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Journal of Chemical and Pharmaceutical Research, 2013, 5(10):320-326

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Molecular docking studies of embelin (simple natural benzoquinone) and its derivatives as a potent tyrosinase inhibitor

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ABSTRACT

In recent years regulation of the enzymatic activity of tyrosinase has been the main focus of investigation due to its potential applications in medicine, agriculture and cosmetics. In the present study, we evaluated its docking behaviour of nine different ligands (such as Coenzyme Q10, L-DOPA, Embelin, Idebenone, Kojic acid, 5-Methyl embelin, Potassium embelate, L-Tyrosine and Vilangin)with the copper-bound Streptomyces castaneoglobisporus tyrosinase & Agaricus bisporus (Mushroom tyrosinase). Autodock 4.0 tool was used to investigate its putative binding residues. Molecular physicochemical and the drug-likeness studies reveal that L-DOPA, Kojic acid and L-Tyrosine complies very well with thumb rule of five. With regard to affinity and binding energy calculationswith the targeted protein (Streptomyces castaneoglobisporus tyrosinase), kojic acid showed least affinity value -3.52 kcal/mol, compared to other chosen ligands. Similarly, in case of Agaricus bisporus (Mushroom tyrosinase), embelin showed least affinity value of -6.56 kcal/mol, compared to all other ligands. Thus, our present molecular docking studies could contribute for the further, development and understanding of tyrosinase inhibitors for the prevention of hyper pigmentation.

Key words: Embelin, Molecular physicochemical properties, Drug-likeness properties, *Streptomyces castaneoglobisporus* tyrosinase, Molecular docking

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INTRODUCTION

Tyrosinase is a copper containing enzyme that is localized in eyes, skin and hair. It is wide spread in virtually all living organisms from bacteria to higher eukaryotes. It is rate limiting enzyme in melanogenesis process and catalyses the first two steps of this process namely: the hydroxylation of tyrosine to 3, 4 Dihydroxy phenylalanine (DOPA) and the oxidation of DOPA to Dopaquinone. It is a trans membrane melanosomal protein. The cytoplasmic domain contains the activation site for protein kinase-C-β. The intra melanosomal portion contains the copper binding catalytic domain responsible for incorporating tyrosine into DOPA and otherwise promoting melanin synthesis. Apart from this tyrosinase also contains two cysteine rich regions, a signal peptide region and an EGF (epidermal growth factor) motif. Two Cu^{2+} ions individually connected with three histidine residues (His) at the active site are charged in their cupric (or) cuprous state and are directly involved in different catalytic reactions via the oxy, deoxy & met states [1]. The copper atoms in the active site plays vital role in tyrosinase catalytic activity. They cause these reactions through electron transfer to the respective substrates. Therefore, chelation of tyrosinase Cu^{2+} by synthetic compounds (or) agents from natural sources has been targeted as a way to inhibit or block tyrosinase catalysis for pharmaceutical purposes, darking problems in agricultural products and cosmetic interests. Indeed, understanding and inhibiting tyrosinase would be an important in medicine due to its clear role in Parkinson's disease [2], melanoma [3] and hyper pigmentation. Tyrosinase also participates in cuticle formation in insects. Moreover, inhibiting tyrosinase can prevent the unwanted darkening of fruits and seafood, which has financial significant [4].

