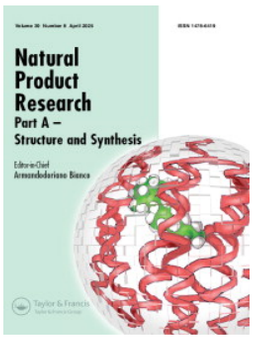

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RAPID COMMUNICATION

Chemical constituents from *symplocos sumuntia* and their anti-inflammatory effect

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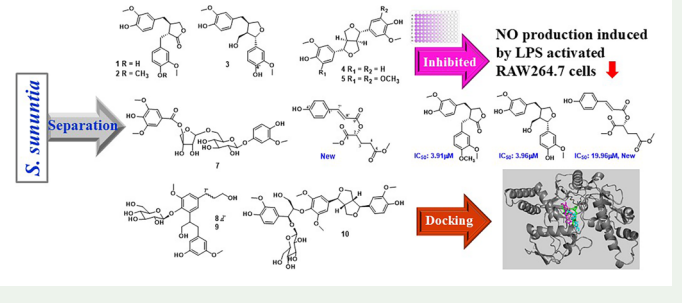
ABSTRACT

Symplocos sumuntia Buch-Ham ex D Don is traditionally used to relieve inflammation in Vietnam. This study described a chemical investigation that led to isolation and identification of one new and nine known compounds. Their structures were determined by using spectroscopic techniques. Compounds **1**–**10** possessed inhibitory activities on NO production induced by LPS activated macrophages. Among them, compounds **2** and **3** demonstrated strong ability to reduce NO production with IC_{50} values of 3.91 ± 0.05 and 3.96 ± 0.24 μM, respectively. Some of the other compounds also reduced NO production in LPS stimulated RAW264.7 cells. *In-silico* study supported hints to the bioactivity of compounds **2** and **3** by analysing the interactions of those when they were docked with protein to create complexes targeting anti-inflammation. Our research revealed the chemical components of this plant and its active ingredients that target inflammation, highlighting its therapeutic potential to improve its value for traditional uses.



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1. Introduction

Inflammation is the defensive reaction of the host body to dangerous stimuli resulting from tissue damage or infection. It creates pro-inflammatory cytokines and mediators during an inflammatory phase, forcing the body to play two roles. However, excess of cytokines and mediators caused adverse effects to tissues and organs (Chen et al. 2018). Among them, mediators may alter the function of tissues and organs which were affected by inflammation and allow them to adapt to conditions stimulated by inducer inflammation. This process continues for a long time, causing tissue and organ failure (Eming et al. 2007, Kany et al. 2019). Therefore, controlling the reactions and stimulation of inflammatory cytokines and mediators has become a therapeutic strategy to manage inflammatory diseases. Traditional medicine has been utilised for a long time to improve human health since it has less negative effects when used to treat ailments (Bernardini et al. 2018). There are numerous potentials for civilisation to develop in the production of food, materials, and medicine due to the high genetic diversity present in natural sources. The evolution of modern medicine has always benefitted greatly from developed natural products, and drug discovery is still greatly aided by them today. Prolonged search for novel medicinal potential in natural resources has produced important discoveries, including analgesics, antibiotics, anticancer medications, and anti-inflammatory compounds (He et al. 2018, Maroon et al. 2010, Veda et al. 2015).

Symplocos sumuntia belongs to the family Symplocaceae. It is well known that *S. sumuntia* is a folk medicine used for relieving cough, hypertension, and inflammation. Previous studies demonstrated the chemical constituents from this plant including phenolics and lignans (Thu Huong et al. 2017). Extract and isolated constituents from this plant showed some anti-inflammatory effects (Lim et al. 2022, Thu Huong et al. 2017). However, there is little report about chemical and biological investigations from this plant until moment. In this study, we described the chemical investigation from EtOH extract of *S. sumuntia*. The isolated compounds were further evaluated for their anti-inflammatory effects on LPS-induced NO production in RAW264.7 cells. In-silico approaches were applied to depict the molecular target of inflammatory effect by using active substances.

