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REVIEW ARTICLE

A Comprehensive Study to Explore Tyrosinase Inhibitory Medicinal Plants and Respective Phytochemicals for Hyperpigmentation; Molecular Approach and Future Perspectives

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Abstract: Tyrosinase is a copper-containing key substance in the pigmentation of mammalian hair and skin. Melanin synthesis is influenced by a variety of extrinsic and internal variables, including hormone fluctuations, inflammation, ageing, and subsequent ultraviolet light exposure. Melasma, senile lentigines, freckles, and diminished colour are all undesirable side effects of excessive melanin production. The current review provides the pursuit of effective and safe tyrosinase inhibitors derived from medicinal plants and ascribes updated inferences on current practices. Commercially available tyrosinase inhibitors provide an even skin tone and are used clinically to treat hyperpigmentation and related disorders. This review focuses on the mechanism of melanogenesis and on experimentally verified potent and natural tyrosinase inhibitors. Bioactive compounds such as phenols, flavonoids, stilbenes, and few traditional herbal formulations from the Indian system of medicine, have been used for long in India and subcontinents for the effective management of melanogenesis and related problems. Scientific information was gathered from different sources of databases such as PubMed, Google Scholar, Springer, Scopus, and Science Direct, as well as the literature found in medicinal plant books. This critically summarized review ensures to aid researchers and enterprises working on tyrosinase inhibitors and on conditions associated with melanogenesis, to get one-step solutions for identifying more safe and effective natural remedies.

Keywords: Hyperpigmentation, anti-browning, tyrosinase, melanogenesis, phenols, flavonoids.

1. INTRODUCTION

Melanin is a heterogeneous collection of biopolymers that imparts colour to human skin, hair, and eyes. Melanin is synthesized in melanosomes, membrane-bound granules, and is subsequently transferred in a ratio of approximately 1:36 from melanocytes to keratinocytes [1]. UVB exposure, α-melanocyte stimulating hormone (α-MSH), melanocortin 1 receptor (MC1R), and agouti-related proteins are a few examples of environmental, hormonal, and genetic factors that may influence melanogenesis [2, 3]. Conceding melanogenesis is a complicated process involving numerous enzymatic and chemical interactions. Enzymes such as tyrosinase and associated proteins TRP-1 and TRP-2 play a critical role in melanin formation. Tyrosinase is a multifunctional copper-containing metalloprotein that contains di-nuclear copper ions and functions as a rate-limiting enzyme in the biosynthesis of melanin. Tyrosinase is the major enzyme response ble for the hyperpigmentation of human skin and enzymatic browning in mammals, fruits, fungi, and vegetables [4].

Melasma, solar lentigine, and post inflammatory skin discoloration are a few examples of frequent hyperpigmentation problems that can occur as a result of various skin conditions like acne, eczema, contact dermatitis, or trauma [5]. Several countries, including the European Union, have banned it from being used in cosmetics because of its harmful effects [6]. This step motivated the scientists to divert their efforts to discovering, isolating, synthesizing, and characterizing new tyrosinase inhibitors derived from herbs for application as food preservatives, in the food industry and skin whitening agents in medicine and in cosmetics [7]. Many physicians have difficulty in treating hyperpigmentation, and an expanded inventory is necessary to aid in the development of topical therapies.

As potential alternatives to the currently available products such as hydroquinone, hydroxyphenolic compounds, corticosteroids, and tretinoin, which possess numerous side effects, including skin irritation, contact dermatitis, and ex-

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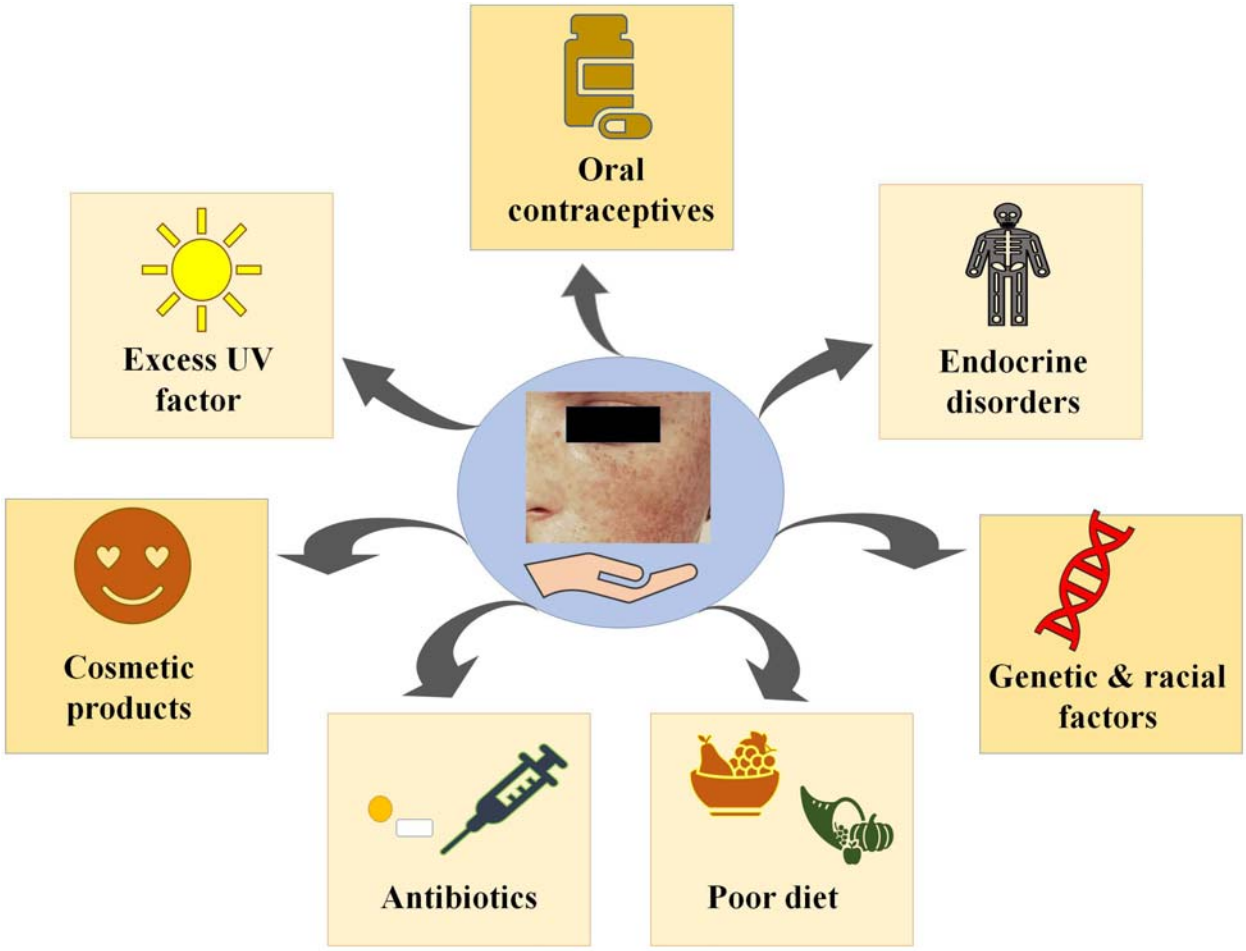


Fig. (1). Causative factors for hyperpigmentation. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

ogenous ochronosis in people with darker skin, a variety of safe and effective skin-lightening botanicals are available in the market in today's time. Natural extracts contain a wide variety of active ingredients that can be used in skin-lightening cosmeceuticals. Furthermore, a study incorporating phytochemicals into current therapy is required to treat hyperpigmentation. Patients nowadays are more interested in natural alternatives, so dermatologists and other healthcare professionals would only benefit from re-acquainting themselves with the pieces of evidence supporting or refuting the use of botanically derived natural products for hyperpigmentation treatment. Excess UV-B rays, hereditary factors, a poor diet of junk food, and other variables have been linked to the creation of brown-black coloured melanin [8], few are depicted in Fig. **(1)**. In the field of cosmeceuticals, the discovery of novel tyrosinase inhibitors for the production of anti-melanogenic drugs has received a lot of attention. Numerous inhibitors have been identified previously, and the purpose of this review is to discover and focus on novel phytoconstituents and conventional formulations capable of inhibiting the catalytic reaction of melanin formation via the enzyme tyrosinase [9, 10].

2. MELANOGENESIS

Melanogenesis is a biological process that occurs within the melanosome. Melanocytes, or pigment-producing cells, are found in the epidermis, the outermost layer of the skin, wherein melanin is produced. Two types of melanin produced by melanosomes are eumelanin and pheomelanin [11]. Pheomelanin is a soluble sulphur-containing pale red-yellow polymer, whereas eumelanin is an insoluble dark brown-black polymer. The activation of tyrosinase, a critical enzyme in melanogenesis, accelerates the process of melanogenesis, particularly when the skin is exposed to external stimuli such as UV light, *etc*. The structural and kinetic properties of tyrosinase have been the subject of much research and review studies [12, 13]; This provides a concise outline of the biochemical properties and their reaction mechanisms. Tyrosinase (monophenol, o-diphenol; oxygen oxidoreductase, EC 1.14.18.1), also known as polyphenol oxidase (PPO) is a multifunctional, glycosylated and copper-containing metalloprotein that contains di-nuclear copper ions in the membrane of melanosome, a vesicle of the melanocytes [4]. It consists of an inner melanosomal domain containing the catalytic region (approximately 90% of the protein), a short transmembrane domain, and a cytoplasmic domain of approximately 30 amino acids. Histidine residues in the inner (catalytic) region of tyrosinase bind with copper ions, which are required for tyrosinase action [12].

3. GENETICS INVOLVED BEHIND BROWNING/ MELANOGENESIS

Browning is frequently ascribed to oxidative polymerization in fruits and fungi, which is theoretically analogous to melanogenesis. The primary distinction is that allomelanin is not constructed using dopaquinone-derived patterns as its primary monomers, but rather with different quinoid building blocks [13]. Over 125 genes are known to regulate skin pigmentation genetically. Together with hormones, genes are responsible for regulating the process of melanin synthesis. They can alter the amount of eumelanin or pheomelanin produced by mammalian skin cells, as well as their survival and function, resulting in variations in skin colour over time [14]. Some people's darker skin helped shield them from the sun's harmful UV radiation [12], whereas lighter skin enabled others in low-sun places to generate vitamin D more effectively (a crucial step in the production of vitamin D) [15]. By examining ethnically, genetically, and phenotypically varied Africans, the study revealed new pigmentation loci that are not highly polymorphic in European populations and appear to affect a variety of traits. DDB1 impacts pigmentation, cellular impact on the mutagenic effect of UVR, [3] and female fertility [15-17].

4. ROLE OF TYROSINASE IN BROWNING

Among the different sources of tyrosinase, *Agaricus bisporus* for mushroom tyrosinase is a plentiful and economical source that bears a high degree of similarity and homology to human tyrosinase [18, 19]. Bourquelot and Bertrand isolated *Agaricus bisporus* tyrosinase for the first time in 1895, a 120 kDa tetramer with two different heavy and light subunits [4]. Tyrosinase catalyzes the hydroxylation of the amino acid tyrosine to L-3,4-dihydroxyphenylalanine (DOPA) by a sequence of enzymatic and spontaneous chemical reactions, which is the initial step in creation of melanin called the Raper–Mason pathway, [20] as shown in Fig. **(2)**. The enzyme also catalyzes the conversion of DOPA to dopaquinone. Eumelanin is produced by a spontaneous or dopachrome tautomerase-dependent reaction in the absence of cysteine or glutathione (DCT, formerly known as tyrosinase-related protein 2 or TRP-2). Dopaquinone oxidizes spontaneously to dopachrome, which is then attacked by DCT, resulting in di-hydroxy carboxylic acid. Pheomelanin is a light red-yellow, sulphur-containing soluble polymer, which is generated when dopaquinone is filled with cysteine. Except for tyrosinase, the remaining reactions are spontaneous and do not need any additional catalysts [21].

The process of tyrosinase catalyzed melanin biosynthesis is divided into two essential steps (i). Catecholase oxidation is the process by which *o*-diphenol is converted to *o*-quinone or *o*-dopaquinone (diphenolase) (ii). Hydroxylation of monophenols to *o*-diphenols or *l*-Tyrosine by *l*-Dopa (monophenolase) or cresolase activity [22].

