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FULL PAPER

# Chemical profiles and antioxidant properties of *Bruguiera gymnorrhiza* fruit extracts from Central Sulawesi, Indonesia

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**Abstract**

*Bruguiera gymnorrhiza* is one of the mangrove species that a source of antioxidants. Antioxidant substances are able to protect cells from oxidative stress and other related diseases. This study aimed to evaluate the chemical profiles, predicted biological activity, and antioxidant activity of the *B. gymnoriza* fruit extracts. The research methods included sampling, extraction (maceration with MeOH:DCM), identification of chemical profiles (GCMS spectra analysis), assaying for computational analysis (PASS server and ADMET), antioxidants (DPPH radical scavenging), and total phenolic content (Folin-Ciocalteu). *Bruguiera gymnorrhiza* fruits was collected from Central Sulawesi, Indonesia. The chemical profiles detected in the *B. gymnorrhiza* fruit extracts, namely isopimaradiene (64.20%); 4-(2-Aminopropyl) phenol (19.06%); dimethylamino-dimethylphosphene oxide (9.40%); 3-amino-2-benzylbutanoic acid (5.46%); and 1,4-dideuteriooctane (1.89%). PASS server analysis showed that the five compounds detected from *B. gymnorrhiza* fruit have the potential as an NF-E2-related factor (Nrf2) stimulant and oxygen scavenger. The ADMET analysis results indicated that *B. gymnorrhiza* fruits could be developed as folk medicine and nutraceutical products.

## 1. Introduction

Mangroves are a forested ecosystem widely distributed in tropical and subtropical areas (Zhu *et al*., 2012; Al-Maqtari and Nagi, 2014; Suh *et al*., 2014). Indonesia is recognized as a centre for biodiversity globally as an archipelago country due to its rich natural habitats, including mangroves (Kusmana, 2014). About 23% of total world mangrove forests are located in Indonesia (Armitage, 2020), with 202 mangroves species, e.g., *Avicennia* sp., *Bruguiera* sp., *Rhizophora* sp., and *Xylocarpus* sp. (Noor *et al*., 2006; Kusmana, 2014). They have been utilized for several purposes, such as wood for house constructions, charcoal (Dahdouh-Guebas *et al*., 2000), food ingredients (Jariyah *et al*., 2014; Analuddin *et al*., 2019; Amin *et al*., 2021), complementary foods (Kardiman *et al*., 2017), food products (Situmorang and Barus, 2015; Wibawanti *et al*., 2018), and folk medicine (Rout and Basak, 2014; Suh *et al*., 2014).

Mangroves have long been used as folk medicine and therapeutics for diarrhoea, indigestion, and inflammation in coastal communities (Rout and Basak, 2014; Suh *et al*., 2014). Their efficacies are related to the level and composition of bioactive compounds. It is expected to have several physiological activities such as anti-fungal (Acharya *et al*., 2020), anti-bacteria (Behbahani *et al*., 2018; Eswaraiah *et al*., 2020), antioxidants (Arulkumar *et al*., 2020; Karim *et al*., 2020), and anti-hemolytic (Karim *et al*., 2020).

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The coast of Central Sulawesi, Indonesia, is the home of various mangrove species such as Rhizophora *mucronata, Sonneratia alba*, *Avicennia marina*, and *Bruguiera gymnorrhiza* (Damanik and Djamaludin, 2012; Lisna *et al*., 2017; Dewanto *et al*., 2018; Alhaffaf *et al*., 2019). *B. gymnorrhiza,* belonging to Rhizophoraceae, is reported as an essential and major mangrove species in the Asia Pacific, including Central Sulawesi (Zhu *et al*., 2012; Kusmana, 2014). It is traditionally used as a medicinal plant (Lin *et al*., 2020). The previous study has revealed that methanol leaves extract of *B. gymnorrhiza* and *Heritiera littoralis* revealed free radical scavenging, anti-haemolytic, cytotoxic, and antibacterial activity (Karim *et al*., 2020). Meanwhile, the aqueous extract of *B. gymnorrhiza* exhibited a protective effect against dextran sulfate sodium (DSS)-induced ulcerative colitis (Chen *et al*., 2020). In addition, the *B. gymnorrhiza* roots extract has been reported to inhibit the *Escherichia coli*, *Staphylococcus aureus,* and urinary tract infections (UTI) bacterial pathogens, e.g., *Pseudomonas aeruginosa* growth (Acharya *et al.,* 2020). However, explorations of *B. gymnorrhiza* fruits have been limited. Even though *B. gymnorrhiza* fruits have reported possessed biological activities, it is therefore related to the chemical profiles and their antioxidant activities.

