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Identification And Characterization Of Shogaol And 6-Gingerol Complex From Madurese Herbal Medicine

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Abstract

Ginger (*Zingiber officinale*) and meniran (*Phyllanthus niruri* L.) is a cultural heritage in Madura ethnic, Indonesia. Madurese herbs were traditionally boiled using pottery which is made from clay. Clay consists of Silica (SiO_2), Aluminum silicate (Al_2O_3), Magnesium (MgO), Calcium (CaO),) Iron (Fe_2O_3) and Potassium (K_2O). This component contributes to the efficacy of traditional Madurese herbal medicine by forming bioinorganic complex compounds. The present study aimed to characterize the bioinorganic complex compounds from Madurese herbal medicine and predict their pharmacokinetics activity. Madurese traditional herbal medicine composition was determined using Liquid Chromatography-Mass Spectrometry/Mass Spectrometry (LC-MS/MS). Then, Fourier-Transform Infrared Spectroscopy (FITR), X-Ray Fluorescence (XRF), Scanning Electron Microscopy (SEM) and X-Ray Diffraction (XRD) analysis were used to determine the functional group, transition metal composition, morphology, and the crystal structure of bioinorganic complex compounds from Madurese traditional herbal medicine, respectively. The pharmacokinetic activity was predicted using ADMET software. The results showed that Fe and Mn bind to hydroxyl groups (-OH) in the 6-gingerol and shogaol compounds to form bioinorganic complex compounds. The morphological structure of Madurese herbal powder was porous slabs. The crystal structures of Madurese herbal powder were amorphous and uniform in size. The pharmacokinetic activity analysis showed that Madura traditional herbal has a high solubility in water and easily absorbed by the body. In conclusion, bioinorganic complex compounds of Madurese traditional herbal medicine can be considered as a therapeutic agent in further research.

Keywords: Characterization, Madurese Traditional Herbal Medicine, Pottery Boiled, Bioinorganic Compound

1. Introduction

Herbal medicine is a traditional medicine that uses several mixtures of medicinal plants [1]. One way of using traditional herbal medicine is by boiling [2]. Herbs are traditionally boiled using pottery from clay. The composition of clay includes Silica (SiO_2), Aluminums Silicate (Al_2O_3), Potassium (K_2O), Calcium (CaO), Magnesium (MgO) and Iron (Fe_2O_3) [2,3]. The physical-mechanical properties of pottery can withstand liquids, withstand heat, absorb water.

Boiling is a simple extraction method to dissolve the active compounds, such as flavonoids, phenols, alkaloids [5,6] Bioactive compounds play an essential role in disease therapy, maintaining health and improve the immune system [7,9] The chemical structure of dissolved active compounds with hydroxyl functional groups (-OH) can form complex bioinorganic compounds with transition metals as their atomic center [10]. The anthocyanin compound in Java Plum fruit (*Syzygium cumini*) can bind to Fe^{3+} metal, forming a bioinorganic complex compound [11]. Bioinorganic complex compounds have several biological activities: antioxidants, anti-inflammatory, anti-tumor, anti-cancer, anti-microbial, anti-viral, anti-diabetic, and anti-obesity [10]. Transition metals, such as Cu, Zn, Mn, and Fe, which are naturally found in medicinal plants, are considered relatively safe, inexpensive, and efficient.

Traditional herbal medicine is a cultural heritage of the Madurese ethnic that is passed down from generation to generation [11]. Madurese traditional herbal medicine was usually made by boiling using pottery at 80°C for 30 minutes. Madurese traditional herbal medicine consists of Ginger and Meniran, which is believed to have a biological effect on maintaining health. Knowledge about the

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chemical compounds and their role in treating or preventing diseases is necessary [12]. The active compounds dissolved during boiling are expected to form bioinorganic complex compounds. Boiling the herbs using pottery is projected to contribute to transition metals in forming bioinorganic complex compounds.

