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Research Article

Understanding the Role of IGF-1 in Regenerative Medicine for Skin Regeneration, the Future of Wound Healing: A Systematic Review

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Abstract

Background: The skin is the outermost layer of the body which serve as a protectivebarrier and plays a huge role in physical appearance. Pathology involving the skin such as chronic non-healing wound, hair loss and aging may affect the wellbeing of the individual leading to mental stress as well as increased morbidity and mortality. Inview of recent development in regenerative medicine, present study aims to pool studies relating to the used of insulin growth factor (IGF-1) in regenerative medicine for various skin conditions and identify the research gap. **Materials and Methods:** Anextensive literature search was done in PubMed Central and PubMed from 2009 to present, 2020. The inclusion criteria include original research related to IGF-1 in skin regeneration done in vivo or in vitro. **Results:** During the search, 208 journals were identified whereby 12 had met the inclusion criteria. Our findings revealed most of thestudies relating to this area were conducted on wound healing (n=11), and one studyis on hair growth (n=1). **Conclusion:** Based on current data, incorporating IGF-1 intoregenerative medicine benefits promotes wound healing which may benefits patients with non-healing diabetic wound, as well as hair growth which serve as aesthetic purposes for those with male or female pattern baldness. However, there were no studies relating to the anti-aging effects of IGF-1 and human studies/clinical trials conducted in this area of study which could be a potential area for future study.

Introduction

Skin diseases are a growing global problem which is rapidly increasing throughout theyears (Martinengo, Olsson et al., 2019). The complications after healing including scarring and hair loss may affect the individual aesthetically while chronic non-healing wounds contributes to morbidityand mortality (Menke, Ward et al., 2007). Current intervention maybe beneficial for certain skin diseases but not all. As such uncontrolled diabetic foot ulcer may leads to amputation which furtherimpairs their quality of life increasing morbidity and mortality (Alrub, Hyassat et al., 2019; AlSadrah, 2019; Weledji & Fokam, 2014). To date, studies on various intervention for skin diseases including diabetic and normal wound healing (Frykberg, Wittmayer et al., 2007; Jannu, Suganthirababu et al., 2019; Weledji & Fokam, 2014), male and female pattern hair loss (Avram & Finney, 2019; Coleman, 2020; Dervishi, Liu et al., 2020), and scar management are still ongoing (Behrouz-Pirnia, Liu et al., 2020; Gauglitz, Korting et al., 2011; Liu, Liu et al., 2019; Waibel, Gianatasio et al., 2020; Wiseman, Ware et al., 2020). In view of current development and trend in regenerative medicine along with the importance of insulin growth factor (IGF-1) in various skin conditions, present study aims to pool studies relating to the used of IGF-1 in regenerative medicine for various skin conditions (Achar, Silva et al., 2014; Amiri, Fathabadi et al., 2014; C. Chen, Hu et al., 2012; Dallman, Pecoraro et al., 2003; Emmerson, Campbell et al., 2012; Gan, Leong et al., 2020; Gomes, Rodrigues et al., 2017; Rudman, Philpott et al., 1997; Trüeb, 2018).

The used of regenerative medicine which includes tissue engineering and cellular therapy for skin regeneration had been widely studied and reviewed (Boyce & Lalley, 2018; Chocarro-Wrona, López-Ruiz et al., 2019; Deptuła, Zieliński et al., 2019; Gan, Leong et al., 2020). It was reported where both tissue engineering and cellular therapy yields positive results in skin regeneration (Boyce & Lalley, 2018; Chocarro-Wrona, López-Ruiz et al., 2019; Deptuła, Zieliński et al., 2019; Lamaro-Cardoso, Bachion et al., 2019; Paganelli, Benassi et al., 2019; Stojic, López et al., 2019). The effectiveness of regenerative medicine in skin regeneration is believed to be the secretomes such as growth factors, and peptides secreted by the cells introduced into the pathological/injured area which acts via paracrine effect to promotes healing (Amiri, Fathabadi et al., 2014; Park, Jun et al., 2019).

IGF-1 is one of the growth factor present during the inflammatory phase in the event of wound healing (Landén, Li et al., 2016; Serra, Barroso et al., 2017). According to Serra, Barroso et al. (2017) IGF-1 promotes fibroblastsproliferation, extracellular matrix synthesis, and angiogenesis which supports skin regeneration. Similarly, studies had reported IGF-1 stimulation or transduction of IGF-1 genes into cells used for regenerative medicine had been reported to yield favorable results to skin regeneration (Bak, Choi et al., 2018; Balaji, LeSaint et al., 2014; Shabbir, Cox et al., 2015). As different types of cells response differently to the growth factors present including IGF-1 (Doorn, van de Peppel et al., 2011), present review will pool studies relating to regenerative

medicine of the skin using IGF-1 stimulation and transduction on different types of cells. We sought to identify the research gap presenton the use of IGF-1 stimulated/transduced cells in skin regeneration. The findings in this review will benefits researchers and clinicians working on skin disorders and aesthetics.

