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A Compendious Review on Tyrosinase Inhibitors from Natural and Synthetic Origin

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ABSTRACT
The review focuses on the recent identification of tyrosinase inhibitors that are specifically involved in the inhibition of tyrosinase catalytic activity and functionality. These inhibitors come from a variety of sources, including natural products, virtual screening, and structure-based molecular docking studies. The enzyme tyrosinase participate in a sequence of oxidative processes that result in the formation of melanin. Tyrosinase is a copper-containing enzyme that catalyses the hydroxylation of monophenols to o-diphenols and the oxidation of o-diphenols to o-quinones, two rate-limiting events in melanogenesis. It acts through various modes such as MITF inhibition; tyrosinase inhibition and enhancement of its degradation; down regulation of MC1R activity; interference with melanosomes, maturation and transfer; desquamation, and chemical peeling. More recently, the crystal structure of mushroom tyrosinase complexes with the highly strong inhibitor tropolone was disclosed, as well as the crystal structures of a few additional tyrosinases and other fungi. To get into insight and prevent against skin-aging disorders, we expect that the updated data offered in this review will aid researchers in the creation of new safe, effective, and skin care or medicine solutions.

Key words: - Molecular docking, MITF inhibition, MC1R activity

I. INTRODUCTION

Indian skin has significant color variation as well as certain distinctive characteristics. In India, pigmentary disorders in particular are of great concern and have a significant psychosocial influence on quality of life.(1) For skin lightening creams and other skin care products, it is estimated that $432 million was spent in India alone in 2010. According to a recent poll, 80% of Indian males use fairness creams, and the market is expanding 18% annually. The primary cause of skin colour, melanin, is reduced by these skin lightening treatments by a molecular mechanism show in statistics pi diagram (Fig.1) (2)

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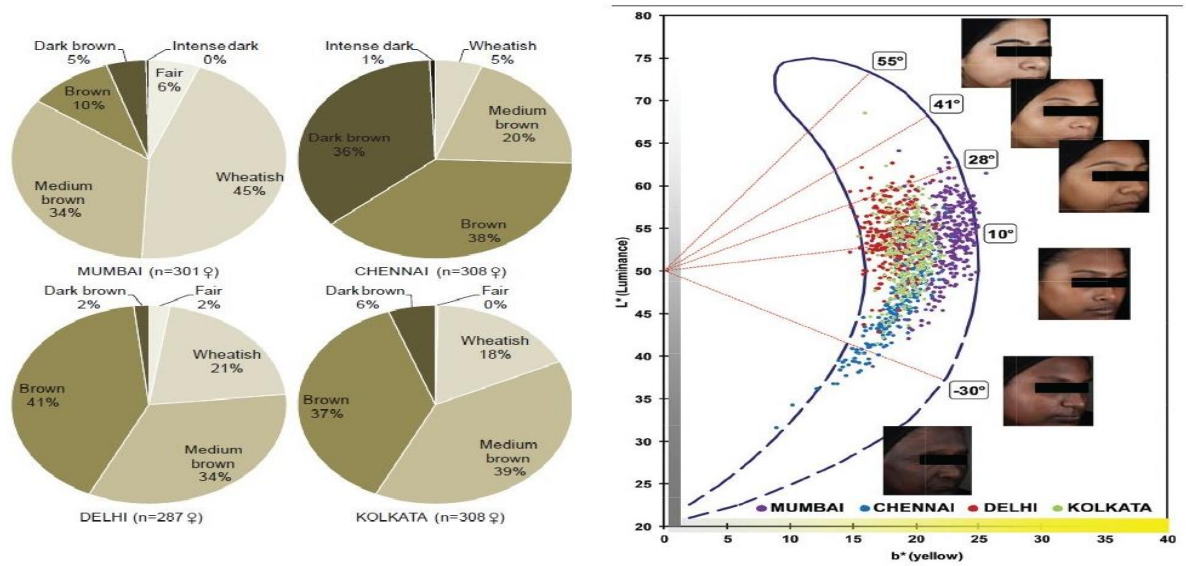

Fig.1Distribution of skin complexions based on dermatologist assessment in Mumbai, Chennai, Delhi, and Kolkata

Melanin is essential for protecting human skin from the detrimental effects of UV sun radiation and for scavenging hazardous medicines and chemicals. It determines our racial and phenotypic characteristics. The formation of an inordinate amount of melanin in various places of the skin as more pigmented patches (melasma, freckles, ephelides, senile lentigines, etc.) may become an aesthetic problem in the future. (3) Up to 10% of skin cells in the epidermis's deepest layer produce melanin, a dark pigment. Melanogenesis begins with the initial step of tyrosine oxidation via an enzyme called tyrosinase when the skin is exposed to UV light. Tyrosine is oxidized by enzymes within particular organelles called melanosomes to create melanin by epidermal melanocyte. This process is known as melanogenesis. The synthesis and expression of numerous melanogenic enzymes and inhibitors play a crucial role in the regulation of melanogenesis at the sub cellular level.(4)

1.1 MELANIN BIOSYNTHESIS

Melanin biosynthesis begins with L-tyrosine, which is oxidized to L-3, 4-dihydroxyphenylalanine and then to dopaquinone with the help of the enzyme tyrosinase. Dopaquinone is formed via cyclization of leukodopachrome and subsequent oxidation to dopachrome and Indole-2 carboxylic acid-5, 6-quinone (DHI), as shown in (Fig. 2). (5)

Dopaquinone is transformed into dihydroxyindole-2-carboxylic acid (DHICA) and oxidized in the presence of the enzyme tyrosine related protein-1 (TRP-1). DHI is further converted to indole quinone by oxidation using the tyrosinase enzyme (IQ). The polymerization of DHICA and IQ produces eumelanin (black-brown). Dopaquinone, on the other hand, is modified by glutathione or cysteine to glutathionyldopa or cysteinyl dopa, which is then transformed to pheomelanin (red-yellow) by producing benzothiazine as an intermediate.(6)

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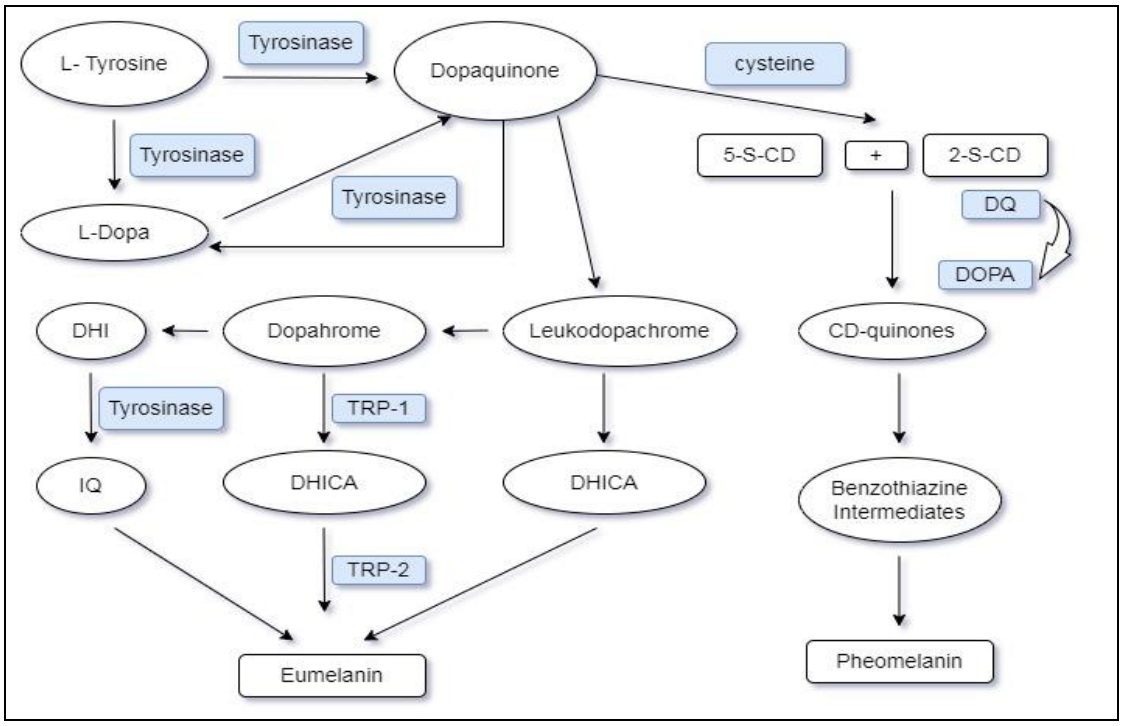

