**Synthesis, Characterization And Cosmetic Application Of (E)-3-(2-Hydoxyphenyl)-N(4-Nitrophenyl) Acrylamide, A Novel Compound** **By Using Green Chemistry Techniques.**

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**Highlights:**

* Chalcones are a class of compounds with anti-oxidant skin activity.
* Green synthesis of chalcones from natural jamun fruit was described.
* Anti-oxidant skin efficacy of naturally derived chalcones was established.

**Abstract:**

Chalcones collectively are defined as a class of pharmaceutically and medicinally important compounds. Very long reaction times, consumption of large quantities of organic solvents, presence of an acid catalyst etc make the synthesis of these compounds very tedious and costly. However, green chemistry techniques are gaining popularity recently, as they are relatively fast and also reduce chemical waste generation. We have employed green chemistry principles for the synthesis of Chalcones and described the method here. Natural jamun fruit juice freeze dry extract was used as natural acid catalyst for the synthesis of (E)-3-(2-Hydoxyphenyl)-N(4-Nitrophenyl) Acrylamide, from 2-Hydroxy cinnamic acid and 4-Nitroaniline and was characterized by FT-IR and NMR. Antioxidant skin efficacy of these products was tested on human subjects and promising effect was observed and reported. Thus, the stated green chemical approach for the synthesis of chalcones was stated to be convenient, affordable, simple, efficient, eco-friendly and cost-effective.

**Keywords:** Green synthesis; Natural jamun fruit juice freeze dried extract; Chalcones; Characterization; antioxidant skin activity.

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**1. Introduction:**

Green chemistry approach involves the usage of less expensive, less polluting reaction media, eliminating the usage of hazardous and costly solvents and finally producing the same outcome in a more eco-friendly process as compared to the traditional chemistry approach [1]. Solvent-free reaction conditions are increasingly becoming popular among the chemists who routinely perform organic reactions, as most of solvents are highly toxic, flammable and costly. On the other hand, the solvent-free reactions are faster, simpler and highly efficient and are highly selective. Separation and purification of the final desired outcome becomes easy by using the solvent-free green chemistry approach as compared to the conventional solvents [2]. Natural Fruit juices are gaining popularity among the chemists as potential organic solvents. Various pharmaceutically interesting compounds can be synthesized by using the fruit juices [3]. This was discussed and was proved time and again by many different chemists, in various organic transformation reactions [4,5]. This high interest in using fruit juices can be attributed to the relatively non-toxic, safe, inexpensive and environmentally benign nature of the fruit juices compared to the conventional organic solvents [6]. Chalcones were chosen for the current study as they can be used as intermediates for the synthesis of lot many pharmaceutically important molecules [7]. Chalcones exhibit moderate antibacterial, antifungal, herbicidal and clinical properties, largely attributed to their azomethine linkage [8-10]. They also possess catalytic and photo chromic properties [11]. Chalcones are produced by the condensation reaction between primary amines and carbonyl compounds. This was first reported by Hugo Schiff in 1864. The most prevalent structural feature of the Chalcones is the azomethine group with a general formula RN=CH-R1, where R and R1 are alkyl, aryl, cycloalkyl or heterocyclic groups. Aryl substituted Chalcones are more stable than their alkyl counterparts. Similarly, Chalcones of aliphatic aldehydes are less stable and are prone to polymerization, whereas aromatic aldehydes strong bonding and stability [12]. Having said this, usage of eco-friendly green chemistry methods, can be used for the synthesis of Schiff base and many researchers have reported this, with considerable and notable disadvantages such as lengthy reaction times, used high reaction temperatures, costly dehydrating reagents/catalysts and the need to use special apparatus, etc [13, 14].

Jamun tree belongs to family Myrtacea. The seeds of the Jamun fruit are employed in numerous therapies like Ayurveda, Unani and ancient Chinese medication. Wine and vinegar also are made up of the fruit. Jamun fruit is wealthy in antioxidant that has been noted to possess an incredible impact on skin. It's been well-tried to embellish and lighten skin. The antioxidant nature of the Jamun may produce anti-aging effect because it helps skin in fighting free radicals, manufacturing collagen, aids in skin regeneration and rising skin texture. Scars and blemishes may be lightened by applying Jamun seed powder on to the affected areas of skin.

