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Natural and synthetic flavonoid derivatives as new potential tyrosinase inhibitors: a systematic review

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Tyrosinase is a multifunctional glycosylated and copper-containing oxidase that is highly prevalent in plants and animals and plays a pivotal role in catalyzing the two key steps of melanogenesis: tyrosine's hydroxylation to dihydroxyphenylalanine (DOPA), and oxidation of the latter species to dopaquinone. Melanin guards against the destructive effects of ultraviolet radiation which is known to produce considerable pathological disorders such as skin cancer, among others. Moreover, the overproduction of melanin can create aesthetic problems along with serious disorders linked to hyperpigmented spots or patches on skin. Several skin-whitening products which reduce melanogenesis activity and alleviate hyperpigmentation are commercially available. A few of them, particularly those obtained from natural sources and that incorporate a phenolic scaffold, have been exploited in the cosmetic industry. In this context, synthetic tyrosinase inhibitors (TIs) with elevated efficacy and fewer side effects are direly needed in the pharmaceutical and cosmetic industries owing to their protective effect against pigmentation and dermatological disorders. Furthermore, the biological significance of the chromone

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skeleton and its associated medicinal and bioactive properties has drawn immense interest and inspired many researchers to design and develop novel anti-tyrosinase agents based on the flavonoid core (2-arylchromone). This review article is oriented to provide an insight and a deeper understanding of the tyrosinase inhibitory activity of an array of natural and bioinspired phenolic compounds with special emphasis on flavonoids to demonstrate how the position of ring substituents and their interaction with tyrosinase could be correlated with their effectiveness or lack thereof against inhibiting the enzyme.

1. Introduction

Tyrosinase (E.C. 1.14.18.1) is a multifunctional copper-containing oxidase enzyme^{1,2} and is biologically significant because of the key role it plays in the biosynthesis of melanin pigment in living organisms.³⁻⁶ It catalyzes the *o*-hydroxylation of polyphenolic substrates to diphenol (catechol) derivatives, which further oxidize to *o*-quinone products.⁷ Tyrosinase is known as a rate-limiting enzyme that catalyzes the hydroxylation of L-tyrosine to L-DOPA and 3,4-dihydroxyphenylalanine to dopaquinones which can cause unusual melanin pigment accumulation in the outermost layer of the skin.⁸ In this context, the standard tyrosinase inhibitors (TIs) such as kojic acid, tropolone, hydroquinone and mercury are clinically effective and may function as medicines for facial aesthetic treatments and other more serious dermatological disorders related to melanin hyperpigmentation in human skin. In addition, they are used in cosmetics as skin-whitening agents and in agriculture as bio-insecticides.⁹⁻¹² These inhibitors typically work by chelating with Cu²⁺ cation in the active site of tyrosinase or replacing it, as in the case of mercury, thus inhibiting the substrate-enzyme interaction and disrupting the ensuing electrochemical oxidation process. Over the past decade, a number of naturally occurring and synthetic TIs have been reported,¹³⁻¹⁵ though most of these inhibitors have associated toxic effects and low efficacy problems. In addition to providing pigmentation necessary for photoprotection, tyrosinase is also responsible for a variety of biological processes in arthropods including wound healing, cuticle sclerotization, and protective encapsulation. In plants, it is responsible for promoting enzymatic browning processes in damaged crops following harvest handling and managing. Thus, the production of efficient and harmless TIs is therefore essential not only for insect control, but also for use in the cosmetic, food, medical and agricultural industries.¹⁶

Despite extensive efforts to design and synthesize TIs, such compounds are scant and only few (*e.g.*, PTU, anthracene, tropolone, and arbutin) have been employed in cosmetics and as therapeutic agents.¹⁷⁻²¹ However, because of poor safety profiles, adverse effects, or low efficacy, only a handful of them have been continued and put into practice.²²⁻²⁹ Undoubtedly, now more than ever, there is an urgent need to identify and develop more efficient and safer tyrosinase inhibitors.

1.1 The role of tyrosinase enzyme in the biosynthesis of melanin pigment

Melanin is the essential pigment formed by the dermal cells in the deepest layer of the epidermis known as the basal layer. It is produced by specialized cells called melanocytes through a multi-step chemical process where the amino acid tyrosine is oxidized, followed by polymerization. Melanogenesis is initiated in the skin following exposure to UV radiation and is

able to dissipate almost completely the absorbed UV radiation. Thus, melanin performs an essential role in shielding the skin from the detrimental impacts of the sun's ultraviolet rays.³⁰⁻³² Even though melanin primarily exhibits a photoprotective role in human skin, the accretion of melanin in various parts of the skin results in more pigmented spots and patches that could become an aesthetic problem.^{33,34} In worst cases, frequent exposure to UV radiation may be associated with increased risk of a cancer of melanocytes known as malignant melanoma. Furthermore, the enzymatic browning on the sliced surface of fresh fruits and vegetables can reduce the shelf life and impact their quality.^{35,36} Melanogenesis is the mechanism that leads to the development of dark molecular stains, *i.e.*, melanin. When the skin is exposed to frequent and excessive UV radiation, abnormal melanin pigment formation occurs, creating severe aesthetic deformity especially common among elderly and middle-aged people. The biosynthesis of melanin can also be triggered by free radicals. As a countermeasure, antioxidants that can detoxify free radicals prevent oversupply of melanin. Few examples of antioxidants used as melanogenesis inhibitors include vitamin C and reduced glutathione. The benefit of developing tyrosinase chemistry is expected to provide deeper understanding of how to increase shelf life of products and efficiently increase farming yields while simultaneously minimizing economic loss.³⁷⁻⁴¹

As stated earlier, melanocytes are cells produced in the dermal basal layer and are important in melanogenesis, the process of biosynthesizing melanin. Melanocytes are melano-blasts formed-dendritic cells that are unpigmented cells originating from neural crest cells of the embryos. These are mainly involved in melanin pigment synthesis. Each melanocyte is surrounded by about 36 keratinocytes which are the primary type of cell present in the outermost layer of the skin. After synthesizing melanin, it is stored inside melanosomes and subsequently transferred, using extended dendrites, to the outermost layer of suprabasal keratinocytes.⁴² Fig. 1 shows that skin pigmentation is caused by keratinocyte cornification which includes the mature melanosomes which are biosynthesized, used to store melanin and transferred by the melanocytes to the keratinocytes. Eventually, keratinocytes undergo a process of cornification or programmed cell death and migrate, along with the engulfed melanin, to the skin surface. Cornification forms the outermost skin barrier known as the cornified layer.

With tyrosinase being the main enzyme that boosts up the process of melanin formation, tyrosinase inhibitors represent key inhibitory agents to combat the excess production of melanin. On the other hand, since the biosynthesis of melanin can also be triggered by free radicals, various natural and synthetic antioxidant systems able to scavenge such radicals may control excess production of melanin.⁴³⁻⁴⁶



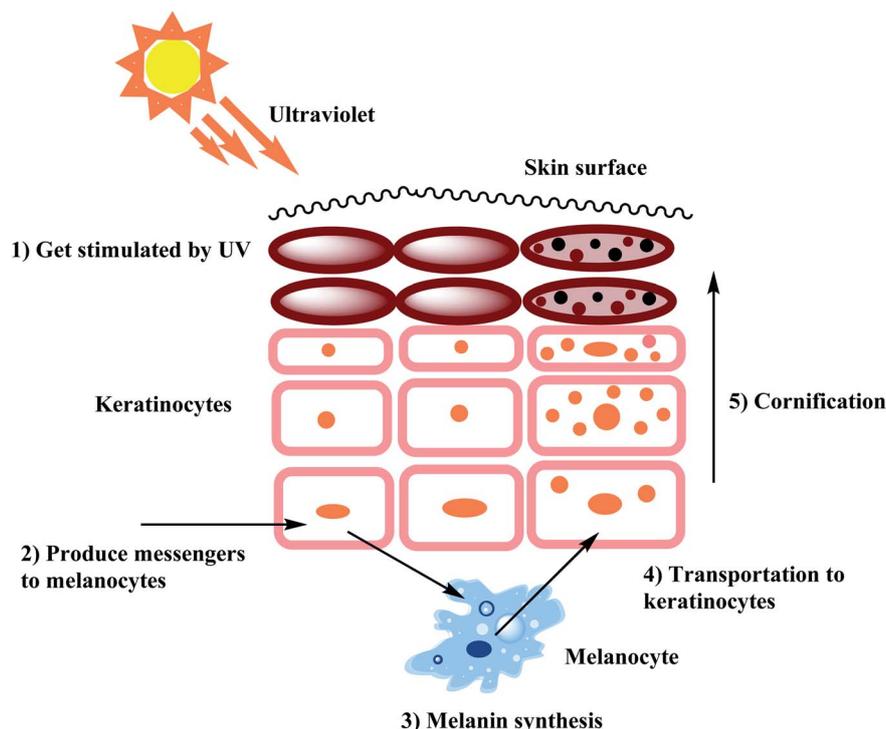


Fig. 1 Mechanism of skin pigmentation.

2. Properties of various kinds of tyrosinase

2.1 Properties of mushroom tyrosinase

Tyrosinases have been extracted and refined from a variety of natural sources including some herbs, animals, and microbes. Although in many cases the isolated enzymes were sequenced, especially those extracted from humans, very few were properly characterized or probed. Recently, a new tyrosinase produced by Sahara soil actinobacteria was isolated and chemically characterized to detect novel enzymes useful for biotechnological purposes. Heretofore, among the various sources of tyrosinase, the *Agaricus bisporus* mushroom is the most common and inexpensive tyrosinase source where the enzyme exhibits high level of structural resemblance and homology to the human tyrosinase. Tyrosinase, a 120 kDa tetramer with two isolated intense and light subunits, was isolated from *Agaricus bisporus* by Bourquelot and Bertrand in 1895. It binds to six histidine residues and has three domains and two copper-binding sites that interact with molecular oxygen in the tyrosinase active site. Additionally, its structure is stabilized by the presence of disulfide linkage. Recently, a 50 kDa *Agaricus bisporus* (H-subunit) tyrosinase isoform with a high specific activity of over 38 000 U per mg has been identified and purified.^{47–52a}

2.2 Properties of mammalian tyrosinase

Tyrosinases found in different living species are often very diverse in terms of chemical structure, structural properties, distribution in various tissues, and cellular location. The mammalian tyrosinase is

characterized as single membrane-spanning transmembrane protein.^{52b} In humans, this enzyme is sorted into organelles known as melanosomes^{52c} and the catalytically active site of the protein is situated within melanosomes. Notably, only a short, enzymatically superfluous part of the protein extends into the cytoplasm of the

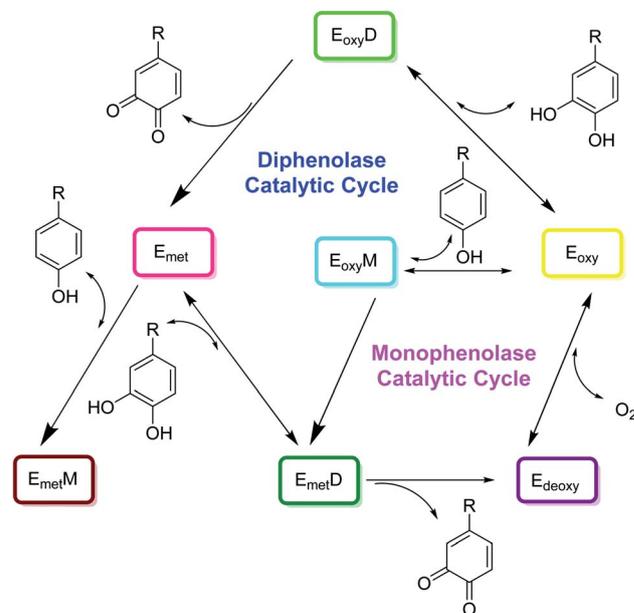


Fig. 2 Catalytic cycle for the hydroxylation of monophenol and the conversion of o-diphenol to o-quinone by the two types of tyrosinase, E_{oxy} , E_{met} , and E_{deoxy} .²⁴