Fig.2 Melanin Biosynthesis

1.2 SIGNALING PATHWAYS TO REGULATE MELANOGENESIS

A signaling pathway involves a melanogenesis master regulator that up regulates melanogenesis enzymes TYR, TRP-1, and TRP-2 by binding to the motif in their promoter regions as shown in Fig. 3.

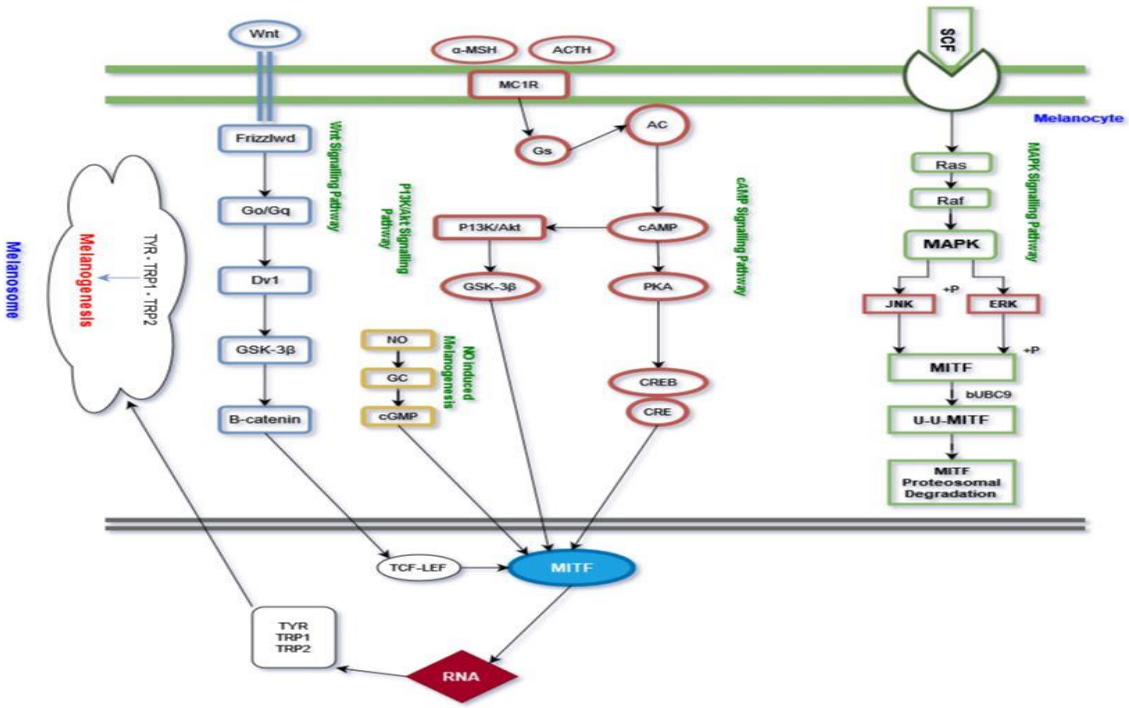

Fig.3Common signaling pathways involved in the regulation of melanogenesis

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The Microphthalmia-associated transcription factor (MITF), which has been shown to activate more than 25 genes in pigment cells, has emerged as an important regulator not only of melanocyte development, proliferation, and survival, but also of the expression of enzymes and structural proteins required for melanin production.(7)

The activation or inhibition of MITF activity stimulates or inhibits the production of melanogenesis-related enzymes, hence boosting or inhibiting melanogenesis. α – melanocyte - stimulating hormone (α-MSH) regulates melanogenesis via cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) mediated pathway. When α -MSH binds to its receptor, melanocortin 1 receptor (MC1R), on the melanocyte membrane, it activates adenylate cyclase (AC) to create cAMP, which then phosphorylates protein kinase A (PKA). Phosporylated PKA phosphorylates cAMP-response element binding (CREB) protein in the nucleus and in turn, up regulates MITF. Ultimately, MITF efficiently activates the melanogenesis-related enzymes and stimulates melanogenesis.(8)

β -MSH and adrenocorticotropic hormone (ACTH), also stimulate melanogenesis via the same pathway. cAMP also influences MITF post-translational modification by inhibiting phosphatidylinositol 3-kinase (PI3K), which reduces Akt phosphorylation and so stimulates glycogen synthase kinase 3β (GSK) activity by decreasing p-GSK levels. The activated GSKβ, phosphorylate MITF and leading to stimulation of melanogenesis by up regulation of MITF. The extracellular signal-regulated kinase (ERK) or JNK pathway, in contrast to other signalling pathways, controls melanogenesis by causing the MITF protein to degrade. When ERK is active, MITF is phosphorylated and ubiquitinated before being degraded by the proteasome. As a result of stimulating the ERK pathway, MITF activity is reduced, limiting melanogenesis.(9)

Melanogenesis in mammals is regulated at several levels, beginning with the genetic level during embryo development, progressing to the cellular level via melanosome formation control, to the subcellular level where gene expression encoded by melanogenesis-related enzymes such as tyrosinase, TRP-1 and TRP-2, and finally to the transport of melanin pigment from melanocyte to keratinocytes where it produces colour. Melanogenesis inhibitors are important skin-whitening agents used extensively in the cosmetic industry. Skin-whitening creams work by reducing skin pigmentation. Numerous methods can be used to depigment skin, with the modulation of tyrosinase activity being one of the main focuses. Tyrosinase is the rate-limiting enzyme in the synthesis of melanin, making it the most visible target for hyperpigmentation suppression. Tyrosinase inhibition with high efficacy and minimal side effects has long been a challenge in dermatological and cosmetic sciences. As a result, the primary emphasis was placed on using approaches such as virtual screening and structure-based molecular docking investigations. (10),(11).

