

REVIEWER'S REPORT

Manuscript No.: IJAR-58973

Title: APPLICATION OF THERAPEUTIC ULTRASOUND IN KNEE OSTEOARTHRITIS: AN INTEGRATIVE REVIEW OF RANDOMIZED CLINICAL TRIALS.

Recommendation:

Accept as it is

Accept after minor revision.....

Accept after major revision ...YES.....

Do not accept (*Reasons below*)

Rating	Excel.	Good	Fair	Poor
Originality		☐		
Techn. Quality			☐	
Clarity		☐		
Significance		☐		

Reviewer's ID: JPR- 094

Detailed Reviewer's Report

Reviewer's Report

1. Overall Assessment

The manuscript, ***"Application of Therapeutic Ultrasound in Knee Osteoarthritis: An Integrative Review of Randomized Clinical Trials,"** addresses a clinically relevant topic in physiotherapy and conservative management of knee osteoarthritis. The manuscript attempts to synthesize recent evidence regarding conventional therapeutic ultrasound, LIPUS, phonophoresis, and focused ultrasound.

The topic is potentially valuable; however, the current manuscript has important concerns regarding **study eligibility, methodological rigor, inclusion of studies that do not directly evaluate therapeutic ultrasound in knee osteoarthritis, search strategy, quality appraisal, data synthesis, and strength of the conclusions**. In particular, several included studies use ultrasound only as a component of a multimodal intervention or were conducted in healthy participants, which makes it difficult to conclude that therapeutic ultrasound itself is responsible for the reported benefits.

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2. Strengths of the Manuscript

1. ****Clinically relevant topic:**** Knee osteoarthritis is a major cause of pain, disability, and reduced quality of life, making evaluation of conservative treatment modalities important.
2. ****Focus on recent evidence:**** The review attempts to summarize RCT evidence from 2020–2026, providing a contemporary perspective.
3. ****Different ultrasound modalities are considered:**** The manuscript discusses conventional therapeutic ultrasound, LIPUS, phonophoresis, and focused ultrasound/neuromodulation.
4. ****Use of PICO/PICOS framework:**** The authors have appropriately attempted to structure the research question using PICO and PICOS.
5. ****Relevant clinical outcomes:**** Pain, WOMAC, Lequesne index, range of motion, gait parameters, and other functional outcomes are considered.
6. ****Recognition of heterogeneity:**** The authors appropriately identify differences in ultrasound frequency, intensity, duty cycle, treatment duration, and combination therapies as important limitations.
7. ****Recent emerging technology:**** Discussion of focused ultrasound neuromodulation provides an interesting perspective on the future development of ultrasound-based treatment.
8. ****The manuscript identifies an important clinical issue:**** The observation that ultrasound combined with therapeutic exercise may provide greater benefits than ultrasound alone is clinically meaningful.

3. Weaknesses / Major Concerns

Major Concern 1: Inconsistency between eligibility criteria and included studies

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The manuscript states that studies published between ****2020 and 2026**** were eligible, but the Results section states that the identified RCTs were published between ****2024 and 2026****.

The authors should clearly explain:

- * How many studies were identified for 2020–2023?
- * Were there no eligible RCTs during this period?
- * How many records were retrieved initially?
- * How many were excluded during screening and for what reasons?

A PRISMA-style flow diagram would substantially improve transparency.

Major Concern 2: Several included studies do not directly evaluate therapeutic ultrasound as the intervention

This is probably the ****most important methodological problem****.

For example, ****Ikeda et al. (2024 and 2026)**** involved healthy participants rather than patients with knee osteoarthritis. Therefore, these studies do not meet the stated population criterion of adults with knee OA.

Similarly, ****Kamal et al. (2025)**** appears to investigate gait training/physical performance, with ultrasound being part of a conventional protocol rather than the primary intervention.

The authors should reconsider whether such studies belong in the main evidence synthesis.

****Recommendation:**** Studies involving healthy participants should either be excluded from the systematic clinical evidence synthesis or placed in a clearly separated ****“mechanistic/experimental evidence”**** section.

Major Concern 3: Lack of isolation of the ultrasound effect

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A considerable proportion of the included trials combine ultrasound with other interventions such as:

- * exercise,
- * TENS,
- * hot packs,
- * laser therapy,
- * shockwave therapy,
- * gait training.

