Review

Thymosin Beta-4 and TB-500 in Tissue Healing, Regeneration, and Musculoskeletal Repair: A Scoping Review

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Scoping Review

Thymosin Beta-4 and TB-500 in Tissue Healing, Regeneration, and Musculoskeletal Repair: A Scoping Review

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Featured Application

This review provides clinicians and researchers with a structured map of the TB4 and TB-500 literature, helping distinguish biologic plausibility and preclinical signal from direct human clinical evidence.

Abstract

Thymosin beta-4 (TB4) and the related compound commonly referred to as TB-500 are widely discussed in tissue healing and musculoskeletal medicine, but the scope and nature of the supporting literature remain unclear. We conducted a scoping review to map the evidence on TB4 and TB-500 in tissue healing, regeneration, and musculoskeletal repair. PubMed, Europe PMC, and ClinicalTrials.gov were searched through March 2026. English-language in vitro, animal, human, and registered clinical trial sources directly evaluating TB4, TB-500, or included derivatives in repair-related contexts were eligible. Of 1772 records identified, 80 studies were included. The evidence base was weighted toward mixed and in vitro designs, and most studies evaluated TB4 rather than TB-500. The most common tissue categories were wound/skin/soft tissue, vascular/endothelial, ocular/cornea, and bone. Direct musculoskeletal tissue categories such as tendon, ligament, muscle, cartilage, and spine/intervertebral disc were comparatively sparse. Human evidence was concentrated in ocular/cornea and wound/skin/soft tissue settings, whereas direct TB-500 evidence was limited to a single included study. Overall, the mapped literature supports the popular interest in several repair-related pathways but remains unevenly distributed and largely preclinical, with limited human evidence directly relevant to musculoskeletal applications.

Keywords: thymosin beta-4; TB-500; scoping review; tissue healing; musculoskeletal repair; regenerative medicine; sports medicine

1. Introduction

Peptides are short chains of amino acids that have played an important role in therapeutics for more than a century, beginning with the introduction of insulin in 1921. Advances in peptide synthesis, structural modification, and delivery systems have accelerated development in this therapeutic class, and more than 80 peptide drugs have now been approved worldwide, with more than 170 additional peptide agents in active clinical development and many more in preclinical study [1]. At the same time, public interest has expanded beyond regulated peptide therapeutics to investigational and unapproved peptides promoted for tissue healing, recovery, and performance, giving this area growing clinical and policy relevance [2,3].

Thymosin beta-4 (TB4) is a multifunctional and widely distributed 43-amino-acid peptide and the most abundant beta-thymosin in the human body [4]. It has been implicated in several biologic

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processes relevant to tissue repair, including promotion of angiogenesis and cell proliferation and inhibition of apoptosis and inflammation [4]. A related compound commonly referred to as TB-500 has been promoted for tissue healing and musculoskeletal injury recovery despite limited clinical evidence [4]. However, the extent, types, and musculoskeletal relevance of the available evidence across preclinical and human studies remain unclear. No comprehensive scoping review has specifically mapped the literature on TB4 and TB-500 in tissue healing, regeneration, and musculoskeletal repair.

This uncertainty is especially important in the current regulatory and public-policy context. The U.S. Food and Drug Administration currently list TB4 fragment (LKKTETQ) among bulk drug substances that may present significant safety risks in compounding because of limited human exposure and safety data [5]. The World Anti-Doping Agency also classifies TB4 and its derivatives, including TB-500, as prohibited substances under the 2026 Prohibited List [6]. More broadly, recent sports medicine and peptide reviews have emphasized that patient demand, direct-to-consumer marketing, and off-label or unapproved peptide use are expanding faster than the human evidence base [2,3]. In this setting, the purpose of this scoping review is to map the existing literature on TB4 and TB-500 in tissue healing, regeneration, and musculoskeletal repair across preclinical and clinical research. Specifically, this review aims to characterize the tissues studied, summarize the mechanisms of action and study designs represented in the literature, determine whether human clinical studies exist, and identify gaps relevant to musculoskeletal medicine and orthopedic applications.

2. Methods

2.1. Protocol and Reporting Framework

This scoping review was conducted to map the available literature on thymosin beta-4 (TB4) and TB-500 in tissue healing, regeneration, and musculoskeletal repair across preclinical and clinical research. The objective was to characterize the extent, range, and nature of the evidence, including study designs, tissues studied, proposed mechanisms of action, and major evidence gaps, rather than to estimate treatment effectiveness or perform quantitative pooling. The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [7]. A protocol was registered prospectively in the Open Science Framework before data extraction commenced April 2nd, 2026 (https://doi.org/10.17605/osf.io/jtdh4).

2.2. Eligibility Criteria

Eligibility criteria were developed using the population, concept, and context framework for scoping reviews. Sources of evidence were eligible if they directly evaluated TB4, TB-500, or an included derivative in relation to tissue healing, regeneration, repair, or relevant biologic mechanisms. Eligible evidence included in vitro studies, animal studies, human clinical studies, and registered clinical trials involving musculoskeletal tissues or related repair contexts, including tendon, ligament, muscle, bone, cartilage, wound healing, and broader tissue regeneration models relevant to musculoskeletal healing. Studies evaluating angiogenesis, fibrosis, inflammation, cell migration, collagen deposition, histologic healing, biomechanical strength, or related repair outcomes were eligible when they directly involved TB4 or TB-500. Review articles, editorials, opinion pieces, conference abstracts without full text, duplicate records, studies not involving TB4 or TB-500, and studies unrelated to tissue healing or regeneration were excluded. Studies focused exclusively on unrelated organ systems without relevance to tissue repair or regeneration were also excluded. Only English-language sources were included. No publication year restrictions were applied.

