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REVIEW ARTICLE

Microorganisms as a source of tyrosinase inhibitors: a review

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Abstract Tyrosinase is the main enzyme responsible for enzymatic browning of fruits post-harvest and melanogenesis in mammals, an undesirable phenomenon. This encouraged researchers to seek potent tyrosinase inhibitors for application in the food and cosmetics industries. Despite an increased knowledge of tyrosinase inhibitors from plants and synthetic sources in the past few years, inhibitors of microbial origin are under-explored. Thus, this article surveys tyrosinase inhibitors produced by microorganisms and hence, serves as an updated database of tyrosinase inhibitors from microbial sources.

Keywords Inhibitor · Melanogenesis · Bacteria · Fungi · Tyrosinase

Introduction

Over the past several years, tyrosinase (EC 1.14.18.1) has been studied extensively in a wide area of research. Tyrosinase enzyme is ubiquitous in nature, found in both prokaryotes as well as eukaryotes. There are several examples of well-characterized tyrosinases from prokaryotes. The first well-described tyrosinase was reported in *Streptomyces* sp. (Lerch and Ettinger 1972; Katz et al. 1983); however, this enzyme has also been reported from other genera, such as *Bacillus megaterium*, *Rhizobium* sp., *Symbiobacterium thermophilum*, *Pseudomonas maltophilia*, *Sinorhizobium meliloti*, *Marinomonas mediterranea*, *Thermomicrobium roseum*, *Bacillus thuringiensis*, *Pseudomonas putida* F6 and *Ralstonia solanacearum* (Liu et al. 2004; Ruan et al. 2005; Claus and Decker 2006; Dalfard et al. 2006; Hernández-Romero et al. 2006; McMahon et al. 2007; Shuster and Fishman 2009). In eukaryotes, they serve several other functions apart from melanin production. They are important for wound healing and serve as primary immune response in plants, sponges, and many invertebrates (Van Gelder et al. 1997; Cerenius and Söderhäll 2004; Müller et al. 2004), and are also involved in sclerotization in arthropods (García-Borrón and Solano 2002).

Recently, enzyme inhibitors have been gaining attention as indispensable tools, not only for the study of the respective enzyme structure but also for their potential in pharmaceuticals and agriculture (Imada 2004). Tyrosinase plays a key role in melanogenesis in mammals and enzymatic browning in fruits and fungi, through a series of reactions leading to the formation of a dark pigment, melanin (Chang 2009). Although melanin plays an important role in the phytoprotection of human skin from UV rays, depigmentation is an esthetic problem in a wide range of human populations (Solano et al. 2006; Brenner and Hearing 2008). In addition, browning of fruits and mushrooms post-harvest is undesirable, as it reduces the commercial value of the product. The development of tyrosinase inhibitors has also become a better alternative in controlling insect pests, as the enzyme also plays an important role in developmental and defensive functions in insects (Sugumaran 2002). Due to these varied applications, tyrosinase inhibitors have been gaining importance as the best alternative for these approaches.

Tyrosinase inhibitors have been discovered and reviewed from various natural and synthetic sources (Kim and Uyama 2005; Khan 2007; Parvez et al. 2007; Schurink et al. 2007; Likhitwitayawuid 2008; Lin et al. 2008; Chang 2009, 2012a; Loizzo et al. 2012; Chan et al. 2014; Chen et al. 2015; Kilimnik and Dembitsky 2016). However, limited literature

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has been reviewed about tyrosinase inhibitors produced by microorganisms. Microorganisms produce several bioactive compounds and have potential as important new sources of tyrosinase inhibitors. Hence, this article reviews several tyrosinase inhibitors produced by microorganisms in the literature for use in the depigmentation of hyperpigmented skin and other applications.

Biochemical characteristics of tyrosinase

In this section, we give a brief overview of tyrosinase from bacteria, plants and fungi, with more emphasis on mushroom tyrosinase. Because of difficulties in producing tyrosinase from humans in large quantities, its three-dimensional structure is still unknown. Tyrosinase is a polyphenol oxidase enzyme which uses molecular oxygen to catalyze sequential reactions, such as (i) hydroxylation of monophenols to o-diphenols, followed by (ii) oxidation of o-diphenols to o-quinones. The quinones self-polymerize or react with other substances to form melanin. They belong to a large group of proteins, namely type 3 copper proteins, responsible mainly for the first step in melanin synthesis. Both copper atoms are coordinated by conserved three histidine residues. In melanin synthesis, three types of tyrosinase, namely oxy, met, and deoxy, with different binuclear copper structures are involved. The resting form of tyrosinase consists of a mixture of met and oxy forms, with 85% of the met form (Sánchez-Ferrer et al. 1995; Kim and Uyama 2005; Claus and Decker 2006).

The first crystal structure of tyrosinase was determined from *Streptomyces castaneoglobisporus* (Matoba et al. 2006). The low sequence homology between tyrosinase of different sources can be related to the differences in their structure and function. In fungal tyrosinases, one histidine residue is linked by thioether bond to the side chain of a cysteine residue. This feature is not found in bacterial tyrosinase. Haudecoeur et al. (2014) reported that there was some similarity and difference between the binding sites of tyrosinase from different origins using the same set of molecules. Selinheimo et al. (2007) also compared the characteristics of fungal and plant tyrosinases and suggested that the enzymes showed different features in terms of substrate specificity, stereo-specificity, inhibition, and ability to crosslink the model protein; however, they had similar reaction mechanisms to produce identical quinone radicals. In a recent study, it was found that, although monophenols and diphenols bind and orient identically at the active site, only monophenols rotate during the reaction, thus enabling enzymes with only diphenolase activity to have two constraints to prevent monophenolase activity. They also proposed a conserved water molecule at the active site that mediates deprotonation of monophenol at the active site (Goldfeder et al. 2014). Kanteev et al. (2015) also suggested that the active site flexibility and substrate deprotonation is crucial for the monophenolase activity of type 3 copper proteins. Asn and Glu residues are highly conserved in type 3 copper proteins and are assumed to play a role in the activation of the conserved water molecule. We have listed in Table 1 tyrosinases from different microbial sources.

Melanogenesis in mammals

Melanin is an important pigment in mammals, synthesized and distributed in the skin and hair bulbs, that absorb free radicals generated within the cytoplasm and also protect the host from various types of ionizing radiation (Seiberg et al. 2000; Schaffer and Bolognia 2001). In mammals, a mixture of two types of melanin, eumelanin (brown or black pigment) and pheomelanin (red or yellow pigment), are found. The formation of melanin occurs through a series of oxidative reaction, where tyrosine is converted to dihydroxyphenylalanine (DOPA) and, further, to dopaquinone by tyrosinase. Dopaquinone is further auto-oxidized to dihydroxyindole or to dihydroxyindole-2-carboxylic acid (DHICA) by dopachrome tautomerase and DHICA oxidase to form eumelanin. Subsequently, pheomelanin is formed (Raper 1928; Kobayashi et al. 1995; Borges et al. 2001).

Melanogenesis is regulated by three different signaling pathways: protein kinase C-mediated pathway, cAMP-mediated pathway, and mitogen-activated protein kinase (MAPK) pathway. Although there are three enzymes active in the process of melanogenesis, tyrosinase plays the key role in the formation of melanin, whereas the rest adjust the type of pigment formed (Kobayashi et al. 1995). Microphthalmia-associated transcription factor (MITF) is phosphorylated by MAPK, which is essential for its activation as well as degradation. cAMP serves as a starting point of several interacting signaling cascades in melanin synthesis as well as regulating melanin production and PI3K. Stimulation with cAMP inhibits PI3K signaling, thereby increasing the synthesis of melanin via increased transcription of tyrosinase and TRP-1 (tyrosinase-related protein 1). Therefore, the activation of PI3K or protein kinase B (AKT) signaling reduces melanogenesis via the downregulation of MITF expression, as AKT is an effector of PI3K (Bertolotto et al. 1998; Hemesath et al. 1998; Meinkoth et al. 1991; Xu et al. 2000; Hennessy et al. 2005).

Due to the increased treatments for skin fairness, there has been a demand for the prevention of skin pigmentation in the cosmetics industry. This has lead to an increased interest on potent tyrosinase inhibitors, to prevent melanogenesis. Although several tyrosinase inhibitors have been reported from natural and synthetic sources, only a few of them are used as skin-whitening agents. Solano et al. (2006) suggests that, although tyrosinase inhibition is the most common approach, a new innovative combined approach improved the transdermal delivery system and enabled efficient

