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Review Article

An examination of natural and synthetic tyrosinase inhibitors

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ABSTRACT

The enzyme responsible for this process is known as tyrosinase, which is sometimes referred to as polyphenol oxidase, monophenol oxidase, phenolase, or catecholase. It is present in humans, plants, microbes, and fungi. Melanin pigments, found in both plants and animals, require this enzyme as an essential component. Tyrosinase is present in animal creatures, particularly in the pigments of the skin, hair, and eyes. Tyrosinase can cause darkening in foods that is unrelated to their inherent color. Beverages such as fruit juice and wine may experience a decline in appearance and flavor, as well as the occurrence of turbidity and precipitation. The unwanted phenomenon of browning in fruits and vegetables, which is frequently caused by enzymatic processes, needs to be avoided. Tyrosinase enzyme inhibitors are employed to hinder the catalytic oxidations that lead to browning by the tyrosinase enzyme. Currently, these basic ingredients are commonly found in skin whitening solutions, particularly in the field of cosmetics. In addition, tyrosinase inhibitors have practical applications in the treatment of skin problems associated with melanin pigmentation. Furthermore, tyrosinase inhibitors competitively and reversibly hinder the activity of human melanocyte tyrosinase, hence impeding the production of melanin.

Numerous substances possess the ability to hinder the activity of the enzyme tyrosinase. Ongoing studies are being conducted on several derivatized compounds to increase inhibition. This article explores the inhibitory effects of many compounds, including kojic acid, azelaic acid, flavonoids, arbutin-deoxyarbutin, curcumin and its derivatives, and copper chelators, on the enzyme tyrosinase.

Keywords: Azelaic acid, flavonoids, inhibitors, kojic acid, tyrosinase

1. INTRODUCTION

Tyrosinase (EC 1.14.18.1) is an important member of the polyphenoloxidase enzymes, containing the amino acid histidine in its active site. Tyrosinase is a metalloenzyme that possesses two copper atoms as cofactors. Tyrosinase is an enzyme that catalyzes the oxidation of monophenols (monophenolase activity) and *o*-diphenols (diphenolase activity) to reactive oquinones. Both tyrosinase activities exhibit wide substrate specificities, however they display a greater preference for L-isomers as substrates compared to D-isomers. Since the initial biochemical studies, it has been discovered that the enzyme is widely distributed, ranging from bacteria to mammals. The most extensively studied tyrosinases are obtained from *Streptomyces glausescens*, *Neurospora crassa*, and *Agaricus bisporus*. The central copper-binding domain of tyrosinase, which has conserved amino acid residues, including three histidines, is the most significant characteristic seen in the enzyme from many sources. A tyrosinase molecule can

accommodate a pair of copper atoms, with each atom of the bidentate copper cluster forming chemical bonds with three histidines [1].

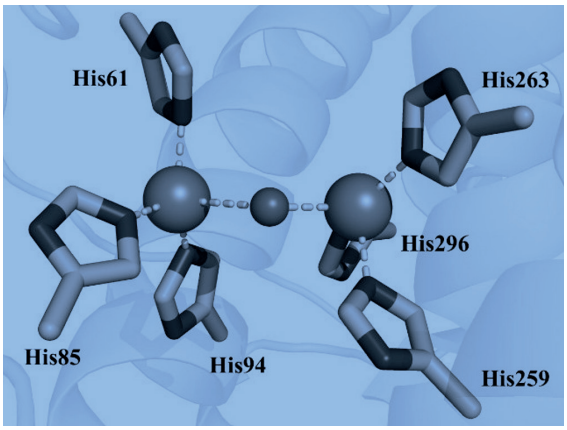

Figure 1. Active site of the crystal structure of *Agaricus bisporus* mushroom tyrosinase (Protein Data Bank, PDB ID 2Y9W) [2].

Tyrosinase is an enzyme that is present in many different kinds of organisms and is essential for the creation of melanin pigments. The enzyme tyrosinase helps plants make lignin, which is important for their defense mechanisms and growth. Factors in the environment, heavy metal exposure, and ultraviolet (UV) radiation can all increase tyrosinase activity. Plants protect themselves from oxidative stress through the antioxidant chemicals phenolic and flavonoid, which are produced in response to tyrosinase activity. Furthermore, it causes plants to undergo enzymatic browning [3]. Apart from inducing enzymatic browning in plants, it also causes animals to produce melanin. Mammals have melanin in their hair, eyes, skin, and inner ears. It plays a vital role in pigmentation. The biological process known as melanogenesis is responsible for the synthesis of melanin, an intricate polymer possessing an indolic structure. The pigment melanin is the cause of the different skin tones that people have. It is also essential for protecting skin from the sun's harmful UV radiation. Melanocytes contain specialized organelles called melanosomes, which are where the process of creating melanin takes place. The critical catalytic step that regulates the rate at which melanin is produced is controlled by the enzyme tyrosinase. Tyrosinase-induced hyperpigmentation can lead to a number of skin disorders, such as melasma, age spots, freckles, and malignant melanoma.

