

## HONEY AS A TREATMENT FOR DIABETIC FOOT ULCER: A SYSTEMATIC REVIEW

Ide Bagoes Insani, Nurina Widayanti, Aliyya Rifki

*Research Assistant of Lingkar Studi Bedah Plastik, Jakarta, Indonesia*

### ABSTRACT

**Background :** Increased number of antibiotic-resistance bacteria has made honey widely reused as a modern wound treatment, including for Diabetic Foot Ulcer (DFU) treatment. Researchers have studied mean duration of wound healing and effectivity of honey dressing compared to other substances, such as povidone iodine, normal saline or alginate. This systematic review was conducted to objectively evaluate mean duration of wound healing using topical honey dressing compared to other substances in the treatment of DFU.

**Method :** All RCT and CCT trials were collected from 4 electronic databases using keywords "Honey", "Honey dressing", "Diabetic foot ulcer", and "Diabetic ulcer". We included all English literatures with year of publication from January 2006 to November 2016; studies comparing honey with other substances; and patients with DFUs. Qualitative assessment of these studies were scored using Jadad Scale.

**Result :** A total of 5 studies involving 517 participants were included. None of 5 studies obtained full Jadad score in quality assessment due to lack of description on randomization method, blinding and dropouts. Three studies reported significantly shorter mean duration of wound healing in honey dressing compared to normal saline and alginate dressing. Other 2 studies reported insignificant difference compared to povidone iodine, although honey still has shorter mean duration of wound healing. Two studies reported less pain during dressing changes in honey dressing group.

**Conclusion :** Honey dressing was superior than control group (normal saline, alginate, and povidone iodine) in reducing mean duration of wound healing in DFU patients. It was also proven to cause less pain during dressing changes. Due to high heterogeneity we are unable to carry out a meta-analysis.

**Keywords:** *diabetic foot ulcers; honey dressing; duration of wound healing; systematic review*

**Latar Belakang:** Meningkatnya jumlah bakteri yang resisten terhadap antibiotik membuat madu kembali digunakan dalam pengobatan luka modern, termasuk kasus Ulkus Kaki Diabetik (UKD). Para peneliti telah mempelajari rerata durasi penyembuhan luka dan efektivitas *dressing* madu dibanding zat lain, seperti povidone iodine, salin normal atau *alginate*. *Review* sistematik ini dibuat untuk mengevaluasi secara objektif rerata durasi penyembuhan luka dengan madu topikal dibandingkan dengan zat lain dalam pengobatan UKD.

**Metodologi:** Seluruh penelitian RCT dan CCT diambil dari 4 *database* elektronik dengan menggunakan kata kunci "Honey", "Honey dressing", "Diabetic foot ulcer", dan "Diabetic ulcer". Kami memasukkan seluruh penelitian berbahasa Inggris dengan tahun publikasi antara Januari 2006 hingga November 2016; penelitian yang membandingkan madu dengan zat lain; dan pasien dengan UKD. Penilaian kualitas dari penelitian tersebut menggunakan *Jadad Scale*.

**Hasil:** Terdapat total 5 studi dengan 517 peserta. Dari kelima studi tersebut, tidak ada yang mendapatkan nilai Jadad yang sempurna karena tidak menyebutkan metode randomisasi, penyamaran dan *drop out*. Tiga penelitian melaporkan bahwa rerata durasi penyembuhan luka pada *dressing* madu lebih pendek secara signifikan dibandingkan dengan *dressing* larutan salin dan *alginate*. Dua penelitian lainnya melaporkan bahwa tidak ada perbedaan yang signifikan antara *dressing* madu dengan povidon iodine, walaupun *dressing* madu tetap menunjukkan rerata durasi penyembuhan luka yang lebih singkat. Dua penelitian melaporkan penggantian *dressing* madu menimbulkan rasa nyeri yang lebih ringan. Tidak ada yang mendapatkan nilai penuh dalam penilaian kualitatif karena kurangnya penjelasan mengenai metode acak, buta dan *dropout*.