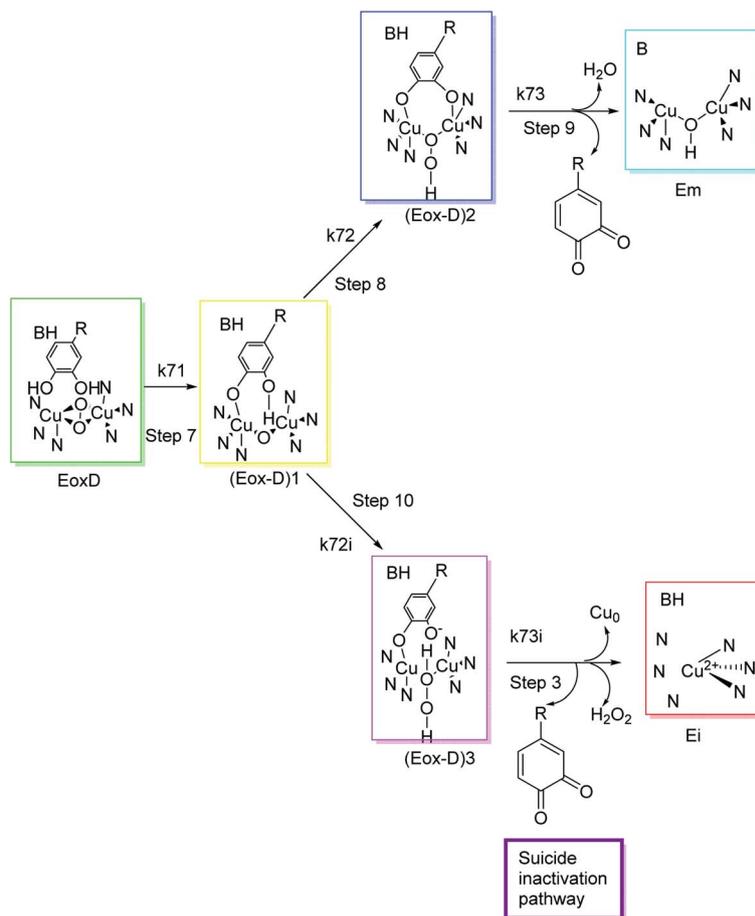


Fig. 3 Molecular mechanism of tyrosinase suicide deactivation by oxidation of an *o*-diphenol substrate. The curly arrows showed that deprotonation results in the reduction of copper from bivalent to zero-valent form, and the elimination of an *o*-quinone and tyrosinase inactivation.⁶²

melanocyte. Among the different known types of tyrosinases, the mushroom tyrosinase is known to exhibit the highest homology with mammalian tyrosinase and is the only commercially available enzyme and may be purchased through several chemical vendors.^{52d}

2.3 Properties and significance of human tyrosinase

In humans, melanin is biosynthesized in melanosomes, which are organelles located inside melanocytes in skin and hair, and retinal pigment epithelium cells in the eye.^{52e} Three tyrosinase-

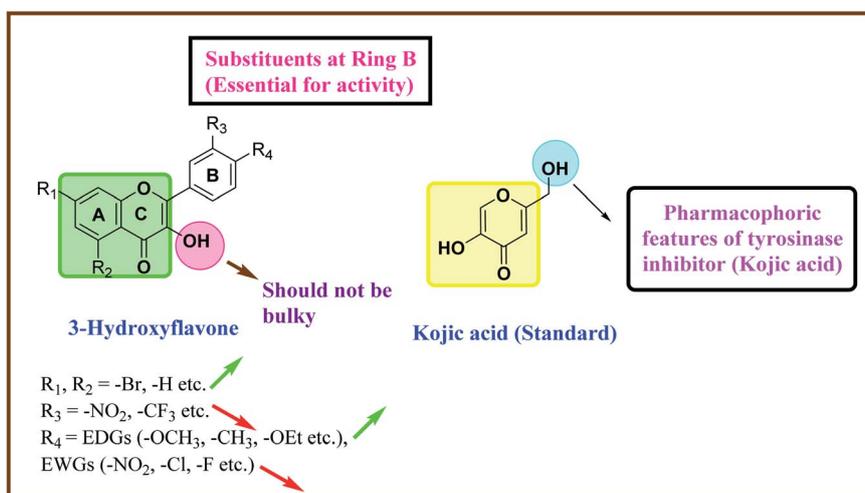


Fig. 4 Comparative SAR study of the most potent subclass (flavonol) among flavonoids with standard kojic acid. The green arrow indicates increased activity and the red arrow indicates decreased activity.



like enzymes are involved in its biosynthesis, tyrosinase (TYR) and tyrosinase-related proteins 1 and 2 (TYRP1 and TYRP2). Recent developments on the structure of TYR and TYRPs and their function by virtue of the crystal structure of human TYRP1, which represents the first available structure of a mammalian melanogenic protein have been reviewed by X. Lai *et al.*^{52f} Combining the preceding structure with those found for tyrosinases from other lower eukaryotes and mutagenesis studies of catalytically active domains, have provided deeper insight into the mechanism of action of TYR and TYRPs proteins. In addition, a TYRP1-based homology model of TYR has now given the necessary foundation to gene map and investigate mutations associated with albinism, as well as to design specific anti-melanogenic agents. Mutations in the TYR or TYRP1 genes leads to oculocutaneous albinism (OCA1 and OCA3, respectively), a group of autosomal recessive conditions involving underproduction of melanin in skin, hair and eyes. Further,

TYR and TYRP1 variants are closely associated with the development of melanoma, a malignant tumor of melanocytes responsible for the majority skin cancer related deaths.^{52g} On the other hand, overproduction of melanin or abnormal distribution may lead to pigmentation disorders, such as over-tanning, age spots and melasma,^{52g} which has triggered the development of skin-whitening products to lower the melanin content. Nowadays, inhibition of melanin biosynthesis is being considered as a rational therapeutic strategy to treat advanced melanotic melanomas.^{52h}

2.4 Reaction mechanism of tyrosinase

The catalytic cycle of tyrosinase involves two steps as shown in Fig. 2. First, monophenols are hydroxylated to *o*-diphenols by a monophenolase activity, and diphenols are hydroxylated by a diphenolase activity. In the second step, tyrosinase oxidizes *o*-

Table 1 Structures of some mushroom tyrosinase inhibitors³⁶

Compound name	Compound structure	Source
Arbutin		Extracted from the dried leaves of bearberry plant in the genus <i>Arctostaphylos</i>
Tropolone		Isolated from <i>Pseudomonas lindbergii</i>
Kojic acid		Obtained from a few species of <i>Aspergillus</i>
Cuminaldehyde		Obtained from essential oils
Oxyresveratrol		Obtained from the extract of heartwood
Cupferron		Obtained from natural samples rich in organic matter
<i>p</i> -Coumaric acid		Obtained from pollens



diphenols to *o*-quinones. There exist a variety of chemical reactions that are coupled simultaneously to the enzymatic reaction in which two *o*-dopaquinone molecules react with each other to produce an *o*-diphenol fragment and a dopachrome particle (Fig. 2). Later on, when the tyrosinase molecule reacts with an *o*-diphenol, it is possible to investigate diphenolase behavior on its own. They form met-tyrosinase that furtherly joins the *o*-diphenol activating the complex E_mD . This complex then oxidizes the *o*-diphenols into *o*-quinone and subsequently the enzyme is transformed into the deoxytyrosinase form. E_d exhibits high affinity for O_2 , initiating the oxy-tyrosinase form, which furtherly attaches to another *o*-diphenol fragment, forming a new multifaceted $E_{ox}D$ complex.

Later, *o*-diphenol is oxidized once more to *o*-quinone and E_m is formed, completing the catalytic cycle. Following these enzymatic reactions, two *o*-quinone molecules react together, producing dopachrome and regenerating an *o*-diphenol

molecule. Although diphenolase activity may be reviewed independently, this is not valid for monophenolase activity because chemical reactions of diphenolase and monophenolase production take place simultaneously. Furthermore, the monophenolase activity is expressed by tyrosinase in a given time interval. There are two new complexes formed by monophenolase activity. One is $E_{ox}M$ and the second one is E_mM . $E_{ox}M$ is an active form and converts into E_mD , which is primarily an intermediate in the catalytic cycle. The *o*-quinones products thus formed by these two oxidation cycles can react spontaneously with one another to form oligomers.^{24,53–56}

3. Tyrosinase inhibition

Owing to the essential function of tyrosinase in the tanning process and melanogenesis, many studies describing the identification of TI's from both biological and synthetic sources

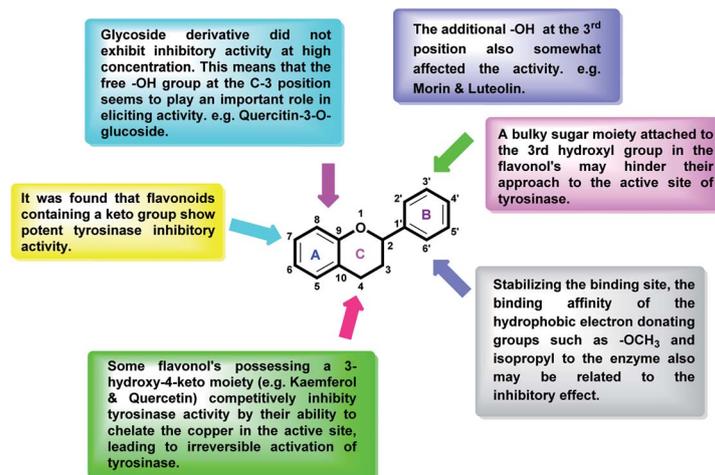
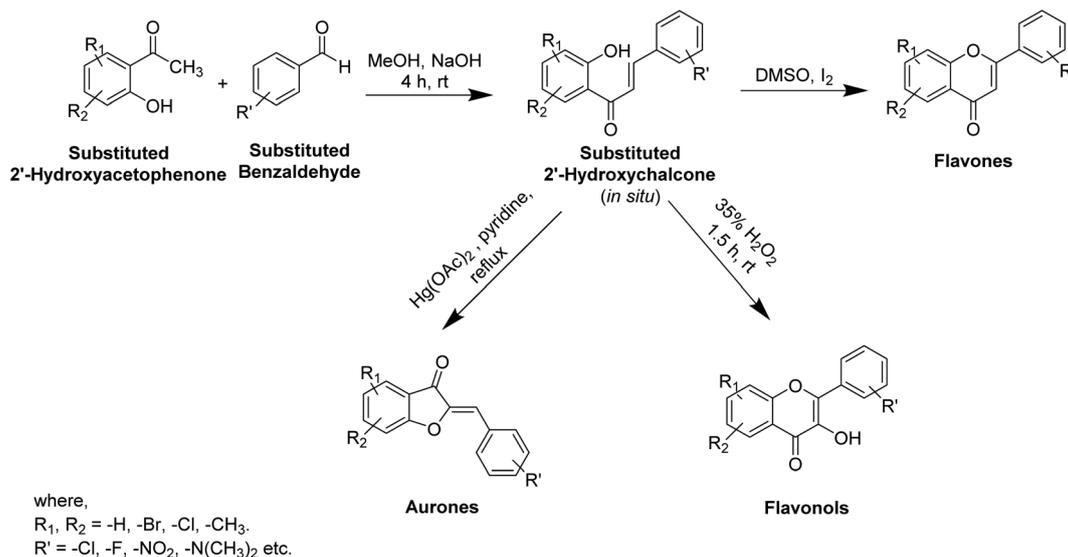


Fig. 5 General structure of flavonoids and relevant pharmacophoric structural features.



Scheme 1 Synthesis of some flavonoids from substituted 2'-hydroxychalcone.



have been reported. Typically, the activity of TIs is estimated in the presence of a tyrosine or *L*-dopa substrate, and the activity is evaluated based on dopachrome formation.^{57–61}

3.1 Tyrosinase inhibition mechanism

Different classes of compounds can prevent melanogenesis, for example, unique TIs and inactivators, different enzymatic substrates, dopaquinone foragers, non-specific enzyme denaturants, and nonspecific enzyme inactivators attach to the enzyme and hinder its process. Suicide inactivators were commonly registered for the treatment of hyperpigmentation. To describe tyrosinase suicide deactivation (Fig. 3), two pathways have been proposed. In the first pathway, it has been suggested that the conformational changes initiated by the inhibitor's complex in the

3D structures of tyrosinase may rationalize the suicide deactivation. Conversely, in the second pathway, suicide deactivation may take place following the proton transfer to the peroxy bridge on the *oxy*-tyrosinase active site.⁶²

Moreover, to determine the inhibitory mechanism, the IC_{50} value could be premeditated in the kinetics studies of enzyme and inhibitor's screening to compare the inhibitory strength of an inhibitor with that of a standard and other inhibitors. Though the inhibitory values can be incomparable owing to different assay conditions (various substratum development time, concentrations, and numerous tyrosinase sources), a positive standard could be used for this purpose to normalize values.^{63,64} Unfortunately, many researchers have not determined IC_{50} values of novel TIs nor applied positive standards in

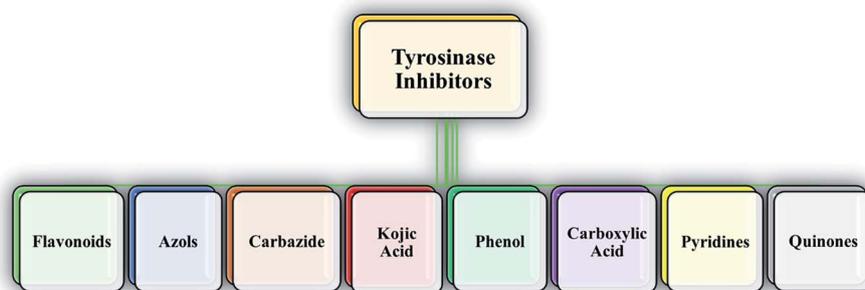


Fig. 6 Representative anti-tyrosinase scaffolds.

