

ORIGINAL ARTICLE

‘HONEY OINTMENT’: A NATURAL REMEDY OF SKIN WOUND INFECTIONS

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Background: Honey is a gift of nature, principally identified and valued to possess antimicrobial and anti-inflammatory activity and has been used as a natural remedy of wounds since ancient times. The objectives of this study were to evaluate the antimicrobial activity of honey against micro-organisms, to formulate a honey ointment and to evaluate the efficacy of such ointment by conducting clinical trials on skin wound infection. **Methods:** This experimental study was conducted at Department of Pharmaceutics, Faculty of Pharmacy, University of Karachi and Out-patient Department of Dermatology, Fauji Foundation Hospital, Rawalpindi from November 2009 to October 2010. The antimicrobial activity of Pakistani floral sources (*Trachysperm copticum*, *Acacia nilotica species indica*, *Zizyphus*) honey samples was investigated by disc diffusion method against freshly isolated wound infecting bacteria (*Staphylococci aureus*, *Staphylococci epidermidis*, *Streptococcus faecalis*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Escherichia coli*, *Proteus vulgaris* and *Candida albicans*), and *Staphylococci aureus* ATCC 6538, *Pseudomonas aeruginosa* ATCC 9022, *Escherichia coli* ATCC 25922, *Candida albican* ATCC 15146. An ointment containing 20% active antimicrobial honey was formulated. The efficacy of such ointment was evaluated by passing thought clinical trials. A total number of 27 patients (23 skin wound infection, and 4 diabetic foot ulcer) were involved in the study. Thin layer of newly formulated honey ointment on gauze were applied two to three times per day till complete healing. **Results:** In microbiological assay the honey samples were found to exhibit a very promising antimicrobial activity against all the micro-organisms tested. In clinical trial very significant results (99.15%) healing was observed in skin wound infections cases with mean healing time of 5.86 (2–20) days, and 95% diabetic foot ulcers healed with the mean healing time of 20 (8–40) days. **Conclusion:** Newly formulated ointment containing 20% active antimicrobial honey is very effective and alternative low-cost product for the treatment of wound infections.

Keyword: antimicrobial activity, honey ointment, wound infection, diabetic foot ulcer

INTRODUCTION

Honey is a unique gift of nature. The last scripture ‘The Holy Quran’ intimates honey as treatment for all kinds of diseases. It is endowed with the possession of antimicrobial, analgesic, anti inflammatory, haemostatic and healing enhancing properties.¹

Honey samples from different region have been reported to exhibit *in vitro* antimicrobial activity against wide range of pathogens, e.g., *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Salmonella species*, *Shigella sonnei*, *Klebsiella pneumoniae*, *Citrobacter freundii*, *Alcaligenes faecalis*, and *Mycobacterium phlei*.² Blaser *et al*³ applied medical honey on wounds of seven patients, colonised or infected with methicillin-resistant *Staphylococcus aureus*; the results indicated that clinical signs of infection were controlled and complete healing was achieved where antiseptics and antibiotics had failed.

Due to the antibiotic resistance in bacteria or same side-effects of antibiotic product, there is reintroduction of the natural products into modern medical practice in Australia and Europe. The United State authority also gave clearance of Medi honey as a wound dressing Product.⁴

Various physicochemical properties of honey are useful in the treatment of wounds. The high osmolarity of honey slows down the bacterial reproduction⁵. The pH of honey is sufficient to inhibit microbial growth.^{6,7} The additional bactericidal effect is also produced by hydrogen peroxide of honey in a slow release manner.⁸ Wahdan extracted phytochemicals (caffeic and ferulic acid) from honey as the possible cause of antimicrobial activity.⁹

