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SHORT COMMUNICATION

Docking studies of sesquiterpene lactones isolated from *Ambrosia maritima* L. reveals their potential anti-inflammatory and cytotoxic activities

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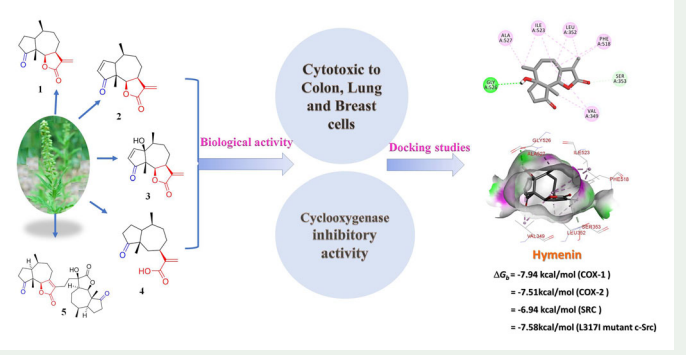
ABSTRACT

Five sesquiterpene lactones were isolated and identified from *Ambrosia maritima* L. Hymenin showed highest cytotoxic activity against HCT-116, A-549, and MCF-7 cell lines (IC_{50}= 3.83 ± 0.2, 5.48 ± 0.3, 10.1 ± 0.6 µg/mL, respectively). Damsin has significant COX-2 inhibitory activity (IC_{50}=33.97 ± 1.62 µg/mL) while hymenin showed highest selectivity to COX-1 (IC_{50} = 18.21 µg/mL) and significant inhibition of NO (IC_{50}=18.19 ± 0.75 µg/mL). The docking study revealed nice fitting into COX-1/2 and a higher binding affinity for maritimolide towards human Src kinase compared to the native ligand, Bosutinib. Results suggested that both COXs/Src kinase inhibition could contribute even partially to the overall mechanism of cytotoxic activity of the five compounds. The structure-activity relationship revealed that α-methylene-γ-lactone moiety enhances the cytotoxic activity, OH group at C-1 increase activity of hymenin. However, the reduction of the double bond at C-2 as in damsin resulted in a significant decrease in activity against HCT-116 and MCF-7 cells.



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1. Introduction

Ambrosia maritima L. (Asteraceae) is an annual herbaceous plant widely distributed in African countries (Saeed et al. 2015) especially near water catchment. It is well known in Egypt under the name of 'Damsissa'. Traditionally, the decoction of the whole plant is used to relief gastrointestinal disturbance and kidney inflammation. The herb acts also as antispasmodic and has been used to relief of bronchial asthma and frequent urination (Abdelgaleil et al. 2011; Dirar et al. 2014). Previous phytochemical analysis of *A. maritima* revealed the presence of pseudoguaianolide sesquiterpene lactones, coumarins, triterpenes, and sterols(Helal et al. 2014; Ahmed et al. 2019). Sesquiterpene lactones (SLs) have diverse biological activities with interesting therapeutic mechanisms, including antiinflammatory, antitumor, antimicrobial, and antiviral properties (Merfort 2011; Saeed et al. 2015). As *A. martima* L. is one of the tradinonal plants indigenous to Egypt, this work aims to the isolation and structure elucidation of SLs from *A. maritima* growing. *In vitro* evaluation of the cytotoxic activity of these compounds using HCT-116 cells (coloncarcinoma cell line), A-549 cells (lungcarcinoma cell line) and MCF-7 cells (breast carcinoma cell line). Estimation of the anti-inflammatory activity of the isolated compounds by evaluating *in vitro* inhibition of cyclooxygenase enzymes and NO. The structure–activity relationships (SARs) of the structurally related isolated SLs were determined. The results were explained through molecular modeling studies.

2. Results and discussion

2.1. Isolation of SLs from *A. maritima* methylene chloride extractive

Phytochemical investigation of CH_2Cl_2 – soluble extractive resulted in the isolation of five SLs, identified as damsin (**1**) ambrosin (**2**) hymenin (**3**) damsinic acid (**4**) (Abdelgaleil et al. 2011), and maritimolide (**5**) (Jakupovic et al. 1987).

