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# Effect of a Proprietary *Arctostaphylous uva-ursi* Standardized Extract (UvaZen-VArb™) on Melanin Regulation and Skin Applications- An *In-silico* Molecular Docking Study

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***Author's contribution***

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## ABSTRACT

Zenherb labs Pvt. Ltd., Mumbai, developed a proprietary *Arctostaphylous uva-ursi* standardized extract (AUSE), (branded as UvaZen-VArb™). The current study is an attempt to get insights of the interaction of bioactives against target proteins involved in skin health pathways like melanogenesis. A molecular docking approach was adopted to understand the protein-ligand interactions and predict the most probable mechanism(s) of beneficial skin health effects imparted by this cosmeceutical ingredient. Four phytoconstituents were docked against 15 shortlisted target proteins using Autodock Vina tool. Drug likeliness was assessed on the basis of ADMET properties and Lipinski's Rule of 5. Arbutin, gallic acid, quercetin and rutin in AUSE demonstrated good docking scores and bioactivities for melanin regulation, cell growth, proliferation and differentiation-hair, skin and nail.

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## 1. INTRODUCTION

Human skin consists of 3 layers namely- hypodermis, dermis and epidermis. The skin colour is dependent on melanin, a pigment produced by the melanocytes in the melanosomes [1]. Melanin is formed from an amino acid L-tyrosine, through a cascade of reactions called melanogenesis. The colour variability depends on the degree of melanin oxidation. Most prevalent types of melanin are- eumelanin (formed in brown and black subtypes), and pheomelanin (resulting in yellow and red tones). Tyrosinase is the key enzyme regulating melanin production [2]. Drugs inhibiting the activity of tyrosinase and collagenase find applications in cosmeceutical products, for their skin protective roles and delayed ageing [3,4].

Tyrosinase (EC 1.14.18.1), a copper containing enzyme, catalyses the first 2 steps of melanin production that determines the color of skin and hair-a hydroxylation (L-Tyrosine to 3,4-dihydroxyphenylalanine, *i.e.* L-DOPA) and an oxidation reaction (L-DOPA to L-dopaquinone). Inhibiting tyrosinase has been used to regulate melanin production and aid treatment of hyper-pigmentation, melasma, damaged skin and related conditions [5]. Several cosmetics are available commercially that constitute tyrosinase and / or collagenase inhibitors like hydroquinones and derivatives, retinoic acid etc. However, their teratogenic and irritant properties are posing problems to their applications. Thus, there's a need for natural extracts that can serve similar functions. Melanogenic inhibitory effects have been reported for multiple classes of phytochemicals like flavonoids, hydroquinones, phenolics, furans, alkaloids etc. [6]. Cosmetic products are a part of countless individual's daily lives and consumer behaviour has witnessed a paradigm shift. Skin and sun care products constitute the major segment in the cosmetics market [7]. Customers prefer using products where natural ingredients have been used. Safety and efficacy are two of the most important aspects in cosmeceuticals products.

*Arctostaphylous uva-ursi* (bearberry), also referred simply as uva-ursi, is a low-lying perennial evergreen shrub. Uva-ursi, has long been revealed of its application in treating urinary tract infections and is, without doubt the plant of great demand for cosmeceutical applications especially for formulating skin lightening products. The leaves and berries of uva-ursi are rich in hydroquinones (majorly arbutin-up to 17%), tannins, flavonoids and elements like iron and magnesium and are well known in the cosmetics industry [8].

The current work revolves around molecular docking of 4 phytochemicals (ligands) from this proprietary preparation against 15 proteins that are involved in different functions related to skin health. We aim to understand the mechanisms adopted by these phyto-constituents in bringing about skin whitening or skin repair or melanin regulation and other associated roles. Drug-likeliness studies were also carried out to check if these bioactives were orally bioactive.

## 2. MATERIALS AND METHODS

### 2.1 Sample

The product under study is a standardized extract of *Arctostaphylous uva-ursi* -AUSE (branded as UvaZen-VArb™). It is developed by Zenherb labs to harness its cosmeceutical potential through the presence of phyto-actives.

