Review

Natural and Bioinspired Phenolic Compounds as Tyrosinase Inhibitors for the Treatment of Skin Hyperpigmentation: Recent Advances

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Abstract: One of the most common approaches for control of skin pigmentation involves the inhibition of tyrosinase, a copper-containing enzyme which catalyzes the key steps of melanogenesis. This review focuses on the tyrosinase inhibition properties of a series of natural and synthetic, bioinspired phenolic compounds that have appeared in the literature in the last five years. Both mushroom and human tyrosinase inhibitors have been considered. Among the first class, flavonoids, in particular chalcones, occupy a prominent role as natural inhibitors, followed by hydroxystilbenes (mainly resveratrol derivatives). A series of more complex phenolic compounds from a variety of sources, first of all belonging to the *Moraceae* family, have also been described as potent tyrosinase inhibitors. As to the synthetic compounds, hydroxycinnamic acids and chalcones again appear as the most exploited scaffolds. Several inhibition mechanisms have been reported for the described inhibitors, pointing to copper chelating and/or hydrophobic moieties as key structural requirements to achieve good inhibition properties. Emerging trends in the search for novel skin depigmenting agents, including the development of assays that could distinguish between inhibitors and potentially toxic substrates of the enzyme as well as of formulations aimed at improving the bioavailability and hence the effectiveness of well-known inhibitors, have also been addressed.

Keywords: pigmentary disorders; mushroom tyrosinase; human tyrosinase; melanin; depigmenting agent; inhibition mechanism; phenolic compounds; resorcinol; hydroxycinnamic acids; chalcones

1. Introduction

The quest for skin lighteners and agents capable of controlling hyperpigmentation disorders is growing at a sustained pace particularly in Asian countries. Most of the strategies explored so far focus on the control of the activity of tyrosinase, which is the main, rate-limiting enzyme involved in the biosynthesis of melanins, the pigments responsible for skin pigmentation in mammals [1–5].

This work will provide an overview of the tyrosinase inhibition properties of natural phenolic compounds, phenols inspired by active compounds of natural origin, or synthetic phenols as appeared in the literature (data source: SciFinder®, search terms: tyrosinase inhibition) in the last five years. Patents were excluded since the main aim of this review is an update of those compounds that have a potential for further development, though possibly not yet ready for a straightforward use in cosmetics.

Beside product efficacy, cytotoxicity, solubility, cutaneous absorption, and stability, other critical issues that should be carefully considered when developing a new tyrosinase inhibitor include adverse effects derived from action of the enzyme itself on the product as largely documented in the recent case of rhododendrol, a depigmenting agent on the market capable of inducing leukoderma [6–8]. In this perspective the different mechanisms by which tyrosinase inhibition occurs will be presented in the following paragraphs.

Given the difficulties of obtaining mammalian tyrosinase, most of the studies have been carried out on fungal (mushroom) tyrosinase, which however exhibits somewhat different substrate specificity [9]. Starting from consideration of the structural features of the most widely investigated classes of tyrosinase inhibitors, a rationalization of the structural requirements to get the inhibitory activity, stemming also from model or docking studies, will be offered. Finally, issues of toxicity of potential tyrosinase inhibitors and the limitations of the *in vitro* studies using mushroom tyrosinase will be discussed in the perspective of developing effective and safe tyrosinase inhibitors. Data on recent trends in cosmetic formulations to improve bioavailability and efficiency of well-known tyrosinase inhibitors will be also presented.

2. Skin Pigmentation and Hyperpigmentary Disorders

Skin pigmentation in humans is dependent mainly on the quantity, type, and distribution of melanins in the epidermis. The resulting pigmentation can be changed by phenomena of light reflection and diffusion, or by the presence of pigments of a different kind, occasionally present in the skin [10,11].

Apart from the hemoglobin and the biliary pigments, melanins are the only pigments to be biosynthesized in humans. They are produced in melanocytes lying in the epidermis at the dermal-epidermal junction and then transferred in the form of organelles termed melanosomes to neighboring keratinocytes in the skin (Figure 1) [12–15].

Figure 1. Schematic representation of melanosome transfers from melanocytes to keratinocytes and melanogenesis pathway inside melanocytes.

Under normal physiological conditions, pigmentation has a beneficial effect on the photoprotection of human skin against harmful UV injury [16]. However increased pigmentation, especially on the face, such as in the case of melasma, solar lentigo (age spots), and lentigo simplex (freckles), presents a significant cosmetic bother and can cause distress to the affected individual. Increased melanin synthesis and accumulation occurs also in other skin problems and systemic or idiopathic diseases [17–22].

Hyperpigmentation can also occur through inflammation of the skin, chronic heat exposure, hormonal imbalance, mechanical stimulation, and medication applications.

