The Anticancer Activity of Phytoconstituents of the Stem of *Bouea macrophylla*

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Gandaria (*Bouea macrophylla* Griff) is a typical Asian plant that is commonly found in Indonesia with various secondary metabolite compounds such as phenolic, flavonoid and terpenoid. The purpose of this study was to isolate secondary metabolites from the stem extract of *B. macrophylla* and determine their activity against cancer cells MCF-7, A549, MDA-MB 231 and HCC-1954. The isolation of the compounds was conducted using various chromatographic techniques, the determination of the chemical structure of the isolates was performed using physicochemical methods including mass spectrometer and nuclear magnetic resonance, the determination of anticancer activity was carried out using 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) i.e. MCF-7 and A549 cell lines; and dimetiltiazol-2-ilm) -2,5-diphenyltetrazolium bromide (MTT) for MDA-MB 231 and HCC-1954 cell lines. Four compounds namely stigmasterol (1), fustin (2), garbanzol (3) and methyl galat (4) were successfully isolated from the stem extract of *B. macrophylla*, which was obtained from Serang Regency, Indonesia. These compounds were then tested their anticancer activity against the cancer cells of Michigan Cancer Foundation-7 (MCF-7), human alveolar epithelial cells (A549), human breast cancer cell line-1954 (HCC-1954) and M.D. Anderson-Metastatic Breast-231 (MDA-MB-231). The results of anticancer test indicated that based on the IC50 values for all compounds tested, the compounds 2 and 4 were more active on HCC-1954 cell with IC50 values of 134.35 ± 44.62 and 153.69 ± 12.54 µg/mL, respectively, while the compound 3 was found to be the most active against MDA-MB-231 cell line with IC50 value of 233.41 ± 91.57 µg/mL.

Keywords: Anticancer, B. Macrophylla, Cytotoxicity, Phytoconstituents.

The *B. macrophylla* (Anacardiaceae) is a high fruit-producing plant rich in antioxidant compounds. It is common in Indonesia, especially on the islands of Sumatra, Java, Kalimantan and Maluku.1,2 The methanol extract of *B. macrophylla* fruit has antioxidant activity with an IC50 value of
16.29 mg/mL. The methanol extract and the fruit skin as well as the fruits of B. macrophylla has been reported to be active as antioxidant. The fruit of B. macrophylla contains compounds of flavonoid class with an antioxidant activity value of IC$_{50}$ 2.43 µg/mL, using in vitro 2,2-Diphenyl-1-Picrylhydrazyl (DPPH) radical scavenging activity method. The antioxidant activity has an important correlation with anticancer activity. Kulsum et al. (2018) reported that the activity of antioxidants is proportionally correlated with anticancer activity in the test of amla and ginger extract with a probability value under 0.05. Their results indicated that compounds in the extract with an excellent antioxidant activity also have good anticancer activity. Gandaria has been reported to show a good antioxidant activity; thus it makes gandaria has possibility to show a good anticancer activity, too.

Andina and Musfirah reported that the ethanol extract of B. macrophylla leaves has strong antioxidant activity with an IC$_{50}$ value of 55.83 µg/mL. They also demonstrated that the antioxidant activity of the ethanol extract of the stem bark of B. macrophylla with an IC$_{50}$ value of 20.03 µg/mL is greater than that of the leaf ethanol extract with an IC$_{50}$ value of 55.83 mg/mL. According to Rudiana et al. (2018) the ethyl acetate extract from gandaria stems (B. macrophylla) has the best antioxidant activity compared to n-hexane and methanol extracts with an IC$_{50}$ value of 4.89 µg/mL.

The seed extract of B. macrophylla has been reported to have anticancer activity against human hypopharyngeal FaDu (HTB-43), MCF-7 and MDA-MB-231 cells with IC$_{50}$ values of 34.36; 59.07; 28.65 µg/mL, respectively. The seed extract of B. macrophylla contains pentagalloyl glucose and ethyl gallate compounds, which can inhibit MCF-7 cells through the apoptotic pathway. Besides that, the seed extract of B. macrophylla can inhibit the growth of leukemia and lung cancer cells with IC$_{50}$ values ranging from 3 to 45 µg/mL.