Many studies have reported the characterization of active compounds from herbal ingredients. However, this study focused on the characterization of bioinorganic complex compounds in Madurese herbs formed during the boiling process using pottery. This study provides an overview of functional groups, transition metal percentages, bioinorganic complex compound sizes, and pharmacokinetics of traditional Madura herbal extracts. The characterization of bioinorganic complex compounds can be used as a scientific basis in the treatment and advanced analysis as a therapeutic agent in several diseases.

2. Material and Methods

Sample Preparation

Ingredients used in Jamu Madura, Indonesia, include Ginger (*Zingiber officinale*) and Meniran (*Phyllanthus niruri* L.). The samples were dried and then mashed in the grinder at a speed of 25,000 rpm for 10 minutes. The samples were sifted using a size of 200 mesh.

Extraction of Madurese Traditional Herbal Medicine

Many 100 g of ginger powder was dissolved in 4 L water (ratio of 2:1), then boiled in pottery at a temperature of 80ºC for 30 min and filtered using filter paper. The filtrate was then freeze-dried.

Liquid Chromatography-Mass Spectrometry and Liquid Chromatography (LCMS/MS) analysis

Madurese traditional herbal medicine composition was analyzed using LC-MS/MS (Shimadzu-8030, Kyoto, Japan). The tool settings used the following criteria: drying gas flow rate (17 L/min); gas pressure collision (230 kPa); hot block temperature (400°C); gas desolvation (nitrogen); gas flow rate of desolvation (3 L/min); nitrogen; interface voltage (4.5 kV); gas collision (argon); and the temperature of the desolvation line (250°C).

The chromatography separation process was used Kinetex column C18 (particle size 2.6 µm, dimensions 2.1 mm x 100 mm, USA). The temperature of the column was maintained at 35°C. The following gradient program was applied to the analyte with a motion phase consisting of 10 mM of acetone and ammonium acetate. The flow rate and injection volume is 0.2 mL/min and 10 µL, respectively [13].

Fourier Transform Infrared Spectrophotometer (FTIR) analysis

Dry powder from water solvent extract by boiling clay method was used for FTIR analysis. Spektra IR is recorded using FTIR (Shimadzu, IR Affinity1, Japan). 10 mg of dried extract of Madurese traditional herbal medicine were added with 1 mg/100 mg potassium bromide. FTIR spectra were collected at frequency regions of 4000–400 cm^{-1} by adding 10 scans and a resolution of 2 cm^{-1} [14].

X-ray Dispersion Fluorescence (XRF) analysis

The X-ray Dispersion Fluorescence Methods (XRF) is a non-destructive method used to determine the elements from the raw plant material without any chemical treatment and helps ascertain the nutritional role. In XRF analysis, samples are synergized with X-rays produced by sources in the instrument. Madurese traditional herbal extract was analyzed for content of trace elements by spectroscopy PAN-alytical's MiniPal 4 type [15].

Scanning Electron Microscope (SEM) analysis

Madurese traditional herbal extract morphology was examined using Jeol JSM-5300 Scanning Electron Microscope (SEM), Tokyo, Japan. The sample was placed on an aluminium buffer in a high vacuum evaporator then analyzed under an electron scanning microscope [12].

X-ray Diffraction (XRD) analysis

Crystal characterization in Madura traditional herbal extract was done using XRD (Xpert MPD). Samples were scanned using copper (Cu). Kα radiation at 20 mA, 36 kV with a wavelength of 1.54056 Å. The angular scanning area in 2θ is from 100 to 900 (step size 0.01, time per step 10 s, divergence gap width (DS) 0.25º, receiver gap width (RS) 12.75 mm. The sample is calibrated at 50º before analysis. This process shows X-ray diffraction, which is then recorded as a diffraction pattern [16,17].

Pharmacokinetic Bioinorganic Compound and ADMET Properties Prediction

ADME is a software for predicting pharmacokinetic properties of drug-like compounds from their molecular structures. This software is a predictions strategies which evaluated designed inhibitors by using Lipinski's rule of five.[16] Swiss ADME software is a web/online based device used to estimate the behaviour of medicinal compounds [18].

