REVIEW

Topical phenytoin for wound healing: a narrative review

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Abstract

Background In 1937, oral phenytoin medication was introduced as an anti-epileptic drug. For many years, researchers have shown interest in how topical phenytoin may be used to promote wound healing in various wounds.

Purpose This review article aims to summarise and critically appraise the clinical evidence available on the effects of topical phenytoin on wound healing.

Methods By using the keywords phenytoin, injuries, wound, wound care, and wound healing, we extracted articles published up to April 2022 through a search in PubMed, ISI Web of Science, SID, Google Scholar and Scopus.

Result We identified 17 studies performed on human subjects and eight on rats. Phenytoin effectiveness is also compared with other wound care substances, including tretinoin, silver sulfadiazine, EUSOL, honey, dexamethasone and hypericin.

Conclusion This review illustrated the significant effects and rare adverse events of topical phenytoin on wound healing.

Keywords wound healing, phenytoin, wounds, review

For referencing Qadirifard MS et al. Topical phenytoin for wound healing: a narrative review. Wound Practice and Research 2024;32(2):66-78.

DOI https://doi.org/10.33235/wpr.32.2.66-78

Submitted 21 April 2023, Accepted 13 December 2023

Introduction

In 1937, oral phenytoin medication was introduced as an anti-epileptic drug[1]. Many clients who had been managed in this way presented with gingival hyperplasia[2–4]. This was discerned in about 20% of patients during chronic treatment with topical phenytoin due to increased manufacture of inflammatory fibroblasts, cytokines, growth factors and genetic susceptibility[5]. The apparent stimulatory effect of phenytoin on connective tissue has propounded the possibility of using it in wound healing[6]. Studies have shown that topical phenytoin promotes the healing of traumatic wounds, venous stasis, diabetic ulcers, decubitus ulcers, burns, leg ulcers, pyoderma gangrenosum ulcers, chronic wounds and leprosy trophic ulcers[7–10]. Different types of

phenytoin are usable orally, by injection, and topically[11–13]. Intravenous phenytoin is often considered the drug of the first choice in benzodiazepine-resistant status in convulsive status epilepticus[14]. An intervention review by Hao et al[15] assessed the effects of topical phenytoin on the rate of healing of pressure ulcers. Their data showed a need for further studies. Nevertheless, the topical form has a significant impact on healing wounds. This study therefore aimed to outline the healing effects of phenytoin on a variety of wounds.

Material and methods

This study aimed to gather and present information on the therapeutic potential of topical phenytoin on wound healing by covering original articles on this subject published up to December 2022. For this purpose, several databases such as Scopus, Google Scholar, Web of Science and PubMed were thoroughly searched. These keywords included phenytoin, injuries, wound, wound care, and wound healing.

A total of 364 studies were found. Of these, 36 articles were excluded since they evaluate gingival hyperplasia, and 72 were duplicates. Out of the 256 remaining articles, 172 were irrelevant. From 84 potentially relevant articles, 52 articles were excluded due to unsuitable study types. Finally, 26 articles were included in the narrative review. Some researchers used phenytoin in their study but did not give details on how phenytoin's effect was measured on wound healing. Most papers failed to describe treatment allocation and randomisation in the trials (see Figure 1 regarding why these articles were excluded).

Studies performed on human and rat subjects (Tables 1 & 2) were included in the review. Knowing the effects of drugs on animals can give us a more comprehensive view of the drug mechanism, and it can be used in humans if it is safe for animals. Animal studies are better for finding the mechanism of the drug, and they improve our understanding of the science. Since animal studies have valuable data, we therefore included them in our study. Studies reported the effects of phenytoin in a variety of wound healing. In the mentioned articles, a description of any adverse events was rarely reported. Phenytoin has been compared with other wound care drugs in order to better evaluate its effect on different types of wounds.

The quality of both animal and human studies was assessed using the checklist from https://jbi.global/critical-appraisal-tools. Two authors assessed the quality of the studies using the mentioned checklist and, in the case of the conflicts, a third author made the final decision.

Results

The mechanism of phenytoin's action

Phenytoin is a drug from the group of hydantoins that is used as an anticonvulsant drug. Because of the chemical effect on sodium and calcium channels in the nerve tissue of the brain, it inhibits them and prevents the generation of action

