

Supplementary Table 1 Search strategies for the effects of capsaicin or menthol on abdominal pain in IBS (RCTs), which were performed through August 2024.

Pubmed	Web of Science	Embase	Cochrane Library
1. "Irritable Bowel Syndrome"[Mesh]	1. (((TS=(Irritable Bowel Syndrome)) OR TS=(Irritable Bowel Syndromes)) OR TS=(Irritable Colon)) OR TS=(Mucous Colitides)) OR TS=(Mucous Colitis)	1. irritable bowel syndrome'/exp	1. MeSH descriptor: [Irritable Bowel Syndrome] explode all trees
2. (((Irritable Bowel Syndrome[Title/Abstract]) OR (Irritable Bowel Syndromes[Title/Abstract])) OR (Irritable Colon[Title/Abstract])) OR (Irritable Colon[Title/Abstract]) OR (Mucous Colitis[Title/Abstract])	2. ((((((((((TS=(Capsaicin)) OR TS=(Capsaicine)) OR TS=(8-Methyl-N-Vanillyl-6-Nonenamide)) OR TS=(8 Methyl N Vanillyl 6 Nonenamide)) OR TS=(Antiphlogistine Rub A-535 Capsaicin)) OR TS=(Axsain)) OR TS=(Zostrix)) OR TS=(Capzasin)) OR TS=(NGX-4010)) OR TS=(NGX4010)) OR TS=(Capsin)	2. 'irritable bowel syndrome':ti,ab	2. (Irritable Bowel Syndrome):ti,ab,kw OR (Irritable Bowel Syndromes):ti,ab,kw OR (Irritable Colon):ti,ab,kw OR (Mucous Colitides):ti,ab,kw OR (Mucous Colitis):ti,ab,kw
3. ("Irritable Bowel Syndrome"[Mesh]) OR (((Irritable Bowel Syndrome[Title/Abstract]) OR (Irritable Bowel Syndromes[Title/Abstract])) OR (Irritable Colon[Title/Abstract])) OR (Irritable Colon[Title/Abstract]) OR (Mucous Colitis[Title/Abstract])	3. TS=(random*)	3. 'irritable bowel syndromes':ti,ab	3. MeSH descriptor: [Capsaicin] explode all trees
4. "Capsaicin"[Mesh]		4. 'irritable colon':ti,ab	4. (Capsaicin):ti,ab,kw OR (Capsaicine):ti,ab,kw OR (Axsain):ti,ab,kw OR (Zostrix):ti,ab,kw OR (Capzasin):ti,ab,kw
5. ((((((((((capsaicin[Title/Abstract]) OR (Capsaicine[Title/Abstract])) OR (8-Methyl-N-Vanillyl-6-Nonenamide[Title/Abstract])) OR (8 Methyl N Vanillyl 6 Nonenamide[Title/Abstract])) OR (Antiphlogistine Rub A-535 Capsaicin[Title/Abstract])) OR (Axsain[Title/Abstract])) OR		5. 'mucous colitides':ti,ab	5. (Capsin):ti,ab,kw OR (8 Methyl N Vanillyl 6 Nonenamide):ti,ab,kw OR (NGX 4010):ti,ab,kw OR (NGX4010):ti,ab,kw
		6. 'mucous colitis':ti,ab	6. (random*):ti,ab,kw
		7. #1 OR #2 OR #3 OR #4 OR #5 OR #6	7. #1 OR #2
		8. 'capsaicin'/exp	8. #3 OR #4 OR #5
		9. 'capsaicin':ab,ti	9. #6 AND #7 AND #8
		10. 'capsaicine':ab,ti	10. MeSH descriptor: [Menthol] explode all trees
		11. '8-methyl-n-vanillyl-6-nonenamide':ab,ti	
		12. '8 methyl n vanillyl 6 nonenamide':ab,ti	
		13. 'axsain':ab,ti	
		14. 'zostrix':ab,ti	
		15. 'capzasin':ab,ti	
		16. 'antiphlogistine rub a-535 capsaicin':ab,ti	

