Journal of
Inflammatory Diseases
(Previous Title: The Journal of Qazvin University of Medical Sciences)

Summer 2021, Volume 25, Number 2

Review Paper

Wound Healing by Semelil: A Structured Review With a Focus on Diabetic Foot Ulcers

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Citation Makarem S, Farzam SS, Allami A. Wound Healing by Semelil: A Structured Review With a Focus on Diabetic Foot Ulcers. Journal of Inflammatory Diseases. 2021; 25(2):127-136. http://dx.doi.org/10.32598/JQUMS.25.2.667.9

http://dx.doi.org/10.32598/JQUMS.25.2.667.9

Article info:
Received: 18 Sep 2020
Accepted: 05 Oct 2020
Publish: 01 Jul 2021

Keywords:
Diabetic Foot Ulcer, Treatment, Semelil

ABSTRACT

Diabetic Foot Ulcer (DFU) is a common complication of diabetes mellitus. Among the various non-invasive treatment modalities used for the improvement of DFUs healing, topical herbal therapies are regaining an increasing body of interest. In this report, the authors review the literature and discuss wound healing with a focus on DFUs with Semelil. In this Structured review, we searched for articles published between 2008 and 2021, in the international and national databases with keywords "Melilotus officinalis", "Semelil", "Angipars", and "diabetic foot ulcer", "wound management". Eligible articles (n=26) were identified according to inclusion and exclusion criteria. This review showed no complications with the application of Semelil and consensus on the positive effects of the found medication. In summary, our review showed that Semelil may be a valuable non-invasive treatment for wound healing in DFUs patients and reduces the wound size for four weeks without major adverse side effects.

1. Introduction

Diabetes mellitus (DM) is one of the most common metabolic disorders that is associated with increased morbidity and mortality. The prevalence of DM has gradually increased in the present century [1]. Diabetes-related complications, especially diabetic foot ulcers (DFUs) have negative effects on patient perceptions of quality of life. Foot ulceration is the most common lower extremity complication in patients with DM [2]. The lifetime risk of a foot ulcer for diabetic patients may be as high as 25 percent [3]. The difficulty of healing of DFUs is one of the most common health problems in DM patients [4]. There are several surgical and medical options, which already have been introduced for the treatment of DFUs [5]. Even with the best available care, at least 25 percent of DFUs are not fully healed after six months of treatment, and this frequently leads to amputation of the leg [6].

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Wound healing is a complex process and is delayed in DM patients due to vascular insufficiency and decreased blood flow [7, 8]. In the early stages and in the absence of signs/symptoms of infection, management of DFUs can be conservative (bed rest and adequate pain management with anti-inflammatory drugs). A more aggressive approach (wound debridement and broad-spectrum antibiotic treatment) is needed for advanced stages and in the presence of signs/symptoms of infection [9-11]. Among the various non-invasive treatment modalities used for the improvement of DFUs healing, topical herbal therapies are regaining an increasing body of interest. In this report, the authors reviewed the literature on Melilotus officinalis extract (Semelil) effect on wound healing with a focus on ulcers in DM patients.

Search strategy

In this review, we searched for articles published between January 1, 2008, and July 2, 2021, in the following electronic databases: international databases of PubMed, ScienceDirect, and Web of Science), the national database of SID, and Google Scholar for both English and Persian language articles with the following keywords: "Melilotus officinalis", "Semelil", "Angipars", and "diabetic foot ulcer", "wound management", as the medical subject heading (MeSH). We also reviewed related articles and hand-searched reference lists. Each reference in relevant papers was checked for forward and backward citations of searched citations (to find more articles). Titles and abstracts were screened to identify eligible articles according to agreed inclusion and exclusion criteria. Full papers of potentially eligible studies were retrieved for a more detailed assessment. We selected papers for this structured review if they could fulfill the following criteria. Study designs of the included studies were cellular, in vitro, and *in vivo* (animal and human) experimental studies, randomized controlled trials (RCTs), retrospective and prospective uncontrolled studies, cross-sectional studies, and review studies. Case reports were excluded. The following data were extracted from identified papers: first authors' name, year of the study, study design, sample size, number of groups, and outcome. A summary of the literature search and the process of study selection are shown in Figure 1.

2. Results

Finally, after a backward and forward search of citations and deletion of overlapping studies, 26 studies were found on Semelil effects, including cellular and *in vitro* studies (n=4), and *in vivo* [animal (n=10) and human experimental (n=12)] studies. According to the findings in Table 1, four cellular and *in vitro* studies, ten animal experimental studies, and 12 human studies were found. Only an animal study conducted by Sharif et al. in 2019 did not show a positive effect on wound healing in diabetic rats [12].

