

# WHAM evidence summary: Papaya-based products for treating wounds

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## CLINICAL QUESTION

What is the best available evidence on the effectiveness of papaya-based products for wound healing?

## KEYWORDS

Papaya, pawpaw, papain, wounds, debridement

## SUMMARY

Despite a long history in low-to-middle resource countries of clinical use of papaya for managing wounds, limited high level research has been conducted on the effectiveness of papaya-based products. Evidence was available for natural papaya pulp wound dressings, commercial papain extract products (withdrawn from market in some countries due to the risk of anaphylaxis) and an experimental papaya filtrate product (not commercially available). Most studies were conducted in hard-to-heal wounds requiring debridement and the studies were generally at a high risk of bias.

Level 1 evidence<sup>1</sup> and Level 2 evidence<sup>2</sup> for papaya pulp dressings demonstrated an improvement in wound tissue type. Level 3 evidence<sup>3-5</sup> suggested papaya pulp dressings were associated with improvement in wound tissue type, reasonable healing rates and reduction in requirement for further surgical interventions. Level 1 evidence<sup>6-9</sup> for commercial papain products showed improvements in wound tissue type<sup>6, 7</sup> and reduction in wound surface area<sup>8, 9</sup>. Other Level 1 evidence<sup>10</sup> failed to demonstrate effectiveness, and Level 4 evidence was mixed.<sup>10-12</sup>

## CLINICAL PRACTICE RECOMMENDATIONS

All recommendations should be applied with consideration to the wound, the person, the health professional and the clinical context.

**There is insufficient evidence to make a graded recommendation on the effectiveness of papaya-based products for promoting wound healing.**

**Evaluate the individual's risk of allergic reaction (e.g., previous latex allergy) and licensing guidance in the geographic region before using papaya-based products. Cease use of natural papaya pulp dressings if the person experiences adverse outcomes (Grade B).**

## SOURCES OF EVIDENCE

This summary was developed using methods published by the Joanna Briggs Institute (JBI)<sup>13-17</sup>.

Table 1: Levels of evidence for clinical studies

Level 1 Evidence	Level 2 Evidence	Level 3 Evidence	Level 4 Evidence	Level 5 Evidence
<b>Experimental Designs</b>	<b>Quasi-experimental Designs</b>	<b>Observational – Analytic Designs</b>	<b>Observational –Descriptive Studies</b>	<b>Expert Opinion/ Bench Research</b>
1.c randomised blinded trials (RCT) <sup>1, 6-9, 18, 19</sup>	2.c Quasi-experimental prospectively controlled studies <sup>2</sup>	3.e Observational study without a control group <sup>3-5</sup>	4.d Case studies <sup>10-12, 20, 21</sup>	5.b Expert consensus <sup>22</sup> 5.c Bench research/single expert opinion <sup>23-27</sup>

The summary is based on a systematic literature search in English combining search terms that describe wounds and papaya. Searches were conducted in Embase, Medline, PubMed, Global Health, the Cochrane Library, Allied Health and Complementary Medicine and Google Scholar databases for dates up to December 2021. Searches were also conducted in ten healthcare journals from low-and-middle resource countries. Evidence was limited to clinical studies in humans. Studies were assigned a level of evidence (see Table 1) based on JBI's hierarchy<sup>13-17</sup>. Recommendations are made based on the body of evidence and are graded according to the system reported by JBI<sup>13-17</sup>.

## BACKGROUND

Papaya (*Carica papaya*, also called pawpaw) is a tropical plant originating from Southern Mexico and Central America that is now cultivated in tropical and subtropical regions worldwide. Many parts of the tree (e.g., fruit, leaves, seeds and bark) have been used in traditional medicine<sup>26</sup>. Biochemical analysis of papaya has identified several protease enzymes (e.g., papain and chymopapain) with debriding properties that are purported to remove slough and non-viable tissue and prepare the wound bed for healing. Papaya extract has also been reported to have antimicrobial properties<sup>9, 23, 24, 26</sup>. Papaya-based treatment is reported to be cost-effective<sup>7, 11</sup>, and papaya pulp dressings have been successfully applied and managed by patients/unskilled carers in community settings<sup>1, 18</sup>.