1.3 THE ROLE OF TYROSINASE IN THE MELANIN BIOSYNTHESIS

Melanogenesis is a complex process involving several enzymatic and chemical reactions, with enzymes such as tyrosinase and other tyrosinase-related proteins (TYR-P1 and TYR-P2) playing an important part in melanin formation. Tyrosinase is a multifunctional copper-containing metalloenzyme with binuclear copper ions that acts as a rate-limiting enzyme in the formation of melanin. Tyrosinase inhibitors are a family of crucial therapeutic antimelanoma medications, however only a small number of substances are recognised to function as safe and efficient tyrosinase inhibitors.(12)

II) TYROSINASE INHIBITORS

Melanin biosynthesis can be reduced by avoiding UV exposure, decreasing tyrosinase, limiting melanocyte metabolism and proliferation, or removing melanin through corneal ablation. For hyperpigmentation disorders such melasma and post-inflammatory hyperpigmentation, typical topical remedies include hydroquinone bleaching, retinoid anti-inflammatory therapy, and tyrosinase inhibitor usage. Numerous tyrosinase inhibitors that inhibited monophenolase, diphenolase, or both of these activities have been discovered in natural and synthetic sources. (13)

2.1 MUSHROOM TYROSINASE INHIBITORS

Mushrooms have been consumed by humans since ancient times, not only as a staple of the diet but also as a delicacy due to its appealing flavour and aroma. Because of the variety of adverse effects induced by traditional drugs, the usage of mushrooms with medicinal characteristics is increasing day by day. Mushrooms have been

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identified as powerful candidates in clinical research among natural goods due to their ease of availability and low cost. Over the last 30 years, the enzyme tyrosinase (polyphenol oxidase, EC 1.14.18.1) has received a great deal of attention as a critical instrument in a range of studies. Since the first biochemical investigations on mushrooms were undertaken in 1895, natural and synthetic sources have been provided in (Tables 1&2). (14)

Table 1Some Mushroom Tyrosinase Inhibitors from Natural Sources

Inhibitor	Source
Kaempferol	Crocus Sativus
Quercetin	Heterotheca Inuloides
Kurarinone	Sophora Flavescens
Arbutin	Gvae Grsi

Table 2 Some Mushroom Tyrosinase Inhibitors from Synthetic Sources

Inhibitor	Type of Inhibition
Cinnamaldehyde	Noncompetitive
Cinnamic acid	Mixed
Captopril	Noncompetitive
Tropolone	Competitive

Tyrosinase from the mushroom *Agaricus bisporus* is commonly utilised as an *in vitro* enzymatic model for creating skin whitening agents that target human tyrosinase. Because mushroom tyrosinase (mTYR) is commercially available (Fig. 4), the majority of study has been conducted using this enzyme. (15)

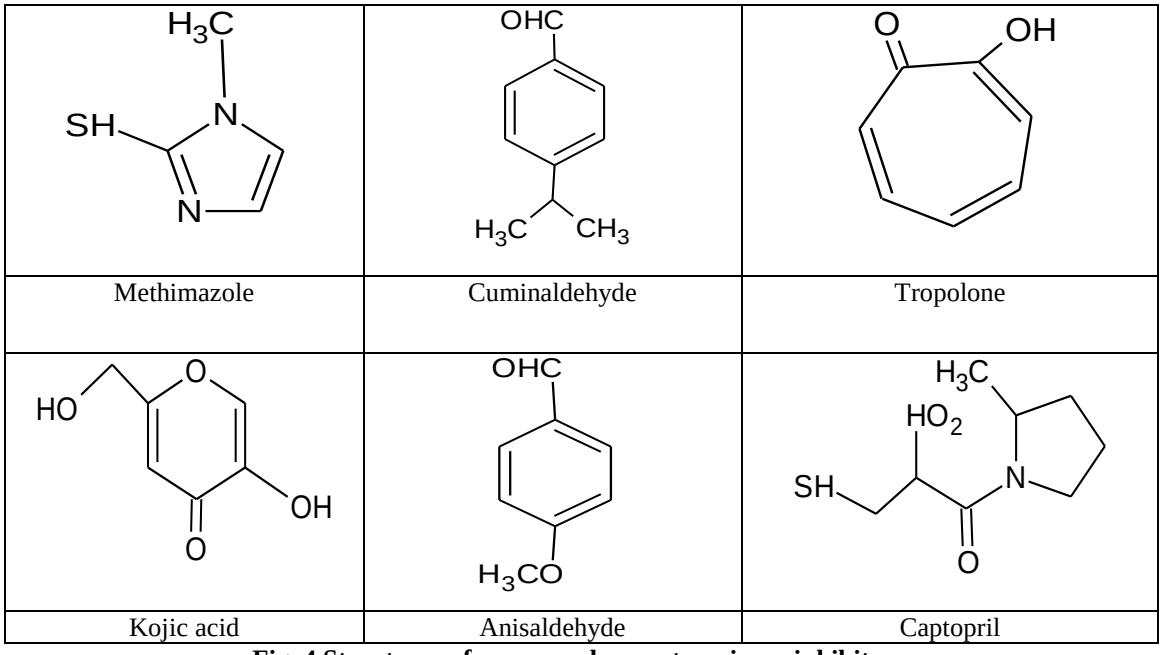

Fig. 4 Structures of some mushroom tyrosinase inhibitors

2.2 HUMAN TYROSINASE INHIBITORS

Human tyrosinase (hsTYR) is a type-3 copper-containing metalloenzyme that belongs to the TYR (EC 1.14.18.1) family, which also includes enzymes from plants, fungi, bacteria, and mammals. The molecular weight of this glycoprotein is 67 kDa, and it is made up of 529 amino acids, including an 18-residue N-terminal signal sequence

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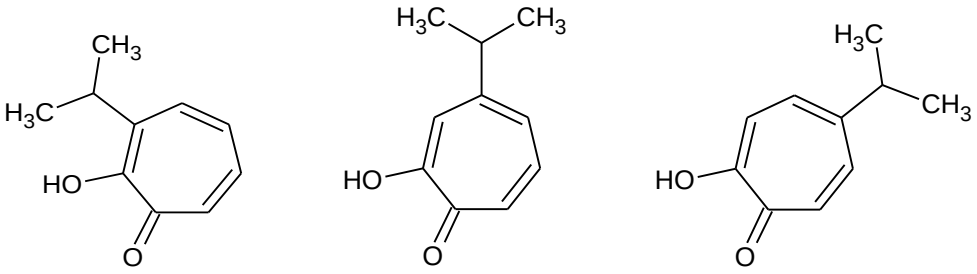
and six or seven N-glycosylated sites. Its active site is composed of two close, magnetically coupled copper centres linked by an aquo(hydroxo) ligand in the met state (hsTYR's reactive state) and coordinated by six histidine residues (H180, H202, H211 for CuA, H363, H367, H390 for CuB) that are highly conserved among tyrosinases, catechol oxidases, and hemocyanins. Although the enzyme can oxidise a wide range of monophenolic and diphenolic substrates, its physiological role is to use molecular oxygen to perform the o-hydroxylation of L-tyrosine to LDOPA (monophenolase activity) and the subsequent oxidation of L-DOPA in dopaquinone (diphenolase activity). The creation of melanin pigments begins with this twofold oxidation process and continues primarily without the use of enzymes. Tyrosinase-related proteins 1 and 2 (hsTYRP1 and hsTYRP2), the only other enzymes known to play a role in melanogenesis, are very similar to hsTYR, albeit the function of hsTYRP1 is uncertain and may instead be related to hsTYR protection.(16)

For instance, there are many different tyrosinase inhibitors that can be used, and a few of them with strong inhibitory effects are listed below. Almost all of the inhibitors have been tested against the tyrosinase found in mushrooms (Figure 5) for their inhibitory effects on both mushroom tyrosinase and human tyrosinase (hTYR) in an effort to discover novel inhibitors against human tyrosinase. The findings demonstrated that human tyrosinase activity was efficiently suppressed by b- and c-thujaplicins (b and c) in a dose-dependent manner, with IC50 values of 8.98 and 1.15 lM, respectively. Particularly, c-thujaplicin [c] outperformed kojic acid (IC501417 lM) by a wide margin.(2)



