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Wound Healing Potential of Selected Drug Molecules Obtained from Terpenoids

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ABSTRACT

Skin is the vital organ of the human system; however, due to its high exposure to the external environment, it was susceptible to various traumatic conditions. During the time of trauma human body played a significant role in the activation of various biological processes for enhancing the wound healing activity in case of damaged tissues. However, in case of skin tissue defects, to enhance the angiogenesis minimal scar formation, several pharmaceutical products were paving their way into the market. Now a days there was a rising worldwide utilization of several bioactive compounds obtained from terpenoids. Terpenoids are 5-carbon compound isoprene with oxygen-containing functional groups were isolated from several plants demonstrates a wide range of activities such as antioxidant, anti-inflammatory and anti-microbial activity. Furthermore, due to their excellent cytoprotective activity, terpenoids based products had played a significant role in wound healing activity. Moreover, in our study, because of their excellent wound healing capability, we reviewed about the few drug molecules such as Tocopherol, Farnesol, Betulin, Retenoic acid, Coenzyme Q10. However, now a day's terpenoids were utilized in several wound-healing formulations because of their excellent anti-inflammatory, re-vascularization and re-epithelization characteristics. Finally, this review focuses on the role of a few drug products obtained from terpenoids as an ideal topical wound healing agent in modern medicine.



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INTRODUCTION

Skin is the vital organ of the human system that acts as a protective layer for the internal organs and prevents the entry of the harmful microorganisms (Chuong *et al.*, 2002). However, due to its high exposure to the external environment, it was susceptible to various traumatic conditions such as (burns, and lesions etc.) (Guo and DiPietro, 2010; Bishop, 2008). Moreover, during the skin tissue defects, several mediators (such as growth factors, cytokines and chemokines etc.) played a significant role in enhancing the tissue regeneration process of skin wounds. The human body activates a complex cascade of biological processes towards healing and regenerating the damaged or destroyed tissue

at the time of the injury (Kumar *et al.*, 2010; Shaw and Martin, 2009; Cotran *et al.*, 2005). Furthermore, in case of skin tissue defects, to enhance the angiogenesis minimal scar formation, several pharmaceutical products were paving their way into the market (Rustad and Gurtner, 2012; Groeber *et al.*, 2011).

(Boateng *et al.*, 2008; Gurtner *et al.*, 2008) Terpenoids are 5-carbon compound isoprene with oxygen-containing functional groups were isolated from several plants demonstrates a wide range of roles like cytoprotective and anti-microbial activity (Cox-Georgian *et al.*, 2019). Even though significant importance was given to antioxidant properties, the terpenoids can also exercise immunomodulatory effect by means of various signalling mechanism (i.e. protein kinase and lipid kinase) (Kim *et al.*, 2020). Terpenoids play a major role in many molecular action pathways for wound healing by interacting with various forms of genes and enzymes. Furthermore, due to their excellent cytoprotective activity the terpenoids based products had played a significant role in wound healing activity (Forni *et al.*, 2019).

Moreover, in this review, we discussed about the few terpenoid based products and their importance in the wound healing activity.

Moreover, Figure 1. Represents a few examples of Terpenoids and their importance in wound healing activity; Figure 2; Represents the tocopherol and Farnesol in wound healing activity; Figure 3. Represents the betulin, retenoic acid and coenzyme Q10 in wound healing activity. Whereas, Tables 1, 2, 3 and 4. Represents the significance of terpenoids (i.e. Tocopherol, Farnesol, Betulin, Retenoic acid, Coenzyme Q10) in wound healing activity.

Drug molecules involved in Topical wound healing

Tocopherol

One of the main complications in diabetics is delayed wound healing. The early stage of the inflammation is critical for better prognosis during the wound healing process. Gamma-tocopherol (GT) is one of the antioxidant nutrients considered to control inflammatory conditions. Shin *et al.* (2017) investigated the impact of GT supplementation in early cutaneous wound healing in diabetic mice on pathways associated with inflammation, oxidative stress and apoptosis. Moreover, the anti-inflammatory, antioxidant characteristics of the gamma-tocopherol decreased the inflammation and oxidative stress and thus promoted cutaneous wound healing in case of diabetic mice. Eventually, it was concluded that the ideal neutraceutical nature

of the gamma-tocopherol played a significant role in the diabetic delayed wound healing (Shin *et al.*, 2017).