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2.3. Information Sources and Search Strategy

Searches were conducted in PubMed, Europe PMC, and ClinicalTrials.gov using database-specific adaptations of controlled vocabulary and keyword terms related to thymosin beta-4/TB-500 and tissue healing, regeneration, or musculoskeletal repair. The final search was executed on March 26th, 2026. Limits included English language only, with no publication year restriction. The complete database-specific search strategies for PubMed, Europe PMC, and ClinicalTrials.gov are provided in Supplementary Appendix S1.

2.4. Selection of Sources of Evidence

Records retrieved from all sources were imported for screening and deduplication. Records were managed in Rayyan during deduplication and title and abstract screening. Included studies and extracted data were subsequently transferred to Microsoft Excel for data charting and synthesis. Title and abstract screening and full-text screening were conducted independently by two reviewers. Disagreements were resolved through discussion and consensus. If eligibility was unclear at the title and abstract stage, the record was advanced to full-text review to avoid premature exclusion. Screening was not blinded to author names, journal names, or publication year.

2.5. Data Charting Process

Data were charted using a standardized Microsoft Excel extraction form developed for this review. Pilot extraction was performed on a small number of included studies to refine the extraction fields before final charting. One reviewer extracted data from each included study, and a second reviewer verified the extracted data for accuracy and completeness. Discrepancies were resolved through discussion and review of the full text until consensus was reached. Extractors had access to full study information, including authors, journals, and study results. Authors of included studies were not contacted for additional data or clarification. Missing information was recorded as not reported.

2.6. Data Items

The following variables were charted from each included source of evidence: author, year of publication, study type, country when available, tissue studied, injury or disease model, intervention type, dose when reported, route of administration when reported, comparator or control condition, mechanisms studied, outcomes measured, key findings, and study limitations or notes. Mechanisms of interest included angiogenesis, inflammation, fibrosis, cell migration, and collagen deposition. Outcomes of interest included healing, regeneration, histologic outcomes, and biomechanical strength. Mechanism categories were assigned using prespecified dominant domains. “Not explicitly mechanistic” was used for studies that reported repair-related, functional, histologic, safety, or other outcomes without explicitly evaluating a named biologic pathway. “Other” was used for studies with a mechanistic focus that did not fit the prespecified categories of angiogenesis, cell migration, inflammation, fibrosis, or collagen/ECM remodeling. Data charting was designed to support descriptive mapping of the literature rather than quantitative effect size extraction. The final charted dataset and coding definitions are provided in Supplementary File S2.

2.7. Critical Appraisal

No formal risk of bias assessment or methodological quality appraisal was performed. This approach was chosen because the purpose of the review was to map the literature and summarize study characteristics, tissues studied, mechanisms, and research themes rather than evaluate treatment effectiveness or exclude studies based on methodological quality. Accordingly, studies were not excluded based on study quality.

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2.8. Synthesis of Results

Extracted data were synthesized using descriptive and narrative methods. Studies were organized into tables and grouped by study type, tissue studied, intervention type, mechanisms of action, and outcomes measured. The synthesis focused on identifying research trends, commonly studied tissues and mechanisms, the balance of preclinical and clinical evidence, and major gaps in the literature relevant to musculoskeletal healing and regeneration. No meta-analysis, pooled effect estimation, publication bias analysis, or sensitivity analysis was performed.

3. Results

3.1. Study Selection

The search identified 1772 records from PubMed, Europe PMC, and ClinicalTrials.gov. After removal of 266 duplicate records, 1506 records underwent title and abstract screening, of which 1382 were excluded. Full-text review was performed for 124 reports. Forty four full-text reports were excluded for the following reasons: did not evaluate a relevant repair-related outcome or mechanism (n = 15), did not address musculoskeletal healing, regeneration, or repair (n = 12), did not directly evaluate TB4, TB-500, or an included derivative (n = 11), not original primary research (n = 2), ClinicalTrials.gov record corresponded to a published manuscript (n = 3), and duplicate identified during full-text screening (n = 1). Eighty studies were included in the final scoping review (Figure 1).

