Systematic review

Effectiveness of conventional management and *Carica papaya* on influencing wound healing: A systematic review and meta-analysis

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ABSTRACT

Protease enzymes found in the Indian papaya, also called *Carica papaya*, are known to have de-sloughing and wound healing properties. It was found that *Carica papaya* applied to a lesion enhanced phagocytic cell killing of bacteria. Green papaya is rich in papain and chymopapain, two potent digestive enzymes that can break down dead tissue and have anti-inflammatory properties. To compare the effectiveness of conventional and *Carica papaya* management in wound healing the systematic review and meta-analysis is conducted. Based on PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines, a systematic review is conducted. While using the search terms 'Diabetic foot ulcer, conventional management, wound healing, *Carica papaya'* in the MEDLINE, Google Scholar, and PubMed databases. *Carica papaya* has a good beneficial effect on reducing necrosis and is frequently utilized in the management of wound healing. None of the studies have demonstrated any adverse impacts of *Carica papaya* on wound healing.

Keywords: *Carica papaya*; papain; wound healing; proteolytic enzymes.

INTRODUCTION

The Indian papaya, also known as *Carica papaya*, contains protease enzymes that are known to have de-sloughing and wound healing properties. A proteolytic enzyme called papain is obtained from the papaya plant's raw fruit. Proteolytic enzymes can help break down proteins into amino acids and peptides, which are smaller protein fragments. Proteins known as proteolytic enzymes are used to break down necrotic material that remains after cell death. They are typically produced as precursors by endogenous protein synthesis, whose activation is highly controlled. In both pathological and normal circumstances, these activated enzymes have a variety of uses (1, 2). They control the maturation and proliferation of cells, the production and turnover of collagen, the formation and removal of perivascular fibrin cuffs seen in leg ulcers and venous insufficiency, and the elimination of dead tissues after inflammation (3).

It was discovered that applying *Carica papaya* to a lesion helped phagocytic cells more effectively kill bacteria. The primary enzyme in *Carica papaya*, papain, is a recognized natural remedy for edema and inflammation related to surgical procedures. *Carica papaya* reveal antibacterial activity against a variety of microbes, including the bacteria *Staphylococcus aureus, B. cereus, B. subtilis, E. coli, Enterobacter cloacae, Proteus vulgaris, K. pneumoniae, S. typhi, P. aeruginosa,* and *Shigella flexner* (4).

In India the prevalence of diabetes mellitus (DM) has reached epidemic levels. Diabetic patients experience lower extremity disease twice as frequently as non-diabetics, including peripheral neuropathy, foot ulcers, peripheral artery disease, and lower extremity amputation. The traditional trio of nerve damage, ischemia, and infection describes diabetic foot ulcers. There is a higher risk of infections and slow wound healing due to the metabolic pathways in DM, which include lowered cell and growth factor responses, reduced peripheral blood flow, and lowered local angiogenesis. As a result, gangrene, deformities, and peripheral nerve injury are predisposed to occur in the foot. Pharmacological studies on papaya have been conducted. Two powerful digestive enzymes (papain and chymopapain), which can break down dead tissue and have anti-inflammatory effect, are abundant in green papaya (5). Therefore, a systematic review and meta-analysis are performed to examine the effectiveness of traditional medical treatment in comparison to *Carica papaya.*

METHODS

A PRISMA (preferred reporting items for systematic reviews and meta-analyses)-based systematic review is conducted (Fig.1) and registered to PROSPERO (CRD42023429114).