Hydroquinone was well known for tyrosinase inhibition activity; however now it was banned due to its toxicity [5]. Similarly hydroquinone derivative namely Alkyl hydroquinone 10 (Z)-heptadecenyl hydroquinone [HQ17(1)] was reported to inhibit tyrosinase activity as well as melanin production [6]. Anthraquinones are known as moderate to strong inhibitors of tyrosinase. Tyrosinase was inhibited by emodin (Anthraquinone derivative) [7]. Another anthraquinone namely 1,5 dihydroxy-7-methoxy-3-methyl anthraquinone was reported to exhibit 72 fold more anti-tyrosinase activity compared to standard compound (Kojic acid). Similarly physcion (1,8 dihydroxy-2-methoxy-3-methyl anthraquinone) another anthraquinone was also reported to exhibited tyrosinase inhibitory activity, which was on par with kojic acid [7]. Regulation of the enzymatic activity of tyrosinase has been the main focus of investigation due to its potential applications in medicine, agriculture and cosmetics [8]. Therefore, in the present study we evaluated its docking behaviour with nine different ligands (such as Coenzyme Q_{10}, L-DOPA [Levo-3,4dihydroxy phenyl alanine], Embelin, Idebenone, Kojic acid (4, 5 Hydroxy-2-(hydroxymethyl)-4-H-pyran-4-one), 5-Methyl embelin, Potassium embelate [without potassium unless otherwise mentioned], L-Tyrosine [Levo tyrosine] and Vilangin) and investigated its putative binding residues using autodock 4.0.

EXPERIMENTAL SECTION

Molecular descriptors analysis

Molinspiration was used to calculate thirteen descriptors such as logP, polar surface area, molecular weight, number of atoms, number of O or N, number of OH or NH, number of rotatable bonds, volume, drug likeness (includes GPCR ligand, ion channel modulator, kinase inhibitor and nuclear receptor ligand) [9] and number of violations to Lipinski's rule for all ligands taken for the analysis [10].

Ligand preparation

Chemical structures of ligands such as Coenzyme Q10 [CID no: 5281915], L-DOPA [CID no: 6047],embelin [CID no: 3218], idebenone [CID no:3686], kojic acid [CID no: 3840], 5-O-methyl embelin [CID no: 171489], potassium embelate [CID no: 23677950], L-Tyrosine [CID no: 6057] and vilangin[CID no: 417182] were retrieved from Pubchem compound database [11].

Target protein Identification and preparation

The three dimensional structures of the copper-bound *Streptomyces castaneoglobisporus* tyrosinase (Oxy form, PDB id: 1WX2) and *Agaricus bisporus* (Mushroom tyrosinase, Deoxy form, PDB id: 2Y9W) were obtained from the RCBS Protein data bank [12]. The proteins were pre-processed separately by deleting the ligand as well as the crystallographically observed water molecules (water without Hydrogen bonds).

Docking setup

Docking was performed using Autodock 4. Autodock combines energy evaluation through precalculated grids of affinity potential employing various search algorithms to find the suitable binding position for a ligand on a given protein [9]. Kollman united atom charges and polar hydrogens were added to the protein PDB using Autodock tools [9]. All rotatable bonds in the ligands were kept free to allow for flexible docking. Grid size was set to 40 x 40 x 40 grid points (x, y and z), with spacing between grid points kept at 0.375 Å. The Lamarckian genetic algorithm was chosen to search for the best conformers. Standard docking protocol was applied. One hundred independent docking runs were carried out for each ligand was generated by using genetic algorithm searches.

RESULTS AND DISCUSSION

Molecular physicochemical and the Drug-Likeness are the two properties that are significant for considering a compound to become a successful drug candidate. The rule formulated by Lipinski Co-workers [13] considered as the thumb rule, where the rule describes molecular properties important for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism, and excretion ("ADME"). LogP (Octanol-water partition coefficient) is used as significant tool in both quantitative structure-activity relationship (QSAR) studies and rational drug design as a measure of molecular hydrophobicity. LogP value less than 5 will be preferred for drug likeness property. The preferred range of molecular weight for drug likeness property was in range between160 to 480 g/ mol as reported by Tambunan and Wulandari [14]. With regard to the preferred number of N, O (hydrogen bond acceptors) and OH & NH (hydrogen bond donors)10 and or less than 10 and 5 and or less than 5,which compliance with the rule number three and four respectively. Further, the preferred number of rotatable bonds (rotb) is 15 and or less than 15, which compliance with the rule number five. In the present study LogP value of L-DOPA was -2.199, followed by L-Tyrosine and kojic acid as -1.71 & -0.88 of LogP values respectively. The molecular weight of the ligand was calculated as 142.11 g/mol (kojic acid),181.191 g/mol (L-Tyrosine) & 197.19 g/mol (L-DOPA) respectively. Hence all the three ligands, agrees with this rule number two. Furthermore, all the three ligands, in the present study comply very well with all the five rules and exhibited nil violation of rule as shown in the table1.