2.2. Cytotoxic activity of the isolated SLs

Hymenin (**3**) exhibited the highest cytotoxic effect on HCT-116 cells, A-549 cells and MCF-7 cells followed by ambrosin (**2**) with high cytotoxic effect on HCT-116 cells and MCF-7 cells then damsin (**1**). Finally, maritimolide (**5**) showed the least cytotoxic effects on A-549 cells, MCF-7 cells and HCT-116 cells (Table S1).

2.3. Structure–activity relationship

Most of the structural modifications in hymenin resulted in decrease in its cytotoxic activity (Figure 1) (Marzouk 2015; Malki et al. 2018).

2.4. COX-1 and COX-2 inhibitory activity

Hymenin and ambrosin showed the highest inhibition of COX-1 with $IC_{50} = 18.21$, 49.73 μg/mL, respectively. While damsin ($IC_{50} = 33.97$ μg/mL) and damsinic acid ($IC_{50} = 36.80$ μg/mL) were the most active against COX-2 compared to celecoxib® ($IC_{50} = 91.75$ and 2.79 μg/mL for COX-1 and COX-2, respectively) (Table S2).

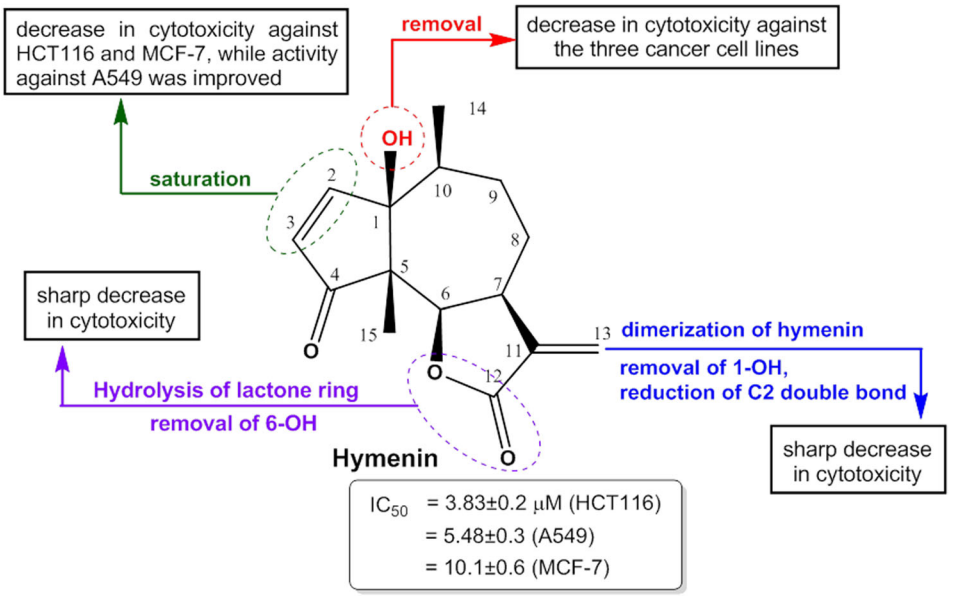

Figure 1. SAR of cytotoxic activity of compounds (**1–5**).

2.5. Nitric oxide inhibitory assay

This assay defined by Griess (1879). Many modifications to the original reaction have been described. Hymenin showed potent selectivity against NO (Table S2).

2.6. The relation between results of COX-1/2 inhibitory activity and anticancer activity

The relationship between inflammation and cancer has been discussed in many articles (Gouda et al. 2019). However, the relative contributions of COX-1 and/or COX-2 to cancer progress in different organs appear unclear (Gouda et al. 2019). Other study showed clear evidence that a selective COX-1 inhibitor as mofezolac, suppresses azoxymethane-induced colon tumor development, as evaluated in terms of tumor incidence (Kitamura et al. 2002). The results (Table S2) revealed hymenin which displayed the best cytotoxic activity, showed high inhibitory activity against COX-1 and weak inhibitory activity against COX-2. It is nearly six times more selective for COX-1 over COX-2.

