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Pharmacological Screening for Burn Wound Healing Potential of Traditional Plant *Cassia fistulia* in Rats

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ABSTRACT

Skin is a vital organ which performs several functions such as thermoregulation, homeostasis, metabolic, neurosensory and immunologic functions. Burns, with their devastating consequences, are known as one of the most common forms of injury. Herbal products could be extensively preferable for treating many ailments due to their widespread accessibility and the vast experiential data retrieved from traditional medicine. *Cassia fistula* has been traditionally used to treat skin disorders and injuries. In the present study, the healing effect of aqueous and ethanolic extracts of leaves of *Cassia fistula* has been evaluated in second-degree burn wound in rats. The preliminary phytochemical screening revealed the presence of tannins, alkaloids, cardiac glycosides, steroids, carbohydrates, flavonoids, saponins, and phenols as phytoconstituents. From day 4 to day 21, both aqueous and ethanolic extracts of *Cassia fistula* leaves were observed to have a significant effect during treatment and also the test drugs were found to play a role in accelerating the rate of epithelialization. Cell viability in both cell lines was significantly decreased when compared to the control cells. The hydroxyproline level was found to be substantially elevated in aqueous and ethanolic extracts of *Cassia fistula* leaves treated groups. The efficacy of *Cassia fistula* leaves in improving wound healing was also discovered by histopathological analysis of the cream-treated rat wound tissues.

Keywords: *Cassia fistulia*, burn wound healing, epithelization, cytotoxicity, hydroxypyroline.

1. INTRODUCTION

Skin is a vital organ which performs several functions such as thermoregulation, homeostasis, metabolic, neurosensory and immunologic functions. It is also a physical barrier against infections; thus, when it is injured, pathogens can have a direct access to the deep tissues.[1] Burns, with their devastating consequences, are known as one of the most common forms of injury. The destructive outcomes of burns include physical disabilities as well as mental and emotional disorders.[2,3] Many synthetic drugs have been used to improve the wound healing process. However, they can pose problems such as allergy and drug resistance. These cases force scientists to seek alternative drugs for wound healing process.[4]

Herbal products could be extensively preferable due to their widespread accessibility and the vast experiential data retrieved from traditional medicine. However, modern scientific methods should be applied to confirm the claims about the beneficial effects of herbal compounds.[5]

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In India, herbal-based treatments like Ayurveda, Siddha, and Unani have been used to cure various diseases and physiological abnormalities. World Health Organization (WHO) estimates that 80% of the people living in developing countries almost exclusively using traditional medicine.[6] *Cassia fistula* (Leguminosae) have been traditionally used to treat skin disorders and injuries.[7] It is distributed in various regions including Asia, South Africa, China, West Indies and Brazil. Phytochemical tests are carried out on the plant to identify the presence of plant secondary metabolites such as coumarins, flavonoids, and mainly phenolic compounds such as fistucacidin, epiafzelechin, epiafzelechin-3-O-glucoside, epicatechin, rhein, procyanidin B2, biflavonoids, triflavonoids, glucosides, sennoside A and B, chrysophenol and physcion isolated from the leaves. It has been claimed that different parts of this plant have been demonstrated to possess several medicinal values such as antitumor activity, antioxidant activity, hypoglycemic, hepatoprotective, antibacterial, hypocholesterolaemic, and antidiabetic.[8-12]

In the present study, the healing effect of aqueous and ethanolic extracts of leaves of *Cassia fistula* has been evaluated in second-degree burn wound in rats.

2. MATERIAL AND METHODS

2.1 Chemicals and Reagents

Distilled water, ethanol, glycerine, propyl paraben etc. were obtained from standard sources. Chloramine-T was prociured from Sigma Aldrich, Hyderabad, India.

