*Sexual Medicine*, 2024, **12**, qfae088
https://doi.org/10.1093/sexmed/qfae088
**Review**

# Effects of therapy in experimental models of Peyronie's disease: a scoping review

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## Abstract

**Background:** Peyronie's disease (PD) is a fibrotic disorder affecting the penile tunica albugínea, with unclear pathophysiology despite centuries of recognition.

**Aim:** This scoping review maps the effects of interventions in basic PD research, synthesizing evidence from in vivo and in vitro studies to guide future investigation.

**Methods:** In October–November 2023, a systematic search was conducted across PubMed, Embase (Ovid), Science of Web, and Scopus, following SRYCLE's guidelines. Relevant studies were screened for data on interventions targeting PD in vivo and in vitro, with no language or time restrictions.

**Outcomes:** Primary outcomes included changes in extracellular matrix (ECM) proteins, myofibroblast activity, and plaque size.

**Results:** Of 683 articles screened, 40 studies were included. Key interventions such as phosphodiesterase inhibitors and stem cell therapies reduced ECM proteins and myofibroblast activity, particularly in early-stage PD models. However, none of the studies adhered to the ARRIVE guidelines, highlighting a gap in reporting standards.

**Clinical translation:** Findings suggest potential benefits of early and multimodal treatment strategies, but further human trials are needed to bridge the gap in clinical practice.

**Strengths and limitations:** This review systematically synthesizes animal and cellular research on PD, highlighting significant preclinical findings. However, the lack of standardized reporting and limited human studies restricts direct clinical applicability.

**Conclusion:** Further research should prioritize adherence to reporting standards, optimize treatment timing, and explore combination therapies to advance PD management.

**Keywords:** fibrotic plaque; pathophysiology; preclinical studies; stem cell therapy; biomolecular effects; transforming growth factor (TGF-ß1).

## Introduction

Peyronie's disease (PD) is an acquired condition characterized by fibrotic plaque formation in the penile tunica albugínea (TA).[1,2] This may cause penile curvature, hinder penetration, and lower the quality of life in the affected men[3] and their partners.[4] Some aspects of the disease are known, others are presumed, and others are unknown.

The present literature concludes that PD is more prevalent in patients with diabetes mellitus,[5,6] Dupuytren disease[7] and hypertension.[6] We also know it has a significant impact on men's health, and depression is more often seen in men with PD.[3,8-10]

PD's prevalence ranges widely from 3.2% to 20.3%[5,11,12] and peaks in the sixth decade.[13,14]

Micro-trauma to the erect penis[15] and genetic predisposition[16,17] are believed to trigger an abnormal wound-healing process mediated by Transforming Growth Factor beta1 (TGF-$\beta$1),[1,2] a key regulator of fibrosis.

## The formation of fibrosis

Fibrosis in PD involves complex signaling pathways.[18] TGF-$\beta$1 promotes the transformation of fibroblasts into myofibroblasts (MFBs) through the TGF $\beta$1/SMAD (Small Mothers Against Decapentaplegic) pathway, resulting in exces-

**Received:** October 8, 2024. **Revised:** December 17, 2024. **Accepted:** December 25, 2024

sive production of extracellular matrix (ECM) components such as collagen and fibronectin. Dysregulated ECM balance leads to scar tissue formation, while pathways like YAP/-TAZ (transcriptional coactivator with PDZ-binding motif) and RhoA/ROCK (Rho-associated protein kinase) further influence fibrosis. Usually, MFBs undergo apoptosis after healing, but in PD, persistent activation leads to tissue scarring and dysfunction.[19]

In animal research, factors indicative of reduced fibrosis include increased smooth muscle cells, $\alpha$-SMA, increased induced nitric oxygen synthase (iNOS), and Matrix-Metalloproteinase (MMPs). Conversely, factors promoting fibrosis include increased TGF-ß1, Fibrin, TIMPs (Tissue inhibitor of Metalloproteinases), PAI-1, and CTGF, activated by TGF-ß1 (see Figure 2).

A consensus statement from the European Society of Sexual Medicine (ESSM)[20] reviewed animal models in PD research and provided guidelines on best practices for reporting study design, technique, and results. While valuable, it excluded in-vitro studies and did not address broader interventions or pathways.

Yang et al.[21] analyzed six studies and conducted a systematic narrative review on using stem cells in PD treatment. Their review highlighted the inhibition of the TGF $\beta$1/Rho/ROCK (Rho-kinase) and TGF $\beta$1/Smad2 pathways by adipose-derived stem cells and their associated immunological effects. Unlike these previous works,[20,21] our scoping review includes five additional animal studies, incorporates diverse stem cell types, and evaluates full-text articles and abstracts, providing a more comprehensive perspective.

Despite ongoing research efforts, PD's precise etiology and pathophysiology remain elusive. This scoping review synthesizes evidence from in vivo and in vitro studies to evaluate the effects of various interventions on PD in its acute and chronic phases, aiming to consolidate current knowledge and identify research gaps.

## Material and methods

The scoping review's search strategy was conducted using a step-by-step guide to identify all relevant animal studies developed by SYRCLE[22] and reported according to the quality standards described in the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews" (PRISMA-ScR)[23]; see Supplementary A. In our scoping review, we also followed the Joanna Briggs Institute (JBI) for Scoping Review.[24] Our protocol was registered and uploaded to the Open Science Framework on 26 November 2023.[25]

### Eligibility criteria

Eligibility criteria were set according to Population, Concept, and Context. We included all experimental models with animal and human tunica albugínea (TA) cells in the population. In the concept, we had effects reported on collagen-, elastin fibers, and anti-fibrotic factors when non-surgical treatments were investigated. We looked at the geographic distribution of the research, what models were used, and whether the research was to highlight possibilities in the prevention or treatment of PD. Concerning context, academic studies from all countries and all years were included.

### Search strategy

MHW developed and refined the search strategy in cooperation with an experienced librarian. As recommended by JBI, a three-step search strategy was utilized. Grey literature and abstracts from conferences were included if they provided sufficient data in the text and when they did not represent preliminary findings of a later published article. We contacted one author group as two different conference abstracts of the same study had different results, and the correct result was clarified.

