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Original Article

NOVEL TOPICAL ANTI-AGING HERBAL COMPOSITION

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ABSTRACT

Objective: Anti-aging formulations are among the premier skin care products in the global market that are in huge demand. Different treatments are available to slow down skin aging, but are very expensive and are often found to produce adverse reactions to the skin in prolong use. Hence, present study has been designed to formulate poly herbal anti-aging skin care products and their evaluation thereon.

Methods: Anti-aging herbal skin care cream, gel and serum were prepared using two medicinal plants *Hippophae salicifolia* and *Celosia argentea* along with three bioactives caffeine, rutin and bakuchiol. The formulations were evaluated for physicochemical parameters like pH, texture analysis, acid value, short-term stability study, etc. Phenolics and flavanoid content were determined. Anti-aging potential was gauged by *in silico* studies using the glide tool of 'Schrodinger'.

Results: Cream, gel and serum showed good physical appearance and were free from gritty particles and with smooth texture. Accelerated stability studies indicated insignificant changes in physicochemical parameters of the formulations. Based on the docking score and interaction with amino acid, compounds present in the plant extracts and bioactive showed good anti-aging activity.

Conclusion: The prepared herbal anti-aging formulations were found to be stable and exhibited good potential as an anti-aging combination. So, they can be used as an effective combination to protect skin from aging.

Keywords: Anti-aging, Bakuchiol, *Celosia*, *In silico,* Polyherbal, Sea buckthorn

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INTRODUCTION

Skin aging is a complex biological process characterized by irregular pigmentation, increased wrinkling, loss of elasticity, dryness and roughness [1-3]. Herbal antioxidants stimulate collagen and elastin formation and reduce the degradation of structural components, thereby repair cutaneous photo damage [4]. Vitamins, ascorbate, carotenoids, polyphenols and flavanoids constitute an exogenous type of antioxidants [5, 6]. Vitamin A (retinol) and vitamin C play important role in biosynthesis of collagen and has positive effects not only on extrinsic but also, on intrinsic skin aging regulating collagen metabolism [2, 7]. L-ascorbic acid, interacts with copper ions at the active site of the tyrosinase enzyme thereby decreasing melanin formation [8]. Bakuchiol, a retinol-like anti-aging compound from *Psoralea corylifolia* has advantages like antioxidant potential, photochemical and hydrolytic stability and ease to formulate due to miscibility with diverse emollients and solubilizers [9, 10]. Caffeine protects skin from oxidative stress-induced senescence through activating the A2AR/SIRT3/AMPK-mediated autophagy [11, 12]. Rutin, an antioxidant, also increases skin elasticity and decreases wrinkles by regulating enzymes in the extracellular matrix [13]. *Hippophae salicifolia* (sea buckthorn) is rich in vitamins, flavonoids, phenolics and carotenoids [14]. Betalains and phenolics isolated from *C. argentea* are shown to possess antioxidant and tyrosinase inhibitory activity [15]. *In silico* anti-aging activity was performed for theses bioactives in glide tool of Schrodinger to investigate the binding mode into the active site of three different enzymes playing important role in aging.

MATERIALS AND METHODS

Procurement of materials

H. salicifolia was collected from Uttarakhand and authenticated by a taxonomist of Herbal Research and Development Institute, Gopeshwar, Uttarakhand, whereas seeds of *C. argentea* was procured from the local market of Ahmedabad, Gujarat and verified by comparing its morphological characteristics available with literature [16]. The hydro-alcoholic extracts (70%) were prepared by reflux method, and bakuchiol, caffeine and rutin were procured from Pharmacognosy laboratory repository.

Glyceryl monostearate, cetyl alcohol, isopropyl myristate, triethanolamine, carbopol, phenoxy ethanol, ethyl hexyl glycerin, butylated hydroxyl toluene (BHT) and sodium hydroxide used were of analytical grade.

Preparation of formulations

The hydro-alcoholic extracts of *H. salicifolia* and *C. argentea along* with bakuchiol, caffeine and rutin were included as active pharmaceutical ingredients (API) (table 1).

Cream

Ingredients of the oil phase and aqueous phase were melted separately using a water bath at 70 °C. Phenoxy ethanol, ethyl hexyl glycerin, and API were added into an aqueous phase and heated. Oil phase was mixed with above with constant stirring and finally, rose oil was added as a fragrance [17].