Table: 1 Analysis of descriptors using Molinspiration online software tool

	Ligands		
Molecular Physicochemical properties	Kojic acid	L-Tyrosine	L-DOPA
Log A (Octanol-Water partition coefficient)	-0.88	-1.71	-2.199
TPSA (Polar surface area)	70.667	83.55	103.778
natoms (Number of non hydrogen atoms)	10.0	13.0	14.0
MW (Molecular weight)	142.11	181.191	197.19
nON (Number of hydrogen bond acceptors [O and N atoms])	4	4	5
nOH NH (Number of hydrogen bond donors [OH and NHgroups])	2	4	5
nviolations (Number of Rule of 5 violations)	0	0	0
nrotb (Number of rotatable bonds)	1	3	3
Volume (Molecular volume)	117.432	163.981	171.999
Drug likeness (or) Bioactivity score			
GPCR ligand	-1.99	-0.08	-0.04
Ion channel modulator	-1.38	0.41	0.39
Kinase inhibitor	-1.54	-0.68	-0.60
Nuclear receptor ligand	-1.72	-0.20	-0.17
Protease inhibitor	-1.22	-0.04	-0.01
Enzyme inhibitor	-0.21	0.27	0.29

Similarly, in our earlier report [15] molecular physicochemical and the drug-Likeness properties were studied for other ligands such as CoenzymeQ$_{10,}$ embelin, idebenone, 5-methyl embelin, potassium embelate and vilangin respectively.

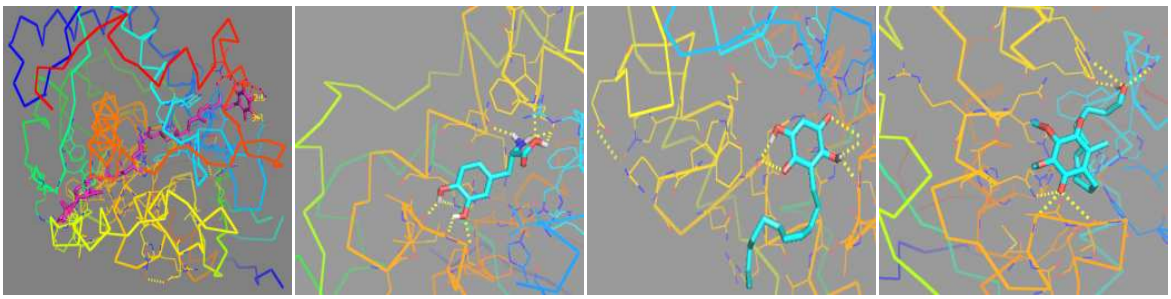
Molecular docking studies serve as boon to the field of Drug design and development, which also helps in screening small molecules by orienting and scoring them in binding sites of protein [16]. With regard to affinity and binding energy calculations, each chosen ligands displayed different affinities with the targeted protein (*Streptomyces castaneoglobisporus* tyrosinase). Expect CoenzymeQ$_{10}$ (+1739.37 kcal/mol) and Vilangin (+49.36 kcal/mol) all other seven ligands showed very good affinity, as shown in the table 2 & figure1. Where kojic acid showed least affinityvalue of -3.52 kcal/mol, compared to other six ligands namely L-DOPA, L-Tyrosine, embelin, idebenone, 5-methyl embelin and potassium embelate.