Data analysis

FTIR and XRD data was analyzed using OriginPro® 2019 (OriginLab Corporation, Suite 303 Northampton, MA 01060, United States) and QUALX2.0 for Windows (Software Ic, Institute of Crystallography – CNR – Bari), respectively.

3. Results and Discussion

Boiling was a simple extraction method used by the community to make traditional herbal medicine. Boiling can dissolve several active compounds that dissolve in polar solvents, such as water, alcohol and derivatives. The boiling process penetrated the matrix in traditional Madurese herbs. It dissolves active compounds, one of which is 6-gingerol and shogaol compounds that belong to the phenolic group at a temperature of 80ºC for 30 minutes [7,19]. The compounds 6-gingerol and shogaol have a high solubility in water at 37–100ºC for 1 h [20,21]. The compound 6-gingerol turns into shogaol at 120ºC–150ºC [22]. The process of boiling Madurese traditional herbal medicine was shown in Figure-1

Based on LC-MS/MS results, 6-gingerol and shogaol compounds were found in Time Retention (RT) 12.761 with an area of 127.585.87 which offers more abundance of 6-Gingerol compounds than shogaol compounds found in Retention Time (RT) 15.745 with an area of 13.798.004.97. The abundance of 6-gingerol compounds in ginger is more than in shogaol compounds [23]. The results of the chromatogram in the LC-MS/MS analysis were shown in Figure-2.

The compounds 6-gingerol and shogaol had hydroxyl fungi (-OH) clusters in aromatic rings (Figure-3). Hydroxyl groups (-OH) in 6-gingerol and shogaol compounds (Figure-3) can bind to transition metals such as Fe, Mn, Zn, Cu (Table-1). According to Sodhi & Paul [23], the active compounds of herbal ingredients can form bioinorganic complex compounds with transition metal Fe and Cu as therapeutic agents [24]. The formed bioinorganic complex compounds have different characteristics to their bioactive compounds [20, 25, 26]. The compounds 6-gingerol and shogaol have characteristics in carbon (C) bond, aromatic ring and the hydroxyl group (-OH) that determine its capability [27].

Fig.-1. Madurese traditional herbal medicine boiling using pottery

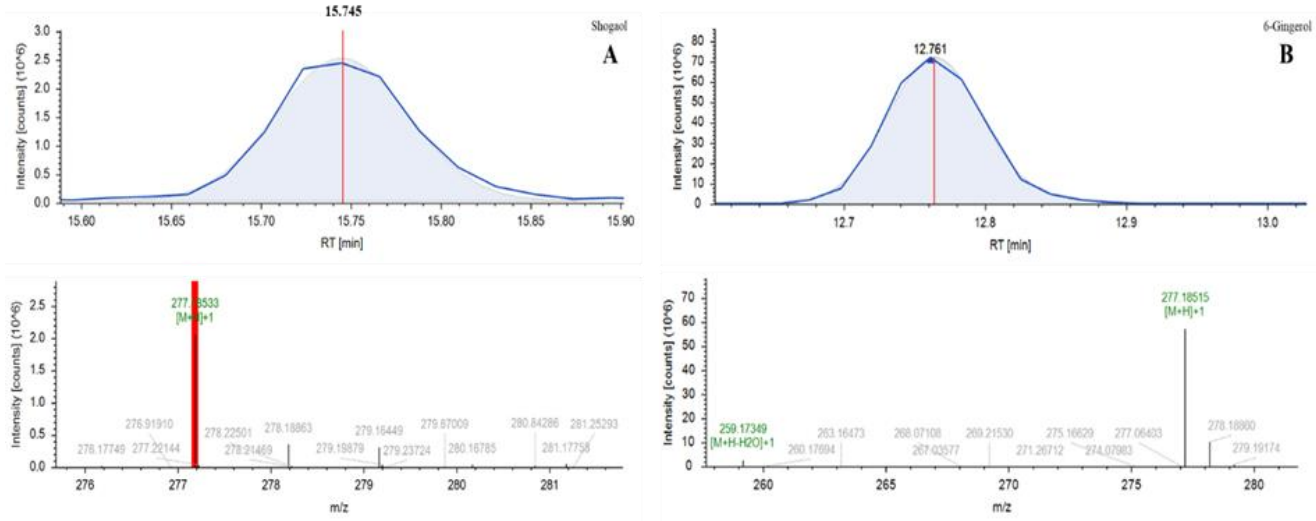


Fig.-2. Comparison chromatogram from Shogaol (A), 6-Gingerol (B) based on LC-MS/MS analysis