Consequently, it is difficult to determine whether the observed improvement resulted from ultrasound or from the accompanying treatment.

For example, if both groups receive ultrasound and one group additionally receives exercise, superiority of the combination does ****not demonstrate the independent efficacy of ultrasound****.

The manuscript should therefore distinguish between:

****A. Evidence for ultrasound alone****

and

****B. Evidence for ultrasound as an adjunct to another treatment.****

This distinction is essential for a clinically meaningful conclusion.

Major Concern 4: No formal risk-of-bias or methodological quality assessment

The manuscript describes itself as an integrative review but does not provide a systematic assessment of the methodological quality of the included RCTs.

Important domains should be assessed, including:

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- * random sequence generation,
- * allocation concealment,
- * participant/personnel blinding,
- * outcome assessor blinding,
- * incomplete outcome data,
- * selective reporting,
- * sample-size calculation,
- * intention-to-treat analysis,
- * attrition/dropout,
- * baseline comparability.

A recognized tool such as ****RoB 2**** would be appropriate for randomized trials.

Without quality assessment, all included studies appear to contribute equally to the conclusion, which may be misleading.

Major Concern 5: Search strategy requires improvement

The search strategy is described as:

> `"therapeutic ultrasound" OR "low-intensity pulsed ultrasound" OR "phonophoresis" AND "knee osteoarthritis" AND "randomized controlled trial"``

The Boolean structure is potentially problematic because ****AND/OR operators should be grouped using parentheses****.

A more appropriate structure would be conceptually:

****("therapeutic ultrasound" OR "low-intensity pulsed ultrasound" OR phonophoresis OR "focused ultrasound") AND ("knee osteoarthritis" OR "knee OA") AND ("randomized controlled trial" OR randomized OR randomised)****

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The complete search strategy for each database should be reported so that the review can be reproduced.

Major Concern 6: Google Scholar search is insufficiently reproducible

Google Scholar is mentioned as a database, but the manuscript does not explain:

- * search date,
- * number of results screened,
- * search limitations,
- * screening procedure,
- * whether the first 100/200/etc. results were examined.

This should be clarified.

Major Concern 7: No information on duplicate removal and study selection

The methodology does not adequately describe:

- * how duplicate records were removed,
- * how titles/abstracts were screened,
- * whether full-text screening was performed,
- * whether screening was performed by one or two reviewers,
- * how disagreements were resolved.

For a literature review intended to synthesize clinical evidence, these details are important.

Major Concern 8: The conclusion appears stronger than the evidence supports

The conclusion states that therapeutic ultrasound has a *****“favorable analgesic and functional effect”****.

However, the manuscript itself acknowledges:

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- * substantial parameter heterogeneity,
- * small samples,
- * multimodal interventions,
- * lack of ultrasound-only comparisons,
- * differences in outcome measures,
- * inclusion of mechanistic studies in healthy participants.

Therefore, the evidence does not appear sufficiently homogeneous to conclude broadly that therapeutic ultrasound itself is consistently effective.

The conclusion should be more cautious, for example:

> Current evidence suggests that some ultrasound-based interventions may provide additional benefits for pain and functional outcomes when incorporated into multimodal rehabilitation programs; however, the independent clinical efficacy of therapeutic ultrasound remains uncertain because of substantial heterogeneity and limited ultrasound-specific comparisons.

4. Key Points That Should Be Addressed

Methodological key points

1. Provide a ****PRISMA flow diagram****.
2. Clearly report the ****number of records identified, screened, excluded, and included****.
3. Explain why no studies from ****2020–2023**** appear in the final table despite the stated search period.
4. Provide the ****complete database-specific search strategies****.
5. Clarify the Boolean operators and use of parentheses.
6. Explain duplicate removal and screening procedures.
7. State whether screening/data extraction was performed by one or multiple reviewers.
8. Include a ****risk-of-bias assessment****.
9. Provide the methodological quality of each included RCT.
10. Consider reporting the review according to an appropriate reporting guideline.

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Scientific key points

1. Separate ****ultrasound monotherapy**** from ****ultrasound as an adjunct****.
2. Remove or separately classify studies involving ****healthy participants****.
3. Clearly distinguish ****therapeutic ultrasound**** from ****diagnostic ultrasound**** and ultrasound-guided procedures.
4. Discuss the clinical relevance of the differences in VAS/WOMAC rather than relying only on statistical significance.
5. Report treatment parameters consistently:
 - * frequency,
 - * intensity,
 - * duty cycle,
 - * treatment duration,
 - * treatment frequency,
 - * treatment area,
 - * coupling medium.
6. Discuss adverse events and safety more systematically.
7. Avoid attributing effects to ultrasound when the intervention contains multiple components.
8. Consider whether phonophoresis should be analyzed separately from conventional therapeutic ultrasound because it involves ****drug delivery plus ultrasound****.