Gel

Accurately weighed carbopol 980 was dispersed in 100 ml distilled water containing all the extracts/bioactives dissolved previously, allowed to swell for half an hour and stirred for 30 min. Sodium hydroxide was added dropwise to obtain the gel at the required consistency, followed by the addition of preservatives [18].

Serum

Isopropyl myristate and the different extracts, along with bioactives were mixed properly. Finally, the preservative butylated hydroxyl toluene was added [19].

Stability study and evaluation of formulations

The accelerated stability studies of formulated cream were carried out at 40±2 °C/75 %±5% RH for three months according to ICH guideline. The formulations were evaluated for different

pharmaceutical parameters like after feel, determination of pH, type of smear, dispersion ability, homogeneity, texture analysis, extrudability, grittiness, skin irritation, and acid value, saponification value, estimation of phytoconstituents etc [17-22].

Table 1: Composition of formulations

Ingredients	Cream	Gel	Serum
	(%w/w)		
APIs	0.5	0.5	0.5
Stearic acid	5	-	-
Glyceryl monostearate	2	-	-
Cetyl alcohol	3	-	-
Isopropyl myristate	3	-	0.3
Dimethicon	1-2	-	-
Triethanolamine	0.1	-	-
Ethyl hexyl glycerin	0.1	0.1	-
Phenyl ethanol	0.5	0.5	-
BHT	-	-	0.1
Water	q. s.	q. s.	-
Carbopol 980	-	0.5	-
18% NaOH solution	-	0.5	-
Fragrance	q. s.	q. s.	q. s.

Anti-aging activity

Anti-aging activity was carried out by the *in silico* method in GLIDE (Grid-based Ligand Docking with Energetics) tool of Schrödinger Maestro, LLC, and New York-2. Molecular docking studies were performed to investigate the binding mode into the active site of three different enzymes playing crucial role in anti-aging mechanism: fibroblast collagenase, native porcine pancreatic elastase, and human hyaluronidase. The crystal structures of these enzymes as PDB (Protein Data Bank) Codes 1CGL, 1QNJ, and 2PE4, respectively, were selected [23-26] and retrieved from PDB (https://www.rcsb.org/). All the enzyme structures were prepared using protein preparation wizard of the Maestro. The proteins were pre-processed first where the missing hydrogens were added, followed by hydrogen bonding assignment optimization, removal of water and other hetero molecules from the crystal structures, applying OPLS3e force field of Schrödinger suite. The 3D structures of plant metabolites were drawn in 3D builder tool of Maestro. The resulting structures were prepared in LigPrep tool keeping all the default parameters constant. In the case of 1CGL, the receptor grid was generated by considering the centroid of the original position of the co-crystalized ligand molecule, (N-[(1s)-3-{[(benzyloxy) carbonyl]amino}-1-carboxypropyl]-l-leucyl-N-(2-morpholin-4-ylethyl)-l-phenylalaninamide). The active sites were located around of Val216 and Tyr 75 residue for 1QNJ and 2PE4 respectively. Glide extra precision mode (XP) was used for docking. Evaluation of receptor-ligand complexes was carried out according to the docking score and potential intermolecular interactions, such as hydrogen bonding, hydrophobic interactions, cation–π, and π–π stacking between ligand and amino acid residues of the crystal structures.

RESULTS AND DISCUSSION

Physical properties of cream, gel and serum as well as percentage of total phenolics and flavanoid content estimated are shown in table 2.

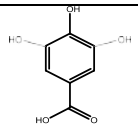
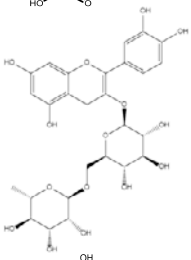
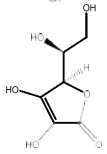
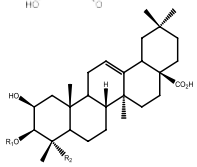
Table 2: Evaluation of formulations

