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Research Article

Complex Compound with Transitional Metal of *Akway* Bark (*Drimys piperita* Hook F.) as Low Molecular Weight Scavenging Antioxidant: A Computational Study

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ABSTRACT

Akway (*Drimys piperita* Hook f.) was known as an endogenous plant of Indonesia. This plant was investigated as a free radical scavenger based on paramagnetic properties. This study aimed to identify the bioactive compound and the role of Fe metals ions to enhance the free radical scavenger capacity as Low molecular weight antioxidant (LWMA) of *akway*. This study was designed by ultra-performance liquid chromatography (UPLC) coupled with ultra-high-resolution time of flight-mass spectrometry detector (TOF-MS), docking (Pyrex and Discovery Studio 2016 Client) and pharmacokinetic properties prediction (SwissADME). UPLC-TOF-MS analysis showed that herbal *akway* bark has five molecular formula ($C_4H_3N_{10}O_2^{1-}$, $C_{14}H_{19}N_4O_9^{1-}$, $C_4H_7N_6O_5^{1-}$, $C_{15}H_{28}NO_3^{1+}$, and $C_{23}H_{32}NO_7^{1+}$). The docking was illustrated the complex binding *akway* formula with Fe and its role as a metal donor and metal acceptor. It also confirmed on pharmacokinetics properties prediction which molecular compounds of *akway* have aqueous solubility. It meant the herbal *akway* bark complexed to Fe could be a low molecular weight antioxidant and it could be escalated free radical scavenger capacity.

Keywords: Akway, Antioxidant, Endogenous plant, Herbal medicine, Metal acceptor, Metal donor, Molecular formula

Introduction

A free radical scavenger or antioxidant is a molecule adequate for decreasing or inhibiting the other molecule's oxidation. Oxidation transfer electron from a substance to an agent of oxidation [1]. At the same time, free-radicals are produced subsequently start chain reactions to decay the animal cells. Antioxidants have delayed this reaction by eliminating free radical agents and inhibiting other oxidation reactions by oxidizing themselves [2, 3]. Antioxidants are compounds with various molecular and chemical structures and are either lipid (hydrophobic) or water-soluble (hydrophilic). They are either synthesized within the human body or are admitted within food and beverage [4].

Akway (*Drimys piperita* Hook f.) is a woody plant that contains aromatic compounds. This plant is originated from Pegunungan Arfak District, West Papua, Indonesia. *Akway* bark was locally used Sougb tribe to boost vitality by boiling the bark into the water and drink it as a herbal beverage [5, 6]. Based on previous research on phytochemical screening, extracts of *akway* contained several bioactive compounds such as alkaloids, flavonoids, glycoside, tannins, and saponins [7]. The preliminary research was done to investigate

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the paramagnetic properties of *akway* as a free radical scavenger. It was showed ease of DPPH free radical activity following an addition of *akway* bark by electron spin resonance (ESR) analysis. Complex *akway*-DPPH (as free radical agent) compared to DPPH indicated a decrease in the resonance curve. *Akway* bark as an herbal medicine was found could be a radical scavenger that reduces unpaired DPPH electron [6].

Therefore, identifying *akway*'s small molecules is important for continuing the bioinformatics study and their effects as antioxidants or free radical scavengers. Under these conditions, ultra-performance liquid chromatography (UPLC) coupled with time-of-flight mass spectrometry (Q-TOF-MS/MS) accommodates appropriate structural information about the bioactive compounds for the separation and identification of complex mixtures [8, 9, 10].

Low molecular weight antioxidant (LWMA) complex is an active compound in herbal medicine with the role as a radical scavenger. It is known in bioinorganic chemistry, which contained metal ions such as Fe, Cu, Zn, and Mn and promised pharmaceutical agents. In the complex compound of plant, LWMA is free from a physical and chemical bond with other macromolecules [11, 12, 13]. The LMWA either bond as a part of endogenic enzymes in cellular metabolism or LMWA themselves by other protein components containing transition metal. Side by protein, non-nutrient like phenolic compounds (flavonoid, alkaloid, phenolic acid, and lignans) could regulate the free radicals by inhibiting it from catching in Haber-Weiss reaction [11, 14, 15].