3. Tyrosinase and its Key Role in Melanin Synthesis

Melanogenesis is a complex pathway involving a combination of enzymatic and chemical catalyzed reactions. Melanosomes produce two types of melanin: eumelanin, a brown-black or dark polymer, and pheomelanin, a red-yellow polymer, formed by intervention of cysteine (Figure 1). The melanogenesis process is initiated with the oxidation of L-tyrosine to dopaquinone by tyrosinase. The formation of dopaquinone is a rate-limiting step in melanin synthesis because the remainder of the reaction sequence can proceed spontaneously at a physiological pH value. Following its formation, dopaquinone undergoes intramolecular cyclization to produce leucodopachrome. The redox exchange between leucodopachrome and dopaquinone then gives rise to dopachrome and L-3,4-dihydroxyphenylalanine (L-dopa), which is also a substrate for tyrosinase and is oxidized to dopaquinone again by the enzyme. Finally, dopachrome undergoes a rearrangement to give 5,6-dihydroxyindole (DHI) and 5,6-dihydroxyindole-2-carboxylic acid (DHICA) (Figure 1). This latter process is catalyzed by tyrosinase related protein-2 (TRP-2), known also as dopachrome tautomerase (DCT). Ultimately, DHI and DHICA are oxidized to melanin pigments. Tyrosinase related protein 1 (TRP-1) is believed to catalyze the oxidation of DHICA to melanin. Although all the three enzymes, tyrosinase, TRP-1, and TRP-2 are involved in the melanogenesis pathway, tyrosinase is exclusively necessary for melanogenesis [11,23–30].

Tyrosinase (EC 1.14.18.1, monophenol, *ortho*-diphenol: oxygen oxidoreductase) is a multifunctional membrane bound type-3 copper-containing glycoprotein located in the membrane of the melanosome. From the structural point of view, two copper ions are surrounded by three histidine residues that are responsible for the catalytic activity of tyrosinase. Substrates for tyrosinase are generally either phenols, which undergo monooxygenation (monophenolase or cresolase activity), or catechols, which undergo oxidation (diphenolase or catecholase activity), leading in both cases to *ortho*-quinones (Figure 2a) [31,32]. Although the view that phenol oxidation involves a hydroxylation step followed by catechol oxidation is still commonly claimed in the literature [33,34], in the monophenolase mechanism the *ortho*-quinone is formed directly from the phenol, and catechol formation is not an intermediate step [35]. During the catalytic cycle the oxidation states of the copper atoms change to give different forms of the enzyme (Figure 2b–d).

The active site of the enzyme has three states: *oxy*, *met*, and *deoxy* forms. The oxidation of phenols to *ortho*-quinones by *oxy*-tyrosinase is the most important function of the enzyme and it is by this process that L-tyrosine is converted to dopaquinone in the biosynthesis of melanins (Figure 2b). Mechanistically, the oxygen of the phenol is believed to bind to CuA followed by electrophilic monooxygenation of the ring leading to a complex in which the substrate is bound to both copper ions. In a further step such complex undergoes homolytic dissociation to give the *ortho*-quinone and *deoxy*-tyrosinase. The *deoxy*-tyrosinase then binds oxygen to regenerate *oxy*-tyrosinase and the phenol-oxidation cycle continues until the phenol and/or oxygen are depleted [35].

Figure 2. (a) Tyrosinase-catalyzed reactions; (b–d) oxidation states of tyrosinase and their conversions by phenols/catechols [35].

Oxy-tyrosinase is able to oxidize catechols in addition to phenols. In many cases, a higher specific activity for catechol oxidation than for the corresponding phenol oxygenation has been observed [36]. This is possibly a consequence of the ease of substrate orientation on binding to the active site: whereas monohydric phenols bind to CuA, catechols initially bind to the active site through the CuB. The oxidation cycle of catechols involves two steps (Figure 2c,d) and in both the binding of the catecholic substrate occurs by deprotonation of the adjacent hydroxyl groups such that the oxygens are coordinated with the two active site copper atoms. In the first step, in which oxy-tyrosinase is converted to met-tyrosinase (Figure 2c), the catechol/enzyme complex dissociates with the release of one of the oxygen atoms from the peroxy conformation of the bound dioxygen yielding the corresponding *ortho*-quinone and water. The resultant met form of the enzyme retains the oxidation state of the active site copper ions [Cu(II)] to which the remaining oxygen atom is coordinated, probably in a protonated form. Overall, the catechol has reduced the peroxy bridge with formation of water and has been oxidized to an *ortho*-quinone. In the second stage of the catechol cycle, a second molecule of catechol reduces the active site Cu(II) ions to Cu(I) giving deoxy-tyrosinase and a second molecule of *ortho*-quinone (Figure 2d). The oxidation states of the active site copper ions [Cu(II)] are then restored by binding dioxygen (Figure 2b) [35].

Tyrosinases have been isolated and purified from different sources such as plants, animals, and microorganisms. Although many of them (such as human) have been sequenced, only few have been characterized. Mushroom tyrosinase from *Agaricus bisporus* is a major and cheap enzyme, with high

similarity and homology compared to human tyrosinase [1,37,38]. Due to the above-mentioned good properties, the structural, functional, and biochemical characteristics of mushroom tyrosinase have been studied extensively as a model system for screening of tyrosinase inhibitors and melanogenic studies, enzyme-catalyzed reactions, and enzyme-inhibitor structural studies so far [1,39–41]. Tyrosinase from *A. bisporus* is a 120 kDa tetramer, which was first isolated by Bourquelot and Bertrand in 1895 [42]. It has three domains and two copper binding sites composed of six histidine residues able to interact with molecular oxygen in the active site. It should be cautioned that tyrosinase from mushroom is very different from human tyrosinase. Mushroom tyrosinase is a tetramer enzyme present in the cytosol of the cells, while human tyrosinase is a monomeric and inactive glycosylated membrane bound form. Furthermore, tyrosinases from different sources exhibit quite different substrate specificity, e.g., human tyrosinase shows higher (up to 6-fold) affinity for L-DOPA oxidation activity than the mushroom tyrosinase [31]. In addition, the amino acid sequence identity between human and mushroom tyrosinase is only very limited (23%) [41].

