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Photobiomodulation (PBM): a therapeutic technique targeting fibroblast cell regeneration and survival in diabetic wounds

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In injury, fibroblasts are key for disintegrating the fibrin clot, secreting collagen proteins, and constructing extracellular matrix. Altered fibroblast function is among the common characteristics of delayed wound healing and development of chronic wounds. Thus, treatment methods for effective wound healing require agents that affect the complexed wound milieu, including fibroblast cells. Diabetes mellitus (DM) is a common cause of impaired fibroblast cell function, delayed wound healing, development of chronic ulcers, and limb amputation. Photobiomodulation (PBM) promotes fibroblast cell proliferation, migration, release of growth factors and wound healing. Yet, its use is limited largely due to an incomplete understanding of its underlying mechanisms at the molecular and cellular level. In this review, we summarise the involvement of fibroblast cells in wound healing, and the effect of PBM on fibroblast cell function and diabetic wound healing. PubMed, Google Scholar, and Research Gate were used to find pertinent academic articles.

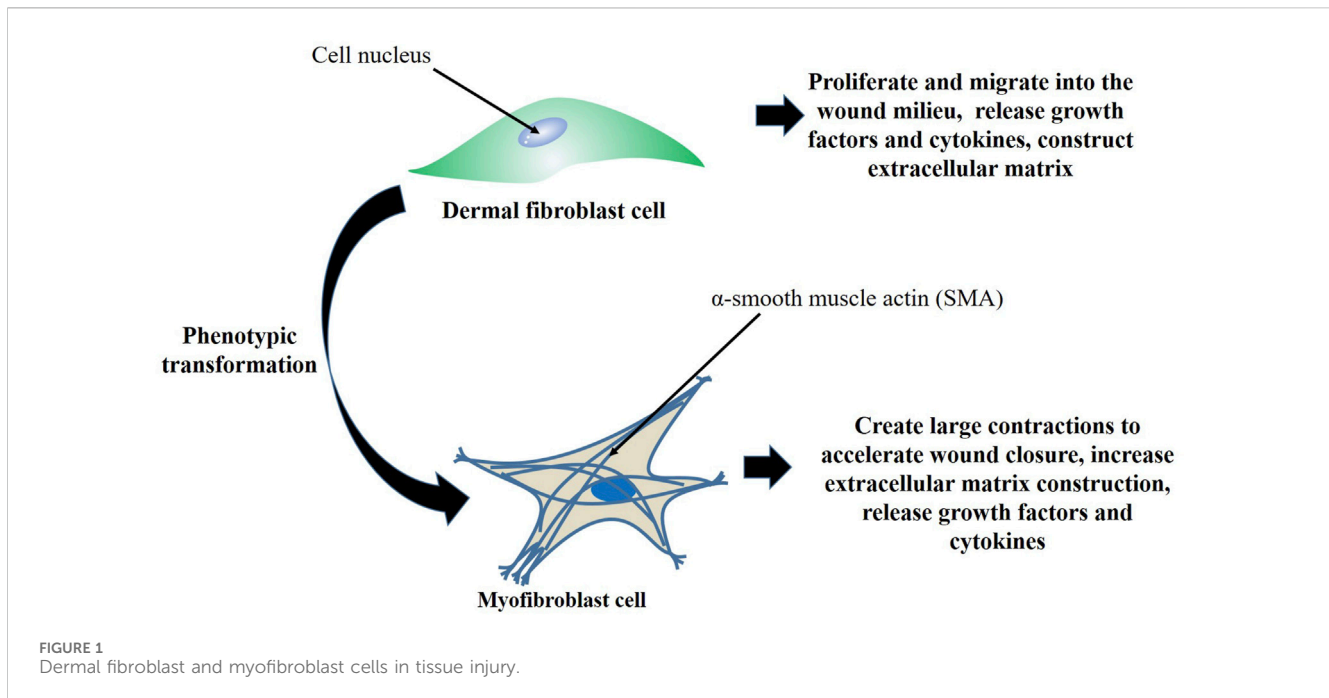
KEYWORDS

fibroblasts, diabetes, fibroblast dysfunction, wound healing, photobiomodulation, diabetic wound