Table 1 Tyrosinase of different origins

Source	Molecular weight (kDa)	pI	References
Gram-positive bacteria			
Streptomyces glaucescens	30.9	–	Lerch and Ettinger (1972); Kim and Uyama (2005)
Streptomyces antibioticus	30.6	7.17	Katz et al. (1983); Claus and Decker (2006)
	14.9	6.54	
Streptomyces avermitilis	33.5	9.33	Claus and Decker (2006)
	13.6	6.64	
Streptomyces nigrifaciens	18	–	Nambudiri et al. (1972); Claus and Decker (2006)
Streptomyces castaneoglobisporus	31	6.20	Matoba et al. (2006)
	13	6.42	
Streptomyces coelicolor	33.1	9.66	Claus and Decker (2006)
	19.3	7.15	
Streptomyces galbus	31.3	9.33	Claus and Decker (2006)
	12.9	6.69	
Streptomyces griseus	35.5	8.90	Claus and Decker (2006)
	13.7	11.8	
Streptomyces lincolnensis	30.7	6.84	Michalik et al. (1975); Claus and Decker (2006)
	14.2	7.10	
Streptomyces lavendulae	31	6.8	Claus and Decker (2006)
	17	11.9	
Streptomyces tanashiensis	31.3	6.84	Claus and Decker (2006)
	12.5	9.39	
Streptomyces sp. KY-453	29	9.9	Yoshimoto et al. (1985); Claus and Decker (2006)
Streptomyces michiganensis	32	9.0	Philipp et al. (1991); Claus and Decker (2006)
	34.5		
Bacillus cereus	28.5	5.47	Claus and Decker (2006)
Bacillus thuringiensis	16.8	4.87	Liu et al. (2004); Ruan et al. (2005)
Corynebacterium efficiens	46.4	5.16	Claus and Decker (2006)
Bacillus megaterium	31	–	Shuster and Fishman (2009)
Gram-negative bacteria			
Marinomonas mediterranea	74.5	4.84	Claus and Decker (2006)
Marinomonas mediterranea	53.1	4.85	Claus and Decker (2006)
Marinomonas mediterranea	28.6	9.89	Claus and Decker (2006)
Nitrosomonas europaea	53.9	5.26	Claus and Decker (2006)
Rhizobium etli (Rh.e.)	67.4	7.28	Claus and Decker (2006); Cabrera-Valladares et al. (2006)
Sinorhizobium meliloti	54.1	4.65	Claus and Decker (2006)
Ralstonia solanacearum	44	8.44	Hernández-Romero et al. (2005); Claus and Decker (2006)
Stenotrophomonas maltophilia	18.6	9.27	Claus and Decker (2006)
Pseudomonas melanogenum	–	–	Yoshida et al. (1974); Claus and Decker (2006)
Thermomicrobium roseum	43	4.9	Kong et al. (2000); Claus and Decker (2006)
Vibrio tyrosinaticus	38.5	–	Pomerantz and Murthy (1974); Claus and Decker (2006)
	41		
Fungi			
Pycnoporus sanguineus	45	4.5–5.0	Halaouli et al. (2005); Halaouli et al. (2006)
Trichoderma reesei	43.5	9.0	Selinheimo et al. (2006)
Aspergillus oryzae	67	–	Ichishima et al. (1984); Halaouli et al. (2006)
Lentinula edodes	54–55	4.3–4.7	Kanda et al. (1996); Halaouli et al. (2006)
	15–50		
Neurospora crassa	46	8.3–8.5	Lerch (1983); Halaouli et al. (2006)
Agaricus bisporus	13.4	4.7–5.0	Solomon et al. (1996)
	43		
Mammals			
Human melanocyte	66.7	–	Solomon et al. (1996)

screening tests for validating their efficacy and safety. Currently, arbutin, gentisic acid, hydroquinone, and aloesin isolated from plants as well as 4-n-butylresorcinol, deoxyarbutin, kojic acid, ascorbic acid, and azelaic acid are used in the cosmetics industry, with strong inhibition against tyrosinase (Solano et al. 2006; Parvez et al. 2007; Lin et al. 2008; Gillbro and Olsson 2011).

Enzymatic browning of plant-derived foods

The browning of fruit and vegetables is of great concern in the food industry, as it reduces its economic value. Browning occurs due to various reasons, such as microbial spoilage, mechanical damage and enzymatic reactions. Due to their thin and epidermal layer, the respiration rate of vegetables and fruits is high; hence, they tend to lose their quality post-harvest. Enzymatic browning is a major concern in damaged fruits during post-harvest handling and processing, where tyrosinase enzyme plays a key role (Mayer 1987). Tyrosinase causes oxidation of the phenolic compounds in fruits, causing undesirable changes in color, flavor and texture, thereby reducing its marketability. The extent of browning depends on various factors, such as concentration of the enzyme and substrate, oxygen availability, pH and temperature (Zheng et al. 2008). Tyrosinase catalyzes the hydroxylation of phenolic substrate tyrosine to DOPA via its monophenolase activity, which is further oxidized to dopaquinone by its diphenolase activity. Further, these quinones are powerful electrophiles, which can be attacked by water, other polyphenols, amino acids, peptides and proteins, leading to Michael-type additions. This is further converted to melanin through a series of reactions (Busch 1999).

The appearance of a product has been an essential attribute in the food industry and, therefore, several methods have been incorporated to reduce or stop enzymatic browning, such as blanching, microwave, autoclaving, application of chemicals, modified atmospheric packing, controlled atmospheric control, etc. (Singh et al. 2010; Ioannou and Ghoul 2013). However, these processes alter the quality, texture, and nutrient content of the product. Several enzyme inhibitors, namely citric acid, ascorbic acid and kojic acid, have been used for the prevention of browning (Loizzo et al. 2012; Ioannou and Ghoul 2013). However, since safety is the main concern in the food industry, the search for a considerably safe tyrosinase inhibitor from a natural source is an eminent topic of research.

Tyrosinase inhibitors

Tyrosinase inhibitors are widely used in cosmetology and agriculture. There are several tyrosinase inhibitors derived from natural and synthetic sources (Parvez et al. 2007; Lin et al. 2008). Some authors use "melanogenesis inhibitors" as the terminology for tyrosinase inhibitors; however, this is attributed to the inhibition of melanin synthesis, regardless of its mode of action. Thus, tyrosinase inhibition could be due to one of the following reasons, which could mislead the definition of an enzyme inhibitor:

1. Reducing agents causing chemical reduction of dopaquinone, e.g., ascorbic acid
2. o-Dopaquinone scavengers which react with dopaquinone to form a colorless product, e.g., thio-containing compounds
3. Alternative substrate with good affinity for the enzyme forming a different product, e.g., phenolic compounds
4. Non-specific enzyme inactivators such as acids and bases which inactivate the enzyme
5. Specific enzyme inactivators or suicide substrates
6. True inhibitors which bind to the enzyme and inhibit its activity

The true inhibitors can be subdivided further into three categories based on their mode of inhibition, such as competitive inhibitors, mixed type inhibitors, and non-competitive inhibitors (Chang 2009, 2012b). The inhibitors mainly comprise copper-binding agents and compounds binding on active sites (Mayer and Harel 1979; Robb 1984). Substrate analogues include numerous aromatic acids, phenols and their derivatives, and a few non-aromatic compounds, which mainly behave as competitive inhibitors (Walker and McCallion 1980; Menon et al. 1990; Nicolas et al. 1994). As the enzyme is a metalloenzyme, metal chelaters such as carbon monoxide, cyanide, azide ions, thiourea derivatives, kojic acid, tropolone, etc. could inhibit its activity. Inhibitors from natural sources have been preferred over synthetic sources, with microbial sources being an important area for exploration of some novel and safe inhibitors for application in various sectors.

Tyrosinase inhibitors from fungi

Fungi produce diverse bioactive compounds, including antibiotics, enzymes, enzyme inhibitors, growth promoters, etc., exploited in the agriculture, food, and pharmaceutical industries. Fungi from different genera have been found to demonstrate anti-tyrosinase activity. One of the genera, *Aspergillus*, was found to produce several compounds having tyrosinase inhibitory activity (Fig. 1). Kojic acid (5-hydroxy-2-(hydroxymethyl)-gamma-pyrone), a well-studied tyrosinase inhibitor, was reported from *A. albus* (Saruno et al. 1979), *A. candidus* (Wei et al. 1991), *A. niger* (Vasantha et al. 2014), and *Penicillium* sp., a good chelator and also a scavenger of free radicals. Saruno et al. (1979) reported kojic acid with 80% inhibition by *A. albus*, whereas Vasantha et al. (2014) reported *A. niger* S16 producing kojic acid that showed 84%

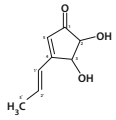
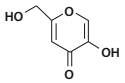
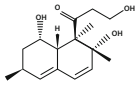
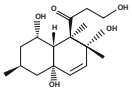
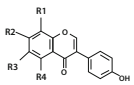
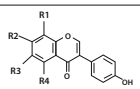
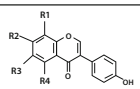
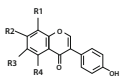
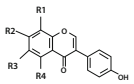
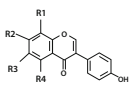
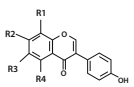
Compound	Structures	Mechanism
Terrein	IC_{50} = n.d 	• Down regulation MITF via induction of ERK activity. • Inhibtion of MITF promoter activity.
Kojic acid	IC_{50} = 61.9 μM 	• Chelate copper at its active site. • Competitive inhibition
Decumbenone A	IC_{50} = 74 μM 	• Not Known
Decumbenone C	IC_{50} = 0.9 μM 	• Not Known
6,7,4′- Trihydroxyisoflavone	IC_{50} = 9 μM  R1=R4=H, R2=R3=OH	• Competitive inhibition of monophenolase activity
7,8,4′- Trihydroxyisoflavone	IC_{50} = 191 μM; 181 μM  R1=R2=OH, R3=R4=H	• Irreversible inhibition of monophenolase and diphenolase activity.
5,7,8,4′- Tetrahydroxyisoflavone	IC_{50} = 184 μM; 212 μM  R1=R2=R4=OH, R3=H	• Irreversible inhibition of monophenolase and diphenolase activity.
Daidzein (7,4′-Dihyroxyisoflavone)	IC_{50} = 203 μM  R1=R3=R4=H, R2=OH	• Competitive inhibition of monophenolase activity.
Glyceitein (6-Methoxy ,7,4′-dihydroxyisoflavone)	IC_{50} = 218 μM  R1=R4=H, R2=OH, R3=OCH3	• Competitive inhibition of monophenolase activity.
Daidzin (4′-Hydroxyisoflavone-7-O-glucoside)	IC_{50} = 267 μM  R1=R3=R4=H, R2=OGlc	• Competitive inhibition of monophenolase activity.
Genistin (5,4′-Dihydroxyisoflavone-7-O-glucoside)	IC_{50} = 343 μM  R1=R3=H, R2=OGlc, R4=OH	• Competitive inhibition of monophenolase activity.

