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Pentacylic triterpenes from *Lavandula coronopifolia*: structure related inhibitory activity on α-glucosidase

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ABSTRACT

Ten pentacyclic triterpenes (**1**-**10**) were isolated from *Lavandula coronopifolia*. We evaluated their α-glucosidase inhibitory activity, and found that the aglycones, **1**, **2**, **3**, **4, 7** and **10** showed superior IC_{50} values to the positive control. In order to explain the structural requirements for α-glucosidase inhibitory activity, eleven derivatives were prepared, including one new compound, 2-formyl-(A)1–19α-hydroxy-1-norursane-2, 12-dien-28-oic acid **10c**. The results demonstrated that a free hydroxyl at ring-A and a free carboxylic group at position 28 are key structural features for the α-glucosidase inhibitory activity, also that an ursane skeleton is optimum for the activity. Additionally, enzyme kinetic analysis of pomolic acid **2**, the most potent compound, revealed that it inhibited α-glucosidase in a mixed-type manner. The molecular docking simulation validated this type of inhibition and highlighted the role of the C-3 hydroxyl and C-28 carboxylic groups in interaction with the enzyme *in silico*.

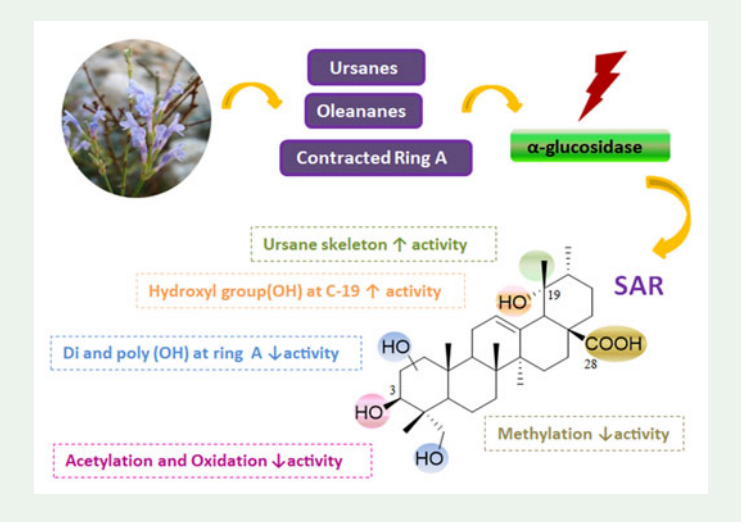
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1. Introduction

The enzyme α-glucosidase is a key enzyme in the digestive system that breaks down dietary carbohydrates into absorbable glucose (Zhang et al. 2017). α-Glucosidase inhibitors can delay glucose absorption from the small intestine and hence lower postprandial glucose and insulin levels, accordingly, they are widely used in treatment of type 2 diabetes (Van De Laar et al. 2005).

Lavandula coronopifolia Poire is a shrub-like perennial, growing in rocky habitat and desert plains (Lis-Balchin 2003). Reviewing the literature, it was clear that the plant chemistry and biological activity is under investigated. Few studies reported hepatoprotective (Farshori et al. 2015) and antimicrobial (Ait Said et al. 2015) activities of *L. coronopifolia*. Also flavonoids (El-Garf et al. 1999) and triterpenes (Singab et al. 2000) were previously isolated from the plant. The majority of *Lavandula* species are traditionally used to treat diabetes, furthermore the plant is among the medicinal plants that used for the management of diabetic mellitus in the Ethiopian and Eritrean flora (Meresa et al. 2017). In this study we afford a rational for its use in management of diabetes.

Our chemical investigation of *L. coronopifolia* resulted in isolation of ten pentacyclic triterpenes; five of them are reported for the first time from the plant. Eleven derivatives were prepared by esterification, acetylation and oxidation. We investigated the α-glucosidase inhibitory activity of the natural pentacyclic triterpenes as well as the prepared derivatives. The IC_{50} values displayed by these related triterpenes revealed an insight on some essential structural features of α-glucosidase inhibitory activity. Additionally, we investigated the possible inhibition mechanism of the most potent compound, pomolic acid **2** by enzyme kinetics and docking study.