The searches were conducted from 10 October to 10 November 2023 (the most recent searches were Scopus: 6/11, PubMed + Web of Science 7/11, and Ovid 10/11). For a complete search strategy for Medline/PubMed, see Supplementary B.

A literature search was initially conducted in MEDLINE/PUBMED and EMBASE/OVID to identify articles, index terms, and keywords. For the "Peyronie's disease" filter, we created the following search strategy: *(Peyronie's disease) OR (Peyronie's disease) OR (Induratio penis plastica) OR (Penile induration) OR (penile fibromatosis) OR (Fibromatosis, Penile) OR (Peyronie's Disease)) OR (Peyronie's Disease) OR (Plastic Induration of the Penis) OR (Cavernitis, Fibrous) OR (Cavernitides, Fibrous) OR (Fibrous Cavernitides) OR (Fibrous Cavernitis) OR (Peyronie's Disease)*. In each database, free-text terms and index terms were searched when available. In Medline (Ovid), penile induration as [MeSH] was also explored.

For the "animal" filter, we used an already comprehensive search string created by SYRCLE.[26] These two search filters were combined with an AND in MEDLINE (Ovid), EMBASE (Ovid), WEB OF SCIENCE (Clarivate), and SCOPUS (Elsevier). However, the animal research filter only existed for the first three, so it was adapted for SCOPUS (Elsevier). Any disagreements at each stage of the selection process were resolved through discussion.

### Data extraction

Two independent reviewers (MHW and RK) reviewed and sorted the articles. The template was customized and refined after testing the data extraction template from Covidence with five randomly selected articles. These articles were used to pilot the template and ensure its effectiveness.

## Results

### Study selection

After the database searches, 683 articles remained after removing duplicates. After title and abstract screening, 64 articles underwent full-text review, and 40[27-66] studies were included for data extraction (Figure 3). The included articles were published between 1986 and 2023 and predominantly within the last decade. None adhered to the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines, introduced in 2010.[67]

Most studies were primary articles (n = 35, 87.5%), with about one-third (n = 12, 30%) originating from North America. The rat (Sprague Dawley or Male Fisher) was the most frequently used animal model (n = 21, 72.4%) injected with TGF-ß1 to induce PD. Cellular studies primarily utilized human TA from PD patients (n = 12, 67.2%) (Table 1). Research focused

**Table 1.** Charactetistics of the included articles.

| *Type of evidence source* | N (%) Total = 40 | *Animal PD model used* | N (%) Total = 29 |
|---|---|---|---|
| Primary article | 35 (87,5) | **Sprague–Dawley (SD) or Male Fisher rats with TGF-ß1, once or repeated** | 21 (72.4) |
| Conference abstracts | 5 (12,5) | **SD Rats with fibrosis and thrombin** | 5 (17.2) |
| *The region where the studies were conducted* | Total = 40 | **SD rats with TGF-ß1+ Aethoxysklerol** | 1 (3.4) |
| North America | 12 (30.0) | **Mice** | 1 (3.4) |
| Asia | 10 (25.0) | **SD rats with allograft** | 1 (3.4) |
| Europe | 5 (12,5) | ***Cellular* PD *model used*** | Total = 18 |
| Multiple regions | 7 (17.5) | **TA from human, no PD** | 4 (22.5) |
| Middle East | 4 (10.0) | **TA from human, with PD** | 12 (67,2) |
| South America | 1 (2.5) | **TA from rats** | 2 (11.2) |
| Oceania | 1 (2.5) | ***Interventions*** | Total 41 |
| Africa | 0 | **Drugs** | 20 (50) |
| *Focus of research* | Total = 40 | **Biomolecular/biological treatment** | 17 (42,5) |
| Prevention/early PD | 15 (37,5) | **Manipulation (ESWT, traction, vacuum)** | 4 (10) |
| Treatment of PD | 19 (47,5) | | |
| Both | 6 (15,0) | ***Report of an effect*** | Total 40 |
| *Mode of administration in animals* | Total 29 | **Positive effect (or partial) in intervention investigated.** | 38 |
| Oral | 9 (31) | **No antifibrotic effect** | 2 |
| Intratunical/intracavernosal | 17 (59) | | |
| Topical | 3 (10) | | |

mainly on existing or newly developed drugs and biomolecular or biological therapies. Delivery methods included intratunical/intracavernosal injection 17 (59%), oral administration 9 (31%), and topical intervention 4 (10%). Interventions targeted both the prevention or acute phase (n = 15, 37.5%) and the chronic phase (n = 19, 47.5%), with a few addressing both phases (n = 6, 15%) (see Table 2 [animal studies] and Table 3 [cellular studies]). Most studies (n = 38, 95%) reported partial or complete effects, with only two showing no histopathological improvements.[32,35] The most commonly reported effects were on extracellular matrix proteins, specifically Collagen I, Collagen III, and Elastin (n = 28, 70%) (see Table 4). The next most frequent effect was the reduction of TGF-$\beta$1 (n = 7, 17.5%), all observed in animal studies. Additionally, five studies (12.5%)[34,39,40,57,60] focused on the intervention's ability to reduce curvature, and seven (17.5%)[34,37,38,45,56,60,62] reported a reduction in plaque size.

## Drugs

Phosphodiesterase inhibitors (PDEi), including PDE5i and pentoxifylline, were independently studied.[64] PDE5i were further investigated with selective estrogen receptor modulators (SERM)[50] and statin.[59] They showed inhibitory effects on forming ECM proteins, reduced MFBs, and plaque size.

With pentoxifylline, a downregulation of SMAD1/5 was found to augment its effect. SMAD1/5 complexes also with SMAD4 and translocate to the nucleus, regulating the transcription of target genes. Additionally, an increase in I-SMAD6 expression due to pentoxifylline was observed[58] (see number 7 in Figure 1). PDE5i-specific effects are suggested to be mediated by elevated cyclic guanosine monophosphate (cGMP) levels[64] and PDE3 (number 13 in Figure 2).[47]

A synergistic effect was noted with PDE5i and SERM[50] or PDE5i and simvastatin[59] combinations. MFB formation was inhibited within a critical treatment window of 24–36 hours post-TGF-$\beta$1 induction. Statins' individual effects may result from CTGF suppression by inhibiting the ROCK pathway (number 3 in Figure 1).

