WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 7, 705-718. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF AN ANTI-OXIDANT PRODUCT FROM BETEL LEAF EXTRACT

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Article Received on
22 April 2021,

Revised on 12 May 2021,
Accepted on 02 June 2021

DOI: 10.20959/wjpr20217-20723

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ABSTRACT

Antioxidants are compounds that inhibit oxidation. Oxidation is a chemical reaction that can produce free radicals, thereby leading to chain reactions that may damage the cells of organisms. Antioxidants provide protection against Reactive Oxygen Species (ROS) i.e. free radicals contributing to cellular aging, atypical pigmentation, mutagenesis, carcinogenesis. *Piper betel* leaves are a rich source of such natural bioactive compounds namely antioxidants. The use of natural antioxidants is of growing interest, especially in food science and complementary medicines, because some synthetic antioxidants are harmful to human health. The antioxidant activity of *P. betel* is previously researched by many researchers, and also a work on the formulation of antioxidant cream is done. Considering the following researches into consideration this study is focused on the formulation and evaluation of an antioxidant peel-off mask comprising the ethanolic leaves extract of *P. betel*. The in-vitro free radical scavenging activity was studied by using Hydrogen Peroxide (H_2O_2) solution. The ethanolic leaves extract possesses remarkable antioxidant properties which are observed at increasing concentrations. The formulation comprises 2% of ethanolic extract and was formulated by the addition of six different phases using Polyvinyl alcohol (PVP) as a film former. The formulation was subjected to standard evaluation process on parameters like physical evaluation, pH, peel test, thickness measurement, thermodynamic stability study, stability testing, and hydrogen peroxide radical scavenging activity assay. The evaluation of formulated peel-off masks showed satisfactory results and can be a potential cosmetic product when worked on further. Further studies can be conducted on the enhancement of the parameters to market an effective, stable and cost-effective cosmetic product on a large scale.

KEYWORDS: *Piper betel*, Desipaan, hydrogen peroxide radical scavenging test, antioxidant peel-off mask, cosmetic product.

INTRODUCTION

Antioxidants are compounds that inhibit oxidation. Oxidation is a chemical reaction that can produce free radicals, thereby leading to chain reactions that may damage the cells of organisms. Antioxidants terminate these chain reactions. To balance the oxidative stress, plants and animals maintain complex systems of overlapping antioxidants. Antioxidants provide protection against Reactive Oxygen Species (ROS)[1,2,3] i.e. free radicals contributing to cellular aging, mutagenesis, carcinogenesis, and coronary heart disease.[4] These substances are sometimes called **"free-radical scavengers".**[2,3]

Piper betel leaf is a potential reservoir for reducing oxidative stress. Betel leaves are a rich source of natural bio-active compounds such as secondary metabolites and antioxidants.[7,8] Phenolic compounds[3] are the most abundant secondary metabolites in plants, playing a key role in pigmentation, growth, and reproduction of the plant, together with resistance to pathogens and predators. This is largely due to potent astringency.[8] They have been shown to provide anti-allergic, anti-inflammatory, antioxidant, hepatoprotective, anti-viral, and anti-carcinogenic activities.[5] However, probably the most important has been devoted to their antioxidant activity, their ability to reduce the free radical formation and to scavenge free radicals *in vivo*.[2,7,9] By visibly reducing pore size and revealing firmer skin, a post-peel-off can help someone look years younger by boosting your complexion's appearance to look brighter and displaying anti-aging appearance.[10]

The use of natural antioxidants[8] is of growing interest, especially in food science and complementary medicines, because some synthetic antioxidants are harmful to human health. The evaluation of antioxidant potential is, however, a crucial issue, because plants contain two main types of antioxidants, polar (phenolic) and non-polar (vitamin E), and there is no single method suitable for the assessment of both types. Secondly, the complex composition of plant extracts can lead to contradictory results if the antioxidant activity is evaluated by a single method. So, at least two methods for evaluating antioxidant activity are therefore recommended. DPPH scavenging activity[11], Hydrogen peroxide scavenging (H2O2)[6], Nitric oxide scavenging activity, Ferric thiocyanate (FTC) method, Total radical-trapping antioxidant parameter (TRAP) method, Ferric reducing-antioxidant power (FRAP) assay, Metal chelating activity, etc. are used methods for evaluation of proton donating antioxidants,

like phenolic compounds, from plants. Test for determination of phenolic compounds are ferric chloride test and lead acetate test.[9]

