International Journal of Research in Engineering and Science (IJRES)
ISSN (Online): 2320-9364, ISSN (Print): 2320-9356
www.ijres.org Volume 9 Issue 5 ǁ 2021 ǁ PP. 09-13

A Review of Some Significant Developments in Textile Wound Dressings for Treatment of Diabetic Foot Ulcers

Dr.N.Gokarneshan
Department of costume design and fashion
Dr.SNS Rajalakshmi college of arts and science
Coimbatore India.

Dr.U.Ratna
Department of textiles and clothing
Avinashilingam institute of home science and higher education for women
Coimbatore India.
[1] Corresponding author: N.Gokarneshan:

Abstract
The article reviews some recent developments in the textile wound dressings for treatment of diabetic ulcers. Given their severity and non-healing nature, diabetic chronic wounds are a significant concern to the 30.3 million Americans diagnosed with diabetes mellitus. Peripheral arterial diseases, neuropathy, and infection contribute to the development of these wounds, which lead to an increased incidence of lower extremity amputations. Early recognition, debridement, offloading, and controlling infection are imperative for timely treatment. However, wound characterization and treatment are highly subjective and based largely on the experience of the treating clinician. Functional wound dressing with tailored physicochemical and biological properties is vital for diabetic foot ulcer (DFU) treatment. Our main objective in the current study was to fabricate Cellulose Acetate/Gelatin (CA/Gel) electrospun mat loaded with berberine (Beri) as the DFU-specific wound dressing. The wound healing efficacy of the fabricated dressings was evaluated in streptozotocin-induced diabetic rats.
Key words: *Diabetic foot ulcer, Nano composite, Non woven fabrics, Electrospun mat, Wound dressing, Nanofibres.*

Date of Submission: 27-04-2021 Date of acceptance: 11-05-2021

I. INTRODUCTION

One of the major causes of death in North America is diabetes mellitus, and has become a cause of increasing health concern that affects more than 9% of the population above teenage [1,2]. Diseases like peripheral arterial disease, neuropathy, limited joint mobility, abnormal foot pressures, minor trauma, and foot deformity relate to diabetes and pose major health risks. Improved treatment of diabetes could significantly decrease associated healthcare costs, given that the cost of healing a single ulcer, infected ulcer, and amputation are estimated at $8000, $17,000, and $45,000, respectively [3]. Diabetes mellitus is classified as a metabolic disease that has various complications such as chronic wounds, arterial damage, and neuropathy resulting from uncontrolled blood sugar. The wound healing process is a complex and multiphase process that is delayed in diabetic patients because of various complexities [4,5]. In such patients, owing to low interaction between growth factors and their target site, the angiogenesis and re-epithelialization are not sufficient. Another deleterious effect arising from neutrophil infiltration is severe inflammation. Furthermore, factors like intense inflammation, limited nutrients and poor blood circulation lead to another complication known as diabetic foot ulcer (DFU). Despite the tremendous breakthroughs over the last decades, effective treatment of DFU remains a challenge [6-8].

II. SMART WOUND DRESSINGS

There exists a certain possibility of developing a chronic wound in patients afflicted with diabetes. Chronic wounds associated with diabetes include foot, venous and pressure ulcers [9]. Diabetic foot ulcers (DFUs) can be categorized into chronic, non-healing wounds which lead to a disruption in the skin and the healing process is prolonged causing frustration to the patient. With a global prevalence of 6.3%, DFUs place a heavy burden on public health [10]. The onset of diabetic ulcer results in peripheral neuropathy and causes damage to the peripheral nerves in the limbs. It renders the limb insensitive in feeling excessive pressure or pain from minor injuries. The lack of response to what may initially be minor incidents, combined with the poor blood circulation and impaired healing capacity of diabetic patients eventually leads to ulceration [11]. Those affected by DFUs and other chronic wounds are at increased risk for lower extremity amputation due to the threat of osteomyelitis and/or sepsis resulting from wound infection. Several studies have concluded that 85% of amputations are preceded by ulcers, and the incidence of new ulcer formation at a collateral wound site may be up to 50% [12,13].