The effective prophylactic agent of honey prevents bacterial growth, and further cross-infection from external contamination.^{4,10} Chemical debridement action of honey in Fourier’s gangrene and decubitus ulcers is greatest advantage that separated slough more quickly.¹¹ The antimicrobial property of honey also kills the malodor producing anaerobes, bactericides species.⁶ Honey’s rapid anti-inflammatory activity soon suppresses the inflammation so that the raised amount of exudate decreases, that decreases swelling, pain and absorption of odema fluid.¹¹ Also it controls the hypertrophic scarring resulting in less scar tissue.^{12,13} It improves circulation and supplies more oxygen and nutrient to facilitate the tissue repair and healing.⁶

The application of honey stimulates the epithelialisation growth.^{11,13} The acidic nature of honey also responsible to released oxygen in high quantity from the haemoglobin in wound site which promotes the granulation tissue to repair wounds.⁷ In treatment with honey the wounds become sterile within 7–10 days and promote the formation of healthy granulation tissue.¹⁴ Most important, honey is non-toxic, non-irritating, bactericidal, and more comfortable than other dressings.¹⁵

Based on growing evidences of effectiveness, use of honey as a natural antimicrobial wound healing agent has increased significantly.¹⁶ Recently, several honey-based wound dressing products for the treatment of wounds, on sale as medical product, are accepted by control authorities and have been introduced in the market for treatment of wide range of wound infections.¹⁷ There is need for a product which combines antimicrobial activity with wound healing stimulating properties.¹⁸

The aims of present study were to develop an ointment containing active antimicrobial honey and to evaluate the efficacy of such newly formulated ointment by conducting the clinical trials on patients suffering from skin wound infections.

MATERIAL AND METHODS

Three Pakistani floral sources (*Trachyspermum copticum*, *Acacia nilotica species indica*, *Zizyphus*) honey were evaluated by CLSI (formerly NCCLS) reference disc diffusion (Kirby Bauer) method against freshly isolated micro-organisms (*Staphylococci aureus*, *Staphylococci epidermidis*, *Streptococcus faecalis*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Escherichia coli*, *Proteus vulgaris* and *Candida albicans*) and *Staphylococci aureus* ATCC 6538, *Pseudomonas aeruginosa* ATCC 9022, *Escherichia coli* ATCC 25922, *Candida albican* ATCC 15146.

Ointment was prepared with the following ingredients: White Soft paraffin (Merck) 100 gm, Liquid paraffin (Merck) 100 gm, Lanolin (Merck) 100 gm, Crude honey (antimicrobial potential) 200 gm to make (with white soft paraffin) 1,000 gm. Tubes and plastic jars were filled under aseptic conditions. For sterilisation of the product an effective dose of gamma radiation was applied. The ointment was store at room temperature (5–25 °C).

To assess the effectiveness of newly formulated honey ointment containing 20% active antimicrobial honey, clinical trials were conducted under the supervision of doctors at out patient department of dermatology Fauji Foundation Hospital Rawalpindi from November 2009 to October 2010. The protocol of study was approved by the Research Committee, Department of Pharmaceutics, Faculty of Pharmacy, University of Karachi. The study design was

experimental and non-comparative. All patients were informed about aims and objectives of the study, and informed consent in writing from all patients was obtained before inclusion. Patients who could not respond on due date or applying any other treatment along with topical honey treatment were excluded. A total number of 27 (n=23 skin wound infection and n=4 diabetic foot ulcers) patients were included in the study. Before the study the patient underwent a thorough physical examination. The sex, age distribution and social economic data are shown in Table-2. Assessment of wound infections was made on visual observations for any sign of increased redness, pain, infection, pus formation, inflammation, swelling or heat with in or around the wound. Clinical history, observation, available data, laboratory testing of informative material was used for the diagnosis. Each wound cleaned with normal saline, then dressed with the thin layer of the newly formulated honey ointment on gauze. The treatment for wound management was continued 2–3 times daily till the complete healing with clinical assessment is made at alternate day during treatment. An evaluation response of the clinical trials was assessed in accordance with the criteria of visual observation of wound healing under the supervision of doctors, as visual appearance of the skin condition is one of the basic parameter in comparing the efficacy of different treatment method.¹⁹ This study used reduction in wound size as a measure of wound healing, as wound is considered ‘closed and healed’ if the repairs of the epidermis due to the out-growth of epithelial cells at the edge of wounds are observed. Size of wound was measured in mm² by tracing infection boundaries on a transparent paper before and after treatment. The healed area was calculated by subtracting the wound area after treatment from the area of wound before treatment.²⁰ Wound healing percentage was calculated by using the following formula of Baie and Sheikh²¹:

$$\% \text{ of wound contraction} = \frac{\text{Healed Area}}{\text{Total area of the wound before treatment}} \times 100$$

