groups containing amine were positioned at C-12 (Fig. (**9**):**94-101**) [29]. Results from human glioblastoma (U87) and breast cancer (MCF-7) cell lines showed that all these derivatives exhibited poor potency compared to Andro, suggesting that the introduction of hydrophilic groups at C-12 were adverse to cytotoxic activity. Actually, compounds with aromatic ring (**97-101**) showed better potency than their analogs with aliphatic chain or ring (**94-96**) while too large substituent in position C-12 (**101**) was found to be adverse to inhibitory activities.

In contrast, a number of Andro derivatives (Fig. (**9**):**102-110**) which had the lactone moiety substituted by aromatic ring or heterocycles were synthesized and evaluated for their cytotoxic activity against nine human cancer cell lines (breast (MCF-7/ADR, MCF-7), colon (SW620, HT29), lung (H522), melanoma (UACC62), ovarian (OVCAR8), and prostate (DU145, PC3)) using the NCI standard Protocol [30]. Good activity was observed on compounds **102-104** while the others exhibited poor activity. In fact, as the essential role of the lactone moiety plays in the anti-cancer activity, substitution of this moiety was rarely conducted for further modification.

More recently, He *et al.* [31, 32] obtained a series of biotransformed products (Fig. (**10**)) from Andro by *Rhizopus stolonifer* (ATCC12939) and *Aspergillus ochraceus* (ATCC1008). Compounds **115** and **119** showed better cytotoxic activities than Andro (with IC_{50} values of 2.2 and 2.1 μM against MCF-7, respectively) when tested against human breast cancer (MCF-7), human colon cancer (HCT-116) and leukemia (HL-60) cell lines. Nevertheless, the conversion of β-hydroxyl into the keto of Andro (**116-118**) showed poor cytotoxic activities.

ANTIDIABETIC ACTIVITY

The results obtained from streptozotocin-induced diabetic rats showed that Andro could lower plasma glucose by promoting glucose utilization [33]. It was also deduced that α-glucosidase inhibitory activity might be one of the reasons for the antidiabetic effects of *Andrographis paniculata* [34]. Compounds **30** and **68** (Fig. (**11**)) (the inhibiting percentage was 16.5 and 34.2, respectively) displayed certain α-glucosidase inhibitory activity while compound **120** had no effect at 100μM, implicating that the flexible chain between the γ-butyrolactone moiety and the two six-member rings

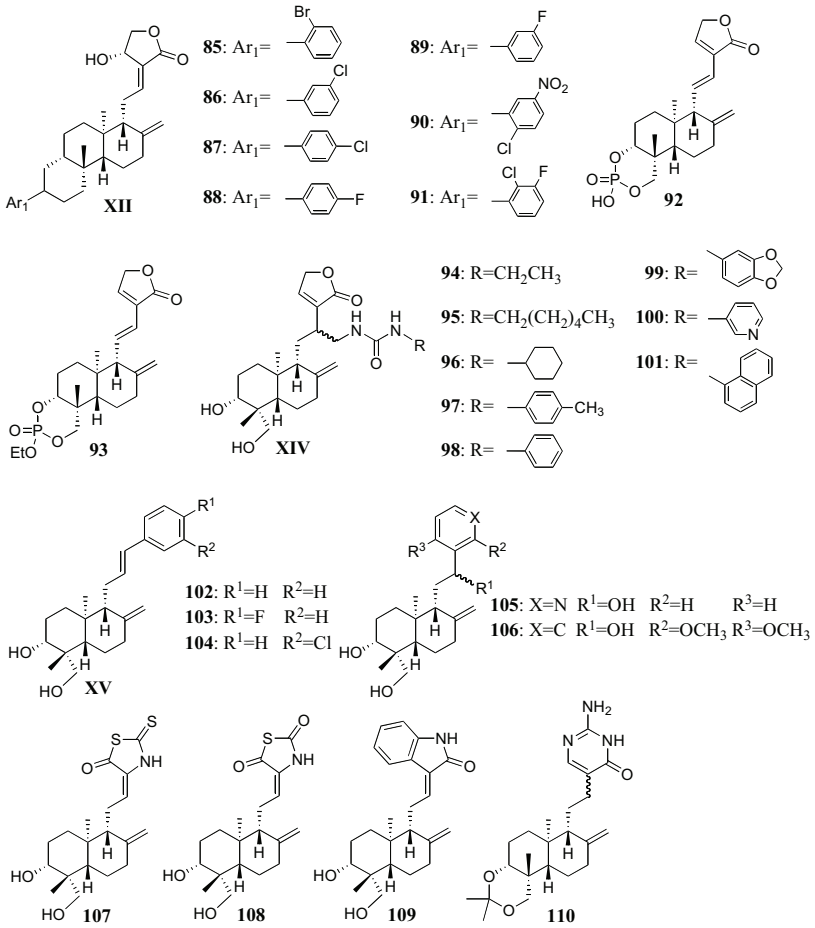


Fig. (9). Chemical structure of Andro derivatives studied for cytotoxic activities *in vitro*.