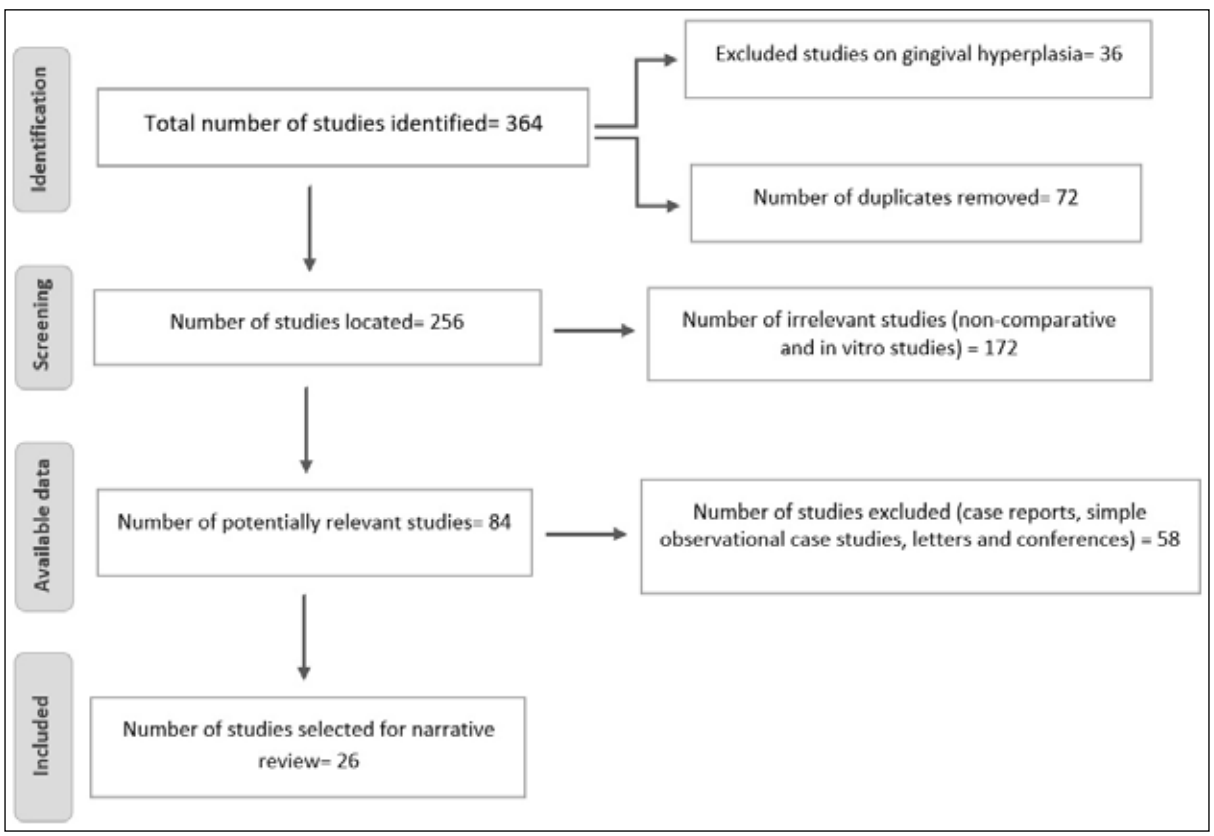

Figure 1. Number of papers located and selected on phenytoin therapy and wound healing

Table 1. Characteristics of studies on human subjects

Type of intervention/ control	Type of patients/ wounds	Mean age range of subjects (years)	No. of subjects, PTH: control	Dose of phenytoin	Root of administration	Period/type of study and design	Results and outcome measures	Dropout number/ adverse events
Layegh et al. (2005)[16]								
PTH vs. topical solution of tretinoin	Patients with chronic ulcers	20–60	30 (15:15)	Phenytoin cream 1%	Topical	6 weeks/clinical trial, prospective controlled	↓ Ulcer size, depth & pain in the PTH group ($p<0.05$)	No AE; no dropouts reported
Carneiro et al. (2002)[17]								
PTH vs. SSD	Patients with burn wounds	68.7% under age 5	64 (32:32)	Unknown	Topical	2 weeks/clinical trial, prospective randomised controlled	↓ Pain ↑ Wound healing in the PTH group ($p<0.01$)	No AE; no dropouts reported
Sepaskhah et al. (2020)[18]								
PTH vs. fluocinolone	Patients with cutaneous lichen planus	Over 8 years old	48 (23:25)	PTH 2% dissolved in 3mg phenytoin capsules & 30g of PTH 1%	Topical	8 weeks/clinical trial, prospective, double-blind, randomised controlled study	↓ Erythema size in PTH and fluocinolone groups ($p<0.05$)	No AE; no dropouts reported
Lodha et al. (1991)[19]								
PTH vs EUSOL	Patients with a large abscess cavity	Unknown	40 (20:20)	300mg of phenytoin-sodium	Topical	4 weeks/clinical trial, prospective controlled	Significantly earlier mean rate of wound reduction in the PTH group ($p<0.05$)	Transient burning sensation following application
Malhotra & Amin (1991)[20]								
PTH vs topical zinc	Patients with leprosy ulcers	60% in both groups, 30–50	72 (50 PTH: 22 zinc)	Unknown	Topical	12 weeks/clinical trial, prospective controlled	↑ Healing ($p<0.0001$) ↑ Granulation tissue formation ↓ Ulcer area	No AE; no dropouts reported
Carneiro et al. (2003)[21]								
PTH vs. EUSOL	Patients with venous leg ulcer	PTH: 32.50±14.87; Control 34.2±14.72	102 (50:52)	Unknown	Topical	4 weeks/clinical trial, prospective controlled blinded assessment	↓ Pain ($p<0.01$) ↓ Ulcer surface ($p<0.05$) ↑ Granulation ($p<0.001$) in the PTH group	No AE; no dropouts reported
Oluwatosin et al. (2000)[22]								
PTH vs. PTH + honey vs. honey	Hospitalised patients with leg ulcers	8–95 (Mean 44.2)	50 (25:25)	200mg of topical phenytoin powder per 1ml of natural honey	Topical	4 weeks/clinical trial, prospective controlled blinded assessment	↑ Granulation tissue ($p<0.05$) & healing in the PTH group (22% PTH group and 0% in the other groups PTH is a better topical agent than honey	No AE; no dropouts reported
Dubhashi & Sindwani (2015)[23]								
Honey vs. PTH vs. saline	Patients with chronic wounds	20–80	150 (50:50:50)	0e5cm: 100mg 5e9cm: 150mg 10e15cm: 200mg >15cm: 300mg	Topical	3 weeks/clinical trial, prospective controlled	↓ Pain & wound area ↑ granulation tissue in PTH & honey (2.5 times earlier) Honey provides quicker pain relief and removes malodour more effectively than PTH	No AE; no dropouts reported

