How Natrol misrepresents the research on Promensil

Natrol's claims in ads and on the label

Natrol's Promensil magazine ad says: "Why promensil?...22 clinical studies can't be wrong. Promensil provides more than relief from hot flashes! Promensil is a natural alternative for menopause that is clinically proven to safely relieve hot flashes, night sweats, sleep disturbances and mood swings while promoting breast health, heart health and emotional well-being...If you are experiencing menopause symptoms, don't suffer any longer, get Promensil today and get back in control of your days and your nights."



Natrol's Promensil television ad says: "Try the

only supplement proven to reduce menopause symptoms. Plus maintain heart and breast health. Now available: Promensil Post-Menopause, the 2 in 1 bone and heart health supplement. Visit promensil.com."

Natrol's Promensil label says: "Balance your hormones, Stay in Control. Relieves hot flashes. Relieves night sweats. Promotes breast health. Promotes heart health. Clinically proven & doctor recommended. Natural relief for menopausal symptoms and more. Why do women around the world use Promensil? Clinical research has shown that in cultures consuming a natural diet abundant in isoflavones women have fewer and milder menopausal symptoms. Promensil's active ingredients are Red Clover isoflavones, which complement the body's declining estrogen levels around menopause, so relieving menopausal symptoms and promoting breast health and heart health. Independent research has proven Promensil to be the only product to contain the amount of isoflavones claimed on the package."

The 22 "can't be wrong" studies

You won't find a list of 22 "can't be wrong" clinical studies on either Natrol's or Promensil's websites. Here is the list of the 22 studies that Natrol provided to CSPI. We have kept their numbering from (1) to (22) and annotated each with a summary of the results. Natrol included studies testing two other red clover supplements, Rimostil and Menoflavon.

Natrol's list of 22 studies actually contains only 17 relevant studies. Studies (1), (2), and (5) are the same study. Natrol counted it three times. Studies (15) and (18) are the same study. Natrol counted it twice. Studies (10) and (20) are pharmacokinetic studies that



traced the digestion, absorption, and metabolism of red clover supplements and didn't look for or find any health benefits, so it doesn't belong on this list.

Does Promensil relieve hot flashes or overall menopausal symptoms?

The totality of the evidence does not support these claims.

Five of the studies tested the effect of Promensil on hot flashes. Three of the five, including the largest two and the longest one, found the supplement <u>ineffective</u> for reducing the average number of daily hot flashes. Promensil did not lessen the frequency of hot flashes in 86 British women (1), 23 Australian women (7), or 84 U.S. women (12). Two small trials of 15 Peruvian women (4) and of 15 Dutch women (16) found that Promensil reduced the average number of daily hot flashes from 7 to 4 and 5 to 4, respectively, after two to four months.

Five of the studies tested the effect of Promensil on overall menopausal symptoms. Four of the five, including the largest two and the longest one, found the supplement ineffective for lessening the severity of menopausal symptoms, as measured by the widely used Greene Climacteric Scale. This Scale tracks the severity of psychological, physical, and vasomotor symptoms. Promensil did not relieve menopausal symptoms in 86 British women (1), 23 Australian women (7), 84 U.S. women (12), or 15 Dutch women (16). The one Promensil trial that detected an effect on symptoms, a small trial of 15 middle-class Peruvian women, provided no details about the scale used (4). A sixth trial using a different red clover product called Menoflavon and employing an older menopausal symptom scale called the Kupperman index found that two tablets a day for 3 months improved symptoms in 53 Ecuadoran women (18).

(1) Atkinson C, Warren RM, Sala E, et al. Red-clover-derived isoflavones and mammographic breast density: a double-blind, randomized, placebo-controlled trial [ISRCTN42940165]. Breast Cancer Res. 2004;6:R170-R179. [PMID 15084240]

Promensil did not reduce hot flashes or other menopausal symptoms in 86 women and did not increase breast density (unlike conventional HRT). "...(O)ur findings suggest that the isoflavone supplement at the dose given was not acting as an oestrogen or as an anti-oestrogen." Novogen provided the pills, analyzed the urine for isoflavones, and provided research support for one of the authors.

