INTERNATIONAL JOURNAL OF CURRENT ADVANCED RESEARCH
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 13; Issue 7; July 2024; Page No.3177-3182
DOI: http://dx.doi.org/10.24327/ijcar.2024.3182.1686

Research Article

ESTERIFICATION REACTION AND ANTIOXIDANT ACTIVITY OF XANTHONE DERIVATIVE FROM MANGOSTEEN PEEL (*Garcinia mangostana L.)*

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ARTICLE INFO

Article History:
Received 12th June, 2024
Received in revised form 22th June, 2024
Accepted 16th July, 2024
Published online 28th July, 2024

Key words:

Antioxidant, Esterification, *Garcinia mangostana*, Mangosteen, Xanthone

ABSTRACT

Mangosteen peel (*Garcinia mengostana* L.) contains bioactive compounds from xanthone derivatives as the largest component. Xanthones are active as antioxidants, anti-inflammatory, anti-fungal, anti-cancer and anti-allergic. Mangosteen peel powder was extracted by maceration with ethanol, and then fractionated with n-hexane and chloroform. The results of the fractionation were tested for antioxidant activity and total phenolics. The xanthone derivative obtained was carried out by an esterification reaction with anhydrous acetic acid using sulfuric acid catalyst. The results of the phytochemical test of the ethanol extract of mangosteen peel contain secondary metabolites such as alkaloids, flavonoids, terpenoids, phenols, and saponins. The results of the phenol test on the chloroform fraction obtained a total phenol content of 77939.94 mg GAE/100 mL. The results of the antioxidant activity test showed that the n-hexane fraction was the most active antioxidant with IC_{50} 114.8 µg/mL, chloroform fraction (202.59 µg/mL), water (407.36 µg/mL), and ethanol crude extract (482.36 µg/mL). Antioxidant activity after the esterification reaction decreased compared to before esterification with IC_{50} 219.29 µg/mL. Compounds that can be identified from the esterification reaction of the chloroform fraction of mangosteen peel are manopiranoside; 1,3,6-triolate-α-mangosteen; 1,3,6-trihydroxy-α-mangosteen; 3-O-acetyl- α-mangosteen; 3,6-di-O-acetyl-α-mangosteen; 3,6,7-tri-O-acetyl-α-mangosteen.

INTRODUCTION

Mangosteen (*Garcinia mangostana* L.) is a tropical plant and in Southeast Asia is widely used as a traditional medicine. Mangosteen peel extract can be used topically to prevent skin aging, protect skin damage from UV-B rays and free radicals, increase skin elasticity, prevent skin inflammation, and protect skin from hyperpigmentation. Mangosteen extract is also used as a mouthwash, toothpaste, dental floss, dental plaque, mouth spray, healthy beverages, deodorant, and treats various diseases such as gonorrhoea, kidney infection, diarrhea, dysentery, and abdominal pain (Abate *et al*. 2022; Xu *et al*. 2016; Janardhanan *et al*. 2017).

Mangosteen peel contains bioactive compounds such as xanthones, pectin, phenolic acids, tannins, anthocyanin, flavonoids, phenolics, and organic acids (Kurniawan *et al*. 2021; Yuvanatemiya *et al*. 2022; Rizaldy *et al*. 2021). Mangosteen peel also contains vitamins B1, B2, C, iron, niacin, protein, calcium, polysaccharides, catechins, polyphenols, carbohydrates, protein, fat, and fiber (Mayefis *et al*. 2019; Kurniawan *et al*. 2021). Xanthones in mangosteen peel contain the major component α-mangosteen (69.02%), followed by γ-mangosteen (17.86%) (Yuvanatemiya *et al*. 2022; Martemucci *et al*. 2022; Mohammad *et al*. 2019). Alpha-mangosteen and γ-mangosteen have activities as antioxidants, anti-inflammatories, and anticancer (Tran *et al*. 2021). Xanthones show significance in inhibiting the growth of colon cancer cells, and inhibiting the growth of the mosaic virus in tobacco (Mohammad *et al*. 2019; Cin & Kinghorn. 2008; Ruan *et al*. 2017). Xanthones are active as antioxidants, anti-inflammatory, antifungal, anticancer, hypo-allergenic, anti-malarial, anti-diabetic, anti-tuberculosis, anti-viral, immunomodulatory, and antibacterial (Ragasa *et al*. 2016; Mayefis *et al*. 2019; Kurniawati *et al*. 2011; Abate *et al*. 2022; Kurniawan *et al*. 2021). The pectin in mangosteen peel contains 65% galacturonic acid which is active as an antioxidant and has the potential to be used as a matrix for biomedical applications (Wathoni *et al*. 2019). Polyphenolic compounds in mangosteen can prevent degenerative diseases and tumor cell proliferation (Abate *et al*. 2022). Mangosteen peel contains high xanthone which has antioxidant activity.

