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RESEARCH ARTICLE

Phonopheresis Versus Topical Salvadora Persica in Healing of Full-Thickness Wound: An experimental Study

Hesham Galal Mahran[1], Mohamed A.S. Aborehab[2,3]

1. Department of Physical Therapy for Surgery, Faculty of Physical Therapy, Cairo University, Egypt.
2. Department of Pharmaceutics, Faculty of Pharmacy, Umm Al-Qura University, KSA.
3. Department of Pharmaceutics, Faculty of Pharmacy, Minia University, Egypt.

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Corresponding Author

Dr. Hesham Galal Mahran

Abstract

Objective: To compare and investigate the effect of phonopheresis and topical salvadora persica on wound healing in rats. **Design:** Randomized, controlled trial. **Settings:** University animal laboratory. **Animals:** 45 adult albino male rats allocated to A, B and C groups. **Interventions**: After anesthesia, a wound area of 5cm^2 was made on the upper dorsum of all rats. Group A was treated with phonopheresis, with frequency of 1MHz, intensity of 0.5W/cm^2 and duty cycle of 40%, group B received sham phonopheresis while group C received sham ultrasonic, and treatment duration for all was six minutes/session/8 sessions. Wounds were captured by digital camera and were measured using trace method. **Outcome measures:** healing represents decreased in wound surface area. **Results:** there was a significant sequential reduction in wound surface area throughout 1st, 3rd, 5th and 8th sessions in all three groups. There was significant difference between; mean of W.S.A in group (A) and mean of W.S.A in group (B) at3rd ,5th and 8th sessions as *p* value (.09), (0.029) and (0.004) respectively, also there was significant difference between; mean of W.S.A in group (A) and mean of W.S.A in group (C) at **3rd,** 5th and 8th sessions as *p* value (0.003),(0.00001) and (0.00001) respectively, while there was significant difference between; mean of W.S.A in group(B) and mean of W.S.A in group (C) at **3rd,** 5th and 8th sessions as p value (0.024), (0.00001) and (0.021) respectively. **Conclusion:** phonophersis and topical salvadora persica gel have satisfied effect on wound healing. In addition, better healing provided by phonopheresis

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INTRODUCTION

Wound is a breach formed in the normal continuum of the cellular and molecular structure of the body, thereby creating a disruption in the cellular, anatomic and as well as in their functional continuity. Wound healing or wound repair is an intricate process in which the skin or organ or tissue repairs itself after injury (Nilani et al., 2011).Wound can be healed by as spontaneous process in the organism through a cascade of events, which starts by switching on various chemical signals in the body. Healing of full thickness wound which extends through the entire dermis involves more complex well-regulated biological events. The healing process begins with the clotting of blood and is completed with remodeling of the cellular layers of the skin. The whole process can broadly be classified into 5 overlapping phases, namely, inflammation, granular tissue formation, re-epithelialization, matrix production and remodeling (Janis et al., 1996)

Open wounds have been treated with medicines and a range of natural and synthetic materials in an attempt to speed healing. Despite considerable laboratory and clinical study no single therapy has proved beneficial for all types of wounds and problems related to wound healing are still the cause of significant morbidity and mortality (Low and Reed, 1993).Some researchers found that some physical methods as constructive, adjunctive niches in facilitating and accelerating wound healing, and also improving scar quality, they include; therapeutic ultrasound, laser treatments, hydrotherapy, negative pressure therapy, hyperbaric oxygen and electro stimulation(A ghamsari et al., 1996)

Therapeutic ultrasound has a frequency of 0.75–3.00 MHz, and most machines used to deliver it are set at a frequency of either 1 or 3 MHz. The absorption coefficient of ultrasound in soft tissue increases linearly with frequency, so using higher frequencies (say 3 rather than 1 MHz) reduces the penetration depth by about one-third and vice versa. In the continuous mode, it is characterized by the production of biophysical and thermal effects, whereas in the pulsed mode it reduces the thermal effect due to the cyclical interruption of energy emission, while maintaining the biological effect. It has been suggested that the non-thermal effects of ultrasound, including cavitation and acoustic micromassage, are more important for the treatment of soft tissue lesions than the thermal effects (Watson, 1996)

