

Different Natural and Synthetic Tyrosinase Inhibitors and their Application

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Abstract: Tyrosinase plays an important role in melanin synthesis by directly regulating the amount of melanin produced unlike other enzymes, which can only modify the synthesized melanin in the biochemical pathway. Tyrosinase is basically involved in the pigmentation of skin, eyes and hair in mammals which provides protection against UV rays. Tyrosinase is an oxygen oxidoreductase enzyme which acts with other compounds as donor and incorporates an oxygen atom for depicting its principal characteristic. This enzyme is also used for the therapeutic purposes namely L-DOPA drug, which is used to treat Parkinson's disease, manufacturing of lincomycin antibiotic and treating various neurological diseases. This enzyme has also been used in the food bioprocessing, agricultural and environmental industries. Inhibition of tyrosinase pose various strategies to develop new depigmenting agents which consequently has great applications in medical and cosmetic products. Natural and synthetic tyrosinase inhibitors has been reported. The tyrosinase inhibitors forms an important class of clinical antimelanoma drugs out of which very few comes out as effective and safe.

Keywords- Tyrosinase, Melanogenesis, Tyrosinase inhibitors, Melanin, Dopakinone

1. Introduction

Tyrosinase is a widely distributed multi-copper enzyme which plays a major role in enzymatic browning and melanogenesis in various organisms including mammals (Zolghadri et al., 2019). Tyrosinase plays an important role in synthesis of melanin substrate (Mendes et al., 2014). Melanin is responsible for the safety against the destructive ultraviolet radiation that can cause cancer (Lee et al., 2016). There are many skin whitening ingredients which inhibit tyrosinase activity. Skin pigmentation is human prototype trait. Melanogenesis is a complicated process in which the pigment melanin component is formed by a melanocyte into the skin in melanosomes (Pillaiyar et al., 2017). The melanocyte connects with the immune, inflammatory and endocrine and central nervous system and its activity is regulated by extrinsic and intrinsic factor such as ultraviolet radiation, hormonal changes, age (D'Mello et al., 2016). So melanin is a primary determinant of skin, eye and hair color. These are important for human prototype traits and plays an important role in the human skin homeostasis like protecting from ultraviolet radiation and the enzyme which is involved in the melanogenesis is tyrosinase (Kim et al., 2005). The structure of Tyrosinase varies from species to species, however they share some of the fundamental features such as it has three functional states, met, deoxy and oxy. Met- tyrosinase binds reversibly with molecular oxygen. The most important function of tyrosinase is the oxidation of phenols to *ortho*-quinones which is the process of biosynthesis of melanin by conversion of L-tyrosine to dopaquinone (Panzella et al., 2019).

Inhibition of tyrosinase pose various strategies to develop new depigmenting agents which consequently has great applications in medical and cosmetic products (Casanola martin et al., 2013). The development of natural, semi-synthetic and synthetic inhibitors have been done various methods of screening (Zolghadri et al., 2019).

Melanin and its types

Melanin is a complex polymer derived from the tyrosine amino acid. Melanin is responsible for determining skin and hair colour. Melanin plays a major role in avoiding the harmful effects of ultraviolet radiation and oxidative stress induced by various environmental pollutants on the skin (Brenner et al., 2008). Melanin is a group of natural pigments found in most organisms. Melanin is formed by a multi-stage chemical process known as melanogenesis, where polymerization follows the oxidation of the amino acid tyrosine (Bonaventure et al., 2013). The pigments of melanin are formed in a specialised cell group known as melanocytes. Melanocytes are produced from unpigmented precursor cells called melanoblasts, which come from the cells of the embryonic neural crest (Sviderskaya et al., 2001).

There are three basic types of melanin

1. Eumelanin
2. Pheomelanin
3. Neuromelanin

Eumelanin: There are two types of eumelanin

- a) Brown eumelanin

b) Black eumelanin

An aggregate of pigment molecules, each made up of cross-linked 5,6-dihydroxyindole (DHI) and 5,6-dihydroxyindole-2-carboxylic acid (DHICA) polymers, and is responsible for the black or brownish pigmentation of skin, feathers, hair, fur, eyes, scales, etc. Eumelanin is produced through the process of melanogenesis, which includes a series of catalysed chemical reactions, starting from tyrosine, and with tyrosinase as the key enzyme. In humans, it accounts for the pigmentation of the skin and hair. In particular a small quantity of black eumelanin (in the absence of other pigments as well) results in grey hair. A small amount of brown eumelanin (in the absence of other pigments as well) results in blond hair. A defective tyrosinase production leads to the disruption of melanin production (including eumelanin) and therefore results in oculocutaneous albinism.