Research related to *akway* has not been completed. Bioinformatics study becomes the base of this research to identify the bioactive compound of *akway* (*D. piperita* Hook f.) and the role of Fe metals ions to enhance the free radical scavenger capacity of *akway*.

Material and Methods

Preparation of Akway bark

Fresh harvested *Akway* (*D. piperita* Hook f.) bark samples were collected from Pegunungan Arfak district, Manokwari, West Papua, Indonesia. It was air-dried at room temperature (25°C) for 24h. After that, 1000 g of *akway* bark was milled to form a powder. The powder was then boiled to 100°C for 15 minutes using water at the ratio of solid : water at 1 : 5. The suspension was sonicated for 30 min and freeze-dried, then stored in the freezer.

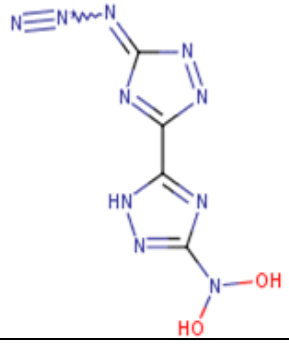
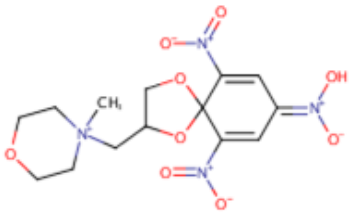
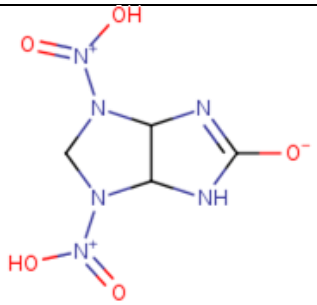
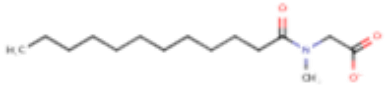
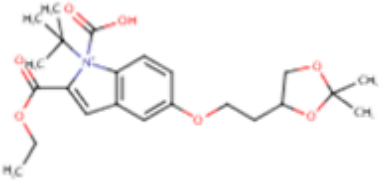
Identify of bioactive compound

An ultra-performance liquid chromatography (UPLC) coupled with ultra-high-resolution time of flight-mass spectrometry detector (TOF-MS) (Eppendorf, Jerman) assay was conducted for the identification of bioactive compound which contained on freeze-dried suspension [16]. Chromatographic separations were performed with mobile phase RSLC 120 C18 (2.2 µm; 120 Å 2.1 × 100 mm, Eppendorf, Jerman). The pump was associated with a gradient binary solvent system: Methanol 10 % with 5 mM ammonium acetate (A) and Methanol with 5 mM ammonium acetate (B). The mobile phase was arranged consecutively in a linear gradient as follows: 0-1 min, 99% A and 1% B; 3 min, 61% A and 39% B; 14-16 min, 1% A and 99% B; and 16.1-20 min, 99% A and 1% B. The ionization source was performed with electrospray ionization (ESI) to acquire mass spectra and scanning range 50-1000 m/z in positive and negative modes. UPLC-TOF-MS has obtained the molecular formula and their mass-to-charge ration (m/z) of *akway* bark.

Computational modeling

Prediction of metal-compound interaction is essential for the success of computational approaches. Molecular docking was well known as computational modeling that aims to predict the demanded orientation of a ligand to its receptor when these are bind to each component to establish a stable complex material [17]. The molecular formula of *akway* bark was confirmed to the PubChem database and was found the 2D structure (Table 1). It was docked with the Fe molecule (CID: 27284) to evaluate how the metal transition was to enhance the antioxidant properties of *akway* bark. Docking site and conformational properties were analyzed using Pyrex and Discovery Studio 2016 Client [18, 19]. Docking was run by entering the molecular formula of *akway* bark and Fe molecule to Pyrex. Subsequently, it was analyzed by Discovery Studio 2016 Client to comprehend the molecular structure, binding affinity, and prove the role of Fe molecule to *akway* bark component as low molecular weight antioxidant. The docking process was well done by AutoDock Vina using the different vina search box (Table 1).

