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REVIEW ARTICLE

Honey as an Alternative in the Management of Contemporary Wound Healing: A Systematic Review

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ABSTRACT

Introduction: In recent times, the traditional honey has shown a revival as a topical treatment for a variety of wounds. The aim of this systematic review is to assess the available evidence and further evaluate the role of honey in modern wound care management.

Methods: The databases which were used for this purpose include the PubMed and the ISI web of science. The review only contains the studies being conducted on humans. The review only contains the studies being conducted on humans covering burns, ulcers and other types of wounds (like traumatic, postoperative, malignant wounds). Under "design," research designs namely, RCTs and CCTs were included.

Result: In all three of the identified wound types, honey as a dressing with healing promoting properties is supported by evidence, whereas, the other known properties of honey like debridement, deodorizing, anti-inflammatory and wound pain-reducing effects are found to be less supported by the pieces of evidence.

Interpretation: Many limitations were quite evident in the included studies related to the methodology, quality, and sample size. This review tries to reveal all such limitations and gaps and also recommends certain suggestions for the future research.

Keywords: Burns, Healing, Honey, Manuka, Pain, Ulcers, Wound.

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INTRODUCTION

Indigenous medicine (also popularly called as traditional medicine) embraces the expertise and information that has been originated in various civilizations over generations before the origin of modern medicine. According to the World Health Organization (WHO), traditional therapies are those practices which incorporate the knowledge and beliefs pertaining to indigenous plants, animals, minerals, spiritual healing techniques, which are either applied as a combination therapy or sometimes individually to diagnose, treat and prevent the ailments or in nutshell, to maintain a healthy well-being.[1] Over the last decade, the traditional or indigenous medicines has become increasingly popular[2-4] and with this rising popularity, the concomitant interest in the scientific community for these therapies has also been observed. Many herbal products have so far been studied and claimed to possess many therapeutic properties. One such natural product of therapeutic promise is honey.

Honey bears a special mention as a medicinal product since ancient times in numerous studies,[5,6,8-10] the first such reference was discovered in "Edwin Smith papyrus" (2600–2200 BC) in the wound management followed by Greeks and Romans who used honey for preventing wound decomposition by either adding animal or vegetable fat into it or by incorporating honey into many other ointments.[9,11-13] Many other descriptions like using cooked honey as an astringent by the famous Arab doctor, Avicenna (980–1037), for reducing wound exudation,[15] using honey as a cleanser in case of gunshot wounds are available for the reference.[15,16] The popularity of honey remained in the picture until the dawn of antibiotics (1940).[17,18]

There has been a profound change observed in the epidemiology of soft tissue infections due to *S. aureus* especially in Maori and Pacific populations in New Zealand. The most commonly affected age group is below 5 years of age group.[19,20] The prevalence of Methicillin-resistant *S. aureus* is found to be 8–10%, but it varies in different regions. There is a growing concern of emergence of community-onset MRSA (CA-MRSA) and SWP ST30 (South West Pacific) resistant clones in New Zealand. Apart from their resistance to β-lactam antimicrobials, their resistance to most commonly used topical fusidic acid in New Zealand is also noteworthy.[21]

Though antibiotics are essential for reducing the worldwide encumbrance due to fast-growing infectious diseases but, it is complementing this fact with the development of antibacterial resistance resulting in the waning effect of antibiotics. All this along with the growing cognizance for natural medicines has shown a revival in the interest for unfurling the antimicrobial and wound healing properties of honey in the scientific community.[5,15,18]

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Honey is a viscid, carbohydrate-rich solution collected, altered and stored by the honey bee, *Apis mellifera*.[12] The chief constituents of honey are sugar (75–79%) and water (20%),[11,13] but it also contains proteins, vitamin B-complex, minerals, and antioxidants like flavonoids, vitamin C, enzyme-like invertase, amylase, glucose oxidase and catalase, metals like selenium[4,24] and organic acids (0.57%), which are responsible for its acidic nature.[23,24] The specific proportions of all these constituents may vary depending on the type of the plant, the season of nectar collection, topography, the age of honey and any treatment whatsoever done since the time of its harvest.[13]

The immunomodulatory properties of honey relevant to the wound repair are based on many mechanisms. Firstly, its anti-bacterial activity due to the production of hydrogen peroxide by the enzymatic activity on the wound exudates,[4,8,23,25] secondly, providing less 'free' water for the growth of microbes. The high sugar content of the honey also causes bacterial death due to osmosis.[13,26] The third effect of honey can be explained by its acidic nature (ranging between 3.2 and 4.5) which for bacterial growth is not ideal (7.2–7.4).[22,26,27]