Therefore, in this study, we reported *B. gymnorrhiza* fruit extract's chemical profiles with GCMS, the prediction of biological activity with PASS server and ADMET analysis, and antioxidant activity with DPPH radical scavenging and total phenol content with Folin-Ciocalteu.

## 2. Materials and methods

### *2.1 Sampling location*

*Bruguiera gymnorrhiza* fruits were collected from the coastal area of Tomini Bay in Laemanta, Parigi Moutong, Central Sulawesi, Indonesia (-0.1847 S and 120.0088 E) (Figure 1) in April 2020. Mangrove fruits were randomly taken from a mangrove tree *B. gymnorrhiza* followed by identification based on Noor *et al*. (2006). After collection, the *B. gymnorrhiza* fruits were washed with water to eliminate the presence of contaminants.

### *2.2 Materials*

Free radical 2,2-Diphenyl-1-Picrylhydrazyl (DPPH, Merck-1898664), distilled water, dichloromethane (DCM, $CH_2Cl_2$; (Merck- 106050), methanol (MeOH, $CH_3OH$; Merck- 107018), Folin-Ciocalteu reagent (Merck-109001), gallic acid ($C_6H_2(OH)_3CO_2H$, Merck-842649; purity ≥ 98%), $Na_2CO_3$ were purchased from CV Amani Media Malang and CV Intraco Makassar, Indonesia.

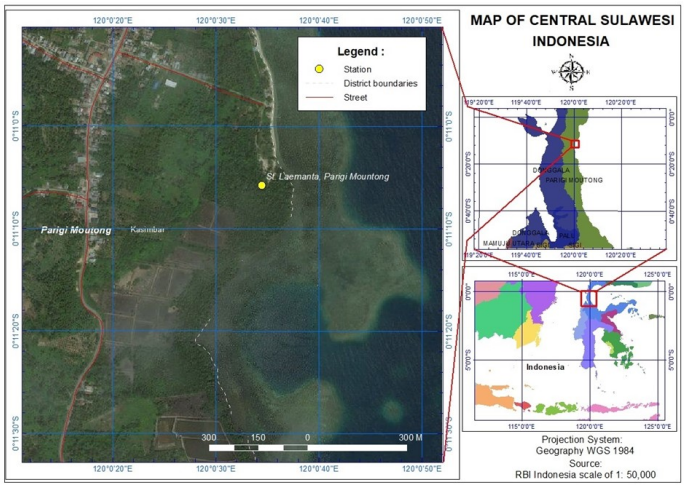


Figure 1. Sample coordinates for *Bruguiera gymnorrhiza* from Laemanta, Central Sulawesi, Indonesia

### *2.3 Preparation of Bruguiera gymnorrhiza extracts*

Before extractions, 500 g of *B. gymnorrhiza* fruits were dried at 50-60ºC using an oven (Finco OV50) for 15-20 hrs. After drying, the samples were pounded into flour. The crude extract of *B. gymnorrhiza* (100 g) was obtained by extraction with the combination of MeOH and DCM (1: 1) for 48 hrs (Hsiao *et al*., 2015; Putra *et al*., 2016). The filtrate obtained by the extraction was filtered with filter paper (Whatman No. 42). The filtrate was vacuum-concentrated at 40-45°C using a rotary evaporator (EYELA N-1100) to obtain the crude extracts. The extraction process was carried out three times. Then, the extracts were weighed and dissolved in 30% MeOH then stored at 4-5ºC for further analysis.