Antioxidants are compounds that can bind to free radicals, causing them to become unreactive. Antioxidants can inhibit the oxidation process in other compounds. Radical compounds can cause oxidative damage to lipids, proteins, DNA structures, and nucleic acids. (Lobo *et al*. 2011; Jung *et al*. 2016; Ifeanyi O.E., 2018). As an antioxidant, xanthone works by chelating metals, capturing free radicals, and inhibiting lipid peroxidation (Pinto *et al*. 2005). Melia *et al*. (2019) evaluated the antioxidant activity of mangosteen peel using

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the DPPH method, it obtained ethanol fraction with an IC_{50} of 210.45 µg/mL. The hydroxy groups in xanthone increase their ability as antioxidants because they can chelate metals and act as free radical scavengers (Wen, 2017).

Xanthones contain active groups such as hydroxy, methoxy, ketone, and prenyl groups which can be derivatized to produce higher bioactivity (Wen, 2017). Xanthone contains three hydroxy groups which allow for esterification reactions to be carried out. The hydroxy group in the ortho position with the methoxy group is easier to esterification. The methoxy group activates the ring so that electrons will collect more on the hydroxy group, this will make it easier to be attacked by H^+. The prenyl group also acts as a ring activator but it is weaker than methoxy, while the keto group has the property of deactivating the ring so that the electrons in the hydroxy group are more attracted to the keto group which makes the hydroxy group more difficult attacked by H^+. The influence of neighboring groups also causes steric hindrance which affects the esterification reaction (Rosyda *et al*. 2020; Kurniawan *et al*. 2021).

MATERIAL AND METHODS

Materials

The material used in this study was ripe mangosteen purchased at a traditional market in Denpasar. The peels were cut into small pieces and then dried in the open air. After drying, the peels were finely ground to form a powder.

The chemicals used are pro-analytical, such as ethanol, methanol, chloroform, n-hexane, 1,1-diphenyl-2-picrylhydrazyl (DPPH), sodium hydroxide, sodium acetate, boric acid, hydrochloric acid, silica gel GF_{254}, silica gel for columns, acetic anhydrous acid, phytochemical test reagents.

Equipment

The equipment used in this study was a set of reflux instruments, Erlenmeyer, beakers and other glassware, Perkin Elmer FTIR spectrophotometer, Secoman S 1000 UV Vis Spectrophotometer, Buchii rotary vacuum evaporator, LCMS/MS Parkin Elmer.

Procedures

Extraction of Mangosteen Peel

The extraction followed the method of Hyun *et al*. (2006) with slight modifications. 500 g of dried mangosteen peel powder was extracted by maceration with ethanol (4 x 1.5 L) at room temperature for 1 day. The extract obtained was then filtered and the solvent evaporated using a rotary vacuum evaporator. The concentrated ethanol extract was then dissolved with 500 mL of distilled water. The water extract was then fractionated with n-hexane (3 x 500 mL) and chloroform (3 x 500 mL). The fractionated extract was then evaporated. The crude (ethanol), water, n-hexane, and chloroform extracts were then tested for their antioxidant activity.

Phytochemical Test of Mangosteen Peel Ethanol Extract

Phytochemical analysis was performed on the concentrated ethanol extract of mangosteen peel. The secondary metabolites tested included terpenoids, steroids, flavonoids, alkaloids, phenols, tannins, and saponins.