5. Significance of the Manuscript

The manuscript has ****moderate potential significance**** because it addresses an important clinical question and focuses on newer ultrasound technologies.

Its strongest potential contribution is the identification of the apparent trend that:

****ultrasound-based treatment may be more useful as an adjunct to active rehabilitation rather than as a stand-alone intervention.****

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The discussion of LIPUS and focused ultrasound neuromodulation is also potentially interesting because these technologies represent newer applications beyond traditional thermal therapeutic ultrasound.

However, the scientific significance is currently reduced by the methodological limitations and inappropriate mixing of:

- * clinical RCTs in knee OA,
- * multimodal rehabilitation trials,
- * phonophoresis studies,
- * focused ultrasound neuromodulation,
- * and mechanistic studies in healthy volunteers.

A more rigorous classification of these evidence categories would substantially increase the manuscript's value.

6. Specific Recommendations for Revision

Table 1 should be revised

I recommend adding the following columns:

Author/year	Sample	OA severity	Intervention	Ultrasound parameters	Comparator	Duration	Primary outcomes	Main results	Risk of bias
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

This would make comparison between studies much easier.

The studies should also be classified into separate groups:

****Group 1 – Conventional therapeutic ultrasound in knee OA****

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****Group 2 – LIPUS in knee OA****

****Group 3 – Phonophoresis in knee OA****

****Group 4 – Focused ultrasound/neuromodulation****

****Group 5 – Mechanistic studies in healthy participants****

This would prevent inappropriate pooling of fundamentally different interventions and populations.

7. Minor Comments

1. The title should preferably use *****“randomized controlled trials”***** rather than “randomized clinical trials” if that is the actual study design being included.
2. There are several grammatical and formatting issues that require language editing.
3. The term *****“knee osteoarthritis”***** should be used consistently rather than alternating unnecessarily between KOA and knee OA.
4. “Key words:-” should be formatted as *****“Keywords:”*****.
5. The reference formatting should be checked carefully for consistency.
6. Complete DOI links should be provided consistently rather than only the DOI suffix in Table 1.
7. The phrase *****“Source: prepared by the author”***** is acceptable, but the methodology used to construct the table should be clearly described.
8. The clinical significance of reported changes should be discussed in addition to ***p*-values**.
9. The manuscript should discuss adverse events and tolerability of ultrasound interventions.

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10. The distinction between ****high-intensity continuous ultrasound (HICUS)**** and conventional therapeutic ultrasound should be clearly explained.

8. Recommendation to the Editor

****Recommendation: MAJOR REVISION****

****Rationale:**** The manuscript addresses an important and clinically relevant topic and contains potentially useful recent evidence. However, substantial methodological and interpretive problems need to be corrected before the manuscript can be considered suitable for publication.

The most important revisions are:

1. ****Correct the eligibility/inclusion of studies that do not meet the population/intervention criteria.****
2. ****Separate direct therapeutic-ultrasound evidence from multimodal and mechanistic evidence.****
3. ****Provide a transparent study-selection process/PRISMA flow diagram.****
4. ****Add formal risk-of-bias/quality assessment.****
5. ****Improve and fully report the search strategy.****
6. ****Moderate the conclusions so that they do not overstate the independent efficacy of therapeutic ultrasound.****
7. ****Clarify the actual contribution of ultrasound when it is combined with exercise, shockwave therapy, TENS, laser, or other interventions.****

Yes. Based on the manuscript you provided, “Major Revision” is justified mainly because there are several internal methodological contradictions and problems with the selection and interpretation of the included studies. Below is a line-by-line reviewer justification, with the line number, issue, and reason .