4. Jeri A. The use of an isoflavone supplement to relieve hot flushes. Female Patient. 2002:27:35-37. [PMID Not Indexed]

Promensil reduced the frequency and intensity of hot flashes in 15 postmenopausal Peruvian women. "This study demonstrates that dietary supplementation with red clover-derived isoflavones is an effective alternative for relief of vasomotor symptoms in postmenopausal women..." Financial support not described.



7. Knight DC, Howes JB, Eden JA. The effect of Promensil, an isoflavone extract, on menopausal symptoms. Climacteric. 1999;2:79-84. [PMID 11910671]

Promensil had no effect on the frequency of hot flashes or on other menopausal symptoms or on vaginal maturation in 23 postmenopausal women taking 40 mg or 160 mg/d. HDL rose in those taking 40 mg but not in those taking 160 mg. The authors suspected that inadvertent use of dietary isoflavones in the placebo group may have affected the results. Funded by Novogen. One of the authors is a Novogen employee.

12. Tice JA, Ettinger B, Ensrud K, Wallace R, Blackwell T, Cummings SR. Phytoestrogen supplements for the treatment of hot flashes: the Isoflavone Clover Extract (ICE) Study: a randomized controlled trial. JAMA. 2003;290:207-214. [PMID 12851275]

Neither Promensil nor Rimostil reduced the frequency of hot flashes or affected anxiety, depression, or sexual desire in 165 menopausal women. Women taking Promensil (but not Rimostil) had slightly fewer hot flashes during weeks 4 to 7 of the study, but not before or after this period. "...(N)either supplement had a clinically significant effect on hot flashes or other menopausal symptoms when compared with a placebo." Funded by Novogen.

16. van de Weijer PH, Barentsen R. Isoflavones from red clover (Promensil) significantly reduce menopausal hot flush symptoms compared with placebo. Maturitas. 2002;42:187-193. [PMID <u>12161042</u>]

Promensil reduced the frequency of hot flashes but not overall menopausal symptoms in 16 postmenopausal women. Funded by Novogen.

18. Hidalgo LA, Chedraui PA, Morocho N, Ross S, San Miguel G. The effect of red clover isoflavones on menopausal symptoms, lipids and vaginal cytology in menopausal women: a randomized, double-blind, placebo-controlled study. Gynecol Endocrinol. 2005;21:257-264. [PMID <u>16373244</u>]

This is the same study as (15). A red clover extract decreased menopausal symptoms and triglycerides and improved vaginal karyopyknotic, cornification and basal cell matural indices in 53 postmenopausal Ecuadoran women. It did not affect blood pressure, total cholesterol, or LDL. Pills were provided by Melbrosin International of Vienna, Austria.

Does Promensil promote "heart health," as Natrol's ad claims?

The totality of the evidence looking at the established risk factors for heart disease does not support this claim.

Eight studies (2, 8, 9, 11, 13, 17, 18, 22) found <u>no effect</u> of Promensil on total cholesterol. One unpublished study found that Promensil lowered total cholesterol in postmenopausal Peruvian women (3).

Six studies (2, 8, 9, 11, 13, 18) found no effect of Promensil on LDL levels.



Four studies (2, 8, 9, 11) found <u>no effect</u> of Promensil on HDL levels. One study (7) found that HDL rose with 40 mg of Promensil but not with 160 mg a day, suggesting that the change at 40 mg was just random variation. Another study (17) found that HDL levels rose in postmenopausal but not in premenopausal women.

Five studies (2, 9, 18, 21, 22) found <u>no effect</u> of Promensil on blood pressure. One study (11) found an effect of Promensil on daytime blood pressure but not on overall 24-hour blood pressure.

