TRADITIONAL AND INTEGRATIVE MEDICINE

Trad Integr Med, Volume 9, Issue 1, Winter 2024

Review

Wound Healing Agents as Described by Avicenna in the *Canon of Medicine*

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Received: 17 Dec 2022 **Revised:** 16 Jul 2023 **Accepted:** 18 Jul 2023

Abstract

Topical wounds are common complications, and it is necessary to find new remedies and approaches for their treatment. In this study, Avicenna's definitions of topical wounds and his treatment strategies are investigated and compared with contemporary findings. Data were extracted from the fourth chapter of the fourth volume of *the Canon of Medicine* and databases of PubMed, Scopus and Google Scholar using keywords of wound healing, Avicenna, Persian medicine, etc. Avicenna tries to clarify categorizations, semiology, pathophysiology, dressing, remedies and treatment strategies for wound. Many of his descriptions—like callus and the importance of angiogenesis in wound healing—are close to current definitions. He also mentioned to strategies like using gauze in dressing, control of bleeding and swelling (inflammation), washing and clearing wounds, using suture and surgery in some cases and also prescribing tonic foods. Furthermore, the efficacy of many natural remedies mentioned by Avicenna like *Boswellia sacra* Flück., *Hordeum vulgare* L., *Prangos ferulacea* Lindl., *Quercus persica* Jaub. & Spach, *Brassica oleracea* L., and *Plantago major* L. have been evaluated and approved by contemporary investigations. These results demonstrate the impact of Avicenna's knowledge on wounds and wound healing process. Therefore, besides historical impact, it is important as a novel natural source to find new medicaments based on this ancient knowledge.

Keywords: History of medicine; Integrative medicine; Persian medicine; Phytotherapy; Wound healing; Avicenna

http://doi.org/10.18502/tim.v9i1.15093

Citation: Zargaran A, Soleymani S, Mazhari M, Mirghazanfari SM. **Wound Healing Agents as Described by Avicenna in the *Canon of Medicine***. Trad Integr Med 2024;9(1):105-113. http://doi.org/10.18502/tim.v9i1.15093

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Introduction

Topical wounds are common complications with various causes, from simple cuts in the skin to pathological and malignant causes [1]. In 2004, a report stated that chronic wounds involved more than six million people in the United States (US). They were considered as the main costly skin disorders, with $9.7 billion spent on them in one year in US alone [2]. Therefore, it is necessary to find new ways and beneficial treatments to heal wounds, as well as eliminate scars so as to reduce the cost of treatment and increase patients' well-being [3]. Although there are too many suggested remedies and methods to heal topical wounds like drugs (e.g. phenytoin and collagen-based biomaterials), autologous stem cell therapy, and so on, no way is completely sufficient and cost-efficient [4].

Traditional systems of medicine are, as a group of schools of medicines, mostly rooted in the history that can be a good source of hypotheses for current medicine. Persian medicine (PM) is one of the traditional system of medicines, dating back 7,000 years, as one of the oldest schools of medicine, rooted in antiquity. Medical science was flourished in the early Islamic and medieval era (9–12th century AD) under the guidance of Persian physicians like Haly Abbas (949–982 AD), Rhazes (865–925 AD), and Avicenna (980–1032 AD) [5]. Ibn Sina, who was known as Avicenna in the West, was one of the most outstanding scientists of that era. He was born in Afshane, north-east of Old Persia (980 AD) and died in Hamedan, a city in the west of Persia (1032 AD) [6]. He made great contributions to the field of medical science. His main and most important medical text book is *The Canon of Medicine*. It is a huge medical encyclopedia in five volumes [7]. Avicenna comprehensively discussed the types of wounds, traumas, and wound-healing methods and remedies in the fourth chapter of the fourth volume of *the Canon of Medicine* (Figure 1) [8]. In this study, Avicenna's definitions of topical wounds and his treatment strategies are investigated and compared with contemporary findings.