Table: 2 Affinity and binding energy calculations for chosen ligands with the targeted protein (*Streptomyces castaneoglobisporus* tyrosinase)

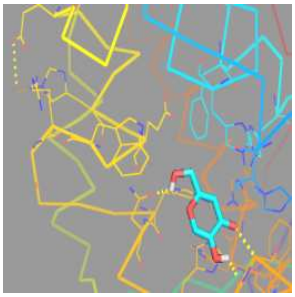
Ligand	Lowest binding energy (kcal/mol)	Mean binding energy (kcal/mol)
Coenzyme Q$_{10}$	+4.89 X 10^6	+5.03 X 10^6
L-DOPA*	-5.53	-4.82
Embelin	-4.79	-3.77
Idebenone	-4.17	-2.03
Kojic acid	-3.52	-3.44
5-Methyl embelin	-5.24	-3.95
Potassium embelate	-5.10	-4.07
L-Tyrosine**	-5.24	-5.03
Vilangin	+49.36	+199.64

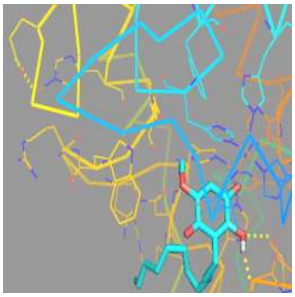
**-L-DOPA; means Levo -3,4 Dihydroxy phenyl alanine.*
***-L-Tyrosine; means Levo-Tyrosine.*

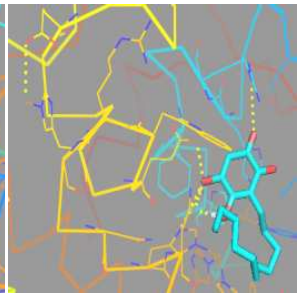
Figure: 1 Docking results of chosen ligands with the targeted protein (*Streptomyces- castaneoglobisporus* tyrosinase)

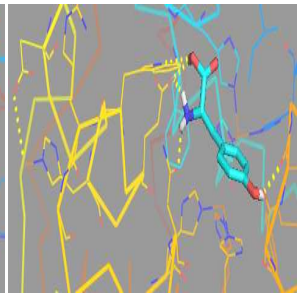


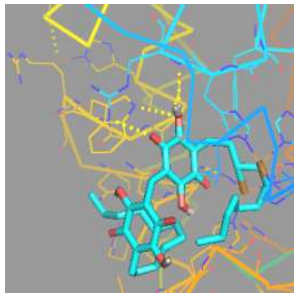
CoenzymeQ$_{10}$ **L-DOPA** **Embelin** **Idebenone**


Kojic acid


5-Methyl embelin


Potassium embelate


L-Tyrosine

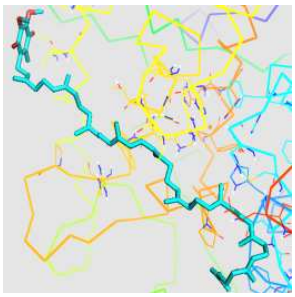

Vilangin

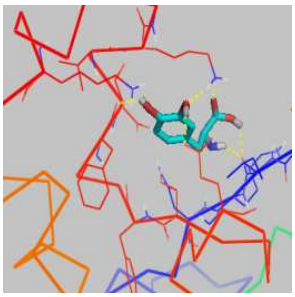
Similarly with regard to affinity and binding energy calculations, each chosen ligands displayed different affinities with the targeted protein (Mushroom tyrosinase). Expect CoenzymeQ_{10} (+3.71 kcal/mol) all other eight ligands showed very good affinity, as shown in the table 3 & figure 2. Where Embelin showed least affinity value of -6.56 kcal/mol, compared to other seven ligands namely potassium embelate, L-DOPA, 5-methyl embelin, L-Tyrosine, idebenone, kojic acid and vilangin.

