

VOLUME 14 NO. 1

JUNE 2017

ISSN 1675-7009

SCIENTIFIC RESEARCH JOURNAL

Institute of Research Management and Innovation

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Rabuyah Ni, Mohammad Isa Mohamadin, Vivien Jong Yi Mian

Bioadsorption of Multiple Heavy Metal Ions by *Rhizophora Apiculata* sp. and *Elaeis Guineensis* sp.

M.B. Nicodemus Ujih, Mohammad Isa Mohamadin, Millaa-Armila Asli, Bebe Norlita Mohamed

Microwave Assisted Synthesis and Characterisation of Trinuclear Zinc(II) Schiff Base Complexes Derived from *m*-phenylenediamine and Salicylaldehyde

Karimah Kassim, Muhamad Azwan Hamali

Identification of Pathogenic Bacteria Isolated from Raw and After Sand Filtration Water at Lubok Buntar Water Treatment Plant

Nur Hafizah Zakaria, Husnul Azan Tajarudin, Mohd Sharizal Mohd Sapongi Mohamad Fared Murshed

Analysing Population Structure of *Elaeis Oleifera* Germplasm using Model-Based Approach Programme STRUCTURE

Wan Nurhayati Wan Hanafi, Farida Zuraina Mohd Yusof, Rajinder Singh, Ahmad Kushairi Din, Rajanaidu Nookiah, Maizura Ithnin

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Scientific Research Journal is a journal by Institute of Research Management & Innovation (IRMI), Universiti Teknologi MARA, Bangunan Wawasan, Level 3, 40450 Shah Alam, Selangor Darul Ehsan, Malaysia. E-mail: irmiuitm@salam.uitm.edu.my

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SCIENTIFIC RESEARCH JOURNAL

Institute of Research Management & Innovation (IRMI)

Vol. 14 No. 1

June 2017

ISSN 1675-7009

- 1. Synthesis, Spectral Characterisation and Antimicrobial Properties of Cu(II) and Fe(II) Complexes with Xanthone** 1
Rabuyah Ni
Mohammad Isa Mohamadin
Vivien Jong Yi Mian
- 2. Bioadsorption of Multiple Heavy Metal Ions by *Rhizophora Apiculate sp.* and *Elaeisis Guineensis sp.*** 15
M.B. Nicodemus Ujih
Mohammad Isa Mohamadin
Millaa-Armila Asli
Bebe Norlita Mohamed
- 3. Microwave Assisted Synthesis and Characterisation of Trinuclear Zinc(II) Schiff Base Complexes Derived from *m*-phenylenediamine and Salicylaldehyde** 29
Karimah Kassim
Muhamad Azwan Hamali

- 4. Identification of Pathogenic Bacteria Isolated from Raw and After Sand Filtration Water at Lubok Buntar Water Treatment Plant** 41
Nur Hafizah Zakaria
Husnul Azan Tajarudin
Mohd Sharizal Mohd Sapingi
Mohamad Fared Murshed
- 5. Analysing Population Structure of *Elaeis Oleifera* Germplasm using Model-Based Approach Programme STRUCTURE** 53
Wan Nurhayati Wan Hanafi
Farida Zuraina Mohd Yusof
Rajinder Singh
Ahmad Kushairi Din
Rajanaidu Nookiah
Maizura Ithnin

Synthesis, Spectral Characterisation and Antimicrobial Properties of Cu(II) and Fe(II) Complexes with Xanthone

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Accepted: 31 May 2017

Received: 26 January 2017

ABSTRACT

The new complexes [CuL₂(H₂O)₂] and [FeL₂(CH₃O)₂] in which L = β-mangostin were synthesised and characterised. The structure of the ligand, β-mangostin was confirmed using NMR and the purity of ligand was determined using HPLC. Both Cu(II) and Fe(II) complexes were prepared by reaction between the ligand and the acetate of the metals in one-step reaction. The synthesised compounds have been characterised using UV-Visible, FTIR and CHNS analyser. Ligand and metal complexes were tested against bacteria to assess on their antimicrobial properties using Minimum Inhibitory Concentrations (MICs) and Minimum Bactericidal Concentrations (MBCs) method. The elemental analysis and spectra data suggested octahedral geometry for both Cu(II) and Fe(II) complexes. The IR spectroscopy revealed that the chelation of Cu²⁺ and Fe²⁺ ion occurred with hydroxyl and carbonyl group at C₉ and C₁ respectively of β-mangostin. Both Cu(II) and Fe(II) complexes showed stronger inhibition against Pseudomonas aeruginosa, Proteus vulgaris, Klebsiella pneumoniae and Salmonella pneumonia at concentration 900 mg/mL and Escherichia coli at 450 mg/mL compared to the ligand itself.