The literature search identified several methods of applying papaya-based products to a wound:

- Natural papaya pulp dressing: Raw pulp from the fruit is prepared and applied directly to the wound bed.
- Commercial processed preparations: Products containing papain enzyme are available in gel, cream, impregnated dressings and other topically applied formulations. Papain is sometimes combined with other active agents including urea and chlorophyllin-copper complex to enhance its action<sup>25</sup>. Due to the risk of severe allergic response, papain-based topical agents are banned by the (USA) Food and Drug Administration<sup>22</sup>.
- Experimental processed formulation: A product prepared as papaya and peach (10-1 by volume), with the fruit flesh treated in a series of processes (titled OPAL001) to form two products—a filtrate and a cream<sup>11, 12</sup>. The mechanism of activity for the product

were hypothesised to be related to either proinflammatory response, antioxidant effect and/or vasorelaxation<sup>12</sup>. The product is not currently listed with the Therapeutic Goods Administration in Australia where it was developed.

Although no serious adverse reactions were identified in the studies in this evidence summary, papaya has been associated with severe allergic reaction and anaphylaxis, including cross-reactivity in people with latex allergy. This has led to withdrawal of commercial papain-based products from the market in some countries, including the USA<sup>22, 26</sup>. Anaphylactic reaction is reported to occur at a rate of 1%;<sup>27</sup> the response might be associated with the concentration of active ingredients, which is generally higher in processed preparations compared with the natural fruit pulp<sup>26</sup>.

## CLINICAL EVIDENCE FOR PAPAYA FOR IMPROVING CLINICAL OUTCOMES IN CHRONIC WOUNDS

### Studies reporting papaya pulp dressing for wound healing outcomes

One RCT<sup>1</sup> compared the efficacy of two methods of debridement—enzymatic debridement using papaya pulp dressings and mechanical debridement using wet-to-dry saline dressings. Following randomisation, 128 participants were enrolled in the study. Of these, 93% had a chronic wound (7% hard wound dehiscence following surgery). There was a significant improvement in granulation tissue formation with papaya dressings compared to wet-to-dry dressings in the third and fourth weeks ( $p < 0.001$ ) and superior reduction in slough/necrotic tissue for the papaya dressing group compared to the wet-to-dry dressing group at each weekly assessment point (week four,  $p = 0.0082$ ). However, this did not translate to a significant difference in either reduction in mean wound size at four weeks ( $p = 0.08$ ) or complete wound healing at three months (papaya 78% versus saline 72%,  $p = 0.488$ )<sup>1</sup> (Level 1).

A quasi-experimental study<sup>2</sup> assessed papaya pulp dressing prepared using fresh ripe fruit for healing diabetic foot ulcers. A convenience sample of 60 participants was assigned to either an experimental or control treatment ( $n = 30$  in each group). The papaya dressings were changed daily for 14 days,

while the control group received unspecified routine treatment. A significant improvement in healing occurred over time in the group receiving papaya dressing, as measured using the mean healing score on the Bates-Jensen Wound Assessment Tool (BWAT; pre-test  $26.37 \pm 7.73$  versus post-test  $51.10 \pm 6.81$ ,  $p < 0.001$ ). A significant difference between the experimental and control group was also reported ( $p < 0.001$ )<sup>2</sup> (Level 2).

A prospective study<sup>3</sup> followed 94 patients who underwent a surgical procedure to treat a diabetic foot ulcer: amputation ( $n = 31$ ) or surgical debridement ( $n = 63$ ). Thereafter and in conjunction with oral antibiotic therapy, papaya pulp dressings were used for 89% ( $n = 74$ ) of patients. The grated papaya was prepared, applied daily and covered with sterile gauze. Average healing time, defined as achieving healthy granulation tissue with epithelialised wound edges was 21.56 days (range from 17 to 28 days). Further surgery was required for ten patients<sup>3</sup> (Level 3).