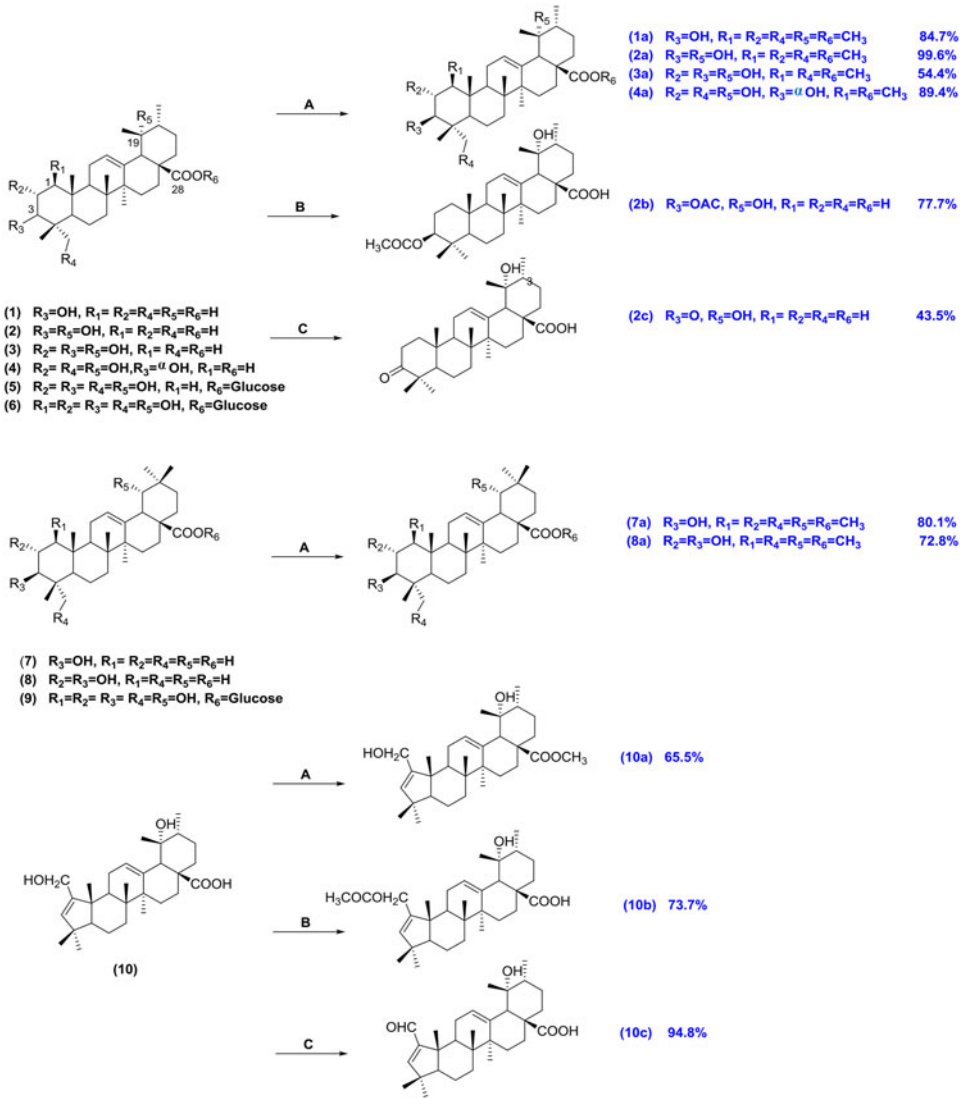


Figure 1. Structures of triterpenes isolated from *L. coronopifolia* (**1**-**10**) and the prepared derivatives, A: $(CH_3)_3SiCHN_2$/20% MeOH in Benzene, B: $(CH_3CO)_2O$/Pyridine, C: PCC/DCM, D: Jones/Acetone.

2. Results and discussion

2.1. α-*Glucosidase assay*

A series of natural pentacylic triterpenes (**1**-**10**) were isolated from *L. coronopifolia* (Figure 1). These triterpenes have different hydroxylation pattern and belong to three types of skeletons: ursane, oleane and ring-A contracted triterpene skeleton. Upon investigating the α-glucosidase inhibitory activity of these related structures, we could determine a preliminary insight toward their structure activity relationship. Following, eleven derivatives were prepared by methylation (**1a**-**4a**, **7a, 8a, 10a**) at free

carboxylic group (C-28), acetylation (**2 b**, **10 b**) and oxidation (**2c**, **10c**) of free hydroxyl group of ring-A at (C-3 or C-1 in case of ring-A contracted type). These transformations were made in order to elucidate the role of these functional groups in the activity.