Fig. 1 Structures of tyrosinase inhibitors from *Aspergillus* sp. (*n.d* not defined)

competitive inhibition of mushroom tyrosinase with an IC_{50} value of 61.9 μM. Based on several studies, kojic acid at a minimum level of exposure or consumption was found to have negligible toxicity to humans (Burdock et al. 2001; Nohynek et al. 2004). Apart from kojic acid, the *Aspergillus* genus produces diverse compounds with anti-tyrosinase activity. *Aspergillus niger* produces metallothioneins, which are strong tyrosinase inhibitors having strong avidity to chelate copper at its active site (Goetghebeur and Kermasha 1996). An inhibitor of melanin formation, decumbenone A, was isolated from *P. decumbens* and *A. sulphureus*; in addition, the *Aspergillus* genus also produced a new potent decaline derivative, decumbenone C, showing cytotoxic activity against human melanoma cells with an IC_{50} value of 0.9 μM (Fujii et al. 2002; Zhurayleva et al. 2012). Terrein was isolated for the first time from *A. terreus*, which inhibited melanin synthesis by the downregulation of MITF via the induction of ERK activity and inhibition of MITF promoter activity (Raistrick and Smith 1935; Kim et al. 2007, 2008). A melanogenesis inhibitor isolated from *Penicillium* sp. 20135 was also identified as terrein,

which inhibited melanin formation in B16 melanoma cells; however, neither inhibited mushroom tyrosinase nor demonstrated cytotoxic activity in a cell-based assay (Park et al. 2004; Kim et al. 2005). In addition, Chang et al. (2007) reported seven isoflavones from soygerm koji fermented with *A. oryzae* BCRC 32288 having anti-tyrosinase activity. Five compounds, 6,7,4′-trihyroxyisoflavone (IC_{50} = 9 μM), daidzein (IC_{50} = 203 μM), glycitein (IC_{50} = 218 μM), daidzin (IC_{50} = 267 μM), and genistin (IC_{50} = 343 μM), showed inhibitory activity against the monophenolase activity of tyrosinase by competitive inhibition. The other two compounds, 7,8,4′-trihyroxyisoflavone and 5,7,8,4′-tetrahydroxyisoflavone, irreversibly inhibited both monophenolase with IC_{50} values of 191 μM and 184 μM, respectively, as well as diphenolase activity with IC_{50} values of 181 μM and 212 μM, respectively, of tyrosinase. Additionally, dietary daidzein, a phytoestrogen component of soy, did not show toxicity to the female reproductive tract in rats (Lamartiniere et al. 2002). Tyrosinase inhibition activity (56.18%) was also found in rice bran fermented with *A. oryzae* (Razak et al. 2015).

Another genus found to produce diverse compounds having anti-tyrosinase activity is *Trichoderma* (Fig. 2). Lee et al. (1995) reported a particular strain of *T. harzianum* MR304 to produce a melanin synthesis inhibitor, MR304-1, identified as an isocyanide compound, which inhibited melanogenesis inhibition in *S. bikinienesis*, B16 melanoma cells [minimum inhibitory concentration (MIC) = 0.05 μg/mL], and mushroom tyrosinase (IC_{50} = 0.25 μg/mL). *Trichoderma harzianum* isolated from soil was also reported to produce several melanin synthesis inhibitors. Two new tyrosinase inhibitors, MR566A (IC_{50} = 1.72 μM) and MR566B (IC_{50} = 47 μM), along with a new oxazole compound MR93B (IC_{50} > 6000 μM), six known isocyanide compounds, and MR93A (IC_{50} > 6000 μM), were isolated showing inhibition against mushroom tyrosinase, melanogenesis inhibition in *S. bikinienesis*, and B16 melanoma cells. The isocyanide compounds were identified as 1-(1,4,5-trihydroxy-3-isocyanocyclopenten-2-enyl)ethanol, 2-hydroxy-4-isocyano-α-methyl-6-oxabiocyclo[3.1.0]hex-3-ene-3methanol, 4-hydroxy-8-isocyano-1-oxaspiro[4.4]cyclonon-8-en-2-one, MR304A, methyl-3-(1,5-dihydroxy-3-isocyanocyclopent-3-enyl)prop-2-enoate, and an unidentified compound with IC_{50} values of 3.6, 4.9, 0.089, 47, 1.72, and 0.0014 μM, respectively (Lee et al. 1997a, b). Lee et al. (1997a, b) proposed that the isocyano group in the compounds plays a vital role in inhibiting the activity of mushroom tyrosinase enzyme. Imada et al. (2001) reported mushroom tyrosinase inhibitor produced by *Trichoderma* sp. H1-7 isolated from a marine environment as having 1000–2500 U/mL inhibitory activity. A competitive inhibitor of tyrosinase (5.4×10^5 U/mL) similar to the structure of homothallin II was isolated from *T. viridae* strain H1-7 from marine sediments which inhibited the enzyme by binding to the copper active site. In addition, this strain produced seven different melanogenesis inhibitors, with not all of them showing inhibition of tyrosinase (Tsuchiya et al. 2008).

Marine fungi live in a unique environment with stressful conditions of pH, temperature, salinity, oxygen nutrients, and light, and, therefore, serve as promising candidates for novel bioactive compounds. On investigation, few known and novel compounds with tyrosinase inhibition activity have been reported from marine-derived fungi (Fig. 3). Two derivatives of kojic acid, kojic acid dimethyl ether and kojic acid monomethyl ether, as well as phomaligol A, were identified from broth of marine-derived fungi *Alternaria* sp. isolated from marine green algae having tyrosinase inhibitory activity (Li et al. 2003). Similarly, two compounds, 6-n-pentyl-α-pyrone and myrothenone A, identified from marine-derived fungi *Myrothecium* sp. MFA 58 isolated from algae were stronger than kojic acid (IC_{50} = 7.7 μM), with IC_{50} values of 0.8 and 6.6 μM, respectively (Li et al. 2005). Zhang et al. 2007 reported a pyrone derivative, 6-[(E)-hept-1-enyl]-α-pyrone, exhibiting anti-tyrosinase activity (IC_{50} = 4.5 μM) isolated from *Botrytis* sp. Two sesquiterpene compounds were isolated from a marine-derived fungi *Pestalotiopsis* sp. Z233, isolated from algae, 1β,5α,6α,14-tetraacetoxy-9α-benzoyloxy-7β*H*-eudesman-2β,11-diol and 4α,5α-diacetoxy-9α-benzoyloxy-7β*H*-eudesman-1β,2β,11-tetraol, having tyrosinase inhibitory activity. These compounds were induced by abiotic stress elicitation by $CuCl_2$ with IC_{50} values of 14.8 μM and 22.3 μM, respectively (Wu et al. 2013).

Apart from marine fungi, several other fungal groups are reported for anti-tyrosinase activity (Fig. 4). Azelaic acid (1,7-heptanedicarboxylic acid) produced by yeast, *Pityrosporum ovale*, has a cytotoxic effect on the melanocytes of primary cutaneous melanoma. It is a straight chain, saturated dicarboxylic acid which inhibits tyrosinase by competing for the α-carboxylate binding site of the L-tyrosine substrate of the enzyme (Schallreuter and Wood 1990). Nevertheless, azelaic acid is a known compound that has been previously reported as non-toxic (Töpert et al. 1989). In addition, yeasts also produce cytosolic proteins, metallothioneins characterized by the selective binding of a large amount of heavy metal ions and high cysteine content. *Neurospora crassa* is also reported to produce a copper metallothionein, which serves as a metal donor for apotyrosinase (Lerch 1981). Tanaka et al. (1996) reported an anti-melanoma compound from *Talaromyces* sp. FO-3182, which reduced the melanin content of B16 melanoma cells. Melanocin A was isolated from the fermentation broth and mycelia extract of *Eupenicillium shearii* F80695, showing inhibition against mushroom tyrosinase (IC_{50} = 0.009 μM) and B16 melanoma cells (MIC = 0.9 μM) due to the presence of isocyanide group in the compound (Kim et al. 2003). Two steroids were isolated from the fungus *Cunninghamella elegans*, 17α-ethynyl-11α,17β-dihyroxyandrost-4-en-3-one (IC_{50} = 5950 μM) and 17α-ethyl-11α,17β-dihyroxyandrost-4-en-3-one (IC_{50} = 1720 μM), having tyrosinase inhibition activity (Choudhary et al. 2005).

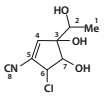
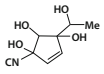
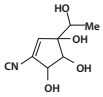
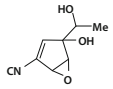
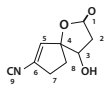
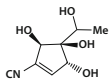
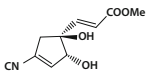
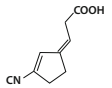
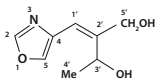
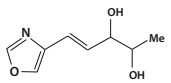
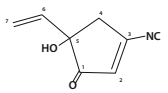
Compound	Structures		Mechanism
MR566A 1-(3-chloro-1,2-dihydroxy-4-isocyano-4-cyclopenten-1-yl)ethanol		IC_{50} = 1.72 μM	• Isocyano group in the compound plays role in inhibition of the enzyme
MR566B 1-(1,2,3-trihydroxy-3-isocyano-4-cyclopenten-1-yl)ethanol		IC_{50} = 47 μM	• Isocyano group in the compound plays role in inhibition of the enzyme
1-(1,4,5-Trihydroxy-3-isocyanocyclopenten-2-enyl)ethanol		IC_{50} = 3.6 μM	• Isocyano group in the compound plays role in inhibition of the enzyme
2-Hydroxy-4-isocyano-α-methyl-6-oxabicyclo[3.1.0]hex-3-ene-3-methanol		IC_{50} = 4.9 μM	• Isocyano group in the compound plays role in inhibition of the enzyme
4-Hydroxy-8-isocyano-1-oxaspiro[4.4]cyclonon-8-en-2-one		IC_{50} = 0.089 μM	• Isocyano group in the compound plays role in inhibition of the enzyme
MR304A		IC_{50} = 47 μM	• Isocyano group in the compound plays role in inhibition of the enzyme
Methyl-3-(1,5-dihydroxy-3-isocyanocyclopent-3-enyl)prop-2 enoate		IC_{50} = 1.72 μM	• Isocyano group in the compound plays role in inhibition of the enzyme
Unidentified		IC_{50} = 0.0014 μM	• Isocyano group in the compound plays role in inhibition of the enzyme
MR93B 4-[(1Z)-3-hydroxy-2-hydroxymethyl-1-propen-1-yl]oxazole		IC_{50} >6000 μM	• Not Known
MR93A		IC_{50} >6000 μM	• Not Known
Homothallin II		IC_{50} = 5.4 x 10^5 Units/mL	• Competitive inhibition

Fig. 2 Structures of tyrosinase inhibitors from *Trichoderma* sp.

Entomopathogenic fungi are a source of several potential bioactive compounds. Three new polyphenolic tyrosinase inhibitors were isolated from an entomopathogenic fungi *Paecilomyces gunnii*, paecilomycones A, B, and C, having IC_{50} values of 110, 170, and 140 μM, respectively, which compete for the active binding site of the enzyme and, in addition, the number of hydroxyl groups present in these compounds also plays a vital role in its inhibitory activity (Lu et al. 2014).