Keywords: β-mangostin, copper(II) complex, iron(II) complex, antimicrobial, xanthenes

INTRODUCTION

Xanthenes are naturally oxygenated heterocycles with γ -pyron moiety fused with two benzene rings (Figure 1). There has been strong interest of this class of compounds due to their unique chemical structures containing different types of substituent in different positions, which leads to a large variety of pharmacological activities [1, 2]. They have remarkable biological and pharmacological properties such as antibacterial, antioxidant, antiviral, anticancer, anti-inflammatory and antifungal. Consequently, researchers tend to isolate xanthone derivatives from natural product and also tend to synthesise these compounds as novel drug candidates [3]. The major secondary metabolites that can be isolated from *Garcinia mangostana* are α -mangostin, β -mangostin, and γ -mangostin containing xanthone scaffold [4]. Simultaneously, synthetic and medicinal chemistry studies of xanthone derivatives have been performed [5]. In contrast, there are only a few reports that deal with complexation of metal ions with xanthone derivatives.

Coumarins and flavonoid as secondary metabolites have attracted more interest among researchers to check whether its metal complexes are more biologically effective than the ligand itself. Quercetin (Figure 2) and Morin (Figure 3) are examples of flavonoids forming metal complexes that have better antibacterial and cytotoxic properties as compared to its ligand. The metal complexes were formed via chelation of hydroxyl and carbonyl group of the ligands. The location of chelation is influenced by the anion used in metal, the ratio of starting material and pH value. Farhan [6] proposed that metal chelation with hydroxyl and carbonyl are at C₅ and C₄ respectively. The reaction condition was in the presence of ammonia at pH 7-8 and molar ratio 1:2 of copper(II) chloride and morin in ethanolic solution. While, Panhwar *et al.* [7] suggested that chelation with hydroxyl and carbonyl group at C₃ and C₄ respectively in equal molar of copper(II) sulphate and morin in methanol. Besides, Bukhari *et al.*, [8] proposed chelation also occurred in copper(II)-quercetin complex utilising 1:2 proportion of copper(II) sulphate and quercetin in methanol.

Up to this point, complexation having xanthenes as a ligand only involves synthetic xanthenes. The synthetic xanthone was prepared via reaction of dihydroxyxanthone with crown ether [9] and piperidinyl [10] respectively. The macrostructure of crown ether helps to stabilise the

Cu(II) complexes formed whereas piperidinyl structure contributes basicity properties to encourage formation of Cu(II) and Zn(II) complexes with simple oxygenated xanthones (Figure 4 and Figure 5).

In this work, the natural occurring xanthone, β -mangostin from *Garcinia mangostana* were used as ligand to synthesise novel antibacterial agents through complexation process involving copper and iron. Subsequently, β -mangostin, Cu(II) and Fe(II) complexes were characterised and tested for antimicrobial properties.