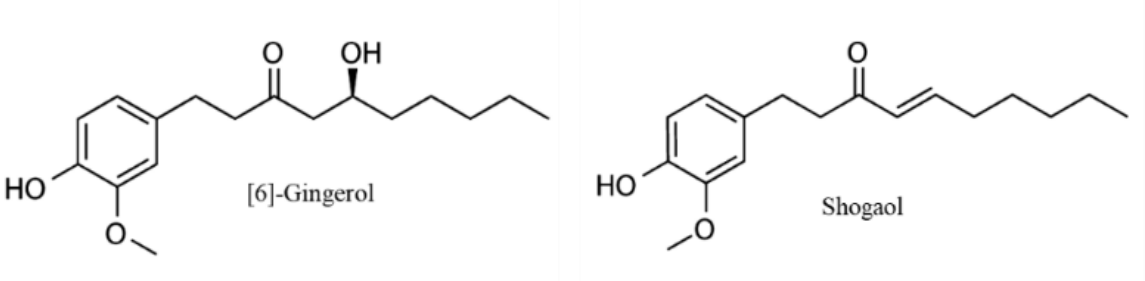


Fig.-3. Hydroxyl group (-OH) at 6-Gingerol and Shogaol

FTIR analysis was used to investigate the functional group of traditional Madura herbal extract by analyzing interferogram signals produced from interferometer detectors. Analysis of functional group on Madura traditional herbal extract was used wavelengths of 4000-400 cm^{-1} because most molecules show peaks in the infrared area [28]. The results of the functional group of Madurese traditional herbal medicine extract were shown in Figure-4.

Table-1. Transition metal content in Madurese traditional herbal extract (%)

Elements	Pottery
Fe	0.97 ± 0.03
Mn	1.00 ± 0.01
Cu	0.26 ± 0.01
Zn	0.05 ± 0.02
Mo	6.14 ± 0.04

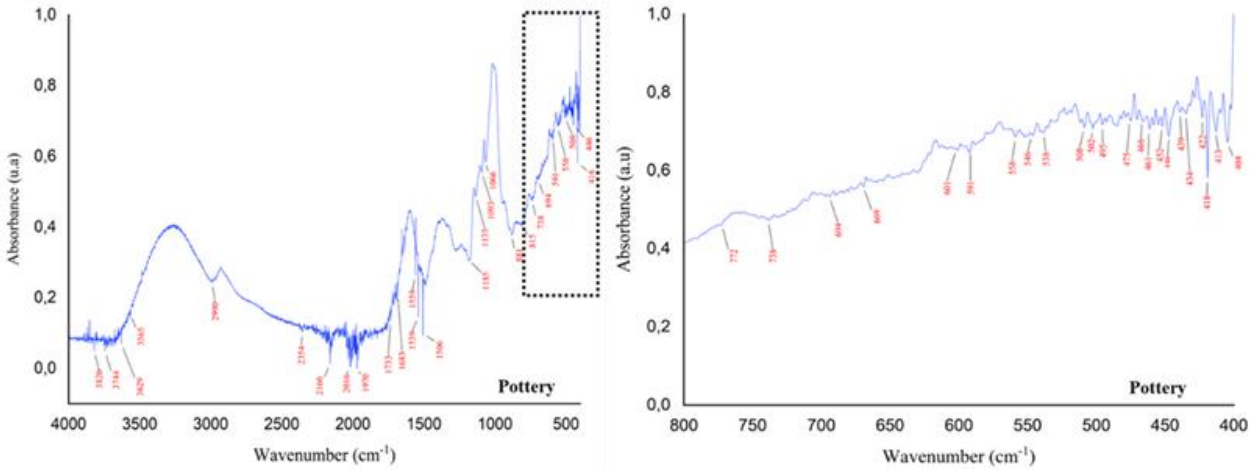


Fig.-4. Identification of function group in Madurese traditional herbal medicine extracted with boiling methods using pottery using FTIR analysis