AIM & OBJECTIVE

The existence of many researches and research papers on various activities of *Piper betel* has been made. However, there is still no sign for establishing marketed formulation on this ancient betel leaf which is also cost-effective. This project seeks to formulate and evaluate an antioxidant product prepared out of betel leaf. The research will use ethanol as a solvent for the isolation of an antioxidant component in Soxhlet apparatus.

MATERIALS AND METHODS

A. MATERIALS

A.i. Active ingredient: *Piper betel* leaves (Desipaan).

A.ii. Chemicals: Ethanol (C_2H_5OH), Polyvinyl alcohol (PVA), Glycerol (glycerine), Polyethylene glycol (PEG), Polysorbate 20 (Tween 20), Methanol (CH_3OH), Hydrogen peroxide (H_2O_2), Phosphate buffer pH 7.4, Distilled water.

A.iii. Apparatus and Instruments: Soxhlet extractor, Volumetric flasks, Vernier caliper, Beakers, Test tubes, Porcelain dish, Glass rod/stirrer, Measuring cylinders, Pipette, Petri plates, Rubber piping, Cotton, Weighing balance, Water pump, Uninterruptible power supply (UPS), Water bath, Heating mantle, Hot air oven, Laboratory stirrer, Magnetic stirrer, Refrigerator, Mixer grinder, UV-VIS double beam spectrophotometer, Digital pH meter.

B. METHODS

B.i. Collection of leaves

Fresh leaves of Desipan variety were collected from Paan Galli near Gol Deval Temple, Sardar Vallabhbhai Patel Rd, Khetwadi, Bhuleshwar, Mumbai, Maharashtra 400004. Leaves were purchased at 0.50 Rs/leaf and a total of 200 leaves were purchased.

B.ii. Preparation of sample for extraction

The leaves were washed with clean water and dried in the air under shade for 48 hours (Fig. 1). Avoid blackening of leaves due to frequent touching and excess of drying. The dried leaves were coarsely ground in a mixer grinder (Fig. 2). The coarse powder was stored in an airtight container for further use.[13]

Fig. 1: Drying of leaf under shade

Fig. 2: Coarsely powdered dried leaves

B.iii. Extraction procedure

The siphon tube of extractor was blocked with cotton. A 20 g of coarse powder was weighed and filled in the sample tube and cotton was placed above it. 2 ceramic chips were put in the flask. The assembly (Fig. 3) was set up with a condenser over a heating mantle. The condenser was assembled with inlet and outlet pipes using water pumping motor. Ethanol[15] was poured from above until 2 cycles run through the siphon tube i.e. approximately 200 ml. The heating mantle was set to 70^0C. The extraction process is carried out until the ethanol in the siphon tube becomes colorless; the approximate time required is 3 hours. Once the extraction process is completed, the assembly is turned off. The extract was then transferred to a porcelain dish and kept over a water bath for solvent evaporation (Fig. 4). Once the solvent is evaporated, the extract is dried and the percentage yield was calculated. The extract is then stored in an airtight container at 4^0C for further study.[13] The extracted product is a waxy brownish red compound.

[***Note:*** if the extracted compound does not dry completely and feels sticky, then defatting is preferred. In this the extraction is first carried out with petroleum ether and then regular process as mentioned above.]

B.iv. Phytochemical analysis

Antioxidant activity of the betel leaf is because of the phenolic contents of leaves.