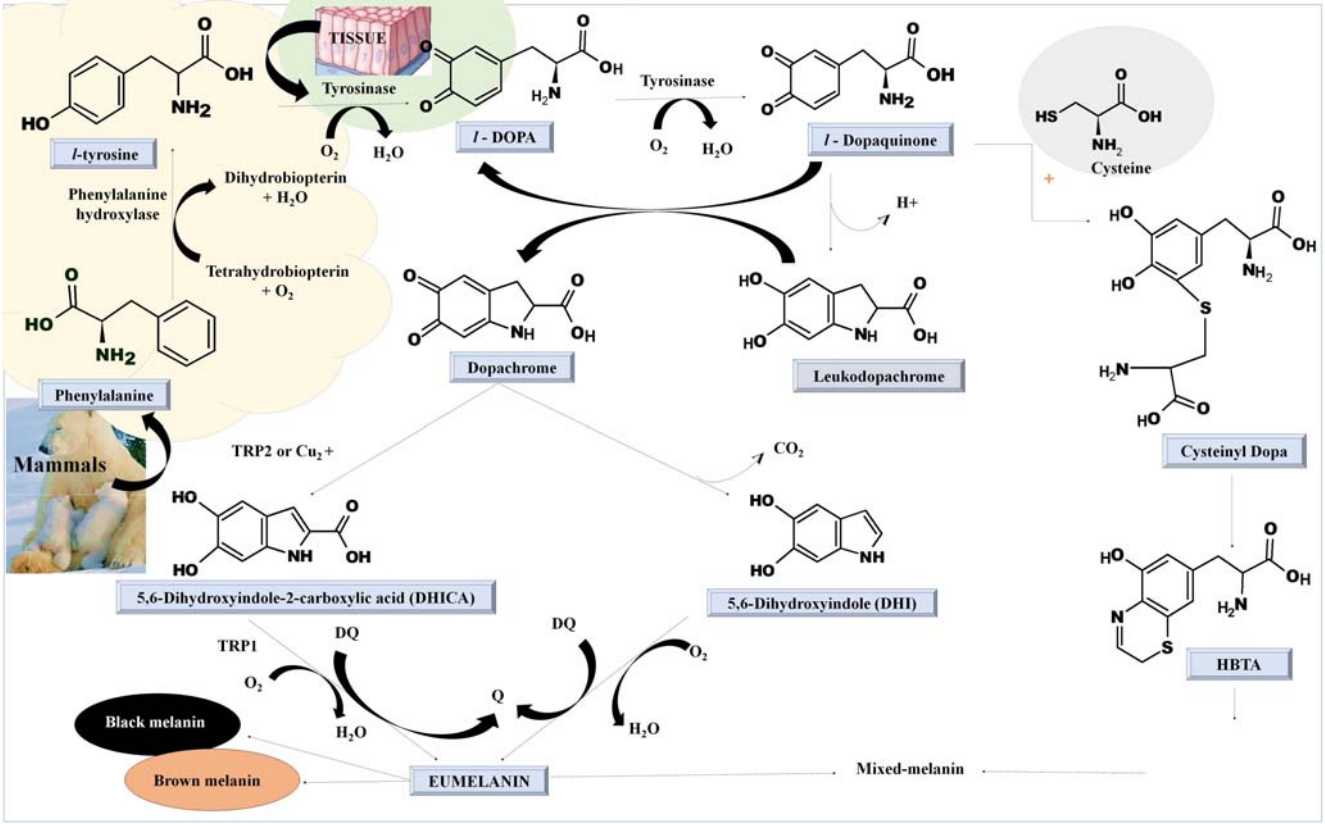


Fig. (2). Raper-mason pathway. Tyrosinase catalyses the first step in the synthesis of melanin (brown, black and mixed melanin), the hydroxylation of the amino acid L-tyrosine to L-3,4-dihydroxyphenylalanine (l- DOPA) by a series of enzymatic and spontaneous chemical events. TRP-1, tyrosinase related protein-1; TRP-2, tyrosinase related protein-2; L- DOPA, L-3, 4-dihydroxyphenylalanine; HBTA, 5-hydroxy-1, 4-benzothiazinylalanine. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

5. CATECHOL OXIDATION

Diphenolase is a self-contained reaction that involves two oxidation steps: first, the peroxy-bridge of the active site of the oxy-form of tyrosinase is reduced to *o*-diphenol, yielding the corresponding *o*-quinone and water molecule, and then the oxy-form is converted to met-form. Another phase occurs when the active site of the copper ions in met form is reduced by *o*-diphenol, resulting in the formation of the de-oxy form of tyrosinase enzyme and a molecule of *o*-quinone as a result of the reduction. The met-form gets attached to the *o*-diphenol, resulting in the formation of metD complex. This combination oxidizes the *o*-diphenol to *o*-quinone, which is then deoxidized by the enzyme tyrosinase into de-oxy form. This de-oxy form of tyrosinase has a greater affinity towards oxygen, hence, it combines with it to form the oxy-form, which in turn binds with another *o*-diphenol molecule and ultimately results in the formation of a complex *oxy-D form*. By binding with oxygen, tyrosinase maintains the oxidation state of the active site of copper ions Cu^{+} to $Cu^{2+,}$ as depicted in Fig. **(3)**. When the *o*-diphenol is oxidized to *o*-quinone, the catalytic cycle ends and the Met form is produced once again [23].

Both diphenolase and monophenolase are active concurrently. Tyrosinase exhibits monophenolase activity after a lag period. This period is proportional to the amount of monophenol used and is necessary for the enzyme to accumulate *o*-diphenol in the reaction media. Additionally, the lag time is an autocatalytic mechanism that is based on tyrosinase dependent DOPA as it acts upon tyrosine as a substrate. Tyrosinase has two active binding sites: one for the substrate (*o*-monophenol) and another for the reductant (oxygen) (*o*-diphenol or exogenously added AH2). When exogenous AH2 is not present, the hydroxylation reaction has a lag time, which is a complex equilibrium between the enzymatic and chemical steps to reach the steady state in terms of diphenol concentrations to achieve this concentration, a small amount of enzyme in the oxy form must be present. Here as shown in Fig. **(4),** the de-oxy form is converted to the oxy form, as previously stated in the diphenolase cycle. Now, this oxy form of tyrosinase binds with a molecule of *o*-monophenol to form a complex oxy-T form along with an intermediate metD form of tyrosinase (a stage in the catalytic cycle formed by binding of *o*-diphenol with met form) thus making the cycle comes to an end [4, 22].

6. NATURAL TYROSINASE INHIBITORS

These days, focused observation has been directed at the black market for products such as hydroquinone, corticosteroids, and tretinoin, as well as the associated health problems such as the generation of reactive oxygen species, oxidative damage to membrane lipids and proteins, permanent loss of melanocytes resulting in irreversible loss of inherited skin colour. [24]. These products are manufactured legally in other nations and illegally sold in countries such as India [12].

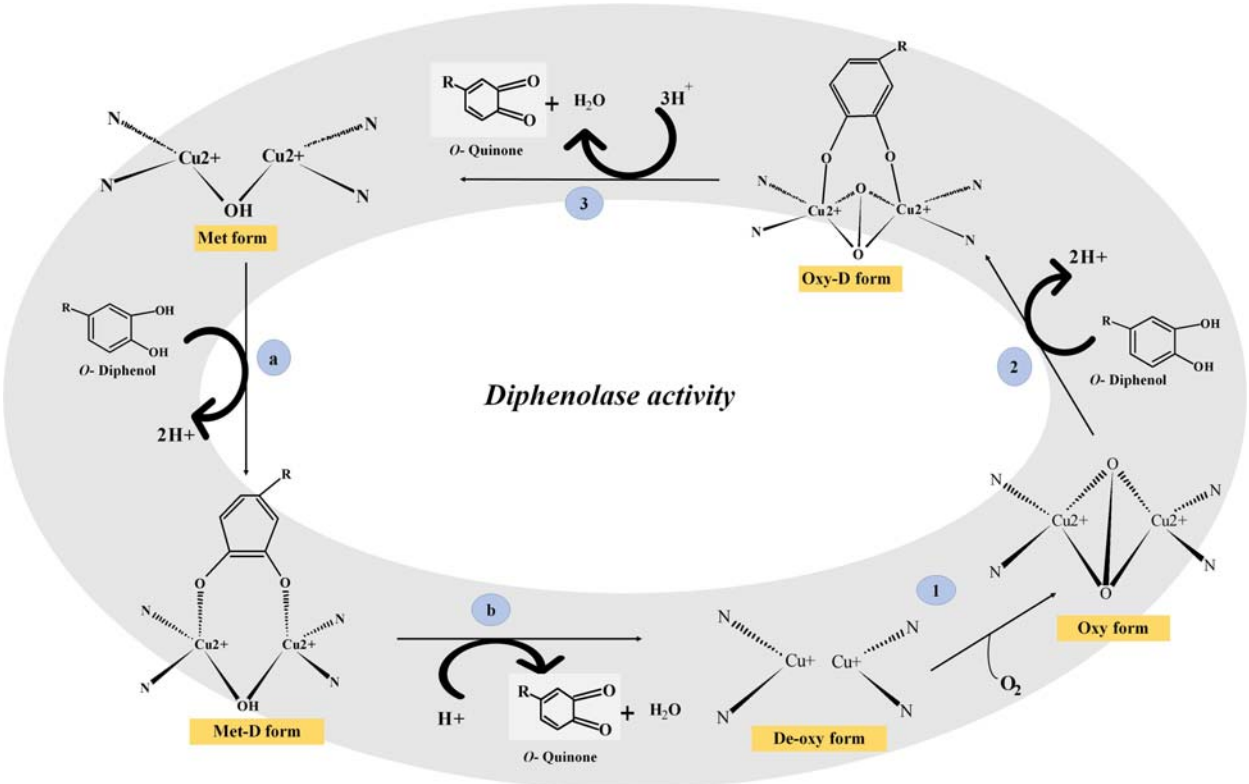


Fig. (3). Catechol oxidation or diphenolase catalytic cycle. A two-step oxidation process, firstly (steps **1-3**), Peroxy-bridge of the active site of Oxy-form is reduced by o-Diphenol yielding the corresponding o-quinone and water molecule. De-oxy form of tyrosinase actively binds to an oxygen molecule to yield Oxy-form of tyrosinase enzyme. Oxy-form further releases an o- quinone and water molecule to produce Met-form; second (steps **a** & **b**) Active site of copper ions of Met-form is reduced by o-Diphenol and giving De-oxy form of tyrosinase enzyme and a molecule of o-quinone. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

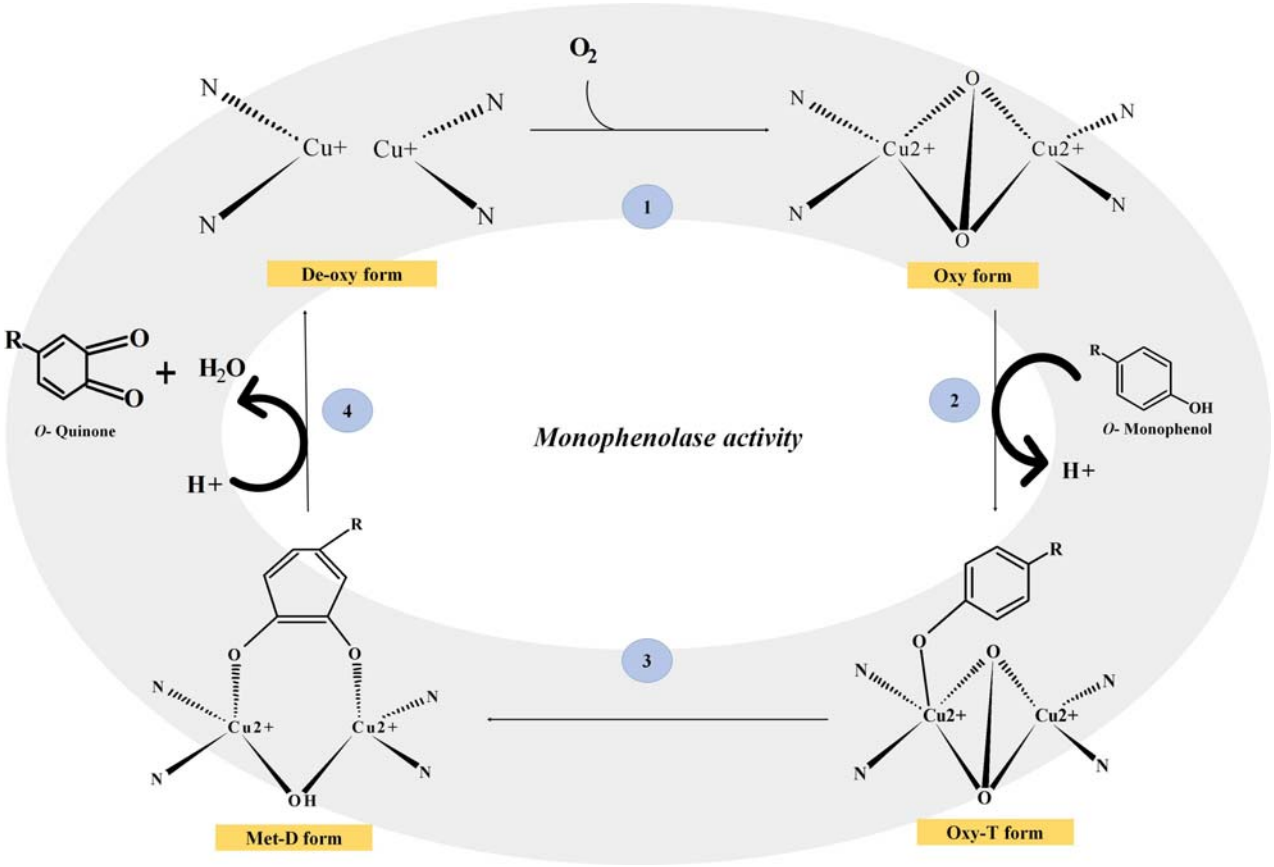


Fig. (4). Cresolase or monophenolase catalytic cycle. De-oxy form of tyrosinase enzyme is transformed into Oxy-form which binds to a molecule of o-Monophenol to give a complex Oxy-T form, and an intermediate met-D form is produced that again forms De-oxy form along with o- quinone and a water molecule (steps **1-4**). (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