Hydroxyl functional group (-OH) found in the range of wavelength areas 3900-3300 cm^{-1} was in the wavelength areas 3820, 3744, 3629, 3565 cm^{-1}. Hydroxyl groups (-OH) are also found in wavelength numbers 1500-400 cm^{-1}. According to Joshi [27] and Coates [28], the absorption of the O-H function group at a wavelength of 3600-3300 cm^{-1}, the C-H function group at a wavelength of 3000-2800 cm^{-1}, C=O function group at wavelength 1850-1640 cm^{-1}, C=C function group at wavelength 1680-1400 cm^{-1}, C-O function group at wavelength 1300-1000 cm^{-1}, and wavelength 1500-400 cm^{-1} are characteristic (fingerprint) compounds of plants. In addition, there is a unique bond in the number of wavelengths [28,29]. The absorption of functional groups in the wavelength area of 4000-400 cm^{-1} with the boiling of pottery was shown in Table-2.

Hydroxyl groups (OH) can bind to transition metals such as Fe, Mn, Cu, Zn (Table-1) at wavelengths between 1200-400 cm^{-1} [30,31]. According to Nakamoto [30] and Liu & Guo [31], the absorption of Mn-O stretch at a range of ≈ 1200 - 400 cm^{-1}; Fe-O stretch at a range of ≈ 900 - 500 cm^{-1}; Cu-O stretch at a range of ≈ 700 - 400 cm^{-1}; Zn-O stretch

at a range of ≈ 650 - 400 cm^{-1}; Mo-O stretch at a range of ≈ 600 - 500 cm^{-1} [31,32].

Transition metals are essential elements needed in plant metabolisms, such as photosynthesis, redox reactions, and electron transfer processes [20,25]. Chlorophyll is a matrix of cells whose constituents consist of transition metals [26]. The content of transition metal in Madurese traditional herbal extract was presented in Table-1. Transition metals molybdenum (Mo), manganese (Mn), iron (Fe) has the possibility of bonding with active compounds forming bioinorganic complex compounds. The formation of bioinorganic complex compounds was influenced by the abundance of transition metals and binding energy. 6-gingerol and shogaol compounds can bond with Fe and Mn transition metals because the binding energy was relatively small (-0.6 kcal/mol) (Table-3). The transition metals can bind to flavonoid compound groups such as quercetin, crysin, luteonin, kaempferol, hesperidin, and naringin naringenin, apigenin, silibinin, and morin [31]. Pottery also contributed to the abundance of iron transition metals (Fe) because the pottery constituent material contains Iron (Fe_2O_3), and affecting the formation of complex compounds.

Table-2. Functional group absorption value in Madurese traditional herbal extract based on FTIR analysis

Wavenumber (cm^{-1})	Boiled Pottery methods (cm^{-1})	Function group
3900-2700 cm^{-1} (X-H Stretch region)		
3900-3300	3820, 3744, 3629, 3565	Alcohol O-H Almine N-H alkyne C-H
3300-2500	2990	Acid O-H
3200-3000	2990	Aromatic (sp^2) =C-H Alkene (sp^2) =C-H
3000-2800	2990	Alkyl (sp^3) C-H
2400-2100 cm^{-1} (C≡X Stretch region)		
2400-2100	2354, 2160	Nitrile C≡N
2100-1500 cm^{-1} (C=X Stretch region)		
2050-1750	2016, 1970	Anhydride C=O
1750-1700	1733	Aldehyde C=O Ketone C=O Ester C=O Acid C=O
1700-1640	1683	Amide C=O
1680-1620	-	Alkene C=C
1600-1400	1559, 1539, 1506	Aromatic C=C
1500-400 cm^{-1} (Fingerprint areas)		
1300-1000	1185, 1135, 1093, 1066	C–O
1500-400	881, 815, 772, 738, 694, 669, 601, 591, 558, 546, 538, 508,502, 495, 475, 466, 461, 452, 446, 439, 434, 422, 418, 413, 404	Fingerprint area