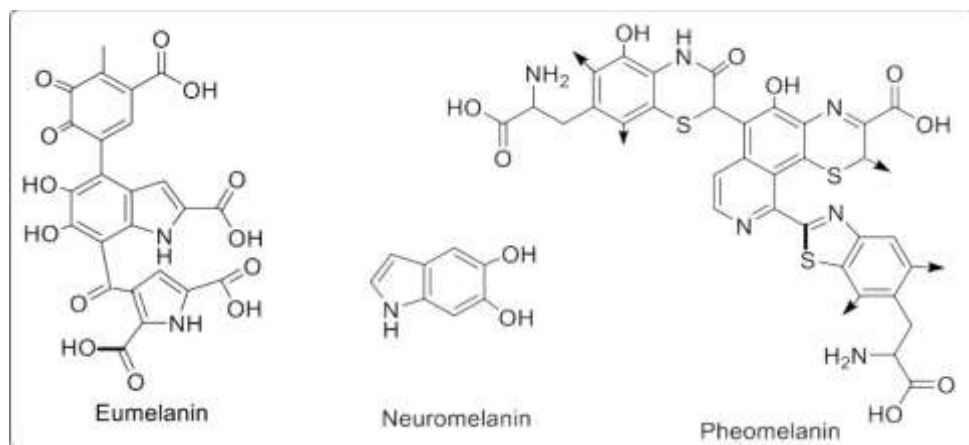


Figure 1: Structure of the melanin types

Pheomelanin

A type of melanin pigment consisting of units of benzothiazine that is responsible for yellow and pink to red hues or pigments such as hair, lips, etc. In humans, this pigment occurs in relatively large amounts in lips, nipples, vagina, and glans penis. It also accounts for hair red pigmentation. If present in the skin in large amounts, the skin will have a pinkish hue. Red heads will, therefore, have a pinkish skin colour. Similar to eumelanin, the biosynthesis pathway of pheomelanin begins at tyrosine. It proceeds to the route with an end result of alanyl-hydroxy-benzothiazine in the presence of glutathione or cysteine.

Neuromelanin

A type of melanin pigment present in parts of the brain, particularly in the neurons of substantia nigra and locus ceruleus. Neuromelanin is made up of a polymer of 5,6-dihydroxyindole monomers. Similar to eumelanin, it is synthesized directly from L-DOPA through the catalytic activity of tyrosine hydroxylase and aromatic acid decarboxylase.

3.1 Melanin biosynthesis

Melanin synthesis starts with the tyrosine and involves a series of steps that lead to black- brown eumelanin and yellow pheomelanin (Hearing et al., 1987). Biosynthesis begins with the conversion of L-tyrosine amino acid into L-3,4-dihydroxyphenylalanine (L-dopa) and the subsequent conversion of L-dopa into dopaquinone by tyrosinase (Lee et al., 2016). In melanin biosynthesis the conversion of L-tyrosine into Dopaquinone is a very important step (Faccio et al., 2012). Dopaquinone is converted into dopachrome which is further transformed into dihydroxyindole-2-carboxylic acid (DHICA) which further converts into Indole- 5,6 quinone carboxylic acid and forms the black form of eumelanin and dihydroxyindole (DHI) by an auto oxidation reaction (Ullah et al., 2011-2015) converts into Indole-5,6 quinone from the brown form of eumelanin and the completion of these reactions results into the formation of eumelanin. On the other side, dopaquinone can be transformed into cysteinyl-dopa in the presence of cysteine amino acid and these are further converted into pheomelanins (Chang et al., 2012). Eumelanin is responsible for the skin's brown / black colour, while pheomelanin imparts a pink or red colour to skin.

3.2 Chemical classification of tyrosinase inhibitors:

1. Natural inhibitors and their derivatives
2. Synthetic inhibitors and their derivatives

3.3.1 Natural tyrosinase inhibitors and their derivatives

The natural species have evolved safety methods from harmful ultraviolet radiation, so nature is an innumerable source or tyrosinase inhibitor. So number of studies or researches have been dedicated to identify inhibitors from plant, fungi, bacteria, mammals and marine algae. Tyrosinase inhibitors from natural and synthetic sources attract

more attention compared to chemically synthesized compounds (Lee et al., 2016).