2.7. Computational studies (molecular docking studies)

2.7.1. Docking study into COX-1/2 enzymes

Compounds (**1**–**5**) displayed binding free energy (ΔG_b) in the range of −7.94 to −10.37 kcal/mol compared to −8.43 kcal/mol for ibuprofen, where, maritimolide was the most active as COX-1 inhibitor (Table S3). The results revealed that hymenin has higher affinity toward COX-1 than COX-2, which is matched with the results of the *in vitro* COX inhibition assay. Hymenin exhibited one conventional hydrogen bond with GLY525 with bond distance of 2.17 Å, one carbon hydrogen bond with SER353

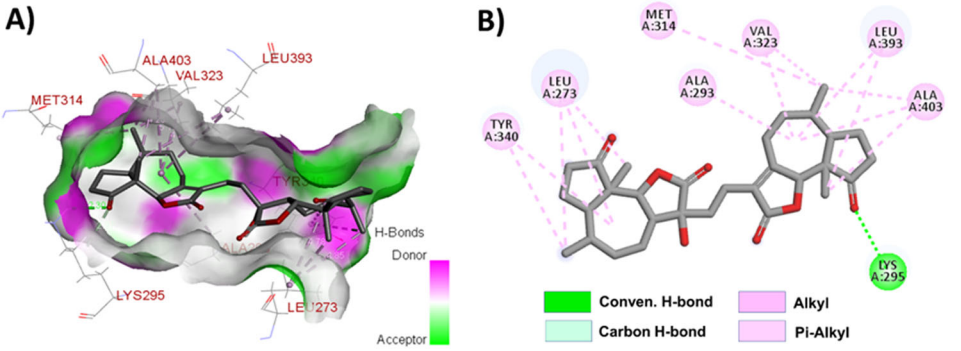

Figure 2. Binding modes of Maritimolide into the active site of human Src kinase (pdb: 4MXO): (A) 3D binding mode of Maritimolide into Src kinase; (B) 2D binding mode of Maritimolide into Src kinase; receptor surface shown as H-bond donor (pink) and acceptor (bright green); hydrogen atoms were omitted for clarity.

and ten hydrophobic interactions of alkyl and pi-alkyl types which contributed to the overall binding free energy. In addition, the isolated compounds exhibited binding free energy (ΔG_b) in the range of −7.44 to −8.06 kcal/mol toward COX-2 compared to −10.78 kcal/mol for Sc-588 (Table S4). Damsin displayed the highest affinity to COX-2. On the other hand, hymenin displayed only five hydrophobic interactions of the alkyl and pi-alkyl types with amino acids in COX-2 (Figure S28). The findings are in concordance with the results of COX-1/2 inhibitory assay.

2.7.2. Docking study into human Src/L317I mutant c-Src kinases

Recently, oncogenic protein kinase such as Src kinase was emerged as a promising target in the discovery of new anticancer agents (Irby and Yeatman 2000). Accordingly, we have performed a study into both Src and mutant Src kinases to evaluate the binding affinities/mode into the two kinases. The results revealed the ability of the tested compounds to bind to the same binding site of bosutinib in Src kinase with ΔG_b in the range of −6.94 to −10.45 kcal/mol compared to −9.18 kcal/mol for bosutinib (Table S5 and Figure S35). They exhibited several hydrogen bonding interactions with amino acids in the active site indicating that they can interrupt the open/closed Src kinase form which could contribute to their cytotoxic activity (Saeed et al. 2015). Maritimolide displayed the highest binding affinity toward Src kinase ($\Delta G_b = 10.45$ kcal/mol) and exhibited one conventional hydrogen bond with LYS295 (Figure 2). However, maritimolide displayed the weakest cytotoxic activity against the tested cancer cell lines. This could be attributed to its high molecular volume.

One the other hand, the results of the docking study into mutant c-Src kinase revealed high binging free energies ($\Delta G_b = -6.67$ to −11.04 kcal/mol) for the compounds (**1**–**5**) compared to −11.79 kcal/mol for dasatinib (Table S6).