This enzyme is essential for the proper functioning of melanin pigments, which can be found in numerous plant and animal species. Melanin biosynthesis is catalyzed by it in three steps: (i) tyrosine undergoes hydroxylation to form 3,4-dihydroxyphenylalanine (DOPA); (ii) DOPA is oxidized to dopakinone; and (iii) indolequinone is produced by oxidation of 5,6-dihydroxyindole (DHI). The reaction changes two types of melanin into completely different substances. A brownish-black pigment called eumelanin and a reddish-yellow pigment called pheomelanin are both present; eumelanin is insoluble in water and possesses a polymer structure [4]. Figure 2 shows the process, which includes various complex enzymatic reactions.

Melanin synthesis regulation involves three critical enzymes. Three proteins: human tyrosinase (hTYR), tyrosinase-related protein-1 (TYRP-1), and tyrosinase-related protein-2 (TYRP-2). A copper center distinguishes hTYR from TYRP-1 and TYRP-2, which both contain two zinc centers. Nitric oxide, MAPK, MC1R/a, PI3K/Akt, Wnt/b-catenin, and other signaling pathways within melanocytes regulate melanogenesis. Overactive or activated tyrosinase could be the consequence of signaling pathway disruption. Albinism and vertigo are disorders caused by a decrease in the functionality of the enzyme tyrosinase and related enzymes.

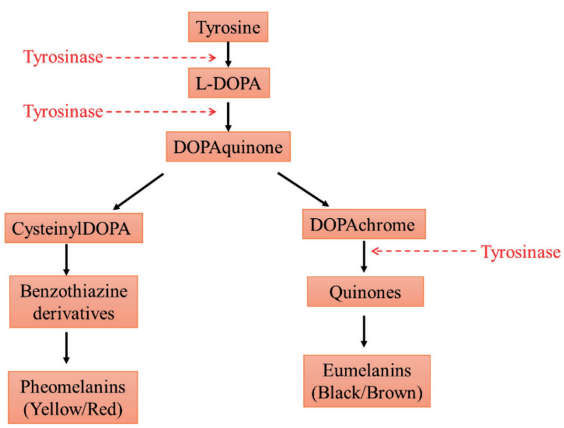

Figure 2. Tyrosinase enzyme pathway of melanin synthesis

When this gene is overexpressed, it can cause hyperpigmentation, which manifests as brown spots, age spots, freckles, and the like. A person's standard of living may suffer as a result of this. Furthermore, it has the ability to develop into malignant melanoma, an extremely dangerous and difficult-to-treat skin cancer that can be fatal if left untreated [5].

The study of enzymes and their applications is an evolving discipline. There has been a lot of study into the best ways to isolate and purify enzymes from plants and animals, particularly in the last several years. The tyrosinase enzyme has numerous uses in food, health, cosmetics, agricultural, and other related industries due to its involvement in numerous critical reactions. Being present in so many different types of produce gives it a significant foothold in the food business [6].

It catalyzes reactions of oxidation of phenolic compounds leading to the formation of pigments responsible for color changes in fruits, vegetables or processed food products. In the food industry, it causes adverse appearance and taste changes, turbidity and precipitation in beverages such as fruit juice, causing damage. Tyrosinase inhibitors are used in the food industry to eliminate the undesirable conditions caused by the tyrosinase enzyme. In addition, the activity of the tyrosinase enzyme is important to enhance the color and flavor of foodstuffs such as dried fruits, coffee, tea, cocoa [7].

Abnormal production of melanin pigment causes significant aesthetic issues because it is involved in melanin formation. Because of their capacity to prevent the enzymatic browning of food items and their skin-lightening effects, tyrosinase inhibitors find widespread use in the cosmetics industry. Additionally, neurodegeneration has been associated with Parkinson's disease, and tyrosinase has been found to induce dopamine neurotoxicity. A degeneration of dopaminergic neurons in the brain causes Parkinson's disease, a neurodegenerative condition. So, many Parkinson's disease drugs and studies have focused on blocking tyrosinase [8].