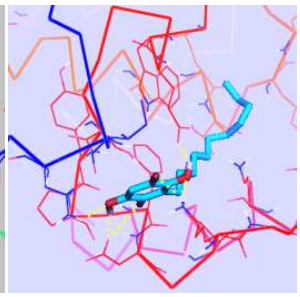
Table: 3 Affinity and binding energy calculations for chosen ligands with the targeted protein *Agaricus bisporus* (Mushroom tyrosinase)

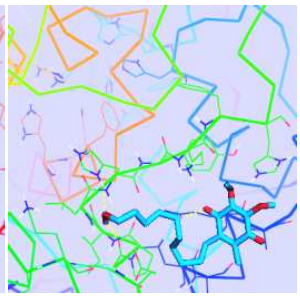
Ligand	Lowest binding energy (kcal/mol)	Mean binding energy (kcal/mol)
Coenzyme Q_{10}	+3.71	+5.01
L-DOPA	-5.85	-5.18
Embelin	-6.56	-6.56
Idebenone	-5.42	-4.51
Kojic acid	-5.24	-4.92
5-Methyl embelin	-5.84	-4.79
Potassium embelate	-6.00	-5.25
L-Tyrosine	-5.44	-5.05
Vilangin	-3.39	-3.39

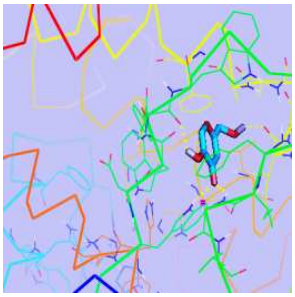
Figure: 2 Docking results of chosen ligands with the targeted protein *Agaricus bisporus* (Mushroom tyrosinase)

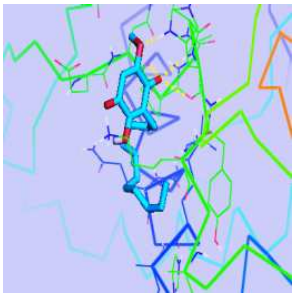

CoenzymeQ_{10}

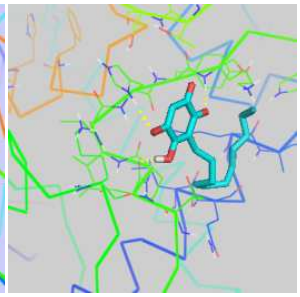

L-DOPA

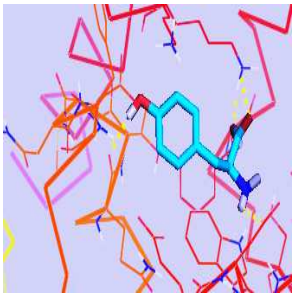

Embelin


Idebenone


Kojic acid


5-Methyl embelin


Potassium embelate


L-Tyrosine

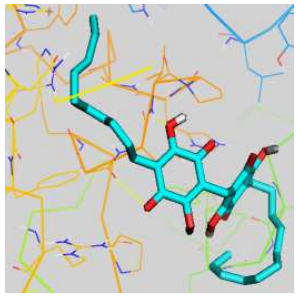

Vilangin

Table: 4 Interaction sites, bond sites and bond distance, between *Streptomyces –castaneoglobisporus* tyrosinase and chosen ligands