**Kesimpulan:** *Dressing* madu lebih unggul dibandingkan grup kontrol (larutan salin, *alginate*, dan povidone iodine) dalam menurunkan rerata durasi penyembuhan luka pada pasien UKD. Terbukti pula bahwa rasa nyeri yang ditimbulkan saat penggantian *dressing* madu lebih ringan dibanding substansi lain. Heterogenitas muncul akibat kurangnya jumlah penelitian yang diterbitkan dan tidak adanya standarisasi metode aplikasi madu terhadap luka, oleh karena itu kami menyarankan penelitian lebih lanjut dalam bidang ini.

**Kata Kunci :** *diabetic foot ulcers; honey dressing; duration of wound healing; systematic review.*

*Received: 5 September 2016, Revised: 19 September 2016, Accepted: 1 November 2016*

ISSN 2089-6492 ; E-ISSN 2089-9734

This Article can be viewed at [www.jprjournal.com](http://www.jprjournal.com)

## INTRODUCTION

Honey has been used in wound care since ancient times. The Egyptians started using honey for wound treatment at least since 3000 years BC and it became an important part of the ancient Egyptians wound care methods<sup>1</sup>. The introduction of antibiotics in modern medicine led to a decrease use of topical honey as wound treatment until recent studies reported that antibiotic-resistance bacteria including *Methicillin Resistant Staphylococcus Aureus* (MRSA) were found in infected wound in the last few years. As the consequence of misused antibiotics and antibiotics resistance, honey is widely reused as modern wound treatment. Several modern studies have proven the benefits of honey for wound treatment. Based on study published by Jurnal Plastik Rekonstruksi (JPR) in 2012, honey has antibacterial effect towards bacteria such as *Pseudomonas A.*, *Staphylococcus A.* and MRSA<sup>2</sup>. Due to its moisturizing nature, honey can also accelerate migration of fibroblast, keratinocyte and macrophage into the wound<sup>3,4</sup>. Antibacterial effect of honey is one of the main characteristics profitable for wound treatment as it has low osmolarity, low acidity level (pH) and low hydrogen peroxide activity<sup>2</sup>. There are also other benefits of honey as wound treatment, such as : inhibits inflammation, absorbs exudate and eliminates odors<sup>1</sup>.

On the other hand, some epidemiological studies show tendency of increased incidence and prevalence of Diabetes Mellitus type-I and type-II around the world including Indonesia<sup>5</sup>. WHO predicts that the number of diabetic patients will increase in the next few years. In Indonesia population, WHO predicts that the number of people with Diabetes Mellitus will increased from 8.4 million in 2000 to 21.3 million in 2030<sup>6</sup>. Uncontrolled blood glucose level will lead to complications (15-25%) such as infection, gangrene and soft tissue-hard tissue (bone) damaged. Diabetic Foot Ulcer (DFU) is one of the most common complications among diabetic patients and it may lead to amputation of the lower leg which will have a negative impact on the patient's quality of life<sup>7</sup>. DFU also imposes huge burden to the worldwide health care system with at least 33% of all costs for diabetic complication treatment was spent for the treatment of DFU<sup>8</sup>. Topical honey - for its benefits (wound healing properties and cost effectiveness) - is widely used to treat wounds including diabetic foot ulcers. There are several randomized controlled trials and controlled clinical trial reporting the use of topical honey for diabetic foot ulcer treatment.

However, we are still lacking systematic review on the use of topical honey for diabetic foot ulcers treatment. According to this reason, the authors planned this review.

## METHOD

The aim of this study was to review and to analyze published randomized controlled trials (RCTs) and clinical controlled trial (CCTs). The search strategy was developed in four electronic databases<sup>9</sup>: PubMed, ProQuest, Mendeley, and Perpustakaan.go.id. Search terms composed of four items: "Honey", "Honey dressing", "Diabetic foot ulcer", and "Diabetic ulcer". These phrases were combined using Boolean operators "OR" and "AND". Filters have been used to restrict non-english language publication and to specify year of publication. All trials were screened by title and abstract, retrieved potentially relevant articles in full text, and assessed them for the inclusion criteria.