Ultrasound may be used to increase the penetration of pharmacologically active drugs through the skin. This technique is known as sono- or phonophoresis (Mitragotri, 2005)**.**Phonophoresis facilitates the transdermal absorption of a drug by thermal effects such as an increase in tissue temperature and by mechanical effects such as cavitation and acoustic streaming (Amit and Jaideep, 2002). Sonophoresis occurs because ultrasound waves stimulate micro-vibrations within the skin epidermis and increase the overall kinetic energy of molecules making up topical agents. The drugs are absorbed through the transcellular, intercellular and appendageal pathways (Mitragotri, 1996)**.**When utilizing ultrasound for TDD, increased blood flow in target tissues can decrease the ability of the desired medication to reach target tissues. As the medication passes the stratum corneum of the skin, increased blood flow can cause the drug to be taken into the blood stream more rapidly before reaching target tissues (Bronaugh and Maibach, 1991)**.**So in our study we decided to select pulsed ultrasound (non-thermal) with power density (0.5W/cm2) and 1 Mhz in order to compare and invetigate the effect of phonopheresis and topical salvadora persica on treatment of full thickness wound in rats. As there were no or limited research studies investigated the effect miswak or salvadora persica in healing of wound so our study may be considered new trend in direction of evaluating effect of miswak aqueous extract topical and transdermal delivery through ultrasonic therapy on healing of wound.

Salvadora persica, L., the toothbrush tree, locally called miswak, is a member of the Salvadoraceae family has been used by different Islamic communities as tooth brushes which has been scientifically proven to be very useful in the prevention of tooth decay, even when used without any other tooth cleaning methods(Salehi et al., 2006)**.**Studies reported that extracts of miswak possess several biological activities, including antibacterial (Firas and Khudir, 2008)**.**(Al Lafi and Ababneh, 1995)**.**Antifungal(Al Bagieh et al.,1994).And anti-plasmodial effects(Ali et al.,2002)**.**Leaves of Salvadora persica have carminative, antiseptic and anti-fungal action (Sarvesh et al., 2007)**.**Extract of S. persica shows hypolipidemic activity in rats (Galati and Monforte,1999)**.**Chemical analysis of S. persica miswak has demonstrated the presence of b-sitosterol and m-anisic acid; chlorides, salvadourea, and gypsum; organic compounds, such as pyrrolidine, pyrrole, and piperidine derivatives; glycosides, such as salvadoside and salvadoraside; and flavonoids, including kaempferol, quercetin, rutin, and a quercetin glucoside (Farooqi and Srivastava, 1968)**.**Benzyl isothiocyanate (BITC) was isolated from S. persica roots. BITC is a chemopreventive agent that is thought to prevent cariogenic and other genotoxic compounds from reaching or reacting with target sites on the treated tissue (Al Dosari et al., 1992)**.**BITC was found to have virucidal activity against Herpes simplex virus 1(Al Bagieh, 1992)**.**BITC might prevent carcinogenic and other genotoxic elements to access and/or react with targeted sites (Hecht, 1992)**.**

In addition to Salvadorine, an alkaloid present in S. persica miswak, may exert a bactericidal effect and stimulate the gingival (Farooqi and Srivastava, 1968)**.**Salvadora persica also possess the flavonoids and flavonoids glycosides (Manu et al., 2013)**.**Salvadora persica is a unique plant with anti-inflammatory, analgesic, antibacterial, antifungal, anti-ulcer, anti-seizure, antioxidant, anti-platelet, diuretic & lipid lowering activities hidden within a single plant(Hoor et al.,2014)**.**

Antibacterial activities of salvadora persica

The aqueous extract of S. persica miswak was demonstrated to have an in vitro inhibitory effect on the growth of Candida albicans which may be attributed to the high sulfate content of the sticks (Farooqi and Srivastava, 1968)**.**In another in vitro study, the derivatives of S. persica miswak demonstrated strong antimicrobial effects on the growth of Streptococcus sp. and Staphylococcus aureus (Al Lafi and Ababneh, 1995)**.**Benzyl isothiocyanate (BITC) is the

main antibacterial component of S. persica root chewing sticks has high killing activity against the Gram-negative periodontal pathogens A. actinomycetemcomitans and P. gingivalis (Abier et al., 2011). In a recent study, the strongest antibacterial activity was shown by the aqueous extract against E. faecalis(Sarmad, 2013)**,**(Al Bayati and Sulaiman,2008)**.**Recent study showed that ethanolic extract of S. persica has good antifungal activity compared to clotrimazole(Al Bagieh,1992)**.**