As shown in Table S1, compounds **2**, **1**, **10**, **2a**, **7**, **2c**, **10c**, **2 b** and **3** showed considerable α-glucosidase inhibitory activity, with IC_{50} values of 5.3, 17.5, 19.2, 58.5, 69.5, 116.8, 160.4, 170.2 and 178.4 μM, respectively. Meanwhile compounds **8a** and **4** were less active with IC_{50} values of 225.7 and 231.0 μM, respectively. All were superior to acarbose, the positive control, 371.9 μM. Compound **3a** showed comparable IC_{50} value to acarbose, 392.1 μM, while the IC_{50} values of the remaining compounds were >400 μM.

Regarding the skeleton, the IC_{50} value of oleanolic acid **7** was almost four times of that of ursolic acid **1**, which suggested the effect of the ursane skeleton on the activity. Also the IC_{50} value of hyptadienic acid **10** was almost three times of that of pomolic acid **2**, suggesting that the contracted ring-A might weaken the activity. These findings suggested that an ursane skeleton with six membered ring-A, is the most optimum for the α-glucosidase inhibitory activity.

Regarding C-28 site, all the prepared methyl ester derivatives, **1a**-**4a**, **7a**-**8a** and **10a** showed dramatically reduced activity as compared to their parent free acid; suggesting that a free carboxylic group at position 28 is essential for activity. Even though compound **2a** displayed superior IC_{50} value to the positive control, still the activity is reduced about 10 times upon on esterification.

Regarding hydroxyl substituents, we investigated the C-3 hydroxyl of pomolic acid **2** and C-1 hydroxyl of hyptadienic acid **10**. The prepared acetyl derivatives **2 b** and **10 b**, also the oxo derivatives **2c** and **10c**, showed greatly raised IC_{50} values as compared to their parent triterpene. These results suggested the importance of a free hydroxyl group at ring-A. This is in accordance with previous literature, confirming that C-3 hydroxyl group is essential for activity (Fatmawati et al. 2013) since it interacts with the enzyme through hydrogen bonding (Wu et al. 2015). It is worth to note that acetylation had a higher negative impact on activity than oxidation, since the oxo-derivatives were slightly more active than the acetyl derivatives, which will be more cleared later on.

At the same time, the 19α-hydroxy ursolic acid **2**, showed three times reduced IC_{50} value as compared to ursolic acid **1**, suggesting that the presence of a hydroxyl group at position 19, is important for eliciting the activity. Meanwhile the presence of di or poly hydroxyl substituents in ring-A at positions 1, 2 and 23 had a negative impact on the activity. This was demonstrated by the decreased activity of the ursanes; 2α-hydroxy pomolic **3** and 2 α, 23 dihydroxy pomolic **4** as compared to pomolic acid **2**; also for the oleane; 2α-hydroxy oleanolic **8** as compared to oleanolic acid **7**, suggesting that hydroxylation at ring-A specifically at positions 2 and 23 dramatically decreases the activity.

The poly hydroxylated 28-*O*-glucosyl derivatives **5**, **6** and **9** displayed poor inhibitory effects with IC_{50} value >400 μM, confirming our previous suggestion on the role of free carboxylic group and that di or poly hydroxyl substituents at ring-A weakens the activity.

It is worth to note that among the tested triterpenes, pomolic acid **2** was found to be the most potent inhibitor on α-glucosidase, possessing all the favorable features

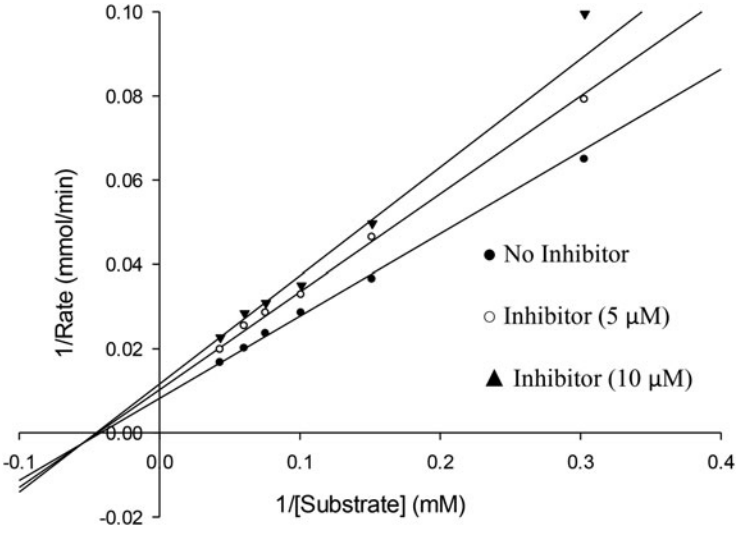


Figure 2. Lineweaver-Burk plot for the inhibition mode of compound 2 against α-glucosidase at different concentrations of inhibitor (0, 5, 10 μM).

for the α-glucosidase inhibitory activity, an ursane skeleton, a free hydroxyl group at C-3, free carboxylic group (C-28) and a hydroxyl group at C-19. Pomolic acid derivatives also displayed strong activity despite being reduced about thirty times by acetylation in **2 b**, about twenty times by oxidation in **2c** and about ten times by esterification in **2a**.