### 2.2 Ligand Preparation

Four bioactives from this standardized *Uva ursi* extract, have been shortlisted as ligands for the molecular docking study, based on thorough literature search (Table 1). Three-dimensional structures of the ligands were procured from PubChem (https://pubchem.ncbi.nlm.nih.gov/) in .SDF format (Table 1), and later converted to pdbqt format.

### 2.3 Retrieval of Target Proteins and it's Preparation

Target proteins involved in skin health were shortlisted based on thorough literature surveys. The 15 targets chosen were- 4XIF, 4GYY, 2HFP, 2P54, 4ZRY, 3LCK, 1K6F, 1MFR, 5YLC, 4MID, 1EST, 2GOO, 3SL9, 2R53 and 2Q3Z (Table 2). Three dimensional structures were downloaded from RCSB (www.rcsb.org). The proteins were prepared prior to docking by removing the heteroatoms and water molecules. Hydrogen bonds and Kollman's charges were further added to ready the protein structures for docking. Protein structures were saved in the pdbqt format.

## 2.4 Docking Using Autodock Vina

Study of the ligand-protein interactions were carried out by molecular docking using AutoDock Vina 1.5.6. Objectives of molecular docking are the identification of a ligand that binds to a specific receptor binding site and the identification of its preferred, energetically most favourable, binding pose. Grid parameters for each protein were generated to create a grid-box, which would allow free movement of ligands.

### 2.4.1 ADME Profiling

ADME Profiling was performed to check the important properties such as Absorption, distribution, metabolism and excretion. ADMET profiling also predicts how orally bioavailable the drug is, based on compliance to Lipinski's rule of 5. ORISIS Property Explorer was used to predict the logS value for all the compounds based on the SMILES notations. Bioactivity scores were predicted using the Molinspiration tool which calculates the Bioactivity score based on the structure and its functional groups present in the ligands. This analysis was performed from Drulito as well as calculation of molecular properties using Molinspiration (www.molinspiration.com).

### 2.4.2 Drug likeness calculations

Drug-likeness may be defined as a complex balance of various molecular properties and structure features which determine whether a particular molecule is similar to the known drugs. *In vivo* efficacy in terms of bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability etc., is influenced by parameters like hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and flexibility, presence of various pharmacophoric features etc.

## 3. RESULTS AND DISCUSSION

Ligands and proteins can exist in different combinations. Docking is one of the approaches for rational drug design. Molecular docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex, like hand in glove. Often, in search of lead molecules, a large library of molecules is virtually screened, unlike the current study, where only 4 bioactives were shortlisted for detailed insights to underlying mechanisms of promoting skin health.

## 3.1 Molecular Docking Studies

Autodock Vina was used to carry out the current docking studies. Autodock Vina is popular, user-friendly and vastly cited amongst the reputed publications [9]. Understanding of the ideal orientation in which the ligand-protein interacts, may be used to predict the binding affinities between two molecules with the help of scoring functions. Depending on the objective of study, the ligands of interest could either be an agonist (triggering a biological response) or an antagonist (suppressing the agonist facilitated response). Force-field based approaches try to estimate the absolute free binding energies (calculated as kcal/mol).

Fifteen protein targets (4XIF, 4GYY,2HFP,2P54, 4ZRY, 3LCK, 1K6F, 1MFR, 5YLC, 4MID, 1EST, 2GOO, 3SL9, 2R53 and 2Q3Z), were docked to assess their binding scores with respect to different classes of proteins playing significant roles in skin health and repair (some representative poses illustrated in Fig. 1).

The results suggest that phytochemicals have higher binding scores with the target proteins and are potential candidates for cosmeceutical applications. The results, calculated by Autodock Vina, are presented in Table 3. Favorable intermolecular interactions decrease the enthalpy and this negative free binding energy is energetically favorable [10].

In general, all the four ligands selected in the study have demonstrated decent binding scores with good bioactivities. The target proteins shortlisted were directly or indirectly involved in the functions of influencing the skin pigmentation through regulated melanin production. Melano-genic inhibitory effects have been reported for multiple classes of phytochemicals like flavonoids, phenolics, furans, alkaloids *etc.* [11]. Molecular docking approach has been adopted for understanding the key target protein interact-tion in various conditions like breast cancer [12], hepatitis [13], SARS Covid 2 infection [14] etc.