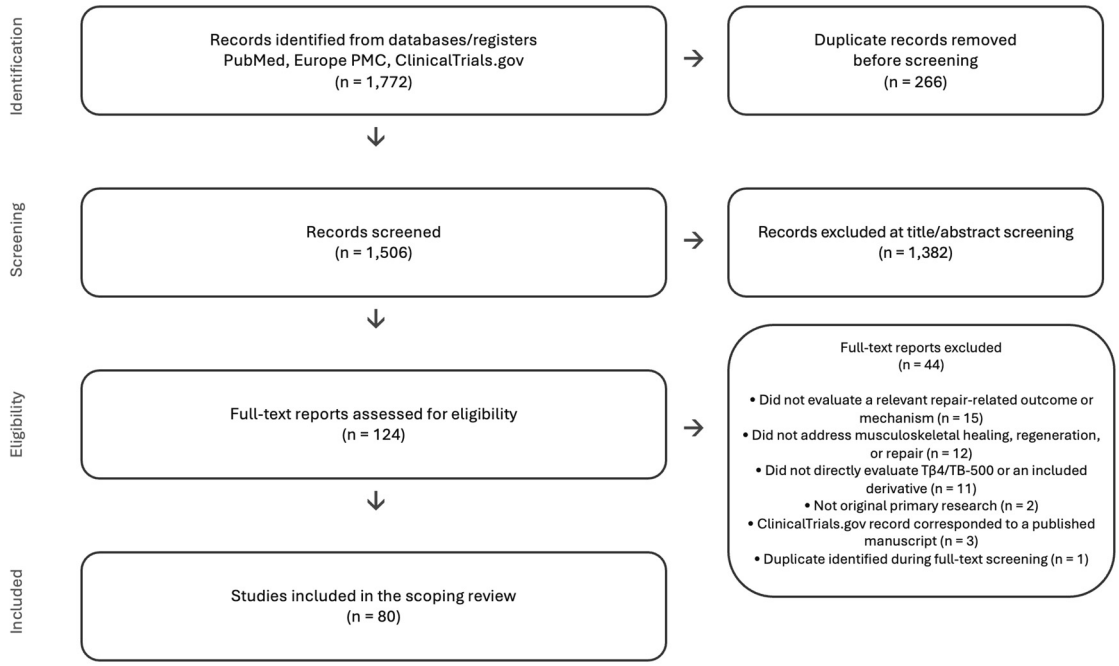

Figure 1. PRISMA flow diagram of study selection. Flow diagram showing record identification, deduplication, screening, full-text eligibility assessment, exclusion reasons, and final inclusion.

3.2. Characteristics of Included Sources of Evidence

Overall, the evidence base was weighted toward mixed and in vitro designs. Of the 80 included studies, 27 (33.8%) were coded as mixed studies, 23 (28.8%) as in vitro studies, 19 (23.8%) as human studies, and 11 (13.8%) as animal studies. By tissue, the literature was concentrated in wound/skin/soft tissue (22/80, 27.5%) and vascular/endothelial settings (17/80, 21.3%), followed by ocular/cornea (8/80, 10.0%), bone (7/80, 8.8%), and Multiple/other (7/80, 8.8%). Smaller categories included cartilage (4/80, 5.0%), adipose/fat graft (3/80, 3.8%), ligament (3/80, 3.8%), tendon (2/80, 2.5%), Multiple (2/80, 2.5%), Other/Not reported (2/80, 2.5%), spine/intervertebral disc (2/80, 2.5%),

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and muscle (1/80, 1.3%). The distribution of included studies across tissue categories and study types is shown in Figure 2.