Historical Perspective

Healing wounds and injuries is an important and old technique in the history of medicine. It was also important for military physicians and surgeons, helping them survive casualties [9]. In Chinese mythology, a farmer or an emperor learned the technique of healing wounds from a snake when using an herb (called snake grass) to heal another snake or his own wounds. But documentation shows that Chinese healers, at least from 17th century AD, used wine for wound care, and there was a special type of physicians who were called ulcer doctors in 11th century AD [10]. The first written evidence of applying linen bandages and drugs (willow and a paste of honey, grease, and lint) for wound healing in ancient Egypt is found in the *Ebers Papyrus*, dating back to 1550 BC [11]. Wound healing methods were advanced in ancient Persia, too. Herodotus (the father of history) indicated that as opposed to the Greeks, the Persians in the Achaemenid era (550–330 BC) used clean bandages and myrrh salves for injuries [12]. Pahlavic manuscripts belonging to the Sassanid kingdom (224–637 AD) show that the Persians knew about blood circulation and its role in spreading infection, as well as the importance of cleaning the wounds to avoid infection [12]. Also, a Greek barber invented a syringe (named *pyūlkos*) to suck pus out of wounds in 280 BC [11].

Figure 1. One Page of the book of The Canon of medicine on wound; written by Avicenna (980-1032 AD).

Wound Healing in Avicenna's The Canon of Medicine

In this study, Avicenna's definitions of topical wounds and his treatment strategies are investigated and compared with contemporary findings. Data were extracted from the fourth chapter of the fourth volume of *the Canon of Medicine* and citation databases of PubMed, Scopus and Google Scholar using keywords of wound healing, Avicenna, Persian medicine, etc.

General categorizations of injuries

Avicenna categorized wounds generally and commented on their progress based on the location of injuries. The categories including the injuries located only on flesh, or on bones, accompanied by injury to vessels and sinews. He believed that injuries solely on flesh have the best prognosis with faster healing, and bone fractures have the worst prognosis. Healing of vessels

and injuries to sinews are intermediate and need more care than just flesh wounds [8]. He believed that injuries in some critical internal organs like heart, brain, kidney, liver, intestine, and bladder are too dangerous and can lead to death unless these injuries are minor [8].

Types of wounds

Avicenna categorized wounds into two main groups: internal and superficial. As it was mentioned, Avicenna believed that internal wounds can be dangerous and life-threatening. Moreover, he described a prognosis for patients with internal wounds: If they have vomiting, hiccoughs, and diarrhea, they will die [8]. Current findings show that upper GI bleedings can lead to vomiting and melena, and that massive ones can cause complicated and lethal conditions [13].

He also mentioned that such wounds can be either on the surface or have a deep root in the layers of the skin and muscle. Avicenna has divided superficial wounds into the following types: A simple scratch, smooth without any damage and loss of flesh; round wounds; angular and polygonal; a scratch with loss of a part of flesh.

Semiology and pathophysiology

Avicenna stated that wounds on muscles are accompanied with pain and edema. However, such wounds can get deeper, and the mass of edema may flow into them if they accrue. He explained that repairing skin and flesh involves "creating a meaty skin without hair growth" [8] that is a clear description of a callus [14]. Then, he categorized scars into two types: when they are like a pit or a waste jut depending on less or more meat on the wound. He also mentioned fistula in some deep wounds causing discharge of pus, and encouraged physicians to make a way for discharge of pus by using lancet in some deep wounds. There is also evidence that Avicenna was aware of angiogenesis in wound healing: "vessels like flesh; can grew up by generating the new branches and compensate the missed ones" [8] that importance of angiogenesis in wound healing is accepted by current findings [15].

Prognosis

Avicenna believed that pus and infection can be occurred in swollen wounds, therefore prevention of wound swelling leads to better prognosis. Although there are no current findings supporting this theory, it needs more investigations.