2. Results and discussions

2.1. Structural determination of isolated compound

Compound **6** was obtained as an amorphous powder. The infra-red spectrum of **6** revealed the absorption bands characterised for OH (3462 cm^{-1}), C=O (1756–1707 cm^{-1}), C=C (1368 and 1109 cm^{-1}) groups. Its high resolution mass data showed a basic ion peak at *m/z* 345.0924 (calc. for $C_{16}H_{18}O_7Na^+$, 345.0945), another ion peak at *m/z* 147.0432 indicating for a *p*-coumaric moiety.^{1}H-NMR spectrum of **6** displayed a characteristic signal for a *trans*-coupling system at δ_H 7.66 (1H, d, *J* = 15.9 Hz, H-7′) and 6.37 (1H, d, *J* = 15.9 Hz, H-8′), an AABB coupling spin system at δ_H 7.49 (2H, d, *J* = 8.7 Hz, H-2′/6′) and 6.82 (2H, d, *J* = 8.7 Hz, H-3′/5′), an oxygenated proton at δ_H 5.12 (1H, dd, *J* = 4.8, 8.0 Hz, H-2), two methoxy groups at δ_H 3.75 (3H, s, 1–O–CH_3) and 3.68 (3H, s, 5-O–CH_3), and two methylene groups at δ_H 2.51 (2H, m, H-4) and 2.22 (2H, m, H-3)

(Table S1, Supplementary materials). The DEPT spectrum of **6** exhibited seven CH groups at δ_C 72.3 (C-2), 113.7 (C-8′), 116.6 (C-3′/5′), 131.1 (C-2′/6′), 147.4 (C-7′), two CH_3 groups at δ_C 52.0 (5-OCH_3), 52.6 (1-OCH_3), and two CH_2 groups at δ_C 27.2 (C-3), 30.0 (C-4). HMBC spectrum showed the correlations of H-2′/6′ (δ_H 7.49) to C-2′/6′ (δ_C 131.1)/C-4′ (δ_C 161.4)/C-7′ (δ_C 147.4), and those of H-7′(δ_H 7.66) to C-2′/6′ (δ_C 131.1)/C-9′ (δ_C 168.0), that allowed to establish the partial structure of *trans*-coumaroyl moiety (Figure S8, Supplementary materials). In addition, 2-hydroxyglutarate moiety was established by COSY correlations from H-3 (δ_H 2.22) to H-2 (δ_H 5.12)/H-4 (δ_H 2.51), that approved the side chain C-2 (δ_C 72.3)/C-3 (δ_C 27.2)/C-4 (δ_C 30.0). On the other hand, HMBC spectrum also revealed the correlations of H-3 (δ_H 2.22) to C-2 (δ_C 72.3)/(C-1) (δ_C 172.4)/C-5 (δ_C 174.5), and those of methoxy groups at δ_H 3.75 and 3.68 to (C-1) (δ_C 172.4)/C-5 (δ_C 174.5), respectively, that confirmed its partial structure. The chemical shift value at H-2 (δ_H 5.12) shifted down field, comparing to those of free 2-OH group (Berger et al. 2021, Hahn and Nahrstedt 1993), suggesting esterification at C-2. Indeed, HMBC correlation between H-2 (δ_H 5.12) and C-9′ (δ_C 168.0) (Figure S6) was observed. Thus, the planar structure of **6** was established. The configuration at 2*α*-OH was proposed by analysis of its NMR data of H-2 at δ_H 5.12 (dd, $J = 4.8$, 8.0 Hz) comparing to those of 5.14 (dd, $J = 4.7$, 7.8 Hz) and 5.07 (dd, $J = 4.1$, 8.5 Hz) of D- and L-2-hydroxyglutaric acid derivatives (Bal et al. 2002), respectively. To our knowledge, this is a new compound with a trivial named symplocosol A, and its structure is depicted in Figure 1.