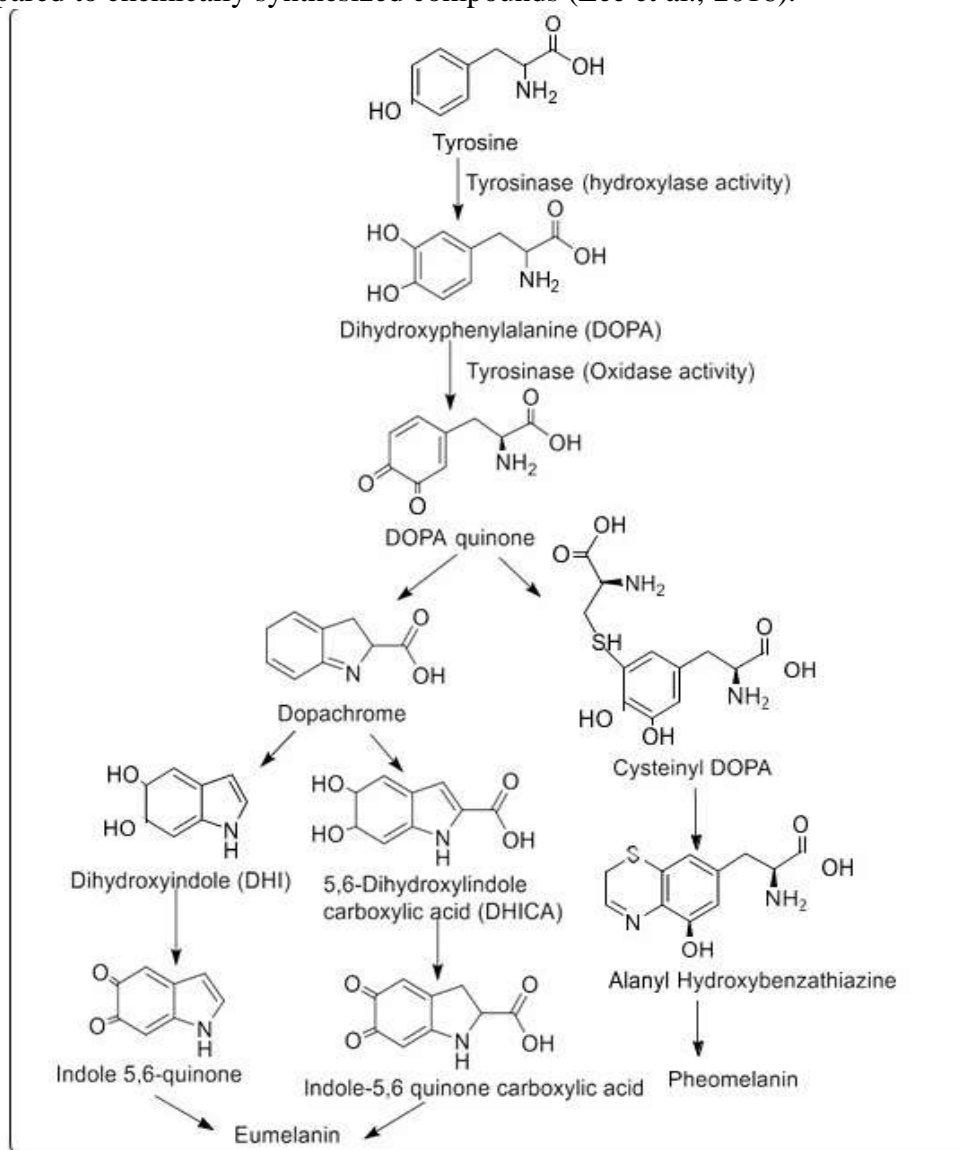


Figure 2: Biosynthesis of the melanin

Flavonoids

Flavonoids are one of the most frequently studied polyphenol derivatives in leaves, seeds, bark, plants and flowers, consisting of phenols and pyrane rings. Over 4,000 flavonoids have been reported to date and provide protection against ultraviolets, herbivores and pathogens. The largest proportion of newly discovered natural tyrosinase inhibitors are occupied by flavonoids (Harborne et al., 2000). Flavonoids are subdivided into six groups: flavanols, flavones, flavonols, flavanones, isoflavones and anthocyanidins (Zolghadri et al., 2019). They vary in the A- and B-ring conjugation and in the substituent configuration, such as hydroxy, methoxy, glycosides, etc. The flavonoid composition is consistent with both substrate and tyrosinase inhibitor roles (Lee et al., 2016). The inhibitory activity against tyrosinase is shown by some flavonoids, such as kaempferol, morin and quercetin, while others such as rhamnetin and catechin, serve as substrates and suppress tyrosinase activity by being a cofactor. The inhibitory efficacy of flavonoids on mushroom tyrosinase is strongly associated with melanin synthesis in melanocytes (kim et al., 2005). Many flavonoid compounds have been isolated and tested while looking for effective tyrosinase inhibitors from natural products for their inhibitory activity on mushroom tyrosinase from different natural sources such as *Trifolium nigrescens Subsp Petrisavi* (Demirkiran et al., 2013), *mung bean* (Yao et al., 2012), *Morus yunnanensis* (Wang et al., 2012), *Bhagwa* and *Arakta cultivar* (Fawole et al., 2012), *Maackia fauri* (Kim et al., 2010), *pleurotus ostreatus* (Alam Net al., 2010) and