

Pirfenidone: A Review of its Dermatologic Uses

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INTRODUCTION

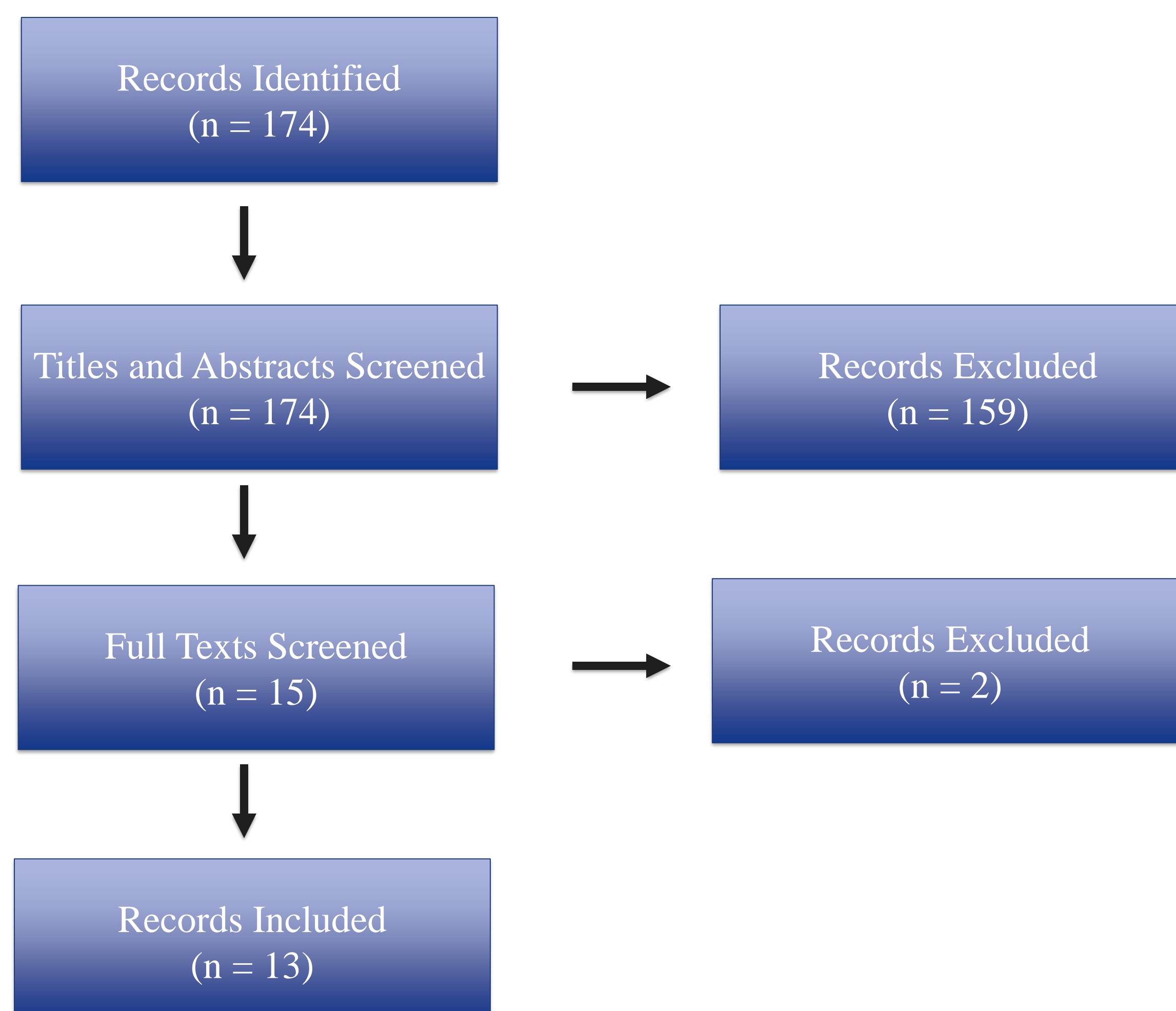
Fibrosis, characterized by the excessive accumulation of extracellular matrix components, leads to tissue scarring and impaired organ function. Skin fibrosis, often resulting from trauma, surgery, or burns, can significantly impact a patient's quality of life by causing disfigurement and functional impairments.¹

Pirfenidone, an anti-fibrotic agent, is currently approved for use in treating idiopathic pulmonary fibrosis, showing its ability to slow down the progression of fibrosis in lung tissue.² Its mechanism involves inhibiting transforming growth factor-beta (TGF- β), a key regulator of fibrotic processes.³⁻⁷ Although pirfenidone is primarily administered orally, other countries have explored its topical application to manage skin fibrosis, particularly in the treatment of scars.