Type of intervention/ control	Type of patients/ wounds	Mean age range of subjects (years)	No. of subjects, PTH: control	Dose of phenytoin	Root of administration	Period/type of study and design	Results and outcome measures	Dropout number/ adverse events
Lavaf et al. (2017)[24]								
PTH vs. honey vs. placebo	Nulliparous women with episiotomy	18–35	120 (40:40:40)	200mg of phenytoin-sodium	Topical	2 weeks/clinical trial, prospective controlled	↓ Wound size in PTH & natural honey groups compared with placebo ($p<0.01$) Honey showed better results than PTH in the process of wound healing	No AE; no dropouts reported
Simpson et al. (1965)[25]								
PTH vs. control	Hospitalised patients with venous leg ulcers	40–77	30 (15:15)	Phenytoin cream 1%	Topical	13 weeks/clinical trial, prospective randomised controlled double-blinded study	Deterioration in the control group ↓ Ulcer area in the PTH group ($p<0.05$)	No AE; no dropouts reported
Tabrizi et al. (2022)[26]								
PTH vs. control	Patient with stage II of medication-related osteonecrosis of the jaw (MRONJ)	59.8±7.11	20 (10:10)	5% topical phenytoin (250mg/5ml) + tetracycline (tetracycline Najo 1%)	Topical	12 month/a comparative study, randomly allocated to control and PTH groups	↑ Wound healing in the PTH group ($p<0.05$)	No AE; no dropouts reported
Zanardini Pereira et al. (2010)[27]								
PTH vs. cream without PTH	Patient with skin wound from excision of melanocytic nevi	16–77	200 (100:100)	20g phenytoin 0.5% + 20g cream	Topical	60 days	↓ Healing time ↑ Intense epithelisation Smaller wound area ($p < 0.05$)	Allergic contact dermatitis; no dropout reported
Hajong et al. (2016)[28]								
PTH mixed with normal saline vs. normal saline	Patients with diabetic foot ulcers (grade I and II)	Unknown	100 (50:50)	Phenytoin 100–200mg	Topical	45 days	↓ Healing time (epithelialisation and 50% wound contracture) ($p<0.05$)	No AE; no dropouts reported

PTH=topical phenytoin therapy; SSD=silver sulphadiazine; TAT=topical antibiotic therapy; AE=adverse events; VS=versus; ↑=increase; ↓=decrease

Table 2. Characteristics of studies on rat subjects are included.

Type of intervention/control	Type of patient/wounds	No. of subjects, PTH: control	Dose of phenytoin	Root of administration	Type of study/period	Results and outcome measures	p value	Dropout number/ adverse events
Shamseddini et al. (2006)[29]								
PTH vs. 1% SSD vs. 0.06% estrogen cream vs. their combination	Male Albino rats with skin wounds	30 rats in 6 groups (5 each)	Phenytoin cream 1%	Topical	4 weeks/clinical trial	Healed size rate in cm^2: PTH: 0.131 SSD: 0.206 PTH+ SSD: 0.154 Oestrogen: 0.208	p<0.05	No AE; no dropouts reported
Taheri et al. (2015)[30]								
PTH vs. laser vs. PTH + laser	Male Albino rats with skin wounds	60 rats in 4 groups (15 each)	Phenytoin cream 1%	Topical	4 weeks/clinical trial	↑ wound surface area reduction and collagen ↓ polymorphonuclear cells in laser + PTH group	p<0.05	No AE; no dropouts reported
Meena et al. (2011)[31]								
PTH vs. Dex vs. PTH + Dex vs. SSD vs control	Either sex of Wistar rats/burn wound	30 rats in 5 groups (6 each)	Preweighed PTH base (2.5g) added to liquid paraffin (12.5ml) in a mortar while triturating	Topical	4 weeks/clinical trial	PTH promotes burn wound healing by decreasing the period of epithelialisation and increasing wound contraction	p<0.05	No AE; no dropouts reported
Sayar et al. (2014) [32]								
PTH vs. HP cream vs saline	Male Wistar rats/ second-degree burn wound	20 rats in 3 groups	PTH 3% & 3g of phenytoin powder combined with 100g of simple ointment base	Topical	4 weeks/clinical trial	↑ collagen content and VEGF level in the PTH group	p<0.05	No AE; no dropouts reported
Ai et al. (2017)[33]								
PNAg	Male Sprague-Dawley rats/dermal wound	30 rats in 3 groups	PNAg 0.25g/kg	Topical	24 days/clinical trial	PNAg accelerates dermal wound healing	p<0.05	
Saddik et al. (2020)[34]								
PTH-loaded CuNP	Adult Sprague-Dawley rats/open excisional wound	12 rats in 3 groups	1mg PTH powder added plain CuNP in HPMC gel (1% w/w)	Topical	1 week/clinical trial	PTH-loaded CuNP accelerates epidermal regeneration	p<0.05	
Mirnezami et al. (2018)[35]								
PTH vs. SSD vs. oestrogen in skin wound	Male Wistar rats/ skin wound	32 rats in 4 groups (8 each)	Phenytoin cream 1%	Topical	2 weeks/clinical trial	↑ wound reduction in the PTH group	p<0.01	No AE; no dropouts reported
Mulaalwar et al. (2016)								
PTH vs. povidone iodine	Male and female Sprague Dawley rats	32 rats in 4 groups (8 each)	PTH cream 1% (1g of PTH powder + 99g of petroleum jelly)	Topical	10 days	↑ wound tensile strength	p<0.001	No AE; no dropouts reported
			PTH cream 2% (2g of PTH powder + 98g of petroleum jelly)			↑ collagen synthesis	p<0.05	

PTH=topical phenytoin therapy; HP=hypericin; HPMC=hydroxypropylmethylcellulose; Dex=Dexamethasone; CuNP=copper nanoparticles; PNAg: Phenytoin silver; SSD=silver sulphadiazine; AE=adverse events; VS=versus; ↑=increase; ↓=decrease

potentials. One of the side effects of phenytoin that was observed after its long-term use was hyperplasia of patients' gums which became the basis for further studies on the effect of phenytoin on wound healing[8,9].