Furthermore, nine additional compounds **1**−**5**, and **7**−**10** were isolated and their structures were identified as matairesinol (**1**) (Rahman et al. 1990), arctigenin (**2**) (Rahman et al. 1990), lariciresinol (**3**) (Xie et al. 2003), pinoresinol (**4**) (Brenes et al. 2000), syringaresinol (**5**) (Bajpai et al. 2018), ecdysantherol C (**7**) (Song et al. 2014), manglieside D (**8**) (Kiem et al. 2008), icariside E_3 (**9**) (Miyase et al. 1988), and hedyotol C 7″-O-β-D-glucopyranoside (**10**) (Yin et al. 2016). Among isolates, compounds **3**, **5**, **7**−**10** were isolated for the first time from this plant.

2.2. Anti-inflammatory activity

Isolated compounds (**1**−**10**) were also examined for their anti-inflammatory effect against NO production induced by LPS activated RAW264.7 macrophages. All isolated compounds dose-dependently inhibit NO production. Particularly, compounds **2** and **3** significantly inhibited NO production with IC_{50} values of 3.91 ± 0.05 and 3.96 ± 0.24 μM, respectively. Compounds **4**−**6** exhibited moderate inhibition in LPS-induced NO production with IC_{50} values of 17.44 ± 1.30, 19.84 ± 1.15, and 19.96 ± 0.48 μM, respectively. Whereas other compounds demonstrated weak activity with IC_{50} values ranging from 30.80 μM to 84.14 μM. Dexamethasone was used as a positive control with an IC_{50} value of 3.24 ± 0.07 μM (Table S2, Supplementary materials). All tested compounds did not cause any effect to viability of RAW264.7 cells (data not shown), suggesting that these compounds are potential selectivity towards anti-inflammatory effect. A structural activity relationship was deduced based on the above observation. Compounds **1** and **2** displayed a similar structure. However, compound **2** strongly inhibited NO production than compound **1**. Therefore, CH_3-4 functional group may promote inhibitory effect towards NO production at tested conditions.