α-Thujaplicin β-Thujaplicin γ-Thujaplicin

Compound	Tyrosinase inhibition IC50 (μm)	
	Human	Mushroom
α-Thujaplicin	>1000	9.53
β-Thujaplicin	8.98	0.09
γ-Thujaplicin	1.15	0.07
Kojic acid	571.17	53.70

Fig. 6 Structures of different human tyrosinase inhibitors

Although considerable amounts of hTyr may be extracted from human melanoma metastases, it is unknown if this is the original form of hTyr. Furthermore, the approach is plainly unsuited for laboratory-scale continuous enzyme synthesis. Human tyrosinase has been found to be transiently expressed in a variety of animal cell lines. Unfortunately, yields were consistently low, making comprehensive characterization of the resulting preparations impossible. Many tyrosinase inhibitors have been used as skin-whitening treatments, including hydroquinone (HQ), arbutin, kojic acid, azelaic acid, L-ascorbic acid, ellagic acid, and tranexamic acid (Table 3).(17)

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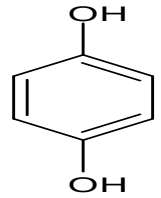
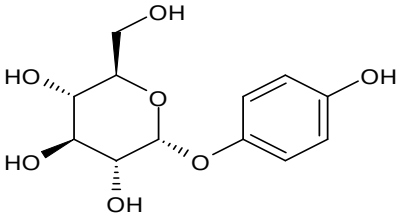
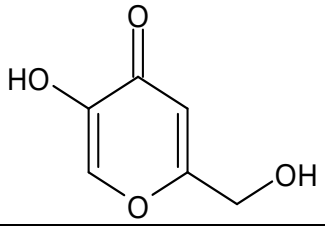
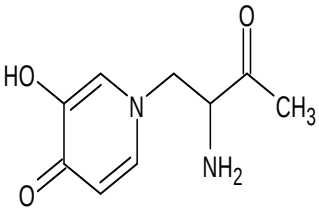
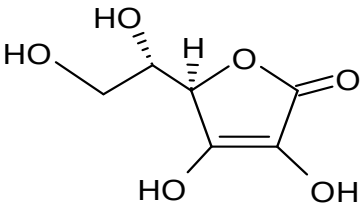
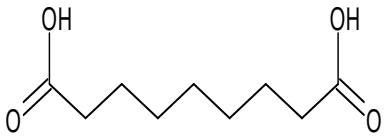
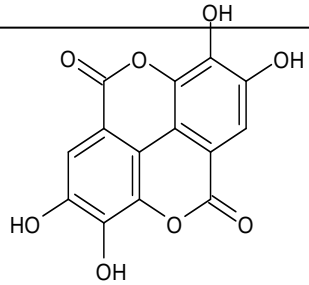
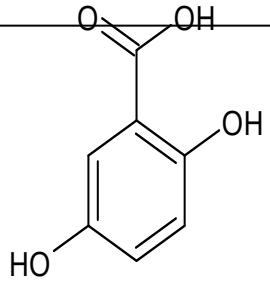
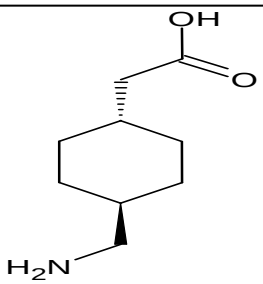
Table 3 Chemical structure of well-known skin lightening agents as tyrosinase inhibitors

		
Hydroquinone	Arbutin	Kojic acid
		
L- Minosine	L- Ascorbic acid	Azelic acid
		
Ellagic acid	Gentisic acid	Tranexamic acid

III. STRUCTURAL DIVERSITY OF TYROSINASE

3.1 CRYSTAL STRUCTURE OF TYROSINASE

Tyrosinase is a multi-subunit binuclear copper-containing metalloenzyme expressed by human melanocytes. The enzyme crystal structure of Agaricus bisporus mushroom tyrosinase (mTYR) was presented using molecular and biological techniques (Fig. 5A). mTYR is an H2L2 tetramer with a molecular mass of 120 kDa. The H subunit's tyrosinase domain is made up of 13 -helices, 8 short -strands, and several loops. The L component is shaped like a lectin and has 12 antiparallels -strands with 150 amino acids apiece. Each copper ion in the tyrosinase active site can interact strongly with three particular amino acid residues that are positioned in two antiparallels -helices of the H- subunit at an angle of roughly 90 degrees (Fig. 5B). (18),(19)

Cu (II) is dsp2 hybridised, resulting in four dsp2 orbitals, three of which can form coordination interactions with histidine residues. One copper ion, for example, coordinates with N_2 atoms of His 61, His 85, and His 94, while the other copper ion correlates with His 259, His 263, and His 296. Two copper ions are linked together by an intracellular water molecule. Six histidine residues' side-chain conformations are restricted by Phe 90 and Phe 292. A covalent thioether bond between His 85 and Cys 83, as well as hydrogen bonds between the Nd1 atom on His 61, His 94, His 259, His 263, and the peptide carbonyl oxygen atom, help to keep geometric shape of active site well-ordered. (19)

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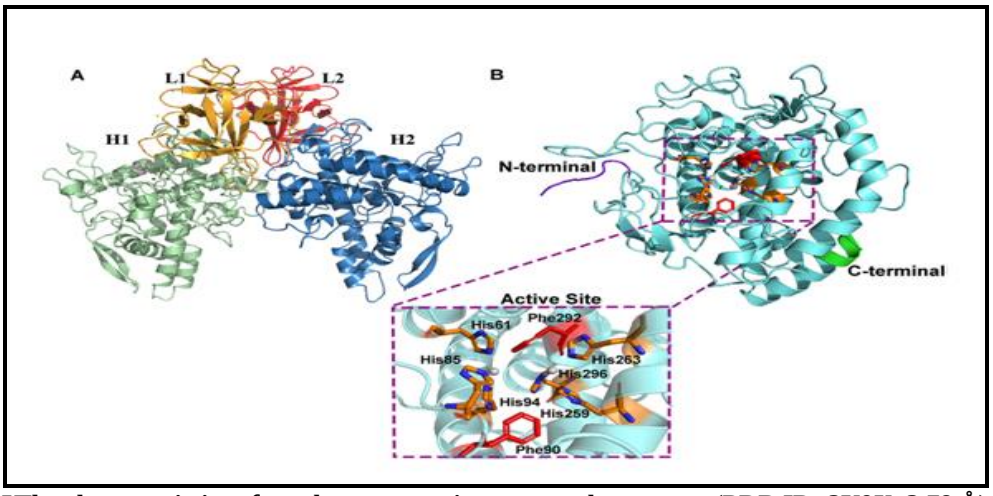


Fig.5The characteristics of mushroom tyrosinase crystal structure (PDB ID: 2Y9X, 2.78 Å)

Fig. 5A The side view of mushroom tyrosinase H_2L_2 tetramer structure. H-L dimer interactions are between H1 (green), L1 (yellow), H2 (blue) and L2 (red).
Fig. 5B The H subunit bearing the active center is performed by the cartoon model with the N-terminal (purple) and C terminal (green).