Methodology

Literature Review

A comprehensive search of basic science journals in PubMed Central and PubMed was performed to identify studies related to IGF-1 in tissue healing. The search was performed in PubMed Central and PubMed is due to its reliability and the availability for related literatures. The keywords used were (i) IGF-1 'OR' (ii) Insulin Growth Factor-1 'AND' (iii) Mesenchymal Stem Cells 'AND' (iv) Tissue Healing from year 2009up to the present, 2020.

Selection of Research Articles

The selection of articles where conducted according to PRISMA guidelines and includes primary studies related to IGF-1 in tissue regeneration done *in vivo* or *in vitro*which are related to skin regeneration. Review articles such as narrative or systematicreview, news, letters, editorials, case studies or studies that does not relate IGF-1 to skin regeneration were excluded.

Data Extraction and Management

The literatures were reviewed in three phases (Figure 1) before being included. In brief, the identified articles were reviewed based on its title and abstract followed by its full text. Literatures that do not met our inclusion criteria were eliminated during any phase of our study.
The literatures were reviewed by one reviewer whereas another reviewer was assigned to review and confirm the included literatures. Differences in opinion were resolved by discussion between the reviewers. Hence, the literatures included in this study were the result from the mutual agreement between both reviewers. All data extraction was carried out and recorded on a data collection form base of the followings: (1) References which includes the author(s) name and year; (2) Study design; (3) Study population; (4) Intervention; (5) Types of skin research being studied
(6) Follow-ups; (7) Results relating to IGF-1 in skin regeneration.

Results

A total of 160 and 52 articles were retrieved from PubMed Central and PubMed respectively (Figure 1). Four duplicated journals were excluded. During screening andupon the agreement of the two reviewers, 196 articles were excluded due to the non-fulfilment of inclusion criteria. The excluded articles including reviews, editorials and studies which are not related to the integumentary system. During the selection process, the reviewer had identified studies which uses differenttypes of cells other than mesenchymal stem cells (MSCs). Upon deliberation, studies which has IGF-1 related to keratinocytes, alveolar type II epithelial cells (AvT-IICs), mononuclear cells (MNCs) and any form of fibroblasts including dermal fibroblasts (DFs) and foreskin fibroblasts were also included. Such decision were due to keratinocytes and AvT-IICs were cells differentiated from MSCs and therefore share the same lineages although they the not MSCs (Dos Santos, Borçari et al., 2019; Ma, Gai et al., 2011; Mishra, Mishra et al., 2016; Sasaki, Abe et al., 2008). The inclusion of studies whichuses MNCs were also due to previous studies which reported where MSCs are part ofMNCs and that MNCs also have the capability to differentiate into various tissues (Dolati, Yousefi et al., 2019).As the term MSCs is relatively a broad term where such cells were also known as fibroblasts by Friedenstein, Chailakhjan et al. (1970) who were the firstpioneer who discover MSCs. Hence, studies using any form of fibroblasts were included in this present review. Thus, upon the agreement of the reviewers, 12 articleswere included in present

review. Our findings include eight studies which consist of an in vivo component and four studies which consists only in vitro findings. Most of the literatures relating to IGF-1 stimulated or transduced cells were on wound healing except one in vivo study whichwere on hair growth. Our findings revealed the role of IGF-1, its expression and secretion had been studied on cells namely keratinocytes, hDPs (human dermal papilla cells), hBM-MSCs (human bone marrow mesenchymal stem cells), hAT-MSCs(human adipose tissues derived mesenchymal stem cells), mAT-MSCs (mouse adipose tissues derived mesenchymal stem cells), hA-MSCs (human amniotic mesenchymal stem cells), hDT-MSCs (human dermal tissues derived mesenchymal stem cells), hUCB-MSCs (human umbilical cord blood mesenchymal stem cells), human dermal fibroblasts (hDFs), foreskin fibroblasts, MNCs, AvT-IICs, and hUVECs(human umbilical vein endothelial cells) (Table 1). Most of these studies had reportedpositive results on skin regeneration.

