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FORMULATION AND EVALUATION OF *PLUMERIA ALBA* LEAVES HYDROGEL FOR CHRONIC WOUND MANAGEMENT

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Abstract-

As we see, wound is a major problem now a days due to disturbances in the four phases of wound healing due to which wound healing is delayed and become chronic, and our conventional treatments such as antibiotics face challenges in it. To overcome these limitations, the herbal hydrogels such as *Plumeria alba* hydrogel is a novel and advanced drug delivery system that provides moist environment, infection control and other parameters for better treatment in diabetic wound healing. In this research, research, we will observe that a potential plant leaves of *Plumeria alba* leaves are selected, collected, authentication was done and pre-formulation studies and micromeritics studies were performed. Then, a herbal hydrogel was developed and evaluated for different parameters. The diabetes was induced in Wistar rats and excision wound model were induced to study diabetic wound healing study of 21 days. In this research study, a very potential plant was selected to improve the wound healing activity of diabetic patients. The *Plumeria alba* leaves was selected as a strong candidate and herbal hydrogel were developed and characterized. The parameters such as ash value, foaming index, angle of repose and other micromeritics studies were performed such as bulk and tap density carr's and dates and hausner's ratio.After, extraction of leaves were performed by using Soxhlation, and phytochemical analysis of extracted leaves were performed. There are other parameters of leaves extract are also evaluated such as, TLC, fluorescence analysis and FTIR. After that, the herbal hydrogel of *Plumeria alba* leaves were developed by using polymers by applying physical blending method using HPMC- Carbopol composite hydrogel base. The hydrogel were formulated in four different formulations such as F1 (1% w/w), F2 (3% w/w), F3 (5% w/w), F4 (10% w/w). These four formulations were evaluated for different parameters such as, viscosity (100% of F3), spread ability (100% of F1), droplet size (210 nm of F4) and PI. (0.73 of F1) and drug entrapment efficiency is 83.8% of F3. If we observe all parameters of all four parameters of all four formulation, then F3 is best. The *in vitro* drug release study is also performed. The anti-microbial activity is very important for wound healing, and it is performed by agar well diffusion method and cork borer method and zone of inhibition.

Keywords- Chronic wound**,** Agar well diffusion method, Plumeria alba leaves hydrogel, Streptozoticin, etc.

Introduction-

When there is a disturbance in the normal anatomy of skin or underlying tissue, it is known as wound. It can be of any type of wound such as chemical, physical or biological. If we take any definition of wound such as

such as Merriam-Webster Medical Dictionary, “A wound is a physical damage to the human or animal system in which the skin gets cracked or break or mucus membrane get harmed with the underlying tissue. A wound is responsible for discontinuation of skin lining or underlining tissue [1].

The wound healing is divided into four steps such as, Hemostasis, inflammation, proliferation and remodeling. When a wound or injury occurs, the first step hemostasis initiates immediately in which vessels get constrict and platelets clogging starts for the control of bleeding. After that, conversion of fibrinogen into fibrin gets started to clot the blood. Then, in next step, that is inflammation, the neutrophils and macrophages are appointed at the surface of wound within one and half days of the wound occurs. They recruit various chemokines and cytokines such as components like C3a and C5a and transforming growth factor beta to provide them to pathogens and phagocytosis cells. The cytokines, TGF- β and interleukin 10 are released when inflammatory phase gets converted into anti- inflammatory phase. After that matrix metalloproteins enzymes splits the extracellular matrix (ECM) to allow movement of the cells. In the third step, proliferation, the growth factors stimulate the fibroblast and ECM are produced in the form of hyaluronan, fibronectin and collagen, after that epithelial barrier takes place by the process of re- epithelialization. Then, there is last step, that is remodeling, in which the tissue tensile strength gets stronger and the wound size gets smaller with the help of interaction myofibroblast with ECM, then in result a mature scar bis developed at the place of wound [2].