Hydroquinone, an established skin whitening agent, was used as the positive control for the docking study. The ligand-protein interactions results are indicating the molecular mechanisms through which the bioactives are able to affect the skin health. For example: All the 4 ligands demonstrate anti-inflammatory properties and show potential in use for treatment of skin inflammation conditions like discoloration, brown patch development etc.

Peroxisome proliferator-activated receptors (PPAR) are known to play role(s) in the formation of the epidermal barrier and in sebocyte differentiation [15]. PPARs are common research targets in understanding and treatment of multiple skin disorders like hyperpigmentation, acne, psoriasis. PPARα and β are especially crucial for skin repair post injury. Arbutin principally regulates melanogenesis and promotes differentiation and proliferation of skin cells through PPARs [16]. PPARs Many of PPAR-alpha target genes down-regulated in inflamed skin. All ligands are controlling the melanocyte differentiation process and are essential for maintaining the skin-barrier permeability. When compared with hydroquinone, all 4 bioactives are much more efficient in binding to the collagen protein (ProProGly-triple helix) responsible for imparting elasticity and smoothness to the skin [17].

The melanocortin 1 receptor (MC1R), also known as melanotropin receptor, is one of the most significant influencers regulating skin pigmentation and UV response. Binding of melanocortin ligands (like melanocyte stimulating hormone or adrenocorticotropic hormone) to MC1R promotes crucial UV-resistance physiologic changes in melanocytes and protects the skin from UV damage and regulates melanin formation. Gallic acid, quercetin and rutin demonstrated good binding with the 5YLC receptor. Thus, the bioactives could be used for potential application in UV repair formulations.

Another key target protein is bone morphogenetic protein (BMP) and consists of a family of dimeric proteins (BMP-2 to BMP-15). BMP receptor is a metalloprotease that cleaves pro-collagen I, II & III and structurally similar (30-50%) with the transforming growth factor-beta (TGF-β). BMP-2, specifically targets tyrosinase gene expression and thus regulates the melanin synthesis [18]. (Lower binding scores of rutin to BMP receptors are indicative of their functions involved in skin morphogenesis, anti-wrinkle effect and wound repair [19]. Quercetin, and Rutin were more effective compared to gallic acid and arbutin in binding to transglutamase, an important enzyme involved in the keratinocytes differentiation, which in turn, is responsible for epidermal barrier and prevents from chemical and physical damage [20]. Multiple *in vitro* and *in vivo* studies with urva-ursi extracts have demonstrated anti-melanogenic activities, attributed to the high arbutin content, making this plant significant to the cosmetics industry [21].

## 3.2 Drug-Likeliness and Bioactivity Prediction

Drug likeness calculations are based on qualitative parameters that help understand how drug-like a substance is, with respect to factors like bioavailability. A traditional method to evaluate drug-likeness is to check compliance to Lipinski's rule of 5, which includes the numbers of hydrophilic groups, molecular weight, solubility and hydrophobicity to predict the oral bioavailability of a drug (Lipinski, 2000). It evaluates the candidate molecules for the following parameters: (a) clogP ≤ 5; (b) Molecular weight (MW) ≤ 500 g/mol; (c) Number of hydrogen bond acceptors (sum of N and O atoms) ≤ 10 and (d) Number of hydrogen bond donors sum of OH and NH groups) ≤ 5 [22]. Additionally, Number of rotatable bonds (nRotb) ≤ 10 and Polar surface area (PSA) < 140 Å2, are also assessed based on additions by Veber et al. [23]. The simplicity of these criteria to remove outlier molecules made them very easy to implement with the use of specific software. Thus, this rule moved rapidly up in the hierarchy of medicinal chemistry concepts, from being a set of alert criteria in the minds of the medicinal chemists to a commandment engraved in the high altars of do's and don'ts of drug seekers [24].

The drug-likeness properties of molecules were analysed based on Lipinski rule of 5. Overall, the drug likeliness or the pharmacokinetics parameters analysed for the docked compounds were good for the oral consumption. These results demonstrated that the compounds were biologically active. (Table 4). Overall, the drug likeliness or the pharmacokinetics parameters analyzed for the docked compounds demonstrated good scores and biological activities. These findings suggest that bioactive compounds from AUSE, under study, are eligible lead candidates for use in skin-whitening treatments. Uva-ursi, is naturally rich in arbutin (about 17%) and finds several cosmeceutical applications, especially as a powerful skin whitening agent. It is known to block epidermal melanin biosynthesis by inhibiting the enzymatic oxidation of tyrosine and L-3,4-dihydroxyphenylalanine (L-DOPA) [25].