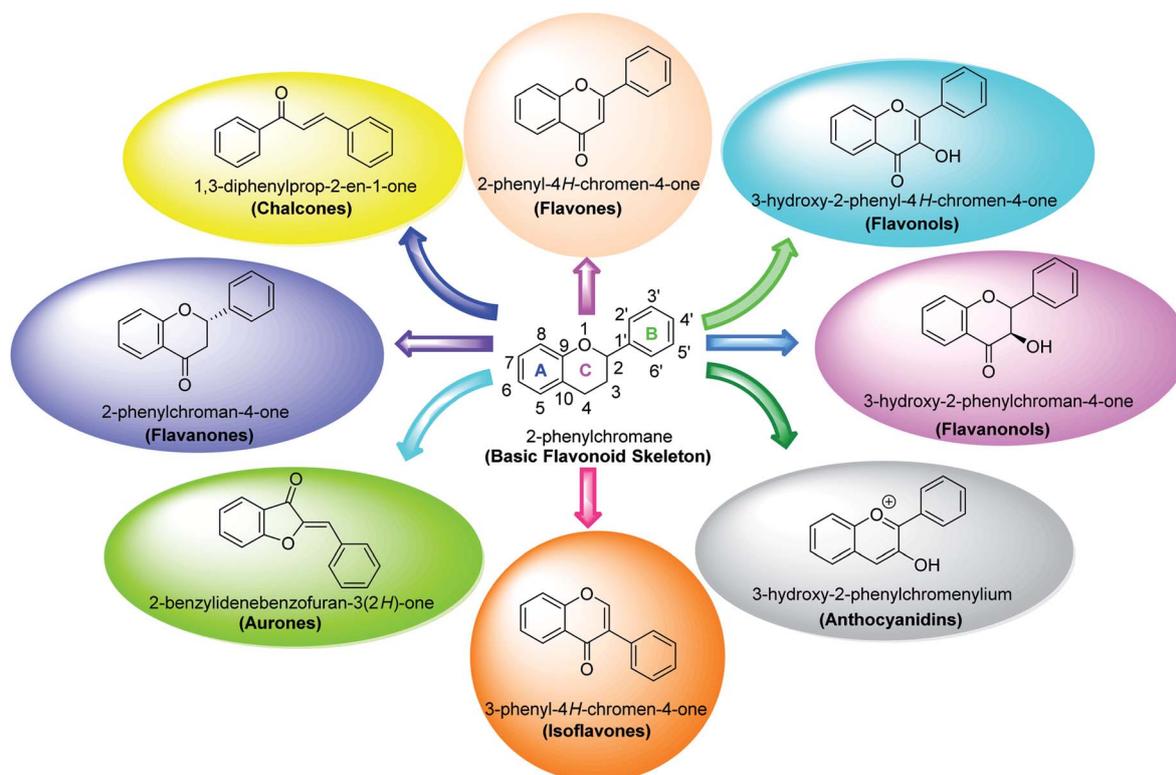


Fig. 7 Various sub-classes of flavonoids.⁸⁹

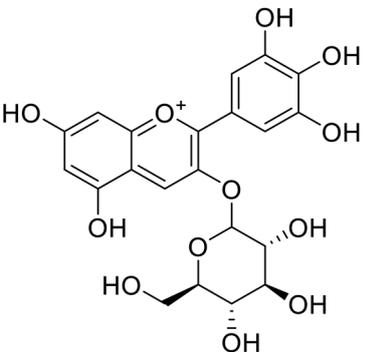
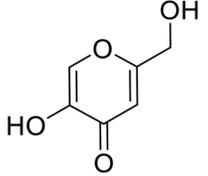


Table 2 Chemical structures of natural anthocyanidins and IC₅₀ values against mushroom tyrosinase

Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
1	Malvidin		45	31
2	Peonidin		22	31
3	Pelargonidin		78	31
4	Haginin A		5.0	31
5	Delphinidin		20.9	31
6	4-(8,8-Dimethyl-2 <i>H</i> ,8 <i>H</i> -pyrano[2,3- <i>f</i>]chromen-3-yl)benzene-1,3-diol		0.09	31
7	Cyanidin-3- <i>O</i> -glucoside		18.1	140



Table 2 (Contd.)

Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
8	Delphinidin-3-O-glucoside		7.5	31
Standard	Kojic acid		59.3	31 and 140

their research like kojic acid, hydroquinone and arbutin which are typically used as standards. Though amongst various kinds of TIs, few inhibitors such as azelaic acid, kojic acid, tranexamic acid, ellagic acid and L-ascorbic acid have been identified in cosmetic products as skin-whitening agents. Despite the good safety profile of these drugs, several studies failed to prove their outcome as useful skin lightening agents in clinical trials.^{65–67}

From a structural point of view, the two divalent copper ions that are surrounded by three histidine residues are responsible for the catalytic activity of tyrosinase. A docking study (*in silico*) revealed that the various TIs expressed their inhibitory potential through hydrophobic π -alkyl, hydrophobic π - σ , hydrophobic π - π T-shaped, and hydrophobic π - π stacked type interactions with His263, Phe264, Ala286, Val283, and His85 amino acid residues inside of the activation loop of targeted tyrosinase biological molecule.^{52d}

After an extensive structure–activity relationship studies, the SAR data suggest that among all the flavonoid derivatives, the flavonol class stands out and offers the most potent inhibitory activity due to its structural resemblance with that of the standard inhibitor kojic acid. In particular, the phenyl- γ -benzopyran core structure plays a vital role in tyrosinase inhibitory activity. It is noted though that variation in the activity of these inhibitors is attributed to variability in the positions and nature of substituents on the aryl ring (B) as well as the nature of ring B. Introducing halogen atoms into ring A of 2-phenylchromones enhances the electron density along with the hydrophobicity of the molecules and fosters strong bonding interactions. The structure of such inhibitors is therefore customizable and may be tuned to achieve optimum potency. The aforementioned results suggest that 3-hydroxyflavone molecules can serve as fascinating candidates for the treatment of tyrosinase-related

ailments and as lead compounds for the development of potent new tyrosinase inhibitors (Fig. 4).

4. Natural and synthetic sources of inhibitors

4.1 Natural phenolic tyrosinase inhibitors and their sources

Living organisms have developed shielding mechanisms to safeguard against the destructive actions of UV radiations. Hence, nature has a multitude of tyrosinase inhibitor sources. Several investigators have described the isolation of tyrosinase inhibitors from mycological metabolites, plants, and aquatic algae, among other sources. Tyrosinase inhibitors from natural resources commonly attract more interest compared to synthetic ones to meet cosmetic demand and requirements. The IC₅₀ values for the current TIs in the literature are incomparable because of the differences in assay conditions, such as substrate concentration, different time of incubation, and various lots of tyrosinases (Table 1). Henceforth, many researchers have been using the most recognized TI, for example, kojic acid as a standard to adjust and normalize the reported inhibitory activity values.^{68–72}

4.2 Synthetic phenolic tyrosinase inhibitors

In recent years, numerous studies have addressed the development of new TIs based on natural structural motifs, yet designed to overcome issues related to chemical stability, effectiveness, and isolated yield.^{9,73} Thus, bioinspired by the various structural scaffolds of natural tyrosinase and the existing research course to design useful synthetic compounds (Fig. 5), synthetic inhibitors with new structural moieties as well as analogs of natural compounds have been synthesized (Scheme 1).^{74,75}

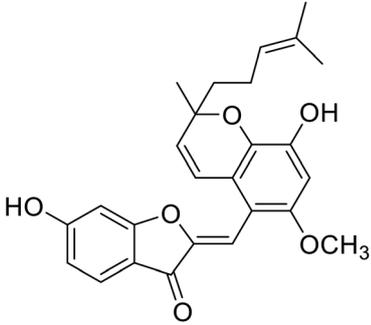
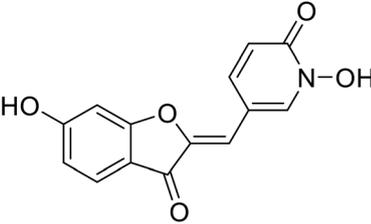
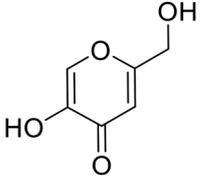


Table 3 Chemical structures of natural aurones and IC₅₀ values against mushroom tyrosinase

Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
9	4,6,4'-Trihydroxyaurone		38	35
10	Altilisin J		98.5	107
11	Aurone		12.3	31
12	Altilisin H		85	107
13	7-Hydroxy-2-(4-hydroxybenzylidene) benzofuran-3(2H)-one		31.7	106
14	5-Hydroxy-2-(4-hydroxybenzylidene) benzofuran-3(2H)-one		38.4	106



Table 3 (Contd.)

Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
15	Attilisin I		88.9	107
16	2-Hydroxypyridine <i>N</i> -oxide aurone		1.5	111
Standard	Kojic acid		167	107 and 111

Various potent or weak synthetic (Scheme 1) and natural inhibitors have been reported for tyrosinase.^{76–78} Flavonoids, the most abundant and commonly studied polyphenols, are benzo- γ -pyrones comprising of pyrene and phenolic rings (Fig. 5). Broadly spread in the flowers, seeds, barks, and leaves, more than 4000 flavonoids have been discovered up to date. Flavonoids are accountable for the distinguished blue and red colors of wines, berries, and a variety of vegetables. Flavonoids can be divided into eight different classes, including aurones, chalcones, flavonols, flavones, flavanols, flavanones, and anthocyanins. Various flavonoid classes are characterized by oxygen-containing five or six-membered heterocyclic rings, and by variation in the position of ring B, and by $-\text{OH}$, $-\text{CH}_3$, and $-\text{OCH}_3$ groups widely spread in various distinct patterns around the rings.^{79–81} Besides flavonoids, other polyphenols, which are also known as TIs, include coumarin and stilbenes derivatives (Fig. 6).⁸² Detailed investigations have proven that few flavonoids are very powerful and effective inhibitors and are discussed in this segment.^{83–86}

5. Flavonoids

Flavonoids belong to a class of naturally occurring plant polyphenolic secondary metabolites that are broadly dispersed in the plant kingdom and therefore commonly consumed in diet. Generally, they are identified as compounds having the $\text{C}_6\text{--C}_3\text{--C}_6$ carbon framework as a core structure consisting of 15-carbon atoms. These often comprise two phenyl rings,

designated as A and B, and a heterocyclic ring. Biological studies performed on natural and synthetic analogs of flavonoids have uncovered a considerably broad range of bioactivities manifested by these species which include anxiolytic, anti-microbial, anti-cancer, anti-inflammatory, anti-ulcer, and thrombosis.^{85,87–90}

Certain flavonoids commonly found in herbs, vegetables, or obtained from synthetic routes, have shown promising prospects as potential TIs among polyphenolic compounds. There is a considerable connection and correlation between the flavonoid's inhibitory potency on tyrosinase and melanin formation in melanocytes.