When the normal stages of healing is not successful, then wound healing process gets delayed and universally known as chronic wound. We can say that, the chronic wound cannot be healed and remains unhealed for at least 2-3 months, even when the treatment is on ongoing. The inflammation in chronic wounds remain constant due to which the wound cannot be healed. There are various chronic wounds such as, infection, diabetes, burn, impaired blood supply, venous insufficiency, other systemic conditions and pressure ulcers. In chronic wounds, the substance remains entrapped in inflammation phase and cannot be released due to which tissue cannot be regenerate and wound become more complicated [3- 4].

The chronic wound is when considered by its definition, it is the condition in which inflammation phase become delayed and converted into a severe pathological condition due to which healing cannot takes place easily and breaks its coordination with the other phase of wound healing. The chronic wounds are responsible for major complicated conditions [5].

The conventional treatment involves various types of medication and major amount of antibiotics such as gentamicin, vancomycin, silver sulfadiazine, neomycin, mupirocin, bacitracin, ciprofloxacin and many more, are become major reason of side effects, adverse effects, or neutralization of therapeutic potential. These conventional treatments are very important and helped us from starting in the healing of wound, but they are loaded with lots of disadvantages and limitations too [6,7,8].

The novel drug delivery system, that has strong capacity of water absorption, and the polymer makes a crosslinked 3d network with the swelling water capacity is known as hydrogel. Their high potential of water absorption make them a suitable candidate for wound healing and other biomedical benefits. The polymer used in the manufacturing of hydrogel contains various functional groups such as, hydroxyl, carboxyl, amide, sulphonic groups which act as the backbone of the side chains enhance their hydrophilic behavior and make them suitable and potential candidate for hydrogel [9]. There are such types of hydrogel are also present that carry hydrophobic functional group and can be mixed with hydrophilic polymers to increase the efficiency of hydrogel and make them stable [10,11]. There are different types of networking is possible in hydrogel depending upon their physical properties such as, semi- crystalline, supramolecular, amorphous and hydrocolloidal aggregates [12].

To make hydrogel better and more effective, the antibiotics and other synthetic drugs are replaced by natural origin bioactive compound in which mostly belongs to plant sources, and such types of hydrogels are known as herbal hydrogel. These natural drugs are derived from the plants leaves, flowers, roots, stems, rhizomes, etc. and elevate the properties of hydrogel polymers more. There various types of hydrogels are formulated such as curcumin loaded hydrogel, aloe vera based hydrogel, neem incorporated hydrogel, etc.

Frangipani is also other name of *Plumeria alba*, and its family name is Apocynaceae. Plumeria Alba comes under small tree and shrubs. The cultivation of flowers has been done in South America, Mexico, Central America, extending to Brazil. They are also propagating in tropical and sub-tropical regions also. Plumeria alba is a native of America and have lactiferous properties. Sometimes it is cultivated in graden and if we are talking about its height, 4.5 m height can be reaches. Different properties such as purgative, diuretic, hypotensive and cardiotonic contains latter species of *Plumeria alba*. The plant of Plumeria alba also contains amyrin acetate, a combination of amyrins, ß- sitosterol, scopotetin, and iridoids such as plumieride, plumieride isoplumericin, plumieride, coumerate, and coumarate glucoside.

Materials and Methods-

The Plumeria alba leaves were collected from local field of Varanasi, UP, and its authentication was done in BHU, Varanasi, UP. HPMC, Carbopol, triethanolamine, phenoxy ethanol and caprylyl glycol was purchased from Paras Chemicals. Weighing balance, beaker, measuring cylinder, petri dish, TLC plate , etc are used.

Collection and authentication of Plumeria alba leaves-

The plant was collected from local field of Varanasi, U.P. and then authenticated by BHU, Pharmacognosy department. The collected plant was dried in the shed at the room temperature and grinded into powder for further study.

Fig 1- Powdered dried plant

Preformulation studies-

Microscopic study of the plant [13]-

The dissection of fresh leaf of Plumeria alba leaves was performed. And thinnest section was cut and observed under a microscope for its microscopic study and to know the leaf features better.