Detailed Reviewer Comments — Line by Line

Line(s)	Issue identified	Reason / Reviewer justification
2	Title says “Integrative Review of Randomized Clinical	The title suggests that only RCT evidence is synthesized, but the manuscript subsequently includes healthy-volunteer

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Line(s)	Issue identified	Reason / Reviewer justification
	Trials"	mechanistic studies. The title and actual study selection are therefore inconsistent.
6–8	Abstract states RCTs from 2020–2026	The Results section (lines 114–119) says the included trials were actually from 2024–2026 . The authors must clarify whether eligible studies from 2020–2023 existed and, if excluded, provide reasons.
8–10	Broad claim covering continuous US, LIPUS, phonophoresis and focused US	These are substantially different interventions with different mechanisms and clinical purposes. Combining them under one therapeutic-ultrasound category may lead to an inappropriate overall conclusion.
9–11	"Most consistent outcomes were pain reduction and functional improvement"	This conclusion is difficult to support because many included studies used multimodal interventions , making it impossible to determine how much improvement was attributable specifically to ultrasound.
10	"Combining ultrasound with exercise was superior to isolated application"	This statement requires careful qualification. Some studies compare combinations with different interventions rather than directly comparing ultrasound + exercise versus ultrasound alone.
11	"Parameter heterogeneity limits conclusions"	This is appropriately acknowledged, but the same heterogeneity should also result in a more cautious conclusion than the one currently presented.

Introduction

Line(s)	Issue	Reason
18–23	General description of OA	Appropriate background, but references should be provided for epidemiology, socioeconomic burden, and progression to arthroplasty.
24–30	Therapeutic US, LIPUS, phonophoresis and focused US presented together	These technologies should be clearly differentiated. Conventional therapeutic US, LIPUS, phonophoresis and focused ultrasound neuromodulation are not interchangeable interventions.
30	"broadened the clinical applications of this technology in knee osteoarthritis"	This statement may overgeneralize the evidence. Focused ultrasound neuromodulation is an emerging technology and should not be presented as an established extension of conventional therapeutic US without qualification.
31–33	Combination with exercise and shockwave therapy	Combination treatment creates a major confounding issue . Improvement cannot necessarily be attributed to ultrasound.
34–40	Heterogeneity acknowledged	Good observation, but the methodology does not subsequently provide a formal method for dealing with this heterogeneity.
42–48	Mechanistic evidence introduced	Mechanistic evidence from healthy participants should not be used directly to establish therapeutic efficacy in patients with knee OA. Biological plausibility is not equivalent to clinical effectiveness.
45	Ikeda studies cited	The later table confirms these studies were conducted in healthy participants . Therefore, they do not satisfy the stated PICO population of patients with knee OA.
46–48	Inflammatory markers cited	Reduction in inflammatory markers following combined LIPUS +

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Line(s)	Issue	Reason
	from combined treatment	shockwave treatment cannot establish that LIPUS alone caused the effect.
50–53	Research question specifies patients aged 20–70 years with knee OA	This creates a direct contradiction with the inclusion of healthy participants in lines 167–172.
54–60	Objective includes “critical analysis”	A critical analysis requires formal assessment of methodological quality/risk of bias, which is not adequately reported later.

Methodology

Lines 61–67

Issue	Reason
Integrative review methodology is described, but the actual implementation is insufficiently detailed.	The authors mention six steps but do not provide sufficient information about screening, reviewers, duplicate removal, quality assessment, or risk of bias.

Lines 68–85 — PICO/PICOS

Line(s)	Issue	Reason
72–73	Population = men and women aged 20–70 with knee OA	This criterion is violated by Ikeda et al. , whose participants were healthy.
74–76	Intervention includes US alone or combined with other interventions	This very broad criterion creates difficulty in determining the independent effect of ultrasound.
77–79	Comparator includes exercise, laser, shockwave etc.	Comparators are highly heterogeneous, making direct synthesis problematic.
80–82	Primary outcomes include pain/function plus biomechanical and biochemical outcomes	These outcomes are very different in clinical meaning and should preferably be separated into primary clinical outcomes and exploratory/mechanistic outcomes.
83–85	PICOS restricted to RCTs	This makes the inclusion of mechanistic healthy-volunteer studies particularly problematic, even though they are crossover randomized studies. Their population does not meet PICO .

Search Strategy

Lines 86–93

This is one of the areas requiring substantial revision.

Line(s)	Issue	Reason
87–88	Four databases listed	The authors should provide the date of the search for each database.
89–90	Boolean search string	The search expression lacks adequate parentheses around OR terms. Boolean precedence can change which records are retrieved.