Wound healing has different stages, which include inflammation, re-epithelialisation, formation of granulation tissue, wound contraction and tissue regeneration, respectively, and these stages overlap. The restoration and re-strengthening of the skin and the size of the final scar depend on how these steps are performed. Fibroblasts and keratinocytes play an essential role in healing, but cell matrix, growth factors, cytokines and their receptors are also important[30].

Based on the studies, it is stated that the use of phenytoin reduces pain and inflammation, and increases the speed of wound healing, but the mechanisms involved are not known[8,30].

In general, phenytoin stimulates the connective tissue by increasing the activity of growth factors, mediators and various cytokines, stimulating the proliferation of fibroblasts and myofibroblasts, increasing the formation of granulation tissue, and stimulating the production of extracellular matrix and proteins such as collagen. As a result, more collagen is deposited, and the strength of the wound increases, thereby accelerating wound healing. On the other hand, phenytoin prevents collagen breakdown by reducing tissue collagenase activity[8,30].

The increase in the activity of growth factors is mediated by increasing the gene expression of the platelet-derived growth factor beta chain in macrophages and monocytes. Also, phenytoin reduces oedema and wound secretion. It inhibits glucocorticoid activity and causes neovascularisation. Phenytoin reduces pain by stabilising the membrane. Moreover, with direct and indirect effects on inflammatory cells, it reduces the bacteria in the wound[30].

Phenytoin effects on wound in different ways. It activates gp130-JAK-STAT3 pathway which leads to increased vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs) and collagen level, and also increased NF-κB and transforming growth factor beta (TGF-ß1). On balance, it leads to increased granulation tissue and decreased healing time, inflammation and wound and erythema size (Figures 2 & 3)[33].

Cytochrome p450 isozyme found in epidermal tissue and skin appendages such as sebaceous glands and hair follicles can break down phenytoin. Absorption of topical phenytoin is related to wound fluid and its pH, and its effect on wound healing is related to its dose[8].

Tretinoin versus phenytoin

Topical tretinoin has been found to stimulate epithelial cells and improve healing markedly. It also has been used in the improvement of photoaged skin disease for a long time, and using it on wounds has shown significant efficiency[36]. Studies have shown that tretinoin treatment increases

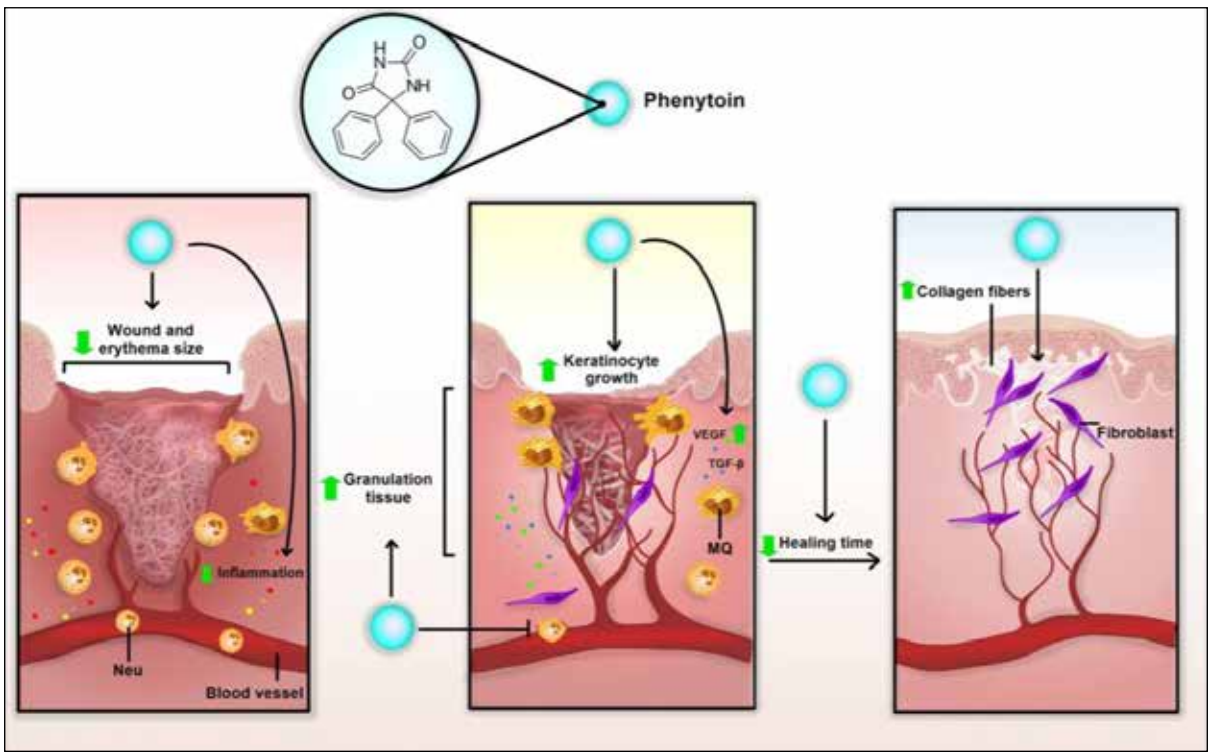

Figure 2. Potential mechanism of topical phenytoin in wound healing. Topical phenytoin can reduce inflammation, wound and erythema size, and healing time. Phenytoin can also induce granulation tissue, keratinocyte growth and collagen fibre, accelerating wound healing procedure

granulation tissue, new collagen formation, and new vascular tissue in 1–4 weeks[37]. Layegh et al[16] compared phenytoin and tretinoin effects on the ulcers of human subjects. Out of a total of 15 patients, 18 ulcers were treated with 1% topical phenytoin and 19 ulcers were treated with 0.05% tretinoin. The phenytoin group represented a decrease in ulcer surface area. Before using phenytoin, 44.4% of ulcers were without pain; however, after introducing phenytoin, 100% of ulcers had no pain. After 6 weeks of treatment with phenytoin, the ulcer size, depth and pain reduction were significant ($p<0.05$) (Table 1).