Caddeo *et al.* (2018) suggested the successful production of vesicular formulations that could be used to help regulate oxidative stress of wound and thus improve healing of a wound. Form of polysorbate used to make tocopherol loaded transfersomes weakly affected the properties and efficiency of the vesicles, but the transfersomes containing Tween 80 can be considered as the most promising formulation since the vesicles were small (76 nm) and capable of absorbing the highest amount of tocopherol (90 per cent). Additionally, they have been able to enhance the deposition of tocopherol in the different skin strata to a better degree and to ensure complete closure of the wound. Additional studies, such as targeted in vivo experiments, are required to confirm the antioxidant and wound healing activities of the loaded tocopherol transfersomes prepared in vitro (Caddeo *et al.*, 2018).

Zahid *et al.* (2019) synthesised an electrospun fibers resembling ECM matrix, promote healing of skin defects. Moreover, the characteristics of bi-layer membranes depending on PCL and PLA which were filled with α -tocopherol acetate. The PLA Monolayer degradation rate was significantly lesser than PCL Monolayer electrospun fibers. Compared with monolayer and bi-layer membranes, the co-spun membranes exhibited a significant biodegradability. The addition of α -tocopherol acetate to the electrospun membranes has been found to slightly enhance the rate of degradation. Studies of swelling indicated that bi-layered membranes are capable of absorbing water. Wound healing assay revealed about the significant role of the electron spun fibers in assisting the cellular migration, and proliferation at the scratch site. CAM assay demonstrated important angiogenic behavior of the membranes loaded with α -tocopherol acetate. Finally, the developed tocopherol acetate-based electron spun fibers were proved to be useful in wound healing studies (Zahid *et al.*, 2019).

Bonferoni *et al.* (2018b) demonstrated that incorporation of the poorly soluble that the encapsulation in chitosan oleate of poorly soluble hydrophobic molecules allows for fast dispersion in hydrophilic formulations such as freeze-dried dressings. In the present case, the combination of chitosan oleate nanocarriers incorporating AgSD and α Tph resulted in a dressing whose influence on tissue regeneration was dose-dependent, as the wound healing was observed more quickly after 4 mg (BD-4) dressing was applied compared to 2 mg (BD-2). It appears

Table 1: Represents the significance of tocopherol in wound healing activity.

Sl. No	Name of the Drug	Name of the Author	Significance	Reference
1.	Tocopherol	(Shin et al., 2017)	The anti-inflammatory, antioxidant characteristics of the gamma-tocopherol decreased the inflammation and oxidative stress and thus promoted cutaneous wound healing in case of diabetic mice.	14
2.	Tocopherol	(Caddeo et al., 2018)	Faster rate of tocopherol absorption resulted in fastening of the wound healing process in case of the skin wounds.	15
3.	Tocopherol	(Zahid et al., 2019)	Addition of α -tocopherol acetate to the electrospun membranes has been found to enhance the rate of degradation	16
4.	Tocopherol	(Bonferoni et al., 2018b)	Dose-dependent effect of tocopherol bioactive dressing acts as an effective and flexible hemoderivative aid for the treatment of wounds.	17
5.	Tocopherol	(Bonferoni et al., 2018a)	Tocopherol loaded nanoemulsions confirmed the cellular proliferative effect in case of keratinocytes and fibroblasts cell culture.	18

Table 2: Represents the significance of farnesol and betulin in wound healing activity.

Sl. No	Name of the Drug	Name of the Author	Significance	Reference
1.	Farnesol	(Wu et al., 2019)	Improved collagen synthesis and enhanced the reepithelization process in case of topical wound model	19
2.	Farnesol	(Wu et al., 2018)	Exert the strongest UVB-screening effects along with excellent diffusive property.	20
3.	Betulin	(Färber and Daniels, 2016)	Enhanced the wound healing process in case of topical wounds.	21
4.	Betulin		Oleogel shown excellent efficacy, tolerability, reepithelization and revascularization in case of burnt wound patients.	22

Table 3: Represents the significance of Retenoic acid in wound healing activity.

Sl. No.	Name of the Drug	Name of the Author	Significance	Reference
1.	Retenoic Acid	(Arantes et al., 2020)	Enhanced the wound healing activity by improving the collagen synthesis, reepithelization and revascularization in damaged skin portion of the diabetic mouse model.	23
2.	Retenoic Acid	(Pourjafar et al., 2017)	MSCs with ATRA improved cell therapy efficacy by stimulating survival signaling pathways	24
3.	Retenoic Acid	(Kitano et al., 2001)	Excellent biocompatibility and reepithelization potential all-trans-retinoic acid played a crucial role in skin wound studies.	25

