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Characterization, development and evaluation of a cream by using terminalia chebula and cucumber sativus extracts

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Abstract---Background: Continual exposure to the sun's ultraviolet radiation damages skin. Freckles are little brown patches that develop on the skin after repeated sun exposure. Terminalia chebula and Cucumber Sativus extracts-infused water in oil (W/O) emulsion is created, that has anti-freckle and emollient effect. Methodology: Base with no extract and formulation containing three different extract concentrations 4% of Terminalia Chebula with 1% Cucumber Sativus, 5% T. Chebula with 2% C. Sativus and 6% of T. Chebula with 3% of C.

Sativus are formulated and after 4 weeks of study and their stability parameters are evaluated at 8°C, 25°C, 40°C and 40°C $\pm$ 75RH. Different parameters such as anti freckle effect, skin melanin, skin moisture content, sebum level and TEW loss level are investigated by applying these formulations on the volunteer's cheeks for 4 weeks. Results: Skin melanin levels, sebum level, moisture level and TEW loss level of three formulations containing both plant extracts are significant statistically ($p < 0.05$). Skin melanin level and TEW loss are decreased after application of cream. But skin moisture and sebum level are increased after application of formulation. Conclusion: All three formulations have anti freckle response and exert whitening effect and positive rejuvenating effect on the skin due to combination of both plant extracts.

Keywords---Terminalia Chebula, Cucumber Sativus, Melanin, freckles, moisture, sebum, transepidermal loss.

Introduction

Continual exposure to the sun's ultraviolet radiation damages skin and increases the risk of skin cancer, despite the fact that the sun is a key source of vitamin D, which helps to build strong bones. Freckles, however, are little brown patches that develop on the skin after repeated sun exposure (Olson, Gaylor & Everett, 1973). The overproduction of melanin, which is required to darken the skin and hair color, results in the formation of these patches. In addition to all of these factors, melanin is a pigment that is photoprotective and shields the skin from UV damage (Brenner & Hearing, 2008).

Melanin, a pigment made by specialized cells called melanocytes, plays a key role in determining skin color. These melanocytes are found in the epidermis layer of the skin. The two forms of melanin that are produced by the skin are different. The two forms of eumelanin—brown and black—that determines the colour of the skin and hair and pheomelanin, which determines the colour of the lips, nipples, and other pinkish areas of the body (Gortner, 1912). Free radical oxygen species (ROS), which are formed after exposure to the sun's rays, are crucial for the development of freckles by either an exogenous or an endogenous process. Moreover, this causes the lipids, proteins, and carbohydrates that are present on the skin's surface to oxidize, damaging the skin and causing it to become dull, rough, and freckled (Ratz-Lyko, Arct & Pytkowska, 2012).

Modern cosmaceuticals that are used to improve attractiveness and act as anti-oxidants can suppress oxidation free radical reactions and oxidation processes because they contain vitamin E, vitamin c, and ferulic acid, which shields the skin from harm. Oil in water (o/w) and water in oil (w/o) are the two varieties of creams (Zhu, et al. 2004). Moreover, this solution lessens freckles that appear on the skin to darken it. A plant extract of Terminalia Chebula and Cucumber Sativus, which removes freckles from the skin, is also added to a cream to increase its anti-freckle efficacy (Lee, et al. 2005).

The plant genus *Terminalia* contains 250 species, including *Terminalia chebula*. Termed as "Myrobalans" in English and "harad" in Hindi. Moreover, *T. chebula* has cardiogenic, diuretic, laxative, and antitussive effects (Muhammad, et al. 2012; Bag, Bhattacharyya & Chattopadhyay, 2013). The anti-oxidant and anti-freckle effects of *T. chebula* are the most significant of all of them. Due to its amazing ability to cure skin wounds, this plant is often referred to as the "King of Medicine" (Suguna, et al. 2002).

Cucumis sativus is a plant belonging to family cucurbitaceae having 750 species. The species contain cylindrical to spherical fruits that grows annually up to 62cm long and 10cm diameter (Tatlioglu, 1993). Glycosides, flavonoids and tannins present in the plant are responsible for the whitening effect, emollient and moisturizer effect on the skin (Shah, et al. 2013).