Estradiol, akin to Tamoxifen, interacts with estrogen receptors and is thought to reduce phosphorylated SMAD2 and inhibit the ROCK signaling pathway (number 3 in Figure 1).

Animal studies investigating the potential antifibrotic drug effects revealed histopathological effects. Two studies on the activin receptor-like kinase (ALK) inhibitor,[60,62] which inhibits the TGF-$\beta$1 type 1 receptor, were included. One study[60] investigated the properties of ALK inhibitor treatment, noting reduced pSMAD2 and hydroxyproline expression with injections on Day 30. Another study[62] 11 years later examined the early ALK inhibitor properties, finding reductions in pSMAD2, hydroxyproline, MFBs, and inflammation cells in the plaque.

A new drug derived from Chinese herbal medicine, the Xiaojin pill demonstrated MMP2 and 9 and iNOS reduction compared with sham groups. Colchicine[38] and mitomycin (MMC)[54] exhibited anti-fibrotic effects in the early stages of TGF-$\beta$1 induced PD. Conversely, mycophenolate mofetil (MMF)[28] showed significantly reduced Collagen III levels when administrated 30 days post-TGF- $\beta$1 induction. When injected into the plaque in a PD rat model, Verapamil, known for its hypertensive and anti-fibrotic properties, promoted the downregulation of collagen and MFBs.[34]

Terfenadine (H1 receptor antagonist), Ebastine (H3 receptor antagonist), and Solifenacin (muscarinic receptor antagonist) were investigated on fibroblasts from PD patients. The results showed concentration-dependent inhibition of MFBs in PD-derived cells.[49] In an older study, collagenase displayed plaque dissolution[42] and efficient degradation of ECM proteins[37] in vitro.

Pirfenidone[32] was also investigated but exhibited no histopathological effects on PD plaques.

## Effects of manipulation

Manipulative therapies showed mixed results: Low- and high-intensity li-ESWT combined with collagenase yielded no additional effects beyond collagenase alone.[63] A vacuum erection device (VED) decreased TGF-$\beta$1, SMAD2, SMAD3, and

**Table 2.** Characteristics of animal studies (drug, biomolecular, and manipulation).

| Animal studies (drugs) | Primary article | Conference abstract | Fibrosis induced by: | | | | Intervention | | | Intervention administered: | | | | Prevention/ early treatment | Treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | TGF-$\beta$1 | Fibrin | Thrombin | Surgery | Drug | Biomolecular | Manipulation | Oral | Intratunical | Intracaver-nosal | Topical | | |
| Antoniassi et al, 2020[28] | x | | x | | | | x | | | x | | | | x | x |
| Cevik et al, 2023[32] | x | | x | | | | x | | | x | | | | | x |
| Chung et al, 2013[34] | x | | x | | x | | x | | | | x | | | | x |
| El-Sakka et al, 1999[38] | x | | x | | | | x | | | x | | | | x | x |
| Ferrini et al, 2006[40] | x | | x | | | | x | | | x | | | | x | x |
| Geng et al., 2019[43] | x | | x | | | | x | | | x | | | | | x |
| Ilg et al, 2019[50] | x | | x | | | | x | | | x | x | | | x | |
| Kaya et al., 201[54] | x | | x | | | | x | | | | | x | | x | |
| Song et al., 2019[62] | x | | | x | x | | x | | | x | | | | x | |
| *Soubra et al.*, 2022[63] | | x | x | | | | x | | x | | x | | x | | x |
| Valente et al., 2003[64] | x | | x | | | | x | | | x | | | | x | |
| **Animal studies (Biomolecular)** | | | | | | | | | | | | | | | |
| Akman et al, 2013[27] | x | | x | | | | | x | | | x | | | x | |
| Castiglione et al, 2013[29] | x | | x | | | | | x | | | x | | | x | |
| Castiglione et al, 2019[30] | x | | x | | | | | x | | | x | | | | x |
| Castiglione et al, 2019[31] | x | | x | | | | | x | | | x | | | x | |
| Culha et al, 2019[35] | x | | x | | | | | x | | | x | | | | x |
| Davila et al, 2004[34] | x | | | x | x | | | x | | | x | | | | x |
| Ferrini et al, 2002[41] | x | | x | | | | | x | | | | | | x | |
| Ferretti et al, 2012[39] | | x | | | | x | | x | | | x | | | | x |
| Gocke et al., 2014[45] | x | | x | | x | | | x | | | x | | | x | x |
| Gocke et al., 2015[44] | x | | x | | | | | x | | | x | | | x | x |
| Hakim et al, 2020[46] | x | | x | | | | | x | | | x | | | | x |
| Kim et al, 2014[61] | x | | | x | x | | | x | | x | | | | | |
| Kwon et al., 2014[55] | x | | | x | x | | | x | | | x | | | | x |
| Ryu et al., 2009[60] | x | | x | | | | | x | | | x | | | (x) | |
| Wang et al, 2022[65] | x | | x | | | | | x | | | x | | | x | x |
| Yang et al., 2020[66] | x | | x | | | | | x | | | x | | | x | |
| **Animal studies (manipulation)** | | | | | | | | | | | | | | | |
| Li et al., 2018[54] | x | | x | | | | | | x | | | | x | | x |
| Lin et al., 2017[57] | x | | x | | x | | | | x | | | | x | | x |
| *Soubra et al.*, 2022[63] | | x | x | | | | x | | x | | x | | x | | x |