### *2.4 Chemical profiles screening using GCMS*

The chemical components of *B. gymnorrhiza* fruits extract were profiled using Gas Chromatography-Mass Spectrometry (GCMS). The analysis was performed on an HP 6890 GCMS system (Hewlett-Packard, California, USA) equipped with a capillary column (Agilent 19091S -433 HP-5MS; 30 m x 250 µm i.d.; Santa-Clara, California, USA). The carrier gas was helium at a flow rate of 1 mL/min. The oven temperature was set at 325° C. The pre-oven temperature was 150°C held at 2°C/ min. It ran for 10°C/min and was then increased to 240° C, holding time for 11 mins. The total running time was 24 mins. The scanning range was 50 - 550 amu. Structural assignments were based on analysis of mass spectral fragmentation patterns and compared with mass spectra in the National Institute of Standards and Technology (NIST) and Wiley's compound profile database (Tanod *et al*., 2019).

### *2.5 Prediction of biological activity*

The chemical profiles from *B. gymnorrhiza* fruits extract by GCMS were predicted through Prediction of

 

Activity Spectra for Substances (PASS)-way2Drug server (http://www.pharmaexpert.ru/passonline/index.php). PASS server is used to predict the chemical compounds' biological activity (Aisiah *et al*., 2020; Riyadi, Romadhon, Anggo *et al*., 2020). The structural target compounds obtained from the National Centre for Biotechnology Information (https://pubchem.ncbi.nlm.nih.gov/) in the form of canonical SMILE were used to predict their biological activity. The chemicals profile structure was also used to estimate their ADMET (absorption, distribution, metabolism, excretion, and toxicity) through AdmetSAR (http://lmmd.ecust.edu.cn/admetsar2).

### *2.6 Determination of total phenol contents*

Total phenolic content (TPC) of *B. gymnorrhiza* fruits extract was determined by the Folin-Ciocalteu (FC) reagent method (Blainski *et al*., 2013 and Lamuela-Raventós, 2017). The gallic acids (1 mg/mL) were used as a standard by diluting ethanol: distilled water (1: 1). Gallic acid solutions were diluted in serial dilution with concentrations 5, 20, 40, 60, 80, and 100 µg/mL. From each dilution concentration, 1 mL of gallic acid was taken, and 9 mL of distilled water was added. Then those aliquots were mixed with 1 mL of FC reagent (homogenization) and incubated for 8 mins at room temperature. After incubation, 3 mL of 20% $Na_2CO_3$ was added, and the mixture was allowed to stand at room temperature for 2 hrs. The absorbance was measured at 750 nm. The standard curve for gallic acid was prepared with gallic acid concentration (µg/mL) with an absorbance value.

The aliquot (1 mg/mL extract) was added with 10 mL of distilled water + 1 mL of FC reagent and incubated as described above. Then TPC content was measured at 750 nm. *B. gymnorrhiza* fruits extract's total phenolic content was then calculated based on a gallic acid standard curve and expressed as mg of gallic acids equivalent (GAE)/g extract.

### *2.7 DPPH radical scavenging activity*

DPPH is a free radical, stable at room temperature, which produces a violet solution in ethanol. Antioxidants' presence will reduce the colour and change into uncoloured ethanol solution (Clarke *et al.*, 2013). The total free radical scavenging capacity of Free radical scavenging capacity was assessed according to the previously reported method using a stable DPPH (Molyneux, 2004; Dewanto *et al*., 2019). The extract was expressed as the $IC_{50}$, which is the antioxidant concentration required to quench 50% of the initial DPPH under the experiment treatment. Vitamin E, known as the strong DPPH radical scavenger (Yu *et al*., 2002), was used as the positive control. The $IC_{50}$ value was converted to the vitamin E equivalent. Each evaluation was performed in triplicate.

*Bruguiera gymnorrhiza* fruit extracts (200 µg/mL) in ethanol solution was prepared and diluted into several concentrations (20, 40, 60, 80, 100 µg/mL). 2 mL aliquot of each concentration was reacted with 50 µM DPPH ethanol solution. The mixtures were homogenized and stand for 30 mins in the dark at room temperature before reading against a blank at 517 nm (UV-VIS spectrophotometer T90 + PG Instruments Ltd).