The total sample size of 12 clinical studies was 730 and five studies had focused on DFU healing (Table 2). Most of the human studies were on oral and topical administration of Semelil. Table 2 shows the wound characteristics of patients. The patients' age, weight, fasting blood sugar (FBS), and DM duration were reported in five, two, one, and two studies, respectively. Three studies had reported the condition of the wound before and after the intervention. Two studies were without the control group. All the studies (total sample size of 171) showed that the medication had improved wound healing. No relevant cross-sectional study was found.

3. Discussion and Literature Review

M. officinalis, known as yellow melilot and yellow sweet clover as an annual/biennial plant is a member of the Fabaceae family. Eurasia and, more specifically, the Mediterranean region of central Europe to Tibet, is the native range of sweet clover [37]. M. officinalis has been used traditionally for anti-inflammatory and antioedematous activities, its anti-aging effect on the skin, for the treatment of sprains, and as a spasmolytic, phlebotomist, sedative, and diuretic [38, 39]. M. officinalis is used for treating post-surgical tissue swelling in Japan [40], and spleen disease, gutting, diphtheria, and larvae in China [41]. It is also known as a drug against aggregation, as well as for its antioxidative and hepatoprotective properties in the Netherlands, Austria, and Poland [42-44]. In Germany, the use of sweet clover to treat hemorrhoids, vein problem, and blunt injuries have been approved by the German Commission E [45]. It was regarded as a drug against edema and renal vein circulation in the United Kingdom [46], and as a poultice on purulent wounds and ulcers in Russia [47]. The Melilot herb was mentioned in the European Pharmacopoeia [48].

ANGIPARS™, a phytotherapeutic drug formulation (herbal medicine), is produced from the extract of M. officinalis for wound healing applications. M. officinalis is the major ingredient of ANGIPARSTM [49, 50]. This drug has been formulated by Iranian scientists in recent years [26]. Melilotus, coumarin, and flavonoids are the main constituents of Semelil. The most abundant biologically active substances are kaempferol, quercetin glycosides, and triterpene saponins. It also contains

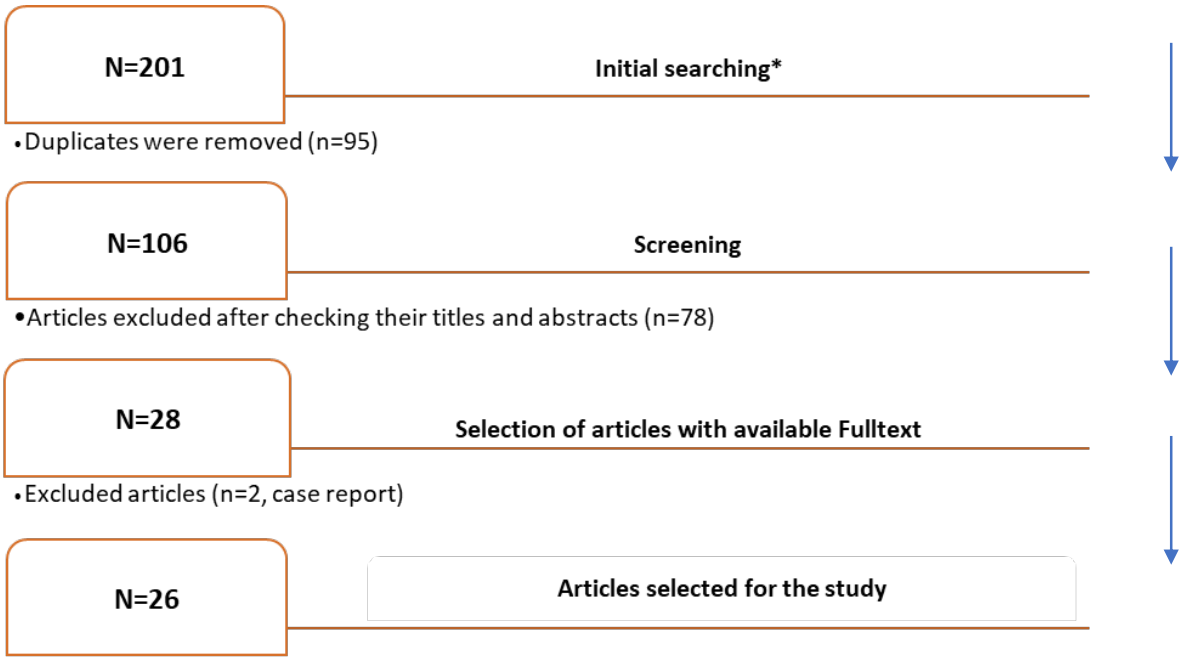

Figure 1. Summary of the literature search and study selection.

selenium, fructose, sodium phosphoglycerol, urea, and 7-hydroxycoumarin.

Semelil is effective in wound healing due to its chemical composition and its content. This herbal extract can improve the process of wound healing by increasing angiogenesis. Angiogenesis improves the tissue blood flow and increases oxygenation, which is the main mechanism of Semelil action in wound healing. [24].