other various medicinal plants (Azizuddin et al., 2011). Flavonoids may act in a number of different ways on the various components of blood such as platelets, monocytes, low density lipoprotein (LDL) and smooth muscles. Platelets are key participants in atherogenesis and pro-inflammatory mediators such as thromboxane A₂, PAF and serotonin are produced from them. Flavonoids may inhibit platelet adhesion, aggregation and secretion. Flavonoids with antiplatelet activity include chalcone and isoflavone isolated from the seeds of *Psoralea corylifolia* (Harborne et al., 2000). Flavonoid derivative from twigs of *Cudrania tricuspidata* and *stepogennia* a flavanone derivative showed the best tyrosinase inhibitory activity.

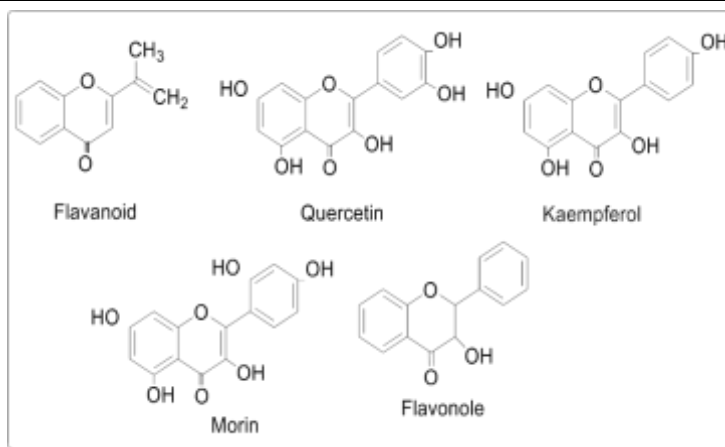


Figure 3: Structure of the natural tyrosinase inhibitors

Flavonols

Many flavonols were isolated from plants and some were recognised as inhibitors of tyrosinase. Usually, the inhibitory mode of flavonol inhibitors is competitive inhibition of tyrosinase oxidation of L-dopa and the 3-hydroxy-4-keto moiety of the flavonol structure plays a key role in copper chelation (Kubo et al., 2000). Many flavonol inhibitors such as quercetin from *olea europaea* (Omar et al., 2018), galagin from *Alpinia officinarum* (Lu YH et al., 2007), morin from *Cudrania cochinchinesis* (Zheng et al., 2011) and kaempferol from *Hypericum laricifolium* (Quispe YN et al., 2017) and *crocus sativa* (Kubo et al., 1999) act as tyrosinase inhibitors. So the discovered flavonol inhibitors according to their strength are ranked as follows: quercetin > kaempferol > galagin > morin (Xie et al., 2003). Inhibitors of flavonol have a little ability in the application of skin whitening.