There have been several studies of secondary metabolites from Basidiomycetes with different biological activities, with few studies on tyrosinase inhibition and depigmentation of skin. We have reviewed compounds serving as tyrosinase or melanogenesis inhibitors isolated from mycelia or fruiting bodies of mushrooms (Fig. 4). Two tyrosinase inhibitors have been isolated, purified, and characterized from the mushroom *Agaricus hortensis* with competitive and non-competitive inhibition, respectively (Madhosingh and Sundberg 1974). Similarly, two isomeric compounds having tyrosinase inhibitory activity were isolated from the lipophilic fractions *Albatrellus confluens* and identified as neogrifolin (IC_{50} = 25 μM) and grifolin (IC_{50} = 760 μM), the activities of which are affected by the position of the

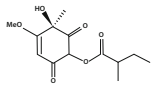
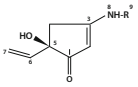
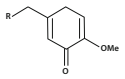
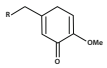
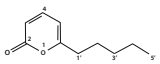
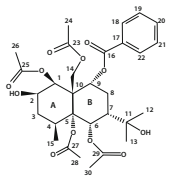
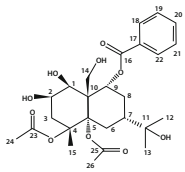
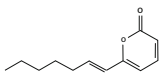
Compound	Structures		Mechanism
Phomaligol A		IC_{50} = n.d	• Not Known
Myrothenone A	R = CHO 	IC_{50} = 6.6 μM	• Not Known
Kojic acid di-methyl ether	R = Me 	IC_{50} = n.d	• Not Known
Kojic acid monomethyl ether	R = H 	IC_{50} = n.d	• Not Known
6-n-pentyl-α-pyrone		IC_{50} = 0.8 μM	• Not Known
1β,5α,6α,14-tetraacetocy-9α-benzolyloxy-7β*H*-eudesman-2β,11-diol		IC_{50} = 14.8 μM	• Not Known
4α,5α-diacetoxy-9α-benzoyloxy-7β*H*-eudesman-1β,2β,11-tetraol		IC_{50} = 22.3 μM	• Not Known
6-[(E)-hept-1-enyl]-a-pyrone		IC_{50} = 4.5 μM	• Not Known

Fig. 3 Structures of tyrosinase inhibitors from marine-derived fungi (*n.d* not defined)

farnesyl group on the aromatic ring (Misasa et al. 1992). Neogrifolin was also isolated from mushroom *Polyporus confluens*, which showed 100% tyrosinase inhibition at 50 ppm (Minosasa et al. 1991). Melanogenesis inhibitor, 2-amino-3H-phenoxazin-3-one was identified from the mushroom *A. bisporus* (Lu et al. 2002). Sharma et al. (2004) reported the methanolic extract of an edible mushroom *Dictyophora indusiata* non-competitively inhibiting mushroom tyrosinase activity and was identified as 5-hydroxymethyl-2-furfural (HMF). However, the carcinogenic potential of HMF in food was found to be contradictory due to limited data from toxicity studies and, therefore, there is a need for improvement in the risk assessment for HMF (Abraham et al. 2011; Capuano and Fogliano 2011). Two tyrosinase inhibitors, 5-hydroxymethyl-2-furaldehyde (IC_{50} = 720 μM) and protocatechualdehyde (IC_{50} = 2.896 μM), were isolated from the fruiting body of a medicinal mushroom *Phellinus linteus*. Protocatechualdehyde competitively binds to the copper active site with its hydroxyl group and possibly chelating the copper in tyrosinase, whereas 5-hydroxymethyl-2-furaldehyde is a non-competitive inhibitor which may form a Schiff base with primary amino groups in the enzyme, rather than binding to the active site (Kang et al. 2004). A chromene type compound, daedalin A (IC_{50} = 194 μM), was reported from the mycelia culture broth of the mushroom *Daedalea dickinsii*, which competitively inhibited tyrosinase, for its substrate L-tyrosine. Further studies on the application of this compound in an in vitro human skin model substantiated its activity on suppressing melanogenesis without affecting cell viability by directly inhibiting tyrosinase activity in melanocytes (Morimura et al. 2007, 2009).

Tyrosinase inhibitors from bacteria

Bacterial metabolites represent a diverse array of chemical compounds with different biological activities. Several reports of tyrosinase inhibition by bacteria have been discussed in this

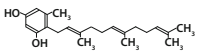
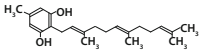
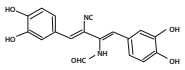
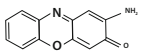
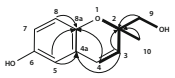
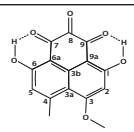
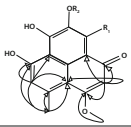
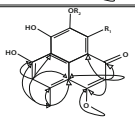
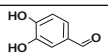
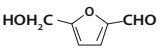
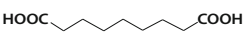
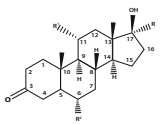
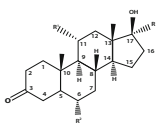
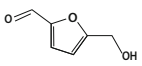
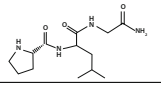
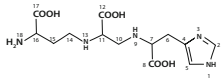
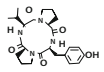
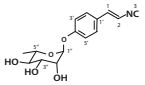
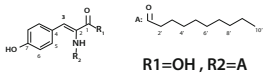
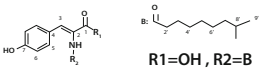
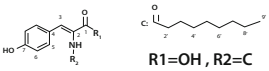
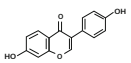
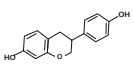
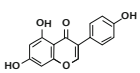
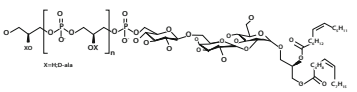
Compound	Structures	Mechanism
Neogrifolin	IC_{50} = 25 μM 	• Not Known
Grifolin	IC_{50} = 760 μM 	• Not Known
Melanocins A	IC_{50} = 0.009 μM 	• Isocyanide group in the compound plays a role in inhibition of the enzyme
2-amino-3H-phenoxazin-3-one	IC_{50} = n.d 	• Not Known
Daedalin A	IC_{50} = 194 μM 	• Competes with the substrate L-tyrosine of the enzyme tyrosinase.
Unidentified	IC_{50} = n.d 	• Not Known
Paecilomycones B	IC_{50} = 170 μM 	• Competes for the active binding site of the enzyme.
Paecilomycones A	IC_{50} = 110 μM  R1=OH R2=H	• Competes for the active binding site of the enzyme.
Paecilomycones C	IC_{50} = 140 μM  $R1=NH_2$ R2=H	• Competes for the active binding site of the enzyme.
Protocatechualdehyde	IC_{50} = 2.9 μM 	• Competes with copper active site of the enzyme with its hydroxyl group. • Chelates copper in the active site of the wnzyme.
5-Hydroxymethyl-1,2-furfural (HMF)	IC_{50} = n.d 	• Non-Competitevly inhibits by forming a Schiff base with primary amino groups in the enzyme.
Azelaic acid	IC_{50} = n.d 	• Competes for the α-carboxylate binding site of L-tyrosine substrate of the enzyme.
17 α-ethynyl-11 α,17β-dihydroxyandrost-4-en-3-one	IC_{50} = 5950 μM  R=-C≡C, Δ^4 R1=OH R2=H	• Not known
17 α-ethyl-11 α,17β-dihydroxyandrost-4-en-3-one	IC_{50} = 1720 μM  R=-H_2C—CH_3,Δ^4 R1=OH R2=H	• Not known
5-Hydroxy-xymethyl-2-furaldehyde	IC_{50} = 720 μM 	• Not-competitive inhibition

Fig. 4 Structures of tyrosinase inhibitors from other fungi (*n.d* not defined)

article (Fig. 5). Among them, *Streptomyces* sp. serves as a potential source of several bioactive compounds, including enzyme inhibitors (Umezawa 1972). There have been several reports on tyrosinase inhibition from the genus *Streptomyces*.

Compound	Structures		Mechanism
Melanostatin		IC_{50} > 703.3 μM	• Inhibits tyrosinase through post-translational modification of the enzyme or other moduatory proteins.
Amphistin		IC_{50} = 6.8 μM	• Inhibits tyrosinase through post-translational modification of the enzyme or other moduatory proteins.
Cyclo(-L-Pro-L-Tyr-L-Pro-L-Val-)		IC_{50} = n.d	• Not Known
Byelyankacin		IC_{50} = 0.0021 μM; 0.03 μM	• Isocyanide group binds to copper active site of the enzyme.
Albocycline K3		IC_{50} = n.d	• Not Known
OH-3984 K1		IC_{50} = n.d	• Not Known
OH-3984 K2	R=H 	IC_{50} = n.d	• Not Known
Thalassotalic acid A	 R1=OH , R2=A	IC_{50} = 130 μM	• Not Known
Thalassotalic acid B	 R1=OH , R2=B	IC_{50} = 470 μM	• Not Known
Thalassotalic acid C	 R1=OH , R2=C	IC_{50} = 280 μM	• Not Known
12815 A (Streptochlorin)		IC_{50} = 9 μM	• Competitive inhibition
12815 B		IC_{50} = 1086 μM	Not Known
Daidzein		IC_{50} = n.d	• Suppresses gene encoding melanocortin receptor-1. • Interferes with phosphorylation MAPK, extracellular signal regulated kinase and glycogen synthase kinase. • Decreases expression of tyrosinase, TRP-1 and TRP-2.
Equol		IC_{50} = n.d	• Suppresses gene encoding melanocortin receptor-1. • Interferes with phosphorylation MAPK, extracellular signal regulated kinase and glycogen synthase kinase. • Decreases expression of tyrosinase, TRP-1 and TRP-2.
Genistein		IC_{50} = n.d	• Suppresses tyrosinase activity and expression through positive regulator, MITF and MAPK inactivation.
Lipoteichoic acid		IC_{50} = n.d	• Reduces activity and expression of tyrosinase. • Degrades MITF via regulation of signaling and RNA stability of proteins involved in melanogenesis.
Uracil		IC_{50} = n.d	• Down-regulation of transcription gene encoding melanocortin 1 receptor. • Decreases phosphorylation of cAMP response element-binding protein. • Represses expression of MITF