Other activities of salvadora persica

The ethyl acetate extract of S. persica shows potent anti-inflammatory activity to be nearly the same of indomethacin activity, and these results may be due to the presence of flavonoids in ethyl acetate extract. S. persica revealed potent antioxidant capacity which may be due to the furan derivatives and also may be attributed to the presence of antioxidant enzymes(Saleh and Jalaluddin, 2013)**.**It has been reported that benzyl isothiocyanate isolated from SalvadoraPersica affected HSV–1 replication (Mahmoud,2008)**.**

MATERIALS AND METHODS

A)-Animals

Forty five adult male albino rats approximately 4 months of age at study initiation, and weighed 200-250 gm. obtained from animal house of faculty of medicine, Umm Al Qura University were individually housed in stainless steel cages with wire-mesh flooring in a controlled environment at 23-25°C and 50% humidity with a 12 h artificial light cycle on a 12:12-h dark-light cycle (07.00-19.00 lights on). Food (#5322 Purina Certified Rat Ration, and available ad libitum for all. Animals were housed in solid bottomed cages; food and water were maintained on a pellet diet and tap water ad libitum during the entire period of the study.

B)-Instruments and chemicals

Chemicals:

-Carbopol 934P and Glycerol were purchased from Himedia, India**.**
-Triethanolamine was purchased from Sigma-Aldrich, Germany.
-Herbs/plants: 3kilograms of green sticks of miswak (arak).

Instruments

1-Salvadora persica aqueous extraction and gel formation instruments:

-Freeze Dryer (CHRIST, Germany).

-Hot Plat stirrer (IKA, Germany).

2-Treatment instrument: Ultrasonic device (model pulson200. Manufacturer; GymnaUniphy N.V. Belgium) was used with a probe 1.9 cm^2 in diameter in this study.

3-Measuring instrument**:** Transparent film, Metric graph paper and digital camera (Canon INC., made in Japan).

Procedures:

A) -Aqueous extracts (H_2O) preparation: The green sticks of S. persica were cut into small pieces and freeze-dried for 24 hrs, then they were ground to powder using laboratory ball mill. The fine powdered stems were macerated in distilled water with constant stirring till complete exhaustion of the powder (discoloration of the supernatant). The extract was then filtered through Whatman No. 1 filter paper, and the filtrate was then dried using a freeze drier. The obtained dried mass was stored in air-tight closed bottles and kept in a freezer at –20 ºC for further work (Manu et al., 2013)**.**

B)-Procedure for Formulations of Gel: Carbopol 934P (1gm) and the measured quantity of extract (to prepare 5% gel) were dispersed in 80 ml of distilled water with continuous mixing using a magnetic stirrer at 800 rpm for 1 h. Glycerol 5 ml was added to the mixture under continuous stirring. The mixture was then neutralized by drop-wise addition of tri ethanolamine. Mixing was continued until a transparent gel was formed. Fresh gel formulation was prepared for each treatment (Ramane et al., 2013)**.**

C)-Wound Surgery: For all Forty five rats, local preparation of the upper dorsal skin was done; as upper dorsal skin of rats was shaved by electrical clipper, disinfected with 70% alcohol, then all rats were anesthetized by inhalation (diethyl ether). After anesthesia, the area for wound was measured (2x2.5 cm). A full-thickness excisional wound was performed as 5 cm^2 wound area was excised from the dorsal aspect of all rats. The same researcher performed all surgical procedures.

D)-Experiment design: After wound surgery, rats were randomly divided into three equal groups; A, B and C. (15 animals in each group):
1. Control group (C) (sham ultrasonic): Fifteen rats were received ultrasonic therapy in off mode
2. Topical group (B) (sham phonopheresis): Fifteen rats were received topical salvadora persica gel and ultrasonic was used therapy in off mode.
3. Phonopheresis group (A): Fifteen rats were received topical salvadora persica gel and ultrasonic therapy was used in on mode.
The treatment was started in each group after 2 hours of the surgical procedure.

Interventions

A)-Treatment:

-Standard cleaning of all wounds by alcohol.