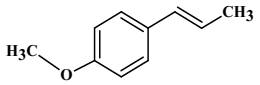
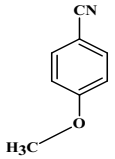
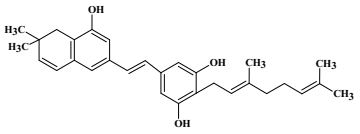
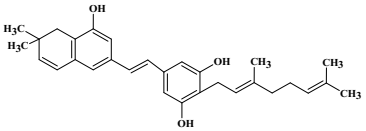
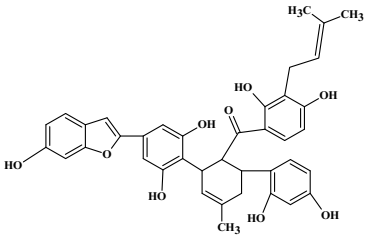
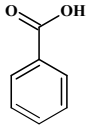
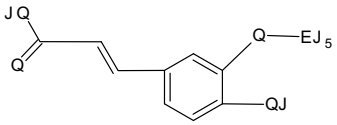
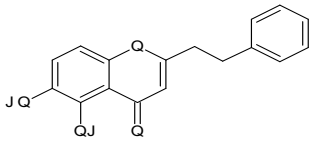
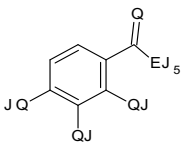
Apart from these studies, the increased public interest and demand for hypo-pigmenting chemicals in natural therapy approaches over the last few years is evident, as they are safe, economical, and effective. Plants, microbes, and fungi have recently garnered attention for their ability to synthesize bioactive that inhibit tyrosinase activity. Additionally, experimental studies have proved strong tyrosinase inhibition by a variety of phytoconstituents such as phenols, flavonoids, and glycosides, as listed in Table **1**, as well as a mechanistic approach to tyrosinase enzyme inhibition is also illustrated in Fig. (**5**). These compounds inhibit the migration of melanosomes conveying eumelanin to keratinocytes, so limiting excessive melanin formation and thereby hyperpigmentation.

7. PHENOLS

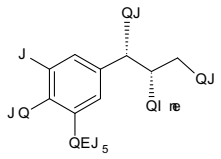
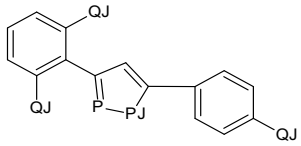
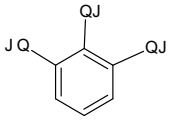
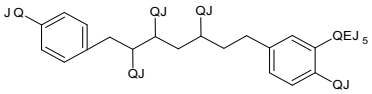
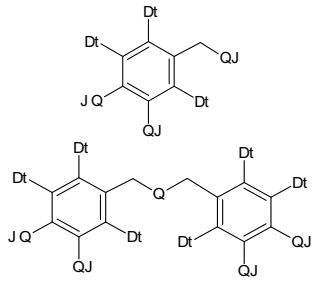
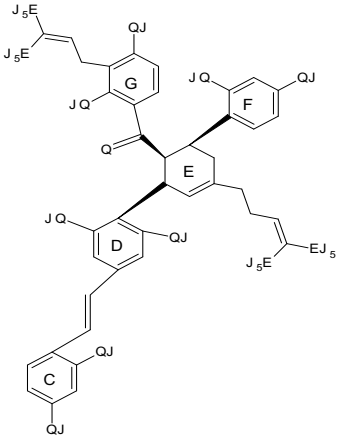
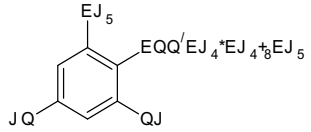
Phenols are organic compounds that contain one or more hydroxyl groups that are chemically linked to an aromatic hydrocarbon group [25]. Numerous recent studies have demonstrated that phenolic compounds such as trans-anethole effectively inhibit the enzyme tyrosinase, hence inhibiting UV-induced melanogenesis in the fruit of *Foeniculum vulgare* (Apiaceae) [26].

Anisnitrile (4-methoxybenzonitrile) obtained from the seeds of *Pimpinella anisum* L. and *Cuminum cyminum* L. inhibits mushroom tyrosinase and *o*-diphenolase, as does apigenin extracted from *Onosma frutescens* Lam (Boraginaceae) [27-29]. Revoltella *et al*. reported that benzoic acid from *Pinus uncinata* Subsp. (Pinaceae) needle (leaves) was a potent inhibitor of the tyrosinase enzyme in HPTLC bioautographic experiment [30]. The primary component of phenolic compounds in pomegranates is punicalagin, an antioxidant and anti-tyrosinase ellagitannin containing 16 dissociable-OH (*Punica granatum* L., Lythraceae) [31]. Rhamnetin from the leaves of *Aristotelia chilensis* (Elaeocarpaceae) inhibited tyrosinase in a mixed manner [32]. Caftaric acid from unripe *Vitis vinifera* L. (Vitaceae) inhibits the monophenolase mushroom tyrosinase [33]. Chalcomoracin from the leaves of *Morus alba* L. (Moraceae) [34], chlorogenic acid from the aerial part of *Valeriana dioscoridis* Sp. (Caprifoliaceae) [35] and quercetin from the leaves and stem bark of *Tibouchina semidecandra* L. (Melastomataceae) [36] tend to inhibit mushroom tyrosinase enzyme. *Laricifolium* Juss. (Clusiaceae) aerial part inhibits mushroom tyrosinase by using spectrophotometric analysis [37]. Caricapapayol is a compound derived in flowers of *Carica papaya* L. (Caricaceae) [38], 6, 3′, 4′-trihydroxy-5, 5′-diisopropyl-2, 2′-dimethylbiphenyl from the aerial part of *Thymus vulgaris* L. (Lamiaceae) [39], agar wood of *Aquilaria crassna* Pierre ex Lecomte (Thymelaeaceae) contains 5, 6-dihydroxy-2-(2-phenylethyl) chromone and 5, 6-dihydroxy-2-(2-phenylethyl) chromone [40], and ellagic acid from the leaves of *Psidium guajava* Linn. (Myrtaceae) have been shown to have good

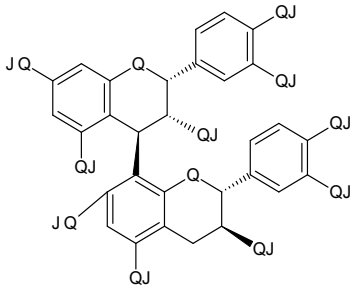
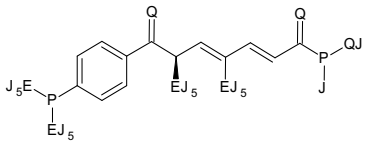
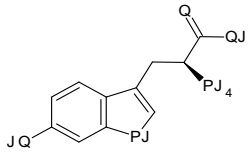
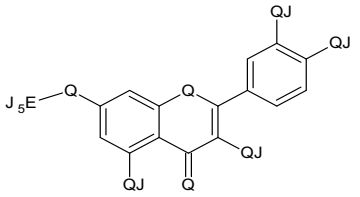
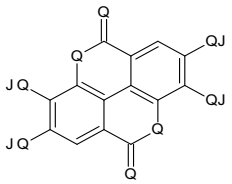
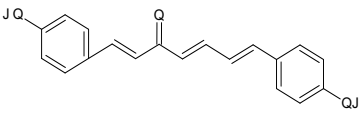
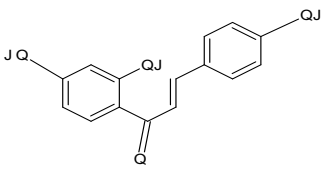
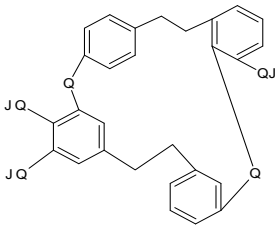
Table 1. Phytoconstituents having potential tyrosinase inhibitory activity.

S. No.	Plant Constituent	Source (Name, Family, Part Used)	Method/Model Used	Tyrosinase inhibition (IC_{50}, Pearson Coefficient, Inhibitory Concentration)	Structure	Refs.
Phenols						
1	Trans-anethole	*Foeniculum vulgare* (Apiaceae) Fruit	UV-induced melanogenesis	8.954 µM		[26]
2	Anisnitrile	*Pimpinella Anisum* L. and *Cuminum cyminum* L. Seeds	Mushroom diphenolase inhibition	111.1 µM		[27]
3	Caricapapayol	*Carica papaya*. L. (Caricaceae) Flowers	Mushroom tyrosinase inhibition	14.3 µM		[38]
4	Caftaric acid	Unripe grape juice	Mushroom monophenolase inhibition	30 µM		[29, 33]
5	Chalcomoracin	*Morus alba* L. (Moraceae) Leaves	Mushroom tyrosinase inhibition	5.61 µM		[34]
6	Benzoic acid	*Pinus uncinata* Subsp. (Pinaceae) Needles (leaves)	HPTLC autographic assay	552 µM		[30]
7	Ferulic acid	Tetragonioides (Pallas) Kuntze	B16F10 cells stimulated with α-melanocyte stimulating hormone	20 µM		[94, 95]
8	5,6-Dihydroxy-2-(2-phenylethyl) chromone	*Aquilaria crassna* Pierre ex Lecomte (Thymelaeaceae) Agar wood	Monophenolase tyrosinase inhibition	172.6 µM		[40]
9	Gallacetophenone	*Rosa canina* L. (Rosaceae) Fruit	Effect on 3D human skin	1000 µM (70% Inhibition)		[42]

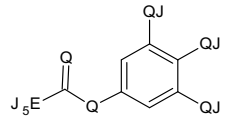
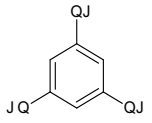
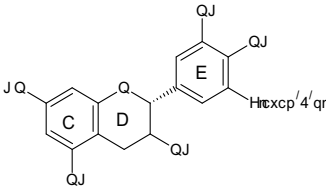
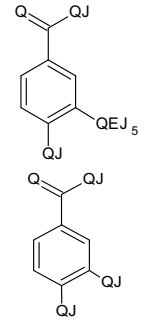
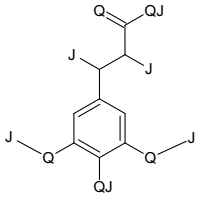
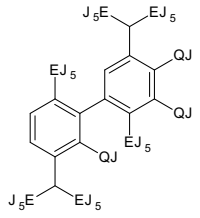
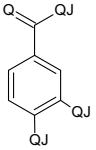
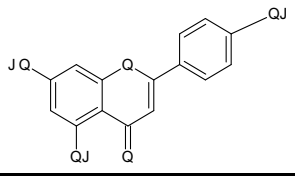
(Table 1) Contd….

S. No.	Plant Constituent	Source (Name, Family, Part Used)	Method/Model Used	Tyrosinase inhibition (IC_{50}, Pearson Coefficient, Inhibitory Concentration)	Structure	Refs.
10	Guaiacyl glycerol 8-O-βD-glucopyranoside	*Piper aduncum* L. (Piperaceae) Leaves	Monophenolase tyrosinase inhibition	41.3 µM		[96]
11	Pyrazole	*Matricaria recutita* L. (Asteraceae) -	Mushroom tyrosinase inhibition	28.20 µM		[97]
12	Pyrogallol	*Piper aduncum* Linn. (Piperaceae) Leaves	Diphenolase mushroom tyrosinase inhibition	772 µM		[96]
13	Rhoiptelol C	*Juglans mandshurica* Maxim. (Juglandaceae) Bark	Phenol oxidase inhibitory effects	1500 µM		[98]
14	2,3,6-tribromo-4,5-dihydroxybenzyl methyl alcohol bis-(2,3,6-tribromo-4,5-dihydroxybenzyl methyl ether)	*Symphyocladial atiuscula* (Harvey) Yamada (Rhodomelaceae) Algae	Mushroom tyrosinase inhibition	10.78 and 2.92 µM		[99]
15	Macrourin E	*Morus macroura* Miq. (Moraceae) Stem	Mushroom tyrosinase inhibition	0.39 µM		[100]
16	n-Octyl orsellinate	*Parmotrema tinctorum* Despr. (Parmeliaceae) Lichen	Mushroom tyrosinase inhibition	500 µM		[101]

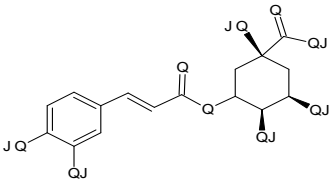
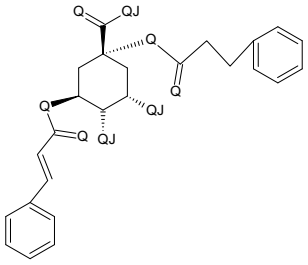
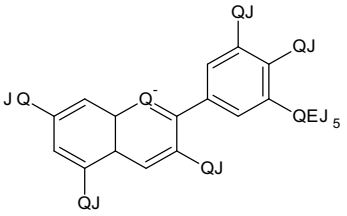
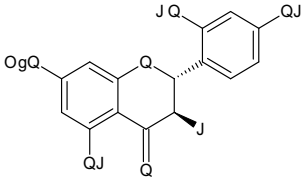
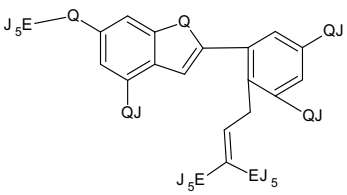
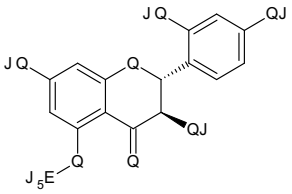
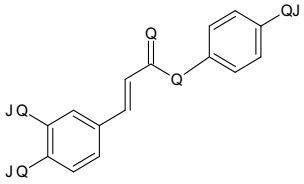
(Table 1) Contd….