Five studies (2, 8, 9, 11, 17) found <u>no effect</u> of Promensil on triglycerides levels. One study (18) found a decrease. Triglycerides are considered an emerging risk factor for heart disease.

Promensil improved arterial compliance in 17 postmenopausal women (8) and arterial stiffness in 34 postmenopausal women (21). These markers are not currently recognized as risk factors for heart disease.

2. Atkinson C, Oosthuizen W, Scollen S, Loktionov A, Day NE, Bingham SA. Modest protective effects of isoflavones from a red clover-derived dietary supplement on cardiovascular disease risk factors in perimenopausal women, and evidence of an interaction with ApoE genotype in 49-65 year-old women. J Nutr. 2004;134:1759-1764. [PMID 15226466]

This is the same trial as (1) above. Promensil did not change total cholesterol, LDL, HDL, triglycerides, fibrinogen, systolic blood pressure, or diastolic blood pressure among all the women. "...(T)here was no significant effects of the isoflavone supplement...on the cardiovascular risk factors measured in this population of women as a whole." There was a suggestion that Promensil might lower triglycerides in perimenopausal women and plasminogen activator inhibitor type 1 (which is involved in clotting), but the authors pointed out that the "sample sizes were small and a larger study is required to confirm these findings." Novogen provided the pills.

3. Jeri A. Effects of isoflavone phytoestrogens on lipid profile in postmenopausal Peruvian women. Paper presented at: 10th World Congress on the Menopause; 2002; Berlin, Germany.

In this unpublished, un-peer-reviewed study, Promensil is reported to have reduced total cholesterol by 10.2% in postmenopausal Peruvian women. Support not described.

8. Nestel PJ, Pomeroy S, Kay S, et al. Isoflavones from red clover improve systemic arterial compliance but not plasma lipids in menopausal women. J Clin Endocrinol Metab. 1999;84:895-898. [PMID <u>10084567</u>] Erratum in: J Clin Endocrinol Metab. 1999:84:3647



Promensil significantly improved arterial compliance in 17 postemenopausal women, but did not affect total cholesterol, LDL, HDL, or triglycerides. Funded by Novogen.

9. Howes JB, Sullivan D, Lai N, et al. The effects of dietary supplementation with isoflavones from red clover on the lipoprotein profiles of post menopausal women with mild to moderate hypercholesterolaemia. Atherosclerosis. 2000;152:143-147. [PMID 10996349]

Isoflavones from red clover did not affect total cholesterol, LDL, HDL, triglycerides, or blood pressure in 66 postmenopausal women. "...(I)soflavone supplementation using the extract from red clover chosen does not have a significant impact on plasma lipid profiles of postmenopausal women with moderately elevated plasma cholesterol levels." Funded by Novogen.

11. Howes JB, Tran D, Brillante D, Howes LG. Effects of dietary supplementation with isoflavones from red clover on ambulatory blood pressure and endothelial function in postmenopausal type 2 diabetes. Diabetes Obes Metab. 2003;5:325-332. [PMID 12940870]

Red clover isoflavones lowered daytime blood pressure by an average of 8/4 in 18 postmenopausal type 2 diabetics, but had no effect on overall 24-hour blood pressure. It also increased forearm vascular resistance in response to L-nitromonomethylarginine (L-NMMA), a measure of endothelial function. The isoflavones had no effect on total cholesterol, LDL, HDL, trigylcerides, or fasting blood glucose. Funded by Novogen.

13. Knudson Schult T, Ensrud KE, Blackwell T, Ettinger B, Wallace R, Tice JA. Effect of isoflavones on lipids and bone turnover markers in menopausal women. Maturitas. 2004;48:209-218. [PMID <u>15207886</u>]

Neither Promensil nor Rimostil had an effect on markers of bone turnover or on total cholesterol and LDL. The red clover isoflavones may have had effects on HDL and triglycerides, but these were "small in magnitude." "This study suggest little clinical benefit from isoflavone supplementation." Novogen provided the pills.