- As wound dimensions were approximately (20mm x 25mm x 2m) so amount of salvadora gel calculated and used to cover wound cavity through using a syringe was $1cm^3$.Adding more 0.5 cm^3 of salvadora gel used for cover boundaries of wound. This amount (1.5 cm^3) was used throughout all time of experiment

-In both groups; A and B: salvadora persica gel was used to fill the wound cavity.

-In group C: there is no salvadora persica gel was used

-Sterile plastic drape was applied to all wounds and surrounding tissues to prevent any cross-contamination of the device. The plastic drape should overlap wound margins by at least 4 cm and its surrounding ends fixed on rats skin by adhesive tape (Biagio et al., 2009). Pulsed ultrasonic (applicator 1.9 cm^2) was applied over plastic drape and movement was begun over the wound cavity or wound scab then over wound margins in all groups. Perfect grasping rats so that wound area is between thumb and index as act as barrier to keep gel within wound area. **Figure (1).**

-Ultrasonic therapy was in on mode only in group (A) and with the following parameters; pulsed duty cycle 40% (4ms on, 6ms off) and Power density (0.5 W/cm^2).

-While in both groups B and C., ultrasound was in off mode as treatment was applied with no current (sham method) aiming to control any effect of handling or movement of ultrasonic head over the wound. In all groups, moving of ultrasonic applicator was done for 6 minutes per day, day after day, three treatments per week and for eight sessions, as 3 minutes within wound boundaries and other 3 minutes over wound margins.

-Gel and plastic drape were removed and the wound was dried, cleaned and disinfected by povidone solution at the end of each session.

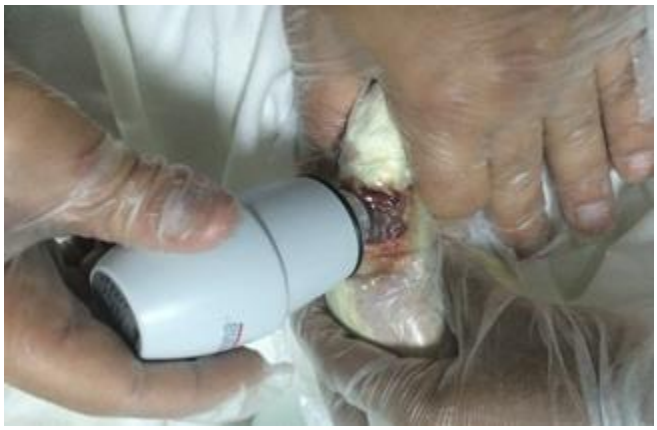


Figure (1): Treatment procedures; rat grasping and U.S application over wound through sterile plastic drape.

B-Measurement:

-The wound area was measured by placing a transparent tracing paper over the wound and tracing it out then the tracing paper was placed on 1 mm2 graph sheet, and traced out. The millimeter squares were counted and the area

was recorded. In each group, measurement of wound area was repeated 4 times (1st, 3rd, 5th and 8th sessions).Every wound area was photographed by digital camera at (1st, 3rd, 5th and 8th sessions) in all groups.
-Results were collected and analyzed using SPSS program v(16), as means and standard deviations were calculated in addition to using repeated measures ANOVA test to compare mean values within a group and one way ANOVA to compare mean values between groups considering *p* value less than (0.05) as significant point.

RESULTS

All forty five rats were homogeneous in terms of characteristics; all rats were adult albino male rats approximately 4 months of age, weighed approximately 200-250 gm each, fed the same type of food (#5322 Purina Certified Rat Ration, and available ad libitum), and subjected to the same surgical procedure with same surgeon .

A)-Compare within each group:

Results from repeated measures ANOVA test revealed a significant sequential reduction in wound surface area throughout treatment phases (1st, 3rd, 5th and 8th sessions) in all three groups as *p* value < 0.05. Results also revealed significant differences in means of wound surface area (WSA) between; 3rd session mean results and 1st session mean results , 5th session mean results and 3rd session mean results , 8th session mean results and 5th session mean results in all groups as *P* values (0.0001) < (0.05) for all. These all results are shown in tables; (1),(2) and (3) also are shown in figures (2&4).