IV. INHIBITORS FROM SYNTHETIC AND NATURAL ORIGIN

A) CHALCONE

Chalcone is a class of chemical compounds with the backbone structure 1,3-diaryl-2-propen-1-one (Fig. 6) that can be isolated and purified from natural sources or synthesised completely. Chalcone is regarded as a privileged scaffold due to its diverse biological activities. (20)(21)

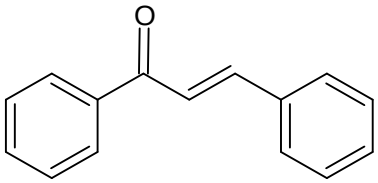
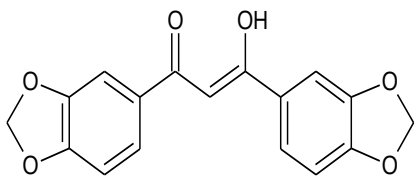
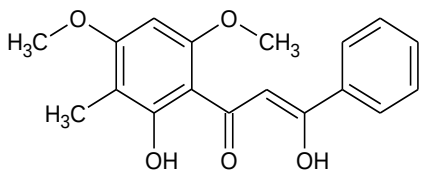


Fig.6 Chalcones

4.1 INHIBITORS FROM NATURAL ORIGIN

In nature, chalcones with simple substituents such as hydroxyls, methoxyls, prenyls, and glycosides are prevalent are shown in (Table 4). (22)

Table 4 Unique chalcones isolated from various plant sources

 Galiposin	 2-hydroxy-4,6-dimethoxy-3-methyl

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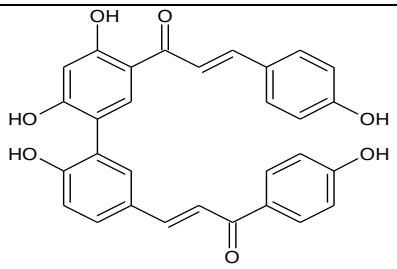
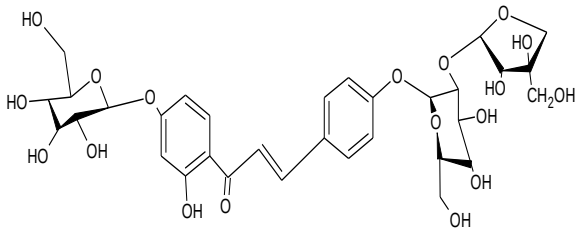


Bisdesmosidic tri glycoside

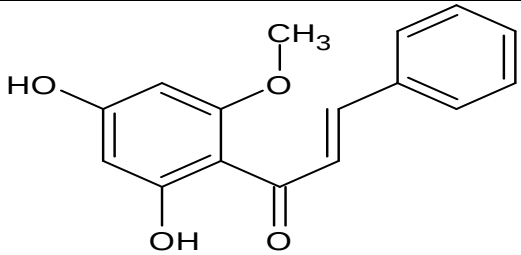


Rhuschalcone

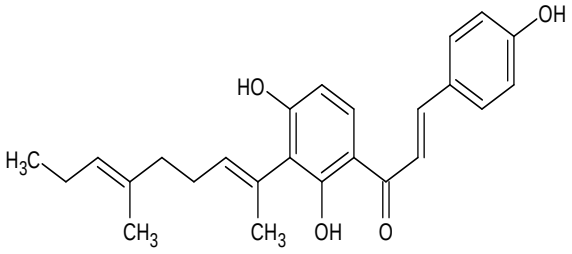
Two unusual -OH chalcones, for example, have been reported from a natural source. Galiposin is the first bis (methylenedioxy) chalcone discovered from a natural source, derived from *Galipea granulosa* (Rutaceae). Similarly, aerial parts of *Leptospermum scoparium* (Myrtaceae) are utilised to produce 2-hydroxy-4, 6-dimethoxy-3-methyl chalcone. Similarly, a bisdesmosidic try glycoside isolated from the roots of *Glycyrrhiza aspera* (Leguminosae) has been characterised as an uncommon chalcone with unique bonding of three sugar moieties. Rhuschalcone is a bichalcone produced by C-C linking two isoliquiritigenin units isolated from Rhus pyroides. This C-C connected bichalcone is extremely uncommon in nature. Nonetheless, some of the chalcones obtained from plant sources with unique bonding and substitutions are detailed here (Table 4). (23)

Four anti-tyrosinase chalcones 2′, 4′-dihydroxy-6′-methoxy-chalcone, Xanthoangelol isolated from *Loran thus acutifolius* dichloromethane extract, two naturally occurring chalcones of *Piper methysticum*, *flavokawain A* (2′-hydroxy-4, 4′, 6′-trimethoxychalcone) and *flavokawain B* (4′, 6′-Dimethoxy-2′-hydroxychalcone), have exhibited their ability to suppress melanogenesis in MSH-induced B16/F10 cells and zebrafish without causing any hazardous side effects. The monophenolase and diphenolase activities of tyrosinase were reduced by chalcones derived from Humulus lupulus methanol extract, such as xanthoumol B and xanthoumol C. More potent inhibition was reported in chalcones having an isoprenyl group at ring A. The isolated flavonoids from *Greyia radlkoferi* 2′, 4′, 6′-trihydroxydihydrochalcone were found to be the most efficient tyrosinase inhibitors among the extracted flavonoids. Furthermore, molecular docking investigations revealed that Cu2+ ion contact at the active site had an influence on tyrosinase. (24) The chemical structures of the natural chalcones with anti-tyrosinase activities are detailed here (Table 5).

Table 5 Chalcones with anti-tyrosinase activity.



2′,4′-dihydroxy-6′-methoxy-chalcone



Xanthoangelol

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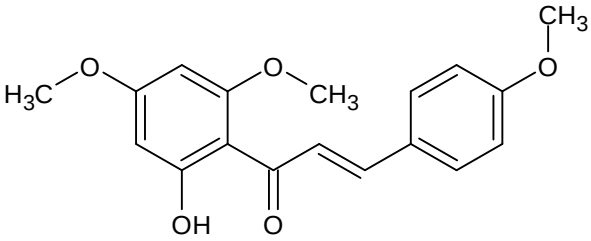

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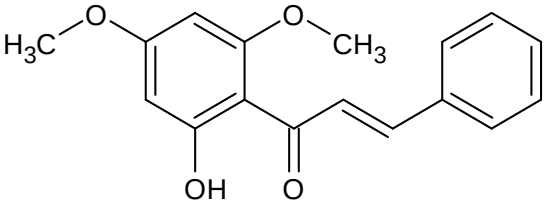

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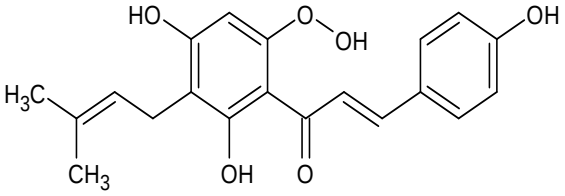

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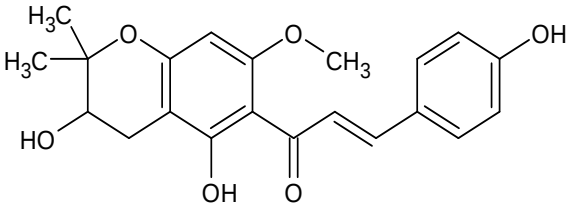

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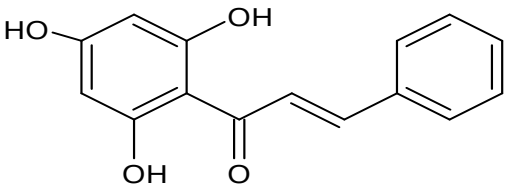