1 Introduction

The global morbidity rate of diabetes mellitus (DM) is increasing, and by 2030 it is estimated to increase from approximately 5%–8% (Liao et al., 2022). Several complications develop as a result of DM, accompanied with high treatment costs, disability, and lowered life expectancy of the affected individual. Diabetic foot ulcers (DFUs) are a critical marker for high mortality in diabetic patients, and is characterised by infection, persistent wound formation, and destruction of the deep tissue. The development of diabetic ulcers is largely due to neuropathy and peripheral arterial disease, and the risk of developing chronic wounds in diabetic patients is reported to have increased to approximately 25% (Jais, 2023). Literature elucidates that in DM, dermal fibroblast activity is reduced, and is closely related to the reduced wound healing process (Evangelatov et al., 2022). Treatment for diabetic ulcers is a challenge, frequently resulting in minor or major limb amputation which increases the mortality rate within 5 years to as high as 39%–68% (Petersen et al., 2020; Liao et al., 2022; Liu et al., 2022; Jais, 2023).

The notion that dermal fibroblasts comprise numerous separate subpopulations is a significant development in the field of skin pathophysiology and provides a fresh viewpoint that could lead to the development of innovative wound remedies (Des Jardins-Park et al., 2018). This review discusses the involvement of fibroblast cells in wound healing, and PBM



as a treatment technique for fibroblast cell regeneration and survival in diabetic wounds. A search was conducted online using terms like “diabetic wound healing,” “fibroblast cell,” “fibroblast cell in wound healing,” “diabetes mellitus,” “effect of photobiomodulation,” and “laser therapy in diabetic wound healing” on PubMed, Google Scholar, and Research Gate. The heterogeneity of healthy fibroblast cells is well explained elsewhere (Liu et al., 2022).

2 Influence of hyperglycaemia on fibroblast cells during skin wound healing

During the skin wound healing process, the granulation tissue is basically composed of ECM, inflammatory cells, small blood vessels, and fibroblast and myofibroblast cells. Myofibroblast cells characteristically differ from normal fibroblasts due to their increased ability to synthesize large amounts of ECM proteins and tighten the wound. They express alpha-smooth muscle actin (α -SMA), an isoform of actin, and is found in the majority of connective tissues of healing wounds (Evangelatov et al., 2022). Fibroblasts are mesenchymal-derived cells, and are widely found in most tissues. This cell type express vimentin, but neither desmin nor α -SMA are expressed, and under normal circumstances, fibroblasts are essential for controlling the turnover of ECM. Fibroblasts are activated in injured tissue, and undergo differentiation into myofibroblasts (Figure 1) that shrink the wound and release ECM proteins to aid in the healing process (Li and Wang, 2011). Fibroblasts possess a variety of functions including creation of the basic tissue and organ framework, and are among the critical cell types for effective wound healing (Dick et al., 2023). Fibroblast cells are responsible for coordinating the entire wound healing process by producing a range of regulatory molecules and interacting with other cell populations involved in the healing mechanism. Injury

provokes the release of cytokines, resulting from platelet degranulation, which sets off an inflammatory response. During this time, tumour necrosis factor- α (TNF- α), inducible nitric oxide synthase (iNOS), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-12 (IL-12), and other pro-inflammatory mediators are further elevated, thereby promoting inflammation and fibroblast cell recruitment and activation (Francesca et al., 2022).

Although fibroblast cells are essential for an acute wounds’ ability to heal, they can also cause fibrosis and excessive scarring, and may prevent a lesion from healing as in the case of ulcerative and diabetic wounds (Samuel et al., 2023). Dysfunctional fibroblast cells is a critical factor in the development of chronic wounds, and abnormal deposition of ECM and collagen often cause permanent organ dysfunction. Research has demonstrated that fibroblasts from chronic wounds have aberrant characteristics, such as reduced proliferation, early senescence, and changed cytokine release patterns, in addition to aberrant MMP and tissue inhibitor of metalloproteinases (TIMP) activity (Wall et al., 2008; Li and Wang, 2011). Furthermore, it has been demonstrated that hyperglycaemia reduces migration, proliferation, and production of collagen, and enhances apoptosis of fibroblast cells (Xuan et al., 2014). Buranasin et al. (Buranasin et al., 2018) elucidated that hyperglycaemia affects fibroblast cell proliferation and migration, elevates inflammation, and hinders the wound healing process.