Jamun fruit juice freeze dry extract is extremely nutritious and is one of the finest and richest sources of vitamin-C, amino acids and minerals. Among all, hydrolysable tannins, flavonoids, citric acid, gallic acid, ellagic acid are reported to possess biological activity. The Chalcones synthesized from berry fruit juice freeze dry extracts were characterized by NMR and FT-IR spectral techniques. The synthesized Chalcones possess the potential for cosmetic skin applications.

**2. Experimental Section.**

Fresh and ripened jamun fruits were obtained from the local market. 2-Hydroxy cinnamic acid and 4-Nitroaniline used for the synthesis of Chalcones were procured from Sigma Aldrich, India. Ethanol was used for the preparation of the jamun fruit juice freeze dry extract.

**2.1. Preparation of jamun fruit juice freeze dry extract.**

Ripened jamun fruit juice freeze dry powder was used for the preparation of the 1%w/v solution. Accurately 1.0 gm of jamun fruit juice freeze dry powder was weighed in to 250 ml flat bottomed flask and about 70 ml ethanol was added to the flask. Contents of the flask were extracted by refluxing on a water bath at 80oC ± 20C for 60 minutes and the dissolved extract was decanted into 100 ml volumetric flask. The residue was washed with 10 ml of ethanol and the same was transferred into the same 100 ml volumetric flask and the volume was made up to the mark with ethanol. The extract was filtered through Whatman no. 1 filter paper. First 25 ml of filtrate was discarded, and the subsequent filtrate was used for the synthesis of Chalcones.

**2.2 Synthesis of Chalcones from jamun fruit juice freeze dry.**

The equimolar amount of 2-Hydroxy cinnamic acid (0.01 mol) with 4-Nitroaniline (0.01 mol) was taken in a beaker. 5.0 ml of jamun fruit juice freeze dry extract was added to the mixture and then kept aside for 2 minutes. The mixture was stirred for 20 minutes at room temperature and kept aside at room temperature until a solid crystal product was formed. Post completion of the reaction, the product was purified and re-crystallized with minimum amount of ethyl acetate. This re-crystallized sample was taken for characterization by NMR and FTIR spectral techniques and reported.

Scheme,1:



2-Hydroxy cinnamic acid 4-Nitro aniline (E)-3-(2-Hydroxyphenyl)-N(4-Nitrophenyl)acrylamide

**2.3. Compound identification by Melting point determination:**

Sufficient quantity of sample was introduced into a capillary tube so that a compact column of 4 mm to 6 mm in height was obtained. Temperature of the bath was raised to about 10°C below the presumed melting point and then the rate of heating was adjusted to about 0.5 °C/min. When the temperature was 5°C below the presumed melting point, the capillary tube was introduced into the instrument. Capillary tube was carefully immersed so that the closed end of the tube was near the centre of the bulb of the thermometer. Temperature at which the last particle passed into the liquid phase was observed and noted.

**2.4. Characterization by Fourier Transform Infrared spectroscopy (FTIR):**

The FTIR spectrum determination of (E)-3-(2-Hydroxyphenyl)-N(4-Nitrophenyl)acrylamide, was carried out using Perkin Elmer spectrometer; model Spectrum two. FTIR spectrometer was operated at the range of 4000-400 cm-1 at the resolution of 4 cm-1.The FTIR spectrum of the compounds gave an absorption band near 1538cm-1 which was a characteristic of C=O and NH group of synthesized Chalcones.

**2.5. Characterization by Nuclear magnetic resonance spectroscopy (NMR):**

Nuclear Magnetic Resonance (NMR) spectroscopy was employed to determine the molecular structure of the Chalcones. NMR can be used to quantitatively analyze mixtures containing known compounds. Unknown compounds can be determined by matching the NMR spectra with the spectral libraries. The basic structure of unknown compounds can also be determined directly using NMR. Molecular conformation in solution and physical properties such as conformational exchange, phase changes, solubility and diffusion etc can be determined later. Subjecting the Chalcones for the NMR analysis, the molecular structure of the compounds was determined individually.