2.2 Collection and Physical Evaluation of Plant Material

The fresh leaves of *Cassia fistula* were collected from the Botanical Herbal Garden, Ranga Reddy District, Telangana, India. The plant was confirmed by Dr. P. V. Prasanna, Botanical Survey of India, Hyderabad, India (Voucher: 734). Physical standards of leaves of *Cassia fistula* were determined. These are rarely constant for crude drugs, but may help in evaluation, especially with reference to moisture content, loss on drying and ash content (total ash, acid insoluble ash, water soluble ash and sulphated ash).[13]

2.3 Different Extractions of Plant Material

The leaves of *Cassia fistula* were cut into small pieces and dried under the shadow one month at room temperature. Then, the small pieces were granulated or powdered by using a blender and sieved to get uniform particles. The final uniform powder was used for the extraction of active constituents and stored in dry, clean air tight glass jars. 250 g of powdered leaves of *Cassia fistula* were packed in Soxhlet apparatus separately and extracted with solvent water and ethanol. The extracts were filtered while hot and the solvents were removed by distillation and the last traces of solvent being removed under reduced pressure. The aqueous and ethanolic extracts were stored in refrigerator for further experimental work.[14]

2.4 Phytochemical Screening

The preliminary phytochemical analysis of aqueous and ethanolic leaf extracts of *Cassia fistula* was screened for the various phytochemical principles such as alkaloids, saponins, glycosides, carbohydrates, flavonoids, tannins, proteins and amino acids, fixed oils, phytosterols and phenols using simple established standard methods.[15,16]

2.5 Preparation of Ointment

The appropriate hydrophilic cream base for delivering aqueous and ethanolic leaf extracts of *Cassia fistula* was prepared according to the previously reported procedure.[17] The vehicle constituents were listed in Table 1. The oil phase was prepared by heating the solid lipid materials at 75°C until it liquefied, and the internal phase was apparently dispersed into the external phase. The solution was mixed well using homogenizer at 200 ± 25 rpm until homogenous, which subsequently was quenched to room temperature. 20 g of aqueous and ethanolic leaf extracts of *Cassia fistula* were separately incorporated into the base cream formula (Fig. 1).

2.6 Acute Dermal Toxicity Studies

The test in the albino rats were performed as per to the OECD draft guideline number 434.

Table 1: Formulation of leaf extracts of *Cassia fistula*

Ingredients	Composition (w/w)
Stearic acid	15
Cetyl alcohol	0.5
Isopropyl myristate	3.0
Glycerin	6.0
Potassium hydroxide	0.5
Sodium hydroxide	0.18
Propyl paraben	0.15
Cassia fistula leaf extract	20
Distilled water	q.s. (100 g)

Selection of dosage was guided by procedures stipulated in OECD draft guidelines. Sighting study was conducted to all extracts tested. The limit dose of 2000 mg/kg was selected for the main study based on the fact that the 1000 mg/kg as a start dose in the sighting study could not show any sign of toxicity when considering animal weight changes for two weeks.[18]

A total of ten animals (all females) were divided into two groups of five animals each for a treatment and a control groups. Approximately 24 hours before the study, fur was removed from the dorsal area of the trunk of the animals by clipping to obtain at least 10% of the body surface area while taking care to avoid abrading the skin. Depending on the type of extract; the test substances were moistened with either sunflower cooking oil or distilled water then applied evenly over a shaved area using a small spatula. Liquid test substances were used undiluted. The test substances were held in contact with the skin with a porous gauze dressing and non-irritating tape throughout a 24-hour exposure period. At the end of the exposure period, residual test substance was removed using water or sunflower oil or both. Cage side observation was made daily, but weight measurement was taken weekly for 14 days. Observation included evaluation of skin and fur, eyes, respiratory effects, salivation, diarrhea, urination, and central nervous system effects such as tremors and convulsion, gait and posture, reactivity to handling or sensory stimuli and altered strength.