Silver sulfadiazine versus phenytoin

Silver sulfadiazine is a topical anti-bacterial substance that incorporates the anti-bacterial effects of both sulfadiazine and silver[39]. It helps wound healing, especially burns, through its steady reactions with serum and other body fluids[40]. Carneiro et al[17] compared phenytoin powder and silver sulfadiazine effects on burn wounds in the human body. After the treatment, 78% of patients in the phenytoin group, compared to 47% in the silver sulfadiazine group, had no pain in the wound area. The differences were statically significant ($p<0.01$). In the trial, 20% of patients in the silver sulfadiazine group ($p<0.05$) did not heal well and changed their treatment to phenytoin; within 48 hours of hospitalisation the wounds healed (Table 1).

Mirnezami et al[35] compared phenytoin cream and silver sulfadiazine on rats with single circular (4mm in diameter) full-thickness skin wounds. The healing duration was 10 days in the phenytoin group and 7.62 days in the silver sulfadiazine group. Wound healing in the phenytoin group was significantly earlier compared to other groups ($p<0.01$) (Table 2). According to Shamseddini et al[29], using phenytoin cream 1% in combination with silver sulfadiazine cream 1% on rat wounds (2cm in diameter) can significantly reduce wound size ($p<0.05$) (Table 2).

EUSOL versus phenytoin

One of the common dressing materials that have been used for decades is EUSOL (Edinburgh University solution of lime), which has the property of generating tissue granulation[41]. Carneiro & Nyawawa[21] compared phenytoin and EUSOL effects on non-malignant chronic leg ulcers. The formation of healthy granulation tissue and clearance of ulcers were significant (0.05%); the mean surface area (cm^2) in the EUSOL group (58.7±18.06) and the phenytoin group (66.5±22.01) significantly decreased after 28 days of treatment ($p<0.05$) (Table 1). A high methodological quality double-blinded trial also on leg ulcers conducted by Simpson et al[25] (Table 1) shows notable ulcer area healing in the phenytoin group. Lodha et al[19] studied the comparison of topical phenytoin and EUSOL effects in the healing of large abscess cavities. On day 30, the percentage of reduction of the wound in the phenytoin group was 99.7% and, by using phenytoin, the mean rate of reduction was 2.02cm^2/day, which was significantly earlier compared to EUSOL with 1.58cm^2/day ($p<0.05$) (Table 1).

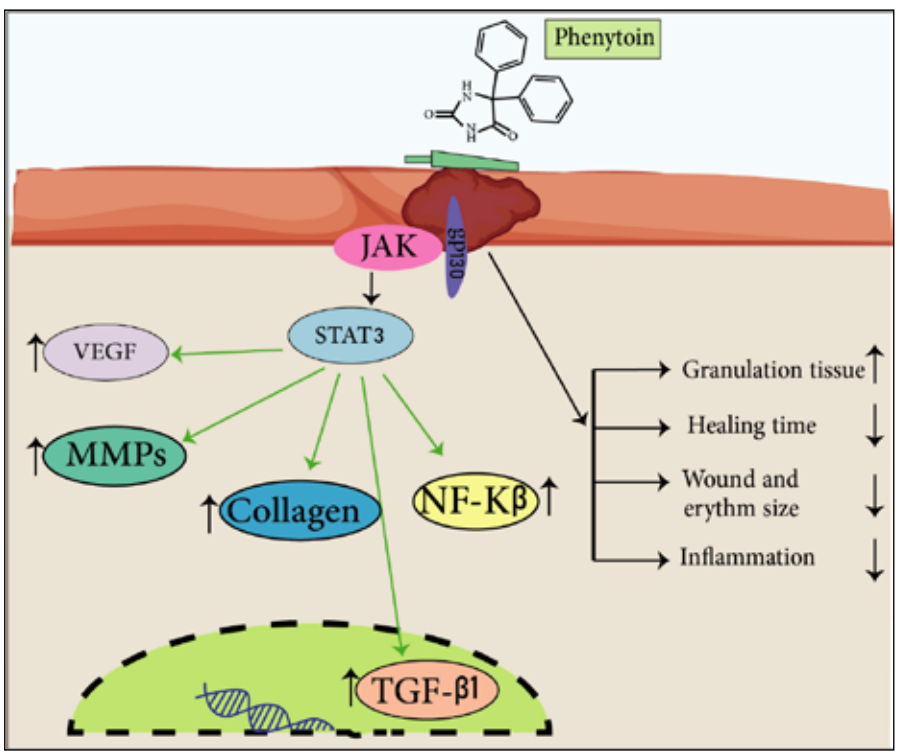

Figure 3. Phenytoin effects wounds in different ways. It activates a gp130-JAK-STAT3 pathway which leads to increase VEGF, MMPs, collagen level and also increases NF-κB and TGF-ß1. On balance, it leads to an increase in granulation tissue and a decrease in healing time, inflammation and wound and erythema size.