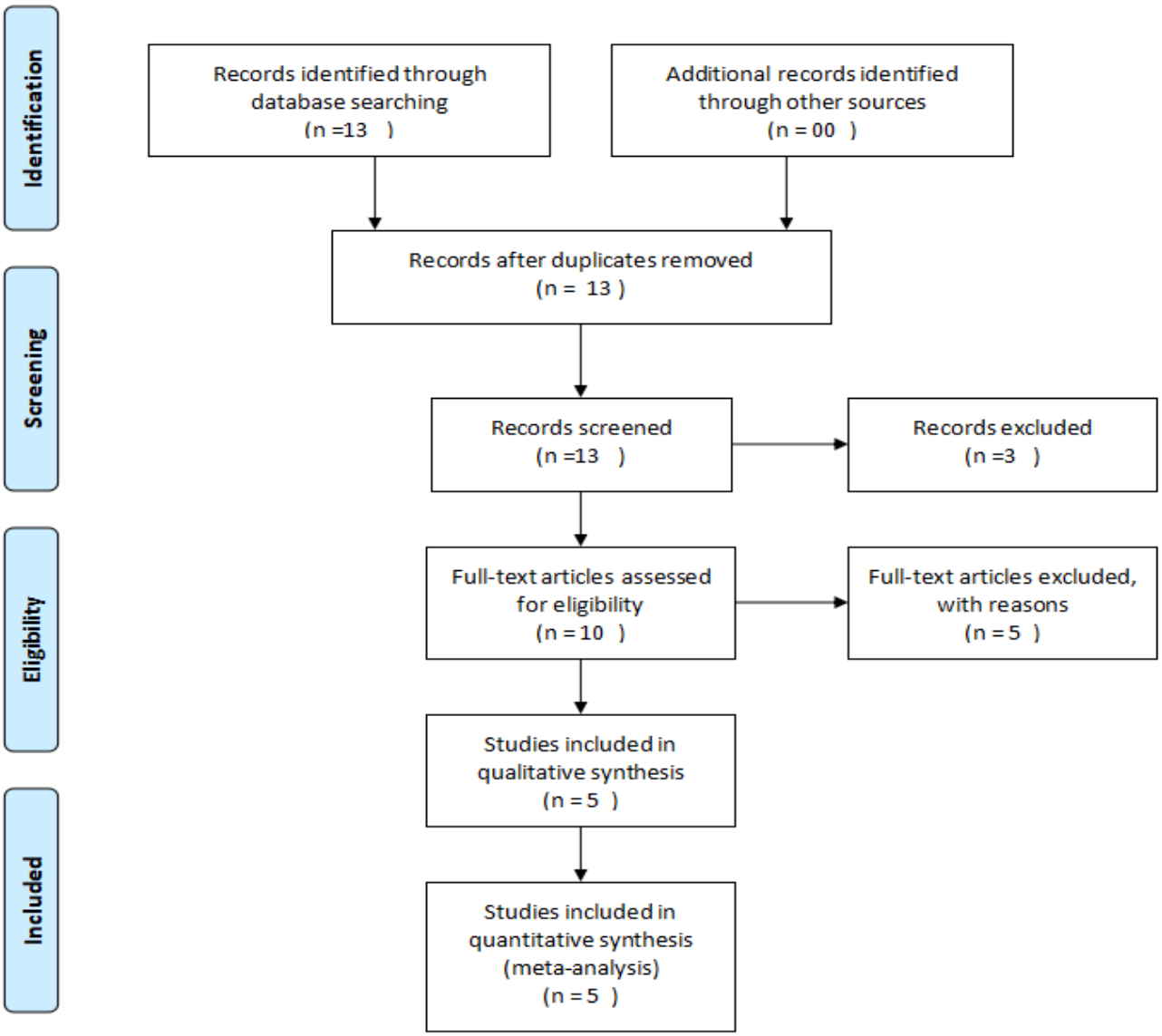


Fig. 1: PRISMA flow chart

Search strategy

The research was conducted independently, and included management of wound healing until May 2023 in the published articles up to the years 2010–2023. Searches for articles are conducted systematically in the MEDLINE, Google Scholar, and PubMed databases. The following search terms were used to find open access articles in the database: 'Diabetic foot ulcer, conventional management, wound healing, *Carica papaya*'. Only English-language articles were selected based on language constraints.

Inclusion criteria

- Articles with full text and open access
- Diabetic, traumatic, and postoperative infective wounds
- Randomized controlled trial and prospective study
- The articles released between 2010 and 2023.

Exclusion criteria

- Burnt wounds
- Articles that perform systematic reviews and meta-analyses.
- Articles published in languages other than English.

Qualitative evaluation

The quality assessment was completed to determine the bias risk in the articles chosen for the study and to confirm that the Cochrane risk of bias method was being applied (Fig. 2). The following quality evaluation standards applied: Random sequence creation, concealment of allocation, selective reporting, additional sources of bias, participant and staff blinding, outcome assessment blinding, and incomplete outcome data are some of the bias-inducing techniques. According to each individual article chosen for the studies, the reviewer's judgements of High, Low, and Unclear risk of bias are evaluated (Fig. 3).