Discussion

Role of IGF-1 in Hair Growth

Hair growth is an important element in aesthetic medicine which is required for those suffering from male/female pattern baldness (alopecia), pathology which damages the hair-bearing regions such as burns, and female to male transgender individuals who seek facial or body hair (Dhingra, Bonati et al., 2019; Norwood, 1975; Stevenson, Wixon et al., 2016; Vachiramon, Aghabeigi et al., 2004). Although various attempt to stimulate hair growth such as the use of minoxidil, finasteride, and low level laser comb therapy, the resultswere inconclusive (van Zuuren, Fedorowicz et al., 2016). In line with that, the used of regenerative aesthetic medicine had begun to gain popularity where platelet rich plasma were one of the key therapy administered for skin regeneration (Elghblawi, 2018; Samadi, Sheykhhasan et al., 2019). Our study reviewed the role of IGF-1 in regenerative medicine since 2009 in skin disorders had identified only one in vivo studies relating to this area (Bak, Choi et al., 2018). According to that study, IGF-1 enhance hair morphogenesis and increases neogenesis in induced telogen-anagen transition C3H/HeJ mice model via paracrine mechanism through AKT/GSK3β/β-cateninpathway (Wnt pathway) (Figure 2). Sadly, there were insufficient data in relation to thisarea and hence, more studies should be done to understand the role of IGF-1 in hair growth.

Role of IGF-1 in Wound Healing

The role of IGF-1 stimulated/overexpressed cells had been widely studied in wound healing. Most studies identified reported where IGF-1 enhance wound healing by stimulating the proliferative and migration potential of MSCs, hDFs, and hBM-MSCs (L. Chen, Xu et al., 2014; Kraskiewicz, Paprocka et al., 2020; Shabbir, Cox et al., 2015; Shim, Park et al., 2013). According to the studies by Shim, Park et al. (2013), hDT-MSCs secreted relatively higher levels of IGF-1 and other peptides namely bFGF, HGF, IGF binding proteins-1 (IGFBP), IGF binding proteins-2 (IGFBP-2), and VEGF into the culture medium compared with non-hDT-MSCs. Using the culture medium to cultured hDFs, the authors had reported an increased in hDFs proliferation and migration leading to enhance wound healing based on wound scratch assay. Similarly, L. Chen, Xu et al. (2014) had culture hBM-MSCs in hypoxic condition which stimulates the increasedlevels of IGF-1 which enhance its proliferation and migration. However, these studies had stimulated their cell of interest with the presence of other growth factors and peptides. As such, culturing cells in hypoxic condition had also been reported to upregulate bFGF and VEGF which might also contributes to enhance cellular proliferation and migration (Lee, Xia et al., 2009). While the study by López, Sarkanen et al. (2018), had reported where IGF-1 did not promote proliferation and migration of hAT-MSCs, human foreskin fibroblasts, human umbilical vein endothelial cells (hUVECs) and keratinocytes. With all these findings reported, we concluded that the role of IGF-1 in stimulating cellular proliferation and migration leading to skin regeneration were also being influenced by the other stimulants, peptides and cell receptors present. However, theoptimal condition to enhance cellular proliferation and migration depends on the type of cells which requires further studies.

Besides promoting cellular proliferation and migration, incorporation of IGF-1 into intervention

also promotes wound healing by enhancing angiogenesis, stimulates cellular differentiation and protein secretion (Balaji, LeSaint et al., 2014; L. Chen, Xu et al., 2014; Garg, Rennert et al., 2014; Ghosh, Gorantla et al., 2013; Jin, Kim et al., 2013; Kim, Zhang et al., 2012; Shabbir, Cox et al., 2015; Weinheimer-Haus, Judex et al., 2014). It had been reported where IGF-1 enhance angiogenesis when coupled with other stimulant such as TGF-β (57). Similarly, Garg, Rennert et al. (2014) seeded mAT-MSCs into hydrogel and reported increase expression of OCT4, VEGF, MCP-1, SDF-1 and IGF-1 which is related to stemness and angiogenesis leading to accelerate wound closure. To date, studieshad reported the importance of IGF-1 in skin regeneration where IGF-1 is seen to actalong with the other stimuli consisting of growth factors, cytokines or peptides presence in the culture medium or secreted by cells to accelerate wound healing. However, no studies identified which characterised all the peptides presence in different types of cells and studied the interaction between them and IGF-1 in promoting skin regeneration and accelerate wound closure. Although Ghosh, Gorantla et al. (2013) had reported where IGF-1 enhance wound closure through Wnt pathway (Figure 2), little did we knew on the mechanism on how IGF-1 interact with all theother growth factors and stimuli to accelerates wound closure.