Because tyrosinase is a copper chelators such as aromatic acids, non-aromatic chemicals phenolic ingredients, can compete to inhibit the enzyme [4]. Numerous tyrosinase inhibitors have been found naturally and synthetically. Hydroquinone, α-arbutin, kojic acid, retinoids, azelaic acid, resveratrol, camptaric acid, chrysosplenetin and phenylethyl resorcinol have been identified as tyrosinase inhibitors [9].

2. TYROSINASE INHIBITORS

In many studies in the literature, inhibitors are evaluated in the presence of tyrosine or DOPA, the substrate of the enzyme, in terms of DOPA-chrome formation. Tyrosinase inhibitors are mainly used

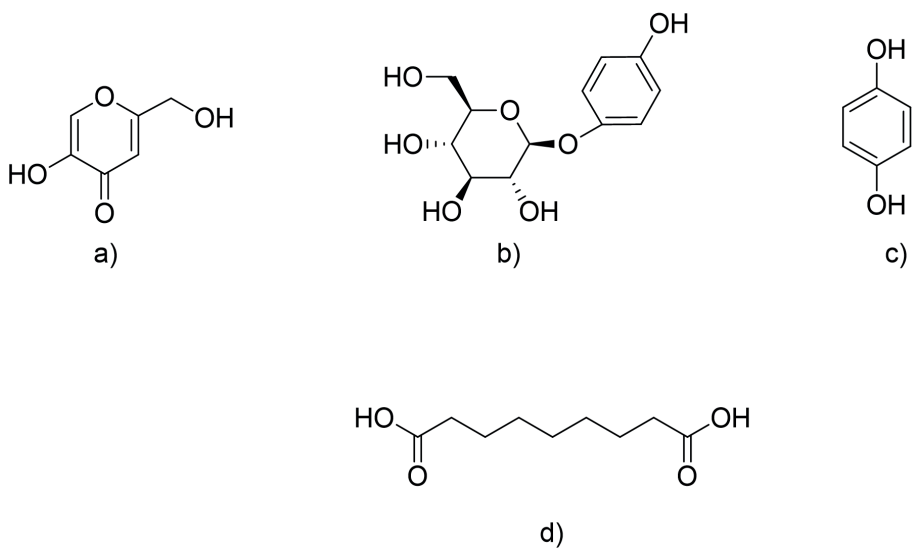

Figure 3. Tyrosinase inhibitors chemical structure a) kojic acid, b) arbutin, c) hydroquinone, d) azelaic acid.

in reference to melanogenesis inhibitors, which interfere to some extent with melanin formation.

2.1. Kojic acid and derivatives

Kojic acid (5-hydroxy-2-(hydroxymethyl)-4*H*-pyran-4-one) (Figure 4) is one of the metabolites produced by various strains of fungi or bacteria such as *Aspergillus* and *Penicillium*. Kojic acid, which is often studied as an inhibitor of tyrosinase, is used as a skin whitener in the cosmetics industry and is also used in the food industry to prevent enzymatic browning [1]. Kojic acid shows a competitive inhibitory effect on monophenolase activity and a quasi-competitive inhibitory effect on the diphenolase activity of fungal tyrosinase. The ability of kojic acid to chelate copper in the active site of the enzyme explains its competitive inhibitory effect. The biological activities of kojic acid are attributed to its γ-pyranone structure containing an enolic hydroxyl group. If the enolic hydroxyl group is retained, the tyrosinase inhibitory activity is completely lost. It acts by chelating copper in the active site of the tyrosinase enzyme. Kojic acid is also an antioxidant and scavenges reactive oxygen species that are excessively released from cells or formed in tissue or blood. Stable metal kojic acid complexes are created when kojic acid reacts with metal salts of aluminum, chromium, cobalt, copper, gold, indium, iron, nickel, manganese, palladium, vanadium, and zinc [10-12].

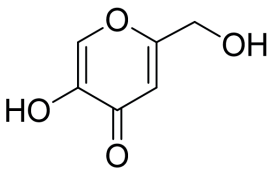

Figure 4. Kojic acid chemical structure

Based on the fact that kojic acid is an inhibitor of tyrosinase enzyme, many derivatives of kojic acid were investigated and its inhibition effect was examined. The low stability of kojic acid has pioneered the search for different derivatives. It has been observed that the C-terminal amine groups in the structure to be involved in the inhibition of tyrosinase enzyme create a high inhibition effect [13,14].

Aromatic side chains can interact with the hydrophobic pocket containing the amino acids His63, His216 and Phe59 surrounding the double-core copper in the active site of the tyrosinase enzyme. As a result, aromatic molecules can exert competitive, semi-competitive and non-competitive inhibition. As a result of conjugation of kojic acid and various amino acids, it was observed that kojic acid-phenyl alanine had a higher inhibition effect than kojic acid and remained stable for more than 3 months [15]. In another study, compounds formed as a result of molecular hybridization of kojic acid and aromatic aldehydes exhibited a strong tyrosinase inhibitory activity. As a result, it was determined that it prevents browning [16].