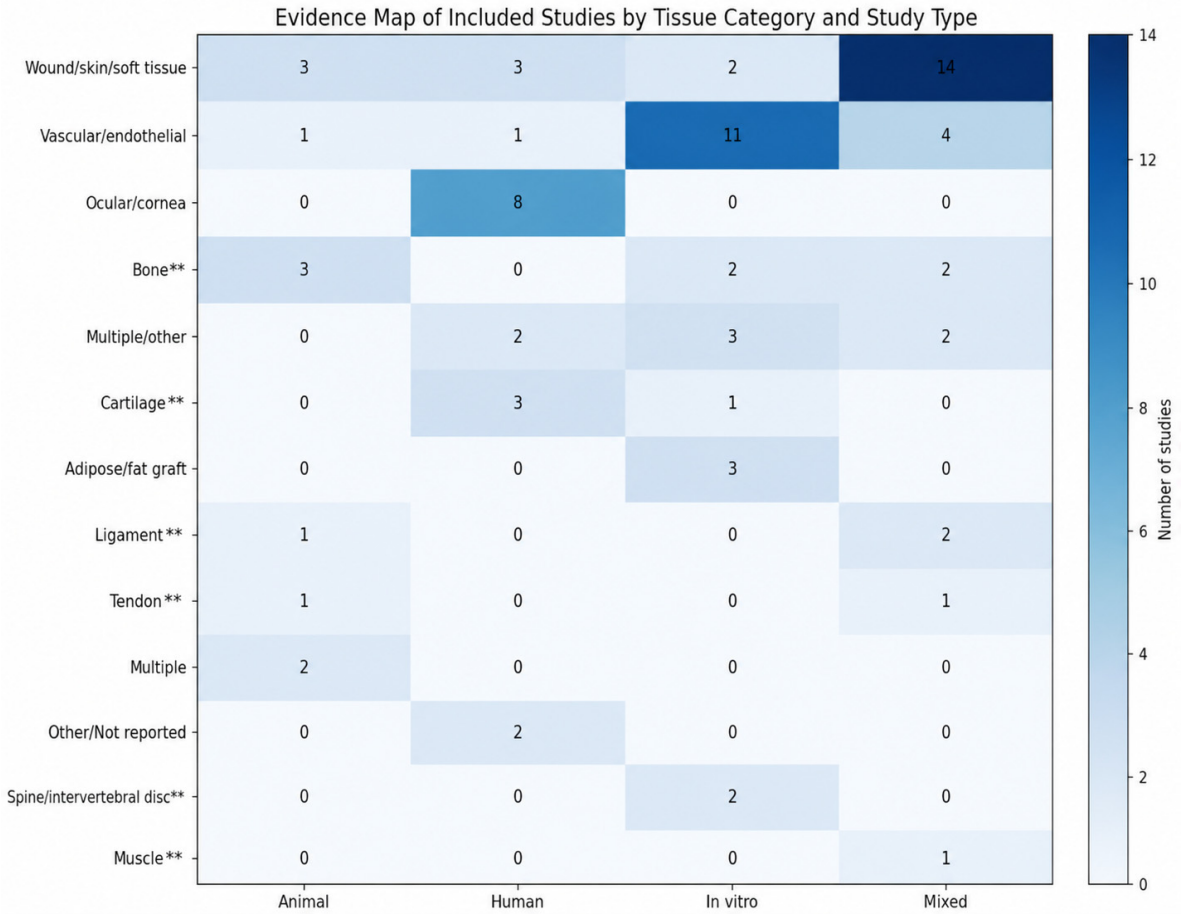

Figure 2. Evidence map of included studies by tissue category and study type. Heatmap summarizing the number of included studies within each cross-classified tissue and study-type cell. ** Denotes musculoskeletal categories.

TB4 accounted for most included interventions (70/80, 87.5%). Five studies (6.3%) were categorized as no direct intervention or endogenous-only, four (5.0%) as derivative or fragment studies, and one (1.3%) as a direct TB-500 study. The most common mechanism categories were not explicitly mechanistic (21/80, 26.3%), meaning no dominant named pathway was directly evaluated, other (19/80, 23.8%), meaning a mechanistic focus was present but did not fit a prespecified mechanism category, and angiogenesis (19/80, 23.8%), followed by cell migration (10/80, 12.5%), inflammation (5/80, 6.3%), collagen/ECM remodeling (4/80, 5.0%), and fibrosis (2/80, 2.5%). Outcome categories were led by molecular/cellular markers (38/80, 47.5%), healing/repair (21/80, 26.3%), and functional outcomes (10/80, 12.5%), with smaller numbers of regeneration (5/80, 6.3%), safety/PK/tolerability (3/80, 3.8%), histology (2/80, 2.5%), and biomechanical strength (1/80, 1.3%). Characteristics of individual included studies are presented in Table 1. Grouped distributions by tissue, study type, and intervention are summarized in Table 2, and mechanism and outcome distributions are summarized in Table 3.

Table 1. Characteristics of included studies.

Study ID	Author	Year	Study type	Tissue studied	Intervention	Primary mechanism category	Primary outcome category	Ref.
1	Lee	2021	Human	Multiple/other	TB4	Not explicitly mechanistic	Functional outcome	[8]
2	Lee	2021	In vitro	Cartilage	No direct intervention/endogenous-only	Other	Molecular/cellular marker	[9]
3	Xi	2025	Mixed	Bone	TB4	Angiogenesis	Regeneration	[10]
4	Adachi	2013	Animal	Bone	TB4	Not explicitly mechanistic	Regeneration	[11]
5	Li	2022	Mixed	Bone	TB4	Angiogenesis	Regeneration	[12]
6	Tokura	2011	Mixed	Muscle	TB4	Cell migration	Molecular/cellular marker	[13]
7	Ahmed	2014	Animal	Tendon	No direct intervention/endogenous-only	Inflammation	Healing/repair	[14]
8	Ehrlich	2012	Mixed	Wound/skin/soft tissue	TB4	Fibrosis	Histology	[15]
9	Rahaman	2024	Mixed	Multiple/other	TB-500	Other	Molecular/cellular marker	[16]
10	Zhang	2025	Mixed	Adipose/fat graft	TB4	Other	Molecular/cellular marker	[17]
11	Yu	2021	Human	Wound/skin/soft tissue	TB4	Other	Functional outcome	[18]
12	Lee	2016	Mixed	Ligament	TB4	Inflammation	Healing/repair	[19]
13	Li	2023	In vitro	Adipose/fat graft	TB4	Other	Molecular/cellular marker	[20]
14	Li	2024	In vitro	Adipose/fat graft	TB4	Angiogenesis	Molecular/cellular marker	[21]
15	Huff	2002	Mixed	Multiple/other	TB4	Collagen/ECM remodeling	Molecular/cellular marker	[22]
16	Malinda	1997	Mixed	Vascular/endothelial	TB4	Cell migration	Molecular/cellular marker	[23]
17	Guarnera	2007	Human	Wound/skin/soft tissue	TB4	Not explicitly mechanistic	Healing/repair	[24]
18	Wyczółkowska	2007	In vitro	Multiple/other	Derivative/fragment	Inflammation	Molecular/cellular marker	[25]
19	Sosne	2015	Human	Ocular/cornea	TB4	Not explicitly mechanistic	Functional outcome	[26]
20	Freeman	2011	In vitro	Vascular/endothelial	TB4	Other	Molecular/cellular marker	[27]
21	Li	2007	Animal	Wound/skin/soft tissue	TB4	Angiogenesis	Healing/repair	[28]
22	Sosne	2015	Human	Ocular/cornea	TB4	Not explicitly mechanistic	Functional outcome	[29]
23	Malinda	1999	Mixed	Wound/skin/soft tissue	TB4	Angiogenesis	Healing/repair	[30]
24	Al-Nedawi	2004	In vitro	Vascular/endothelial	TB4	Other	Molecular/cellular marker	[31]
25	Kim	2020	Animal	Vascular/endothelial	TB4	Angiogenesis	Molecular/cellular marker	[32]
26	Wang	2021	Human	Other/Not reported	TB4	Not explicitly mechanistic	Safety/PK/tolerability	[33]