He mentioned the wounds involved vessels, nerves, and end of muscles have poor prognosis. He also warned against blood loss in such cases and described the symptoms, including change in skin color of the patient, reduction in pulse rate (after weakness and increasing rate), and even fainting [8].

Intervention

Avicenna's general strategies for healing wounds are summarized in table 1. The first step is control of bleeding. Although, he believed that a bit of bleeding in some cases to avoid swelling, infection, and fever is necessary, control of the bleeding was his first strategy facing with wounds. Wound cleansing is the second step. Next step is prescription medicines including pus drier to eliminate infections and swelling, wound healing agents and also medicaments to restore lost flesh. Suggestion of *Saleh al-Kimous* foods as tonic

Table 1. General Avicenna's strategies for wound healing

Acts	Conditions
Control of bleeding	Act on all types of wounds in the first step.
Washing and clearing wounds	To avoid polluting wounds by nothing
Controlling the swelling of the wound	Act in all types of wounds. Avicenna believed that wounds would have good prognosis if they do not be swelled.
Undermine the pus and infections by hot drugs	In the swelled and infected wounds
Dressing the wounds	1- in the simple scratches without any damage and loss of flesh to avoid polluting or wetting the wound 2- In the cases the edges of the wound reach together 3- in the cases you want to press the wounds to discharge infectious and pus or for keeping medicines on the wounds
Suture the wounds	In the cases of round wounds, that the edges of the wound are far from together.
Using medicines	Dryer, deterrent and hot drugs to control swallows and infections.
Surgery	In some deep wound cases, if wet mass (infection and pus) sticks in the inner parts of the skin and flesh; physician should split the wound to discharge them and use cotton to absorb pus
Debridement	In the cases of some unhealed damaged wound tissues
Amputations	In some cases of complicated muscle wound, that causes to convulsion of the patient; the limb should be removed

for patients is the last step [8].

Wound-healing medicine

The types of remedies based on Avicenna's view on wound healing are summarized in table 2. These groups of remedies include meat growing agents; adhesive wound-edge agents; wound-finalizing agents; corrosive agents (*Akkal*) and dressing agents [8].

Meat growing agents

Avicenna believed medicaments that could help to meat growth should have dry quality and coagulate healthy blood to convert it to meat. This can be considered Avicenna's refer to the remedies that can affect the regeneration or repairing of muscle tissue and other related tissues. Also, ulcers should be cleaned and dried before using such drugs, even if it reaches to the bone. Furthermore, choosing the right medicines depends on the wound's temperament (Hot, cold, wet, dry). For example, if the ulcer is wet and infected (filthy), medicines with drying properties should be used. [8].