Test for phenolic compound

a. **Ferric chloride test:** Dissolve a small quantity of the extract in distilled water. To this solution add 2 ml of 5% ferric chloride solution. The formation of blue, green or violet colour indicates the presence of phenolic compound.[13]
b. **Lead acetate test:** Dissolve a small quantity of extract in distilled water. To solution add few drops of lead acetate solution. The formation of a white precipitate indicates the presence of phenolic compounds.[13]

B.v. *In vitro* method of evaluation of antioxidant activity

Hydrogen Peroxide Scavenging Assay of the ethanolic extract-

The ability of plant extracts to scavenge hydrogen peroxide can be estimated according to the method of Ruch et al. (1989). A solution of hydrogen peroxide (40 mM) is prepared in phosphate buffer (50 mM pH 7.4). The concentration of hydrogen peroxide is determined by absorption at 230 nm using a spectrophotometer. Extract (20–60 mcg/mL) in distilled water is added to hydrogen peroxide and absorbance at 230 nm is determined after 10 min against a blank solution containing phosphate buffer without hydrogen peroxide. The percentage of hydrogen peroxide scavenging is calculated as follows:

$$\% \text{ scavenged } (H_2O_2) = [(Ai - At)/Ai] \times 100$$

Where, Ai is the absorbance of the control and At is the absorbance of the test.[9]

B.vi. Formulation procedure: The procedure involves the addition of six different phases;

Table 1: Formulation.[12]

Ingredients	*Optimized concentration*	*Activity*
Polyvinyl alcohol (PVA)	14 g	Film former
Water	100 ml	Base
Glycerine	3 ml	Smoothing agent
Polyethylene glycol (PEG)	1 ml	Surfactant
Tween twenty	0.5 ml	Polymer
Methanol	1 ml	Solvent
Water	0.5 ml	Base
Drug extract	2 g	Antioxidant

Phase I

In this phase 14% cold Polyvinyl alcohol solution is prepared in distilled water by slow addition of 14 g of PVA in 100 ml cold water with continuous stirring with the help of

laboratory stirrer. The process of the addition of PVA should be slow. Solution thickens and foams with the addition of PVA. Then fully dissolved PVA solution is kept for rest overnight for the foam to settle down. A clear, translucent and viscous 14% solution of polyvinyl alcohol is prepared (Graph 1).

Phase II

In this phase, a mixture of Glycerine and PEG in the ratio of 3:1 is prepared by mixing 3ml of glycerine in 1 ml PEG. This mixture is added to phase I at 40^0C temperature and mix well.[12]

Phase III

Add 0.5 g polysorbate (tween – twenty) without any further heating with constant stirring with a glass rod.[12]

Phase IV

Add 1 ml methanol into phase III mixture and mix well.[12]

Phase V

Add 2 g drug and stir well until uniform yellowish golden mixture is prepared (Fig. 5). The product seems to be opaque but on rest, it turns to a clear and translucent mixture (Fig. 6).

Fig. 3: Soxhlet extraction assembly

Fig. 4: Evaporation of solvent

Fig. 5: Preparation of *Phase I*
(PVA solution)

Fig. 6: Phase V.
(on addition of drug)

STATISTICAL ANALYSIS

The data for radical scavenging activity were obtained by using UV-VIS Double beam Spectrophotometer ME 22. The data were presented as ± standard mean deviation (SEM).

RESULTS AND DISCUSSIONS

I. Extraction and Qualitative Phytochemical studies

The percentage yield and nature of the extract are given in Table 2. The percentage yield of the extract is given by;

Amount of extract obtained/Amount of powdered leaves used x 100[16]

The quantitative phytochemical extract showed the presence of phenolic compounds and flavonoids as given in Table 3.[13]

Table 2: Percentage yield and nature of the extract.[13]

Extract	Nature	Yield
Crude Ethanol Extract	Reddish-brown semisolid	37.00 %

Table 3: Phytochemical Analysis of the extract.[14]