Honey versus phenytoin

Natural honey has been used to treat a variety of wounds throughout the ages. It is hygroscopic, and it also can draw moisture out of the environment. This dehydrates bacteria, and its sugar content is also high enough to hinder the growth of microbes. Therefore, it inhibits the growth of different bacterial species that cause wound infections[42–47]. A study conducted by Lavaf et al[24] showed a comparison between using natural honey and phenytoin on the 7th and 14th days of the postpartum period in nulliparous women with episiotomy wounds; 30% of wound reduction in the phenytoin group and 29% in the honey group compared to 8% in the placebo group was observed after 14 days, which was significant (p=0.011). The study's results represented that although both topical phenytoin 1% and natural honey were effective in episiotomy wound reduction, honey showed better results in the process of wound healing. However, neither of them could reduce the pain (Table 1).

Dubhashi and Sindwani[23] studied phenytoin, natural honey and saline effects on chronic wounds. The study revealed that the percentage reduction of wounds using phenytoin 1% is approximately 15.8% which is close to the honey effects (with a 20.6% reduction). However, honey provides quicker pain relief and removes malodour more effectively. Moreover, phenytoin, in comparison to saline effects (with 8.07 reduction), is significantly more practical (p<0.0001) (Table 1). Oluwatosin et al[22] compared phenytoin, natural honey, and their mixture effects on chronic leg ulcers of different sizes (166–262mm^2) in 4 weeks of treatment duration. In the 4th week, a significant difference was observed (p=0.04). The mixture of honey and phenytoin reduced 85.7mm^2 of the ulcer area compared to phenytoin (19.4mm^2) and honey (45.1mm^2) reduction. Thus, they suggested that phenytoin may be a more effective topical agent than honey in treating chronic ulcers (Table 1).

Dexamethasone versus phenytoin

Dexamethasone is a robust anti-inflammatory glucocorticoid used in skin allografts and organ transplantation[48]. The dexamethasone treatments strongly interfere with the synthesis of collagen[49]. Meena et al[31] compared using phenytoin, dexamethasone and a combination of them on burn wounds in different groups of rats. The phenytoin group had the highest collagen production. The mean period of epithelisation and wound contraction was approximately 20% better in comparison with other groups (p<0.05) (Table 2).

Hypericin versus phenytoin

Hypericin (HP) is a phytochemical with significant anti-inflammatory activity[50]. However, its lipophilicity limits its therapeutic applications. The topical form of HP can promote re-epithelialisation in burn wounds and shorten the healing time for superficial burn wounds[51]. VEGF is a platelet-derived growth factor. Its essential role is to stimulate angiogenesis and endothelial cell migration in wound healing[52]. Sayar et al[32] compared HP with phenytoin effects on burn wounds in rats. Using phenytoin in the treatment significantly promoted VEGF production in the wound regions greater than HP and the control group (p<0.05) (Table 2).

Zinc versus phenytoin

Zinc is an essential element in the human body, and its deficiency can lead to delayed wound healing[53,54]. According to the study by Malhotra and Amin[20], which compared zinc and phenytoin on leprosy ulcers, phenytoin reduced ulcer area and increased granulation tissue formation compared to zinc (p<0.0001) and also demonstrated better results than zinc oxide cream in the healing process of chronic trophic leprosy ulcers.

Phenytoin conjugated with silver and copper nanoparticles

Silver nanoparticles have been used for wound healing due to their antimicrobial and anti-inflammatory effects. In a study by Nasr et al, silver interacts with the bacterial cell wall and blocks its respiratory pathway. Silver's anti-inflammatory function decreases the level of some inflammatory mediators such as IL-6 mRNA[55]. In another study, the effects of silver nanoparticles on wound healing in a rabbit model were examined. By evaluating the wound healing process, such as no signs of sepsis in wound closure, longer newly formed epithelium, and thicker granulation, it was concluded that silver nanoparticles could be used in wound healing instead of systemic antibiotics[56]. By changing fibroblasts into myofibroblasts and improving keratinocyte migration and proliferation, silver nanoparticles accelerate the healing process of diabetic wounds and make them tighter. Silver nanoparticles also avoid severe cellular damage by reducing reactive oxygen species (ROS) through the modulation of cytokine production[58].

Ai et al[33] studied the pharmacological action of phenytoin silver. They postulated that regulating the expression levels of collagen I, NF-κB, TGF-ß, MMP-2 and MMP-9 asynchronously promote fibroblast cells (NIH-3T3) and epidermal cells (HaCat) proliferation by regulating Jak/Stat3 pathway; hence phenytoin silver can be used as an effective compound for wound healing. Silver nano compounds promote wound healing by organising fibroblast cells, collagen fibres and blood vessels[33]. Another beneficial trait of silver nanoparticles being used in wound healing is their low toxicity and low concentration in blood, which was indicated in many studies. However, Nasr et al have made a contrary declaration about silver nanoparticle toxicity. They noted that decreasing mitochondrial function can have toxic effects on human fibroblasts and keratinocytes, which are concentration-dependent[55].

Another nano compound used for wound healing is copper nanoparticles. Due to copper nanoparticles' trait, an antimicrobial, anti-inflammatory and angiogenesis-enhancing function, it seems to be a good choice for wound healing. By co-factoring enzymes involved in antioxidant

processes such as superoxide dismutase and cytochrome oxidase, copper nanoparticles showed antioxidant function. It also has immune boosting activity by stimulating the production of IL-2 and, through induction of VEGF, enhances angiogenesis[55]. Copper metabolism in phenytoin therapy was tested by Palm and Hallmans[58]. They found that the level of serum copper was increased by phenytoin therapy, so they claimed that phenytoin might affect the absorption and accumulation of copper, which causes a high level of copper in the blood[58]. Phenytoin-loaded copper increases the expression of dermal procollagen type 1 and decreases the expression of the inflammatory Jak3, which causes accelerated epidermal regeneration and stimulates tissue formation[34].