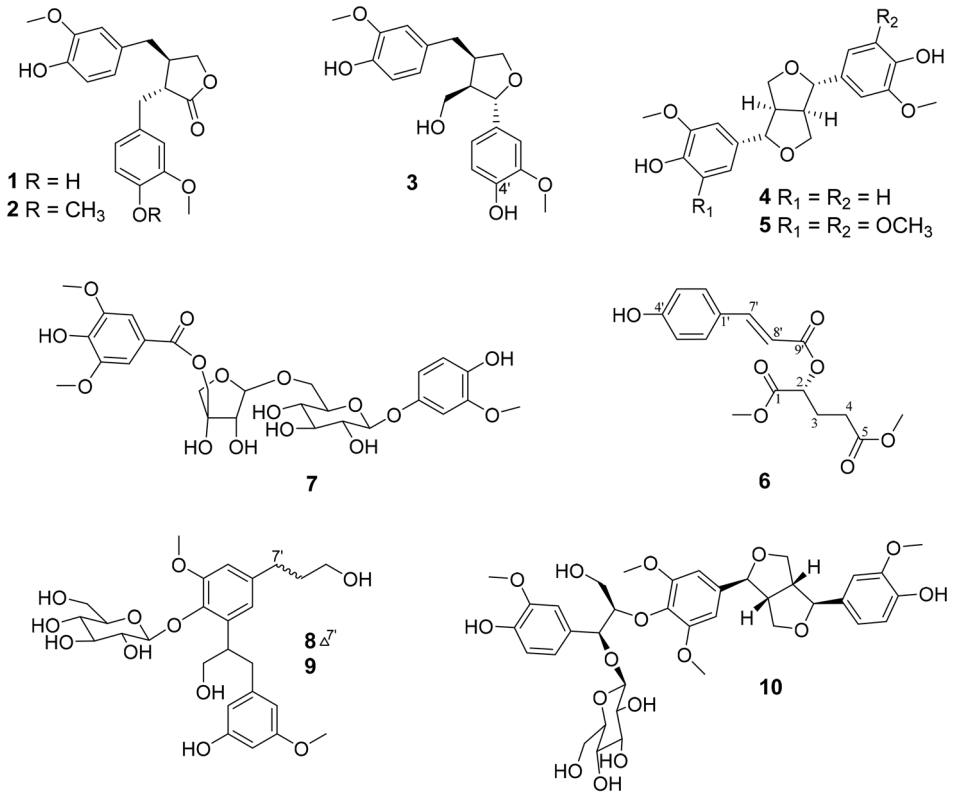

Figure 1. Chemical structures of isolated compounds from *S. sumuntia*. .

2.3. Molecular docking analysis

The active compounds (**2** and **3**) were further prepared as the ligands to form the ligand-protein complexes to verify their bioactivity. To validate the docking protocol, the co-crystalline structure was redocked by using previous report (Arias et al. 2021). The root mean square deviation between native ligand (HEM) and redocked ligand was 1.68 Å (less than limitation of 2.0 Å) (Arias et al. 2021) by calculation of superimposing the original and redocked crystal structure poses of native ligand. This observation indicated that the docking protocol was reliable. Therefore, the active compounds were evaluated for their interactions to binding poses of protein when they were docked into ligand-protein complexes by using 6AV2 protein. As a result, compounds **2**, **3**, and dexamethasone were docked into the same region of binding poses of protein (Figure S9, Supplementary materials). Furthermore, the above isolated compounds displayed significant docking as indicated by their docking scores of −8.76 and −8.73 kcal/mol, respectively, comparing to those of dexamethasone (ΔG = −8.63 kcal/mol) (Table S3, Supplementary materials). As shown in Figure S2, compound **2** may establish the H-bonds with VAL421 and VAL572 residues through forming interactions with oxygen and carboxylic groups, respectively, and further correlated with other hydrophobic interactions with GLU597, TRP592, TRP414, and CYS420 residues. Meanwhile, dexamethasone exhibited conventional hydrogen bonds with amino acids, GLY422, CYS420, VAL421, throughout interacting with hydrogen group of the ligand,

and surrounded by interaction with other hydrophobic including TRP414, GLN425, GLY591, TRP592, TYR593, MET594, GLU597, ILE684, and PRO686 amino acids. Compound **3** showed H-bond interaction with TYR711 residue and correlated with other amino acid of the binding pocket including TRP414, ALA417, ARG419, CYS420, LEU429, SER462, ALA463, ILE464, VAL572, MET575, PHE589, SER590, GLY591, TRP683, and PHE709 residues. These In silco results may support evidence for correlations between ligand and residues of binding pocket of active compounds and protein targeting inflammatory diseases.

3. Conclusion

Multiple chromatographic techniques led to the isolation of a new, symplocosol A, and nine known compounds from *S. sumuntia*. Spectroscopic methods were used to successfully identify the structures of the isolated chemicals. This is the first report for isolation of lariciresinol (**3**), syringaresinol (**5**), ecdysantherol C (**7**), manglieside D (**8**), icariside E_3 (**9**), and hedyotol C 7″-O-β-D-glucopyranoside (**10**) from *S. sumuntia*. Finding from this study highlighted the phytochemicals insight of *S. sumuntia*. These isolated compounds alternated with the expression of NO production induced by LPS activated RAW264.7 cells. Especially, compounds **2** and **3** significantly suppressed NO production in the experimental conditions. The active compounds remarkedly exhibited binding affinity with respective protein through their interactions with residues of the binding pockets of ligand-protein complexes. Bioactivities of constituents of this plant is traditionally used for treating inflammation, indicates that these active ingredients may be developed into functional products for the prevention or treatment of inflammatory diseases.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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