S. No.	Plant Constituent	Source (Name, Family, Part Used)	Method/Model Used	Tyrosinase inhibition (IC_{50}, Pearson Coefficient, Inhibitory Concentration)	Structure	Refs.
17	Procyanidine B2	*Nelumbo nucifera* Gaertn. (Nymphaeaceae)	Mushroom tyrosinase inhibitory activity	52.32 µM		[102]
18	Trichostatin A	Fermented broth of strain *Streptomyces* sp. CA-129531	Mushroom tyrosinase inhibition	2.18 µM		[103]
19	6-hydroxy-L-tryptophan	*Lyophyllum decastes* (Lyophyllaceae) Fruits Fungus	Mushroom tyrosinase inhibition	230 µM		[104]
20	Rhamnetin	*Aristotelia chilensis* (Molina, Stuntz) (Elaeocarpaceae) Leaves	Mixed type tyrosinase inhibition	133.3 µg/mL		[32]
21	Ellagic acid	*Psidium guajava* Linn. (guava) (Myrtaceae) Leaves	Mushroom tyrosinase inhibition	93.7 (% inhibition)		[41]
22	1E,4E,6E)-1,7-bis(4-hydroxyphenyl)-1,4,6-heptatrien-3-one	*Zingiber cassumunar* Roxb. (Zingiberaceae)	Mushroom tyrosinase inhibition	22.96 µg/mL		[105]
23	Isoliquiritigenin	*Genista numidica* Spach Fabaceae (Leguminosae) Aerial parts	Mushroom tyrosinase inhibition	90.2 µg/ml		[106]
24	Marchantin A	*Marchantia polymorpha* L. (Primulaceae) Thalli	Mushroom tyrosinase inhibition	11.97, 7.45 and 9.80 µg/mL		[107]

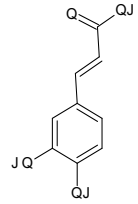
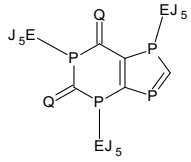
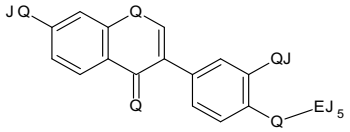
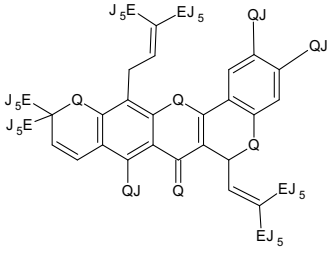
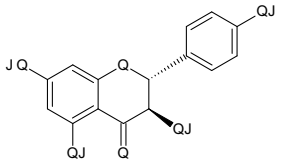
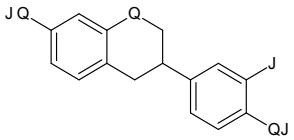
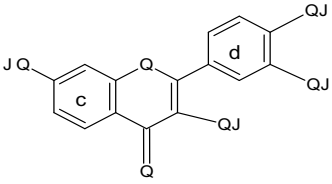
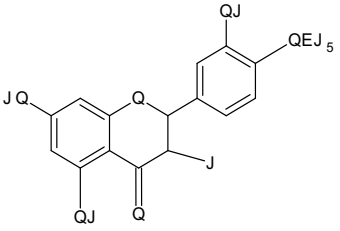
(Table 1) Contd….

S. No.	Plant Constituent	Source (Name, Family, Part Used)	Method/Model Used	Tyrosinase inhibition (IC_{50}, Pearson Coefficient, Inhibitory Concentration)	Structure	Refs.
25	Methyl gallate	Gallarhois	Diphenolase mushroom tyrosinase inhibition	40 µg/mL		[108]
26	Phloroglucinol	Pistachio (*Pistacia vera* L.) (Anacardiaceae) Nuts	Mushroom tyrosinase inhibition	43.6% inhibition		[109]
27	Proanthocyanidins	*Clausenal ansium* (Lour.) (Rutaceae) Fruit carp	Monophenolase and diphenolase tyrosinase inhibition	23.6 and 7.0 µg/ mL		[68]
28	Vanillic acid and protocatechuic acid	*Oryza sativa* L. (Ricebery rice) (Oryzoideae) Rice	B16 cells diphenolase mushroom tyrosinase inhibition	60.08 mg/mL		[110]
29	Trans-sinapic Acid	Unspecified source	diphenolase(L-dopa) mushroom tyrosinase inhibition	88.73µg/ml 10.36 (% inhibition)		[111]
30	6,3′,4′-trihydroxy-5,5′-diisopropyl-2,2′-dimethylbiphenyl (compound 1)	*Thymus vulgaris* L. (Lamiaceae) Aerial part	Mushroom tyrosinase inhibition	35 (% inhibition)		[39]
31	Syringic acid	*Micromeria myrtifolia* Boiss. & Hohen. (Lamiaceae) Aerial part	Mushroom tyrosinase inhibition	Pearson correlation coefficient= 0.432		[112]
32	Apigenin	*Onosma frutescens* Lam. (Boraginaceae) Aerial part	Mushroom tyrosinase inhibition	Pearson correlation coefficient=0.220		[28]

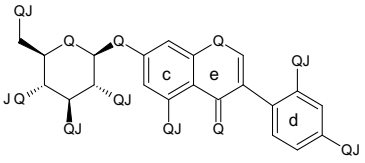
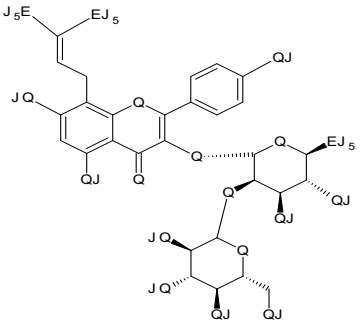
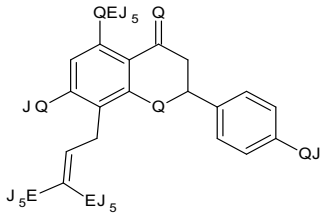
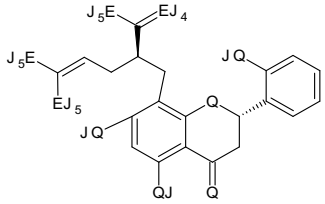
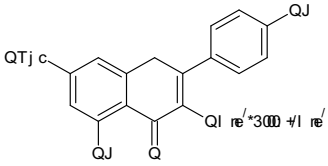
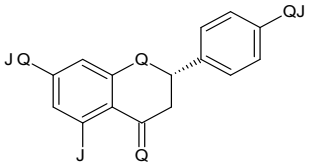
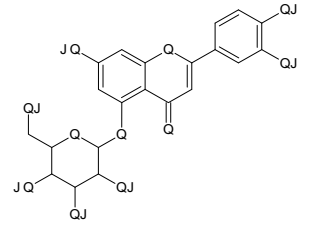
(Table 1) Contd….

S. No.	Plant Constituent	Source (Name, Family, Part Used)	Method/Model Used	Tyrosinase inhibition (IC_{50}, Pearson Coefficient, Inhibitory Concentration)	Structure	Refs.
33	Chlorogenic acid	*Valeriana dioscoridis* Sp. (Caprifoliaceae) Aerial part	Mushroom tyrosinase inhibition	Pearson correlation coefficient=0.804		[35]
34	1, 5-Dicaffeoylquinic acid (1,5-DCQA)	*Inula bifrons* L. (Asteraceae) flowers	Mushroom diphenolase inhibition, modified 96-well microplate method	Pearson correlation coefficient= -0.7047		[113]
			Flavonoids			
1	Petunidin	*Lycium ruthenicum* Murr. (Solanaceae) Dried fruit	Monophenolase (competitive inhibition) Diphenolase (anticompetitive)	1.483 mg/mL 42.16 (% inhibition)		[114]
2	Artocarpanone	*Artocarpus heterophyllous* (AH) (Moraceae) Wood	Mushroom tyrosinase inhibition	2.0 µM 44.56 µg/mL		[55, 56]
3	Artopithecin B	*Artocarpus pithecogallus* C. Y. WU (Moraceae) Dried twigs	Diphenolase mushroom tyrosinase inhibition	37.09 µM		[115]
4	Broussoflavonol J	*Broussoneti apapyrifera* (paper mulberry) (Moraceae) Root bark	Monophenolase mushroom tyrosinase inhibition	9.29 µM		[54]
5	p-hydroxyphenyl caffeate	*Sphagneticola trilobata* (Wedelia) (Asteraceae) Whole plant	*In vitro* tyrosinase inhibitory activity	2.00 µM		[116]

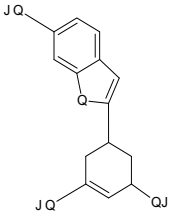
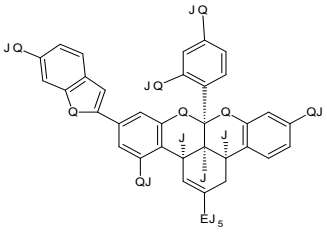
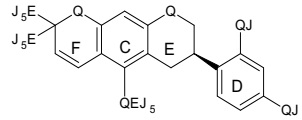
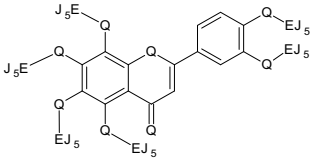
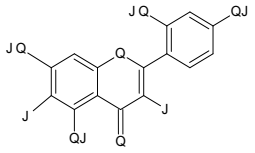
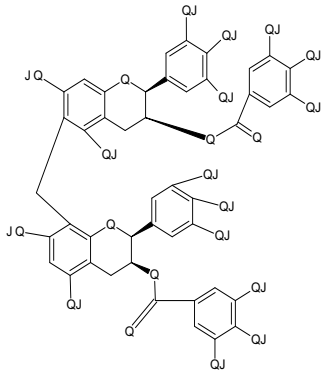
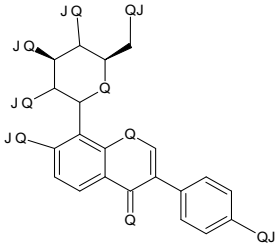
(Table 1) Contd….

S. No.	Plant Constituent	Source (Name, Family, Part Used)	Method/Model Used	Tyrosinase inhibition (IC_{50}, Pearson Coefficient, Inhibitory Concentration)	Structure	Refs.
6	Caffeic acid	*Anthemis chia* L. (Asteraceae) flowers	Mushroom tyrosinase inhibition	Pearson correlation coefficient =0.960		[117]
7	Caffiene	*Camellia* (Theaceae) Pollens	Non-competitive tyrosinase inhibition	18.5 µg/mL		[118]
8	Calycosin	*Pueraria lobata* (Kudzu) (Leguminosae) Roots	Monophenolase and diphenolase tyrosinase inhibition	1.45 and 7.02 µM		[119]
9	Cycloheterophyllin	*Artocarpus lowii* King (Moraceae) Heartwood	Mushroom tyrosinase inhibition	104.6 µM		[120]
10	(+)-Dihydrokaempferol	*Manilkara zapota* L. (Sapodilla plum) (Sapotaceae) Dried bark	Monophenolase Diphenolase	45.35 µM 55.41 µM		[121]
11	Equol, an intestinal metabolite of daidzein	*Glycine max* L. (Soy)	*In vitro* tyrosinase inhibition	100 µM		[122]
12	Fisetin	*Vitis vinifera*. L. (Vitaceae) Fruits	In-vitro Mouse B16-F10 melanoma cells mushroom inhibition	200 µM and 39.9 (% inhibition)		[123]
13	Hesperidin	*Astragalus gymnolobus*, and *A. onobrychis* (Fabaceae) Aerial part	Mushroom tyrosinase inhibition	Pearson correlation coefficient =0.987		[117]

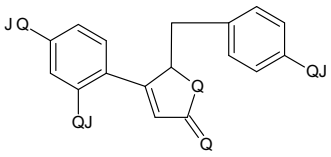
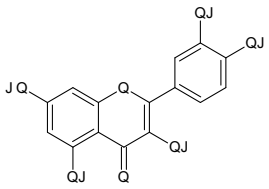
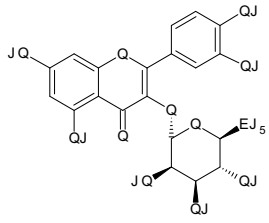
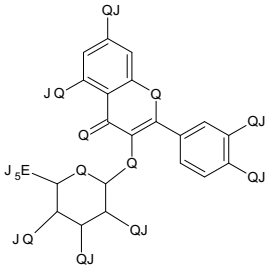
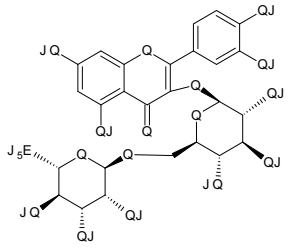
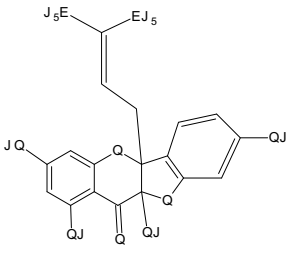
(Table 1) Contd….