Maeda et al. reported that Uva-ursi extract inhibited the tyrosinase activity of cultures of human melanocytes at non-cytotoxic concentrations [16]. Literature cites multiple reports advocating the effectivity of arbutin to be

same as hydroquinones but less toxic, especially the α-arbutin, which exhibits inhibitory activity against mammalian tyrosinase [26,27]. Rutin violated 3 of the parameters (Table 4) of Lipinski's rule of 5 suggesting that this molecule is not good for oral consumption as well as does not follow the ADME properties. However, it's noteworthy that only 51% of the drugs approved by FDA are compliant to Lipinski's rule of five and consumed orally. Further, the biologicals and natural or semi-synthetic natural drugs which do not comply to the rule have established therapeutic effects, which means that if certain phyto-constituents violate 1 or 2 rules of Lipinski's, but demonstrate biological activities, they should be considered for further evaluations [28]. In general, most of the ligands selected in the study have demonstrated good binding scores with decent bioactivities.

Molinspiration is a web-based tool used to predict the bioactivity scores of the shortlisted potential drug candidate compounds for activity with the human receptors such as GPCR ligands, ion channel modulators, kinase inhibitors, nuclear receptor ligands, protease inhibitors and enzyme inhibitors [29,30]. The bioactivity scores of all the ligands can be classified into three classes – Active (>0), Moderately Active (-5.0 – 0.0), Inactive (< -5.0).

**Table 1. Phyto-chemicals (ligands) from AUSE used for the docking study**

| Sr. No | Phyto-constituents (Ligands) | Molecular formula | PubChem ID (CID) |
|---|---|---|---|
| 1 | Arbutin | C12H16O7 | 440936 |
| 2 | Gallic acid | C7H6O5 | 370 |
| 3 | Quercetin | C15H10O7 | 5280343 |
| 4 | Rutin | C27H30O16 | 5280805 |

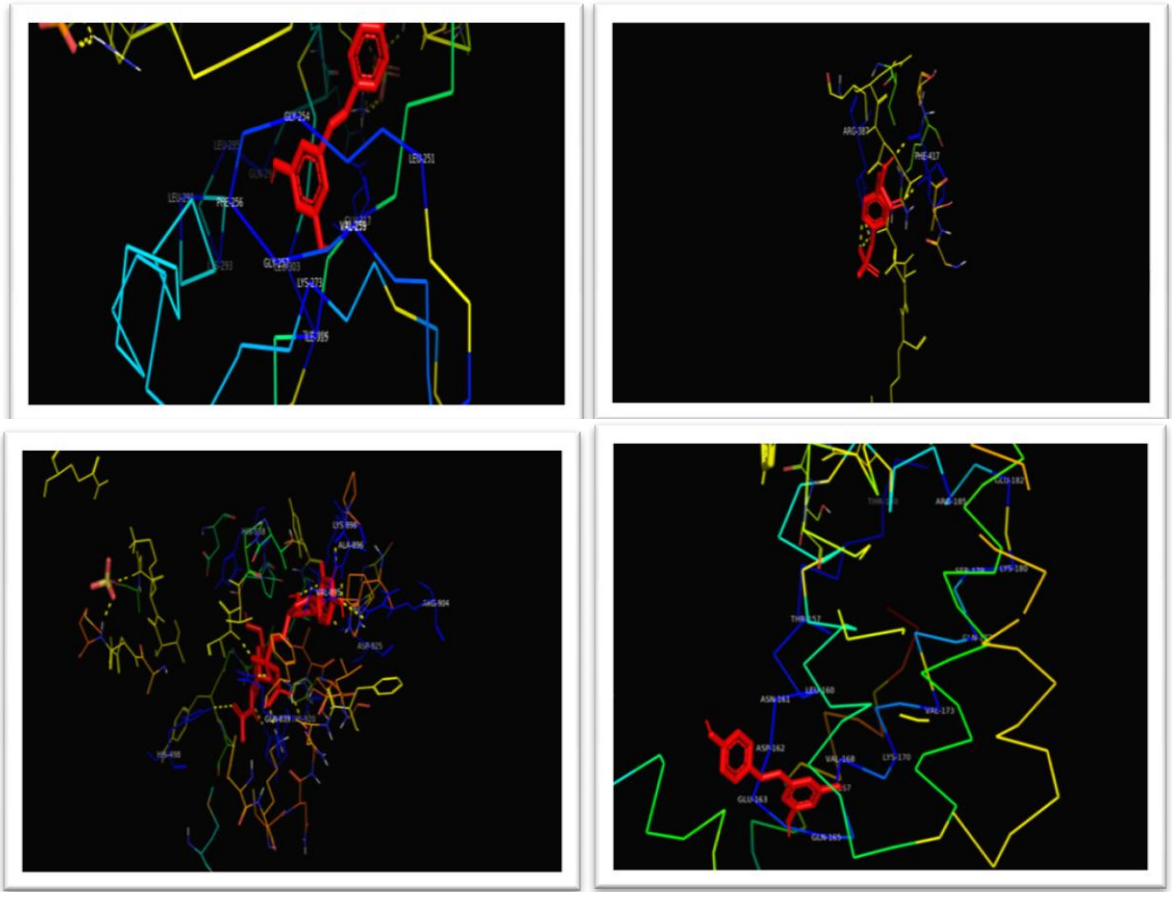
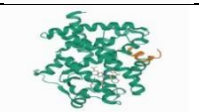
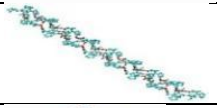
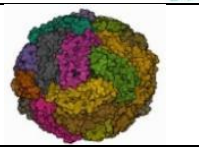