27	Philp	2004	Mixed	Wound/skin/soft tissue	TB4	Angiogenesis	Healing/repair	[34]
28	Reti	2008	In vitro	Wound/skin/soft tissue	TB4	Other	Molecular/cellular marker	[35]
29	Philp	2003	Mixed	Wound/skin/soft tissue	TB4	Angiogenesis	Healing/repair	[36]
30	Dettin	2011	Mixed	Vascular/endothelial	Derivative/fragment	Angiogenesis	Molecular/cellular marker	[37]
31	Guarnera	2010	Human	Wound/skin/soft tissue	TB4	Not explicitly mechanistic	Healing/repair	[38]
32	Kim	2015	In vitro	Vascular/endothelial	TB4	Other	Molecular/cellular marker	[39]
33	Lv	2013	In vitro	Vascular/endothelial	TB4	Angiogenesis	Molecular/cellular marker	[40]
34	Wei	2013	Human	Cartilage	No direct intervention/endogenous-only	Other	Molecular/cellular marker	[41]
35	Ruff	2010	Human	Other/Not reported	TB4	Not explicitly mechanistic	Safety/PK/tolerability	[42]
36	Selmi	2012	In vitro	Vascular/endothelial	TB4	Cell migration	Molecular/cellular marker	[43]
37	Zhu	2016	Human	Vascular/endothelial	TB4	Not explicitly mechanistic	Functional outcome	[44]
38	Kim	2017	Mixed	Wound/skin/soft tissue	TB4	Angiogenesis	Healing/repair	[45]
39	Zhao	2018	Mixed	Wound/skin/soft tissue	TB4	Angiogenesis	Healing/repair	[46]
40	Cierniewski	2012	In vitro	Multiple/other	TB4	Cell migration	Molecular/cellular marker	[47]
41	Ock	2012	In vitro	Vascular/endothelial	TB4	Angiogenesis	Molecular/cellular marker	[48]
42	Philp	2003	Mixed	Wound/skin/soft tissue	TB4	Cell migration	Healing/repair	[49]
43	Ti	2015	Mixed	Wound/skin/soft tissue	TB4	Angiogenesis	Healing/repair	[50]
44	Zhao	2011	In vitro	Vascular/endothelial	TB4	Angiogenesis	Molecular/cellular marker	[51]
45	Qiu	2009	In vitro	Vascular/endothelial	TB4	Cell migration	Molecular/cellular marker	[52]
46	Philp	2006	Mixed	Wound/skin/soft tissue	TB4	Collagen/ECM remodeling	Molecular/cellular marker	[53]
47	Trenkwalder	2015	Mixed	Vascular/endothelial	TB4	Angiogenesis	Functional outcome	[54]
48	Fan	2009	In vitro	Vascular/endothelial	TB4	Collagen/ECM remodeling	Molecular/cellular marker	[55]
49	Choi	2018	In vitro	Bone	TB4	Other	Molecular/cellular marker	[56]
50	Jo	2010	In vitro	Vascular/endothelial	TB4	Angiogenesis	Molecular/cellular marker	[57]
51	Li	2013	In vitro	Vascular/endothelial	TB4	Angiogenesis	Molecular/cellular marker	[58]
52	Wang	2013	Mixed	Wound/skin/soft tissue	TB4	Other	Healing/repair	[59]
53	Zachman	2013	Mixed	Wound/skin/soft tissue	Derivative/fragment	Angiogenesis	Molecular/cellular marker	[60]
54	Lin	2015	Animal	Wound/skin/soft tissue	TB4	Cell migration	Healing/repair	[61]
55	Kim	2014	Animal	Wound/skin/soft tissue	TB4	Inflammation	Healing/repair	[62]
56	He	2026	Mixed	Wound/skin/soft tissue	TB4	Not explicitly mechanistic	Healing/repair	[63]