The exploration of pure phytoconstituents isolation of the stem of B. macrophylla has not been investigated. In our previous work, two compounds, luteolin and naringenin, have been identified in the ethyl acetate extract of B. macrophylla stem using liquid chromatography-mass spectrometry. Still, they were not isolated. The previous works on B. macrophylla mostly focused on the chemical content of their extracts. The present work aims to study the isolation of of secondary metabolites in the stem of B. macrophylla and determined the anticancer activity of the compounds isolated against MCF-7, HCC-1954, MDA-MB-231, and A549 cell lines.

**MATERIALS AND METHODS**

**Plant Material**

The stem of B. macrophylla was obtained from Serang District, Banten Province of Indonesia and identified at the Herbarium Bogoriense, a Center for Biological Research, Indonesian Institute of Research, Cibinong with voucher specimen number of 1068/IPH.1.01./If.07/VI/2018.

**General Experiment**

Thin layer chromatography analysis was carried out using silica gel on an aluminum layer (Merck Kieselgel 60 F254), monitoring TLC under UV lamps 254 and 365 nm. The vacuum liquid chromatography was performed using silica gel 60 G (Merck) as the stationary phase and silica gel 60 (Merck) in chromatography gravity column. The chemical structure of the isolates was determined using spectroscopic techniques including mass spectroscopy (Waters UPLC-MS/MS H-Class TQD), and 1H- and 13C-NMR spectroscopy which were obtained with JEOL ECA 500 with frequencies at 500 MHz and 125 MHz, respectively.

**Extraction and Isolation**

The stem powder of B. macrophylla (7.6 kg) was macerated in stages with n-hexane, ethyl acetate, and methanol (Technical, Pha Che, Indonesia) for 3 x 24 hours each using similar procedure available in the literatures. Each extract was tested anticancer activity against MCF-7, HCC 1954, MDA-MB 231, and A549 cell lines. The n-hexane extract (21 g) was separated by VLC using the mobile phase n-hexane: ethyl acetate: methanol: acetone in a 10% polarity gradient in such a way that the A-B fraction was obtained. Fraction A was purified by CC using n-hexane, ethyl acetate as the stationary phase to produce compound 1 (28 mg).
acetate: ethanol as the mobile phase to produce the A-K fraction. The G fraction (594.70 mg) was purified by CC using \( \text{n-hexane: ethyl acetate: methanol} \) in 10% gradient as the mobile phase to obtain the A-J fraction. The G fraction (594.70 mg) was purified by CC using \( \text{n-hexane: ethyl acetate: methanol} \) in 10% gradient as the mobile phase to produce compound 4 (20 mg).

Anticancer Activity

The anticancer activity of MCF-7 breast adenocarcinoma (ATCC HTB-22) and A549 Lung Carcinoma (ATCC CCL-185) cell lines were analysed using the MTS assay method which were carried out at The Biological Activity Laboratory, the Central Laboratory, Universitas Padjadjaran, Bandung, Indonesia: the cells were cultured on RPMI media (Sigma-Aldrich) containing 10% fetal calf serum, and incubated for 24 hours, and then the antibiotics, and streptomycin. The cells and media were incubated for 2 hours. The MTT reaction was stopped using \( \text{n-hexane} \), and the absorbance of the reaction was measured using an ELISA reader at a wavelength of 550 nm.