Materials and Methods

Materials and Apparatus

Fruits of *T. chebula* and Fresh *Cucumis sativus* were bought at a local market in Sahiwal, Pakistan. Paraffin oil, Polyethylene glycol was purchased from Kohinoor Pharmaceuticals Pvt Ltd. Ethanol and distilled water was taken from the Laboratory of Bahauddin Zakariya University Multan. The following equipment was used for preparation of cream EBA 20 centrifuge, conductivity meter, Corneometer (Courage-Khazaka, Germany), Mexameter (Courage-Khazaka), TEWA meter (Courage-Khazaka), humidity meter, electronic balance, mechanical homogenizer, pH meter, refrigerator, rotary evaporator, UV-1601 ultraviolet spectrophotometer.

Product formulation

Extract of plant *terminalia chebula* was prepared after grinding of plant fruits, then soaked the powder with ethanol and distilled water for 14 days. Likewise *cucumis sativus* is firstly peeled off and crushed into fine pieces then soaked it with ethanol and distilled water for 14 days. After that, filtration was done for both mixtures and filtered marc was again soaked with same solvents for 7 days. Finally, maceration was done and filtrates of both extracts were allowed to dry and after 3 to 4 days, a concentrated extract of *terminalia chebula* and *cucumis sativus* was prepared in the petri dishes.

The creation of a water in oil (W/O) emulsion involved combining the aqueous and oily phases. Paraffin (14%), the emulsifier polyethylene glycol (5%), and distilled water made up the oily phase's components. Initially, the oily and aqueous phases were each heated to a maximum of 75°C. The two phases were then continuously stirred while being combined drop by drop. Finally, extracts from *Terminalia chebula* and *cucumis sativus* were added in various formulations containing 4%, 5%, 6% extracts of *t. chebula* were added in three different formulations having 1%, 2% and 3% extracts of *cucumis sativus* respectively with base in each formulation. The mechanical mixer was used to stir the mixture for 15 minutes at a speed of 2000 rpm, then for 10 minutes at 1000 rpm, and finally for 5 minutes at 500 rpm, until and unless all of the oily phase and aqueous phase had combined and after that lemon oil's few drops were added to

give the mixture a pleasing scent. 2g of xanthan gum was also added to the mixture to increase its thickness. Formulations are named as MO₁; MO₂ and MO₃. The cream was then brought to room temperature and placed in a glass jar with a tight lid.

Characterization properties:

Anti-oxidant activity:

The antioxidant activity is assessed using the DPPH (1, 1- diphenyl-2-picryl hydrazyl) free radical. In the ethanol solution, diluted extract was combined with an equal amount of DPPH. A device called a spectrophotometer was used to test absorbance at 517 nm in wavelength.

Vitamin C is used as standard in this test.

Stability Test:

The three cream samples (MO1, MO2, and MO3) were created. Each sample was stored at a different temperature, including 25°C, 8°C, 40°C, and 40°C with 75% relative humidity at 7, 14, and 28 days, respectively, pH levels and physical, thermal, and organoleptic stability tests were performed. Every sample was kept at a constant temperature of 25°C for formulations.

Assessment of type of cream by Conductivity Test:

To establish which type of formulation is created, all the three formulations (MO₁, MO₂ and MO₃) were under gone with the conductivity tests. Along entire path, a digital conductivity meter is employed.

Spreadability Test:

To determine the spread of the formulation, the spread ability of the formulation was examined. The first glass containing the formulation was placed on another glass surface, and a circle of 1 cm in diameter was drawn on a glass surface that had already been marked. After letting it sit for 5 to 10 minutes, the cream spread's diameter was measured. This test was repeated using the same formulation and methodology every 15 days for two months.