Laser versus phenytoin

In a study on the treatment of excisional wounds made on the body of rats, Taheri et al[30] compared using a low-level diode laser, topical phenytoin, and a combination of them (Table 1). The results indicated no significant difference between laser and phenytoin effects in composing vessels and dense infiltration of lymphocytes. However, more collagen and faster reduction in polymorphonuclear cells in phenytoin and simultaneous laser use were observed, which was statistically significant ($p<0.05$).

Cream versus phenytoin

A study was conducted by Pereira et al; its purpose was to investigate the effect of phenytoin 0.5 versus cream and the possibility of its better therapeutic and cosmetic results in wound healing caused by the removal of the melanocytic mole. In the obtained results, faster recovery and more intense epithelialisation were observed in the treatment with phenytoin, and the final scar was often smaller, round and flat[27].

Povidone iodine versus phenytoin

In the results of Malkalwar et al's animal study comparing the effect of phenytoin and povidone-iodine, it was found that the measured tensile strength of the wound in patients treated with phenytoin is comparatively higher than the group treated with povidone-iodine. Moreover, as a result, topical phenytoin accelerates the wound healing process in the incision wound model[59].

Phenytoin effect on diabetic foot ulcers

A study by Hajong et al[28] was conducted with the aim to investigate the effect of topical phenytoin on the healing of grade I and II diabetic foot ulcers. In this study, it was found that the average wound epithelialisation time and, as a result, the wound healing time, is less when taking phenytoin. This action takes place with the following mechanisms – increased proliferation of fibroblasts, increased granulation, increased collagen deposition, decreased collagenase activity, neo-angiogenesis, and decreased bacterial contamination of the wound[28].

Phenytoin effect on decubitus wound

A study on the efficacy of topical phenytoin on decubitus wound healing in the sacral region of a motionless patient with a stroke was conducted by Pitiakoudis et al[60]. It was found that phenytoin increases wound healing by stimulating lymphocyte chemotaxis and increasing the regulation of angiogenesis. Their study showed that phenytoin benefits as decubitus wound healing and helps the healing process on several levels[60].

Hypothesis about phenytoin in wound healing

In a hypothesis, Namazi states the possible effect of phenytoin on wound healing[61]. According to this hypothesis, due to the inhibitory effect of phenytoin on norepinephrine release, cell mediated immunity and monoamine oxidase activity, as well as its potential capability to fixate the melanosome membrane and motivate melanocytes, phenytoin may be effective against vitiligo. Due to the facilitation of collagen deposition and the inhibition of collagenase activity by phenytoin, its simultaneous topical use with steroids may prevent steroid-induced skin atrophy and, at the same time, enhance the anti-vitiligo effect of these agents[61].

Finally, Table 3, summarises the different topical forms of phenytoin used versus the comparison product.

Discussion

This review sought current evidence on phenytoin and its effectiveness in wound healing. The results showed that the availability of methodological study designs made it nearly possible to analyse the data or extract conclusions about the effectiveness of topical phenytoin in the healing of wounds.

Studies have demonstrated that phenytoin is a non-sedative anticonvulsant with local pain relief and anti-inflammatory function due to its membrane-stabilising action[62]. It can depress repetitive neuronal activities and synaptic transmission selectively[21]. Kumar et al[63] reported that phenytoin elevates the expression of platelet-derived growth factor-ß in macrophages and monocytes, which leads to increased neovascularisation. In many studies, it has been concluded that phenytoin increases epidermal growth factor (EGF), a VEGF that elevates the number of blood vessels, and TGF-ß1, which stimulates the deposition of collagen and fibrosis development and causes re-epithelialisation. Increasing the number of follicles and shortening the telogen phase can help improve hair growth in alopecia. By suppressing voltage-gated sodium channels, phenytoin can control seizures[12].

A large number of studies noted that phenytoin fortifies the arrangement of granulation tissue, fibroblast multiplication (which clarifies the change in granulation tissue arrangement), tolerance of tissue versatility, restraint of glucocorticoid generation, new collagen arrangement, increment in blood vessels, reduction of collagenase movement, and diminishing tissue oedema[38,64]. Phenytoin also is known to have an anti-bacterial effect, especially against *Staphylococcus*