**Table 3.** Characteristics of cellular studies (drug, biomolecular, and manipulation).

| Cellular studies (drugs) | Primary article | Conference abstract | Drug | Biomolecular | Manipulation | Cellular model | | TA from rats | Prevention | Treatment |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | TA from human | TA from PD patients | | | |
| DelCarlo et al, 2009[37] | | x | x | | | | x | | | x |
| Gelbard et al, 1982[42] | x | | x | | | | x | | | x |
| Harding et al, 2023[47] | | x | x | | | | x | | x | |
| Ilg et al., 2020[51] | x | | x | | | | x | | x | |
| Ilg et al., 2023[48] | x | | x | | | | x | | x | |
| Ilg et al., 2023[49] | | x | x | | | | x | | | x |
| Jiang et al, 2015[53] | x | | x | | | | | x | x | |
| Lin et al., 2010[57] | x | | x | | | x | x | | | x |
| Milencovic et al., 2018[59] | x | | x | x | | | x | | x | |
| **Cellular studies (Biomolecular)** | | | | | | | | | | |
| Jiang et al, 2017[52] | x | | | x | | | | x | x | |
| Milencovic et al., 2018[59] | x | | x | x | | | x | | x | |
| **Cellular studies (manipulation)** | | | | | | | | | | |
| Chung et al, 2013[33] | x | | | | x | | x | | | x |

pSMAD2/3 expression,[56] while traction therapy increased MMP8 and reduced $\alpha$-SMA, indicating reduced MFB activity.[33] A comparative study found traction therapy more effective in reducing curvature, while VED treatments[57] preserved smooth muscle in the corpora cavernosa.

## Biomolecular and biomedical effects

Ten articles (25%) focused on the effects of stem cells, utilizing various types: rat-adipose-derived stem cells (rat-ADSC),[39,44,45,52] human ADSC,[29,30] rat-stromal-vascular fraction cells[31,46] rat bone marrow stem cells,[65] and stem cell exomes from urine.[66] Five studies reported reduced ECM content,[29-31,39,46] while Gokce et al.[44,45] found reduced TIMPs and increased MMPs in the TA. Jiang et al.[52] observed a reduction in pSMAD2, MFBs, ECM content, and increased MMPs in TA, while Yang et al.[66] found decreased TIMP 1, 2, 3, MFBs, ECM content alongside increased MMP 1, 3, 9 in TA. Wang et al.[65] reported increased expression of SMAD7 and reduced ECM content. Studies consistently found more significant effects in early-stage PD groups. One study noted that the PD rats model exhibited less fibrosis at two months than at 1 month.[30]

Decorin's antifibrotic effects are attributed to its high affinity for TGF-$\beta$1, neutralizing its activity and resulting in less disorganized collagen in TA.[27] Inhibiting iNOS demonstrated intensified TGF- $\beta$1-induced fibrosis, reactive oxygen species (ROS) levels, and collagen deposition,[41] aligning with a later study that showed iNOS induction led to decreased collagen deposition, TGF- $\beta$1 and PAI-1[36]—Anthocyanin, antioxidants from fruits, reduced expression of TGF-$\beta$1 in a rat model.[61] An adenoviral vector with histone deacetylase blocked the TGF-$\beta$1 pathway, inhibiting fibroblasts and MFBs and accelerating apoptosis in human PD fibroblasts.[55] Platelete-rich plasma (PRP) was ineffective in treating PD rats.[35]

Table 4 and Table 5 summarize the effects reported across interventions mapped to Figs. 1 and 2, illustrating the cellular process targeted. Four articles were excluded from this analysis—three due to no observed effect[32,35,63] and one[39] for limited outcome reporting.

## Discussion

The review identified a range of pharmacological agents, manipulation techniques, and biomolecular interventions studied for their effects on PD in both in vivo and in vitro models. Among the pharmacological agents, PDEi, SERMs, statins, and antifibrotic drugs such as pentoxifylline and verapamil showed promising results in reducing plaque size and fibrosis in animal models. Notably, the potential of combination therapies, such as PDE5i with SERMs or statins, to demonstrate synergistic effects in inhibiting fibrosis and preserving erectile function offers a hopeful outlook for the future of PD treatment.

### Emerging therapies show promise in animal PD models

Manipulation techniques, such as vacuum erection devices (VED) and traction therapy, demonstrated potential in animal models, reducing plaque size and improving erectile function. Cellular therapies utilizing adipose-derived stem cells (ADSCs), bone marrow-derived mesenchymal stem cells (BMSCs), stromal vascular fraction (SVF), and exosomes

**Table 4.** Cellular response from animal studies.

| Animal studies (drugs) | 1. ↓TGF-$\beta$1 | 2. ↓p-SMAD2/3 | 3. Inhibition of ROCK pathway | 4. Effect fibro blasts differenti-ation | 5. Reduction of TIMPs | 6. ↓Myofibro-blasts. | 7. ↑ Smad7 or Smad6 expression | 8. ↓ ECM content | 9. ↓ iNOS | 10. ↑ iNOS | 11. Apoptosis of fibroblast | 12. ↑MMPs in TA | 13. ↓MMP2 and MMP9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Antoniassi et al, 2020[28] | | | | | | | | x | | | | | |
| Chung et al., 2013[34] | | | | | | x | | x | | | | | |
| El-Sakka et al, 1999[38] | x | | | | | | | x | | | | | |
| Ferrini et al, 2006[40] | x | | | | | | | x | | | | | |
| Geng et al., 2019[43] | | | | | | | | | x | | | | x |
| Ilg et al., 2019[50] | | | | | | x | | x | | | | | |
| Kaya et al., 2017[54] | | | | | | | | x | | | | | |
| Song et al, 2019[62] | | x | | | | x | | x | | | | | |
| Valente et al., 2003[64] | | | | x | | | | x | | | x | | |
| **Animal studies (biomolecular)** | | | | | | | | | | | | | |
| Akman et al, 2013[27] | x | | | | | | | | | | | | |
| Castiglione et al, 2013[29] | | | | | | | | x | | | | | |
| Castiglione et al., 2019[30] | | | | | | | | x | | | | | |
| Castiglione et al, 2019[31] | | | | | | | | x | | | | | |
| Davila et al, 2004[36] | x | | | | | | | x | | x | | | |
| Ferretti et al, 2012[39] | | | | | | | | x | | | | | |
| Ferrini et al., 2002[41] | | | | | | | | | x | | | | |
| Gocke et al, 2014[45] | | | | | x | | | | | | | x | |
| Gocke et al., 2015[44] | | | | | x | | | | | | | x | |
| Hakim et al, 2020[46] | | | | | | | | x | | | | | |
| Kim et al, 2014[61] | x | | | | | | | x | | | | | |
| Kwon et al., 2014[55] | x | x | | | | | | x | | | x | | |
| Ryu et al., 2009[60] | | x | | | | | | x | | | | | |
| Wang et al, 2022[65] | | | | | | | x | x | | | | | |
| Yang et al., 2020[66] | | | | | x | x | | x | | | | x | |
| **Animal studies (manipulation)** | | | | | | | | | | | | | |
| Li et al, 2018[54] | x | x | | | | | | | | | | | |
| Lin et al., 2017[57] | x | | | | | x | | | | | | | |