Trials eligible for inclusion in this review were: RCTs and CCTs with year of publication from January 2006 to November 2016 of any authors or participating institutions; English literature; studies comparing between honey (any resources and concentration) versus other substances (pyodine dressing, normal saline dressing, saline soaked gauze dressing, povidone iodine solution 10% diluted with normal saline, and alginate dressing); and patient with diabetic foot ulcers. Exclusion criteria in this review includes: (1) Animal and in-vitro studies, (2) Review articles, intervention protocol, discussion papers, case report, case series, quasi experimental study, case-control and retrospective studies, (3) Studies involving diabetic patients with pressure ulcer, venous ulcer or other chronic wounds.

The quality of all trials were evaluated using Jadad Scale. Those articles were assessed for randomization, double blinding, and withdrawals/dropouts. Total score ranged from 0 to 5, with 0 as the lowest score and 5 as the highest score.

**Disclosure:** *The authors have no financial interest to disclose.*

Outcome parameters of all trials were systematically included in the detailed analysis using RevMan 5.3 from The Cochrane Community and methodological strengths or weaknesses were identified. Mean duration of healing in days were compared as continuous variable. In these studies included, healing was judged by focusing on whether the wound was clean and ready for closure<sup>10,14</sup>; complete epithelialization with no discharge<sup>12</sup>; sterile from microorganisms on swab cultures<sup>14</sup>; and ulcers size (cm<sup>2</sup>)<sup>12</sup>. If standard deviations and means were not provided in the manuscript, we assume the data were normally distributed. Consequently, we calculate standard deviation and mean based on data range and median provided. Heterogeneity was assessed with I<sup>2</sup> recommended by The Cochrane Collaboration.

**METHOD**

From 311 studies searched through electronic databases, any duplication was removed and 276 studies were screened (Figure 1). We found 45 relevant articles based on their titles and abstracts. From those 45 articles, we excluded the following: review articles and editorial articles (n=12); quasi-experimental (n=1); case report/case series (n=3); in-vitro and preclinical studies (n=6); venous ulcer, pressure ulcer, burn wound (n=14); and studies with no comparison (n=1). Eight full text articles assessed for eligibility and 3 full text articles were excluded (Figure 1) due to incomparable outcomes as such: 1 text article analyzed wound area per m<sup>2</sup> as the outcome and 2 other articles analyzed infection clearance as the outcome. Finally, 5 studies were eligible for qualitative and

**Table 1.** Database and Research Terminology

No	Databases	Results	Search Term
1	Pubmed	45	((("diabetic foot ulcer") OR "diabetic ulcer") AND honey) OR "honey dressing"
3	Mendeley	73	title:Honey abstract:"diabetic foot ulcer" or "diabetic ulcer" or ulcer discipline:medicine
4	ProQuest	58	("diabetic foot ulcer" OR "diabetic ulcer") AND honey
5	Perpusnas.go.id	135	((TitleCombined:(honey)) OR (honey dressing)) AND ((diabetic foot ulcer) OR (diabetic ulcer))

**Table 2.** Characteristic of surgery

No	Study	Jadad Score					Total
		Randomised	Double Blind	Withdraw als/ Dropouts	-1 if use innapropriate use of randomization	-1 if use innapropriate method of blinding	
1	Agarwal, 2015 <sup>10</sup>	1	0	0	0	0	1
2	Eldeen, 2012 <sup>11</sup>	1	0	0	0	0	1
3	Imran, 2015 <sup>12</sup>	2	0	1	0	0	3
4	Kamaratos, 2012 <sup>13</sup>	1	1	0	-1	0	1
5	Shukrimi, 2008 <sup>14</sup>	1	0	0	0	0	1