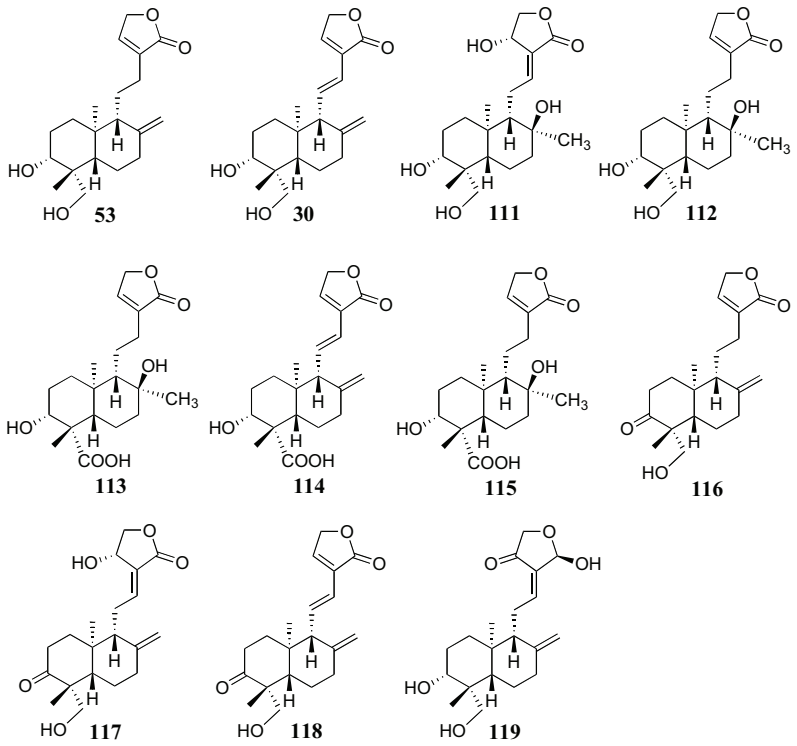


Fig. (10). Chemical structure of biotransformed products studied for cytotoxic activities *in vitro*.