Tests for terpenoids and steroids were carried out with Lieberman Burchad reagent (extract + acetic anhydrous + H_2SO_4). The formation of blue-green color indicates positive steroids, red-purple color indicates positive terpenoids.

The flavonoid test was carried out by the Wilstatter test (extract + metal Mg + concentrated HCl), giving an orange-red color indicating the presence of flavonoids. With Bate Smith-Metcalfe reagent (sample in alcohol + concentrated HCl, heated for 15 minutes), giving a red color indicating the presence of flavonoids.

The alkaloid test was carried out with Wegner, Meyer, and Dragendorff reagents. The presence of flavonoids with the formation of brown, white and red deposits.

Phenol and tannin test, the extract was added with 1% $FeCl_3$ will give a blue to black color indicating the presence of phenol, when then added with concentrated H_2SO_4, a brown precipitate forms indicating the presence of tannins.

Saponin test, the extract in the test tube was added with distilled water and then shaken, the foam was formed, then HCl was added and it turned out that the foam was stable indicating the presence of saponins.

Antioxidant Activity Test

As much as 1 mL of 20 ppm DPPH was put into the cuvette, then incubated for 30 minutes at room temperature. After 30 minutes of incubation, the absorbance was measured with a UV–vis spectrophotometer at a maximum wavelength of 517 nm. As much as 1 mL of crude ethanol extract was put into a cuvette, added 1 mL of DPPH, then vortexed and incubated for 30 minutes, then the absorbance was measured at a maximum wavelength of 517 nm. The same procedure was carried out for the water extract, n-hexane, and chloroform extract. Percent inhibition of anti-radical activity was calculated by the formula:

$I = (Ao - Ae)/Ao \times 100$	……(1)

Where I = Percent Inhibition
Ao = absorbance without extract
Ae = absorbance with extract.

Determination of Total Phenolic Contents

Gallic acid concentrations were made: 100, 125, 150, 175, 200 µg/ml. From each concentration of gallic acid solution, pipet 0.2 mL then add 15.8 mL of distilled water and 1 mL of Folin-Ciocalteu reagent and shake until homogeneous and leave for 8 minutes. Added 3 mL of 10% Na_2CO_3 solution then shaken homogeneously, and then left for 2 hours at room temperature. Measure the absorbance at a maximum absorption wavelength of 765 nm, then create a calibration curve for the relationship between gallic acid concentration (µg/ml) and absorbance. Pipette 0.2 mL of 1 mg/mL mangosteen extract, add 15.8 mL of distilled water and 1 mL of Folin–Ciocalteu reagent then shake. Leave it for 8 minutes then add 3 mL of 10% Na_2CO_3 to the mixture. Leave the solution for 2 hours at room temperature. The absorption was measured using a UV-Vis spectrophotometer at a wavelength of 765 nm, so that the phenol content obtained was obtained as mg gallic acid equivalent/g sample.

Purification and Identification of Xanthone Derivative Active Fractions

The most active extract as antioxidant was purified by column chromatography following the procedure carried out by Hyun *et al*. (2006) using silica gel as the stationary phase and

$CHCl_3$: MeOH as the mobile phase. The extracted column results were then identified for the xanthone derivative using a UV-Vis spectrophotometer with maximum absorption areas of 230 – 245, 250 – 265, 305 – 330, and 340 – 400 nm. To determine the presence of hydroxy groups in xanthone, the extract was identified by a UV-Vis spectrophotometer by adding shear reagents such as NaOH, $AlCl_3$, and $AlCl_3$+HCl. Identification of xanthone derivatives was also carried out using an IR spectrophotometer.

Esterification of Xanthone Derivatives

Xanthone compounds that bind to hydroxy groups were carried out by esterification reactions. Into a 250 mL round bottom flask equipped with a reflux condenser, added xanthone extract (7.4 g), anhydrous acetic acid (26 mmol), and 4 drops of H_2SO_4. The mixture was heated in heating mantle at a temperature of 160-180 ^oC for 1 hour while stirring. The reaction product was cooled to room temperature. The extract obtained was put into a separatory funnel, added 2 mL of 5% Na_2CO_3 followed by the addition of 1 mL of distilled water, then shaken and separated the organic phase. The organic phase obtained was added with anhydrous sodium sulfate. The esterification results were then purified by column chromatography using silica gel as the stationary phase and chloroform: benzene (3:1) as the mobile phase and the antioxidant activity was tested. The results of the esterification reaction were identified by IR spectrophotometer and LCMS/MS.