Fig. 1: Prepared herbal cream

2.7 Pharmacological Activity

2.7.1 Experimental Animal

30 adult albino wistar rats of either sex (160-250 g) were used in the study. The experimental protocol was approved by Institutional Animal Ethics Committee, Central Animal House CPCSEA No.: 1864/PO/Re/S/17/CPCSEA, Shadan Institute of Medical Sciences, Hyderabad, India. The animals were maintained in standard laboratory conditions, 12-hr light/ dark cycle with controlled temperature. All animals were acclimatized to laboratory environment for a week. They were given standard diet pellet and free access to water before the commencement of experiment. All animal procedures were performed in accordance with the approvals from care and use of laboratory animals. The project was approved by Institutional Animal Ethics Committee with protocol no.: IAEC-03/SES/2019/007.

2.7.2 Induction of Burn Wound

The back of the twenty rats were shaved under anesthesia (100/10 mg/kg ketamin, intra peritoneal (*ip*)). Then a deep circular 15 mm diameter burn wound (177 mm^2) was created on their dorsal parts, using an electrical heater (110°C for 10 seconds). The underlying skin was cleaned with normal saline to anticipate spinal shock. The profundity, measure and morphology of the wounds was measured and their recuperating potential was tried with application of standard and test creams for 21 days (Fig. 2).[19]

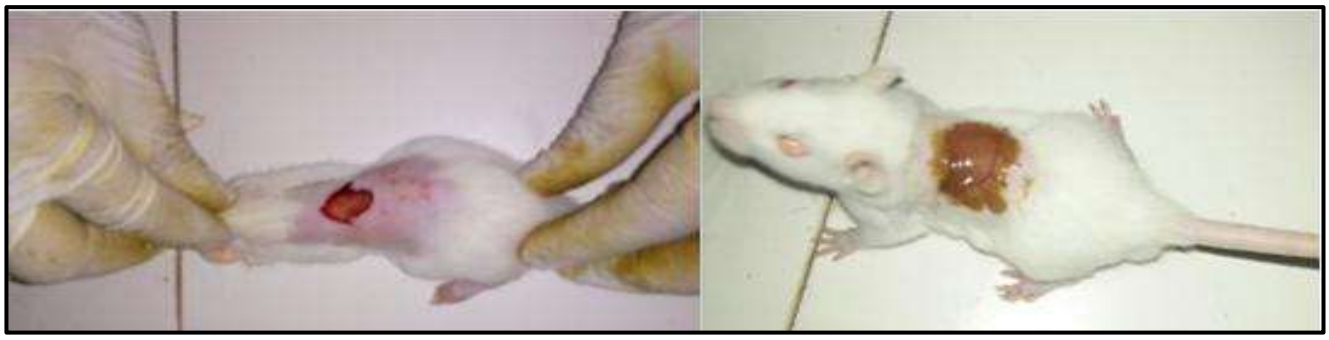

Fig. 2: Application of prepared leaf extracts cream of *Cassia fistula*

2.7.3 Experimental Protocol

The animals were divided into five groups with six animals in each group.

- **GROUP I (Normal Control):** Undergoes shaving only
- **GROUP II (Disease Control):** Acute burn injury group (doesn't received treatment)
- **GROUP III (Standard):** Burn injury + Silversulfadiazine (1% w/w) topically treated group
- **GROUP IV (Treatment I)**: Burn injury + *Cassia fistula* aqueous extract-based cream (20% w/w) topically treated group
- **GROUP V (Treatment I)**: Burn injury + *Cassia fistula* ethanolic extract-based cream (20% w/w) topically treated group

The animals were housed in different cages. Treatment began 24 hours after the burn wound was inducted and lasted 21 days. Daily ointments were added to the wound, which was then dressed with a standard dressing. For 21 days, the dressing was changed every 24 hours. Both rats were sacrificed on day 22 and skin tissues from the burned area were gathered. Each sample was cut into sections, with one section held in 10% formalin to assess histopathological changes and another used to determine the concentration of hydroxyproline.