The DPPH radical scavenging effect in percentage (%) was calculated according to the following equation:

$$\text{DPPH Scavenging Effect (\%)} = \frac{A_{blank} - A_{sample}}{A_{blank}} \times 100\%$$

Where $A_{sample}$ is the absorbance of a sample solution and $A_{blank}$ is the absorbance of the blank solution (containing all reagents except the test sample).

The half of maximum concentration in reducing initial DPPH was calculated from the graph by plotting inhibition concentrations against initial DPPH to obtain a linear regression equation, y = a + bx. Each measurement was carried out in triplicates.

## 3. Results

### *3.1 Sample identification*

Identification was carried out according to Noor *et al*. (2006). The samples included in the *B. gymnorrhiza* based on the leaves' shape and tip, the types of roots, fruit, and flowers. BG's bark has lenticels, and the surface is smooth to rough, dark gray to brown. BG roots are like planks extending to the side at the tree's base and developing several knee roots. Characteristics of BG leaves are skinned green on top and yellow on bottom. The BG leaves shape is elliptical to elliptical-lanceolate and had average length and width 4.5 to 7 cm and 8.5 to 22 cm, respectively. Characteristics of BG fruit are straight, blunt, and dark green-purple when fresh with length (12-30 cm) and diameter (1.5-2 cm) (Figure 2).


Figure 2. *Bruguiera gymnorrhiza* mangrove fruits from Laemanta, Central Sulawesi, Indonesia

 

### *3.2 Chemical profiles of Bruguiera gymnorrhiza fruit extracts*

The GCMS analysis showed the presence of 5 compounds from *B. gymnorrhiza* fruit extracts (Table 1). The chemical profiles were identified through mass spectrometry attached with GC. The total ion chromatogram (TIC) of the GCMS analysis confirms that five compounds and their different retention time (4,700 to 22,824 mins) are presented in Figure 3. The chemical profiles contained in *B. gymnorrhiza* fruits extracts are isopimaradiene (64.20%), 4-(2-Aminopropyl) phenol (19.06%), dimethylamino-dimethylphosphene oxide (9.40%), 3-amino-2-benzylbutanoic acid (5.40), and 1,4-dideuteriooctane (1.89 %).

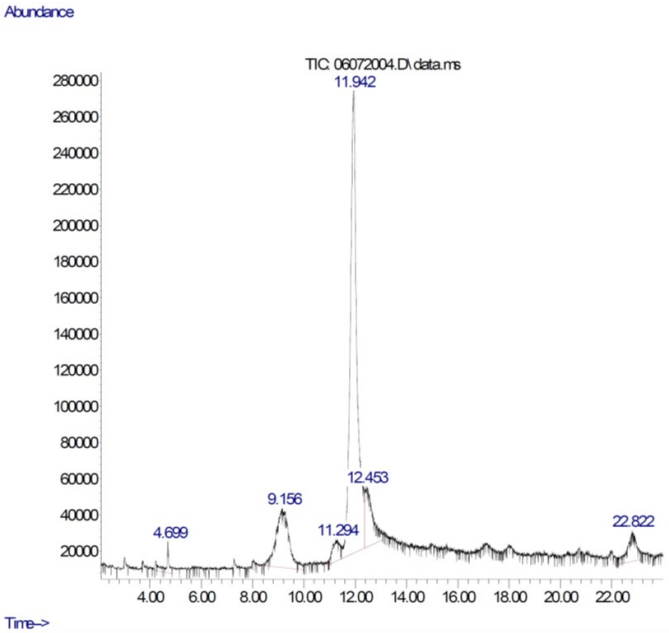


Figure 3. GCMS chromatogram of mangrove fruit extracts *Bruguiera gymnorrhiza*

### *3.3 Biological activity prediction of fruits extracts*

The prediction of biological activity was performed with chemical profiles in *B. gymnorrhiza* fruits extracts and presented in Table 2. The biological activity prediction was used the PASS server. The PASS server could predict compounds' biological activity based on their formula with 95 % accuracy (Filimonov and Poroikov, 2008; Riyadi, Tanod, Wahyudi *et al*., 2020). The biological activity prediction value of the *B. gymnorrhiza* fruits extracts' chemical profiles was expressed as a "probability to be active" (Pa). The chemical profiles are probable to act as antioxidants, free radical scavengers, oxygen scavengers, and NF-E2-related factor (Nrf2) stimulant properties (Figure 4). The PASS server was analysed and dominated by Nrf2 stimulant and oxygen scavenger, which play a role in protecting oxidative stress.