Flavones, Flavanones, Flavanols

Citrus peel contains a large amount of flavonoids as a byproduct of the citrus juice industry. Some of the flavonoids have been identified as inhibitors of tyrosinase, including Nobiletin, Neohesperidin, and Naringin (Zhang et al., 2007). But as compared to Kojic acid, the inhibitory capacity of the three inhibitors was found to be poorly active against mushroom tyrosinase (Itoh et al., 2009). Since no effective inhibitors of tyrosinase have been isolated from citrus fruit to occur, ethanolic extract has been isolated from citrus fruit has shown in vitro inhibitory effects on melanogenesis in melanoma cells and in vivo in brown guinea pigs against UVB-induced dorsal skin pigmentation. The inhibiting function of citrus crude extracts was primarily due to the antioxidant activity of neohesperidin citrus fruit in melanogenesis (Chang et al., 2009). Citrus flavonoids such as hesperidin and naringin, the flavanone glycosides, have been well researched for their toxicities and activities such as increasing vascular integrity, reducing capillary permeability (Garg et al., 2001) and anti-oral carcinogenesis (Sumida et al., 1997). However, there are few studies about its inhibitory effect on tyrosinase. Citrus polymethoxylated flavones, another group like nobiletin and tangeretin, have attracted recent interest for their potent activities against tumors and other targets due to their unique polymethoxyl radicals (Zhang et al., 2006). In comparison to citrus extracts, extracts of the plant *Morus* have been identified as polyphenol rich plant and since many potent tyrosinase inhibitors are isolated from different parts of the plant, they also have strong potential in formulations as skin whitening agents and used as a non-toxic natural therapeutic agent (Lee et al., 2002). Many potent tyrosinase inhibitors were also present at the roots of the *Morus* species in addition to the leaves and stems of the plant, including oxyresveratrol, norartocarpetin, and streppogenin flavanol (Shin et al., 1998), taxifolin collected from the *Polygonum hydropiper* sprout showed similar inhibitory activity of kojic acid in relation to mushroom tyrosinase monophenolase activity (An et al., 2008).

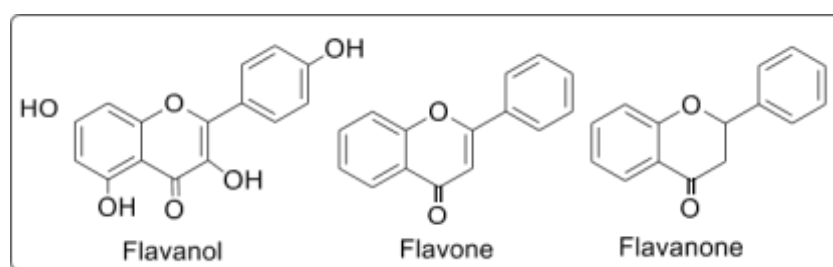
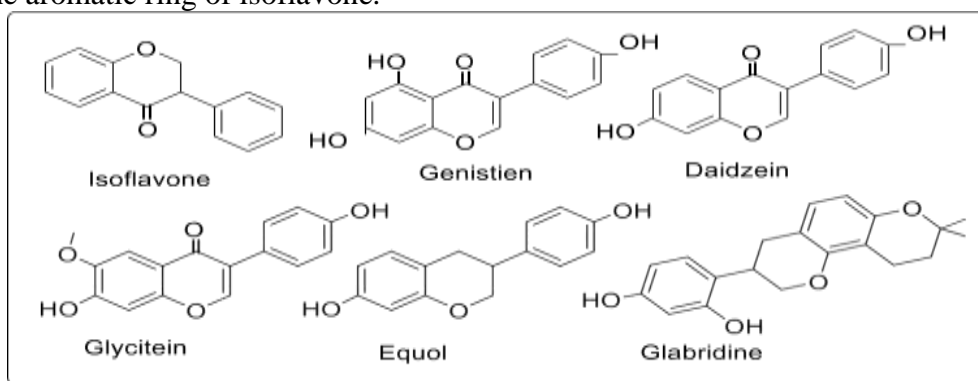


Figure 3: Structure of the Flavanol, Flavone and Flavanone

Isoflavones

Extracts from the roots and seeds of the species *Glycyrrhiza* (Leguminosae) have long been considered to be an effective component of skin whitening agents. The extracts' inhibitory melanogenesis function is caused mainly by isoflavonoids in the plant and two isoflavans have been purified from the roots of *glycyrrhiza* plant and identified as potent tyrosinase inhibitors Glabridine and Glabrene (Yokota et al., 1998). Glyasperin C has recently been isolated from the same part of the plant and has been shown to be twice as active as glabridine (Nerya et al., 2003).

Glabridin had the strongest melanogenesis, even though glyasperin C is the most active inhibitor among them (Kim et al., 2005). Isoflavones are often detected in medicinal plants, such as daidzein, genistein, glycitein, formononetin, and their glycosides (Huang et al., 2010). Tyrosinase inhibition activity of some natural derivatives of o-dihydroxyisoflavone with a variable hydroxyl substituent isolated from five-year-old Korean fermented soybean paste in the aromatic ring of isoflavone.