Major Concerns, Recommendation and Future Directions

To date, most studies had reported incorporation of IGF-1 into skin regeneration yieldsfavourable results. Although these studies had reported IGF-1 enhance migration, proliferation, differentiation, angiogenesis, cell survival and secretion of peptides, cytokines and growth factors which supports skin regeneration, these properties are also the major concern in skin regeneration. The ability of the cells to migrate may guide the cells to the pathological area in promoting healing however, this is also a major concern especially for those patients with multiple pathology such as diabetes.This is because the cells may also have the potential to migrate to the diabetic pancreas instead of the wound. Besides that, IGF-1 had also been widely studied in many cancer studies and had been reported to be one of the contributing factors to cancer (Castejón, Plaza et al., 2020; Christopoulos, Msaouel et al., 2015; Grimberg, 2003; Le Coz, Zhu et al., 2016). Hence, precaution should be taken as IGF-1 overexpress or producing cells may also have the potential to developed into malignant growth considering the ability of IGF-1 to enhance cellular migration and proliferation.

Besides enhancing the ability to proliferate, the role of IGF-1 had been widely studiedin cellular differentiation into osteogenic (Y. Chen, Zhao et al., 2017; Doorn, van de Peppel et al., 2011; Filion, Skelly et al., 2017; Frisch, Venkatesan et al., 2014; Gan, Choy et al., 2021; Hwang, Cho et al., 2014; Kumar & Ponnazhagan, 2012; Osugi, Katagiri et al., 2012; Qi, Xia et al., 2018), chondrogenic (Gan, Choy et al., 2021; Ikeda, Sakaue et al., 2017), adipogenic (Kumar & Ponnazhagan, 2012), and cardiogenic lineages (Gong, Wang et al., 2017). Therefore, it is important to identify all the factorswhich have agonist, antagonist, and synergist effect to IGF-1 in inducing such differentiation to prevent unwanted tissue formation at the treatment area. In additionto that, excessive angiogenesis is a characteristic of most inflammatory and neoplastic skin diseases such as psoriasis, atopic dermatitis, melanoma and vascular neoplasia (Richarz, Boada et al., 2017). Hence, it is still questionable if IGF-1 could effectively treat neoplastic wounds orinduce wound healing and hair growth in patient who also present with inflammatory and neoplastic skin diseases. Also, it's risk and complication for skin regeneration should first being evaluated before translating this approach into clinical trial. Clinical trials should commence with IGF-1 overexpressed or producing cells being introducedlocally on the site of injury instead to systemic delivery to prevent its migration to any undesirable area. In addition to that, although IGF-1 may promote wound healing, it also promotes hair growth. It is also questionable if IGF-1 overexpressed or producingcells will causes excessive hair growth during wound healing at the injured site. Therefore, understanding the mechanism and interaction of IGF-1 with other cells, growth factors and peptides present in the healing environment is crucial before translating this study into clinical trials.

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Gan Quan Fu (Lecturer, UTAR) Co-ordination and design of the project and overall strategy, contribution to data acquisition, literature review and data analysis, and in manuscript preparation.
Ker Woon Choy (Senior Lecturer, Universiti Teknologi MARA) Contributed on data acquisition and as reviewer of the study.
Chai Nien Foo (Assistant Professor, UTAR) Contributed to data analysis and the images in the study.
Chye Wah Yu (Associate Professor, AIMST) Contributed to data analysis and reviewer of the study
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Table 1:
Characteristics of Reviewed Articles

Reference	Study Design	Study Population	Brief Description about the Study	Organ/Tissues Studied	Outcomes Related to IGF-1 and Tissue Healing
Shabbir, Cox et al. (2015)	In Vitro	hBM-MSCs	Incubate both human normal and diabetic wound fibroblasts with MSCs derived exosomes.	Skin (Diabetic Wound Healing)	• hBM-MSCs exosomes induce the expression of a number of growth factors including IGF-1 contributing to increase proliferation and migration of normal and chronic wound fibroblasts and enhance angiogenesis in vitro.
Bak, Choi et al. (2018)	In Vivo	• hUCB-MSCs • hDPCs • Induced telogen- anagen transition C3H/HeJ mice model	• *In Vitro* section involves coculture hDPCs with hUCB-MSCs. hDPCs were then characterised. • *In Vivo* section involves Intradermal injection of hUCB-MSCs into the hair depilated mice and the dorsal skin was harvested for characterisation.	Skin (Hair Growth)	*In Vitro:* • The actions of IGF-1 are modulated by IGFBP-1. (When IGFBP-1 expression increases, the protein concentration of IGF-1 decreases) • IGFBP-1, through the colocalization of an IGF-1 and IGFBP-1, had positive effects on cell viability, proteins and growth factors secretion which promotes hair growth via paracrine mechanism. • The mechanism of IGF-1 in hair growth is through AKT/GSK3β/β-catenin pathway *In Vivo:* • hUCB-MSCs enhanced hair follicle morphogenesis, represented as an increase of follicular neogenesis.