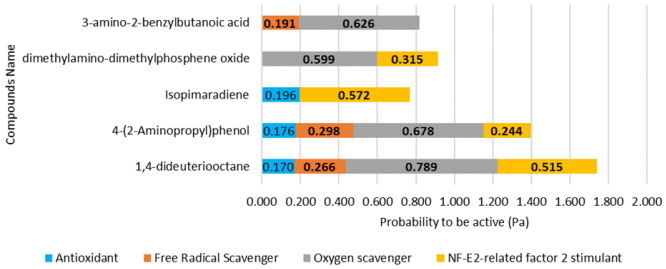


Figure 4. Probability to be active from *Bruguiera gymnorrhiza* fruit extracts profiles with PASS Server

ADMET analysis is an important parameter to determine whether a natural product will reach the body's target when administered orally (Dong *et al*., 2018; Natesh *et al*., 2021). The ADMET properties of compounds are important to the development process of nutraceutical and pharmaceutical products (van de Waterbeemd and Gifford, 2003; Guan *et al*., 2019). The utilization of *B. gymnorrhiza* fruits extracts for human health benefits needs to be satisfied with the ADMET properties before further applications. Therefore, we evaluated the ADMET properties of *B. gymnorrhiza* fruits extracts chemical profiles by using admetSAR (Table 2).

The chemical profiles of *B. gymnorrhiza* fruit extracts showed good human intestinal absorption. However, only dimethylamino-dimethyl phosphene oxide did not show well on the caco-2 permeability (Table 2). Interestingly, none of the selected chemical profile functions is acted as both P-glycoprotein (P-gp) substrate and inhibitor. Furthermore, 4-(2-Aminopropyl) phenol), isopimaradiene, and 3-amino-2-benzyl butanoic acid from the *B. gymnorrhiza* fruits extracts act as substrate of CYP450 2D6, CYP450 3A4, and CYP450 2C9, respectively. In contrast, none of the chemical profiles acts as inhibitors of CYP450 enzymes, which

Table 1. Chemical profiles of *Bruguiera gymnorrhiza* fruit extracts by GCMS

| RT (Min) | Chemical Profiles | Formula | Molecular Weight (g/mol) | Area (%) | Pubchem CID |
|---|---|---|---|---|---|
| 4.700 | 1,4-dideuteriooctane | $C_8H_{18}$ | 116.24 | 1.89 | 151945284 |
| 9.158 | 4-(2-Aminopropyl)phenol | $C_9H_{13}NO$ | 151.21 | 15.93 | 3651 |
| 11.295 | | | | 3.13 | |
| 11.940 | Isopimaradiene | $C_{20}H_{32}$ | 272.5 | 64.2 | 13969536 |
| 12.453 | dimethylamino-dimethylphosphene oxide | $C_4H_{12}NOP$ | 121.12 | 9.4 | 521290 |
| 22.824 | 3-amino-2-benzylbutanoic acid | $C_{11}H_{15}NO_2$ | 193.24 | 5.46 | 541835 |

 