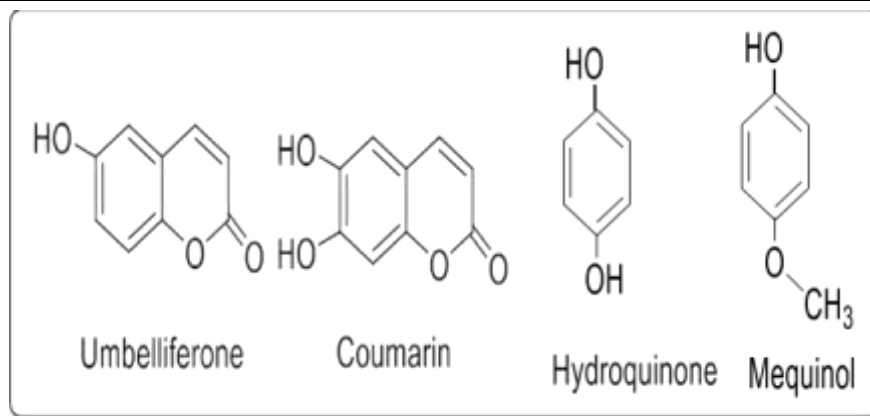


Anthocyanidins

It has been seen that phenolic compounds and anthocyanins isolated from different plants possess anti mushroom tyrosinase activity (Soung et al., 1999; Karioti et al., 2007; Ding et al., 2009). Anthocyanins, including anthocyanidins and their glycosides are commonly found in medicinal plants. It seems that a significant relationship exists between anti-human anthocyanin material and anti-mushroom anthocyanin tyrosinase activity (Jhan et al., 2016). Black soya bean (BS) is widely used as a medicinal food and herb in eastern countries (Astadi et al., 2011). The effects of Black soya are anti-inflammatory and antioxidant (Kim et al., 2008; Kim et al., 2006). Research has shown that, due to their inherent antioxidant activities, anthocyanins in the seed coat of black soybeans (SCBS) are the main active compounds responsible for many biological functions in BS (Choung et al., 2001). So the main objective is that the black soya bean (SCBS) seed coat contains a high volume of anthocyanins and exhibits the activities of antioxidants and anti tyrosinase (Furuta et al., 2003; Astadi et al., 2008; Lee et al., 2009).

Hydroquinone and Its Derivatives

Hydroquinone is commonly found in tea, wheat, berries, beer and coffee, which are commonly used to treat hyperpigmentation (Denton et al., 1952; Amer et al., 1998). By binding to histone covalently, hydroquinone competitively prevents melanin synthesis reacting with copper at the active site, and acting as a weak substrate for tyrosinase (Draelos et al., 2007). Hydroquinone has been regarded as the preferred medication for the long-term treatment of hyperpigmentation. However, the semiquinone-free radicals formed during the enzymatic reaction can cause permanent harm to melanosomes and melanocytes (Findlay et al., 1982). It has also been noted and this medication is rapidly transferred to the vascular system from the epidermis and detoxified within the liver (Wester et al., 1998). Hydroquinone has been banned in cosmetics in most countries due to side effects of long-term use such as permanent depigmentation and exogenous ochronosis. Hydroquinone is a phenolic compound chemically known as 1,4-dihydroxybenzene (Tse et al., 2010). Although hydroquinone's best days are over in the treatment of hyperpigment and its derivatives are also used as skin whitening agents in the cosmetic industry, such as arbutin, deoxyarbutin, and mequinol. B-arbutin is a hydroquinone of b-D-glucopyranoside found in bearberry, cranberry, blueberry and pear leaves (Parej et al., 2001). In cultured melanocytes, the dose dependent inhibition of tyrosinase inhibition is inhibited by b-Arbutin and it is less cytotoxic to melanocytes than hydroquinone (Seo et al., 2012). Arbutins (α - and β -arbutin) are glycosylated hydroquinones that are commercially used in the cosmetic industry. These compounds have an inhibitory function against tyrosinase, a critical enzyme for generating pigments, which leads to the prevention of melanin formation, resulting in a whitening effect on the skin. Although β -arbutin is found in various plants including bearberry, wheat, and pear, α -arbutin and other arbutin derivatives are synthesized by chemical and enzymatic methods (Seo et al., 2012). Regulated trials have shown that arbutin is comparably successful with kojic acid for hyperpigmentation (Garcia et al., 1996). Mequinol, a monomethyl ether hydroquinone, functions as a tyrosinase substrate, thus inhibiting the development of melanin precursors (Draelos et al., 2007).