There are many varieties of honey that are well-researched and sold in the market with different standardization of antibacterial activities like Taulang honey (TH), Manuka honey, Langnese honey, pure unprocessed Indian hive bee honey, pasture honey, jelly bush honey, African jungle honey. Some of the clinically practiced honey include Manuka and Medihoney, although Taulang honey, a multifloral honey from Malaysian jungles is also recently gaining popularity. Unlike Taulang honey, Manuka and Medihoney come from the *Leptospermum scoparium* (*L. scoparium*) species of trees in New Zeal and Australia. Manuka honey has generated interest in the scientific world because of its unique antibacterial property which is independent of peroxide activity.[28-31]

Though apitherapy is considered as an ancient therapy and its revival in today's world is quite evident by its frequent use in a variety of conditions, but the exact level of evidence for its role in wound management is still not clear.[4,5,18,26,32] Thus, the aim of this systematic review is to assess the role of honey in the wound management taking into account the available published literature. This review examines the use of honey in the wound care management, its application in different categories of the wound, and also provides an associated critical evaluation.

METHODS

The systematic review is designed with randomized controlled trials (RCTs) and clinical controlled trials (CCTs). Two databases, namely PubMed and ISI Web of Science were used as a strategy for the search so that most of the published literature can be covered. The items like "honey', "design" and "wound healing", "ulcers", "burns", were executed in the search engine. Under "design", research designs namely, RCTs and CCTs were included. There were no restrictions being applied with reference to the authors, publication year or the investigating institute. The review only contains the studies being conducted on humans covering burns, ulcers and other types of wounds (like traumatic, post-operative, malignant wounds).

Tables 1 and 2 represent a detailed systematic analysis of the study parameters including the methodologies and their strengths and weaknesses. The six categories for the outcome parameters are presented in Table 3.

RESULTS

Description of the Publication

A total of 54 publications were assessed in PubMed and ISI Web of Science (Flow chart 1), out of which 27 studies which were registered for this review for different wound etiologies are presented in Table 4. Though the two publications belong to the same study, in this review, these are included as two different studies as they discuss the primary and secondary outcomes separately. The review does not include any meta-analysis due to the heterogenic nature of the included studies.[33,34]

Outcomes

The analysis of the included works of literature according to the etiological classification of the wound resulted in the following:

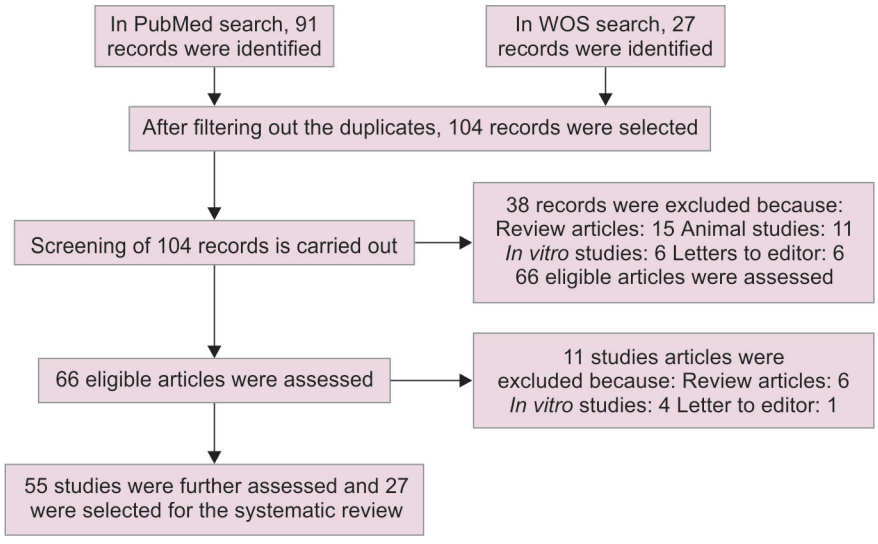
Burns

Seven of the RCTs in the review have examined the impact of pure, undiluted and unrefined honey in the wounds resulted from burns (Table 1). Although the anti-bacterial effect was found to be positive in five of the RCTs, the statistically significant result was found only in four of them (Tables 1 and 2). Only in one study, the tangential excision (TE) followed by skin grafting in the control group resulted in better anti-bacterial effect than the honey intervention group.[40]