◀ **Fig. 5** Structures of tyrosinase inhibitors from bacterial source (*n.d* not defined)

Melanostatin isolated from the fermentation broth of *S. claviver* N924-2 inhibited melanin formation in B16 melanoma cells ($IC_{50} > 703.34$ μM) (Ishihara et al. 1991). Three compounds, OH-3984 K1, OH-3984 K3, and albocycline K3, a macrocyclic compound isolated from *Streptomyces* sp. OH-3984, inhibited melanogenesis of B16 melanoma cells at concentrations of 7.5, 3.8, and 15 μg/mL respectively; however the mechanism of action is unknown (Takamatsu et al. 1993, 1996). Arai et al. (1997) reported melanogenesis inhibitor produced by *Streptomyces* sp. KP-3052, which was identified as amphistin with $IC_{50} = 6.8$ μM against the growth of B16 melanoma cells. Amphistin is a pseudotripeptide with activity similar to melanostatin and feldamycin, which inhibits tyrosinase through post-translational modification of the enzyme or other modulatory proteins. Imada et al. (2001) screened and reported two bacterial isolates, one being actinobacteria producing tyrosinase inhibitor, having 19 and 6 U/mL inhibitory activity, respectively. Chang and Tseng (2006) isolated and screened actinobacteria from forest soil for anti-tyrosinase activity; one bacterial strain, *Streptomyces* sp. TI-B10, showed the highest tyrosinase activity (46 U/mL), which was further improved to 73 U/mL when cultured in YMG medium at pH 8.0 and 30 °C. Chang et al. (2008) reported *S. hiroshimensis* TI-C3 isolated from soil, showing anti-tyrosinase activity (498 U/mL) with enhanced activity (905 U/mL) using glucose and malt extract as the sole carbon and nitrogen sources, respectively. *Streptomyces roseolilacinus* NBRC 12815 produced two compounds, 12815 A ($IC_{50} = 9$ μM) and B ($IC_{50} = 1086$ μM), showing anti-tyrosinase activity against mushroom and mammalian tyrosinases. However, 12815 A was further identified as streptochlorin, which was found to be a competitive inhibitor of tyrosinase with anti-nematode activity and cytotoxicity (Nakashima et al. 2009). This study also suggested that compound 12815 A produced by *S. roseolilacinus* and its companions could be a common feature in related species.

Several studies on melanogenesis inhibitors have been reported from Gram-negative bacteria. Takahashi et al. (2007) reported an *Enterobacter* sp. B20 isolated from soil produced a novel potent melanogenesis inhibitor, byelyankacin, which inhibited tyrosinase ($IC_{50} = 0.0021$ μM) by binding its isocyanide group to the copper active site of the enzyme, and also inhibited melanogenesis of B16-2D2 melanoma cells ($IC_{50} = 0.03$ μM). *Burkholderia cepacia* TKU025, a Gram-negative bacteria isolated from soil, also produced tyrosinase inhibitor (2890 U/mL) in nutrient broth, which was maximized after cultivation in 1% squid pen as a sole C/N source to 5000 U/mL. The inhibitor was stable at varying pH conditions (pH 2–12) and thermostable at 100 °C for 60 min. The partially purified methanol extract of the metabolite exhibited an IC_{50} value of 2 μg/mL (Hsu et al. 2014; Liang et al. 2015). In addition, tyrosinase inhibitors are reported from a marine Gram-negative bacterium, *Thalassotalea* sp. PP2-459 isolated from a marine bivalve and identified as thalassotalic acid A, B, and C, with IC_{50} values of 130, 470, and 280 μM, respectively. Thalassotalic acids are N-acyl dehydrotyrosine derivatives produced by this bacterium, thalassotalic acid A being comparable to the inhibitory activity of arbutin and could be used as a whitening agent or in preventing browning of foods. They suggest that the presence of a carboxylic acid and a straight aliphatic chain increased enzyme inhibition within this structural class of inhibitors (Deering et al. 2016).

Probiotics such as *Lactobacillus* sp. and *Bifidobacterium* sp. have been used in several fermented food products. In addition, the fermented by-products of such probiotic bacteria have been recently explored for bioactive compounds with applications in cosmetics. Several investigators have reported fermented substrates that inhibit tyrosinase activity and melanogenesis. Lactobacilli and bifidobacteria are the two major bacteria involved in fermentation, resulting in producing metabolites suppressing melanogenesis. *Lactobacillus helveticus* produced a novel tyrosinase inhibitor, identified as a cyclic tetra peptide, cyclo(-L-Pro-L-Tyr-L-Pro-L-Val-), by Kawagishi et al. (1993). *Lactobacillus plantarum* M23 isolated from raw milk showed better tyrosinase inhibitory activity as compared to commercial lactic acid bacteria, showing 52.1% tyrosinase inhibition and 32% inhibition of melanoma B16 cells. Tyrosinase inhibition activity was enhanced to 84.05% in fermented milk by the addition of yeast extract and grape, incubated at 37.1 °C for 14.8 h (Heo et al. 2007; Lim and Kim 2012). In addition, Kuwaki et al. (2012) reported a plant-based paste fermented by a lactic acid bacteria and yeast, and extracted with PBS, which demonstrated anti-tyrosinase activity with an IC_{50} value 58.5 mg/mL. *Bifidobacterium adolescentis* culture filtrate was found to decrease melanogenesis of melanoma cell by inhibiting tyrosinase activity mediated by its antioxidant property (Huang and Chang 2012). Tsai et al. (2013) reported *L. rhamnosus* spent culture supernatant showing 71.3% tyrosinase inhibitory activity, where the supernatant showed no difference in activity on heating at 100 °C for 30 min. Chen et al. (2013) reported extracts from *L. plantarum* TWK10 fermented soy milk to inhibit tyrosinase activity (38.33%) and melanin production in B16F0 melanocytes (27.56%) compared to non-fermented soy milk, structurally elucidated as an aglycone isoflavone similar to daidzein, equol, or genistein. These isoflavones have been known to be non-toxic to the reproductive tract of female rats (Fritz et al. 1998; Lamartiniere et al. 2002). Chen et al. (2013) further report the inhibition of melanogenesis by suppressing tyrosinase activity and expression through a positive regulator, microphthalmia-associated transcription factor (MITF) and p38 MAPK inactivation. Daidzein

and equol reduced the melanin content by suppressing gene encoding melanocortin receptor-1, interfering with phosphorylation of p38 MAPK, phosphorylation of extracellular signal regulated kinase and glycogen synthase kinase, and decreasing the expression of tyrosinase, TRP-1, and TRP-2 (Chang and Tsai 2016). Kim et al. (2015) further report a cell wall component of *L. plantarum*, lipoteichoic acid, to inhibit melanogenesis in B16F10 mouse melanoma cells by reducing the activity and expression of tyrosinase and, also, likely by degrading MITF via the regulation of signaling and RNA stability of proteins involved in melanogenesis. Interestingly, the metabolite had no effect on mushroom tyrosinase. *Lactobacillus plantarum* TWK10, an organism responsible for fermenting soy milk, contained a metabolite exhibiting anti-melanogenesis in B16F0 mouse melanoma cells, where the melanogenic inhibitor was identified as uracil. Its activity was found to be due to the downregulation of a transcription gene encoding melanocortin 1 receptor, decreasing phosphorylation of cAMP response element-binding protein, and repressing the expression of MITF (Chang et al. 2015). Exopolysaccharides (EPS) isolated from *L. sakei* Probio 65 have also been reported, with tyrosinase inhibiting activity in the range 13.17–62.85% (Bajpai et al. 2016). Wang et al. (2016) reported tyrosinase inhibition activity in walnuts, Moutan Cortex Radicis, and asparagus root extract fermented by *B. bifidum* with IC_{50} values of 420, 380, and 260 μg/mL, respectively. The study also reports the fermented extract to have low cytotoxic activity as compared to unfermented extracts.

Conclusions

Tyrosinase plays a vital role in the enzymatic browning of food and depigmentation disorders in humans. Thus, targeting tyrosinase inhibitors could be the best solution in preventing such problems. Natural product research still has an enormous unexplored potential with microorganisms representing promising sources producing anti-tyrosinase metabolites in high yields with feasible extraction methods at a reasonable cost. Thousands of bacterial metabolites have been reported with wide application in varied sectors. However, the chemical diversity in the metabolites produced by microorganisms remains an unparalleled resource for the discovery of new compounds for application in the agriculture, cosmetics, and pharmaceutical industries. This review, therefore, compiles an updated database of tyrosinase or melanogenesis inhibitors reported from microbial sources. Tyrosinase inhibitors isolated from natural sources comprise a small group, with the majority of the compounds identified from plant sources and marginally from microbial sources. Although tyrosinase inhibitors isolated from plant sources are diverse, belonging to the family of polyphenol, benzaldehyde derivatives, anthraquinones, lipids, and steroids, inhibitors isolated from fungi are structurally comparable to those from plant sources. Tyrosinase inhibitors from fungi are derivatives of isoflavones and pyrones, along with terpenes, steroids, and alkaloids, which may reversibly or irreversibly inactivate the enzyme. In contrast, tyrosinase inhibitors from bacteria comprise a smaller group, belonging to alkaloids, macrolides, and polyphenols, which competitively inhibit the enzyme. However, profound work on the mechanism of these compounds needs to be established. To conclude, the information provided could serve as leads in the search for new inhibitors from microorganisms with increased efficiency and safety in the food and cosmetics industries.