4. Tyrosinase Inhibition Mechanisms

Among different types of compounds able to inhibit melanogenesis, such as specific tyrosinase inactivators and inhibitors, dopaquinone scavengers, alternative enzyme substrates, nonspecific enzyme inactivators and denaturants, only specific tyrosinase inactivators and reversible inhibitors actually bind to the enzyme and really inhibit its activity [1].

Suicide inactivators have been widely reported for the control of hyperpigmentation processes. To explain the suicide inactivation of tyrosinase, mainly two mechanisms have been proposed. It has been suggested that the conformational changes triggered by the inhibitor compound in the tertiary and quaternary structures of tyrosinase might be the real reason for the suicide inactivation. On the other hand, it has also been proposed that suicide inactivation could occur after the transfer of a proton to the peroxy bridge on the active site of *oxy*-tyrosinase [1,43–45].

As far as the true inhibitors are concerned, four types of mechanism have been described: competitive, uncompetitive, mixed type (competitive/uncompetitive), and noncompetitive. A competitive inhibitor can bind to a free enzyme and prevents substrate binding to the enzyme active site. This is the case of phenolic compounds able to act as copper chelators or compounds structurally mimicking the substrate of tyrosinase. In contrast, an uncompetitive inhibitor can bind only to the enzyme-substrate complex, whereas a mixed inhibitor can bind to both free enzyme and enzyme-substrate complex. Finally, noncompetitive inhibitors bind to the free enzyme and the enzyme-substrate complex with the same equilibrium constant [1,46].

The inhibitory strength is generally expressed as the IC_{50} value, that is the concentration of inhibitor at which 50% of the enzyme activity is inhibited. Of course, it must be considered that IC_{50} values may be incomparable due to the different assay conditions (e.g., substrate and enzyme concentrations, incubation time, source of tyrosinase). Reference compounds commonly used as positive controls in the mushroom tyrosinase inhibition assay are kojic acid and β -arbutin (Figure 3), which however are very poor inhibitors ($IC_{50} > 500 \mu M$) of human tyrosinase [9,47]. Deoxyarbutin has been recently described as a novel tyrosinase inhibitor, with increased skin penetration and binding affinity to human tyrosinase [48–50].

Figure 3. Chemical structures and IC_{50} values [9] against mushroom tyrosinase of the commonly used reference compounds kojic acid and β -arbutin.

5. Natural Phenolic Inhibitors of Mushroom Tyrosinase

Among natural phenolic compounds acting as tyrosinase inhibitors (Supplementary Materials, Table S1), flavonoids are the most representative class. Figure 4 shows the structures of the most potent inhibitors with the corresponding IC_{50} values against mushroom tyrosinase. Among the different subclasses, the highest activity has been determined for chalcones, with 2,2',4,4'-tetrahydroxychalcone exhibiting a very low IC_{50} value ($0.07 \mu M$) [51]. A significant melanogenesis inhibition potential has been reported also for galangin ($IC_{50} = 3.55 \mu M$) [52], isoliquiritigenin ($IC_{50} = 4.85 \mu M$) [53], kaempferol ($IC_{50} = 5.5 \mu M$) [54], and dihydromorin ($IC_{50} = 9.4 \mu M$) [55], belonging to different flavonoid subfamilies, but all characterized by at least one resorcinol moiety. IC_{50} values in the range $20\text{--}150 \mu M$ have instead been reported for catechins [56–59].

Figure 4. Chemical structures and IC_{50} values against mushroom tyrosinase of phenolic compounds belonging to the flavonoid class. Unless otherwise specified, IC_{50} values refer to the diphenolase activity of the enzyme.

Another major class of mushroom tyrosinase inhibitors is represented by hydroxystilbenes (Figure 5). Several derivatives of the parent resveratrol have been described as potential depigmenting agents, with oxyresveratrol ($IC_{50} = 1.7 \mu M$) [55] and particularly dihydroxyresveratrol ($IC_{50} = 0.3 \mu M$) [55] among the most active compounds. Recently, glycosylation has been reported to improve the tyrosinase inhibitory activities of both resveratrol and its methylated analogues pterostilbene and pinostilbene [60].

Figure 5. Chemical structures and IC_{50} values (referring to the diphenolase activity of the enzyme) against mushroom tyrosinase of hydroxystilbenes.

Moving to simple phenols, significant inhibition activity has been described for 4-hydroxybenzyl alcohol ($IC_{50} = 6 \mu M$) [61] and isoeugenol ($IC_{50} = 33.3 \mu M$) [62], which would appear more efficient than resorcinol [55] or rhododendrol [63] themselves. Other inhibitors have been recently isolated from the roots of *Dryopteris crassirhizoma* [64] and leaves of *Piper aduncum* [65] (Figure 6).