Several flavonoids, extracted from biological resources such as *Teretris nigrescens*, *Myristica yunnanensis*, *Pleurotus ostreatus*, roots of *Morus lhou*, and *Palhinhaea cernua*, herbal plants, and other numerous medicinal plants, were analyzed for their inhibitory action on tyrosinase in the search for effective TIs.^{91–94} Flavonoids are categorized into various classes, for instance, isoflavones, flavonols, flavanonols, flavanones, flavan-3,4-diols, anthocyanidins, flavones, aurones, and chalcones (Fig. 7). Other flavonoid subclasses include vinylated and acetylated flavonoids, as well as their glycosides. Few flavonoid glycosides such as myricetin galactoside and quercetin galactopyronaside from *Epilobium tetragonum* have been examined for their TI activities. Remarkably, it has been revealed that far IR irradiation can increase the TI activity of certain flavonoid glycosides.^{95–103} In a review of recent findings, Orhan *et al.* surveyed many tyrosinase inhibitors incorporating the flavonoid scaffold.¹⁰⁴ Many promising TI's from different classes of



Table 4 Chemical structures of synthetic aurones and IC₅₀ values against mushroom tyrosinase

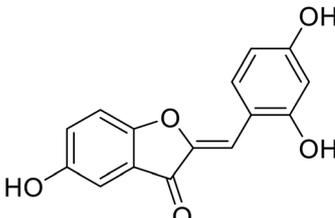
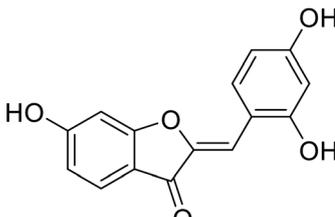
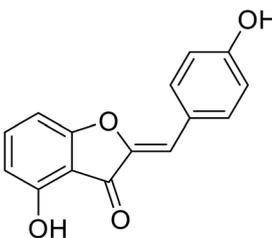
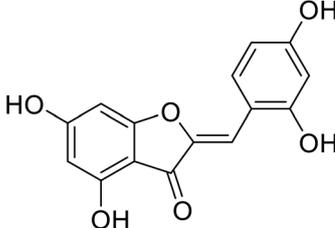
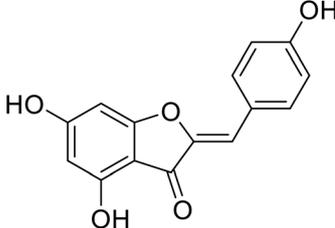
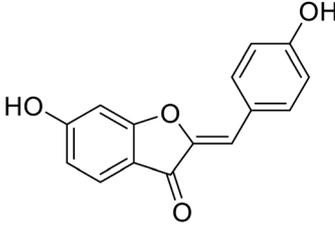
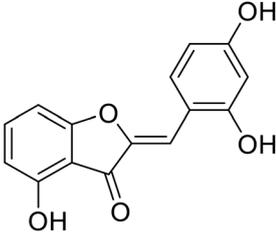
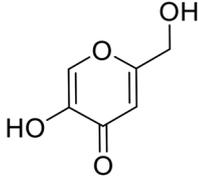
Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
17	2-(2,4-Dihydroxybenzylidene)-5-hydroxybenzofuran-3(2H)-one		>1000	106
18	2-(2,4-Dihydroxybenzylidene)-6-hydroxybenzofuran-3(2H)-one		>1000	106
19	4-Hydroxy-2-(4-hydroxybenzylidene)benzofuran-3(2H)-one		31.7	31
20	2-(2,4-Dihydroxybenzylidene)-4,6-dihydroxybenzofuran-3(2H)-one		300	106
21	4,6-Dihydroxy-2-(4-hydroxybenzylidene)benzofuran-3(2H)-one		38.0	111
22	6-Hydroxy-2-(4-hydroxybenzylidene)benzofuran-3(2H)-one		38.4	31



Table 4 (Contd.)

Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
23	2-(2,4-Dihydroxybenzylidene)-4-hydroxybenzofuran-3(2H)-one		9	106
Standard	Kojic acid		280	31, 106 111

natural and synthetic flavonoids have been summarized and the role of flavonoids has been highlighted and recommended as the focus of future and continued tyrosinase inhibition studies.

5.1 Anthocyanidins

Anthocyanin, also known as common sugar-coupled anthocyanidin, is a flavonoid found in plants and is accountable for the bright color of vegetables and fruits. It has wound healing and antioxidant properties. Anthocyanin is a naturally occurring pigment that can lessen excess free radicals in the body and can decrease the risk of cancer and cardiovascular diseases. *Hibiscus sabdariffa* Linn., an annual herbaceous shrub, is an exceptional resource of anthocyanin. Toxicity reports indicated that anthocyanin from *Hibiscus sabdariffa* can shield rat liver from the poisoning and destructive effect of *tert*-butyl hydroperoxide due to the antioxidant action of the former species. Still, there is no evidence that anthocyanin from *Hibiscus sabdariffa* inhibits melanogenesis. However, compounds **4**, **6**, and **8** (IC₅₀ = 5, 0.09, and 7.5 μM) in Table 2 have shown excellent tyrosinase inhibitory activities.

Anthocyanin molecules are highly unstable and prone to degradation because they are charged. The anthocyanin color persistency is influenced by temperature, presence of enzymes, pH, light, concentration, structure of the anthocyanin, and the existence of complex derivatives such as other phenolic acids, flavonoids, and metals. Anthocyanin has excellent antioxidant impacts but is susceptible to the effect of biological factors. Hence, encapsulating anthocyanin in liposomes will effectively extend the half-life of anthocyanin (Table 2).¹⁰⁵ At the moment and to the best of our knowledge, there is no literature available on synthetic anthocyanins as mushroom TIs.

5.2 Aurones

Aurone itself is a weak inhibitor of the tyrosinase enzyme, but its synthetic derivatives that contain more than two –OH groups residing at the 4', 4, and 6 positions are more potent TIs. Researchers found that natural aurones are most effective against

human tyrosinase. Synthetic aurone derivatives like 2-benzylidenebenzofuran-3(2H)-ones and 2',3'-dihydro-2'-(1-hydroxy-1-methylethyl)-2,6'-dibenzofuran-6,4'-diol are also important TIs.¹⁰⁶

Aurones, natural as well as their synthetic analogs, show a broad array of bioactivities such as antimicrobial, anti-leishmanial, and anticancer. However, these natural biologically active analogs are also specified for their inhibitory action against many kinds of proteins and enzymes. Particularly, natural 4,6,4'-trihydroxyaurone has been recognized as a highly effective inhibitor against human melanocyte-tyrosinase as shown in Table 3. In contrast with the known standard kojic acid, an excellent inhibitor of mushroom tyrosinase, 4,6,4'-trihydroxyaurone showed even superior inhibitory results.^{107,108}

Aurone and its derivatives were discovered as human tyrosinase inhibitors by Okombi *et al.* Moreover, they recognized that aurones themselves are weak blockers, yet their analogs with more than three –OH groups, usually at the 4', 4, and 6 positions, are potent TIs. For example, the most active aurone, compound **9** (Table 3), causes 75% inhibition at 0.1 mM concentration and is very efficient compared to the standard kojic acid.¹⁰⁸

N. T. Mai and his colleagues (2012) have reported three new aurones (compounds **10**, **12**, and **15**) isolated from a plant, *Artocarpus altilis* (Moraceae), which is broadly distributed over the tropical regions of Asia.¹⁰⁹ The isolated compounds were tested for their tyrosinase inhibitory activity (Table 3). The assay was carried out at five different concentrations ranging from 1 to 100 μM for tyrosinase inhibition. All compounds possessed tyrosinase inhibitory activity with IC₅₀ values less than 100 μM. Among them, compounds **12** and **15** showed more potent activities with IC₅₀ values of 85 μM and 88.9 μM, respectively. The results showed that these derivatives had an excellent tyrosinase inhibitory activity.

Dubois *et al.* (2012) showed that the most potent aurones were those bearing a –OH group at the 4'-position of ring B. Believing that aurones interact with the binuclear Cu²⁺ active site through this ring, they surveyed aurones in which the



Table 5 Chemical structures of natural chalcones and IC₅₀ values obtained against mushroom tyrosinase

Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
24	2,4,2',4'-Tetrahydroxy-3-(3-methyl-2-butenyl)-chalcone (TMBC)		0.95	118
25	2,2',4,4'-Tetrahydroxychalcone		0.07	113
26	Isoliquiritigenin		4.85	36
27	Kuwanon J		0.17	36
28	Kuraridin		0.6	27
29	Isobavachromene		15.8	134
30	Morachalcone A		0.14	112
31	4'-O-Methylbavachalcone		48.8	134



Table 5 (Contd.)

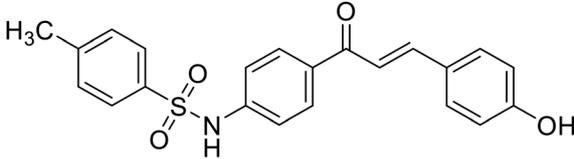
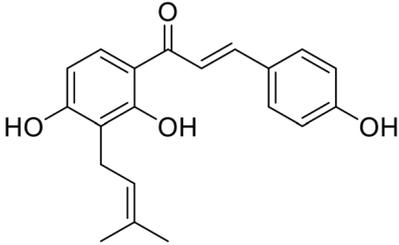
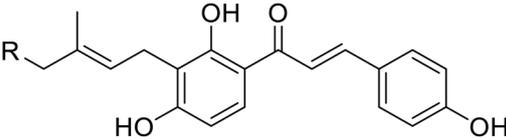
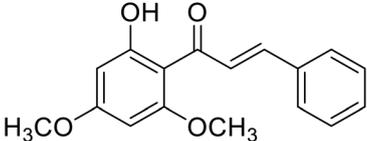
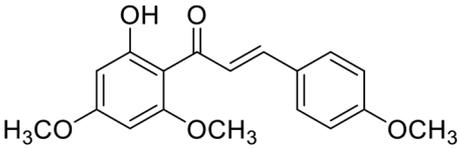
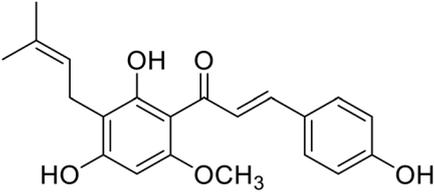
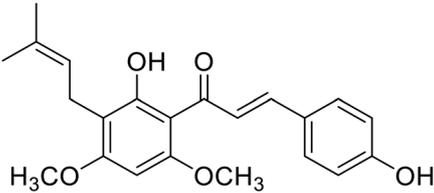
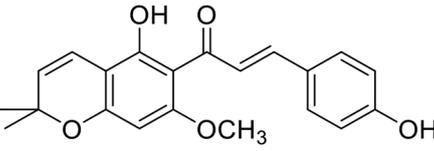
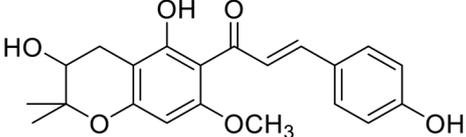
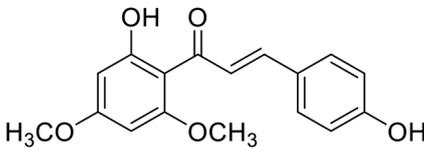
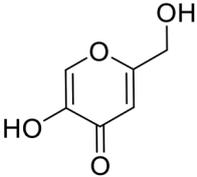
Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
32	4'-(<i>p</i> -Toluenesulfonylamino)-4-hydroxychalcone		23.3	36
33	Isovabachalcone		12.3	134
34	Artocarmitin C		20.6	135
35	Flavokawain B		14.38	29
36	Flavokawain A		14.26	29
37	Xanthohumol		15.4	30
38	4'-O-Methylxanthohumol		34.3	134
39	Xanthohumol C		41.3	30
40	Xanthoumol B		46.7	30



Table 5 (Contd.)

Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
41	Flavokawain C		106.7	29
Standard	Kojic acid		89.5	29, 30, 134 and 135

position of the -OH group on the A ring is fixed in the 6th position. Compound **16** (IC₅₀ = 1.5 μM) was found to promote L-DOPA oxidation, which is mediated by tyrosinase. This particular finding indicated that 2-benzylidene-furan can either act as substrates or as hyperbolic activators.¹¹⁰

Among the synthesized aurone analogs, the one in which B-ring is substituted with a HOPNO group, compound **16** has been determined as an efficient and novel mushroom tyrosinase inhibitor. The hybrid aurone **16** has been constructed by combining an aurone moiety with 2-hydroxypyridine *N*-oxide, an excellent metal chelator.

In 2014, 24 different substituted hydroxylated aurones were synthetically prepared by R. Haudecoeur and his coworkers to evaluate their repressing action towards bacterial and mushroom tyrosinases. The inhibitory behavior of the chemical derivatives depended highly on the hydroxylation patterns of rings A and B and the type of tyrosinase used. Among the new derivatives, 2',4'-dihydroxyaurones were recognized as the best effective mushroom and bacterial TIs. The presence of hydroxy groups in compounds **18**, **19**, and **22** at 4,4'; 6,4'; or 4,6,4' positions was found to be critical for excellent tyrosinase inhibitory potencies in hydroxylated aurones. Based on the aforementioned findings, compounds **18**, **19**, and **22** were evaluated for their IC₅₀ and proved much stronger and better inhibitors (Table 4) than kojic acid (IC₅₀ = 280 μM) and arbutin (IC₅₀ = 8.4 μM).¹¹¹

5.3 Chalcones

Chalcones are comprised of two *trans*-configured aryl rings, separated by 3C atoms, two of which are covalently bonded by a double bond (=) and the third is a carbonyl (C=O) functionality. Several natural acylated chalcones show potent tyrosinase inhibitory properties. Their aromatic rings are substituted with different functional groups: -OH, -OCH₃, -R, and these substituents impact the bioactivities of chalcones. Several chalcones described in the literature show good tyrosinase inhibitory activity.^{8,58,112}

Khatib and colleagues discovered that mono-, di-, tri-, and tetra-substituted hydroxychalcones could inhibit tyrosinase. Compound **28** (Table 5), a prenylated chalcone isolated from the plant *Sophora flavescens*, was highly potent as it exhibited 34 fold activity compared to that of a standard against mushroom tyrosinase monophenolase. More intriguing, the two prenylated chalcones also showed higher activity than their flavanone analogs.^{27,96,97} Kuraridin (a chalcone) was 10 times more active than kurarinone (a flavanone). Compounds **28** and **24** produced 34- and 26-fold TI activities than kojic acid, respectively (Table 5).