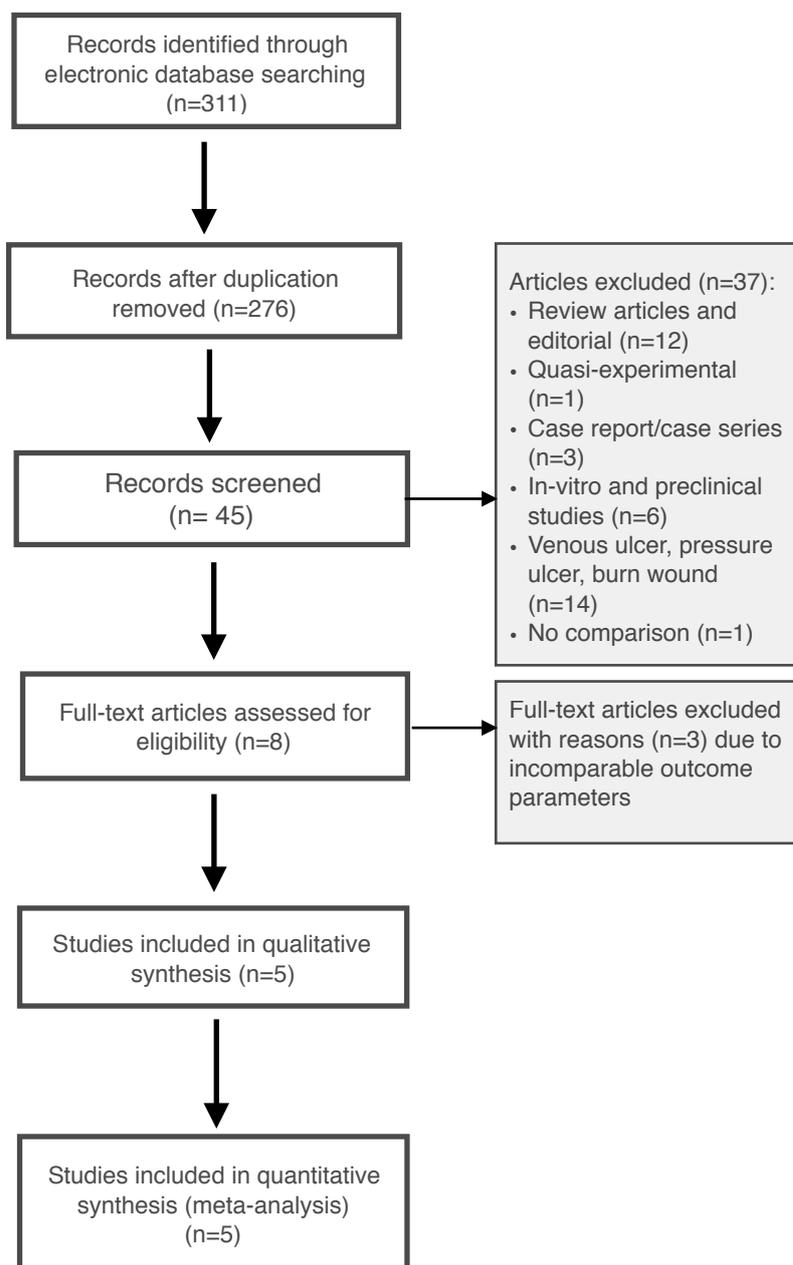


Figure 1. Study flow diagram of search results, studies identified and included in this review

Quality of these studies were analyzed using Jadad Scale (Table 2). Total score varied from 1-3. None of them had full score due to lack of description on randomization method, blinding, and dropouts. We also had to deduct one point in one of the studies because of its inappropriate randomization sequence. From 5 studies included, a total of 517 patients were reported. Two studies compared honey dressing with normal saline dressing; 2 studies compared honey dressing with povidone iodine dressing; and 1 study compared honey dressing with alginate dressing. Three studies reported there are significant reduction in mean duration of

wound healing for honey treatment groups<sup>11,12,13</sup>. The other two studies reported that honey versus povidone iodine dressing showed insignificant difference in mean duration of wound healing, but the mean duration of wound healing in honey group still showed shorter period<sup>10,14</sup>. Two studies reported that patients in honey treatment group had experienced less pain during dressing changes<sup>10,14</sup> (Table 3). All of the studies have similarity in reporting their results of wound healing duration, which was using days as an outcome parameter.