Table 1. The molecular formula of *akway* bark by UPLC-TOF-MS confirmed to PubChem

No.	Retention Time (min)	Identified Molecular Formula	m/z	Intensity (a.u.)	2D Structure	PubChem CID
1.	1.21	$C_4H_3N_{10}O_2^{1-}$	223.0446	2.9×10^4		136877171
2.	1.34	$C_{14}H_{19}N_4O_9^{1-}$	387.1158	3.1×10^4		78168764
3.	1.34	$C_4H_7N_6O_5^{1-}$	219.0483	4.1×10^4		101674670
4.	7.07	$C_{15}H_{28}NO_3^{1+}$	270.2064	2.0×10^5		171502
5.	10.3	$C_{23}H_{32}NO_7^{1+}$	434.2173	2.3×10^4		91539162

It was enhanced to virtual-screen the optimized docking site of Fe binds to *akway* bark compounds [20]. Then, the pharmacokinetics properties, included physicochemical and water solubility of *akway* bark's molecular formulas, were analyzed using SwissADME (http://www.swissadme.ch/) [21].

Results and Discussions

Akway bark is a potential source of natural, free radical scavenger, as has been done in previous research. As a result, java plum (*Syzygium cumini*) and mangosteen (*Garcinia mangostana* Linn.) rind extract were unambi-guously identified and assigned as antioxidant sources. Java plum extract was contained a metal transition complex with anthocyanin, while mangosteen rind extract was included in xanthone which showed a declining resonance curve of electron spin resonance. Additionally, free radical java plum and mangosteen rind extract intensity decreased [13, 22]. UPLC-TOF-MS has been validated and evolved as a current chromatographic analysis to identify and determine substances in complex ma-