According to Nerya *et al.*,²⁷ the location of the -OH groups attached to the aryl rings A and B is the most essential structural feature required to produce strong tyrosinase inhibitory activity of chalcones, and there is a substantial preference for *p*-substituted ring B over substitution at ring A. However, the findings drawn from their recent study revealed conflicting results that chalcones with 2,4-DNPH and resorcinol moieties displayed the greatest tyrosinase inhibitory activity, and the resorcinol subunit on ring B did not contribute effectively to maximize TI action. In the presence of both Cu²⁺ ions and tyrosinase, the catechol on ring A acted like a metal chelator (in the presence of Cu²⁺ ions) and a competitive inhibitor (in the presence of tyrosinase), while the catechol on ring B underwent oxidation to the corresponding *o*-quinone. Compounds **24** and **25** (IC₅₀ = 0.95 and 0.07 μM respectively) are powerful tyrosinase inhibitors.

Likewise, Jun *et al.*¹¹³ synthesized a chalcone series and analyzed their tyrosinase repressive action. The findings were consistent with their prior work,²⁷ and the most active derivative reported was 2,4,2',4',6'-pentahydroxychalcone, showing a 5-fold higher activity than 2,4,2',4'-hydroxychalcone.

Nguyen *et al.*¹¹⁴ recently isolated acylated flavones and chalcones from the wood of *Artocarpus heterophyllus*. Compound **30**, which had a 3000-fold greater activity than kojic acid, was the most active of the isolated compounds with significant TI activity. Many synthetic derivatives of chalcones were developed as effective candidates of tyrosinase



Table 6 Chemical structures of synthetic chalcones and IC₅₀ values against mushroom tyrosinase

Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
42	1-(2-Hydroxy-6-propoxyphenyl)-3-(4-(hydroxymethyl)phenyl)prop-2-en-1-one		26.8	96
43	3-(3-Amino-4-methoxyphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one		9.75	96
44	1,3-Bis(2,4-dihydroxyphenyl) prop-2-en-1-one		0.02	96
45	3-(4-Hydroxyphenyl)-1-phenyl prop-2-en-1-one		21.8	133
46	3-(2,4-Dihydroxyphenyl)-1-(2,4,6-trihydroxyphenyl)prop-2-en-1-one		17.6	133
47	3-(4-Amino-2-methoxyphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one		7.82	112
48	1-(2,4-Dihydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one		8.1	114
49	1-(2,4-Dihydroxyphenyl)-3-(3,4-dihydroxyphenyl)prop-2-en-1-one		29.3	114
50	1-(1-(4-Methoxyphenyl)-3-phenylallylidene)thiosemicarbazide		0.274	123
51	3-(3-Amino-4-methoxyphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one		9.75	112



Table 6 (Contd.)

Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
52	3-(2,4-Dihydroxyphenyl)-1-(3-hydroxynaphthalen-2-yl)prop-2-en-1-one		114.4	116
53	3-(3,5-Dihydroxyphenyl)-1-(3-hydroxynaphthalen-2-yl)prop-2-en-1-one		10.4	116
54	1-(3-Hydroxynaphthalen-2-yl)-3-(pyridin-3-yl)prop-2-en-1-one oxime		12.22	117
55	1-(3-Hydroxynaphthalen-2-yl)-3-(pyridin-4-yl)prop-2-en-1-one oxime		19.45	117
56	3-(4-(Dimethylamino) phenyl)-1-(2-hydroxy-4-methoxyphenyl)prop-2-en-1-one		14.20	112
Standard	Kojic acid		57.9	112, 116, 123 and 133

inhibitors,^{115–117} inspired by their versatile bioactivity and unique structural motif. Some natural and synthetic chalcones, as well as their derivatives, have been reported as new potent depigmenting agents and TIs, according to several studies (Table 6). Up to now, natural chalcone isoliquiritigenin from licorice roots, 2,4,2',4'-hydroxychalcone and three of its analogs with 3'-substituted resorcinol moieties from *Malacosteus australis* (Table 5) 2,4,2',4'-tetrahydroxy-3-(3-methyl-2-butenyl)-chalcone from *Morus nigra*, 2,4,2',4'-tetrahydroxychalcone (IC₅₀ = 0.07 ± 0.02 μM) and morachalcone A (IC₅₀ = 0.08 ± 0.02 μM) from *Morus alba* L. have been designated as tyrosinase inhibitors.¹¹⁵

Tetrahydroxychalcone and its various derivatives (such as naphthyl chalcones and their thiosemicarbazide) have been described as a novel class of TIs (Table 6). Remarkably, compounds 44, 46, 50, and 54 have shown excellent tyrosinase inhibitory activity due to the presence of –OH groups on rings A

and B and the number of –OH groups, while the presence of a catechol group did not correlate with rising tyrosinase inhibition potency.^{116,117}

The synthesized chalcones, compound 47 and compound 51 (Table 6) were proven to be the most potent TIs in a competitive way. Their IC₅₀ values indicated that they were more potent than kojic acid, the reference compound.^{27,118,119}

Nerya *et al.* reported that chalcones are highly potent new depigmenting agents, with their dual effect of antioxidant activity and reductants.^{27,120} Tables 4 and 5 depict chalcone and its analogs showing anti-tyrosinase behaviors (IC₅₀ values).^{121–123}

5.4 Flavones

Flavone belongs to the class of flavonoids having a 2-phenylchromen-4-one backbone. They can be found in some yellow and orange fruits and vegetables, as well as spices.



Table 7 Chemical structures of natural flavones and IC₅₀ values obtained against mushroom tyrosinase

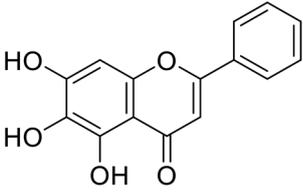
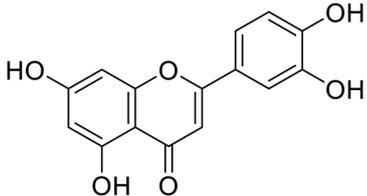
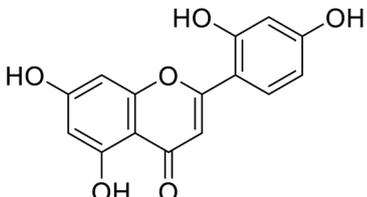
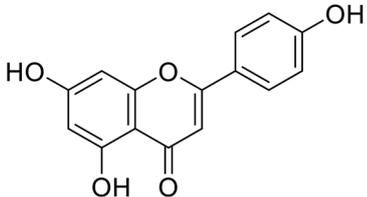
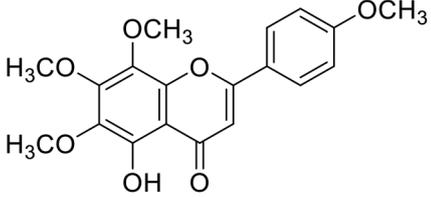
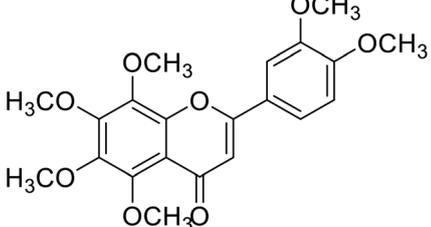
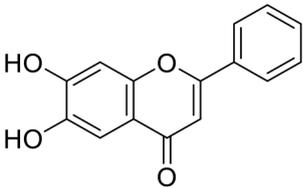
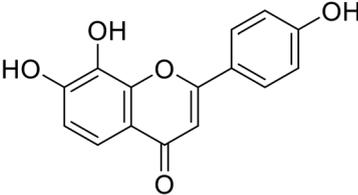
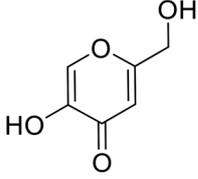
Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
57	Baicalein		110	93
58	Luteolin		20.8	30
59	Norartocarpetin		1.2	86
60	Apigenin		17.3	30
61	Tangeretin		25	87
62	Nobelitin		29.8	124
63	6,7-Dihydroxy-2-phenyl-4H-chromen-4-one		2.8	30



Table 7 (Contd.)

Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
64	4',7,8-Trihydroxyflavone		10.31	94
Standard	Kojic acid		78	30, 86 and 94

Apigenin, lutein, chrysin, and baicalein along with their glycosides, the polymethoxylated flavones tangeretin, and nobiletin, are the most popular flavones.^{86,87,124} Nguyen *et al.*¹¹⁴ have studied the occurrence of compounds **60** and **62** from the methanolic extract of *Artocarpus altilis* with 11 other polyphenolic derivatives for their TI activity.

Shang *et al.*⁹³ discovered a flavone derivative, namely 7,8,4'-trihydroxyflavone, which prevents tyrosinase diphenolase action (Table 7). The proposed binding mechanism involved van der Waals forces and hydrogen bonding, according to the thermodynamics parameters. In addition, docking simulations revealed H-bonding between this compound and the active site residues His244 and Met280. Several hydroxyflavones, such as 6-hydroxyapigenin, baicalein, and 6-hydroxykaempferol, and 6-hydroxygalangin have also been shown as inhibitors of tyrosinase diphenolase activity (Table 7). Another active flavone, compound **57** (5,6,7-trihydroxyflavone), has been obtained from the roots and aerial parts of *Chrysanthemum morifolium* and *Oroxylum indicum* (Indian trumpet flower) (Table 7). The compound shows tyrosinase inhibition by inducing conformational changes within the structure of the target enzyme.^{125,126}

Nihong Guo *et al.* estimated the active site for binding interaction is present at the bottommost cavity of tyrosinase. From docking studies carried out using the same tyrosinase enzyme (PDB: 2Y9X), intermolecular interaction confirmed the binding between tyrosinase and baicalein which effectively produced a docking score of $-6.20 \text{ kcal mol}^{-1}$ for binding conformation. Several adjacent residues which include His85, Val 248, Phe264, Met280, Ser282, Val283, and Ala286 foster hydrophobic interaction with the benzene ring and increase the stability of binding interaction. The phenolic hydroxyl group (C-7) of baicalein and the carbamoyl oxygen atom of Met 280 residue form hydrogen bonding which stabilizes the complex. The C-7 hydroxy group was considered very essential for enhancing its inhibitory activity against tyrosinase.¹²⁷⁻¹²⁹

Jamshaid *et al.*⁸⁷ reported compound **69** as a new synthetic analog of flavone with potential TIs (Table 8). It is obvious from their findings that the indole moiety present at the 2-position of

the flavone motif is responsible for enhanced TI action as reflected by the greater activity obtained relative to the standard. Furthermore, the other substituted synthetic 2-phenylchromones substituted with a nitro group at the 4th position and dimethoxy groups at 3rd and 4th positions on the B ring, respectively, showed extraordinary activity as compared to the standard kojic acid.

5.5 Flavanols

Flavanonols are a diverse subclass of the flavonoid family that includes catechin monomers and epicatechin isomers, as well as oligomeric and polymeric proanthocyanidins and condensed tannins. Flavanols found in the higher plants and medicinal herbs include epicatechin, catechin, *epi*-gallocatechin, ECG, EGCG, and proanthocyanidins. *Astelia neocaledonica* is a prevalent Caledonia tree, which was recognized as an anti-tyrosinase source due to the existence of gallocatechin and tannins. Furthermore, proanthocyanidins from *Clausena lansium* showed excellent TI in a competitive style and demonstrated good melanogenic inhibition activity of B16 cells (Table 9). Another study described that compound **81**, purified from *Annona squamosa* pericarp, could strongly inhibit the monophenolase and diphenolase actions of tyrosinase, competitively.¹³⁰⁻¹³³ Additionally, Kim *et al.*¹³⁴ had shown that catechin-aldehyde poly-condensates reduce the hydroxylation of L-tyrosine and oxidation of L-DOPA by chelation to the tyrosinase active site.