(Zostrix[Title/Abstract])) OR
 (Capzasin[Title/Abstract])) OR (NGX-
 4010[Title/Abstract])) OR (NGX
 4010[Title/Abstract])) OR
 (NGX4010[Title/Abstract])) OR (NGX-
 4010[Title/Abstract])
 6. ("Capsaicin"[Mesh]) OR
 (((((((((((capsaicin[Title/Abstract]) OR
 (Capsaicine[Title/Abstract])) OR (8-Methyl-
 N-Vanillyl-6-Nonenamide[Title/Abstract]))
 OR (8 Methyl N Vanillyl 6
 Nonenamide[Title/Abstract])) OR
 (Antiphlogistine Rub A-535
 Capsaicin[Title/Abstract])) OR
 (Axsain[Title/Abstract])) OR
 (Zostrix[Title/Abstract])) OR
 (Capzasin[Title/Abstract])) OR (NGX-
 4010[Title/Abstract])) OR (NGX
 4010[Title/Abstract])) OR
 (NGX4010[Title/Abstract])) OR (NGX-
 4010[Title/Abstract]))
 7. ((randomized controlled trial[Publication
 Type]) OR (randomized[Title/Abstract])) OR
 (placebo[Title/Abstract])
 8. (((("Irritable Bowel Syndrome"[Mesh])
 OR (((Irritable Bowel

4. #1 AND #2 AND #3
 5. ((TS=(Menthol)) OR TS=(5-
 methyl-2-(1-methylethyl)))
 OR
 TS=((1alpha,2beta,5alpha)-
 Isomer)
 6. #1 AND #3 AND #5

17. 'ngx-4010':ab,ti
 18. 'ngx 4010':ab,ti
 19. 'ngx4010':ab,ti
 20. 'capsin':ab,ti
 21. #8 OR #9 OR #10 OR
 #11 OR #12 OR #13
 OR #14 OR #15 OR
 #16 OR #17 OR #18
 OR #19 OR #20
 22. 'random':ab,ti
 23. 'placebo':ab,ti
 24. #22 OR #23
 25. #7 AND #21 AND
 #24
 26. 'menthol'/exp
 27. 'menthol':ab,ti
 28. 'cyclohexanol':ab,ti
 29. '5-methyl-2-(1-
 methylethyl)':ab,ti
 30. '(1alpha,2beta,5alpha)-
 isomer':ab,ti
 31. #26 OR #27 OR #28
 OR #29 OR #30
 32. #7 AND #24 AND
 #31

11. (Cyclohexanol):ti,ab,kw OR
 (5methyl2(1methylethyl)):ti,ab,kw OR
 ((1alpha,2beta,5alpha)Isomer):ti,ab,kw
 12. #10 OR #11
 13. #6 AND #7 AND #12

Syndrome[Title/Abstract]) OR (Irritable
Bowel Syndromes[Title/Abstract])) OR
(Irritable Colon[Title/Abstract])) OR (Irritable
Colon[Title/Abstract])) OR (Mucous
Colitis[Title/Abstract])) AND
(("Capsaicin"[Mesh] OR
(((((((((((capsaicin[Title/Abstract]) OR
(Capsaicine[Title/Abstract])) OR (8-Methyl-
N-Vanillyl-6-Nonenamide[Title/Abstract]))
OR (8 Methyl N Vanillyl 6
Nonenamide[Title/Abstract])) OR
(Antiphlogistine Rub A-535
Capsaicin[Title/Abstract])) OR
(Axsain[Title/Abstract])) OR
(Zostrix[Title/Abstract])) OR
(Capzasin[Title/Abstract])) OR (NGX-
4010[Title/Abstract])) OR (NGX
4010[Title/Abstract])) OR
(NGX4010[Title/Abstract])) OR (NGX-
4010[Title/Abstract])))) AND (((randomized
controlled trial[Publication Type]) OR
(randomized[Title/Abstract])) OR
(placebo[Title/Abstract]))
9. "Menthol"[Mesh]
10. ((Cyclohexanol[Title/Abstract]) OR (5-
methyl-2-(1-methylethyl[Title/Abstract]))))

OR ((1alpha,2beta,5alpha)-
Isomer[Title/Abstract])

11. ("Menthol"[Mesh]) OR
(((Cyclohexanol[Title/Abstract]) OR (5-
methyl-2-(1-methylethyl[Title/Abstract])))

OR ((1alpha,2beta,5alpha)-
Isomer[Title/Abstract]))