2.2. Kinetic study of pomolic acid 2

Due to its interestingly high inhibitory activity against α-glucosidase, we investigated the possible underlying mechanism of inhibition by pomolic acid **2**. According to the Lineweaver-Burk plot (Figure 2), we concluded that, pomolic acid **2** is a mixed inhibitor (Whiteley 1999). This type of inhibition is similar to noncompetitive inhibition except that binding of the substrate or the inhibitor affect the enzyme's binding affinity for the other (Ha and Bhagavan 2011).

2.3. Molecular docking analysis of pomolic acid 2

In order to validate the results of the enzyme kinetic study, a molecular docking simulation of pomolic acid **2** with α-glucosidase was undertaken (Tables S3-S6, Figures S22-S23). As shown in Figure S23, pomolic acid interacted with both catalytic and allosteric sites on α-glucosidase. At the catalytic site, it displayed three H-bond interactions through C-3 hydroxyl to the amino acid residues His112 and Asp215, and through C-28 carboxylic to Gln353. It also displayed hydrophobic interactions with Tyr72, Tyr158, Phe178, Val216, Phe303, and Arg315. The mentioned residues are also responsible for binding of acarbose, a known comptetive inhibitor, with α-glucosidase (Ali et al. 2017). Moreover, at allosteric site 4, pomolic acid **2** interacted with the amino acid residues

Tyr292 and Ser295 through H-bonding to C-28 and with Trp 14, Lys262, Ile271, and His258 through hydrophobic interactions. Oleanolic acid, a known allosteric inhibitor, interacted with α-glucosidase at the same residues (Ding et al. 2018). These findings are in good agreement with the suggested mixed inhibition mode for pomolic acid **2**.

2.4. Chemistry

Based on analysis of their MS and spectral data as well comparison to literature, the isolated compounds were identified as: ursolic acid (**1**) (Morocho et al. 2018), pomolic acid (**2**) (Sidjui et al. 2014), tormentic acid (**3**) (Woo et al. 2014), myrianthic acid (**4**) (Ojinnaka et al. 1984), nigaichigoside F1 (**5**) (Chen et al. 2013), 1β,2α,3β,19α,23-pentahydroxy-urs-12-en-28-oic acid 28-*O*-β–D-glucopyranosidate (**6**) (Singab et al. 2000), oleanolic acid (**7**), maslinic acid (**8**) (Woo et al. 2014), 1β,2α,3β,19α,23-pentahydroxy-olean-12-en-28-oic acid 28-*O*-β–D-glucopyranosidate (**9**) (Singab et al. 2000) and hyptadienic acid (**10**) (Wang et al. 2009).

Following to isolation, eleven derivatives, including one new compound (**10c**), were prepared by esterification (**1a**-**4a**, **7a**, **8a, 10a**), acetylation (**2 b**, **10 b**) and oxidation (**2c**, **10c**). Theses derivatives were characterized as: ursolic acid methyl ester (**1a**) (Seo et al. 1975), pomolic acid methyl ester (**2a**) (Lontsi et al. 1998), 3-*O*-acetyl-pomolic acid (**2 b**) (Neto et al. 2000), 3-*oxo*-pomolic acid (**2c**) (Cheng and Cao 1992), tormentic acid methyl ester (**3a**) (Lontsi et al. 1998), myrianthic acid methyl ester (**4a**) (Ojinnaka et al. 1984), oleanolic acid methyl ester (**7a**), maslinic acid methyl ester (**8a**) (Seo et al. 1975), hyptadienic acid methyl ester (**10a**), 1-*O*-acetyl-hyptadienic acid (**10 b**) (Rao et al. 1990).