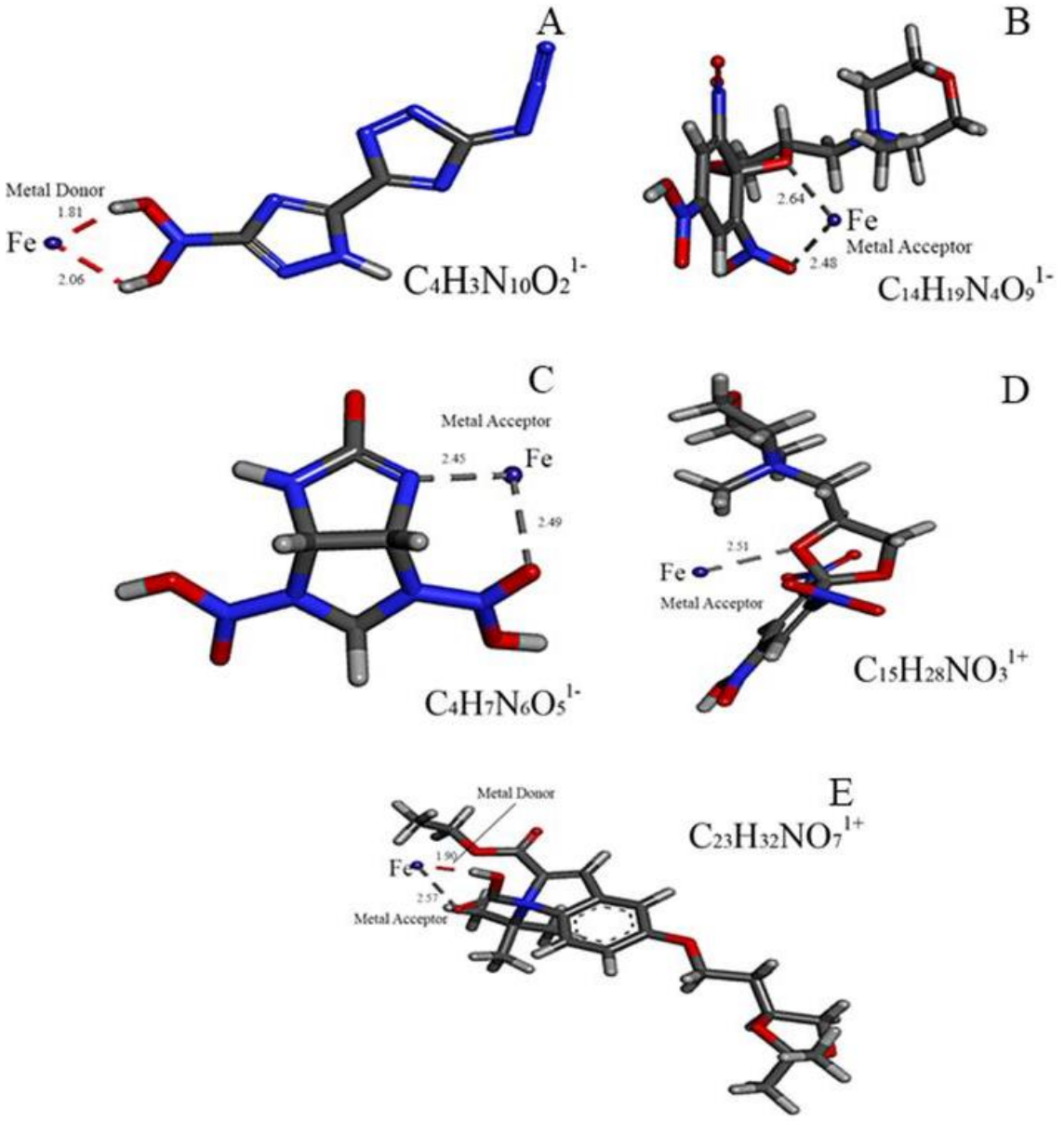


Figure 1. Variabilities of possible complex structures with Fe: $C_4H_3N_{10}O_2^{1-}$ (A); $C_{14}H_{19}N_4O_9^{1-}$ (B); $C_4H_7N_6O_5^{1-}$ (C); $C_{15}H_{28}NO_3^{1+}$ (D) and $C_{23}H_{32}NO_7^{1+}$ (D)

terials [23, 8]. In this study, based on the UPLC-TOF-MS analysis, we were discovered potential bioactive formulas as a precursor and fragment site, and subsequently, it screened to PubChem database. According to Table 1, there were five molecular formulas identified by UPLC-TOF-MS. The molecular formula that appeared are a molecular formula with a high m/z value and a peak intensity at a particular retention time. The molecular formulas have not been identified as specific compounds. However, the molecular formula data by UPLC-TOF-MS become the determinant for data mining in the PubChem database, so the bioinformatics study could be carried out.

Docking was showed an interaction between Fe and the molecular formula(s). The $C_4H_3N_{10}O_2^1$, $C_{14}H_{19}N_4O_9^{1-}$, $C_4H_7N_6O_5^{1-}$, $C_{15}H_{28}NO_3^{1+}$, and $C_{23}H_{32}NO_7^{1+}$ has a number of binding affinity -0.4; -0.6; -0.6, -0.6, -0.4 kcal/mol, respectively. Based on Figure 1, there are Fe (orbicular blue) and crystal structures molecular formula. The type of bond between a metal and molecular formula is metal donor and metal acceptor. $C_4H_3N_{10}O_2^{1-}$ has two metal donor site 1.81Å and 2.06Å. Subsequently, $C_{14}H_{19}N_4O_9^{1-}$, $C_4H_7N_6O_5^{1-}$, and $C_{15}H_{28}NO_3^{1+}$ have metal acceptor sites: 2.64Å and 2.48Å; 2.45Å and 2.49Å; 2.51Å, respectively. Only $C_{23}H_{32}NO_7^{1+}$ has a metal donor site 1.90Å and a metal acceptor site

Table 2. Prediction of Pharmacokinetics Properties *akway* bark's molecular formula by SwissADME software (http://www.swissadme.ch/)