The medical effects of this herbal extract are diverse. Semelil improves the micro-vascularization of tissues and as a result, it improves tissue repairment at the wound site and decreases the rate of recurrence [26, 31, 33]. Semelil has strong antioxidant components, such as flavonoids (kaempferol and quercetin glycosides), oleanene-glucuronide, and 7-hydroxycoumarin [49]. Coumarin, as an active ingredient, is a phenolic substance, which various derivatives of it have anti-inflammatory [51], neuroprotective, and anti-diabetic activities [52]. Also, Semelil increases lymphatic flow and venous return [53]. The clinical tolerability and therapeutic efficacy of M. officinalis were evaluated in patients with chronic venous insufficiency. A significant improvement in the clinical sign and symptoms was obtained after 30 days [54].

Intraperitoneal injection of Semelil in diabetic neuropathic rats significantly improved nerve conduction velocity and sciatic morphological injuries [21]. Also, Semilil was safe with therapeutic efficacy in wound healing in rodents, focal cerebral ischemia in rats and human DFU, and pressure ulcers [55].

The anti-inflammatory effect of M. officinalis extract was observed in cellular, in vitro, and *in vivo* (animal experimental) studies [15, 22]. The effects were evaluated by measuring total leukocyte count, differential leukocyte count, and serum citrulline, a test used for *in vitro* phagocytosis [55]. M. officinalis reduced the activation of circulating phagocytes and lowered citrulline production [38]. Also, the mechanisms, by which M. officinalis extract interferes with inflammation-associated and oxidative stress pathways during sepsis were investigated in induced sepsis in mice. This extract showed marked effects on the pathological manifestation of lung tissue and lung inflammatory response [56].

This extract has been used for the treatment of diabetic foot ulcers. According to the results of pre-clinical and clinical trial studies, Semelil (in oral, topical, and intravenous forms) is effective in decreasing wound size [28, 30]. Systemic application of Semelil has no major adverse effects. Results of an animal study showed no significant difference in hematologic and biochemical laboratory parameters between the Semelil and control groups. Evidence shows that Semelil is well tolerated and has no adverse effects in subacute and chronic toxicity tests [17]. Also, human studies showed that this product is safe and has minimal toxicity [7, 26, 31, 32].

Table 1. List of the studies on Semelil (ANGIPARS) in diabetic foot ulcers treatment (neuropathy, angiogenesis, wound healing, bone formation, and drug toxicity)

First author	Published year	Study design	Sample size	Number of groups	Route of administration	Outcome	Duration of follow up after ending therapy (week)	Efficacy	Ref.
In vitro and Cell Lines									
Navaei-Nigjeh	2015	in vitro	human lymphocytes treated with CP	-	-	viability & oxidative stress markers	3 days	↓ toxic effects	[13]
Asiaei	2016	in vitro	HEPG2 and A549 cell lines	2	-	antioxidant; cytoprotective	-	effective	[14]
Khosroyar	2018	Antioxidant: Regenerative ability of cuprous ions from Cupric ions in the presence of copper Reagent Anti-inflammatory: preventing deformation of protein	12 tubes	2	-	antioxidant and anti-inflammatory activity	-	effective	[15]
Horváth	2021	in vitro	primary sensory neurons and macrophages of rats	3	-	analgesic and anti-inflammatory	-	effective	[16]
Animal Studies									
Abdollahi	2008	experimental	NA	-	I.M. & I.P.	acute, subacute & chronic toxicity	2	no adverse effect	[17]
Farzamfar	2008	experimental	8	2	I.M.	safety & toxicity effects	4	no adverse health or toxic effects	[18]
Fatehi	2013	experimental	48	4	I.P.	oxidative stress	therapeutic properties on tissue injuries (DM)	anti-oxidant and neovascularization effects	[19]
Jafari	2013	experimental	48	6	I.P.	hot plate & tail flick test	8	↓ neuropathic hyperalgesia	[20]
Zangiabadi	2014	experimental	40	5	I.P.	diabetic neuropathy	2	positive effects	[21]
Fatehi	2015	experimental	48	4	I.P.	chemokines and *in vitro* chemotaxis	NA	regulation of angiogenesis & inflammation	[22]
Rasouli-Ghahroudi	2018	experimental	16	2	in bony defects	new bone formation	8	↑ osteogenesis	[23]
Tanideh	2018	experimental	75	5	topical	healing of third-degree Burn in Rat	3	effective	[24]
Amanzadi	2019	experimental	30	5	topical	full-thickness incision wound	2	improved wound healing	[25]
Sharif	2019	experimental	30	5	oral & topical	wounds healing in diabetic rats	2	Ineffective	[12]