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Compliance with ethical standards

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Conflict of interest The authors declare that there is no conflict of interest regarding the publication of this manuscript.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

References

Abraham K, Gürtler R, Berg K, Heinemeyer G, Lampen A, Appel KE (2011) Toxicology and risk assessment of 5-Hydroxymethylfurfural in food. Mol Nutr Food Res 55:667–678. doi:10.1002/mnfr.201000564

Arai N, Shiomi K, Takamatsu S, Komiyama K, Shinose M, Takahashi Y, Tanaka Y, Iwai Y, Liu JR, Omura S (1997) Amphistin, a new melanogenesis inhibitor, produced by an actinomycete. J Antibiot 50(10):808–814

Bajpai VK, Rather IA, Park YH (2016) Partially purified exopolysaccharide from *Lactobacillus sakei* Probio 65 with antioxidant, α-glucosidase and tyrosinase inhibitory potential. J Food Biochem 40(3):264–274. doi:10.1111/jfbc.12230

Bertolotto C, Abbe P, Hemesath TJ, Bille K, Fisher DE, Ortonne JP, Ballotti R (1998) Microphthalmia gene product as a signal transducer in cAMP-induced differentiation of melanocytes. J Cell Biol 142:827–835

Borges CR, Roberts JC, Wilkins DG, Rollins DE (2001) Relationship of melanin degradation products to actual melanin content: application to human hair. Anal Biochem 290:116–125

Brenner M, Hearing VJ (2008) The protective role of melanin against UV damage in human skin. Photochem Photobiol 84(3):539–549

Burdock GA, Soni MG, Carabin IG (2001) Evaluation of health aspects of kojic acid in food. Regul Toxicol Pharmacol 33(1):80–101

Busch JM (1999) Enzymic browning in potatoes: a simple assay for a polyphenol oxidase catalysed reaction. Biochem Educ 27:171–173

Cabrera-Valladares N, Martínez A, Piñero S, Lagunas-Munoz VH, Tinoco R, De Anda R, Vázquez-Duhalt R, Bolívar F, Gosset G

(2006) Expression of the *melA* gene from *Rhizobium etli* CFN42 in *Escherichia coli* and characterization of the encoded tyrosinase. Enzym Microb Technol 38:772–779

Capuano E, Fogliano V (2011) Acrylamide and 5-hydroxymethylfurfural (HMF): a review on metabolism, toxicity, occurrence in food and mitigation strategies. Food Sci Technol 44:793–810

Cerenius L, Söderhäll K (2004) The prophenoloxidase-activating system in invertebrates. Immunol Rev 198:116–126

Chan CF, Huang CC, Lee MY, Lin YS (2014) Fermented broth in tyrosinase and melanogenesis inhibition. Molecules 19:13122–13135

Chang TS (2009) An updated review of tyrosinase inhibitors. Int J Mol Sci 10:2440–2475

Chang TS (2012a) Natural melanogenesis inhibitors acting through the down-regulation of tyrosinase activity. Materials 5:1661–1685

Chang TM (2012b) Tyrosinase and tyrosinase inhibitors. J Biocatal Biotransfor 1:2

Chang CJ, Tsai TY (2016) Antimelanogenic effects of the novel melanogenic inhibitors daidzein and equol, derived from soymilk fermented with *Lactobacillus plantarum* strain TWK10, in B16F0 mouse melanoma cells. J Funct Foods 22:211–223

Chang TS, Tseng M (2006) Preliminary screening of soil actinomycetes for anti-tyrosinase activity. J Mar Sci Technol 14(3):190–193

Chang TS, Ding HY, Tai SS, Wu CY (2007) Mushroom tyrosinase inhibitory effects of isoflavones isolated from soygerm koji fermented with *Aspergillus oryzae* BCRC 32288. Food Chem 105:1430–1438

Chang TS, Tseng M, Ding HY, Tai SS (2008) Isolation and characterization of *Streptomyces hiroshimensis* strain TI-C3 with anti-tyrosinase activity. J Cosmet Sci 59:33–40

Chang CJ, Dai RY, Leu YL, Tsai TY (2015) Effects of the melanogenic inhibitor, uracil, derived from *Lactobacillus plantarum* TWK10-fermented soy milk on anti-melanogenesis in B16F0 mouse melanoma cells. J Funct Foods 17:314–327

Chen YM, Shih TW, Chiu CP, Pan TM, Tsai TY (2013) Effects of lactic acid bacteria-fermented soy milk on melanogenesis in B16F0 melanocytes. J Funct Foods 5:395–405

Chen CY, Lin LC, Yang WF, Bordon J, Wang HMD (2015) An updated organic classification of tyrosinase inhibitors on melanin biosynthesis. Curr Org Chem 19:4–18

Choudhary MI, Sultan S, Khan MTH, Atta-ur-Rahman (2005) Microbial transformation of 17α-ethynyl- and 17α-ethylsteroids, and tyrosinase inhibitory activity of transformed products. Steroids 70:798–802

Claus H, Decker H (2006) Bacterial tyrosinases. Syst Appl Microbiol 29: 3–14

Dalfard AB, Khajeh K, Soudi MR, Naderi-Manesh H, Ranjbar B, Sajedi RH (2006) Isolation and biochemical characterization of laccase and tyrosinase activities in a novel melanogenic soil bacterium. Enzym Microb Technol 39:1409–1416

Deering RW, Chen J, Sun J, Ma H, Dubert J, Barja JL, Seeram NP, Wang H, Rowley DC (2016) N-acyl dehydrotyrosines, tyrosinase inhibitors from the marine bacterium *Thalassotalea* sp. PP2-459. J Nat Prod 79:447–450. doi:10.1021/acs.jnatprod.5b00972

Fritz WA, Coward L, Wang J, Lamartiniere CA (1998) Dietary genistein: perinatal mammary cancer prevention, bioavailability and toxicity testing in the rat. Carcinogenesis 19(12):2151–2158

Fujii Y, Asahara M, Ichinoe M, Nakajima H (2002) Fungal melanin inhibitor and related compounds from *Penicillium decumbens*. Phytochemistry 60(7):703–708

García-Borrón JC, Solano F (2002) Molecular anatomy of tyrosinase and its related proteins: beyond the histidine-bound metal catalytic center. Pigment Cell Res 15:162–173

Goetghebeur M, Kermasha S (1996) Inhibition of polyphenol oxidase by copper-metallothionein from *Aspergillus niger*. Phytochemistry 42: 935–940

Gillbro JM, Olsson MJ (2011) The melanogenesis and mechanisms of skin-lightening agents—existing and new approaches. Int J Cosmet Sci 33:210–221. doi:10.1111/j.1468-2494.2010.00616.x

Goldfeder M, Kanteev M, Isaschar-Ovdat S, Adir N, Fishman A (2014) Determination of tyrosinase substrate-binding modes reveals mechanistic differences between type-3 copper proteins. Nat Commun 5: 4505. doi:10.1038/ncomms5505

Halaouli S, Asther M, Kruus K, Guo L, Hamdi M, Sigoillot JC, Asther M, Lomascolo A (2005) Characterization of a new tyrosinase from *Pycnoporus* species with high potential for food technological applications. J Appl Microbiol 98:332–343

Halaouli S, Asther M, Sigoillot JC, Hamdi M, Lomascolo A (2006) Fungal tyrosinases: new prospects in molecular characteristics, bioengineering and biotechnological applications. J Appl Microbiol 100(2):219–232

Haudecoeur R, Gouron A, Dubois C, Jamet H, Lightbody M, Hardré R, Milet A, Bergantino E, Bubacco L, Belle C, Réglier M, Boumendjel A (2014) Investigation of binding-site homology between mushroom and bacterial tyrosinases by using aurones as effectors. Chembiochem 15(9):1325–1333. doi:10.1002/cbic.201402003

Hemesath TJ, Price ER, Takemoto C, Badalian T, Fisher DE (1998) MAP kinase links the transcription factor Microphthalmia to c-Kit signalling in melanocytes. Nature 391:298–301

Hennessy BT, Smith DL, Ram PT, Lu Y, Mills GB (2005) Exploiting the PI3K/AKT pathway for cancer drug discovery. Nat Rev Drug Discov 4:988–1004

Heo IS, Kim KS, Yang SY, Lee NH, Lim SD (2007) Physiological characteristics and tyrosinase inhibitory activity of *Lactobacillus plantarum* M23 isolated from raw milk. Korean J Food Sci Anim Resour 27(4):501–508

Hernández-Romero D, Solano F, Sanchez-Amat A (2005) Polyphenol oxidase activity expression in *Ralstonia solanacearum*. Appl Environ Microbiol 71(11):6808–6815. doi:10.1128/AEM.71.11.6808-6815.2005

Hernández-Romero D, Sanchez-Amat A, Solano F (2006) A tyrosinase with an abnormally high tyrosine hydroxylase/dopa oxidase ratio. FEBS J 273:257–270

Hsu CH, Nguyen AD, Chen YW, Wang SL (2014) Tyrosinase inhibitors and insecticidal materials produced by *Burkholderia cepacia* using squid pen as the sole carbon and nitrogen source. Res Chem Intermed 40:2249–2258. doi:10.1007/s11164-014-1602-0

Huang HC, Chang TM (2012) Antioxidative properties and inhibitory effect of *Bifidobacterium adolescentis* on melanogenesis. World J Microbiol Biotechnol 28(9):2903–2912

Ichishima E, Maeba H, Amikura T, Sakata H (1984) Multiple forms of protyrosinase from *Aspergillus oryzae* and their mode of activation at pH 3.0. Biochim Biophys Acta 786:25–31

Imada C (2004) Enzyme inhibitors of marine microbial origin with pharmaceutical importance. Mar Biotechnol 6:193–198

Imada C, Sugimoto Y, Makimura T, Kobayashi T, Hamada N, Watanabe E (2001) Isolation and characterization of tyrosinase inhibitor-producing microorganisms from marine environment. Fish Sci 67: 1151–1156

Ioannou I, Ghoul M (2013) Prevention of enzymatic browning in fruit and vegetables. Eur Sci J 9(30):310–341

Ishihara Y, Oka M, Tsunakawa M, Tomita K, Hatori M, Yamamoto H, Kamei H, Miyaki T, Konishi M, Oki T (1991) Melanostatin, a new melanin synthesis inhibitor. Production, isolation, chemical properties, structure and biological activity. J Antibiot 44(1):25–32

Kanda K, Sato T, Ishii S, Enei H, Ejiri S (1996) Purification and properties of tyrosinase isozymes from the gill of *Lentinus edodes* fruiting body. Biosci Biotechnol Biochem 60:1273–1278