**2.6. Sun protection factor of Chalcones compounds:**

Accurately, 10 mg of (E)-3-(2-Hydroxyphenyl)-N(4-Nitrophenyl) acrylamide were weighed in 25ml volumetric flask; 10 ml of ethanol was added and sonicated for 15 minutes. Volume was made up to the mark with ethanol (solution-A) and filtered through Whatman filter paper, rejecting the first 5 ml. 12.5 ml aliquot (solution-A) was transferred to 25ml volumetric flask and diluted to volume with ethanol (0.02 % of Solution-B).

Solution-B was transferred into 1 cm cuvettes and absorbance at UVB range i.e., 290 nm to 320 nm at

every 5 nm wavelength interval was taken in triplicate. This was repeated for each sample and Mansur

equation (2) was applied on the resultant data.

The in vitro SPFs were determined according to the method described. The observed absorbance values at 5 nm intervals (290-320 nm) were calculated by using the following formula.

320  
SPF= C x ∑ EE (λ) x I (λ) x Abs (λ)   
 290

Here, CF = correction factor (10), EE (λ) = erythmogenic effect of radiation with wavelength λ, Abs (λ) = spectro photometric absorbance values at wavelength λ. The values of EE(λ) x I are constants. They were determined by Sayre et al and are given in table.no.1.

Table.No.1: Values of EE (λ) x I at different wavelengths.

|  |  |
| --- | --- |
| Wavelength(λ) | Value of EE x I |
| 290 | 0.0150 |
| 295 | 0.0817 |
| 300 | 0.2874 |
| 305 | 0.3278 |
| 310 | 0.1864 |
| 315 | 0.0837 |
| 320 | 0.0180 |

EE-Erythmogenic effect of radiation, I-Constant.

**2.7 Formulation Preparation:**

Table 2: Composition of emulsion with Chalcones active Novel compounds:

|  |  |  |
| --- | --- | --- |
| **Sl. No** | **Name of the material** | **% composition** |
| 1 | Glycerin monostearate SE grade | 3.0 % |
| 2 | Coconut oil | 4.0 % |
| 3 | Montanova-68 | 3.0 % |
| 4 | Glycerin IP | 4.0 % |
| 5 | Purified Water | upto 100.0% |
| 6 | Euxyl PE 9010 | 0.5 % |
| 7 | Perfume Orange fresh | 0.5 % |
| 8 | Schiff base active compounds((E)-3-(2-Hydoxyphenyl)-N(4-nitrophenyl) acrylamide) | 0.1 % |
| 9 | Citric acid | 0.025 % |

Remarks: Emulsification of the cream was good and the formula meets the cosmetic regulations.

**2.8 Formulation Procedure:**

Preparation of oil-in-water multiple emulsions:- After several pre-formulation studies, the most appropriate primary emulsion was selected for further development of oil-in-water multiple emulsion system. Composition of the same was presented in table 2. Multi-phase emulsions were prepared by the three-step emulsification procedure, which was described here.

Phase-I (Oil phase): Primary emulsion was prepared in a stainless-steel vessel by emulsifying oil and aqueous phases in the presence of coconut oil, heating at 80±20C for 10 minutes, in water bath with continuous stirring until a clear solution was formed.

Phase-II (Water phase): Phase-II was prepared in a stainless-steel vessel by emulsifying glycerin in the presence purified water, heating at 80±20C, in water bath with continuous overhead mixing at 2000 rpm for 10 minutes.

Phase-III: Phase-III was prepared by mixing Euxyl PE 9010, Perfume orange fresh and Schiff base active compounds in a single stainless-steel vessel mix with help of sonication.

Phase-I was then slowly added to phase-II. The aqueous phase was homogenized with the oil phase while heating both the phases at 80±20C, mixing with an overhead stirrer at 2000rpm for 10 minutes. The RPM was then reduced to 1000 rpm and stirred for another 10 minutes. The emulsion was cooled down to room temperature while stirring at a speed of 500 rpm for another 10 minutes. Phase-III was then added slowly to the aqueous phase containing hydrophilic emulsifier, stirring at a speed of 700 rpm for 10 minutes. 0.025 % of citric acid was added and the pH was adjusted to 6.0. A soft cream was formed. Post 48 hours, the product was subjected to evaluation.