Complex compounds formed between 6-gingerol and shogaol with transition metals Fe^{2+} and Mn^{2+} in Madura traditional herbal medicine were predicted. ADMET was used to know its pharmacokinetic character. Bioinorganic complex compounds formed easily soluble in water with TPSA values of 55.76 Å2, 45.63 Å2 smaller than 130 Å2. Solubility of bioinorganic complex compounds was also shown log S values (ESOL, Ali, SILICOS-IT) had met the criteria for solubility of compounds in water between -5 to 6. GI absorption is also high, so the body very easily absorbs it. Madura traditional herbal extract has many pores, so it is easily soluble in water (Figure-5).

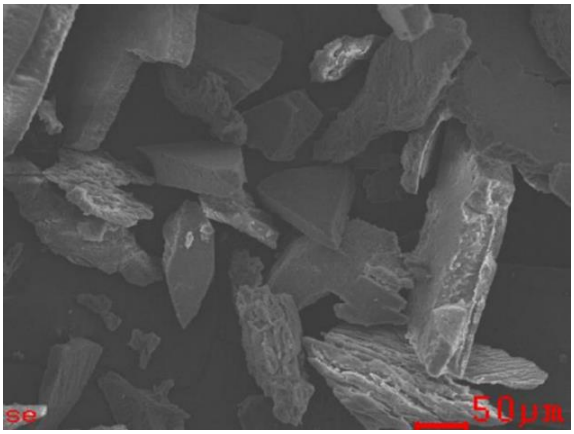
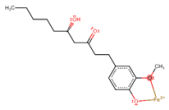
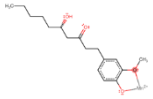
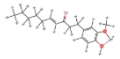
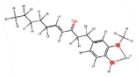


Fig.-5. Morphology of Madurese traditional herbal extract powder using SEM analysis

The morphology of powdered extract of Madurese traditional herbal medicine showed the characteristics of particles such as coarse and irregular, porous particles forming solid slabs (Figure-5). Characterization of crystals formed in bioinorganic complex compounds using X-Ray Diffraction (XRD) analysis. The results of the XRD analysis were shown in Figure-6.

The results of XRD analysis from Madurese traditional herbal extract showed the formation of crystals, and this is shown from the peak pattern formed in the area of 2 thetas 14.32, 19.42, 32.19, 37.23, 54.19. The crystal structure formation is also due to the binding energy needed to form a relatively small bioinorganic complex compound (Table-3). The tapered peak shape indicated the uniformity of the crystal size and type of crystal.

Table-3. Functional group absorption value in Madurese traditional herbal extract

Name Compound	Complex Compound	Binding Affinity (kcal/mol)	Water Solubility			Pharmacokinetics		Lipophilicity		Physicochemical Properties	
			Log S (ESOL)	Log S (Ali)	Log S (SILICOS-IT)	GI Absorption	Log Kp (skin permeation) (cm/s)	Log $P_{o/w}$ (XLOGP3)	Log $P_{o/w}$ (WLOGP)	Num. rotatable bonds	TPSA (Å2)
Gingerol-Fe^{2+}		-0.6	-3.57	-3.95	-5.37	high	-6.22	3.11	3.72	9	55.76
Gingerol-Mn^{2+}		-0.6	-3.57	-3.95	-5.37	high	-6.22	3.11	3.72	9	55.76
Shogaol- Fe^{2+}		-0.6	-4.32	-5.03	-5.91	high	-5.25	4.34	4.39	8	46.53
Shogaol- Mn^{2+}		-0.6	-4.31	-5.03	-5.91	high	-5.24	4.34	4.39	8	46.53