Parameters	Cream	Gel	Serum
Appearance	Creamish brown	Translucent	Transparent creamish
Homogeneity	Good	Good	Good
Removal	Easy	Easy	Easy
After feel	Emollient	Emollient	Emollient
Type of smear	Continuous	--	--
pH	6-7	6-7	6-7
Grittiness	--	No	--
Acid value	7.01±0.03	--	--
Saponification value	11.2±0.02	--	--
Primary skin irritation test	Non-irritant	Non-irritant	Non-irritant
Tube extrudability	Good	--	--
Texture analysis	Good	--	--
Phenolic (%w/w)	0.116-0.121	0.129-0.132	0.026-0.029
Flavanoids (%w/w)	1.779-1.833	2.025-2.095	0.283-0.320

Results of accelerated stability studies depicts that all the physicochemical parameters were well maintained during the period. There were no changes found in colour, emolliency, homogeneity etc. pH in all the formulations was found in the range of 6.02 to 6.04. To find the potential candidate for the treatment of aging, molecular docking studies were performed against 3 protein structures 1CGL, 1QNJ and 2PE4. The docking scores are shown in table 3.

The hydroxyl groups present in the glycone and aglycone part of the plant molecules showed hydrogen bonding interactions with Tyr240, Glu219 and Gly179 in collagenase. In elastase, π-π stacking has been observed between His57 and aromatic ring present in the molecule; and hydrogen bonding was also seen between Arg61, Thr96 amino acid residues and multiple hydroxyl groups present in the molecule. For hyaluronidase, Glu131 and Trp321 amino acid residues were found to form hydrogen bonding with hydroxyl groups present in the molecules. 3D interaction diagrams of compounds with 1CGL, 1QNJ and 2PE4 ligands are showed in fig. 1-3.

Table 3: Docking scores of 1CGL, 1QNJ and 2PE4 with ligands

S. No.	Name of ligand	Structure of ligand	Binding energy (Kcal/mol)		
			1CGL	1QNJ	2PE4
1	Gallic acid		-6.932	-4.427	-6.017
2	Rutin		-9.189	-9.722	-10.591
3	Ascorbic acid		-7.442	-5.156	-4.965
4	Celosin A	 A R_1=Glc-Ara; R_2=CHO	-9.624	-6.327	-6.801
5	Celosin C	C R_1=Glc; R_2=COOH	-6.674	-7.908	-6.045
6	Celosin D	D R_1=Glc-Glc; R_2=COOH	-9.56	-3.965	-7.962

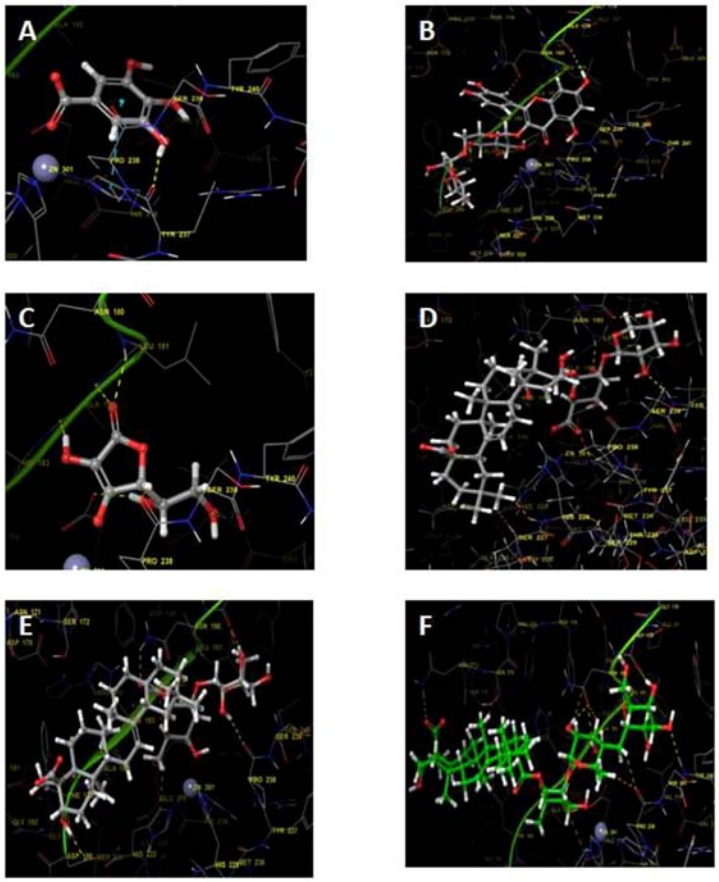


Fig. 1: 3D Interaction diagram with 1CGL (A) Gallic acid (B) Rutin (C) Ascorbic acid, (D) Celosin A (E) Celosin C (F) Celosin D