Coumarins and Its Derivatives

Coumarin derivatives are a significant class of compounds commonly found in plants including edible fruits and vegetables. Coumarin are the heterocyclic compounds that occur naturally, which present an aromatic ring combined with condensed 6-member lactone ring. A range of biological and pharmacological behaviours have been found to exhibit coumarins and their derivatives and, due to their powerful beneficial effects have gained significant interest (Bubols et al., 2013). There are many coumarin derivatives (Liu et al., 2012; Le-The-Thu H et al., 2012; Hassan et al., 2018), which shows the inhibitory effect such as esculetin (Masamoto et al., 2003), umbelliferone and their analogues (Ashraf et al., 2015), phenyl coumarins (Matos et al., 2011), hydroxycoumarins, diamides of thiophosphonic acid, coumarin derivatives of diazaphosphinans (Ueno et al., 1970; Asthana et al., 2015), were assessed on tyrosinase activity. Aloesin is a famous which is a natural hydroxycoumarin glucoside which is isolated from isolated from Aloe vera. In cell-based assays, it does not show any cytotoxicity and does not show any skin irritation in Preliminary human experiments (Jones et al., 2002). Aloesin has shown more murine tyrosinase-inhibitory activity than mushroom tyrosinase. Due to its multifunctional activity in skin care and natural origin, aloesin has therefore been widely used in topically applied cosmetics.

3.3.2 Synthetic tyrosinase inhibitors and their derivatives Benzaldehyde and its derivatives

Isolation of a significant number of benzaldehyde and benzoate derivatives from plants are known as tyrosinase inhibitors, namely benzaldehyde (Maghsaudi et al., 2013), benzoic acid (Duckworth et al., 1970), cinnamic acid (Shi et al., 2005), anisic acid (Kubo et al., 2003), anisaldehyde (Ha et al., 2005) and methoxycinnamic acid derived from *Pulsatilla cernua* (Lee et al., 2002), Vanillic acid from black rice ban (Miyazama et al., 2003). In benzaldehyde type inhibitors, the inhibitory action of tyrosinase stems from their ability to form a Schiff basis with the enzyme as the primary amino group (Kubo et al., 1998). By a copper chelating mechanism tyrosinase is inhibited by benzoate and belongs to a typical HA-type acid tyrosinase inhibitor whose inhibitory mechanism involves the interaction of the non-ionized form of the inhibitor with copper at the active site of the enzyme (Conrad et al., 1994). Both benzaldehyde and benzoate derivatives that occur naturally showed only mild to moderate tyrosinase inhibitory activity in terms of inhibitory strength, although none were stronger than kojic acid. Methyl trans-cinnamate (Huang et al., 2009), salicylic acid (Zhang et al., 2006), flourobenzaldehyde (Huang et al., 2006) and hydroxybenzaldehyde (Kanade et al., 2007) have also been shown bad tyrosinase inhibitors with antityrosinase activity of one to two orders of magnitude lower than Kojic acid activity. The most potent natural benzaldehyde type inhibitor was not known in plants, but in a fungus. Protocatechualdehyde was collected from the fruiting body of *Phellinus linteus* and displayed a 7.8-fold increase in tyrosinase inhibitory activity compared to Kojic acid (Kang et al., 2004).