Table (1): Means of wound surface areas (WSA) at (1st, 3rd 5th and 8thsessions) in group (A) and comparison of means of WSA between every 2 sequent measurements within (A) group.

	Wound Surface Area (M±SD)			
Group	**1st session**	**3rd session**	**5thsession**	**8th session**
(A)	5.00±00	2.12±1.03	0.34±0.11	0.09±0.03
P value		**(0.0001)****	**(0.0001)****	**(0.0001)****	

Table (2): Means of wound surface areas (WSA) at (1st, 3rd 5th and 8th sessions) in group (B) and comparison of means of W.S.A between every 2 sequent measurements within (B) group.

	Wound Surface Area (M±SD)			
Group	**1st session**	**3rd session**	**5th session**	**8th session**
(B)	5.00±00	2.74±0.69	0.73±0.62	0.38±0.30
P value		**(0.0001)****	**(0.0001)****	**(0.0001)****	

Table (3): Means of wound surface areas (WSA) at (1st, 3rd 5th and 8th sessions) in group (C) and comparison of means of WSA between every 2 sequent measurements within (C) group.

	Wound Surface Area (M±SD)			
Group	**1st session**	**3rd session**	**5th session**	**8th session**
(C)	5.00±00	3.30±0.57	1.54±0.17	0.59±0.14
P value		**(0.0001)****	**(0.0001)****	**(0.0001)****	

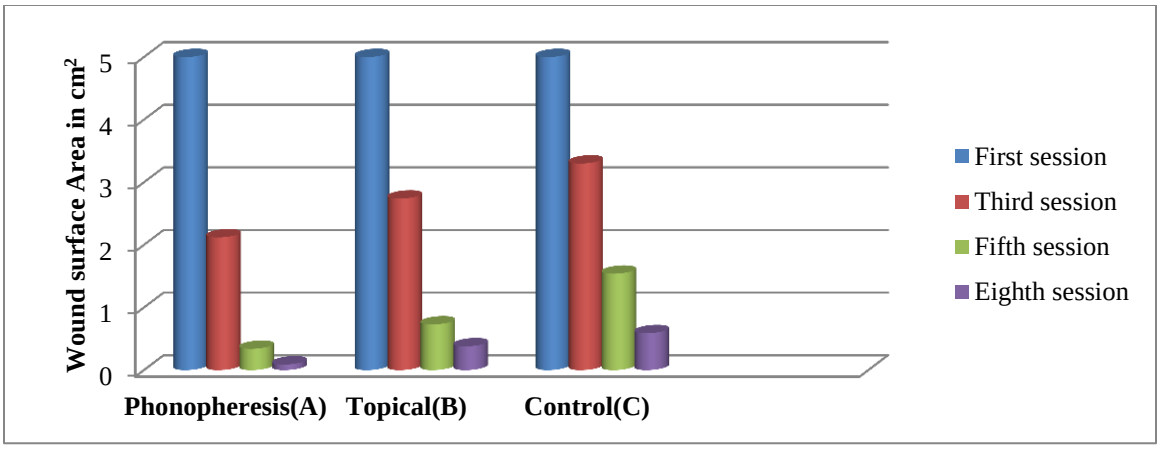


Figure (2): Comparison of means of wound surface area (WSA) among different measurements within each group.

(B)-Compare between groups:

Displayed in Table 4 are results that show differences between mean of WSA in group (A) and mean in group (B) at 3rd, 5th and 8th sessions. One way ANOVA test revealed that; there was no significant (reduction) difference between; mean of W.S.A in group (A) and mean of W.S.A in group (B) at 1st session, while there was significant (reduction) difference between; mean of W.S.A in group (A) and mean of W.S.A in group (B) at 3rd ,5th and 8th session as *p* value (.09), (0.029) and (0.004) respectively. Displayed in Table 5 are results that show differences between means of WSA in group (A) and means in group (C) at 5th and 8th sessions. One way ANOVA test revealed that; there was no significant (reduction) difference between; mean of W.S.A in group (A) and mean of W.S.A in group (C) at1st session, while there was high significant (reduction) difference between; mean of W.S.A in group (A) and mean of W.S.A in group (C) at 3rd, 5th and 8th sessions as *p* value (0.003), (0.00001) and (0.00001) respectively .While in Table 6, results show differences between means of WSA in group (B) and means in group (C) at 3rd, 5th and 8th sessions. One way ANOVA test revealed that; there was no significant (reduction) difference between; mean of W.S.A in group (B) and mean of W.S.A in group (C) at 1st session, while there was significant (reduction) difference between; mean of W.S.A in group (B) and mean of W.S.A in group(C) at 3rd, 5th and 8th sessions as *p* value (0.024), (0.00001) and (0.021) respectively. These results are shown in tables ;(4), (5) and (6) also are shown in figure (3).