Table 2. Remedies mentioned by *Avicenna* for wound healing

Therapeutic group in *Canon*	Persian/Arabic Name of medicine	Common name or Scientific name	Family	Part use/ Formula	Indication in *Canon*	Wound healing effect based on Current Findings
Meat growing agents	*Zangar*	Verdigris (copper sulfate)	-	One tenth in olive oil and wax (preparing a salve)	Good slave for wounds	copper (II) alginate hydrogels showed antibacterial and coagulant activities in wound healing process [16]
	Kondor	*Boswellia sacra* Flueck.	Burseraceae	Gum	For wet temper persons with dry wounds/ for elders	This herb was used as an ingredient in Chinese and Persian multi-herbal remedies which possess wound healing effects in *in vitro* and *in vivo* studies [17]
	Baghali	*Vicia faba* L.	Fabaceae	Flour	For wet temper persons with dry wounds/ for elders	Anti-inflammatory effect/ *in vivo* study [18]
	Jo	*Hordeum vulgare* L.	Poaceae	Flour	For wet temper persons with dry wounds/ for elders	A traditional Persian formulation containing visceral Fat and Barely seed ash accelerated wound healing by decreasing inflammation/ *in-vivo* study [19]
	Zaravand	*Aristolochia olivieri* Collengo	Aristolochiaceae	Root	For dry temper persons with wet wounds/ for elders	-
	Jawsheer	*Prangos ferulacea* Lindl.	Apiaceae	Root	For dry temper persons with wet wounds/ for elders	Enhances collagen production and migration rate of cells as well as possess antibacterial activity/ *in-vitro* study [20]
	Zaj	Alum	-	Burned	For dry temper persons with wet wounds	Alum adjuvant in combination with zein can improve wound healing process with reducing scar formation, by increasing the number of T cells and the expression of resistin-like molecule-α/ *in vivo* study [21]
	Zanbagh	*Syringa × persica* L.	Oleaceae	Flower	For the persons having wounds with the same temper (dry or wet)	-
	Loobia Gorgi	*Lupinus albus* L.	Fabaceae	Seed Flour	For the persons having wounds with the same temper (dry or wet)	Anti-microbial, anti-proliferative, and anti-inflammatory effects/ *in vitro* and *in vivo* studies [22]
	Zoft	Tar	-	-	For elders	Current investigations do not support Tar positive effect on wound healing [23]
	Gav Daneh	*Vicia ervilia* (L.) Willd.	Fabaceae	Seed Flour	For elders	Antimicrobial and anti-inflammatory activities [24]
	Soosan	*Lilium candidum* L.	Liliaceae	Root	For elders	Antiviral/ *in vitro* [41]; anti-inflammatory/ *in vitro* [25]

	Mordar Sang	Litharge	-	In combination with oils		Historical use; it uses is stopped because of probable side effects [26]
	Sefid Ab	Venetian Ceruse (white powder)	-	In combination with myrtle oil and wax		-
Adhesive wound edges agents	*Baloot*	*Quercus persica* Jaub. & Spach.	Fagaceae	leaves		Antibacterial and Wound healing activity [27]
	Bid	*Salix babylonica* L.	Salicaceae	Leaves		Anti-inflammatory/ *in vitro* [28]
	Kalam	*Brassica oleracea* L.	Brassicaceae	Leaves		Increases the number of type I collagen fibers and accelerate wound healing/*in vivo* [29]
	Sib	*Malus pumila* Miller	Rosaceae	Leaves and pine bark		Anti-inflammatory/ *in vitro* [30]
	Barhang	*Plantago major* L.	Plantaginaceae	Leaves		An *ex vivo* study showed the wound healing effect of its leaves extract [31]
	Jegan	*Carex hirta* L.	Cyperaceae	Leaves, macerated in vinegar or wine		-
	Senobar	*Populus tremula* L.	Salicaceae	Pine bark		Anti-inflammatory/ *in vitro* and *in vivo* [32]
	Sarve	*Cupressus sempervirens* L.	Cupressaceae	Leaves and thin branches		Anti-inflammatory and proliferative [33]
	Saghez	*Pistacia atlantica* Desf.	Anacardiaceae	Exudates	For the wounds located close the many vessels	An *in vivo* study showed burn wound healing effect by increasing the concentration of bFGF and PDGF and improving the angiogenesis [34]
	Gerdoo	*Juglans regia* L.	Juglandaceae	Walnut; Rubed in water and salt		A Persian multi herbal formulation containing walnut improved wound contraction/*in vivo* [35]
	Kahoo	*Lactuca sativa* L.	Asteraceae	Leaves; cooked in wine		It Enhances Antioxidant, Analgesic, Anti-Inflammatory, and Anticoagulant Activities/ *in vivo* [36]
	Sir	*Allium sativum* L.	Amaryllidaceae	Burned		An in vivo study showed aged garlic extract effect on wound healing [37]; other studies also approved this effect and also antibacterial activity in dressings enhanced by garlic extract [38]
	Hair	-	-	Burned hair in rose oil and wax	For elders	-
	Mast Torsh	Sour yogurt	-	-	Beneficial for great ulcers	-