S. No.	Plant Constituent	Source (Name, Family, Part Used)	Method/Model Used	Tyrosinase inhibition (IC_{50}, Pearson Coefficient, Inhibitory Concentration)	Structure	Refs.
14	7-(β-Glucopyranosyl)-2' -hydroxygenistein	*Apios americana* (American groundnut) (Fabaceae) Edible tuber	Diphenolase mushroom tyrosinase inhibition	729.3 μM		[124]
15	Ikarisoside B	*Epimedium koreanum* Nakai (Berberidaceae) Dried aerial part	Tyrosinase inhibitory activity	8.7 μM		[125]
16	Isoxanthohumol	*Humulus lupulus* L. (Cannabaceae)	Monophenolase and diphenolase mushroom tyrosinase inhibition	58.4 μM 117.4 μM		[126]
17	kushenol A	*Sophora flavescens* Kushen (Fabaceae) Roots	Invitro tyrosinase inhibition	μM (non-competitive) (>10 μM)		[127]
18	3-O-β-D-Glucosyl-(1→6)-β-D-glucosyl-kaempferol	*Sauropus androgynus* L. Merr. (Euphorbiaceae) Leaves	Mushroom tyrosinase inhibition	94.7 (% melanin content)		[128]
19	Liquiritigenin	*Pueraria lobata* (Wild) Ohwi (Leguminosae) Stem	Mushroom tyrosinase inhibition	25.24 μM		[129]
20	luteolin 5-O-β-d-glucopyranoside	*Cirsium japonicum* var. maackii (Maxim.) Matsum (Compositae) Whole plant	Mushroom tyrosinase inhibition (l-tyrosine) (l-3,4-dihydroxyphenyl-alanine)	2.95 μM 8.22 μM		[130]

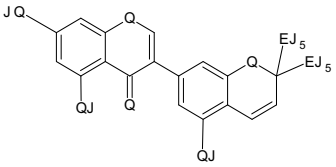
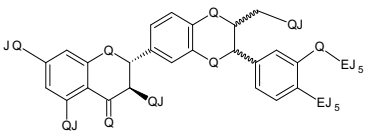
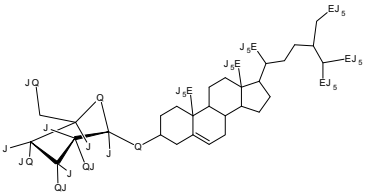
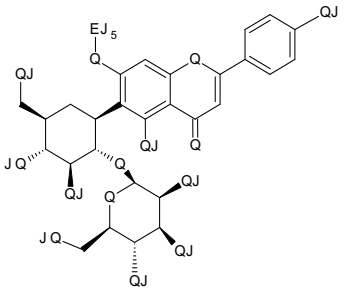
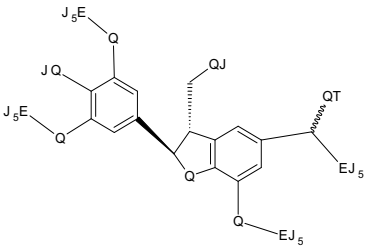
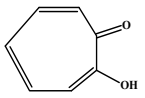
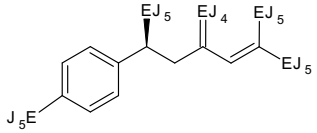
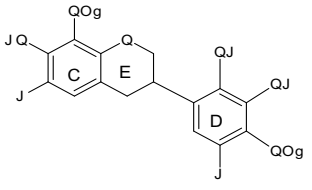
(Table 1) Contd….

S. No.	Plant Constituent	Source (Name, Family, Part Used)	Method/Model Used	Tyrosinase inhibition (IC_{50}, Pearson Coefficient, Inhibitory Concentration)	Structure	Refs.
21	Moracin M	*Morus alba* L. (Moraceae) Twigs	Mushroom tyrosinase inhibition	8.00 µM		[131]
22	Mulberrofuran G	*Morus alba* L. (Mulberry species) (Moraceae) Root bark	Monophenolase mushroom tyrosinase inhibition	6.35 µM		[132]
23	Neorauflavane	*Campylotropis hirtella* (Franch.) Schindl. Roots	Monophenolase Mushroom tyrosinase inhibition	0.03 µM		[47]
24	Nobiletin	*Citrus reticula* L. var. (Rutaceae) Peel	Diphenolase mushroom tyrosinase inhibition	131.92 µM		[133]
25	Norartocarpetin	*Artocarpus rigida* Linn. (Moraceae) Stem	Mushroom tyrosinase inhibition	0.023 µM		[134]
26	Oolonghomobisflavan B	*Camellia sinensis* (L.) Kuntze (Theaceae) Leaves	Cellular tyrosinase and melanogenesis inhibition	34.0 µM and 43.1 µM		[135]
27	Puerarin	*Puerariae lobatae* Radix (Fabaceae) Roots	Monophenolase mushroom tyrosinase inhibition	0.537 mg/mL		[136]

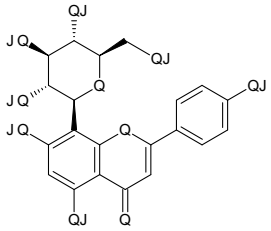
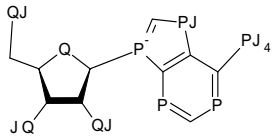
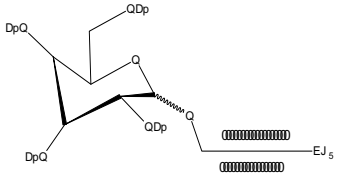
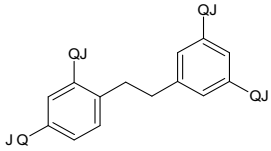
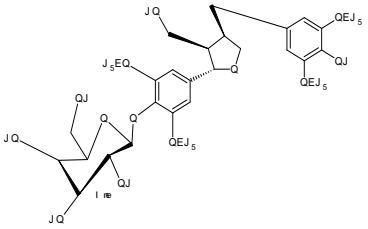
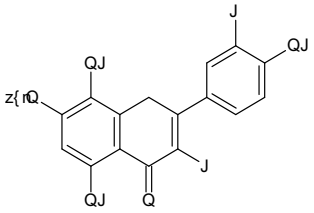
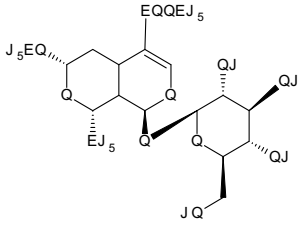
(Table 1) Contd….

S. No.	Plant Constituent	Source (Name, Family, Part Used)	Method/Model Used	Tyrosinase inhibition (IC_{50}, Pearson Coefficient, Inhibitory Concentration)	Structure	Refs.
28	Puerol A	*Amorpha fruticosa* (Leguminosae) Roots	Monophenolase and diphenolase mushroom tyrosinase inhibition *In vitro* B16 melanoma cell inhibition	2.2 µM 3.8 µM 11.4 µM		[137]
29	Quercetin	*Punica granatum* L. (Punicaceae) Rind *Olea europaea* L. (Rubiaceae) Olive *Hypericum laricifolium* Juss	Mushroom tyrosinase inhibition	94.2 (% inhibition) 10.73 µM 14.29 ± 0.3 µ M		[37, 138, 139]
30	Quercitrin	*Gynotroches axillaris* Blume (Rhizophoraceae) Leaves	Mushroom tyrosinase inhibition	59 (% inhibition)		[140]
31	Quercetrine	Unspecified source	Diphenolase (L-dopa) mushroom tyrosinase inhibition	12.23 µg/ml 2.42 (% inhibition)		[111]
32	Rutin	*Eucalyptus camaldulensis* Dehnh (Myrtaceae) Stem	Diphenolase mushroom tyrosinase inhibition	500 µg/mL 65.16 (% inhibition)		[141]
33	Nigragenon E (Sanggenon-type)	*Morus nigra* L. (Moraceae) Twigs	Mushroom tyrosinase inhibition	27.14 µM		[142]

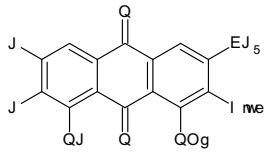
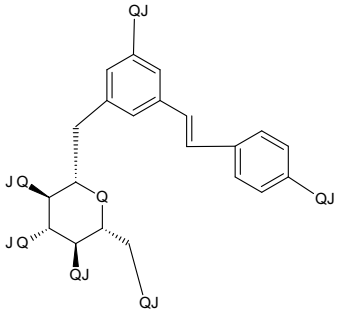
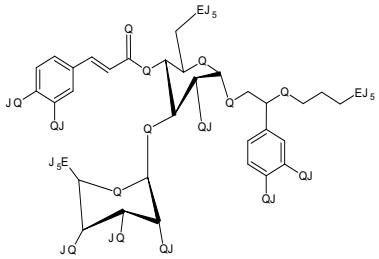
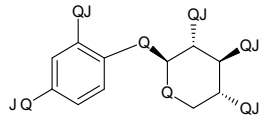
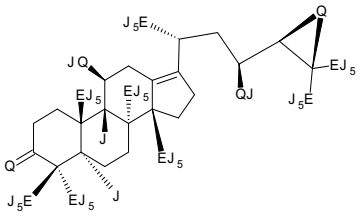
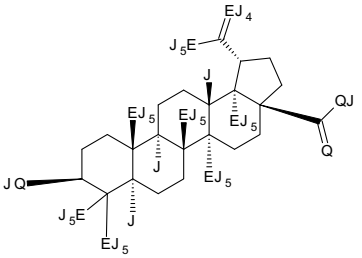
(Table 1) Contd….

S. No.	Plant Constituent	Source (Name, Family, Part Used)	Method/Model Used	Tyrosinase inhibition (IC_{50}, Pearson Coefficient, Inhibitory Concentration)	Structure	Refs.
34	Semilicoisoflavone B	*Glycyrrhiza inflata* Batalin (Leguminosae) Roots and rhizome	Mushroom tyrosinase inhibition	0.25 µM		[143]
35	Silybin (flavonolignans)	*Silybum marianum* (Milk thistle) (Asteraceae) Dried seeds	Monophenolase and diphenolase tyrosinase inhibition (mixed inhibition type)	7.6 µM 44.9 µM		[144]
36	Glycoside of β-sitosterol	*Rhynchospora corymbosa* (Cyperaceae) Whole plant	Diphenolase *in vitro* tyrosinase inhibition assay	43.28 mg/mL		[145]
37	Spinosin	*Ziziphus jujuba* (red date) (Rhamnaceae) Seeds	Mushroom tyrosinase inhibition	47 µM		[146]
38	Tamariscinol U	*Selaginella tamariscina* (Beauv.) Spring (Selaginellaceae) Complete herb	Diphenolase mushroom tyrosinase inhibition	5.75 µM		[147]
39	Tropolone	*Pseudomonas aeruginosa* a secret siderophore pyoverdine	Monophenolase mushroom tyrosinase inhibition	1.2 µM		[148]
40	Turmerone	*Curcuma longa* L. (Zingiberaceae) Rhizome EO.	Diphenolase mushroom tyrosinase inhibition	Inhibition constant = (19.35)		[149]
41	Pterocarpan (3RS)-3-hydroxy-8-methoxy vestitol	*Dalbergia parviflora* Fabaceae Heartwood	Mushroom tyrosinase and murine tyrosinase inhibition melanogenesis in B16-F10 melanoma cells	16.7 µM 59 (% inhibition)		[48]

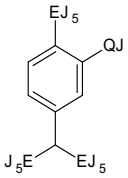
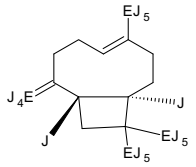
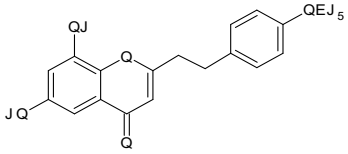
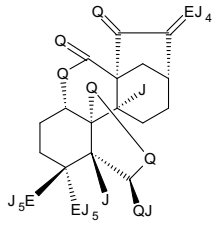
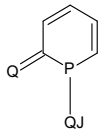
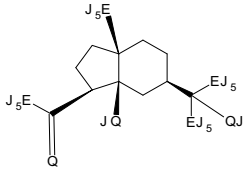
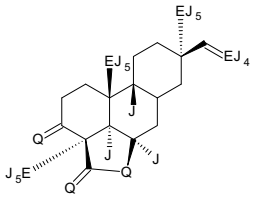
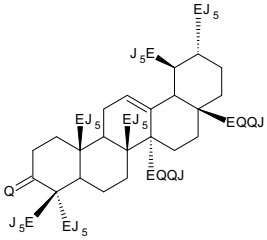
(Table 1) Contd….