Balaji, LeSaint et al. (2014)	In Vivo	• Human Skin (Keratinocytes) • Induced diabetic wound mice.	Ex Vivo: Skin (Diabetic Wound Healing) • 6 mm full thickness punch biopsy human skin samples were embedded in rat tail collagen I gel matrix and were treated with Ad5-CMV-IGF-1 and Ad5-CMV-LacZ vector and were characterised based	*Ex Vivo* • Overexpression of IGF-1 increases basal keratinocytes migration and angiogenesis without increasing VEGF levels on day 7. *In Vivo* • Adenoviral mediated gene transfer of IGF-1 enhances diabetic impaired wound healing by accelerating

			on its viability and VEGF expression levels. In Vivo • Two full-thickness excisional skin wounds were created on the backof mice. • One wound was injected with Ad5-CMV-IGF-1 or Ad5-CMV-LacZ. The other were injected with PBS. • Mice were sacrifices for histological and immunostaining analyses.		epithelial gap closure and promoting granulation tissue formation. • IGF-1 overexpression enhances angiogenesis without increasing VEGF levels (VEGF-independentpathway).
L. Chen, Xu et al. (2014)	In Vivo	• hBM-MSCs • Balb/c nude mice	• *In Vitro* section involves characterising the cellular properties (generic expression, proliferation and migration ability, and protein synthesis) of hBM- MSC cultured in hypoxic condition. • *In Vivo* section involving the application of hypoxic hBM-MSCs culture medium on wounds created on Balb/c nude mice.	Skin (Wound Healing)	*In Vitro* • Hypoxic condition increases mRNA expression levels of IGF-1. • Hypoxia enhances proliferation, migration and angiogenic paracrine effects of BM-MSCs. *In Vivo* • Culture medium from hBM-MSCs cultured in hypoxic condition when applied to wounds created on Balb/c nude mice demonstrated significantly accelerated wound closure relative to the other groups.

Garg, Rennert et al. (2014)	In Vivo	• mAT-MSCs • 8 to 12 weeksold wound induced maleC57Bl/6 mice	• *In Vitro* section of this study involves seeding mAT- MSCs onto collagen hygrogel scaffold andcharacterised. • *In Vivo* section involves placing the seeded or unseeded wound bed of the C57Bl/6 mice.	Skin (Wound Healing)	*In Vitro* • Hydrogel seeded mAT-MSCs results in increase expression of multiple genes related to stemness and angiogenesis including OCT4, VEGF, MCP-1, SDF-1 and IGF-1. *In Vivo* • Mice treated with hydrogels seeded with mAT-MSCs demonstrate

					improves wound closure and vascularisation.
Ghosh, Gorantla et al. (2013)	In Vitro	rAvT-IICs	• rAvT-IICs isolated from male SD rats and were cultured. rAvT-IICs were cultured till day 6 to obtain rAvT-ICs. • The culture medium for rAvT-IICs cells and rAvT- ICs were analysed. • rAvT-IICs were then been treated by IGF-1 and characterised.	Skin (Wound Healing)	• IGF-1 was increased in the culture medium of rAvT-ICs compared to rAvT-IICs. • IGF- 1 plays a significant role in cell differentiation by speeding up the differentiation of rAvT-IICs into rAT-Icells. Such differentiation was through Wnt pathway based on the activation of Wnt5a. • IGF-I or Wnt5a stimulates wound closure.
Jin, Kim et al. (2013)	In Vivo	• MNCs • Non-obese diabetic-severe combined immune deficiency NOD-SCID mice	• *In Vitro* section involves incubation of isolated MNCs with a priming cocktail containing EGF, IGF-1, FGF-2, FLT-3L, Ang-1, GCP-2 and TPO for 15, 30 and 60 min. • *In Vivo* section involves transplantation of the cellsinto the wounds of non- obese diabetic-severe combined immune deficiency (NOD-SCID) mice. The wounds were then being evaluated	Skin (Wound healing)	*In Vitro* • The 30 minutes primed cells demonstrated significantly elevated angiogenic and anti-apoptotic properties with the elevation of IGF-1 and TGF-β. It also demonstrated significantly increased rate of fibroblast-mediated wound closure based on wound scratched assay. *In Vivo* • When the cells were injected into induced NOD/SCID mouse wound model. Those mice transplanted with 30 minutes primed cells demonstrated accelerated wound healing at day 7 and 14.