Configuration Test:

The freshly prepared base formulations [base; MO1; MO2 and MO3] and active formulations underwent a configuration test. To complete the tests, room temperature with 5000 rpm for 10 minutes was provided.

pH Determination:

The pH of each sample was measured using a digital pH meter on freshly manufactured base and active formulation samples. The samples were then all placed in cool and hot stability chambers with varying humidity counts and storage settings, such as 25°C+1°C, 8°C+1°C, 40°C+1°C, and 40°C+1°C with 75% relative humidity. The pH was tested again at a predetermined time interval (fresh, 24 hours, 7 days, 14 days, and 28 days) during the 60-day test period.

Patch test (Burchard test):

A patch test was performed on the forearm of every participant to look for any product sensitivity on the first day. Each healthy volunteer's forearm had a

specific area (4 or 5 cm) chosen for product application. On the right and left arm of healthy volunteers, a very small amount roughly 1g of each formulation containing an active ingredient had been administered. Three categories had undergone testing. In category 1, the first set of six volunteers applied the active formulation MO1 to their right arms while applying the base without the active component to their left arms. The same method is done for categories two and three. Following a 48-hour period of surgical dressing, the area was cleaned with normal saline to check for any erythema of any kind. Findings were graded on a scale of 0 to 3 (absence = 0, normal = 1, mild = 2, and severe = 3) (de Groot, Liem & Weyland, 1985).

Panel test:

A Google questionnaire with 7 parameters questions was given to each participant to be assessed in order to determine the efficacy of the various active formulations (MO1, MO2, and MO3). Each parameter received eleven (11) parameters ranging from +5 to -5, which represent extremely good to extremely poor performance. For all control and active formulations over the 4 week study periods, the average points assigned by each volunteer for each question were determined. Included parameters were:

1. Organoleptic Evaluation
2. Configuration Analysis
3. Electrical conductivity Analysis
4. pH Evaluation
5. Skin Erythema and Melanin test
6. Skin moisture and Skin sebum test
7. Transepidermal water loss test

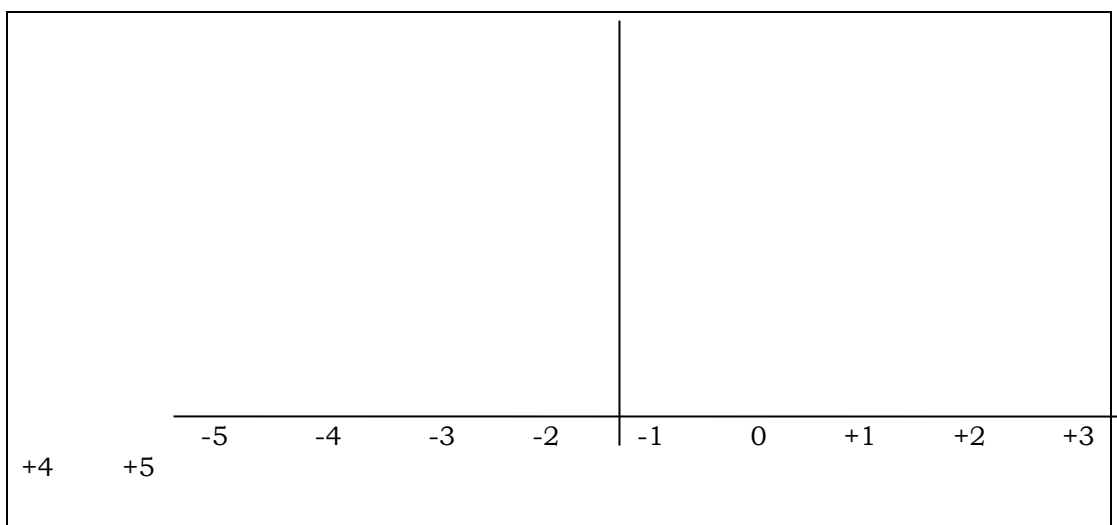


Figure 1: Parameter Graph

Results

Anti-oxidant activity

The anti-oxidant capacity of Cucumber Sativus and Terminalia chebula were assessed using a DPPH (2, 2-Diphenyl-1-picryl hydrazyl Radical) scavenging assay in comparison to the standard (vitamin C).