Compound (**10c**) was identified as 2-formyl-(A)1–19α-hydroxy-1-norursane-2,12-dien-28-oic acid. According to literature, this compound has never been previously described; eventhough, its oleane isomer has been reported (Thao et al. 2014). The ^{1}H-NMR spectrum of compound **10c** was similar to that of hyptadienic acid **10** except for replacement of the oxygenated methylene at $\delta_{(H)}$ 4.08 (H, *dd*, 14.7, 1.8) and 4.17 (H, *dd*, 14.7, 1.7) by an aldehydic proton signal at $\delta_{(H)}$ 9.62 (H, s). In the ^{13}C-NMR spectrum, oxygenated methylene signal was replaced by a carbonyl signal at $\delta_{(c)}$ 191.5 (C-1) corresponding to aldehyde group. It also showed a noticeable downfield shift in positions C-2 and C-3 at $\delta_{(c)}$ 157.1 and 164.2, respectively confirmed oxidation of the secondary alcohol into aldehyde. The molecular formula $C_{30}H_{44}O_4$ was confirmed by the negative molecular ion peak at *m/z* 467.3177 $[M\text{-}H]^-$ in HRESIMS.

3. Experimental

For general experimental procedures, isolation procedures (Figure S20), α-glucosidase assay see supplemental file.

3.1. Plant material

The plant material (2.5 kg) was collected in Feburary, 2017 from Wady Hagol, Suez governorate, Egypt. Authentication was done by Prof. Ibrahim Mashaly, at Ecology and

Botany Department, Faculty of Science, Mansoura University. A voucher specimen has been deposited at the herbarium of the Pharmacognosy Department, Faculty of Pharmacy, Mansoura University (02-17-LC-Mansoura).

Compound (**10c**): 2-formyl-(A)1–19α-hydroxy-1-norursane-2,12-dien-28-oic acid, colorless gum, HRESIMS *m/z* 467.3177 $[M-H]^-$, calcd for ($C_{30}H_{43}O_4$, 467.3161). ^{1}H-NMR: $\delta_{(H)}$ 9.65 (H, *s*, H-1), 6.56 (H, *s*, H-3), 5.46 (H, *s*, H-12), 1.12 (3 H, *s*, Me-23), 1.00 (3 H, *s*, Me-24) , 1.17 (3 H, *s*, Me-25) , 0.92 (3 H, *s*, Me-26) , 1.24 (3 H, *s*, Me-27) , 1.15 (3 H, *s*, Me-29), 0.87 (3 H, *s*, Me-30) .^{13}C-NMR: $\delta_{(c)}$ 191.5 (C-1), 157.1 (C-2), 164.2(C-3), 44.1 (C-4), 62.8 (C-5), 17.3 (C-6), 33.9 (C-7), 41.4 (C-8), 43.5 (C-9), 50.9 (C-10), 26.3 (C-11), 128.0 (C-12), 139.1 (C-13), 41.5 (C-14), 28.9 (C-15), 25.6 (C-16), 48.6 (C-17), 54.4 (C-18), 72.8 (C-19), 41.6 (C-20), 25.9 (C-21), 38.1 (C-22), 22.2 (C-23), 28.9 (C-24), 18.4 (C-25), 19.5 (C-26), 24.2 (C-27), 184.7 (C-28), 27.4 (C-29), 15.2 (C-30).

3.2. Derivatization reactions

The methyl ester derivatives **1a**-**4a** and **7a**, **8a** were prepared by dissolving the start material in 20% MeOH in benzene; followed by addition of trimethylsilyldiazomethane (Urosa et al. 2015). The *O*-acetyl derivatives **2 b** and **10 b** were prepared by dissolving the start material **2** and **10** in pyridine, followed by addition of acetic anhydride (Cheng et al. 2013). Compound **2c** was prepared by treating **2** with PCC in DCM (Sandjo et al. 2011). Compound **10c** was prepared by Jones oxidation (Tağ et al. 2012) of **10**. All the products were purified over silica gel using EtOAc in Hexane as a solvent system.

4. Conclusion

We investigated the structure activity relationship of twenty one related pentacylic triterpenes, as α-glucosidase inhibitors. The results demonstrated that a carboxylic group at C-28 site and a free hydroxyl group at ring-A are crucial structural features for the α-glucosidase inhibitory activity. In the meantime, additional di or poly hydroxyl substituents at ring-A weaken the activity. In contrast, C-19 hydroxyl substitution can elicit the activity. It was concluded that an ursane skeleton is favorable for activity over oleane or ring-A contracted skeletons. Furthermore, enzyme kinetic analysis and molecular docking simulation of pomolic acid **2**, the most active compound, revealed it acted as a mixed inhibitor.

Disclosure statement

No potential conflict of interest was reported by the authors.

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