2.8 Assessment of Burn Wound

2.8.1 Measurement of Wound Contraction and Epithelization

The rate of wound healing was calculated using a digital camera frequently from the second day of treatment, as a percentage reduction in the initial wound region. Image J software was used to analyze the collected photographs in order to assess the wound location. The following equation was used to measure the percentage of wound contraction (WC %):[20]

$$WC = \frac{\text{size on induction day} - \text{size on specific day}}{\text{size on induction day}} \times 100$$

Finally for all the group animals which were treated by standard and test drugs, the epithelization time in days was determined.[21]

2.8.2 Measurement of Tensile Strength

The degree of wound healing was determined by the tensile strength. It indicates how resistant the healed tissue is to cracking under strain and may help determine the healing tissue's consistency. Both of the animals were anesthetized with ketamine hydrochloride (50 mg/kg, i.p., body weight) on the tenth day, the sutures were cut, and the healing tissue was excised from all of the animals. The tensile strength of excised tissue was determined using a tensiometer.[22]

2.8.3 Cytotoxic Assay

The cells were cultured on 96-well plates (2×10^5 cells/mL) in 100 L of full growth medium to conduct the MTT reduction. After 24 hours, the medium was replaced with fresh medium combined with 1000 µg/ml aqueous and ethanolic extracts of *Cassia fistula* leaves. The cells exposed to the trace agent mixture were plated at a density of 2 10^5 cells/mL and incubated for 24 hours in the same way. MTT reduction assay was conducted after 24 hours of incubation.[23]

2.8.4 Hydroxyproline Estimation

The amount of hydroxyproline in excised wound tissues from both rats was measured. Tissues were dried to a constant weight in a hot air oven at 60°C, then hydrolyzed in 6 N HCl for 4 hours at 130°C. The hydrolysates were then neutralized to

pH 7.0 and oxidized for 20 minutes with Chloramine-T. The reaction was stopped after 5 minutes with the addition of 0.4 M perchloric acid and color formed with Ehrlich reagent at 60°C. The samples were analyzed at 557 nm in an ultraviolet spectrophotometer after extensive stirring. A typical curve of pure L-hydroxyproline was used to measure the hydroxyproline content in the tissue samples.[24]

2.9 Histopathological Study

All the animals were anesthetized with ketamine at the end of the investigation; wound tissue specimens were obtained and stored in glass vials containing 10% formalin solution for histological analysis. Parts of wound tissue specimens were microtomized and dyed with hematoxylin and eosin (H & E) dye.

2.10 Statistical Analysis

The data were presented as mean ± standard error of the mean (SEM) and evaluated using one-way ANOVA and Tukey's post-hoc analysis, with $P < 0.05$ being considered important for both values.

3. RESULTS

3.1 Physical Evaluation

The results of physical evaluation of leaves of *Cassia fistula* are shown in Table 2. The moisture content of leaves of *Cassia fistula* was 16.23% indicating that the leaves of *Cassia fistula* are less prone to microbial decomposition and enzymatic deactivation, suggesting more stable for longer periods. The leaves of *Cassia fistula* showed 15.28 % w/w of loss on drying and 0.87% of crude fibre which assures it's most pure and qualitative property. The ash study revealed that total, acid insoluble, water soluble and sulphated ash values were 2.43, 0.21, 1.22 and 0.17 % w/w respectively.

3.2 Yield of Extraction

The amount of leaves extracts of *Cassia fistula* obtained after the Soxhlet process of aqueous extraction was 12 % ethanolic extraction was 10 %.

3.3 Phytochemical Screening

The aqueous extract of *Cassia fistula* leaves posses alkaloids, saponins, cardiac glycosides, carbohydrates, flavonoids, and phenols. The ethanolic extract of *Cassia fistula* leaves possess tannins, alkaloids, cardiac glycosides, steroids, carbohydrates, flavonoids, saponins, phenols, and proteins as phytoconstituents.