Kang HS, Choi JH, Cho WK, Park JC, Choi JS (2004) A sphingolipid and tyrosinase inhibitors from the fruiting body of *Phellinus linteus*. Arch Pharm Res 27(7):742–750

Kanteev M, Goldfeder M, Fishman A (2015) Structure–function correlations in tyrosinases. Protein Sci 24:1360–1369

Katz E, Thompson CJ, Hopwood DA (1983) Cloning and expression of the tyrosinase gene from *Streptomyces antibioticus* in *Streptomyces lividans*. J Gen Microbiol 129:2703–2714

Kawagishi H, Somoto A, Kuranari J, Kimura A, Chiba S (1993) A novel cyclotetrapeptide produced by *Lactobacillus helveticus* as a tyrosinase inhibitor. Tetrahedron Lett 34(21):3439–3440

Khan MTH (2007) Molecular design of tyrosinase inhibitors: a critical review of promising novel inhibitors from synthetic origins. Pure Appl Chem 79(12):2277–2295

Kilimnik A, Dembitsky VM (2016) Anti-melanoma agents derived from fungal species. Mathews J Pharm Sci 1(1):002

Kim YJ, Uyama H (2005) Tyrosinase inhibitors from natural and synthetic sources: structure, inhibition mechanism and perspective for the future. Cell Mol Life Sci 62:1707–1723

Kim JP, Kim BK, Yun BS, Ryoo IJ, Lee CH, Lee IK, Kim WG, Lee S, Pyun YR, Yoo ID (2003) Melanocins A, B and C, new melanin synthesis inhibitors produced by *Eupenicillium shearii* I. Taxonomy, fermentation, isolation and biological properties. J Antibiot 56(12):993–999

Kim WG, Ryoo IJ, Park SH, Kim DS, Lee S, Park KC, Yoo ID (2005) Terrein, a melanin biosynthesis inhibitor, from *Penicillium* sp. 20135. J Microbiol Biotechnol 15(4):891–894

Kim DS, Cho HJ, Lee HK, Lee WH, Park ES, Youn SW, Park KC (2007) Terrein, a fungal metabolite, inhibits the epidermal proliferation of skin equivalents. J Dermatol Sci 46(1):65–68

Kim DS, Lee HK, Park SH, Lee S, Ryoo IJ, Kim WG, Yoo ID, Na JI, Kwon SB, Park KC (2008) Terrein inhibits keratinocyte proliferation via ERK inactivation and G2/M cell cycle arrest. Exp Dermatol 17(4):312–317

Kim HR, Kim H, Jung BJ, You GE, Jang S, Chung DK (2015) Lipoteichoic acid isolated from *Lactobacillus plantarum* inhibits melanogenesis in B16F10 mouse melanoma cells. Mol Cells 38(2):163–170

Kobayashi T, Vieira WD, Potterf B, Sakai C, Imokawa G (1995) Modulation of melanogenic protein expression during the switch from eu- to pheomelanogenesis. J Cell Sci 108:2301–2309

Kong KH, Hong MP, Choi SS, Kim YT, Cho SH (2000) Purification and characterization of a highly stable tyrosinase from *Thermomicrobium roseum*. Biotechnol Appl Biochem 31(2):113–118. doi:10.1042/BA19990096

Kuwaki S, Nakajima N, Tanaka H, Ishihara K (2012) Plant-based paste fermented by lactic acid bacteria and yeast: functional analysis and possibility of application to functional foods. Biochem Insights 5:21–29. doi: 10.4137/BCI.S10529

Lamartiniere CA, Wang J, Smith-Johnson M, Eltoum IE (2002) Daidzein: bioavailability, potential for reproductive toxicity, and breast cancer chemoprevention in female rats. Toxicol Sci 65:228–238

Lee CH, Chung MC, Lee HJ, Kho YH, Lee KH (1995) MR304-1, a melanin synthesis inhibitor produced by *Trichoderma harzianum*. Korean J Appl Microbiol Biotechnol 23(6):641–646

Lee CH, Chung MC, Lee HJ, Bae KS, Kho YH (1997a) MR566A and MR566B, new melanin synthesis inhibitors produced by *Trichoderma harzianum*. I. Taxonomy, fermentation, isolation and biological activities. J Antibiot 50(6):469–473

Lee CH, Koshino H, Chung MC, Lee HJ, Hong JK, Yoon JS, Kho YH (1997b) MR566A and MR566B, new melanin synthesis inhibitors produced by *Trichoderma harzianum*. II. Physico-chemical properties and structural elucidation. J Antibiot 50(6):474–478

Lerch K (1981) Copper monooxygenases: tyrosinase and dopamine β-monooxygenase. In: Sigel H (ed) Metal ions in biological systems. Marcel Dekker, New York, pp 143–186

Lerch K (1983) *Neurospora* tyrosinase: structural, spectroscopic and catalytic properties. Mol Cell Biochem 52:125–138

Lerch K, Ettinger L (1972) Purification and characterization of a tyrosinase from *Streptomyces glaucescens*. Eur J Biochem 31:427–437

Li X, Jeong JH, Lee KT, Rho JR, Choi HD, Kang JS, Son BW (2003) Gamma-pyrone derivatives, kojic acid methyl ethers from a marine-derived fungus *Alternaria* sp. Arch Pharm Res 26(7):532–534

Li X, Kim MK, Lee U, Kim SK, Kang JS, Choi HD, Son BW (2005) Myrothenones A and B, cyclopentenone derivatives with tyrosinase inhibitory activity from the marine-derived fungus *Myrothecium* sp. Chem Pharm Bull 53(4):453–455

Liang TW, Lee YC, Wang SL (2015) Tyrosinase inhibitory activity of supernatant and semi-purified extracts from squid pen fermented with *Burkholderia cepacia* TKU025. Res Chem Intermed 41(9):6105–6116

Likhitwitayawuid K (2008) Stilbenes with tyrosinase inhibitory activity. Curr Sci 94(1):44–52

Lim SD, Kim KS (2012) Optimization of tyrosinase inhibitory activity in the fermented milk by *Lactobacillus plantarum* M23. Korean J Food Sci Anim Resour 32(5):678–684

Lin JW, Chiang HM, Lin YC, Wen KC (2008) Natural products with skin-whitening effects. J Food Drug Anal 16(2):1–10

Liu N, Zhang T, Wang YJ, Huang YP, Ou JH, Shen P (2004) A heat inducible tyrosinase with distinct properties from *Bacillus thuringiensis*. Lett Appl Microbiol 39:407–412

Loizzo MR, Tundis R, Menichini F (2012) Natural and synthetic tyrosinase inhibitors as antibrowning agents: an update. Compr Rev Food Sci Food Saf 11:378–398

Lu Q, Tian M, Liu Y, Yu D (2002) Isolation and structure elucidation of melanin biosynthesis inhibitors H7264 A and B. Zhongguo Kangshengsu Zazhi 27(7):385–386

Lu R, Liu X, Gao S, Zhang W, Peng F, Hu F, Huang B, Chen L, Bao G, Li C, Li Z (2014) New tyrosinase inhibitors from *Paecilomyces gunnii*. J Agric Food Chem 62(49):11917–11923. doi:10.1021/jf504128c

Madhosingh C, Sundberg L (1974) Purification and properties of tyrosinase inhibitor from mushroom. FEBS Lett 49:156–158

Matoba Y, Kumagai T, Yamamoto A, Yoshitsu H, Sugiyama M (2006) Crystallographic evidence that the dinuclear copper center of tyrosinase is flexible during catalysis. J Biol Chem 281:8981–8990

Mayer AM (1987) Polyphenol oxidases in plants—recent progress. Phytochemistry 26:11–20

Mayer AM, Harel E (1979) Polyphenol oxidases in plants. Phytochemistry 18:193–215

McMahon AM, Doyle EM, Brooks S, O'Connor KE (2007) Biochemical characterisation of the coexisting tyrosinase and laccase in the soil bacterium *Pseudomonas putida* F6. Enzym Microb Technol 40:1435–1441

Meinkoth JL, Montminy MR, Fink JS, Feramisco JR (1991) Induction of a cyclic AMP-responsive gene in living cells requires the nuclear factor CREB. Mol Cell Biol 11:1759–1764

Menon S, Fleck RW, Yong G, Strothkamp KG (1990) Benzoic acid inhibition of the α, β, and γ isozymes of *Agaricus bisporus* tyrosinase. Arch Biochem Biophys 280:27–32

Michalik J, Emilianowicz-Czerska W, Switalski L, Raczynska-Bojanowska K (1975) Monophenol monooxygenase and lincomysin biosynthesis in *Streptomyces lincolnensis*. Antimicrob Agents Chemother 8(5):526–531

Minosasa J, Matsui K, Uehara H, Tanaka H (1991) Tyrosinase inhibitors containing neogrifolin. Jpn Kokai Tokkyo Koho, 15 Japanese Patent: JP 03109319 A 19910509 Heisei

Misasa H, Matsui Y, Uehara H, Tanaka H, Ishihara M, Shibata H (1992) Tyrosinase inhibitors from *Albatrellus confluens*. Biosci Biotechnol Biochem 56(10):1660–1661

Morimura K, Yamazaki C, Hattori Y, Makabe H, Kamo T, Hirota M (2007) A tyrosinase inhibitor, Daedalin A, from mycelial culture of *Daedalea dickinsii*. Biosci Biotechnol Biochem 71(11):2837–2840

Morimura K, Hiramatsu K, Yamazaki C, Hattori Y, Makabe H, Hirota M (2009) Daedalin A, a metabolite of *Daedalea dickinsii*, inhibits

melanin synthesis in an in vitro human skin model. Biosci Biotechnol Biochem 73(3):627–632. doi:10.1271/bbb.80695

Müller WE, Grebenjuk VA, Thakur NL, Thakur AN, Batel R, Krasko A, Müller IM, Breter HJ (2004) Oxygen-controlled bacterial growth in the sponge *Suberites domuncula*: toward a molecular understanding of the symbiotic relationships between sponge and bacteria. Appl Environ Microbiol 70:2332–2341