Many flavanols have been extracted from plants, and several have been classified as potent TIs. The inhibitory mode of these natural inhibitors is normally competitive inhibition for the oxidation of L-dopa by tyrosinase where the 3-hydroxy-4-keto moiety (Table 9) of the flavanol structure plays the key role in copper chelation.^{28,135-138} Currently, to the best of our knowledge, there is no literature available on synthetic flavanols as mushroom TIs inhibitors.

5.6 Isoflavones

Isoflavones like daidzein and genistein, as well as their glycosides, are often found in medicinal plants. Park *et al.*



Table 8 Chemical structures of synthetic flavones and IC₅₀ values obtained against mushroom tyrosinase

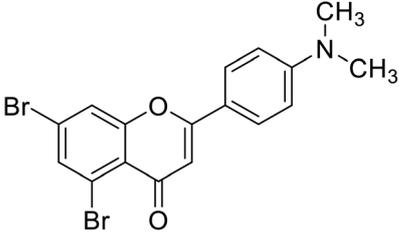
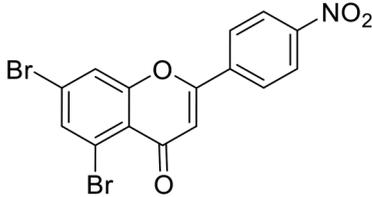
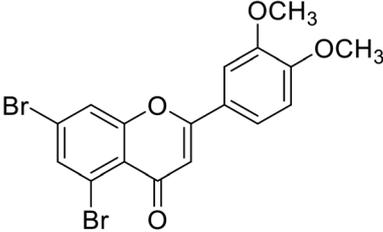
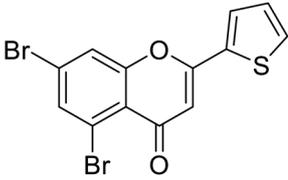
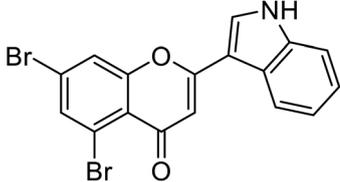
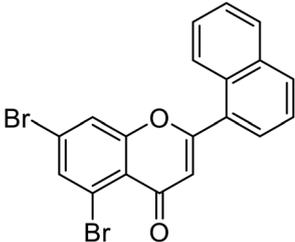
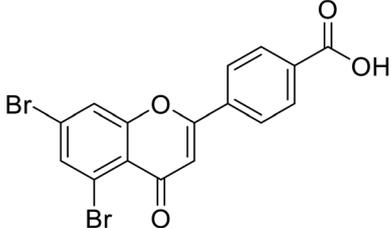
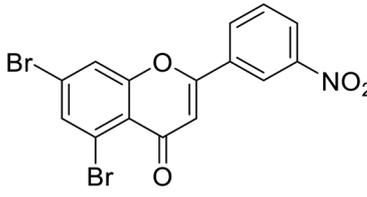
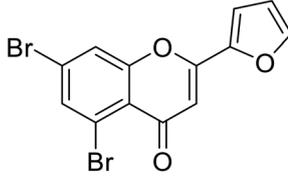
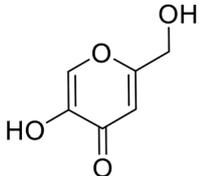
Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
65	5,7-Dibromo-2-(4-(dimethylamino)phenyl)-4H-chromen-4-one		0.57	87
66	5,7-Dibromo-2-(4-nitrophenyl)-4H-chromen-4-one		0.27	87
67	5,7-Dibromo-2-(3,4-dimethoxyphenyl)-4H-chromen-4-one		0.49	87
68	5,7-Dibromo-2-(thiophen-2-yl)-4H-chromen-4-one		0.68	87
69	5,7-Dibromo-2-(1H-indol-3-yl)-4H-chromen-4-one		0.22	87
70	5,7-Dibromo-2-(naphthalen-1-yl)-4H-chromen-4-one		3.41	87
71	4-(5,7-Dibromo-4-oxo-4H-chromen-2-yl)benzoic acid		3.28	87



Table 8 (Contd.)

Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
72	5,7-Dibromo-2-(3-nitrophenyl)-4H-chromen-4-one		3.28	87
73	5,7-Dibromo-2-(furan-2-yl)-4H-chromen-4-one		2.07	87
Standard	Kojic acid		1.79	87

investigated the activity of certain natural dihydroxyisoflavone analogs with a variable –OH group position at the aryl ring of isoflavone isolated from Korean fermented soybean paste in inhibiting tyrosinase. They discovered two trihydroxyisoflavone analogs with different positions of the hydroxyl groups. These produced IC₅₀ values of 5.23 (compound **92**) and 11.2 μM (compound **93**) against mushroom tyrosinase. However, compound **91**, a related derivative, showed no anti-tyrosinase activity (Table 10). As a result, it has been suggested that the C₆ and C₇ –OH groups of the isoflavone scaffold might be significant for inhibiting tyrosinase.¹³⁵

Likewise, compound **93** extracted from soygerm koji, was evaluated by Chang *et al.* They also discovered that 7,8,4'-trihydroxyisoflavone is a potent inhibitor of tyrosinase monophenolase activity, with an IC₅₀ value of 9.2 μM, rendering **93** six times more active than kojic acid. This compound had an irreversible inhibitory effect on both monophenolase and diphenolase activities. It may be concluded that the presence of the –OH group at both the C₇ and C₈ positions could entirely alter the inhibitory effect of the isoflavones from the reversible competitive to the irreversible suicide form ref. 139 and 140. Recently, the two isoflavones 6-hydroxydiadzein (compound **96**) and calycosin (compound **97**), isolated from *Agave americana* were recognized as competitive inhibitors.¹⁴¹ The most active mushroom TI was compound **112**, which was 5 to 9 times higher than arbutin. In the various test intervals, the only oxygenated isoflavones at the C₆ position displayed an excellent anti-tyrosinase activity with IC₅₀ values of 52.3 and 45.8 μM (ref. 142) (Table 10).

In the 7-oxygenated series (Table 10), compounds **107** and **116** possessed notable anti-tyrosinase activity (IC₅₀ = 53.9 and 38.1 μM), whereas the potent TI among the 7,8-dimethylated series was compound **118** (IC₅₀ = 45.8 μM). Noteworthy,

isoflavones having free hydroxyl groups at C₆, C₇, or C_{4'} usually exhibited potent anti-tyrosinase activities. However, the activity becomes erratic when both the C₇ and C_{4'} are hydroxylated in the same motif. For instance, while daidzein and genistein were inactive, 6,4'-dihydroxy-7,8-dimethylisoflavone and 6-hydroxydiadzein were the most potent TIs. In this study, *o*-dihydroxylated series with –OH groups at C₇ and C₈ or C₆ and C₇ appeared to be better mushroom TIs, except the C₇-methoxylated derivatives. This result revealed that the inhibitory manner of the *o*-dihydroxylated series was different from that of the non-*o*-dihydroxylated series.⁴⁶

Basically, *O*-bearing substituents at C_{4'} of ring B seem to contribute to the anti-tyrosinase activity, whereas the –OH or –MeO at C_{2'} and C_{3'} of ring B of an isoflavone tend to attenuate the TI effect. However, the existence of a lipophilic end in hydroxylated isoflavones may contribute to the binding to mushroom tyrosinase.¹⁴³ The synthetic analogs of isoflavones as TIs have not yet been reported in the literature.

5.7 Flavanones

Flavanones may be discerned from other flavonoids by the absence of the covalent double bond '=' connecting the 2nd and 3rd positions of the pyrone ring. A systematic study about the influence of the number and position of –OH groups on the aryl ring indicated the importance of *p*-position on ring B.¹⁴⁴ Naturally occurring flavanones such as streppogenin, bavachinin, alpinetin are primarily found in medicinal herbs and citrus fruits. Streppogenin, a copper chelator flavanone, inhibits tyrosinase reversibly and competitively (Table 11).

Furthermore, docking findings demonstrated that hesperetin chelates a Cu²⁺ ion coordinating with three histidine (His61, His85, and His259) residues within the enzyme's active



Table 9 Chemical structures of natural flavanols and IC₅₀ values obtained against mushroom tyrosinase

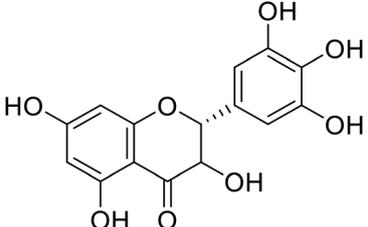
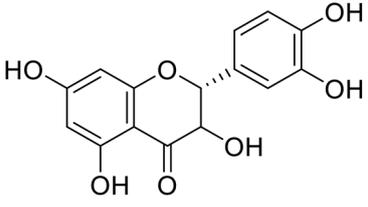
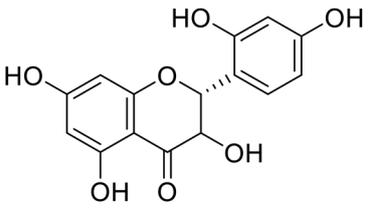
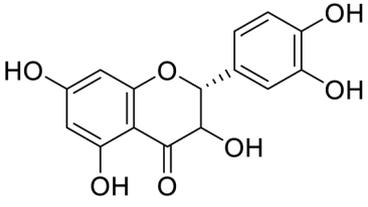
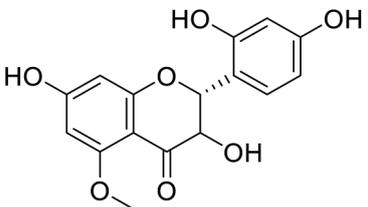
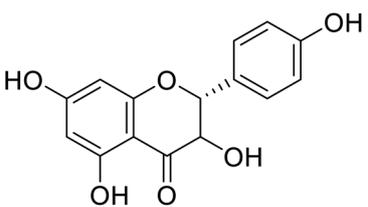
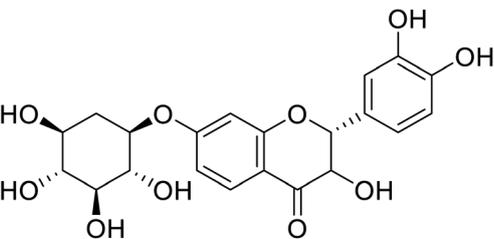
Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
74	Dihydromyricetin		849.88	167
75	Taxifolin		0.24	118
76	Dihydromorin		9.4	10
77	Dihydroxykampherol		>200	58
78	Brousoflavonol J		9.29	96
79	3,5,7-Trihydroxy-2-(4-hydroxyphenyl)chroman-4-one		25	22
80	Chlorophorin		6.6	172



Table 9 (Contd.)