Table 3. Comparison of phenytoin usage and outcomes with control substances

Author	Intervention	Control	Dose of phenytoin	Root of administration	Results and outcome measures
Layegh et al (2005)[16]	PTH	Topical solution of tretinoin	Phenytoin cream 1%	Topical	↓ Ulcer size, depth & pain in the PTH group (p<0.05)
Carneiro et al (2002)[17]	PTH	SSD	Unknown	Topical	↓ Pain ↑ Wound healing in the PTH group (p<0.01)
Sepaskhah et al (2020)[18]	PTH	Fluocinolone	PTH 2% dissolved in 3mg phenytoin capsules & 30g of PTH 1%	Topical	↓ Erythema size in PTH and fluocinolone groups (p<0.05)
Lodha et al (1991)[19]	PTH	EUSOL	300mg of phenytoin-sodium	Topical	Significantly earlier mean rate of wound reduction in the PTH group (p<0.05)
Malhotra & Amin (1991)[20]	PTH	Topical zinc	Unknown	Topical	↑ Healing (p<0.0001) ↑ Granulation tissue formation ↓ Ulcer area
Carneiro & Nyawawa (2003)[21]	PTH	EUSOL	Unknown	Topical	↓ Pain (p<0.01) ↓ Ulcer surface (p<0.05) ↑ Granulation (p<0.001) in the PTH group
Oluwatosin et al (2000)[22]	PTH, PTH + honey	Honey	200mg of topical phenytoin powder per 1ml of natural honey	Topical	↑ Granulation tissue (p<0.05) & healing in the PTH group (22% PTH group and 0% in the other groups PTH is a better topical agent than honey
Dubhashi & Sindwani (2015)[23]	PTH	Saline Honey	0e5cm: 100mg; 5e9cm: 150mg; 10e15cm: 200mg; >15cm: 300mg	Topical	↓ Pain & wound area ↑ granulation tissue in PTH & honey (2.5 times earlier) Honey provides quicker pain relief and removes malodour more effectively than PTH
Lavaf et al (2017)[24]	PTH	Honey vs. placebo	200mg of phenytoin-sodium	Topical	↓ Wound size in PTH & natural honey groups compared with placebo(p<0.01 Honey showed better results than PTH in wound healing
Simpson et al (1965)[25]	PTH	Control	Phenytoin cream 1%	Topical	Deterioration in the control group ↓ Ulcer area in the PTH group (p<0.05)
Tabrizi et al (2022)[25]	PTH	Control	5% topical phenytoin (250mg/5ml) + tetracycline (tetracycline Najo 1	Topical	↑ Wound healing in the PTH group (p<0.05)
Zanardini Pereira et al (2010)[27]	PTH	Cream without PTH	20g phenytoin 0.5% + 20g cream	Topical	↓ Healing time ↑ Intense epithelisation Smaller wound area (p < 0.05)
Hajong et al (2016)[33]	PTH mixed with normal saline	Normal saline	Phenytoin 100–200mg	Topical	↓ Healing time (epithelialisation and 50% wound contracture) (p<0.05)

PTH=topical phenytoin therapy; SSD=silver sulphadiazine; ↑=increase; ↓=decrease

aureus, Escherichia coli, Klebsiella and Pseudomonas species[32,63]. The anti-bacterial action of phenytoin depends on local changes in pH and the improvement of the local circulation[19,21]. Wounds treated with phenytoin had more negative cultures than the other substances used for wound healing[63]. Phenytoin also reduces pain caused by superficial burns and chronic leg ulcers. It also can reduce neuropathic pain and heal leprosy ulcers through faster ulcer volume reduction.

Phenytoin can treat abscess cavities by reducing oedema and inflammation and earlier separation of the slough. It also can inhibit swelling through decreasing oedema, and burn wounds through increasing VEGF and TGF-ß expression. It can heal nasal wounds through increasing EGF and proliferating cell nuclear antigen (PCNA) and CD31[11,19,31,64,65]. EGF is a mitogenic dose-dependent agent that affects increased epithelial cell proliferation and reduced healing time. CD31 is involved in increased angiogenesis[65].

The results of this study showed that debridement, along with local administration of phenytoin and tetracycline, improved the healing process and the recurrence rate after treatment in medication-related osteonecrosis of the jaw (MRONJ) patients[26]. Considering that the wounds of diabetics have a prolonged inflammatory phase, phenytoin is beneficial for people with diabetes due to its anti-inflammatory action. It is also suggested that phenytoin caused increased granulation tissue, decreased wound exudate, and lowered bacterial load within the diabetic wound bed[8,63]. Moreover, phenytoin has been influential in treating leprosy wounds, including a reduction in ulcer area and an increase in healing rate[8,10].

Pressure ulcers are localised injuries in the underlying tissue, skin or both. It is usually the result of pressure on a bony prominence or accompanied by a shear. Pressure ulcers are a costly, painful and widespread healthcare problem. Some studies show that they are unsure whether topical phenytoin can improve ulcer healing in people with grade I and II pressure ulcers. Phenytoin has been shown to reduce the use of analgesics due to the alleviation of pain and decreases hospitalisation period and hospital admission costs[17,21].

Despite phenytoin's benefit, it has some side effects like gingival hyperplasia and hypertrophic granulation tissue, which can be avoided by stopping the treatment, hypertrichosis in long-term phenytoin therapy, and inhibition of potassium channels and initial burning sensation that can be omitted by using sodium-free phenytoin[12,21,63,66].

While most studies and research suggest enhanced and accelerated wound healing using topical phenytoin, there are a few contrary reports. One study showed no significant differences in wound contraction between the control and phenytoin groups[68]. Another study declared that phenytoin did not improve wound healing, and there was slower epithelialisation and even fewer fibroblasts in the phenytoin-treated group. Taheri et al[30] recommend that a combination of phenytoin and laser would have better results and make more collagen fibres. Given phenytoin's pain-relieving and anti-bacterial properties in moving forward wound mending, as well as its accessibility, low cost, ease of utilising and precise security properties, it can be utilised as a treatment methodology for diverse sorts of wounds[63].

Conclusion

The present review summarised and critically appraised the clinical evidence available on the effects of topical phenytoin on wound healing. Through assessment of the comparative trials in this area, an estimation of the improvement level between the phenytoin-treated groups compared with controls was mentioned. Based on the positive growing evidence, phenytoin had a better effect on wound healing than tretinoin, silver sulfadiazine, EUSOL, dexamethasone, HP, saline, zinc, common dressings and cold cream. However, further studies are needed to compare the effects of phenytoin versus honey, fluocinonide and laser on wound healing.

Acknowledgements

We appreciate all included papers' authors.

Conflict of interest

The authors declare no conflicts of interest.

Ethics statement

An ethics statement is not applicable.

Funding

The authors received no funding for this study.

Author contribution

Study concept and design: ND; acquisition of data: MSQ, MQ, GT, FA, SZM, SKR; drafting of the manuscript: MSQ, MQ, GT, FA, SZM, SKR, YS, RT, FS, NP, MP, KG, MD, HM, MF; critical revision of the manuscript for important intellectual content: ND, MF; study supervision: ND. All authors read and approved the final manuscript.

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