The hydroxypyranone moiety of kojic acid serves as a scaffold for tyrosinase inhibitors, as it shows the ability to chelate with copper ions in the tyrosinase active center. The enhancement of kojic acid with functional groups showed an inhibition effect 9-fold higher than that of kojic acid [17].

Numerous studies have examined the inhibitory effects of compounds extracted from plant sources, fungi, and microbes on tyrosinase. Despite kojic acid being the most extensively researched compound, its volatility, potential adverse effects from prolonged exposure, and limited efficacy have prompted

researchers to explore derivatives to mitigate these drawbacks.

Shao et al. synthesized hydroxypyridinone derivatives and formulated variants capable of mitigating the adverse effects of kojic acid. The compounds demonstrated superior efficacy in bleaching compared to kojic acid [18].

A cohort of researchers examining the impact of the benzapyrone ring on tyrosinase inhibition synthesized several derivatives by the conjugation of kojic acid and coumarin including the benzapyrone ring. The findings indicated that the compounds conjugated with coumarin had a greater inhibitory impact on tyrosinase than kojic acid [19,20].

2.2. Azelaic acid and derivatives

Azelaic acid is structurally a 9-carbon straight chain 1,7-heptandicarboxylic acid. It is commonly used

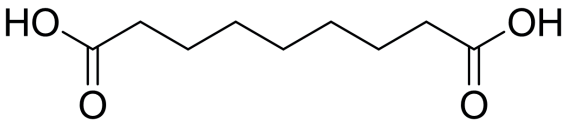

Figure 5. Azelaic acid chemical structure

in the treatment of acne, melanoma, rosacea and hyperpigmentation [21]. Azelaic acid is metabolized by β-oxidation resulting in the formation of malonyl-CoA or acetyl-CoA. Due to its chemical structure, it has the capacity to inhibit tyrosinase and to a much greater extent thioredoxin. Azelaic acid has anti-inflammatory, antibacterial and anti-keratinizing effects and has a significant therapeutic efficacy on acne [22,23].

Azelaic acid inhibits the enzyme tyrosinase. This enzyme is involved in the conversion of tyrosine into DOPA and DOPA-quinone, precursors of melanin. Dicarboxylic acids do not affect normal skin melanocytes, so AZA can be used to treat many types of skin hyperpigmentation and does not cause discoloration of healthy skin near the lesions [23].

In a study with azelaic acid esters, it was found to inhibit the tyrosinase enzyme. It was determined that it completely inhibits L-tyrosine oxidation and stops esterification reactions [24].

2.3. Flavonoids

Flavonoids constitute the principal polyphenolic group in plants, often present in the fruits, vegetables, drinks, and cereals that we eat every day. Flavonoids belong to a class of naturally occurring plant polyphenolic secondary metabolites found in many plants and therefore widely consumed in the diet. In general, they are composed of 15 carbons; a phenyl ring and a heterocyclic ring. Biological studies carried out on natural and synthetic analogues of flavonoids have revealed anti-keratinization, anti-microbial, anti-cancer, anti-inflammatory, anti-ulcer action by these species [25].

Flavonoids, due to their polyhydroxyphenolic structure, are metal chelators that can interact with copper ions in the active site of tyrosinase. Therefore, their species and their derivatives are model compounds for tyrosinase inhibition. Numerous compounds derived from natural products have been reported to be moderate to potent tyrosinase inhibitors [26]. Among these, many flavonoid derivatives have been found to be potent inhibitors of tyrosinase. Four important flavonoid compounds, chrysin, quercetin, naringin and kaempferol, have been shown to play an important role in tyrosinase inhibition [27, 28].

The general structure of flavonoids indicates that keto groups possess significant potential as tyrosinase inhibitors. The -OH group at the C-3 position in the structure is crucial for activity. Flavonoids, including kaempferol and quercetin, possess a 3-hydroxy-4-keto moiety in their structure. This allows it to function as a copper chelator in the inhibition of tyrosinase, thereby obstructing the enzyme's activity. In heterocyclic rings containing 5 or 6 carbon atoms, the presence of -OH and -CH_3 groups, frequently observed around the ring, is indicative of the structure. These groups exhibit an inhibitory effect by influencing the enzymatic activity within the structure [29].