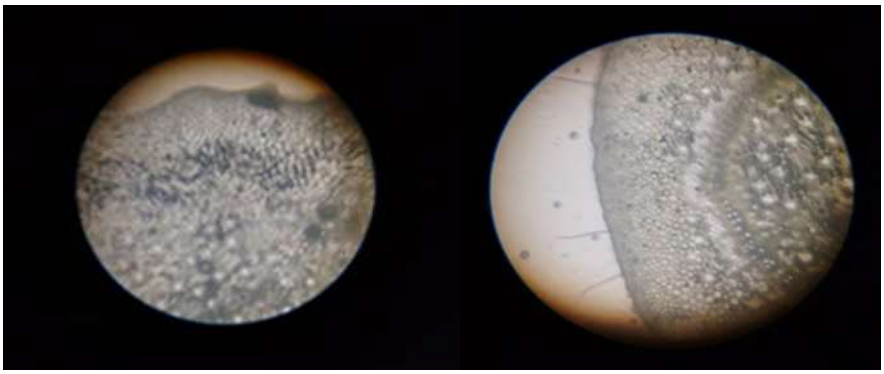

Fig 2- Transverse section of leaf

Powder microscopy [14]-

The dissection of fresh leaf of Plumeria alba leaves was performed. And thinnest section was cut and observed under a microscope for its microscopic study and to know the leaf features better.

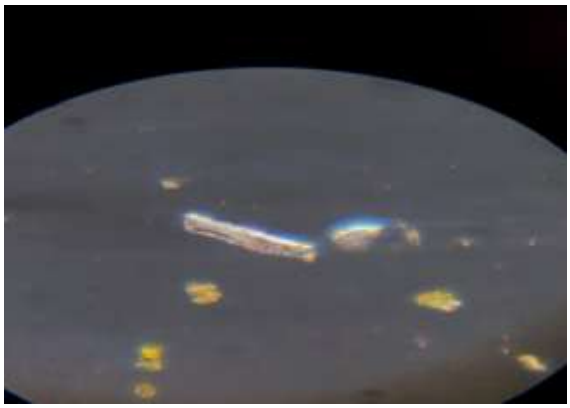

Fig 3- Powder microscopy of leaf.

Micromeritics studies [15]-

The flow properties of powdered dried leaves of *Plumeria alba* leaves are studied and mentioned below.

Angle of repose [16]-

The funnel method is used for determining angle of repose. The leaves dried powder was transferred on a graph paper from a funnel attached to a burette stand and the pile of the powder was circle and diameter was noted and height of the pile is measured, and by using given formula, it is calculated.

$$\text{Angle of Repose } (\theta) = \tan^{-1} h / r$$

Where, h=hight of pile (in cm), r =radius (in cm)

Fig 4- Angle of repose

Determination of Swelling Index [17]-

Transfer the dried powder leaves into a 25 ml measuring cylinder. The internal diameter of the cylinder was measured, the length was marked and 0.2-ml divisions from 0 to 25 ml in an upwards direction marked on the measuring cylinder. Add 25 ml of water and mix it well for ten minutes on a hold for 1 hour. Wait for 3 hours and the measure the sample of swelling index.

Determination of Moisture content [18]-

The 1.50 grams of powdered dried leaves was placed in porcelain dish, which was earlier dried for no moisture at 105 ºC in hot air oven. It was weighed empty and after that with sample and moisture content was calculated.

$$\% \text{ Moisture content} = \text{Total moisture content} / \text{Total wt. of powder} \times 100$$

Bulk Density and Tapped Density [19]-

The 20 grams of leaves powder was transferred into the measuring cylinder with the help of funnel and volume on the measuring cylinder was noted as bulk volume and bulk density was calculated. After that, the measuring cylinder was tapped in a repeated manner for 15 minutes and then tapped volume was noted and tapped density was calculated.