Ligand	Interaction sites	Bond	Bond distance (A°)
Coenzyme Q_{10}	252 th residue Lys of A chain	Lys A 252-NZ···O (Coenzyme Q_{10})	2.0
	50th residue Glu of A chain	Glu A 50-OE··· O (Coenzyme Q_{10})	3.1
L-DOPA	182th residue Glu	Glu 182-OE2··· H(L-DOPA)	1.8
	182th residue Glu	Glu 182-OE2··· H(L-DOPA)	2.0
	184th residue Trp	Trp 184-NE1···O (L-DOPA)	3.0
	191th residue Asn	Asn 191-OD1···H(L-DOPA)	2.0
	194th residue His	His 194-CE1··· H*(L-DOPA)	2.8
	201th residue Met	Met201-O··· H*(L-DOPA)	2.1
	203th residue Thr	Thr 203-O··· H(L-DOPA)	2.0
	206th residue Ser	Ser 206-OG··· O(L-DOPA)	2.7
Embelin	191th residue Asn	Asn 191-OD1···O(Embelin)	3.5
	191th residue Asn	Asn 191-OD1···H(Embelin)	2.1
	203th residue Thr	Thr 203-O···O*(Embelin)	2.2
	206th residue Ser	Ser 206-O···O*(Embelin)	2.0
	206th residue Ser	Ser 206-OG···O(Embelin)	3.4
Idebenone	55th residue Arg	Arg 55-NE···O (Idebenone)	2.8
	182th residue Glu	Glu182-OE2···H(Idebenone)	2.7
	184th residue Trp	Trp 184-NE1··· O(Idebenone)	3.4
	194th residue His	His 194-ND1··· O(Idebenone)	3.5
	201th residue Met	Met 201-O··· O(Idebenone)	2.8
	203th residue Thr	Thr 203-C··· O(Idebenone)	3.0
Kojic acid	191th residue Asn	Asn 191-OD1···H(Kojic acid)	2.2
	203th residue Thr	Thr 203-O···H(Kojic acid)	2.2
	206th residue Ser	Ser 206-OG···O(Kojic acid)	2.8
5-Methyl embelin	203th residue Thr	Thr 203-O···H(5-Methyl embelin)	2.1
	206th residue Ser	Ser 206-OG···O(5-Methyl embelin)	2.6
Potassium embelate	55th residue Arg	Arg 55-NE···O(Potassium embelate)	3.4
	182th residue Glu	Glu 182-OE2··· O(Potassium embelate)	2.7
	190th residue His	His 190-ND1··· O(Potassium embelate)	3.3
	191th residue Asn	Asn 191-CG···H(Potassium embelate)	3.3
	191th residue Asn	Asn 191-CG···O(Potassium embelate)	1.7
L-Tyrosine	182th residue Glu	Glu 182-OE2··· H(L-Tyrosine)	1.8
	182th residue Glu	Glu 182-OE2··· H(L-Tyrosine)	2.0
	184th residue Trp	Trp 184-NE1··· O(L-Tyrosine)	3.2
	191th residue Asn	Asn 191-OD1···H(L-Tyrosine)	2.0
	203th residue Thr	Thr 203-O···O(L-Tyrosine)	2.0
Vilangin	55th residue Arg	Arg 55-NH_2···O (Vilangin)	3.2
	55th residue Arg	Arg 55-N···O* (Vilangin)	3.2
	184th residue Trp	Glu 182-NE1··· O*(Vilangin)	3.3

**-bind with the same Oxygen (or) Hydrogen atom.*

With regard to the interaction sites, bond sites and bond distance, calculated based on the bioinformatics tool for the targeted protein (*Streptomyces castaneoglobisporus* tyrosinase) with that of nine different ligands individually as shown in table 4.