**Table 2.** Characteristic of surgery

Study	Design	Sample Size and Treatment Groups	Type of Honey used	DFU Classification	Outcome
Agarwal, 2015	RCTs	n=36; Honey impregnated dressing versus Povidone iodine 10%	Non-sterile pure honey	Grade II Wagner classification	Mean duration for wound healing showed insignificant difference, however all patients in honey group experienced less pain
Eldeen, 2012	RCTs	Honey dressing n=20; Alginate dressing n=20	Pedyphar ointment	Grade II Wagner classification	Honey treatment group has significantly shorter wound healing duration compared to alginate
Imran, 2015	RCTs	Honey dressing n=179; Normal saline dressing n=169	sterilised Beri ( <i>Ziziphus jujuba</i> ) honey	Grade I and II Wagner classification	Honey impregnated dressing significantly reduced the duration of wound healing in diabetic foot ulcer patients
Kamaratos, 2012	RCTs	Honey dressing n=32; Saline dressing n=31	Manuka honey impregnated dressing	Grade I and II Wagner classification	Duration of healing in patients treated with honey were significantly shorter
Shukrimi, 2008	RCTs	n=30; Honey dressing versus 10% povidone iodine dressing	Non-sterile pure honey	Grade II Wagner classification	Ulcer healing was not significantly different in both study groups. All patients in honey group experienced less pain during dressing

## DISCUSSION

### Outcome of Studies

Although there are two studies reported that honey gives insignificant results, mean duration for wound healing were shorter in honey dressing group. Agarwal<sup>10</sup> mentioned that mean duration for wound healing in honey group was 14.2 days (range 6-25 days) compared to 15.5 days (range 9-37 days) in povidone iodine group. Shukrimi<sup>14</sup> mentioned that mean duration in honey group was 14.4 days (range 7-26 days) compared to 15.4 days (range 9-36 days) in povidone iodine group. They also reported that honey dressing has better result in decreasing wound oedema<sup>10,14</sup>, reducing wound discharge<sup>10</sup> and reducing malodorous discharge<sup>14</sup>. Both studies reported less pain during dressing changes<sup>10,14</sup> in honey dressing group. This is due to the ability of honey to maintain the moisture of the wound without adhesion to the granulating surface<sup>14</sup>. The other three significant studies reported that honey dressing group gave better result in: mean duration of wound healing<sup>11,12,13</sup>, eradication of infection<sup>11</sup>, granulation tissue<sup>11</sup>, and experience of pain<sup>11</sup>. Faster healthy granulation tissue on honey dressing treatment is similar to Subrahmanyam study in 1991<sup>15</sup>. Other experimental study by Kreshanti et al in 2012<sup>16</sup>

also reported that intra-oral honey application significantly precipitates faster epithelialization process.

### Bacteria Colonization

Honey possesses several benefits in treating diabetic foot ulcer. Especially in wounds contaminated with *Pseudomonas A*, *Staphylococcus A*, and *MRSA*<sup>2</sup>. Based on study conducted by Pemayun in Semarang<sup>17</sup>, out of positive cultured specimen of DFU patients admitted in RSUD Kariadi, 70.8% were positive for gram-negative bacilli, 20.8% for gram-positive, and 4.3% for anaerobic bacteria. Most of anaerobic bacteria were cultured from gangrenous specimens. In Indonesia, patients tend to assume that DFUs are common just like wounds in non-diabetic cases<sup>17</sup>. They try to treat their ulcers with traditional treatments such as dried in sunlight exposure or soaked in hot water. After the traditional treatments failed, they started to seek medical attention. Due to this delay of medical treatment, their ulcer has become infected or even gangrenous which are mandatory for surgical debridement or amputation. Hydrogen peroxide activity in honey has been described by White in 1963<sup>18</sup>. This property is very important in inhibiting the growth of anaerobic bacteria that can cause gangrene.