Carr's Index [20]-

For measuring the compressibility of the leaves powder the Carr's index was calculated by using the given formula and putting the value of tapped and bulk density.

Carr's index (% compressibility) = (1 - Db / Dt) × 100

Where, Db = Bulk density, Dt = Tapped density

Hausner Ratio [21]-

With the help of bulk density and tapped density, the Hausner' ratio was calculated.

Hausner ratio =Dt / Db

Where, Db = Bulk density and Dt =Tapped density.

Table 1- Micromeritic studies

S.N.	Parameter	Result
1.	Angle of repose	28.05 (excellent)
2.	Bulk density	0.3
3.	Tapped Density	0.375
4.	Carr's index	20%
5.	Hausenr's ratio	1.25
6.	Ash Value	19%

Determination of Ash value [22]-

The earlier ignited and tared crucible was used and 2 grams of dried leaves powder was placed in it. It is spread evenly and ignited at a temperature of 600 °C, until the color change to white showing the absence of carbon. After that, a desiccator is used to cool it and it is weighed and ash value is calculated.

Fig 5- Ash value

Determination of foaming index [23]-

The coarse powder of the dried leaves about 1 gram was weighed and transferred into a 500 ml conical flask that contains 100 ml of boiling water and a moderate temperature for about 30 minutes. Cool the mixture and

filter it into a 100 ml volumetric flask and dilute it by adding sufficient quantity of water. Then the mixture was transferred into 10 test tubes of the portion like 1 ml, 2 ml, 3 ml, 4 ml till 10 ml and in all test tube the volume was adjusted up to 10 ml by adding water. Then place the stopper in each test tube and shake each of one in vertical direction for 15 seconds, two shakes per second. Then measure the foam height after 15 minutes.

Fig 6- Foaming index

Extraction of *Plumeria alba* leaves [24]-

Soxhlet apparatus used for various phytoconstituents extraction. A thimble containing 50 grams of finely powdered *Plumeria alba* was prepared and thereafter subjected to extraction using 400ml chloroform at a temperature of 610°C. Summarizes the present study including plant extraction, in vitro wound healing studies of the *Plumeria alba* leaves plant.

Fig 7- Soxhlet apparatus

Phytochemical Analysis of Plumeria alba extract [25]-

- **Test for alkaloid-**
  The Dragendroff's test were performed for the alkaloid, in which 2-3 ml of extract was added in dragendroff's reagent and orange brown precipitate was formed.
- **Test for tannins and phenolic compound –**
  For the identification of tannins and phenolic compounds, the extract was added in small quantity in lead- acetate solution and white precipitate was formed.
- **Test for reducing sugar-**
  Benedict test was performed for identification of reducing sugar. The benedict reagent and extract sample was added and mixed in equal quantity in a test tube. In a boiling water bath, heated for 5 minutes and solution appears green.

- **Test for Steroid-**

  Salkowski reaction is performed for analyzing the presence of steroid. The 2 ml of leaves extract was added in a test tube with 2 ml of chloroform and concentrated sulphuric acid. The test tube was shake well. The chloroform layer appears red and acid layer become greenish yellow.

- **Test for Proteins-**

  Million's test was performed for the identification of proteins. Mix 3 ml of extract with 5 mo of reagent. The white precipitate convert into brick red color.

Fig 8- Phytochemical test

Table 2- Preliminary Phytochemical Test-

S.No.	Test for Phytoconstituents	Test	Result
1.	Test for alkaloids	Dragendorff's test	-
2.	Test for tannins & phenolics	Lead acetate test	+
3.	Test for reducing sugar	Benedict's test	+
4.	Test for steroids	Salkowski reaction	+
5.	Test for proteins	Million's test	-
6.	Test for saponins	Foam test	+

Thin Layer Chromatography (TLC) of Plumeria alba extract [26]-

The pre- coated TLC plate was used and a line was drawn by using pencil in the bottom of the plate as baseline. Then the extract was dissolved in the ethyl acetate. With the help of a capillary tube, the sample was spotted on the baseline. The spot was allowed to dry. A TLC chamber was taken and mobile phase chloroform: n-hexane (9:1) is transferred in the chamber in small amount. The chamber was covered with the filter paper for better saturation. Place the TLC plate in the chamber in the upward direction and the solvent should be below the baseline. Cover the chamber and allow the solvent to run. Remove the plate from chamber and mark the solvent front. The plate was dried and observed by staining of iodine. The distance travelled by each compound is measured by calculating the Rf.