	Senobar	*Populus tremula* L.	Salicaceae	Pine bark; in combination with rose oil or myrtle oil		Anti-inflammatory/ *in vitro* and *in vivo* [32]
	Samgh Angedan	*Ferula assa-foetida* L.	Apiaceae	Dried latex		Anti-inflammatory and analgesic/ *in vitro* and *in vivo* [39]
	Mes	Copper	-	A thin layer		copper (II) alginate hydrogels showed antibacterial and coagulant activities in wound healing process [16]
	Kondor	*Boswellia sacra* Flueck.	Burseraceae	Powder of exudates		Antibacterial and anti-inflammatory/ *in vitro* [40]
	Mordar Sang	Litharge	-	In Vinegar		Historical use; it uses is stopped because of probable side effects [26]
	Roonas	*Rubia tinctorum* L.	Rubiaceae			Antioxidative activity/ *in vitro* [40]
	Zaravand	*Aristolochia olivieri* Collengo	Aristolochiaceae	Burned root		-
	Zaj	Alum	-	Burned	For wet ulcers	Alum adjuvant in combination with zein can improve wound healing process with reducing scar formation, by increasing the number of T cells and the expression of resistin-like molecule-α/ *in vivo* study [21]
Wound finalizing agents	*Mazoo*	*Quercus* sp.		Oak gall (Exudate)		Containing tannins; astringent; Anti-inflammatory activity/ *in vivo* [41]
	Anjeer	*Ficus carica* L.	Moraceae	Leaves		Anti-inflammatory and antioxidant [42]
	Jawsheer	*Prangos ferulacea* Lindl.	Apiaceae	Pine Bark		Enhances collagen production and migration rate of cells as well as possess antibacterial activity/ *in-vitro* study [20]
	Zangar	Verdigris (copper sulfate)	-		Only in very wet ulcers	copper (II) alginate hydrogels showed antibacterial and coagulant activities in wound healing process [18]
	Sefid Ab	Venetian Ceruse (white powder)	-	In Vinegar		-
	As	*Myrtus communis L.*	Myrtaceae	Used myrtle oil in combination with vinegar, orally		*In vivo* studies showed its healing effect on skin wounds and intra oral ulcers [43]

Adhesive wound-edge agents

Adhesive wound-edge agents were used to paste two edges of wounds and fuse them. These remedies have too dry quality and affect due to the wetness of the edges. They dry the blood on the wound immediately and do not allow it to get infected. It is better to apply these medicaments in combination with oils and in the form of salves because oils and salves can penetrate into the inner layers of the skin [8]. These drugs could be considered as agents that affect on proliferation stage in wound healing process.

Wound-finalizing agents

Wound-finalizing agents are another remedies that

should be used in the last stage of healing wounds. These drugs have most dryness quality in comparison with others and if they are used in suitable amounts and within the prescribed timeframe, scars and calluses would be disappeared and wounds acquire the consistency of skin [8]. It refers to the remodeling stage of wound healing process.

Corrosive agents (Akkal)

Theis group of medicines help to remove rotten waste meat and unwanted materials on the wounds [8]. It is one of the important issues during wound healing process to avoid forming scars or remove them after healing the wounds.

Dressing

There are three strategies for dressing wounds *in the Canon of medicine*: dressing with bandages having two heads for general wounds; using small triangle pillows on large wounds and then dressing with bandage (this is similar to gauzes currently used for dressing); and using suture in the case that the wound gap is filled (by meat) and then dressing with bandage. Also, it is mentioned that the two edges of a wound should be put together completely before dressing with bandage, to avoid bleeding or causing severe pain. Furthermore, it is recommended to apply lint to fill the wound gap in muscles [8].