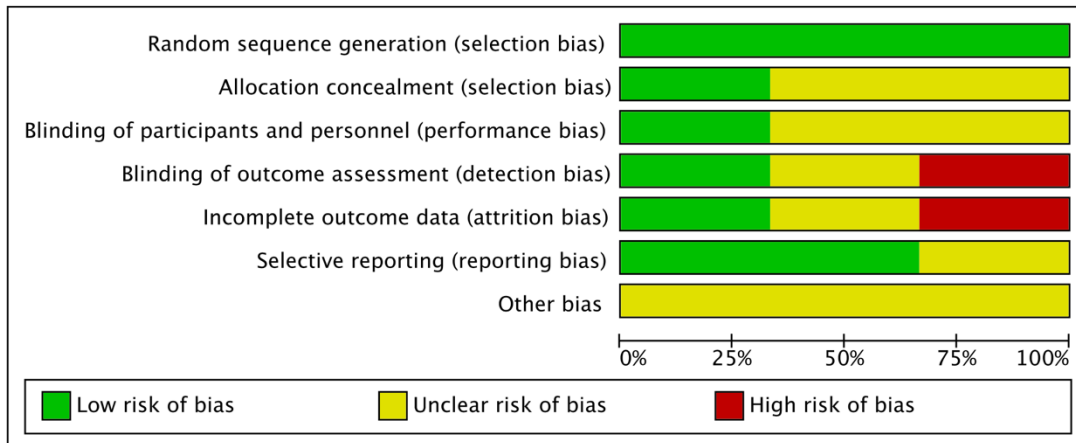
12. (("Irritable Bowel Syndrome"[Mesh])

OR (((((Irritable Bowel
Syndrome[Title/Abstract]) OR (Irritable
Bowel Syndromes[Title/Abstract])) OR
(Irritable Colon[Title/Abstract])) OR (Irritable
Colon[Title/Abstract])) OR (Mucous
Colitis[Title/Abstract]))) AND

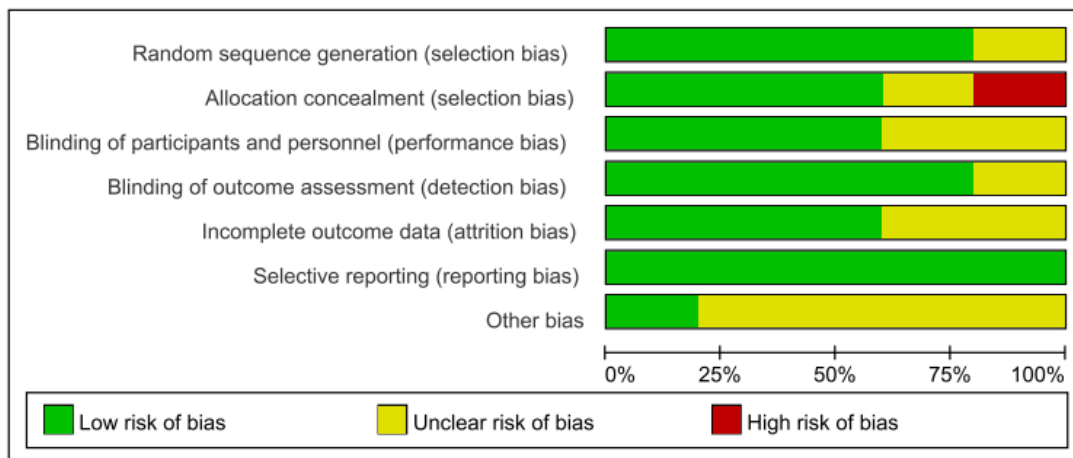
("Menthol"[Mesh]) OR
(((Cyclohexanol[Title/Abstract]) OR (5-
methyl-2-(1-methylethyl[Title/Abstract])))

OR ((1alpha,2beta,5alpha)-
Isomer[Title/Abstract]))) AND

(((randomized controlled trial[Publication
Type]) OR (randomized[Title/Abstract])) OR
(placebo[Title/Abstract]))



Supplementary Figure 1 Risk-of-bias assessment for the capsaicin included studies. Trials with a low or high risk of bias in key domains were categorized as having a “low risk of bias” or “high risk of bias”, respectively. Otherwise, trials were categorized as having an “unclear risk of bias”.



Supplementary Figure 2 Risk-of-bias assessment for the menthol included studies. Trials with a low or high risk of bias in key domains were categorized as having a “low risk of bias” or “high risk of bias”, respectively. Otherwise, trials were categorized as having an “unclear risk of bias”.

Author(s):
Question: Capsaicin compared to placebo for abdominal pain in irritable bowel syndrome
Setting:
Bibliography:

Certainty assessment							N _e of patients		Effect		Certainty	Importance
N _e of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	capsaicin	placebo	Relative (95% CI)	Absolute (95% CI)		
VAS score												
3	randomised trials	not serious	not serious	not serious	not serious	none	59	63	-	SMD 0.34 higher (0.02 lower to 0.7 higher)	⊕⊕⊕⊕ High	

CI: confidence interval; SMD: standardised mean difference

Supplementary Figure 3 GRADE Assessment of researches about RCTs of the effects of capsaicin on abdominal pain in irritable bowel syndrome.