A restricted scope is available for effectively treating diabetic chronic wounds and it becomes necessary to find a solution which takes into account all aspects related to inflammation and repair and is considered crucial. A smart dressing fabricated from optimal material combinations oriented in a specific multi-layered architecture needs to possess qualities that inhibit bacterial growth, manage excess exudate, and promote re-epithelialization, all while maintaining a moderately moist environment [14]. Besides delivering antibiotics and growth factors, composites of natural and synthetic polymers can contribute a similar composition as ECM. The type of scaffold and geometry of fibre can also influence the parameters such as antiobiotic elution, mechanical strength and porous structure. The smart wound dressings can be fabricated so as to tackle the clinical problems. But, they are unable to identify the specific condition of the wound.

Biosensing provides a special set of quantitative merits in real time, like exudate levels, bacteria concentrations, and tissue regeneration. A number of kinds of sensor and potential target biomarkers are available. But, in order to render them useful in sensing the wound environment they should become disposable, biocompatible, able to detect clinically relevant parameters, conform to the shape of the ulcer and have flexible properties similar to the applied dressing. Biochemical sensors offer the required sensitivity. However, miniaturization and integration with a smart dressing could prove relatively difficult in comparison with the use of an impedance or pressure sensor device. The use of a biochemical sensor would provide increased specificity, but these devices are typically limited with respect to shapes for fabrication.

On the other hand, impedance and pressure sensors can be designed as an array which can be implanted into the selected dressing. In order to evaluate the use of biological, impedance, or pressure sensors in the use of real-time detection of the chronic wound environment more research and study needs to be done. Development in the integration of a smart dressing can enable to avoid ulcers and amputation and improve the process of healing. Timely detection of the chronic wound environment and evolving a feedback system can quantify and classify the healing process and enable therapists with a valuable tool for fast detection of the chronic wound degeneration

III. ELECTROSPUN CELLULOSE ACETATE/GELATIN NANOFIBROUS WOUND DRESSING WITH BERBERINE

Since DFU is an acute wound, it needs to be dressed with proper dressing materials able to enhance the healing process and also isolate the wound site from pathogen microorganisms [15,16]. Furthermore, the wound dressing should be capable of absorption of the exerted exudates from the wound and also offer the best possible environment in order to carry out the healing process. Besides, the healing process of DFU requires to be accelerated via bioactive molecules or drugs, and the proposed dressing must be able to load a proper amount of the drug and release it in a sustain release manner[17-19]. A wide range of biomaterials and nanostructured materials have been evaluated as wound dressings for DFU, such as natural and synthetic polymers in the forms of hydrocolloids, hydrogels, foams, and electrospun nanofiber dressing[20,21].

Of the possible options, electrospun nanofibrous mats provide a broad range of prospective possibilities appropriate for wound dressing applications. Electrospinning is a sophisticated and efficient technique which provides a low-cost, scalable, flexible, relatively simple approach for nanofibers fabrication from a wide variety of synthetic and natural substance [22-25]. It is possible to adjust the porosity and the pore size of the electro spun mats to prevent microorganism penetration, while permitting oxygen to smoothly pass through the dressing and reach the area of wound. It is possible to design the water vapor transmission to offer the ideal moisture state in the process of wound healing. The drug loading and sustained delivery is aided by the high surface area of nano fibres.

The intended drugs, natural substance, or bioactive molecules can be adsorbed onto the surface of nanofibers or encapsulated into the nanofibers matrix [26,27]. Moreover, the electrospun nanofibrous dressings are self-standing and their handling during the wound treatment is easy [28-30]. A number of natural as well as synthetic polymers have been used to produce electrospun nano fibers, which have been applied as the wound dressing. Among them, natural polymers have grabbed considerable attention due to their desirable properties. Most of them are biocompatible, non-toxic, biodegradable, abundant, inexpensive, renewable, and versatile [31-33]. Cellulose is one of the most abundant natural polymers on earth, which has various derivatives. Still, the most promising derivative is cellulose acetate (CA), the acetate ester form of cellulose [34,35]. CA is applicable in various applications such as membrane separation, biomedical, textile fibers, cigarette industries, and plastics

[36-39]. The biomedical applications of CA are mainly categorized in drug delivery systems, tissue engineering, and wound dressing [37-40]. Biocompatibility, water absorption abilities, and good interaction with fibroblast cells have mad CA the right candidate for wound dressing applications [41]. Gelatin (Gel) is a widely used natural polymer with fascinating biological properties such as biocompatibility, biodegradability, and bioactivity, which is obtained from collagen hydrolysis [42-44]. Different types of gelatin can be designed, like the hydrogel, layered, freeze-dried, and micro- and nanofibers for various end uses. Due to the presence of cell adhesion domains such as the Arg-Gly-Asp (RGD) domains in the structure of gelatin, it is widely used in tissue engineering and wound dressing applications [45-47].