Rf = Distance traveled by compound / Distance traveled by solvent (Harwood, 1989)

Solvent font =3.2, Sample no. 1= 1.2, Sample no. 2= 2.5,

Retention factor of spot no. 1= 1.2/2.5 , Rf = 0.3

Fig 9- TLC Plate

Fluorescence analysis [27]-

A small amount of powdered sample was taken. Then powder is mixed with distilled water. Then, a glass slide was prepared and observed a U.V chamber to evaluate its purity.

Table 3- Fluorescence analysis of drug powder

Treatment	Day light	UV (254nm)	UV 365 nm)
Powder as such	Greenish brown	Green	Green
Powder +Hcl	Paleyellowish	Dark brown	Dark brown
Powder + Benzene Crystalline	Black	Dark Green	Black
Powder + Hydrogen peroxide	Brown	Dark Green	Black
Powder +Acetic acid	Brown	Dark Green	Yellowish
Powder + sulphuric acid	Black	Green	Black
Powder + Methanol	Black	Green	Brown
Powder + Acetone	Dark green	Green	Dark green

FTIR of *Plumeria alba* leaves extract-

For identifying the drug compound specifically, the Fourier transform infrared spectroscopy were one of the authenticated method which is used [28].There are many significant quality of FTIR due to which it is used

for analysis in pharmaceutical industries such as, it is time saving, easy to use, selective method, fast, sensitive and green and its help to guaranteed regulations conformity through the protocols of validation [29-30].

Formulation of Plumeria alba leaves Hydrogel [31]-

A 4.5 g of HPMC was added to the hot water and continuously stirred until it thickened to obtain A hydrogel (gel made from dissolving 4.5 grams of HPMC). Next, 0.5 g of carbopol was added to the water, then added with 0.25 g of triethanolamine and stirred continuously until B hydrogel (gel made from dissolving 0.5 grams of carbopol + 0.25 grams of triethanolamine was obtained. The two hydrogels were mixed, and then 0.7 g of phenoxy ethanol and 0.3 g of caprylyl glycol were added. A series concentration (1, 3, 5, and 10% w/w) of *Plumeria alba* leaves extract was added to the hydrogel and mixed well via stirring.

Fig 10- 1% w/w Plumeria alba leaves extract incorporated hydrogel

Fig 11- 3% w/w Plumeria alba leaves extract incorporated hydrogel

Fig 12- 5% w/w Plumeria alba leaves extract incorporated hydrogel

Fig 13- 10% w/w Plumeria alba leaves extract incorporated hydrogel

Post evaluation of Plumeria alba hydrogel-

Viscosity Measurement [32]-

The Brookfield viscometer is used for determining the viscosity of all four formulation. It is found that, F3 has better viscosity in comparison of others.

Spreadability [33]-

The spreadability of *Plumeria alba* leaves hydrogel was evaluated and the spreadability was found to be like, 13.56 and so on. These values show that, the hydrogel can br spread easily.

Size and poly-dispersity index-

The droplet size and polydispersity index of the herbal hydrogel was helpful in knowing better behavior of the hydrogel use.

Drug Entrapment Efficiency [34]-

As we increase the polymer concentration such as HPMC and corbopol, the extra space is created for the entrapment of Plumeria alba. Here we calculated the drug entrapment efficiency in percentage.