2.9 **Evaluation of Cream:**

**2.9.1 Physical Properties:** The Cream was observed for color, odor and appearance. The sample was filled in a 50mL borosilicate glass beaker and observed in diffused daylight, viewing vertically against a white back ground.

**2.9.2 Determination of pH:** 10 ± 0.01g of the Cream was weighed accurately and dispersed in 45mL water in a 100mL borosilicate glass beaker. The pH of the suspension was determined using the digital pH meter at 27oC.

**2.9.3 Zeta potential:** The cream was filled in HDPE containers and chamber maintained at 10 ± 1°C,and 30 ± 1°C, and 45 ± 1°C. These samples were further evaluated by using Malvern zeta sizer- nano-ZS, 2600 series instrument. 0.1% samples were prepared in water and studied for zeta potential.

**2.9.4 Total Fatty matter:** Total fatty matter was determined according to the method C specified in the Bureau of Indian Standards (BIS) document no. IS 6608:2004.

**2.9.5 Water content****:** Water content was determined according to the method specified in the Bureau of Indian Standards (BIS) document no. IS 9740.

**2.9.6 Viscosity:** 100g of sample was weighed into a clean and dry 100ml glass beaker. Enough care was taken to avoid air bubbles while transferring. The beaker was covered with aluminum foil and placed in a water bath for about 1 to 2 hours by maintaining temperature at 30°±1oC. Viscosity was measured on Brookfield DV+Pro viscometer using T-96 spindle at 2.5rpm. Triplicate reading of viscosity were taken and the average viscosity was reported.

**2.9.7 Microbial load:** The formulated creams were inoculated on the plates of agar media by streak plate method and a control was prepared without the cream. The plates were placed in the incubator and are incubated at 370C for 24 hours. Plates were taken out after the incubation period and the microbial growth was checked by comparing it with the control. Test method followed was as per the Indian pharmacopeia 2019.

**2.9.8 Heavy metals test: (By ICP-MS).** The samples were digested. The ICP-MS instrument was utilized as per the standard operating procedure. Standard solutions (lead, Arsenic, Cadmium, mercury, iron, cupper, lithium, zinc, selenium, nickel, chromium and Antimony etc)were prepared and injected in the instrument ad the results were calculated.

**2.9.9 Stability studies:** Stability studies were done according to ICH guidelines. The cream formulation was filled in HDPE containers. These containers were charged in stability chambers maintained at 30 ± 2°C/ 65 ± 5 % RH and 40 ± 2°C / 75 ± 5 % RH for one month. At the end of studies, samples were analyzed for the physical properties and viscosity.

**2.9.10 Patch Test:** On the ventral side of the left or right hand of each human volunteer patch containing 1gm. of test formulations was applied on an area of 2.5 cm2. The product was kept in place of front forearm hand. The patch medicament was kept undisturbed for 30 minutes at the same skin site. After 30 minutes (day 1 to 7) the site was evaluated 30 mins after removing the product. Skin reaction was noted. Again, on day 7 site of application was observed and reaction was noted.

**2.9.11 Skin efficacy test:** The response to therapy was evaluated at intervals of two weeks upto the 6th week. The response to the Nourishing skin cream was graded as follows. Response was evaluated on a visual analogue scale of 0-3 (0-Nil, 1- Moderate, 2- Good, 3-Excellent).

The scoring was in turn correlated with response to the treatment as follows:

Grade

0 – No visible improvement.

1 – Poor response is < 25% visible improvement.

2 – Moderate response is -25-49% visible improvement.

3 – Good response is 50-74% visible improvement.

4 – Excellent response is > 75% visible improvement.

All subjects were reviewed for a period of 6 weeks at 2 weeks interval and at each follow-up visit, they were asked about the frequency of application and overall compliance to the treatment. Clinical assessment of skin condition was done objectively (by the investigator) and also subjectively (by subject). Subjects were thoroughly examined after 2 weeks and also at the end of the study. At every check-up the visible response to the usage, any adverse events, and subject compliance were assessed.