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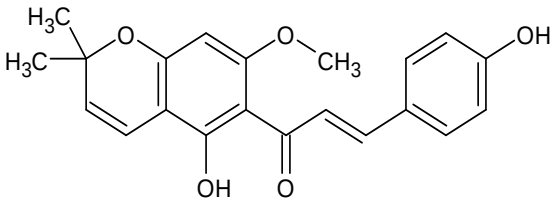

2′,4′,6′-trihydroxydihydrochalcone

The most prevalent chalcone derivatives found in foods such as citrus fruit and apples are phloretin and 2', 4, 4', 6'-tetrahydroxychalcone. Tyrosinase inhibition is high in chalcones containing a resorcinol ring on one side and a catechol moiety on the other. Butein, for example, has high monophenolase activity but low diphenolase activity because it has a catechol subunit on ring A and resorcinol on ring B. Three chalcone derivatives, licuraside, isoliquiritin, and licochalcone A, isolated from the roots of Glycyrrhiza species, were found to competitively inhibit the monophenolase activity of mushroom tyrosinase. (25) Kuraridin, a prenylated chalcone derived from the plant Sophoraflavescens, was discovered to be a powerful tyrosinase inhibitor, with 34 times the activity of kojic acid against mushroom tyrosinase monophenolase activity. Kuraridinol, 2, 4, 2' ,4'-tetrahydroxy-3-(3-methyl-2-butenyl)-chalcone (TMBC), derived from Morus nigra stems, was recently reported to be 26-fold more powerful than kojic acid in diphenolase inhibition of mushroom tyrosinase. (13) Butein inhibits competitively, whereas isoliquiritigenin and 4-hydroxychalcone inhibit semi competitively (Table 6).(26),(27),(28)

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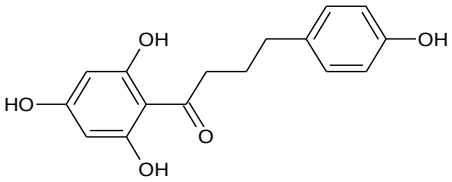
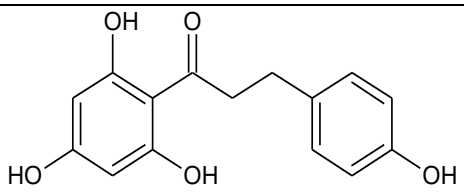
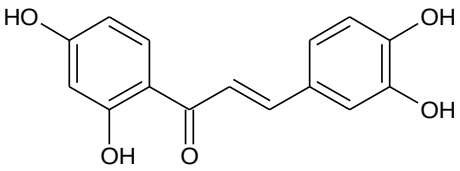
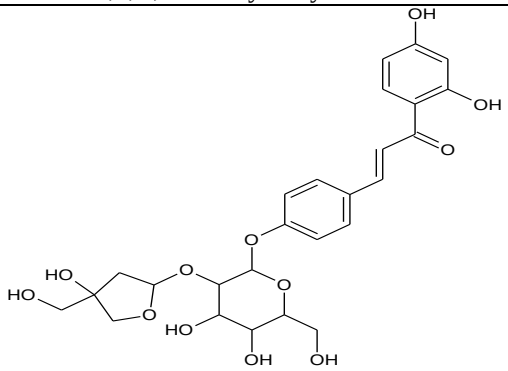
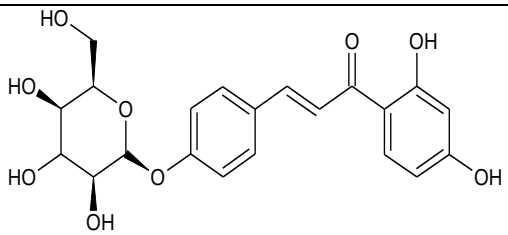
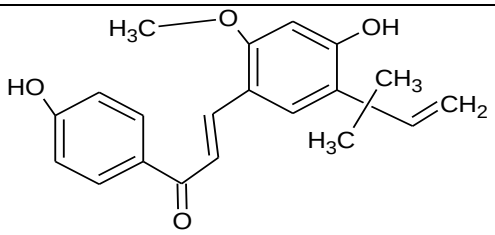
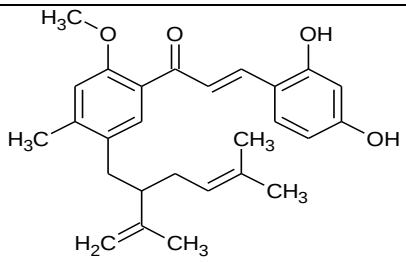
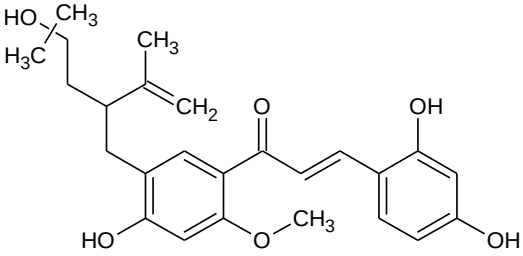
Table 6 Plentiful chalcones as tyrosinase inhibitors in plants

 Phloretin	 2',4,4',6'-tetrahydroxychalcone
 Butein	 Licuroside
 Isoliquiritin	 Licochalcone A
 Kuraridin	 Kuraridinol

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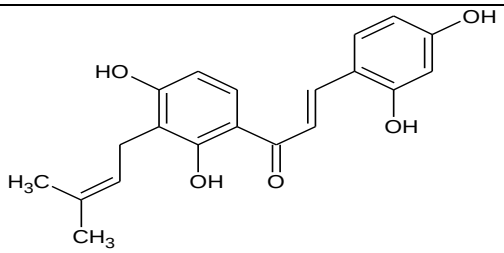
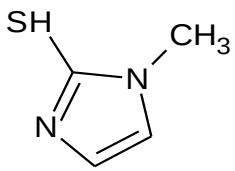
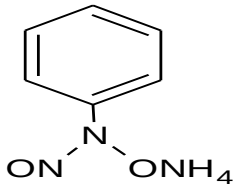
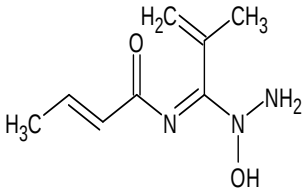
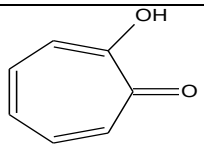
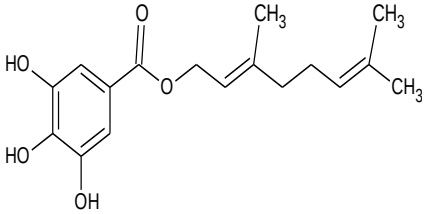
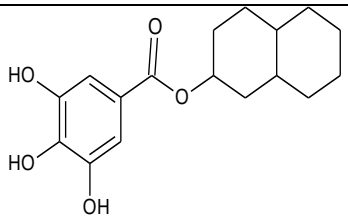
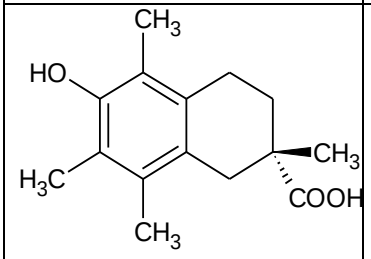
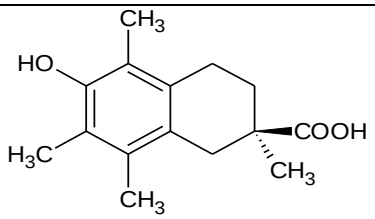
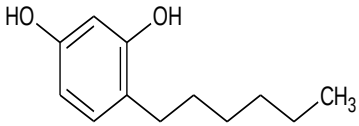