RESULTS AND DISCUSSION

The Isolated Compounds

Four compounds were successfully isolated. The separation is guided by spot pattern. The compounds were as follows: Stigmasterol (1) (Figure 1): colourless crystal, \( ^1\text{H-NMR (in CDCl}_3, 500 \text{ MHz)} \) \( \delta_{\mathrm{H}} \) (ppm): 1.83 (2H, \( m \), H-1); 1.51 (2H, \( t \), H-2); 3.53 (1H, \( m \), H-3); 2.26 (2H, \( d \), \( J=6.5 \text{ Hz} \), H-4); 5.33 (1H, \( d \), \( J=4.9 \text{ Hz} \), H-6); 1.97 (2H, \( m \), H-7); 1.47 (1H, \( m \), H-8); 0.95 (1H, \( m \), H-9); 1.50 (2H, \( m \), H-11); 1.97 (2H, \( m \), H-12); 1.05 (1H, \( m \), H-14); 1.52 (2H, \( m \), H-15); 1.23 (2H, \( m \), H-16); 1.15 (1H, \( m \), H-17); 0.66 (3H, \( s \), H-18); 0.99 (3H, \( s \), H-19); 1.97 (1H, \( m \), H-20); 1.00 (3H, \( d \), \( J=9.7 \text{ Hz} \), H-21); 5.13 (1H, \( m \), H-22); 5.12 (1H, \( m \), H-23); 1.47 (1H, \( m \), H-24); 1.81 (1H, \( m \), H-25); 0.81(3H, \( d \), \( J= \text{ Hz} \), H-26); 0.82 (3H, \( m \), H-27); 1.15 (2H, \( m \), H-28) and 0.78 (1H, \( s \), H-29). \( ^{13}\text{C-NMR (in CDCl}_3, 125 \text{ MHz)} \) \( \delta_{\mathrm{C}} \) (ppm): 36.3 (C-1); 32.5 (C-2); 71.9 (C-3); 42.3 (C-4); 140.9 (C-5); 120.7 (C-6); 32.0 (C-7); 32.0 (C-8); 50.3 (C-9); 36.5 (C-10); 21.4 (C-11); 39.2 (C-12); 42.4 (C-13); 56.9 (C-14); 24.5 (C-15); 29.2 (C-16); 56.2 (C-17); 12.2 (C-18); 19.5 (C-19); 39.9 (C-20); 23.2 (C-21); 138.5 (C-22); 129.4 (C-23); 51.4 (C-24); 31.8 (C-25); 20.0 (C-26); 21.2 (C-27); 25.6 (C-28) and 12.2 (C-29). UPLC-QTOFMS m/z 411.24 [M-] (calculated (calcd.) for \( \text{C}_{29}\text{H}_{48}\text{O} \), m/z 412.69).

Fustin (2) (Figure 1): yellow amorphous, \( ^1\text{H-NMR (in acetone-d}_6, 500 \text{ MHz)} \) \( \delta_{\mathrm{H}} \) (ppm): 6.40 (1H, \( d, J=2.5 \text{ Hz} \), H-8); 6.62 (1H, \( dd, J=8.5 \text{ and } 2 \text{ Hz} \), H-6); 6.86 (1H, \( dd, J=8 \text{ and } 2.5 \text{ Hz} \), H-5'); 6.92 (1H, \( td, J=8 \text{ and } 2 \text{ Hz} \), H-6'); 7.07 (1H, \( d, J=2.5 \text{ Hz} \), H-2'); 7.72 (1H, \( d, J=8.5 \text{ Hz} \), H-5); 4.98 (1H, \( d, J=12 \text{ Hz} \), H-2) and 4.53 (1H, \( d, J=11.5 \text{ Hz} \), H-3). \( ^{13}\text{C-NMR (in acetone-d}_6, 125 \text{ MHz)} \) \( \delta_{\mathrm{C}} \) (ppm): 74.0 (C-3); 85.0 (C-2); 103.1 (C-8); 111.8 (C-6); 115.8 (C-2'); 113.1 (C-10); 115.9 (C-5'); 120.9 (C-6'); 129.8 (C-5); 130.1 (C-1'); 145.8...
Garbanzole (3) (Figure 1): yellow needle crystal. $^1$H-NMR (in acetone-$d_6$, 500 MHz) $\delta_H$ (ppm): 7.70 (1H, d, $J= x$, H-5); 6.60 (1H, dd, H-6); 6.37 (1H, d, H-8); 7.41 (2H, d, H-2’ and 6’); 6.87 (2H, d, H-3’ and H-5’); 5.02 (1H, d, H-2); and 4.45 (1H, dd, H-3). $^{13}$C-NMR (in acetone-$d_6$, 125 MHz) $\delta_C$ (ppm): 84.9 (C-2); 73.9 (C-3); 193.3 (C-4); 129.8 (C-5); 111.8 (C-6); 165.9 (C-7); 103.7 (C-8); 164.6 (C-9); 113.1 (C-10); 129.4 (C-1’); 130.4 (C-2’ and C-6’); 115.9 (C-3’ and C-5’); and 158.9 (C-4’). UPLC-QTOFMS m/z 273.0559 [M+2] (calcd. for C$_{15}$H$_{12}$O$_5$, m/z 272.0559).