**Table 5.** Cellular response from studies with cells.

| Cellular studies (drugs) | 1. ↓TGF-$\beta$1 | 2. ↓p-SMAD2/3 | 3. Inhibition of ROCK pathway | 4. Effect fibroblasts differentiation | 5. Reduction of TIMPs | 6. ↓Myofibroblasts. | 7. ↑ Smad7 or 6 expression | 8. ↓ ECM content | 9. ↓ iNOS | 10. ↑ iNOS | 11. Apoptosis of fibroblast | 12. ↑MMPs in TA | 13. ↓MMP2 and MMP9 | 14. ↓PDE3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DelCarlo et al, 2009[35] | | | | | | | | x | | | | | | |
| Gelbard et al., 1982 | | | | | | | | x | | | | | | |
| Harding et al, 2023[45] | | | | | | x | | | | | | | | x |
| Ilg et al., 2020[49] | | | | | | | | x | | | | | | |
| Ilg et al., 2023[46] | | | | | | x | | | | | | | | |
| Ilg et al., 2023[47] | | | | | | x | | | | | | | | |
| Jiang et al., 2015[51] | | x | | | | | | x | | | | | | |
| Lin et al., 2010[56] | | x | | | | | x | | | | | | | |
| *Milenkovic et al.*, 2018 | | | x | | | | | x | | | | | | |
| **Cellular studies (biomolecular)** | | | | | | | | | | | | | | |
| Jiang et al., 2017[50] | | x | | | | x | | | | | | x | | |
| Milenkovic et al., 2018[57] | | | x | | | | | x | | | | | | |
| **Animal studies (manipulation)** | | | | | | | | | | | | | | |
| Chung et al., 2013[31] | | | | | | x | | | | | | x | | |

from urine-derived stem cells showed beneficial effects in preventing or reducing fibrosis, particularly in early-stage PD models.

## Translating preclinical success to clinical outcome

However, transitioning these findings from animal models to clinical practice remains challenging. One key limitation is the biological differences between human PD and animal models. Rodent models, for instance, tend to exhibit faster disease progression and different healing mechanisms, potentially exaggerating therapeutic responses. Additionally, preclinical studies often rely on surrogate markers such as fibrosis reduction or plaque size, which do not always translate to clinically meaningful outcomes, like improved curvature or erectile function.

## Preliminary human trials explore early intervention strategies for PD

Preliminary human studies have begun to explore the clinical relevance of findings from animal models. For example, positive outcomes from PDE5i and SERM combinations in animal models led to a clinical study by Cellek et al.[68] Their clinical experiences with these combinations emphasized the importance of early intervention based on research done in the nineties where tamoxifen was administered to 36 patients in the acute phase, with the best response in patients with disease duration of less than four months[69] and another study with 25 patients in chronic phase with no statistically significant effect.[70] The reported clinical experience[68] involved 102 men treated within six months of disease onset; fewer progressed than controls who received no treatment or vitamin E. Additionally, the treatment group showed improvement in penile curvature. Nonetheless, further research is needed to identify optimal patient groups and confirm these findings in more extensive trials.

## Limitations in manipulation techniques and ESWT

Experimental studies on manipulation remain limited, partly due to the lack of suitable animal models to study traction and erection devices. Studies exploring manipulation techniques, however, have shown reductions in MFBs and fibrosis markers, such as TGF-$\beta$1 and pSMAD2/3[56,57] in animal models and increased collagen-degrading enzymes like MMP 8.[33] However, newer research suggests MMP2 and MMP-9 may play a more significant[70] role in PD, warranting further investigations. ESWT studies, particularly in combination with CCH, have shown inconclusive results. Human trials have also been inconclusive, with four randomized studies[71,72] involving 268 PD patients showing only modest reductions in penile curvature without statistical significance. Combining ESWT with other modalities at the beginning of the disease, as a treatment taking part in a multi-targeting approach, maybe where ESWT is shown to have the best effect.

## Stem cell therapies show promise in animal models

Stem cell therapies, particularly those using ADSCs, BMSCs, SVF, and exosomes, have shown promise in animal models by modulating fibrosis-associated molecular pathways. However, only two human trials have been conducted with limited sample sizes.[73,74] One with five patients intraplaque injected with placental matrix-derived mesenchymal stem cells[74] and