RESULTS AND DISCUSSION

Mangosteen Peel Extraction Results

Extraction of 500 g of mangosteen peel powder, with a water content of 7.5 %, produced a brown viscous extract weighing 51 g (10.2% yield). The extract was then partitioned to get 0.712 g n-hexane fraction (1.40% yield); 17.785 g chloroform fraction (34.87%); and 30.405 g water fraction (59.62%). The results showed that the most abundant secondary metabolites contained in mangosteen peel extract were polar metabolites. Umami *et al*. (2020) extracted mangosteen peel using ethyl acetate and obtained a yield of 6.69%. Manimekalai *et al*. (2016) extracted the mangosteen peel with several solvents and obtained n-hexane, chloroform, and ethyl acetate fractions with yield of 1; 1.5; 1% respectively,

Phytochemical Test Results of Mangosteen Peel Ethanol Extract

The results of the phytochemical test showed that the ethanol extract of mangosteen peels contains secondary metabolites such as: alkaloids, flavonoids, terpenoids, phenols, and saponins. The results of the Meyer test formed a white precipitate which indicated the presence of alkaloids. The results of the Bate Smith-Metcalfe test showed a change from brown to red indicating the presence of flavonoids. The results with the Lieberman Burchard reagent showed a brown to purple color change indicating the presence of terpenoids, but no blue color was formed so there was no steroid. As a result of the $FeCl_3$ reagent, a color change from brown to black indicated the presence of phenolic compounds, with $FeCl_3$ and H_2SO_4 not forming a brown precipitate indicating the absence of tannin compounds. The addition of distilled water and HCl formed a stable foam which indicated the presence of saponins. Manimekalai *et al*. (2016) conducted a phytochemical test on mangosteen peel and found that the peels contained phenol, flavonoid, and terpenoid. Shafy *et al*. (2019) conducted a phytochemical test on mangosteen peel and found glycosides, phenolics, tannins, resins, flavonoids, alkaloids, terpenoids, and no steroids were found.

Results of the Antioxidant Activity Test of the Partition Result of Mangosteen Fruit Peel

DPPH, a free radical scavenger was applied to test the antioxidant activity. The test results showed that the mangosteen peels have antioxidant activity by reducing the absorbance value of DPPH. The n-hexane fraction was the most active antioxidant with the lowest IC_{50} (114.8 µg/mL), followed by the chloroform fraction (202.59 µg/mL), water (407.36 µg/mL) and ethanol extract (482.79 µg/mL). Zarena and Sanker (2009) reported that mangosteen peel n-hexane fraction has good ability as a scavenger of free radicals with an IC_{50} of 181.21 µg/mL.

The active extract that was carried out by the esterification reaction was the chloroform fraction, because the n-hexane fraction obtained was very small. The ability of antioxidant activity after the esterification reaction has decreased compared to before esterification with IC_{50} of 219.29 µg/mL. Xanthones which have hydroxyl phenol groups are very important as antioxidants because of their ability to reduce their hydroxyl groups. The hydroxyl group can donate its hydrogen free radical and thereby prevent a chain reaction. After xanthone is esterified, the hydroxyl group changes, thereby reducing its ability as a hydrogen radical donor which causes a decrease in antioxidant activity (Jamila *et al*. 2016). The polyphenol structure has stronger antioxidant activity than the monophenol structure. The more hydroxyl groups cause the ability as an antioxidant to increase (Suttirak, W. and Manurakchinakorn, 2014). The hydroxyl group in α-mangosteen at positions C_3 and C_6 plays a very important role in its ability as an antioxidant. The acetylation reaction of the hydroxyl groups at C_3 and C_6 can reduce the ability of antioxidant activity (Tran *et al*. 2021). Antioxidant activity data is shown in Table 1.

Results of Total Phenolic Content, FTIR, and UV-Vis Analysis of the Chloroform Fraction of Mangosteen Peel Extract.

