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Editorial

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# Tyrosinase and Tyrosinase Inhibitors

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Melanin is responsible for skin color and plays an important role in protection of the skin against UV light induced damage. During the melanin biosynthesis pathway, tyrosinase (EC 1.14.18.1) is the rate-limiting enzyme that hydroxylates L-tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA), and L-DOPA is further oxidized to the corresponding *o*-dopaquinone.

## Tyrosinase

Tyrosinase is a well-known copper-containing enzyme and is widely distributed in microorganisms, plants and animals. In fungi and vertebrates, tyrosinase catalyzes the rate-limiting step in the formation of the pigment melanin from tyrosine. In plants, the physiological substrates contain a variety of phenolics. Tyrosinase oxidizes them in the browning pathway, observed when the plant tissues are injured. The tyrosinase extracted from the champignon mushroom, *Agaricus bisporus,* is highly homologous with the mammalian ones. Hence, mushroom tyrosinase is well suited as a model for studies on melanogenesis. Actually, almost all studies on tyrosinase inhibition conducted so far have used mushroom tyrosinase, because only the enzyme is commercially available. Tyrosinase has been ascribed other functions apart from melanin production, including the detoxification of host plant defensive phenols for symbiotic bacteria [1,2], the sclerotisation of insect cuticles [3], and the synthesis of amino acid based antibiotics [4]. Recently, the activities of tyrosinase have been used in several biotechnological applications. Tyrosinase has been applied in numerous of electrochemical biosensors, for a lot of phenolic compounds. Also, tyrosinase has been applied to activate the tyrosine residues in polypeptides for protein cross-linking to chitosan films, as well as in direct protein-protein cross-linking. Besides, tyrosinases could be applied to the removal of phenol from wastewater and the bioconversion of L-tyrosine to L-DOPA [5].

## Tyrosinase Inhibitors

Tyrosinase inhibitors are widely used in dermatological treatments and also applied in cosmetics. There are plenty of tyrosinase inhibitors derived from both natural and synthetic sources, which have been investigated. The definition of "tyrosinase inhibitor" is sometimes ambiguous in research articles. Some authors use that terminology in terms of melanogenesis inhibitors, whose action mainly focus on decreasing melanin formation, regardless of any direct interaction between inhibitor and enzyme. Many potential tyrosinase inhibitors are examined in the presence of L-tyrosine or L-DOPA as the enzyme substrate, and tyrosinase activity is assayed in terms of dopachrome formation. Thus, experimental evaluation of the tyrosinase inhibitors can be accomplished by one of 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 melanogenetic process 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. 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. Also, some chemical compounds reversibly bind to tyrosinase and reduce its catalytic capacity, and they could also be recognized as specific tyrosinase inhibitors. In general, some tyrosinase inhibitors exhibit only weak inhibitory effect due to their reactive and consumable properties toward tyrosinase or the quinone products. The tyrosinase inhibitors could be classified into four types, including competitive inhibitors, uncompetitive inhibitors, mixed type (competitive/uncompetitive) inhibitors, and non-competitive inhibitors. A competitive inhibitor combines with a free tyrosinase that prevents substrate binding. A competitive inhibitor might be a copper ion chelator, tyrosinase substrate analogs, or derivatives of L-tyrosine or L-DOPA. On the other hand, an uncompetitive inhibitor only binds to the tyrosinase-substrate complex. A mixed (competitive and uncompetitive mixed) type inhibitor binds not only with a free tyrosinase, but also with the tyrosinase-substrate complex. For most mixed-type inhibitors, their equilibrium binding constants for the free tyrosinase and the tyrosinase-substrate complex are different. The non-competitive inhibitors could bind to a free tyrosinase and a tyrosinase-substrate complex, with the same equilibrium constant. The tyrosinase inhibitor strength is usually expressed as the inhibitory $IC_{50}$ value, which is the concentration of an inhibitor needed to inhibit half of the enzyme activity, in the tested condition. Usually, in most studies conducted to discover new tyrosinase inhibitors, kojic acid is often used as a positive standard at the same time. Hence, it is suggested to compare the strength of tyrosinase inhibitors with that of kojic acid, and describe the inhibitory strength as a relative inhibitory activity, which is calculated by dividing the $IC_{50}$ value of kojic acid with that of a newly found inhibitor, in the same report. The relative inhibitory activity is also useful to express and compare the inhibitory strength of an inhibitor with others.

## Conclusion

Tyrosinase is a glycosylated and copper-containing oxidase, which catalyzes the first two steps in mammalian melanogenesis, and is responsible for enzymatic browning reactions in damaged fruits. These phenomena have encouraged researchers to seek new potent

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tyrosinase inhibitors, for use in cosmetics and foods. This article briefly describes the characteristics of tyrosinase and tyrosinase inhibitors, which is useful for researchers interested in the field of biocatalysis or biotransformation of tyrosinase.

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