Discussion

Avicenna's words familiarize us with the knowledge of wound healing in a thousand years ago. Although, he believed to humoral theories of medical practice and used these terminologies to define medical matters, many of his descriptions—like callus and the importance of angiogenesis in wound healing—are close to current definitions. The strategies he mentioned are widely used today, such as the use of gauzes in dressing, control of bleeding and swelling (inflammation), washing and clearing wounds, using suture and surgery in some cases, and feeding patients by tonic foods, among others. Some of these strategies, however, must be considered with caution as they—e.g. the use of bleeding in some cases to avoid swelling, infection, and fever—are not approved by current medical practice. But, these methods can be investigated to evaluate their efficacy in the future.

Also, there are his pharmaceutical suggestions that are approved by current findings. His suggestion to apply the medicaments in combination with oils and in the form of salves to penetrate into the inner layers of the skin is supported by current findings. Skin has a lipophilic outer layer, and therefore oily medicaments can be absorbed easier and faster [44].

Nonetheless, the efficacy of many remedies mentioned by Avicenna like *Boswellia sacra* [17], *Hordeum vulgare* [19], *Prangos ferulacea* [20], *Quercus persica* [27], *Brassica oleracea* [29], *Plantago major* [31], Copper [16], Alum [21], *Myrtus communis* [43] and *Pistacia atlantica* [34] for healing the wounds have been evaluated and approved in *ex vivo*, *in vitro*, and *in vivo* models. It is due to their anti-inflammatory, anti-microbial, proliferative, coagulant and collagen producing effects, as well as by increasing collagen fibers, the concentration of bFGF and PDGF, the number of T cells and the expression of resistin-like molecule-α and improving the angiogenesis [16,17, 19-21, 27,29,31,34, 43].

Current research has demonstrated that healing the wounds can be accelerated with the help of medicaments which possess anti-inflammatory, anti-microbial, and coagulant properties, and can thus enhance collagen production, the migration rate of cells, angiogenesis, and the reduction of scar formation [46]. Some of the medicinal herbs and natural remedies mentioned by Avicenna possess such effects according to the current investigations, e.g., antimicrobial efficacy of Verdigris [16], *Lupinus albus* [22], *Vicia ervilia* [24], *Lilium candidum* [41], and *Boswellia sacra* [40]; the anti-inflammatory effect of *Vicia faba* [18], *Lupinus albus* [22], *Vicia ervilia* [24], *Lilium candidum* [25], *Salix babylonica* [28], *Malus pumila* [30], *Populus tremula* [32], and *Ferula assa-foetida* [39]; proliferative effect of *Lupinus albus* [22]; *Cupressus sempervirens* [33], *Boswellia sacra* [40], and *Ficus carica* [42]; astringent effect of *Quercus* sp. [41]; enhancing collagen production by *Prangos ferulacea* [20]; and anticoagulant activity of *Lactuca sativa* [36] has been confirmed by current investigations; but they have not been evaluated as wound healing agents yet. Therefore, by meeting both traditional and current evidence and support, these remedies could be very good candidates for further investigations to evaluate their wound healing effectiveness.

Some other Avicenna's suggestions do not meet current evidence and need more investigations to find if they can have any wound healing efficacy or not.

Finally, discussion on Avicenna's views on wound healing was published previously [45], but current work focused on to present the probable mechanism of actions, in particular for medicinal herbs mentioned by Avicenna, with more details comparing and supporting with new findings.

Conclusion

This study shows the impact of Avicenna's knowledge on wounds and healing the wounds.

It seems that most of his definitions and strategies were supported by current knowledge and many of natural remedies mentioned by Avicenna to heal wounds have been validated by contemporary researches and some

of them are good options for further investigations to reach new natural products facilitating wound healing process. Therefore, these findings are important both historically and also from the standpoint of finding novel natural sources to develop new medicaments based on ancient knowledge.

Conflict of Interests

The authors declare that there is no conflict of interest.

Acknowledgments

This paper is resulted from a research project supported by deputy of research, AJA University of Medical Sciences.

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