TMBC

4.2 INHIBITORS FROM SYNTHETIC ORIGIN

Chalcones are often produced through condensation processes catalysed by bases or acids. Despite the fact that chalcones are a form of, unsaturated ketone that are simple to synthesize, a rising number of innovative procedures and methods have lately been documented Table 7. (29)

Table 7 Inhibitors form synthetic origin

 Methimazole	 Cupferron	 Dopastin
 Tropolone	 Geranyl gallate	 Decahydro-2-naphthyl gallate
 (R)-HTCCA	 (S)-HTCCA	 4-Hexylresorcinol

Methimazole (1-methyl-2-mercaptoimidazole) inhibited both the mono and diphenolase activities of mushroom tyrosinase. It suppressed mushroom tyrosinase activity in two ways: conjugating with o-quinones, resulting in apparent suppression of pigmented product production, and chelating copper at the enzyme's active site. (30)

One of the most effective tyrosinase inhibitors available. Tropolone (2-hydroxy-2, 4, 6-cycloheptatriene), which has a similar structure to o-diphenolic tyrosinase substrates, was found to be an excellent copper chelator. (31) The most

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effective inhibitor for usage in the food sector is 4-Hexylresorcinol. It is also permitted for the control of browning in a number of foods, including fresh and hot-air-dried apple slices, potatoes, avocados and shrimp melanosis. Several synthetic tyrosinase inhibitors have been demonstrated to inhibit monophenolase, diphenolase, or both of these actions (Table 7). (32)

B) THIOSEMICARBAZONES

Thiosemicarbazones are derivatives of thiosemicarbazone with at least one proton substituted (Fig. 7). There are five proton substitution possibilities, and several substances having at least one proton substitution have been shown to be strong tyrosinase inhibitors. The inclusion of electronegative oxygen, sulphur, or nitrogen atoms on the ligand improves ligand coordination. Thiosemicarbazones are typically used as chelating agents, with transition metal ions attaching through sulphur or hydrazine nitrogen atoms on the thiosemicarbazide moiety. Because tyrosinase contains two copper ions in its active site, thiosemicarbazones can chelate the ions and reduce the enzyme's catalytic activity.

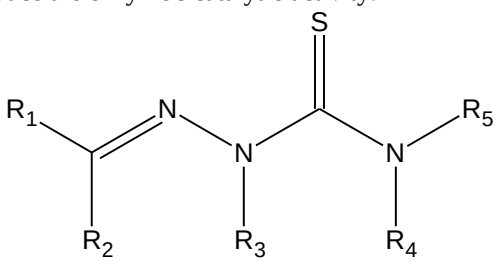
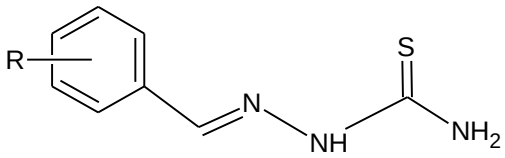


Fig.7 General Structure of thiosemicarbazone derivatives with assigned all possible substitution positions.

Benzaldehyde thiosemicarbazone (Figure 8) was reported few times as potent tyrosinase inhibitor. Because L-tyrosine and Ldopa, which are natural tyrosinase substrates and also contain phenyl groups, are more comparable to thiosemicarbazones, proton substitution with an aromatic ring may increase the affinity of thiosemicarbazones to the enzyme. The high affinity of these substances for the enzyme results from their aromatic rings' van der Waals interactions with the hydrophobic residues in the tyrosinase cavity. (33)



i. R = 2-OH
ii. R = 3-OH
iii. R = 4-OCH3

iv. R = 4-Br

v. R = 2, 4-OH

Fig.8 Structures of hydroxy and methoxy-substituted benzaldehyde thiosemicarbazone derivatives as tyrosinase inhibitors

C) COUMARINS

Lactones of phenylpropanoid acid with an H-benzopyranone nucleus are known as coumarins. The most well-known coumarin-type tyrosinase inhibitor is aloesin (Figure 9a), a naturally occurring hydroxycoumarin glucoside that was isolated from Aloe vera. Due to its natural origin and multifunctional activity in skin care, aloesin demonstrated more inhibitory efficacy towards crude murine tyrosinase than mushroom tyrosinase and has lately been employed in topically applied cosmetics. 9-hydroxy-4-methoxypsoralen (Figure 9b) was extracted from Angelica dahurica and demonstrated six times greater tyrosinase inhibitory action than kojic acid. Interestingly, another purified molecule, cleomiscosin A, had a structure that was very similar to 8'-epi-cleomiscosin A but had a 14-fold lower tyrosinase inhibitory activity when compared to -proton that of 8'-epi-cleomiscosin A. The sole difference between these two compounds is that the proton in the latter is at the same place. (34)

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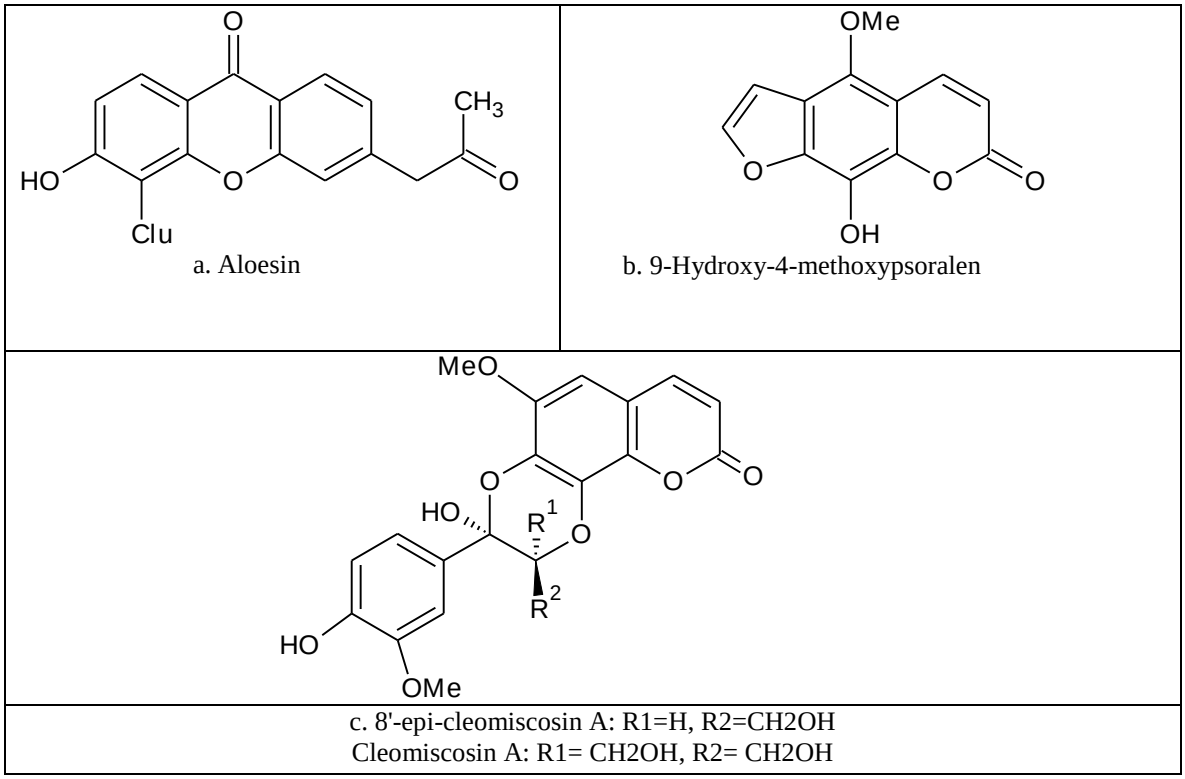

a. Aloesin

b. 9-Hydroxy-4-methoxypsoralen

c. 8'-epi-cleomiscosin A: R1=H, R2=CH2OH
Cleomiscosin A: R1= CH2OH, R2= CH2OH

Fig. 9 Chemical structures of selected tyrosinase inhibitors belonging to Coumarins

