



Title	Chemical Studies on Tyrosinase Inhibitory and Antioxidant Activity of Bromophenols from Rhodomelaceae Algae [an abstract of dissertation and a summary of dissertation review]
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学位論文内容の要旨

博士の専攻分野の名称：博士（水産科学） 氏名：エムディー レアズル イスラム

学位論文題目

Chemical Studies on Tyrosinase Inhibitory and Antioxidant Activity of Bromophenols from Rhodomelaceae Algae

(フジマツモ科海藻由来ブロモフェノール類のチロシナーゼ阻害及び抗酸化活性に関する化学的研究)

Hyperpigmentation and enzymatic browning is mainly caused by the activity of tyrosinase enzyme. Inhibition or delay of this enzymatic reaction is a very popular technique to overcome the problem. Many tyrosinase inhibitors have already been isolated as phenolic compounds from plant, microorganism and marine organism. Moreover, free radicals are continuously generated in a living systems but natural defense mechanism neutralize that radicals. When this balance does not work, there is possibility of arising many diseases from the attack of free radicals. The major objectives of this research were set as screening and identification of potential marine algae; isolation and purification of bioactive compounds, structural elucidation by MS and NMR analysis; inhibitory activity and kinetic study of the inhibitors.

In Chapter 1, Marine algae were collected from Hakodate, Otaru and Nemuro, Japan and screened for DPPH antioxidant assay. Most of algae extract exhibited weak antioxidant activity except red algae of family Rhodomelaceae. Therefore, the marine alga *Odonthalia corymbifera* (Rhodomelaceae) was selected for purification. With the guidance of results of antioxidant assay, the extract was separated by several chromatographic techniques to obtain compounds **R1** and **R2**. Compound **R1** named odonthadione was determined as a new hybrid-type bromophenols consist of coupling between brominated hydroxylated benzyl (BHB) unit and a unique cyclopentene moiety with two ketone groups. Compound **R1** possessing a chiral center showed optically inactive. Thus compound **R1** could be a racemic mixture. Compound **R2** named odonthalol was determined as a new trimer of three BHB units. So far only four trimers have been purified and this compound will include as a new member of this group.

In Chapter 2, eight known bromophenols were isolated from two kinds of Rhodomelaceae algae. Bromophenols were isolated from the two red algae *Neorhodomela aculeata* and *Odonthalia*

corymbifera. The bromophenols were identified as two bromophenol monomers **R3** and **R4**, two symmetric dimers **R5** and **R8**, and four asymmetric dimers **R6**, **R7**, **R9** and **R10**, from their MS and NMR data. Although compounds **R6**, **R7** and **R10** were isomers, they were determined from difference of HMBC correlations.

In Chapter 3, tyrosinase inhibitory and antioxidant activity were compared among the bromophenols isolated. All the bromophenols showed tyrosinase inhibitory activity which comparable to positive control kojic acid. Hybrid bromophenol **R1**, trimer **R2**, dimers **R5-R10** displayed higher inhibition than monomers **R3** and **R4**. Bromophenols **R1-R10** possess catechol moiety that act as copper chelator of tyrosinase and play key role in enzyme inhibition. Number of bromination affected tyrosinase inhibitory activity. These results suggested that tyrosinase activity influence not only from copper chelation but also bromination can enhance inhibitory activity. Bromophenols **R5**, **R8**, **R9** and **R10** showed non-competitive inhibition from Lineweaver-Burk plot analysis. This type of inhibitors may bind other site of the active site, combine with either free enzyme or enzyme-substrate complex, bring change in the structure and shape of enzyme, and the modified enzyme was no longer capable of binding correctly with the substrate. Although effect of bromination is still unclear, bromination may play an important role. The antioxidant activities of bromophenols **R1-R10** were examined by radical scavenging (DPPH & ABTS), metal reducing (CUPRAC & FRAP) and copper-chelation assay. Bromophenols **R1-R10** displayed antioxidant activity in varying degree which was comparable to respective positive controls. Result revealed that antioxidant properties strongly rely on number and position of hydroxy group. Thirteen related phenolic compounds were purchased and compared inhibitory activity with bromophenols **R1-R10** to elucidate inhibition mechanism. Although two dichlorinated compounds showed moderate tyrosinase inhibition, the others displayed weak or no inhibition. These results suggest that tyrosinase inhibition requires catechol moiety and bromine substitution, not other halogen substitution. Bromophenols are multifunctional compounds. Mostly reported tyrosinase inhibitors are phenolic compounds but naturally occurring bromophenol was not investigated for tyrosinase inhibition. These studies have revealed new functionality of bromophenol as tyrosinase inhibitor. Bromine substitutions inhibit tyrosinase activity to a great extent but further investigations are required for clear understanding of inhibitory mechanism. However, marine red algae can be source of bioactive compounds in pharmaceutical industries.