There are six RCTs in the review that examined the wound healing effect of honey, all of which resulted in positive outcomes, thus favoring honey. Three of these studies reported a better and a more rapid process of epithelization, whereas two of these studies showed a catalytic effect in the production of granulation tissue.[39,47]

Though four of the RCTs in the review have silver sulphadiazine (SSD), which is known as a gold standard in wound healing, in the control group, yet honey reported

Flow chart 1: Number of studies included in the systematic review



to have a significant and a healthier antibacterial effect when comparing it to SSD (Tables 1 and 2).

The positive outcome in odor reducing, anti-inflammatory and the debriding effects of honey was reported in a number of trials (Table 2), but on comparing it with the control group, none of the studies has shown any statistically significant difference (Tables 1 and 2).

As far as wound pain is concerned, 3 RCTs mentioned its effect and only one trial reported a positive outcome in favor of honey (Tables 1 and 2).

It is quite evident from these trials that the antibacterial and the healing effects of honey are favorable, whereas, the debriding, anti-inflammatory, odor as well as the pain reducing effects of honey are found to be rather weak and thus, inconclusive.

Ulcers

The wide use of honey in a variety of ulcers like venous, pressure, diabetic, and foot ulcer are discussed in 6 trials (Table 3). Four of the RCTs reported the antibacterial effect of honey and only one of it showed a positive outcome with honey, however not so significant statistically. Two studies discussed the potential action of honey in lowering the incidence of infection and in eliminating the methicillin-resistant *Staphylococcus aureus* (MRSA).[33,34]

Four RCTs reported wound healing stimulating effect of honey, out of which two showed a statistically significant effect,[45] whereas, the anti-inflammatory, debridement and deodorizing properties of honey are weakly supported by one trial each.[38]

As most of the evidence was found to be positive in case of wound stimulating effect of honey, the other properties of honey in ulcers seemed to be inconclusive. However, this can be argued as insufficient evidence for its practical implications in clinical practice.

Other Wounds

There are 14 studies (RCTs) included in this group that belongs to different wound etiologies (Table 3). Out of 14 RCTs, only one study has reported a statistically significant effect on the antibacterial effect of honey[50] (Table 2), whereas, the healing effects of honey are investigated by 12 RCTs. Four of these trials showed a significant result but the majority of these studies are supporting the healing catalytic effects of honey (Table 2).

The anti-inflammatory properties of honey are discussed in 6 RCTs and the debriding effect is reported in 3 RCTs, where 50% is found to be statistically significant in the former and only one was found to be favorable in the latter (Table 2).

In wound pain management, there are only two RCTs in the review that support honey out of 5 RCTs, but those are not statistically significant. As the deodorizing effects of honey in these classes of wounds are not well supported by any of the studies, thus its evidence can be referred to as weak (Table 2).

It can be concluded that honey has a substantial effect on the healing process in these types of wounds as compared to the deodorizing, anti-inflammatory, antibacterial and pain reducing properties where the pieces of evidence were found to be insufficient and weak.

DISCUSSION

After looking at the three above defined wound types, it is quite clear that honey is beneficial as a dressing for the healing of different types of wound. However, there are limited pieces of evidence found in the pieces of literature

Table 1: Description of the included studies with reference to wound class and design