This review aims to investigate the potential of pirfenidone in slowing down skin fibrosis when applied topically, drawing comparisons between its systemic use for pulmonary fibrosis and its emerging role in dermatology. Understanding pirfenidone's broader therapeutic application may pave the way for innovative treatments for scarring and other fibrotic skin conditions.

METHOD

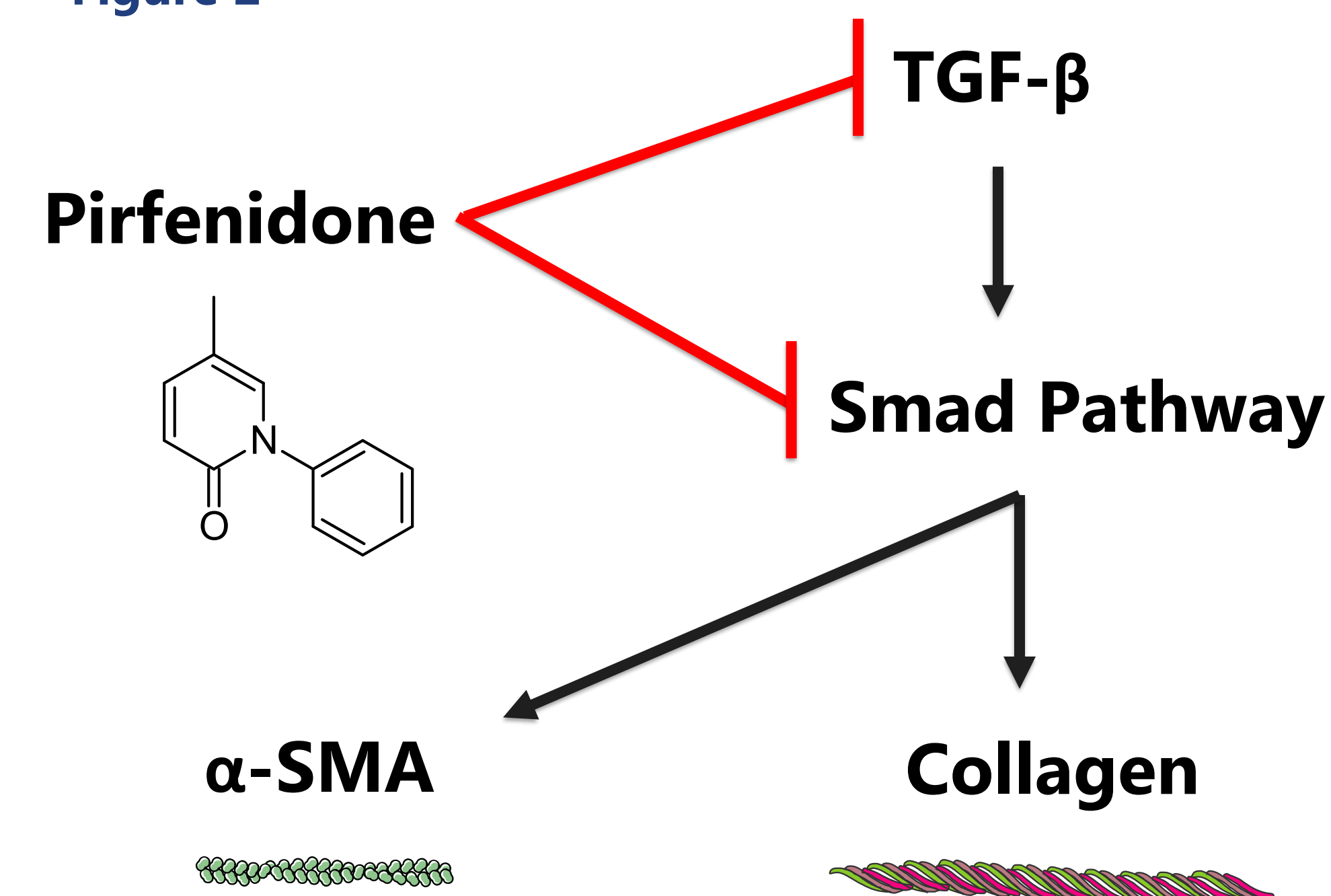
Figure 1



We utilized a systematic approach to our review. Cochrane, EBSCO, Embase, Google Scholar, and PubMed were searched for relevant articles. Key terms included “pirfenidone”, “skin”, and “scar” among others. All articles pertaining to the use of pirfenidone for the treatment of skin conditions were included. Multiple authors were involved in applying the inclusion and exclusion criteria.

MECHANISM

Figure 2



Images from Sevier medical art

The mechanism of pirfenidone's antifibrotic effects are not fully understood. This lack of understanding is due, in part, to the drug having multiple mechanisms of action.²⁻⁷ The best characterized mechanism is pirfenidone's effect on the TGF- β /Smad pathway (Figure 2).