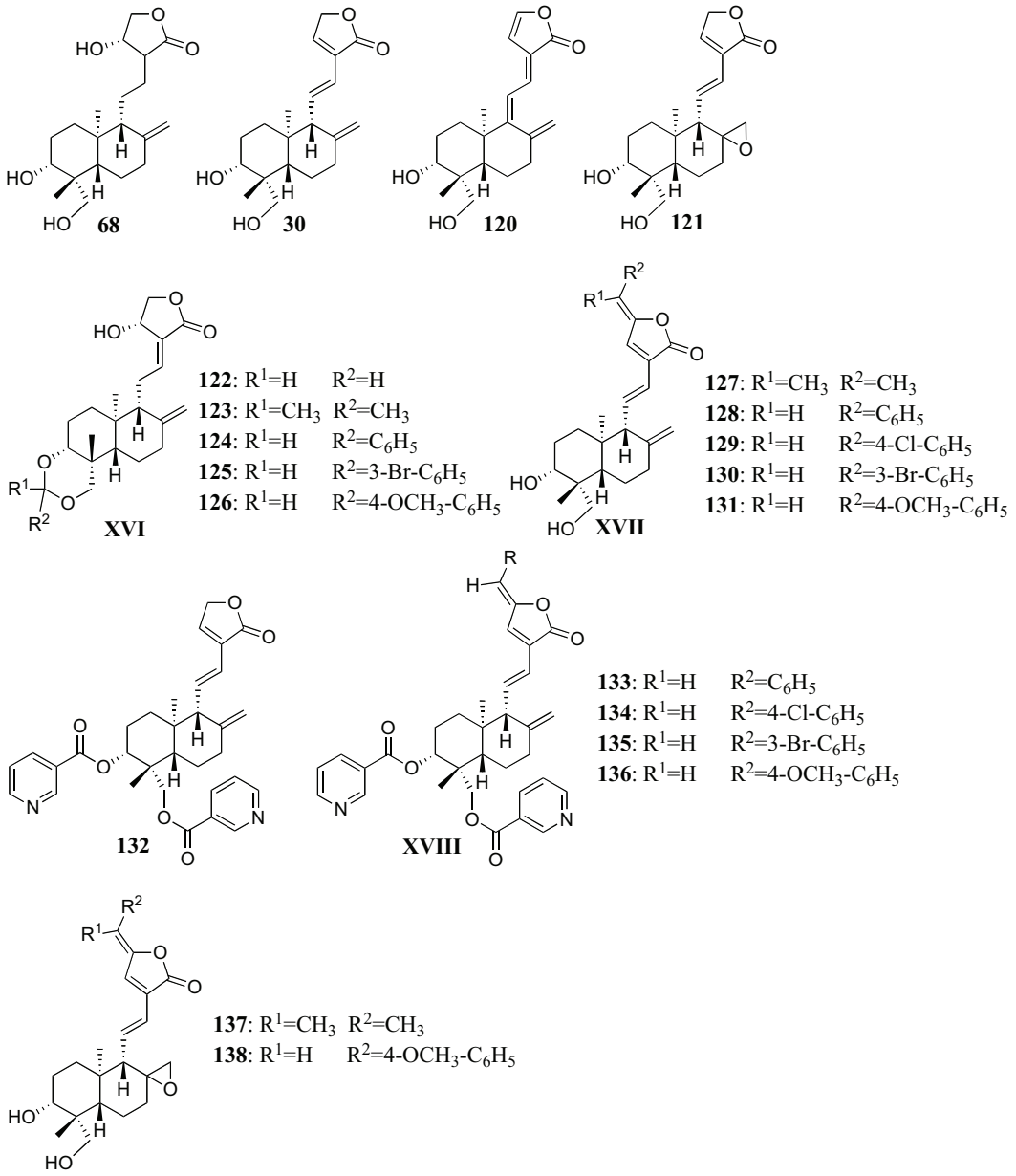


Fig. (11). Chemical structure of Andro analogues studied for α-glucosidase inhibitory activity *in vitro*.

was critical to α-glucosidase activity profile. The epoxidation of $\Delta^{8(17)}$ double bond of Andro (**121**, **137**, **138**) made α-glucosidase inhibitory activity reduced or lost while the introduction of 15-ene-substitution (**127**, **130**, **131**) generated some positive results. Furthermore, certain lipophilic protection of 3, 19-hydroxyls was favorable to the activity profile, as being evidenced from compounds **125**, **126**, and **134** with the inhibition percentage being 49.6, 13.2 and 100, respectively. In fact, compounds **133-136** also exerted higher potency than their analogs **127-131** which left C-3 and C-19 hydroxyls free. Among all the tested derivatives, the most active compound was **134** (IC_{50}, 6μM) which could be ascribed to the presence of lipophilic protective group and 15-ene-substitution [35]. On the other hand, AL-1(**37**) seems to be a potential novel antidiabetic agent due to its protective effects on hypoglycemic and beta cell [36]. Recently, to predict and design new α-glucosidase inhibitors, QSAR studies were also carried out on Andro derivatives [37-39].

ANTIFEEDANT ACTIVITY

The potential antifeedant activity of compounds isolated from *Andrographis paniculata*, against the DBM (diamondback moth, *plutella xylostella*), was first reported by Hermawan *et al.* [40]. The minimum effective dose (MED) of Andro and 14-deoxyandrographolide (**53**) in suppressing the feeding of the DBM larva were 25 and 100 μg/leaf disc (cabbage leaf), respectively [41, 42]. However, Andro did not deter feeding by adults of *Henosepilachna vigntioctopunctata* [43]. Recently, antifeedant activity of Andro and its derivatives (Fig. (**12**)) was determined by a conventional leaf disk method against the third instar larvae of *Mythimna separata* (Walker) under the sublethal

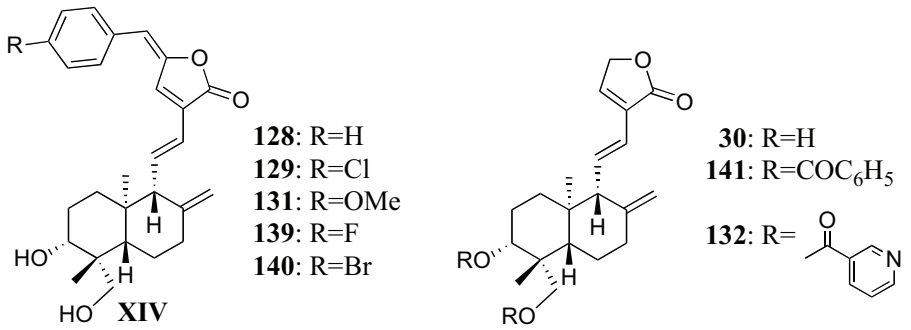


Fig. (12). Chemical structure of Andro analogues studied for antifeedant activity *in vitro*.