Delayed and postponed wound healing in DM is largely due to dysregulated differentiation of fibroblasts to myofibroblasts, disordered action of myofibroblasts, and insufficient deposition of ECM (Wan et al., 2021). Dysfunctional myofibroblasts can cause postponed or suspended wound repair process mostly due to failure in ECM reconstruction (Cialdai et al., 2022). One of the key pathogenic influences in diabetic complications is oxidative stress due to high concentrations of advanced glycation end products (AGEs). Increased oxidative stress is a vital mechanism that triggers

cellular defects and accelerated tissue damage, mostly via the increased reactive oxygen species (ROS) and activated receptor for AGEs (RAGE). During the wound repair process, several pro-inflammatory cytokines and other signalling pathways, including transforming growth factor-beta (TGF β)/Smad, similarly activate fibroblast cells and cellular fibrosis, and, increased expression of MMPs, TGF, Angiotensin II (Ang II), and TNF- α are associated with fibrous tissue remodelling (Zheng et al., 2019). High blood glucose activates the advancement of tissue fibrosis, and during diabetic wound healing is linked to reduced and malfunction of myofibroblasts (Deb et al., 2017). To demonstrate the effect of hyperglycaemia on fibroblasts, Haas et al. (Haas et al., 2021) noted a decreased expression of fibrosis-related genes and myofibroblasts in diabetic wounds. Lerman et al. (Lerman et al., 2003) found a significant reduction in fibroblast cell migration, transformed production of matrix metalloproteinase 9 (MMP-9), and a huge reduction in the production of vascular endothelial growth factor (VEGF) from diabetic mice. In addition, Zheng et al. (Zheng et al., 2019) showed that hyperglycaemia increases the expression of MMP-9, a protein that regulates the pathological remodelling processes involving prolonged inflammation and fibrosis, and intracellular domain of Notch receptor in fibroblasts. Recent studies have shown that hyperglycaemia reduces fibroblast proliferation and migration, and these findings clearly point out the failure of fibroblasts to hastily migrate into the wound milieu, reconstruct the ECM, and effectively promote angiogenesis in DM (Wall et al., 2008; Deng et al., 2021).

3 Therapeutic methods that target fibroblast cells in diabetic wound healing

There are several therapeutic methods that classically focuses on offloading, maintaining a moist environment, and preventing infection and formation of biofilm. Growth factor and cell-based therapies have been used to target and improve the performance of fibroblasts (Berger et al., 2021). Recently, attempts have been made to transform the wound bed into an environment where maximum wound healing may be successfully obtained. In clinical practice, cells including fibroblasts have all been utilised to promote wound healing (You and Han, 2014). Also, nanotechnology-based therapies for chronic diabetic wounds have emerged, with numerous designed nanotechnologies exhibiting distinct qualities and diverse applications for wound repair being put forth (Hamdan et al., 2017). Furthermore, treatment approaches based on stem cells have been suggested, and their potential to enhance both the speed and calibre of wound healing as well as skin regeneration has been demonstrated (Nourian et al., 2019). However, these options are not satisfactory, and many patients still require amputation, with approximately 30% of patients with chronic diabetic wounds undergoing amputation (Deng et al., 2021). In recent years, the understanding of fibroblast cell behaviour in wound healing has led to discoveries of novel therapeutic techniques including photobiomodulation (PBM) (Des Jardins-Park et al., 2018).