S. No.	Plant Constituent	Source (Name, Family, Part Used)	Method/Model Used	Tyrosinase inhibition (IC_{50}, Pearson Coefficient, Inhibitory Concentration)	Structure	Refs.
42	Vitexin	*Otholobium pubescens* (Poir.) J.W. Grimes (Fabaceae)	Mushroom tyrosinase inhibition	350 µM		[150]
			Glycosides			
1	Adenosine	*Angelica dahurica* (Fisch. ex Hoffm.) Benth. et Hook (Apiaceae) Roots	Monophenolase mushroom tyrosinase	11.79 (% inhibition)		[151]
2	Alkynyl O-glycoside	Sugar	*In vitro* on mushroom tyrosinase with L-tyrosine as substrate	54.0 µM		[152]
3	Dihydrooxyresveratrol	*Morus alba* L. (Moraceae) Wood	Mushroom tyrosinase inhibition	0.3 µM		[89]
4	Glucopyranoside	*Opilia amentacea* Var. (Opiliaceae) Leaves	*In vitro* mushroom tyrosinase inhibition	42.1 µM		[153]
5	Hypolaetin-7-O-β-D-glucoside	*Juniperus chinensis* L. (Cupressaceae) Fruit	Mushroom tyrosinase inhibition	50 µM		[154]
6	(7a)-7-O-methylmorroniside	*Vinca major L.* (Apocynaceae) Leaves	Diphenolase mushroom tyrosinase inhibition	64.51µM		[155]

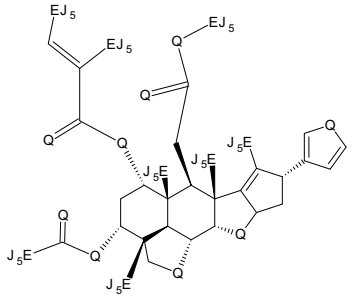
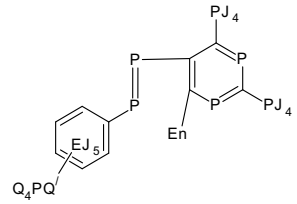
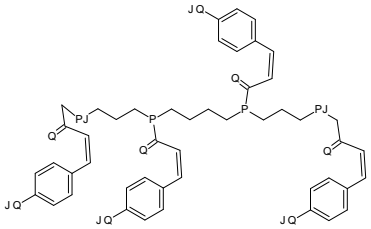
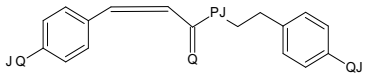
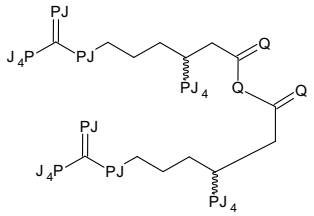
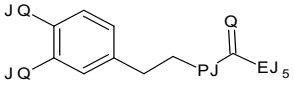
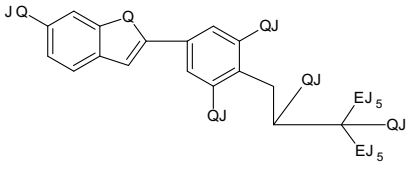
(Table 1) Contd….

S. No.	Plant Constituent	Source (Name, Family, Part Used)	Method/Model Used	Tyrosinase inhibition (IC_{50}, Pearson Coefficient, Inhibitory Concentration)	Structure	Refs.
7	Obtusifolin-2-Oglucoside	Cassia tora L., ''Foetid Cassia' (Leguminosae) Seeds	*In-vitro* tyrosinase inhibition	99.4 µM		[156]
8	Polydatin	*Quercus coccifera* L. Bark	Mushroom tyrosinase inhibition	4.05 µg/mL		[157]
9	Spicaoside	*Chloranthus spicatus* (Thunb.) Makino (Chloranthaceae) Leaves	Mushroom tyrosinase inhibition	15.4 µM		[158]
10	Xyloside	*Isotachis japonica* (Hepaticae) and *Protea neriifolia* (Proteaceae)	Diphenolase mushroom tyrosinase	852 µM		[159]
Terpenoids						
1	Alisol B	*Alisma orientale* Juz. (Alismataceae) Dried rhizome	Effect on mushroom tyrosinase activity, although reduced glutathione, a compound that inhibits tyrosinase activity, significantly inhibited	1 µM and 10 µM		[160]
2	Betulinic acid	*Dillenia indica* L. (Dilleniaceae) Fruit	Monophenolase Diphenolase tyrosinase inhibition	25.66 µM 13.93 µM		[76]

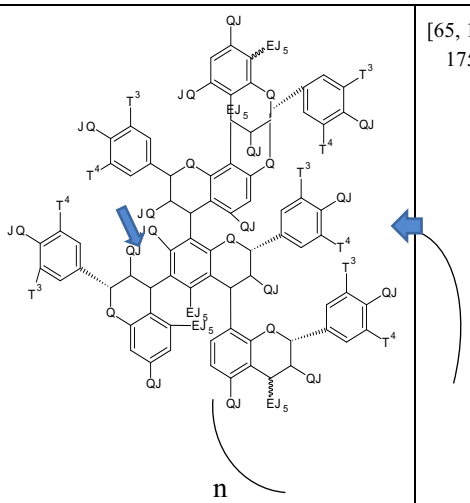
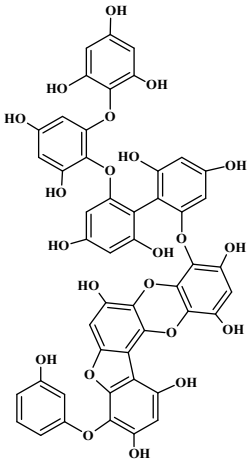
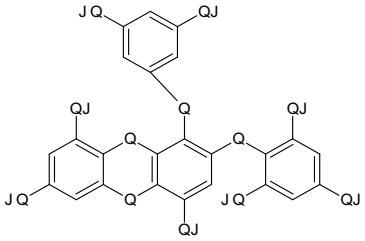
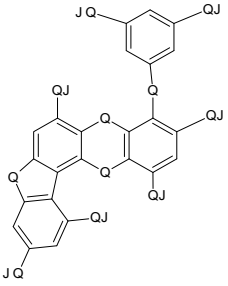
(Table 1) Contd….

S. No.	Plant Constituent	Source (Name, Family, Part Used)	Method/Model Used	Tyrosinase inhibition (IC_{50}, Pearson Coefficient, Inhibitory Concentration)	Structure	Refs.
3	Carvacrol	*Origanum ehrenbergii* (OE) (Lamiaceae) Stem and leaves	Diphenolase mushroom tyrosinase inhibition	45 µg/ml 30 (% inhibition)		[161]
4	β-caryophyllene	*Sideritis albiflora*, ballıbabagiller (Lamiaceae) Oil	Mushroom tyrosinase inhibition	15.2 (% inhibition)		[162]
5	6,8-dihydroxy-2- 2-(4-methoxyphenyl) ethyl chromone	Aquilaria plant (Thymelaeaceae) Agarwood	Mushroom tyrosinase inhibition	51.5 µM		[163]
6	Isodocarpin	*Isodont richocarpus* (Labiatae) Aerial part	Inhibited the expression of tyrosinase, tyrosine-related protein (TRP-1, and TRP-2) mRNA (mechanism of melanogenesis inhibition)	0.19 µM		[104]
7	Hydroxypyridinone (HPO)	Potato	monophenolase activity of mushroom tyrosinase	1.33 µM		[164]
8	5 β, 11 - dihydroxy - iphionan - 4 –one	*Eucalyptus globulus* Labill (Myrtaceae) Leaves	Diphenolase mushroom tyrosinase	14.17 µM		[165]
9	Momilactone A	*Oryza sativa* L. (Poaceae) Roots	Monophenolase tyrosinase inhibition	2.0 mg/mL 37.6 (% Inhibition)		[141]
10	Quafrinoic acid	*Nauclea pobeguinii* (Pellegr.) Merr. (Rubiaceae) Stem bark	Mushroom tyrosinase inhibition	39.4 µg/mL		[166]

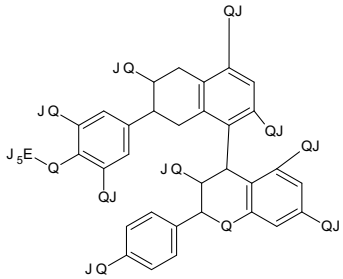
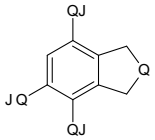
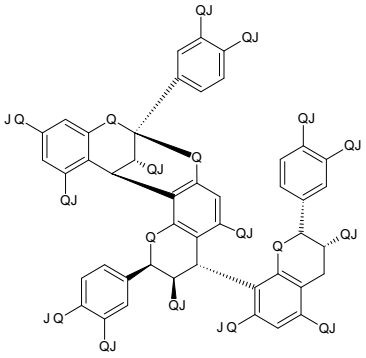
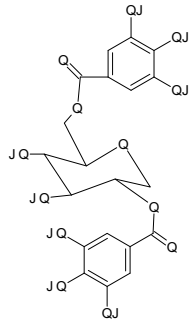
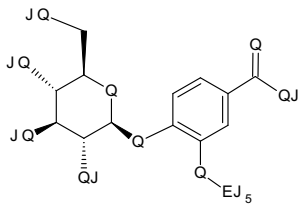
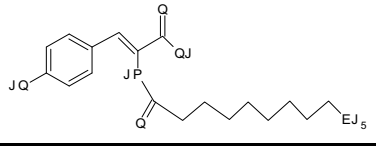
(Table 1) Contd….

S. No.	Plant Constituent	Source (Name, Family, Part Used)	Method/Model Used	Tyrosinase inhibition (IC_{50}, Pearson Coefficient, Inhibitory Concentration)	Structure	Refs.
11	Salannin	Root, bark and seed	Inhibiting expression of MITF, tyrosinase, TRP-1, and TRP-2, α-MSH-stimulated B16 melanoma cells, western blotting	44.86 µM		[167]
			Polyamines			
1	(6-chloro-5-((2-nitrophenyl) diazenyl) pyrimidine-2,4-diamine)	-	Mushroom tyrosinase inhibition	24.68 µM		[168]
2	Mogoline A	*Quercus mongolica* Bee pollen	Mushroom tyrosinase inhibition	85.8 µM		[169]
3	Cis n-coumaroyl tyramine	*Humulus japonicas* Siebold & Zucc. (Cannabaceae) Aerial part	Mushroom tyrosinase inhibition	36.4 µM		[170]
4	(–)-β-homoarginine anhydride	*Trichosanthes truncate* L. (Cucurbitaceae) Roots	Mushroom tyrosinase inhibition	106.9 µM		[171]
5	n-acetyl dopamine	*Protaetia brevitarsis* (Kolbe) Larvae	Mushroom tyrosinase inhibition	44.8 µM		[172]
6	Moracin VN	*Artocarpus heterophyllus* Lam. (Moraceae) Wood	Diphenolase tyrosinase inhibition	0.82 µM		[173]

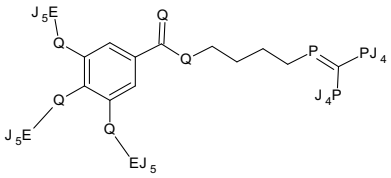
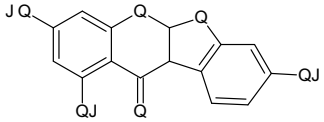
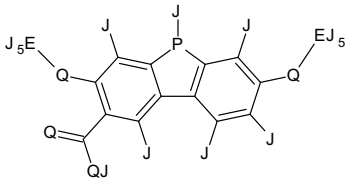
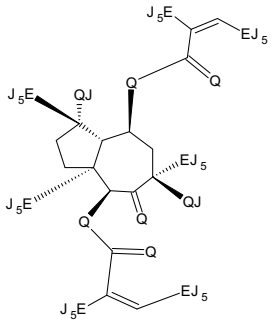
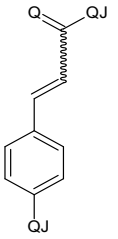
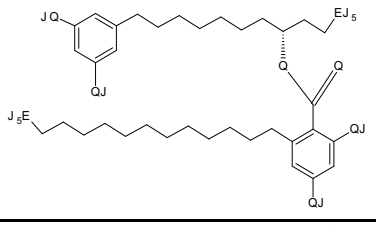
(Table 1) Contd….