Most types of honey can generate  $H_2O_2$  with the activation of glucose oxidase which oxidizes glucose to gluconic acid and  $H_2O_2$ <sup>19</sup>. Nevertheless, the presence of heat or catalase can breakdown this activity.

In 5 of our subjected articles, there are 2 articles assessed wound healing by the eradication of microorganisms on swab cultures<sup>13,14</sup>. Kamaratos<sup>13</sup> showed healing duration of diabetic foot ulcers in patients treated with honey-impregnated dressing was significantly shorter than patients treated with normal saline dressing, which was marked by sterile wounds from any microorganisms, such as: *Pseudomonas*, *E. coli*, *MRSA* and *Proteus sp.* Other article also said that mean duration of wound healing in honey dressing group was shorter (although not significantly) than povidone-iodine dressing group, which was marked by negative culture of *Staphylococcus* and *Streptococcus*<sup>14</sup>.

### Application of Honey Dressing

Debridement was carried out prior to honey application in these 5 included studies.

Currently, there are no standardized method for applying honey dressing. Even in this review, we found different methods of honey application. Three trials was using pure undiluted honey<sup>10,12,14</sup>, while other two was using standardized honey medication (Pedyphar Ointment and Medihoney)<sup>11,13</sup>. However, given the promising evidence, there are several pharmacies that have started to produce standardized honey impregnated dressings. Unfortunately, standardized medical honey is not available yet in our country.

Unstandardized honey application is one of obstacles in using honey for wound dressing. Sudjatmiko<sup>4</sup> proposed that manually prepared honey impregnated dressing should be changed at least once daily or more in presence of excessive exudate. This standardization of honey application is concluded based on: (1) its hygroscopic properties—honey could easily liquefied (decreased viscosity) in contact to body temperature, (2) dry honey dressing can cause gauze to adhere to wound surface thus induce pain in dressing changes, (3) honey can give unpleasant smell if the dressing does not be changed in 3 days. We do hope that there will be more protocols of honey application in the future.

### Strength and Limitation of This Review

The strength of this review lies in the fact that all trials was done in different parts of the world (Greece, India, Malaysia, Pakistan and Egypt) so they were hoped to represent different race of the patients involved.

Limitations of this review include the inability to carry out a meta-analysis. Forest Plot of all trials showed statistically significant effect favouring honey as diabetic foot ulcer treatment, but as we tried to calculate the pooled mean difference based on mean duration of wound healing from each studies, it was to no success due to heterogeneity of the included studies. This heterogeneity due to: unstandardized clinical assessment to determine healed wound; unstandardized age of participants; and unstandardized honey application.

### Recommendation for Future Research

To upgrade the evidence on honey in modern wound care, standardized and validated measurement tools are needed, as well as reliable cost-effectiveness analysis, as they will allow a valid comparison with current practice. Conducting more trials with sufficiently larger sample size and standardization of honey application are needed to determine its statistical significance as wound dressing. We do hope that those trials could determined honey application protocols in the future.

## DISCUSSION

Honey dressing was proven to be effective in reducing mean duration of wound healing compared to Normal Saline dressing and Alginate Dressing. Although it showed insignificant difference compared to Povidone Iodine dressing, mean duration of wound healing in honey dressing groups were still shorter. On the other hand, honey dressing was also proven to cause less pain in dressing changes. The mean difference of wound healing duration between honey dressing and other substances cannot be pooled due to low number of the studies and substantial heterogeneity. We suggested more studies analyzed honey as diabetic foot ulcer treatment as well as its standardized method of application.