The total phenolic content of the chloroform fraction was 77939.94 mg GAE/100 mL. Zarena and Sanker (2009) revealed that the total phenolic content of methanol and ethanol extracts of mangosteen peels were 315.7 ± 0.01 and 431.0 ± 0.07 mg GAE/g respectively. Ibrahim *et al*. (2015) also reported that the total phenolic content of the mangosteen peel methanol extract was 0.0274 mg GAE/g. Meanwhile, Zarena and Sanker (2019) stated that the total phenolic content of mangosteen peel ethyl acetate, n-hexane, and acetone extracts were successively 269.9 ± 0.02, 135.9±0.03, and 205.2±0.02 mg GAE/g.

The results of the FTIR spectral analysis of the chloroform fraction showed that there was a peak at 3419.79 cm^{-1} indicating the OH group, this was supported by the appearance of a peak at 1288.45 cm^{-1} which was the C-O group. The peak of 2968.45 cm^{-1} was a C-H sp^3 group, supported by a peak of 1463.97 cm^{-1} which was a CH_3 group. The peak at 1631.78 cm^{-1} indicated the presence of aromatic C=C, supported by the peak of 839.03 which was an aromatic C-H group.

Table 1 Antioxidant activity test of mangosteen peel fractionation results

Fractions/Extract	Concentration (µg/mL)	Absorbance	% Inhibition	IC_{50}
DPPH	20	0.366	0	
n-hexane	20 40 60 80	0.224 0.219 0.211 0.196	38.798 40.164 42.349 46.448	Y=0.125x + 35.65; R^2 = 0.942 IC_{50} = 114.8 µg/mL
Chloroform	20 40 60 80	0.222 0.217 0.213 0.209	39.344 40.710 41.803 42.896	Y=0.058x + 38.25; R^2 = 0.996 IC_{50} = 202.59 µg/mL
Water	20 40 60 80	0.353 0.344 0.334 0.331	3.552 6.011 8.743 9.563	Y=0.121x + 0.710; R^2 = 0.964 IC_{50} = 407.36 µg/mL
Ethanol	20 40 60 80	0.356 0.350 0.342 0.335	2.732 4.372 6.557 8.470	Y=0.103x + 0.273; R^2= 0.994 IC_{50} = 482.79 µg/mL
Esterifikasi Result	20 40 60 80	0.343 0.332 0.303 0.299	6.284 9.290 17.213 18.303	Y=0.2199x + 1.778; R^2 = 0.9252 IC_{50} = 219.29 µg/mL

The results of UV-Vis analysis of the chloroform fraction showed two absorption peaks at 224.50 and 316 nm. With the addition of NaOH showed a bathochromic shift. Absorption peaks appear at 242 nm (shifted +17.5 nm), and 372 nm (+56 nm). This indicates the presence of free OH groups in xanthone compounds. The addition of $AlCl_3$ showed a bathochromic shift. Absorption peaks appear at 236 nm region (+11.5 nm), and 359 nm (+ 43 nm). This indicates the presence of C=O and OH groups in adjacent positions and dihydroxy groups in the ortho position in xanthone compounds. The addition of $AlCl_3$ and HCl showed a bathochromic shift. Peaks appear at 237 nm (+12.5 nm), and 358 nm (+42 nm). There was no significant peak difference with the $AlCl_3$. The spectra of UV-Vis analysis results are shown in Figure 1.