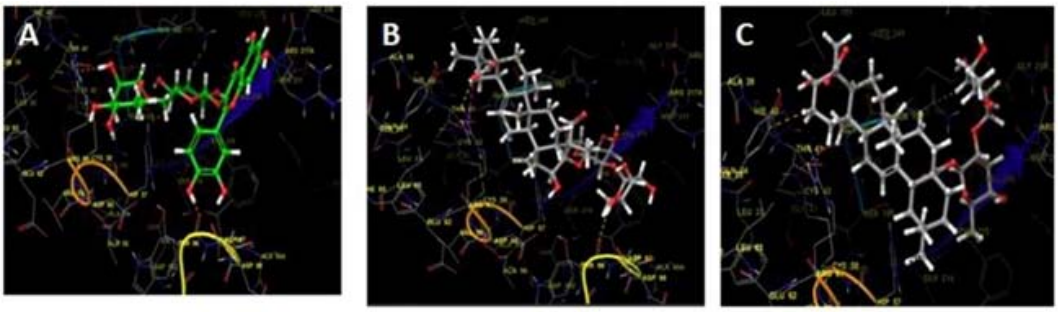


Fig. 2: 3D Interaction diagram with 1QNJ (A) Rutin (B) Celosin A (C) Celosin C

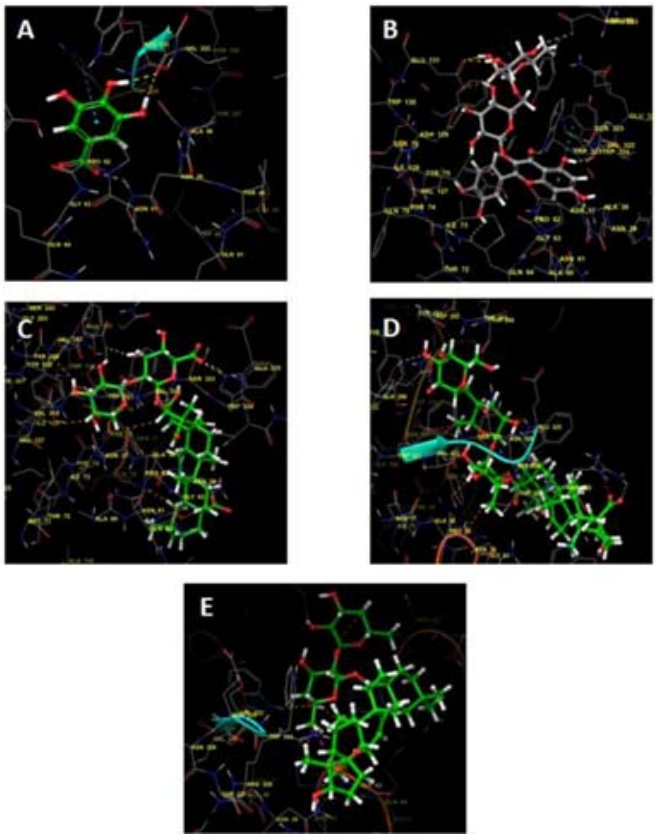


Fig. 3: 3D Interaction diagram with 2PE4 (A) Gallic acid (B) Rutin (C) Celosin A (D), Celosin C (E) Celosin D

CONCLUSION

Although a variety of formulations are available in market for anti-aging, still appear to be limited in pace of tissue regeneration. Hence, we have made an attempt to formulate polyherbal cream, gel and serum containing herbs as well as bioactives, which satisfy almost all the mechanism of anti-aging activity effectively. Physicochemical and phytochemical screenings were performed. All the parameters remained unchanged throughout the stability period for three formulations. The APIs selected showed good anti-aging activity and better binding affinity value against the selected target protein 1CGL, 1QNJ and 2PE4. The study was an endeavour to develop anti-aging herbal formulations based on the combination of herbal extract and bioactives.

ACKNOWLEDGEMENT

Not applicable

ABBREVIATIONS

A2AR: Adenosine A2a receptor; AMPK: Adenosine monophosphate protein kinase; ICH: International Council for Harmonisation; RH: Relative humidity; SIRT3: Sirtuin 3.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Authors hereby declare that there is no conflict of interest.

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