Table (4): Comparison of means of W.S.A between (A) and (B) groups at each measurement.

Group	**1st session**	**3rd session**	**5thsession**	**8th session**
(A)	5.00±00	2.12±1.03	0.34±0.11	0.09±0.03
***P* (value)**	------	**(0.09)**	**(0.029)***	**(0.004)****
(B)	5.00±00	2.74±0.69	0.73±0.62	0.38±0.30

Table (5): Comparison of means of W.S.A between (A) and (C) groups at each measurement.

Group	**1stsession**	**3rdsession**	**5thsession**	**8th session**
(A)	5.00±00	2.12±1.03	0.34±0.11	0.09±0.03
***P* (value)**	------	**(0.003)****	**(0.00001)*****	**(0.00001)****
(C)	5.00±00	3.30±0.57	1.54±0.17	0.59±0.14

Table (6): Comparison of means of W.S.A between (B) and (C) groups at each measurement.

Group	**1st session**	**3rdsession**	**5thsession**	**8th session**
(B)	5.00±00	2.74±0.69	0.73±0.62	0.38±0.30
***P* (value)**	------	**(0.024)***	**(0.00001)*****	**(0.021)***
(C)	5.00±00	3.30±0.57	1.54±0.17	0.59±0.14

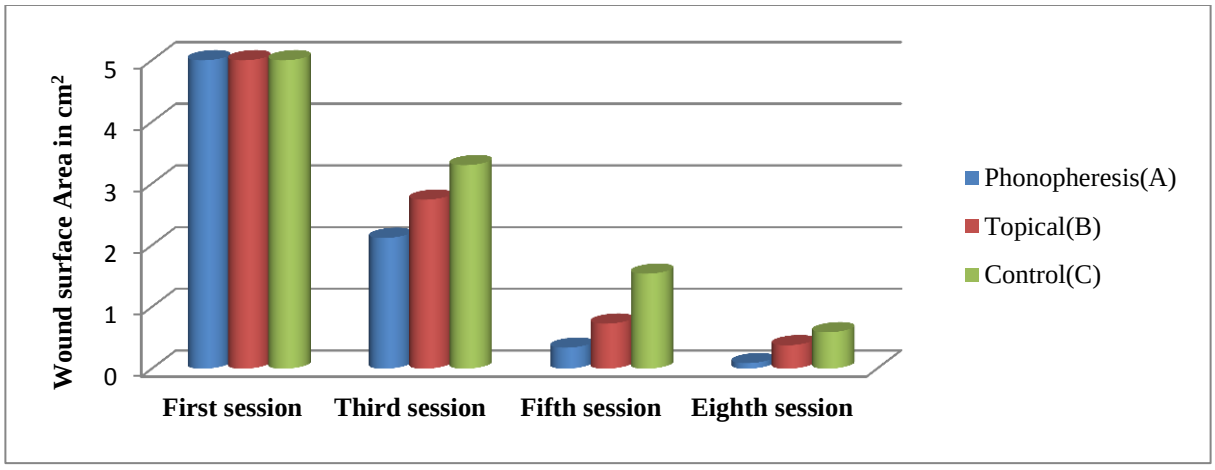
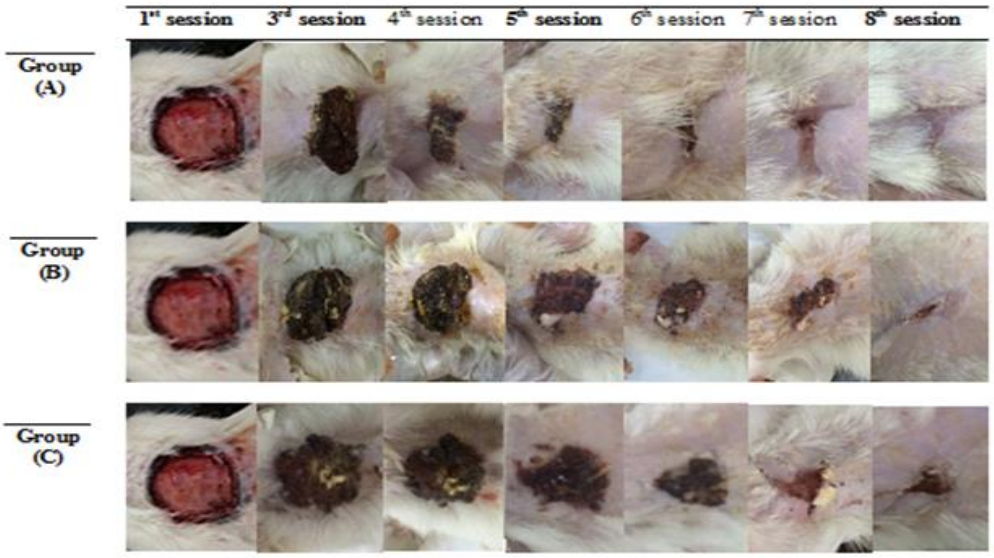