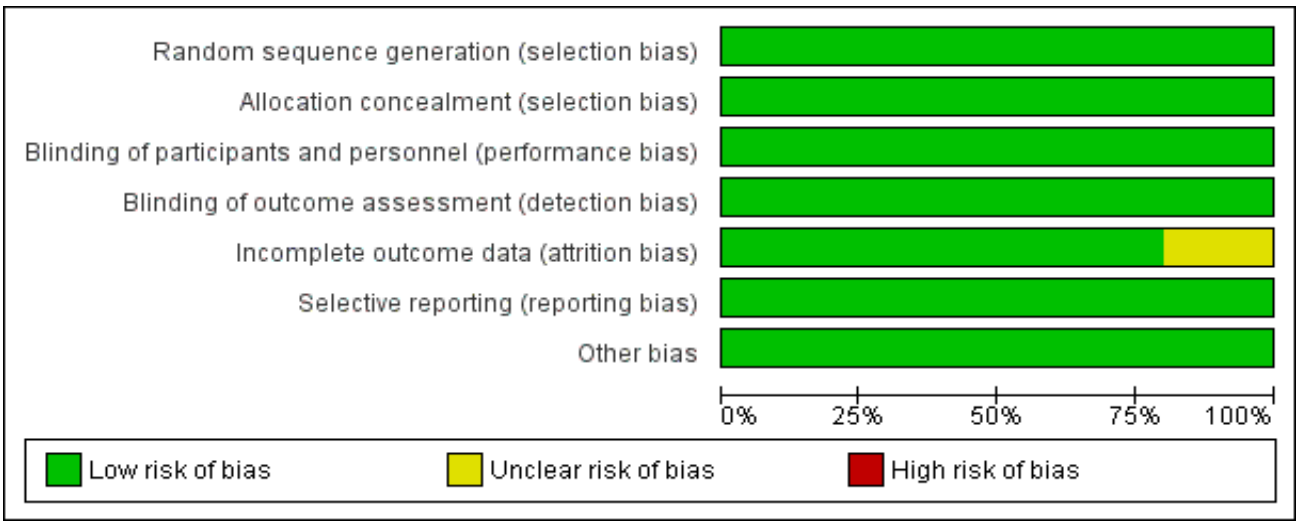


Fig. 2: Percentage of risk of bias included in the study

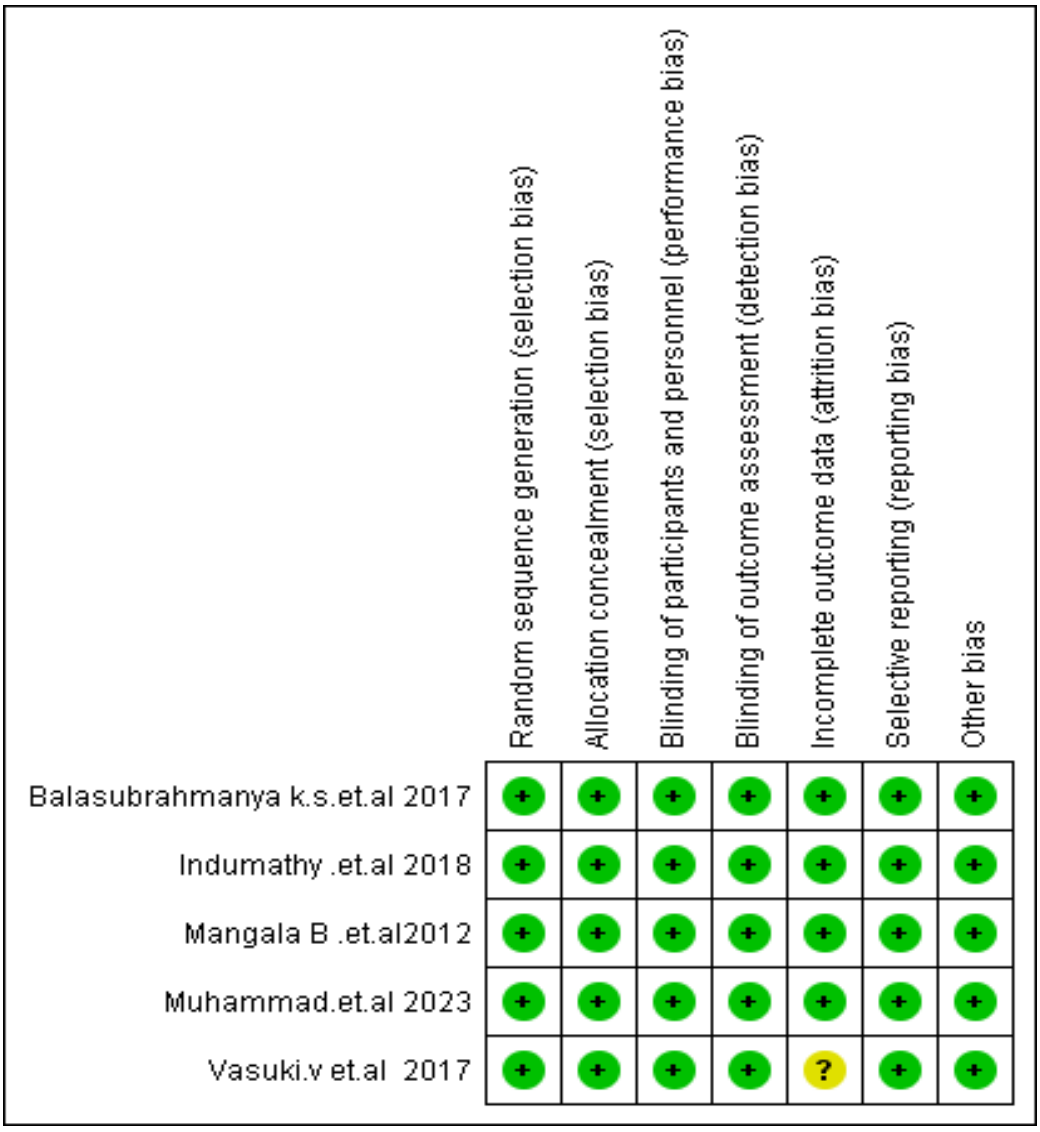


Fig. 3: Summary of risk of bias included in the study

Table 1: Characteristics of the included studies

Authors	Study Design	Study Location	Total no. of participants	Genders	Site of wound	Interventions	Outcome Measures	Outcome
Muhammad *et al.,* (6)	Randomized controlled trail	Lahore, Pakistan	n= 114 Group P:57 Group H:57	Group p M :34 F: 23 Group h M: 29; F: 28	Foot	Group P: Papaya dressing Group H : Hydrogel dressing	PWAT (*photographic wound assessment tool*)	Mean score of PWAT SCORE Group P : 5.09+ 1.65 Group H : 6.02+1.78
Balasubrahmanya *et al.,*(7)	Prospective study	Karnataka (India)	n=60 Group A : 30 Group B: 30	Group A : M: 16 F:14 Group B: M:15; F:15	Foot	Group A : Papain urea Group B: Conventional dressing	1. % of reduction of necrotic tissue 2. Incidence of infection 3. Appearance of granulation 4. Hospital stay	1. Percent decrease in necrotic tissue Group A: 72.27+4.68 Group B: 24.62+3.74 2 Infection Group A: 10 Group B :12 3. Granulation formation Group A: 8.73+2.37 Group B :16.03+4.68 4. Hospital stay Group A: 15.40+4.02 Group B :23.26+5.48