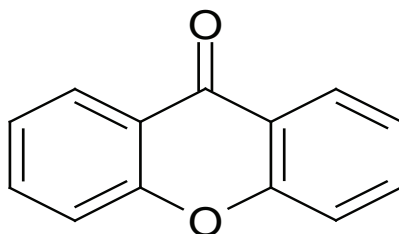


Figure 1: Xanthone

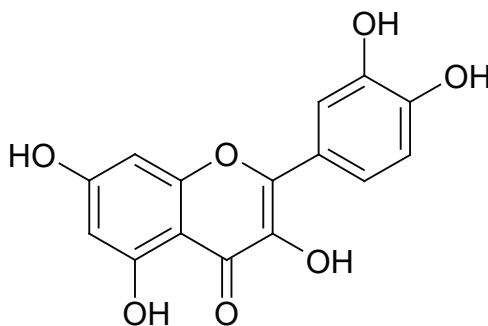


Figure 2: Quercetin

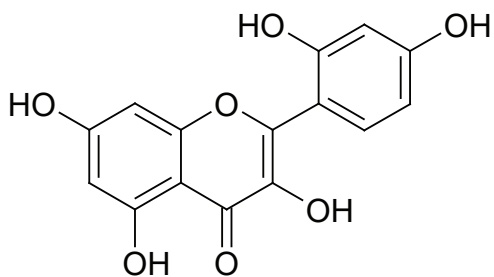


Figure 3: Morin

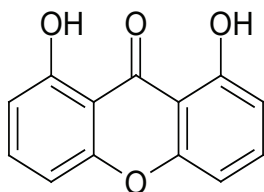


Figure 4: 1,8-dihydroxyxanthone

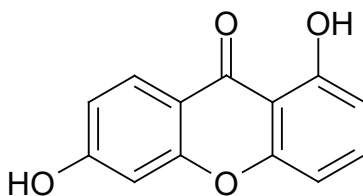


Figure 5: 1,6-dihydroxyxanthone

METHOD

Materials

All reagents and solvents used were analytical grade. Thin Layer Chromatography (TLC) analysis was performed using silica gel 60 F₂₅₄ (Merck), liquid vacuum column chromatography analysis was carried out on silica gel 60 F₂₅₄ (Merck) and gravity column chromatography using silica gel 60 (0.040 – 0.063 mm) (Merck). Cu(II) acetate and Fe(II) acetate were purchased from R & M whereas, nutrient agar and nutrient broth were brought from Bendosen.

Extraction, Isolation and Purification of β -mangostin

The barks sample of *Garcinia mangostana* was collected from Sarawak Forestry Department. The herbarium voucher specimens were kept at Universiti Teknologi MARA Sarawak. The stem barks sample was cut to smaller pieces and air dried at room temperature for few weeks. Then, it was grinded using heavy duty grinder at Sarawak Forestry Department. The air-dried powder of stem barks sample was soaked with chloroform for 48 hours at room temperature. Evaporation of solvents yielded 31.8 g of residues. The crude chloroform extract was isolated with hexane/chloroform, chloroform/ethyl acetate and ethyl acetate/methanol using Liquid Vacuum Chromatography to afford 27 fractions. Fractions 11 until 13 were further isolated using gravity column chromatography, eluted with hexane/chloroform and followed by chloroform/methanol solvent system gradient. Fractions which gave similar spots and same R_f values on the TLC plates of β -mangostin were combined. The purity of β -mangostin was determined using Agilent HPLC Series 1260 Infinity.

Preparation of the Metal Complexes

The copper(II) complex was prepared by the addition of ligand to an ethanolic solution of copper(II) acetate in 1 : 2 ratio. Crystal ligand was formed when the procedure was repeated with iron(II) acetate. Therefore,

β -mangostin complex with iron(II) was prepared by 1 : 2 molar reaction of ligand and iron(II) acetate using methanol in one-pot reaction as describe by Bukhari *et al.* [8]. The resulting complexes were characterised using spectroscopic techniques.

Instrumentation

Elemental analysis was performed using Elemental analyser, vario MICRO cube. The electronic spectra determinations were performed using Perkin-Elmer, Model Lambda 25. Infrared spectra were recorded in 4000-400 cm^{-1} by Perkin-Elmer, Frontier FTIR spectrophotometer in KBr pellets. ^1H and ^{13}C NMR measurements were carried out by Bruker at 400 MHz. HPLC analysis for β -mangostin was performed by Agilent G1316A (150 mm x 4.6 mm, 5 μm) column, the mobile phase was acetonitrile/water (80:20, v/v) mixture at room temperature with one mL min^{-1} flow rate and 5 μl injection loop. UV detector of HPLC was set at 320 nm since this wavelength was a selective wavelength for xanthone scaffold detection and only few other compounds can be ingested at this wavelength [11].

Antimicrobial Properties

β -mangostin, Cu(II) and Fe(II) complexes were evaluated for antimicrobial properties against five gram negative bacteria strains. Unlike gram positive bacteria, Gram-negative bacteria are more resistant against antibodies and most antibiotics because of their impermeable cell wall. Bacteria used were *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Klebsiella pneumonia* and *Salmonella pneumoniae*. Antimicrobial activity was performed using Minimum Inhibitory Concentrations (MICs) and Minimum Bactericidal Concentrations (MBCs) method. Streptomycin sulphate was used as the positive control for antimicrobial test.