No.	Pharmacokinetics Properties	Molecular Formula of *akway* bark (*Drymis piperita* Hook f.)				
		$C_4H_3N_{10}O_2$	$C_{14}H_{19}N_4O_9$	$C_4H_7N_6O_5$	$C_{15}H_{28}NO_3$	$C_{23}H_{32}NO_7$
1.	Molecular weight (g/mol)	223.13	387.32	219.14	270.39	434.50
2.	Num. heavy atoms	16	27	15	19	31
3.	Num. arom. heavy atoms	5	0	0	0	6
4.	Fraction Csp3	-	0.64	0.75	0.87	0.57
5.	Num. rotatable bonds	2	4	2	13	9
6.	Num. H-bond acceptors	10	9	6	3	8
7.	Num. H-bond donors	3	1	3	0	1
8.	Molar Refractivity	-	97.27	52.81	77.14	120.37
9.	Topological polar surface area (Å²)	-	168.31	134.55	60.44	91.29
10.	Solubility (mg/ml)	2.18	30.6	46.2	0.0894	0.0129
11.	Solubility Class	Soluble	Very soluble	Very soluble	Soluble	Moderately soluble

2.57Å. These bonding types were made *akway* bark may assign Fe ion to the human cell body or receive Fe ion. As a result, low molecular weight complex antioxidant which conforms between Fe (also Cu and Ni) and aromatic compound of *akway* bark was assigned as a free radical scavenger. The metals were played as a central atom and aromatic compounds (Table 1) acted as a ligand [11, 14, 24]. A metal complex compound has a strong antioxidant capacity compared to a single compound. Complex compounds with an electron group and metal transition as central atom were performed as electron transfer regulators. Free radical was released or received an electron from central complex compound ion without conforming to a radical complex. Besides, the single compound such as flavonoid, electron discharging to free radical would generate a phenoxy radical. It would be over if the electron met other radical electrons by phenoxy radical termination. Metal ions, like $Fe^{2+}$and Fe^{3+}, will only refine the magnetic properties of complex compound from paramagnetic to diamagnetic conversely. It includes the electron transfer mechanism of hemoglobin [25].

Potential therapeutic based on pharmacological and pharmaceutical sciences were interestingly discussed, especially to modulate the levels of endogenous free radicals by molecules [26]. Reactive oxygen species (ROS), naturally, be products of cell metabolism. They may arrange a beneficial/deleterious character, depending on concentration and generation mode. ROS has been identified as a critical pathogenic element for diseases. On the other hand, the investigation of novel free radical scavenger molecules may promote the therapeutic agents for preventing and recuperating the diseases.

Low molecular weight complexes of transition metals binding to organic or natural components are identified as pharmaceutical agents [26, 11, 14]. Fe, Co, Ni, Mg, Ca, Cu, Zn, and Cr are required to maintain the health and sustainability of the human body because most critical biological functions in humans depend on their presence and their inadequacy may induce any diseases [27]. The body cell needs iron to synthesize oxygen transport proteins (myoglobin and hemoglobin) and for the conformation of heme enzymes and others involved in electron transfer and reduction-oxidation mechanisms [28].

Swiss ADME made pharmacokinetic properties prediction. Based on Table 2, there were physicochemical and solubility of molecular formula which showed that *akway* bark is water-soluble. Estimating the aqueous solubility was done by measuring formula(s) directly from its structure. It was meant the *akway* bark might be a therapeutic agent [21]. The novel of molecular formula of *akway* bark as herbal medicine becomes complete with this study. The study of *akway* is limited to antibacterial activity and essential oil characterizations [5, 29]. Identifying molecular formula and predicting pharmacokinetic properties of *akway*

bark would contribute an insight to further research.

Conclusion

Akway bark as a herbal medicine has five molecular formulas analyzed by UPLC-TOF-MS and their capability to bind to Fe ions as a complex. The binding of Fe and *akway*'s formula are donor and acceptor metals. Therefore, the pharmacokinetic properties showed that *akway* bark-Fe has capability to aqueous soluble so it could be a novel pharmaceutical agent. So, they could be free radical scavengers based on low molecular weight antioxidants.

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