**Fig. 1. Representative images of the ligand-protein docking poses derived from PyMOL -a) Arbutin and 3LCK, b) rutin and 3LCK, quercetin and 4GYY and d) gallic acid and 3SL9**

**Note: Red colour depicts the ligand structure, blue colour represents polar regions and non-polar regions are visualized in yellow colour*

**Table 2. Target proteins involved in skin health functions**

| No. | Proteins | ID | Structures |
|---|---|---|---|
| **1** | Human OGT in complex with UDP-5S-GlcNAc and substrate peptide (keratin-7). | 4XIF |  |
| **2** | Crystal structure of human O-GlcNAc Transferase with UDP-5SGlcNAc and a peptide substrate. | 4GYY |  |
| **3** | Crystal Structure of PPAR Gamma with N-sulfonyl-2-indole carboxamide ligands. | 2HFP |  |
| **4** | A crystal structure of PPAR alpha bound with SRC1 peptide and GW735. | 2P54 |  |
| **5** | Crystal structure of the heterocomplex between coil 2B domains of human intermediate filament proteins keratin 1 (KRT1) [] and keratin 10 (KRT10) | 4ZRY |  |
| **6** | The Kinase domain of Human lymphocyte kinase (LCK), activated form | 3LCK |  |
| **7** | Crystal Structure of the Collagen Triple Helix Model [(Pro-Pro-Gly)10]3 | 1K6F |  |
| **8** | Crystal structure of M Ferritin | 1MFR |  |

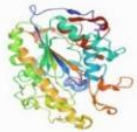
| | | | |
|---|---|---|---|
| **9** | Crystal Structure of MCR-1 Catalytic Domain. | 5YLC |  |
| **10** | ***Crystal Structure of Activin A/BMP2 chimera*.** | 4MID |  |
| **11** | Complex between BMP-2 and 2 BMP receptor IA ectodomains | 1ES7 |  |
| **12** | Complex of BMP-2 bound to BMPR-IA-ECD and ActRII-ECD | 2GOO |  |
| **13** | X-ray structure of Beta catenin in complex with Bcl9 | 3SL9 |  |
| **14** | *Crystal structure analysis of Bone Morphogenetic Protein-6 variant B2 (B2-BMP-6)* | *2R53* |  |
| **15** | *Transglutaminase 2 undergoes large conformational change upon activation* | *2Q3Z* |  |