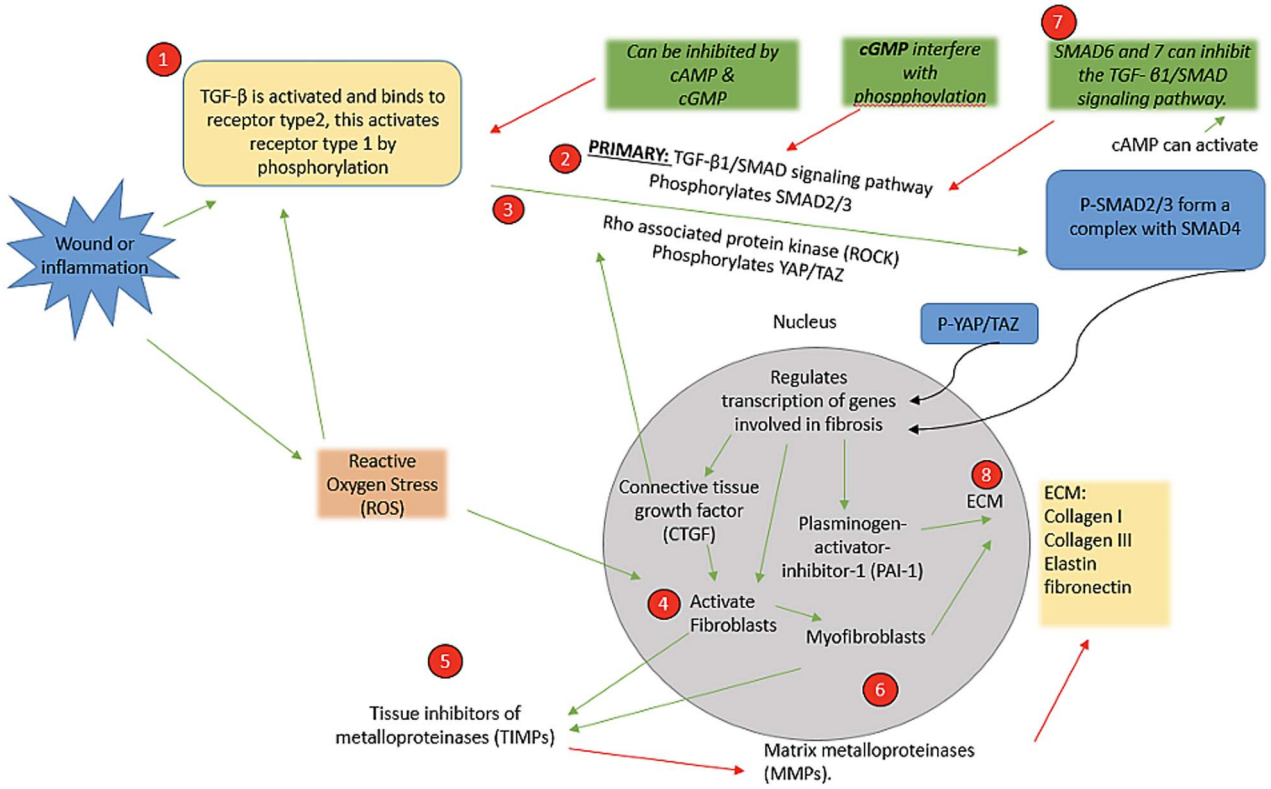


**Figure 1.** A simplified model of fibrosis: The excessive accumulation of extracellular matrix proteins in tissues. TGF- ß1: Transforming growth factor- ß1, cAMP: Cyclic adenosine monophosphate, cGMP: Cyclic guanosine monophosphate, SMAD: Mothers against Decapentap.

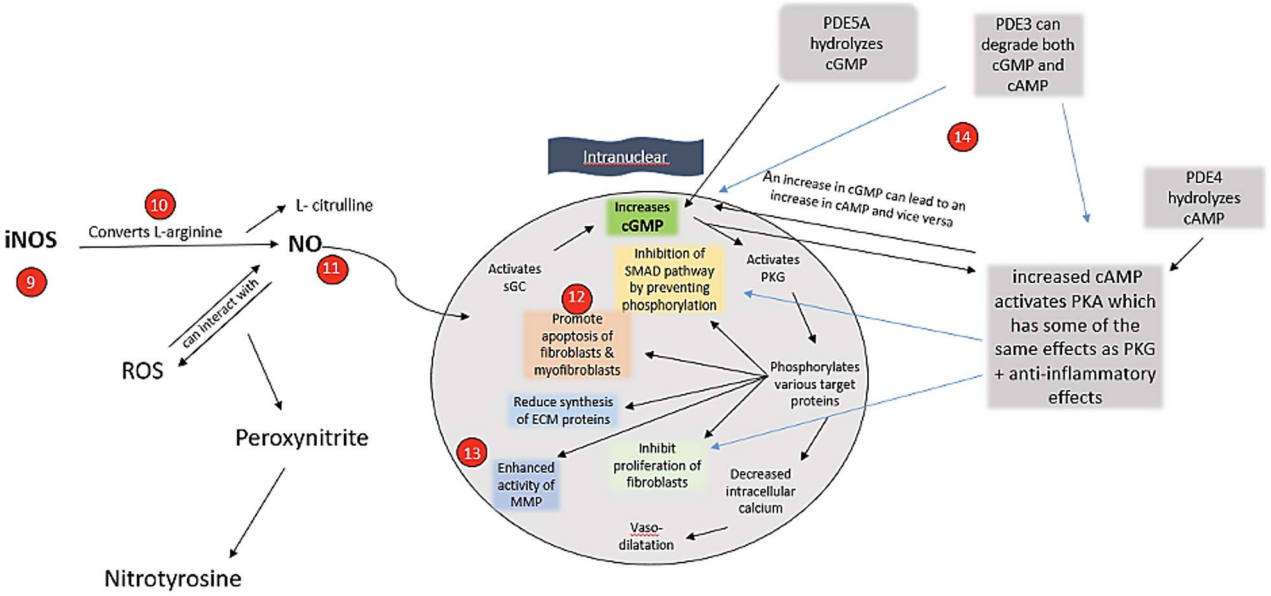


**Figure 2.** iNos is induced by inflammation. ECM: Extracellular matrix iNOS: Inducible Ntrix oxide synthase, MMP: Matrix-metallo-proteinases NO: Nitric oxide, PKG: cGMP-dependent protein kinase, ROS: Reactive oxygen stress, sGC: Soluble guanylate cyclase.

another with SVF combined with ESWT.[73] The importance of early intervention is highlighted, with animal studies consistently showing better outcomes when treatments are initiated early in the disease course. Larger, well-designed human trials are needed to validate these findings.