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Line(s)	Issue	Reason
89–91	Search strategy is not fully reproducible	Exact database-specific search strings, filters, dates and limits should be reported.
88–90	“English and Portuguese descriptors”	The actual Portuguese search terms are not provided.
91–93	PEDro search described differently	The authors should provide the exact PEDro search procedure and number of records retrieved.
87–93	No search date	Since the review includes 2026 , the exact final search date is essential.
87–93	No information about duplicate removal	It is unclear how duplicate citations across PubMed, SciELO, Google Scholar and PEDro were handled.

Eligibility Criteria

Lines 94–104

This section contains a **major internal contradiction**.

Line(s)	Issue	Reason
95	Only RCTs included	Generally appropriate.
96	Publication January 2020–2026	Results only contain studies from 2024–2026. This needs explanation.
96–97	Age 20–70	Some included participants are ≥ 65 , which is acceptable, but exact age distributions should be reported.
97–99	Knee OA required	Ikeda 2024 and Ikeda 2026 involve healthy participants , so they do not satisfy this criterion.
98–99	US alone or combined with another resource	This is too broad to determine the specific therapeutic contribution of US.
100–104	Exclusion criteria	The criteria are not sufficient to explain the exclusion of studies based on intervention characteristics, sample characteristics, or inadequate comparator.

Most serious eligibility problem:

Lines 72–73 say the population must have knee OA.

But:

Lines 167–172 explicitly acknowledge that Ikeda et al. (2024; 2026) were conducted in healthy volunteers.

Therefore, these two studies **should not have been included in the primary evidence synthesis under the stated eligibility criteria**.

This alone is a strong justification for **Major Revision**.

Data Extraction and Synthesis

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Issue	Reason
No description of who performed data extraction	It should be stated whether extraction was performed independently by two reviewers.
No risk-of-bias assessment	This is a major weakness for a review of RCTs.
No quality scoring	The reader cannot determine which studies are methodologically stronger or weaker.
Narrative synthesis only	Narrative synthesis can be appropriate, but the rationale for not performing quantitative synthesis should be stated.
Ultrasound parameters mentioned but not systematically presented	Frequency, intensity, duty cycle, duration and treatment frequency are crucial to this review and should be presented consistently.

Results**Lines 113–119**

Issue	Reason
“set of RCTs published between 2024 and 2026”	Contradicts the stated 2020–2026 search period.
No number of records retrieved	The reader cannot assess the comprehensiveness of the search.
No number excluded	Screening transparency is absent.
No PRISMA flow diagram	Strongly recommended for transparent reporting of literature identification and selection.

Table 1 — Major Problems***Abed et al. (2024)***

The study is relevant, but the intervention contains **metformin phonophoresis + exercise**, phonophoresis alone, and conventional US.

Problem:

The superior outcome in the combination group cannot automatically be interpreted as evidence that **therapeutic ultrasound is effective**.

Reviewer concern:

The effect of **exercise and metformin delivery** needs to be separated from the effect of ultrasound.

Yang et al. (2025)

LIPUS alone vs aerobic exercise vs LIPUS + aerobic exercise is highly relevant.

However:

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The review should report:

exact LIPUS parameters,
treatment frequency,
treatment duration,
sample size in each arm,
baseline comparability,
effect size,
confidence intervals,
adverse events.

Simply stating that the combination was “superior” is insufficient for a critical review.

Khadour et al. (2025)

Major issue:

LIPUS + shockwave therapy was compared with shockwave therapy alone.

Therefore, the study primarily demonstrates the **additional effect of adding LIPUS to shockwave therapy**, not necessarily the effectiveness of LIPUS as an independent treatment.

The conclusion should reflect this distinction.

Ilfeld et al. (2025)

This is a promising study, but it is described as a **pilot feasibility study**.

Issue:

A pilot/feasibility RCT should not be given the same evidentiary weight as a sufficiently powered efficacy RCT.

The authors should clearly distinguish: **feasibility/safety evidence** from **clinical efficacy evidence**.

Sharma et al. (2025)

Issue:

Ibuprofen gel phonophoresis is not equivalent to conventional therapeutic ultrasound.

The therapeutic effect could arise from:

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ibuprofen,
ultrasound-mediated delivery,
placebo/contextual effects,
or the phonophoresis procedure.

Therefore, phonophoresis should preferably be analyzed as a **separate therapeutic modality**.

Atan et al. (2024)

This study is particularly problematic for the review's central question.