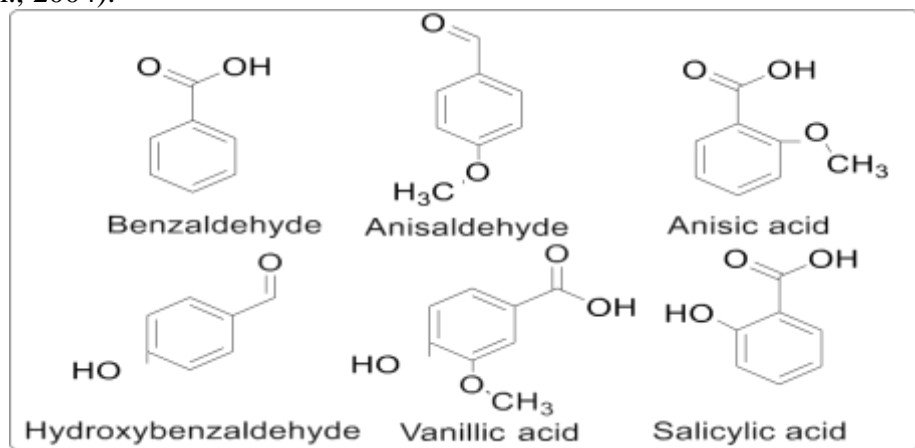


Figure: Benzaldehyde and its derivatives

Kojic Acid and Its Derivatives

Kojic acid which is a slow binding tyrosinase inhibitor and a fungal metabolite which is used as a skin whitening cosmetic for preventing the enzymatic browning (Burdoeket al., 2001; Bentley et al., 2006) and formed by many species of *Asperigillus* and *Penicillium* (Parrish et al., 1966) and it is a good chelator of transition metal ions and a good scavenger of free radiacals (Niwa et al., 1991). However, due to its light instability and the aerobic environment, its use in cosmetics is limited. For transition metal ions such as Cu⁺² and Fe⁺³, kojic acid serves as a bidentate chelator and demonstrates the competitive inhibitory effect of mushroom tyrosinase on monophenolase activity and the mixed inhibitory effect of mushroom tyrosinase on diphenolase activity (Kim et al., 2005; Kahn et al., 1997). Therefore, kojic dipalmitate, in cosmetic formulations, a more stable ester derivative is commonly used as an alternative; however, no research shows that the ester is as powerful as Kojic acid. Kojic acid is a metabolite formed primarily by fungi belonging to the genus aspergillus. A wide range of pharmacological profiles are found in this natural product, such as skin whitening, antioxidants, anti-tyrosinase and anti-tumors (Chang et al., 2009).

Stillbenes

The most popular stilbene is resveratrol. Several stilbene derivatives have been investigated for their tyrosinase inhibitory activity from natural and synthetic sources including: resveratrol from *pleurotus ferulae* (Alam et al., 2012), *Morus alba* (Bernard et al., 2000), *vitis viniferae caulis* (Park et al., 2013), *Carignan* grape juice (Gilly et al., 2001) and synthetic sources (Fransco et al., 2012) oxyresveratrol from *morus australis* (Shin et al., 1998). There are number of synthetic stilbene analogs which shows the anti-tyrosinase activity such as azostilbene (Choi et al., 2002), dihydrognetol (Ohguchi et al., 2003), hydroxy-2-phenylnaphthalenes (Song et al., 2007).

Thiourea Derivatives

One of the most well-known inhibitors of tyrosinase studied in the literature is phenylthiourea (PTU) (Criton M et al., 2008). At the active site of tyrosinase, the PTU sulphur atom binds to both copper ions and blocks the activity of the enzyme.

Azole and Thiazolidine Derivatives

There are number of azole derivatives which shows the tyrosinase inhibitory activity such as DL-3(5-benzazolyl) alanines and alpha-methyl-dopa analogs (Shiin et al., 2001), aryl pyrazoles (Channar et al., 2018), 3,5-diaryl pyrazole derivatives (Bandgar et al., 2010), herterocyclic hybrids based on pyrazole and thiazolidinone scaffolds (Gawande et al., 2013), 3,5-diaryl-4,5-dihydro-1H (Zhou et al., 2013), isoxazolone analogs (Ki et al., 2018), 5-oxazolone derivative (Hamidian et al., 2013), thiazolyl resorcinols (Mann et al., 2018). Therefore, there are many thiazolidone analogs as well which shows the tyrosinase inhibitory activity such as azo-hydrazone tautomeric dyes replaced by thiazolidinone moiety (Razaei et al., 2018), 5-(substituted benzylidene) thiazolidine-2,4-dione derivatives (Ha et al., 2012).

Conclusions

Tyrosinase is basically involved in the pigmentation of skin, eyes and hair in mammals which provides protection against UV rays. Due to increasing attention to the appearance of the skin, Many cosmetic and pharmaceutical companies depend on processes that can enhance skin pigmentation. Melanin synthesis in melanosomes should be inhibited by skin whitening agents because their specific action is to minimise the activity of tyrosinase. However there are currently only a few commercially available antimelanogenic reagents, typically Kojic acid and arbutin. More concrete human tyrosinase studies are needed from a clinical point of view. The invention of new tyrosinase inhibitors are useful for their applications in improving the nutritional value and preventing the melanin related and pigmentation disordersw in human biengs. Inhibitors are of vital importance in seeking innovative and more consumer-compatible approaches towards the decoloration process. Various forms of compounds from both natural and synthetic sources have been tested to obtain stronger inhibitors. However, much more study on tyrosinase inhibitors is necessary to confirm their effectiveness and safety in various applications.

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