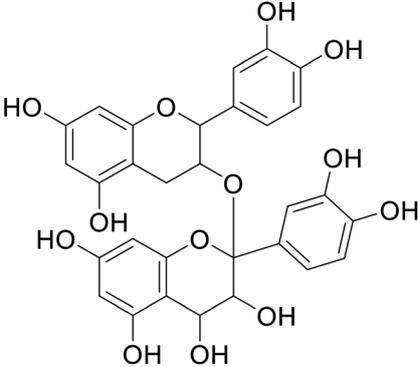
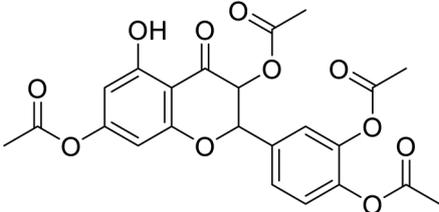
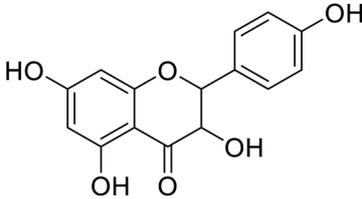
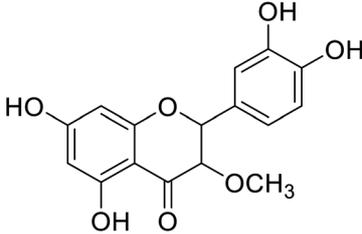
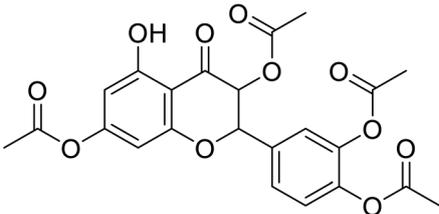
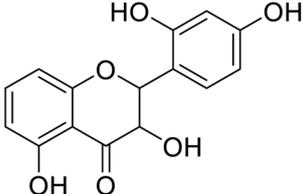
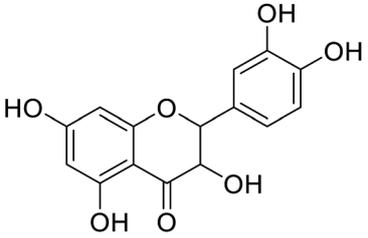
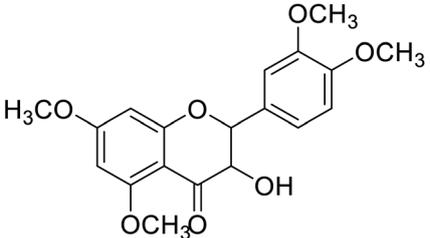
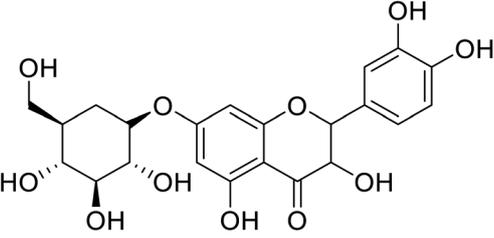
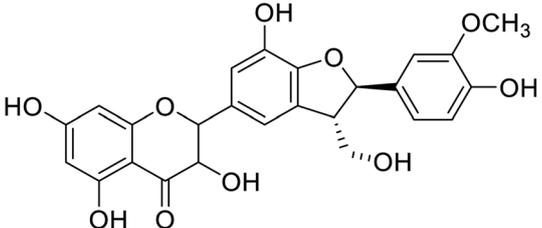
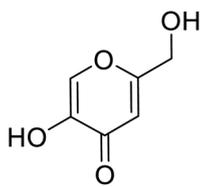
Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
81	Proanthocyanidins		55.01	146
82	4-(3,8-Diacetoxy-5-hydroxy-4-oxochroman-2-yl)-1,2-phenylene diacetate		>230	28
83	3,5,7-Trihydroxy-2-(4-hydroxyphenyl)chroman-4-one		>100	28
84	2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-3-methoxychroman-4-one		>300	28
85	4-(3,7-Diacetoxy-5-hydroxy-4-oxochroman-2-yl)-1,2-phenylene diacetate		>230	28
86	2-(2-Hydroxyphenyl)-3,5,7-trihydroxychroman-4-one		25	28



Table 9 (Contd.)

Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
87	2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxychroman-4-one		>300	28
88	2-(3,4-Dimethoxyphenyl)-3-hydroxy-5,7-dimethoxychroman-4-one		75.8	28
89	2-(3,4-Dihydroxyphenyl)-3,5-dihydroxy-(7,2,3,4-trihydroxy-5-(hydroxymethyl)cyclohexyl)oxychroman-4-one		>200	28
90	3,5,7-Trihydroxy-2,7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-3-(hydroxymethyl)-2,3-dihydrobenzofuran-5-ylchroman-4-one		28.8	28
Standard	Kojic acid		237	28 and 167

site. Chiari *et al.*¹⁴⁴ validated the TI activity of a substituted 6-isoprenoid flavanone isolated from *Dacryopinax elegans* in another report. Among these inhibitors, streptogenin was a stronger inhibitor than the positive controls, arbutin or kojic acid.

Several phenolic compounds isolated from various plants were tested as inhibitors of mushroom tyrosinase. The Moraceae family is an effective supplier of skin-whitening agents^{4, 145–152} (Table 11), and a source of several flavanone analogs that display, in some cases, very low IC₅₀ values. Like compounds in the previous class, these analogs have not been explored as synthetic inhibitors against tyrosinase.

5.8 Flavonols

Plants contain numerous flavonols, some of which have been described as tyrosinase inhibitors. The flavonol's structure, 3-hydroxy-4-keto moiety, is essential in copper chelation, and the inhibitory mode of flavonol inhibitors is normally competitive inhibition for the oxidation of L-dopa by tyrosinase.¹⁵³ Kaempferol, myricetin, quercetin, isorhamnetin, galangin, morin, and their glycosides are the prevalent naturally occurring flavonols, mostly found as O-glycosides.^{154–160} So far, several flavonols such as quercetin from *Olea europaea*, kaempferol from *Hypericum laricifolium*, and *Crocus sativus*,



Table 10 Chemical structures of natural isoflavones and IC₅₀ values obtained against mushroom tyrosinase

Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
91	Daidzein		17.50	30
92	7,3',4'-Trihydroxyisoflavone		52.3	135
93	7,8,4'-Trihydroxyisoflavone		11.21	135
94	3,8-Dihydroxy-9-methoxy pterocarpan		16.7	141
95	3'-Hydroxygenistein		15.9	168
96	6-Hydroxydaidzein		0.009	58
97	Calycosin		1.45	180
98	Cajanin		67.9	58
99	Daidzein-7-O-β-glucopyranose		22.2	58



Table 10 (Contd.)

Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
100	5-Hydroxy-daidzein-7-O-β-glucopyranose		4.39	58
101	7-(β-Glucopyranosyl)-2'-hydroxygenistein		729	58
102	(8,9)-Furanyl-pterocarpan-3-ol		7.18	50
103	Neorauflavane		500	78
104	3'-Hydroxy-8-methoxy vestitol		67.8	50
105	Khrinone B		54.0	50
106	7,8-Dihydroxy-3-(4-hydroxyphenyl)-4H-chromen-4-one		45.8	48
107	7,8-Dihydroxy-3-(3-methoxyphenyl)-4H-chromen-4-one		53.9	48

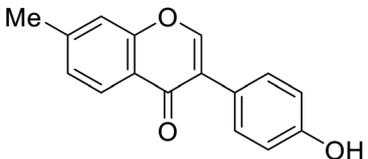
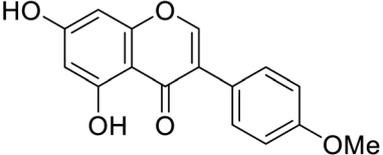
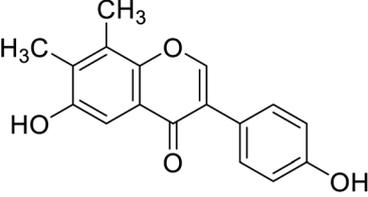
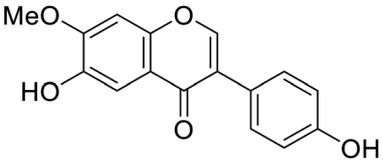
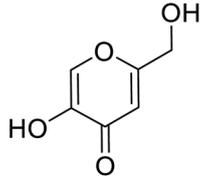


Table 10 (Contd.)

Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
108	3-(3,4-Dihydroxyphenyl)-8-hydroxy-7-methyl-4H-chromen-4-one		129.9	48
109	7,8-Dihydroxy-3-(3-hydroxyphenyl)-4H-chromen-4-one		96.4	48
110	7,8-Dihydroxy-3-(4-methoxyphenyl)-4H-chromen-4-one		50.9	48
111	7,8-Dihydroxy-3-(2-methoxyphenyl)-4H-chromen-4-one		82.8	48
112	6,7-Dihydroxy-3-(4-methoxyphenyl)-4H-chromen-4-one		8.1	68
113	6,7-Dihydroxy-3-(4-hydroxyphenyl)-4H-chromen-4-one		15.6	68
114	5,7-Dihydroxy-3-(2-methoxyphenyl)-4H-chromen-4-one		171.1	68
115	7-Hydroxy-3-(3-hydroxyphenyl)-4H-chromen-4-one		110.9	68



Table 10 (Contd.)

Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
116	3-(4-Hydroxyphenyl)-7-methyl-4H-chromen-4-one		38.1	68
117	5,7-Dihydroxy-3-(4-methoxyphenyl)-4H-chromen-4-one		141.3	68
118	6-Hydroxy-3-(4-hydroxyphenyl)-7,8-dimethyl-4H-chromen-4-one		45.8	68
119	6-Hydroxy-3-(4-hydroxyphenyl)-7-methoxy-4H-chromen-4-one		83.5	68
Standard	Kojic acid		89	48, 68, 135 and 141

quercetin-4'-O-beta-D-glucoside from *Parornix bifurca*, quercetin glucopyranoside and kaempferol glucopyranoside from mulberry leaves, morin and 2,3-*cis*-dihydromorin, 2,3-*trans*-dihydromorin from *Chloropsis cochinchinensis*, were found to act as tyrosinase inhibitors (Table 12). Moreover, it was reported that three 3-hydroxyflavones including kaempferol, galangin, and quercetin inhibit the L-DOPA oxidation process catalyzed by tyrosinase, and apparently, this TI activity arises from their Cu²⁺ chelating ability.^{161–166} Kubo *et al.* assumed that the chelation mechanism by flavonols may be attributed to the free 3-OH group. Remarkably, quercetin acts as a cofactor and does not inhibit monophenolase activity. The common feature of these three flavonols^{167–172} is that they all inhibit diphenolase activity by chelating copper in the enzyme. Furthermore, quercetin glucoside, with an IC₅₀ value of 1.9 μM, inhibited tyrosinase more effectively than the positive standard, kojic acid.^{173–178}

Jamshaid *et al.*,⁸⁵ synthesized some 3-hydroxyflavone derivatives and tested their TI potential against mushroom tyrosinase (Table 13). Fascinatingly, the test analogs 2-(3-

(trifluoromethyl)phenyl)-3-hydroxyflavone (IC₅₀ = 0.280 μM) and 2-(4-chlorophenyl)-3-hydroxyflavone (IC₅₀ = 0.230 μM) were found to be the most potent among all the synthesized derivatives and superior to the positive control kojic acid. The 2-(3-(trifluoromethyl)phenyl)-3-hydroxyflavone possesses a highly electron-withdrawing group (-CF₃) at the *m*-position on ring B. This reveals that the structure fits nicely and strongly interacts with the active site of the envisioned enzyme. Interestingly, 2-(2-(trifluoromethyl)phenyl)-3-hydroxyflavone (IC₅₀ = 0.30 μM), having trifluoromethyl group (-CF₃) at the *o*-position of ring B, was found comparatively less active than its *m*-isomer, but still more active than the standard.

Jamshaid *et al.*,⁸⁷ synthesized substituted flavonols where the most active derivative, which contains a strong EWG (-NO₂) at the *p*-position of the B ring, was 2-(4-nitrophenyl)-3-hydroxyflavone (IC₅₀ = 0.284 μM). Likewise, the replacement of the aromatic B ring with other 5-membered heterocyclic rings such as thiophene (IC₅₀ = 0.347 μM) also produced excellent activity. The TI by 2-(thiophen-3-yl)-3-hydroxyflavone depends



Table 11 Chemical structures of natural flavanones and IC₅₀ values obtained against mushroom tyrosinase

Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
120	5,5',7-Trihydroxy-2',4'-dimethoxy-6-methylflavanone		44.74	68
121	Streppogenin		1.3	68
122	5,7,2'-Trihydroxy-5'-(1''',1'''-dimethylallyl)-8-prenylflavanone		27.5	97
123	Liquiritigenin		22.0	50
124	Bavachinin		143.9	30
125	Corylifolin		23.6	30
126	Alpinetin		450	50



Table 11 (Contd.)

Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
127	Delanin		0.26	144
128	5,7,2'-Trihydroxy-8,3'-diprenylflavanone		68.5	97
129	5,7,2'-Trihydroxy-5'-(1''',1'''-dimethylallyl)-8-prenylflavanone		27.5	142
130	2-(2,4-Dihydroxyphenyl)-7-hydroxychroman-4-one		0.11	4
131	5,7-Dihydroxy-2-(4-hydroxyphenyl)-6-(3-methylbut-2-en-1-yl)chroman-4-one		38.1	4
132	5,7-Dihydroxy-2-(2-hydroxy-4,6-dimethoxy phenyl)-6-methylchroman-4-one		44.74	4



Table 11 (Contd.)