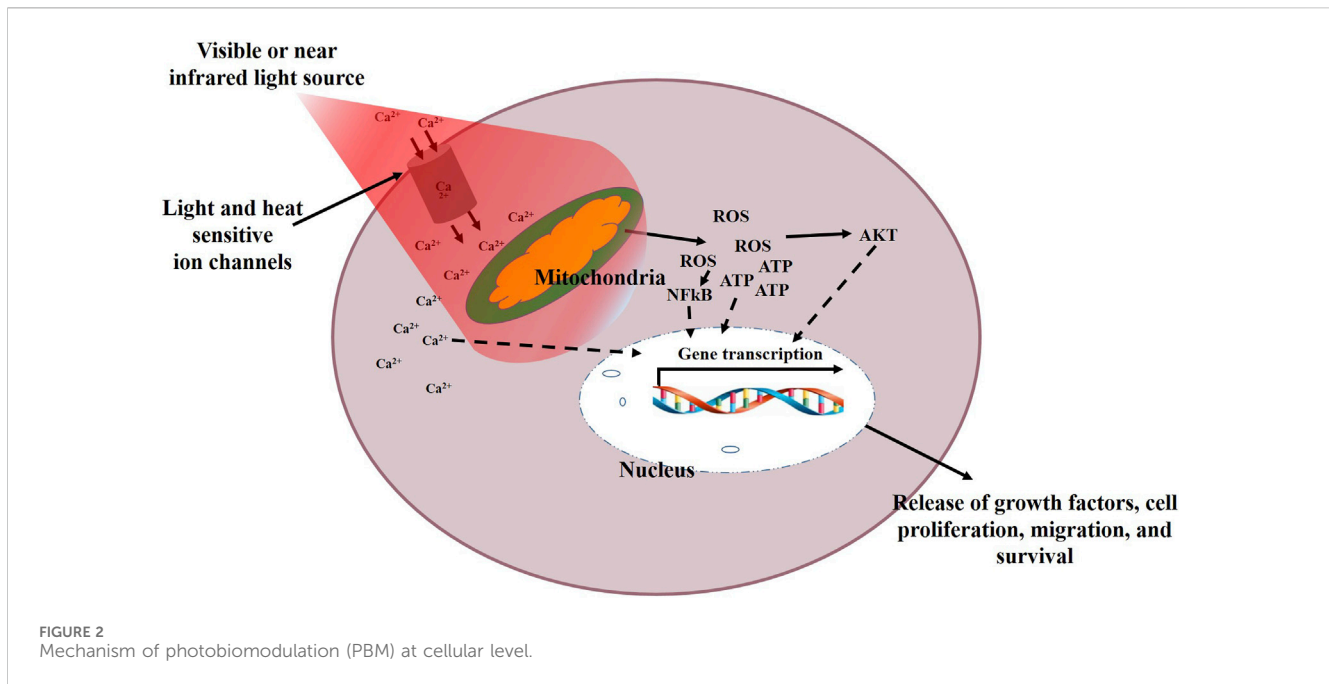
Recently, the application of PBM therapy in medicine has gained a lot of interest. PBM induces a photobiomodulatory effect on tissue and cells to modulate cellular behaviour and enhance tissue repair.

Previously known as low level laser/light therapy (LLLT), PBM is able to induce cellular proliferation, migration, and differentiation without causing tissue or cell's temperature to rise. It is a non-invasive treatment technique effective for pain relief, reduction of inflammation, and enhanced wound healing (Dompe et al., 2020). It is believed that the mitochondria and gated ion channels for light and heat are the likely location for the primary effects of PBM, resulting in enhanced production of ATP and alteration of ROS, leading to downstream stimulation of transcription factors for cell proliferation, migration, and survival (Figure 2). This mechanism involves mitochondrial cytochrome c oxidase (CoX), a membrane protein having a binuclear copper (CuA) and a heme centre (a3-CuB). These proteins facilitate the transportation of electrons from CoX to oxygen in the electron transport chain. It is suggested that CoX represents the primary photoacceptor for the red and near infrared (NIR) light spectrum in mammalian cells (Farivar et al., 2014). The mechanisms of PBM and the mitochondrial redox signalling is well explained elsewhere (Hamblin, 2018). Different from pharmaceutical agents, PBM is described by parameters including wavelength, power output, energy density, frequency, and time of irradiation. It is believed that a reduced dosage may result in an insignificant cellular response, and an excessive dosage may completely impede positive cellular responses and induce apoptosis (Arndt-Schulz law). However, these cell responses have also been reported in some irradiated tumour cells, raising fear that PBM may enhance growth of tumours, as well as highlighting the importance of understanding the effects of PBM at the cell level for proper interpretation of treatment protocols in cancer patients (Tam et al., 2020).