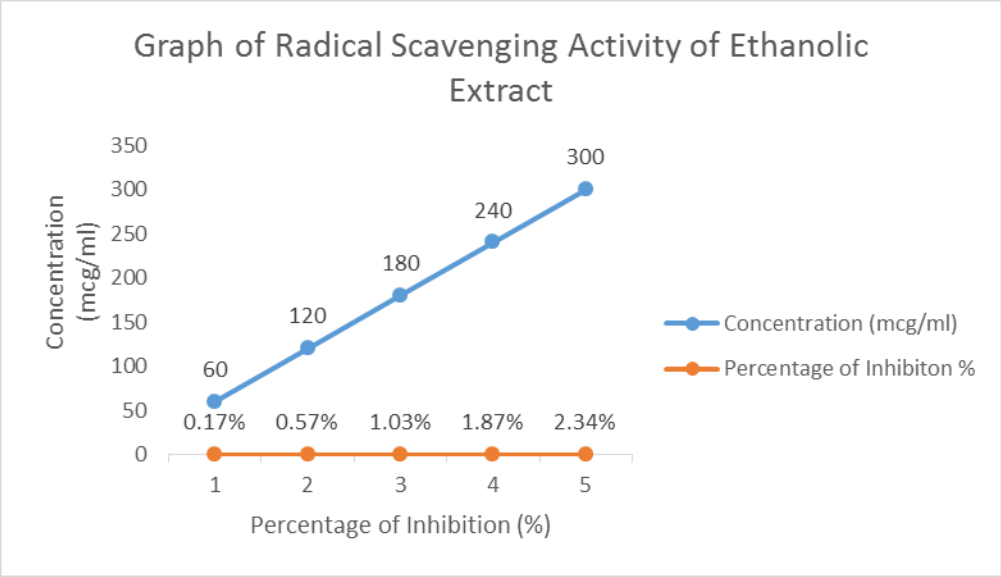
Test	Observation	Inference
Test for phenolic compound: i. Ferric Chloride Test ii. Lead Acetate Test	 Violet colour White precipitate	 Present[13]
Test for flavonoids:	Pink colour	Present[13]

II. Hydrogen Peroxide Radical Scavenging Activity of ethanolic extract[9]

The antioxidant activities of ethanolic leaves extract from *P. betel* were assessed using Hydrogen peroxide radical scavenging activity. The results are shown in Table 4. The graph is shown as Graph 1. Thus, the result can be concluded as the present proposed study that the *P. betel* ethanolic leaves extract possesses remarkable antioxidant properties. The observed antioxidant effects can be attributed majorly to the presence of polyphenolic compounds in the *P. betel* extract.

Table 4: H_2O_2 Radical Scavenging Activity of ethanolic extract ± SEM(0.4022).

Concentrations (microgram/millilitre)	Percentage of inhibition (%)
60	0.168
120	0.573
180	1.027
240	1.869
300	2.34



Graph 1: Radical Scavenging Activity of Ethanolic Extract.

III. Evaluation of Formulation

The formulated peel-off gel (Fig. 6) from the ethanolic extract of *Piper betel* leaves was subjected to the standard evaluation procedures and the results are discussed below. The formulated antioxidant gel evaluated for several physicochemical tests and the results is shown in Table 4. The formulated gel showed a slight odour of the extract and golden yellow coloured peel-off mask. The formulated mask was not greasy after application to the skin. The formulated mask was easily removable by washing with tap water. The gel showed the homogenous distribution of extracts which was confirmed by visual examination. There was no change in the colour of the formulated mask upon keeping for a long time. Different tests on peel-off gel masks are performed given in Tables 6, 7 and 8.

Table 5: Physicochemical Evaluation of Facial Mask.[12]

Parameter	Observation
a. Physical Appearance	Translucent
b. Odour	No Characteristic odour
c. Colour	Golden Yellow
d. Texture	Smooth[12]
e. Phase Separation	No
f. Homogeneity	Homogeneous[13]
g. Immediate skin feel	A film formed after drying, no grittiness
h. Rheological Study	Non-Newtonian
i. After feel	Emollients and slipperiness[13]
j. Removal	Easily removed with tap water (no greasiness)[13]

a. Measurement of pH

The pH of the formulated mask was found to be in the range of 6.0 – 6.5 which is considered a suitable pH for cosmetic skin formulations.[13]

Table 6: Measurements of pH.

Sr.no.	1	2	3
pH	6.3	6.4	6.3

b. Thickness Measurements (Fig. 7)

The thickness of the film determines its ability to attach to the skin and was found to be 0.20[12] mm on an average.