Table 2. Admet profile of *Bruguiera gymnorrhiza* fruit extracts

| ADMET Profile | 1,4-dideuterio Octane | 4-(2-Aminopropyl) phenol) | Isopimara-diene | dimethylamino-pdimethyl phosphene oxide | 3-amino-2-benzyl butanoic acid |
|---|---|---|---|---|---|
| Absorption properties | | | | | |
| Human Oral Bioavailability | + (0.5286) | - (0.5857) | + (0.6571) | + (0.6000) | + (0.8286) |
| Human Intestinal Absorption | + (0.8865) | + (0.9861) | + (0.9828) | + (0.8805) | + (0.9945) |
| Caco-2 Permeability | +(0.9825) | +(0.9499) | +(0.8457) | -(0.5244) | + (0.5957) |
| P-glycoprotein Substrate | -(0.9516) | -(0.8011) | -(0.9000) | -(0.98) | - (0.9485) |
| P-glycoprotein Inhibitor | -(0.9850) | -(0.9903) | -(0.8387) | -(0.988) | - (0.9903) |
| Distribution properties | | | | | |
| Blood-Brain Barrier (BBB) B | +(1.000) | -(0.993) | | +(0.9911) | + (0.8686) |
| Subcellular localization | | | | | |
| Metabolism properties | | | | | |
| CYP450 2C9 Substrate | -(0.8415) | -(1.0000) | -(0.7731) | -(1.0000) | + (0.6409) |
| CYP450 2D6 Substrate | -(0.7215) | +(0.5870) | -(0.7252) | -(0.7913) | -(0.7568) |
| CYP450 3A4 Substrate | -(0.7947) | -(0.7593) | +(0.5636) | -(0.6488) | -(0.7595) |
| CYP450 2C9 Inhibitor | -(0.9349) | -(0.8930) | -(0.5747) | -(0.8930) | -(0.967) |
| CYP450 2D6 Inhibitor | -(0.9373) | -(0.7163) | -(0.9203) | -(0.9491) | -(0.944) |
| CYP450 2C19 Inhibitor | -(0.9540) | -(0.7723) | -(0.500) | -(0.8930) | -(0.8805) |
| CYP450 3A4 Inhibitor | -(0.9877) | -(0.8767) | -(0.8545) | -(0.9724) | -(0.9463) |
| CYP inhibitory promiscuity | -(0.8149) | -(0.9737) | -(0.6444) | -(0.9737) | -(0.9818) |
| Toxicity properties | | | | | |
| Hepatotoxicity | - (0.9500) | - (0.7750) | - (0.7500) | - (0.9500) | + (0.825) |
| Acute Oral Toxicity | | II (0.5359) | II (0.8150) | III (0.6949) | III (0.7484 |
| AMES (Ames mutagenesis) | | -(0.9300) | -(0.9400) | -(0.5800) | |

can interfere degradation process. In addition, all chemical profiles showed a positive response as oral bioavailability, water-soluble, and could bind to proteins in the blood.

### *3.4 Total phenol content*

Phenolic compounds are mainly found in plants. Phenolic compounds have a protective role in human health and are beneficial in food and pharmaceutical products due to their benefits (Salar *et al.*, 2017). The present study evaluated the quantitative estimation of phenolic compounds in BGF extract collected from North Sulawesi, Indonesia. The TPC value of BGF extract was determined by the FC method reported by Blainski *et al.* (2013) and Lamuela-Raventós (2017). Gallic acid was used as a standard for the calibration curve to calculate the TPC with equation y = 0.0101x - 0.0318. The calculated result of TPC was accounted for 27539.60±35.01 mg GAE/100 g dry extract. The results indicated that *B. gymnorrhiza* fruit extracts contained *a* high level of phenolic compounds.

### *3.5 Antioxidant activity analysis using the DPPH method*

The DPPH method has been widely used for antioxidant evaluation due to a stable free radical to evaluate radical scavenging activity (Liu *et al.*, 2004). The level of discoloration exhibits the potency of antioxidants to scavenge free radicals. These phenomena due to the reaction between the 2,2-Diphenyl-1-Picrylhydrazyl and antioxidant compound to form the hydrazine diphenyl picrite (Huliselan *et al.*, 2015; Tanod *et al.*, 2019). DPPH could reduce the exposure of radical proton scavengers (Yamaguchi *et al.*, 1998). The antioxidants reduced the stable DPPH radicals, resulting in decreased absorbance at 517 nm (Behgar *et al.*, 2011). The present study evaluated *B. gymnorrhiza* fruit extracts' antioxidant activity using the DPPH radical scavenging method with more than one concentration and compared the results with vitamin E (Figure 5).