Nakashima T, Anzai K, Kuwahara N, Komaki H, Miyadoh S, Harayama S, Tianero MDB, Tanaka J, Kanamoto A, Ando K (2009) Physicochemical characters of a tyrosinase inhibitor produced by *Streptomyces roseolilacinus* NBRC 12815. Biol Pharm Bull 32(5): 832–836

Nambudiri AMD, Bhat JV, Rao PVS (1972) Conversion of p-coumarate into caffeate by *Streptomyces nigrifaciens*: purification and properties of the hydroxylating enzyme. Biochem J 130:425–433

Nicolas JJ, Richard-Forget FC, Goupy PM, Amiot MJ, Aubert SY (1994) Enzymatic browning reactions in apple and apple products. Crit Rev Food Sci Nutr 34:109–157

Nohynek GJ, Kirkland D, Marzin D, Toutain H, Leclerc-Ribaud C, Jinnai H (2004) An assessment of the genotoxicity and human health risk of topical use of kojic acid [5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one]. Food Chem Toxicol 42:93–105

Park SH, Kim DS, Kim WG, Ryoo IJ, Lee DH, Huh CH, Youn SW, Yoo ID, Park KC (2004) Terrein: a new melanogenesis inhibitor and its mechanism. Cell Mol Life Sci 61:2878–2885

Parvez S, Kang M, Chung HS, Bae H (2007) Naturally occurring tyrosinase inhibitors: mechanism and applications in skin health, cosmetics and agriculture industries. Phytother Res 21:805–816

Philipp S, Held T, Kutzner HJ (1991) Purification and characterization of the tyrosinase of *Streptomyces michiganensis* DSM 40015. J Basic Microbiol 31:293–300

Pomerantz SH, Murthy VV (1974) Purification and properties of tyrosinases from *Vibrio tyrosinaticus*. Arch Biochem Biophys 160(1):73–82

Raistrick H, Smith G (1935) Studies in the biochemistry of micro-organisms: the metabolic products of *Aspergillus terreus* Thom. A new mould metabolic product—terrein. Biochem J 29(3):606–611

Raper HS (1928) The anaerobic oxidases. Physiol Rev 8:245–282

Razak DLA, Rashid NYA, Jamaluddin A, Sharifudin SA, Kahar AA, Long K (2015) Cosmeceutical potentials and bioactive compounds of rice bran fermented with single and mix culture of *Aspergillus oryzae* and *Rhizopus oryzae*. J Saudi Soc Agric Sci. doi:10.1016/j.jssas.2015.04.001

Robb DA (1984) Tyrosinase. In: Lontie R (ed) Copper proteins and copper enzymes, vol 2. CRC Press, Boca Raton, pp 207–241

Ruan L, He W, He J, Sun M, Yu Z (2005) Cloning and expression of *mel* gene from *Bacillus thuringiensis* in *Escherichia coli*. Antonie van Leeuwenhoek 87:283–288

Sánchez-Ferrer Á, Rodríguez-López JN, García-Cánovas F, García-Carmona F (1995) Tyrosinase: a comprehensive review of its mechanism. Biochim Biophys Acta 1247:1–11

Saruno R, Kato F, Ikeno T (1979) Kojic acid, a tyrosinase inhibitor from *Aspergillus albus*. Agric Biol Chem 43(6):1337–1338

Schaffer JV, Bolognia JL (2001) The melanocortin-1 receptor: red hair and beyond. Arch Dermatol 137:1477–1485

Schallreuter KU, Wood JW (1990) A possible mechanism of action for azelaic acid in the human epidermis. Arch Dermatol Res 282:168–171

Schurink M, van Berkel WJH, Wichers HJ, Boeriu CG (2007) Novel peptides with tyrosinase inhibitory activity. Peptides 28:485–495

Seiberg M, Paine C, Sharlow E, Eisinger M, Shapiro SS, Andrade-Gordon P, Costanzo M (2000) Inhibition of melanosome transfer results in skin lightening. J Invest Dermatol 115:162–167

Selinheimo E, Saloheimo M, Ahola E, Westerholm-Parvinen A, Kalkkinen N, Buchert J, Kruus K (2006) Production and characterization of a secreted, C-terminally processed tyrosinase from the filamentous fungus *Trichoderma reesei*. FEBS J 273:4322–4335

Selinheimo E, Nieidhin D, Steffensen C, Nielsen J, Lomascolo A, Halaouli S, Record E, O'Beirne D, Buchert J, Kruus K (2007) Comparison of the characteristics of fungal and plant tyrosinases. J Biotechnol 130:471–480

Sharma VK, Choi J, Sharma N, Choi M, Seo SY (2004) In vitro anti-tyrosinase activity of 5-(hydroxymethyl)-2-furfural isolated from *Dictyophora indusiata*. Phytother Res 18(10): 841–844

Shuster V, Fishman A (2009) Isolation, cloning and characterization of a tyrosinase with improved activity in organic solvents from *Bacillus megaterium*. J Mol Microbiol Biotechnol 17: 188–200

Singh P, Langowski HC, Wani AA, Saengerlaub S (2010) Recent advances in extending the shelf life of fresh *Agaricus* mushrooms: a review. J Sci Food Agric 90:1393–1402

Solano F, Briganti S, Picardo M, Ghanem G (2006) Hypopigmenting agents: an updated review on biological, chemical and clinical aspects. Pigment Cell Res 19:550–571. doi:10.1111/j.1600-0749.2006.00334.x

Solomon EI, Sundaram UM, Machonkin TE (1996) Multicopper oxidases and oxygenases. Chem Rev 96:2563–2605

Sugumaran M (2002) Comparative biochemistry of Eumelanogenesis and the protective roles of phenoloxidase and melanin in insects. Pigment Cell Res 15:2–9

Takahashi S, Iwai H, Kosaka K, Miyazaki T, Osanai Y, Arao N, Tanaka K, Nagai K, Nakagawa A (2007) Byelyankacin: a novel melanogenesis inhibitor produced by *Enterobacter* sp. B20. J Antibiot 60(11):717–720

Takamatsu S, Rho MC, Hayashi M, Komiyama K, Tanaka H, Omura S, Imokawa G (1993) New inhibitors of melanogenesis, OH-3984 K1 and K2. II. Physico-chemical properties and structural elucidation. J Antibiot 46(10):1526–1529

Takamatsu S, Kim YP, Hayashi M, Komiyama K, Imokawa G, Omura S (1996) A new inhibitor of melanogenesis, Albocycline K3, produced by *Streptomyces* sp. OH-3984. J Antibiot 49(5):485–486

Tanaka N, Naganuma M, Fukuda M, Wati Y, Komatsu K, Yoshida S, Komiyama K, Omura S (1996) Novel inhibitor of melanogenesis produced by *Talaromyces* FO-3182. Nippon Koshohin Kagakkaishi 20(1):3–6

Töpert M, Rach P, Siegmund F (1989) Pharmacology and toxicology of azelaic acid. Acta Derm Venereol Suppl 143:14–19

Tsai CC, Chan CF, Huang WY, Lin JS, Chan P, Liu HY, Lin YS (2013) Applications of *Lactobacillus rhamnosus* spent culture supernatant in cosmetic antioxidation, whitening and moisture retention applications. Molecules 18:14161–14171. doi:10.3390/molecules181114161

Tsuchiya T, Yamada K, Minoura K, Miyamoto K, Usami Y, Kobayashi T, Hamada-Sato N, Imada C, Tsujibo H (2008) Purification and determination of the chemical structure of the tyrosinase inhibitor produced by *Trichoderma viride* strain H1-7 from a marine environment. Biol Pharm Bull 31(8):1618–1620

Umezawa H (1972) Enzyme inhibitors of microbial origin. University of Tokyo Press, Tokyo, Japan

Van Gelder CW, Flurkey WH, Wichers HJ (1997) Sequence and structural features of plant and fungal tyrosinases. Phytochemistry 45: 1309–1323

Vasantha KY, Murugesh CS, Sattur AP (2014) A tyrosinase inhibitor from *Aspergillus niger*. J Food Sci Technol 51(10): 2877–2880

Walker JRL, McCallion RF (1980) The selective inhibition of ortho- and para-diphenol oxidases. Phytochemistry 19:373–377

Wang GH, Chen CY, Lin CP, Huang CL, Lin CH, Cheng CY, Chung YC (2016) Tyrosinase inhibitory and antioxidant activities of three *Bifidobacterium bifidum*-fermented herb extracts. Ind Crop Prod 89:376–382

Wei CI, Huang TS, Chen JS, Marshall MR, Chung KT (1991) Production of kojic acid by *Aspergillus candidus* in three culture media. J Food Prot 54(7):546–548

Wu B, Wu X, Sun M, Li M (2013) Two novel tyrosinase inhibitory sesquiterpenes induced by $CuCl_2$ from a marine-derived fungus *Pestalotiopsis* sp. Z233. Mar Drugs 11:2713–2721

Xu W, Gong L, Haddad MM, Bischof O, Campisi J, Yeh ET, Medrano EE (2000) Regulation of microphthalmia-associated transcription factor MITF protein levels by association with the ubiquitin-conjugating enzyme hUBC9. Exp Cell Res 255:135–143

Yoshida H, Tanaka Y, Nakayama K (1974) Properties of tyrosinase from *Pseudomonas melanogenum*. Agric Biol Chem 38(3):627–632

Yoshimoto T, Yamamoto K, Tsuru D (1985) Extracellular tyrosinase from *Streptomyces* sp. KY-453: purification and some enzymatic properties. J Biochem 97(6):1747–1754

Zhang D, Li X, Kang JS, Choi HD, Son BW (2007) A new a-pyrone derivative, 6-[(E)-hept-1-enyl]-a-pyrone, with tyrosinase inhibitory activity from a marine isolate of the fungus *Botrytis*. Bull Kor Chem Soc 28(5):887–888

Zheng ZP, Cheng KW, Chao J, Wu J, Wang M (2008) Tyrosinase inhibitors from paper mulberry (*Broussonetia papyrifera*). Food Chem 106:529–535

Zhuravleva OI, Afiyatullov SS, Vishchuk OS, Denisenko VA, Slinkina NN, Smetanina OF (2012) Decumbenone C, a new cytotoxic decaline derivative from the marine fungus *Aspergillus sulphureus* KMM 4640. Arch Pharm Res 35(10): 1757–1762