Figure (3): Comparison of means of wound surface area (WSA) among different groups at each measurement.



Figures (4): Examples of captured images by digital camera for reduction wound surface area throughout sequent sessions in three groups.

DISCUSSION

Wound healing is a process by which a damaged tissue is restored as closely as possible to its normal state and wound contraction is the process of shrinkage of area of the wound. It mainly depends on the repairing ability of the tissue, type and extent of damage and general state of the health of the tissue (Shivananda et al.,2006). Cutaneous wound repair procedure is accompanied by an ordered and definable sequence of biological events which are starting with wound closure and progressing to the repair and remodeling of the damaged tissue (Phillips et al., 1991). Wound healing process for a full-thickness wound (i.e., damage is imposed to both epidermis and dermis) is comprised of different steps including; epithelialization, wound contraction and scarring. Studies showed that wound healing process could be accelerated and enhanced by the use of natural or synthetized biochemical compounds (csupor et al.,2010). Plant constituents could significantly accelerate and enhance the healing process and augment the quality of wound healing (Al Bayaty et al., 2012).

In this study an excision wound model was employed for the assessment of wound healing effect of transdermal drug delivery (phonopheresis) using of aqueous extract of S. persica gel and topical application of the Spersica gel. The results of this study provided evidences for the ability of the aqueous extract of S. persica introducing in form of phonopheresis and topical to enhance the wound healing process and to shorten the healing period in rats as our study results shown that; a significant sequential reduction in wound surface area throughout treatment phases (1^{st}, 3^{rd}, 5th and 8^{th} sessions) in topical group as there was significant difference between WSA means of every 2 sequent phases as p value <0.05, also show significant (reduction) differences between means of WSA in topical group and means of WSA in control group at 3^{rd}, 5^{th} and 8^{th} sessions as p value <0.05.which ascertain that topical salvadora persica has effect on wound healing in rats. These results may be explained as follow; the preliminary phytochemical studies of aqueous extract of S. persica revealed the presence of flavonoids and alkaloids. Flavonoids are demonstrated to reduce lipid peroxidation not only by preventing or slowing the onset of cell necrosis but also by improving vascularity. Hence, any drug that inhibits lipid peroxidation is believed to increase the viability of collagen fibrils by increasing the strength of collagen fibers, increasing the circulation, preventing the cell damage and by promoting the DNA synthesis (Getie et al., 2002).

Flavonoids are also known to promote the wound-healing process mainly due to their astringent and antimicrobial property, which seems to be responsible for wound contraction and increased rate of epithelialization (Tsuchiya et al., 1996).Thus, wound-healing property of S. persica may be attributed to the phytoconstituents present in it, which may be either due to their individual or additive effect that fastens the process of wound healing. These results may be due to the benzyl isothiocyanate component of the extract in addition to the flavonoids. Also our study results shown that; a significant sequential reduction in wound surface area throughout treatment phases (1^{st}, 3^{rd}, 5th and 8^{th} sessions) in phonopheresis group as there was significant difference between WSA means of every 2 sequent phases as p value <0.05, also show significant (reduction) differences between means of WSA in phonopheresis group and means of WSA. in control group at 3^{rd}, 5^{th} and 8^{th} sessions as p value <0.05.also there was a significant (reduction) differences between means of WSA in phonopheresis group and means of WSA. in topical group at 3^{rd}, 5^{th} and 8^{th} sessions as p value <0.05. and these results inform that salvadora persica phononpheresis had good effect on healing of full thickness wound in rats in addition it had better healing result than topical method had. These results may be due to the following:

A)-Transdermal drug delivery by U.S and long period drug storage for long acting:

The ultrasound mediated increase in the membrane permeability depends on mechanical loosening of connective tissue and depolymerization of hyaluronic acid. In addition to acoustic effects in the medium, ultrasonic waves also change the pressure in the substrate with respect to the ambient pressure. Both the variable pressure and the invariable acoustic radiation pressure modify not only the morphofunctional state of the membrane, but also its ability to transport and redistribute liquids and solid substances between cells and the environment.Intracellular microflows are important factors of the mechanism of biological effect of ultrasound. Such microflow increase the cell sensitivity to physical and chemical factors (El'Pine,1973).

Ultrasound induces loosening of skin epidermis and connective layer and increases the activity of the perspiratory and oil glands. The skin porosity also increases, thereby improving the skin permeability for drugs. Skin pores and oil gland ducts are the main pathways of drug transport through skin in phonophoresis. The solvent used (vaseline, lanolin, water soluble gels, distilled water, etc.) is an important factor of drug transport through skin. Polar solvents facilitate drug transport through perspiratory gland ducts, whereas nonpolar solvents facilitate drug transport through oil gland ducts. Ultrasound modifies the pharmacodynamics of subcutaneous drug transport. For example, drugs can be stored for a long time in subsurface and deeper skin layers. Drug deposition in skin is based on ultrasound mediated permeation of drugs through skin. Lack of active blood and lymph circulation in the outer skin layers also contributes to the process of deposition. It is important to note that the drug is deposited directly at the application site (Ulashchik and Chirkin,1983).

B) -Effect of selected parameters of ultrasonic in our study:

As we selected pulsed form of ultrasonic with low intensity which initiate mainly mechanical effect of ultrasonic which allow drugs to reached and stored in target tissues the advantage which thermal effect not allowed and this consistent with following; Phonophoresis facilitates the transdermal absorption of a drug by thermal effects such as an increase in tissue temperature and by mechanical effects such as cavitation and acoustic streaming (Loyd et al., 2011).The drugs are absorbed through the transcellular, intercellular and appendageal pathways. When utilizing ultrasound for TDD, increased blood flow in target tissues can decrease the ability of the desired medication to reach target tissues. As the medication passes the stratum corneum of the skin, increased blood flow can cause the drug to be taken into the blood stream more rapidly before reaching target tissues (Mitragotri, 1996).

C)-Synergy between ultrasonic therapy and drugs:

In addition to drug effect (salvadora persica) on healing which was mentioned above, ultrasonic has good effect on healing on wound which is consistent with the following; It appears that exposure to ultrasound during the initial 'inflammatory' phase of tissue repair can lead to an acceleration of this phase, although ultrasound is not in itself an anti- inflammatory agent. The second phase of healing is the 'proliferative' stage. This is the stage at which cells migrate to the site of injury and start to divide, granulation tissue is formed, and fibroblasts begin to produce collagen. Ultrasound has been shown to enhance collagen synthesis by fibroblasts and repairing of epithelium (Zhou et al., 2004).

Many laboratory-based studies have been undertaken to understand the effects of ultrasound on wound healing. To date, its effects include cellular recruitment, collagen synthesis, increased collagen tensile strength, angiogenesis, wound contraction, fibroblast and macrophage stimulation, fibrinolysis, and reduction of the inflammatory phase and promotion of the proliferative phase of healing (Ter et al., 1996).

CONCLUSIONS

Both of salvadora persica phonopheresis and Salvadora persica topical application have supporting effect in acceleration wound healing process in rats. In addition phonopheresis method provide more better healing than topical method , so salvadorapersica can be considered as satisfied effective herb/drug as it can be used to accelerate wound healing, this is by introducing it in form of gel through using ultrasonic therapy as phonopheresis in human cases.

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