**Corresponding author :**

Ide Bagoes Insani

ide.bagoes.insani@gmail.com

**Acknowledgement**

*We would like to show our gratitude to dr.Gentur Sudjtmiko, SpB, SpBP-RE(K) for sharing his pearls of wisdom with us during the course of this research.*

**REFERENCES**

1. Sudjtmiko G. Madu Untuk Luka Akut dan Kronis. 2014. Jakarta: Yayasan Lingkar Studi Bedah Plastik; 2014.
2. Diah A, Sundoro A, Sudjtmiko G. Antibacterial Activity of Indonesian Local Honey Against Strains of P. Aeruginosa, S. Aureus and MRSA. JPR. 2012 Mar. 1(2): 177-181.
3. Adifitrian T, Melati N, Sudjtmiko G et al. Application of Honey and Transparent Dressing to Split Thickness Skin Graft Donor Site and Its Effect on Epithelialization Rate. JPR. 2012 Mei. 1(3): 333-337.
4. Raymond B, Sudjtmiko G. Standardization of Honey Application on Acute Partial Thickness Wound. JPR. 2012 Nov. 1(6): 570-574.
5. Perkumpulan Endokrinologi Indonesia. Konsensus Pengelolaan dan Pencegahan Diabetes Melitus Tipe 2 di Indonesia; 2011.
6. Sreedevi C, Car N, Pavlic-Renar I. Dermatologic lesions in Diabetes Mellitus. Diabetologica Croatica; 2002.
7. G.E. Reiber, B.A. Lipsky, G.W. Gibbons, The burden of diabetic foot ulcers, Am. J. Surg. 176 (1998) 5Se10S.
8. Driver VR, Fabbi M, Lavery LA, Gibbons G. The costs of diabetic foot: the economic case for the limb salvage team. JVasc Surg 2010;52(3 Suppl):17S-22S.
9. Sastroasmoro S. Dasar - Dasar Metodologi Penelitian Klinis. Edisi ke-5. Jakarta: Sagung Seto; 2013. P. 267-287.
10. Agarwal A, et al. A Control Trial of Honey-impregnated and Povidone Iodine Dressings in The Treatment of Diabetic Foot Ulcers among North Indian Subjects. *Indian J.Sci.Res.* 2015. 6(2): 7-10.
11. Eldeen M, Fathey R, Hasaballah A, Basal A. Topical Honey versus Alginate as Dressing for Management of Wagner Type 2 Diabetic Foot Ulcer. *Journal of American Science.* 2012. 8(9).
12. Imran M, Hussain MB, Baig M. A Randomized, Controlled Clinical Trial of Honey-Impregnated Dressing for Treating Diabetic Foot Ulcer. *Journal of The College of Physicians and Surgeons Pakistan.* 2015. 25(10):721-725.
13. Kamaratos AV, et al. Manuka honey-impregnated dressings in the treatment of neuropathic diabetic foot ulcers. *International Wound Journal.* 2012.
14. Shukrimi A et al. A Comparative Study Between Honey and Povidone Iodine as Dressing Solution for Wagner Type II Diabetic Foot Ulcers. *The Medical Journal of Malaysia.* 2008. 63(1).3030
15. Subrahmanyam M. Topical Application of Honey in Treatment of Burns. *Br. J. Surg.* 1991. 78(4): 497-8.
16. Kreshanti P, Sudjtmiko G, Bangun K. The Effect of Honey Give As Oral Drops in Precipitating Epithelialization of Lateral Palatal Defects Post Two-Flap Palatoplasty. *Jurnal Plastik Rekonstruksi.* 2012.1(5):504-509.
17. Pemayun TGD, Naibaho NM. Diabetic Foot Ulcer Registry at a Tertiary Care Hospital in Semarang, Indonesia: an Overview of its Clinical Problem and Management Outcome. *Diabetes Management.* 2016. 6(4), 082-089
18. White JW, Subers MH, Schepartz AI. The identification of inhibine, the antibacterial factor in honey, as hydrogen peroxide and its origin in a honey glucose - oxidase system. *Biochimica et biophysica acta.* 1963;73:57 - 70.
19. Mandal MD, Mandal S. Honey: its medicinal property and antibacterial activity. *Asian Pacific Journal of Tropical Biomedicine.* 2011.1(2):154-160.
20. Frykberg et al. Diabetic Foot Disorders: A Clinical Practice Guideline (2006 revision). *The Journal of Foot and Ankle Surgery.* 2006.45(5).