Besides the structural needs, a proper DFU dressing is expected to have an active ingredient for improvement of the healing process or even provide the antibacterial property. Biological functions have been incorporated in the dressings by different kinds of biological, natural, and chemical moieties. Berberine is a natural substance belongs to the alkaloid family found in the rhizome, roots, and stems of various plants such as Oregon grape, Goldenseal, and Barberry [48]. Berberine is known for its anti-diabetic, antimicrobial, and anti-inflammatory activities [49].

Moreover, some studies reported the diabetic wound healing efficacy of berberine [50-53]. Hence, the major focus has been directed towards design of CA/Gel electrospun nanofibrous mat containing berberine as a DFU wound dressing.

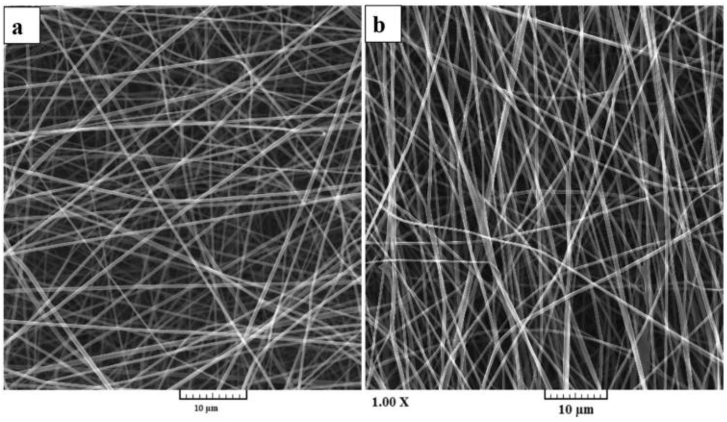

Figure SEM images of the electrospun (**a**) CA/Gel and (**b**) CA/Gel/Beri nanofibers [54].

Diabetic foot ulcers create complications in mellitus diabetes and calls for major care and wound management. In the case of DFU, the healing is slow. Hence it becomes necessary to accelerate the process by use of certain agents. Moreover, the wound site must be isolated from pathogenic microorganisms via a well-designed dressing [54]. Owing to their nanometric scale, high surface to volume ratio, adjustable porosity, and ability to load different drugs and bioactive molecules, electrospun nanofibrous dressings are considered perfect wound dressing. The electrospinning technique has been adopted to design CA/Gel nanofibrous dressing containing berberine after characterization used as a DFU dressing material. It has been shown that the designed dressing is found appropriate as the wound dressing material without causing any adverse effect on the cultured cells and also show antibacterial activity against gram-positive and negative bacterium. Investigations on the STZ-induced diabetic rats have shown that the CA/Gel/Beri dressing improved the process of wound healing. The investigation proves that the designed A/Gel/Beri dressing is considered appropriate dressing material for improvement of the healing process of DFU and also isolate the wound site from the pathogenic microorganisms invasion.

IV. CONCLUSION

Many wound dressings have been designed to address particular clinical presentations, but a prescriptive method is lacking for identifying the particular state of chronic, non-healing wounds.

The authors suggest that recent developments in wound dressings and biosensing may allow for the quantitative, real-time representation of the wound environment, including exudate levels, pathogen concentrations, and tissue regeneration. Development of such sensing capability could enable more strategic, personalized care at the onset of ulceration and limit the infection leading to amputation. This review presents an overview of the pathophysiology of diabetic chronic wounds, a brief summary of biomaterial wound dressing treatment options, and biosensor development for biomarker sensing in the wound environment. It is found that an average nanofiber diameter of 502 ± 150 nm, and the tensile strength, contact angle, porosity, water vapor permeability and water uptake ratio of CA/Gel nanofibers were around 2.83 ± 0.08 MPa, 58.07 ± 2.35°, 78.17 ± 1.04%, 11.23 ± 1.05 mg/cm2/hr, and 12.78 ± 0.32%, respectively, while these values for CA/Gel/Beri nanofibers were 2.69 ± 0.05 MPa, 56.93 ± 1°, 76.17 ± 0.76%, 10.17 ± 0.21 mg/cm2/hr, and 14.37 ± 0.42%, respectively. The antibacterial evaluations demonstrated that the dressings exhibited potent antibacterial activity. The collagen density of 88.8 ± 6.7% and the angiogenesis score of 19.8 ± 3.8 obtained in the animal studies indicate a proper wound healing. These findings implied that the incorporation of berberine did not compromise the physical properties of dressing, while improving the biological activities. In conclusion, our results indicated that the prepared mat is a proper wound dressing for DFU management and treatment.