D) PEPTIDES

Peptides have occupied a significant place in drug discovery research due to their structure, safety, and chemical properties. In recent years, various researches have been conducted on peptides as well as kojic acid hybrids possessing anti-tyrosinase activity. Focusing on the effectiveness of peptides and the problems with the present tyrosinase inhibitors, 16 naturally occurring and synthetic anti-tyrosinase peptides were reported.

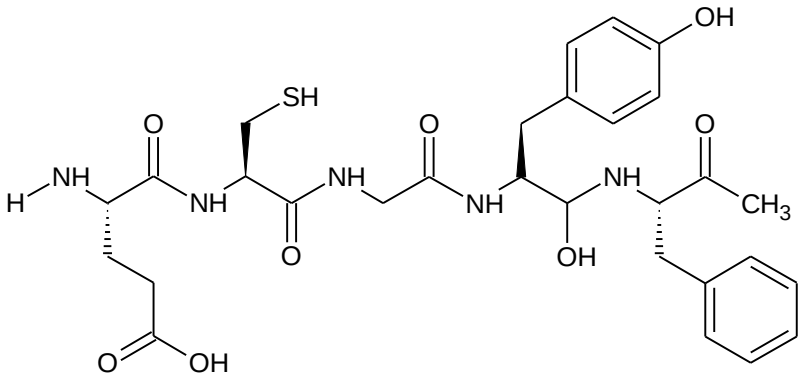

Fig.10 The structure of peptide

Natural peptides

Lactobacillus helveticus anti-tyrosinase cyclotetrapeptide with tyrosine, valine, and two proline residues. Pseudostellaria heterophylla roots contain seven cyclic peptides with tyrosinase inhibitory action [Table 7]. A new cyclic depsipeptide from Oscillatoria agardhii (Oscillapeptin G) containing glyceric acid, glutamine, leucine, 3-amino-6-hydroxy-2-piperidone, two threonine residues, N-methyl tyrosine, isoleucine, and homotyrosine.

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Table 7 Cyclic peptides possessing tyrosinase inhibitory activity from Pseudostellaria heterophylla roots

Pseudostellarins	Structures
A	Cyclo[Gly-Pro-Tyr-Leu-Ala]
B	Cyclo[Gly-Ile-Gly-Gly-Gly-Pro-Pro-Phe]
C	Cyclo[Gly-Thr-Leu-Pro-Ser-Pro-Phe-Leu]
D	Cyclo[Gly-Gly-Tyr-Pro-Leu-Ile-Leu]
E	Cyclo[Gly-Pro-Pro-Leu-Gly-Pro-Val-Ile-Phe]
F	Cyclo[Gly-Gly-Tyr-Leu-Pro-Pro-Leu-Ser]
G	Cyclo[Pro-Phe-Ser-Phe-Gly-Pro-Leu-Ala

Synthetic peptides

A library of proteins and synthesized peptides obtained from different sources such as β-lactoglobulin, α-lactalbumin, β-conglycinin, gliadin, ovalbumin, glycinin, and β-casein. (35)

E) THIOUREA

N-Phenylthiourea (PTU) has long been known to be a tyrosinase inhibitor (Figure 11). The complex crystal structure of PTU and catechol oxidase, both of which belong to the type-3 copper protein group, revealed that the sulphur atom of the thiourea moiety was linked to both copper ions in the enzyme. Meanwhile, van der Waals interactions between amino acid residues (Phe 261, Ile 241, His 244) contributed to PTU's strong affinity for tyrosinase.

The inhibitory activity of phenyl thiourea derivatives against mushroom tyrosinase was determined. The tyrosinase inhibitory actions of the compounds with fluorine atoms at the phenyl ring were greater. Particularly, the molecule (11a) shown noticeably more activity than kojic acid (IC50 14 33.3 lM). Additionally, the mechanism research showed that compound 14a might be an inhibitor that doesn't compete. As a result, when compared to other derivatives and the reference kojic acid (IC50 14 16.8320 0.0621 mM), N-(quinolin-3-ylcarbamo thioyl) hexanamide (11b) displayed the greatest tyrosinase inhibitory action. It was a noncompetitive inhibitor, according to kinetic study, with a Ki value of 0.0087 mM. (36)

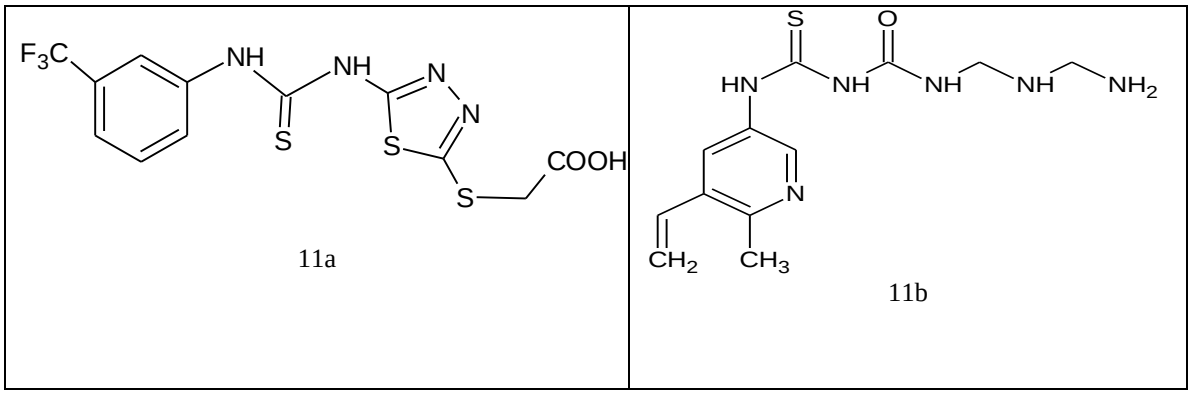

Fig.11. Structures of Thiouurea

CONCLUSION

To identify novel inhibitors with drug-like properties especially on tyrosinase proteins resulted as better depigmenting and lightening agents, various compounds from both natural and synthetic sources have been investigated during the past three decades. Melanocytes play a key role in tanning, and also to other factors secreted by keratinocytes as a consequence of UV exposure. Therefore, understanding the mechanisms by which different factors and compounds induce melanogenesis is of great interest pharmaceutically (as therapy for pigmentary diseases) and cosmeceutically (*e.g.*, to design tanning products with the potential to reduce skin cancer risk). Natural tyrosinase inhibitors are preferred over their synthetic analogs owing to the

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safety and can be used irrespective of the span of time for treatment as they also have other synergistic effects nourishing the skin. Finally, we hope that the information provided in this study, could serve as leads in the search for effective anti-tyrosinase agents from natural and synthetic sources with increased efficiency and safety in the food and cosmetics industries.

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