17. Campbell MJ, Woodside JV, Honour JW, Morton MS, Leathem AJ. Effect of red clover-derived isoflavone supplementation on insulin-like growth factor, lipid and antioxidant status in healthy female volunteers: a pilot study. Eur J Clin Nutr. 2004;58:173-173. [PMID <u>14679383</u>]

Promensil had no effect on IGF status, antioxidant status, total cholesterol, or triglycerides in 7 postmenopausal women. It did raise HDL levels, but the authors pointed out this needed more study since the number of women was small. Promensil had no effect on antioxidant status, total cholesterol, HDL, or triglyucerides in 16 premenopausal women. It had a "relatively weak" effect on IGF status, which the authors pointed out "may, in fact, be negligible." Novogen provided the pills.



18. Hidalgo LA, Chedraui PA, Morocho N, Ross S, San Miguel G. The effect of red clover isoflavones on menopausal symptoms, lipids and vaginal cytology in menopausal women: a randomized, double-blind, placebo-controlled study. Gynecol Endocrinol. 2005;21:257-264. [PMID <u>16373244</u>]

This is the same study as (15). A red clover extract decreased menopausal symptoms and triglycerides and improved vaginal karyopyknotic, cornification and basal cell matural indices in 53 postmenopausal Ecuadoran women. It did not affect blood pressure, total cholesterol, or LDL. Pills were provided by Melbrosin International of Vienna, Austria.

21. Teede HJ, McGrath BP, DeSilva L, Cehun M, Fassoulakis A, Nestel PJ. Isoflavones reduce arterial stiffness: a placebo-controlled study in men and postmenopausal women. Arterioscler Thromb Vasc Biol. 2003;23:1066-1071. [PMID 12714433]

Red clover isoflavones rich in formononetin but not in biochanin improved arterial stiffness in 34 postmenopausal women without improving flow-mediated dilation or blood pressure. Supported by Novogen.

22. Howes JB, Bray K, Lorenz L, Smerdely P, Howes LG. The effects of dietary supplementation with isoflavones from red clover on cognitive function in postmenopausal women. Climacteric. 2004;7:70-77. [PMID: <u>15259285</u>]

Rimostil did not affect scores in standardized cognitive function tests, blood pressure, or cholesterol in 14 postmenopausal women. "Isioflavone supplementation does not appear to have major short-term effects on cognitive function in postmenopausal women." Supported by Novogen.

Does Promensil promote "breast health," as Natrol's ad claims?

One study looked at cyclical mastalgia.

6. Ingram DM, Hickling C, West L, Mahe LJ, Dunbar PM. A double-blind randomized controlled trial of isoflavones in the treatment of cyclical mastalgia. Breast. 2002;11:170-174. [PMID 14965665]

Promensil reduced the "breast pain score" in five women with cyclical mastalgia who took 40 mg/d, but not in seven women with mastalgia who took 80 mg/d. Nine of 12 taking Promensil reported more than a 25% decrease in pain vs two of the six who received a placebo. "We have demonstrated that a commercial preparation of isoflavones may provide relief from mastalgia for most women." Funded by Novogen.

Does Promensil promote "bone health," as Natrol's ad claims?

Promensil had mixed effects on bone health.



5. Atkinson C, Compston JE, Day NE, Dowsett M, Bingham SA. The effects of phytoestrogen isoflavones on bone density in women: a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr. 2004;79:326-333. [PMID 14749241]

This is the same trial as (1) above. Promensil reduced the loss of mineral content and bone mineral density in the lumbar spine but not in the hip. It increased two bone formation markers, but had no effect on markers of bone resorption (breakdown). "...(O)ur findings suggest that, through attenuation of bone loss, the isoflavone supplement has a potentially protective effect on the lumbar spine." Novogen provided the pills, analyzed the urine for isoflavones, and provided research support for one of the authors.