57	Stadelmann	2025	In vitro	Wound/skin/soft tissue	TB4	Cell migration	Molecular/cellular marker	[64]
58	Su	2022	Mixed	Vascular/endothelial	TB4	Collagen/ECM remodeling	Molecular/cellular marker	[65]
59	Paz-González	2023	Human	Cartilage	No direct intervention/endogenous-only	Other	Molecular/cellular marker	[66]
60	Wu	2020	Mixed	Tendon	TB4	Cell migration	Molecular/cellular marker	[67]
61	Sosne	2023	Human	Ocular/cornea	TB4	Not explicitly mechanistic	Healing/repair	[68]
62	Matsuo	2012	Animal	Bone	TB4	Other	Regeneration	[69]
63	Lee	2015	Mixed	Ligament	TB4	Other	Molecular/cellular marker	[70]
64	Spurney	2010	Animal	Multiple	TB4	Not explicitly mechanistic	Functional outcome	[71]
65	Xu	2013	Mixed	Wound/skin/soft tissue	Derivative/fragment	Cell migration	Healing/repair	[72]
66	Choi	2015	In vitro	Bone	TB4	Other	Molecular/cellular marker	[73]
67	Xu	2013	Animal	Ligament	TB4	Not explicitly mechanistic	Biomechanical strength	[74]
68	Brady	2014	Animal	Bone	TB4	Not explicitly mechanistic	Healing/repair	[75]
69	Wang	2015	In vitro	Spine/intervertebral disc	TB4	Other	Molecular/cellular marker	[76]
70	Aki	2018	Human	Cartilage	No direct intervention/endogenous-only	Other	Molecular/cellular marker	[77]
71	Lin	2013	Animal	Multiple	TB4	Not explicitly mechanistic	Regeneration	[78]
72	Tapp	2010	In vitro	Spine/intervertebral disc	TB4	Other	Molecular/cellular marker	[79]
73	Ehrlich	2010	Mixed	Wound/skin/soft tissue	TB4	Fibrosis	Histology	[80]
74	Qiu	2011	In vitro	Multiple/other	TB4	Inflammation	Molecular/cellular marker	[81]
75	ReGenTree, LLC	2007	Human	Ocular/cornea	TB4	Not explicitly mechanistic	Healing/repair	[82]
76	RegeneRx Biopharmaceuticals, Inc.	2011	Human	Multiple/other	TB4	Not explicitly mechanistic	Safety/PK/tolerability	[83]
77	ReGenTree, LLC	2015	Human	Ocular/cornea	TB4	Not explicitly mechanistic	Functional outcome	[84]
78	ReGenTree, LLC	2016	Human	Ocular/cornea	TB4	Not explicitly mechanistic	Functional outcome	[85]
79	ReGenTree, LLC	2019	Human	Ocular/cornea	TB4	Not explicitly mechanistic	Functional outcome	[86]
80	ReGenTree, LLC	2022	Human	Ocular/cornea	TB4	Not explicitly mechanistic	Healing/repair	[87]

Table 1. Study-level characteristics for all 80 included sources in StudyID order. Structured fields reflect the finalized coded workbook, and numeric citations correspond to the final manuscript reference list.

Table 2. Grouped synthesis summary by tissue, study type, and intervention.

Tissue category	Total n	%	Animal	Human	In vitro	Mixed	TB4	TB-500	Derivative/fragment	Endogenous-only / no direct intervention
Wound/skin/soft tissue	22	27.5	3	3	2	14	20	0	2	0
Vascular/endothelial	17	21.3	1	1	11	4	16	0	1	0
Ocular/cornea	8	10.0	0	8	0	0	8	0	0	0
Bone	7	8.8	3	0	2	2	7	0	0	0
Multiple/other	7	8.8	0	2	3	2	5	1	1	0
Cartilage	4	5.0	0	3	1	0	0	0	0	4
Adipose/fat graft	3	3.8	0	0	2	1	3	0	0	0
Ligament	3	3.8	1	0	0	2	3	0	0	0
Tendon	2	2.5	1	0	0	1	1	0	0	1
Multiple	2	2.5	2	0	0	0	2	0	0	0
Other/Not reported	2	2.5	0	2	0	0	2	0	0	0
Spine/intervertebral disc	2	2.5	0	0	2	0	2	0	0	0
Muscle	1	1.3	0	0	0	1	1	0	0	0

Table 2. Grouped summary of distributions by tissue, study type, and intervention across the 80 included studies. Percentages are calculated from the 80 included studies.

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Table 3. Mechanism and outcome summary.

Panel A. Mechanism categories			
Mechanism category	**Count**	**%**	**Most represented tissue(s)**
Not explicitly mechanistic	**21**	**26.3**	**Ocular/cornea (8)**
Other	**19**	**23.8**	**Cartilage (4)**
Angiogenesis	**19**	**23.8**	**Vascular/endothelial (8); Wound/skin/soft tissue (8)**
Cell migration	**10**	**12.5**	**Wound/skin/soft tissue (4)**
Inflammation	**5**	**6.3**	**Multiple/other (2)**
Collagen/ECM remodeling	**4**	**5.0**	**Vascular/endothelial (2)**
Fibrosis	**2**	**2.5**	**Wound/skin/soft tissue (2)**
Panel B. Outcome categories			
Outcome category	**Count**	**%**	**Most represented study type(s)**
Molecular/cellular marker	**38**	**47.5**	**In vitro (23)**
Healing/repair	**21**	**26.3**	**Mixed (11)**
Functional outcome	**10**	**12.5**	**Human (8)**
Regeneration	**5**	**6.3**	**Animal (3)**
Safety/PK/tolerability	**3**	**3.8**	**Human (3)**
Histology	**2**	**2.5**	**Mixed (2)**
Biomechanical strength	**1**	**1.3**	**Animal (1)**

Table 3. Summary of mechanism categories (Panel A) and outcome categories (Panel B) across the included literature. "Not explicitly mechanistic" indicates studies that did not directly evaluate a named biologic pathway. "Other" indicates studies with a mechanistic focus that did not fit the prespecified mechanism categories. Dominant tissue and study type patterns are descriptive summaries from data extraction and do not imply exclusive one-to-one mapping.