Methyl gallate (4) (Figure 1): yellow needle crystal. $^1$H-NMR (in acetone-$d_6$, 500 MHz) $\delta_H$ (ppm): 3.75 ppm (3H, s, -OCH$_3$); 7.07 (2H, s, H-2 and H-6); and 8.19 (1H, s, -OH). $^{13}$C-NMR (in acetone-$d_6$, 125 MHz) $\delta_C$ (ppm): 166.3 (C-7); 145.2 (C-3 and C-5); 137.9 (C-4); 120.9 (C-1); 108.9 (C-2 and C-6); and 51.1 (-OCH$_3$). UPLC-QTOFMS m/z 183.09 [M-] (calcd. for C$_{15}$H$_{11}$O$_5$, m/z 184.15).

Compound 1 is a colorless crystal. The UPLC-QTOFMS spectrum for compound 1 has the molecular formula C$_{29}$H$_{48}$O, m/z 412.69. The
\(^1\)H-NMR spectrum of isolate I is similar to the reference compound reported by others\(^19\) and it showed a typical signal for the group of steroid compound in which the signal accumulated in the area below 2 ppm at\(_{\text{H}}\) was typical for steroids. Four signals in the at\(_{\text{H}}\) region (3H, \(d, J = 9.74\) Hz); 0.81 (3H, s); 0.82 (3H, m); and 0.79 (1H, s) ppm indicated the presence of a methyl signal bound to C-21, C-26, C-27 and C-29, respectively. Furthermore, it is believed that 9 signals indicated the presence of methylene protons in the at\(_{\text{H}}\) region of 1.82 (2H, m); 1.51 (2H, m); 2.26 (2H, \(d, J = 6.5\) Hz); 1.97 (2H, m); 1.50 (2H, m); 1.97 (2H, m); 1.52 (2H, \(m, J = 1.23 (2H, m); 1.15 (2H, m) ppm, which is binds to C-1, C-2, C-4, C-7, C-11, C-12, C-15, C-16 and C-28 respectively. The proton signal from methine is believed to appear at at\(_{\text{C}}\) 1.47 (1H, m); 0.95 (1H, m); 1.05 (1H, m); 1.15 (1H, m); 1.97 (1H, m); 1.47 (1H, m); and 1.81 (1H, m) ppm bound to C-8, C-9, C-14, C-17, C-20, C-24, and C-25, respectively. There is a typical signal for olefinic protons at at\(_{\text{H}}\) 5 ppm and there is a signal for oxygenated protons at at\(_{\text{H}}\) 3 ppm, which is commonly reported in the class of the steroid compound.\(^19, 20\) The signal was detected as an oxygenated proton at at\(_{\text{H}}\) 3.51 (1H, m) ppm.

Rings A, B, and C consist of six carbon or cyclohexane atoms, and ring D consists of five or cycloheptane. Furthermore, most of the steroids have properties, which includes the oxygen functional group (as = O or OH) at C-3, and contains side groups at C-17, many of which contain double bonds at C-4 - C-5 or C-5 - C-26. The carbon signal that appears in the area above at\(_{\text{C}}\) is 100 ppm (140.9; 120.7; 138.5; and 129.4 ppm), which are at C-5, C-6, C-22, and C, respectively. C-23 was confirmed by the presence of two double bonds in the analyzed compound. The double bond signal is reported in the at\(_{\text{C}}\) 140.9 region; 120.7; 138.5; and 129.4 ppm. The methyl signal is believed to be in the at\(_{\text{C}}\) 12.2 (C-18) region; 19.5 (C-19); 23.2 (C-21); 20.0 (C-26); 21.2 (C-27) and 12.2 (C-29) ppm. The signal from the methylene group is believed to be present in the region:\(\text{C} 36.3 (\text{C}-1); 32.5 (\text{C}-2); 42.3 (\text{C}-4); 32.0 (\text{C}-7); 21.4 (\text{C}-11); 39.2 (\text{C}-12); 24.5 (\text{C}-15); 29.2 (\text{C}-16) and 25.6 (\text{C}-28). In addition, the signal in the region 32.0 (C-8); 50.3 (C-9); 56.9 (C-14); 56.2 (C-17); 39.9 (C-20); 51.4 (C-24), and 31.8 (C-25) ppm were believed to indicate the presence of a methine group.