**3.0: Result and Discussion:**

3.1 Melting point: The melting point of the synthesized compound, (E)-3-(2-Hydoxyphenyl)-N(4-nitrophenyl) acrylamide, was determined to be 183.00C.

3.2 Characterization by FTIR:

The (E)-3-(2-Hydoxyphenyl)-N(4-nitrophenyl) acrylamide synthesized from 1.0 % jamun fruit juice freeze dry extract was characterized by FTIR and the spectroscopic data showed the presence of absorption bands at 3001 cm-1, between 1680 to 1630 cm-1 and between 1600 to 1500 cm-1, confirming the presence of –NH group, C=O group and NO2 group respectively (figure 1).



Figure.1: FTIR spectrum of (E)-3-(2-Hydoxyphenyl)-N(4-nitrophenyl) acrylamide.

3.3 Characterization by NMR:

NMR characterization of the synthesized compound was performed and the data was furnished here.

3.3.1 1H NMR:

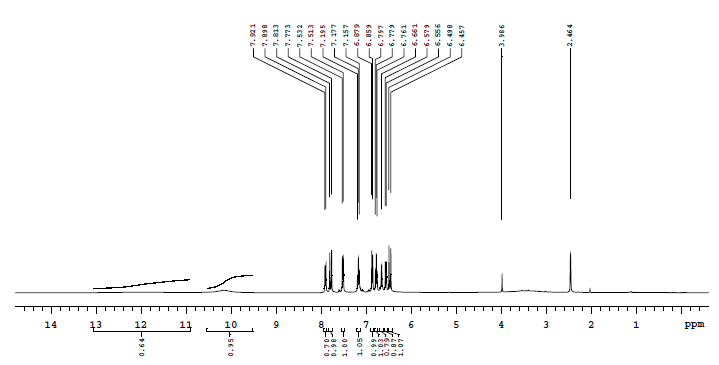


Figure.2: 1H NMR spectrum of (E)-3-(2-Hydoxyphenyl)-N(4-nitrophenyl) acrylamide.

H NMR (400 MHz, dmso) δ 12.07 (s, 1H), 10.16 (s, 1H), 7.91 (d, *J* = 9.0 Hz, 1H), 7.79 (d, *J* = 16.1 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.18 – 7.12 (m, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.78 (t, *J* = 7.4 Hz, 1H), 6.66 (s, 1H), 6.57 (d, *J* = 9.0 Hz, 1H), 6.48 (d, *J* = 16.1 Hz, 1H).

3.3.2 C13 NMR: (Figure 3)

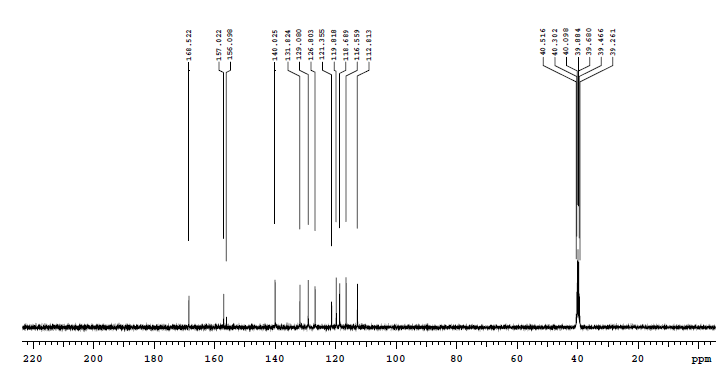


Figure.3: C13 NMR spectrum of (E)-3-(2-Hydoxyphenyl)-N(4-nitrophenyl) acrylamide.

13C NMR (101 MHz, dmso) δ 168.50 (s), 156.99 (s), 156.07 (s), 140.00 (s), 136.09 (s), 131.80 (s), 129.06 (s), 126.79 (s), 124.51 (s), 121.34 (s), 119.80 (s), 118.67 (s), 116.54 (s), 112.80 (s).