S. No.	Plant Constituent	Source (Name, Family, Part Used)	Method/Model Used	Tyrosinase inhibition (IC_{50}, Pearson Coefficient, Inhibitory Concentration)	Structure	Refs.
			Tannins			
1	Condensed tannins	*Acanthus ilicifolius* Linn (Acanthaceae) Leaves *Vigna angularis* (adzuki bean) Seeds *Ficus virens* L. (Moraceae) leaves, fruit and stem bark	Diphenolase mushroom tyrosinase inhibition Monophenolase and Diphenolase tyrosinase inhibition	19.7 µg/mL 130.0 and 35.1 µg/ mL 99-131 mg/mL		[65, 174, 175]
2	974-A	*Ecklonia stolonifera* Okamura (Laminariaceae)	Monophenolase and diphenolase inhibition	1.57 and 3.56 µM		[176]
3	2-phloroeckol	*Ecklonia cava* (Laminariaceae)	Mushroom tyrosinase inhibition	7.0 µM		[177]
4	Fucofuroeckol-A	*Eisenia bicyclis* (Kjellman) Setchell (Laminariaceae) Algae	IBMX-induced melanin formation in B16-F10 melanoma cells	12.5-100 µM		[178]

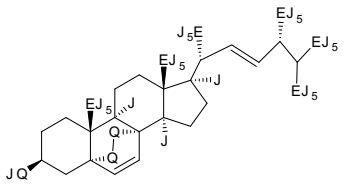
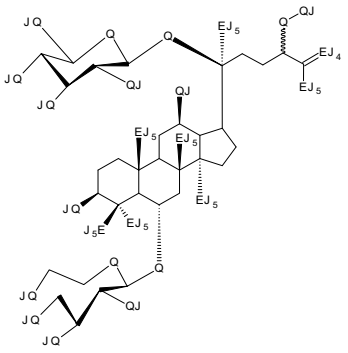
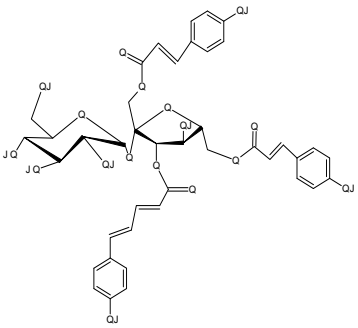
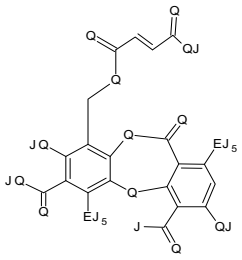
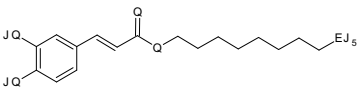
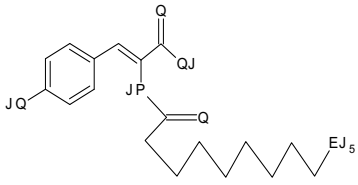
(Table 1) Contd….

S. No.	Plant Constituent	Source (Name, Family, Part Used)	Method/Model Used	Tyrosinase inhibition (IC_{50}, Pearson Coefficient, Inhibitory Concentration)	Structure	Refs.
5	Procyanidins ((Epi)catechin, (epi)gallocatechin, (epi)catechin gallate, and (epi)gallocatechin gallate)	*Leucaena leucocephala*. (Lam.) De Wit. (Fabaceae) Leaf and Fruit	Monophenolase diphenolase tyrosinase inhibition	73.5 µg/mL (leaf) and 27.2 µg/mL (fruit) 27.2 µg/mL (leaf) and 16.1 µg/mL(fruit)		[179]
6	1,3-dihydroisobenzofuran-4,5,7-Triol	*Neolentinus lepideus* (Fr.) Redhead &Ginns (Gloeophyllaceae) Fruiting body	Mushroom tyrosinase inhibition Suppressed melanin accumulation stimulated by α-MSH in the murine melanoma B16 cells	173 µg/mL 15 µg/mL		[180]
7	Aesculitannin B	*Periploca forrestii* Schltr. (Apocynaceae) Stem	α-MSH stimulated melanogenesis *via* detecting the expressions of MITF and tyrosinase on B16-F10 cells by western blot analysis	25 µM 54.6 (% inhibition)		[181]
8	Ginnalin A	*Acer rubrum* L. Red maple	Murine melanoma B16-F10 cells	2500 µM 79.1 (% inhibition)		[182]
9	Vanillic acid-4-O-β-d-glucopyranoside	*Cotula anthemoides* L. (Asteraceae) Aerial part	Mushroom tyrosinase by spectrophotometric methodology	85 µM		[183]
10	Thalassotalic acid A	Marine Bacterium Thalassotalea sp.	*In vitro* inhibition of the enzyme tyrosinase	130 µM		[184]

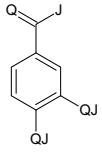
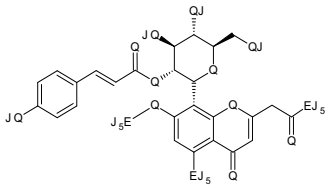
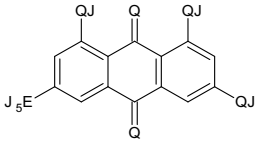
(Table 1) Contd….

S. No.	Plant Constituent	Source (Name, Family, Part Used)	Method/Model Used	Tyrosinase inhibition (IC_{50}, Pearson Coefficient, Inhibitory Concentration)	Structure	Refs.
Alkaloids						
1	10□methoxy□leonurine	*Leonurus japonicas* L. (Labiatae)	Competitive monophenolase tyrosinase inhibitory activity	7.4 µM		[185]
2	Lupinalbin A	*Apios americana* (A. americana) (Leguminosae) Dried tubers	Mushroom tyrosinase inhibitory	10.3 µM		[186]
Coumarins						
1	Clausine K	*Clausena indica* (Dalz) Oliv. (Rutaceae) Fruit	Mushroom tyrosinase inhibition	179.5 µg/ml		[187]
2	Laserpitin	*Angelica keiskei* (Apiaceae or Umbelliferae) Roots	Monophenolase mushroom tyrosinase inhibitory	100 µM		[188]
3	p-coumaric acid	*Lepechinia meyenii* (Walp.) Epling (Lamiaceae)	Monophenolase Diphenolase tyrosinase inhibition	0.30 µM 0.62 µM		[189]
Polysaccharides						
1	Xylorhamnoarabinogalactan I pectic polysaccharide- BAPP1	*Aegle marmelos* L. (Rutaceae) Beal fruit	Mushroom tyrosinase inhibition	28.0 µg/mL	-	[190]
2	Integracin E	*Swintonia floribunda* (Anacardiaceae) Stem bark	Mushroom tyrosinase inhibition	48.2 µM		[191]

(Table 1) Contd….

S.No.	Plant constituent	Source (Name, Family, Part used)	Method/model used	Tyrosinase inhibition (IC50, Pearson coefficient, Inhibitory concentration)	Structure	Refs.
			Steroids			
1	Ergosterol peroxide	*Fagopyrum esculentum* Moench (Polygonaceae) Bee pollen	Mushroom tyrosinase inhibition	202.37 µg/mL		[192]
2	Floral ginsenoside A (FGA)	*Panax ginseng* (C. A. Meyer) (Araliaceae) Berry	Zebrafish model, inhibited melanin biosynthesis in melan-a cells	160 µM 23.9 (% inhibition)		[193]
			Esters			
1	Hydropiperoside	*Persicaria orientalis* L. (Polygonaceae) Air dried roots	Monophenolase and Diphenolase tyrosinase inhibition	50 µM >59 (% inhibition)		[194]
2	Fumarprotocetraric acid	*Cladonia verticillaris* (Raddi) Fr. Lichens	Mushroom tyrosinase inhibition	600 µM 39.8 (% inhibition)		[195]
3	Caffeic acid N-nonyl ester	*Canarium album* L. Olive	Mushroom tyrosinase inhibition	37.5 µM		[196]
			Aldehydes			
1	Thalassotalic acids A	Marine bacterium	Mushroom tyrosinase inhibition	65 µM		[197]

(Table 1) Contd….

S.No.	Plant constituent	Source (Name, Family, Part used)	Method/model used	Tyrosinase inhibition (IC50, Pearson coefficient, Inhibitory concentration)	Structure	Refs.
2	Protocatechuic aldehyde	*Salvia emiltiorrhiza* Radix et Root or rhizome and *Carthamus tinctorius* L. Flowers	Mushroom tyrosinase inhibition	455 µM		[198]
Resins						
1	7-Omethylaloeresin A	*Aloe vera* L. (Xanthorrhoeaceae) Leaf gel	Mushroom tyrosinase inhibition	9.8 µM		[172]
Anthraquinones						
1	Emodin	*Rheum palmatum* L., *R. offcinale* Baill., *R. tanguticum* Maxim. Ex Balf. (Polygonaceae) Rhizome and roots	Mushroom tyrosinase inhibition using l-DOPA (diphenolase)	29.03 µM		[199]

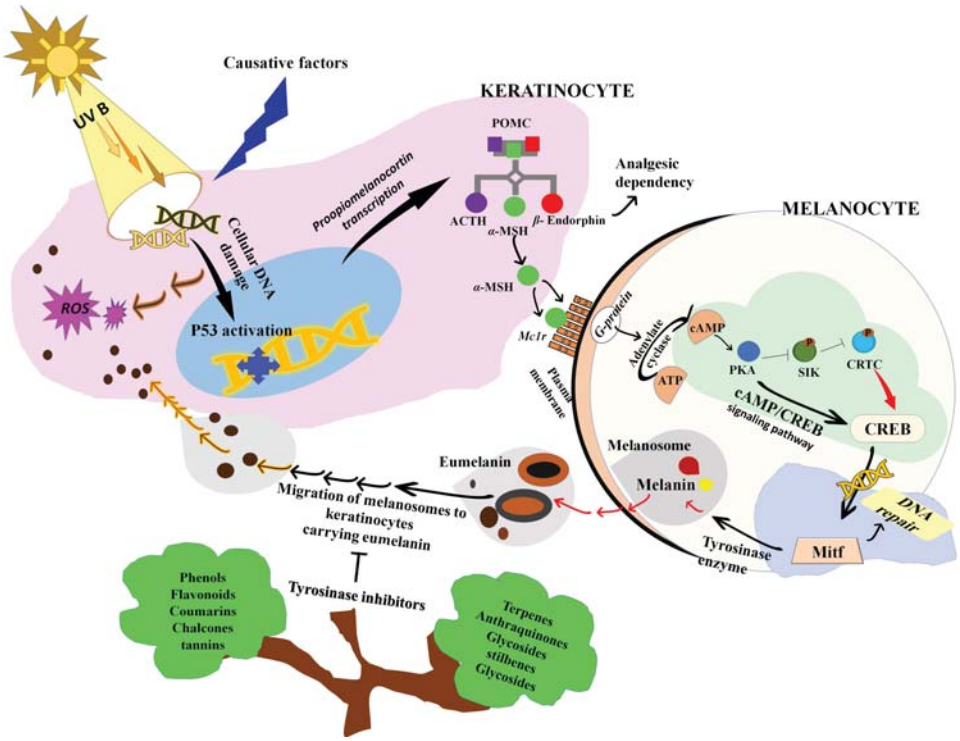


Fig. (5). α-MSH-triggered melanogenesis in melanocytes and inhibition of enzyme tyrosinase by natural inhibitors. Melanocytes, melanin-producing cells, are found in the skin's basal layer. Different signaling pathways produce eumelanin (brown-black) and pheomelanin (yellow-red) in a specialized organelle melanosome within melanocytes, then melanocytes transfer melanin pigments produced by melanosomes to keratinocytes where they get accumulated. **Abbreviations:** UV B, Ultraviolet B; ROS, Reactive oxygen species; POMC, Proopiomelanocortin; α -MSH, Alpha-melanocyte stimulating hormone; MC1R, melanocortin 1 receptor, CRTCs, CREB-regulated transcription co-activators; MITF, microphthalmia inducing transcription factor. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

tyrosinase inhibitory properties [41]. Gallacetophenone from *Rosa canina* L. (Rosaceae) fruit [42] and safflospermidines A from *Helianthus annuus* L. (Bee pollen) have tyrosinase inhibitory effects [43], indicating that phenols are a complex class of potential tyrosinase enzyme inhibitors, and their use could aid in the treatment of hyperpigmentation.

8. FLAVONOIDS

Flavonoids are a varied class of plant pigments with structures similar to or identical to flavones. They have been shown to inhibit tyrosinase due to their capacity to chelate copper in the enzyme's active site [44]. Flavones, flavonols, isoflavones, flavanones, flavanols, and anthocyanidins are the major flavonoids, whereas di-hydroflavones, flavan-3, 4-diols, coumarins, chalcones, di-hydrochalcones, and aurones are minor flavonoids [45]. Flavonoids have shown the ability to suppress the tyrosinase enzyme. Lin *et al*. found that glabridin, a phytoconstituent derived from the roots of *Glycyrrhiza glabra* L. (Fabaceae), suppressed enzyme tyrosinase in cultured B16 murine melanoma cells in guinea pig skin model [46]. In human epidermal melanocytes (HEMn), 2, 3-dihydro-4, 4-di-O-methylamentoflavone from the leaves of *Podocarpus macrophyllus* (Thunb.) Sweet. var (Podocarpaceae) decreased cellular tyrosinase activity and melanin inhibitory action, as well as strongly inhibited both protein and mRNA levels of TRP-2 [47].