3.3. Synthesis by Study Type

Mixed studies comprised the largest study-type category and frequently integrated cell-based assays with in vivo repair models or paired biomaterial and delivery platforms with preclinical repair [10,12,13,15–17,19,22,23,30,34,36,37,45,46,49,50,53,54,59,60,63,65,67,70,72,80]. In vitro studies were the main source of molecular and cellular outcome data and were concentrated in vascular/endothelial, cartilage, adipose/fat graft, and spine/intervertebral disc settings [9,20,21,25,27,31,35,39,40,43,47,48,51,52,55–58,64,73,76,79,81]. Human studies were concentrated in ocular/cornea and wound/skin/soft tissue contexts and more often reported clinical, functional, or safety-type outcomes than direct mechanistic endpoints [8,18,24,26,29,33,38,41,42,44,66,68,77,82–87]. Animal studies formed the smallest study-type category and were more often associated with healing/repair, regeneration, or biomechanical outcomes [11,14,28,32,61,62,69,71,74,75,78].

3.4. Synthesis by Tissue

Wound/skin/soft tissue was the largest tissue category and spanned animal, human, in vitro, and mixed designs [15,18,24,28,30,34–36,38,45,46,49,50,53,59–64,72,80]. Vascular/endothelial was the second largest category and was dominated by in vitro studies [23,27,31,32,37,39,40,43,44,48,51,52,54,55,57,58,65]. Ocular/cornea included only human studies [26,29,68,82,84–87]. Bone included animal, in vitro, and mixed designs [10–12,56,69,73,75].

The direct musculoskeletal tissue categories were less evenly represented. Cartilage evidence was limited and indirect, with included studies consisting of endogenous, transcriptomic, proteomic,

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or secretome-based work rather than direct administered TB4 or TB-500 interventions [9,41,66,77]. Ligament included few studies and was represented by medial collateral ligament and periodontal ligament models [19,70,74]. Tendon was represented by two preclinical studies, one endogenous Achilles tendon-healing study and one mixed tendon tissue-engineering study [14,67]. Muscle was represented by a single mixed study of injury-induced TB4 expression and myoblast chemotaxis [13]. Spine/intervertebral disc studies were limited to in vitro work [76,79], and adipose/fat graft studies were limited to in vitro and mixed designs [17,20,21].

3.5. Synthesis by Intervention, Mechanism, and Outcome

Across study types and tissues, most included studies evaluated TB4 directly, whereas endogenous-only, derivative or fragment, and TB-500 studies accounted for a small minority of the mapped literature (Table 2). Endogenous-only or no direct intervention studies were few and clustered in cartilage and tendon settings [9,14,41,66,77]. Derivative or fragment studies were uncommon and were represented by mast-cell, angiogenesis-focused, and wound-healing preclinical work [25,37,60,72]. Direct TB-500 evidence was limited to a single mixed study centered on metabolite profiling and fibroblast wound-healing screening [16].

Mechanistically, the literature was heterogeneous. The largest categories were not explicitly mechanistic, indicating that no dominant named pathway was directly evaluated, Other, indicating that a mechanistic focus was present but did not fit a prespecified mechanism category, and angiogenesis. Angiogenesis-focused studies were especially common in vascular/endothelial and wound/skin/soft tissue settings [10,12,21,28,30,32,34,36,37,40,45,46,48,50,51,54,57,58,60]. Cell-migration studies were identified across endothelial, wound, tendon, muscle, and adipose settings [13,23,43,47,49,52,61,64,67,72]. Collagen/ECM remodeling and fibrosis were less frequently represented [15,22,53,55,65,80].

3.6. Descriptive Evidence Gaps

Several descriptive gaps were evident in the mapped literature. Direct TB-500 evidence was minimal and limited to a single included study [16]. Human evidence was concentrated in ocular/cornea and wound/skin/soft tissue applications [18,24,26,29,38,63,68,82,84–87]. Direct musculoskeletal tissue categories remained sparsely represented overall, particularly tendon, ligament, muscle, and spine/intervertebral disc. Cartilage evidence was also limited and indirect, with included cartilage studies reflecting endogenous or no direct intervention approaches rather than administered TB4 or TB-500 interventions [9,41,66,77]. In addition, molecular/cellular marker outcomes predominated, whereas biomechanical strength, histology, and safety/PK/tolerability outcomes were less frequent.

4. Discussion

4.1. Main Findings

This scoping review mapped 80 studies addressing TB4 and TB-500 in tissue healing, regeneration, and musculoskeletal repair. Several patterns were consistent across the included literature. First, the evidence base was weighted toward preclinical and mechanistic work rather than human musculoskeletal studies. Second, the tissue distribution was concentrated in wound/skin/soft tissue, vascular/endothelial, and ocular settings, whereas direct musculoskeletal tissues such as tendon, ligament, muscle, cartilage, and spine/intervertebral disc were comparatively sparse. Third, most interventions studied TB4 rather than TB-500, and direct TB-500 evidence was limited to a single mixed experimental study [16].

These findings are broadly consistent with the wider background literature, which describes TB4 as a multifunctional peptide with reported roles in angiogenesis, cell migration, inflammation modulation, and tissue repair while also emphasizing that exploratory biologic promise has outpaced direct clinical validation [1,4,88]. Within the included studies, angiogenesis and cell migration were

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among the most common mechanistic themes [10,12,13,21,23,28,30,32,34,36,37,40,43,45–52,54,57,58,60,61,64,67,72]. At the same time, a substantial portion of the literature was not explicitly mechanistic, and many studies reported molecular or cellular endpoints rather than clinically interpretable healing outcomes. Taken together, the mapped evidence suggests that biologic plausibility and clinical readiness should not be treated as equivalent concepts in this area [1–4,88,89].