The table below lists the anti-oxidant activity of three distinct Terminalia Chebula preparations.

Table 1: Anti-Oxidant Activity Evaluation

MO1 having 4% & 1% extracts	MO2 having 5% and 2% extracts	MO3 having 6% & 3% extracts	Standard (Vitamin C)
73 percent	82 percent	89 percent	97 percent

Stability studies and Organoleptic Evaluation of three Formulations

The results of four weeks of observation show that formulation MO1 does not change color over the course of 28 days at 8°C and 25°C. Yellow is the color of the formulation. However, in the fourth week of the study at 40°C and 40°C + 75% RH temperature, a little change in the hue occurred from Mustard Yellow to Yellowish Orange.

Conductivity test of Formulations

Electrical conductivity tests are done on all of the formulations, whether they are W/O or O/W formulations. At all temperatures, including 8°C and 25°C, 40°C and 40°C + 75% RH, current flows through the formulations MO1, MO2, and MO3. The three creams are W/O in nature and stable at all temperatures, as seen by the conductivity meter's NO rating for all three creams.

Configuration test for Formulations

In the formulations MO1, MO2, and MO3 at all temperatures (8°C and 25°C, 40°C, and 40°C + 75% RH), no phase separation is seen; nevertheless, a small sedimentation at 40°C at day 28 occurs. It demonstrates that creams remain stable at temperatures for a full 28 days. While creams should be maintained at low temperatures to prevent deterioration in order to retain integrity, formulas are stable at all temperatures for four weeks.

pH determination of Formulations

When MO1 is first created, its pH value is 5.9; after 28 days, it decreases to 5.5, 5.4, 5.3, and 5.1 at temperatures of 8°C, 25°C, 40°C, and 40°C + 75% RH, respectively. Newly synthesized MO2 has a pH value of 6.0, which decreases to 5.4, 5.3, 5.2, and 5.1 after 28 days at the corresponding temperatures (8°C, 25°C, 40°C, and 40°C + 75% RH). MO3 has a pH value of 6.2 when it is first created, and it decreases to pH values of 5.5 at 8°C, 5.4 at 25°C, 5.3 at 40°C, and 5.2 at 40°C + 75% RH after 28 days.

Spreadability of all Formulations:

Freshly created MO1 formulation has a spreadability of 3.5, and it gradually gets better over the course of 60 days, rising to 3.9, 4, 4.2, and 4.3.

The Freshly prepared MO2 formulations have spreadability in range of 3.8, and by day 60, it gradually rises to 4.4, 4.5, 4.6, and 4.8.

Freshly created MO3 formulation has a spreadability of 4.0, and it gradually rises to 4.6, 4.8, 4.9, and 5.0 at the 60th day, correspondingly.

Statistical Analysis

Statistical tools used for this study are Google questionnaire, Microsoft Excel, SPSS v.24 and Analysis of Variance and sample paired t-test.

Skin melanin level of Base and MO₁, MO₂ and MO₃

After using the base and the formulations MO₁, MO₂, and MO₃ for each week of the study's four-week duration, changes in the skin's melanin level were seen. Figure 1 displays the outcomes.

To determine if results are significant or not in statistics, statistical tests are run. However, a paired sample t-test reveals results between the melanin effects of the MO₁, MO₂, and MO₃ formulations of Cucumber Sativus & Terminalia chebula are statistically significant (p values = 0.025, 0.023, and 0.02 respectively). The ANOVA test indicates insignificant (p value < 0.05) results between the melanin effect of a formulation with respect to time.

Skin Sebum level of MO₁, MO₂ and MO₃ and base

For 4 weeks study period, the % variations in the sebum level of skin were observed by applying the base and formulations MO₁, MO₂ and MO₃ in all weeks. Results are shown in the figure 2.

Statistical tests are performed to check the significance or insignificance of obtained results. ANOVA test indicates insignificant (p value < 0.05) results for checking sebaceous effect of a formulations MO₁, MO₂ and MO₃ of Cucumber Sativus & terminalia chebula with respect to time but after applying paired sample t-test, results sebum effect of sebaceous glands of MO₁ formulation of is significant (p value= 0.03, 0.025 and 0.02 respectively) to statistics.