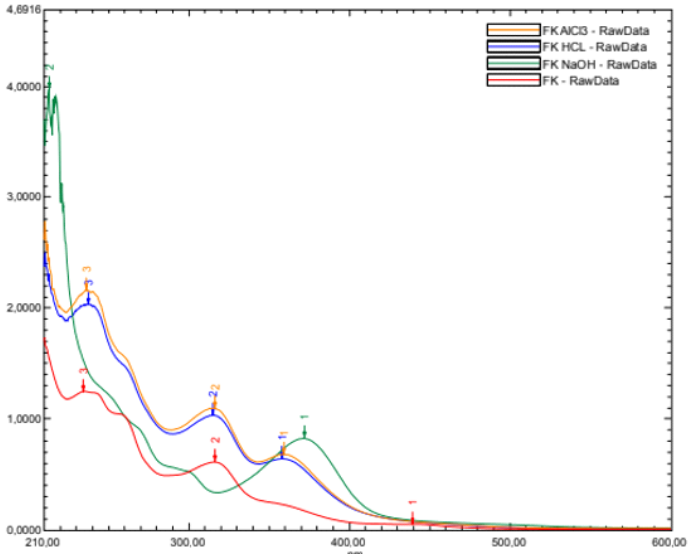

Fig. 1 Spectra UV-Vis of the chloroform fraction with the addition of NaOH, $AlCl_3$, $AlCl_3$ + HCl shift reagents

Results of the Esterification Reaction of the Chloroform Fraction of Mangosteen Peel Extract

The results of the esterification reaction after column chromatography were obtained 4 fractions, including fraction 1 which was dark brown with a weight of 0.370 g; fraction 2 was light brown with a weight of 0.375 g; fraction 3 was yellow with a weight of 0.035g; and fraction 4 was light yellow with a weight of 0.028g. Fraction 1 which gave the brownest colour was identified by FTIR and LCMS/MS spectra. FTIR results showed an absorption peak at 3658.96 cm^{-1} indicating the presence of OH groups. The peaks of 2293.52 cm^{-1} and 2879.78 cm^{-1} indicate the C-H sp^3 group, this was supported by the peaks of 1485.19 cm^{-1} and 1386.82 cm^{-1} which were the CH_3 and CH_2 groups. The peak at 1786.08 cm^{-1} indicates the C=O group. The peak of 1298.09 cm^{-1} indicates the C-O ester group.

The results of the LCMS/MS analysis obtained several compounds that could be identified, such as: manopiranoside (4-hydroxy-2-methoxyphenyl α-D-mannopyranoside) (retens ion time, tR 6.55); α-mangosteen (7-methoxy-2,8-bis-(3-methyl-2-bute-1-yl)-9-oxo-9H-xanthena-1,3,6-triolate); 1,3,6-triolate-α-mangosteen (tR 8.04); α-mangosteen (1,3,6-Trihydroxy-7-methoxy-2,8-bis(3-methyl-2-buten-1-yl)-9H-xanthen-9-one); 1,3,6-trihydroxy-α-mangosteen (tR 10.46). The esterification reaction shows that xanthone can undergo an esterification reaction to produce xanthone monoacetate (1,6-dihydroxy-7-methoxy-2,8-bis(3-methyl-2-buten-1-yl)-9-oxo-9H-xanthen-3-yl acetate; 3-O-acetyl- α-mangosteen (tR 11.384); xanthone diacetate (1-hydroxy-7-methoxy-2,8-bis(3-methyl-2-buten-1-yl)-9-oxo-9H-xanthene-3,6 -diyl diacetate; 3,6-di-O-acetyl-α-mangosteen (tR 13,866 and 15,8); xanthone triacetate (7-methoxy-2,8-bis(3-methyl-2-buten-1-il)-9-oxo-9H-xanthene-1,3,9-triyl triacetate; 3,6,7-tri-O-acetyl-α-mangos-teen (tR 12.832 and 14.723).

The UPLC spectra is shown in Figure 2 and the MS spectra is shown in Figure 3. Abate *et al.* (2022) identified xanthone

derivative in the chloroform fraction of mangosteen peel extract obtained mangostanol, garcinon, gamma mangosteen, gudraxanton, 8-deoxygartanin, garsinon, and beta mangosteen. Li *et al*. (2019) identified xanthone derivative compounds in the ethanol extract of mangosteen peels and found several compounds such as garsicon, isomangosteen, α-mangosteen, γ-mangosteen, smeatxanthon. Alfa mangosteen has a good potential in preventing skin damage due to exposure to Ultra Violet B (UV B) rays, treating Alzheimer's disease, schizophrenia, anti-depression, antioxidant, anti-diabetic, anti-inflammatory, and anti-obesity (Rizaldy *et al*. 2021; Rohman *et al*. 2020; Cruz, 2015). 3,6-di-O-acetyl-α-mangosteen is toxic to HT-29 colon cancer cells (Ren *et al*. 2011). 3,6-di-O-acetyl-α-mangosteen has stronger anticancer and antidiabetic activity than α-mangosteen (Umami *et al*. 2020).