Various transcription factors including nuclear factor kappa B (NF- κ B) are regulated with the status of cellular redox to activate several intracellular signalling pathways for nucleic acid and protein synthesis, progression of cell cycle, and activation of enzymes. This process stimulates cell differentiation, increases cell proliferation and migration, and release of cytokines and growth factors. PBM modifies cellular transcription factors and gene expression resulting in various phenotypic cellular variations (Khalkhal et al., 2020). Different researchers have elucidated on the advantages of PBM in advancing human fibroblast cell proliferation and survival when used at appropriate parameters (Almeida-Lopes et al., 2001; Rani et al., 2005).

4 Effect of photobiomodulation (PBM) on fibroblast cells in diabetic wound healing

The equations should be inserted in editable format from the equation editor. Several studies have demonstrated the effect of PBM on fibroblast cell proliferation and migration in diabetic wound healing. *In vitro*, PBM has demonstrated a significant increase in the proliferation rate of human fibroblasts (Kreiser et al., 2002). When Khadra et al. (Khadra et al., 2005), used PBM using a diode laser at a fluence of 1.5 and 3 J/cm² at a wavelength of 830 nm, they noted a significant improvement in human fibroblast cell attachment and proliferation on titanium discs. Using a diode laser at a wavelength of 670 nm, 780 nm, 692 nm, and 786 nm at a fluence of 2 J/cm², Almeida-Lopes et al. (Almeida-Lopes et al., 2001) noted a significant



increase in human fibroblast proliferation. Jere et al. (Jere et al., 2021) noted a significant increase in fibroblast cell migration when they used PBM at a wavelength of 660 nm and energy density of 5 J/cm² on diabetic wounded and hypoxic diabetic wounded human fibroblasts. Furthermore, when Rajendran et al. (Rajendran et al., 2021) used PBM at a wavelength of 660 nm (fluence of 5 J/cm², and power density of 11.2 mW/cm²), or 830 nm (fluence of 5 J/cm², and power density of 10.3 mW/cm²), they observed enhanced migration in irradiated diabetic wounded fibroblast cells. Giannakopoulos et al. (Giannakopoulos et al., 2023) noted an increased activation of cellular migration and proliferation when they tried to investigate the role of red light at a wavelength of 661 nm on 3T3 fibroblast cell proliferation and migration. Similarly, Zhao et al. (Zhao et al., 2022) aimed to assess and relate the outcomes of 630 nm and 810 nm PBM on the proliferation of mouse fibroblast cells (L929) in wound healing *in vitro* and *in vivo*. They noted that both 630 nm and 810 nm irradiation significantly stimulated cell proliferation and migration. In another study, Oyebole and Houreld, (Oyebole and Houreld, 2022), noted a significantly increased human fibroblast cell proliferation and migration when they investigated the potential of PBM at 830 nm in accelerating cell proliferation and migration.

The differentiation of fibroblasts to myofibroblasts is regulated by different growth factors and the stiffness of the ECM (Sassoli et al., 2016). When Oyebole and Houreld, (Oyebole and Houreld, 2021), used diode lasers at a wavelength of 830 nm and 660 nm at a fluence of 5 J/cm² on diabetic human fibroblast cells they reported successful initiation of fibroblast cell differentiation into myofibroblasts at a wavelength of 660 nm than 830 nm. However, they noted better results at a wavelength of 660 nm than at a wavelength of 830 nm. It should be noted that this was *in vitro*, and most studies make use of NIR as it has a deeper penetration depth than red light. Myofibroblasts demonstrate the competence to release ECM proteins and adopt a contractile phenotype to regulate tissue remodelling and wound contraction. Lau et al. (Lau et al., 2015) assessed the effects of near infrared (808 nm) PBM on diabetic wounds in rats at a fluence of 5 J/

cm² with power densities of 0.1 W/cm², 0.2 W/cm² and 0.3 W/cm² and exposure time of 50 s, 25 s and 17 s, respectively. They noted that wound contraction was optimised with a power density of 0.1 W/cm², and that PBM was able to enhance epithelialisation and collagen fibre synthesis, indicating effective transformation of fibroblasts to myofibroblasts. When Sassoli et al. (Sassoli et al., 2016) assessed NIH/3T3 fibroblast cells cultured in medium with reduced serum and additional TGF-β1 that were irradiated with a 635 nm diode laser at a fluence of 0.3 J/cm², they noted that PBM inhibited TGF-β1-induced fibroblast differentiation to myofibroblast. They observed a significant reduction in the formation of stress fibres, α-SMA and expression of type-1 collagen, indicating that PBM at a lower fluence may negatively affected the differentiation of fibroblasts to myofibroblasts, critical for the reduction of fibrosis.