**Table 3. Summary of binding scores of selected ligands against the 15 target proteins**

| Bioactives | Target proteins | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1K6F | 1MFR | 2HFP | 2P54 | 4ZRY | 3LCK | 4XIF | 4GYY | 5YLC | 4MID | 1ES7 | 3SL9 | 2GOO | 2R53 | 2Q3Z |
| Arbutin | -4.3 | -5.5 | -5.4 | -5.4 | -4.9 | -6.1 | -5.9 | -6.0 | -4.9 | -4.4 | -5.4 | -5.1 | -5.4 | -6.6 | -5.5 |
| Gallic acid | -4.0 | 4.8 | -5.2 | -5.2 | -4.0 | -6.4 | -5.9 | 5.2 | -6.8 | -4.6 | -4.9 | -5.2 | -4.9 | -4.3 | -5.5 |
| Quercetin | -4.2 | -6.6 | -6.5 | -6.5 | -5.9 | -7.6 | -6.5 | -7.1 | -6.0 | -4.5 | -6.5 | -3.9 | -5 | -4.1 | -6.4 |
| Rutin | -4.0 | -5.3 | -6.1 | -6.1 | -6.3 | -8.6 | -7.6 | -8.9 | 6.3 | -6.6 | -6.0 | -4.3 | -5.7 | -5.5 | -7.0 |
| Hydroquinone | -2.7 | -2.7 | -5.3 | -1.3 | -5.3 | -4.3 | -5.2 | -4.5 | -4.3 | -3.9 | -4.2 | -4.8 | -4.7 | -4.2 | -2.7 |

**Table 4. Drug likeliness evaluation of phyto-constituents (ligands)**

| Bioactives (ligands) | Parameters of Lipinski's Rule of 5 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **miLogP** | **TPSA** | **natom** | **MW** | **Non** | **nOHNH** | **nrotb** | **violations** |
| **Arbutin** | -0.81 | 119.61 | 19 | 272.25 | 7 | 5 | 3 | 0 |
| **Gallic acid** | 0.59 | 97.98 | 12 | 170.12 | 5 | 4 | 1 | 0 |
| **Quercetin** | 1.68 | 131.35 | 22 | 302.24 | 7 | 5 | 1 | 0 |
| **Rutin** | -1.06 | **269.43** | 43 | **610.52** | **16** | 10 | 6 | 3 |

*# miLogP- Octanol-water partition coefficient logP, TPSA-Topological polar surface area, Natoms-number of atoms, MW-molecular weight, nON-number of Oxygen Nitrogen, nOHNH-number of OH and NHn, nrotb-number of rotatable bonds and violations: number of rules violated; **

**Table 5. Bioactivity scores of the selected phyto-constituents (ligands) from AUSE**

| Ligands | GPCR | Ion channel | Kinase inhibitor | Nuclear receptor | Protease inhibitor | Enzyme inhibitor |
|---|---|---|---|---|---|---|
| **Arbutin** | 0.05 | 0.12 | -0.13 | 0.04 | -0.09 | 0.46 |
| **Gallic acid** | -0.77 | -0.26 | 0.88 | -0.52 | 0.94 | -0.17 |
| **Quercetin** | -0.06 | -0.19 | 0.28 | 0.36 | -0.25 | 0.28 |
| **Rutin** | -0.05 | -0.52 | -0.14 | -0.23 | -0.07 | 0.12 |

## 4. CONCLUSION

The docking scores, analysis of the interactions of the compounds suggest that all the bioactives selected in this study have the ability to bind to multiple targets involved in functions promoting skin health, especially skin pigment regulation. UVA ZenVArb acts through binding on 11 different receptors directly or indirectly affecting skin pigmentation through melanogenesis. In terms of overall drug likeness, this proprietary extract contains 2 more molecules in addition to arbutin with similar likeliness. These can also be explored for added oral and topical applications Thus, this *in silico* study on the compounds of the AUSE, advocates the huge potential of arbutin, gallic acid, quercetin, and rutin as potent cosmeceutical agents. Hence, UvaZenVArb could have a potential to show 3x better efficacy in terms of controlling skin pigmentation through various modes. Nevertheless, further in vitro, *in vivo* and quantification studies may be attempted to further establish the key bioactives of these proprietary plant extracts that are claimed to have beneficial effects on the human skin health.

## DISCLAIMER

The products used for this research are commonly and predominantly used products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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