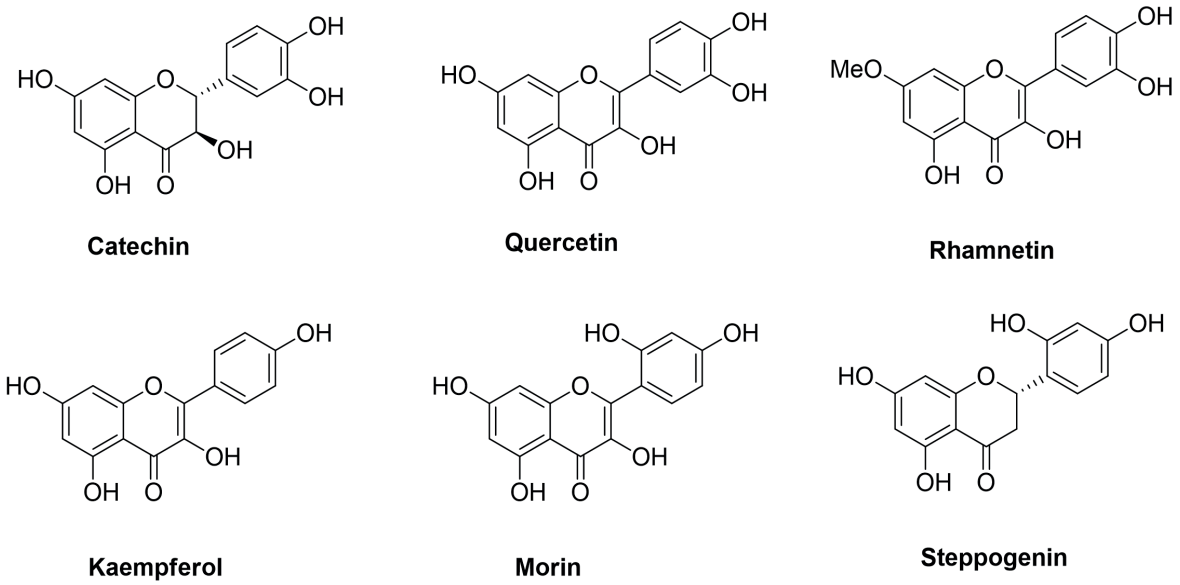

Figure 6. Chemical structures of flavonoids

Chrysin (5,7-dihydroxyflavone) is a natural flavonoid derived from many plants and has anti-melanogenesis effects [30]. Naringin (5,7,4-trihydroxyflavone) is another type of flavonoid with tyrosinase inhibition activity [31]. Quercetin (5,7,3,4-tetrahydroxyflavonol) also shows tyrosinase inhibitory effects through inhibition of diphenolase activity [32]. Rocchitta et al. demonstrated in their study that the structure of quercetin exhibited an inhibitory effect through hydrogen bonding interactions with the His85, His244, Thr261, and Gly281 residues of tyrosinase [20]. Kaempferol (5,7,4-trihydroxyflavonol) is another flavonoid inhibitor whose anti-tyrosinase effects have often been proven [33].

In a study, the tyrosinase inhibition effects of flavonoids such as kaemferol and quercetin were investigated. The compounds competitively inhibited the tyrosinase enzyme and showed a higher inhibition effect than kojic acid [34].

2.4. Arbutin-deoxyarbutin and derivatives

Arbutin (hydroquinone-O-*β*-D-glucopyranoside), a natural polyphenol isolated from the bearberry plant *Arctostaphylos uva-ursi* (L.) Sprengel, has whitening and anticancer properties. Arbutin is a compound in which the D-glucose molecule is linked to hydroquinone. D-glucose exists in aqueous solution in *α*, *β* or *γ*-anomeric form; the compound in which the *β*-anomer of D-glucose binds to hydroquinone is called *β*-Arbutin (this stereoisomer is called arbutin) and the compound in which the α-anomer of D-glucose binds to hydroquinone is called *α*-Arbutin. Both forms of arbutin are hydroxylated at the *ortho* position of the catechol group by oxytyrosinase, resulting in a complex formed by hydroxylated mettyrosinase [35,36].

Due to its glucose composition, arbutin is regarded as more dependable than hydroquinone. Arbutin is highly hydrophilic, so skin penetration is relatively low. Arbutin is resistant to light and unstable at pH 2. Arbutin can undergo partial hydrolysis to hydroquinone in the presence of water, which in turn can be oxidized to benzoquinone [37]. *α*-Arbutin is 10 times more effective than *β*-arbutin in inhibiting tyrosinase, but α-arbutin is easily degraded by heat [37,38].