Wound category	*Author*	*Sample size*	*Intervention used*	*Wound etiology*
Ulcers: RCTs	Gethin and Cowman[20]	n = 108: HG = 54; CG = 54	HG: Manuka Honey, UMF 18+; CG: hydrogel	Venous leg ulcer
	Gethin and Cowman[19]	n = 108: HG = 54; CG =54	HG: Manuka Honey, UMF 18+; CG: hydrogel	Venous leg ulcer
	Jull et al.[23]	n= 368: HG = 187; CG = 181	HG: Manuka, CG: UMF 12+; standard dressings	Venous and mixed ulcer
	Yapucu Gunes[59]	n = 50; HG = 15; CG =11 (but in 26 subjects)	HG: Raw, unpasteurized, natural honey; CG: Dressing of ethoxy-diaminoacridine plus Nitrofurazone	Stage 2 and 3 pressure ulcers
	Shukrimi et al.[50]	n = 30: HG = 14; CG = 16	HG: Pure and non-sterile honey; CG: povidone -iodine 10% dressing	Type-2 diabetic foot ulcer
Ulcers: CCT	Oluwatosin et al.[38]	n = (but in 38 50 subjects)	HG: Unprocessed and undiluted honey; CG: Mixture of phenytoin and honey	Ulcer: Post-traumatic
Burns: RCT	Baghel et al.[6]	n = 78; HG = 37; CG = 41	HG: Pure, undiluted; CG: SSD	Burns (1st and 2nd degree)
	Malik et al.[32]	n = 150 (intra-individual design)	HG: Langnese honey; CG: SSD	Burns (2nd degree)
	Subrahmanyam[45]	n = 104; HG = 52; CG = 52	HG: Undiluted,pure but unprocessed honey; CG: SSD	Burns with TBSA < 40% (superficial)
	Subrahmanyam[48]	n = 92: HG = 46; CG = 46	HG: Undiluted and unprocessed honey ; CG: Polyurethan film	Burns with TBSA < 40% (Partial thickness)
	Subrahmanyam[47]	n = 100: HG = 50; CG = 50	HG: Indian hive bee unprocessed, pure and honey; CG: potato peel (boiled)	Burns with TBSA < 40% (Partial thickness)
	Subrahmanyam[49]	n = 50; HG = 25; CG = 25	HG: Unprocessed , pure and undiluted honey; CG: SSD	Burns with TBSA < 40% (superficial)
	Subrahmanyam[47]	n = 50; HG = 25; CG = 25	HG: Indian hive bee (unprocessed) honey; CG: skin graftingand (TE)	Burns with TBSA < 30% (full thickness)
Other: RCTs	Chang et al.[11]	n = 48: HG = 16; Budesonide group = 16; Gentamicin group = 16	HG: Manuka CG: saline solution honey;	Endoscopic sinus surgery
	English et al.[18]	n = 30: HG = 14; CG = 16	HG: Manuka honey, UMF 15; CG: Wrigley's sugarless chewing gum	Gingivitis ulceration
	Lund-Nielsen et al.[29]	n = 69: HG = 34; CG = 35	HG: Manuka honey, CG:silver-coated bandage UMF12+; nanocrystalline	Malignant wound
	McIntosh Thomson[30]	n = 100: HG= 52; CG = 48	HG: Manuka honey; CG: paraffin-impregnated tulle grass	Surgical wound of toe-nail
	Robson et al.[41]	n = 105: HG = 52; CG = 53	HG: Medihoney; CG: standard conventional treatment	Eczematous, mixed wounds
	Robson et al.[40]	n = 49: HG = 25; CG = 24	HG: Medihoney, Antibacterial Wound Gel; CG: conventional dressings	Free tissue grafting for head and neck cancer
	Moolenaar et al.[33]	n = 24: HG = 12; CG = 12	HG: Honeysoft (multifloral) honey CG: paraffin gauze	Skin toxicity induced by radiotherapy
	Mphande et al.[36]	n = 40: HG = 22; CG = 18	HG: Malawi honey; CG: Malawi sugar	Mixed: trauma, post-surgical, ulcers
	Khanal et al.[26]	n = 40: HG = 20; CG = 20	HG: beehive honey from Western Ghats (India) CG: lignocaine gel	oral mucosal inflammation after radiotherapy
	Ingle et al.[22]	n = 82; HG = 42; CG = 40	HG: Monofloral CG: hydrogel aloe honey;	Traumaticskin lesions

(Contd...)

(Contd...)

Wound category	*Author*	*Sample size*	*Intervention used*	*Wound etiology*
	Al-Waili and Saloom[4]	n = 50; HG = 26; CG = 24	HG: Undiluted, crude honey; CG: povidone-iodine gel and 70% ethanol	Postsurgical wounds after C-section and hysterectomy
	Abdulrhman et al.[1]	n = 90; HG = 30; CG = 30; HOPE = 30	HG: Non-sterile Egypt honey; CG: HOPE (a mixture of propolis, benzocaine gel, olive oil, and beeswax)	Oral mucosal inflammation after chemotherapy
	Okeniyi et al.[37]	n = 43; HG = 23; CG = 32	HG: Crude CG: EUSOL and undiluted honey	Abscess injury
Other: CCTs	Misirlioglu et al.[34]	n = 88	HG: Unprocessed honey; CG: paraffin and hydrocolloid dressing	Skin graft site of the donor

n: sample size; HG: honey group; CG: control group; SSD: Silver Sulphadiazine; TBSA: total body surface area; UMF: unique manuka factor; TE: tangential excision

Table 2: Outcomes of the studies with reference to design and wound class.