Table 2: Physical evaluation of leaves of *Cassia fistula*

S. No.	Parameters	Values (% w/w)
1	Moisture content	16.23
2	Loss on drying	15.28
3	Crude fibre content	0.87
4	Total ash	2.43
5	Acid insoluble ash	0.21
6	Water soluble ash	1.22
7	Sulphated ash	0.17

3.4 Acute Dermal Toxicity

The aqueous and ethanolic extracts of *Cassia fistula* leaves caused no harmful symptoms or death in any animals who lasted for up to 14 days after receiving a single dose of 2000 and 1000 mg/kg body weight on the first day. Behavioral variations were found for the first 6 to 14 hours after the application of the extract. The animals in the extract-treated group were average and showed no apparent differences in appearance, skin symptoms, ventilation, water and food absorption, postural anomalies, or hair loss.

3.5 Effect of *Cassia fistula* Leaves on Wound Contraction and Epithelization

From day 4 to day 21, both aqueous and ethanolic extracts of *Cassia fistula* leaves were observed to have a tentative effect during treatment. The credentials discovered spontaneously on day 21 favor the test drug's possible curative benefit, which was shown by increased wound contracting as compared to disease control group ($P < 0.001$). In terms of epithelialization rate, the test drugs were found to play a role in accelerating the rate of epithelialization and took less time to complete the process as compared to the disease control group ($P < 0.001$) (Table 3).

3.6 Effect of *Cassia fistula* Leaves on Tensile Strength

A good wound healing agent must have effective tensile strength to improve the viability of collagen fibrils. In contrast to the disease control group, both aqueous and ethanolic extracts of *Cassia fistula* leaves showed a strong ($P < 0.001$) action on increasing tensile strength (Table 4).

3.7 Cytotoxic Assay

According to Table 4, cell viability in both cell lines was significantly decreased ($P < 0.001$) when compared to the control cells. The viability assessed by the MTT reduction assay in all the cell lines were significantly decreased. In this assay, the CTC_{50} for aqueous extracts of *Cassia fistula* leaves in the fibroblast cells was 780 ± 5 µg/mL and for ethanolic extracts was >1000 µg/mL (Table 4).

3.8 Effect of *Cassia fistula* Leaves on Tissue Hydroxyproline

The improved viability or microcirculation of collagen fibrils across the wound region was confirmed by increased hydroxyproline content, which was indirectly responsible for increasing the collagen amount. In comparison to the control group animals, the hydroxyproline level was found to be substantially ($P < 0.001$) elevated in aqueous and ethanolic extracts of *Cassia fistula* leaves treated animals respectively. The results are shown in Table 4.

Table 3: Effect of *Cassia fistula* leaves on % wound contraction and epithelization period

Groups	Wound Contraction on Different Days (%)						Epithelization Period (Days)
	2nd	6th	10th	14th	18th	21st	
Normal Control	-	-	-	-	-	-	-
Disease Control	5.57 ± 1.22	16.76 ± 0.75	35.13 ± 0.54	56.43 ± 1.64	79.49 ± 0.56	84.41 ± 1.04	24.85 ± 1.28
Standard Control	11.61 ± 1.16***	26.74 ± 0.34***	46.56 ± 0.21***	70.12 ± 1.22***	88.12 0.24***	96.36 ± 1.34***	33.71 ± 1.33***
Aqueous Extract	18.12 ± 0.88***	26.92 ± 1.07***	50.11 ± 0.89***	69.13 ± 1.87***	87.65 ± 0.75***	95.36 ± 1.20***	31.23 ± 1.65***
Ethanolic Extract	17.23 ± 0.14***	26.82 ± 0.25***	49.36 ± 1.44***	67.83 ± 0.94***	87.62 ± 0.68***	94.45 ± 1.31***	29.65 ± 1.23**

*All values are represented as mean ± SEM. Data were analyzed by one-way ANOVA, followed by Tukey's post hoc test. **P < 0.01, ***P < 0.001, when compared to the disease control group.*

Table 4: Effect of *Cassia fistula* leaves on tensile strength, cell viability and hydroxyproline content

