Discovering Inhibitors of Tyrosinase Enzyme from Zingiberaceae for Depigmentation Agents

Karina Muthia[1], Fride Rindu Alami[1], Nyi Mekar Saptarini[1,2], Jutti Levita[1*]

[1]*Department of Pharmaceutical Analysis and Medicinal Chemistry, Faculty of Pharmacy, Universitas Padjadjaran*
Jl. Raya Bandung-Sumedang km.21 Jatinangor, West Java, Indonesia 45363.
[2]*School of Pharmacy, Bandung Institute of Technology, Labtek VII, Ganesha 10 Bandung 40132, Indonesia.*

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Abstract:
Tyrosinase enzyme, which has two copper ions in its catalytic site, involved in skin pigmentation by catalyzing three oxidation reactions on melanogenesis, that are conversion of L-tirosine to L-DOPA, L-DOPA to dopaquinone, and 5,6-dihydroxyindole to 5,6-indolequinone. An inhibition of melanogenesis was proven in vitro by bioactive compounds of Zingiberaceae plants, which are ethyl p-metoxycinnamate, galangin (IC_{50} 10 μM), 6-gingerol (IC_{50} 25-100 μM), 4-hydroxypanduratin-A (IC_{50} 23.2 μM), isopanduratin-A (IC_{50} 10.6 μM), kaempferol (IC_{50} 0.23 μM), and kaempferida. In this paper we studied the interaction of these compounds with tyrosinase enzyme using AutoDock Vina. The interactions were then compared to arbutin (hydroquinone-β-D-glucoside), kojic acid, and hydroquinone, which have been well known as depigmentation agents in cosmetics. All bioactive compounds of Zingiberaceae plants were able to interact with tyrosinase. Compared to others, kaempferol showed the lowest inhibition constant value (Ki 2.7 μM) and two metal interactions with both copper ions, Cu501 and Cu502, which means that this compound was predicted as the strongest inhibitor of tyrosinase enzyme. Kaempferol interacted with tyrosinase by blocking the entrance of the enzyme's catalytic site, therefore it will prevent the substrate to react with the enzyme. It can be concluded that bioactive compounds of Zingiberaceae can be developed as an inhibitors of tyrosinase.

Key words: *Arbutin, gingerol, kaempferol, kojic acid, melanogenesis, molecular docking, Zingiberaceae*

Introduction

Tyrosinase enzyme, which has two copper ions in its catalytic site, involved in skin pigmentation by catalyzing three oxidation reactions on melanogenesis, that are: (1) conversion of L-tyrosine to L-DOPA, (2) L-DOPA to dopaquinone, and (3) 5,6-dihydroxyindole to 5,6-indolequinone. Tyrosinases catalyze the oxidations of both monophenols (cresolase or monophenolase activity) and O-diphenols (catecholase or diphenolase activity) into reactive O-quinones. The term tyrosinase refers to its typical substrate, tyrosine [1], therefore by inhibiting this substrate, melanogenesis or furthermore, skin pigmentation, could be prevented.

Tyrosinase inhibitors or competitive antagonists of tyrosine are commonly used in dermatological treatments as depigmentation agents. There is plenty of tyrosinase inhibitors derived from either plants or synthetic sources, which have been investigated. An inhibition of melanogenesis was proven in vitro by bioactive compounds of Zingiberaceae plants, which are ethyl p-metoxycinnamate (EPMC), galangin (IC_{50} = 10 μM), 6-gingerol (IC_{50} = 25–100 μM), 4-hydroxy-panduratin-A (IC_{50} = 23.2 μM), isopanduratin-A (IC_{50} = 10.6 μM), kaempferol (IC_{50} = 0.23 μM), and kaempferida [2,3,4].

The mechanism of action of tyrosinase inhibitors can be accomplished by one of the following: (a) Reducing agent such as ascorbic acid causes chemical reduction of dopaquinone, and reduces O-dopaquinone to L-DOPA, thus avoiding formation of dopachrome and melanin; (b) O-Dopaquinone scavenger such as most thio-containing compounds could react with dopaquinone, to form colorless products. Then the melanogenesis is slowed down, until all the scavengers are consumed; (c) Some phenolic compounds act as alternative tyrosinase substrates, their quinoid reaction products absorb in a spectral range different from that of dopachrome. When these phenolics exhibit a good affinity for tyrosinase, dopachrome formation is prevented, hence they could be regarded as tyrosinase inhibitors; (d) Nonspecific tyrosinase inactivators such as acids or bases, which non-specifically denature the enzyme and inhibit its activity. Those acids or bases are sometimes mistakenly regarded as tyrosinase inhibitors [4]. Actually, the specific tyrosinase inhibitors should be catalyzed by tyrosinase and form covalent bond with the enzyme, thus irreversibly inactivating the enzyme during catalytic reaction [5].

In this paper, we studied the binding modes of galangin, EPMC, kaempferol, 6-gingerol, 4-hydroxypanduratin-A, isopanduratin-A, and kaempferida, bioactive compounds of Zingiberaceae, with tyrosinase enzyme using AutoDock Vina for discovering depigmentation agents from natural sources.

***Corresponding author:** Jutti Levita,
E-mail: jutti.levita@unpad.ac.id