Figure 6. Chemical structures and IC_{50} values (referring to the diphenolase activity of the enzyme) against mushroom tyrosinase of simple phenols.

Low IC_{50} values against both monophenolase and diphenolase activity of mushroom tyrosinase have been very recently reported for *p*-coumaric and caffeic acid [66], belonging to the cinnamic acid family (Figure 7).

Figure 7. Chemical structures and IC_{50} values against mushroom tyrosinase of cinnamic acid derivatives. Unless otherwise specified, IC_{50} values refer to the diphenolase activity of the enzyme.

The IC_{50} values together with structural formulas for other phenolic compounds widely distributed in nature that have been the subject of studies that appeared in the last five years [53,62,63,67–82] are also reported in Figures 4–8.

A series of more complex phenolic compounds have been isolated from several plants and evaluated as inhibitors against mushroom tyrosinase. The *Moraceae* family, in particular, has proven to be an important source of potential skin whitening agents [73,83–87] (Figure 9), leading to compounds with in some cases very low IC_{50} values, such as norartocarpetin (from the stems of *Artocarpus rigida*,

$IC_{50} = 0.023 \mu M$) [87], morachalcone A (from the twigs of *Artocarpus pithecolobus*, $IC_{50} = 0.77 \mu M$) [83], and artocarpinone (from the wood of *Artocarpus heterophyllus*, $IC_{50} = 2.0 \mu M$) [73], all belonging to the flavonoid family and characterized by the presence of resorcinol ring(s).

Figure 8. Chemical structures and IC_{50} values against mushroom tyrosinase of natural phenolic compounds. Unless otherwise specified, IC_{50} values refer to the diphenolase activity of the enzyme.

Figure 9. Chemical structures and IC_{50} values (referring to the diphenolase activity of the enzyme) against mushroom tyrosinase of phenolic compounds isolated from *Artocarpus* species (Moraceae family).

Potent mushroom tyrosinase inhibitors have been isolated also from plants of the genus *Morus* [55,88–91] (Figure 10): noticeable examples are 2,3',4-trihydroxydihydrostilbene ($IC_{50} = 0.8 \mu M$) [55], the benzofuran moracin M ($IC_{50} = 8.0 \mu M$) from mulberry (*Morus alba*) wood [55], and isoprenylated flavanons from *Morus nigra*, such as kuwanon J ($IC_{50} = 0.17 \mu M$) and sanggenon O ($IC_{50} = 1.15 \mu M$) [91] (Figure 10).

Figure 10. Chemical structures and IC_{50} values (referring to the diphenolase activity of the enzyme) against mushroom tyrosinase of phenolic compounds isolated from *Morus* species (*Moraceae* family).

A series of flavonoids derivatives from the root bark of *Broussonetia papyrifera*, first of all broussonetiflavonol J ($IC_{50} = 9.29 \mu M$), have been found to be more active than kojic acid as inhibitors of the monophenolase activity of the enzyme [92] (Figure 11). Prenylated flavanones from the roots of *Dalea pазensis* Rusby also proved to be quite effective as mushroom tyrosinase inhibitors [93]. On the contrary, biflavonoids not containing a 1,3-benzenediol from *Solanum nigrum* (Figure 11) were only poor tyrosinase inhibitors, with IC_{50} values $> 190 \mu M$ [94].

Figure 11. Chemical structures and IC_{50} values (referring to the diphenolase activity of the enzyme) against mushroom tyrosinase of flavonoids isolated from different plants.

A pterocarpan ($IC_{50} = 16.7 \mu M$) and some isoflavones and isoflavans isolated from *Dalbergia parviflora* (Figure 11) have been also recently reported as inhibitors of the diphenolase activity of mushroom tyrosinase [95].

Increasing attention has been devoted to condensed tannins, which have shown promising activities as inhibitors of both monophenolase and diphenolase activity of mushroom tyrosinase (Table 1) [96–107]. Particularly active were prodelphinidins and procyanidins from the fruit pericarp of *Clausena lansium* Skeels [102], as well as the complex mixtures isolated from *Persea Americana* [106], Longan bark [99], and from leaves and fruit of *Leucaena leucocephala* [97].

Table 1. IC_{50} values against mushroom tyrosinase reported for condensed tannins isolated from different plants.

Source	IC_{50} ($\mu g/mL$) (Monophenolase Activity)	IC_{50} ($\mu g/mL$) (Diphenolase Activity)
<i>Vigna angularis</i> [96]	130.0	35.1
<i>Leucaena leucocephala</i> [97]	52.3	16.1
<i>Vigna radiata</i> [98]	80	20
Longan [99]	43.7	11.5
<i>Prunus cerasifera</i> [100]	738.37	137.69
<i>Annona squamosa</i> [101]	46.5	37.3
<i>Clausena lansium</i> [102]	23.6	7.0
<i>Ficus altissima</i> [104]	256.7	41.3
<i>Rhododendron pulchrum</i> [105]	200	200
<i>Persea americana</i> [106]	40	19.5

Very potent (IC_{50} values in the range 0.10–7.5 μM) mushroom tyrosinase inhibitors have been isolated from licorice (Figure 12), the most active belonging to the isoflavan class [108–110]. Structurally related compounds and paeoniflorin derivatives isolated from San-Bai decoction proved less active (IC_{50} in the range 35.54–171.13 μM) [111] (Figure 12).