Table 7: Measurements of Thickness.

Formulated Sample	Thickness (mm)
Film 1	0.30
Film 2	0.20
Film 3	0.20

Fig. 7: Thickness measurement of film.

c. Stability Testing

The visual testing was done at each temperature. The formulation was found to be stable and good until 40°C. As the temperature rises the formulation starts to get viscous and solidifies at 60°C and becomes unstable completely at 8°C.[12] The results are given in Table 8.

Table 8: Stability Testing.

Temperature(°C)	Physical Appearance
10	Stable[12]
20	Stable[12]
30	Stable[12]
40	Stable[12]
50	Viscosity increases[12]
60	Film forming and Solidification[12]

d. Hydrogen Peroxide Radical Scavenging Activity of Mask[9]

The formulated product is subjected to radical scavenging activity of hydrogen peroxide. The results are shown in Table 9. Hence, the results can be inferred as, the present proposed study that the formulated product possesses phenomenal antioxidant properties since the percentage of inhibition (%) is found to be **5.28%**. The observed antioxidant effects can be attributed majorly to the presence of polyphenolic compounds in the *P. betel* extract.

Table 9: H_2O_2 Radical Scavenging Activity of Formulated Mask.

Sample Concentration	Percentage of Inhibition
1g	5.28

CONCLUSION

- The results of this investigation show that the response of the Betel leaf as an antioxidant can drastically reduce the oxidative destruction without any harmful effects and can act as a remedy for skin ailments.
- It is observed that methanol has a substantial amount of chemical toxicity and is flammable whereas solvent ethanol is less chemically toxic and less corrosive, safe for human use with adequate amount of extraction yield of 37%.
- Results reveal that the efficiency of the antioxidant peel-off mask is directly proportional to time. As the time of the rest of the peel-off mask on the face is increased the performance of the antioxidant activity is increased as well. However, a decrease in resting time will show a considerable amount of effects. These results can be clearly understood by the radical scavenging activity.
- The Thermodynamic testing and stability test evaluated signifies that the product remains stable till 40-45^{o} C which indicates that the product must remain stable at room temperature until its shelf life.
- Hence, it can be concluded that this antioxidant peel-off mask is a multifunctional mask applicable for anti-aging, anti-wrinkle, for reducing fine lines, reducing pore size and provides tightening effect to the skin, clearing the pores and shedding off the dead skin cells.
- The thesis concludes that the commendable activity of *Piper betel* leaf as an antioxidant overcomes oxidation and provides ample of cosmetically elegant product that will create more impact in the future cosmetic product establishment.

ACKNOWLEDGEMENT

The authors express sincere regards to **Mr. Anirudh Rushi** the principal, St. Wilfred's College of Arts, Commerce and Science, Panvel for his co-operation, authors also extend regards to **Dr. Deenanath Jhade** the principal, St. Wilfred's Institute of Pharmacy, Panvel, Maharashtra, India for providing the facilities to carry out the work.

CONFLICT OF INTEREST

The authors declare no conflict of interest for current work.

AUTHORS CONTRIBUTION STATEMENT

Mr. Pravin Borana and **Miss Kazeema Kazi** are the prime authors of this work and **Mr. Vijay Ikale** sir hold the position of guide for the work. Selection of *Piper betel* leaf for study was done by both the authors together because of common interest. **Miss Kazeema K** conceptualized and gathered the data with regard to this work. **Mr. Pravin B** obtained the sources and materials to be needed. The plan of work and methodology was created by both the authors whereas, **Mr. Vijay Ikale** guided the authors with the same. The analysis was carried out by both the authors decidedly and the data was analyzed by the guide. Both the authors and guide discussed on the final report of the work and contributed to the final manuscript.

FUNDING ACKNOWLEDGEMENT

We acknowledge the machines and chemicals needed for the study were provided by the Department of Pharmaceutics, St. Wilfred's Institute of Pharmacy, Panvel, Maharashtra, India. The specimens of leaves needed were purchased by the authors themself.

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