Kim, Zhang et al. (2012)	In Vivo	• hA-MSCs • hAT-MSCs • hDFs • 12 to 14 weeks male STZ induced diabeticNOD/SCID mice.	• *In Vitro* section involves culturing hA-MSCs, hAT- MSC and HDFs in a low- glucose DMEM and characterised them. • *In Vivo* section involves treating the full excisional wound created on the	Skin (Diabetic Wound Healing)	*In Vitro* • hA-MSCs showed significantly higher expression of the IGF-1(27- fold), when compared to hAT-MSCs. • hA-MSCs culture medium significantly increased the rate of fibroblast wound closure to those culture media obtained from hAT-

			dorsal surface each side ofthe midline of the mice with the cells and analysedit.		MSCs, hDFs and control group at 48 hours based on scratch wound analysis. *In Vivo* • hA-MSCs treated wounds displayed accelerated wound healing at 7, 10 and 14 days, compared with those treated with hAT-MSCs and hDFs. • Histological analysis at day 14 showed that hA-MSCs-treated wounds displayed enhanced reepithelialisation when compared to those treated with hAT-MSCs andhDFs. • Cells in hA-MSCs treated wounds possess high keratinocyte differentiation and cell survival potential.

Kraskiewicz, Paprocka et al. (2020)	In Vivo	• hAT-MSCs • NOD/SCID female mice	*In Vitro* • hAT-MSCs were isolated from patients with venous stasis ulcer and healthy patients and were transfected with pSV3-neo and hTERT plasmids. The transfected cells were distinguished and cells that demonstrated high proliferation rate were selected for expansion. The cultures of the cells were then be characterisedbased on its secretory profile and capability to enhance angiogenesis. *In Vivo* • The cultures of the cells and were injected into	Skin Wound and Tumorogenesis	*In Vitro* • Cytokines including angiogenin, growth-regulated oncogene, IL-6, IL-8, VEGF, IGF-1, and matrix metalloproteinase were found positive in all hAT-MSCs supernatants. • Supernatant treatment significantly enhanced the survival of fibroblasts, endothelial cells, and keratinocytes in the in vitro chronic wound model. It improves the proliferation of fibroblasts. *In Vivo* • The supernatant treatment does notcause tumorogenesis in vivo.

			NOD/SCID female mice for Tumorigenicity assay.		
López, Sarkanen et al. (2018)	In Vitro	• Human Keratinocytes • hAT-MSCs • Human Foreskin fibroblasts • hUVECs	The protein and growth factor (EGF, IGF-I, IL-6, PDGF-B, TNF-a, TGF-β, FGF-a and VEGF, and KGF) concentration were measured for both platelet rich plasma or adipose tissue extract and the cultures were used in human keratinocyte, human foreskin fibroblast, hUVECs and hAT-MSCs cell culture. The cells were then been characterised based on its proliferation and migration capabilities.	Skin (Wound Healing)	• All growth factors except KGF is significantly higher in platelet rich plasma compare to adipose tissue extract. • Both platelet rich plasma and adipose tissue extract did not promote proliferation of hAT-MSCs, human foreskin fibroblasts and hUVECs. However, adipose tissue extracts significantly induce the proliferation of keratinocytes. • Adipose tissue extracts significantly induce the migration of human foreskin fibroblasts and hA-MSC as compare to platelet rich plasma and control group. • There was no difference in the migration abilities for hUVECcultured in adipose tissue extract, platelet rich plasma and the control group. • Human keratinocytes cultured in adipose tissue extract or platelet rich plasma demonstrated better migration and faster wound closure as compared to the control group. • Hence the combination of growth factors and IGF-1 doesn't necessarily enhance migration and proliferation.

Shim, Park et al. (2013)	In Vitro	Normal hDFs	Conditioned medium used for hDT-MSCs culture were usedin culturing Normal hDFs. ThehDFs were characterised.	Skin (Wound Healing)	• hDT-MSCs secreted relatively higher levels of bFGF, HGF, IGFBP-1, IGFBP-2, IGF-1, and VEGF compared with non- hDT-MSCs. • UVA-irradiated Normal hDFs cultured in hDT-MSCs cultured

					condition medium demonstrated increased wound healing process via wound scratch assay by enhancingits migration and proliferation.
Weinheimer-Haus, Judex et al. (2014)	In Vivo	• Induced Diabetic Wound Mice	• *In Vivo* section of this study involves administering low intensity vibration on the wound created on the dorsum of the mice and characterised it in comparison to the non-vibration group.	Skin (Wound Healing)	In Vivo • Low intensity vibration led to higher levels of growth factors namely IGF-1 and VEGF but not TGF-β1 at the injury site at day 7 post wounding. • Low intensity vibration leads to increased re-epithelialization and granulated tissue formation on day 7in addition to higher collagen deposition and robust increase in angiogenesis. On day 15, low intensity vibration treated group demonstrated better wound closure and higher macrophages level as compare to the control group.