Figure 12. Chemical structures and IC_{50} values (referring to the diphenolase activity of the enzyme) against mushroom tyrosinase of phenolic compounds isolated from *Glycyrrhiza* species and San-Bai decoction.

IC_{50} values in the range 28–42 μM have been reported for two lignans isolated from *Opilia amentacea* leaves [112] (Figure 13), whereas particularly effective against the monophenolase activity of the enzyme were flavonolignans from the seeds of *Silybum marianum* (IC_{50} in the range 1.7–4.9 μM) (Figure 13) [113] as well as, although with a lower strength, hydroxylated phenones from *Syzygium polyanthum* leaves [114] (Figure 14).

Figure 13. Chemical structures and IC_{50} values against mushroom tyrosinase of lignans isolated from *Opilia amentacea* and *Silybum marianum*. Unless otherwise specified, IC_{50} values refer to the diphenolase activity of the enzyme.

Figure 14. Chemical structures and IC_{50} values against mushroom tyrosinase of phenolic compounds isolated from *Syzygium polyanthum* and *Humulus lupulus*.

Higher inhibition against monophenolase than diphenolase activity of mushroom tyrosinase were reported also for xanthohumol and other chalcones isolated from *Humulus lupulus* [115] (Figure 14).

Several *p*-coumarate esters from *Breynia officinalis* leaves have been described as mushroom tyrosinase inhibitors, the most active of which being seguinoside A *p*-coumarate (IC_{50} = 16.9 μ M) [116]

(Figure 15), whereas less effective were feruloyl sucrose esters from *Oryza sativa* roots [117] and epicatechin glucosides isolated from *Breynia fruticosa* [118] (Figure 15).

Figure 15. Chemical structures and IC_{50} values against mushroom tyrosinase of phenolic compounds isolated from *Breynia* and *Oryza sativa* species. Unless otherwise specified, IC_{50} values refer to the diphenolase activity of the enzyme.

Interestingly, polyamine derivatives comprising coumaroyl and caffeoyl moieties from bee pollen of *Quercus mongolica* have been also described as tyrosinase inhibitors [119].

Finally, moderate-high activity has been very recently reported for phenylethylchromones isolated from the agarwood of *Aquilaria* plants [120,121] and anthraquinones from *Cassia tora* seeds [122] (Figure 16).

Figure 16. Chemical structures and IC_{50} values (referring to the diphenolase activity of the enzyme) against mushroom tyrosinase of phenolic compounds isolated from *Aquilaria* and *Cassia tora* species.

6. Synthetic Phenolic Inhibitors of Mushroom Tyrosinase

In the last years several studies have been directed to the development of novel tyrosinase inhibitors inspired by natural scaffolds, which should overcome stability, efficacy, and isolation yield issues. One of the main exploited scaffolds is hydroxycinnamic acid: indeed several hydroxycinnamic acid analogues have been synthesized through the most disparate approaches [123–141], leading in some cases to very potent mushroom tyrosinase inhibitors (Figure 17), such as 2,4-dihydroxycinnamides ($IC_{50} = 0.0112$ – $0.16 \mu M$) [132,133]. A thiophenyl derivative of 2,4-dihydroxycinnamic acid has also exhibited a very low IC_{50} value ($0.013 \mu M$) against the monophenolase activity of the enzyme [134]. An IC_{50} value of $1.10 \mu M$ for the monophenolase activity of mushroom tyrosinase has been instead calculated for a cyclopentanone compound related to 3-hydroxy-4-methoxycinnamic acid [135]. Quite low IC_{50} values have been reported also for dihydrolipoic acid conjugates of caffeic acid and its methylester [136,137], as well as for thiochromanone compounds [138], diamides [139], or esters [140,141] related to *p*-coumaric acid.

Figure 17. Chemical structures and IC_{50} values against mushroom tyrosinase of synthetic hydroxycinnamic acid derivatives. Unless otherwise specified, IC_{50} values refer to the diphenolase activity of the enzyme.

Similar scaffolds are chalcones [142–156], characterized by an enone moiety linked to a phenyl ring as well. Particularly active as mushroom tyrosinase inhibitors are 2,2',4,4'-tetrahydrochalcone ($IC_{50} = 0.08 \mu M$) and its derivatives [149], followed by azachalcones ($IC_{50} = 1.70$ – $2.30 \mu M$) [150], chalcone oximes ($IC_{50} = 4.5$ – $8 \mu M$) [151], and a chalcone based pyrazoline ($IC_{50} = 4.72 \mu M$) [152] (Figure 18). Quite low IC_{50} values have been reported also for chalcone-21 ($IC_{50} = 6.8 \mu M$) [153], 6-methoxy-3,4-dihydronaphthalenone chalcone-like derivatives ($IC_{50} = 6.19 \mu M$) [154], aminochalcones [155], and indenone chalcone-like derivatives [156] (Figure 18).

Figure 18. Chemical structures and IC_{50} values (referring to the diphenolase activity of the enzyme) against mushroom tyrosinase of synthetic chalcone derivatives.