The table says:

“Therapeutic US + TENS + hot pack in all groups.”

Problem:

If ultrasound was provided to all groups, the study does **not determine the efficacy of ultrasound**.

The observed difference appears to be attributable primarily to the treadmill intervention.

Therefore, this study provides limited evidence concerning the independent effectiveness of therapeutic ultrasound.

Cp et al. (2024)

Again:

US + isometric strengthening was used as baseline treatment.

The comparison is essentially conventional treatment versus conventional treatment + shockwave therapy.

Problem:

The study demonstrates the additional value of shockwave therapy, **not the independent efficacy of ultrasound**.

It should therefore not be used as strong evidence supporting therapeutic ultrasound efficacy.

Ikeda et al. (2024)

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Critical eligibility problem

The table itself states:

“healthy”

This violates the stated PICO population:

“men and women aged 20 to 70 years with ... knee osteoarthritis.”

Therefore, this study should be:

excluded from the main clinical evidence synthesis, or

placed in a separate section titled something such as:

“Mechanistic evidence from healthy participants.”

Ikeda et al. (2026)

Exactly the same concern applies.

The study involves:

“healthy”

participants.

Therefore, it does not answer the review question concerning therapeutic ultrasound in **patients with knee OA**.

It can support **biological plausibility**, but not clinical efficacy in OA.

Kamal et al. (2025)

The manuscript itself says:

“ultrasound was used only for baseline characterization.”

This is a very important problem.

If ultrasound was not the therapeutic intervention being evaluated, this study should **not be included as evidence for therapeutic ultrasound**.

It appears to evaluate gait/physical performance rather than the therapeutic effect of ultrasound.

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This study should be removed from the main review unless the authors can demonstrate that therapeutic ultrasound was actually administered as an intervention.

Lines 124–136 — Conventional Ultrasound

The heading suggests evidence concerning conventional therapeutic ultrasound.

However, both examples are **multimodal interventions**.

Problem:

The reader cannot determine the independent contribution of ultrasound.

Therefore, this section should be renamed, for example:

“Therapeutic ultrasound as a component of multimodal rehabilitation.”

That would make the interpretation scientifically more accurate.

Lines 137–147 — LIPUS

This is one of the stronger sections.

However:

Yang et al.

The combination of LIPUS + exercise being superior does not necessarily prove that LIPUS itself is clinically superior.

Khadour et al.

LIPUS + shockwave vs shockwave alone provides evidence for **incremental benefit**, not LIPUS monotherapy.

Therefore, the wording “synergistic effect” should be used cautiously unless the study statistically tested an interaction/synergy.

Lines 148–158 — Phonophoresis

Major conceptual issue:

Phonophoresis is not simply another “ultrasound modality” in the same sense as conventional US or LIPUS.

It involves **ultrasound-assisted transdermal drug delivery**.

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Therefore, the pharmacological effect of the delivered drug is an important confounder.

The review should analyze:

conventional therapeutic ultrasound

And **phonophoresis** separately.

Lines 159–165 — Focused Ultrasound

This section is reasonable but needs caution.

Problem:

The authors describe it as:

“promising”

But a pilot study primarily establishes feasibility/safety and provides preliminary efficacy information.

Therefore, “promising” should be accompanied by language emphasizing that **clinical effectiveness remains uncertain**.

Lines 166–172 — Healthy Participants

This is perhaps the clearest justification for major revision.

The authors explicitly state:

“although carried out in healthy volunteers”

Yet these studies were included in the review.

Reviewer decision:

They do not satisfy the predefined population criterion and should not be part of the primary clinical evidence synthesis.

They may be retained only as **supportive mechanistic evidence**, clearly separated from RCT evidence in patients with OA.

Discussion — Lines 173–192

Lines 174–176

The manuscript states:

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therapeutic ultrasound ... has a “favorable and consistent effect”

Problem:

This is **too strong** given the evidence presented.

Why?

Because:

several studies use multimodal therapy;

some studies don't test ultrasound independently;

two studies involve healthy participants;

one study appears not to evaluate therapeutic ultrasound as the intervention;

interventions and ultrasound parameters are heterogeneous;

no formal risk-of-bias assessment is presented.

Therefore, “favorable and consistent” should be softened.

Lines 177–181

The statement that combination with exercise produces greater gains is reasonable, but it should not be interpreted as proof that ultrasound itself is responsible.