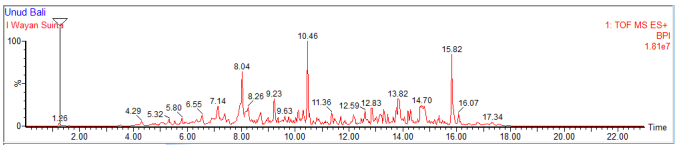

Fig. 2 UPLC spectra of esterified mangosteen peel extract in the chloroform fraction

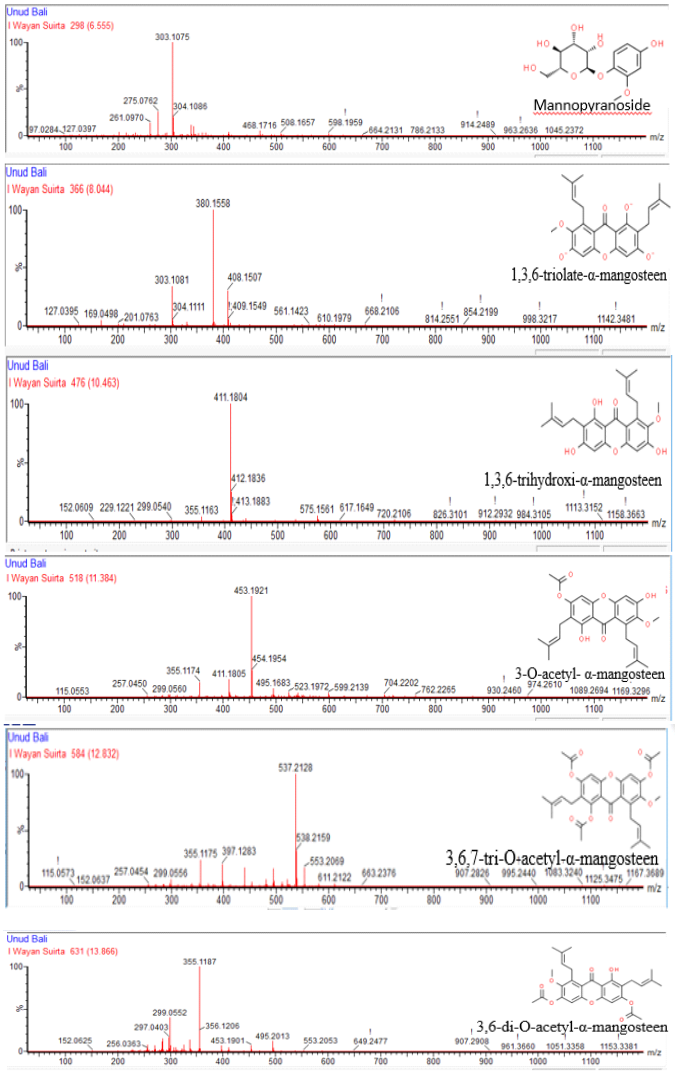

Fig. 3 MS spectra of esterified mangosteen peel extract in the chloroform fraction

CONCLUSIONS

Mangosteen peel fractionation results have a stronger antioxidant activity than crude ethanol extract. The chloroform fraction extract had stronger antioxidant activity than the esterified product. Compounds that can be identified from the esterification reaction of the chloroform fraction of mangosteen peel are manopiranoside; 1,3,6-triolate-α-mangosteen; 1,3,6-trihydroxy-α-mangosteen; 3-O-acetyl- α-mangosteen; 3,6-di-O-acetyl-α-mangosteen; and 3,6,7-tri-O-acetyl-α-mangosteen.

It is necessary to purify the esterification results in order to obtain a pure mangosteen ester and it is also necessary to test its bioactive activity.

Acknowledgments

The author would like to thank Udayana University for funding this research through the PNBP Fund with the agreement number: B/78.345/UN14.4.A/PT.01.03/2022

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