Deoxyarbutin, another derivative of hydroquinone, is clinically more effective and safer than arbutin in the treatment of hyperpigmentation. Deoxyarbutin is a second generation hydroquinone derivative. Deoxyarbutin is less cytotoxic than other hydroquinone derivatives [39,40].

After removal of all hydroxyls in the glycoside side chain, *β*-arbutin is converted to deoxyarbutin. This

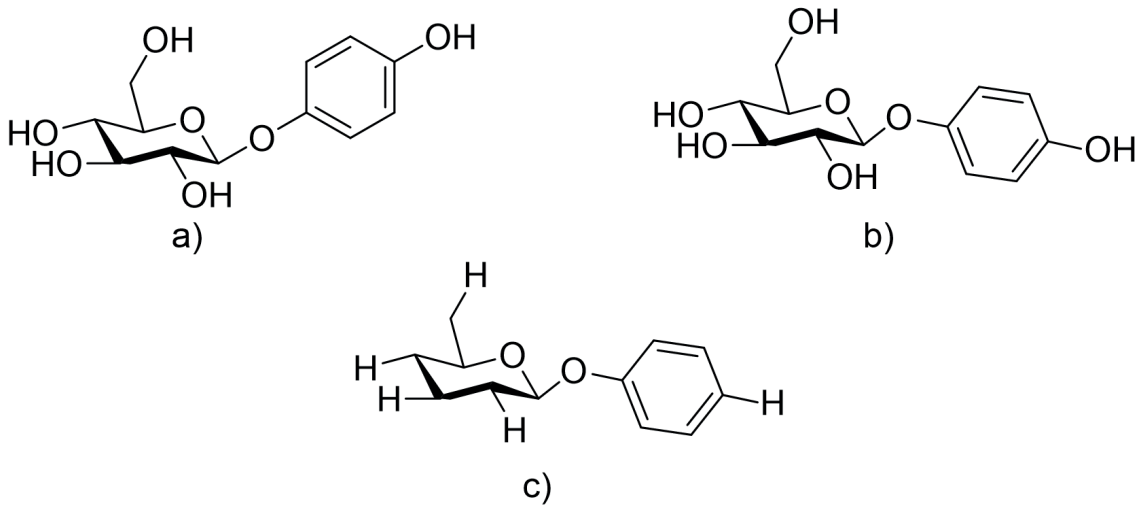

Figure 7. The molecular structure of a) *β*-arbutin, b) *α*-arbutin, c) deoxy-arbutin

procedure results in increased lipo-solubility of deoxyarbutin compared to *β*-arbutin. Deoxyarbutin shows a stronger tyrosinase enzyme inhibition than hydroquinone and *β*-arbutin [41]. The activity of arbutin and its derivatives is related to particle size, spatial structure and electrostatic potential around the benzene ring [42].

Studies have shown that arbutin, deoxyarbutin and their derivatives inhibit the activity of the tyrosinase enzyme and prevent the oxidative polymerization of melanogenic intermediates, which is common for antioxidant compounds that provide protection from reactive oxygen species produced by UV radiation. In addition, arbutin and its derivatives were found to inhibit the maturation of melanoma cells. The *in vitro* study showed that arbutin is gradually oxidized in the presence of tyrosinase, which makes its effect prolonged in the presence of antioxidants such as L-ascorbic acid [42]. In several studies, *α*- and *β*-arbutin inhibited melanin formation in B16 cells induced by α-melanocyte stimulating hormone (α-MSH) and blocked thyronazinase activity [43–45]. Acetylated arbutin exhibits enhanced tyrosinase inhibitory potential, likely due to the increased solubility and improved membrane penetration conferred by the acetyl group in lipid-containing systems [44]. There is reason to be optimistic about the potential of phenolic compound derivatives as tyrosinase inhibitors in the stages of melanomagenesis. By inhibiting the production of melanin in B16F10 cells, the active phenolic and alkylhydroquinone components found in the extract of the *Rhus succedanea* L. tree demonstrated a tyrosinase inhibitor effect. Upon conducting comparisons with hydroquinone, it was determined that the active alkylhydroquinone component exhibited an IC_{50} value of 37 μM. Conversely, the IC_{50} value of hydroquinone was found to be exactly 70 μM. It was observed, as a consequence of the data that was obtained, that the heptadecenyl chain that was present in the structure of the active component was responsible for the oxidation of the hydroquinone ring. As a consequence of this, a more efficient derivative inhibitor molecule was purified from hydroquinone [46].