RESULTS

Table-1 illustrates the broad spectrum antimicrobial results of honey samples of three different floral sources of Pakistan against standard ATCC micro-organisms and clinical isolates. Table-2 shows the clinical evaluation of the efficacy of newly formulated honey ointment on patients. Table-3-a–c summarise the demographic features of the total numbers of 27 patients (skin wound infection=23, diabetic foot ulcers=4).

Pictures show the representative photographs before and after treatment. The application newly formulated honey ointment showed very promising results. Table-4 shows the percentage of healing and mean healing time of the wounds.



Case D.2: Before Treatment



Case W.2: After Treatment with Honey Ointment



Case D.2: After Treatment with Honey Ointment



Case W.12: Before Treatment



Case W.2: Before Treatment



Case W.12: After Treatment with Honey Ointment

Table-1: Antimicrobial activity of honey samples of different floral sources of Pakistan against standard micro-organisms and clinical isolates

Antimicrobial agent	Trachysperm copticum honey	Acacia nilotica species indica	Zizyphus honey
	Diameter of Zone of inhibition (mm)		
<i>Staphylococcus aureus</i>	23.7±0.9	28±0.3	31.3±0.8
<i>Staphylococcus epidermidis</i>	22.7±0.8	24.7±0.3	20.7±0.7
<i>Streptococcus faecalis</i>	17.7±0.3	18.3±0.3	18.7±0.3
<i>Pseudomonas aeruginosa</i>	20±0	22.3±0.3	23.7±0.8
<i>Klebsiella pneumoniae</i>	17.3±0.3	20±0	20.7±1.2
<i>Escherichia coli</i>	26.3±1.2	26.3±0.8	30.3±0.8
<i>Proteus vulgaris</i>	20.3±0.3	18.7±0.3	27.7±0.3
<i>Candida albican</i>	17.3±0.3	19±0.6	17.3±0.3
<i>Staphylococcus aureus ATCC 6538</i>	26±1	16.7±0.3	18.3±0.3
<i>Pseudomonas aeruginosa ATCC 9022</i>	16.7±0.3	16.3±0.3	17±0.6
<i>Escherichia coli ATCC 25922</i>	18.3±0.3	19±0.6	16.3±0.3
<i>Candida albican ATCC 15146</i>	10±0	13±0	13±0.6

Note: Value represent mean of triplicate determination ± SE

Table-2: Clinical efficacy of newly formulated honey ointment on skin wound infection (n=27)

Case No.	Age (year)	Health Status		Site	Wound area before treatment (mm ²)	Wound area after treatment (mm ²)	Healed area (mm ²)	Healing %	Healing duration (days)
w.1	10	Poor	Average	Good	216	0	216	100	04
w.2	1.5			Good	78	0	78	100	06
w.3	42	Poor	Average	Left hanh % elbow	480	0	480	100	03
w.4	20			Right hand	10595	0	10595	100	04
w.5	36	Poor	Average	Head (right side)	750	0	750	100	03
w.6	43			Right hand	180	0	180	100	02
w.7	48	Poor	Average	Good	192	0	192	100	06
w.8	52			Good	72	0	72	100	04
w.9	50	Poor	Average	Good	660	0	660	100	06
w.10	30			Good	266	0	266	100	06
w.11	52	Poor	Average	Good	117	0	117	100	07
w.12	32			Good	6300	0	6300	100	08
w.13	15	Poor	Average	Good	36	2×3.5=7	29	80.55	08
w.14	40			Good	1350	0	1350	100	06
w.15	50	Poor	Average	Good	96	0	96	100	06
w.16	49			Good	80	0	80	100	04
w.17	28	Poor	Average	Good	288	0	288	100	07
w.18	29			Good	70	0	70	100	20
w.19	60	Poor	Average	Left index finger	48	0	48	100	04
w.20	40			Good	132	0	132	100	05
w.21	59	Poor	Average	Good	91	0	91	100	06
w.22	49			Good	420	0	420	100	06
w.23	27	Poor	Average	Good	27300	0	27300	100	06
D.1	60			Good	400	0	400	100	12
D.2	52	Poor	Average	Good	256	0	256	100	08
D.3	48			Good	130	4×6.5=26	104	80	40
D.4	55	Poor	Average	Good	48	0	48	100	20