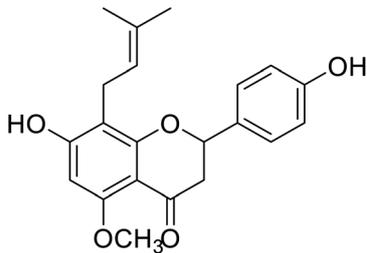
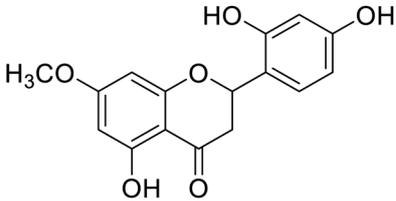
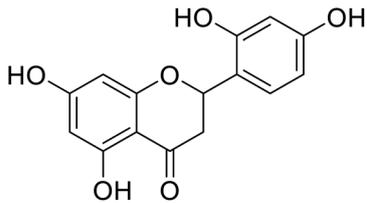
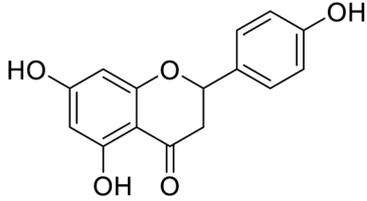
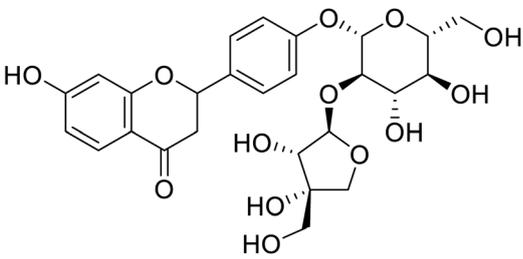
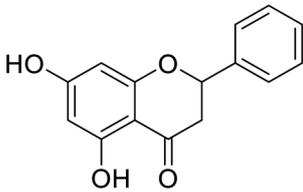
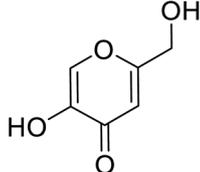
Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
133	7-Hydroxy-2-(4-hydroxyphenyl)-5-methoxy-8-(3-methylbut-2-en-1-yl)chroman-4-one		77.4	4
134	2-(2,4-Dihydroxyphenyl)-5-hydroxy-7-methoxychroman-4-one		2.0	4
135	2-(2,4-Dihydroxyphenyl)-5,7-dihydroxychroman-4-one		1.76	4
136	5,7-Dihydroxy-2-(4-hydroxy phenyl)chroman-4-one		>300	4
137	(3,4-Dihydroxy-4-(hydroxymethyl)tetrahydrofuran-2-yl)oxy-(4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxyphenyl-7-hydroxychroman-4-one		88.91	4
138	5,7-Dihydroxy-2-phenyl chroman-4-one		>500	4
Standard	Kojic acid		310	4, 30 and 50



Table 12 Chemical structures of natural flavonols and IC₅₀ values obtained against mushroom tyrosinase

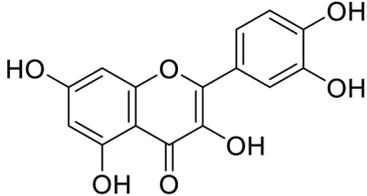
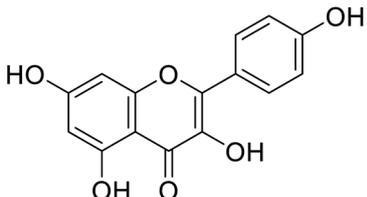
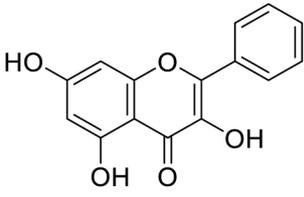
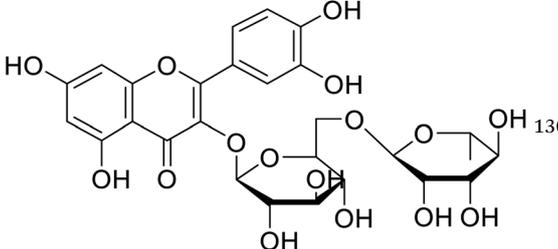
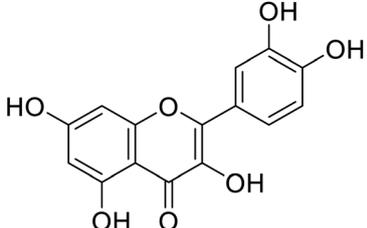
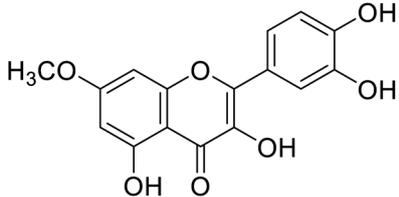
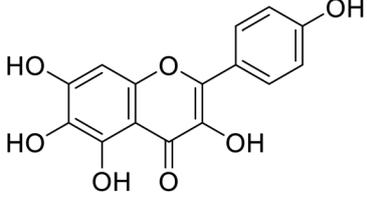
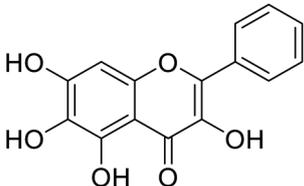
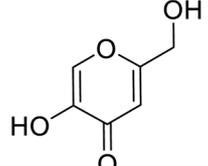
Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
139	Quercetin		10.73	58
140	Kaempferol		5.5	71
141	Galangin		3.55	38
142	Rutin		130	101
143	2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one		53.4	31
144	2-(3,4-Dihydroxyphenyl)-3,5-dihydroxy-7-methoxy-4H-chromen-4-one		72.5	31
145	6-Hydroxykaempferol		124	31



Table 12 (Contd.)

Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
146	6-Hydroxygalangin		182	31
Standard	Kojic acid		318	31, 38, 58 and 71

on the ability of a 'S' atom to coordinate with the dinuclear Cu²⁺ in the enzyme's active site. The high inhibitory potential may be due to the electronegativity of the two -OCH₃ groups at *o*- and *p*-positions of the B-ring which fits appropriately in the active pocket of the target enzyme. Moreover, the 5,7-dibromo-2-(4-chlorophenyl)-3-hydroxyflavone has an EWD (-Cl) at 4th position on ring B. Perhaps, this functionality and its location have suitable interactions with the enzyme's active site. Subsequently, the next most active derivative, which contains a strong EWG (-NO₂) at the 3rd position on the B ring, is 5,7-dibromo-2-(3-nitrophenyl)-3-hydroxyflavone. Excitingly, the *p*-NO₂ substituted 5,7-dibromo-3-hydroxyflavone displayed enhanced activity as compared to its *m*-analog (Table 13).

6. Conclusions and perspectives

Pigment disorders are triggered by the upregulation or downregulation of tyrosinase. Because of the cosmetically significant issue of abnormal pigmentation and its impact on the quality of life and the development of life-threatening diseases, there is a great demand for melanogenesis inhibitors. The regulation of melanogenesis is a complicated process which involves several cellular factors. Tyrosinase, the central culprit in the enzymatic pathway of melanogenesis, has emerged as the most important target for the treatment of clinical and aesthetic hyperpigmentation. The enzyme catalyzes the first and only rate-limiting step in melanogenesis. Plants have always played a significant role as supply for drug lead compounds. In particular, some plants are rich in polyphenols, which form building blocks for the biosynthesis of chalcone, flavones, and flavonols, among others, which further form proanthocyanins and function as antioxidants. However, as these phytoconstituent have poor solubility and stability when formulated in different matrices, their bioavailability becomes a major concern. Pleasingly, their synthetic structural analogs offer interesting anti-tyrosinase activities, and thus help in the

development of customized chemical agents with desired features to maximize inhibitory activity, stability, and safety for long-term use in skincare. Consequently, in recent years, many inhibitors have been identified and shown to act against tyrosinase.

It is fascinating to note that, regardless of the variety of natural inhibitors, many TI's are phenolic in nature. Several investigators had considered suitable skeletons based on natural compound structures and created new synthetic inhibitors. Among all the natural and synthetic flavonoid derivatives, the preceding survey of tabulated compounds and their inhibitory results suggest that the flavonol moiety can serve as an effective scaffold and a lead structural feature and foundation for the further development of novel tyrosinase inhibitors. For flavonols (3-hydroxyflavones), vicinal positions of the hydroxyl group and keto functionality play a significant role in chelating with Cu²⁺ ions to render them the most potent anti-tyrosinase agents.

Useful provisions have been proposed by molecular modeling studies that outline the essential structural elements required for the manifestation of inhibitory actions of natural compounds, providing a guide for the design of more efficient synthetic bioinspired chemical repressors. Hence, it is important to assess the efficiency and safety of inhibitors by examining *e.g.*, whether the candidate inhibitor is a tyrosinase substrate being altered on exposure to the enzyme. Future research guidelines on pigmentation regulation by tyrosinase modulation also include the production of highly specific assays of enzymatic activity, as well as the proper use of novel formulations to enhance the efficiency of the inhibitors by increasing their bioavailability. In conclusion, we expect that this review will serve as helpful reference to the medicinal chemists working on melanogenesis, specifically on various tyrosinase enzymes, to develop lead tyrosinase inhibitors with drug-like characteristics.

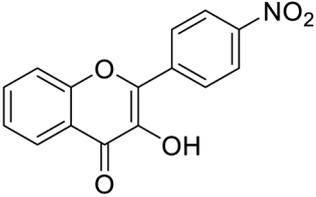
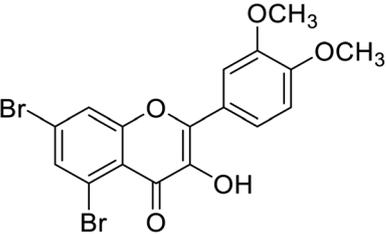
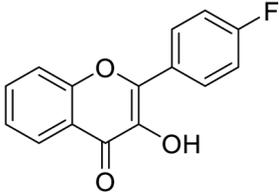
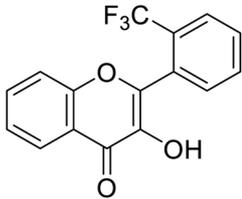
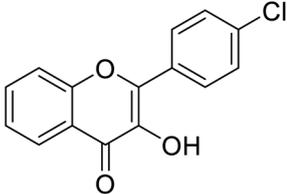
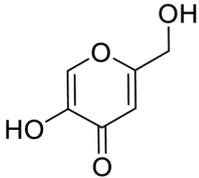


Table 13 Chemical structures of synthetic flavonols and IC₅₀ values obtained against mushroom tyrosinase

Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
147	5,7-Dibromo-2-(4-chlorophenyl)-3-hydroxy-4 <i>H</i> -chromen-4-one		0.71	87
148	5,7-Dibromo-3-hydroxy-2-(3-nitrophenyl)-4 <i>H</i> -chromen-4-one		0.15	87
149	5,7-Dibromo-2-(4-fluorophenyl)-3-hydroxy-4 <i>H</i> -chromen-4-one		2.36	87
150	5,7-Dibromo-2-(4-(dimethylamino)phenyl)-3-hydroxy-4 <i>H</i> -chromen-4-one		0.50	87
151	5,7-Dibromo-3-hydroxy-2-(naphthalen-1-yl)-4 <i>H</i> -chromen-4-one		0.564	87
152	5,7-Dibromo-3-hydroxy-2-(<i>p</i> -tolyl)-4 <i>H</i> -chromen-4-one		0.126	87
153	3-Hydroxy-2-(thiophen-2-yl)-4 <i>H</i> -chromen-4-one		0.347	85



Table 13 (Contd.)

Compound no.	Compound name	Chemical structures	IC ₅₀ values (μM)	Reference
154	3-Hydroxy-2-(4-nitrophenyl)-4H-chromen-4-one		0.284	85
155	5,7-Dibromo-2-(3,4-dimethoxyphenyl)-3-hydroxy-4H-chromen-4-one		0.093	87
156	2-(4-Fluorophenyl)-3-hydroxy-4H-chromen-4-one		0.799	85
157	3-Hydroxy-2-(2-(trifluoromethyl) phenyl)-4H-chromen-4-one		0.30	85
158	2-(4-Chlorophenyl)-3-hydroxy-4H-chromen-4-one		0.230	85
Standard	Kojic acid		1.79	85 and 87

Abbreviations

DOPA	Dihydroxyphenylalanine;
TI's	Tyrosinase Inhibitors
PTU	1-Phenyl-2-thiourea
UV	Ultraviolet
kDa	Kilo dalton
E _m	Met-tyrosinase

E _{ox}	Oxy-tyrosinase
IC ₅₀	Half maximal inhibitory concentration
IR	Infrared
HOPNO	2-Hydroxypyridine <i>N</i> -oxide
TMBC	2,4,2',4'-Tetrahydroxy-3-(3-methyl-2-butenyl) chalcone
His	Histamine
Val	Valine
Phe	Phenylalanine
Met	Methionine



Review

Ser	Serine
Ala	Alanine
ECG	Epicatchin gallate
EGCG	Epigallocatechin gallate
EWG	Electron-withdrawing group

Conflicts of interest

Hereby, I declare that we have no conflicts of interest.

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The authors would like to thank the Deanship of Scientific Research at Umm Al-Qura University for supporting this work under grant number 18-SCI-1-02-0006. The authors are also grateful to the Higher Education Commission of Pakistan (HEC) for providing financial assistance under the Project No. (NRPU-6484).

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