Organism
h: Human; m: Mice; r: Rat
Tissues Derived
A: Amniotic; AT: Adipose Tissue; BM: Bone Marrow; DT: Dermal Tissues; UCB: Umbilical Cord Blood
Cell Types
AvT-ICs: Alveolar Type I Cells; AvT-IICs: Alveolar Type II Cells; DFs: Dermal Fibroblasts; DPCs: Dermal Papilla Cells; MNCs: Mononuclear cells MSCs: Mesenchymal Stem Cells; UVECs: Umbilical Vein Endothelial Cell
Growth Factors
Ang: Angiopoietin; bFGF: Basic Fibroblast Growth Factor; EGF: Epidermal Growth Factor; FGF: Fibroblast Growth Factor; FLT: FMS-like tyrosine kinase; GCP: Granulocyte Chemotactic Protein; GDF-5: Growth Differentiation Factor-5; HGF: Hepatocyte Growth Factor; IGF-1: Insulin Growth Factor-1; IGFBP-1: Insulin Growth Factor Binding Proteins-1; IL: Interleukin; KGF: Keratinocyte Growth Factor; MGF: Mechano Growth Factor; PDGF: Platelet Derived Growth Factor; TGF-β: Transforming Growth Factor-β; TNF: Tumor Necrosis Factor; TPO: Thrombopoietin; VEGF: Vascular endothelial growth factor; **Cell Transduction**
Ad: Adenoviral Transfer Vector; CMV: Cytomegalovirus promoter; hTERT: Human Telomerase Reverse Transcriptase; pSV3-neo: Vertebrate/E.coli Plasmid Vector