Indumathy *et al.,*(8)	Randomized controlled trail	India	n=60 Experimental Group :30 Control Group :30	-	Foot, Ankle Forefoot	Experimental Group: papaya dressing Control Group: conventional dressing	Bates Jensen wound assessment scale (BJWAS)	Control Group: 26.73+7.73 Experimental Group : 51.10+6.81
Mangala *et al.,*(9)	Randomized controlled trail	India	n= 64 Group A: 32 Group B :32	-	Post-caesarean section	Group A: Hydrogen peroxide Group B: Papaya dressing	1.Duration of granulation development 2.hospitalization	1. Duration granulation development Group A: 6.2+1.6, Group B :2.5+ 0.5 2. hospitalization duration Group A: 19.2+5.8 Group B :12.92+4.6
Vasuki *et al.,* (10)	Randomized controlled trail	India	n= 100 Group 1 :50 Group 2 :50	Group 1 M: 27; F: 23 Group 2 M: 28 F: 22	1. Abdomen 2. Ankle 3. Foot 4. Gluteus 5. Leg 6. Arm 7. Elbow 8. Scrotum 9. Thigh 10. Hip	Group 1 : papaya dressing Group 2 : normal saline dressing	1. Culture 2. Ulcer size 3. Slough/ necrotic tissue 4. Granulation tissue formation	Slough/necrotic tissue Group 1 :10.5+0.70 Group 2:13.15+3.45 Ulcer size Group 1 :2.50+1.50 Group 2:2.15+1.29

Quantitative evaluation

The quantitative evaluation was established from the data extraction in accordance with the study's outcome measure. For the quantitative analysis, a forest plot was utilized with a fixed effect of standardized mean difference and a 95% confidence interval in RevMan.