Wound category	*Author*	*Antibacterial effect*	*Healing catalytic effect*	*Debridement*	*Anti-inflammatory*	*Odour reducing effect*	*Wound pain reducing effect*
Ulcers: RCTs	Gethin and Cowman[20]	1+	#	#	#	#	2+
	Gethin and Cowman[19]	>/<	2+	1+	#	#	#
	Jull et al.[23]	//	//	#	#	#	#
	YapucuGunes[59]	#	2+	#	#	#	#
	Shukrimi et al.[50]	//	//	#	1+	1+	#
Ulcers: CCT	Oluwatosin etal.[38]	#	1-	#	#	#	#
Burns: RCT	Baghel etal.[6]	2+	2+	1+	#	#	#
	Malik et al.[32]	1+	2+	#	>/<	#	#
	Subrahmanyam[45]	2+	2+	>/<	#	>/<	1+
	Subrahmanyam[48]	2+	2+	>/<	#	>/<	>/<
	Subrahmanyam[47]	2+	2+	#	#	#	//
	Subrahmanyam[49]	>/<	2+	1+	1+	#	#
	Subrahmanyam[47]	%	#	#	#	#	#
Other: RCTs	Chang et al.[11]	#	//	#	//	#	#
	Englishetal.[18]	>/<	#	#	2+	#	#
	Lund-Nielsenet al.[29]	#	//	//	//	//	//
	McIntoshand Thomson[30]	#	%	#	#	#	//
	Robson etal.[41]	#	1+	>/<	#	#	#
	Robson et al.[40]	//	>/<	#	#	>/<	#
	Moolenaaret al.[33]	#	1+	#	#	#	1+
	Mphande et al.[36]	1+	1+	#	#	#	1+
	Khanal et al. [46]	#	2+	#	2+	#	#
	Ingle et al.[22]	#	1+	#	#	#	#
	Al-Waili and Saloom[4]	2+	2+	#	>/<	#	>/<
	Abdulrhman et al.[1]	#	2+	#	#	#	#
	Okeniyi etal.[37]	#	2+	2+	2+	#	#
Other: CCTs	Misirlioglu etal.[34]	#	2+	#	#	#	2+

1+: result in favor of honey and not significantly different; 2+: results significantly different and in favor of honey; %: results significantly different and in disadvantage of honey; #: results not reported; >/<: not compared; 1-: results not significantly different and not in favor of honey; //: no significant difference between the honey and ot her therapy regimens

regarding its deodorizing, anti-inflammatory and wound pain-reducing effects.

The antibacterial properties of honey have been shown by the included studies as the strongest, especially in burns. One of the studies has also compared it withTEfollowedbyskin graftinginthird-degreeburns,[40] where the comparison seems to be inappropriate as the application of topical honey is only recommended in first and second-degree burns (superficial).[4,58] Nevertheless, these pieces of evidence should be reviewed with caution as out of the 7 RCTs, 5 belonged to the same researcher. Moreover, six studies have used undiluted, unprocessed and natural honey which might be seen as an unfavorable fact as far as replication and generalization of future research is concerned.

For the ulcers and other wound categories, the pieces of evidence can be classified from moderate to weak for the anti-bacterial effects of honey. The studies do not support

Table 3: Wound etiology by design

Wound etiology:	*RCT*	*CCT*	*Total*
Ulcer	5	1	6
Burns	7	0	7
Other wounds	13	1	14
Total	25	2	27

the much popular recommendation of Manuka and Medi honey for their anti-bacterial function.[9,29-31] Under ulcer wound category, only three trials (3 RCTs) have used this honey, and only one has reported the antibacterial effect of honey.[34] Thus, with the limited evidence available for these medical kinds of honey, their recommendations for medical use cannot be established. Moreover, the results from the best-implemented trial by Jull and associates[12] also confirmed that Manuka honey is not a clinically relevant aid for the wound management when compared to the standard treatment (Table 4).

It can also be commented from this review that the MRSA elimination capacity of honey, as reviewed by few studies[29,59] can be further investigated in the light of the recent upsurge in the antibiotic resistance. However, this comment should be deduced cautiously as wounds of different etiology are discussed under this wound category; therefore, one may find this conclusion to be difficult to generalize.