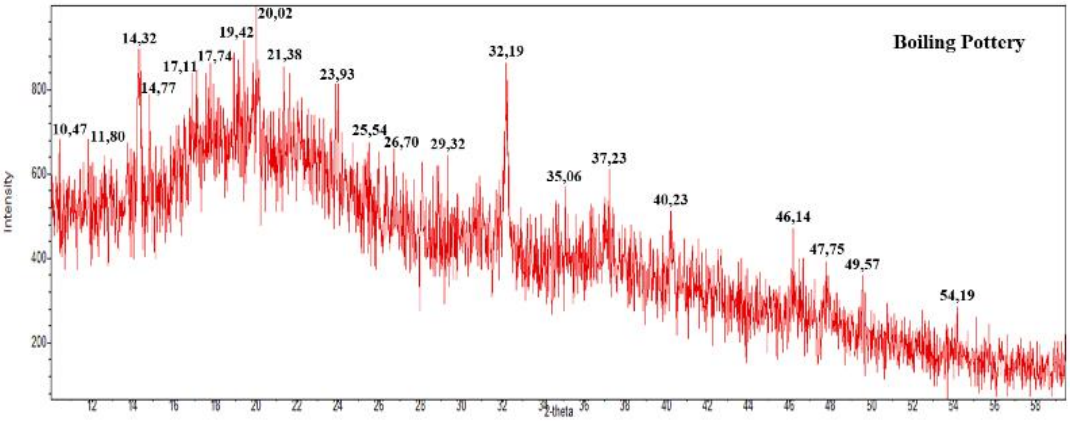


Fig.-6. Crystal structure pattern in Madurese traditional herbal extract using X-Ray Diffraction (XRD) analysis

In ADMET analysis predicted bioinorganic complex compounds formed with the composition of one active compound: one transition metal, thus allowing the crystals formed to have a small size and amorphous. The highest peak indicated the number of crystals formed. The more pointed peak showed the uniformity of the size of the crystals formed.

Boiling is one of the dissolving processes of compounds often used by the local community [3,32]. The physical-mechanical properties of pottery can withstand liquids, withstand heat, and absorb water [4]. The thermal conductivity of pottery may differ from other containers made of stainless steel and aluminums. Therefore, dissolved active compounds will differ and affect the character of bioinorganic complex compounds and pharmacokinetics. 6-gingerol and shogaol have a high solubility in water at 37ºC–100ºC for 1 h [33,34]. The compound 6-gingerol turns into shogaol at 120ºC – 150ºC [21,22].

It is also a concern for further research on whether temperature and time variations affect the character and profile of the bioinorganic complex compounds that are formed. Changes in the profile characteristics of bioinorganic complex compounds in the processing process will affect the activity and efficacy of traditional Madurese herbs. The activity of bioinorganic complex compounds is also influenced by pharmacokinetics, solubility, dissolved particle size, and physicochemical properties. Bioinorganic complex compounds have various activities, such as antioxidants, anti-inflammatory, anti-bacterial. Bioinorganic compounds have structural stability and solubility as therapeutic agents to overcome health problems, such as cancer, tuberculosis, anemia and energy management disorders. It can also be used as a follow-up study for in vivo trials and clinical trials on bioinorganic compound candidates.

4. Conclusion

The use of herbal medicine as an alternative treatment can be an option to overcome some diseases. Madurese traditional herbal medicine, which boiled using pottery at 80ºC for 30 minutes, could dissolved the compound 6-gingerol and shogaol. The formation of bioinorganic complex compounds occurs in hydroxyl groups (-OH) of 6-gingerol and shogaol, found in wavenumbers of 3900 cm^{-1} – 2700 cm^{-1} and fingerprint areas (1500 cm^{-1} – 400 cm^{-1}). The binding energy required to interact between 6-gingerol and shogaol compounds with the transition metals Fe^{2+} and Mn^{2+} was -0.6 kcal/mol, allowing bioinorganic complex compounds. Pharmacokinetic of the formed bioinorganic complex have water-soluble properties and are easily absorbed by the body. The morphology of Madura traditional herbal extract has many pores, indicated that the extract is easily soluble. The crystal structure formed is indicated by forming a peak at the number 2 theta, namely 14.32, 19.42, 32.19, 37.23, 54.19; the spiky peak shape showed the uniformity of crystal size and amorphous.

Conflict of interest

There is no conflict of interest

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