TGF- β receptors promote fibrosis by phosphorylating Smad proteins. Smad will then translocate to the nucleus and increase expression of fibrotic molecules such as α -SMA and collagen fibers. Interestingly, while pirfenidone will decrease collagen I mRNA levels (Col1A1) in many cell types, the same effect has not been measured in skin fibroblasts.^{3,5} Collagen protein deposition is still significantly reduced however, suggesting pirfenidone plays a post-transcriptional role in attenuating fibrosis.

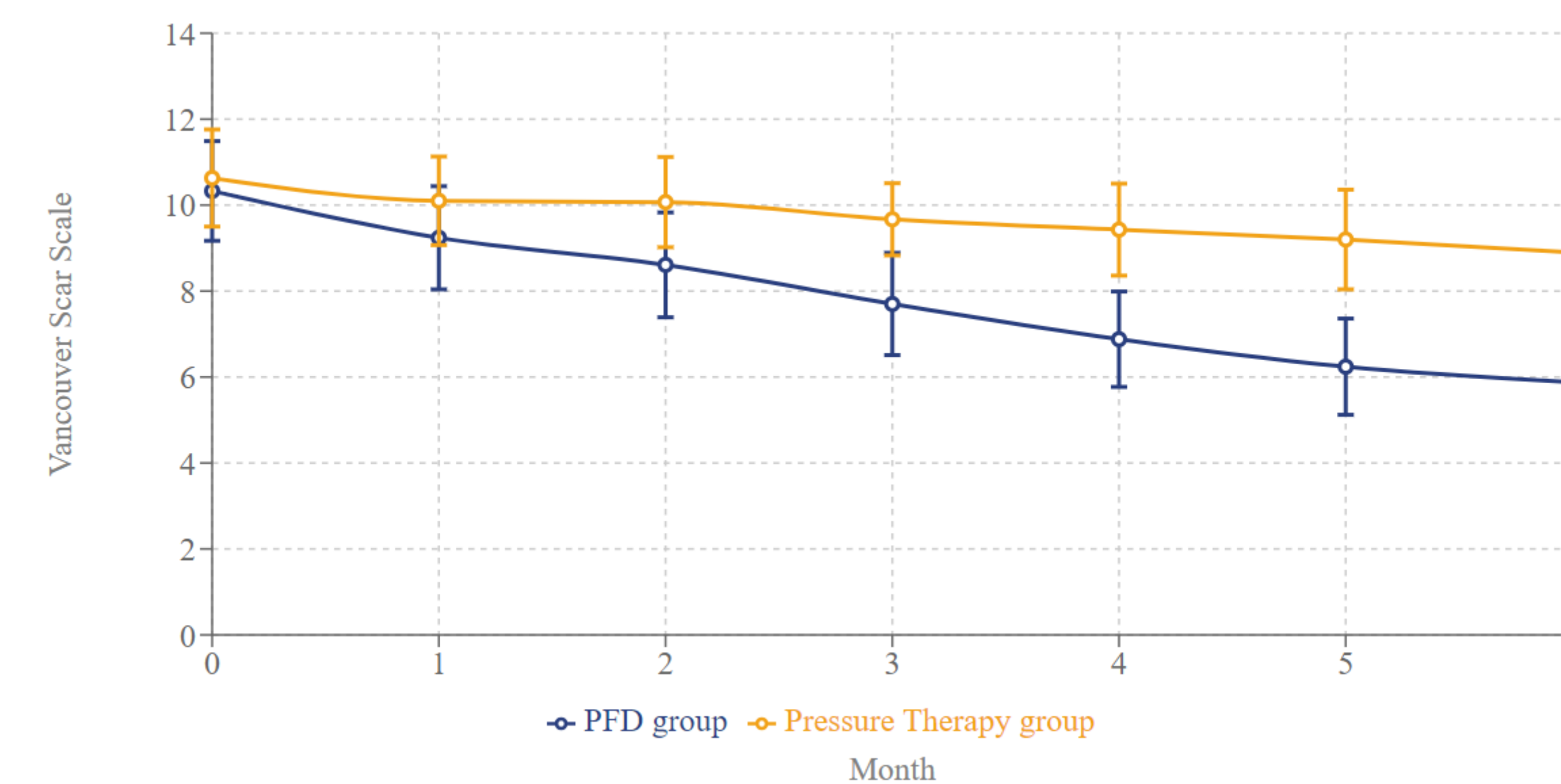
Pirfenidone has other mechanisms of action that may be distinct from collagen and actin synthesis. Its effects include regulating immune cells², downregulating Notch signaling⁸, and impairing the epithelial-mesenchymal transition.⁹ More work is needed to fully elucidate the mechanism by which pirfenidone inhibits scarring in the skin.