RESULT AND DISCUSSION

Structural Elucidation of β -mangostin

The ligand, β -mangostin was isolated as fine yellow needle with melting point of 174 – 175°C (Lit. 175 – 176°C, [12]). β -mangostin was obtained via column chromatography and eluted with chloroform hexane mixture in 9:1 ratio and showed good agreement with Gopalakrishnan *et al.*, [13]. Figure 6 shows the structure of β -mangostin with molecular formula of $C_{25}H_{28}O_6$. Meanwhile, the IR spectrum showed the presence of hydroxyl group at 3399 cm^{-1} and chelated carbonyl group at 1647 cm^{-1} . The absorption bands are situated at 1600, 1571, 1458 and 1278 cm^{-1} and are related to carbon vibration in benzene rings. The purity of isolated β -mangostin determined from HPLC analysis was 98%. Table 1 represents 1H -NMR, ^{13}C -NMR and DEPT of β -mangostin. 1H -NMR and ^{13}C -NMR result was compared with reported data by Sen *et al.* [14], Al-Massarani *et al.*, [15] and Syam *et al.* [16] before identified as β -mangostin.

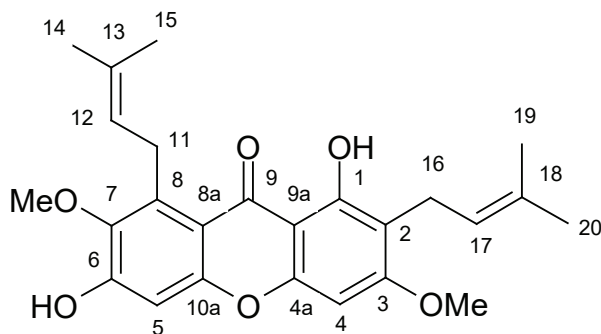


Figure 6: β -mangostin

Table 1: $^1\text{H-NMR}$, $^{13}\text{C-NMR}$ and DEPT of β -mangostin in acetone- d_6

Carbon	δ_{C}	δ_{H}	DEPT
1	159.63	13.66 (1H, s, OH)	C
2	110.94	-	C
3	163.5	-	C
4	90.00	6.53 (1H, s)	CH
4a	155.31	-	C
5	101.83	6.87 (1H, s)	CH
6	156.69	-	C
7	143.70	-	C
8	137.25	-	C
8a	111.18	-	C
9	182.06	-	C
9a	103.27	-	C
10a	155.42	-	C
11	26.00	4.15 (2H, d, $J = 6.6$ Hz)	CH_2
12	122.41	5.22 (2H, t, $J = 7.3$ Hz)	CH
13	130.66	-	C
14	25.05	1.67 (3H, s)	CH_3
15	16.97	1.84 (3H, s)	CH_3
16	21.02	3.34(2H, d, $J = 7.2$ Hz)	CH_2
17	123.78	5.29 (2H, t, $J = 6.7$ Hz)	CH
18	130.62	-	C
19	25.00	1.65 (3H, s)	CH_3
20	17.40	1.79 (3H, s)	CH_3
7-OMe	60.46	3.99 (3H, s)	CH_3
3-OMe	55.67	3.81 (3H, s)	CH_3

Physical Properties of Metal Complexes

The metal complexes $[\text{CuL}_2(\text{H}_2\text{O})_2]$ and $[\text{FeL}_2(\text{CH}_3\text{O})_2]$ appeared as green and dark brown complex respectively. They are stable at room temperature. The percent yield of Cu(II) and iron(II) were 72% and 83% respectively. Elemental analysis suggested the ratio between metal to ligand was 1:2. Table 2 displays the actual and experimental values of carbon and hydrogen for both metal complexes.

Table 2: Elemental analysis of copper (II) and iron (II) complexes

Metal complexes	Theoretical value		Experimental result	
	C (%)	H (%)	C (%)	H (%)
$\text{CuL}_2(\text{H}_2\text{O})_2$	62.6	5.4	63.4	6.1
$\text{FeL}_2(\text{CH}_3\text{O})_2$	64.5	5.8	64.5	6.4

Spectroscopic Study of Metal Complexes

IR spectra of β -mangostin showed the shifting of $\nu(\text{C}=\text{O})$ peak from 1647cm^{-1} to 1615 and 1610cm^{-1} for Cu(II) and Fe(II) respectively. The carbonyl frequency in the ligand is shifted to lower frequency. Thus, this showed that the electron density in the carbonyl was slightly decreased probably due to back bonding process. It was in a good agreement with Shen *et al.*, [9] and Wang *et al.*, [10]. Moreover, a broad band was observed at 3438 cm^{-1} and 3429 cm^{-1} for Cu (II) and Fe (II) complex respectively suggesting that the oxygen from hydroxyl also involved in coordination bond with the Cu^{2+} and Fe^{2+} ion.