3. Conclusion

Five pseudoguaianolide sesquiterpene lactones were isolated from the methylene chloride fraction of *A. maritima* L. Hymenin showed significant cytotoxic activity

against the tested cell lines and also it showed significant inhibition of NO. *In vitro* COX-1 and COX-2 inhibitory activity revealed that damsin has significantly inhibited COX-2 enzyme. The results of cytotoxic and cyclooxygenase inhibitory activity were confirmed through a molecular modeling study. The results of the docking studies suggested that the anticancer potential of the isolated compounds could be mediated by inhibition of Src kinase and partially through the inhibition of COXs enzymes. SAR study revealed that the presence of α-methylene-γ-lactone moiety enhance the cytotoxic activity against tested cell lines. Also, the presence of OH group at C-1 increase activity of hymenin. However; the reduction of the double bond at C-2 as in damsin resulted in significant decrease in cytotoxic activity against both HCT-116 and MCF-7 cells and improved activity against A-549 cells compared to ambrosin.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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References

Abdelgaleil S, Badawy M, Suganuma T, Kitahara K, Abdelgaleil S. 2011. Antifungal and biochemical effects of pseudoguaianolide sesquiterpenes isolated from *Ambrosia maritima* L. Afr J Microbiol Res. 5(21):3385–3392.

Ahmed RH, Mustafa DE, Mohamed YS. 2019. Anti-diabetic plants used in sudanese folk medicine and their phytochemical constituents: a review. J Adv Res Pharmaceutical Sci Pharmacol Interventions. 3(1):6–13.

Dirar AI, Mohamed MA, Ahmed WJ, Mohammed MS, Khalid HS, Garelnabi EA. 2014. Isolation and characterization of potential cytotoxic leads from *Ambrosia maritima* L. (Asteraceae). J Pharmacognosy Phytochem. 3(4): 38–41.

Gouda AM, Beshr EA, Almalki FA, Halawah HH, Taj BF, Alnafaei AF, Alharazi RS, Kazi WM, AlMatrafi MM. 2019. Arylpropionic acid-derived NSAIDs: new insights on derivatization, anticancer activity and potential mechanism of action. Bioorg Chem. 92:103224.

Griess P. 1879. Bemerkungen zu der Abhandlung der HH. Weselsky und Benedikt 'Ueber einige Azoverbindungen' . Ber Dtsch Chem Ges. 12(1):426–428.

Helal EG, Abou-Aouf N, Khattab SM, Meselhy AERA, Abu-Amara TM. 2014. The effects of *Ambrosia maritime* L. (Damsissa) on some biochemical and histological parameters of diabetic albino rats. EJHM. 57 (1587):612– 625.

Irby RB, Yeatman TJ. 2000. Role of Src expression and activation in human cancer. Oncogene. 19(49):5636–5642.

JakupovicJ, Sun H, Geerts S, Bohlmann F. 1987. New pseudoguaianolides from *Ambrosia maritima*. Planta Med. 53(1):49–51.

Kitamura T, Kawamori T, Uchiya N, Itoh M, Noda T, Matsuura M, Sugimura T, Wakabayashi K. 2002. Inhibitory effects of mofezolac, a cyclooxygenase-1 selective inhibitor, on intestinal carcinogenesis. Carcinogenesis. 23(9):1463–1466.

Malki WH, Gouda AM, Ali HE, Al-Rousan R, Samaha D, Abdalla AN, Bustamante J, Elmageed ZYA, Ali HI. 2018. Structural-based design, synthesis, and antitumor activity of novel alloxazine analogues with potential selective kinase inhibition. Eur J Med Chem. 152:31–52.

Marzouk A. 2015. Investigating Volutaria abyssinica as a potential source for cytotoxic sesquiterpenoids. J Am Sci. 11:73–81.

Merfort I. 2011. Perspectives on sesquiterpene lactones in inflammation and cancer. Curr Drug Targets. 12(11):1560–1573.

Saeed M, Jacob S, Sandjo LP, Sugimoto Y, Khalid HE, Opatz T, Thines E, Efferth T. 2015.Cytotoxicity of the sesquiterpene lactones neoambrosin and damsin from *Ambrosia maritima* against multidrug-resistant cancer cells. Front Pharmacol. 6:267