2.5. Curcumin and derivatives

Curcumin is commonly regarded as a prototypical example of phenylpropanoid compounds due to its chemical structure. The compound is called 1,7-bis(4-Hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione [47]. Curcumin is a plant-derived polyphenol obtained from *Curcuma longa* L., also known as turmeric. Turmeric is a powdered rhizome of this plant that is commonly used to enhance the color and taste of food. It is also traditionally believed to have medicinal properties for treating inflammatory illnesses and other diseases. Curcumin, also known as diferuloylmethane, possesses both anticancer and tyrosinase enzyme inhibitory effects Curcumin, at

concentrations between 25-110 μM, was discovered to possess inhibitory effects on melanin formation via activating the Akt/PKB signaling pathway. This activation can hinder the process of melanogenesis by decreasing MITF levels and blocking the action of the enzyme tyrosinase [48,49].

Phenolic chemicals, known for their antioxidant properties, can aid in the prevention and relief of various chronic diseases resulting from oxidative stress. Research has demonstrated that curcumin and its derivatives have a greater inhibitory effect on the tyrosinase enzyme compared to kojic acid. Furthermore, research has demonstrated that the *β*-phenyl-*α*, *β*-unsaturated carbonyl structure seen in curcumin derivatives is strongly associated with the ability to block tyrosinase. Coumaric acids are compounds that are derived from mono-hydroxylated cinnamic acid in the phenyl group. Among these compounds, *p*-coumaric acid is the most prevalent type. *p*-Coumaric acid is present in substantial amounts in numerous fruits, vegetables, and cereals. *p*-Coumaric acid is a potent antioxidant known for its ability to eliminate reactive oxygen species (ROS) and free radicals [50,51]. Research has demonstrated that derivatives of *p*-coumaric acid exhibit a distinct ability to inhibit the enzyme tyrosinase [52,53]. Furthermore, *p*-coumaric acids were examined for their impact on melanin creation in B16F10 cells and were observed to decrease melanin production [54].

The polyphenolic content of curcumin has become significant in scientific research focused on its antioxidant properties and potential as an anticancer agent. The literature has examined the effect of curcumin on tyrosinase inhibition, specifically regarding its whitening properties and its implications for melanoma and other skin cancer types [55].

2.6. Copper chelators

The majority of drugs that chelate copper ions in the active site of the tyrosinase enzyme have the ability to inhibit the tyrosinase enzyme. Tropolone is an established tyrosinase inhibitor due to its ability to chelate copper. Tropolone derivatives were synthesized based on the structure of the tiny seven-membered ring, and it was discovered that these derivatives have the ability to block the tyrosinase enzyme [56]. The researchers conducted an investigation on the red tembul leaves to determine the effect of their alkaloids, tannins, and flavonoid content as tyrosinase inhibitors. The results of the investigation show promising outcomes [57].

The study utilized ilapia skin collagen hydrolysate to examine the potential for TYR inhibition. The results indicated that TYR inhibitory peptides had a greater ability to chelate copper [58].

2.7. Resveratrol and derivatives

Resveratrol (3,4',5-trihydroxy-*trans*-stilbene) has been the subject of extensive research over the past decade due to its diverse bioactivities, which include anti-inflammatory and antioxidant properties, as well as effects on cancer, neurodegenerative diseases, and aging. Resveratrol has demonstrated the ability to mitigate neuroinflammation and oxidative stress, primarily through the enhancement of neurotransmitter release. Recent studies indicate that resveratrol exhibits an inhibitory effect on the tyrosinase enzyme [59].

The antioxidant efficacy of resveratrol is contingent upon the redox potential of the phenolic hydroxyl group and the capacity for electron delocalization attributed to its conjugated configuration. The antioxidant mechanism of resveratrol encompasses the reduction of reactive oxygen species (ROS) generation, the scavenging of free radicals, and the enhancement of antioxidant biosynthesis. Moreover, its phenyl ring has lately garnered significant interest owing to its potential chemopreventive and chemotherapeutic properties [60,61].

The bioavailability of resveratrol is limited owing to its chemical instability and poor solubility. The inhibition of tyrosinase by resveratrol derivatives was examined to mitigate these drawbacks [62].

Oxyresveratrol (*trans*-3,5,2′,4′-tetrahydroxystilbene) possesses an additional hydroxyl group, distinguishing it from resveratrol. A study conducted in 2021 demonstrated that oxyresveratrol exhibits a more potent inhibitory effect on tyrosinase activity, attributed to its capacity to form a greater number of hydrogen bonds in comparison to resveratrol [62,63].