First author	Published year	Study design	Sample size	Number of groups	Route of administration	Outcome	Duration of follow up after ending therapy (week)	Efficacy	Ref.
wHuman Studies									
Larijani	2008	multicenter RCT	69	2	I.V.	efficacy & safety	4	effective without adverse effect	[26]
Masoompour	2008	before-after clinical trial	10	1	I.V.	efficacy & safety	8	effective without adverse effect	[7]
Shamimi	2008	RCT	18	2	I.V.	treatment of pressure ulcers	during hospitalization	effective	[27]
Bahrami	2008	RCT	21	3	oral & topical	efficacy & safety	6	effective without adverse effect	[26]
Heshmat	2008	phase I clinical trial	6	1	escalating I.V. doses	MTD & DLT	8	MTD: 10 cc/day	[28]
Hemmatabadi	2008	RCT	61	2	oral	antioxidant	12	deoxyguanosine↓, no significant change in TNFα or CRP levels	[29]
Ebrahimi	2009	before-after clinical trial	75	1	oral & topical	ABI & TBI	24	↑ in ABI and TBI after 6 weeks, no side effects or toxicity	[30]
Bahrami	2010	RCT	40	2	oral	efficacy & safety	12	enhanced wound healing within weeks 2 to 4 of treatment	[31]
Zanboori	2010	RCT	300	2	oral & topical	efficacy & safety	12	effective, no significant side effects	[32]
Bakhshayeshi	2011	RCT	49	2	oral	diabetic peripheral neuropathy	12	limited evidence of efficacy	[33]
Hasani-Ranjbar	2012	RCT	61	2	oral	bone resorption & formation markers	12	no beneficial or harmful effects on bone	[34]
Radmanesh	2012	markov computer simulation model	20	2	oral & topical	cost effectiveness	20	cost-effective	[35]

MTD: Maximum tolerated dose; DLT: dose-limiting toxicity; ABI: ankle-brachial index; TBI: toe brachial index; IM: intramuscular; IP: intraperitoneal injection; IV: intravenous; CP: chlorpyrifos; RCT: randomized controlled clinical trial.

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Table 2. Wound area status before and after intervention on diabetic foot ulcers studies

First author	Published year	Control group	Pre-treatment	Post-treatment	Follow-up (week)	Ref.
Larijani	2008	Yes	E 479.9±379.7 mm^2	E: 198.9±143.7 mm^2	4	[26]
Masoompour	2008	No	123.2±110 mm^2	69.6±60 mm^2	8	[7]
Bahrami	2008	Yes	916.7±228.6 mm^2	137.5±41.7 mm^2	6	[36]
Bahrami	2010	Yes	E: 63.9±2.5 cm^2	4.2±15.2 cm^2	12	[31]
Ebrahimi	2015	No	E: 6.05±11.1 cm^2	E: 1.1±3.5 cm^2	24	[30]

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Semelil can be recommended in diabetic foot ulcer treatment, especially when other treatments have not been effective. Semelil should be used when signs and symptoms of infection and a significant vascular occlusion in the lower extremity have resolved. Also, the wound must be completely debrided and all necrotic tissue removed. Semelil along with other treatments would be more effective [32]. A study showed that it could reduce the wound size, by at least 50% after eight weeks [7]. The suggested oral dose of Semelil (capsule) is 100 mg twice daily and the topical treatment is done with Semelil gel 3% once daily. Each course of treatment is two weeks and the maximum duration of treatment in the studies was 45 days. Systemic administration of Semelil is contraindicated in patients with severe renal failure, concurrent use of anticoagulant medications, and thrombocytopenia [49].

Our study has some limitations. First, at this stage, we cannot make strong recommendations for practice and change guidelines related to the management of diabetic foot ulcers and more research is needed the support our findings. Because the published studies on the ANGIPARS™ effect have been done only in Iran, future studies need to be done in other countries. Also, because studies were very heterogeneous, it was appropriate to summarize the data narratively and not attempt a statistical (meta-analytic) summary. Second, we limited our review to Persian and English language studies. Other limitations were the small sample size and the use of an intermediate or short-term outcome of selected studies, and the likelihood of publication bias.

Conclusion

The results of our structured review confirm the healing properties of the herbal extracts. Our review showed that Semelil may be a valuable non-invasive treatment for wound healing in DFUs patients and reduce the wound size for weeks without any significant adverse effects.

Ethical Considerations

Compliance with ethical guidelines

This study was performed in compliance with the Helsinki Declaration.

Conflict of interest

The authors declared no conflicts of interests.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Acknowledgments

The authors thank the staff of Bu-Ali Sina hospital for their support during the study.

Authors' contributions

Conceptualization, Writing - original draft, and Data analysis: Abbas Allami and Saeideh Makarem; Writing - review, editing, Project administration, and Resources: Abbas Allami; Supervision: Seyed Saeed Farzam.

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