## The iNOS modulation in PD

The modulation of iNOS in PD is complex. iNOS, the enzyme responsible for producing nitric oxide (NO), demonstrated reduced levels in some treatments[41,43] while increased in others.[36] When investigating the potential effect of NO, it is crucial to recognize NO's dual role in fibrosis and protein remodeling. Moderate NO concentrations can exert an anti-fibrotic effect by inhibiting fibroblast activation, collagen deposition, and MFB differentiation. In contrast, excessive NO levels generate reactive nitrogen species, promoting oxidative stress and exacerbating fibrosis. This oxidative stress can damage cellular components,

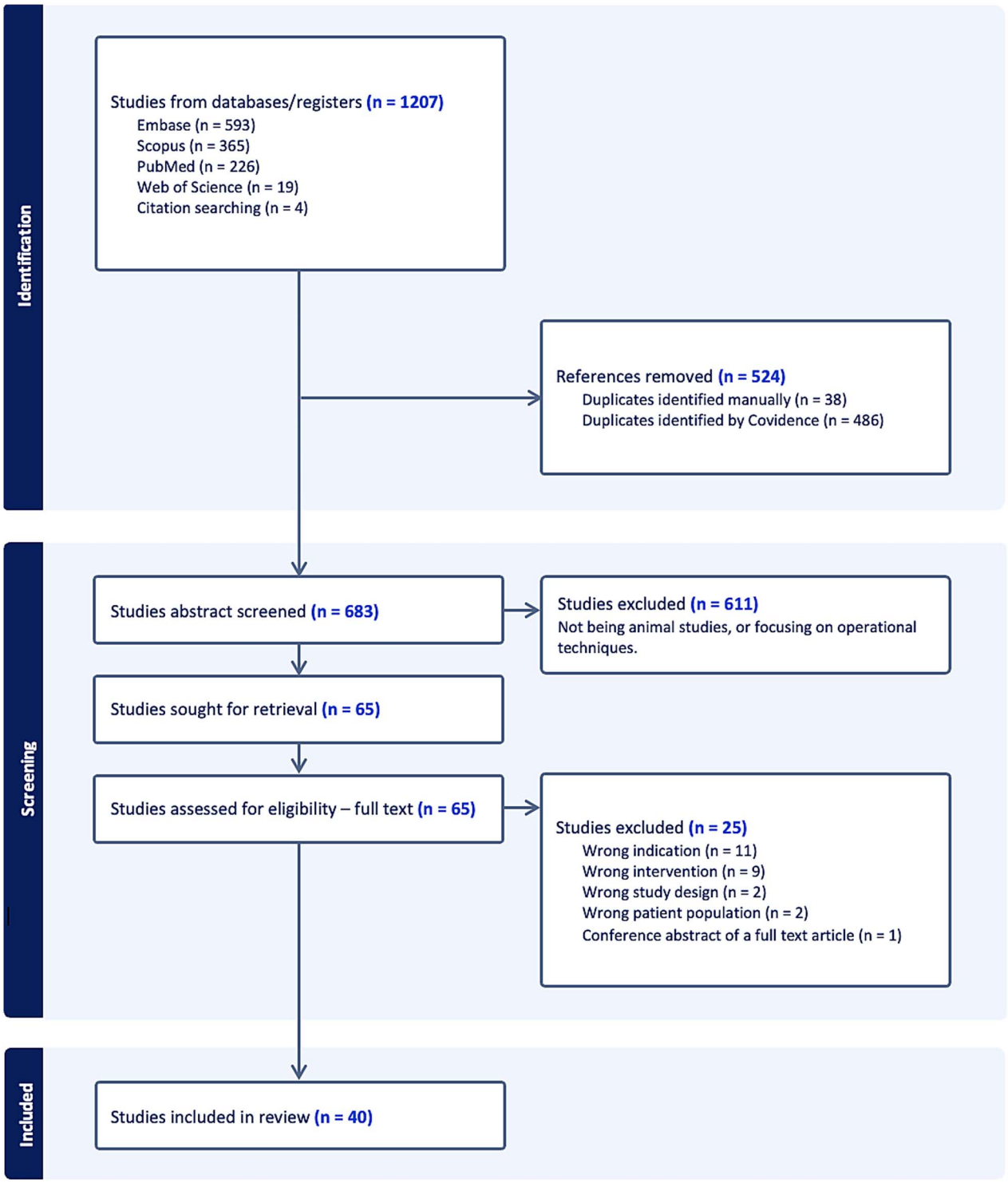


**Figure 3.** PRISMA flowchart.

exacerbating tissue injury and inflammation, ultimately promoting fibrosis. Therefore, the context of iNOS modulation is critical to understanding its therapeutic potential.[75]

## Importance of accurate measurement and fibrosis markers

Another frequently reported effect of interventions is the reduction of ECM proteins, particularly Collagen I, Collagen III, and Elastin. However, only some studies specify the methods used to quantify these reductions. Hydroxyproline, an amino acid indicative of tissue collagen content, is a common measure of fibrosis. The activation of fibroblasts into MFBs, typically identified by an $\alpha$-SMA expression,[50] is another important marker. MFBs commonly express both $\alpha$-SMA and vimentin, whereas smooth muscle cells express $\alpha$-SMA but not vimentin. Therefore, information on both protein markers could be valuable to include when reporting on effects.

### Inconsistent methods and defining acute vs. chronic phases in animal research

The widely used PD animal model involving TGF-$\beta$1 injection into the TA[1] presents challenges. The model was developed as TGF-$\beta$1 was found to be upregulated in human PD plaque.[76] However, spontaneous reduction in fibrosis is seen after 60 days,[28] complicating long-term studies. Additionally, inconsistently reporting on the TGF-$\beta$1 injection method (injection to the TA under vision/injection of the midshaft of the rat penis) may affect the interpretation of results. Although the measures in that area are small, it could be anticipated that this also may develop fibrosis in various degrees and influence the interpretation of results. This agrees with ESSM,[20] which recommends a detailed description of PD in induction but does not stress the importance of standardized injection methods.