Data extraction

Researchers separately extract the following information from each article: study design, total "n" participants, study location, gender, interventions, type of wounds, outcome measures, and outcome (Table 1).

RESULTS

Characteristics of included studies

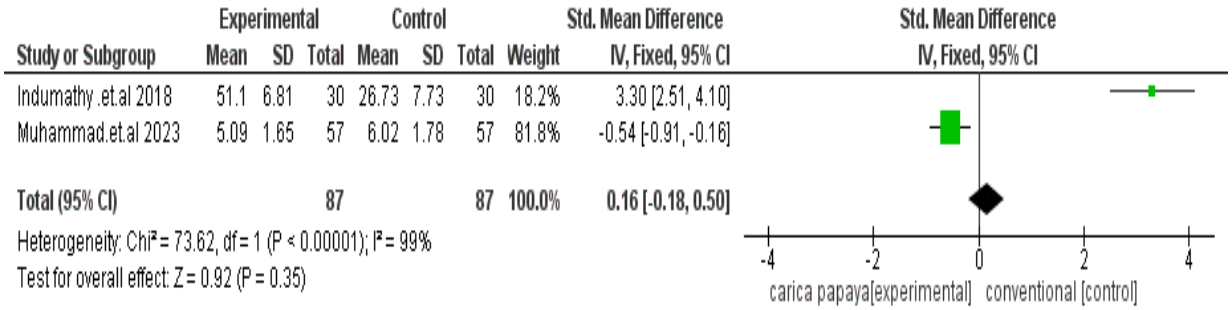
Five studies in total have met the criteria for eligibility, and it turns out that four of them were conducted in India and one was carried out in Pakistan. One prospective study and four randomized control trials comprise the five studies. Each of the five studies has undergone quantitative analysis.

PWAT and BJWAS outcome measurement

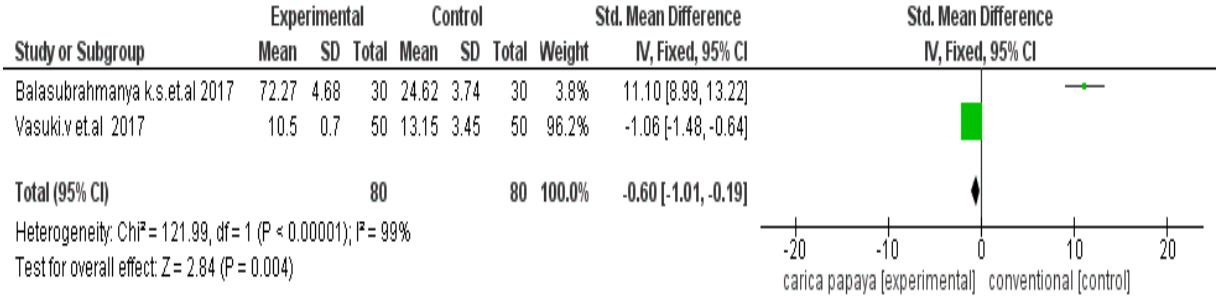
Two studies out of five correspond to the criteria. The study's outcome measures of PWAT and the BJWAS, suggest that *Carica papaya* management is insignificant compared to conventional management (Graph 1).

Decreased tissue necrosis

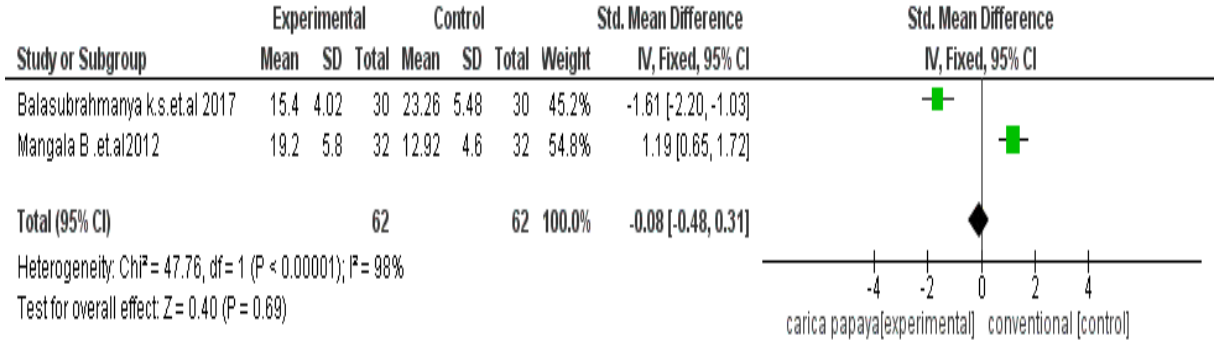
Out of five studies, two fulfil the criteria for eligibility. According to the study's outcome metrics, which included a decrease in tissue necrosis, *Carica papaya* management differs significantly from conventional management (Graph 2).