As to other natural phenol-inspired synthetic compounds [157–161], the best results have been reported for a carvacrol derivative containing a 3,5-dihydroxyphenyl moiety (IC_{50} = 0.0167 μ M) [159] (Figure 19). Good inhibition properties have been exhibited also by some rhododendrol glycosides (IC_{50} = 0.56–9.15 μ M) [160] and eugenol derivatives (IC_{50} ca. 8 μ M) [161] (Figure 19).

Figure 19. Chemical structures and IC_{50} values (referring to the diphenolase activity of the enzyme) against mushroom tyrosinase of synthetic phenolic compounds.

Of course, the most potent inhibitory activity is still attributed to resorcinol derivatives [162–170], although these compounds often suffer from toxicity concerns (the case of rhododendrol is emblematic [6–8]) (see below). Low IC_{50} values (0.39–3.62 μ M) have been reported for resorcinol

alkyl glucosides [166] (Figure 19), whereas thiamidol, which is currently one of the most potent skin depigmenting agent on the market, is not so active against mushroom tyrosinase ($IC_{50} = 108 \mu M$) [9]. Alkyl resorcinols, such as 4-butylresorcinol or 4-hexylresorcinol, also exhibited very low IC_{50} values (Figure 19), particularly against the monophenolase activity ($IC_{50} = 0.077 \mu M$ for 4-butylresorcinol) [167,168]. Rather low IC_{50} values have been determined also for resveratrol derivatives such as (E)-2,3-bis(4-hydroxyphenyl)acrylonitrile ($IC_{50} = 5.06 \mu M$) [169] and dihydroxyresveratrol glucosides [170] (Figure 19).

Coumarins are another class of compounds able to efficiently inhibit mushroom tyrosinase [171–174]. Coumarin dimers and derivatives containing a tetracyclic skeleton exhibited IC_{50} values in the range 1.7–2.9 μM [172] (Figure 20), whereas even higher activity has been reported for synthetic 3-heteroaryl coumarins [173] and umbelliferone-thiazolidinedione hybrids [174] (Figure 20).

Figure 20. Chemical structures and IC_{50} values (referring to the diphenolase activity of the enzyme) against mushroom tyrosinase of synthetic coumarin derivatives.

7. Human and Animal Tyrosinase Phenolic Inhibitors

In the last five years, several natural and synthetic phenolic compounds have been described also as inhibitors of tyrosinase from animal and human sources. Most of these studies used B16 murine melanoma cell lines as a model [52,55,75,85,95,96,99,114,122,123,127–129,132–135,138,139,151,153,155,163,175–205], although some papers using zebrafish as an *in vivo* whole animal model have also been published [55,116,206]. As to the human sources, data on inhibition of human recombinant or purified tyrosinase [9,207], human melanoma cells [130,136], normal human melanocytes [208–211], or human skin models consisting of reconstructed three-dimensional human epidermis [212–215] have been published (Figure 21). The results of clinical trials have also been reported for well recognized skin depigmenting agents [216,217] such as thiamidol, that, as stated also above, is one of the most striking examples of a pigmentation inhibitor exhibiting significant higher activity on human than on mushroom tyrosinase [9,218]. This nicely exemplifies the differential effects of tyrosinase inhibitors on the human and mushroom enzymes, likely due to the presence of additional amino acids in the hydrophobic substrate-binding pocket of mushroom tyrosinase [218].

Figure 21. Chemical structures and inhibitory potency (where available) of the main human tyrosinase inhibitors.

Of course, care should be taken when cellular or in vivo models are considered, since several alternative or additional biochemical mechanisms can be operative, involving e.g., tyrosinase expression and interference with the complex signaling pathways in melanogenesis, which could result in melanin reduction as well. As an example, it has been reported that both ferulic and caffeic acid inhibited melanin production in B16 melanoma cells, but ferulic acid reduced tyrosinase activity by directly binding to the enzyme, whereas no binding was observed in the case of caffeic acid [177]. Apart from the direct inhibition of tyrosinase activity, the anti-melanogenic activity of resorcinol in B16F10 cells has been attributed to the inhibition of cAMP signaling and activation of p38 MAPK [179]. The same applies e.g., to moracin J [181], 4,5-dicaffeoylquinic acid [183], chrysin [187], casuarictin [178], and synthetic compounds [135,136,153,197], which have been reported to both inhibit intracellular tyrosinase activity and regulate melanogenesis-related protein expression.

In any case, there is no doubt that human tyrosinase inhibitors are really important in the perspective of cosmetics development.

8. Structural Requirements for the Design of Tyrosinase Inhibitors

Several inhibition mechanisms have been reported for the tyrosinase inhibitors described above, highlighting the importance of key structural moieties as responsible for the observed effects. As an example, in silico analysis showed that the flavonoids spinosin and swertiajaponin act as competitive inhibitors of the enzyme by binding to the active site through hydrogen bonding and hydrophobic interactions [212,214], as is the case also for condensed tannins from different sources based on molecular docking [96,98,99]. Chelation of copper ions by adjacent hydroxyl groups on the B ring has also been suggested as a feasible inhibition mechanism for proanthocyanidins [101,102,106]. Copper chelation as well as hydrophobic and hydrogen bonding within the active site resulting in secondary structural changes have been validated for brazilein, too [190]. Generally, the number and location of phenolic hydroxyl groups significantly affect the tyrosinase inhibitory activity in the case of flavonoids [62]. The presence of sugar moieties as well as the glycosylation pattern is also important:

for example, flavanol containing 5-O- and 7-O-sugar moieties are more potent inhibitors compared to related not glycosylated compounds [118]. Interestingly, quercetin-3-O- α -L-rhamnopyranoside possesses tyrosinase inhibition activity whereas 3-glycosylated flavonols were not active, suggesting that the rhamnosyl group at C-3 played an indispensable role in the anti-tyrosinase activity [59]. The impact of chemical structure on the tyrosinase inhibition properties is emblematic also in the case of hydroxystilbene compounds, in which the presence of the inter-ring double bond, or of methylated or glucosylated phenolic moieties strongly affect the IC₅₀ value [55,60,63].

The presence of the sulfur atom able to chelate the copper ions has been described as essential for the inhibitory activity in the case of bis(4-hydroxybenzyl) sulfide from *Gastrodia elata* [209].

An interaction driven mainly by electrostatic forces has instead been brought forth in the case of aloe-emodin, and this would induce changes in conformation of the enzyme preventing binding of the substrate [79]. Interactions with specific amino acid residues in the active site pocket of the enzyme have been evidenced by molecular dynamics simulation in the case of pyrogallol [77] and quercetin-7-O- α -L-rhamnoside [182]. Binding via Met280 residue has been in particular predicted for baicalein [71]. In the case of obtusin derivatives, different interactions inside and/or outside the active site of the enzyme have been proposed [122].

Interactions with specific amino acids in the tyrosinase binding pocket has been predicted also for synthetic inhibitors, such as hydroxylated chalcone derivatives [151,155], 2-(3, 4-dihydroxybenzylidene) malononitrile [215], or carvacrol derivatives featuring a 2,4-dihydroxyphenyl moiety, able to interact with amino acid HIS85 through the 2-hydroxy group [159]. Other important structural requirements have been also underlined: for example, a three carbons tether with a diamide-link in dimeric cinnamoyl analogues is required to efficiently inhibit melanin production on α -MSH stimulated B16F1 cells [139]. The same has been reported for the alkyl spacer in the case of resorcinol alkyl glucosides [166]. The presence of resorcinol and glucose moieties has also reported to be important [162]. Hydrogen bonds and aromatic (hydrophobic) interactions with tyrosinase have been predicted by docking simulation for the potent inhibitor MHY2081 [129].

9. New Trends in the Search for Tyrosinase Inhibitors

Recently, a rather large number of studies have been directed to the development of novel assays for the search and assessment of tyrosinase inhibitors. These have been prompted in part by the need to avoid interferences due to color development associated to the oxidation of phenolic compounds acting as substrates of mushroom tyrosinase [219,220].

As an example, a colorimetric assay based on a combination of chitosan-stabilized platinum nanoparticles, catechol, tyrosinase, and 3,3',5,5'-tetramethylbenzidine as the probe being oxidized to a yellow diamine has been proposed [221]. A microreactor-detector based on the use of a gold disk for tyrosinase immobilization and a carbon disk as a working electrode able to amperometrically detect dopaquinone formation starting from L-tyrosine has also been described [222]. Immobilized tyrosinase has been used also coupled to capillary electrophoresis [223,224].

A different approach is based on thin layer chromatography (TLC) bioautographic assay, with the reported advantages of a low cost and sensitive methodology [225], whereas ultrafiltration coupled with HPLC has been proposed as a strategy for identification of specific inhibitors of the enzyme [226].

The use of dopamine functionalized quantum dots exhibiting strong fluorescence undergoing quenching upon dopamine oxidation by the enzyme have also been proposed [227].

Alternatives to mushroom tyrosinase have also been developed, such as recombinant tyrosinase from *Polyporus arcularius* overproduced in *Escherichia coli* [228].

Perhaps one of the main drawbacks of the “classic” mushroom tyrosinase inhibition assay is that it does not enable to distinguish between skin whitening tyrosinase inhibitors and leukoderma inducing phenols, that is compounds which are readily oxidized by the enzyme leading to the generation of cytotoxic reactive quinones [229]. To this aim, a convenient screening method was reported, involving spectrophotometric monitoring of the incubation mixtures followed by reduction with NaBH₄ and

HPLC analysis. Under these conditions it was indeed possible to differentiate potential toxic enzyme substrates, such as rhododendrol, raspberry ketone, and *p*-substituted phenols, from tyrosinase inhibitors like ellagic acid [38].

Another issue to take into account is the possibility that the inhibitor compound may react with dopaquinone to give an adduct that is not further oxidized. In this way dopaquinone is subtracted from the melanogenic pathway and a decrease of pigmentation is observed though the activity of the enzyme that has not been affected to any extent. This could be the case of compounds comprising a resorcinol moiety [230], like phenylethyl resorcinol and resveratrol derivatives, or a thiazolidine unit that may undergo ring opening disclosing the thiol functionality [231]. Of course, the possible toxicity associated with the occurrence of this diverted reaction pathways should be carefully evaluated.