13. Knudson Schult T, Ensrud KE, Blackwell T, Ettinger B, Wallace R, Tice JA. Effect of isoflavones on lipids and bone turnover markers in menopausal women. Maturitas. 2004;48:209-218. [PMID 15207886]

Neither Promensil nor Rimostil had an effect on markers of bone turnover or on total cholesterol and LDL. The red clover isoflavones may have had effects on HDL and triglycerides, but these were "small in magnitude." "This study suggest little clinical benefit from isoflavone supplementation." Novogen provided the pills.

Effects of Promensil on the uterus and vagina

14. Imhof M, Gocan A, Reithmayr F, et al. Effects of a red clover extract (MF11RCE) on endometrium and sex hormones in postmenopausal women. Maturitas. 2006;55:76-81. [PMID 16513301]

A red clover extract raised testosterone levels and decreased endometrial thickness in 109 postmenopausal women. Pills were provided by Melbrosin International of Vienna, Austria.

15. Chedraui P, Hidalgo L, San Miguel G, Morocho N, Ross S. Red clover extract (MF11RCE) supplementation and postmenopausal vaginal and sexual health. Int J Gynaecol Obstet. 2006;95:296-297. [PMID <u>17007858</u>]

In an un-peer-reviewed study, a red clover extract improved vaginal karyopyknotic, cornification and basal cell maturation, dyspareunia, and libido in 53 postmenopausal Ecuadoran women. Funded by Melbrosin International of Vienna, Austria.

19. Woods R, Colville N, Blazquez J, Cooper A, Whitehead MI. Effects of red clover isoflavones (Promensil) versus placebo on uterine endometrium, vaginal maturation index and the uterine artery in healthy postmenopausal women. Paper presented at: Annual Meeting of the British Menopause Society; July 3-4, 2003; Manchester, England.

In an un-peer-reviewed abstract, Promensil improved the "vaginal maturation index" for the change in percentage of cells in the superficial layer. Promensil did not affect the



"pulsatility" index of the uterine artery or endometrial thickness. "Longer studies assessing the endometrium would be needed to confirm this positive effect." Support not described.

Effect of Promensil on cognition

22. Howes JB, Bray K, Lorenz L, Smerdely P, Howes LG. The effects of dietary supplementation with isoflavones from red clover on cognitive function in postmenopausal women. Climacteric. 2004;7:70-77. [PMID: 15259285]

Rimostil did not affect scores in standardized cognitive function tests, blood pressure, or cholesterol in 14 postmenopausal women. "Isoflavone supplementation does not appear to have major short-term effects on cognitive function in postmenopausal women." Supported by Novogen.

Observational studies

10. Setchell KD, Brown NM, Desai P, et al. Bioavailability of pure isoflavones in healthy humans and analysis of commercial soy isoflavone supplements. J Nutr. 2001;131(suppl 4):1362S-1375S. [PMID <u>11285356</u>]

This was an "observational" study, according to the authors. It observed the bioavailability of pure isoflavones in healthy humans and did not test for any health benefits.

20. Howes J, Waring M, Huang L, Howes LG. Long-term pharmacokinetics of an extract of isoflavones from red clover (Trifolium pratense). J Altern Complement Med. 2002;8:135-142. [PMID 12006121]

This is a two-week pharmacokinetic study of Promensil's absorption and metabolism. It did not look for or find health benefits.

Here is the complete list of 22 studies.

PMID refers to the Medline ID number for each study. The links are to abstracts in PubMed.