Groups	Tensile Strength (g)	Cell Viability against MTT Assay			Hydroxyproline (µg/100 mg tissue)
		Test Conc. (µg/ml)	Cytotoxicity (%)	CTC_{50} (µg/ml)	
Normal Control	-	500	18.17	-	42.68 ± 0.22
Disease Control	234.56 ± 0.28	500	19.13	-	44.29 ± 0.34
Standard Control	472.52 ± 0.33***	500	24.19***	-	47.95 ± 0.69***
Aqueous Extract	867.34 ± 0.87***	1000	39.37***	780 ± 5	46.12 ± 0.71***
Ethanolic Extract	776.87 ± 0.53***	1000	29.32***	>1000	43.61 ± 0.11**

*All values are represented as mean ± SEM. Data were analyzed by one-way ANOVA, followed by Tukey's post hoc test. **P < 0.01, ***P < 0.001, when compared to the disease control group.*

3.9 Histopathological Study

The histopathological studies of the tissue of the excision wound were performed on the 22nd day and histopathological features of the tissue of all groups of animals were shown in Figure 4. Group I (normal control) animals had normal skin texture with no pathological modifications. Animals in Group II (disease control) had diseased and inflammatory cells, as well as decreased collagen fibers, fibroblast cells, and blood vessels, as well as visible scar tissue. Increased fibroblast cells, collagen fibers, and blood vessels, as well as decreased inflammatory cells, were seen in Group III (standard). In comparison to the disease control, the group IV (aqueous extract) group had significantly more fibroblast cells, blood vessels, and well-organized collagen fibers. There was less cellular necrosis in group V (ethanolic extract), as well as more collagen fibers and blood vessels. The extract ointment-treated and control groups all demonstrated epithelial tissue proliferation and keratinization.

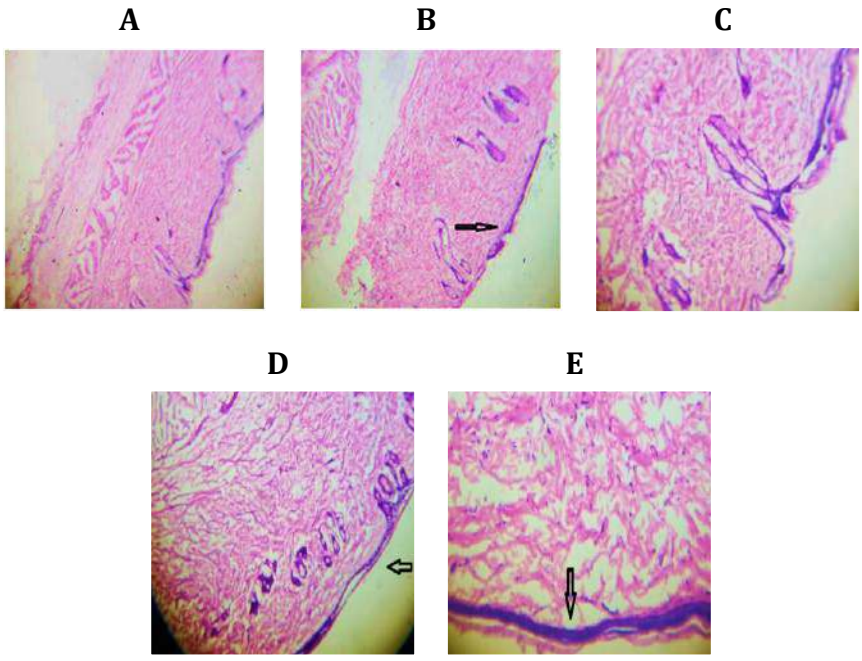

Fig. 4: Histopathology of skin tissue

Photomicrograph of histopathological section of wound tissue of rats of (A) group I (normal control) animal wound tissue, (B) group II (disease control) animal wound tissue, (C) group III (standard) animal wound tissue, (D) group IV (aqueous extract) animal wound tissue and (E) group V (ethanolic extract) animal wound tissue.