Another emerging research trend is the development of new formulations for improving the bioavailability and hence the efficiency of tyrosinase inhibitors to be used as skin depigmenting agents. As an example, a polyethylene glycol/polycaprolactone (PEG/PCL) copolymer has shown good encapsulation efficiency toward the potent skin lightening agent adamantan-1-yl-N-(2,4-dihydroxybenzyl)-2,4-dimethoxybenzamide (known as AP736) [232]. On the same line, hybrid poly (lactic-co-glycolic acid) (PLGA) microspheres have been proposed to improve the encapsulation and control the release of amphiphilic compounds such as phenylethyl resorcinol, leading to 40% enhancement of tyrosinase inhibition in mouse melanoma cells [233]. Ethosomes formulations as well as nanostructured lipid carriers (NLCs) with high encapsulation efficiency and stability have also been developed for the delivery of phenylethyl resorcinol into the skin, exhibiting higher tyrosinase inhibition compared to other formulations in B16 melanoma cells [234,235]. Increased loading and chemical stability was achieved also by the use of smartPearls combined with the UV absorber Tinosorb S [236].

SmartPearls consisting of mesoporous silica particles have been combined also with glabridin to enhance its water solubility by a factor higher than four and therefore improve its dermal bioavailability [237]. A 20-fold increase of tyrosinase inhibition activity has also been reported for a glabridin/hydroxypropyl- β -cyclodextrin inclusion complex [238].

Gallic acid-loaded cationic niosomes composed of Brij 52/cholesterol/cetyltrimethylammonium bromide at 7:3:0.65 have shown high stability and tyrosinase inhibition in B16F10 melanoma cells, due to controlled release of the phenol over 24 h [239].

Monoolein and lauroylcholine chloride-based vesicles have proven efficient at delivering 3-hydroxycoumarin to the deeper skin layers [240]. NLCs as well as solid lipid nanoparticles (SLNs) have been employed instead for resveratrol encapsulation, enhancing its tyrosinase inhibitory activity [241,242]. Good results have been obtained also with nanoparticles from calli of resveratrol-enriched rice [243].

SLNs for encapsulation of curcumin and a synthetic inhibitor, (Z)-5-(2,4-dihydroxybenzylidene)thiazolidine-2,4-dione (MHY498), have also been described [244,245].

Improved performance as a cosmetic ingredient has been finally reported for dextran-rosmarinic acid conjugates [246].

10. Conclusions and Perspectives

The regulation of melanogenesis is highly complex and a number of cellular factors are involved in this process. Tyrosinase, the central enzymatic system of melanogenesis, catalyzing the rate-limiting step of the pathway, has become one of the most important targets for the control of hyperpigmentary disorders of pathological or cosmetic relevance. As a result, in recent years, an impressive number of inhibitors have been reported that exert their action at the level of tyrosinase.

In general, given the availability and the ease of purification, tyrosinase from *Agaricus bisporus* mushroom is the most frequently used model for screening potential candidates in the development of skin-whitening substances, while human and mouse melanocytic lysates are used to a lesser extent.

It is interesting to note that despite the diversity of natural inhibitors, a large number of tyrosinase inhibitors are phenolic in nature. Many researchers have designed appropriate scaffolds inspired by the structure of natural compounds and developed novel synthetic inhibitors. A valuable support in these studies has been provided by the molecular docking approach that allowed to rationalize the critical structural elements responsible for the inhibitory activity of natural compounds providing a guide for the design of more effective synthetic bioinspired inhibitors. In particular, from the survey of the recent literature reported in this paper the presence of at least one 2,4-dihydroxyphenyl (resorcinol) moiety stands as an essential factor to achieve effective tyrosinase inhibition properties. However, hydroxycinnamic acids possibly “activated” by suitable substituents are emerging as valid alternative depigmenting agents which, even though in most cases are of synthetic origin, should not, in principle, present toxicity issues associated with the entrapment of dopaquinone as briefly discussed in the previous paragraphs.

More in general, there are several issues that should be carefully considered in the development of the research in the field of tyrosinase inhibitors for the treatment of skin hyperpigmentation.

At present, though a wide range of tyrosinase inhibitors from natural and synthetic sources have been reported, only a few of them, in addition to being effective, are known as safe compounds. No significant advances concerning toxicity issues of tyrosinase inhibitors seem to emerge from the literature survey carried out for this review, the relevant papers just reporting the results of in vitro cytotoxicity experiments [49,52,75,81,95,126,129,131–133,136,137,147,163,176–178,184,185,192,198,202,203,207,210,212,214,215,239,240,242,245] and only a few of in vivo experiments on zebrafish [130,206,209]. Therefore, it is essential to examine the efficacy and safety of inhibitors by checking e.g., whether or not the candidate inhibitor is substrate of tyrosinase being modified on exposure to the enzyme. Once this first level of safety assessment has been passed, in vivo experiments using reconstructed three-dimensional human epidermis that has mostly replaced animal models tests should be carried out before the compound could be considered for clinical trials in the perspectives of its use in medicinal and cosmetic applications. Future directions of the research on pigmentation control by tyrosinase modulation also include the development of highly specific assays of the enzymatic activity as well as the appropriate use of innovative formulations for boosting the efficacy of the inhibitors by enhancing their bioavailability.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2079-9284/6/4/57/s1>, Table S1: Main natural phenolic inhibitors of mushroom tyrosinase.

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