5 Photobiomodulation (PBM) enhanced release of growth factors by fibroblast cells in diabetic wound healing

The wound healing process is largely regulated by mitogenic mediators including cytokines and growth factors that are produced by occupant and infiltrating cells within the wound milieu (Chen et al., 2014). The dermal fibroblast cells are critical for reconstructing the injured tissue, and produce essential growth factors and cytokine that contribute to the wound healing process. According to Rahbar et al. (Rahbar et al., 2020) dysfunctional fibroblast cell proliferation and communication within the dermis is the major cause of disrupted wound healing in DM. In DM the production of the mitogenic factors and their downstream cellular signalling that promote fibroblast cell activity is altered, further diminishing the wound healing process (Huang et al., 2018). Several studies have shown that PBM induces impaired diabetic fibroblasts for effective and enhanced diabetic wound healing. Rahbar et al. (Rahbar et al., 2020) demonstrated that PBM at a wavelength of 632.8 nm and a fluence of 0.5 J/cm² stimulates the release

of 7 growth factor/cytokines [eotaxin-3, brain-derived neurotrophic factor (BDNF), fibroblast growth factor 6 and 7 (FGF-6 and -7), fractalkine, fit-3ligand, and granulocyte chemotactic protein (GCP-2)] mainly involved in cell-to-cell communication and cell proliferation in diabetic fibroblast cells. Literature shows that PBM induces therapeutic benefits and increases the healing of diabetic wounds via the release of growth factors including FGFs (Kasowanjete et al., 2022). Karkada et al. (Karkada et al., 2023) showed that PBM stimulates the release of IL-6 and bFGF in human skin fibroblasts (HSFs) cultured in high glucose concentration medium. In addition, Khoo et al. (Khoo et al., 2014) observed a significant increase in the expression of FGF, platelet-derived growth factor (PDGF) and VEGF in irradiated diabetic fibroblast cells with a single dose of PBM at a wavelength of 810 nm and a fluence of 1 J/cm². This suggests that PBM may play a critical role in diabetic wound healing by stimulating fibroblasts and the release of growth factors. Literature shows that PBM enhances wound healing, particularly diabetic wounds, and its effect in cellular function as a result of growth factor and cytokine production (Oyebode and Houreld, 2021). Research on the impact of repeated exposures to PBM on the responses of injured skin fibroblasts shows that appropriate energy density or fluence and exposure frequency can enhance the responses of injured fibroblasts and encourage cell migration and proliferation by promoting mitochondrial activity and preserving viability without adding to the stress or harm to the injured cells. The results show that the stimulatory effect is determined by the cumulative effect of lower dosages, while multiple exposure at larger concentrations produces an inhibitory effect that causes more damage (Rocha Júnior et al., 2007).

6 Conclusion

During the wound healing process, fibroblast cells play a key role in all the phases of wound healing, and crosstalk with other types of cells via the production of chemokines, growth factors, MMPs, and construction of ECM. In an effort to close and remodel the wounded tissue, fibroblasts differentiate into contractile myofibroblasts, which are responsible for increased production and construction of ECM, mainly aimed at reestablishing the normal function of the tissue after injury. Fibroblast dysfunction, therefore, is a distinctive attribute of impaired wound healing and the development of chronic non-healing wounds. For this reason, most therapeutic techniques target the regulation and progression of fibroblast cell performance. Diabetic wounds are problematic to heal, become chronic, and may necessitate limb amputation. However, the

molecular and cellular modifications that lead to this deficiency is not completely known. PBM is a novel treatment technique that is able to induce and enhance tissue repair, and research shows that it compensates most impairments in diabetic fibroblast cells. Could this non-invasive and cheap treatment technique with limited side effects be effective in mitigating fibroblast dysfunction in diabetic wound healing? Due to controversy surrounding the use PBM, more research may be critical to understand its effect, at a cellular and molecular level, and the optimal dosage of PBM in diabetic wound healing.

Author contributions

SJ: Conceptualization, Writing—original draft, Writing—review and editing. NH: Writing—review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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