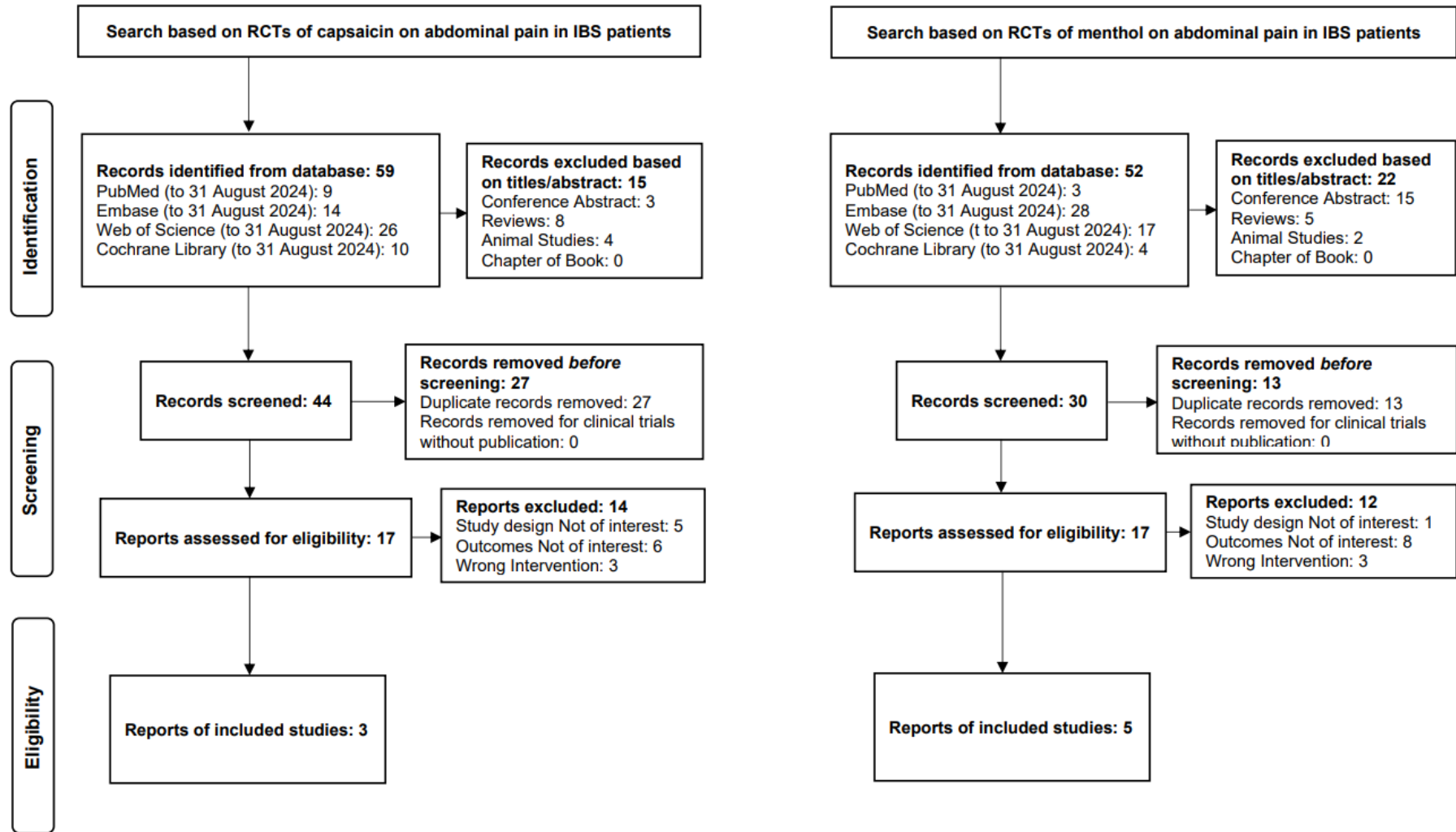
Author(s):
Question: Menthol compared to placebo for abdominal pain in irritable bowel syndrome
Setting:
Bibliography:

Certainty assessment							N _e of patients		Effect		Certainty	Importance
N _e of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	menthol	placebo	Relative (95% CI)	Absolute (95% CI)		
IBS symptom scores												
5	randomised trials	not serious	not serious	not serious	not serious	none	179	184	-	SMD 0.38 lower (0.67 lower to 0.1 lower)	⊕⊕⊕⊕ High	

CI: confidence interval; SMD: standardised mean difference

Supplementary Figure 4 GRADE Assessment of researches about RCTs of the effects of menthol on abdominal pain in irritable bowel syndrome.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

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