Table 1. Summary of the Most Effective of Andro Derivatives in the Studied Biological Activities. [1]When Several Compounds were Active Only the Most Potent are Referred.

Biological Activity	Specific Effect(s)	Active Compound(s)[1]	Refs
Anti-inflammatory	Inhibition on LPS-induced TNF-α and IL-6 release in mouse macrophages	5, 6, 7	[7]
	Inhibition on LPS-induced COX-2 expression in mouse macrophages	20	[8]
	Inhibition of TNF-α, IL-6, MIP-2, and nitric oxide secretions from LPS/IFN-γ stimulated RAW 264.7 cells	34-36	[9, 10]
Antibacterial	Inhibition of pyocyanin and protease produced and excreted by *P. aeruginosa*	AL-1(37), 52	[12, 13]
	Inhibition of EPS and pyocyanin produced and excreted by *P. aeruginosa*	AL-1(37)	[14]
	Synergistic inhibition of biofilms formation of *P. aeruginosa* combined with various antibiotics	AL-1(37)	[14]
Antivirus	Inhibition of avian influenza A (H9N2 and H5N1) and human influenza A H1N1viruses	AL-1	[15]
	Inhibition of HSV-1in infected Vero cell lines	IPAD(54)	[16, 17]
	Inhibition of C8166 cells	13, 64	[18-20]
Antitumor	Cytotoxicity to human breast (MCF-7/ADR), CNS (U251), colon (SW620), lung (H522), ovarian (SKOV3), prostate (DU145), and renal (A498) cancer cell lines	72, 74-76	[24]
	Cytotoxicity to human leukemic cell lines (U937, K562, and THP1) and normal cell lines (NIH3T3 and L132)	77, 80	[25]
	Cytotoxicity to 60 NCI cancer cell lines	85-91	[26]
	Cytotoxicity to human glioblastoma (U87) and breast cancer (MCF-7) cell lines	98, 101	[29]
	Cytotoxicity to human breast (MCF-7/ADR, MCF-7), Colon (SW620, HT29), Lung (H522), Melanoma (UACC62), Ovarian (OVCAR8), and Prostate (DU145, PC3) cell lines	102-104	[30]
	Cytotoxicity to human breast cancer (MCF-7), human colon cancer (HCT-116) and leukemia (HL-60) cell lines	115, 119	[31, 32]
Antidiabetic	Inhibition of α-glucosidase	134, AL-1(37)	[34-36]
Antifeedant	Inhibition of the DBM larva	Andro(1)	[41, 42]
	Inhibition of the third instar larvae of *Mythimna separata*	30, 139,140	[44]

concentration of 2.0 mg/ml [44]. Compounds **30**, **139** and **140** exhibited strong antifeeding rates at the level of 116.1-125.0% and 43.1-52.4% within 24 h and 48 h, respectively. In addition, compound **140** showed a mortality rate of 10.0% at 24 h while **139** presented a mortality rate of 16.7% at 48 h.

CONCLUSION

Andro exhibiting impressive biological activities attracts much attention from many researchers. Due to its moderate activity and poor water solubility, large numbers of Andro derivatives were synthesized for the improvement of

biological activities and water solubility. Following these studies, various biological activities and corresponding SAR of Andro and its derivatives were presented continuously, which gave pharmaceutical chemists more confidence for drug discovery. For instance, the number and position of double bond may play an important role for anti-inflammatory activity while the suitable lipophilic group at C-14 hydroxyl is necessary for antibacterial activity. Also, the modification of three hydroxyls is vital for antitumor activity while the proper length of carbonchain at C-15 is favorable to antidiabetic activity. In fact, although no drugs from Andro and its derivatives were approved by FDA, several leads were obtained for various biological activities, such as compound **34** for anti-inflammatory, AL-1 for antibacterial and antidiabetic, IPAD for antivirus, and compound **77** for antitumor. Recently, discovery and development of the antivirus potency of Andro and its derivatives provide a new approach for drug research. Due to the involvement with the early step of HSV-1 replication, IPAD may play a key role of combination therapy with other antiviral drugs. In addition, although the potential anti-HIV and antifeedant of Andro and its analogues do not gain evident progress, it is still a promising field for further investigation.

To conclude, studies on Andro and its derivatives result in several novel active agents that can serve as the leads and scaffolds for drug discovery. We have refined all the information available and hope that researchers will benefit from it.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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