Where CoenzymeQ$_{10}$ does not exhibited any interaction or binding. Glutamic acid (Polar amino acid) at (Glu) 55th position was one of putative binding residues for idebenone, potassium embelate and vilangin ligands respectively. Glutamic acid (Polar amino acid) at (Glu) 182th position was one of putative binding residues for L-DOPA, idebenone, potassium embelate and L-Tyrosine ligands respectively. Tryptophan (Aromatic amino acid) at (Trp) 184th position was one of putative binding residues for L-DOPA, idebenone, L-Tyrosine and vilangin ligands respectively. Histidine (Aromatic amino acid) at (His) 190th position was one of putative binding residues for potassium embelate ligand. Asparagine (Polar amino acid) at (Asn) 191th position was one of putative binding residues for L-DOPA, embelin, kojic acid, potassium embelate and L-tyrosine ligands respectively. Methionine (Polar amino acid) at (Met) 201th position was one of putative binding residues for L-DOPA and idebenone ligands respectively. Threonine (Polar amino acid) at (Thr) 203th position was one of putative binding residues for L-DOPA, embelin, idebenone, 5-Methyl embelin and L-tyrosine ligands respectively. Serine (Polar amino acid) at (Ser) 206th position was one of putative binding residues for L-DOPA, embelin, kojic acid and 5-Methyl embelin ligands respectively. With reference to affinity and binding energy calculations, with the targeted protein (*Streptomyces castaneoglobisporus* tyrosinase), in our earlier study [17] we reported molecular docking of L-Cysteine with that of *Streptomyces castaneoglobisporus* tyrosinase. Similarly, several reports were available to substantiation use of *Streptomyces castaneoglobisporus* tyrosinase as targeted protein for docking studies [18-19]. Similarly with reference to affinity and binding energy calculations, with the targeted protein (Mushroom tyrosinase), several reports were available to substantiation use of Mushroom tyrosinase as targeted protein for docking studies [20-21].
Similarly with regard to the interaction sites, bond sites and bond distance, calculated based on the bioinformatics tool for the targeted protein (Mushroom tyrosinase) with that of nine different ligands individually as shown in table 5.

Table: 5 Interaction sites, bond sites and bond distance, between *Agaricus bisporus* (Mushroom tyrosinase) and chosen ligands

Ligand	Interaction sites	Bond	Bond distance (A°)
Coenzyme Q_{10}	219thresidue Ala	Ala 219-O···O(Coenzyme Q_{10})	2.3
L-DOPA	17th residue Ile	Ile17-O··· H(L-DOPA)	2.2
	17th residue Ile	Ile17-O··· H(L-DOPA)	2.0
	359th residue Glu	Glu 359-OE2··· H(L-DOPA)	1.9
	368th residue Phe	Phe368-O···H(L-DOPA)	2.1
	372th residue Lys	Lys372-HZ3···O(L-DOPA)	2.2
Embelin	19th residue Asn	Asn 19-HD2···O(Embelin)	2.4
	359th residue Glu	Glu359-CD···H(Embelin)	1.8
	369th residue Asp	Asp369-OD1···O(Embelin)	3.2
	369th residue Asp	Asp369-OD1···H(Embelin)	1.9
	372th residue Lys	Lys372-HZ3···O(Embelin)	2.1
Idebenone	44th residue Gln	Gln44-OE1···O (Idebenone)	2.7
	174th residue Asn	Asn 174-O··· H(Idebenone)	2.1
	178th residue His	His 178-HD1··· O(Idebenone)	2.2
Kojic acid	136th residue Trp	Trp 136-HE1···O*(Kojic acid)	1.9
	140th residue Tyr	Tyr 140-O···H(Kojic acid)	2.0
	149th residue Gly	Gly149-HN···O*(Kojic acid)	2.1
	217thresidue Ile	Ile 217-O···H(Kojic acid)	1.9
5-Methyl embelin	174th residue Asn	Asn174-O···O*(5-Methyl embelin)	2.5
	178th residue His	His178-HN···O*(5-Methyl embelin)	2.3
	178th residue His	His178-O···O*(5-Methyl embelin)	2.7
	178th residue His	His178-HD1···O(5-Methyl embelin)	1.8
Potassium embelate	174th residue Asn	Asn174-O···H(Potassium embelate)	2.1
	178th residue His	His 178-HD1··· O(Potassium embelate)	2.2
	180th residue Lys	Lys 180-HN··· O(Potassium embelate)	2.8
L-Tyrosine	307th residue Gln	Glu 307-O··· H(L-Tyrosine)	2.1
	379th residue Lys	Lys379-HZ2···O(L-Tyrosine)	2.8
	379th residue Lys	Lys379-HZ2···O(L-Tyrosine)	1.7
	357th residue Asp	Asp357-OD1···H(L-Tyrosine)	1.9
Vilangin	281th residue Gly	Gly281-O···O (Vilangin)	3.3
	283th residue Val	Val283-HN···O (Vilangin)	1.8