Skin Moisture content of MO₁, MO₂ and MO₃ and base

After using the base or formulations MO₁, MO₂, and MO₃ for each week of the study's four-week duration, changes in the skin's moisture content were noted in percentage terms. Figure 3 displays the outcomes.

The moisturizing effects of the formulations MO₁, MO₂, and MO₃ of Terminalia chebula are not statistically significant (p value 0.05) when tested using the analysis of variance (ANOVA). However, when tested using the paired sample t-test, the moisturizing effects of the MO₁, MO₂, and MO₃ formulations of Terminalia chebula are statistically significant (p values = 0.04, 0.035, and 0.03 respectively).

Trans epidermal water loss (TEWL) of MO₁, MO₂ and MO₃ and base

After applying base against the formulations MO₁, MO₂, and MO₃ for each week of the four-week trial period, a change in the moisture level of the skin was noted in percentage terms. Figure 4 displays the outcomes.

To determine if results are significant or not for statistics, statistical tests are run. For the TEWL effect of the formulations MO₁, MO₂, and MO₃ of *Terminalia chebula* with respect to time, the results of the analysis of variance test (ANOVA) are non-significant (p value 0.05), but after applying the paired sample t-test, the results are significant (p value= 0.05, 0.04, and 0.03 respectively).

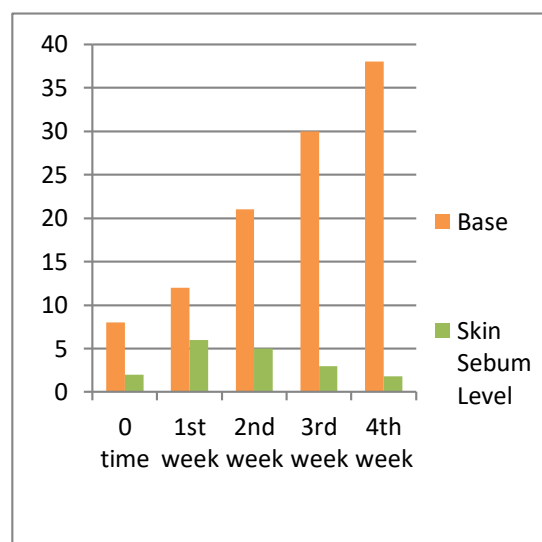
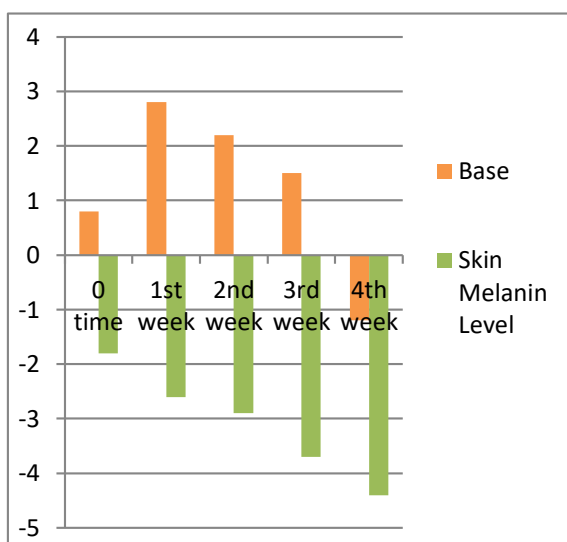


Fig 2:% change in the “Skin melanin” level

Fig 3:% changes in the “Skin sebum” level

Orange bars = base/ control, **Green bars** = active formulation MO₁, MO₂ and MO₃