In vitro drug release Study [35]-

The Franz diffusion cell is used to study the in vitro drug release study of *Plumeria alba* leaves hydrogel. For the permeation of Plumeria alba from the hydrogel to the membrane, the egg membrane is used as diffusion membrane. The study was performed after 8 hours of the formulation. In these formulations, where gelling agent is high, there is low permeation of *Plumeria alba*.

Antimicrobial Activity [36]-

Antibacterial Activity Test-

For evaluating the anti- bacterial activity of Plumeria alba leaves hydrogel, the agar diffusion method was used. [37].

Cork Borer Method-

By using a vortex mixer, in a petri dish, 20 ml of sterile nutrient agar was poured. By using the borer five well were created in which three of them were filled with 300 µL, 600 µL, and 900 µL of the *Plumeria alba* leaves hydrogel while a fourth was filled with a standard antibiotic (Ciprofloxacin). The plates were left at room temperature for 2 hours to allow diffusion before microbial growth began, and then incubated at 37 °C for 24

hours. Antibacterial activity was assessed by measuring the diameter of the inhibition zones with a ruler [38-40].

Zone of inhibition [41]-

The in vitro antibacterial properties of *Plumeria alba* leaves were evaluated. The antibacterial potential of the *Plumeria alba* leaves against two pathogenic bacterial species *Lactobacillus* and *Staphylococcus aureus* was assessed using the agar well diffusion method. The *Plumeria alba* leaves was dissolved in an appropriate solvent, sterilized through filtration using Whatman filter paper, and then stored at 4°C. To determine the zone of inhibition (ZOI), *Lactobacillus* and *S. aureus* were used, and Ciprofloxacin served as the standard antibiotic to enable comparison of the results. Three concentrations (300 µL, 600 µL, and 900 µL) of *Plumeria alba* leaves, along with standard drugs, were prepared in double-distilled water using nutrient agar tubes. The zones of bacterial inhibition surrounding the disks were measured, including the diameter of the disks themselves. The susceptibility of the bacterial species to the *Plumeria alba* leaves was determined based on the size of the inhibition zones.

Result-

- **Organoleptic properties of *Plumeria alba* leaves**

S.No	Color	Odor	Taste	Texture
1	Dark green	Characteristic	Bitter	Smooth

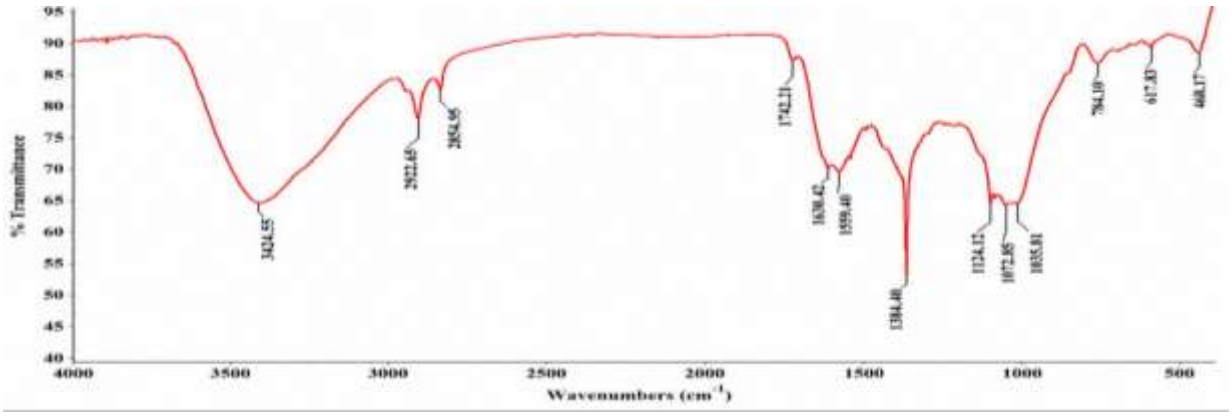

Fig 14- FTIR of *Plumeria alba* leaves

Characterization of Hydrogel-

Table 4- Evaluation parameters of *Plumeria alba* Hydrogel

S. No	Parameters	F1	F2	F3	F4
1	Viscosity (%)	67.5	90.9	100	90.0
2	Spreadability (%)	100	88.6	63.8	70.1
3	Droplet size (nm)	406	353	260	210
4	Polydispersity index	0.73	0.51	0.30	0.18