Defining PD's acute and chronic phases in animal models is essential for consistency. In this review, the acute phase post-TGF-$\beta$1 injection was defined as 0-30 days, while the chronic phase ranged from 21 to 45 days, and after fibrin injection, 0 to 1 day, and 15 to 21 days, respectively—the shorter period after fibrin injection is expected due to faster plaque formation.

However, studies in which interventions are initiated after 30 days are divided. Some researchers[60] argue that this represents an early, unstable, and progressive phase of PD in humans as the model has not yet developed a curvature.

### Key molecular targets for therapy

The development of fibrotic plaque in PD is driven by an imbalance between profibrotic and antifibrotic processes, involving key molecules like TGF-ß1, fibrin, PAI-1, increased TIMPs NO, IFN-$\alpha$, and IFN-$\gamma$, Decorin microRNA. Understanding these mechanisms can help target therapies.

### Limitations of trichome staining in fibrosis assessment

Trichrome staining is commonly used to assess fibrosis by visualizing collagen deposition, but it has limitations. It does not capture the dynamic processes underlying fibrosis, such as fibroblast activation, myofibroblast differentiation, and ECM turnover. More comprehensive evaluation methods, such as immunohistochemistry for markers like $\alpha$-SMA and vimentin or molecular imaging to track changes in ECM content and cellular behavior, would provide a better understanding of how therapies affect fibrosis. Additionally, what constitutes a "sufficient" reduction in fibrosis markers to predict success in human studies is unclear. A modest decrease in collagen I or III may not translate into functional improvements unless accompanied by changes in other key factors like MMPs or TGF-$\beta$1 levels. Therefore, more robust criteria are needed to define successful fibrosis reduction and functional recovery.

### Emphasizing multi-modal strategies for optimal treatment outcomes

Numerous studies support early treatment initiation, demonstrating greater efficacy when interventions begin promptly. This necessitates a paradigm shift in PD management, moving towards earlier and multimodal treatment strategies, which is on its way. We need to think of treatment sooner and with more modalities. These findings underscore the need for personalized treatment approaches and further research to optimize timing and modality combinations.

### Balancing fibrosis inhibition and tissue regeneration

Regenerative therapies, including stem cell-based approaches, have shown great promise in animal models by reducing ECM content and modulating fibrosis. However, translating these findings into clinical practice has been slow. Human trials have been limited to small cohorts, and results could be more consistent. Achieving the right balance between inhibiting fibrosis and promoting tissue regeneration remains a significant challenge. Moreover, the optimal timing for regenerative interventions, particularly in PD's acute versus chronic phases, must be better understood. Future studies should focus on optimizing stem cell delivery methods, exploring combination therapies, and investigating the long-term effects of these interventions in more extensive clinical trials.

### Knowledge gaps and future directions

Despite the progress made in understanding PD and exploring potential treatments, several knowledge gaps and areas for future research have been identified.

First, the precise mechanisms driving PD development and progression are not fully understood. Future studies should focus on unraveling the molecular pathways involved in PD pathophysiology, including the role of TGF-$\beta$1 and other signaling molecules.

Second, standardized animal models that better replicate human PD are needed. This would improve the predictive value of preclinical findings and facilitate the development of new treatments.

Third, the optimal timing, duration, and combination of interventions for PD treatment remain unclear. Future research should aim to elucidate the optimal treatment regimens and identify patient-specific factors that may influence treatment outcomes.

Finally, consensus is needed on defining PD's acute and chronic phases in experimental models to ensure consistency across studies.

It could be helpful to redo some of the studies for future studies, as we now have greater knowledge of some mechanisms and pathways. There should also be an increased focus on combination treatments, such as drug-added manipulation interventions or stem cell-added manipulation. A game-changing focus would be on treatments the patient can attend a few times or can do at home.

### Strengths and limitations

The review provides a comprehensive overview of the current experimental research on PD adhering to established protocols and utilizing a well-defined search strategy. However, the heterogeneity of the studies complicates comparisons and the drawing of definitive conclusions. Potential selection bias is also a limitation, as some studies may have been excluded if their primary focus was physiological processes rather than treatment outcomes. The studies focus little on possible side effects and safety concerns, which are crucial for clinical translation. There are limitations to the animal models in replicating human PD accurately, which can complicate the translation of findings.

## Conclusions

The scoping review provides a comprehensive overview of the current landscape of preclinical research on PD treatments.

Despite these findings, PD's precise etiology and pathophysiology remain elusive and necessitate further research. The review underscores the importance of early, multimodal treatment strategies and calls for more well-conducted human trials to validate the efficacy of these interventions. Future research should also focus on refining animal models, standardizing study protocols, and exploring the mechanisms underlying the observed effects to develop targeted therapies for PD.

While numerous interventions have shown promise in animal models, further research is needed to translate these findings into effective therapies for human patients. By addressing the identified knowledge gaps and advancing our understanding of PD pathophysiology, we can move closer to developing targeted and personalized treatments for this debilitating condition.

## Acknowledgments and disclosures

None.

## Author contributions

M.H.W.: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, software & resources, Writing—original draft, Visualization, Writing—review & editing, R.K.: Formal analysis, Methodology, software & resources, Supervision, Writing—review & editing, B.S.L.: Formal analysis, Supervision, Writing—review & editing, L.L.: Conceptualization, Formal analysis, Supervision, Writing—review & editing.

## Supplementary material

Supplementary material is available at *Sexual Medicine* online.

## Funding

The work was generously supported by The Region of Southern Denmark [grant number 20/14248], The Louis-Hansen Fund [grant number 20-2B-7413], the Lizzi and Mogens Staal Fund [grant number 2021-0456], The Karola Jørgensen Fund, The Marie and Børge Kroghs Fund, The Senior Doctors Research Fund OUH [grant number 128-A5326], The Fund for Gentle Surgery OUH and the PhD fund of the executive board of the Hospital of South West Denmark [grant number 20-55755]. These funding sources, crucial to our research, were managed independently and did not influence the trial design, data collection, analysis, or publication.

## Conflicts of interest

None declared.

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*Sexual Medicine*, 2024, 12, qfae088
https://doi.org/10.1093/sexmed/qfae088
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