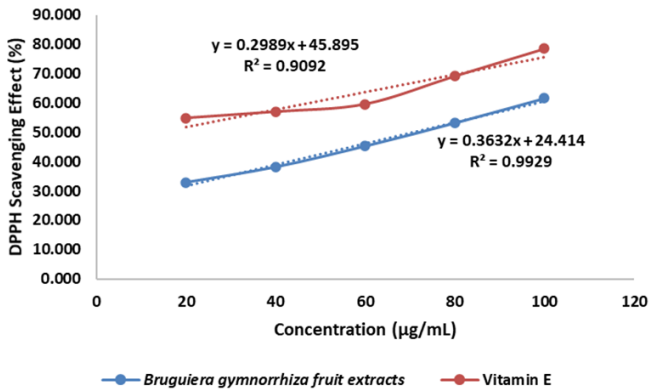


Figure 5. DPPH scavenging effect from *Bruguiera gymnorrhiza* mangrove fruit extracts

The *B. gymnorrhiza* fruit extracts were also

 

evaluated for the inhibitory effect of DPPH radicals for $IC_{50}$ determination (Table 3). The *B. gymnorrhiza* fruit extracts possessed antioxidant activity because they could donate hydrogen atoms/electrons to react with DPPH radicals. The results showed a *B. gymnorrhiza* fruit extracts concentration dependent on free radical scavenging and comparable with synthetic antioxidants (vitamin E). The results indicated that *B. gymnorrhiza* fruit extracts have strong antioxidant activity ($IC_{50}$: 70.45±0.49 μg/mL), however its activity lower than vitamin E ($IC_{50}$: 13.72±1.02 μg/mL).

Table 3. $IC_{50}$ of *Bruguiera gymnorrhiza* mangrove fruit extracts using the DPPH Radical Scavenging, compared with vitamin E.

| Mangrove fruits extract | $IC_{50}$ (μg/mL) |
|---|---|
| *Bruguiera gymnorrhiza* | 70.45±0.49 |
| Vitamin E | 13.72±1.02 |

## 4. Discussion

*Bruguiera gymnorrhiza,* a medicinal food plant, is widely distributed in Indonesia (Kusmana, 2014). *Bruguiera gymnorrhiza* has been used for several purposes, such as vegetables, firewoods (Kusmana *et al*., 2018), and folk medicine (Ahmed *et al*., 2007). The present study reported the characteristics of chemical profiles and antioxidants properties of *B. gymnorrhiza* fruit extracts. This study also predicted the biological activity related to antioxidant and ADMET properties of chemical profiles in *B. gymnorrhiza* fruit extracts. The major chemical profiles identified by GCMS from the *B. gymnorrhiza* fruit extracts were dominated by Isopimaradiene (terpenoids component) and 4-(2-Aminopropyl) phenol (phenolics component) (Figure 3 and Table 1). Plant phenolics denote a major group of compounds with antioxidants properties (Adesegun *et al*., 2009; Pandey and Rizvi, 2009; Lin *et al*., 2016). Phenolics reported have the ability to strong reactive oxygen species (ROS)-scavenging activity, dropping nitrite levels, and downregulated cyclooxygenase-2 (COX-2) expression, which can play a vital role in human health (Lin *et al*., 2009; Rodríguez-López *et al*., 2020). In addition, terpenoids are also reported as antioxidant potential (Mohandas and Kumaraswamy, 2018). Terpenoids have a hydroxyl group that may act as an antioxidant due to their relatively complex cyclic structure (consisting of alcohol, aldehyde, or carboxylic acid) (Dewanto *et al*., 2019).