CLINICAL TRIALS

Oral pirfenidone has been studied extensively for its use in idiopathic pulmonary fibrosis. There is interest in repurposing the drug for a variety of fibrotic diseases. Skin conditions represent a promising area for the use of pirfenidone because topical application can avoid many of the drug's side effects. Despite this, there is limited clinical data to support the use of topical pirfenidone.

Our search identified 3 clinical trials evaluating the use of pirfenidone for skin conditions. Armendariz-Borunda et al. recruited 63 pediatric patients with hypertrophic scars to evaluate an 8% pirfenidone gel. Patients in the treatment group (33) were instructed to apply the gel 3 times daily for six months. Control patients (30) were treated with pressure therapy. The patients were then evaluated every month using the Vancouver Scar Scale. Pirfenidone showed a significant reduction in scar severity as compared to pressure therapy (Figure 3).¹⁰

Figure 3



Adapted from Armendariz-Borunda et al. 2012. PFD = pirfenidone

Rodriguez-Castellanos et al. studied the effects of pirfenidone on 12 patients with localized scleroderma. After 6 months, they found a statistically significant effect on a clinical scar scale, durometer readings, as well as improvement in the histologic appearance of skin.¹¹

Mecott et al. studied oral pirfenidone 600mg given once daily to patients with second degree burns. They were only able to recruit 8 patients to the trial. The primary outcome was thickness of re-epithelialized dermis after 7 days of treatment. Patients given pirfenidone had significantly more epithelium at day 7. They also had a healthier histologic and gross appearances compared to patients receiving standard of care (Figure 4).¹²

Figure 4



Images from Mecott et al. 2020. The patient in part A was treated with pirfenidone, the patient in part B was not. Pictures were taken 7-8 days after presenting with a second-degree burn.

CONCLUSION

Pirfenidone shows promise as an antifibrotic agent for skin conditions. However, there are significant hurdles to using it dermatologically in the United States. Currently oral pirfenidone is FDA approved only for use in idiopathic pulmonary fibrosis. A topical pirfenidone application would need to be compounded. More research is needed to understand pirfenidone's mechanism of action and clinical effect on the skin.

REFERENCES

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