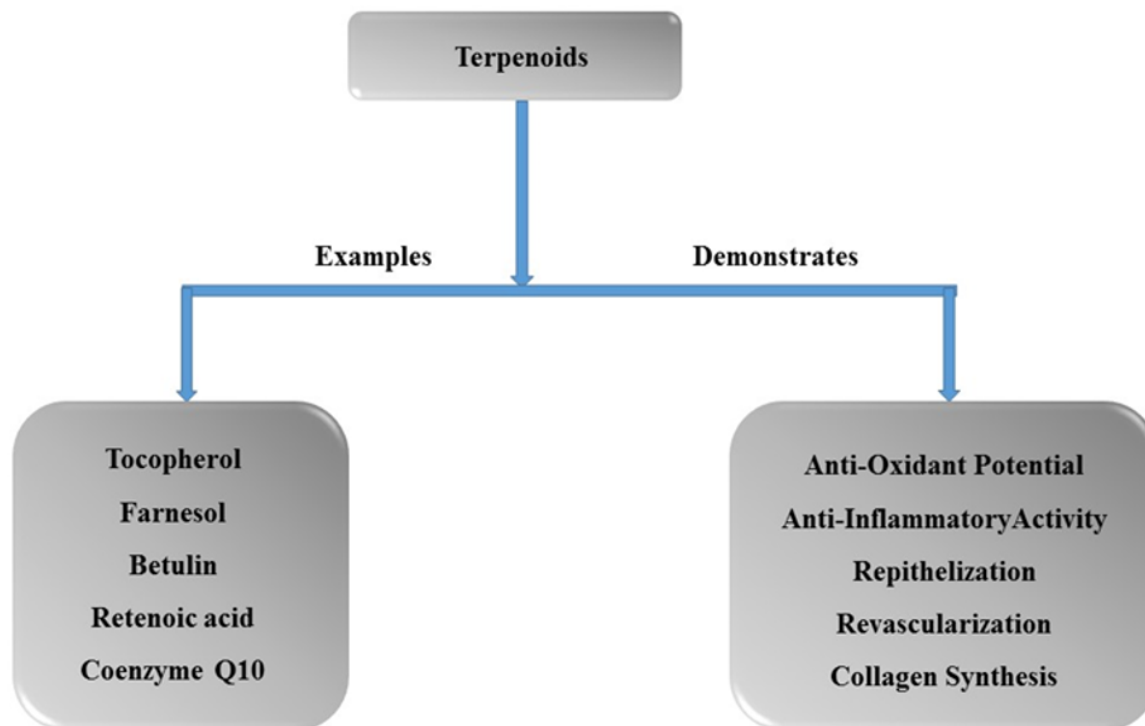


Figure 1: Represents a few examples of Terpenoids and their characteristics in wound healing activity.

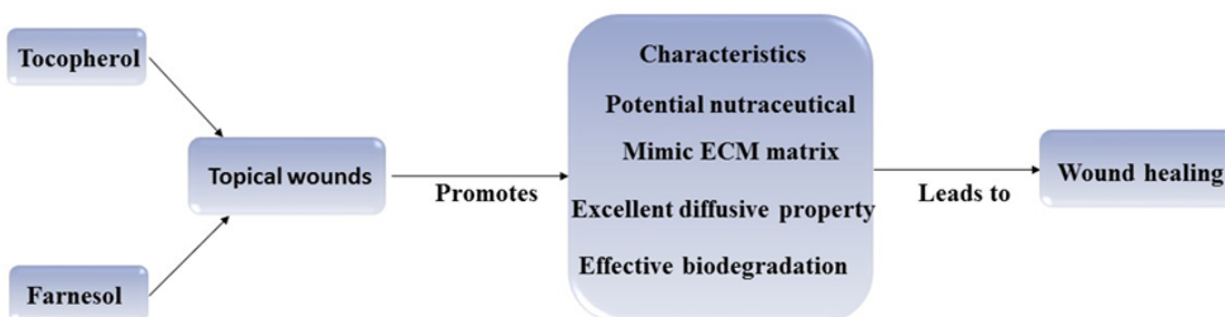
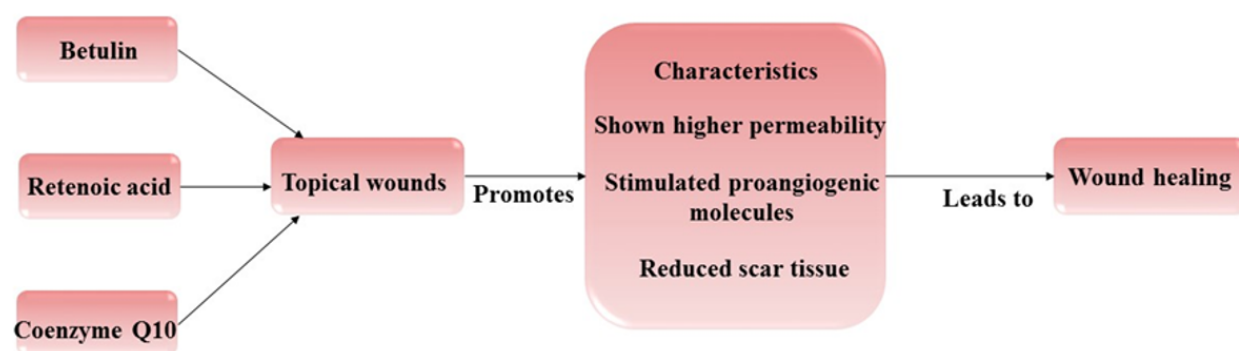