5	Drug entrapment efficiency (%)	63.5	68.9	83.8	69.3

Table 5- *In vitro* drug release study of *Plumeria alba* Hydrogel

Time (in min)	F1	F2	F3	F4
0	0	0	0	0
30	4.3	3.5	4.1	2.6
60	8.4	7.4	9	4.4
90	12.3	10.5	13.9	9.5
120	18.2	17.5	21.6	12.5
150	23.7	20.8	25.7	16.7
180	28.5	25.5	31	19.8
210	36.3	29.4	37.5	23.8
240	45.5	35.5	46.2	29.5

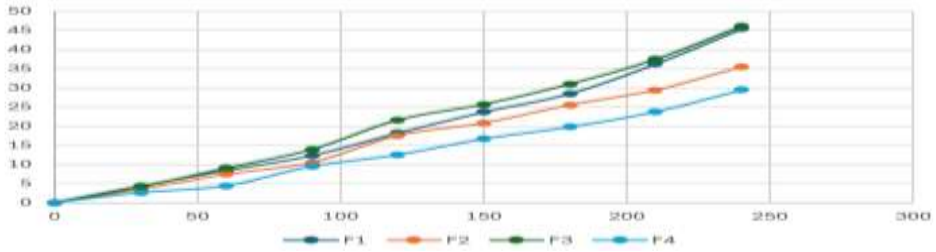

Fig 15- *Invitro* drug release profile

Antibacterial activity of *Plumeria alba* hydrogel-

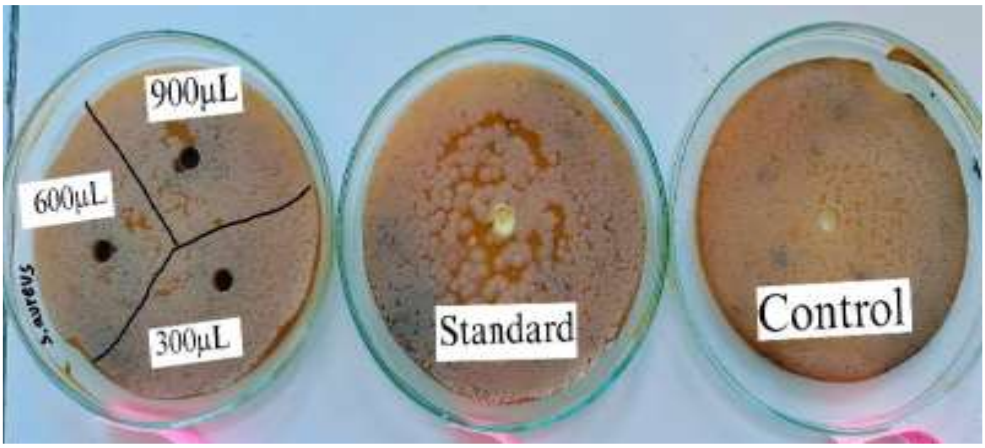

Fig 16- *Staphylococcus aureus*

Fig 17- *Lactobacillus*

Conclusion- As we see, wound is a major problem now a days due to disturbances in the four phases of wound healing due to which wound healing is delayed and become chronic, and our conventional treatments such as antibiotics face challenges in it. To overcome these limitations, the herbal hydrogels such as *Plumeria alba* hydrogel is a novel and advanced drug delivery system that provides moist environment, infection control and other parameters for better treatment in wound healing.From the above research, result and discussion, it was concluded that, *Plumeria alba* leaves hydrogel is effective and have great potential in the wound healing treatment.

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