Another significant difference between the ligand and its metal complex was observed from UV spectrum. The UV spectrum of copper(II) complex showed a broad band at 22000cm^{-1} (450 nm) which presumably corresponded to $d-d$ transition with octahedral arrangement as described by Yousef *et al.* [17]. While, Iron(II) complex has a broad band at 19157cm^{-1} (522 nm) [18] indicating an octahedral environment to the surrounding metal. The chelation of Cu(II)- β -mangostin and Fe(II)- β -mangostin complexes with bidentate ligand occurred with hydroxyl and carbonyl group at C_9 and C_1 respectively. The proposed structures of the complexes

are shown in Figure 7. The chelation formation in this study was similar to Farhan [6](2013) and Wang *et al.* [10].

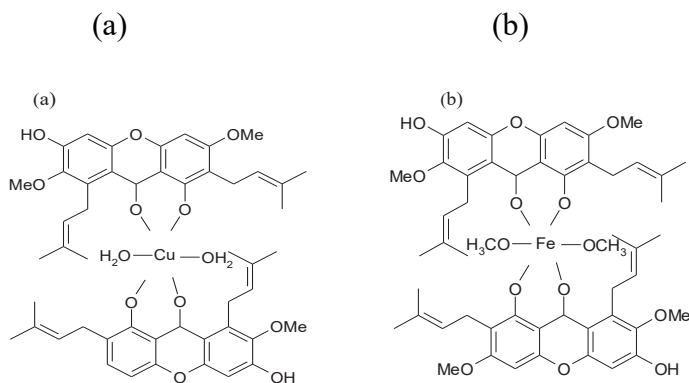


Figure 7: Proposed structure for (a) Cu(II) and (b) Fe(II) complexes

Antimicrobial Activity

Table 3 illustrates the classification of antimicrobial properties adopted from Pessini *et al.* [19]. The evaluation of antibacterial against bacteria is given in Table 4. β -mangostin was inactive against five Gram-negative bacteria strains. However, both metal complexes exhibited moderate inhibition towards *Escherichia coli* and weak inhibition to other bacteria.

Table 3: Classification of antimicrobial properties [19]

Antibacterial properties	Range (ppm)
Strong inhibition	< 100
Moderate inhibition	100 - 500
Weak inhibition	500 - 1000
Inactive inhibition	>1000

Table 4: MICs (MBCs) of ligand and metal complexes against range of microorganisms

Microorganisms	MIC (MBC) ppm		
	β -mangostin	Cu- β -mangostin complex	Fe- β -mangostin complex
<i>Pseudomonas aeruginosa</i>	1800	900	900
<i>Protes vulgaris</i>	1800	900	900
<i>Klebsiella pneumonia</i>	1800	900	900
<i>Salmonella pneumoniae</i>	1800	900	900
<i>Escherichia coli</i>	1800	450	450

CONCLUSION

Two new metal complexes containing copper and iron were successfully synthesized with general formula of $[\text{CuL}_2(\text{H}_2\text{O})_2]$ and $[\text{FeL}_2(\text{CH}_3\text{O})_2]$. The elemental analysis and spectra data suggested the octahedral geometry for both Cu(II) and Fe(II) complexes. The IR spectroscopy showed that the oxygen of the carbonyl and hydroxyl of β -mangostin formed a coordination bond with Cu^{2+} and Fe^{2+} ion. The newly synthesized compounds, Cu(II) and Fe(II) complexes exhibited better activity towards antimicrobial than ligand itself, indicating that it has a good potential as bactericide.

ACKNOWLEDGEMENT

The authors wish to thank Universiti Teknologi MARA (UiTM) for the facilities and to Ministry of Higher Education for financial support through Fundamental Research Grant Scheme (FRGS) grant (FRGS/1/2014/ST01/UiTM/02/3).

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