Figure 2: Represents the role of tocopherol and farnesol in wound healing activity.

Table 4: Represents the significance of coenzyme Q10 in wound healing activity.

Sl. No	Name of the Drug	Name of the Author	Significance	Reference
1.	Coenzyme Q10	(Choi <i>et al.</i> , 2009)	Shown strong antioxidant activity in the silica- and zymosan-induced reactive oxygen system utilizing Raw 264.7 cells.	26
2.	Coenzyme Q10	(Ryu <i>et al.</i> , 2020)	Shown a higher permeation efficacy fast wound healing effect in keratinocytes and fibroblasts cell culture.	27

**Figure 3: Represents the betulin, retenoic acid, coenzyme Q10 in wound healing activity.**

to support the formulation's bioactive behaviour, owing to the combined action of chitosan and chitosan oleate correlated with antioxidant involvement. The positive *in vivo* findings demonstrated the protective effect of encapsulation to the denaturing effect of AgSD, and the positive stimulation of α TphNE to the keratinocytes and fibroblasts previously observed *in vitro*. The combination of PL with bioactive 2 mg dressing (PL-BD) greatly enhances the dressing effect and also indicates an increase of PL efficacy on the promotion of wound healing. Therefore the bioactive dressing may be an effective and flexible hemoderivative aid for the treatment of wounds. The dose-dependent effect of bioactive dressing makes this a versatile method in treating a wound. In addition, the combination of PL with the bioactive help can be modulated to achieve the best healing effect at the lowest PL quantities. In addition, since PL preparation requires freezing steps, hemoderivative doses can be safely processed, treated and combined with the dressings without patients needing to make any efforts (Bonferoni *et al.*, 2018b).

Bonferoni *et al.* (2018a) demonstrated that Chitosan oleate (CS-OA) is ideal for stabilizing α Tph-loaded NEs, which are readily miscible in wound

exudate. Further, the ideal characteristics of the chitosan and oleic acid played a significant role in successful incorporation of tocopherol that aims to heal wounds. Furthermore, the findings of both polymer and drug-loaded nanoemulsions cell line studies demonstrated about the ideal proliferation of the fibroblasts and keratinocytes at the site of tissue defects. Finally, the incorporation of the tocopherol into chitosan oleate nanoemulsion enhanced the stability and thus improved the skin wound healing process (Bonferoni *et al.*, 2018a).

Farnesol

Given the inhibition of fibroblast proliferation at high concentrations, Wu *et al.* (2019) developed a farnesol / HPMC gel for enhancing the healing process in case of skin wounds. Further, the liposome incorporated farnesol gel effectively enhanced the reepithelization and collagen synthesis in case of burnt wound defects when compared to untreated, HPMC, SSC treated group. Finally, the Farnesol gel proved to be an ideal alternative for enhancing the post-burn wound healing process (Wu *et al.*, 2019).

Farnesol, a naturally occurring organic compound of 15 carbon chains, has diverse microbiological and cellular functions. Wu *et al.* (2018) developed a Farnesol gel for the treatment and management of UV

induced sunburn. Further, the various concentration of HPMC gel in fibroblasts demonstrated excellent intact nuclei and cytoplasm, which is similar to that of those without UVB exposure. Furthermore, in vitro characterisation studies indicated about the excellent diffusive potential and UV burn screening effects of the developed formulation. Finally, due to its excellent anti-inflammatory, antioxidant and cellular proliferative potential farnesol based gel formulations played a significant role in skin restoration studies (Wu *et al.*, 2018).

Betulin

Because of its excellent anti-inflammatory and permeability characteristics, betulin played a significant role in the acceleration of the wound healing activity. According to Färber and Daniels (2016) the outer bark of birch triterpenes obtained from birch bark are known for activating the healing activity in case of skin wounds. Moreover, the characterisation studies revealed about the excellent viscosity and permeability of the developed formulation. Further, the in vivo studies revealed about the excellent re-epithelization in case of the developed foams. Finally, the contactless application of the betulin loaded W/ O Proved to be promising for skin wound healing studies (Färber and Daniels, 2016).