W=Wound, D=Diabetic

Table-3-a: Types of wound in patients (n=27)

Wound Type	Total Patients	Males	Females
Wide variety wounds	23	22	1
Diabetic foot ulcer	4	3	1
Total	27	25	2

Table-3-b: Age distribution of the patients (n=27)

Wound Type	Age Groups (Years)				
	1-10	11-20	21-30	31-40	≥41
Wide variety wounds	2	2	4	4	11
Diabetic	-	-	-	-	4
Total	2	2	4	4	15

Table-3-c: Patient's occupation (n=27)

Wound Type	Service	Business	Household	Other
Wide variety wounds	15	4	1	3
Diabetic	2	1	1	-
Total	17	5	2	3

Table-4: Percentage of healing and mean healing time of wounds (n=27)

Lesion	Healing (%)	Mean Healing Time (days)	Range (days)
Skin wounds (n=23)	99.15	5.86	2-20
Diabetic foot ulcer (n=4)	95	20	8-40

DISCUSSION

To formulate the honey ointment as semi-solid form and to assure the effectiveness of ointment for use as antimicrobial agent selection of honey is important criteria for clinical application.²² During the present study, in microbiological assay the Pakistani honey samples were found to exhibit very promising antimicrobial activity against wound infecting micro-

organisms. Thus honey that demonstrates activity in the disc diffusion method is recommended for utilisation in modern wound care products. The newly developed ointment containing 20% active antimicrobial honey is very effective and formidable in proliferation of wound infecting bacteria. It may have significant indication for clinical use in the cleansing of wounds and enhancing the rate of wound healing.

Wound healing is fundamentally connective tissue response, consists of step wise process of homeostasis, inflammation, re-epithelialisation, granulation and finally reshaping.²³ The application of newly formulated honey ointment showed in addition to excellent antimicrobial and anti-inflammatory activity significant sign of improvement in wound healing: exudate management, reduction in pain and oedema, deodorisation, re-epithelialisation at the edge of wound and promotion of granulation tissue.

By application of newly formulated ointment all the skin wound infection cases healed 99.15% within the mean healing time of 5.86 days. The large variation in the duration of healing time may be attributed to the size of lesions, age, sex and socioeconomic status. All reported signs and symptoms of the patients, i.e., swelling/oedema, pus/exudation of fluid, bleeding, infection, inflammation, redness, vesicles, localizes pain, erythema, localised heat, cellulites and itching gently subsided in the early 3–5 days application of honey ointment dressing. Clinical evaluations of the efficacy of honey ointment for use in treating of wounds were undertaken at each dressing change by the doctors. During the treatment even at last follow-up no infection complication was noted in all patients. Doctors and dermatologist judged the severe effectiveness and gave a valued status to honey in treatment of infected wounds.