Exercise is already an established active treatment for knee OA.

The authors should discuss whether ultrasound provides **additional clinically meaningful benefit over exercise alone**.

Lines 182–188

Problem:

The manuscript uses inflammatory and biomechanical findings to support clinical effectiveness.

However:

biological plausibility $\neq$ clinical efficacy.

Reduction of inflammatory markers or fat-pad stiffness does not automatically establish meaningful improvement in pain or function.

These should be described as **mechanistic/supportive evidence**.

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Lines 189–192

The focused ultrasound discussion is interesting, but it should be clearly described as **early-stage evidence** rather than evidence supporting established therapeutic use.

Lines 193–209 — Limitations

This is actually a good section, but there is an important problem:

The authors identify many of the same problems that undermine their own conclusion.

They acknowledge

heterogeneity,

small samples,

variable outcomes,

inability to isolate ultrasound effects,

age discrepancies.

Yet the conclusion still states that therapeutic ultrasound “**exerts a favorable analgesic and functional effect.**”

The conclusion should therefore be revised to correspond to the limitations.

Conclusion — Lines 210–219

Major concern

The conclusion is stronger than the methodology supports.

The statement:

“therapeutic ultrasound ... exerts a favorable analgesic and functional effect”

should be modified.

A more defensible conclusion would be:

“Current evidence suggests that some ultrasound-based interventions may provide additional improvements in pain and functional outcomes when incorporated into multimodal rehabilitation programs; however, the independent clinical efficacy of therapeutic ultrasound remains uncertain because of substantial heterogeneity,

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limited ultrasound-specific comparisons, and methodological limitations of the available trials.”

This would be much more scientifically appropriate.

References — Lines 220–260

The references need careful verification and formatting.

Issues to check:

Verify every DOI.

Verify that every cited article is actually an RCT.

Verify that the population matches the manuscript's eligibility criteria.

Verify that ultrasound was actually used therapeutically.

Verify sample sizes.

Verify treatment parameters.

Verify whether the reported outcomes accurately reflect the original publications.

Ensure consistent reference formatting.

Provide complete DOI information in Table 1 rather than only DOI suffixes.

Why I Recommend MAJOR REVISION, Not Minor Revision

The problems are **not merely grammar, formatting, or presentation issues**. They affect the **validity of the review's central conclusion**.

The five most important reasons are:

1. Eligibility contradiction

The review requires knee OA patients, but **Ikeda 2024 and 2026 used healthy participants**.

2. Questionable inclusion of Kamal et al.

The manuscript itself says ultrasound was used only for **baseline characterization**, which does not appear to satisfy the therapeutic intervention criterion.

3. Ultrasound effect cannot be isolated

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Several studies administer ultrasound together with exercise, TENS, hot packs, shockwave therapy, laser, etc. Therefore, the review cannot confidently attribute benefits to ultrasound.

4. No formal risk-of-bias assessment

For a review claiming to critically synthesize RCT evidence, this is a significant methodological omission.

5. Conclusion overstates the evidence

The manuscript concludes that therapeutic ultrasound has a favorable and consistent effect despite substantial heterogeneity and limited evidence for ultrasound as an independent treatment.

Final Reviewer Recommendation

Recommendation: MAJOR REVISION

Reviewer justification:

The manuscript addresses a clinically relevant and potentially valuable topic; however, substantial methodological and interpretative issues currently limit the validity of its conclusions. The principal concerns include inconsistencies between the predefined eligibility criteria and the included studies, particularly the inclusion of healthy participants; questionable inclusion of studies in which ultrasound was not the therapeutic intervention; extensive use of multimodal interventions that prevents isolation of the specific effect of ultrasound; insufficient description of the study-selection process and search strategy; absence of a formal risk-of-bias assessment; and conclusions that appear stronger than warranted by the available evidence. The authors should revise the eligibility and classification of studies, separate direct ultrasound evidence from adjunctive and mechanistic evidence, provide transparent study-selection and quality-assessment procedures, and moderate the conclusions accordingly. These issues require substantial methodological revision rather than minor editorial correction.

Most critical reviewer comment: *The authors should not claim that therapeutic ultrasound is consistently effective in knee OA until studies in which ultrasound is only one component of multimodal treatment, studies involving healthy participants, and studies where ultrasound is not the therapeutic intervention are appropriately reclassified or excluded.*