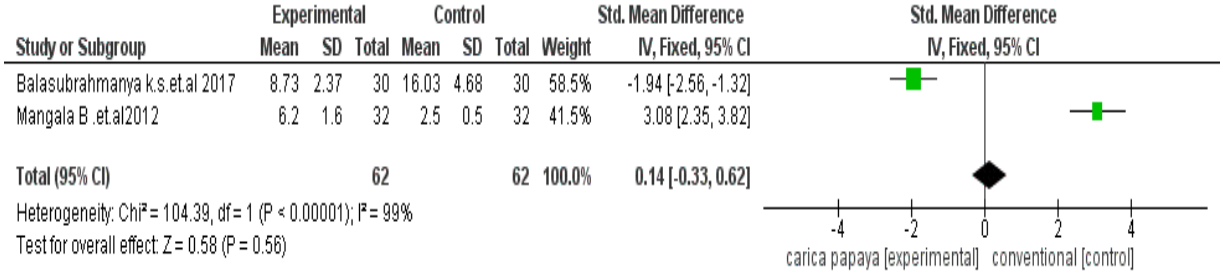
Graph 1: Comparison of *Carica papaya* and conventional management with outcome measure of PWAT and BJWAS



Graph 2: Comparison of *Carica papaya* and conventional management with outcome measure of reduction of tissue necrosis



Graph 3: Comparison of *Carica papaya* and conventional management with outcome measure of duration of hospitalization



Graph 4: Comparison of *Carica papaya* and conventional management with outcome measure of granulation tissue formation

Hospital-stay duration

Two of the five studies meet the qualifying criteria. The length of hospital stay was one of the outcome indicators for the study that showed a negligible difference between conventional and *Carica papaya* therapy (Graph 3).

Granulation tissue formation

The qualifying criteria are met by two of the five studies. The management of *Carica papaya* differs insignificantly from conventional management, according to the study's outcome measures, involving a granulation tissue formation (Graph 4).

DISCUSSION

The most frequent cause of hospitalization and prolonged hospital stays is a diabetic foot ulcer, which has an influence on both the economic burden and suffering of human beings. The diabetic foot was primarily caused by neuropathy and modifications to the macro- and microvasculature (11-13). The main cause was sensory neuropathy, which resulted in injuries despite feeling pain, ulcers, and infection. A change in the structure of the epidermis and tissue damage brought on by macrovascular and microvascular alterations prevents healing by causing ulceration and infection. All these variables cause

gangrene, which ultimately necessitates amputation. When the margins of the wound were covered in developing epithelium and good granulation tissue, the wound was deemed healthy. The papaya dressing demonstrated noticeably quick enzymatic debridement and quick healing (14). It speeds up the healing process. Hemostasis, inflammation, proliferation, and remodeling are the four carefully and meticulously planned stages of wound healing, which is a typical biological process in the human body. All four stages must take place in the right order and amount of time for a wound to heal successfully. Numerous factors may affect one or more stages of this process, which could lead to inappropriate or impaired wound healing (15). Rats given a papain-based wound cleanser showed improved collagen deposition and the presence of skin organelles, demonstrating the cleanser's effectiveness in accelerating wound healing (16,17). The findings show that 3% papain gel can enhance cutaneous wound healing in mice through reduced local inflammatory response, enhanced angiogenesis, and improved organization of collagen deposition. In its current state, a papain-urea product cannot be deemed safe for use in patients with serious burns as an enzymatic debriding agent (18,19).

Limitation and suggestion

Frequency of dressing, quantitative, and qualitative *Carica papaya* extraction to be applied for wound injury in blindness, and since no study has documented about the negative event in *Carica papaya* intervention, more study needs to be done.

CONCLUSION

In this systematic review and meta-analysis done among various wounds injuries on management with conventional and *Carica papaya* dressing had a positive influence on wound healing properties. From the meta-analysis, the study concludes that the extraction of *Carica papaya* can be widely used in management of wound healing and has a good beneficial effect on reduction of necrosis. None of the studies have shown the adverse effect of *Carica papaya* while managing wound healing.

CONFLICT OF INTEREST

Throughout the review, the researchers had no conflicts of interest.

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