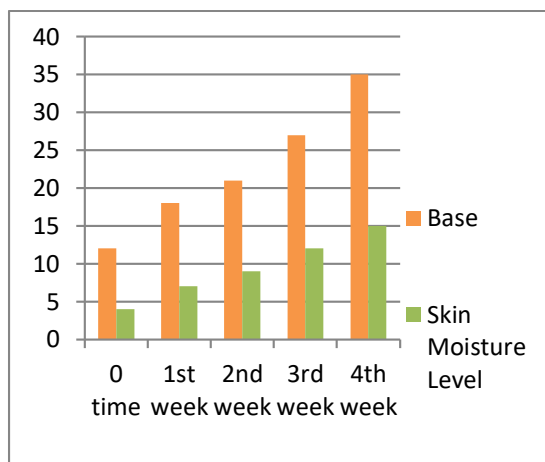


Fig 4: % changes in the "Skin moisture" level

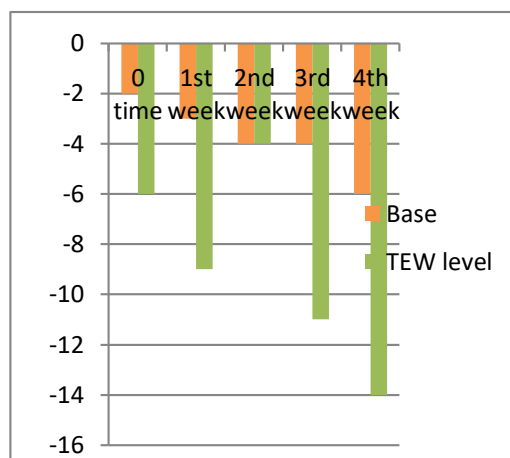


Fig 5: % changes in the "Skin TEW Loss" level

Orange bars = control, **Green bars** = active formulation MO₁, MO₂ and MO₃

Discussion

Physical test is first test that was performed on formulation which gives information about the stability of the cream (formulation). For this purpose, we performed liquefaction test, change of color and odor, phase separation. If there would be any change in these factors, then the formulation will be considered as unstable formulation. After observing the formulation for 4 weeks, results shows no change of color occurs in all three formulations MO₁, MO₂, MO₃ in 28th day at temperature 8°C and 25°C. Yellow is the colour of the formulation. However, in the fourth week of the study at 40°C and 40°C + 75% RH temperature, a little change in the hue occurred from Mustard Yellow to Yellowish Orange. This occurs because formulations are sensitive to minor deterioration at high temperatures.

All three formulations, MO₁, MO₂, and MO₃, exhibit no phase separation. It demonstrates that creams remain stable at temperatures for a full 28 days. Creams should be kept at a low temperature to preserve their integrity and avoid deterioration. At all temperatures, including 8°C and 25°C, 40°C and 40°C + 75% RH, current is passed through all three formulations, MO₁, MO₂, and MO₃. Conductivity meters for all three creams display NO values, indicating that they are all W/O.

pH determines the stability of all three formulations. 4.5 to 6 is the normal pH of the skin. Average value of pH is 5.5. So, it is considerable to notice that all the formulations MO₁, MO₂, MO₃ that are to be applied on the skin, must have pH in this range. This pH supports the body from infection. pH is tested for all three formulations MO₁, MO₂, MO₃ at every temperatures 8°C and 25°C, 40°C and 40°C ± 75% RH that had in the range of skin pH. Because of degradation of chemical components of cream, value of pH decreases continuously until 28th day with some variation. Other reason for reduction in the pH value is hydrolysis and ionization reactions and production of acidic metabolites in the formulations (Monteiro, et al. 2009).

pH is low at low temperatures 8°C and 25°C. But at high temperatures 40°C and 40°C $\pm$ 75% RH, pH will be high which indicates high temperatures effects pH of formulations. If the pH of formulations is in the range of skin pH then formulations are effective, safe to use and not irritated for the skin. Spreadability index is term used to denote formulation absorption into the skin. It indicates the easy application, uniformity and a valuation of viscosity of formulation. Storage stability and formulation acceptance by customers is described by spreadability. Value should not be varied and must be within the mandatory limits. If values will be expanded, it results in phase separation, liquefaction and cracking of cream. Spreadability of all formulations increases by increasing of temperatures which indicates high absorption, high acceptability and better stability of formulation even at low thermal stability (Riley, 1997).