A second prospective study<sup>4</sup> reported outcomes for 135 patients receiving papaya pulp dressings for diabetic foot ulcers (Grade 1-3 on Wagner's classification system). Prior to commencing the second-daily dressing regimen, 96 patients (71.11%) required surgical debridement. Mean healing time, defined as achieving healthy granulation tissue and epithelialised wound edges, was  $19.65 \pm 3.47$  days (range 14 to 29 days)<sup>4</sup> (Level 3).

A study<sup>5</sup> that included patients who were receiving combined therapy for diabetic foot ulcers ( $n = 43$ ) tested the effect of papaya pulp dressings on healing. The papaya dressings were changed every two days. Healing time, defined as achieving healthy granulation tissue with epithelialised wound edges, ranged from 18 to 29 days (mean  $19.23$  days  $\pm 3.624$ ) and 88% of the ulcers required no further surgical intervention after papaya dressings commenced<sup>5</sup> (Level 3).

A case study reported effective use of papaya pulp dressings to heal a post-radiation sacral ulcer. The wound had received surgical debridement, honey dressings, negative pressure wound therapy and failed flap surgery prior to commencing papaya treatment. Second-daily papaya pulp dressing led to healthy granulation after six weeks, allowing the patient to undergo a follow-up successful flap repair<sup>21</sup> (Level 4.d).

## Studies reporting processed papaya-based preparations for wound healing outcomes

In the largest RCT<sup>6</sup> exploring processed papaya-based products, 100 participants with hard-to-heal, sloughy wounds received either papain-urea or collagenase debriding ointment. Treatment was commenced when the wound was stable (no healing observed over the preceding eight weeks) and continued for four weeks, with weekly assessment. The papain-urea group showed statistically significantly superior reduction in slough/necrotic tissue over time ( $89.22\% \pm 15.16\%$  versus  $82.51\% \pm 17.45\%$ ,  $p = 0.043$ ). Between-group difference was not statistically significant in the first three weeks, and the small difference observed in week four may not be clinically significant. Percent of granulation tissue was statistically significantly greater for the papain-urea group at every weekly assessment, including baseline (week four: papain-urea  $6.82\% \pm 8.15\%$  versus collagenase  $3.58\% \pm 3.09\%$ ,  $p = 0.01$ )<sup>6</sup> (Level 1).

Sixty participants with diabetic foot ulcers were randomly assigned to receive either papain-urea or an unidentified conventional wound dressing to explore the effectiveness of a commercially available papaya-based debriding agent.<sup>7</sup> Both treatments were applied second-daily. The papain group achieved statistically significantly greater reduction of necrotic tissue ( $72.27\% \pm 4.68\%$  versus  $24.63\% \pm 3.74\%$ ,  $p = 0.03$ ) and faster granulation ( $8.73 \pm 2.37$  days versus  $16.03 \pm 4.68$  days,  $p = 0.001$ ). The superior outcome led to faster hospital discharge<sup>7</sup> (Level 1).

In a small, double-blind RCT<sup>18</sup>, 8% papain gel was compared to both fibrin gel and a non-active gel control for the healing of chronic venous ulcers ( $n = 55$  people with  $n = 63$  ulcers). Individual ulcers were randomised to one of the three groups and assessed at baseline then every 15 days. Neither fibrin gel nor papain gel improved ulcer healing compared to the control. This conclusion was based on the following: complete wound healing rates were similar in all groups (fibrin gel 14.3%, papain gel 21.1% and control 30.4%,  $p = 0.43$ ) and no statistically significant difference between groups in reduction in wound area ( $p = 0.62$ ).

All groups achieved improvements in exudate levels, signs of local wound infection and edge epithelisation by day 60 (all  $p > 0.05$ ). Two participants (one in each of the active treatment groups) reported mild pain<sup>18</sup> (*Level 1*).

In a small, non-blinded RCT, Rodrigues et. al. (2015)<sup>8</sup> reported on the effectiveness of 2% papain gel compared to 2% carboxymethyl cellulose gel for healing venous leg ulcers. Twenty-one participants were randomised, of which 18 participants ( $n = 28$  ulcers) completed the 12-week study. The results showed a statistically significant reduction in wound area for ulcers treated with papain, particularly between the fifth and 12<sup>th</sup> week of treatment ( $p = 0.032$ ) and this was statistically significant compared to the control group ( $p = 0.006$ ). However, the rate of complete healing was low (two ulcers treated with papaya and no control group ulcers completely healed in 12 weeks) and the amount of exudate and devitalised tissue were similar in both groups ( $p > 0.05$  for both)<sup>8</sup> (*Level 1*).