2.8. Heterocyclic Compounds and Derivatives Containing Triazole and Thiazole

Heterocyclic compounds are cyclic structures that incorporate oxygen, nitrogen, or sulfur, with at least one heteroatom present. Quintuple-ring aromatic heterocyclic compounds exhibit remarkable stability. Heterocyclic compounds are utilized across various domains. Heterocyclic compounds that contain nitrogen and sulfur are commonly utilized for pharmacological and biological activity. Thiazoles, comprising both nitrogen and sulfur atoms in their rings, are incorporated into numerous pharmaceutical active ingredients as biologically active compounds. Triazoles are five-membered heterocyclic compounds containing three nitrogen atoms. These molecules are often examined for their derivatives because of their biological activity [64–68].

A 2019 study compared the effects of tyrosinase inhibition using kojic acid as a positive control and synthesized a novel heterocyclic amide compound featuring a new triazole and thiazole ring. The researchers investigated the inhibitory effect of the synthesized compound on the fungal tyrosinase enzyme. The presence of two methylene groups in the derivative structure enhanced its activity due to the steric effect. A comparison of the derivative molecule with kojic acid revealed an activity enhancement of approximately 15-20 times. The findings with various derivatives indicated that the polar and bulky substituents on the phenyl ring in the derivative molecules adversely affected the activity. The same research group examined the inhibitory effects of derivatives resulting from modifications at the C-3 and N-4 positions of the triazole ring. They synthesized various derivatives by substituting the ethyl group in the triazole ring with a benzyl group in place of the attached acetamide group. The synthesized heterocyclic derivative compounds exhibited lower IC_{50} values than standard molecules and demonstrated potential as inhibitory agents [65,69,70].

In a further promising study, the synthesized derivative molecule was formed via a hydrogen bond between cysteine and the amino group of the thiazole ring. The interactions between the thiazole ring and histidine were established through hydrogen bond formation. The tyrosinase inhibition studies of this new derivative molecule indicated a promising IC_{50} value in comparison to the standard molecule [71].

Shakila et al. synthesized indole-triazole derivatives incorporating N-acetamide by linking an indole ring to the carbon of the triazole ring. The synthesized compounds were evaluated for their potential as tyrosinase inhibitors, yielding IC_{50} values ranging from 0.033 to 0.142 μM. The IC_{50} values obtained indicated a substantial inhibitory effect, showing a marked difference in comparison to standard molecules [72].

3. CONCLUSION

This study summarizes and critically analyzes studies on isolated compounds with possible tyrosinase inhibitory action. The enzymatic oxidation of phenols by the enzyme tyrosinase is responsible for the browning of nutrients. Consequently, there is a degradation of crucial amino acids, a decrease in the ability to be digested, and a decline in nutritional value, along with the creation of harmful substances. The occurrence of these unwanted browning events is a significant challenge, and it is imperative to explore potent tyrosinase inhibitors to address this issue. Melanin has a crucial function in safeguarding the skin from the development of skin cancer caused by exposure to sunlight. Nevertheless, the excessive synthesis of melanin pigment poses both cosmetic and medicinal concerns in humans. Nevertheless, tyrosinase inhibitors are employed in medical practice to treat some conditions associated with excessive melanin pigmentation, and they also play a significant role in the fields of cosmetics and pharmaceuticals due to their ability to lighten the skin. Numerous natural and synthetic compounds and their derivatives have been shown to inhibit tyrosinase effectively; nevertheless, the majority have not undergone clinical investigation. At now, only a limited number of chemicals are used in topical dermatological formulations. However, there are only a limited number of commercially accessible tyrosinase inhibitors. The limited applicability of

these substances is a result of their high intercellular toxicity and low stability, which raises concerns. This article reviews the capacity of several chemicals to hinder the tyrosinase enzyme, as well as the molecules that can beyond the constraints and exhibit a stronger inhibitory impact. The advancement of inhibitors in the literature and modifications to enhance inhibitor activity are significant considerations. The design of natural or synthetic tyrosinase inhibitors is a significant research topic, driven by considerations of high bioavailability, low cytotoxicity, and effective inhibition. This review examines the inhibitory effects of various derivatives, particularly phenolic and heterocyclic compounds, on tyrosinase activity. It highlights the significance of understanding structural modifications in the identification of new inhibitors. This review aims to provide guidance and a comprehensive strategy for the development of novel, effective, highly active, and safe tyrosinase inhibitors for enhanced practical applications in the future.

Ethical approval

Not applicable because this article does not contain any studies with human or animal subjects.

Author contribution

Conceptualization, G.D.; Data collection and/or processing, G.D.; Investigation, G.D.; Writing—original draft preparation, G.D.; Writing—review and editing, G.D. The author has read and agreed to the published version of the manuscript.

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The author declared that there is no conflict of interest.

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