The antioxidants are harmless, safe to use and used for topical application as medicinal cream for freckles. A dark brown to black pigment is present in the skin that is called melanin. Melanocytes produce melanin pigment inside the melanosomes that represents the color of skin. It is a biopolymer. Certain diseases such as melasma, solar lentigo and hyperpigmentation are caused by excessive production and accumulation of melanin pigment in the skin. When skin is exposed to the UV light of sun, melanocyte stimulating hormones are secreted from the pituitary glands. The process by which melanin is produced and then distributed to the skin and hair follicles is called as melanogenesis. Several enzymes such as Tyrosinase that are present in the melanosomes, are responsible for producing the melanin (Prota, 2012).

Ethanol extract of *Terminalia chebula* with *Cucumber Sativus* and three different formulations have inhibitory action for melanogenesis and reduce formation of melanin pigment which in turn reduces the darkness of skin. It brightens the skin by reducing the skin freckles and other diseases of skin. After exposing to ultraviolet radiation of sun, an inflammatory reaction is produced on the skin is called erythema. Signs of inflammation such as redness, heat, tenderness, and edema are seen on the skin. By applying different formulations of *terminalia chebula* with *cucumber sativus*, erythema and inflammation level in the skin decreases (Schwartz & Nervi, 2007). *Terminalia chebula* has high concentration of tannin which has two major constituents such as gallic acid and ellagic acid and possess potent anti inflammatory property which reduces redness, inflammation and erythema level on the skin. Water content is increased inside the dermis by moisturizing the skin (Akhtar, et al. 2012). Cucumber extract maintains the lipid barrier by attracting, holding and redistributing the water level in the skin. Appearance and integrity of skin is maintained by moisturization. After application of three different formulations, moisturizing effect of skin is increased because Vitamin C and A are major constituents found in the *Cucumber Sativus* (Lodén, 1995). Collagen biosynthesis of dermis is enhanced by vitamin C content of *terminalia chebula* which in turn improves hydration and moisturizing of skin. Cucurbitacin D present in the cucumber plant is responsible for the inhibition of melanin synthesis (Stojiljković, et al. 2013). There are the glands present in each hair follicle which form an oily substance called as sebum. Because formulation is W/O emulsion by nature and this property of formulation enhances sebum level of skin. Along with this, it also contains viscous and thick liquid such as paraffin oil which also increases sebum level of the skin. It is abbreviated as

transepidermal water loss (Shi, et al. 2015). If this loss of water is increased, it indicates the impaired water barrier of cream on the skin. Paraffin oil is an oily and viscous fluid in the formulation of terminalia chebula. It increases the oily barrier and prevents the water loss from the skin epidermis. Vitamin C is also present in the terminalia chebula which is a major constituent to reduce transepidermal water loss (Distante & Berardesca, 2020; Sultanbawa, 2016).

Conclusion and Future directions

A stable topical formulation (cream) is formulated that is a W/O emulsion. Cream contains terminalia chebula & Cucumber Sativus extract which reduces the production of melanin from the skin and a whitening effect is produced on the skin. Skin erythema level is reduced due to Anti-inflammatory property of terminalia chebula. Moisturizing and Cooling effect of skin is increased due to Vitamin C and A constituent of Cucumber Sativus. TEWL is reduced due to oily and viscous component of formulation that is paraffin oil; it also produces anti-wrinkle effect on the skin.

Oily skin people are not suitable for using this cream because excess amount of oil is produced from the skin after application of cream, and oil can cause acne problem to the oily skin. But people having melasma, freckles, psoriasis and wrinkles are best target for using cream having terminalia chebula & Cucumber Sativus extract.

In-vivo studies of cream show that formulation affects the different parameters of cream such as melanin level, moisturizing level, skin erythema level and TEWL loss level and increases whitening effect on the skin and also remove freckles. So it is not only used as cosmeceutics but also pharmaceuticals. Finally it is concluded that formulation containing drug Terminalia Chebula & Cucumber Sativus reduces skin freckles that developed due to UV radiation of sun and genetics as well.

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