In the RCTs on burn wound etiology, the link between the antibacterial effect and the rapid wound healing is found to be clear as compared to other wound types. This can be interpreted as, in case of burn injuries, there is no other underlying pathology contrary to other wounds where the chronicity of the wounds poses an influencing effect on the healing process.

For the treatment protocol, it is important to mention the various considerations like the choice of the honey which was found to be described imprecisely in some studies, for example, in few trials, even the non-sterilized, natural and nonmedical honey was used, which implies that there can be possible risks associated with the contamination.[28,31] The use of the same type of the standard bandage, the mentioning of the person responsible for changing the dressings and the frequency of its changes make the studies more repeatable. It should be noted that any deviation from the recommended protocol in any investigation degrades its quality and rationality. Such studies should be better avoided for any references.

Honey, as a single therapy, is used only in 10 studies[14,28,46,47,53,55,27,39-41] and in few studies, it was used after the standard therapy.[35] This creates challenges in drawing conclusions and thus leads to limitations with reference to repetition and generalization of the outcomes of these studies. The exact arm of the therapy in the studies must be known wherein it is very clear that the research groups have received equal standard therapy and that the topical intervention (honey or any other control product) is undoubtedly the only variable under investigations. This allows making the clear judgment that the difference in the results is only because of the topical treatment.

Table 4: Outcome categories

Outcome group	*Outcome parameter*
Antibacterial effect	Complete eradication or partial reduction of pathogens
Healing catalytic effects	Ranging from reduced wound size, increased granulation and epithelialization, reduced healing time
Debridement effect	Reduced debris and necrosed tissue
Anti-inflammatory effect	Reduced signs of inflammation like redness, swelling, puss formation
Deodorizing effect	Reduced bad odor
Wound pain effect	Reduced existing pain of the wound after honey application

The analysis of the cost-effectiveness is also important while we compare the interventions and make a conclusion. In this review, many studies have reported honey as a cost-effective treatment,[36,37,39,41,48,49] but in only one study this was calculated by using the Incremental cost-effectiveness ratio (ICER) factor and the result came out to be in the favor of control group and not the honey group.[32]

Insight on the Methodology of the included Studies

The sample size varies largely in the included studies and a power analysis was executed in advance in only 11 studies to determine the population size.[24,31,33,34,42,51]

Out of these 11 studies, only 4 studies had the desired number of participants,[31,42,49,59] and in rest of the 7 studies, 3 RCTs could not gather the required number of subjects owing to the high cost and limited time frame of the study.[24,33,34] To have the results validated and representative, one must consider in advance the power analysis, predefined selection criteria, primary and secondary outcomes. Unfortunately, these parameters are not clear in case of the included studies in this review. Many studies have used different and nonvalidated measurement tools and thus introduced measurement bias. Although this bias can be corrected by blinding the investigator,[58] but no such corrections were being implemented in any of these studies.

One of the most commonly encountered limitations in case of using honey in wound care is the inability to blind due to the staining of the wound and the surrounding skin and the apparent smell of honey.[31,33] Nevertheless, few studies have used single blinding (8 RCTs),[30,31,34,36,38,43,46] whereas, in some double blinding was done (3RCTs).[42,44,49] For an independent and qualitative judgment of the outcomes, while assessing the wounds, one must strive for at least a single blinding.[57]

Review's Strengths and Weaknesses

The review discusses about various views on the usage of honey worldwide in 3 different types of wound classes. Moreover, it also highlights the caveats present in the included studies as far as methodology and results are concerned.

The limitation of this review lies in its inability to perform a meta-analysis due to the heterogenic nature of the included studies. As this review includes only the published literature, Jull and associates[59] mentioned the potential introduction of the publication bias.

FUTURE RESEARCH RECOMMENDATIONS

On a thorough evaluation of the studies, many gaps have been observed in the review and thus the recommendation of honey in the clinical management of the wound remains inconclusive. It is absolutely necessary to perform the power analysis, stratification of the wound and the simultaneous corrections of the confounding factors. There should be clear mentioning of the type of honey used. Only gamma-sterilized honey-impregnated dressings must be recommended owing to its standard composition and quality besides its easy usage.

The validated and standardized measurement tools along with a reliable cost-effectiveness analysis are also recommended to allow a fair comparison between honey and the standard current practice in the modern wound care management.

The Consort guidelines for the randomized controlled trials must be strictly abided by the investigator while reporting any results.

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