The quaternary carbon group containing 3 signals was predicted in the at\(_{\text{C}}\) 140.9 (C-5) region; 36.5 (C-10) and 42.4 (C-13) ppm. Figure 1 shows that the methyl proton at position C-29 at\(_{\text{H}}\) -0.78 correlates with C-26 (at\(_{\text{C}}\) -20.0) and C-28 (at\(_{\text{C}}\) -25.6). The methyl proton at position C-18 (at\(_{\text{H}}\) -0.66) correlates with C-12, C-13, C-14 and C-17 with each value at\(_{\text{C}}\), namely 39.2; 42.4; 56.9; and 56.2 ppm. The methyl proton at position C-19 (at\(_{\text{H}}\) -0.99) correlates with C-1, C-5, C-9, and C-10 with values of at\(_{\text{C}}\) -36.3, at\(_{\text{C}}\) -141, at\(_{\text{C}}\) -50.1 and at\(_{\text{C}}\)

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**Fig. 4.** HMBC correlation of garbanzol

**Table 1.** Toxicity of extract and compound 1-4

<table>
<thead>
<tr>
<th>No</th>
<th>Sample</th>
<th>MCF-7</th>
<th>A549</th>
<th>HCC-1954</th>
<th>MDA-MB-231</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Stigmasterol (1)</td>
<td>1209.25 ± 47.92</td>
<td>5757.60 ± 4173.23</td>
<td>853.53 ± 103.87</td>
<td>553.60 ± 121.35</td>
</tr>
<tr>
<td>2</td>
<td>Fustin (2)</td>
<td>377.94 ± 9.17</td>
<td>359.31 ± 3.58</td>
<td>134.35 ± 44.62</td>
<td>5704.28 ± 289.08</td>
</tr>
<tr>
<td>3</td>
<td>Garbanzole (3)</td>
<td>248.16 ± 83.12</td>
<td>568.77 ± 98.13</td>
<td>427.05 ± 122.71</td>
<td>233.41 ± 91.57</td>
</tr>
<tr>
<td>4</td>
<td>Methyl gallate (4)</td>
<td>351.75 ± 3.80</td>
<td>388.84 ± 9.75</td>
<td>153.69 ± 12.54</td>
<td>311360.41 ± 262865.2</td>
</tr>
</tbody>
</table>
Fig. 5. The comparison of anticancer activity test for all compounds isolated.
showed 8 signals of methine carbon ($\delta_c$, 74.0; 85.0; 103.1; 111.8; 115.8; 115.9; 120.9; 129.8 ppm) and there were 7 carbon signals quaternary ($\delta_c$, 113.1; 130; 1; 145.8; 146.6; 164.6; 165.8; 193.2 ppm). The $^{13}$C-NMR spectrum shows a signal at a shift below 100 ppm, namely at $\delta_c$ 85.0 and 74.0 ppm as a characteristic of saturated carbon $sp^3$ which binds to electronegative atoms such as oxygen. The carbon signal at 193.2 ppm shift is characterized by carbonyl carbon, which has a range shift between 185-220 ppm. The 2D NMR COSY spectrum of $^1$H-$^1$H correlation shows that there is a correlation between H-3 ($\delta_h$ 4.53 ppm) with H-2 ($\delta_h$ 5.00 ppm) and H-5 ($\delta_h$ 7.72 ppm) with H-6 ($\delta_h$ 6.62 ppm). This confirms that the basic structure of the isolate is a flavonoid with 2 protons in ring A and ring B, each of which is correlated. The results of the 2D NMR HMQC spectrum analysis showed that there were 8 correlations between the proton and the carbon signal. The correlation shows a direct bond between protons and carbon, namely the proton-carbon signal. The correlation shows a direct bond were 8 correlations between the proton and the carbon. Furthermore, HMQC 2D spectrum shows a direct correlation between protons and carbon. The correlation signal appears up to 7 signals at $\delta_h$ 4.55 (H-3); 5.03 (H-2); 6.37 (H-8); 6.60 (H-6); 6.87 (3'/5'); 7.41 (2'/6'); and 7.70 (H-5) ppm with carbon at $\delta_c$ signal 73.9 (C-3), respectively; 84.9 (C-2); 103.7 (C-8); 111.8 (C-6); 115.9 (C-3'/5'); 120.4 (C-2'/6'); and 129.8 (C-5) ppm. 2D HMBC analysis was performed, and the structure of the isolate was believed to be a flavonoid. This is reinforced by the signal that appears at $\delta_c$ 5.04 ppm (C-2), which correlates with $\delta_c$ 73.9 (C-3); 193.3 (C-4); 129.4 (C-1'); 130.4 (C-2'/6'). This signal shows the correlation between the C and B rings of flavonoids. The important HMBC correlation of 3 was shown in Figure 4.