Healing of burn wounds remains challenging now a days because of the lack of the angiogenesis and reepithelization at the damaged site. Frew *et al.* (2019) developed a betulin loaded oleogel for accelerating the wound healing activity in case of burnt wound patients. Further, the developed oleogel shown excellent efficacy and tolerability when compared to marketed formulations (Octenilin gel). Furthermore, the developed oleogel shown excellent reepithelization and revascularization in case of 84.9 % of patients when compared to its counterparts. Finally, the biocompatibility of the betulin loaded oleogel proved to be promising for burn wound healing studies (Frew *et al.*, 2019).

Retenoic acid

Restoration skin defects in diabetic wounds was crucial for minimising cases of limb amputations in the diabetic patients worldwide. Arantes *et al.* (2020) designed and characterized a solid lipid nanoparticles retenoic acid incorporated chitosan solid lipid nanoparticles for enhancing the wound healing activity of skin defects in case of a diabetic mouse model. Further, the characterisation studies revealed about the size uniformity, biocompatibility and controlled release of the developed solid lipid nanoparticles. Furthermore, the in vivo study data revealed that the developed retenoic acid loaded solid lipid nanoparticles successfully enhanced the

wound healing activity by improving the collagen synthesis, reepithelization and revascularization in damaged skin portion of the diabetic mouse model. Finally, it was identified that retenoic acid loaded solid lipid nanoparticles proved to be a promising approach for the treatment of skin defects in diabetic wounds (Arantes *et al.*, 2020).

Stem cell therapy is considered an ideal option for the treatment of a variety of wounds. However, the therapeutical approaches involving cellular therapy, chemical and pharmacological preconditioning proved to be promising for enhancing the wound healing activity. Pourjafar *et al.* (2017) in his study, examined the efficacy of the retenoic acid loaded mesenchymal stem cells (MSC) in case of skin wounds. Further, the gene expression studies demonstrated about the excellent anti-inflammatory and angiogenic potential of the MSC preconditioned retenoic acid-treated groups. Finally, MSC Preconditioned retenoic acid played a significant role in improvising the cellular proliferation and migration process which in turn ultimately resulted in the acceleration of wound healing activity (Pourjafar *et al.*, 2017).

Due to its excellent biocompatibility and reepithelization, potential all-trans-retinoic acid played a crucial role in skin wound studies. Moreover, in order to accelerate the wound healing activity, Kitano *et al.* (2001) utilised the all-trans-retinoic acid as a topical formulation. Further, the in-vitro characterisation studies demonstrated the importance of the retinoic acid in case of keratinocyte growth factor proliferation. Further, the in vivo analysis provided the evidence for the reepithelization, revascularization and fibroblast proliferation in case of retinoic acid-treated groups. Finally, it was proved that the retenoic acid has extended its influence in diabetic wound-related studies (Kitano *et al.*, 2001).

Coenzyme Q10

Due to its excellent anti-inflammatory and antioxidant potential coenzyme, Q10 played a significant role in wound healing studies. Choi *et al.* (2009) performed various characterisation studies in order to evaluate the extent of healing in case of CoQ10 treated groups. Moreover, the in-vitro characterisation studies revealed about the extent of fibroblast proliferation, antioxidant, and anti-inflammatory potential of the coenzyme Q10 at the skin wound site. Even though the coenzyme Q10 did not show the antioxidant potential in case of DPPH free radical scavenging activity it has shown excellent antioxidant activity in case of silica- and zymosan-induced reactive oxygen species based cell culture system.

Finally, the coenzyme Q10 proved to be promising for wound healing studies (Choi *et al.*, 2009).

In order to enhance the permeability and solubility of coenzyme Q10, Ryu *et al.* (2020) developed a coenzyme Q10 based microemulsion. However, out of several developed formulations coenzyme Q10 emulsions of 2: 1 (surfactant/ cosurfactant) ratio shown excellent permeability along with keratinocytes and fibroblast proliferation in case of treated groups. Finally, due to the excellent penetrability microemulsion system enhanced the therapeutic outcome of the coenzyme Q 10 molecule (Ryu *et al.*, 2020).

CONCLUSION

Terpenoids are potential bioactive compounds that are present in several plant-based products. However, a significant number of studies demonstrated about the significance of terpenoids as a wound-healing agent. Further, the structure-activity relationship of the various wound models has yet to be explored in order to determine about the processes involved in terpenoid based wound healing. Another topic yet to be explored is the regulation of the use of terpenoids and their dosage as wound care products.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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