REFERENCES

[1]. Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States; Centers for Disease Control and Prevention: Atlanta, GA, USA, 2014.

[2]. Reiber, G.; Lipsky, B.; Gibbons, G. The burden of diabetic foot ulcers. Am. J. Surg. **1998**, 176, 5S–10S.

[3]. Dahiru, I.; Amaefule, K.; Okpe, I.; Ibrahim, A.; Muazu, S. An overview of diabetic foot disease. Niger. J. Basic Clin. Sci. **2016**, 13, 1.

[4]. Wynn, M. The efficacy of negative pressure wound therapy for diabetic foot ulcers: A systematised review. *Journal of Tissue Viability* (2019).

[5]. Dow, C. *et al*. Diet and risk of diabetic retinopathy: A systematic review. *European journal of epidemiology* **33**, 141–156 (2018).

[6]. Jeffcoate, W. J., Vileikyte, L., Boyko, E. J., Armstrong, D. G. & Boulton, A. J. Current challenges and opportunities in the prevention and management of diabetic foot ulcers. *Diabetes care* **41**, 645–652 (2018).

[7]. Aldana, P. C. & Khachemoune, A. Diabetic Foot Ulcers: Appraising Standard of Care and Reviewing New Trends in Management. *American Journal of Clinical Dermatology*, 1–10 (2019).

[8]. Braun, L. R., Fisk, W. A., Lev-Tov, H., Kirsner, R. S. & Isseroff, R. R. Diabetic foot ulcer: an evidence-based treatment update. *American Journal of Clinical Dermatology* **15**, 267–281 (2014).

[9]. Siddiqui, A.R.; Bernstein, J.M. Chronic wound infection: Facts and controversies. Clin. Dermatol. **2010**, 28, 519–526.

[10]. 10.. Zhang, P.; Lu, J.; Jing, Y.; Tang, S.; Zhu, D.; Bi, Y. Global epidemiology of diabetic foot ulceration: A systematic review and meta-analysis. Ann. Med. **2017**, 49, 106–116.

[11]. Jeffcoate, W.J.; Harding, K.G. Diabetic foot ulcers. Lancet **2003**, 361, 1545–1551.

[12]. Moxey, P.W.; Gogalniceanu, P.; Hinchliffe, R.J.; Loftus, I.M.; Jones, K.J.; Thompson, M.M.; Holt, P.J. Lower extremity amputations—A review of global variability in incidence. Diabet. Med. **2011**, 28, 1144–1153.

[13]. Health Statistics|NIDDK. Available online: https://www.niddk.nih.gov/health-information/healthstatistics#category=diabetes.

[14]. Elizabeth G, Craig M and Jordon G, SmartWound Dressings for Diabetic ChronicWounds, Bioengineering 2018, 5, 51; doi:10.3390/bioengineering5030051.

[15]. Moura, L. I., Dias, A. M., Carvalho, E. & de Sousa, H. C. Recent advances on the development of wound dressings for diabetic foot ulcer treatment—a review. *Acta biomaterialia* **9**, 7093–7114 (2013).

[16]. Broussard, K. C. & Powers, J. G. Wound dressings: selecting the most appropriate type. *American Journal of Clinical Dermatology* **14**, 449–459 (2013).

[17]. Mulder, G., Armstrong, D. G. & Seaman, S. Standard, appropriate, and advanced care and medical-legal considerations: Part onediabetic foot ulcerations. *Wounds* **15**, 92–106 (2003).

[18]. Jannesari, M., Varshosaz, J., Morshed, M. & Zamani, M. Composite poly (vinyl alcohol)/poly (vinyl acetate) electrospun nanofibrous mats as a novel wound dressing matrix for controlled release of drugs. *International journal of nanomedicine* **6**, 993 (2011).

[19]. Tamer, T. *et al*. MitoQ loaded chitosan-hyaluronan composite membranes for wound healing. *Materials* **11**, 569 (2018).