References

1. Atkinson C, Warren RM, Sala E, et al. Red-clover-derived isoflavones and mammographic breast density: a double-blind, randomized, placebo-controlled trial [ISRCTN42940165]. Breast Cancer Res. 2004;6:R170-R179. [PMID 15084240]
2. Atkinson C, Oosthuizen W, Scollen S, Loktionov A, Day NE, Bingham SA. Modest protective effects of isoflavones from a red clover-derived dietary supplement on cardiovascular disease risk factors in perimenopausal women, and evidence of an interaction with ApoE genotype in 49-65 year-old women. J Nutr. 2004;134:1759-1764. [PMID 15226466]



- 3. Jeri A. Effects of isoflavone phytoestrogens on lipid profile in postmenopausal Peruvian women. Paper presented at: 10th World Congress on the Menopause; 2002; Berlin, Germany.
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- 6. Ingram DM, Hickling C, West L, Mahe LJ, Dunbar PM. A double-blind randomized controlled trial of isoflavones in the treatment of cyclical mastalgia. Breast. 2002;11:170-174. [PMID 14965665]
- 7. Knight DC, Howes JB, Eden JA. The effect of Promensil, an isoflavone extract, on menopausal symptoms. Climacteric. 1999;2:79-84. [PMID <u>11910671</u>]
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- 11. Howes JB, Tran D, Brillante D, Howes LG. Effects of dietary supplementation with isoflavones from red clover on ambulatory blood pressure and endothelial function in postmenopausal type 2 diabetes. Diabetes Obes Metab. 2003;5:325-332. [PMID 12940870]
- 12. Tice JA, Ettinger B, Ensrud K, Wallace R, Blackwell T, Cummings SR. Phytoestrogen supplements for the treatment of hot flashes: the Isoflavone Clover Extract (ICE) Study: a randomized controlled trial. JAMA. 2003;290:207-214. [PMID 12851275] 13. Knudson Schult T, Ensrud KE, Blackwell T, Ettinger B, Wallace R, Tice JA. Effect of isoflavones on lipids and bone turnover markers in menopausal women. Maturitas. 2004;48:209-218. [PMID 15207886]
- 14. Imhof M, Gocan A, Reithmayr F, et al. Effects of a red clover extract (MF11RCE) on endometrium and sex hormones in postmenopausal women. Maturitas. 2006;55:76-81. [PMID <u>16513301</u>]
- 15. Chedraui P, Hidalgo L, San Miguel G, Morocho N, Ross S. Red clover extract (MF11RCE) supplementation and postmenopausal vaginal and sexual health. Int J Gynaecol Obstet. 2006;95:296-297. [PMID 17007858]
- 16. van de Weijer PH, Barentsen R. Isoflavones from red clover (Promensil) significantly reduce menopausal hot flush symptoms compared with placebo. Maturitas. 2002;42:187-193. [PMID 12161042]
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antioxidant status in healthy female volunteers: a pilot study. Eur J Clin Nutr. 2004;58:173-173. [PMID 14679383]

- 18. Hidalgo LA, Chedraui PA, Morocho N, Ross S, San Miguel G. The effect of red clover isoflavones on menopausal symptoms, lipids and vaginal cytology in menopausal women: a randomized, double-blind, placebo-controlled study. Gynecol Endocrinol. 2005;21:257-264. [PMID 16373244]
- 19. Woods R, Colville N, Blazquez J, Cooper A, Whitehead MI. Effects of red clover isoflavones (Promensil) versus placebo on uterine endometrium, vaginal maturation index and the uterine artery in healthy postmenopausal women. Paper presented at: Annual Meeting of the British Menopause Society; July 3-4, 2003; Manchester, England. 20. Howes J, Waring M, Huang L, Howes LG. Long-term pharmacokinetics of an extract of isoflavones from red clover (Trifolium pratense). J Altern Complement Med. 2002;8:135-142. [PMID 12006121]
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- 22. Howes JB, Bray K, Lorenz L, Smerdely P, Howes LG. The effects of dietary supplementation with isoflavones from red clover on cognitive function in postmenopausal women. Climacteric. 2004;7:70-77. [PMID: 15259285]

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