**-bind with the same Oxygen atom.*

Alanine (Non-polar amino acid) at (Ala) 219th position was only putative binding residue for CoenzymeQ$_{10}$. Asparagine (Polar amino acid) at (Asn) 174th position was one of putative binding residues for 5-Methyl embelin, potassium embelate and idebenone ligands respectively. Histidine (Aromatic amino acid) at (His) 178th position was one of putative binding residues for 5-Methyl embelin, potassium embelate and idebenone ligands respectively. Glycine at (Gly) 281th position and Valine (Non-polar amino acid) at (Val) 283th position were putative binding

residues for vilangin ligand respectively. Glutamate (Polar amino acid) at (Gln) 307th position, Asparatic acid (Polar amino acid) at (Asp) 357th position and Lysine (Polar amino acid) at (Lys) 379th position were putative binding residues for L-Tyrosine ligand respectively. Isoleucine (Non-polar amino acid) at (Ile) 17th position, Glutamic acid (Polar amino acid) at (Glu) 359th position, Phenylalanine (Aromatic amino acid) at (Phe) 368th position and Lysine (Polar amino acid) at (Lys) 372th position were putative binding residues for L-DOPA ligand respectively. Tryptophan (Aromatic amino acid) at (Try) 136th position, Tyrosine (Aromatic amino acid) at (Phe) 140th position, Glycine at (Gly) 149th position and Isoleucine (Non-polar amino acid) at (Ile) 217thpositionwere putative binding residues for kojic acid ligand respectively.Glutamate (Polar amino acid) at (Gln) 44th position & Lysine (Polar amino acid) at (Lys) 180th position was one of putative binding residues for idebenone and potassium embelateligands respectively. Asparagine (Polar amino acid) at (Asn) 19th position, Glutamic acid (Polar amino acid) at (Asn) 359th position, Asparatic acid (Polar amino acid) at (Asp) 369th position and Lysine (Polar amino acid) at (Lys) 372th position were putative binding residues for embelin ligand respectively. With reference to the interaction sites, bond sites and bond distance, calculated based on the bioinformatics tool for the targeted protein (*Streptomyces castaneoglobisporus* tyrosinase). Nithitankool co-workers [18] reported that all docked ligands interacts with Ile 42, Asn191, Thr203 and Ser206 residues of *Streptomyces castaneoglobisporus* tyrosinase. Joonho Park and Nack-Do Sung [19] also reported that most of thiosemicarbazone analogues studied were interacts mainly with Glu182 and Asn191 residues of *Streptomyces castaneoglobisporus* tyrosinase. Similarly with reference to the interaction sites, bond sites and bond distance, calculated based on the bioinformatics tool for the targeted protein (Mushroom tyrosinase). Yin co-workers [20] reported that phthalic acid interacts with Glu67 and Leu73 residues of *Agaricus bisporus* tyrosinase (2ZMX chain A). Wang co-workers [21] reported that fucoidan interacts with His 56, 80, 249, 253, Cys78, Glu246 and Pro268 residues of *Agaricus bisporus* tyrosinase (2Y9X).

CONCLUSION

Regulation of the enzymatic activity of tyrosinase has been the prime focus of investigation due to its potential applications in various fields such as medicine, agriculture and cosmetics. Indeed, inhibiting and understanding tyrosinase would be a significant in medicine due to its clear role in melanoma, hyper pigmentation and Parkinson's disease. Hence, our present study results provide new insight in understanding the, embelin as a potent tyrosinase inhibitor. Thus, our present molecular docking studies could contribute for the further, development and understanding of tyrosinase inhibitors for the prevention of hyper pigmentation.

Acknowledgement
All the authors, thanks the IADVL-L'OREAL, India for financial assistance in the form of Pigmentation Research Grant-2012 is gratefully acknowledged.

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