[20]. Dhivya, S., Padma, V. V. & Santhini, E. Wound dressings–a review. *BioMedicine* **5** (2015).

[21]. Ehterami, A. *et al*. A promising wound dressing based on alginate hydrogels containing vitamin D3 cross-linked by calcium carbonate/d-glucono-δ-lactone. Biomedical Engineering Letters, 1–11 (2020).

[22]. Samadian, H., Zakariaee, S. S. & Faridi-Majidi, R. Evaluation of effective needleless electrospinning parameters controlling polyacrylonitrile nanofibers diameter via modeling artificial neural networks. The Journal of The Textile Institute, 1–10 (2018).

[23]. Samadian, H., Mobasheri, H., Hasanpour, S. & Faridi-Majid, R. In Journal of Nano Research. 78–89 (Trans Tech Publ).

[24]. Massoumi, B., Massoumi, R., Aali, N. & Jaymand, M. Novel nanostructured star-shaped polythiophene, and its electrospun nanofibers with gelatin. *Journal of Polymer Research* **23**, 136 (2016).

[25]. Vicente, A. C. B. *et al*. Influence of process variables on the yield and diameter of zein-poly (N-isopropylacrylamide) fiber blends obtained by electrospinning. *Journal of Molecular Liquids* **292**, 109971 (2019).

[26]. Sun, Y. *et al*. Electrospun fibers and their application in drug controlled release, biological dressings, tissue repair, and enzyme immobilization. *RSC Advances* **9**, 25712–25729 (2019).

[27]. Nikmaram, N. *et al*. Emulsion-based systems for fabrication of electrospun nanofibers: Food, pharmaceutical and biomedical applications. *RSC Advances* **7**, 28951–28964 (2017).

[28]. Mirjalili, M. & Zohoori, S. Review for application of electrospinning and electrospun nanofibers technology in textile industry. *Journal of Nanostructure in Chemistry* **6**, 207–213 (2016).

[29]. Hassiba, A. J. *et al*. Review of recent research on biomedical applications of electrospun polymer nanofibers for improved wound healing. *Nanomedicine* **11**, 715–737 (2016).

[30]. Júnior, L. P., Silva, D. B. D. S., de Aguiar, M. F., de Melo, C. P. & Alves, K. G. Preparation and characterization of polypyrrole/organophilic montmorillonite nanofibers obtained by electrospinning. *Journal of Molecular Liquids* **275**, 452–462 (2019).

[31]. Zhu, Y., Romain, C. & Williams, C. K. Sustainable polymers from renewable resources. *Nature* **540**, 354 (2016).

[32]. Massoumi, B. *et al*. A novel bio-inspired conductive, biocompatible, and adhesive terpolymer based on polyaniline, polydopamine, and polylactide as scaffolding biomaterial for tissue engineering application. *International journal of biological macromolecules* **147**,

[33]. 1174–1184 (2020).

[34]. Jaymand, M. Chemically Modified Natural Polymer-Based Theranostic Nanomedicines: Are They the Golden Gate toward a de Novo Clinical Approach against Cancer? *ACS Biomaterials Science & Engineering* (2019).

[35]. Shimizu, M., Kusumi, R., Saito, T. & Isogai, A. Thermal and electrical properties of nanocellulose films with different interfibrillar structures of alkyl ammonium carboxylates. Cellulose, 1–9 (2019).