Another non-blinded small RCT<sup>19</sup> ( $n = 29$  randomised,  $n = 26$  analysed) compared papain-urea to collagenase in non-infected pressure injuries. Participants were treated with moist-to-moist saline dressings in a screening period for up to two weeks prior to commencing the trial. After four weeks of treatment, papain-urea ointment was deemed to be statistically significantly ( $p < 0.05$ ) superior for reducing wound size, with no pain or discomfort experienced by participants<sup>19</sup> (*Level 1*).

Several case studies<sup>10-12</sup> reporting use of OPAL001 papaya-based products have been published. In the first report, 11 quadriplegic patients with Category/Stage 2 and 4 pressure injuries received OPAL001 products in conjunction with contemporary wound dressings. Complete healing was achieved for nine of the pressure injuries after 6 days to 14 weeks of treatment<sup>11</sup>. In the second case report, removal of non-viable tissue and healing was achieved for two diabetic foot ulcers, one venous leg ulcer and an ulcerated skin graft in individuals with impaired vascular function<sup>10</sup>. The third case report<sup>12</sup> detailed reduction in hyperkeratosis and the size of a sacral pressure injury after four weeks of treatment with OPALA filtrate and cream. Ongoing self-treatment with OPALA cream achieved resolution of hyperkeratosis, but the pressure injury deteriorated<sup>12</sup> (all *Level 4*).

## CLINICAL EVIDENCE FOR PAPAYA FOR TREATING SURGICAL WOUND DEHISCENCE

An RCT<sup>9</sup> compared the safety and efficacy of papaya pulp dressings with hydrogen peroxide solution in patients with wound dehiscence post-caesarean section ( $n = 63$ ). Participants received concurrent antibiotics selected following culture and sensitivity. Time required to develop healthy granulation tissue in the hydrogen peroxide group was  $6.2 \pm 1.6$  days compared to the papaya group at  $2.5 \pm 0.5$  days ( $p < 0.05$ ). Only 3.2% of the papaya dressing group required additional surgical debridement compared with 56% of the hydrogen peroxide group ( $p < 0.05$ ). Minor adverse events (e.g., local irritation) were reported but not significantly different to those associated with hydrogen peroxide<sup>9</sup> (n.b., hydrogen peroxide is not recommended for irrigating wounds) (*Level 1.c*).

A case study<sup>20</sup> reported that the use of a papain-urea-chlorophyllin product applied to post-surgical sternal wound dehiscence was associated with complete healing after 31 days of second-daily treatment. The patient received concurrent negative pressure wound therapy<sup>20</sup> (*Level 4.d*).

## CONSIDERATIONS FOR USE

- Papaya-based products facilitate breakdown of necrotic and nonviable tissues that contain protein and the debriding action is from the top downward in the wound. Debridement should be ceased when the wound bed is cleared of slough and necrotic tissue<sup>25</sup>.
- There is no standardised method of preparing papaya pulp dressing. Studies variably use ripe, semi-ripe or unripe fruit pulp<sup>9</sup>. Enzymatic content of the pulp is reported to potential decrease as the fruit ripens, suggesting raw or semi-ripe fruit is more effective<sup>1, 4, 9</sup>. Antimicrobial properties are reported to remain consistent as fruit ripens<sup>1, 4, 9</sup>.
- The following preparation method for papaya pulp dressings is reported:
  - Remove the skin and seeds from papaya fruit<sup>2, 5</sup>.
  - Either grate the fruit pulp<sup>9, 21</sup>, or mash it to a paste.
  - Apply the papaya pulp to wound bed after cleansing the wound.<sup>9, 21</sup>