3.4 Sun protection factor:

Sun protection factor value for the compound (E)-3-(2-Hydoxyphenyl)-N(4-nitrophenyl) acrylamide, was determined to be 36.72, at a concentration of 0.02%.

3.5 Product evaluation: The final cream formulation was evaluated for various physical, microbiological and chemical parameters and the results were tabulated in table.no.3.

Table.No.3:- Results of evaluation of formulation.

|  |  |  |
| --- | --- | --- |
| Sl.No | Test parameters | Observations |
| 1 | Appearance | Soft viscous cream |
| 2 | Color | White |
| 3 | Odour | Mild orange note |
| 4 | pH (10 % solution in water) | 5.83 |
| 5 | Zeta potential | |
|  | 10 ± 1°C | -48.5 |
| 30 ± 1°C | -42.2 |
| 45 ± 1°C | -33.3 |
| 6 | % of TFM | 7.98 % |
| 7 | % of water content | 81.91 % |
| 8 | Viscosity at 300c, T-96 spindle, 2.5 rpm | 1,52,000 cps |
| 9 | Microbial load | |
|  | Total aerobic count CFU/gm | < 10 cfu/gm |
| Yeast and Mould count CFU/gm | < 10 cfu/gm |
| Escherichia coli /g | Absent |
| Staphylococcus.aureus /g | Absent |
| Pseudomonas .aeruginosa /g | Absent |
| Salmonella /g | Absent |
| 10 | Heavy metal test | |
|  | Lead | BQL (0.034) |
| Arsenic | BQL (0.005) |
| Cadmium | BQL (0.007) |
| Mercury | BQL (0.016) |
| 12 | SPF value (1% of solution) | 33.36 |
| 13 | Stability study | No oil separation |

3.6 Patch test: AAMC/IEC/111

All the 24 volunteers of 3 different groups (A, B & C) in this study completed the study as planned. No volunteer was withdrawn from the therapy either for adverse effects or other reasons. Erythema and edema scores for each volunteer are shown in Table 4. As depicted, none of the volunteers developed any signs and symptoms of skin irritation.

3.7 Skin efficacy test:

At the end of 6 weeks of study, there was visible improvement in the moisturizing effect of the skin with overall response shown as none of subjects with poor response, 1 subject with fair response, good response in 7 subjects and excellent response in 22 subjects. The overall response in feeling and softness of skin shows that 1 subject showed fair response, 6 with good response and 23 with excellent response. The overall response of the soothing effect was, 1 with fair response, 6 with good response and 23 with excellent response. Overall appearance of skin and after feel was represented as none of subject with poor response, 3 with fair response, 6 with good response and 21 with excellent response (Table. 4).

Table.no.4: Skin appearance and feel responses.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Table 4: Overall response (n=30) | | | | |
| Response score | Moisturizing effect | Feeling and softness of skin | Soothing effect | After feel/Overall appearance of skin |
| No response | - | - | - | - |
| Poor response | 00 | - | - | 00 |
| Fair response | 01 | 01 | 01 | 03 |
| Good response | 07 | 06 | 06 | 06 |
| Excellent response | 22 | 23 | 23 | 21 |

Thus, significant symptomatic relief was observed after 6 weeks of application of Nourishing Skin Cream. This clinical trial indicated that Nourishing Skin Cream is effective in subjects producing excellent moisturizing effect, feeling and softness of skin and soothing effect.

**4.0 Conclusion:**

In the present study, a novel eco-friendly, green chemical method of synthesis of (E)-3-(2-Hydoxyphenyl)-N(4-nitrophenyl) acrylamide, from natural acids by jamun fruit juice freeze dry powder was described. The solvent-free green approach is non-polluting and easily doable, thus falling under the category of green synthetic approach of Chalcones. The novel method described here is safe and eco-friendly and involves only a mild reaction conditions. The antioxidant skin efficacy and sun protection factor value of the chalcones were determined and novel formulations with these fruit derived actives had demonstrated excellent physical and chemical stability over the tested study period. Visual appearance, color, viscosity, pH and fragrance of the formulations showed that there was no significant variation during this study period. The formulation had demonstrated no skin irritation and other dermatological adverse effects and thus can be incorporated in daily skin care regime.

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