Based on the $^1$H-NMR spectrum of compound 4, there is CH$_3$ (-OCH$_3$), which is oxygenated at $\delta_h$ 3.75 ppm (3H, s). A typical aromatic signal appears at $\delta_h$ 7.07 (2H, s) with a symmetrical plane, hydroxy proton (-OH) appears at $\delta_h$ 8.19 (1H, s). Seven carbon signals that are a C = O signal at $\delta_c$ 167.9 ppm (indicating the presence of carbon ester), one signal indicates the presence of aromatic carbon (C-OH) at $\delta_c$ 145.2 ppm, at $\delta_c$ 137.9 ppm indicates aromatic carbon (C-OH), $\delta_c$ 120.9 contains aromatic carbon (C-C), $\delta_c$ 108.9 ppm contains aromatic carbon (C-H), at $\delta_c$ 51.1 indicates the presence of –O-CH$_3$. These values are in agreement with reported values available in the literature.

**Anticancer Activity of Extracts and Compounds 1-4**

The anticancer activity against MCF-7 and A549 was measured using the MTS assay method, while the anticancer activity of HCC-1954 and MDA-MB 231 cells was measured using the MTT assay method and the results of the anticancer activity test are shown on the Table 1 and the comparison of their IC$_{50}$ values are shown in Figure 5.

All compounds 1 – 4 were assayed for their anticancer property against MCF-7, A549, HCC-1954 and MDA-MB231 cell lines. All isolated compounds exhibited moderate anticancer activity against almost cell lines tested. Compounds 2 and 4 were more active on HCC-1954 cell with IC$_{50}$ values of 134.35 ± 44.62 and 153.69 ± 12.54 µg/
mL, respectively than other isolated compounds. It presumably that the anticancer activity increase with the absence or with the decreasing number of hydroxyl groups. Additionally, among all isolated compounds, compound 3 gave the most active in the anticancer activity test against MDA-MB-231 cell line with IC₅₀ value of 233.41 ± 91.57 µg/mL. While compounds 2 and 3 demonstrated respectable anticancer activity against MCF-7, A549, and HCC-1954 cell lines with IC₅₀ values ranging from 134.35 ± 44.62 to 568.77 ± 98.13 µg/mL. The compounds 2 and 3 are flavanones containing a chiral carbon on chroman-4-one ring which is flexible. According Woo et al., the wide range of the flavanone bioactivity may be due to its chiral structure. In addition, the carbonyl group at C-4 on the flavan skeleton is very important for anticancer activity.

However, the structure-activity relationship study is required to provide better understanding of their anticancer activity. The results of the anticancer test for the compounds isolated in this work are lower compared to other compounds reported by others both in the synthetic compounds such as organotin (IV) carboxylates or other isolated compounds from other plants although the cell lines used were different. However, the results reported in this work are believed still very important results in attempts to find new candidate for anticancer drugs.

CONCLUSIONS

Four compounds namely stigmasterol (1), fustin (2), garbanzol (3), and methyl gallate (4) were successfully isolated from the stem of B. macrophylla. These compounds were well characterized and the characterization data obtained were similar to the known compounds previously published. These compounds were tested for their anticancer activities against 4 cell lines. The result showed based on the IC₅₀ values of compounds 2 and 4 were more active on HCC-1954 cell with IC₅₀ values of 134.35 ± 44.62 and 153.69 ± 12.54 µg/mL, respectively. The compound 3 was the most active against MDA-MB-231 cell line with IC₅₀ value of 233.41 ± 91.57 µg/mL.

Data availability

Data can be made available upon request from the corresponding author.