4.2. Relevance to Musculoskeletal and Sports Medicine

From a musculoskeletal and sports medicine perspective, the central finding of this review is not that TB4 or TB-500 lack biologic activity. Rather, it is that the published literature does not match the way these peptides are often discussed in clinical, performance, or public-facing settings [1–3,90–92]. Human evidence in this review was concentrated in ocular/cornea and wound/skin/soft tissue applications [18,24,26,29,38,63,68,82,84–87]. No human interventional studies of administered TB4 or TB-500 were identified in tendon, ligament, muscle, bone, cartilage, adipose/fat graft, or spine/intervertebral disc categories; the human cartilage studies were endogenous/no direct intervention studies rather than administered peptide interventions [9,41,66,77]. This disconnect is clinically relevant because peptides have attracted increasing attention in regenerative medicine and sports medicine more broadly, while TB4- and TB-500-related products remain under regulatory and anti-doping scrutiny [1,3,5,6,90,91].

Another important point is that the literature captured under the umbrella of TB4 and TB-500 is not methodologically uniform. The mapped studies included direct peptide administration, endogenous-expression studies, derivative or fragment work, and biomaterial-assisted or cell-assisted delivery strategies [9,14,16,19,25,37,60,67,72]. These approaches are biologically related, but they are not interchangeable when the question is whether a specific peptide or peptide-labeled product has clinically useful effects [4,9,16,25,37,60,67,72,88]. That distinction is especially important in musculoskeletal medicine, where clinical interest often focuses on direct treatment claims for tendon, ligament, cartilage, muscle, or bone injury, yet the underlying literature remains concentrated elsewhere. That mismatch may be amplified by online marketing, gray-market distribution, and user-driven discussion forums that can blur the difference between mechanistic signal, product labeling, and clinically validated use [90–92].

4.3. Implications for Future Research

The clearest research gap is the absence of direct human musculoskeletal interventional studies of administered TB4 or TB-500. Future work should prioritize clearly defined clinical indications in tendon, ligament, muscle, cartilage, and bone rather than relying on extrapolation from ocular, wound, or vascular models. Within preclinical research, greater consistency in tissue-specific models, dose selection, route of administration, comparator choice, and endpoint reporting would make the literature easier to interpret across studies. More work is also needed to separate peptide effects from platform effects in combination studies pairing TB4 with scaffolds, hydrogels, exosomes, or stem cell-based approaches [10,12,20,21,50,67].

A second priority is clearer intervention definition. The current literature includes TB4, TB-500, and shorter derivative or fragment constructs, but these categories are often discussed together despite limited direct equivalence data [16,25,37,60,72]. Future studies should distinguish these interventions explicitly and report formulation, sequence, dose, route, and comparator details in a way that supports translation and reproducibility. For clinicians and researchers, that would make it easier to determine whether a study meaningfully informs a specific musculoskeletal use case or instead reflects a related but different biologic strategy. More broadly, the preclinical literature should be interpreted with the same caution applied in other areas of biomedical translation, where encouraging animal and mechanistic signals often fail to translate cleanly into human benefit [89].

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4.4. Limitations of This Scoping Review

This review has several limitations. As a scoping review, it was designed to map the literature rather than evaluate treatment efficacy, and no formal risk of bias or methodological quality appraisal was performed [7]. The search was limited to PubMed, Europe PMC, and ClinicalTrials.gov, and only English-language sources were included. Grey literature capture was limited, conference abstracts without full text were excluded, and authors were not contacted for missing information. Accordingly, some relevant evidence may not have been captured.

The synthesis also relied on structured categorization of dominant tissue, mechanism, intervention, and outcome domains. For studies spanning multiple tissues or mechanistic pathways, those classifications necessarily simplified more complex experimental designs. In addition, the literature was heterogeneous across study type, intervention format, and reported outcomes, so quantitative pooling was neither planned nor appropriate. These limitations should be kept in mind when interpreting the breadth of the mapped literature and the relative prominence of specific categories within it.

5. Conclusions

In this scoping review, the literature on TB4 and TB-500 in tissue healing, regeneration, and musculoskeletal repair was broad but uneven. The mapped evidence was dominated by preclinical studies, concentrated in wound/skin/soft tissue, vascular/endothelial, and ocular settings, and centered on TB4 rather than TB-500. Human evidence directly relevant to musculoskeletal applications was limited, and direct TB-500 evidence was minimal.

Overall, the available literature supports biologic interest in several repair-related pathways but provides limited human clinical evidence for musculoskeletal use. Future work should prioritize clearly defined musculoskeletal indications, direct human studies, and better separation of TB4, TB-500, and derivative interventions. In broader context, these findings support a cautious distinction between mechanistic interest and clinically actionable evidence in a landscape shaped by strong public enthusiasm, online commercialization, and limited direct validation [3,89–92].

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org and can be downloaded at: https://doi.org/10.17605/osf.io/jtdh4, Supplementary Appendix S1: Electronic search strategies for PubMed, Europe PMC, and ClinicalTrials.gov; Supplementary File S2: final charted dataset, coding definitions, and screening summary.

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Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Definition
ECM	extracellular matrix
FDA	U.S. Food and Drug Administration
PCC	population, concept, and context
PK	pharmacokinetic
PRISMA-ScR	Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
TB4	thymosin beta-4
TB-500	peptide commonly referred to as TB-500
WADA	World Anti-Doping Agency

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