4. DISCUSSION

Wound healing is a complex mechanism that occurs when the skin and other soft tissues are damaged. Wound healing is a complex mechanism involving several biochemical reactions aimed at restoring the weakened cellular structure to its original condition.[25] Inflammation, proliferation, and remodeling are three sequential steps of the traditional wound healing cascade.[26]

With their antioxidant, anti-inflammatory and antimicrobial properties, plants have a lot of potential for wound and burn management and care.[27] The healing ability of aqueous and ethanolic extracts of *Cassia fistula* leaves was investigated in this study, and the findings indicated that it is a strong potential for burn wound. Alkaloids, cardiac glycosides, sugars, flavonoids, saponins, phenols, and phenolics were found in the aqueous extracts of Cassia fistula leaves, whereas tannins, alkaloids, cardiac glycosides, steroids, carbohydrates, flavonoids, saponins, phenols, and proteins were found in the ethanolic sample. Recent research has indicated that flavonoids, triterpenoids, and tannins play an important role in wound healing by a variety of pathways, including wound contracting, improved epithelialization, and avoidance of secondary bacterial infection, both of which may have complicated and slowed wound healing.[28] Tannin-

containing herbal products are considered to have medicinal applications because they facilitate wound healing and reduce infection complications due to their antibacterial properties. Furthermore, tannins can cause proteins in damaged tissues to precipitate, resulting in the forming of a scab. They may use this property to reduce tissue edema and exudation, as well as the permeability of capillaries in the wound.[29]

At maximum concentrations, the aqueous and ethanolic extracts of *Cassia fistula* leaves had no harmful impact in rats, indicating that the extracts are non-toxic. The astringent, anti-inflammatory, and antimicrobial efficacy of aqueous and ethanolic extracts of *Cassia fistula* leaves can be due to their strong phenolic and flavonoidal content in the current research. The healing effect of aqueous and ethanolic extracts of *Cassia fistula* leaves may be due to a variety of mechanisms, including increased rate of re-epithelialization and vascularity, scavenging of destructive free radicals, inflammation reduction, and infection control through antioxidant, anti-inflammatory, and antimicrobial. As a result, the use of aqueous and ethanolic extracts of *Cassia fistula* leaves in burn wound injuries has been confirmed in this report.

Collagen is an essential factor that essentially plays an important role in wound strength and tissue matrix integrity. It is found in the granulation tissue of healing wounds. The regulated synthesis and deposition of new collagens, as well as their subsequent maturation, are critical to wound healing.[30] Wound contraction in aqueous and ethanolic extracts of *Cassia fistula* leaves treated ointment indicates improved venerability of collagen synthesis, which may be attributable to the existence of phenolic compounds, but flavonoids, which have antiviral and antibacterial properties, can avoid secondary wound infections.[31]

The MTT assay revealed that the extract was toxic to the cells, with the amount of damage being proportional to the concentration. Unwanted reactions, particularly in herbal extracts where antioxidants directly react with MTT, can result in high background absorbance values.[32] In the current study, this occurred only in few instances. The amount of hydroxyproline in the blood was also measured as a biochemical indicator of collagen turnover. Significantly improved hydroxyproline levels in the granulation tissue of rats treated with aqueous and ethanolic extracts revealed an elevated level of collagen content, resulting in rapid wound healing, and this venerable finding may be attributed to the presence of flavonoid. The efficacy of aqueous and ethanolic extracts of *Cassia fistula* leaves in improving wound healing was also discovered by histopathological analysis of the cream-treated rat wound tissues.

5. CONCLUSION

Subsequently, the findings of this study showed that the aqueous and ethanolic extracts of *Cassia fistula* leaves contain phytoconstituents that facilitate natural healing and may be used as an important wound healing agent. *Cassia fistula* leaves ointment; both aqueous and ethanolic extracts effectively stimulate wound strength and improve the rate of epithelialization, tensile strength, and collagen viability across the wound region. More research is required to isolate the active compounds responsible for wound healing, and attempts are being made to produce a commercial wound healing preparation.

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