Diabetic foot ulcers are the most frequently occurring wounds, with increase prevalence among the elderly. Standard therapy for ulcers require debridement of necrotic tissue, and the treatment of wounds infection if present²⁴. Honey is a natural, economical and moist dressing substance has been known to possess antimicrobial, anti-inflammatory, wound debridement, deodorising wounds, and wound healing properties.^{11,25} In the present clinical trial three male and one female patient with diabetic foot ulcers were treated during April–June 2010. Honey ointment containing 20% active antimicrobial honey was applied three times per day for the treatment of wounds. Diabetic foot ulcer cases healed 95% within the mean healing time of 20 days (range 8–40 days) (Table-4).

Pictures show the representative photographs before and after treatment. Present results are in confirmation with Makhdoom²⁶ who observed promising results of honey in the treatment of 12 diabetic foot wounds patients. Moloney *et al*²⁷ also applied ointments

comprising honey or honey derivatives for the treatment of diabetic ulcers patients.

Whenever there is tissue injury there is always a possibility of infection, fluid loss and wound shock. Chronic wounds often show raised bacterial colonisation and elaborate such virulence factors that can resist wound healing. Honey has a powerful inhibiting effect on the growth of wide range of pathogen.^{2,9,11} The first function of the application of the newly formulated honey ointment is to create favourable moist and clean environment for wound healing and to inhibit the wound infecting bacteria by its powerful antimicrobial activity. In our study all the honey samples used in the *in vitro* antimicrobial assay exhibited broad spectrum antimicrobial activity against wound infected bacteria (Table-1). Two to three times daily application of such ointment containing 20% active antimicrobial honey to infected site were effective, the wounds were free of bacteria and healed more rapidly with out infection complication. Thus significant inhibition of microbial species by honey ointment *in vivo* demonstrated the potential of honey to clear infection, remove malodours, and prevent cross infection.

Chronic and non-healing wounds, necrotic and devitalised wounds require debridement to free the wounds of all these obstructions which cause bacterial growth and impairment of wound healing.⁶ During clinical trial it was observed that newly formulated honey ointment significantly enhance the rate of wound contraction and acts as a very powerful wound debridement. Van den Berg *et al*²⁸ reported the efficacy of honey in the treatment of wounds due to chemical debridement of dead tissues from wounds.

The anti-inflammatory properties of honeys resolve pain.²⁹ Patients complain pain in very inflamed wounds, the application of the newly formulated honey ointment resolve the inflammation due to its anti-inflammatory property and alleviate the pain.

Topical use of honey effect significantly on the area of epithelialisation and granulation tissue.³⁰ High concentration of sugar and high level of amino acids (glycine and methionine) of honey are favourable for early formation of granulation tissues.³¹ Minerals and vitamins of honey also contribute the formulation of granulation of tissue.³² The application of newly formulated honey ointment on infected wound extracts the fluid from the surrounding tissue and facilitates a moist wound healing environment that promotes the period of epithelialisation in the periphery of wound and accelerates healing process due to its bactericide properties. The efficacy of Pakistani honey on excision model of rats have also been demonstrated by Iftikhar³³ who found that topical use of honey reduces the period of epithelialisation and enhances the rate of wound contraction.

Thus the promising evidences of clinical trials suggest the continued application of honey ointment as a natural alternative product in all phases of wound cases (infected wounds, non-healing wounds, superficial wounds, diabetic foot ulcer, bed sores, superficial cuts, punctures and scratches). This is in confirmation with Simon *et al*³⁴ who applied a honey based product usefully on wounds of different nature as an alternative treatment approach. The honey samples of different floral sources of Pakistan used in the study exhibited broad spectrum antimicrobial activity may be substantially important as there is explosive rise in difficult and hard to heal surgical skin wound infections due to the resistance with *Staphylococcus aureus*³⁵ and *Pseudomonas aeruginosa*³⁶.

CONCLUSION

The significantly achieved results of honey against wound infecting bacteria are conducive and led to development of a new honey ointment formulation. Clinical trials prove that newly formulated ointment containing 20% antimicrobial active honey is natural and significantly more effective for treatment of skin wound infections and it provides a broader range of antimicrobial, anti-inflammatory properties. It promotes wound debridement, maintains a moist wound environment, deodorise wound and stimulates healing processes.

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