**Table 2: Summary of the evidence for papaya-based treatments**

Study	Papaya-based treatment	Number receiving papaya	Type of wounds	Clinical setting	Treatment duration	Mean healing time or percent healed	Other reported outcomes
<b>Level 1 evidence</b>							
Alvarez et. al. (2002) <sup>19</sup>	Papain-urea ointment	N=26	Pressure injuries	Nursing home; USA	4 weeks	Not reported	Change in wound area
Balasubrahmanya et. al. (2017) <sup>7</sup>	Papain-urea ointment	N=30	Diabetic foot ulcers	Acute care hospital; India	Not reported	8.73±2.37 days (granulation)	Percent necrotic tissue
de Araújo et. al. (2017) <sup>18</sup>	8% papain gel	N=19	Venous ulcers	Community; Brazil	15 days	21% wounds (complete healing)	Change in wound area
Vijaykumar et. al. (2011) <sup>6</sup>	Papain-urea ointment	N=50	Hard-to-heal wounds	Acute care hospital; India	4 weeks	Not reported	Percent necrotic tissue Percent granulation tissue
<b>Level 2 evidence</b>							
Papaya pulp dressing	N=30	Diabetic foot ulcers	Acute care hospital; India	14 days	Not reported	Change in BWAT score	
<b>Level 3 evidence</b>							
Ch et. al. (2014) <sup>5</sup>	Papaya pulp dressing	N=43	Diabetic foot ulcers	Outpatient department; Pakistan	4 weeks	19.23±3.62 days (granulation)	Surgical debridement or amputation
Rabari et. al. (2016) <sup>4</sup>	Papaya pulp dressing	N=135	Diabetic foot ulcers	Outpatient department; India	14-29 days	19.65±3.47 days (granulation)	Surgical debridement or amputation
Rajaram et. al. (2015) <sup>3</sup>	Papaya pulp dressing	N=74	Diabetic foot ulcers	Acute care hospital; India	4 weeks	21.56 days (granulation)	Surgical debridement or amputation
<b>Level 4 evidence</b>							
Baldwin and Bonham (2011) <sup>12</sup>	OPALA filtrate and cream	N=1	Pressure injury	Community; Australia	> 12 months	Not followed to complete healing	-
Graves et. al. (2008) <sup>11</sup>	OPAL001	N=11	Pressure injuries	Community; Australia	Up to 14 weeks	Up to 14 weeks (complete healing)	-
Melano et. al. (2004) <sup>20</sup>	papain-urea-chlorophyllin ointment	N=1	Surgical wound dehiscence	Acute care hospital; USA	31 days	31 days (complete healing)	-
Mitchell (2011) <sup>10</sup>	OPAL001	N=4	diabetic foot ulcers, venous leg ulcer, skin graft	Community; Australia	Up to 14 weeks	Not followed to complete healing	-
Nwankwo et. al. (2021) <sup>21</sup>	Papaya pulp dressing	N=1	Post-radiation ulcer	Acute care hospital; Nigeria	6 weeks	6 weeks	-

- Covered with sterile gauze<sup>9</sup>.
- Change the papaya pulp dressing daily<sup>2, 5</sup> or second daily<sup>9, 21</sup>.
- Unused papaya paste should be placed in cold storage<sup>5</sup>.

### CONFLICTS OF INTEREST

The author declares no conflicts of interest in accordance with International Committee of Medical Journal Editors (ICMJE) standards.

## ABOUT WHAM EVIDENCE SUMMARIES

WHAM evidence summaries are consistent with methodology published in

Munn Z, Lockwood C, Moola S. The development and use of evidence summaries for point of care information systems: A streamlined rapid review approach, *Worldviews Evid Based Nurs*. 2015;12(3):131-8.

Methods are provided in detail in resources published by the Joanna Briggs Institute as cited in this evidence summary. WHAM evidence summaries undergo peer-review by an international review panel. WHAM evidence summaries provide a summary of the best available evidence on specific topics and make suggestions that can be used to inform clinical practice. Evidence contained within this summary should be evaluated by appropriately trained professionals with expertise in wound prevention and management, and the evidence should be considered in the context of the individual, the professional, the clinical setting and other relevant clinical information.

## PUBLICATION

This evidence summary has been published in *WCET@ Journal*:

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