Inhibition of mushroom tyrosinase *o*-diphenolase utilizing *l*-DOPA as a substrate has been reported in B16-F10 melanoma cells by pterocarpan ((6aR, 11aR)-3, 8-dihydroxy-9-methoxy pterocarpan) from the heartwood of *Dalbergia parviflora* Roxb. (Fabaceae) [48], couAG from *Carthamus tinctorius* L., eupafolin, a phytochemical from the dried aerial portion of *Phyla nodiflora* [49], neorauflavane from *Campylotropis hirtella* (Franch.) Schindl. (Leguminosae) [47] and 20, 40 -dihydroxy-50 -(1, 1- dimethylallyl)-8-prenylpinocembrin (8PP) from the aerial part of *Dalea elegans* L. Gillies ex Hook. et Arn. (Fabaceae). Peralta *et al*. discovered *in vitro* inhibition of mTYR and its effect on meterplanogenesis in B16 cells [50]. Using a modified dopachrome technique with a substrate, *l*-DOPA or *l*-tyrosine, Piao *et al.* found that 5-methyl-7-methoxy 2-(29-benzyl-39-oxobutyl) chromone from *Aloe vera* (Liliaceae) leaves [51], and heartwood of *Artocarpus incises* L. f. (Moraceae) inhibited the enzyme [52]. Competitive inhibition of mushroom tyrosinase diphenolase was also detected in Flemichin D from the roots of *Flemingia philippinensis* Merr. Et Rolfe (Fabaceae), with fluctuating IC_{50} values [53]. This diphenolase competitive inhibition of mushroom tyrosinaseis reported in broussoflavonol J from the root bark of *Broussonetia papyrifera* L. (Moraceae), [54], artocarpanone from the wood of *Artocarpus heterophyllous* (Moraceae) and from the root of *Artocarpus integer* (Thunb.) Merr. (Moraceae), [55, 56], isoeugenol from the flower bud of *Eugenia caryophyllata* Tunb. (Myrtaceae) [57] and asebogenin from the aerial part of *Piper elongatum* Vahl. (Piperaceae) inhibited about more than 70% [58] as well. Broussonin C, in a study by Baek *et al*. from the roots of *Broussonetia kazinoki* (Moraceae), strongly inhibited the enzyme tyrosinase [59]. In contrast, competitive inhibition of mushroom tyrosinase monophenolase in B16-F10 melanoma cells was detected in safflomin A and safflomin B from the flower of *Carthamus tinctorius* L. (Compositae) [60]. Dose dependent inhibition of enzyme tyrosinase is seen in various studies like rutin, a flavonoid in fruits of *Filipendula ulmaria* (L.) Maxim. (Rosaceae)[61], flemichin D from the roots of *Flemingia philippinensis* Merr. Et Rolfe (Fabaceae) [53], berberine from the stem-bark of *Berberis aristata* DC. (Berberidaceae) [62], broussonin C from the root of *Broussonetia kazinoki* (Moraceae) [59] and kuraridin from the dried roots of *Sophora flavescens* AIT (Fabaceae) [63]. Sanggenon D, a compound found in the root bark of *Morus mongolica* Schneider (Moraceae), was detected as a potent inhibitor of the enzyme tyrosinase [64]. All of these findings show that flavonoids are a powerful inhibitor of the pigment melanin.

9. TANNINS AND CATECHINS

To determine how the condensed tannins responded, the rate of dopachrome synthesis was calculated as a function of the enzyme and *l*- DOPA concentrations. The hydroxyl group on the B ring of condensed tannins may act as a chelator for the copper ions in the enzyme. Additionally, condensed tannins are capable of converting *o*-quinones, a product of enzymatic activity, into colorless molecules [65]. Compounds such as 7-phloroeckol isolated from the leafy thalli of the plant *Ecklonia cava* Kjellman (Laminariaceae) inhibited the potential tyrosinase enzyme, allowing a strong tyrosinase inhibitor to be more effective than the positive control kojic acid on B16-F10 melanoma cells [66]. *In vitro* monophenolase inhibition employing monophenolase as the substrate produced tyrosinase inhibitory activity in gallic acid and catechins from *Eugenia dysenterica* DC. (Myrtaceae) leaves [67] and condensed tannins from leaves, fruit, and stem bark of *Ficus virens L*. (Moraceae) [65]. Proanthocyanidins from the fruit pericarp of *Clausena lansium* Skeels (Rutaceae) [68], (2R, 3R)-3-acetyl7-methoxy-(−)-epicatechin 5-O-(6-isobutanoyl)-β-D-glucopyranoside, and (2R, 3R)-3-acetyl-7-methoxy- (−)-epicatechin 5-O-6-(2-methylbutanoyl)-β-D-glucopyranoside[69] from *Breynia fruticose* (Euphorbiaceae), epicatechin-3-gallate and (-)-gallocatechin 3-O-gallate from the leaves of *Camellia sinensis* L. (Theaceae) [70, 71] in the presence of various inhibitory concentrations inhibited mushroom tyrosinase. The inhibition kinetics on the diphenolase activity of mushroom tyrosinase by tannins from *Rhizophora stylosa* Griff. (Rhizophoraceae) bark resulted in enzyme inhibition [72], as well as compound inhibition of (2R, 3R)-3-acetyl7-methoxy-(−)-epicatechin 5-O-(6-isobutanoyl)-β-D-glucopyranoside and (2R, 3R)-3-acetyl-7-methoxy- (−)-epicatechin 5-O-6-(2-methylbutanoyl)-β-D-glucopyranoside from *Breynia fruticose* (Euphorbiaceae) [69].

10. COUMARINS

Coumarins are benzopyrene polyphenols found in plants. Monophenolase tyrosinase inhibition is a type of inhibition in which coumarin prevents monophenol from binding to oxygenated tyrosinase, thereby preventing the enzyme from producing the oxygenated D-form. The hydroxycoumarin biosynthetic pathway, which begins with cinnamic acid, produces 7-hydroxycoumarin or umbelliferone (Umbelliferae and Rutaceae), which is strongly inhibited by monophenolase tyrosinase [73], also 7- methoxycoumarin from the

Table 2. Traditional marketed formulations.

S. No.	Formulation	Type of Formulation	Company Name	Uses
1	Chandan Lepa	Cream	Veyangoda Sanjeewaka Ayurvedic Products	Skin toner
2	ArogyavardhiniGutika Rasa	Solution	Unjha Ayurvedic Pharmacy	Skin diseases
3	Azafran	Soap	Azafran Innovation Ltd.	Active skin brightener
4	Anti-Tan	Face wash	VLCC	Washes away impurities and reduces tan
5	Tribhuvan Kirtiras	Powder	Bhavya Ayurvedic Medicine	Applied to dark patches of skin
6	MukhakantikaraLepa	Paste (Lepa)	Muniyal Ayurveda	Improves glow on face
7	Kumkumadi Tailam	Oil	La'Conde beauty	Increases skin complexion and texture, acne scars, blemishes, acne, white and blackheads, dark circles, sun tan, and wrinkles
8	Nalpamaradi	Face cream	Neev	For skin de-tan and lightening
9	Ubtan	Face mask	Skin Beauty	De-tan and improves the glow of the skin
10	Body Ubtan	Body mask	Patanjali Ayurved Ltd.	Exfoliates dead cells and lightens dark marks with a traditional age-old
11	Yauvana	Face pack	Earth N secrets	Tightening/Brightening/whitening and glowing skin
12	Skin-a-Fair	Fairness cream	Khadi	Effectively whitens the skin

leaves of *Eupatorium triplinerve* Vahl (Asteraceae) showed higher IC_{50} inhibition compared to kojic acid, the positive control. [74] Few terpenes like α-santalolfrom *Santalum album* L. (Santalaceae) form an inhibition zone against enzyme tyrosinase [75]. Betulinic acid from the fruit of *Dillenia indica* L. [76] and broussonetones Q from the leaves of *Broussonetia papyrifera L.* (Moraceae) are reported potent inhibitors of Mushroom tyrosinase i=enzyme [77]. Diphenolase inhibition is seen in many coumarins like 7- methoxycoumarin from the leaves of *Eupatorium triplinerve* Vahl (Asteraceae) and in, *in vitro* B16 mouse melanoma with about 83% inhibition [74]. Diazaphosphinines have inhibition over enzyme tyrosinase [78], a compound seguinoside A *p*-coumarate from *Breynia offcinalis* Hemsley (Euphorbiaceae) [79], betulinic acid from the fruit of *Dillenia indica* L. (Dilleniaceae) [76], ursolic acid from the fruit pulp and seeds of *Madhuca latifolia* (J. Konig) J.F.Macbr. (Sapotaceae) showed dose dependent inhibition [80]. Betulinic acid from the roots of *Vitis amurensis* (Vitaceae) inhibited tyrosinase, TRP-1 and TRP-2 in, *in vitro* B16-F10 cell line [81]. Bisabolangelone from an undisclosed source also inhibited tyrosinase in B16 cells, resulting in a 99% reduction in α-MSH-induced melanin formation [82].

11. ANTHRAQUINONES AND GLYCOSIDES

In a study, Altun *et al*. found that few anthraquinones, such as hypericin from *Hypericum perforatum* L. (Hypericaceae) leaves, lawsone (2- hydroxy-1,4 napthaquinone) and hennotannic acid from *Lawsoniai nermis* L. (Lythraceae) showed about 44% of mixed competitive inhibition by mushroom tyrosinase diphenolase [83], and 50% of noncompetitive monophenolase inhibition was observed [84]. The chalcone 2, 4, 2', 4',-hydroxycalcone, isolated from the stems of *Morus australis* (shimaguwa) (Moraceae), has been shown to be effective against murine B16 melanoma cells [85]. Two known glycosidal compounds, 7R, 8S-dihydrodehydrodic oniferyl and 7R,8S-dihydrodehydrodic alcohol-9-O-β-D glucoside from the seeds of *Crataegus pinnatifida* Bunge (Rosaceae) [86], 2,3-dimethyl-4-hydroxymethylphenyl-1-hydroxymethyl-O-b-D -glucopyranoside from the aerial part of *Eryngium tricuspidatum* L. (Apiaceae) [87] and 6-methoxysorigenin-8-O-glucoside from the heartwood of *Rhamnus nakaharai* Hayata (Rhamnaceae) tend to inhibit mushroom tyrosinase monophenolase in a dose dependent manner [88].

12. STILBENES

Stilbenes are classified as diarylethenes because they have an ethylene moiety in the middle and inhibit the enzyme tyrosinase. Few stilbenes like oxyresveratrol (2, 3, 4, 5-tetrahydroxystilbene) and steppogenin from the twigs of *Morus alba* Lin. (Moraceae) tend to inhibit mushroom tyrosinase enzyme with 97.3% inhibition, of murine tyrosinase [21] and mushroom tyrosinase inhibition. Chaita e *et al*., in a study, showed *in vitro* B16-F10 melanoma cell tyrosinase inhibition by dihydroxy resveratrol and 2, 4, 30-trihydroxydihydrostilbene from the wood of *Morus alba* L. (Moraceae) [89]. Phytoconstituents like artogomezianol and

alasin A from the roots of *Artocarpus gomezianus* Wall ex Tre'c (Moraceae) showed diphenolase inhibition [90] and also a few anisaldehyde from the seeds of *Pimpinella anisum* L. (Umbelliferae) showed mushroom tyrosinase inhibition with *l*-DOPA or *l*-tyrosine as substrate [91]. Diphenolase inhibition of trans, cis-2, 6-nonadiena from the fruit skin of *Cucumis sativus* L. cv. (Cucurbitaceae) 4-tert-butylcatechol with a pharmacokinetic inhibition of Ki = 3.4 mM [92] and norbixin from seeds of *Bixa orellana* annatto (Bixaceae) and crocin and bixin from the stigma of *Crocus sativus* L. (Iridaceae) inhibited cell–free mixed competitive inhibition [93] (Table **1**).

13. TRADITIONAL APPROACHES FOR DEPIGMENTATION

The depigmentation or anti-browning process entails the application and administration of few traditional remedies, as given in Table **2**.

CONCLUSION

Due to the critical role of tyrosinase in the enzymatic browning of food and depigmentation disorders in humans, its inhibitors have been extensively studied. Medicinal herbs from traditional systems of medicine and other sources must be evaluated to identify promising leads that could be used to treat pigmentation by acting as anti-browning agents. Natural sources such as plants and microbes, as well as their active metabolites, have shown tremendous potential as organic anti-tyrosinase sources, as previously stated. However, the majority of the compounds identified from natural sources were isolated from plants, but recently, microorganisms are also being explored as potential sources of tyrosinase inhibitors. It is interesting that despite the diversity of natural inhibitors, a large number of tyrosinase inhibitors are mainly phenolic and flavonoid-based. Many researchers have created innovative synthetic inhibitors and devised appropriate scaffolds based on the structure of natural substances.

The primary goal of this review is to provide a comprehensive list of experimentally verified potent and natural tyrosinase inhibitors as one-step sources. However, despite the existence of a wide range of tyrosinase inhibitors from natural and synthetic sources, only a few of them, in addition to being effective, are known as safe compounds. Therefore, it is recommended to examine the efficacy and safety of inhibitors by *in vivo* models, along with *in vitro* and docking experiments, especially for their application in food and medicinal products. Additionally, the collaborative efforts of imperative aspects of numerous researches were summarised for the development of effective and safe anti-tyrosinase drugs derived from natural and synthetic sources for beneficial applications in the food and cosmetic industries.

LIST OF ABBREVIATIONS

CRTCs	=	CREB-regulated transcription co-activators
DCT	=	Dopachrome taut-ome-rase
DDB1	=	Damage-specific DNA binding protein 1
DOPA	=	Dihydroxyphenylalanine
HBTA	=	5-hydroxy-1, 4-benzothiazinylalanine
HEMn	=	Human epidermal melanocytes
HPTLC	=	High performance thin layer chromatography
MC1R	=	Melanocortin 1 receptor
MITF	=	Microphthalmia inducing transcription factor
POMC	=	Proopiomelanocortin
PPO	=	Polyphenol oxidase
ROS	=	Reactive oxygen species
RP-HPLC	=	Reverse phase high performance liquid chromatography
SPF	=	Sun protection factor
TRP-1	=	Tyrosinase-related protein-1
TRP-2	=	Tyrosinase-related protein-2
UF	=	Ubtan formulation
UVR	=	Ultraviolet radiation
α-MSH	=	α-melanocyte stimulating hormone.

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CONFLICT OF INTEREST

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