Figures

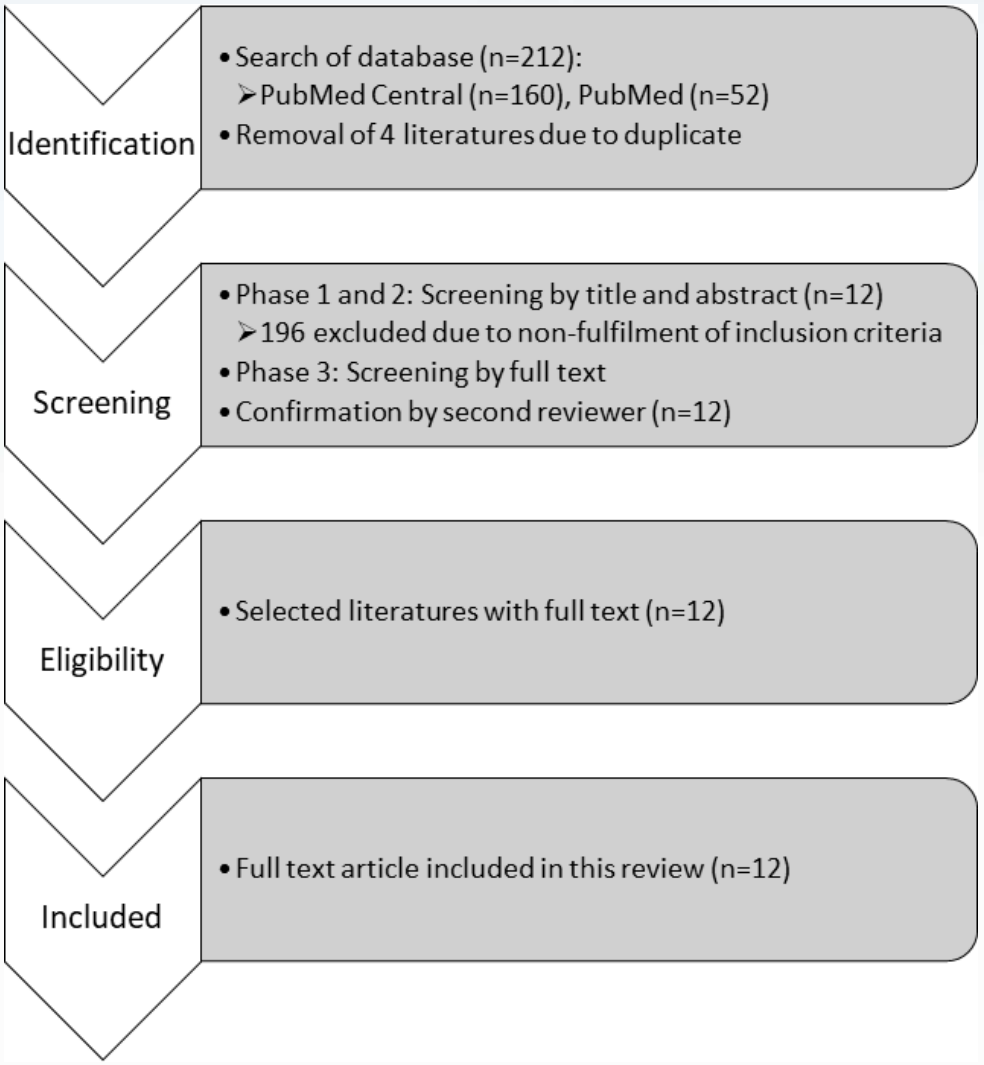

Figure 1: Article Selection Process

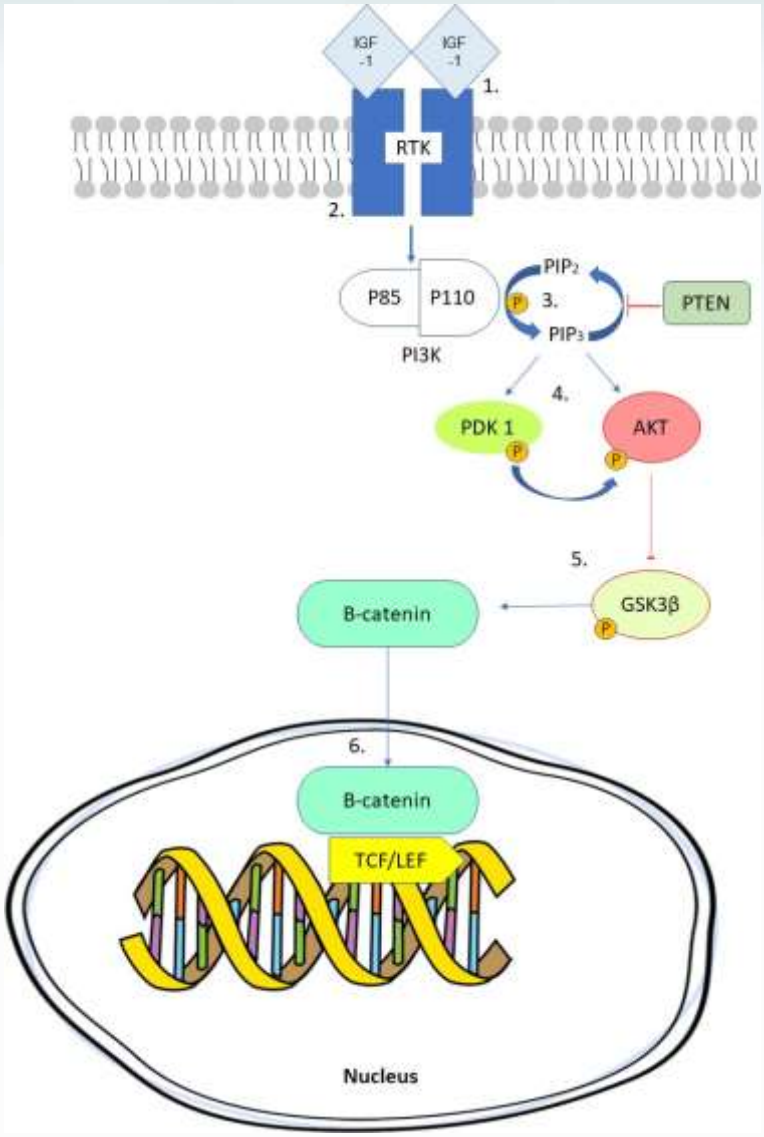

Figure 2: AKT/GSK3β/β-catenin pathway (Wnt pathway)

IGF-1 binds to receptor tyrosine kinase (IGF-1 receptor). 2. Phosphorylation oftyrosine kinase which activates PI3K. 3. PI3K phosphorylates PIP2
(phosphatidylinositol 4,5-bisphosphate) into PIP3 (phosphatidylinositol (3,4,5)- trisphosphate). 4. PIP3 activates AKT (protein kinase B) via PDK1 (phosphoinositide-dependent protein kinase-1). 5. AKT activation inhibits GSK3β. 6.
Inhibition of GSK3β activity leads to an accumulation of β-catenin in the cytoplasm.β-catenin eventual translocation into the nucleus to act as a transcriptional coactivator of transcription factors that belong to the TCF/LEF family.