The predictive of *B. gymnorrhiza* fruit extract chemical profiles by PASS-Server of the major compounds are related to antioxidant properties. Isopimaradiene, a diterpenoid, has been reported to have anti-oxidative and anti-inflammatory properties (Kim and Kim, 2009; Tungcharoen *et al*., 2019) and anti-bacterial activity (Rijo *et al*., 2009). Meanwhile, 4- (2-Aminopropyl) phenol is exerted antioxidant activities, free radical scavenger, $O_2$ scavenger, and NF-E2-related factor 2 (Nrf2) stimulant. Nuclear factor erythroid 2-related factor 2 (Nrf2) plays an important role in regulating the antioxidant proteins to protect against oxidative damages (Hwang and Jeong, 2010; Barajas *et al*., 2011; Ma, 2013; Cui *et al*., 2016). Under oxidative stress conditions, activated Nrf2 translocate into the nucleus and modulates antioxidant-related genes' expression at the transcriptional level (Johnson *et al*., 2008). Oxygen scavengers could prevent oxidation and quality foodstuff changes (Byun *et al*., 2011; Lalpuria *et al*., 2012; Mu *et al*., 2013). This compound has one phenol ring and one $NH_2$ bond. H atoms in the phenol and $NH_2$ ring act as electron donors to react as free radicalizers such as reactive oxygen species (ROS) (Lobo *et al*., 2010).

The present study has been found that *B. gymnorrhiza* fruit extracts possessed higher antioxidant potential and phytochemical content. The antioxidant potential is comparable with synthetic antioxidant vitamin E. The results revealed that *B. gymnorrhiza* fruit extracts exhibited strong antioxidant activity ($IC_{50}$ 70.45). This activity is higher than methanol extract of *B. gymnorrhiza* fruit extracts collected from the Odisha coast, India (Rout *et al*., 2015) and *B. gymnorrhiza* extract collected from Bangladesh (Hosen *et al*., 2020). Some factors are related to the different antioxidant activity of BG, e.g., the polarity of solvents (Jacoeb *et al*., 2013), the maturity of fruits (Sudirman *et al*., 2014), geographical locations (Rout *et al*., 2015; Hosen *et al*., 2020).

Our data showed a high level of phenolic content. This level is considerably higher than ethanol: methanol (1: 1) of *B. gymnorrhiza* fruit extracts (21.9 mg GAE/g powder) (Hosen *et al*., 2020). The extract contains 4- (2-Aminopropyl) phenol and -amino-2-beunzylbutanoic acid with an aromatic ring structure with a hydroxyl group (typical of phenolic compounds).

None of the selected chemical profiles functions as P -glycoprotein (P-gp) substrate and inhibitors. P-gp transporter acts as a protective barrier to keep toxins out of the body and as a cellular defence system to protect the accumulation of foreign materials in the human body (Marzolini *et al.*, 2004; Szakács *et al.*, 2008; Quan *et al.*, 2012; Cloos *et al.*, 2018). After absorption in the intestine, compounds flow to the blood then metabolized in the liver. The liver CYP450 enzyme family could break down the compounds and eliminate them from the human body (Natesh *et al*., 2021). According to the

 

ADMET analysis, 4-(2-Aminopropyl) phenol, isopimaradiene, and 3-amino-2-benzyl butanoic acid from the *B. gymnorrhiza* fruit extracts act as a substrate of CYP450 2D6, CYP450 3A4, and CYP450 2C9, respectively. Possibly, they will metabolize through those enzymes in the liver. Interestingly, all compounds are not showing any toxicity in the liver. Compound No. 1 – 3 showed class II toxicity, while compounds No. 4-5 exhibited class 3 toxicity. According to the GHS United Nations 2015, the toxicity of any compounds taken orally was classified into six categories based on the $LD_{50}$ ranges. Class 1- fatal ($LD_{50} \leq 5$), class 2- fatal ($5 < LD_{50} \leq 50$), class 3- toxic ($50 < LD_{50} \leq 300$), class 4- harmful ($300 < LD_{50} \leq 2000$), class 5- may be harmful ($2000 < LD_{50} \leq 5000$), and class 6, $LD_{50} > 5000$ is considered as non-toxic (Drwal *et al*., 2014).

## 5. Conclusion

It can be concluded that *B. gymnorrhiza* fruit extracts from Central Sulawesi could be developed as a folk medicine, nutraceutical, and functional food ingredient with antioxidant properties in a certain amount that is safe for consumption.

## Conflict of interest

The authors declare no conflict of interest.

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