[36]. Karaj-Abad, S. G., Abbasian, M. & Jaymand, M. Grafting of poly [(methyl methacrylate)-block-styrene] onto cellulose via nitroxidemediated polymerization, and its polymer/clay nanocomposite. *Carbohydrate polymers* **152**, 297–305 (2016).
[37]. Hondo, H., Saito, T. & Isogai, A. Preparation of oxidized celluloses in a TEMPO/NaBr system using different chlorine reagents in water. *Cellulose* **26**, 3021–3030 (2019).
[38]. Yaich, A. I., Edlund, U. & Albertsson, A.-C. Barriers from wood hydrolysate/quaternized cellulose polyelectrolyte complexes. *Cellulose* **22**, 1977–1991 (2015).
[39]. Arca, H. C., Mosquera-Giraldo, L. I., Taylor, L. S. & Edgar, K. J. Synthesis and characterization of alkyl cellulose ω-carboxyesters for amorphous solid dispersion. *Cellulose* **24**, 609–625 (2017).
[40]. Khoshnevisan, K., Maleki, H., Samadian, H., Doostan, M. & Khorramizadeh, M. R. Antibacterial and antioxidant assessment of cellulose acetate/polycaprolactone nanofibrous mats impregnated with propolis. *International journal of biological macromolecules* **140**, 1260–1268 (2019).
[41]. Taepaiboon, P., Rungsardthong, U. & Supaphol, P. Vitamin-loaded electrospun cellulose acetate nanofiber mats as transdermal and dermal therapeutic agents of vitamin A acid and vitamin E. *European Journal of Pharmaceutics and Biopharmaceutics* **67**, 387–397
[42]. (2007).
[43]. Tungprapa, S., Jangchud, I. & Supaphol, P. Release characteristics of four model drugs from drug-loaded electrospun cellulose acetate fiber mats. *Polymer* **48**, 5030–5041 (2007).
[44]. Gouma, P., Xue, R., Goldbeck, C., Perrotta, P. & Balázsi, C. Nano-hydroxyapatite—Cellulose acetate composites for growing of bone cells. *Materials Science and Engineering: C* **32**, 607–612 (2012).
[45]. Pishnamazi, M. *et al*. Microcrystalline cellulose, lactose and lignin blends: Process mapping of dry granulation via roll compaction. *Powder Technology* **341**, 38–50 (2019).
[46]. Liu, X. *et al*. Antimicrobial electrospun nanofibers of cellulose acetate and polyester urethane composite for wound dressing. *Journal of Biomedical Materials Research Part B: Applied Biomaterials* **100**, 1556–1565 (2012).
[47]. Yue, K. *et al*. Synthesis, properties, and biomedical applications of gelatin methacryloyl (GelMA) hydrogels. *Biomaterials* **73**, 254–271 (2015).
[48]. Kuijpers, A. J. *et al*. Cross-linking and characterisation of gelatin matrices for biomedical applications. *Journal of Biomaterials Science, Polymer Edition* **11**, 225–243 (2000).
[49]. Massoumi, B., Ghandomi, F., Abbasian, M., Eskandani, M. & Jaymand, M. Surface functionalization of graphene oxide with poly (2-hydroxyethyl methacrylate)-graft-poly (ε-caprolactone) and its electrospun nanofibers with gelatin. *Applied Physics A* **122**, 1000
[50]. (2016).
[51]. Li, M., Guo, Y., Wei, Y., MacDiarmid, A. G. & Lelkes, P. I. Electrospinning polyaniline-contained gelatin nanofibers for tissue engineering applications. *Biomaterials* **27**, 2705–2715 (2006).
[52]. Huang, Y., Onyeri, S., Siewe, M., Moshfeghian, A. & Madihally, S. V. *In vitro* characterization of chitosan–gelatin scaffolds for tissue engineering. *Biomaterials* **26**, 7616–7627 (2005).
[53]. García, A., Culebras, M., Collins, M. N. & Leahy, J. J. Stability and rheological study of sodium carboxymethyl cellulose and alginate suspensions as binders for lithium ion batteries. *Journal of Applied Polymer Science* **135**, 46217 (2018).
[54]. Gulfraz, M. *et al*. Comparison of the antidiabetic activity of Berberis lyceum root extract and berberine in alloxan-induced diabetic
[55]. rats. *Phytotherapy Research* **22**, 1208–1212 (2008).
[56]. El-Wahab, A. E. A., Ghareeb, D. A., Sarhan, E. E., Abu-Serie, M. M. & El Demellawy, M. A. *In vitro* biological assessment of Berberis vulgaris and its active constituent, berberine: antioxidants, anti-acetylcholinesterase, anti-diabetic and anticancer effects. *BMC complementary and alternative medicine* **13**, 218 (2013).
[57]. Pashaee, M. The effect of hydroalcoholic extract of Berberis vulgaris on wound healing of diabetic wistar rats. *Journal of Chemical Health Risks* **6** (2016).
[58]. Hadi Samadian1, Sina Zamiri2, Arian Ehterami3, Saeed Farzamfar4, Ahmad Vaez5,
[59]. Hossein Khastar6, Mostafa Alam7, Armin Ai8, Hossein Derakhshankhah1, Zahra Allahyari9,10,
[60]. Arash Goodarzi11 & Majid Salehi12,1, Scientific Reports | *(2020) 10:8312* | https://doi.org/10.1038/s41598-020-65268-7.